Overview information for

Nicotine

NICOTINE REFERENCES					
Author Name	Title	Journal	Volume	Page number(s)	Year
Mallock N, Schulz T, Malke S, Dreiack N, Laux P, Luch A.	Levels of nicotine and tobacco-specific nitrosamines in oral nicotine pouches	Tobacco Control	33(2)	193-199	2024
Keyser BM, Flockton H, Weidman RA, Payne R, Rowe J, Jordan KG.	In vitro permeation of nicotine and tobacco specific nitrosamines from smokeless tobacco product extracts in a 3D buccal tissue model	Toxicology Letters	392	36-45	2024
Joshi J, Pandit A, Shah F.	Nicotine mediated epithelial modulations: An in-vitro evidence	Journal of Oral Biology and Craniofacial Research	13(6)	796-800	2023
Susanne Back, Anna E Masser, Lars E Rutqvist, Johan Lindholm	Harmful and potentially harmful constituents (HPHCs) in two novel nicotine pouch products in comparison with regular smokeless tobacco products and pharmaceutical nicotine replacement therapy products (NRTs)	BMC chemistry	17(1)	9	2023
Benowitz NL.	The Central Role of pH in the Clinical Pharmacology of Nicotine: Implications for Abuse Liability, Cigarette Harm Reduction and FDA Regulation.	Clin Pharmacol Ther.	May;111(5)	1004-1006	2022
Cheetham AG, Plunkett S, Campbell P, Hilldrup J, Coffa BG, Gilliland S 3rd, Eckard S.	Analysis and differentiation of tobacco-derived and synthetic nicotine products: Addressing an urgent regulatory issue.	PLoS One.	Apr 14;17(4)	e0267049	2022
Horinouchi T, Miwa S.	Comparison of cytotoxicity of cigarette smoke extract derived from heat-not-burn and combustion cigarettes in human vascular endothelial cells.	J Pharmacol Sci.	Nov;147(3)	223-233	2021
MacLean RR, DeVito EE, Eid T, Parida S, Gueorguieva R, Sofuoglu M.	Threshold dose for intravenous nicotine self-administration in young adult non-dependent smokers.	Psychopharmacology (Berl).	Aug;238(8)	2083-2090.	2021

Chavarrio Cañas JE, Monge-Palacios M, Grajales-González E, Sarathy SM.	Early Chemistry of Nicotine Degradation in Heat-Not-Burn Smoking Devices and Conventional Cigarettes: Implications for Users and Second- and Third-Hand Smokers.	J Phys Chem A.	Apr 22;125(15)	3177-3188	2021
Ho JTK, Tyndale RF, Baker TB, Amos CI, Chiu A, Smock N, Chen J, Bierut LJ, Chen LS.	Racial disparities in intensity of smoke exposure and nicotine intake among low-dependence smokers.	Drug Alcohol Depend.	Apr 1;221	108641	2021
Kuiper N, Coats EM, Crawford TN, Gammon DG, Loomis B, Watson CH, Melstrom PC, Lavinghouze R, Rogers T, King BA.	Trends in Manufacturer-Reported Nicotine Yields in Cigarettes Sold in the United States, 2013-2016.	Prev Chronic Dis.	Nov 25;17	E148.	2020
Lei X, Goel R, Sun D, Bhangu G, Bitzer ZT, Trushin N, Ma L, Richie JP Jr, Xiu G, Muscat JE.	Free Radical and Nicotine Yields in Mainstream Smoke of Chinese Marketed Cigarettes: Variation with Smoking Regimens and Cigarette Brands.	Chem Res Toxicol.	Jul 20;33(7)	1791-1797	2020
St Helen G, Nardone N, Addo N, Dempsey D, Havel C, Jacob P 3rd, Benowitz NL.	Differences in nicotine intake and effects from electronic and combustible cigarettes among dual users.	Addiction.	Apr;115(4)	757-767.	2020

Smith TT, Koopmeiners JS, Hatsukami DK, Tessier KM, Benowitz NL, Murphy SE, Strasser AA, Tidey JW, Blount BC, Valentin L, Bravo Cardenas R, Watson C, Pirkle JL, Donny EC.	Mouth-Level Nicotine Intake Estimates from Discarded Filter Butts to Examine Compensatory Smoking in Low Nicotine Cigarettes.	Cancer Epidemiol Biomarkers Prev.	Mar;29(3)	643-649.	2020
Pauwels CGGM, Boots AW, Visser WF, Pennings JLA, Talhout R, Schooten FV, Opperhuizen A	Characteristic Human Individual Puffing Profiles Can Generate More TNCO than ISO and Health Canada Regimes on Smoking Machine When the Same Brand Is Smoked	Int J Environ Res Public Health.	17(9)	3225	2020
Yu C, Yu J, Zhang H, He Z, Sha Y, Liu B, Wang Y.	A facile approach for rapid on-site screening of nicotine in natural tobacco.	Environ Pollut.	259	113841	2020
Benowitz NL, St Helen G, Nardone N, Cox LS, Jacob P.	Urine Metabolites for Estimating Daily Intake of Nicotine From Cigarette Smoking.	Nicotine Tob Res.	22(2)	288-292	2020
Nelson JM, Cuadra GA, Palazzolo DL.	A Comparison of Flavorless Electronic Cigarette-Generated Aerosol and Conventional Cigarette Smoke on the Planktonic Growth of Common Oral Commensal Streptococci.	Int J Environ Res Public Health.	16(24)	5004	2019
Marusich JA, Wiley JL, Silinski MAR, Thomas BF, Meredith SE, Gahl RF, Jackson KJ.	Comparison of cigarette, little cigar, and waterpipe tobacco smoke condensate and e-cigarette aerosol condensate in a self-administration model.	Behav Brain Res.	372	112061	2019

McEwan M, Coburn S, Ghosh D, Simms L, Giles L, Yuki D, Ashley M, Roemer E, Sohn HO, Proctor C.	Assessment of priority tobacco additives per the requirements of the EU Tobacco Products Directive (2014/40/EU): Part 3, Smoking behavior and plasma nicotine pharmacokinetics.	Regul Toxicol Pharmacol.	104	29-38	2019
Li X, Luo Y, Jiang X, Zhang H, Zhu F, Hu S, Hou H, Hu Q, Pang Y.	Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes.	Nicotine Tob Res.	21(1)	111-118	2019
Lorkiewicz P, Riggs DW, Keith RJ, Conklin DJ, Xie Z, Sutaria S, Lynch B, Srivastava S, Bhatnagar A.	Comparison of Urinary Biomarkers of Exposure in Humans Using Electronic Cigarettes, Combustible Cigarettes, and Smokeless Tobacco.	Nicotine Tob Res.	21(9)	1228-1238	2019
Cai B, Li Z, Wang R, Geng Z, Shi Y, Xie S, Wang Z, Yang Z, Ren X.	Emission level of seven mainstream smoke toxicants from cigarette with variable tobacco leaf constituents.	Regul Toxicol Pharmacol.	103	181-188	2019
Thirión-Romero I, Pérez-Padilla R, Zabert G, Barrientos-Gutiérrez I.	Respiratory Impact Of Electronic Cigarettes And "Low-Risk" Tobacco.	Rev Invest Clin.	71(1)	17-27	2019
Ha TN, Madison MC, Kheradmand F, Altman KW.	Laryngeal inflammatory response to smoke and vape in a murine model.	Am J Otolaryngol.	40(1)	89-92	2019
Taylor AE, Richmond RC, Palviainen T, Loukola A, Wootton RE, Kaprio J, Relton CL, Davey Smith G, Munafò MR.	The effect of body mass index on smoking behaviour and nicotine metabolism: a Mendelian randomization study.	Hum Mol Genet.	28(8)	1322-1330	2019
Mercincavage M, Lochbuehler K, Wileyto EP, Benowitz NL, Tyndale RF, Lerman C, Strasser AA.	Association of Reduced Nicotine Content Cigarettes With Smoking Behaviors and Biomarkers of Exposure Among Slow and Fast Nicotine Metabolizers: A Nonrandomized Clinical Trial.	JAMA Netw Open.	1(4)	e181346. doi: 10.1001/jamanetworkopen.2018.1346	2018

Zhang H, Pang Y, Luo Y, Li X, Chen H, Han S, Jiang X, Zhu F, Hou H, Hu Q	Enantiomeric composition of nicotine in tobacco leaf, cigarette, smokeless tobacco, and e-liquid by normal phase high-performance liquid chromatography	Chirality.	30(7)	923-931	2018
Soule EK, Ramôa C, Eissenberg T, Cobb CO.	Differences in puff topography, toxicant exposure, and subjective response between waterpipe tobacco smoking men and women.	Exp Clin Psychopharmacol.	26(5)	440-447	2018
Son Y, Wackowski O, Weisel C, Schwander S, Mainelis G, Delnevo C, Meng Q.	Evaluation of E-Vapor Nicotine and Nicotyrine Concentrations under Various E-Liquid Compositions, Device Settings, and Vaping Topographies.	Chem Res Toxicol.	31(9)	861-868	2018
Franzen KF, Willig J, Cayo Talavera S, Meusel M, Sayk F, Reppel M, Dalhoff K, Mortensen K, Droemann D.	E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study.	Vasc Med.	23(5)	419-425	2018
d'Adesky ND, de Rivero Vaccari JP, Bhattacharya P, Schatz M, Perez-Pinzon MA, Bramlett HM, Raval AP.	Nicotine Alters Estrogen Receptor-Beta-Regulated Inflammasome Activity and Exacerbates Ischemic Brain Damage in Female Rats.	Int J Mol Sci.	19(5)	pii: E1330. doi: 10.3390/ijms19051330	2018
Condorelli RA, La Vignera S, Duca Y, Zanghi GN, Calogero AE.	Nicotine Receptors as a Possible Marker for Smoking-related Sperm Damage.	Protein Pept Lett.	25(5)	451-454	2018
Ohshima Y, Iwata K, Ibi M, Matsumoto M, Katsuyama M, Yabe-Nishimura C.	Nicotine and methyl vinyl ketone, major components of cigarette smoke extracts, increase protective amyloid-β peptides in cells harboring amyloid-β precursor protein.	J Toxicol Sci.	43(4)	257-266	2018
Tombolini F, Pigini D, Tranfo G, Paci E, Carosi I, Marini F, Bauleo L, Ancona C, Forastiere F.	Levels of urinary metabolites of four PAHs and cotinine determined in 1016 volunteers living in Central Italy.	Environ Sci Pollut Res Int.	25(29)	28772-28779.	2018

Reinikovaite V, Rodriguez IE, Karoor V, Rau A, Trinh BB, Deleyiannis FW, Taraseviciene-Stewart L.	The effects of electronic cigarette vapour on the lung: direct comparison to tobacco smoke.	Eur Respir J.	51(4)	pii: 1701661. doi: 10.1183/13993003.01661-2017	2018
Marinucci L, Balloni S, Fettucciari K, Bodo M, Talesa VN, Antognelli C.	Nicotine induces apoptosis in human osteoblasts via a novel mechanism driven by H(2)O(2) and entailing Glyoxalase 1-dependent MG-H1 accumulation leading to TG2-mediated NF-kB desensitization: Implication for smokers-related osteoporosis.	Free Radic Biol Med.	117	6-17	2018
Zhang G, Wang Z, Zhang K, Hou R, Xing C, Yu Q, Liu E	Safety Assessment of Electronic Cigarettes and Their Relationship with Cardiovascular Disease	Int J Environ Res Public Health.	15(1)	E75	2018
Wei Y, Lai B, Liu H, Li Y, Zhen W, Fu L.	Effect of cigarette smoke extract and nicotine on the expression of thrombomodulin and endothelial protein C receptor in cultured human umbilical vein endothelial cells	Mol Med Rep.	17(1)	1724-1730	2018
Goel R, Trushin N, Reilly SM, Bitzer Z, Muscat J, Foulds J, Richie JP Jr	A Survey of Nicotine Yields in Small Cigar Smoke: Influence of Cigar Design and Smoking Regimens	Nicotine Tob Res.	20(10)	1250-1257	2018
Teichert A, Brossard P, Felber Medlin L, Sandalic L, Franzon M, Wynne C, Laugesen M, Lüdicke F	Evaluation of Nicotine Pharmacokinetics and Subjective Effects following Use of a Novel Nicotine Delivery System.	Nicotine Tob Res.	20(4)	458-465	2018
Leavens EL, Driskill LM, Molina N, Eissenberg T, Shihadeh A, Brett EI, Floyd E, Wagener TL.	Comparison of a preferred versus non-preferred waterpipe tobacco flavour: subjective experience, smoking behaviour and toxicant exposure.	Tob Control.	27(3)	319-324	2018
Rosenberry ZR, Pickworth WB, Koszowski B.	Large Cigars: Smoking Topography and Toxicant Exposure	Nicotine Tob Res.	20(2)	183-191	2018

El-Hellani A, Salman R, El-Hage R, Talih S, Malek N, Baalbaki R, Karaoghlanian N, Nakkash R, Shihadeh A, Saliba NA	Nicotine and Carbonyl Emissions From Popular Electronic Cigarette Products: Correlation to Liquid Composition and Design Characteristics.	Nicotine Tob Res.	20(2)	215-223	2018
Kaur G, Pinkston R, Mclemore B, Dorsey WC, Batra S.	Immunological and toxicological risk assessment of e-cigarettes.	Eur Respir Rev.	27(147)		2018
Wei Y, Lai B, Liu H, Li Y, Zhen W, Fu L.	Effect of cigarette smoke extract and nicotine on the expression of thrombomodulin and endothelial protein C receptor in cultured human umbilical vein endothelial cells.	Mol Med Rep.	17(1)	1724-1730	2018
Arany I, Hall S, Dixit M.	Age-dependent sensitivity of the mouse kidney to chronic nicotine exposure.	Pediatr Res.	82(5)	822-828	2017
Kaisar MA, Kallem RR, Sajja RK, Sifat AE, Cucullo L.	A convenient UHPLC-MS/MS method for routine monitoring of plasma and brain levels of nicotine and cotinine as a tool to validate newly developed preclinical smoking model in mouse.	BMC Neurosci.	18(1)	71	2017
Hiler M, Breland A, Spindle T, Maloney S, Lipato T, Karaoghlanian N, Shihadeh A, Lopez A, Ramôa C, Eissenberg T.	Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience.	Exp Clin Psychopharmacol.	25(5)	380-392	2017
Havel CM, Benowitz NL, Jacob P 3rd, St Helen G.	An Electronic Cigarette Vaping Machine for the Characterization of Aerosol Delivery and Composition.	Nicotine Tob Res.	19(10)	1224-1231	2017

Faulkner P, Ghahremani DG, Tyndale RF, Cox CM, Kazanjian AS, Paterson N, Lotfipour S, Hellemann GS, Petersen N, Vigil C, London ED.	Reduced-Nicotine Cigarettes in Young Smokers: Impact of Nicotine Metabolism on Nicotine Dose Effects.	Neuropsychopharmacology.	42(8)	1610-1618	2017
Zuo Y, Garg PK, Nazih R, Garg S, Rose JE, Murugesan T, Mukhin AG.	A programmable smoke delivery device for PET imaging with cigarettes containing (11)C-nicotine.	J Neurosci Methods.	283	55-61	2017
Pickworth WB, Rosenberry ZR, Koszowski B.	Toxicant exposure from smoking a little cigar: further support for product regulation.	Tob Control.	26(3)	269-276	2017
Lee MS, LeBouf RF, Son YS, Koutrakis P, Christiani DC.	Nicotine, aerosol particles, carbonyls and volatile organic compounds in tobacco- and menthol-flavored e-cigarettes.	Environ Health.	16(1)	42	2017
Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P 3rd, Benowitz NL.	Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study.	Nicotine Tob Res.	19(2)	160-167	2017
Fogli S, Saba A, Del Re M, Pistelli F, Aquilini F, Zucchi R, Palla A, Breschi MC, Carrozzi L, Danesi R.	Application of a pharmacokinetic/pharmacogenetic approach to assess the nicotine metabolic profile of smokers in the real-life setting.	J Pharm Biomed Anal.	131	208-213.	2016
Cravo AS, Bush J, Sharma G, Savioz R, Martin C, Craige S, Walele T.	A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks	Regul Toxicol Pharmacol.	81 Suppl 1	S1-S14	2016
Ross KC, Gubner NR, Tyndale RF, Hawk LW Jr, Lerman C, George TP, Cinciripini P, Schnoll RA, Benowitz NL.	Racial differences in the relationship between rate of nicotine metabolism and nicotine intake from cigarette smoking.	Pharmacol Biochem Behav.	148	1-7	2016

Wray JM, Gass JC, Miller EI, Wilkins DG, Rollins DE, Tiffany ST. .	A comparative evaluation of self-report and biological measures of cigarette use in nondaily smokers	Psychol Assess.	28(9)	1043-50	2016
Coffa BG, Coggins CRE, Werley MS, Oldham MJ, Fariss MW.	Chemical, physical, and in vitro characterization of research cigarettes containing denicotinized tobacco.	Regul Toxicol Pharmacol.	79	64-73	2016
Krebs NM, Chen A, Zhu J, Sun D, Liao J, Stennett AL, Muscat JE.	Comparison of Puff Volume With Cigarettes per Day in Predicting Nicotine Uptake Among Daily Smokers.	Am J Epidemiol.	184(1)	48-57	2016
O'Connell G, Graff DW, D'Ruiz CD.	Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents (HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers.	Toxicol Mech Methods.	26(6)	443-54.	2016
Göney G, Çok İ, Tamer U, Burgaz S, Şengezer T.	Urinary cotinine levels of electronic cigarette (e-cigarette) users.	Toxicol Mech Methods.	26(6)	414-8	2016
Sosnowski TR, Kramek-Romanowska K.	Predicted Deposition of E-Cigarette Aerosol in the Human Lungs.	J Aerosol Med Pulm Drug Deliv.	29(3)	299-309	2016
Perkins KA, Kunkle N, Karelitz JL, Michael VC, Donny EC.	Threshold dose for discrimination of nicotine via cigarette smoking.	Psychopharmacology	233(12)	2309-17	2016
D'Ruiz CD, Graff DW, Robinson E.	Reductions in biomarkers of exposure, impacts on smoking urge and assessment of product use and tolerability in adult smokers following partial or complete substitution of cigarettes with electronic cigarettes.	BMC Public Health.	Jul 11;16:543.	doi:10.1186/s12889-016-3236-1	2016
McAdam K, Eldridge A, Fearon IM, Liu C, Manson A, Murphy J, Porter A.	Influence of cigarette circumference on smoke chemistry, biological activity, and smoking behaviour.	Regul Toxicol Pharmacol.	Sep 12. pii: S0273-2300(16)30258-6		2016

Haziza C, de La Bourdonnaye G, Merlet S, Benzimra M, Ancerewicz J, Donelli A, Baker G, Picavet P, Lüdicke F.	Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement.	Regul Toxicol Pharmacol.	81	489-499.	2016
Kibet J, Kurgat C, Limo S, Rono N, Bosire J.	Kinetic modeling of nicotine in mainstream cigarette smoking.	Chem Cent J.	Oct 12;10:60.		2016
Iskandar AR, Mathis C, Schlage WK, Frentzel S, Leroy P, Xiang Y, Sewer A, Majeed S, Ortega-Torres L, Johne S, Guedj E, Trivedi K, Kratzer G, Merg C, Elamin A, Martin F, Ivanov NV, Peitsch MC, Hoeng J.	A systems toxicology approach for comparative assessment: Biological impact of an aerosol from a candidate modified-risk tobacco product and cigarette smoke on human organotypic bronchial epithelial cultures.	Toxicol In Vitro.	Nov 16. pii: S0887-2333(16)	30231-4	2016
Walele T, Sharma G, Savioz R, Martin C, Williams J	A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part A: Pharmacokinetics	Regul Toxicol Pharmacol.	74	187-92	2016
Richter P, Steven PR, Bravo R, Lisko JG, Damian M, Gonzalez-Jimenez N, Gray N, Keong LM, Kimbrell JB, Kuklenyik P, Lawler TS, Lee GE, Mendez M, Perez J, Smith S, Tran H, Tyx R, Watson CH.	Characterization of SPECTRUM Variable Nicotine Research Cigarettes.	Tob Regul Sci.	2(2)	94-105	2016

Dong J, Segawa R, Mizuno N, Hiratsuka M, Hirasawa N.	Inhibitory effects of nicotine derived from cigarette smoke on thymic stromal lymphopoietin production in epidermal keratinocytes.	Cell Immunol.	302	19-25.	2016
Wang H, Li X, Guo J, Peng B, Cui H, Liu K, Wang S, Qin Y, Sun P, Zhao L, Xie F, Liu H.	Distribution of toxic chemicals in particles of various sizes from mainstream cigarette smoke.	Inhal Toxicol.	28(2)	89-94	2016
Pazo DY, Moliere F, Sampson MM, Reese CM, Agnew-Heard KA, Walters MJ, Holman MR, Blount BC, Watson CH, Chambers DM.	Mainstream Smoke Levels of Volatile Organic Compounds in 50 U.S. Domestic Cigarette Brands Smoked With the ISO and Canadian Intense Protocols	Nicotine Tob Res.	18(9)	1886-94	2016
Ross KC, Gubner NR, Tyndale RF, Hawk LW Jr, Lerman C, George TP, Cinciripini P, Schnoll RA, Benowitz NL.	Racial differences in the relationship between rate of nicotine metabolism and nicotine intake from cigarette smoking	Pharmacol Biochem Behav.	148	1-7	2016
Mercincavage M, Souprountchouk V, Tang KZ, Dumont RL, Wileyto EP, Carmella SG, Hecht SS, Strasser AA.	A Randomized Controlled Trial of Progressively Reduced Nicotine Content Cigarettes on Smoking Behaviors, Biomarkers of Exposure, and Subjective Ratings	Cancer Epidemiol Biomarkers Prev.	25(7)	1125-33	2016
Kubota M, Yanagita M, Mori K, Hasegawa S, Yamashita M, Yamada S, Kitamura M, Murakami S.	The Effects of Cigarette Smoke Condensate and Nicotine on Periodontal Tissue in a Periodontitis Model Mouse	PLoS One.	11(5)	e0155594	2016
Agnew-Heard KA, Lancaster VA, Bravo R, Watson C, Walters MJ, Holman MR.	Multivariate Statistical Analysis of Cigarette Design Feature Influence on ISO TNCO Yields	Chem Res Toxicol.	29(6)	1051-63	2016

Titz B, Boué S, Phillips B, Talikka M, Vihervaara T, Schneider T, Nury C, Elamin A, Guedj E, Peck MJ, Schlage WK, Cabanski M, Leroy P, Vuillaume G, Martin F, Ivanov NV, Veljkovic E, Ekroos K, Laaksonen R, Vanscheeuwijck P, Peitsch MC, Hoeng J.	Effects of Cigarette Smoke, Cessation, and Switching to Two Heat-Not-Burn Tobacco Products on Lung Lipid Metabolism in C57BL/6 and Apoe-/- Mice-An Integrative Systems Toxicology Analysis	Toxicol Sci.	149(2)	441-57.	2016
Tilp C, Bucher H, Haas H, Duechs MJ, Wex E, Erb KJ.	Effects of conventional tobacco smoke and nicotine-free cigarette smoke on airway inflammation, airway remodelling and lung function in a triple allergen model of severe asthma	Clin Exp Allergy.	46(7)	957-72	2016
Picavet P, Haziza C, Lama N, Weitkunat R, Lüdicke F.	Comparison of the Pharmacokinetics of Nicotine Following Single and Ad Libitum Use of a Tobacco Heating System or Combustible Cigarettes	Nicotine Tob Res. May;	18(5)	557-63	2016
Husari A, Shihadeh A, Talih S, Hashem Y, El Sabban M, Zaatari G	Acute Exposure to Electronic and Combustible Cigarette Aerosols: Effects in an Animal Model and in Human Alveolar Cells	Nicotine Tob Res.	18(5)	613-9	2016
Uchiyama S, Hayashida H, Izu R, Inaba Y, Nakagome H, Kunugita N.	Determination of nicotine, tar, volatile organic compounds and carbonyls in mainstream cigarette smoke using a glass filter and a sorbent cartridge followed by the two-phase/one-pot elution method with carbon disulfide and methanol	J Chromatogr A.	1426	48-55	2015
Ogden MW, Marano KM, Jones BA, Morgan WT, Stiles MF	Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 2. Biomarkers of exposure	Biomarkers	20(6-7)	391-403	2015

Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobes DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK.	Randomized Trial of Reduced-Nicotine Standards for Cigarettes	N Engl J Med.	373(14)	1340-9	2015
Thorne D, Dalrymple A, Dillon D, Duke M, Meredith C.	A comparative assessment of cigarette smoke aerosols using an in vitro air-liquid interface cytotoxicity test.	Inhal Toxicol.	27(12)	629-40	2015
Marco E, Grimalt JO.	A rapid method for the chromatographic analysis of volatile organic compounds in exhaled breath of tobacco cigarette and electronic cigarette smokers	J Chromatogr A. 10.1016	1410	51-9	2015
Yan X, Zhang L, Hearn BA, Valentín-Blasini L, Polzin GM, Watson CH.	A High Throughput Method for Estimating Mouth-Level Intake of Mainstream Cigarette Smoke	Nicotine & Tobacco Research	17(11)	1324-30	2015
Tilp C, Bucher H, Haas H, Duechs MJ, Wex E, Erb KJ.	Effects of conventional tobacco smoke and nicotine-free cigarette smoke on airway inflammation, airway remodeling and lung function in a triple allergen model of severe asthma	Clin Exp Allergy	e-publication		2015
Ferrari M, Zanasi A, Nardi E, Morselli Labate AM, Ceriana P, Balestrino A, Pisani L, Corcione N, Nava S	Short-term effects of a nicotine-free e-cigarette compared to a traditional cigarette in smokers and non-smokers	BMC Pulm Med.	e-publication		2015

Benowitz NL, Nardone N, Dains KM, Hall SM, Stewart S, Dempsey D, Jacob P 3rd.	Effect of reducing the nicotine content of cigarettes on cigarette smoking behavior and tobacco smoke toxicant exposure: 2-year follow up.	Addiction	110(10)	1667-75	2015
Verde Z, Reinoso-Barbero L, Chicharro L, Garatachea N, Resano P, Sánchez-Hernández I, Rodríguez González-Moro JM, Bandrés F, Santiago C, Gómez-Gallego F	Effects of cigarette smoking and nicotine metabolite ratio on leukocyte telomere length	Environ Res	140	488-94	2015
Zuo Y, Mukhin AG, Garg S, Nazih R, Behm FM, Garg PK, Rose JE.	Sex-specific effects of cigarette mentholation on brain nicotine accumulation and smoking behavior	Neuropsychopharmacology	40(4)	884-92	2015
Hecht Stephen S; Carmella Steven G; Kotandeniya Delshanee; Pillsbury Makenzie E; Chen Menglan; Ransom Benjamin W S; Isaksson Vogel Rachel; Thompson Elizabeth; Murphy Sharon E; Hatsukami Dorothy K	Evaluation of Toxicant and Carcinogen Metabolites in the Urine of e-Cigarette Users Versus Cigarette Smokers.	Nicotine & Tobacco research	17(6):	704-9	2015
Ashley M, Dixon M, Prasad K.	Relationship between cigarette format and mouth-level exposure to tar and nicotine in smokers of Russian king-size cigarettes	Regulatory Toxicology and Pharmacology	70(1)	430-7	2014
Jarvis MJ, Giovino GA, O'Connor RJ, Kozlowski LT, Bernert JT.	Variation in nicotine intake among U.S. cigarette smokers during the past 25 years: evidence from NHANES surveys.	Nicotine & Tobacco Research	16(12)	1620-8	2014

O'Connor Richard J; Schneller Liane M; Caruso Rosalie V ; Stephens W Edryd ; Li Qiang ; Yuan Jiang; Fong Geoffrey T	Toxic metal and nicotine content of cigarettes sold in China, 2009 and 2012.	Tobacco Control	e-publication		2014
Hammond David; O'Connor Richard J	Reduced Nicotine Cigarettes: Smoking Behavior and Biomarkers of Exposure among Smokers Not Intending to Quit.	Cancer epidemiology, biomarkers & prevention	23	2032-40	2014
Koszowski Bartosz; Rosenberry Zachary R; Viray Lauren C; Potts Jennifer L; Pickworth Wallace B	Make your own cigarettes: toxicant exposure, smoking topography, and subjective effects.	Cancer epidemiology, biomarkers & prevention	23	1793-803	2014
Naik Pooja; Fofaria Neel; Prasad Shikha; Sajja Ravi K; Weksler Babette; Couraud Pierre-Olivier; Romero Ignacio A; Cucullo Luca	Oxidative and pro-inflammatory impact of regular and denicotinized cigarettes on blood brain barrier endothelial cells: is smoking reduced or nicotine-free products really safe?.	BMC neuroscience	15	51	2014
Lin Bencheng; Zhang Huashan; Lin Zhiqing; Tian Lei; Fang Yanjun; Li Xiang; Nie Cong; Xi Zhuge	Comparison of in vitro toxicity of mainstream cigarette smoke particulate matter from nano- to micro-size.	Food and chemical toxicology	64	353-60	2014
Wisniewska Ewa; Dylik Anna; Kulza Maksymilian; Florek Ewa; Piekoszewski Wojciech; Senczuk-Przybylowska Monika; Marszalek Andrzej	Exposure to ethanol and tobacco smoke in relation to level of PCNA antigen expression in pancreatic and hepatic rat cells.	Pharmacological reports	65	914-26	2013

Boue Stephanie; De Leon Hector; Schlage Walter K; Peck Michael J; Weiler Horst; Berges An; Vuillaume Gregory; Martin Florian; Friedrichs Baerbel; Lebrun Stefan; Meurrens Kris; Schracke Nadine; Moehring Michaela; Steffen Yvonne; Schueller Jutta; Vanscheeuwijck Patrick; Peitsch Manuel C; Hoeng Julia	Cigarette smoke induces molecular responses in respiratory tissues of ApoE(-/-) mice that are progressively deactivated upon cessation.	Toxicology	314	112-24	2013
Feltes Bruno Cesar; de Faria Poloni Joice; Notari Daniel Luis; Bonatto Diego	Toxicological effects of the different substances in tobacco smoke on human embryonic development by a systems chemo-biology approach.	PloS one	8	e61743	2013
Jacob Peyton 3rd; Abu Raddaha Ahmad H; Dempsey Delia; Havel Christopher; Peng Margaret; Yu Lisa; Benowitz Neal L	Comparison of nicotine and carcinogen exposure with water pipe and cigarette smoking.	Cancer epidemiology, biomarkers & prevention	22	765-72	2013
Inaba Yohei; Ohkubo Tadamichi; Uchiyama Shigehisa; Kunugita Naoki	Determination of nicotine, tobacco-specific nitrosamine and mutagenic activity of whole tobacco in Japanese cigarettes.	Nihon eiseigaku zasshi. (Japanese journal of hygiene)	68	46-52	2013
Ljungberg Liza U; Persson Karin; Eriksson Andreas C; Green Henrik; Whiss Per A	Effects of nicotine, its metabolites and tobacco extracts on human platelet function in vitro.	Toxicology in vitro	27	932-8	2013

Allam E; Delacruz K; Ghoneima A; Sun J; Windsor L J	Effects of tobacco on cytokine expression from human endothelial cells.	Oral diseases	19	660-5	2013
Siu May; Mladjenovic Nemanja; Soo Evelyn	The analysis of mainstream smoke emissions of Canadian 'super slim' cigarettes.	Tobacco control	22	e10	2013
Yin Wei; Rubenstein David A	Differences between mainstream and sidestream tobacco smoke extracts and nicotine in the activation and aggregation of platelets subjected to cardiovascular conditions in diabetes.	Diabetes & vascular disease research	10	57-64	2013
Green B.T.,Panter K.E.,Lee S.T.,Brown D.R.	Piperidine alkaloids: Human and food animal teratogens	Food and Chemical Toxicology	50	2049-2055	2012
Zoli M., Picciotto M.R.	Nicotinic Regulation of Energy Homeostasis	Nicotine & Tobacco Research	online	21-Jan	2012
Chakrabarti A.,Sood N.,Hota D.,Sahai A.K.	Nicotine Reversal of Anticonvulsant Action of Topiramate in Kainic Acid-Induced Seizure Model in Mice	Nicotine & Tobacco Research	13(11)	1084-1091	2011
Demirhan O.,Demir C.,Tunc E.,Inandiklioglu N.,Sutcu E.,Sadikoglu N.,Ozcan B.	The genotoxic effect of nicotine on chromosomes of human fetal cells: The first report described as an important study	Inhalation Toxicology	23(13)	829-834	2011
Holloway A.C.,Inman M.D.,Petre M.A.,Petrik J.,Ellis R.,Labiris N.R.	Fetal and Neonatal Exposure to Nicotine Disrupts Postnatal Lung Development in Rats: Role of VEGF and its Receptors	International Journal of Toxicology	online	10-Jan	2011
Chen L.,Nishioka T.,Guo J.,Yamamoto D.,Huppi P.,Chen C.Y.	Nicotine, Through Upregulating Pro-Survival Signaling, Cooperates With NNK to Promote Transformation	Journal of Cellular Biochemistry	109	152-161	2010
Jana K.,Samanta P.K.,De D.K.	Nicotine Diminishes Testicular Gametogenesis, Steroidogenesis, and Steroidogenic Acute Regulatory Protein Expression in Adult Albino Rats: Possible Influence on Pituitary Gonadotropins ...	Toxicological Sciences	116(2)	647-659	2010

Solarino B.,Rosenbaum F.,Riesselmann B.,Buschmann C.T.,Tsokos M.	Death due to ingestion of nicotine-containing solution: Case report and review of the literature	Forensic Science International	195	e19-e22	2010
Ashraf, M. Ejaz, S. Kim, B. Lim, C.W. Nawaz, M.	Cigarette smoke condensate and total particulate matter severely disrupts physiological angiogenesis	Food and Chemical Toxicology	47(3)	601-614	2009
Ashraf, M. Ejaz, S. Kim, B. Lim, C.W. Nawaz, M.	Anti-angiogenic and teratological activities associated with exposure to total particulate matter from commercial cigarettes	Food and Chemical Toxicology	47(2)	368-376	2009
Berger, A. Hamm, J.T. Misra, M. Mitchell, M. Vulimiri, S.V.	Effects of Mainstream Cigarette Smoke on the Global Metabolome of Human Lung Epithelial Cells	Chem. Res. Toxicol.	22	492-503	2009
Berndt-Weis, L. Douglas, G.R. Halappanavar, S. Stampfli, M.R. Williams, A. Yauk, C.L.	Toxicogenomic Analysis of Mainstream Tobacco Smoke-Exposed Mice Reveals Repression of Plasminogen Activator Inhibitor-1 Gene in Heart	Inhalation Toxicology	21(1-4)	78-85	2009
Bhattacharya, A. Chakrabarti, G. Das, A.	Cigarette Smoke Extract Induces Disruption of Structure and Function of Tubulin-Microtubule in Lung Epithelium Cells and in Vitro	Chem. Res. Toxicol.	22	446-459	2009
Chen, C.-C. Chen, R.-M. Pan, W.-C. Shen, Y.-C. Ueng, Y.-F.	Suppressive effect of tobacco smoke extracts on oral P-glycoprotein function and its impact in smoke-induced insult to oral epidermal cells	Toxicology Letters	185	116-123	2009
Chen, H.-W. Ku, H.-J. Lii, C.-K. Wang, T.-S.	Cigarette Smoke Extract Induces Expression of Cell Adhesion Molecules in HUVEC via Actin Filament Reorganization	Environmental and Molecular Mutagenesis	50	96-104	2009
Kim, I.k. Kim, K.-N. Kim, M.-K. Lee, J. Sohn, S.-H.	Effect of tobacco compounds on gene expression profiles in human epithelial cells	Environmental Toxicology and Pharmacology	27	111-119	2009
Kumaravel, T.S. Massey, E.D. McEwan, M. Thorne, D. Wilson, J.	Measurement of oxidative DNA damage induced by mainstream cigarette smoke in cultured NCI-H292 human pulmonary carcinoma cells	Mutation Research	673	08-Mar	2009

Al-Mugotir, M. Bitterman, P. Fang, Q. Kim, H. Kobayashi, T. Liu, X. Mao, L. Rennard, S. Togo, S. Wang, X.	NF-kappaB mediates the survival of human bronchial epithelial cells exposed to cigarette smoke extract	Respiratory Research	9(66)	11-Jan	2008
Aufderheide, M. Gressmann, H.	Mutagenicity of native cigarette mainstream smoke and its gas/vapour phase by use of different tester strains and cigarettes in a modified Ames assay	Mutation Research	656	82-87	2008
Balharry, D. BeruBe, K.A. Sexton, K.	An in vitro approach to assess the toxicity of inhaled tobacco smoke components: Nicotine, cadmium. formaldehyde and urethane	Toxicology	244	66-76	2008
Carter, J.D. Crissman, K. Dailey, L.A. Foronjy, R.F. Ghio, A.J. Hilborn, E.D. Pinkerton, K.E. Richards, J.H. Stonehuerner, J. Uyeminami, D.	Particulate Matter in Cigarette Smoke Alters Iron Homeostasis to Produce a Biological Effect	Am J Respir Crit Care Med	178	1130-1138	2008
Casola, A. Castro, S.M. Garofalo, R.P. Guerrero-Plata, A. Kolli, D.	Cigarette Smoke Condensate Enhances Respiratory Syncytial Virus-Induced Chemokine Release by Modulating NF-kappa B and Interferon Regulatory Factor Activation	Toxicological Sciences	106(2)	509-518	2008
Coggins, C.R.E. Friedrichs, B. Gerstenberg, B. Gomm, W. Meurrens, K. Patskan, G.J. Podraza, K.F. Schnell, P. Stabbert, R. Terpstra, P. Veltel, D. Weber, S.	Toxicological Comparisons of Three Styles of a Commercial U.S. Cigarette (Marlboro) with the 1 R4F Reference Cigarette	Inhalation Toxicology	20(5-8)	695-721	2008

DeMarini, D.M. Gudi, R. Kehl, M. Kirby, P.E. Polzin, G. Rao, M. Recio, L. Richter, P.A. Szkudlinska, A.	Genotoxicity of 10 cigarette smoke condensates in four test systems: Comparisons between assays and condensates	Mutation Research	650	15-29	2008
Edmiston, J. Flora, J.W. Langston, T.B. Li, G. McKinney, W. Rana, G.S.J.B. Secrist, R.	Identification of in vitro differential cell secretions due to cigarette smoke condensate exposure using nanoflow capillary liquid chromatography and high-resolution mass spectrometry	Anal Bioanal Chem	391	2845-2856	2008
Edmiston, J.S. Kane, D.B. McKinney, W.J. Oldham, M.J. Scian, M.J.	Characterization of a Whole Smoke In Vitro Exposure System (Burghart Mimic Smoker-01)	Inhalation Toxicology	XX	10-Jan	2008
Edvinsson, L. Xu, C.-B. Zhang, W. Zhang, Y. Zheng, J.-P.	Lipid-Soluble Smoke Particles Upregulate Vascular Smooth Muscle ETB Receptors via Activation of Mitogen-Activating Protein Kinases and NF-kappaB Pathways	Toxicological Sciences	106(2)	546-555	2008
Kaushik, G. Kaushik, T. Khanduja, K.L. Khanduja, S. Pathak, C.M.	Cigarette smoke condensate promotes cell proliferation through disturbance in cellular redox homeostasis of transformed lung epithelial type-II cells	Cancer Letters	270	120-131	2008
Klus, H. Muller, L. Thielen, A.	Tobacco smoke: Unraveling a controversial subject	Experimental and Toxicologic Pathology	60(2-3)	141-156	2008
Ambrose, V. Dickson, S.J. Fowles, J. Hampton, S. Lea, R.A. Miller, J.H. Truman, P.	Tobacco particulate matter is more potent than nicotine at upregulating nicotinic receptors on SH-SY5Y cells	Nicotine & Tobacco Research	9(8)	793-799	2007
Aufderheide, M. Gressmann, H.	A modified Ames assay reveals the mutagenicity of native cigarette mainstream smoke and its gas vapour phase	Experimental and Toxicologic Pathology	58	383-392	2007
Avunduk, M.C. Civelek, S. Guven, C. Isik, A.C.U. Yardimci, S.	Morphologic Alteration Induced by Short-Term Smoke Exposure in Rats	ORL	69	13-17	2007

Baty, C.J. Choi, A.M.K. Guo, F. Karlsson, J.M. Kauffman, H.F. Kim, H.P. Lee, J.S. Liu, F. Postma, D.S. Ryter, S.W. Slebos, D.-J. van der Toorn, M. Wang, X. Watkins, S.C.	Mitochondrial Localization and Function of Heme Oxygenase-1 in Cigarette Smoke-Induced Cell Death	Am J Respir Cell Mol Biol	36	409-417	2007
Bergren, D.R.	Tobacco Smoke is an Adjuvant for Maintained Airway Sensitization in Guinea Pigs	Journal of Asthma	44	723-728	2007
Choi, A.M.K. Dong, Y. Feghali-Bostwick, C.A. Li, C. Matthay, M.A. Ning, W. Sun, J.	Cigarette Smoke Stimulates Matrix Metalloproteinase-2 Activity via EGR-1 in Human Lung Fibroblasts	Am J Respir Cell Mol Biol	36	480-490	2007
Churg, A. Kerstjens, H.A.M. Postma, D.S. Timens, W. Whittaker, P. Wright, J.L.	Airway Remodeling in the Smoke Exposed Guinea Pig Model	Inhalation Toxicology	19	915-923	2007
Coggins, C.R.E.	An Updated Review of Inhalation Studies with Cigarette Smoke in Laboratory Animals	International Journal of Toxicology	26	331-338	2007
Geerlings, M. Hylkema, M.N. Kerstjens, H.A. Luinge, M.A. Melgert, B.N. Postma, D.S. Schouten, J.P. Timens, W.	Effects of 4 months of smoking in mice with ovalbumin-induced airway inflammation	Clinical and Experimental Allergy	37	1798-1808	2007
Hayes, J.R. Meckley, D.R. Nelson, P.R. Stavanja, M.S. Swauger, J.E. Van Kampen, K.R.	Effect of a flue-curing process that reduces tobacco specific nitrosamines on the tumor promotion in SENCAR mice by cigarette smoke condensate	Food and Chemical Toxicology	45	419-430	2007

Hitchman, K. Kerepesi, L. Lu, B. Meng, Q.R. Wisse, L.	Cytotoxicity and Gene Expression Profiles in Cell Cultures Exposed to Whole Smoke from Three Types of Cigarettes	Toxicological Sciences	98(2)	469-478	2007
Ho, C.-Y. Lan, M.-Y. Lee, T.-C. Yang, A.-H.	Cigarette smoke extract induces cytotoxicity on human nasal epithelial cells	Am J Rhinol	21	218-223	2007
Hu, J. Tian, F. Xu, Y.-j. Zhang, Z.-x.	Effect of cigarette smoke extract on proliferation of rat pulmonary artery smooth muscle cells and the relevant roles of protein kinase C	Chin Med J	120(17)	1523-1528	2007
Iann, M.C. Johnson, M. Martin, M.B. Reiter, R. Richards, J.K. Shah, M.S. Singh, B. Stoica, A. Wang, A.	Effects of Tobacco Smoke Condensate on Estrogen Receptor-a Gene Expression and Activity	Endocrinology	148(10)	4676-4686	2007
Lauterbach, J.H. Momin, R.A. Rickert, W.S. Trivedi, A.H. Wright, W.G.	Effect of Smoking Conditions and Methods of Collection on the Mutagenicity and Cytotoxicity of Cigarette Mainstream Smoke	Toxicological Sciences	96(2)	285-293	2007
Meurrens K, Ruf S, Ross G, Schleef R, von Holt K, Schluter K-D	Smoking accelerates the progression of hypertension-induced mycocardial hypertrophy to heart failure in spontaneously hypertensive rats.	Cardiovascular Research	76	311-322	2007
Ayres, P.H. Curtin, G.M. Meckley, D.R. Nelson, P.R. Stavanja, M.S. Swauger, J.E.	DBA/2 mouse skin is unresponsive to dermal tumor promotion by cigarette smoke condensate	Experimental and Toxicologic Pathology	58	125-132	2006
Baginski, T.K. Dabbagh, K. Satjawatcharaphong, C. Swinney, D.C.	Cigarette Smoke Synergistically Enhances Respiratory Mucin Induction by Proinflammatory Stimuli	Am J Respir Cell Mol Biol	35	165-174	2006
Bauter, M.R. Chida, A.S. Kilty, I. Maggirwar, S.B. Rahman, I. Seweryniak, K. Shafiq, N. Yang, S.-R.	Cigarette smoke induces proinflammatory cytokine release by activation of NF-kB and posttranslational modifications of histone deacetylase in macrophages	Am J Physiol Lung Cell Mol Physiol	291	46-57	2006

Borlak, J. Gebel, S. Gerstmayer, B. Kuhl, P. Meurrens, K. Muller, T.	The Kinetics of Transcriptomic Changes Induced by Cigarette Smoke in Rat Lungs Reveals a Specific Program of Defense, Inflammation, and Circadian Clock Gene Expression	Toxicological Sciences	93(2)	422-431	2006
Brys, A.M. Gideon, K.M. Harbo, S.J. Jones, R. Lee, M.K. Meng, Q.R. Renne, R.A.	Gene Expression Profiling in Lung Tissues from Mice Exposed to Cigarette Smoke, Lipopolysaccharide, or Smoke Plus Lipopolysaccharide by Inhalation	Inhalation Toxicology	18	555-568	2006
Callicutt, C.H. Cox, R.H. Hsu, F. Kinser, R.D. Laffoon, S.W. Lee, P.N. Podraza, K.F. Sanders, E.B. Seeman, J.I.	The role of ammonia in the transfer of nicotine from tobacco to mainstream smoke	Regulatory Toxicology and Pharmacology	46	17-Jan	2006
Diekmann, J. Muller, B.L. Tewes, F.J. Wooten, J.B.	Involvement of Semiquinone Radicals in the in Vitro Cytotoxiticity of Cigarette Mainstream Smoke	Chem. Res. Toxicol.	19	1602-1610	2006
Espiritu, I. Maronpot, R.R. Witschi, H.	Lung tumors in 2 year old strain A/J mice exposed for 6 months to tobacco smoke	Cancer Letters	241	64-68	2006
Feng, Z. Hu, W. Hu, Y. Tang, M.-s.	Acrolein is a major cigarette-related lung cancer agent: Preferential binding at p53 mutational hotspots and inhibition of DNA repair	PNAS (Proceedings of the National Academy of Sciences)	103(42)	15404-15409	2006
Friedrichs, B. Van Miert, E. Vanscheeuwijck, P.	LUNG INFLAMMATION IN RATS FOLLOWING SUBCHRONIC EXPOSURE TO CIGARETTE MAINSTREAM SMOKE	Experimental Lung Research	32	151-179	2006
Fukano, Y. Yoshida, T. Yoshimura, H.	Heme oxygenase-1 gene expression in human alveolar epithelial cells (A549) following exposure to whole cigarette smoke on a direct in vitro exposure system	Experimental and Toxicologic Pathology	57	411-418	2006
Hayakawa, K. Hiramatsu, N. Kasai, A. Kitamura, M. Maeda, S. Yao, J.	High Levels of Dioxin-Like Potential in Cigarette Smoke Evidenced by In vitro and In vivo Biosensing	Cancer Res	66(14)	7143-7150	2006

Hur, G.Y. In, K.H. Jung, H.C. Jung, K.H. Kang, E.J. Kang, K.H. Kim, J.H. Lee, S.Y. Lee, S.Y. Shim, J.J. Shin, C. Yoo, S.H.	Peroxisome proliferator-activated receptor-y inhibits cigarette smoke solutioninduced mucin production in human airway epithelial (NCI-H292) cells	Am J Physiol Lung Cell Mol Physiol	291	84-90	2006
Jumarie, C. Morin, A. Porter, A. Prefontaine, D.	In vitro bioactivity of combustion products from 12 tobacco constituents	Food and Chemical Toxicology	44	724-738	2006
Kropotov, A. Krutilina, R. Leutenegger, C. Pleskach, N. Serikov, V.B. Suh, J.H. Tomilin, N.V.	Cigarette Smoke Extract Inhibits Expression of Peroxiredoxin V and Increases Airway Epithelial Permeability	Inhalation Toxicology	18	79-92	2006
Lin, S. Talbot, P. Wu, M. Yu, R.	Cigarette Smoke Toxicants Alter Growth and Survival of Cultured Mammalian Cells	Toxicological Sciences	93(1)	82-95	2006
Mendes, E. Randhawa, K. Wanner, A.	Acute Effect of Cigarette Smoke and Nicotine on Airway Blood Flow and Airflow in Healthy Smokers	Lung	184	363-368	2006
Renne RA, Yoshimura H, Yoshino K, Lulham G, Minamisawa S, Tribukait A, Dietz DD, Lee KM & Westerberg RB	Effects of flavouring and casing ingredients on the toxicity of mainstream cigarette smoke in rats.	Inhalation Toxicology	18	685-706	2006
Aliaga, C. Dennis, P.A. Desai, D. El-Bayoumy, K. Fiala, E.S. Reinhardt, J. Seibert, E. Sodum, R.S. Sohn, O.S. Tsurutani, J. Wang, C.-X.	Induction of preneoplastic lung lesions in guinea pigs by cigarette smoke inhalation and their exacerbation by high dietary levels of vitamins C and E	Carcinogenesis	26(3)	605-612	2005

Arts, J.H.E. Buttner, A. Haussmann, H.-J. Stinn, W.	Cigarette Mainstream Smoke and Gas Phase-Depleted Particulate Phase Enhance Lung Tumorigenicity in the A/J Mouse	SOT Conference, New Orleans, 2005	Poster NewOrleans 05	2	2005
Barr, E.B. Belinsky, S.A. Finch, G.L. Gigliotti, A.P. Grimes, M.J. Hahn, F.F. Hobbs, C.H. Hutt, J.A. March, T.H. Mauderly, J.L. Seilkop, S.K. Vuillemenot, B. R.	Life-span inhalation exposure to mainstream cigarette smoke induces lung cancer in B6C3F1 mice through genetic and epigenetic pathways	Carcinogenesis	26(11)	1999-2009	2005
Bartalesi, B. Cavarra, E. Fineschi, S. Lucattelli, M. Lungarella, G. Lunghi, B. Martorana, P.A.	Different lung responses to cigarette smoke in two strains of mice sensitive to oxidants	Eur Respir J	25 (1)	15-22	2005
Bombick, B.R. Doolittle, D.J. Fields, W.R.	Gene Expression in Bronchial Epithelial Cells Following In Vitro Exposure to Cigarette Smoke Condensate	CORESTA 2005	SSPT23	16-Jan	2005
Bottlaender, M. Coulon, C. Dolle, F. Ottaviani, M. Syrota, A. Valette, H.	Acute inhibitor of Cardiac Monoamines Oxidase A after Tobacco Smoke Inhalation: Validation Study of [11C] Befloxatone in Rats Followed by a Positron Emission Tomography Application in Baboons.	The Journal of Pharmacology and Experimental Therapeutics	314(1)	431-436	2005
Boyle, J.O. Dannenberg, A.J. Duffield-Lillico, A.J. Gross, N.D. Morrow, J.D. Moskowitz, C.S. Subbaramaiah, K. Williams, M.K.	Levels of Prostaglandin E Metabolite, the Major Urinary Metabolite of Prostaglandin EZ, Are Increased in Smokers	Clin Cancer Res.	11(16)	6087-6093	2005
Chaudhuri, S.P. John, L. Pillai, B. Sharma, G.	Cigarette smoke extract induces changes in growth and gene expression of Saccharomyces cerevisiae	Biochemical and Biophysical Research Communications	338	1578-1586	2005

Chen, K. Chen, L. Gao, S. Li, W. Rich, C.B. Stone, P. Zhao, Y.	Transcriptional and Posttranscriptional Inhibition of Lysyl Oxidase Expression by Cigarette Smoke Condensate in Cultured Rat Fetal Lung Fibroblasts	Toxicological Sciences	87(1)	197-203	2005
Dawe, D.E. Fattouh, R. Inman, M.D. Jordana, M. Pouladi, M.A. Richards, C.D. Robbins, C.S. Stampfli, M.R. Vujicic, N.	Mainstream Cigarette Smoke Exposure Attenuates Airway Immune Inflammatory Responses to Surrogate and Common Environmental Allergens in Mice, Despite Evidence of Increased Systemic sensitization	Journal of Immunology	175	2834-2842	2005
Ejaz, S. Seok, K.B. Woong, L.C.	Toxicological Effects of Mainstream Whole Smoke Solutions on Embryonic Movements of the Developing Embryo	Drug and Chemical Toxicology	1	14-Jan	2005
Gottschalk, R.W.H. Kleinjans, J.C.S. Moonen, E.J. van Delft, J.H.M. van Herwijnen, M.H. van Leeuwen, D.M.	Differential Gene Expression in Human Peripheral Blood Mononuclear Cells Induced by Cigarette Smoke and Its Constituents	Toxicological Sciences	86(1)	200-210	2005
Hamm, J.T. Misra, M. Morrissey, R.L. Rajendran, N. Yee, S.F.	Focal Proliferative Lesions in A/J Mouse Lung Following 5-Month Exposure to Mainstream Cigarette Smoke	SOT Conference, New Orleans, 2005	PosterNewOrleans 05	2	2005
Hartman, H. Holloway, G. Millet, S. Sheabar, F. Ye, J.	Evaluation of Cigarette Smoke Cytotoxicity Under In Vitro Conditions	SOT Conference, New Orleans, 2005	SOT Poster March 05	1	2005
Haussmann, H.-J. Meurrens, K. Ruf, S. Schleef, R. Schluter, K.-D. von Holt, K.	Influence of Sub-Chronic Cigarette Smoke Exposure on the Progession of Myocardial Hypertrophy in Spontaneously Hypertensive Rats (SHR)	SOT Conference, New Orleans, 2005	Poster NewOrleans 05	2	2005

Heuer, L.S. Kaul, R. Pinkerton, K.E. Thao, N.N. Wenman, W.M. Wiedeman, J.A.	Tobacco smoke induces a persistent, but recoverable state in Chlamydia pneumoniae infection of human endothelial cells	Microbial Pathogenesis	39	197-204	2005
Hirano, Y. Ishii, H. Kobayashi, M. Kubo, S. Masunaga, Y. Shimizu, Y. Takahashi, K.	Cytokine and chemokine expression in cigarette smoke-induced lung injury in guinea pigs	Eur Respir J	26	993-1001	2005
Hoffmann, H. Hogel, J. Isner, C. Speit, G.	Genetic polymorphisms and the effect of cigarrette smoking in the comet assay	Mutagenesis	20(3)	359-364	2005
Witschi, H.	Carcinogenic Activity of Cigarette Smoke Gas Phase and Its Modulation by Beta-Carotene and N-Acetylcysteine	Toxicological Sciences	84	81-87	2005
Zhong, K.	Effect of Smoking on the Volatile SulfuretedCompounds (VSCs)inOral Cavity	CORESTA 2005	SSPT37	16-Jan	2005
Ahmad, A. Allen, R.H. Panayiotidis, M.I. Stabler, S.P. White, C.W.	Cigarette smoke extract increases S-adenosylmethionine and cystathionine in human lung epithelial-like (A549) cells	Chemico-Biological Interactions	147	87-97	2004
Aufderheide, M. Knebel, J.W. Ritter, D.	Comparative Assessment of Toxicities of Mainstream Smoke from Commercial Cigarettes	Inhalation Toxicology	16	691-700	2004
Aufderheide, M. Mohr, U.	The use of the modified CULTEX system for the direct exposure of bacteria to mainstream cigarette smoke	Coresta Congress, Kyoto, Japan		08-Jan	2004
Ayres, P.H. Curtin, G.M. Higuchi, M.A. Mosberg, A.T. Swauger, J.E.	Lung Tumorigenicity in A/J and rasH2 Transgenic Mice Following Mainstream Tobacco Smoke Inhalation	Toxicological Sciences	81	26-34	2004
Ayres, P.H. Higuchi, M.A. Sagartz, J.W. Shreve, W.K.	Comparative Subchronic Inhalation Study of Smoke From the 1R4F and 2R4F Reference Cigarettes	Inhalation Toxicology	16	20-Jan	2004
Baker RR & Bishop LJ	The pyrolysis of tobacco ingredients	Journal Analytical and Applied Pyrolysis	71	223-311	2004
Baker RR, Massey ED & Smith G	An overview of the effects of tobacco ingredients on smoke chemistry and toxicity	Food and Chemical Toxicology	42	53-83	2004

Barakat, A.I. Douglas, G.R. Mariano, N.F. Soghomonians, A. Thirkill, T.L.	Effect of Aqueous Tobacco Smoke Extract and Shear Stress on PECAM-1 Expression and Cell Motility in Human Uterine Endothelial Cells	Toxicological Sciences	81	408-418	2004
Barankin, B. Bird, G. Freiman, A. Lauzon, G.J. Metelitsa, A.I.	Cutaneous Effects of Smoking	Journal of Cutaneous Medicine and Surgery	8(6)	415-413	2004
Barr, E.B. Bechtold, W. E. Belinsky, S.A. Finch, G.L. Gigliotti, A.P. Hahn, F.F. Hobbs, C.A. March, T.H. Mauderly, J.L. Seilkop, S.K.	Chronic Inhalation Exposure to Mainstream Cigarette Smoke Increases Lung and Nasal Tumor Incidence in Rats	Toxicological Sciences	81	280-292	2004
Bosio, A. Gebel, S. Gerstmayer, B. Haussmann, H.-J. Muller, T. Van Miert, E.	Gene expression profiling in respiratory tissues from rats exposed to mainstream cigarette smoke	Carcinogenesis	25 no 2	169-178	2004
Carchman, R.A. Gaworski, C.L. Meisgen, T.J. Podraza, K.F. Reininghaus, W. Roemer, E. Rustemeier, K. Stabbert, R. Veltel, D.J.	Chemical composition, cytotoxicity and mutagenicity of smoke from US commercial and reference cigarettes smoked under two sets of machine smoking conditions	Toxicology	195	31-52	2004
Chaung, Y.H. Chen, H.W. Chien, M.L. Lii, C.K. Wang, T.S.	Extracts from cigarette smoke induce DNA damage and cell adhesion molecule expression through different pathways	Chem.-Biol. Interactions	150	233-241	2004
Chen, D. Hayata, I. Minamihisamatsu, M. Morishima, H. Sugahara, T. Wang, C. Wei, L. Yuan, Y. Zhang, W.	Effect of Smoking on Chromosomes Compared with That of Radiation in the Residents of a High-Background Radiation Area in China	J. Radiat. Res.	45 (3)	441-446	2004

Curtin, G.M. Hanausek, M. Mosberg, A.T. Slaga, T.J. Walaszek, Z.	Short-Term In Vitro and In Vivo Analyses for Assessing the Tumor-Promoting Potentials of Cigarette Smoke Condensates	Toxicological Sciences	81	14-25	2004
DeMarini, D.M.	Genotoxicity of tobacco smoke and tobacco smoke condensate: a review	Mutation Research	567	447-474	2004
Dolas, S.S. Maru, G. B. Pakhale, S.S. Thapliyal, R.	Evaluation of DNA Damage in Mice Topically Exposed to Total Particulate Matter from Mainstream and Sidestream Smoke from Cigarettes and Bidis	Mutagenesis	19	413-421	2004
Fuciarelli, A.F. Lee, K.-M. McKinney, W.J. Obot, C. J. Renne, R.A.	Characterization of Mainstream Cigarette Smoke-Induced Biomarker Responses in ICR and C576I/6 Mice	Inhalation Toxicology	16	701-719	2004
Garg, R. Hansch, C. Martin, P. Perfetti, T.A. Smith, C.J.	Percutaneous penetration enhancers in cigarette mainstream smoke	Food and Chemical Toxicology	42	15-Sep	2004
Geerlings, M. Hylkema, M.N. Kerstjens, H.A.M. Klok, P. A. Luinge, M.A. Melgert, B.N. Postma, D.S. Timens, W. van der Strate, B.W.A.	Short-Term Smoke Exposure Attenuates Ovalbumin-Induced Airway Inflammation In Allergic Mice	Am J Respir Cell Mol Biol	30	880-885	2004
Goldstraw, P. Pastorino, U. Ratcliffe, C. Tetley, T.D. Vanden Bon, E.J. Witherden, I.R.	Primary Human Alveolar Type II Epithelial Cell Chemokine Release Effects of Cigarette Smoke and Neutrophil Elastase	Am J Respir Cell Mol Biol	30	500-509	2004
Hayes, J.R. Meckley, D.R. Mosberg, A.T. Swauger, J.E. Van Kampen, K.R.	A responsive, sensitive, and reproducible dermal tumor promotion assay for the comparative evaluation of cigarette smoke condensates	Regulatory Toxicology and Pharmacology	39	135-149	2004
Hirose, M. Lee, I.S. Mori, Y. Nishikawa, A. Tanaka, T.	Cigarette Smoking, Metabolic Activation and Carcinogenesis	Current Drug Metabolism	5 (5)	363-373	2004

Intorp, M. Roper, W. Wieczorek, R.	HOFFMANN ANALYTES AND CIGARETTE SMOKE IN VITRO TOXICITY REVISITED - HOW DO THE DATA COMPARE?	Coresta Congress, Kyoto, Japan		08-Jan	2004
Lipowicz, P.J. Piade, J.-J. Poget, L. Sanders, E.B. Seeman, J.I. Synders, J.P. Trowbridge, C.G.	On the Deposition of Volatiles and Semivolatiles from Cigarette Smoke Aerosols: Relative Rates of Transfer of Nicotine and Ammonia from Particles to the Gas Phase	Chem. Res. Toxicol.	17	1020-1037	2004
Samet, J.M.	Adverse effects of smoke exposure on the upper airway	Tob. Control	13 sup.1	57-60	2004
Abbott, B.D. Rogers, J.M.	Screening for Developmental Toxicity of Tobacco Smoke Constituents	Toxicological Sciences	75	227-228	2003
Aggarwal, B.B. Gairola, C.G. Potdar, P. Shishodia, S.	Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF-kB activation through inhibition of IkBa kinase in human lung epithelial cells:correlation with suppression of COX-2, ...	Carcinogenesis	24(7)	1269-1279	2003
Andreoli, C. Gigante, D. Nunziata, A.	A review of in vitro methods to assess the biological activity of tobacco smoke with the aim of reducing the toxicity of smoke	Toxicology in Vitro	17	587-594	2003
Aoshiba, K. Koinuma, M. Nagai, A. Yokohori, N.	IMMUNOHISTOCHEMICAL EVALUATION OF OXIDATIVE STRESS IN MURINE LUNGS AFTER CIGARETTE SMOKE EXPOSURE	Inhalation Toxicology	15	1029-1038	2003
Arey, J. Iv, M. Riveles, K. Talbot, P.	Pyridines in cigarette smoke inhibit hamster oviductal functioning in picomolar doses	Reproductive Toxicology	17	191-202	2003
Aufderheide, M. Knebel, J.W. Ritter, D.	EXPOSURE OF HUMAN LUNG CELLS TO INHALABLE SUBSTANCES: A NOVEL TEST STRATEGY INVOLVING CLEAN AIR EXPOSURE PERIODS...	Inhalation Toxicology	15	67-84	2003
Ayres, P.H. Kinsler, S. Mosberg, A.T. Pence, D.H. Shreve, W.K.	RAT SUBCHRONIC INHALATION STUDY OF SMOKE FROM CIGARETTES CONTAINING FLUE-CURED TOBACCO CURED EITHER BY DIRECT-FIRED OR HEAT-EXCHANGER CURING PROCESSES	Inhalation Toxicology	15	819-854	2003

Bagnasco, M. Balansky, R.M. Bennicelli, C. Camoirano, A. Cartiglia, C. D'Agostini, F. De Flora, S. Izzotti, A. Longobardi, M.G. Lubet, R.A. Tampa, E.	Modulation of cigarette smoke-related end-points in mutagenesis and carcinogenesis	Mutation Research	523-524	237-252	2003
Balansky, R.M. Bennicelli, C. Camoirano, A. D'Agostini, F. De Flora, S. Izzotti, A. Lubet, R.A. Wang, Y. You, M. Zhang, Z.Q.	Molecular Alterations and Lung Tumors in 53 Mutant Mice Exposed to Cigarette Smoke	Cancer Res	63	793-800	2003
Barnes, P.J. Buttery, L.D.K. Habib, M. Hoyt, J.C. Polak, J.M. Robbins, R.A. Springall, D.R.	CIGARETTE SMOKE DECREASES INDUCIBLE NITRIC OXIDE SYNTHASE IN LUNG EPITHELIAL CELLS	Experimental Lung Research	29	12	2003
Bosio, A. Bulles, H. Friedrichs, D. Gebel, S. Gerstmayer, B. Koeser, A. Schlage, W.K.	Gene Expression Profiling of Two 3T3 Cell lines Exposed to Cigarette Smoke Fractions Reveals Differences in the Induction of Xenobiotic-Metabolizing Enzymes	9th International Inhalation Symposium (June 11-14) Hannover Germany	June	1	2003
Budhiraja, R. Chalkley, R. Cooray, S. Hassour, P.M. Kayyali, U.S. Lanzillo, J.J. Pennella, C.M.	Upregulation of xanthine oxidase by tobacco smoke condensate in pulmonary endothelial cells	Toxicology and Applied Pharmacology	188	59-68	2003
Dybing, E. Fowles, J.	Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke	Tob. Control	12	424-430	2003
Fowler, C.J. Sandberg, M. Tiger, G.	Effects of Water-Soluble Cigarette Smoke Extracts Upon The Release of Beta-Hexosaminidase from RBL-2H3 Basophilic Leukaemia Cells In Response To Substance P Compound 48-80 Concanavalin A and Antigen	Inflammation Research	52	461-469	2003

Green, C.R. Rodgman, A.	Toxic Chemicals in Cigarette Mainstream Smoke – Hazard and Hoopla (part1)	Beiträge zur Tabakforschung	20 no 8 (part1)	481-545	2003
Green, C.R. Rodgman, A.	Toxic Chemicals in Cigarette Mainstream Smoke - Hazard and Hoopla (part 2)	Beiträge zur Tabakforschung	20 no 8 (part 2)	481-545	2003
Green, C.R. Rodgman, A.	Toxic Chemicals in Cigarette Mainstream Smoke - Hazard and Hoopla (part 3)	Beiträge zur Tabakforschung	20 no 8 (part 3)	481-545	2003
Ishihara, A. Kita, T. Nakashima, T. Nakatani, T.	EFFECTS OF EXPOSURE TO CIGARETTE SMOKE AT DIFFERENT DOSE LEVELS ON EXTENSOR DIGITORUM LONGUS MUSCLE FIBRES IN WISTAR-KYOTO AND SPONTANEOUSLY HYPERTENSIVE RATS	Clinical and Experimental Pharmacology and Physiology	30	671-677	2003
Ortug, C.	Scanning electron microscopic findings in respiratory nasal mucosa following cigarette smoke exposure in rats	Annals of Anatomy	185	207-210	2003
Altuntas, I. Dane, S. Gumustekin, K.	EFFECTS OF CIGARETTE SMOKING ON LIPID PEROXIDATION	Journal of Basic and Clinical Physiology and Pharmacology	13(1)	69-73	2002
Bosio, A. Gebel, S. Haussmann, H.-J. Janssen, U. Knorr, C. Muller, T.	Kinetics of gene expression profiling in Swiss 3T3 cells exposed to aqueous extracts of cigarette smoke	Carcinogenesis	23 no 5	741-748	2002
Carmines EL	Evaluation of the potential effects of ingredients added to cigarettes. Part 1: Cigarette design, testing approach and review of results.	Food and Chemical Toxicology	40	77-91	2002
Coggins, C.R.E.	A MINIREVIEW OF CHRONIC ANIMAL INHALATION STUDIES WITH MAINSTREAM CIGARETTE SMOKE	Inhalation Toxicology	14	991-1002	2002
Degrell, P. Mazak, I. Molnar, G.A. Nagy, J. Vas, T. Wagner, L. Wagner, Z. Wittmann, I.	Cigarette Smoke and Its Formaldehyde Component Inhibit Bradykinin-Induced Calcium Increase in Pig Aortic Endothelial Cells	Endothelium	9	103-108	2002
Garg, R. Hansch, C. Morton, M.J. Perfetti, T.A. Rodgman, A. Selassie, C.D. Smith, C.J.	The Relative Toxicity of Substituted Phenols Reported in Cigarette Mainstream Smoke	Toxicological Sciences	69	265-278	2002

Haginaka, J. Kagota, S. Kunitomo, M. Yamaguchi, Y.	Participation of peroxynitrite in oxidative modification of LDL by aqueous extracts of cigarette smoke	FEBS Letters	512	218-222	2002
Ji, L. Melkonian, G. Riveles, K. Talbot, P.	Identification of Pyridine Compounds in Cigarette Smoke Solution That Inhibit Growth of the Chick Chorioallantoic Membrane	Toxicological Sciences	69	217-225	2002
Krause, G. Scherer, G. Wolz, L.	The Comet Assay with MCL-5 Cells as an Indicator of Genotoxic Treatment with Chemicals and Cigarette Smoke Condensate	ATLA	30	331-339	2002
Paschke T, Scherer G & Heller W	Effects of ingredients on cigarette smoke composition and biological activity: A literature overview.	Beitrage zur Tabakforschung International	20	107-247	2002
Rustemeier K Stabbert R Haussmann H J Roemer E L carmines E L	Evaluation of the potential effects if ingredients added to cigarettes. Part 2: Chemical composition of mainstream smoke.	Food and Chemical Toxicology	40	93-104	2002
Aoki, N. Hasumura, Y. Hioki, Y. Homori, M. Ishikawa, K. Kawaro, K. Maki, A. Yanagisawa, A. Yasumura, Y. Yoshiro, H.	Acute effects of cigarette smoking on platelet-dependent thrombin generation	European Heart Journal	22	56-61	2001
Coggins, C.R.E.	A Review of Chronic Inhalation Studies with Mainstream Cigarette Smoke, in Hamsters, Dogs, and Nonhuman Primates	Toxicologic Pathology	29	550-557	2001
PERFETTI T.A.;GORDON B.M.;COLEMAN W.M.III	Determination of the transfer efficiency of d-nicotine to mainstream smoke.	Int. Contributions to Tobacco Research	19-5	237-44.,	2001
Avalos, J.T. Bombick, B.R. Borgerding, M.F. Chepiga, T.A. Doolittle, D.J. Morton, M.J. Murphey, P.A. Swager, J.E.	A comparison of the mainstream smoke chemistry and mutagenicity.,of a representative sample of the US cigarette market with two Kentucky reference cigarettes (Kl R4F and Kl R5F)	Food and Chemical Toxicology	38	949-962	2000

Coleman III, W.M. Dull, G.M. Gordon, B.M. Miller, C.W. Morgan, W.T. Norman, A.B. Perfetti, T.A.	The Transfer of Nicotine from Nicotine Salts to Mainstream Smoke	Beiträge zur Tabakforschung International	19	141-158	2000
Hansch, C. Smith, C.J.	The Relative Toxicity of Compounds in Mainstream Cigarette Smoke Condensate	Food and Chemical Toxicology	38	637-646	2000
Maitani, T. Satake, M. Sekita, S. Sugimoto, N. Yamada, T. Yun, Y.S.	Two New Alkaloids from Cigarette Smoke Condensate	Chem. & Pharm. Bull	48	1990-1991	2000
Carchman, R.A. Gomm, W.A. Meisgen, T.J. Roemer, E. Tewes, F.J.	CIGARETTE PARAMETERS THAT INFLUENCE THE MUTA-GENICITY OF MAINSTREAM SMOKE CONDENSATE.	Toxicological Sciences	48	125	1999
COOK C.J.;LAUTERBACH J.H.;PANNELL W.T.;PRICE B.F.;BOWSER W.M.;PINION D.O.;SPENCER A.K.	Transfer of semi-volatile components from tobacco to smoke.	CORESTA Meet. Smoke-Techno Groups/Réunion Groupes Techno-Fumée, Innsbruck,	abstr. ST21		1999
Fournier, J.A. Paine III, J.B. Seeman, J.I. Waymack, B.E.	The Form of Nicotine in Tobacco. Thermal Transfer of Nicotine and Nicotine Acid Salts to Nicotine in the Gas Phase	J. Agric. Food Chem.	47	5133-5145	1999
Gaworski CL, Heck JD, Bennett MB & Wenk ML	Toxicologic evaluation of flavour ingredients added to cigarette tobacco: skin painting bioassay of cigarette smoke condensate in SENCAR mice.	Toxicology	139	1-17	1999
SEEMAN J.I.;FOURNIER J.A.;PAINE J.B. III	Aspects of the thermal behavior of nicotine and its salts with carboxylic acids.	CORESTA Meet. Smoke-Techno Groups/Réunion Groupes Techno-Fumée, Innsbruck	abstr. ST 18		1999
Aufderheide, M. Jarck, P. Knebel, J.W. Koch, W. Lodding, H. Massey, E. Pohlmann, G. Windt, H.	Micronucleus induction in V79 cells after direct exposure to whole cigarette smoke	Mutagenesis	13(2)	145-149	1998

Gaworski CL, Dozier HM, Heck JD, Gerhart JM, Rajendran N, David RM, Brennecke LH & Morrissey R	Toxicologic evaluation of flavour ingredients added to cigarette tobacco: 13-week inhalation exposures in rats.	Inhalation Toxicology	10	357-381	1998
KALAITZOGLOU M.;SAMARA C.	Comparative study of cigarettes produced in Greece.	Bull. Spéc. CORESTA, 1998, Congrès Brighton,	abstr. ST27	p. 174,	1998
Ashida, K. Itoh, T. Kamisaki, Y. Kishimoto, Y. Nakamoto, K. Wada, K.	SUBSTANCES IN THE AQUEOUS FRACTION OF CIGARETTE SMOKE INHIBIT LIPID PEROXIDATION IN SYNAPTOSOMES OF RAT CEREBRAL CORTEX	Biochemistry and Molecular Biology International	42(1)	10-Jan	1997
Ayres, P.H. Bombick, D.W. Doolittle, D.J.	CYTOTOXICITY ASSESSMENT OF WHOLE SMOKE AND VAPOR PHASE OF MAINSTREAM AND SIDESTREAM CIGARETTE SMOKE FROM THREE KENTUCKY REFERENCE CIGARETTES	Toxicology Methods	7	177-190	1997
Ohshima, H. Yoshie, Y.	Synergistic induction of DNA strand breakage by cigarette tar and nitric oxide	Carcinogenesis	18(7)	1359-1363	1997
SEEMAN J.I.;FOURNIER J.A.;PAINE J.B.III	Thermal transfer of nicotine and nicotine acid salts to nicotine in the gas phase.	Tob. Chem. Res. Conf.,	abstr. 11.	51	1997
Kalra, V.K. Rattan, V. Shen, Y. Sultana, C.	Cigarette smoke condensate-induced adhesion molecule expression and transendothelial migration of monocytes	American Journal of Physiology	270	1624-1633	1996
Doolittle, D.J. Fulp, C.W. Lee, C.K. Payne, V.M. Rees, D.C. Steele, R.H.	A comparison of the mutagenicity of mainstream cigarette smoke condensates from a representative sample of the U.S. cigarette market with a Kentucky reference cigarette (KlR4F)	Mutation Research	342	179-190	1995
Eiro, H.	Effects of cigarette tobacco tar by gastric administration on murine pulmonary tumorigenesis	Journal of Toxicologic Pathology	8	377-384	1995
Baumann, H. Krivan, V. Reus, U. Schneider, G.	Multi-element characterization of tobacco smoke condensate	Fresenius Journal of Anal. Chem.	348	218-225	1994
Doolittle, D.J. McKarns, S.C.	A Quantitative Approach to Assessing Intercellular Communication: Studies on Cigarette Smoke Condensates	Toxicology and Applied Pharmacology	111	58-68	1991

Burns, A.R. Dunn, L.A. Hogg, J.C. Hosford, S.P. Walker, D.C.	Respiratory epithelial permeability after cigarette smoke exposure in guinea pigs	J Appl Physiol	66(5)	2109-2116	1989
Gonzalez-Rothi, R.J. Harris, J.O.	Effect of low-yield-cigarette smoke inhalation on rat lung macrophages	Journal of Toxicology and Environmental Health	17	221-228	1986
Hudgens, R.W. Sonnenfeld, G.	Effect of Sidestream and Mainstream Smoke Exposure on in Vitro Interferon - alpha/beta Production by L-929 Cells	Cancer Res	46	2779-2783	1986
KAMESWARA RAO B.V.;MURTHY P.S.N.;CHAKRABORTY M.K.	Chemical studies on Lanka tobacco (indigenous to India) and its smoke. 3. Alkaloids.	VIth Ntl Symp. Tob., Rajahmundry,	abstr. 76	p. 59	1986
Schmahl, D. Zeller, W.J.	Relevance of Gas and Particulate Phases of Tobacco Smoke for Lung Cancer Formation	Cancer Detection and Prevention	9	91-97	1986
Gairola, C.	Genetic effects of fresh cigarette smoke in Saccharomyces cerevisiae	Mutation Research	102	123-136	1982
HOFFMANN D.;ADAMS J.D.;VINCHKOSKI N.;TSO T.C.	On the fate of nicotine-14C during leaf curing and smoking.	Bul. Spéc. CORESTA , Symposium Winston-Salem,	abstr S04	p. 14,	1982
NAGORSKI B.	Predicting alkaloid contents in the main stream smoke of cigarette based on the alkaloid values in tobacco.	Biul. Inf. centr. Lab. Przem. Tyton.,	04-Jan	p. 47-56	1982
Boyd, C.H. Dansie, D.R. Henry, C.J. Kouri, R.E. Rasmussen, R.E.	DNA Replication and Unscheduled DNA Synthesis in Lungs of Mice Exposed to Cigarette Smoke	Cancer Res	41	2583-2588	1981
Coggins, C.R.E. Fouillet, X.L.M. Lam, R. Morgan, K.T.	Cigarette smoke induced pathology of the rat respiratory tract: a comparison of the effects of the particulate and vapour phases	Toxicology	16	83-101	1980
Lam, R.	Transient epithelial loss in rat larynx after acute exposure to tobacco smoke	Toxicology Letters	6	327-335	1980
Bernfeld, P. Homburger, F. Pai, K.J. Soto, E.	Cigarette Smoke Inhalation Studies in Inbred Syrian Golden Hamsters	J Natl Cancer Inst (JNCI)	63(3)	675-689	1979
Akin, F. J. Benner, J.F.	Induction of Aryl Hydrocarbon Hydroxylase in Rodent Lung by Cigarette Smoke : A Potential Short-Term Bioassay	Toxicology and Applied Pharmacology	36	331-337	1976

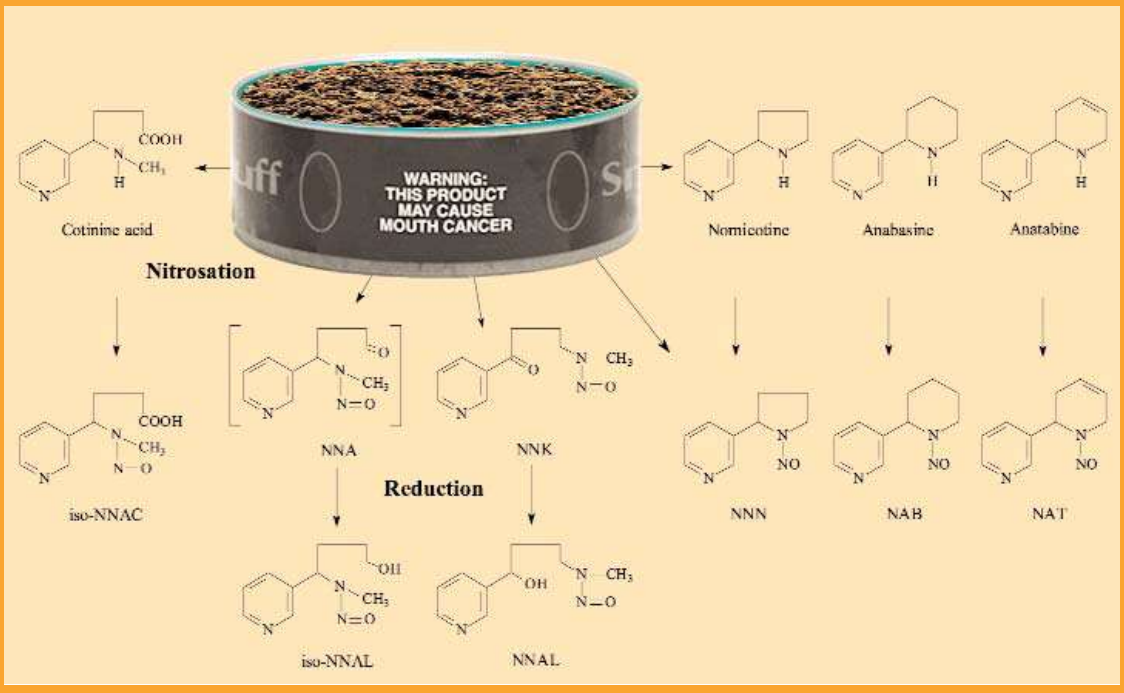
JENKINS R.W.;COMES R.A.	Exogenous versus endogenous transfer of nicotine during smoking.	Int. J. appl. Radiat. Isot.	27-5/6	p. 323-4	1976
Ames, B.N. Kier, L. D. Yamasaki, E.	Detection of Mutagenic Activity in Cigarette Smoke Condensates	Proc. Natn. Acad. Sci. USA	71 no 10	4159-4163	1974
Leuchtenberger, C. Leuchtenberger, R. Zbinden, I.	Gas Vapour Phase Constituents and SH Reactivity of Cigarette Smoke Influence Lung Cultures	Nature	247	565-567	1974
Chevalier, H.-J. Dontenwill, W. Harke, H.-P. Lafrenz, U. Reckzeh, G. Schneider, B.	Investigations on the Effects of Chronic Cigarette-Smoke Inhalation in Syrian Golden Hamsters	J Natl Cancer Inst (JNCI)	51	1781-1832	1973
Houseman, T.H.	Studies of Cigarette Smoke Transfer Using Radioisotopicallv Labelled Tobacco Constituents Part II: The Transference of Radioisotopically Labelled Nicotine to Cigarette Smoke	Beiträge zur Tabakforschung	7(3)	142-	1973
Dontenwill, W. Elmenhorst, H. Harke, H.-P. Misfeld, J. Reckzeh, G. Timm, J. Weber, K.H.	Experimentelle Untersuchungen über die tumorerzeugende Wirkung von Zigarettenrauch-Kondensaten an der Mäusehaut	Z. Krebsforsch.	73	285-304	1970
Leuchtenberger, C. Leuchtenberger, R.	Cytologic and Cytochemical Effects on Primary Mouse Kidney Tissue and Lung Organ Cultures after Exposure to Whole Fresh Smoke	Cancer Res	29	862-872	1969
Benedict, R. C. Stedman, R.L.	Complexity of Enzymatic Inhibition by Cigarette Smoke	Experientia	24 no 12	1205-1206	1968
Kobashi, Y. Sakaguchi, S.	The Influence of Inorganic Salts on the Combustion of Cigarette and on the Transfer of Nicotine on to Smoke	Agric. Biol. Chem.	25	200-205	1961
Izawa, M. Kobashi, Y. Sakaguchi, S.	Combustion Temperatures of Some Unblended Cigarettes and the Transfer of Nicotine into Cigarette Smoke	Bull. Agr. Chem. Soc. Japan	24	274-277	1960
Izawa, M. Kobashi, Y. Sakaguchi, S.	On the Influence of Moisture Content in Cigarettes on Combustion Temperature and Transferred Amount of Nicotine into Cigarettes Smoke	Bull. Agr. Chem. Soc. Japan	23	532-535	1959

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 89

Smokeless Tobacco and Some Tobacco-specific *N*-Nitrosamines



LYON, FRANCE
2007

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 89

Smokeless Tobacco and Some Tobacco-specific *N*-Nitrosamines

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

5–12 October 2004

2007

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, life-style factors and biological and physical agents, as well as those in specific occupations.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed.

The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported by Cooperative Agreement 5 UO1 CA33193 awarded since 1982 by the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the European Commission, Directorate-General EMPL (Employment, and Social Affairs), Health, Safety and Hygiene at Work Unit, and since 1992 by the United States National Institute of Environmental Health Sciences.

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

Distributed by WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int).

IARC Library Cataloguing in Publication Data

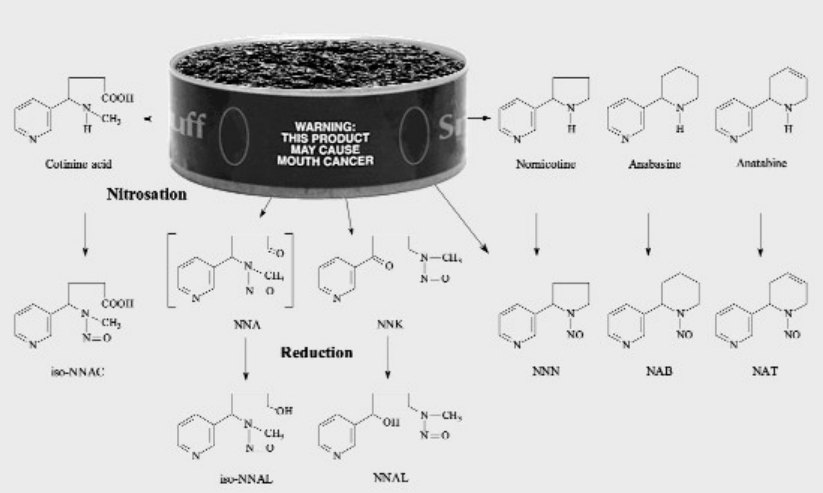
Smokeless Tobacco and Some Tobacco-specific *N*-Nitrosamines/
IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2004 : Lyon, France)

(IARC monographs on the evaluation of carcinogenic risks to humans ; v. 89)

1. Carcinogens 2. Nitrosamines – adverse effects
3. Tobacco, Smokeless – adverse effects
I. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans II. Series

ISBN 978 92 832 1289 8 (NLM Classification: W1)
ISSN 1017-1606

PRINTED IN FRANCE



Cover legend:

Schematic diagramme of the metabolism of nicotine, an addictive chemical present in all tobacco products. The tobacco-specific *N*-nitrosamines NNK, NNN, NAB and NAT are reviewed in the second Monograph of this volume.

Cover design: Georges Mollon, IARC

SMOKELESS TOBACCO

Smokeless tobacco was considered by a previous IARC Working Group in 2004 (IARC, 2007a). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Smokeless tobacco products

The term smokeless tobacco implies use of unburned tobacco in the finished products. A variety of smokeless tobacco products are available, for oral or nasal use. Products intended for oral use are sucked, chewed (dipped), gargled or applied to the gums or teeth, while fine tobacco mixtures are usually inhaled into the nostrils.

Table 1.1 summarizes for each smokeless tobacco product its mode of use, the main ingredients included, the WHO regions in which the product is used, and some specification of the countries is which the product is used most commonly or specifically (DHHS, 2001; IARC, 2007a; European Commission, 2008). Smokeless tobacco products that contain areca nut are commonly used in India, other countries in South Asia, and in migrant populations from these countries. These products may be mentioned here for comparison but are reviewed in the *Monograph* on Betel Quid and Areca Nut in this volume.

1.2 Chemical composition of smokeless tobacco

The tobacco used in a particular product has a decisive influence on its chemical composition, and varies with tobacco species, growing, curing, processing and storage. During product manufacture, tobacco is blended to achieve a specific nicotine content and pH. The pH strongly influences the concentration of unprotonated nicotine, the bioavailable form of nicotine, while the nitrite/nitrate content strongly influences the levels of carcinogenic nitrosamines in the product. Other tobacco components are alkaloids which include nicotine (85–95% of total alkaloids), terpenes, polyphenols, phytosterols, carboxylic acids, aromatic hydrocarbons, aldehydes, ketones, amines, nitriles, *N*- and *O*-heterocyclic hydrocarbons, pesticides, and metallic compounds. Flavour-type additives are also present (Bates *et al.*, 1999). Ammonia, ammonium carbonate and sodium carbonate are applied to control nicotine delivery by raising pH and subsequently the level of unprotonated nicotine which is most readily absorbed through the mouth into the bloodstream (Djordjevic *et al.*, 1995).

Table 1.1 Smokeless tobacco products, ingredients, and use by WHO region

Tobacco product	Mode of use	Ingredients	WHO Region					
			AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Oral use								
Betel quid with tobacco[a]	Chewing	Betel leaf, areca nut, slaked lime, tobacco in various forms			X		X	X
Chimó	Sucking	Paste of crushed and boiled tobacco leaves, sodium bicarbonate, sugar, wood ash, flavourings		X[b]				
Chewing tobacco	Chewing	See Tobacco chewing gum						
Chewing tobacco twist/ roll	Chewing	Dark, air- or fire-cured tobacco leaves treated with tobacco extract, flavourings		X[c]				
Creamy snuff	Other	Finely ground tobacco with aromatic substances (manufactured commercially)					X	
Dry snuff	Sucking	Fire- or air-cured, fermented powdered tobacco	X[d]	X[c]	X[e]	X[f]	X[g]	
Gudhaku	Other	Paste of powdered tobacco and molasses					X[g]	
Gul	Other	Powdered tobacco, molasses and other ingredients					X[g]	
Gutka[a]	Sucking	Sun-dried finely chopped tobacco, areca nut, slaked lime, catechu, flavourings, sweeteners (manufactured commercially)					X	
Iq'mik	Chewing	Fire-cured tobacco leaves with punk ash		X[h]				
Khaini	Sucking	Sun-dried or fermented coarsely crushed tobacco leaves					X[i]	
Khiwam	Chewing	Paste of tobacco extract, spices, additives					X[j]	
Loose leaf	Chewing	Small strips of air-cured, shredded cigar tobacco leaves (manufactured commercially)		X[c]		X		
Maraş	Sucking	Sun-dried powdered tobacco leaves, wood ash, water				X[k]		
Mawa[a]	Chewing	Sun-cured areca nut, crushed tobacco leaves, slaked lime					X[j]	
Mishri	Sucking	Tobacco toasted on hot metal plate and powdered					X[g]	
Moist snuff	Sucking	Air- or fire-cured tobacco, processed into fine particles (fine-cut) or strips (long-cut), with stem and seeds		X[c]		X[l]		
Naswar/nass	Sucking	Sun-dried, powdered tobacco, ash, oil, flavourings, colourings, slaked lime (optional)	X[d]		X[m]	X		
Plug chewing tobacco	Chewing	Heavy-grade or cigar tobacco top leaves immersed in liquorice or sugar, pressed into a plug		X[c]				
Red tooth powder	Other	Fine tobacco powder, many additional ingredients (manufactured commercially)					X	
Shammah	Sucking	Powdered tobacco, lime, ash, black pepper, oils, flavourings			X[n]	X		
Snus	-	See moist stuff		X[c]		X[l]		

Table 1.1 (continued)

Tobacco product	Mode of use	Ingredients	WHO Region					
			AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Saffa	-	*Toomback* rolled into a ball	X[q]					
Tobacco tablet	Sucking	Compressed powdered tobacco, mint, eucalyptus		X[c]				
Toombak	Sucking	Dried, fermented, ground and matured tobacco leaves, sodium bicarbonate	X[q]					
Tuibur	Other	Tobacco water					X[r]	
Zarda	Chewing	Tobacco leaves boiled with lime and spices until dry, colourings; chewed with areca nut and spices			X		X	
Nasal use								
Dry snuff	Sniffing	Fire-cured, fermented and powdered tobacco	X[s]		X	X[t]	X	
Liquid snuff	Sniffing	Powered tobacco mixed with ash from plants, oil, lemon juice, herbs	X[u]					

[a] These products contain areca nut and are reviewed in the*Monograph* on Betel Quid and Areca Nut in this volume.
[b] Specific to Venezuela, used by young boys and urban teenagers
[c] Used in the USA
[d] Used principally in South Africa; dry snuff is mostly inhaled.
[e] Common in North Africa, notably in Tunisia as*neffa*
[f] Used in Germany, Georgia and the United Kingdom
[g] Used as dentifrice, mostly by women, in various parts of India
[h] Specific to native American tribes of North-West Alaska
[i] Used in India, Bangladesh and Nepal
[j] Specific to India
[k] Specific to remote regions of Turkey
[l] Used in Sweden, Norway and Finland
[m] Common in Afghanistan, Islamic Republic of Iran, Pakistan and central Asia
[n] Common in the Middle East, particularly in Saudi Arabia and Yemen
[o] Used in Sweden and Denmark
[p] Specific to Japan (new product)
[q] Specific to Sudan, used by men
[r] Specific to eastern States of India
[s] Used by several tribes in South Africa, namely Bantus
[t] Used in the United Kingdom
[u] Specific to tribes in East Africa
AFRO, African Region; AMRO, Regions of the Americas; EMRO, Eastern Mediterranean Region; EURO, European Region; SEARO, South East Asian Region, WPRO, Western Pacific Region; the countries included in each region are available at http://www.who.int/about/regions/en/

1.2.1 Nicotine content in smokeless tobacco

The majority of commercial tobacco products are made from *N. tabacum* species, grown throughout the world with an alkaloid content that varies greatly. In randomly cultivated varieties examined, the alkaloid content ranged between 0.17 and 4.93%.

N. rustica species is cultivated in eastern Europe, Asia Minor and Africa, and the cured leaves may contain up to 12% nicotine. *Toombak* from Sudan, which contains *N. rustica* tobacco, had the highest reported levels of nicotine (Idris *et al.*, 1991; Prokopczyk *et al.*, 1995). In 17 brands of moist snuff from the USA, the nicotine content ranged from 0.47 to 3.43%.The nicotine content of Swedish snus ranges from 0.5–1.7% (Idris *et al.*, 1998; Stepanov *et al.*, 2008).

1.2.2 Carcinogenic compounds in smokeless tobacco

Multiple carcinogens have been identified in smokeless tobacco (IARC, 2007a) including:

(a) Tobacco-specific N-nitrosamines

Tobacco-specific *N*-nitrosamines include the carcinogens *N*′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

Tobacco-specific *N*-nitrosamines are formed from tobacco alkaloids (nicotine, nornicotine, anatabine, anabasine, and nitrite) primarily during tobacco curing, fermentation and ageing. The nitrate or nitrite content, the mode of curing and the various steps of processing are the main determining factors for the yields of tobacco-specific *N*-nitrosamines in tobacco.

IARC (2007a) compiled an international comparison of the concentrations of NNN and NNK in smokeless tobacco products. The ranges vary widely and are product- and country-specific. In some moist snuff brands in the USA, the highest concentrations of NNN and NNK measured were 135 and 17.8 μg/g tobacco, respectively. In home-made *toombak* from Sudan, values as high as 3085 and 7870 μg/g dry wt tobacco, respectively, have been reported (Idris *et al.*, 1991; Prokopczyk *et al.*, 1995).

(b) N-Nitrosamino acids

The amino acids present in tobacco, and probably also the proteins with secondary amino groups, are amenable to *N*-nitrosation. Since 1985, numerous studies have reported the presence of *N*-nitrosamino acids in smokeless tobacco products (IARC, 2007a).

To date, 11 *N*-nitrosamino acids have been identified in smokeless tobacco: *N*-nitrososarcosine (NSAR), *N*-nitrosoazetidine-4-carboxylic acid (NAzCA), 3-(methylnitrosamino)propionic acid (MNPA), 4-(methylnitrosamino) butyric acid (MNBA), *N*-nitrosoproline (NPRO), *N*-nitrosohydroxyproline (NHPRO), *N*-nitrosopipecolic acid (NPIC), *N*-nitrosothiazolidine-4-carboxylic acid (NTCA), *N*-nitroso-2-methylthiazolidine-4-carboxylic acid (MNTCA), 4-(methylnitrosamino)-4-(3-pyridyl)butyric acid (*iso*-NNAC) and 2-(methylnitrosamino)-3-phenylpropionic acid (MNPhPA) (Ohshima *et al.*, 1985; Tricker & Preussmann, 1988; Hoffmann *et al.*, 1995). Of these, NSAR, MNPA, MNBA and NAzCA have been established as carcinogens in experimental animals.

The concentration of *N*-nitrosamino acids depends on the nitrate or nitrite content of tobacco; they are formed during prolonged storage, particularly under adverse conditions of temperature and relative humidity. The concentrations reported in USA moist snuff samples were in the range of 5.7 to 13.45 μg/g dry wt. Highest amounts of MNPA were found in Indian *zarda* (up to 18 μg/g) and in moist snuff (up to 70 μg/g).

Table 1.2 PAHs in moist snuff brands marketed in the USA

Compound	Mean ± SD of 23 brands (ng/g dry weight)
Naphthalene	1726 ± 392.3
Acenaphthylene	110.5 ± 42.9
Acenaphthene	105.1 ± 53.8
Fluorene	826.5 ± 287.0
Phenanthrene	4700 ± 1571
Anthracene	844.2 ± 277.8
Fluoranthene	1404 ± 537.4
Pyrene	1292 ± 428.5
Benz[*a*]anthracene	193.6 ± 71.3
Chrysene	232.1 ± 109.8
Methylchrysenes	92.6 ± 35.0
Benzo[*b*]fluoranthene + Benzo[*f*]fluoranthene	107.0 ± 69.5
Benzo[*k*]fluoranthene	19.6 ± 6.6
Benzo[*e*]pyrene	52.4 ± 23.8
Benzo[*a*]pyrene	55.8 ± 21.5
Indeno[*c,d*]pyrene	20.5 ± 12.1
Benzo[*g,h,i*]perylene	18.0 ± 8.3
Dibenz[*a,h*]anthracene	7.5 ± 1.9

From Stepanov *et al.* (2010)

(c) Volatile N-nitrosamines

These include *N*-nitrosodimehtylamine (NDMA), *N*-nitrosopyrrolidine (NPYR) and *N*-nitrosopiperidine (NPIP).

Levels of volatile *N*-nitrosamines formed from volatile amines and nitrosating agents in smokeless tobacco products worldwide have been summarized (IARC, 2007a). The highest amounts were found in moist snuff (NDMA up to 265 ng/g dry wt and NPYR up to 860 ng/g dry wt).

(d) PAHs

These include benzo[a]pyrene, benz[a] anthracene, chrysene, benzofluoranthenes, and dibenz[a,h]anthracene.

Levels of various PAHs in 23 moist snuff brands marketed in the USA were determined by Stepanov *et al.* (2010) and are summarized in Table 1.2.

(e) Other carcinogenic compounds and constituents

Levels of the volatile aldehydes formaldehyde, acetaldehyde, acrolein and crotonaldehyde in smokeless tobacco products ranged from 0.207–10.6, 0.97–72.3, 0.27–7.85, and 0.55–19.4 µg/g dry weight tobacco, respectively (Stepanov *et al.*, 2010).

Uranium was reported in Indian snuff at a concentration of about 3 pCi/g tobacco (Sharma *et al.*, 1985). Levels of polonium-210 in commercial moist and dry snuff in the USA were reported to be 0.16–1.22 and 0.23–0.39 pCi/g, respectively.

In several parts of the world, smokeless tobacco is invariably chewed with lime which is responsible for highly alkaline pH (Nair *et al.*, 1990, 1992), facilitating absorption of nicotine in the oral mucosa.

1.2.3 Comparison of new and traditional smokeless tobacco products

Newer types of smokeless tobacco products are appearing on the market. These products are sold as small pouches and do not require spitting. Similar to Swedish snus, they have been manufactured with additional controls to inhibit nitrosamine formation, and are being promoted as reduced risk products. Levels of carcinogens in these newer products are compared to those in traditional products in Table 1.3 (Stepanov *et al.*, 2008).

1.3 Prevalence of use

1.3.1 Prevalence of smokeless tobacco use among adults

Several surveys have evaluated the prevalence of smokeless tobacco use at different times and targeting different populations in the WHO regions (AFRO, African Region; AMRO, Region of the Americas; EURO, European Region; EMRO, Eastern Mediterranean Region; SEARO,

Table 1.3 Mean levels of selected carcinogens in newer and traditional smokeless tobacco products

	Newer products (n = 12)	Traditional products (n = 5)
NNN (μg/g dry weight)	2.05	4.41
NNK (μg/g dry weight)	0.231	1.20
Benzo[*a*]pyrene (ng/g dry weight)	3.12	38.2
Fluoranthene	10.0	400
Benzo[*b*]fluoranthene + Benzo[*k*]fluoranthene (ng/g dry weight)	2.76	38.3
Formaldehyde (μg/g dry weight)	3.23	8.43
Acetaldehyde (μg/g dry weight)	6.16	35.7
Crotonaldehyde (μg/g dry weight)	9.12	2.98

NNN, *N*′-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
From Stepanov *et al.* (2008)

South-East Asian Region; WPRO, Western Pacific Region). The major surveys that form the basis of this report are (Table 1.4):

- the Global Adult Tobacco Survey conducted during 2009–10 among adults aged 15 years or more in 14 middle and low-income countries in AMRO, SEARO, EURO, EMRO and WPRO;
- the national level STEPS noncommunicable risk factor survey (2006–09) was conducted in 8 countries in AFRO, and a few countries in SEARO, EURO (Georgia), EMRO and WPRO (Mongolia), in adults aged 15–64 years, except for AFRO (age group, 25–64 years);
- the Demographic and Health Surveys (2003–10) provide prevalence on smokeless tobacco use among adults aged 15–49 years in countries in AFRO (16), EURO (4), EMRO (2), WPRO (8);
- some other surveys such as the Behavioural Risk Factor Survey, the National Smoking/Tobacco/Drug use Survey, health cost studies, and national health, public health or morbidity surveys.

The prevalence of smokeless tobacco use reported in the various surveys are not directly comparable because of the different methodologies and time periods; however, they provide a snapshot of the global smokeless tobacco burden. Large variations are observed between countries (Table 1.5), between sex within a country, and sometimes within a country (Table 1.6). Those countries with a high prevalence (≥ 10%) represent about 25% of the global adult population. They include, by WHO region:

- in AFRO: Benin (men, 13%), Madagascar (men 23%; women, 20%), Mauritania (women, 28%), South Africa (women, 11%);
- in EMRO: Yemen (men, 15%);
- in EURO: Norway (men, 17.0%; women, 5.0%), Sweden (men, 26%), Uzbekistan (men, 22.5%);
- in SEARO: Bangladesh (men, 26%; women, 28%), India (men, 33%; women 11–18%), Myanmar (men, 51.4%; women, 16.1%), Nepal (men, 31%), Sri Lanka (men, 24.9%);
- in WPRO: Cambodia (women, 12.7%).

A few countries have medium prevalence (between 5% and 10%); these include:

- in AFRO: Benin, Cape Verde, Malawi in women; Lesotho, Mali, Mauritania, Swaziland, Zimbabwe in men;
- in AMRO: USA in men;

- in EMRO: Tunisia in men; Yemen in women;
- in EURO: Finland, Iceland and Kyrgyzstan in men; Norway and Sweden in women;
- in SEARO: Sri Lanka and Thailand in women.

In most countries, current prevalence of smokeless tobacco use is higher among men than among women. Some exceptions are found at all levels of prevalence (in women and men, respectively): Bangladesh (27.9, 26.9), Barbados (0.6, 0), Cambodia (12.7, 0.7), Cape Verde (5.8, 3.5), Malaysia (3.1, 0.5), Mauritania (28.3, 5.7), South Africa (10.9, 2.4), Thailand (6.3, 1.3) and Viet Nam (2.3, 0.3).

Demographic health survey data indicate that in countries in AFRO and SEARO smokeless tobacco is more prevalent in rural compared to urban areas, and higher among low-income compared to high-income groups. Also, prevalence generally increases with increasing age.

Some countries warrant more detailed information of their pattern of smokeless tobacco use, and are presented below.

1.3.2 Country specific data

(a) India

The India Global Adult Tobacco Survey (2009–10) revealed that 26% of all adults use smokeless tobacco in some form, 21.4% daily and 4.5% occasionally. Prevalence in men (32.9%) is higher than in women (18.4%), and is higher in rural (29.3%) than urban areas (17.7%). Large variations are observed between States, from around 5% in Himachal Pradesh, Goa and Chandigarh to 49% in Bihar (India GATS Report, 2009–10).

Khaini is the most commonly used smokeless tobacco product (11.6%), followed by *gutka* (8.2%). Prevalence of *khaini* chewing is significantly higher among men (18%) than among women (5%); 13.1% men and 2.9% women chew *gutka*; 6.2% (7.5% men, 4.9% women) of adults use betel quid with tobacco; 4.7% (3.3% men, 6.3% women) use tobacco products such as *mishri, gul, gudakhu* for oral application (dentifrice); and 4.4% uses some other products, such as snuff for nasal application and some local products. The pattern of use of smokeless tobacco products also varies widely in different States of India (Table 1.6) (India GATS Report, 2009–10).

Proportion of dual tobacco users (smoking+smokeless) is 19.4% among men and 5.3% among women (Sinha *et al.*, 2011).

(b) Bangladesh

In Bangladesh the most prevalent form of smokeless tobacco is betel quid with tobacco (24.3%), followed by *gul* (5.3%), *sada pata* (1.8%), *khaini* (1.5%) and others (1.4%) (BAN GATS Report, 2009). Use decreases with increasing education and socioeconomic level in both men and women, by a steeper rate among women compared to men. Among current users, those with the highest prevalence of use of *gul* and *khaini* were labourers among men (7.5% and 2.8%, respectively) and homemaker among women (5.7% and 1.4%, respectively) (BAN GATS Report, 2009).

Proportion of dual tobacco users (smoking+smokeless) is 22.5% among men and 2.5% among women (Sinha *et al.*, 2011).

(c) Canada

Unchanged from surveys conducted in 2008 and 2009, 8% of Canadians aged 15 years and older reported having ever tried smokeless tobacco products in 2010. In 2009, 11% of young adults aged 20 to 24 years reported ever using smokeless tobacco and 1% having used it within the past 30 days. There has been a shift in the distribution of past-30-day smokeless tobacco users from youth towards older adults: in 2003, 23% of users were aged 15–19 years and 14% were older than 45 years, whereas in 2009, 16% of smokeless tobacco users were 15 to 19 years old and 33% were aged 45 and older.

Table 1.4 Surveys and articles used to compile the information presented*

Bangladesh GATS report Government of the People's Republic of Bangladesh, Ministry of Health and Family Welfare; World Health Organization, Country Office for Bangladesh. Global Adult Tobacco Survey: Bangladesh Report 2009. Dhaka, 2009. http://www.searo.who.int/LinkFiles/Regional_Tobacco_Surveillance_System_GATSBAN_FullReport2009.pdf

Canada CTUMS Canadian Tobacco Use Monitoring Survey (CTUMS) 2010, http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_2010/ann_summary-sommaire-eng.php

Central Statistical Office (CSO) [Swaziland], and Macro International Inc. 2008. *Swaziland Demographic and Health Survey 2006–07.* Mbabane, Swaziland: Central Statistical Office and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR202/FR202.pdf

Central Statistical Office (CSO) [Zimbabwe] and Macro International Inc. 2007. *Zimbabwe Demographic and Health Survey 2005–06.* Calverton, Maryland: CSO and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR186/FR186.pdf

Central Statistical Office (CSO), Ministry of Health (health ministry), Tropical Diseases Research Centre (TDRC), University of Zambia, and Macro International Inc. 2009. *Zambia Demographic and Health Survey 2007.* Calverton, Maryland, USA: CSO and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR211/FR211[revised-05-12-2009].pdf

Department of Health, Medical Research Council, OrcMacro. 2007. *South Africa Demographic and Health Survey 2003. Pretoria: Department of Health.* http://www.measuredhs.com/pubs/pdf/FR206/FR206.pdf

Ghana Statistical Service (GSS), Ghana Health Service (GHS), and ICF Macro. 2009. *Ghana Demographic and Health Survey 2008.* Accra, Ghana: GSS, GHS, and ICF Macro. http://www.measuredhs.com/publications/publication-FR221-DHS-Final-Reports.cfm

Global Tobacco epidemic report World Health Organization. World Report on the Global Tobacco Epidemic, 2009: Implementing Smoke-Free Environments. Geneva: WHO, 2009.

Global Tobacco epidemic report World Health Organization. World Report on the Global Tobacco Epidemic, 2011 Geneva: WHO, 2011.

India GATS report Government of India, Ministry of Health and Family Welfare. Global Adult Tobacco Survey: GATS India 2009–2010. Mumbai, 2010. http://www.searo.who.int/LinkFiles/Regional_Tobacco_Surveillance_System_GATS_India.pdf

Institut National de la Statistique (INSTAT) et ICF Macro. 2010. *Enquête Démographique et de Santé de Madagascar 2008–2009.* Antananarivo, Madagascar: INSTAT et ICF Macro. http://www.measuredhs.com/pubs/pdf/FR236/FR236.pdf

Institut National de la Statistique et de l'Analyse Économique (INSAE) [Bénin] et Macro International Inc. 2007: *Enquête Démographique et de Santé (EDSB-III) – Bénin 2006.* Calverton, Maryland, USA: Institut National de la Statistique et de l'Analyse Économique et Macro International Inc. http://www.measuredhs.com/publications/publication-FR197-DHS-Final-Reports.cfm

Kenya National Bureau of Statistics (KNBS) and ICF Macro. 2010. *Kenya Demographic and Health Survey 2008–09.* Calverton, Maryland: KNBS and ICF Macro. http://www.measuredhs.com/publications/publication-FR229-DHS-Final-Reports.cfm

Liberia Institute of Statistics and Geo-Information Services (LISGIS) [Liberia], Ministry of Health and Social Welfare [Liberia], National AIDS Control Program [Liberia], and Macro International Inc. 2008. *Liberia Demographic and Health Survey 2007.* Monrovia, Liberia: Liberia Institute of Statistics and Geo-Information Services (LISGIS) and Macro International Inc. http://www.measuredhs.com/publications/publication-FR201-DHS-Final-Reports.cfm

Lund M, Lindbak R. *Norwegian Tobacco Statistics 1973–2006.* Oslo: Norwegian Institute for Alcohol and Drug Research; 2007. Sirus skrifter No. 3/2007.

Lundqvist G, Sandström H, Ohman A, Weinehall L. Patterns of tobacco use: a 10-yr follow-up study of smoking and snus habits in a middle-aged Swedish population, Scand J Public Health. 2009, 37:161–7

Ministry of Health and Social Services (MoHSS) [Namibia] and Macro International Inc. 2008. *Namibia Demographic and Health Survey 2006–07.* Windhoek, Namibia and Calverton, Maryland, USA: MoHSS and Macro International Inc. http://www.measuredhs.com/publications/publication-FR204-DHS-Final-Reports.cfm

Ministry of Health and Social Welfare (MOHSW) [Lesotho] and ICF Macro. 2010. *Lesotho Demographic and Health Survey 2009.* Maseru, Lesotho: MOHSW and ICF Macro. http://www.measuredhs.com/publications/publication-FR241-DHS-Final-Reports.cfm

Table 1.4 (continued)

MMWR August 27, 2010, 59(33), 487–92, Tobacco use among Middle and High school students –USA 2000–2009
MMWR August 6, 2010/59(30);946–950, Any tobacco use in 13 states-Behavioural Risk factor Surveillance System 2008
National Bureau of Statistics (NBS) [United Republic of Tanzania] and ICF Macro. 2011. *United Republic of Tanzania Demographic and Health Survey 2010.* Dar es Salaam, United Republic of Tanzania: NBS and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR243/FR243[24June2011].pdf
National Institute of Population Research and Training (NIPORT), Mitra and Associates, and Macro International. 2009. *Bangladesh Demographic and Health Survey 2007.* Dhaka, Bangladesh and Calverton, Maryland, USA: National Institute of Population Research and Training, Mitra and Associates, and Macro International. http://www.measuredhs.com/pubs/pdf/FR207/FR207[April-10-2009].pdf
National Population Commission (NPC) [Nigeria] and ICF Macro. 2009. *Nigeria Demographic and Health Survey 2008.* Abuja, Nigeria: National Population Commission and ICF Macro. http://www.measuredhs.com/publications/publication-FR222-DHS-Final-Reports.cfm
National Statistics Directorate (NSD) [Timor-Leste], Ministry of Finance [Timor-Leste], and ICF Macro. 2010. *Timor-Leste Demographic and Health Survey 2009–10.* Dili, Timor-Leste: NSD [Timor-Leste] and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR235/FR235.pdf
Sinha DN, Palipudi KM, Rolle I *et al.* (2011). Tobacco use among youth and adults in member countries of South-East Asia region: Review of findings from surveys under the global tobacco surveillance system. Indian J Public Health, 55:169–176. PMID:22089684
Statistics Indonesia (Badan Pusat Statistik—BPS) and Macro International. 2008. *Indonesia Demographic and Health Survey 2007.* Calverton, Maryland, USA: BPS and Macro International. http://www.measuredhs.com/pubs/pdf/FR218/FR218[27August2010].pdf
Statistics Sierra Leone (SSL) and ICF Macro. 2009. *Sierra Leone Demographic and Health Survey 2008.* Calverton, Maryland, USA: Statistics Sierra Leone (SSL) and ICF Macro. http://www.measuredhs.com/pubs/pdf/FR225/FR225.pdf
Uganda Bureau of Statistics (UBOS) and Macro International Inc. 2007. *Uganda Demographic and Health Survey 2006.* Calverton, Maryland, USA: UBOS and Macro International Inc. http://www.measuredhs.com/pubs/pdf/FR194/FR194.pdf

*, Exceptionally, the most recent updates of well established ongoing surveys and reports, published after the meeting, were included in this *Monograph*. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.

Table 1.5 Highest and lowest prevalence of smokeless tobacco use by WHO regions and by sex

	Men		Women	
WHO region	**Lowest**	**Highest**	**Lowest**	**Highest**
AFRO	0.8% in Gambia	22.6% in Madagascar	0.2% in Ghana	28.3% in Mauritania
AMRO	0.0% in Barbados	6.9% in USA	0.2% in Guyana & Dominican Republic	0.6% in Barbados
EMRO	1.3% in Saudi Arabia	15.1% in Yemen	0.1% in Libyan	6.2% in Yemen
EURO	0.2% in Switzerland & Latvia	26.0% in Sweden	0% in Switzerland & Ukraine	5% in Kyrgyzstan
SEARO	1.3% in Thailand	51.4% in Myanmar	0.3% in Indonesia	27.9% in Bangladesh
WPRO	0.3% in Viet Nam	2.8% in Mongolia & Philippines	0.1% in the People's Republic of China	12.7% in Cambodia

(d) USA

According to the Behavioural Risk Factor Surveillance System survey (2008), conducted in 13 States, prevalence varied from 0.5% (New Jersey) to 8.8% (West Virginia). Dual use of cigarette and smokeless tobacco products varied from 0.2% (Delaware) to 1.8% (West Virginia).

In an overall analysis of users' demographic characteristics, prevalence of smokeless tobacco use was higher among men (6.3%) than women (0.3%); more prevalent among non-Hispanic whites (4.1%) compared to other ethnic groups; highest in the youngest age group (18–24 years) and decreased steadily with age. Users of smokeless tobacco were almost equally distributed between the sextiles of annual income (3.0 to 3.8%).

(e) Europe

In Europe, countries with a high prevalence of smokeless tobacco use are Norway, Sweden and Uzbekistan.

In Sweden, a 10-year follow-up study of smoking and snus [Swedish moist snuff] habits in a middle-aged Swedish population showed that use of snus increased from 3.1% to 6.0% among women and from 24.6% to 26.3% among men. The number of people who used both snus and cigarettes was stable: 0.5% to 0.8% from baseline to follow-up for women and 4.1% to 3.3% for men. Whereas nearly all snus users in Sweden are daily users, almost half of snus users in Norway use it only occasionally.

1.3.3 Prevalence of smokeless tobacco use among youth

The Global Youth Tobacco Survey (GYTS) is a school-based survey of students aged 13–15 years that uses a two-stage sampling design. In a first stage, schools are selected based on the probability proportional to the enrolment of students in schools. In a second stage, classes are selected randomly. It uses standard questionnaire, field methodology and analysis. The Survey has core questions that spans seven thematic areas pertinent to tobacco. In addition, countries can include country-specific questions that allow assessment of tobacco unique to the country [smokeless tobacco use may include betel quid with tobacco.]

In AFRO, all countries surveyed reported a prevalence of smokeless tobacco use among youth above 5%, ranging from 5.4% in Swaziland to 16.4% in Congo. Among boys, it varied from 5.2% in Seychelles to 18.3% in Congo, whereas among girls, from 4.8% in Togo to 15.8% in Namibia. Prevalence was higher among boys than girls in most countries, except in Uganda where

Table 1.6 Highest and lowest prevalence of use of selected smokeless tobacco products in India, by State

	Lowest	Highest
Betel quid	0.5% in Punjab, Himachal Pradesh, Chandigarh and Uttrakhand	32.8% in Tripura
Dentifrice	0.4% in Tripura	28.35 in Chattishgarh
Khaini	0.5% in Tamil Nadu	32.6% in Jharkhand
Gutka	0.6% in Puducherry	17.0% in Madhya Pradesh

it was higher among girls (9.6% versus 8.6%) (Asma *et al.*, 2011). Four countries (Botswana, Congo, Lesotho and Namibia) are particularly noteworthy: these countries reported the highest prevalence in both sexes (11.3–16.4%), the highest prevalence in boys (11.3–18.3%), the highest prevalence in girls (11.4–15.8%), and similar prevalence in boys and girls.

In AMRO, prevalence of smokeless tobacco use among youth varied from 3.5% in Panama to 9.8% in Barbados. Among boys, it varied from 3.8% in Panama to 11.5% in Barbados, whereas among girls, it varies from 2.6% in Venezuela to 8.5% in Jamaica. Most notably, smokeless tobacco use among boys was above 10% in Barbados, Dominican Republic and Grenada. Girls in most countries used less smokeless tobacco than boys, except in Jamaica (8.5% for both) and Peru (boys, 4.3%; girls, 4.8%) where boys and girls had comparable prevalence (Asma *et al.*, 2011).

In SEARO, all countries surveyed reported a prevalence of smokeless tobacco use among youth above 5%, ranging from 4.9% in Bangladesh to 9.4% in Bhutan. Among boys, it ranged from 5.8% in Bangladesh to 14.1% in Bhutan whereas among girls, it varies from 2.7% in Myanmar to 6% in India. In all countries more boys than girls used smokeless tobacco products (Asma *et al.*, 2011).

In EURO, prevalence of smokeless tobacco use among youth is lower than in other WHO regions, ranging from 1.1% in Montenegro to 6.9% in Estonia. While it ranged from 1.1% in Montenegro to 9.4% in Estonia among boys, it varied from 0.7% in Serbia to 4.5% in Estonia among girls. Except for Estonia (6.9%), all countries reported a prevalence among youth below 5%. Also, in all countries boys used more smokeless tobacco than girls (Asma *et al.*, 2011).

In EMRO, prevalence of smokeless tobacco use among youth varied from 1.6% in Oman to 12.6% Djibouti. Among boys, it varied from 2% in Libyan Arab Jamahirya to 15.2% in Djibouti, whereas among girls, it varied from 0.9% in Oman and Tunisia to 9% in Djibouti. Prevalence of smokeless tobacco use among youth was highest in Djibouti (12.6%), where it is also highest among boys and girls separately. Boys generally used more smokeless tobacco than girls, except in Libyan Arab Jamahirya and Yemen where girl users slightly outnumbered boy users (Asma *et al.*, 2011).

In WPRO, prevalence of smokeless tobacco use among youth varies from 2.1% in Macau to 8.7% in Cook Islands. Among boys, it varies from 2.2% in Macau to 10.5% in Cook Islands, whereas among girls, it varies from 2.1% in Macau to 7.3% in Cook Islands. Prevalence of smokeless tobacco use among youth in Cook Island and Republic of Korea is above 5% for boys and girls combined, as well as separately for boys and girls. Prevalence among boys was generally higher than among girls (Asma *et al.*, 2011).

In summary, among the countries included in the GYTS survey 2007–2010, the prevalence of smokeless tobacco use among youth aged 13–15 years exceeds 5% in all or most countries in AFRO, AMRO and SEARO, in Djibouti, Islamic Republic of Iran, Qatar, Syrian Arab Republic and Yemen in EMRO, and in the Cook Islands and Republic of Korea in WPRO (Asma *et al.*, 2011).

In general, prevalence among boys was higher than among girls, although in several countries prevalence was similar, or higher among girls.

In several countries, smokeless tobacco use among 13 to 15 year-old men is higher than that among adult men (aged 15 years or more). These include Albania, Argentina, Brazil, the Dominican Republic, Guyana, Lesotho, Mexico, Namibia, Saudi Arabia, Tunisia and Uganda. Similarly, in Albania, Argentina, Barbados, Brazil, Dominican Republic, Guyana, Kyrgyzstan, Libyan Arab Jamahirya, Mexico, Saudi Arabia, Swaziland, Uganda and Yemen, smokeless tobacco use among 13–15 year women is higher than that in adult women.

2. Cancer in Humans

2.1 Oral use

2.1.1 Cancers of the oral cavity and pharynx

(a) Overview of studies

Studies of smokeless tobacco and oral and pharyngeal cancer have been conducted in North and South America, Europe, Asia, and Africa. All of the studies reported here examined oral cancer risks associated with use of unsmoked tobacco that was not part of a betel quid. Evidence regarding betel quid is presented in the *Monograph* on Betel Quid in this volume. This section focuses on the predominant smokeless tobacco products and behaviours in the countries in which the studies were conducted, for example on chewing tobacco and snuff in North America, snus in northern Europe, *shammah* in Saudi Arabia and Yemen, *toombak* in Sudan, and a variety of types in South Asia (see Table 1.1 for their mode of use, ingredients and region of use). The studies typically examine cancers arising in intra-oral sites, which are predominantly squamous cell in origin (Canto & Devesa, 2002), but some include other sites as well, such as the oropharynx, hypopharynx, or larynx. Studies involving smokeless tobacco and nasopharyngeal cancer are discussed in another chapter.

The previous *Monograph* (IARC, 2007a) concluded that there was *sufficient evidence* in humans that smokeless tobacco causes cancer of the oral cavity. Studies published since include updates on mortality and incidence for one of the cohorts reviewed previously (Accortt *et al.*, 2002, 2005), two new cohort studies (Luo *et al.*, 2007; Roosaar *et al.*, 2008); case–control studies from Sweden (Rosenquist, 2005; Rosenquist *et al.*, 2005) and India (Sapkota *et al.*, 2007); and three meta-analyses (Weitkunat *et al.*, 2007; Boffetta *et al.*, 2008; Lee & Hamling, 2009).

Because tobacco smoking is a risk factor for oral and pharyngeal cancers (IARC, 2004), and tobacco smoking is often positively correlated with smokeless tobacco use (Tomar, 2002), addressing confounding by smoking is important in the examination of causality related to smokeless tobacco. Heavy alcohol use is another important risk factor and can potentially confound the relationship between tobacco use and risk of oral and pharyngeal cancer (IARC, 2010, 2012).

While analysis restricted to non-smokers and non-alcohol drinkers eliminates the possibility of confounding due to smoking and alcohol drinking, the sample sizes can be small in study populations in regions where these behaviours are common. Adjusting statistically for smoking and alcohol can alternatively be used to address confounding by these factors in populations where these behaviours are common and can provide unbiased estimates that may be more stable if there is no residual confounding within smoking/drinking categories used in the adjustment. There is *sufficient evidence* that human papillomavirus (HPV) 16 causes oral cancer in humans (IARC, 2007b). Studies have shown that the prevalence of HPV DNA is negatively correlated with tobacco smoking and alcoholic beverage consumption (Gillison *et al.*, 2000), suggesting that positive confounding by HPV is

not likely to account for a spurious association between smokeless tobacco and oral cancer.

The specific name of the smokeless tobacco product will be used whenever available. In the USA, where moist snuff and chewing tobacco are both common, the term "smokeless tobacco" refers to use of either. Most publications provide data on "ever" versus "never" use of these products, usually defined as using the product or not for some minimal length of time such as a year. Due to the large body of evidence, this *Monograph* will focus on studies published since IARC (2007a).

(i) Cohort studies

Ever lifetime use or ever daily use of smokeless tobacco and risk of oral and pharyngeal cancers was examined in six cohort studies conducted in the USA (Zahm *et al.*, 1992; Accortt *et al.*, 2002, 2005; Henley *et al.*, 2005), Sweden (Luo *et al.*, 2007; Roosaar *et al.*, 2008), and Norway (Boffetta *et al.*, 2005). Mortality data were analysed in four studies (Zahm *et al.*, 1992; Accortt *et al.*, 2002; Henley *et al.*, 2005; Roosaar *et al.*, 2008), four (Accortt *et al.*, 2005; Boffetta *et al.*, 2005; Luo *et al.*, 2007; Roosaar *et al.*, 2008) analysed cancer incidence. None of the studies excluded persons diagnosed in the first 1 or 2 years of follow-up nor did they collect information on changes in behaviours, such as smokeless tobacco or smoking cessation or initiation, after the baseline (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.1.pdf).

Ever use of smokeless tobacco was associated with a statistically significant threefold increased risk of death from oral cancer and an 8.7 fold increased risk of death from pharyngeal cancer in one study from the USA (Zahm *et al.*, 1992). Risks were greater among those with more frequent use, but adjustment was not performed for tobacco smoking and therefore this study will not be considered further in this section.

Ever use of smokeless tobacco was not associated with risk for cancer in four cohorts (Accortt *et al.*, 2005; Boffetta *et al.*, 2005; Henley *et al.*, 2005; Luo *et al.*, 2007). In one cohort the age-adjusted standardized mortality ratio for oral cancer associated with ever smokeless tobacco use was not elevated (Accortt *et al.*, 2002) and the age-adjusted standardized incidence ratio for smokeless tobacco use and oral cancer was statistically lower than expected (Accortt *et al.*, 2005). The expected number of oral cancer deaths among ever smokeless tobacco users in this cohort was zero, suggesting limited statistical power to detect elevated risks.

In the Cancer Prevention Study I and II cohorts (Henley *et al.*, 2005; CPS-I and CPS-II, respectively), the hazard ratio (HR) for death from oral and pharyngeal cancer in CPS-I for current use of smokeless tobacco versus never use among men who never used any other form of tobacco was 2.0 (95%CI: 0.5–7.7), based on four deaths adjusting for alcohol consumption, fruit/vegetable intake and other factors. The corresponding HR in CPS-II was 0.9 (95%CI: 0.1–6.7), based on one death adjusting for similar factors as CPS-I.

In the Norwegian cohort (Boffetta *et al.*, 2005), the HR for ever use of smokeless tobacco was 1.1 (95%CI: 0.5–2.4), for oral, pharynx or salivary gland cancer after adjusting for age and smoking. Among non-smokers in a cohort of 280 000 Swedish male construction workers, the relative risk of developing oral cancer was 0.8 (95%CI: 0.4–1.7), adjusting for attained age and body mass index (BMI) (Luo *et al.*, 2007).

One cohort study in Sweden involved 9 860 men who participated in an oral examination (Roosaar *et al.*, 2008). An elevated relative risk (RR) of 3.1 (95%CI: 1.5–6.6) was found for ever daily use of snus compared to never daily use of snus controlling for calendar period, area of residence, alcohol consumption, smoking, and an interaction variable for age and smoking. Among

the never-smokers in the cohort, the relative risk for ever daily use of snus was 2.3 (95%CI: 0.7–8.3).

All cohort studies had at least 12 years of follow-up. No increased risk of oral cancer was observed for the three cohorts with 12–26 years of follow-up (Accortt *et al.*, 2002, 2005; Henley *et al.*, 2005; Luo *et al.*, 2007). One study with 35 years follow-up found no association of smokeless tobacco and oral cancer risk (Boffetta *et al.*, 2005) and another study with 27–29 years follow-up had significant positive findings among smokers only (Roosaar *et al.*, 2008).

(ii) Case–control studies

Many case–control studies examined smokeless tobacco and oral and pharyngeal cancer (Broders, 1920; Moore *et al.*, 1953; Wynder & Bross, 1957; Wynder *et al.*, 1957a, b; Peacock *et al.*, 1960; Chandra, 1962; Vogler *et al.*, 1962; Vincent & Marchetta, 1963; Martinez, 1969; Keller, 1970; Browne *et al.*, 1977; Jafarey *et al.*, 1977; Williams & Horm, 1977; Wynder & Stellman, 1977; Westbrook, 1980; Winn *et al.*, 1981a; Wynder *et al.*, 1983; Stockwell & Lyman, 1986; Young *et al.*, 1986; Blot *et al.*, 1988; Spitz *et al.*, 1988; Franco *et al.*, 1989; Goud *et al.*, 1990; Blomqvist *et al.*, 1991; Maden *et al.*, 1992; Marshall *et al.*, 1992; Mashberg *et al.*, 1993; Spitz *et al.*, 1993; Kabat *et al.*, 1994; Bundgaard *et al.*, 1995; Idris *et al.*, 1995a; Muscat *et al.*, 1996; Lewin *et al.*, 1998; Muscat & Wynder, 1998; Schildt *et al.*, 1998; Schwartz *et al.*, 1998; Wasnik *et al.*, 1998; Chelleng *et al.*, 2000; Merchant *et al.*, 2000; Rosenquist *et al.*, 2005; Rosenquist, 2005; Sapkota *et al.*, 2007). Two studies were of cancer of the salivary gland (Keller, 1969; Muscat & Wynder, 1998), one reported on hypopharyngeal cancer (Sapkota *et al.*, 2007), and one on nasopharyngeal cancer (Chelleng *et al.*, 2000). The same study was reported on twice in two instances (Wynder & Bross, 1957; Wynder *et al.*, 1957a; Rosenquist, 2005; Rosenquist *et al.*, 2005). Additionally, one cross-sectional study was conducted, but the comparability of the two surveys analysed to yield risk estimates was uncertain (Sterling *et al.*, 1992).

Nearly half the studies addressed potential confounding by tobacco smoking. In three (Broders, 1920; Stockwell & Lyman, 1986; Keller, 1970), smokeless tobacco information was probably obtained from medical records and, if ascertainment of smokeless tobacco use was more likely from cases than from controls, measurement error might account for the findings and these studies will not be considered further. The remaining 15 studies were conducted in the USA (Vogler *et al.*, 1962; Martinez, 1969; Williams & Horm, 1977; Winn *et al.*, 1981a; Blot *et al.*, 1988; Mashberg *et al.*, 1993; Kabat *et al.*, 1994), Sweden (Lewin *et al.*, 1998; Schildt *et al.*, 1998; Rosenquist, 2005; Rosenquist *et al.*, 2005), India (Chandra, 1962; Wasnik *et al.*, 1998; Sapkota *et al.*, 2007), Pakistan (Merchant *et al.*, 2000), and Sudan (Idris *et al.*, 1995a) (Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.2.pdf).

Five studies were population-based (Williams & Horm, 1977; Blot *et al.*, 1988; Lewin *et al.*, 1998; Schildt *et al.*, 1998; Rosenquist *et al.*, 2005); positive findings were observed in the majority of them (Williams & Horm, 1977; Blot *et al.*, 1988; Lewin *et al.*, 1998) and in all of the hospital-based studies except one (Mashberg *et al.*, 1993). One study (Winn *et al.*, 1981a) also included death certificate cases and controls.

Several case–control studies of oral cancer addressed potential confounding by tobacco smoking either by statistically controlling for tobacco smoking or by restricting to non-smokers. Odds ratios (OR) for ever versus never use of smokeless tobacco overall, or for at least one of the major cancer subtypes, was statistically significantly elevated in eight studies, with odds ratios for oral cavity cancer ranging from 3.9 to 34.5 (Vogler *et al.*, 1962; Martinez, 1969; Williams & Horm, 1977; Winn *et al.*, 1981a; Blot *et al.*, 1988; Kabat *et al.*, 1994; Idris *et al.*, 1995a; Wasnik *et al.*, 1998; Merchant *et al.*, 2000) and

in one study of hypopharyngeal cancer in India (Sapkota *et al.*, 2007). In case–control studies conducted in Sweden, there was no association with use of smokeless tobacco in 2 studies (Schildt *et al.*, 1998; Rosenquist, 2005) or in another study (Lewin *et al.*, 1998) that controlled for smoking and alcohol intake. However, when Lewin *et al.*, 1998 restricted the analysis to non-smokers the odds ratio for head and neck cancer associated with ever use of smokeless tobacco was 4.7 (95%CI: 1.6–13.8). [Rosenquist (2005) was based on a relatively small sample size of 132 cases and 320 controls.]

In one case–control study conducted in the USA (Vogler *et al.*, 1962) and another of *toombak* users in Sudan (Idris *et al.*, 1995a), neither statistical adjustment for tobacco smoking nor restriction to non-smokers was done. However, confounding by smoking was not likely to have a major effect on the risk estimates from these studies. The proportions of smokers in the case and control groups were low in the rural women in the study of Vogler *et al.* (1962) among whom positive findings were found. In the study in Sudan less than 10–12% of the two case groups and in a hospital-based control groups smoked; in the population-based control group 21% were smokers, but most had smoked for less than one year (Idris *et al.*, 1995a).

In a meta-analysis Boffetta *et al.* (2008) included studies published through 2007 that provided information about non-smokers and studies that adjusted for tobacco smoking. The summary estimate for the 11 studies of oral cancer (6 of them also including pharyngeal cancer) was 1.8 (95%CI: 1.1–2.9) overall. For the USA, it was 2.6 (95%CI: 1.3–5.2) and for northern European countries, 1.0 (95%CI: 0.7–1.3) (Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.3.pdf).

Another meta-analysis included 40 studies published through May 2008 (Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.4.pdf) but excluded studies in Asian or African populations (Lee & Hamling, 2009). In addition to the studies in the meta-analysis by Boffetta *et al.* (2008), 15 other studies were included: (Moore *et al.*, 1953; Wynder & Bross, 1957; Wynder *et al.*, 1957, 1983; Peacock *et al.*, 1960; Vincent & Marchetta, 1963; Martinez, 1969; Keller, 1970; Browne *et al.*, 1977; Wynder & Stellman, 1977; Young *et al.*, 1986; Spitz *et al.*, 1988; Franco *et al.*, 1989; Blomqvist *et al.*, 1991; Maden *et al.*, 1992; Marshall *et al.*, 1992; Sterling *et al.*, 1992; Zahm *et al.*, 1992; Spitz *et al.*, 1993; Bundgaard *et al.*, 1995; Muscat *et al.*, 1996; Schwartz *et al.*, 1998) and one unpublished study by Perry and colleagues in 1993. Among never-smokers the odds ratio was 1.72 (95%CI: 1.01–2.94) based on 9 studies; further adjustment for alcohol in the three studies where this was possible yielded an odds ratio among never-smokers of 1.87 (95%CI: 0.82–4.27). The estimate for never-smokers among the studies conducted in the USA was 3.33 (95%CI: 1.76–6.32), and decreased with additional adjustment for alcohol drinking (1.58; 95%CI: 0.52–4.81), based on two studies among never-smokers. Corresponding estimates for snuff use in never-smokers in Scandinavia were 1.01 (95%CI: 0.71–1.45; 4 studies) and 2.30 (95%CI: 0.67–7.92; 1 study) adjusted for alcohol drinking. For studies published since 1990, the corresponding estimates were 1.24 (95%CI: 0.80–1.90; 7 studies) in never-smokers and 1.87 (95%CI: 0.82–4.27; 3 studies) adjusted for alcohol drinking.

Lee & Hamling (2009) updated an earlier meta-analysis (Weitkunat *et al.*, 2007) of 32 studies through 2005, excluding studies conducted in Asian populations. Weitkunat *et al.* (2007) did not include three studies (Rosenquist *et al.*, 2005; Luo *et al.*, 2007; Roosaar *et al.*, 2008), but provided sex- and tobacco type- specific estimates not reported by Lee & Hamling (2009). For smokeless tobacco, the overall smoking-adjusted relative risk was 1.35 (95%CI: 1.04–1.76), and for chewing tobacco and snuff, the estimates were 1.42 (95%CI: 0.99–2.03; 6 studies) and

1.28 (95%CI: 0.76–2.14; 7 studies). For men the smoking-adjusted estimate was 1.15 (95%CI: 0.97–1.37) and for women 2.51 (95%CI: 1.73–3.64). For case–control studies with hospital-based controls, the estimates were 1.41 (95%CI: 1.18–1.68) and for studies with population-based controls 0.99 (95%CI: 0.69–1.42). Smoking-adjusted relative risks for smokeless tobacco were elevated only for studies conducted before 1980: 2.02 (95%CI: 1.28–3.20) for earlier than 1969, 2.67 (95%CI: 1.83–3.90) for 1970–1979, compared with 0.97 (95%CI: 0.71–1.31) for 1980–1989, and 1.10 (95%CI: 0.88–1.37) for 1990 or later.

(b) Dose–response evidence

In this and subsequent sections, the relative risks and odds ratios are either among non-smokers or are adjusted for tobacco smoking. Dose–response relationships were observed in several studies.

(i) Duration and intensity

Williams & Horm (1977) found that the odds ratio for oral cavity cancers in men associated with heavy use of smokeless tobacco was higher than for moderate use. Lewin *et al.* (1998) also reported relative risks for head and neck cancer that increased with increasing intensity of oral snuff use. Of the case–control studies that examined duration, higher risks of oral cancer with greater numbers of years of snuff use were noted for cancers of the gum/buccal mucosa, but not for other cancers of the mouth/pharynx category (Winn *et al.*, 1981a). No increase with years of snus use was observed in two Swedish case–control studies (Lewin *et al.*, 1998; Rosenquist *et al.*, 2005). In a study in Sudan (Idris *et al.*, 1995a), the odds ratio for use of *toombak* for more than 11 years was greater than that for fewer years of use.

(ii) Cessation

In two cohort (Boffetta *et al.*, 2005; Luo *et al.*, 2007) and three case–control studies (Lewin *et al.*, 1998; Schildt *et al.*, 1998; Rosenquist *et al.*, 2005), risks were not significantly elevated in either current or former smokeless tobacco users. No studies provided information on time since stopping.

(c) Comparison of types of smokeless tobacco by geographical location

(i) Northern Europe

Four studies from this area found no overall association between use of snus and oral cancer (Lewin *et al.*, 1998; Schildt *et al.*, 1998; Boffetta *et al.*, 2005; Rosenquist, 2005). One case–control study (Rosenquist, 2005) examined users of fermented and not fermented snuff and observed no risk for either type. In Sweden before 1983, snuff was fermented as part of the manufacturing process, and this process is conducive to formation of tobacco-specific *N*-nitrosamines. In one cohort study (Roosaar *et al.*, 2008) the relative risk for ever daily use of snus was 3.1 (95%CI: 1.5–6.6, adjusted for smoking, calendar period, area of residence, alcohol consumption and a variable to account for the interaction between age and smoking) and 2.3 (95%CI: 0.7–8.3) among non-smokers with adjustment for calendar period, area of residence and alcohol consumption. In a case–control study, among non-smokers, the odds ratio for cancers of the oral cavity, pharynx and oesophagus combined was 4.7 (95%CI: 1.6–13.8) (Lewin *et al.*, 1998).

(ii) USA

In the USA chewing tobacco and moist snuff are the predominant forms of smokeless tobacco. In five case–control studies of oral cancer, the odds ratio for ever use of smokeless tobacco were statistically significantly elevated overall for use of one or other type, ranging from 4.2 to 34.5 (Martinez, 1969; Williams & Horm, 1977; Williams *et al.*, 1977; Winn *et al.*, 1981a; Blot *et al.*, 1988; Kabat *et al.*, 1994). No association with use of either of these products was observed in 2 cohort studies (Accortt *et al.*, 2002; 2005;

Henley *et al.*, 2005) and one case–control study (Mashberg *et al.*, 1993).

The odds ratio for chewing tobacco was not statistically significantly elevated in two studies (Mashberg *et al.*, 1993; Kabat *et al.*, 1994); but was in a third (Martinez, 1969). For snuff, one study found no association (Mashberg *et al.*, 1993) and in three others statistically significant elevated risks were observed, ranging from 4.2 to 34.5 (Winn *et al.*, 1981a; Blot *et al.*, 1988; Kabat *et al.*, 1994). In one case–control study in the southern USA positive associations were observed among non-smoking women who were snuff dippers, but a significant association was observed for white, but not black women; dry snuff was the predominant form of snuff used by women in that area (Winn *et al.*, 1981a). Elevated odds ratios persisted with control for poor dentition (Winn *et al.*, 1981b), use of mouthwashes (Blot *et al.*, 1983), fruits and vegetables (Winn *et al.*, 1984), type of respondent (self versus proxy), and alcohol consumption (Winn, 1986).

(iii) Africa, Middle East, and Asia

In Sudan the majority of a consecutively accrued series of oral cancer cases used *saffa*, an oral snuff, a moistened, powdered tobacco treated with sodium sesquicarbonate (Elbeshir *et al.*, 1989). Also, in Sudan *toombak* use was higher in oral cancer cases with squamous cell-carcinomas in sites with direct contact with the quid (e.g. floor of mouth) than cases with less or no contact (e.g. palate) (Idris *et al.*, 1995b). The odds ratio for *toombak* use was 7.3 (4.3–12.4) comparing hospital-based cases with oral cancers in direct contact with the quid versus hospital controls, and 1.4 (0.8–2.5) for cases with oral cancers not usually in direct contact with the quid (Idris *et al.*, 1995a), adjusting for age, sex, tribe and residence. Ten to twelve percent of the cases and hospital controls smoked. Twenty-one percent of population controls smoked, although most had smoked for less than one year.

Case series from Saudi Arabia have noted a high frequency of use of *shammah* or *al-shammah* in series of oral, pharyngeal, and laryngeal cancer cases (Amer *et al.*, 1985; Ibrahim *et al.*, 1986; al-Idrissi, 1990; Allard *et al.*, 1999).

In Pakistan, ever using *naswar* was associated with an odds ratio of 9.5 (95%CI: 1.7–52.5; adjusted for cigarette smoking and alcohol consumption) (Merchant *et al.*, 2000). Reports based on small series of users in which potential confounding by tobacco smoking could not be ruled out also noted higher frequencies of *naswar* use in oral cancer cases than controls or oral cancers among *naswar* users (Aleksandrova, 1970; Nugmanov & Baimakanov, 1970).

In India, a case–control study of buccal mucosa cancer observed an odds ratio of [2.7] for men and [2.5] for women associated with tobacco chewing among non-smokers (Chandra, 1962). In a cross-sectional survey, the period prevalence of oral and oropharyngeal cancer among persons who used *pattiwala*, sun-cured tobacco leaf only, was 1.17 per 100 persons compared to 0.36 among non-chewers of tobacco (Wahi, 1968) [tobacco smoking was not accounted for]. A case–control study of oropharyngeal cancer, using a smokeless tobacco product for teeth cleaning was associated with an odds ratio of 5.2 (95%CI: 2.5–11.8), adjusted for smoking (Wasnik *et al.*, 1998). In another case–control study in India, snuffing tobacco nasally or orally, generally using *naswar*, was associated with elevated odds ratios for hypopharyngeal cancer in never-smokers and in analyses adjusted for tobacco smoking and alcohol consumption (Sapkota *et al.*, 2007). [The Working Group noted that in the Sapkota *et al.* (2007) study, snuff use was nasal as well as oral so the role of oral use could not be separately determined.] In the same study, odds ratios for hypopharyngeal cancer among never-smokers were significantly elevated for *zarda* and non-significantly elevated for *khaini*, after adjusting for centre, age, sex, socioeconomic status, alcohol consumption and tobacco snuffing.

(d) Interactions

In one study in the USA that provided odds ratios for smokers only, smokeless tobacco users only, and smokers who also used smokeless tobacco, each compared to non-users of either, there was no evidence of an interaction between smokeless tobacco use and smoking (Winn *et al.*, 1981a), nor was there any evidence of an interaction between smokeless tobacco use and alcohol consumption in a similar analysis of that study population (Winn, 1986).

2.1.2 Precancerous lesions of the oral cavity

(a) Overview of studies

Studies on the natural history of oral cancer suggest that several types of potentially malignant lesions and conditions precede the development of cancer of the oral cavity. Oral precancerous lesions of relevance are leukoplakia and erythroplakia. The term leukoplakia will be used below to describe white lesions and erythroplakia to describe red lesions. Several classification systems for the lesions have been used (Axéll *et al.*, 1976; Pindborg, 1980, Greer & Poulson, 1983; Pindborg *et al.*, 1996), all involving visual inspection of the oral cavity and a diagnosis based on clinical appearance of the lesions to identify the causes of the white and red oral lesions. Smokeless tobacco use has previously been identified as a risk factor for oral premalignant lesions (IARC, 2007a). Histological and clinical changes occur in the mucosa of snuff users in as few as 2–7 days after initiation of use (Payne *et al.*, 1998). Furthermore, the location of the lesion in the mouth has been shown to correspond to where the smokeless tobacco is typically placed (Salem *et al.*, 1984; Zaridze *et al.*, 1986; Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Ayo-Yusuf *et al.*, 2000).

Since IARC (2007a) one cross-sectional study has been published in the USA (Fisher *et al.*, 2005), one from Sweden (Roosaar *et al.*, 2008), and one from Yemen (Scheifele *et al.*, 2007). Cross-sectional studies and case series from many parts of the world have reported that leukoplakia occurs more commonly among smokeless tobacco users and that persons with lesions are more frequently smokeless tobacco users. Many cross-sectional studies were conducted in the USA (Greer & Poulson, 1983; Poulson *et al.*, 1984; Offenbacher & Weathers, 1985; Wolfe & Carlos, 1987; Creath *et al.*, 1988; Cummings *et al.*, 1989; Stewart *et al.*, 1989; Ernster *et al.*, 1990; Grady *et al.*, 1990; Creath *et al.*, 1991; Daniels *et al.*, 1992; Sinusas *et al.*, 1992; Grasser & Childers, 1997; Tomar *et al.*, 1997; Martin *et al.*, 1999; Lee *et al.*, 2000; Shulman *et al.*, 2004; Fisher *et al.*, 2005; Sinusas & Coroso, 2006). The types of smokeless tobacco implicated are snus in Sweden (Salonen *et al.*, 1990; Rolandsson *et al.*, 2005), Finland (Jungell & Malmström, 1985), and Denmark (Roed-Petersen *et al.*, 1972; Roed-Petersen & Pindborg, 1973; Rolandsson *et al.*, 2005), chewing tobacco in the United Kingdom (Tyldesley, 1971) and India (Jacob *et al.*, 2004), *nass* (*naswar*) in Uzbekistan (Zaridze *et al.*, 1985, 1986; Evstifeeva & Zaridze, 1992), *toombak* in Sudan (Idris *et al.*, 1996; Ahmed *et al.*, 2003; Ahmed & Mahgoob, 2007), snuff (finely ground fermented tobacco leaf with the wet ash of an Amaranthus species plant) in South Africa (Ayo-Yusuf *et al.*, 2000), *shammah* in Yemen (Scheifele *et al.*, 2007) and Saudi Arabia (Salem *et al.*, 1984; Mani, 1985).

Table 2.5 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.5.pdf) includes cross-sectional and case–control studies of smokeless tobacco and leukoplakia, listed by country. Eight reports from the USA adjusted for tobacco smoking, either through statistical adjustment or restriction to non-smokers, one in schoolchildren (Tomar *et al.*, 1997) and the others in adults (Shulman *et al.*, 2004; Ernster *et al.*, 1990; Grady *et al.*, 1990; Daniels *et al.*, 1992; Greene *et al.*, 1992; Martin *et al.*, 1999; Fisher *et al.*, 2005). The prevalence rate ratio or odds ratio for oral leukoplakia in

current smokeless tobacco users exceeded those of non-users for smokeless tobacco overall in four studies from the USA (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Fisher *et al.*, 2005) for snuff in four studies (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Fisher *et al.*, 2005) and for chewing tobacco in two (Ernster *et al.*, 1990; Tomar *et al.*, 1997) but not in a third (Fisher *et al.*, 2005).

In Uzbekistan *nass* (*naswar*) use was positively associated with oral leukoplakia in non-smokers (Zaridze *et al.*, 1986) and after adjusting for smoking, alcoholic beverage consumption, and age (Evstifeeva & Zaridze, 1992). In India, oral precancerous lesions (oral leukoplakia, submucous fibrosis, erythroplakia, and multiple lesions) were associated with tobacco chewing after adjusting for age, sex, BMI, pack–years of smoking, and years of drinking alcohol (Thomas *et al.*, 2003; Jacob *et al.*, 2004).

(b) Dose–response evidence

(i) Duration and intensity

Strong dose–response relationships have been observed in studies in the USA with intensity and duration of use of smokeless tobacco, snuff or chewing tobacco. The prevalence odds ratio for mucosal lesions increased with increasing intensity (amounts used per day or week) and duration (months, years, minutes or hours per day with tobacco in the mouth; shorter time since last used) of use of smokeless tobacco (chewing tobacco and snuff) (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999; Fisher *et al.*, 2005). Baseball players who used smokeless tobacco only during the playing season had a lower prevalence rate of oral lesions than year-long users, but higher than non-users (Greene *et al.*, 1992).

In Uzbekistan there was a trend of greater odds ratios for pre-leukoplakia and leukoplakia with the number of times *nass* was used per day, earlier age at initiation of the habit, years used, and lifetime intake (Evstifeeva & Zaridze, 1992). In Yemen, there was a dose–response relationship with number of minutes *shammah* was kept in the mouth and the risk was reduced if the mouth was rinsed after using the product (Scheifele *et al.*, 2007).

(ii) Cessation

The prevalence or prevalence odds ratio for oral lesions were higher in current than in former users in studies in the USA (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Shulman *et al.*, 2004; Fisher *et al.*, 2005). Former users generally had higher prevalence or prevalence odds ratio (although not always statistically significantly elevated) than never users (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Fisher *et al.*, 2005). In Uzbekistan, both former (OR, 3.00; 95%CI: 1.08–8.32) and current users (OR, 3.86; 95%CI: 2.60–5.72) had statistically significantly elevated odds ratios associated with *nass* use (Evstifeeva & Zaridze, 1992).

(c) Severity of lesions

The percentage of more severe leukoplakia lesions (degree 3 and 4) was higher with increasing amount of use, longer duration of use, shorter time since last use of snuff, and exposure time in the mouth in studies in the USA (Ernster *et al.*, 1990; Grady *et al.*, 1990; Daniels *et al.*, 1992; Greene *et al.*, 1992; Tomar *et al.*; 1997; Martin *et al.*, 1999). Basal-cell hyperplasia was observed in 4% of 132 lesion biopsies from snuff users, while no hyperplasia was found in the 6 biopsies from chewing tobacco users (Daniels *et al.*, 1992). Severe epithelial atypia was observed in *toombak* users (38%) in a case series in Sudan (Ahmed *et al.*, 2003). Also in Sudan greater duration of *toombak* use was associated with greater severity of the lesions (Idris *et al.*, 1996). In a South African study, lesions were more severe among those with more minutes per day of use and the users of the commercial brand compared to home-made snuff (Ayo-Yusuf *et al.*, 2000).

(d) Types

The prevalence of lesions was higher among snuff users compared with tobacco chewers in several studies (Ernster *et al.*, 1990; Greene *et al.*, 1992; Tomar *et al.*, 1997; Martin *et al.*, 1999). Among snuff users, the prevalence of lesions and the relative risk varied depending on the brand used (Grady *et al.*, 1990; Greene *et al.*, 1992; Martin *et al.*, 1999). In Yemen (Scheifele *et al.*, 2007) the prevalence odds ratio was higher for using black *shammah* compared to white *shammah*. Greater frequency of more severe lesions has been found in users of loose snus compared to men using portion-bag snus (Andersson & Axéll, 1989; Andersson *et al.*, 1994; Rolandsson *et al.*, 2005).

(e) Reversal or progression of lesions

Table 2.6 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.6.pdf) provides information from studies that examined reversal or progression of lesions. In men with leukoplakia that were re-examined 1–21 days after the first examination, 15% of the lesions resolved and 18% improved by one degree (Grady *et al.*, 1991). Smaller lesions were most likely to have resolved in men who decreased or stopped smokeless tobacco use, among users of chewing tobacco compared with those of snuff, among light users, and among seasonal users only. Disappearance or regression of lesions was not associated with duration of smokeless tobacco use or the number of days between the initial examination and follow-up. In a study of military recruits, 97% of the oral lesions observed at the initial examination had completely resolved six weeks after they ceased using tobacco (Martin *et al.*, 1999). In a study in Denmark, there was a lower percentage of snuff users whose lesions transformed to dysplasia or malignancy compared to patients with leukoplakia who did not use snuff (Roed-Petersen & Pindborg, 1973).

Men in Sweden with snus-induced lesions followed over 27–29 years did not have a higher risk of oral cancer (not smoking adjusted) compared to the entire Swedish population (Roosaar *et al.*, 2006). A subset of men had a repeat oral examination 19–22 years after the baseline. Among those who stopped snus entirely or used it less than once per day, 6.1% had a lesion at the follow-up exam. Lesions were still present with the same or lesser severity in 91% of the men who continued use of loose snuff or changed to portion-bag snuff and 8.7% had a worse lesion. Of those who used snus for more hours per day at the follow-up than at baseline, 12.1% had a worse lesion. In an earlier study, after 3–6 months, snus users with oral lesions who used portion-bag snus were more likely to have less severe lesions and users who stopped using snus or who changed to portion bags and changed the placement of the snus in the mouth had no lesions at the original site (Larsson *et al.*, 1991). Snus users who changed to snus with a lower pH and lower nicotine concentrations had less severe lesions after 24 weeks (Andersson & Warfvinge, 2003).

In a 10 year follow up study in India, Gupta *et al.* (1980) reported significantly higher malignant transformation in a group of smokeless tobacco users with precancer.

2.1.3 Cancer of the oesophagus

(a) Overview of studies

Studies of smokeless tobacco and oesophageal cancer have been conducted in North America, Europe and Asia. All of the studies reported here examined oesophageal cancer risks associated with use of unsmoked tobacco that was not part of a betel quid. Evidence regarding betel quid is presented in the *Monograph* on Betel Quid in this volume. These studies generally focused on the predominant smokeless tobacco products and behaviours in the countries in which the studies were conducted.

Two studies (Zendehdel *et al.*, 2008; Nasrollahzadeh *et al.*, 2008) have been published since the previous *Monograph* (IARC, 2007a).

Major risk factors for oesophageal cancers are tobacco smoking, betel quid chewing, heavy alcohol consumption (only for squamous cell carcinomas of the oesophagus) (IARC, 2004, IARC, 2010) and BMI (for adenocarcinoma of the oesophagus) (Kubo & Corley, 2006), making these factors potential confounders in studies of smokeless tobacco. [The Working Group notes that betel quid chewing and smokeless tobacco use are nearly always mutually exclusive in certain geographic regions.]

In two cohort studies (Boffetta *et al.*, 2005; Zendehdel *et al.*, 2008) smokeless tobacco use and oesophageal cancer has been examined (Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.7.pdf); both addressed potential confounding by smoking and included incident cases occurring in the first few years of follow-up.

One of the cohort studies was conducted in Norway and study participants were followed for 35 years for cancer incidence (Boffetta *et al.*, 2005). The relative risk for oesophageal cancer was 1.4 (95%CI: 0.6–3.2) for ever use of snuff compared to never use, adjusted for age and smoking. In a Swedish cohort study (Zendehdel *et al.*, 2008) the relative risk for squamous cell carcinoma of the oesophagus among non-smoking men who used only snuff compared to never users of tobacco was 3.5 (95%CI: 1.6–7.6) adjusting for age and BMI.

Several case–control studies in the USA have been conducted that did not include odds ratio among non-smokers or did not adjust statistically for smoking behaviours (Wynder *et al.*, 1957; Wynder & Bross, 1961; Wynder & Stellman, 1977; Pottern *et al.*, 1981). Of the seven case–control studies of smokeless tobacco and oesophageal cancer that did so (Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.8.pdf), two were conducted in Sweden (Lewin *et al.*, 1998; Lagergren *et al.*, 2000), three in the USA (Martinez, 1969; Williams & Horm, 1977; Williams *et al.*, 1977; Brown *et al.*, 1988), one in India (Phukan *et al.*, 2001) and one in the Islamic Republic of Iran (Nasrollahzadeh *et al.*, 2008). Because the survival rate for oesophageal cancer is poor (Crew & Neugut, 2004), case–control studies may be susceptible to selection bias from not interviewing study cases who died before the time of interview or measurement error due to obtaining information from proxy interviews (Winn, 1986).

Three case–control studies from the USA (one from Puerto Rico) showed no association between use of smokeless tobacco and oesophageal cancer (Martinez, 1969; Williams & Horm, 1977; Williams *et al.*, 1977; Brown *et al.*, 1988) after adjusting for smoking or restricting the analysis to non-smokers. The proportion of proxy interviews needed to ascertain smokeless tobacco use in these studies was 45% (Williams & Horm, 1977; Williams *et al.*, 1977), at least 69% (Brown *et al.*, 1988), and 12% (Martinez, 1969).

Both of the Swedish case–control studies were population-based and adjusted the analyses for smoking and alcohol intake (Lewin *et al.*, 1998; Lagergren *et al.*, 2000). In one of them that involved both squamous cell and adenocarcinoma, no proxy interviews were permitted (Lagergren *et al.*, 2000). The odds ratio for users of smokeless tobacco only compared to non-users of tobacco was 1.4 (95%CI: 0.9–2.3) for squamous cell carcinoma of the oesophagus and 1.2 (95%CI: 0.7–2.0) for adenocarcinoma of the oesophagus adjusting for age, tobacco smoking, alcohol drinking and other factors. In the other Swedish study (Lewin *et al.*, 1998) on squamous cell carcinoma, most were interviewed about a month after the case's diagnosis date. The odds ratio for ever use of snuff was 1.2 (95%CI: 0.7–2.2), adjusting for age, region, tobacco smoking and alcoholic beverages.

In a hospital-based case–control study from India an association between smokeless tobacco and oesophageal cancer was found (Phukan *et al.*, 2001). Relative to persons who neither used smokeless tobacco nor smoked, the odds ratio for persons who used only *chadha* (a type of smokeless tobacco) but did not chew betel quid nor smoke was 3.2 (95%CI: 1.6–9.5) for men and 6.2 (95%CI: 2.4–12.1) for women, adjusting for alcohol. In a study in the Islamic Republic of Iran cases were interviewed at the time of diagnosis (there were no proxy interviews), and only histologically confirmed squamous cell carcinoma were included (Nasrollahzadeh *et al.*, 2008); when use of different tobacco products was examined in a multivariate model, there was a significant positive association with *nass* use only compared to never users of any tobacco product, after adjustment for education, ethnicity, and total intake of fruit and vegetables.

In a meta-analysis of studies published through 2007 (Boffetta *et al.*, 2008; Table 2.9, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.9.pdf), only studies from Europe and the USA that provided information about non-smokers and studies that included smokers but adjusted for tobacco smoking were included. The overall estimate of effect for the five studies of oesophageal cancer was 1.6 (95%CI: 1.1–2.3). In a second meta-analysis Lee & Hamling (2009) included studies from Europe and the USA of smokeless tobacco and oesophageal cancer through May 2008, including and two studies that did not adjust for smoking (Wynder & Bross, 1961; Wynder & Stellman, 1977; Table 2.10, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.10.pdf). The overall relative risk among never-smokers was 1.91 (95%CI: 1.15–3.17) and the smoking-adjusted relative risk 1.13 (95%CI: 0.95–1.36). For Scandinavian studies, the summary relative risk in never-smokers was 1.92 (95%CI: 1.00–3.68; one study) and 1.10 (95%CI: 0.92–1.33) when smoking adjusted. For studies from the USA, the relative risks restricted to never-smokers or adjusted for smoking were identical, 1.89 (95%CI: 0.84–4.25).

(b) Dose–response evidence

(i) Duration and intensity

In one case–control study (Lagergren *et al.*, 2000), there were no significant increases in risk for years of use up to 25 years, adjusted for smoking, alcohol, and other factors. For more than 25 years of use, the odds ratio for snuff use controlling for smoking, alcohol intake and other factors was 2.0 (95%CI: 0.9–4.1) for squamous cell carcinoma of the oesophagus and 1.9 (95%CI: 0.9–4.0) for adenocarcinoma of the oesophagus. The odds ratio for use of 15–35 quids per week for squamous cell carcinoma was 2.1 (95%CI: 1.0–4.4) and for adenocarcinoma, 2.0 (95%CI: 1.0–4.3). Corresponding estimates for using more than 35 quids per week were 1.0 (95%CI: 0.4–2.4) and 0.8 (95%CI: 0.3–2.0), respectively. In another case–control study (Lewin *et al.*, 1998), the odds ratio for smokeless tobacco users of more than 50 g per week was 1.9 (95%CI: 0.8–3.9) adjusting for smoking and alcohol intake among other factors. In the Islamic Republic of Iran study (Nasrollahzadeh *et al.*, 2008), there were significant positive exposure-response relationships for frequency of use per day of *nass*, cumulative use (frequency times duration), and duration of *nass* use. However, these findings were not controlled for tobacco smoking.

(ii) Cessation

In one case–control study of oesophageal cancer (Lewin *et al.*, 1998), there was no association with snuff use for former or current smokeless tobacco users compared to never smokeless tobacco users.

(c) Types

In northern Europe, the predominant form of smokeless tobacco is snus. Of the four studies from that geographic region – two cohort

(Boffetta *et al.*, 2005; Zendehdel *et al.*, 2008) and two case–control (Lewin *et al.*, 1998; Lagergren *et al.*, 2000) – all of the odds ratios were greater than 1.0, but statistically significantly elevated only in one study (Zendehdel *et al.*, 2008). The odds ratios in the three studies from the USA where snuff and chewing tobacco are used, were not statistically significantly elevated (Martinez, 1969; Williams & Horm, 1977; Brown *et al.*, 1988).

In India, among non-smokers, statistically significantly elevated odds ratios associated with chewing *chadha* were reported for both men and women adjusting for alcohol consumption (Phukan *et al.*, 2001). In a study in the Islamic Republic of Iran, *nass* users had a significantly increased risk of oesophageal cancer (Nasrollahzadeh *et al.*, 2008).

It was noted in a report on a case series in Sudan that use of tobacco in the form of *toombak* under the tongue or in the labiodental groove was common in an area where oesophageal cancer incidence rates were high (Babekir *et al.*, 1989).

(d) Histology

Two studies analysed squamous cell cancer and adenocarcinoma separately (Lagergren *et al.*, 2000; Zendehdel *et al.*, 2008); in the other studies (Brown *et al.*, 1988; Phukan *et al.*, 2001; Nasrollahzadeh *et al.*, 2008), most (if not all) of the cases had squamous cell carcinomas. Statistically significantly elevated odds ratios were found for ever use of smokeless tobacco and squamous cell carcinomas in one study (Zendehdel *et al.*, 2008), in another study (Lagergren *et al.*, 2000) for users of 15–35 quids per week, and in a third study of predominantly squamous cell carcinomas (Phukan *et al.*, 2001). In a fourth study from the Islamic Republic of Iran that assessed squamous cell carcinomas, *nass* use was found to have a significant positive association with oesophageal cancer (Nasrollahzadeh *et al.*, 2008).

Two studies provided odds ratios for use of smokeless tobacco and adenocarcinoma of the oesophagus; in one the odds ratio was statistically significantly elevated for ever users (Zendehdel *et al.*, 2008) and in the other (Lagergren *et al.*, 2000) users of 15–35 quids per week had an increased risk for adenocarcinoma of the oesophagus.

(e) Population characteristics

In the study in India (Phukan *et al.*, 2001), significantly elevated odds ratios were observed in both men and women.

(f) Subsites of cancers of the upper aerodigestive tract

In some studies smokeless tobacco-associated risks were examined only for oral cancer or provided oral cavity cancer-specific findings. Of these studies, statistically significantly elevated odds ratios for ever use of smokeless tobacco were noted in seven (Chandra, 1962; Williams & Horm, 1977; Blot *et al.*, 1988; Idris *et al.*, 1995a; Merchant *et al.*, 2000) but no association in two (Schildt *et al.*, 1998; Accortt *et al.*, 2002, 2005; Luo *et al.*, 2007). Some other studies provided estimates for the oral cavity plus one or more of the pharynx, lip, salivary gland, oesophagus, and larynx. Of these four had positive findings (Kabat *et al.*, 1994; Lewin *et al.*, 1998; Wasnik *et al.*, 1998; Roosaar *et al.*, 2008) and four had relative risks below one or close to approximately equal to one (Mashberg *et al.*, 1993; Boffetta *et al.*, 2005; Henley *et al.*, 2005; Rosenquist, 2005). In studies providing information separately for the pharynx, estimates were positive for women with 20 or more years of snuff use in the USA (Winn *et al.*, 1981a); for hypopharyngeal cancer, estimates were positive in one study in India (Sapkota *et al.*, 2007) and below one in two other studies (Williams & Horm, 1977; Lewin *et al.*, 1998).

2.1.4 Cancer of the pancreas

Three cohort studies (Zheng *et al.*, 1993; Boffetta *et al.*, 2005; Luo *et al.* 2007), three population-based case–control studies (Williams & Horm 1977; Farrow & Davis, 1990; Alguacil & Silverman, 2004) and two hospital based case–control studies (Muscat *et al.*, 1997; Hassan *et al.*, 2007) in North America and in Europe investigated the association between the use of smokeless tobacco and pancreatic cancer.

(a) North America

(i) Cohort study

In the Lutheran Brotherhood Insurance Society cohort with 20 years follow-up, a relative risk of 1.7 (95%CI: 0.9–3.1, based on 16 deaths) adjusted for age, alcoholic beverages and smoking was found for male ever users of smokeless tobacco (Zheng *et al.*, 1993).

(ii) Case–control studies

No association was found with smokeless tobacco in two population-based case–control studies (Williams & Horm 1977; Farrow & Davis, 1990). In a population-based case–control study that restricted analyses to lifelong non-smokers of cigarettes, a non-significantly 40% increase in risk for pancreatic cancer (95%CI: 0.5–3.6) was found in those who used smokeless tobacco regularly compared to non-users of tobacco (Alguacil & Silverman, 2004). Among tobacco chewers who were not current cigarette smokers, an elevated risk of 3.6 (CI: 1.0–12.8) was seen when compared to never-smokers and long-term quitters (≥ 20 years) in one hospital-based case–control study (Muscat *et al.*, 1997) and no association with chewing tobacco or using snuff was noted in an another hospital-based case–control study (Hassan *et al.*, 2007). None of the studies adjusted for BMI or alcohol, which are potentially important risk factors for pancreatic cancer (Table 2.11, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.11.pdf).

In a meta-analysis of four studies from the USA, the summary relative risk for pancreatic cancer among users of smokeless tobacco was 1.4 (95%CI: 0.7–2.7) (Boffetta *et al.*, 2008).

(iii) Duration and intensity

Only a few studies assessed risk in relation to duration and intensity of use, assessing oz per week or grams per day and duration of use. In one study (Alguacil & Silverman, 2004), the odds ratio for those who used > 2.5 oz of smokeless tobacco a week compared to non-users of tobacco was 3.5 (95%CI: 1.1–10.6) and for those who used smokeless tobacco for more than 20 years was 1.5 (95%CI: 0.6–4.0), adjusted for age, sex, race, cigar smoking and study area.

(b) Europe

In the Norwegian Cohort Study followed up for 35 years the relative risk for pancreatic cancer for ever use of snuff (snus) was 1.67 (95%CI: 1.12–2.50; 45 cases), adjusted for smoking and age (Boffetta *et al.*, 2005). Among ever users of snuff, the relative risk was 0.85 (95%CI: 0.24–3.07, based on three cases) in never-smokers. In the Swedish construction worker cohort study, analyses were restricted to never smoking men at the time of entry into the study (Luo *et al.*, 2007). Average follow-up was 20 years and 83 pancreatic cancers were recorded. Compared to never users of any tobacco product, and after adjustment for age and BMI, the relative risk for never smoking current users of snus was 2.1 (95%CI: 1.2–3.6; 18 cases) and in never-smokers who used ≥ 10 g/day snus was 2.1 (95%CI: 1.1–3.8) (Table 2.12, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.12.pdf).

A meta-analysis showed a summary relative risk for pancreatic cancer among users of smokeless tobacco based on the two above cohort studies of 1.8 (95%CI: 1.3–2.5) (Boffetta *et al.*, 2008).

2.1.5 Other cancers

(a) Cancer of the stomach

Four cohort studies (Kneller *et al.*, 1991; Chao *et al.*, 2002; Boffetta *et al.*, 2005; Zendehdel *et al.* 2008) and 4 case–control studies (Williams & Horm, 1977; Hansson *et al.*, 1994; Ye *et al.*, 1999; Phukan *et al.*, 2005) investigated the association between stomach cancer and use of smokeless tobacco. Phukan *et al.* (2005) also reported exposure to *tuibur* (Table 1.1).

(i) Cohort studies

In the USA, non-significantly elevated risks associated with smokeless tobacco use were observed among never-smokers compared to men who never used tobacco in the Lutheran Brotherhood cohort study with 20 years follow-up (Kneller *et al.*, 1991) and in the CPS-II cohort study with 18 years follow-up (Chao *et al.*, 2002). In the cohort study from Norway (35 years follow-up), a non-significantly elevated risk for snuff use was found (Boffetta *et al.*, 2005). A total of 343 822 men were analysed in the construction worker cohort study from Sweden (33 years follow-up) and a significant positive relative risk was seen among non-smoking snus users aged 70 and over for cancer in the non-cardia region of the stomach when compared to never users of any tobacco product (Zendehdel *et al.*, 2008; Table 2.13, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.13.pdf).

(ii) Case–control studies

Williams & Horm (1977), Hansson *et al.* (1994) and Ye *et al.* (1999) found no significant associations with the use of smokeless tobacco products or snuff. The study by Phukan *et al.* (2005) showed a significantly elevated risk for chewing tobacco alone among non-betel quid users (adjusted for tobacco smoking, alcohol drinking, *tuibur*, education, occupation, income) and for *tuibur* use (adjusted for tobacco smoking, alcohol drinking, education, occupation, income) (Table 2.14, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.14.pdf).

(iii) Dose–response evidence

In one study, risk increased with cumulative dose of tobacco chewing and for *tuibur* use (p for trend < 0.001), each adjusted for other confounding factors (Phukan *et al.*, 2005).

(iv) Cessation

Phukan *et al.* (2005) found that risk decreased with years of cessation of *tuibur* use, although the test for trend was not significant.

(b) Cancer of the colon and rectum

In the US Veterans' cohort study with 26 years follow-up (Heineman *et al.*, 1995), smokeless tobacco users had a relative risk of 1.2 (95%CI: 0.9–1.7; based on 39 deaths) for cancer of the colon and 1.9 (95%CI: 1.2–3.1; based on 17 deaths) for cancer of the rectum compared to those who had never used tobacco. No new data have been published since the previous *IARC Monograph* (IARC, 2007a).

(c) Cancer of the extra-hepatic bile duct

In a population-based case–control study in Los Angeles County, USA (Chow *et al.*, 1994) an odds ratio of 18 (95%CI: 1.4–227.7; based on 3 cases) was found for chewing tobacco and cancer of the ampulla of Vater. [All cases of cancer of the ampulla of Vater who chewed tobacco also smoked.] There have been no new studies published since the previous *IARC Monograph* (IARC, 2007a).

(d) Cancers of the digestive system combined

A reduced risk with use of smokeless tobacco was seen in the case–control study by Sterling *et al.* (1992) and in the National Health and Nutrition Examination Survey (NHANES I) follow-up study that analysed 6805 men and women aged

45–75 years at baseline (1971–75) (Accortt *et al.*, 2002). The entire NHANES I cohort was reassessed between 1982 and 1984 and analysed 7787 subjects aged 45 and over at baseline. The results showed non-significantly elevated risks for those aged 65 years and over in men and aged 45–64 years in women (Accortt *et al.*, 2005). [The analysis was limited to incident diseases that required an overnight stay in health care facility. Hence, there is a possibility of underrepresentation of the actual number of cancer cases that occurred in the cohort. Analysis was based on a small sample size, 414 exclusive smokeless tobacco users, and chewing tobacco and snuff use were not analysed separately. Pipe and cigar use was not controlled for in the analysis.]

The hazard ratio for men who reported current use of smokeless tobacco and never used other tobacco products was significantly elevated after adjustment for age, race, educational level, BMI, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake and aspirin use in the CPS I cohort but not in the CPS II cohort (additionally adjusted for status and type of employment) (Henley *et al.*, 2005).

(e) Cancer of the gall bladder

One case–control study in India found positive associations with chewing *khaini* [raw tobacco with lime] and cancer of the gall bladder (OR, 1.65; 95%CI: 0.78–3.49) or chewing tobacco alone (OR, 2.71, 95%CI: 1.22–6.02), unadjusted for other potential confounding factors (Shukla *et al.*, 2008).

(f) Cancers of the respiratory tract

(i) Nasal cavities

Brinton *et al.* (1984) in a case–control study found non-significant sex-adjusted odds ratios for tobacco chewers or snuff users while Stockwell & Lyman (1986) found an odds ratio for smokeless tobacco of 3.3 (95%CI,0.4–25.9), adjusted for age, race, sex and tobacco use. [The Working Group noted that information about tobacco use was obtained from medical records and ascertainment bias cannot be ruled out.] No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(ii) Larynx

In a case–control study in Florida, USA, a significantly elevated odds ratio for smokeless tobacco use, adjusted for age, race, sex and tobacco smoking was found (Stockwell & Lyman, 1986). [The Working Group noted that information about tobacco use was obtained from medical records and ascertainment bias cannot be ruled out.] From a case–control study in Sweden Lewin *et al.* (1998) reported no significant association for current and former use of snuff, adjusted for age, smoking and alcoholic beverages. No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(iii) Lung

The NHANES follow-up study ascertained incident cases (Accortt *et al.*, 2005) and deaths from lung cancer (Accortt *et al.*, 2002). Never-smoking women who ever used smokeless tobacco had significantly higher mortality compared to never tobacco users. In men, no deaths from lung cancer occurred among those who were never-smokers and used smokeless tobacco. Estimates of the relative risk were adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, recreational physical exercise and fruit/vegetable intake. The results for cancer incidence (Accortt *et al.*, 2005) showed significantly elevated risks in women aged 65 years and over, based on small numbers of cases among exclusive smokeless tobacco users ($n < 4$ cases). No incident cases of lung cancer occurred in men who used smokeless tobacco. Risk was adjusted for age, race and poverty index ratio. [The Working Group noted limitations to this study. See section on cancers of the digestive system *(d)*.]

In the Cancer Prevention Study I (CPS-I) in the USA, the hazard ratio for lung cancer for current smokeless tobacco users who never used other tobacco products was non-significantly elevated and the corresponding hazard ratio in the CPS-II cohort was significantly elevated, after adjusting for age, race, level of education, BMI, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake, aspirin use and status and type of employment (for CPS-II only) (Henley *et al.*, 2005). The magnitude of effect was similar for those who chewed tobacco but never used snuff and for those who used snuff but never chewed tobacco. In the Norwegian cohort study the relative risk adjusted for age and smoking was non-significantly reduced for ever users of snus compared to never users (Boffetta *et al.*, 2005). In the Swedish construction worker cohort study with 279 897 men followed for an average of 20 years there was no significant association for snus use among never-smokers (Luo *et al.*, 2007).

Henley *et al.* (2007) used CPS II data to compare mortality among former cigarette smokers who switched to smokeless tobacco (switchers) with those who quit using tobacco entirely (quitters), based on tobacco use ascertained at baseline and followed-up for 20 years. In a subset of the cohort that examined uptake of tobacco after baseline, the proportions of persons taking up cigarette smoking was very low. Compared with quitters, the relative risk of lung cancer was 1.5 (95%CI: 1.2–1.7) for all switchers, 1.3 (95%CI: 1.1–1.6) for switchers to tobacco chewing only, 1.8 (95%CI: 1.2–2.5) for snuff only, and 1.9 (95%CI: 1.2–2.9) for tobacco chewing and snuff combined. Compared with men who never used any tobacco product, the relative risk of lung cancer was 3.9 for quitters and 5.6 for switchers (statistically significant but 95% confidence intervals were not provided). Risk estimates were adjusted for age, number of cigarettes formerly smoked per day, number of years smoking cigarettes, age at which they quit smoking cigarettes, race, educational level, BMI, exercise level, alcohol consumption, employment type, employment status, fat consumption, fruit and vegetable intake and aspirin use. The analysis was restricted to men because women were not asked whether or not they used smokeless tobacco.

The case–control study of lung cancer by Williams & Horm (1977) reported non-significant risk for smokeless tobacco use in men, adjusted for age, race, and smoking.

(g) Sarcoma

In the US Veterans' cohort, the relative risk for soft-tissue sarcomas associated with smokeless tobacco use compared to persons who never used tobacco products was 1.5 (95%CI: 0.8–2.7) (Zahm *et al.*, 1992). In a population-based case–control study conducted in the USA, the unadjusted odds ratio for ever use of smokeless tobacco was 1.8 (95%CI: 1.1–2.9); the risk was highest for those diagnosed at age 80 years or above (3.2; 95%CI: 1.0–10.1). Risks were elevated but not significantly so when analysed by anatomical site of the soft-tissue sarcoma (upper gastrointestinal; lung, pleura and thorax; head, neck and face) or by cell type (fibromatous; adipose, myomatous) (Zahm *et al.*, 1989). No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(h) Cancer of the breast

Spangler *et al.* (2001, 2002) conducted a case–control study in Cherokee Native American women and reported a non-significant elevated risk of breast cancer for use of smokeless tobacco. [There was no medical verification of breast cancer and the time relationship between use of smokeless tobacco and breast cancer diagnosis was not reported.] A prospective cohort study of the US population (NHANES I) showed a positive but non-significant association with smokeless tobacco (snuff or chewing tobacco) in women aged 45 years and over based on five breast cancer cases, however the hazard ratios

were below one when stratified by age (Accortt *et al.*, 2005). [The Working Group noted limitations to this study. See Section on cancer of the digestive system, 2.1.5 *(d)*.]

(i) Cancer of the uterine cervix

In a population-based case–control study elevated risks for cervical cancer, adjusted for smoking, age and race, for use of chewing tobacco or snuff were reported (Williams & Horm, 1977). No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(j) Cancer of the prostate

In two cohort studies significantly elevated risks were found among users of smokeless tobacco compared to never users of tobacco (Hsing *et al.*, 1990, 1991). Putnam *et al.* (2000) reported no association with use of snuff and chewing tobacco. [The Working Group noted that data were not presented to support this.] In one case–control study (Hayes *et al.*, 1994) and one cohort study (Accortt *et al.*, 2005) non-significantly elevated risks of prostate cancer associated with chewing tobacco were found.

(k) Cancer of the penis

In a case–control study of cancer and the penis in India, the relative risk for snuff users was 4.2 (95%CI: 1.6–11.3), adjusted for smoking, tobacco chewing and phimosis (Harish & Ravi, 1995). [It was not clear whether snuff was used orally or nasally.] No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(l) Cancer of the urinary bladder

Population-based case–control studies conducted in three provinces of Canada (Howe *et al.*, 1980), in the USA (Hartge *et al.*, 1985; Slattery *et al.*, 1988) and in Alberta and Ontario provinces of Canada (Burch *et al.*, 1989) did not show a significant association between chewing tobacco and bladder cancer. No association with snuff use was seen in the Norwegian cohort (Boffetta *et al.*, 2005).

(m) Cancer of the kidney

Four case–control studies (Goodman *et al.*, 1986; McLaughlin *et al.*, 1995; Muscat *et al.*, 1995; Asal *et al.*, 1988) and one cohort study (Boffetta *et al.*, 2005) evaluated the risk associated with smokeless tobacco use. The adjusted risk for chewing tobacco in non-smokers was not significantly elevated in two case–control studies (Goodman *et al.*, 1986; McLaughlin *et al.*, 1995) and in one cohort study in Norway (Boffetta *et al.*, 2005). In two studies, a significant association was reported for ever use of smokeless tobacco (Asal *et al.*, 1988; Muscat *et al.*, 1995) but there was no adjustment for potential confounders in either study. A dose–response relationship was observed: odds ratio 2.5 (95%CI: 1.0–6.1) for chewing 10 times or fewer per week and 6.0 (95%CI: 1.9–18.7) for chewing 11 or more times per week (Muscat *et al.*, 1995), although there was no adjustment for smoking and other potentially confounding factors.

(n) Cancer of the brain

From a population-based case–control study in the USA (Zheng *et al.*, 2001), no significantly increased risk of brain cancer was reported for either men or women with the use of snuff or chewing tobacco. [Data to support this were not presented.] No new studies were identified since the previous *IARC Monograph* (IARC, 2007a).

(o) Non-Hodgkin lymphoma

Two population-based case–control studies of non-Hodgkin lymphoma in men were conducted in the USA (Brown *et al.*, 1992a; Schroeder *et al.*, 2002). Schroeder *et al.* (2002) found an increased risk for t(14;18)-positive non-Hodgkin lymphoma cases who started chewing tobacco ≤ 18 years of age, after adjusting for age and state (OR, 2.5;

95%CI: 1.0–6.0). No significant associations were observed in the study by Brown *et al.*, (1992a) for any non-Hodgkin lymphoma subtype or overall.

Bracci & Holly (2005) from a population-based case–control study of non-Hodgkin lymphoma conducted in the USA reported significantly elevated risks for non-Hodgkin lymphoma and for follicular and diffuse large cell types in those who used smokeless tobacco. Risk estimates were adjusted for age, level of education and level of average weekly alcohol consumption. [The results are based on only seven cases and six controls.]

(p) Leukaemia

Brown *et al.* (1992b) conducted a population-based case–control study in the USA of chewing tobacco/snuff only and risk for leukaemia. Non-significant elevated risks were seen for all leukaemias, chronic myelogenous leukaemia, chronic lymphocytic leukaemia and myelodysplasia. In the Swedish construction worker cohort study (average follow-up 22.2 years), non-significantly elevated risks for acute lymphocytic and chronic myelogenous leukaemias and no association in men for snuff dipping and acute myelogenous leukaemia and multiple myeloma were found (Fernberg *et al.*, 2007).

(q) Myeloma

In a population-based case–control study in the USA, Brown *et al.* (1992a) compared users of smokeless tobacco only with never users of tobacco and found an odds ratio of 1.9 (95%CI: 0.5–6.6; based on 5 cases). A Swedish construction worker cohort study showed no association for myeloma in men with snuff dipping (Fernberg *et al.*, 2007).

(r) Cutaneous squamous cell carcinoma

Odenbro *et al.* (2005) analysed the Swedish cohort study and found a relative risk of 0.64 (95%CI: 0.44–0.95) for the association between snuff dipping and the incidence of cutaneous squamous cell carcinoma.

2.2 Nasal use

There are no cohort or case–control studies that examined the association between nasal snuff use and nasal cancer.

2.2.1 Cancers of the oral cavity and pharynx

(a) Overview of studies

Three case–control studies from India investigated the association between nasal snuff use and cancer of oral and pharyngeal subsites (Table 2.15, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-03-Table2.15.pdf).

Sankaranarayanan *et al.* (1989a) focused on cancer of the anterior two-thirds of tongue and floor of the mouth; the age-adjusted odds ratio was 4.27 (95%CI: 1.24–14.67; men only) for occasional nasal snuff users and 3.02 (95%CI: 0.94–9.60) for daily snuff users. For cancer of the gingiva the odds ratio for regular snuff use was 3.04 (95%CI: 0.67–12.65) after adjustment for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use (Sankaranarayanan *et al.*, 1989b). For cancer of the buccal and labial mucosa, the age-adjusted odds ratio was 3.98 (95%CI: 1.53–10.34) for regular nasal snuff users and 2.28 (95%CI: 0.74–7.03) for occasional nasal snuff users (Sankaranarayanan *et al.*, 1990a). After adjusting for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use, the odds ratio associated with ever snuff use was 2.93 (95%CI: 0.98–8.77).

In a multicentre case–control study of cancer of the hypopharynx in India, Sapkota *et al.* (2007) found an odds ratio of 2.85 (95%CI: 1.15–7.08) for tobacco snuffing among never-smokers who did not chew tobacco or a non-tobacco product, adjusting for alcohol use, and other factors [The Working Group noted that snuff use was oral as

well as nasal so the role of nasal use could not be determined separately.]

(b) Dose–response evidence

In the study of cancer of the gingiva (Sankaranarayanan *et al.*, 1989b), the age-adjusted odds ratio for daily nasal snuff use was 3.90 (95%CI: 1.19–12.70) and that for occasional use was 3.78 (95%CI: 1.05–13.54). When categories of high versus low defective nasal snuff use were compared, the odds ratios were significantly elevated for the category of lower intensity for cancers of the tongue (Sankaranarayanan *et al.*, 1989a) and of the buccal and labial mucosa (Sankaranarayanan *et al.*, 1990a).

2.2.2 Other cancers

No new studies were identified since the previous *IARC Monograph* (IARC, 2007a) for the sites listed except for cancer of the nostril.

(a) Cancer of the oesophagus

A case–control study of oesophageal cancer form India showed an age-adjusted odds ratio for daily snuff use of 2.39 (95%CI: 0.81–7.04) and that for occasional use of 3.59 (95%CI: 1.20–10.67) (Sankaranarayanan *et al.*, 1991). [Estimates were not adjusted for smoking or betel quid chewing.]

(b) Cancer of the paranasal sinuses

Shapiro *et al.* (1955) studied Bantu cases of paranasal sinus cancer from radiation therapy department records from 1949–51 of a group of hospitals in South Africa. The authors noted that a high proportion (80%) of the antral cancer cases reported 'prolonged and heavy' use of snuff in contrast to 34% of Bantu men with cancer at other sites. The product snuffed by Bantus typically contained powdered tobacco leaves and an ash from aloe plants or other species, with the occasional addition of oil, lemon juice and herbs; typical use was 'one teaspoonful' per day (Keen *et al.*, 1955). [The Working Group noted that the source and nature of the control group was not described.]

(c) Cancer of the larynx

A case–control study from India (Sankaranarayanan *et al.*, 1990b) of laryngeal cancer showed a non-significant risk for snuff use.

(d) Cancer of the lung

Hsairi *et al.* (1993) conducted a case–control study of bronchial cancer in Tunisia. The odds ratio for ever use of inhaled snuff ('tabac à priser'), adjusted for age, sex, cigarette use, water pipe and cannabis use was 2.2 (95%CI: 0.9–5.6).

(e) Carcinoma of the nostril

Sreedharan *et al.* (2007) reported a case of squamous cell carcinoma in the right nostril in a 69-year-old woman in Karnataka, south India, with a history of daily snuff usage of more than 2 g for a duration of 30 years.

2.3 Synthesis

2.3.1 Oral use

(a) Oral cavity and pharynx

Smokeless tobacco was positively associated with cancers of the oral cavity in a cohort study in northern Europe and several case–control studies, some of which that adjusted for smoking and others that adjusted both for smoking and alcohol. There were elevated risks for every type of smokeless tobacco studied: snuff and chewing tobacco in the USA, snus in northern Europe, *toombak* in Sudan, smokeless tobacco used as a dentifrice in India and *naswar* in Pakistan. Case series implicate *shammah* used in Saudi Arabia as a risk factor for oral cancer. Not all reports were positive, namely some studies in Scandinavia and the USA, including two cohorts with small sample sizes. The evidence is strongest for the

oral cavity, with some indication of increased risks for the hypopharynx, or oropharynx and hypopharynx combined. Dose–response relationships with intensity of use were noted in one study and with duration in another. It is unclear whether risks are elevated in former smokeless tobacco users. Three meta-analyses of studies from northern Europe and the USA were generally consistent. In one meta-analysis an overall relative risk of 1.8 (95%CI: 1.1–2.9) was computed for studies that adjusted for smoking or among non-smokers; in another the relative risk was 1.72 (95%CI: 1.01–2.94) among never-smokers and 1.87 (95%CI: 0.82–4.27) when further adjusted for alcohol among never-smokers. In conclusion, there is strong evidence in humans that smokeless tobacco causes cancer of the oral cavity.

(b) Precancerous lesions

Studies in many countries have observed that oral lesions are more common in smokeless tobacco users than non-users, regardless of the type of smokeless tobacco used. The types include snus, snuff, chewing tobacco, smokeless tobacco used as a dentifrice, *naswar*, *toombak*, and *shammah*. In many studies the oral lesions were observed to be in the place in the mouth where users in that geographic region typically place the smokeless tobacco. The prevalence of the lesions increased with various exposure metrics of increasing intensity and duration of use, such as amounts used per day, time kept in mouth, duration of use in months or years. Although some lesions in young persons resolve, the prevalence of lesions in older adult users of these products remains elevated even in former users. There is some evidence from three studies that a small proportion of the lesions among smokeless tobacco users can progress to oral cancer over a period of years, although the rates vary, are not adjusted for any medical intervention to remove the lesions, smoking has not been taken into account, and the follow-up periods are highly variable. Use of smokeless tobacco causes leukoplakia and erythroplakia, both considered precancerous, with a much higher risk of progressing to cancer than normal mucosa.

(c) Oesophagus

Nine studies evaluated the association between smokeless tobacco use and oesophageal cancer. The risks for ever use of smokeless tobacco compared to never use were statistically significantly elevated in one cohort study from Sweden and case–control studies from the Islamic Republic of Iran and India. In a Swedish case–control study, increased risks were observed with 15–35 quids used per week. Smoking could be ruled out as a potential confounder in all of the studies, as well as alcohol intake in two. No increased risk was observed in the three studies from the USA, which included a significant proportion of proxy respondents. Two meta-analyses found that, overall and for the Nordic countries, the estimates of effect for smokeless tobacco use were significantly elevated. The two studies published since the previous *Monograph* on Smokeless Tobacco showed a positive significant association with oesophageal cancer and were adjusted for major confounders. Four of five studies of squamous cell carcinomas and both studies of adenocarcinoma showed significantly positive results.

(d) Pancreas

In North America, 3 case–control studies showed no association, one cohort study and two case–control studies showed a non-significant increased risk and one case–control study showed a borderline significant increase in risk. While these studies accounted for smoking, none adjusted for BMI or alcohol, potentially important risk factors for pancreatic cancer. In Europe, two cohort studies showed a significant increase in risk of pancreatic cancer associated with snuff use. Both studies controlled for smoking; one study adjusted for BMI and also showed that the highest risks were seen in the highest exposure

Table 3.1 Carcinogenicity studies of application of smokeless tobacco to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mouse, CAF1 and Swiss (sex NR) Wynder & Wright (1957)	40, 30 controls Skin application 3 × /wk of unburnt cigarette tobacco 50% methanol extract, (dose NR), controls received whole tar extract; 24 mo	Skin (papillomas): CAF1–11/40 (27%), 16/30 (53%) in controls (8 converted to carcinoma) Swiss–3/40 (7%) (1 converted to carcinoma), 16/30 (53%) in controls (3 converted to carcinoma)	NR NR	No adequate control groups

mo, month or months; NR, not reported

category. There is good evidence to support a causal association between smokeless tobacco use and pancreatic cancer.

(e) Stomach

One cohort study in Sweden showed a significantly higher risk among non-smoking snus users aged 70 years and over for cancer in the non-cardia region of the stomach, not adjusted for alcohol use. One case–control study in India showed significantly higher risks for chewing tobacco alone and for *tuibur* users, with dose-dependent increases in risk. Risk decreased with cessation of *tuibur* use. The risk was not statistically significant in the other studies. Despite some positive findings for chewing tobacco in two different countries and for tobacco smoke-infused water, it was not considered strong enough to conclude for a causal association.

(f) Lung

In summary, in two cohort studies significant positive associations between smokeless tobacco use and lung cancer were found while in three cohort studies and one case–control study there was no association. In one of the positive cohort studies switching from cigarette smoking to smokeless tobacco significantly increased the risk for lung cancer compared to never-tobacco users, and the risk was of greater magnitude than for quitting all together (RR, 3.9 versus 5.6).

2.3.2 Nasal use

Strong positive associations for cancers of the tongue and floor of mouth, gingiva and buccal and labial mucosa were observed in one study in India. In one positive study snuff use was oral as well as nasal so the role of nasal use could not be determined separately.

3. Cancer in Experimental Animals

Since the previous *IARC Monograph* on Smokeless Tobacco (IARC, 2007a), only one new study has been published. The collective evidence for the carcinogenicity of smokeless tobacco in experimental animals is summarized below.

3.1 Chewing tobacco, unburned cigarette tobacco, *mishri* and *naswar*

3.1.1 Mouse

Topical application of unburned cigarette tobacco induced skin papillomas in mice (Wynder & Wright, 1957; Table 3.1). Similar treatment with

Table 3.2 Carcinogenicity studies on administration of smokeless tobacco with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse, Paris albino XVII x 57 black (sex NR) Ranadive *et al.* (1963)	11–36 animals/ group Totally alkaloid free extract, twice/wk for 95 wk + croton oil/dose and duration not specified, controls received acetone	Papillomas: 22/35 (63%) Controls–3/19 (16%) Carcinomas: 10/35 (27%) Controls–0/19	$P > 0.001$ $P = 0.0097$
Mouse, ICR Swiss (F) Bock *et al.* (1964, 1965)	30 animals/group A single DMBA application of 125 µg DMBA in 0.25 mL acetone + 0.25 mL acetone extract of unburnt tobacco 2.5 from cigarettes/d, 5 × / wk; controls received a single application of DMBA 125 µg 36 wk	16 papillomas in 7/30 (23%) mice Controls–0/30	$P > 0.01$
Mouse, ICR Swiss (F) Van Duuren *et al.* (1966)	20 animals/group 150 µg DMBA in 0.1 ml acetone once + (after 2–3 wk) reconstituted extract of flue-cured cigarette tobacco leaf, 25 mg in 0.1 ml solvent, tobacco extract, 3 × /wk; 52 wk	Papillomas: 5/14 (36%) Controls–0/12	$P = 0.04$

d, day or days; F, female; NR, not reported; wk, week or weeks

chewing tobacco extract for 95 weeks followed by croton oil increased the incidence of skin papillomas and carcinomas in mice (Ranadive *et al.*, 1963; Table 3.2). Application of chewing tobacco extract to benzo[*a*]pyrene-initiated mouse skin promoted development of a few skin papillomas and carcinomas in mice (Ranadive *et al.*, 1963). In mice initiated with 7,12-dimethylbenz[a]anthracene (DMBA) applied topically, application of a barium hydroxide extract of unburned tobacco promoted skin papilloma development (Bock *et al.*, 1964; Table 3.2). Skin-tumour-promoting activity of unburned tobacco was reported in some DMBA-initiated mice in two additional studies (Bock *et al.*, 1965; Van Duuren *et al.*, 1966; Table 3.2). Application of brown or black *mishri* extracts to DMBA-initiated skin increased significantly the total incidence of papilloma and carcinoma in Swiss mice (Kulkarni *et al.*, 1989; Table 3.3). Administration of chewing tobacco extracts to the oral mucosa (Mody & Ranadive, 1959), skin painting with chewing tobacco extracts (Mody & Ranadive, 1959; Ranadive *et al.*, 1976), or intravesicular or intravaginal application of *jarda* (Randeria, 1972) did not induce tumours in mice.

Inhalation of powdered tobacco leaves led to a significant increase in the incidence of tumours of the lung and liver in strain A mice (Hamazaki & Murao, 1969; Table 3.4). Mice given chewing tobacco extract by oral intubation developed lung adenocarcinoma and hepatocellular carcinoma in one study [with incomplete reporting of the distribution of different neoplasms] (Bhide *et al.*, 1984). Adding black or brown *mishri* in the diet increased significantly the incidence of forestomach papilloma in Swiss mice (Kulkarni *et al.*, 1988; Table 3.5).

Table 3.3 Carcinogenicity studies of *mishri* alone or with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse Swiss (M) Kulkarni *et al.*, (1989)	30 animals Topical/a single application of 200 nmol DMBA; 24 mo	No tumours	
	29 animals 200 nmol DMBA + 2.5 mg per application of black *mishri* extract, 5 d/wk for 20 wk; 24 mo	Skin papillomas: 4/29 (14%)	$P < 0.05$
	30 animals Topical application of black *mishri* extract, 2.5 mg per application, 5 d/wk for 20 wk; 24 mo	No skin tumours	
	30 animals 200 nmol DMBA + 2.5 mg per application of brown *mishri* extract, 5 d/wk for 20 wk; 24 mo	Skin papillomas: 4/30 (13%)	$P < 0.05$

d, day or days; M, male; mo, month or months; wk, week or weeks

3.1.2 Rat

Administration of chewing tobacco extract by gavage to vitamin-A-sufficient rats induced benign tumours in the lung and forestomach while similarly treated vitamin-A-deficient rats developed benign tumours in the stomach and pituitary gland and "lymphoma" in the lung [extremely rare tumour in rats] (Bhide *et al.*, 1991; Table 3.6).

Administration of *mishri* by gavage to vitamin-A-sufficient or vitamin-A-deficient rats increased significantly the proportion of tumour-bearing rats in both groups. Lung adenomas and forestomach papillomas developed in vitamin-A-sufficient animals while multiple neoplasms including lung lymphoma [an extremely rare tumour in rats] pituitary adenoma and forestomach papilloma occurred in vitamin-A-deficient animals. Control animals did not develop tumours (Ammigan *et al.*, 1991; Table 3.5). No tumours appeared when chewing tobacco extract was applied to the oral mucosa (Gothoskar *et al.*, 1975). Adding black or brown *mishri* in the diet increased significantly the incidence of forestomach papillomas in male and female Sprague-Dawley rats (Kulkarni *et al.*, 1988; Table 3.5).

3.1.3 Hamster

Application of a chewing tobacco extract to the cheek pouch of Syrian golden hamsters produced squamous cell papillomas and/or carcinomas in a small number of animals (Rao, 1984; Table 3.7). Adding black or brown *mishri* in the diet significantly increased the incidence of forestomach papillomas (Kulkarni *et al.*, 1988; Table 3.5). Implantation of chewing tobacco in the cheek pouch (Peacock & Brawley, 1959; Peacock *et al.*, 1960; Dunham & Herrold, 1962; Summerlin *et al.*, 1992), or application of chewing tobacco extract (Suri *et al.*, 1971; Ranadive *et al.*, 1976) or *jarda* (Kandarkar *et al.*, 1981) to the cheek pouch did not induce tumours.

Application of *naswar* to the cheek pouch for life increased incidence of tumours in treated

Table 3.4 Carcinogenicity studies of inhalation of smokeless tobacco in experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mouse, Strain A (M) Hamazaki & Murao (1969)	80 animals/group Inhalation of powdered tobacco leaf, dose (NR), alternate days, controls were untreated; 30 mo	Treated– Lung tumours 12/75 (16%; alveologenic carcinomas 6, squamous cell carcinomas 3, malignant adenomas 3) Leukaemia 11/80 (15%) Hepatocellular carcinomas 3/75 (4%) Controls– Malignant lung adenomas 1/80 Leukaemia 2/80 Hepatocellular carcinomas 0/80 Controls– Malignant lung adenomas 1/80 Leukaemia 2/80 Hepatocellular carcinomas 0/80	Lung tumours: $P < 0.001$ Leukaemias: $P < 0.01$ $P < 0.01$	The incidence of lung tumours and leukaemia was significantly increased in treated animals, the incidence of lung and liver tumours in the untreated controls was unusually low

M, male; mo, month or months, NR, not reported

Table 3.5 Carcinogenicity studies of oral administration of *mishri* alone or with modifiers to experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mouse, Swiss (M, F) Kulkarni *et al.* (1988)	26 animals/sex/group Black *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–11/24 (46%) F–11/26 (42%)	$P < 0.01$ *vs* controls
	26 animals/sex/group Brown *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–14/26 (54%) F–11/26 (42%)	$P < 0.01$ *vs* controls
	27 M, 31 F (controls) No *mishri* tobacco, standard diet only; 25 mo	Forestomach (papillomas): M–3/27 (11%) F–1/31 (3%)	$P < 0.01$ *vs* controls
Rat Sprague Dawley (M, F) Kulkarni *et al.* (1988)	27 M, 24 F Brown *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–10/27 (37%) F–9/24 (37%)	$P < 0.01$ *vs* controls
	25 M, 30 F No *mishri* tobacco, standard diet only; 25 mo	Forestomach (papillomas): M, F–0%	$P < 0.01$ *vs* controls
Hamster Syrian Golden (M, F) Kulkarni *et al.* (1988)	23 M, 26 F Black *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–10/23 (43%) F–7/26 (27%)	$P < 0.01$ *vs* controls $P < 0.02$ *vs* controls
	28M, 20F Brown *mishri* 10% in diet for 20 mo; 25 mo	Forestomach (papillomas): M–12/28 (43%) F–5/20 (25%)	$P < 0.01$ *vs* controls $P < 0.01$ *vs* controls
	23 animals/sex No *mishri* tobacco, standard diet only; 25 mo	Forestomach (papillomas): M–2/23 (9%) F–1/23 (4%)	
Rat Sprague Dawley (M) Ammigan *et al.* (1991)	30 or 31 animals/group VitA sufficient diet + 3 mg *mishri* extract per application by gavage 5 × /wk; 21 mo Controls received VitA sufficient diet + 0.0.5 ml per application DMSO by gavage 5 × /wk; 21 mo	Lung (adenomas and stomach papillomas): 8/30 (27%) Controls–0/31	Total tumour incidence treated *vs* controls $P < 0.001$
	30 animals/group Vit A deficient diet + 3 mg *mishri* extract per application by gavage 5 × /wk; 21 mo Controls received Vit A deficient diet + 0.05 ml per application DMSO by gavage 5 × /wk; 21 mo	28/30 (93%) Controls–0/30	Total tumour incidence Vit deficient *vs* controls $P < 0.001$

F, female; M, male; mo, month or months; *vs*, versus; wk, week or weeks

Table 3.6 Carcinogenicity studies of oral administration of chewing tobacco in experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rat Sprague Dawley (M) Bhide *et al.* (1991)	29, 31 controls Diet containing shark liver oil + tobacco by gavage, 3mg tobacco extract (vaccum dried powder of 100 g tobacco extracted with 1L dichloromethane) in 0.05 ml DMSO, 5 × /wk; controls received diet containing shark liver oil + 0.05 ml DMSO 5 d/wk; 21 mo	Lung (adenomas):3/29 (10%) Forestomach (papillomas): 3/29 (10%) Controls–0/31	$P < 0.05$ χ^2 test	
	31, 30 controls Diet containing shark liver oil + tobacco by gavage, diet without shark liver oil + tobacco by gavage; controls received diet without shark liver oil + 0.05 ml DMSO, 5 × /wk; 21 mo	Lung (lymphomas): 22/31 (71%) Pituitary (adenomas): 19/31 (61%) Stomach (papillomas): 24/31 (77%) Controls–0/30	$P < 0.001$ χ^2 test	Primary lymphoma of the lung is extremely rare in rats

d, day or days; mo, month or months; wk, week or weeks

Table 3.7 Carcinogenicity studies of application of smokeless tobacco to the oral mucosa or cheek pouch of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Hamster Syrian golden (M) Suri *et al.* (1971)	11–12 animals/group Banarasi Tobacco-DMSO extract/not specified; application to the cheek pouch 3 × /wk for 21 wk; controls received DMSO; 21 wk	No tumours found in treated and control animals Leukoplakia: 8/12 (67%)		Short duration of exposure, tobacco/DMSO dose not specified
Hamster Syrian golden (F) Rao (1984)	20, 10 controls Topical application to the cheek pouch of lyophilised aqueous tobacco extract, 1 mg in 0.05 mL water twice/d for 6 mo; controls received topical application of 0.05 mL water; 12 mo	Squamous cell papillomas and carcinomas: 3/17 (18%) Controls–no tumours	NR	Statistics not provided

D, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.8 Carcinogenicity studies of administration of naswar with known carcinogens or modifiers to the skin of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	SSignificance	Comments
Hamster Syrian golden (M, F) Kiseleva *et al.* (1976)	33 M, 28 F *Naswar* introduced as dry powder in the left buccal pouch (mixture of tobacco 45%, lime 8%, ash 30%, plant oil 12% and water 5%, dose (NR); life time	13 animals with tumours: Liver–6 Mixed–1 Adrenal gland–3 Forestomach–1 Uterus/ovary–1 Skin (melanoma)–1 Large intestine–1	Tumour frequency higher than in controls $P < 0.05$	Dose of *naswar* not specified Tumour type not specified genderwise
	24 M, 13 F *Nas* introduced as sunflower oil suspension in the left buccal pouch	Liver: 1 Uterus/ovary: 2 Skin (Papilloma): 1	Tumour frequency higher than in controls, $P < 0.05$	
	46 M, 40 F *Nas* introduced as sunflower oil suspension in the left buccal pouch	13 animals with tumours: Liver–4 Mixed–1 Adrenal gland–3 Forestomach (papillomas)–4 Uterus/ovary–1 Skin (papilloma)–1 Pancreas–1	Tumour frequency higher than in controls $P < 0.05$	
	41 M, 9 F *Nas* suspension in sunflower oil introduced in oesophagus	No tumours		
	31 M, 19 F *Nas* suspension in sunflower oil applied to dorsal skin	3 animals with tumours: Liver–1 Adrenal gland–1 Forestomach (papilloma)–1		
	41 M, 69 F Untreated controls	2 animals with tumours: Stomach–1 Adrenal gland–1		

Table 3.8 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	SSignificance	Comments
Hamster Syrian golden (M, F) Milievskaja & Kiseleva (1976)	184 animals *Naswar* introduced in the buccal pouch as dry powder or 50% suspension in sunflower oil; life time	Buccal pouch: 0 Forestomach: 5 Liver: 13 Adrenal gland: 6 Others: 9	NR	The number of animals that survived at the time of first tumour appearance was small High mortality was seen even in control animals
	30 animals DMBA only introduced in the buccal pouch once	Buccal pouch: 1 Stomach: 2		
	30 animals 0.1 g DMBA only + *naswar* introduced in the buccal pouch as dry powder or 50% suspension in sunflower oil; life time 110 untreated controls	Buccal pouch: 0 Stomach: 5 Others: 1 Stomach: 1 Adrenal gland: 1		

F, female; M, male; NR, not reported

Table 3.9 Carcinogenicity studies of oral administration of snuff to experimental animals

Reference Species, strain (sex)	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Stenström *et al.* (2007)	5.9% snuff diet (snus mixed with powdered standard mouse show); 6 mo	Gastric carcinoma in situ		
Mouse, wild type, FVB (M)	8, 11 controls	0/8 Controls: 0/11	NR	
Wild type, FVB *Helicobacter pylori* infected (M)	20, 8 controls	9/17 Controls: 0/11	NR	Gastric carcinoma in situ invading the mucosa and submucosa
INS-GAS (M)	8 animals/group	4/8 Controls: 2/8	NR	
INS-GAS (M) *Helicobacter pylori*-infected (M)	22, 8 controls	12/12 Controls: 2/8	NR	Gastric carcinoma in situ invading the mucosa

M, male; mo, month or months; NR, not reported

Table 3.10 Carcinogenicity studies of snuff to the oral mucosa or cheek pouch of experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rat, Sprague Dawley (M) Johansson *et al.* (1989)	30 animals/group Snuff insertion in lip canal, 100 mg per application twice/d, 5 d/wk, controls received cotton pellet dipped in saline; 108 wk	Squamous cell carcinomas: 5 (lip–1, hard palate–2, nasal cavity–1, forestomach–1)	All squamous cell tumours
		Squamous cell carcinomas in situ: hard palate–1	$P < 0.01$
		Squamous cell papillomas: 3 (lip–1, hard palate–1, nasal cavity–1) Undifferentiated lip sarcomas: 2 Controls: no tumours	Malignant squamous cell tumours $P < 0.05$
Rat, Sprague-Dawley (M) Johansson *et al.* (1991)	38, 30 controls Snuff inserted in surgically created lip canal, moist snuff,150–200 mg/ application twice/d, 5 d/wk for 104 wk, controls received a cotton pellet dipped in saline once/d 5 d/wk for 100 wk	Sarcoma of the lip: 10/38 (26%)	Comparison of sarcoma $P < 0.01$
		Squamous cell carcinomas and papillomas of the oral cavity: 3/38 (8%) (lip palate and buccal mucosa), Controls–1/30 (3%) sarcoma of the lip	Comparison of all tumours $P < 0.01$

d, day or days; M, male; wk, week or weeks

hamsters compared to controls (Kiseleva *et al.*, 1976; Milievskaja & Kiseleva, 1976; Table 3.8).

3.2 Snuff

3.2.1 Mouse

Addition of snuff (snus) to the diet induced stomach tumours in gastrin transgenic mice but not in wild-type mice unless they were infected with *Helicobacter pylori* (*H. pylori*). Feeding snuff to *H. pylori*-infected transgenic mice increased gastric carcinoma incidence 2-fold versus control transgenic mice (Stenström *et al.*, 2007; Table 3.9).

3.2.2 Rat

Application of snuff to the oral mucosa (Chen, 1989) or swabbing of lips and oral cavity with a snuff extract (Hecht *et al.*, 1986) did not induce tumours.

In one study, the administration of snuff in a surgically created lip canal did not induce tumours in the oral cavity (Hirsch *et al.*, 1984) while a squamous cell carcinoma of the oral mucosa developed in one rat in another study (Hirsch & Johansson, 1983). Insertion of snuff in a surgically prepared lip canal induced a squamous cell carcinoma in the lip canal, a papilloma in the oral cavity and an olfactory tumour (Hecht *et al.*, 1986).

Insertion of snuff in a surgically prepared lip canal induced squamous cell carcinoma in the lip, hard palate, nasal cavity and forestomach and a carcinoma in situ in the hard palate. In addition, the treated animals developed squamous cell papillomas in the lip, hard palate and nasal cavity and two undifferentiated lip sarcomas. The incidence of all squamous cell tumours, squamous cell carcinomas and the total number of tumours in the treated group were significantly greater than in controls (Johansson *et al.*, 1989; Table 3.10).

In another independent study, the insertion of snuff in the surgically prepared lip canal induced two squamous cell papillomas in the lip,

Table 3.11 Carcinogenicity studies of snuff with known carcinogens or modifiers to experimental animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rat, Sprague-Dawley (M) Johansson *et al.* (1991)	40 animals/group with surgically created lip canal Group 1: DMBA in mineral oil – 70 mg solution + a cotton pellet containing saline 1 × /d, 5 d/wk + snuff 150–200 mg/application. Group 2: DMBA initiation as for control group + snuff in the lip canal twice/d, 5 d/wk. Group 3: Controls initiated with cotton pellets containing 0.1% DMBA in mineral oil in lip canal 3 × / wk for 4 wk only, 104 wk	Sarcomas of the lip: 9/40 (22%) Squamous cell carcinomas and papillomas of the oral cavity (lip, palate, and buccal mucosa): 3/40 (7%) Controls: 0/40	Significant increase in lip sarcoma over Group 1
	38, 40 controls Group 4: Initiation with 4 NQO as for control group + snuff in the lip canal twice/d, 5 d/wk, 70 mg 4NQO sol + cotton pellet containing saline 1 × /d, 5 d/wk + snuff 150 – 200 mg/application. Group 5: Controls initiated with 4 NQO (0.5% in propylene glycol) in cotton pellet placed in lip canal 3 × / wk for 4 wk only, 70 mg 4NQO sol + cotton dipped in saline inserted in the lip canal once/d, 5d/wk; 100 wk	Sarcoma of the lip: 25/38 (66%) Controls–1/40 (2%) Squamous cell carcinomas and papillomas of the oral cavity (lip, palate, and buccal mucosa): 8/38 (21%) Controls–9/40 (22%)	Significant increase in lip sarcoma over control
Hamster Syrian golden (M) Park *et al.* (1986)	15–20 animals/group Cheek pouches inoculated with HSV1 or HSV2 (groups 1 and 1'), once/mo for 6 mo (no snuff); 6 mo	No tumours 0/19 (HSV1) No tumours 0/16 (HSV2)	
	Cheek pouches inoculated with HSV1 once/mo + snuff 150 mg/pouch, in both pouches twice/d, 5 d/wk for 6 mo; 6 mo (Group 2)	Invasive squamous cell buccal pouch carcinomas: 10/20 (50%)	Increase in carcinoma $P < 0.05$ Group 2 *vs* Group 1
	Cheek pouches inoculated with HSV2 once a mo + Snuff 150 mg/pouch in both pouches twice/d, 5 d/wk for 6 mo; 6 mo (Group 3)	Invasive squamous cell buccal pouch carcinoma: 11/20 (55%)	Increase in carcinoma $P < 0.05$ Group 3 *vs* Group 1'

Table 3.11 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Hamster Syrial golden (M) Gijare *et al.* (1990)	15 or 20 animals/group Application of 0.125 mg DMBA in 50 µl oil, twice/wk for 1 mo to both cheek pouches 0.25% in liquid paraffin; 6 mo	Cheek pouch tumours: 10/15 (66%) Forestomach tumours: 15/15 (100%)	NR
	Application of 0.125 mg DMBA in 50 ml oil, twice/wk for 1 mo + 50 µl snuff in liquid paraffin 20 mg per cheek pouch twice/wk to both cheek pouches 0.25% in liquid paraffin + Manglorian snuff; 6 mo	Cheek pouch tumours: 3/20 (15%) Forestomach tumours: 20/20 (100%)	NR
	Application of 50 µl snuff in liquid paraffin, 20 mg per cheek pouch twice/wk to both cheek pouches; 6 mo	Cheek pouch tumours: 0/20 Forestomach tumours: 17/20 (85%)	NR
	Application of 0.125 mg DMBA in 50 ml oil, twice/wk for 1 mo + 50 µl scented snuff in liquid paraffin 20 mg per cheek pouch twice/wk to both cheek pouches 0.25% in liquid paraffin + Scented snuff; 6 mo	Cheek pouch tumours: 2/20 (10%) Forestomach tumours: 19/20 (95%)	NR
	Untreated controls	No tumours	

d, day or days; M, male; mo, month or months; NR, not reported; *vs*, versus; wk, week or weeks

10 lip sarcomas and three squamous cell carcinomas in the hard palate. In the control group, a lip sarcoma occurred in one rat. The total incidence of epithelial and mesenchymal tumours of the lip and oral cavity and the incidence of lip sarcoma was significantly greater in snuff-treated rats than in controls (Johansson *et al.*, 1991; Table 3.10).

In one study, animals were repeatedly administered snuff extracts by the subcutaneous route. No local tumours developed in either treated or control groups (Schmähl, 1965).

Application of snuff to the surgically created lip canal of rats infected with HSV 1 resulted in the development of squamous cell carcinoma of the oral cavity in 2/7 (28%) rats and a retroperitoneal sarcoma developed in one rat. In the group exposed to snuff alone, one rat each developed a squamous cell carcinoma of the anus and a retroperitoneal sarcoma (Hirsch *et al.*, 1984).

In animals whose hard palate was treated with 4-Nitroquinoline 1-oxide (4NQO), repeated application of snuff did not enhance the incidence of benign and malignant oral cavity tumours over that in animals treated with 4NQO alone (Johansson *et al.*, 1989). However, in another study, application of snuff to a 4NQO-treated surgically created lip canal increased the incidence of lip sarcoma (Johansson *et al.*, 1991; Table 3.10).

3.2.3 Hamster

In hamsters infected with HSV1 or HSV2, insertion of snuff in the cheek pouch increased significantly the incidence of squamous cell carcinoma over that in animals infected with HSV1 or HSV2 and not administered snuff (Park *et al.*, 1986; Table 3.11). Application of a snuff suspension alone to the cheek pouch resulted in the development of stomach papillomas but did not increase the forestomach papilloma incidence in animals initiated with DMBA (Gijare *et al.*, 1990). In one study, chronic feeding of snuff and calcium hydroxide induced a pancreatic carcinoid in one animal only (Dunham *et al.*, 1975) but did not induce any tumours in another study (Homburger *et al.*, 1976). Snuff instillation in the cheek pouch did not induce tumours in six studies (Peacock & Brawley, 1959; Peacock *et al.*, 1960, Dunham & Herrold, 1962; Dunham *et al.*, 1975; Homburger *et al.*, 1976; Park *et al.*, 1986).

3.3 Synthesis

In animals administered various smokeless tobacco preparations, consistent increases were observed for forestomach, lung, oral cavity and nasal tumours in rats; lung, skin, forestomach and liver tumours in mice; and oral cavity (cheek pouch) and forestomach tumours in hamsters.

4. Other Relevant Data

See Section 4 of the *Monograph* on Tobacco Smoking in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of smokeless tobacco. Smokeless tobacco causes cancers of the oral cavity, oesophagus and pancreas.

There is *sufficient evidence* in experimental animals for the carcinogenicity of smokeless tobacco.

Smokeless tobacco is *carcinogenic to humans (Group 1).*

References

Accortt NA, Waterbor JW, Beall C, Howard G (2002). Chronic disease mortality in a cohort of smokeless tobacco users. *Am J Epidemiol*, 156: 730–737. doi:10.1093/aje/kwf106 PMID:12370161

Accortt NA, Waterbor JW, Beall C, Howard G (2005). Cancer incidence among a cohort of smokeless tobacco users (United States). *Cancer Causes Control*, 16: 1107–1115. doi:10.1007/s10552-005-0247-0 PMID:16184477

Ahmed HG, Idris AM, Ibrahim SO (2003). Study of oral epithelial atypia among Sudanese tobacco users by exfoliative cytology. *Anticancer Res*, 23: 2C1943–1949. PMID:12820484

Ahmed HG & Mahgoob RM (2007). Impact of Toombak dipping in the etiology of oral cancer: gender-exclusive hazard in the Sudan. *J Cancer Res Ther*, 3: 127–130. PMID:17998740

al-Idrissi HY (1990). Head and neck cancer in Saudi Arabia: retrospective analysis of 65 patients. *J Int Med Res*, 18: 515–519. PMID:2292333

Aleksandrova HM (1970) [Role of nass in the development of pathological changes in the mouth] In Russian. In:*Epidemiology of Malignant Tumours* Alma-Ata: Nauka Publishing House, 243–246.

Alguacil J & Silverman DT (2004). Smokeless and other noncigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews. *Cancer Epidemiol Biomarkers Prev*, 13: 55–58. doi:10.1158/1055-9965.EPI-03-0033 PMID:14744733

Allard WF, DeVol EB, Te OB (1999). Smokeless tobacco (shamma) and oral cancer in Saudi Arabia. *Community Dent Oral Epidemiol*, 27: 398–405. PMID:10600072

Amer M, Bull CA, Daouk MN *et al.* (1985). Shamma usage and oral cancer in Saudi Arabia. *Ann Saudi Med*, 5: 135–140.

Ammigan N, Nair UJ, Lalitha VS, Bhide SV (1991). Carcinogenicity studies of masheri: pyrolysed tobacco product, in vitamin-A-deficient Sprague Dawley rats. *J Cancer Res Clin Oncol*, 117: 50–54. PMID:1997470

Andersson G & Axéll T (1989). Clinical appearance of lesions associated with the use of loose and portion-bag packed Swedish moist snuff: a comparative study. *J Oral Pathol Med*, 18: 2–7. PMID:2746515

Andersson G, Björnberg G, Curvall M (1994). Oral mucosal changes and nicotine disposition in users of Swedish smokeless tobacco products: a comparative study. *J Oral Pathol Med*, 23: 161–167. PMID:8046653

Andersson G & Warfvinge G (2003). The influence of pH and nicotine concentration in oral moist snuff on mucosal changes and salivary pH in Swedish snuff users. *Swed Dent J*, 27: 67–75. PMID:12856395

Asal NR, Risser DR, Kadamani S *et al.* (1988). Risk factors in renal cell carcinoma: I. Methodology, demographics, tobacco, beverage use, and obesity. *Cancer Detect Prev*, 11: 359–377. PMID:3390857

Asma S, Palipudi K, Sinha DN (2011).* Smokeless tobacco and public health in India, a scientific monograph presented during Stakeholders Meeting; New Delhi, India, October 17

Axéll T, Mörnstad H, Sundström B (1976). The relation of the clinical picture to the histopathology of snuff dipper"s lesions in a Swedish population. *J Oral Pathol*, 5: 229–236. PMID:820845

Ayo-Yusuf OA, Swart TJ, Ayo-Yusuf IJ (2000). Prevalence and pattern of snuff dipping in a rural South African population. *SADJ*, 55: 610–614. PMID:12608224

Babekir AR, el Fahal AH, Alla AH (1989). Oesophageal cancer in Sudan. *Trop Doct*, 19: 33–34. PMID:2922814

Bates C, Jarvis M, Connolly G (1999) *Tobacco Additives: cigarette engineering and nicotine addiction.Action on Smoking and Health.*, http://www.ash.org.uk/html/regulation/html/additives.html

Bhide SV, Ammigan N, Nair UJ, Lalitha VS (1991). Carcinogenicity studies of tobacco extract in vitamin A-deficient Sprague-Dawley rats. *Cancer Res*, 51: 3018–3023. PMID:2032240

Bhide SV, Shah AS, Nair J, Nagarajrao D (1984). Epidemiological and experimental studies on tobacco-related oral cancer in India. *IARC Sci Publ*, 851–857. PMID:6398309

Blomqvist G, Hirsch JM, Alberius P (1991). Association between development of lower lip cancer and tobacco habits. *J Oral Maxillofac Surg*, 49: 1044–1047, discussion 1048–1049. PMID:1653824

Blot WJ, McLaughlin JK, Winn DM *et al.* (1988). Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res*, 48: 3282–3287. PMID:3365707

Blot WJ, Winn DM, Fraumeni JF Jr (1983). Oral cancer and mouthwash. *J Natl Cancer Inst*, 70: 251–253. PMID:6571933

Bock FG, Moore GE, Crouch SK (1964). Tumor promoting activity of extracts of unburned tobacco. *Science*, 145: 831–833. PMID:14163329

Bock FG, Shamberger RJ, Myers HK (1965). Tumour-promoting agents in unburned cigarette tobacco. *Nature*, 208: 584–585.

Boffetta P, Aagnes B, Weiderpass E, Andersen A (2005). Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer*, 114: 992–995. doi:10.1002/ijc.20811 PMID:15645430

Boffetta P, Hecht S, Gray N *et al.* (2008). Smokeless tobacco and cancer. *Lancet Oncol*, 9: 667–675. doi:10.1016/S1470-2045(08)70173-6 PMID:18598931

Bracci PM & Holly EA (2005). Tobacco use and non-Hodgkin lymphoma: results from a population-based case-control study in the San Francisco Bay Area, California. *Cancer Causes Control*, 16: 333–346. doi:10.1007/s10552-004-4324-6 PMID:15953976

Brinton LA, Blot WJ, Becker JA *et al.* (1984). A case-control study of cancers of the nasal cavity and paranasal sinuses. *Am J Epidemiol*, 119: 896–906. PMID:6731431

Broders AC (1920). Squamous-cell epithelioma of the lip. A study of five hundred and thirty-seven cases. *JAMA*, 74: 656–664.

Brown LM, Blot WJ, Schuman SH *et al.* (1988). Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *J Natl*

Cancer Inst, 80: 1620–1625. doi:10.1093/jnci/80.20.1620 PMID:3193480

Brown LM, Everett GD, Gibson R *et al.* (1992a). Smoking and risk of non-Hodgkin's lymphoma and multiple myeloma. *Cancer Causes Control*, 3: 49–55. doi:10.1007/BF00051912 PMID:1536913

Brown LM, Gibson R, Blair A *et al.* (1992b). Smoking and risk of leukemia. *Am J Epidemiol*, 135: 763–768. PMID:1595675

Browne RM, Camsey MC, Waterhouse JA, Manning GL (1977). Etiological factors in oral squamous cell carcinoma. *Community Dent Oral Epidemiol*, 5: 301–306. PMID:272257

Bundgaard T, Wildt J, Frydenberg M *et al.* (1995). Case-control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control*, 6: 57–67. PMID:7718736

Burch JD, Rohan TE, Howe GR *et al.* (1989). Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer*, 44: 622–628. doi:10.1002/ijc.2910440411 PMID:2793235

Canto MT & Devesa SS (2002). Oral cavity and pharynx cancer incidence rates in the United States, 1975–1998. *Oral Oncol*, 38: 610–617. PMID:12167440

Chandra A (1962). Different habits and their relation with cheek cancer. *Chittaranjan Cancer Hosp Calcutta natl Cancer Res Cent Bull*, 33–36.

Chao A, Thun MJ, Henley SJ *et al.* (2002). Cigarette smoking, use of other tobacco products and stomach cancer mortality in US adults: The Cancer Prevention Study II. *Int J Cancer*, 101: 380–389. doi:10.1002/ijc.10614 PMID:12209964

Chelleng PK, Narain K, Das HK *et al.* (2000). Risk factors for cancer nasopharynx: a case-control study from Nagaland, India. *Natl Med J India*, 13: 6–8. PMID:10743368

Chen SY (1989). Effects of smokeless tobacco on the buccal mucosa of HMT rats. *J Oral Pathol Med*, 18: 108–112. PMID:2746519

Chow WH, McLaughlin JK, Menck HR, Mack TM (1994). Risk factors for extrahepatic bile duct cancers: Los Angeles County, California (USA). *Cancer Causes Control*, 5: 267–272. doi:10.1007/BF01830247 PMID:8061176

Creath CJ, Cutter G, Bradley DH, Wright JT (1991). Oral leukoplakia and adolescent smokeless tobacco use. *Oral Surg Oral Med Oral Pathol*, 72: 35–41. PMID:1891243

Creath CJ, Shelton WO, Wright JT *et al.* (1988). The prevalence of smokeless tobacco use among adolescent male athletes. *J Am Dent Assoc*, 116: 43–48. PMID:3422665

Crew KD & Neugut AI (2004). Epidemiology of upper gastrointestinal malignancies. *Semin Oncol*, 31: 450–464. doi:10.1053/j.seminoncol.2004.04.021 PMID:15297938

Cummings KM, Michalek AM, Carl W *et al.* (1989). Use of smokeless tobacco in a group of professional baseball players. *J Behav Med*, 12: 559–567. PMID:2634109

Daniels TE, Hansen LS, Greenspan JS *et al.* (1992). Histopathology of smokeless tobacco lesions in professional baseball players. Associations with different types of tobacco. *Oral Surg Oral Med Oral Pathol*, 73: 720–725. PMID:1279496

DHHS; Department of Health and Human Services (2001). Summary of Findings from the 2000 National Household Survey on Drug Abuse. Substance Abuse and Mental Health Services Administration, Office of Applied Studies, NHSDA Series H-13, DHHS Publication No. (SMA) 01-3549. Rockville, MD.

Djordjevic MV, Hoffmann D, Glynn T, Connolly GN (1995). US commercial brands of moist snuff, 1994. I. Assessment of nicotine, moisture, and pH. *Tob Control*, 4: 62–66. doi:10.1136/tc.4.1.62

Dunham LJ & Herrold KM (1962). Failure to Produce Tumors in the Hamster Cheek Pouch by Exposure to Ingredients of Betel Quid; Histopathologic Changes in the Pouch and Other Organs by Exposure to Known Carcinogens. *J Natl Cancer Inst*, 29: 1047–1059.

Dunham LJ, Snell KC, Stewart HL (1975). Argyrophilic carcinoids in two Syrian hamsters (Mesocricetus auratus). *J Natl Cancer Inst*, 54: 507–513. PMID:46277

Elbeshir EI, Abeen HA, Idris AM, Abbas K (1989). Snuff dipping and oral cancer in Sudan: a retrospective study. *Br J Oral Maxillofac Surg*, 27: 243–248. PMID:2742810

Ernster VL, Grady DG, Greene JC *et al.* (1990). Smokeless tobacco use and health effects among baseball players. *JAMA*, 264: 218–224. PMID:2355443

European Commission (2008). SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks), Scientific opinion on the Health Effects of Smokeless Tobacco Products

Evstifeeva TV & Zaridze DG (1992). Nass use, cigarette smoking, alcohol consumption and risk of oral and oesophageal precancer. *Eur J Cancer B Oral Oncol*, 28B: 29–35. PMID:1422467

Farrow DC & Davis S (1990). Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int J Cancer*, 45: 816–820. doi:10.1002/ijc.2910450504 PMID:2335385

Fernberg P, Odenbro A, Bellocco R *et al.* (2007). Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: a nationwide cohort study in Sweden. *Cancer Res*, 67: 5983–5986. doi:10.1158/0008-5472.CAN-07-0274 PMID:17575169

Fisher MA, Bouquot JE, Shelton BJ (2005). Assessment of risk factors for oral leukoplakia in West Virginia. *Community Dent Oral Epidemiol*, 33: 45–52. PMID:15642046

Franco EL, Kowalski LP, Oliveira BV *et al.* (1989). Risk factors for oral cancer in Brazil: a case-control study. *Int J Cancer*, 43: 992–1000. PMID:2732011

Gijare PS, Rao KV, Bhide SV (1990). Modulatory effects of snuff, retinoic acid, and beta-carotene on DMBA-induced hamster cheek pouch carcinogenesis in relation to keratin expression. *Nutr Cancer*, 14: 253–259. PMID:1707524

Gillison ML, Koch WM, Capone RB *et al.* (2000). Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst*, 92: 709–720. doi:10.1093/jnci/92.9.709 PMID:10793107

Goodman MT, Morgenstern H, Wynder EL (1986). A case-control study of factors affecting the development of renal cell cancer. *Am J Epidemiol*, 124: 926–941. PMID:3776975

Gothoskar SV, Sant SM, Ranadive KJ (1975). Effect of 'tobacco and lime on oral mucosa of rats' fed on vitamin B deficient diet. *Indian J Cancer*, 12: 424–429. PMID:1221046

Goud ML, Mohapatra SC, Mohapatra P *et al.* (1990). Epidemiological correlates between consumption of Indian chewing tobacco and oral cancer. *Eur J Epidemiol*, 6: 219–222. PMID:2361546

Grady D, Greene J, Daniels TE *et al.* (1990). Oral mucosal lesions found in smokeless tobacco users. *J Am Dent Assoc*, 121: 117–123. PMID:2370378

Grady D, Greene J, Ernster VL *et al.* (1991). Short term changes a surprise with smokeless tobacco. Oral lesions. *J Am Dent Assoc*, 122: 62–64. PMID:1999587

Grasser JA & Childers E (1997). Prevalence of smokeless tobacco use and clinical oral leukoplakia in a military population. *Mil Med*, 162: 401–404. PMID:9183161

Greene JC, Ernster VL, Grady DG *et al.* (1992) *Oral mucosal lesions: Clinical findings in relation to smokeless tobacco use among US baseball players. In: Smokeless tobacco or health: An International Perspective*. Bethesda, MD: National Institutes of Health.

Greer RO Jr & Poulson TC (1983). Oral tissue alterations associated with the use of smokeless tobacco by teenagers. Part I. Clinical findings. *Oral Surg Oral Med Oral Pathol*, 56: 275–284. PMID:6195576

Gupta PC, Mehta FS, Daftary DK *et al.* (1980). Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. *Community Dent Oral Epidemiol*, 8: 283–333. doi:10.1111/j.1600-0528.1980.tb01302.x PMID:6937277

Hamazaki Y & Murao T (1969). On the Carcinogenic Factors of Tobacco Leaf Powder. I. Inhalation of tobacco leaf powder. *J Karyopathol Esp Tumor Tumorvirus*, 12: 163–178.

Hansson LE, Baron J, Nyrén O *et al.* (1994). Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Sweden. *Int J Cancer*, 57: 26–31. doi:10.1002/ijc.2910570106 PMID:8150537

Harish K & Ravi R (1995). The role of tobacco in penile carcinoma. *Br J Urol*, 75: 375–377. doi:10.1111/j.1464-410X.1995.tb07352.x PMID:7735804

Hartge P, Hoover R, Kantor A (1985). Bladder cancer risk and pipes, cigars, and smokeless tobacco. *Cancer*, 55:901–906. doi:10.1002/1097-0142(19850215)55:4<901::AID-CNCR2820550432>3.0.CO;2-Q PMID:3967183

Hassan MM, Abbruzzese JL, Bondy ML *et al.* (2007). Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: a case-control study. *Cancer*, 109: 2547–2556. doi:10.1002/cncr.22724 PMID:17492688

Hayes RB, Pottern LM, Swanson GM *et al.* (1994). Tobacco use and prostate cancer in blacks and whites in the United States. *Cancer Causes Control*, 5: 221–226. doi:10.1007/BF01830240 PMID:8061169

Hecht SS, Rivenson A, Braley J *et al.* (1986). Induction of oral cavity tumors in F344 rats by tobacco-specific nitrosamines and snuff. *Cancer Res*, 46: 4162–4166. PMID:3731083

Heineman EF, Zahm SH, McLaughlin JK, Vaught JB (1995). Increased risk of colorectal cancer among smokers: results of a 26-year follow-up of US veterans and a review. *Int J Cancer*, 59: 728–738. doi:10.1002/ijc.2910590603 PMID:7989109

Henley SJ, Connell CJ, Richter P *et al.* (2007). Tobacco-related disease mortality among men who switched from cigarettes to spit tobacco. *Tob Control*, 16: 22–28. doi:10.1136/tc.2006.018069 PMID:17297069

Henley SJ, Thun MJ, Connell C, Calle EE (2005). Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control*, 16: 347–358. doi:10.1007/s10552-004-5519-6 PMID:15953977

Hirsch JM & Johansson SL (1983). Effect of long-term application of snuff on the oral mucosa: an experimental study in the rat. *J Oral Pathol*, 12: 187–198. PMID:6410027

Hirsch JM, Johansson SL, Thilander H, Vahlne A (1984). Effect of long-term application of snuff and herpes simplex virus 1 on rat oral mucosa. Possible association with development of oral cancer. *IARC Sci Publ*, 829–836. PMID:6099829

Hoffmann D, Djordjevic MV, Fan J *et al.* (1995). Five leading U.S. commercial brands of moist snuff in 1994: assessment of carcinogenic N-nitrosamines. *J Natl Cancer Inst*, 87: 1862–1869. doi:10.1093/jnci/87.24.1862 PMID:7494230

Homburger F, Hsueh SS, Russfield AB *et al.* (1976). Absence of carcinogenic effects of chronic feeding of snuff in inbred syrian hamsters. *Toxicol Appl Pharmacol*, 35: 515–521. PMID:944469

Howe GR, Burch JD, Miller AB *et al.* (1980). Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *J Natl Cancer Inst*, 64: 701–713. PMID:6928984

Hsairi M, Achour N, Zouari B *et al.* (1993). Etiologic factors in primary bronchial carcinoma in Tunisia*Tunis Med*, 71: 265–268. PMID:8212345

Hsing AW, McLaughlin JK, Hrubec Z *et al.* (1991). Tobacco use and prostate cancer: 26-year follow-up of US veterans. *Am J Epidemiol*, 133: 437–441. PMID:2000853

Hsing AW, McLaughlin JK, Schuman LM *et al.* (1990). Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. *Cancer Res*, 50: 6836–6840. PMID:2208150

IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, 83: 1–1438. PMID:15285078

IARC (2007a). Smokeless tobacco and some tobacco-specific N-nitrosamines. *IARC Monogr Eval Carcinog Risks Hum*, 89: 1–592. PMID:18335640

IARC (2007b). Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum*, 90: 1–636. PMID:18354839

IARC (2010). Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum*, 96: 1–1428.

IARC (2012). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F.

Ibrahim EM, Satti MB, Al Idrissi HY *et al.* (1986). Oral cancer in Saudi Arabia: the role of alqat and alshammah. *Cancer Detect Prev*, 9: 215–218.

Idris AM, Ahmed HM, Malik MO (1995a). Toombak dipping and cancer of the oral cavity in the Sudan: a case-control study. *Int J Cancer*, 63: 477–480. PMID:7591252

Idris AM, Ahmed HM, Mukhtar BI *et al.* (1995b). Descriptive epidemiology of oral neoplasms in Sudan 1970–1985 and the role of toombak. *Int J Cancer*, 61: 155–158. PMID:7705940

Idris AM, Ibrahim SO, Vasstrand EN *et al.* (1998). The Swedish snus and the Sudanese toombak: are they different? *Oral Oncol*, 34: 558–566. doi:10.1016/S1368-8375(98)00047-5 PMID:9930371

Idris AM, Nair J, Ohshima H *et al.* (1991). Unusually high levels of carcinogenic tobacco-specific nitrosamines in Sudan snuff (toombak). *Carcinogenesis*, 12: 1115–1118. doi:10.1093/carcin/12.6.1115 PMID:2044192

Idris AM, Warnakulasuriya KA, Ibrahim YE *et al.* (1996). Toombak-associated oral mucosal lesions in Sudanese show a low prevalence of epithelial dysplasia. *J Oral Pathol Med*, 25: 239–244. PMID:8835821

Jacob BJ, Straif K, Thomas G *et al.* (2004). Betel quid without tobacco as a risk factor for oral precancers. *Oral Oncol*, 40: 697–704. PMID:15172639

Jafarey NA, Mahmood Z, Zaidi SH (1977). Habits and dietary pattern of cases of carcinoma of the oral cavity and oropharynx. *J Pak Med Assoc*, 27: 340–343. PMID:413946

Johansson SL, Hirsch JM, Larsson PA *et al.* (1989). Snuff-induced carcinogenesis: effect of snuff in rats initiated with 4-nitroquinoline N-oxide. *Cancer Res*, 49: 3063–3069. PMID:2497972

Johansson SL, Saidi J, Osterdahl BG, Smith RA (1991). Promoting effect of snuff in rats initiated by 4-nitroquinoline-N-oxide or 7,12-dimethylbenz(a) anthracene. *Cancer Res*, 51: 4388–4394. PMID:1907884

Jungell P & Malmström M (1985). Snuff-induced lesions in Finnish recruits. *Scand J Dent Res*, 93: 442–447. PMID:3864218

Kabat GC, Chang CJ, Wynder EL (1994). The role of tobacco, alcohol use, and body mass index in oral and pharyngeal cancer. *Int J Epidemiol*, 23: 1137–1144. PMID:7721514

Kandarkar SV, Hasgekar NN, Sirsat SM (1981). Optical and ultrastructural pathology of vitamin A pretreated hamster cheek pouch–exposed to lime (Ca(OH)2) and tobacco over total life span. *Neoplasma*, 28: 729–737. PMID:7339502

Keen P, De Moor NG, Shapiro MP *et al.* (1955). The artiology of respiratory tract cancer in the South African Bantu; clinical aspects. *Br J Cancer*, 9: 528–538. doi:10.1038/bjc.1955.54 PMID:13304212

Keller AZ (1969). Residence, age, race and related factors in the survival and associations with salivary tumors. *Am J Epidemiol*, 90: 269–277. PMID:5823440

Keller AZ (1970). Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. *Am J Epidemiol*, 91: 486–499. PMID:5438996

Kiseleva NS, Milievskaja IL, Căklin AV (1976). Development of tumours in Syrian hamsters during prolonged experimental exposure to nas. *Bull World Health Organ*, 54: 597–605. PMID:1088508

Kneller RW, McLaughlin JK, Bjelke E *et al.* (1991). A cohort study of stomach cancer in a high-risk American population. *Cancer*, 68: 672–678. doi:10.1002/1097-0142(19910801)68:3<672::AID-CNCR2820680339>3.0.CO;2-T PMID:2065291

Kubo A & Corley DA (2006). Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 15: 872–878. doi:10.1158/1055-9965.EPI-05-0860 PMID:16702363

Kulkarni J, Lalitha VS, Bhide S (1989). Weak carcinogenic effect of masheri, a pyrolysed tobacco product, in mouse skin tumor models. *J Cancer Res Clin Oncol*, 115: 166–169. PMID:2497102

Kulkarni JR, Lalitha VS, Bhide SV (1988). Carcinogenicity studies of masheri, a pyrolysed product of tobacco. *Carcinogenesis*, 9: 2137–2138. PMID:3180350

Lagergren J, Bergström R, Lindgren A, Nyrén O (2000). The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer*, 85: 340–346. doi:10.1002/(SICI)1097-0215(20000201)85:3<340::AID-IJC8>3.0.CO;2-N PMID:10652424

Larsson A, Axéll T, Andersson G (1991). Reversibility of snuff dippers' lesion in Swedish moist snuff users: a clinical and histologic follow-up study. *J Oral Pathol Med*, 20: 258–264. PMID:1890661

Lee JJ, Hong WK, Hittelman WN *et al.* (2000). Predicting cancer development in oral leukoplakia: ten years of translational research. *Clin Cancer Res*, 6: 1702–1710. PMID:10815888

Lee PN & Hamling JS (2009). Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med*, 7: 36 doi:10.1186/1741-7015-7-36 PMID:19638245

Lewin F, Norell SE, Johansson H *et al.* (1998). Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. *Cancer*, 82: 1367–1375. doi:10.1002/(SICI)1097-0142(19980401)82:7<1367::AID-CNCR21>3.0.CO;2-3 PMID:9529030

Luo J, Ye W, Zendehdel K *et al.* (2007). Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet*, 369: 2015–2020. doi:10.1016/S0140-6736(07)60678-3 PMID:17498797

Maden C, Beckmann AM, Thomas DB *et al.* (1992). Human papillomaviruses, herpes simplex viruses, and the risk of oral cancer in men. *Am J Epidemiol*, 135: 1093–1102. PMID:1321561

Mani NJ (1985). Preliminary report on prevalence of oral cancer and precancerous lesions among dental patients in Saudi Arabia. *Community Dent Oral Epidemiol*, 13: 247–248. PMID:3862510

Marshall JR, Graham S, Haughey BP *et al.* (1992). Smoking, alcohol, dentition and diet in the epidemiology of oral cancer. *Eur J Cancer B Oral Oncol*, 28B: 9–15. PMID:1422474

Martin GC, Brown JP, Eifler CW, Houston GD (1999). Oral leukoplakia status six weeks after cessation of smokeless tobacco use. *J Am Dent Assoc*, 130: 945–954. PMID:10422398

Martinez I (1969). Factors associated with ccer of the esophagus, mouth, and pharynx in Puerto Rico. *J Natl Cancer Inst*, 42: 1069–1094. PMID:5793187

Mashberg A, Boffetta P, Winkelman R, Garfinkel L (1993). Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. *Cancer*, 72: 1369–1375. PMID:8339227

McLaughlin JK, Lindblad P, Mellemgaard A *et al.* (1995). International renal-cell cancer study. I. Tobacco use. *Int J Cancer*, 60: 194–198. doi:10.1002/ijc.2910600211 PMID:7829215

Merchant A, Husain SS, Hosain M *et al.* (2000). Paan without tobacco: an independent risk factor for oral cancer. *Int J Cancer*, 86: 128–131. PMID:10728606

Milievskaja IL & Kiseleva NS (1976). Comparative study of the carcinogenic activities of nas and some chemical carcinogens when introduced into the buccal pouch of the Syrian hamster. *Bull World Health Organ*, 54: 607–614. PMID:829414

Mody JK & Ranadive KJ (1959). Biological study of tobacco in relation to oral cancer. *Indian J Med Sci*, 13: 1023–1037. PMID:14423157

Moore GE, Bissinger LL, Proehl EC (1953). Intraoral cancer and the use of chewing tobacco. *J Am Geriatr Soc*, 1: 497–506. PMID:13069216

Muscat JE, Hoffmann D, Wynder EL (1995). The epidemiology of renal cell carcinoma. A second look. *Cancer*, 75: 2552–2557. doi:10.1002/1097-0142(19950515)75:10<2552::AID-CNCR2820751023>3.0.CO;2-1 PMID:7736400

Muscat JE, Richie JP Jr, Thompson S, Wynder EL (1996). Gender differences in smoking and risk for oral cancer. *Cancer Res*, 56: 5192–5197. PMID:8912856

Muscat JE, Stellman SD, Hoffmann D, Wynder EL (1997). Smoking and pancreatic cancer in men and women. *Cancer Epidemiol Biomarkers Prev*, 6: 15–19. PMID:8993792

Muscat JE & Wynder EL (1998). A case/control study of risk factors for major salivary gland cancer. *Otolaryngol Head Neck Surg*, 118: 195–198. PMID:9482552

Nair UJ, Friesen M, Richard I *et al.* (1990). Effect of lime composition on the formation of reactive oxygen species from areca nut extract in vitro. *Carcinogenesis*, 11: 2145–2148. doi:10.1093/carcin/11.12.2145 PMID:2176136

Nair UJ, Obe G, Friesen M *et al.* (1992). Role of lime in the generation of reactive oxygen species from betel-quid ingredients. *Environ Health Perspect*, 98: 203–205. doi:10.2307/3431271 PMID:1486850

Nasrollahzadeh D, Kamangar F, Aghcheli K *et al.* (2008). Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer*, 98: 1857–1863. doi:10.1038/sj.bjc.6604369 PMID:18475303

Nugmanov SN, Baimakanov SS (1970) [The results of an epidemiological study of oro-pharyngeal tumours in Kazakhstan following the WHO project] In Russian. In:*Epidemiology of Malignant Tumours* Alma-Ata: Nauka Publishing House, 227–231.

Odenbro A, Bellocco R, Boffetta P *et al.* (2005). Tobacco smoking, snuff dipping and the risk of cutaneous squamous cell carcinoma: a nationwide cohort study in Sweden. *Br J Cancer*, 92: 1326–1328. doi:10.1038/sj.bjc.6602475 PMID:15770206

Offenbacher S & Weathers DR (1985). Effects of smokeless tobacco on the periodontal, mucosal and caries status of adolescent males. *J Oral Pathol*, 14: 169–181. PMID:3920367

Ohshima H, Nair J, Bourgade MC *et al.* (1985). Identification and occurrence of two new N-nitrosamino acids in tobacco products: 3-(N-nitroso-N-methylamino) propionic acid and 4-(N-nitroso-N-methylamino) butyric acid. *Cancer Lett*, 26: 153–162. doi:10.1016/0304-3835(85)90021-7 PMID:3978605

Park NH, Sapp JP, Herbosa EG (1986). Oral cancer induced in hamsters with herpes simplex infection

and simulated snuff dipping. *Oral Surg Oral Med Oral Pathol*, 62: 164–168. PMID:3462612

Payne JB, Johnson GK, Reinhardt RA, Schmid M (1998). Histological alterations following short-term smokeless tobacco exposure in humans. *J Periodontal Res*, 33: 274–279. PMID:9777594

Peacock EE Jr & Brawley BW (1959). An evaluation of snuff and tobacco in the production of mouth cancer. *Plast Reconstr Surg Transplant Bull*, 23: 628–635. PMID:13667478

Peacock EE Jr, Greenberg BG, Brawley BW (1960). The effect of snuff and tobacco on the production of oral carcinoma: an experimental and epidemiological study. *Ann Surg*, 151: 542–550. PMID:14431201

Phukan RK, Ali MS, Chetia CK, Mahanta J (2001). Betel nut and tobacco chewing; potential risk factors of cancer of oesophagus in Assam, India. *Br J Cancer*, 85: 661–667. doi:10.1054/bjoc.2001.1920 PMID:11531248

Phukan RK, Zomawia E, Narain K *et al.* (2005). Tobacco use and stomach cancer in Mizoram, India. *Cancer Epidemiol Biomarkers Prev*, 14: 1892–1896. doi:10.1158/1055-9965.EPI-05-0074 PMID:16103433

Pindborg JJ (1980) *Oral cancer and precancer.* Bristol: John Wright.

Pindborg JJ, Reichart PA, Smith CJ *et al.* (1996) *Histological typing of cancer and precancer of the oral mucosa. In: International Histological Classification of Tumours.*2nd Ed., Sobin LH (ed) Geneva: World Health Organaization.

Pottern LM, Morris LE, Blot WJ *et al.* (1981). Esophageal cancer among black men in Washington, D.C. I. Alcohol, tobacco, and other risk factors. *J Natl Cancer Inst*, 67: 777–783. PMID:6944547

Poulson TC, Lindenmuth JE, Greer RO Jr (1984). A comparison of the use of smokeless tobacco in rural and urban teenagers. *CA Cancer J Clin*, 34: 248–261. PMID:6432238

Prokopczyk B, Wu M, Cox JE *et al.* (1995). Improved Methodology for the Quantitative Assessment of Tobacco-Specific N-Nitrosamines in Tobacco by Supercritical-Fluid Extraction. *J Agric Food Chem*, 43: 916–922. doi:10.1021/jf00052a013

Putnam SD, Cerhan JR, Parker AS *et al.* (2000). Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. *Ann Epidemiol*, 10: 361–369. doi:10.1016/S1047-2797(00)00057-0 PMID:10964002

Ranadive KJ, Gothoskar SV, Khanolkar VR (1963). Experimental studies on the etiology of cancer types specific to India (a)oral cancer (b) Kangri cancer. *Acta Unio Int Contra Cancrum*, 19: 634–639. PMID:14050624

Ranadive KJ, Gothoskar SV, Rao AR *et al.* (1976). Experimental studies on betel nut and tobacco carcinogenicity. *Int J Cancer*, 17: 469–476. PMID:1279039

Randeria JD (1972). Tobacco induced changes in the bladder buccal and vaginal mucosae. *Indian J Med Res*, 60: 694–698. PMID:4663237

Rao AR (1984). Modifying influences of betel quid ingredients on B(a)P-induced carcinogenesis in the buccal pouch of hamster. *Int J Cancer*, 33: 581–586. PMID:6327538

Roed-Petersen B, Gupta PC, Pindborg JJ, Singh B (1972). Association between oral leukoplakia and sex, age, and tobacco habits. *Bull World Health Organ*, 47: 13–19. PMID:4538900

Roed-Petersen B & Pindborg JJ (1973). A study of Danish snuff-induced oral leukoplakias. *J Oral Pathol*, 2: 301–313. doi:10.1111/j.1600-0714.1973.tb01848.x PMID:4136500

Rolandsson M, Hellqvist L, Lindqvist L, Hugoson A (2005). Effects of snuff on the oral health status of adolescent males: a comparative study. *Oral Health Prev Dent*, 3: 77–85. PMID:16173384

Roosaar A, Johansson AL, Sandborgh-Englund G *et al.* (2006). A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users. *Int J Cancer*, 119: 392–397. PMID:16470839

Roosaar A, Johansson AL, Sandborgh-Englund G *et al.* (2008). Cancer and mortality among users and nonusers of snus. *Int J Cancer*, 123: 168–173. PMID:18412245

Rosenquist K (2005). Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. *Swed Dent J Suppl*, 1791–66. PMID:16335030

Rosenquist K, Wennerberg J, Schildt EB *et al.* (2005). Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Otolaryngol*, 125: 991–998. PMID:16193590

Salem G, Juhl R, Schiødt T (1984). Oral malignant and premalignant changes in 'Shammah'-users from the Gizan region, Saudi Arabia. *Acta Odontol Scand*, 42: 41–45. PMID:6585122

Salonen L, Axéll T, Helldén L (1990). Occurrence of oral mucosal lesions, the influence of tobacco habits and an estimate of treatment time in an adult Swedish population. *J Oral Pathol Med*, 19: 170–176. PMID:2366203

Sankaranarayanan R, Duffy SW, Day NE *et al.* (1989a). A case-control investigation of cancer of the oral tongue and the floor of the mouth in southern India. *Int J Cancer*, 44: 617–621. doi:10.1002/ijc.2910440410 PMID:2793234

Sankaranarayanan R, Duffy SW, Nair MK *et al.* (1990b). Tobacco and alcohol as risk factors in cancer of the larynx in Kerala, India. *Int J Cancer*, 45: 879–882. doi:10.1002/ijc.2910450517 PMID:2335391

Sankaranarayanan R, Duffy SW, Padmakumary G *et al.* (1989b). Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India. *Br J Cancer*, 60: 638–643. doi:10.1038/bjc.1989.330 PMID:2803939

Sankaranarayanan R, Duffy SW, Padmakumary G *et al.* (1990a). Risk factors for cancer of the buccal and

labial mucosa in Kerala, southern India. *J Epidemiol Community Health*, 44: 286–292. doi:10.1136/jech.44.4.286 PMID:2277249

Sankaranarayanan R, Duffy SW, Padmakumary G *et al.* (1991). Risk factors for cancer of the oesophagus in Kerala, India. *Int J Cancer*, 49: 485–489. doi:10.1002/ijc.2910490402 PMID:1917146

Sapkota A, Gajalakshmi V, Jetly DH *et al.* (2007). Smokeless tobacco and increased risk of hypopharyngeal and laryngeal cancers: a multicentric case-control study from India. *Int J Cancer*, 121: 1793–1798. doi:10.1002/ijc.22832 PMID:17583577

Scheifele C, Nassar A, Reichart PA (2007). Prevalence of oral cancer and potentially malignant lesions among shammah users in Yemen. *Oral Oncol*, 43: 42–50. PMID:16759897

Schildt EB, Eriksson M, Hardell L, Magnuson A (1998). Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Int J Cancer*, 77: 341–346. PMID:9663593

Schmähl D (1965). Examination of chewing tobaco extract for cancerogenic effects in rats*Arzneimittelforschung*, 15: 704–705. PMID:5899252

Schroeder JC, Olshan AF, Baric R *et al.* (2002). A case-control study of tobacco use and other non-occupational risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma (United States). *Cancer Causes Control*, 13: 159–168. doi:10.1023/A:1014397920185 PMID:11936822

Schwartz SM, Daling JR, Doody DR *et al.* (1998). Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst*, 90: 1626–1636. PMID:9811312

Shapiro MP, Keen P, Cohen L, De Moor NG (1955). Malignant disease in the Transvaal. II. Tumours of the musculo-skeletal system. III. Cancer of the respiratory tract; first statistical report of the radiation therapy department of the Johannesburg group of hospitals. *S Afr Med J*, 29: 95–101. PMID:14358867

Sharma PK, Lal N, Nagpaul KK (1985). Study of trace amounts of U in snuff. *Health Phys*, 48: 811–812. PMID:4039716

Shukla VK, Chauhan VS, Mishra RN, Basu S (2008). Lifestyle, reproductive factors and risk of gallbladder cancer. *Singapore Med J*, 49: 912–915. PMID:19037558

Shulman JD, Beach MM, Rivera-Hidalgo F (2004). The prevalence of oral mucosal lesions in U.S. adults: data from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Am Dent Assoc*, 135: 1279–1286. PMID:15493392

Sinha DN, Palipudi KM, Rolle I *et al.* (2011).* Tobacco use among youth and adults in member countries of South-East Asia region: Review of findings from surveys under the global tobacco surveillance system. *Indian J Public Health*, 55: 169–176. doi:10.4103/0019-557X.89946 PMID:22089684

Sinusas K & Coroso JG (2006). A 10-yr study of smokeless tobacco use in a professional baseball organization. *Med Sci Sports Exerc*, 38: 1204–1207. PMID:16826015

Sinusas K, Coroso JG, Sopher MD, Crabtree BF (1992). Smokeless tobacco use and oral pathology in a professional baseball organization. *J Fam Pract*, 34: 713–718. PMID:1593245

Slattery ML, West DW, Robison LM (1988). Fluid intake and bladder cancer in Utah. *Int J Cancer*, 42: 17–22. doi:10.1002/ijc.2910420105 PMID:3391705

Spangler JG (2002). Corrections to Spangler *et al.* 2001b *Ethn Dis*, 12: 158–159.

Spangler JG, Michielutte R, Bell RA *et al.* (2001). Association between smokeless tobacco use and breast cancer among Native-American women in North Carolina. *Ethn Dis*, 11: 36–43.

Spitz MR, Fueger JJ, Goepfert H *et al.* (1988). Squamous cell carcinoma of the upper aerodigestive tract. A case comparison analysis. *Cancer*, 61: 203–208. PMID:3334949

Spitz MR, Fueger JJ, Halabi S *et al.* (1993). Mutagen sensitivity in upper aerodigestive tract cancer: a case-control analysis. *Cancer Epidemiol Biomarkers Prev*, 2: 329–333. PMID:7688625

Sreedharan S, Hegde MC, Pai R *et al.* (2007). Snuff-induced malignancy of the nasal vestibule: a case report. *Am J Otolaryngol*, 28: 353–356. doi:10.1016/j.amjoto.2006.10.008 PMID:17826541

Stenström B, Zhao CM, Rogers AB *et al.* (2007). Swedish moist snuff accelerates gastric cancer development in Helicobacter pylori-infected wild-type and gastrin transgenic mice. *Carcinogenesis*, 28: 2041–2046. PMID:17389611

Stepanov I, Jensen J, Hatsukami D, Hecht SS (2008). New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine Tob Res*, 10: 1773–1782. doi:10.1080/14622200802443544 PMID:19023828

Stepanov I, Villalta PW, Knezevich A *et al.* (2010). Analysis of 23 polycyclic aromatic hydrocarbons in smokeless tobacco by gas chromatography-mass spectrometry. *Chem Res Toxicol*, 23: 66–73. doi:10.1021/tx900281u PMID:19860436

Sterling TD, Rosenbaum WL, Weinkam JJ (1992). Analysis of the relationship between smokeless tobacco and cancer based on data from the National Mortality Followback Survey. *J Clin Epidemiol*, 45: 223–231. doi:10.1016/0895-4356(92)90082-X PMID:1569419

Stewart CM, Baughman RA, Bates RE (1989). Smokeless tobacco use among Florida teenagers: prevalence, attitudes, and oral changes. *Fla Dent J*, 60: 38–42. PMID:2599145

Stockwell HG & Lyman GH (1986). Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck. *Head Neck Surg*, 9: 104–110. doi:10.1002/hed.2890090206 PMID:3623935

Summerlin DJ, Dunipace A, Potter R (1992). Histologic effects of smokeless tobacco and alcohol on the pouch mucosa and organs of the Syrian hamster. *J Oral Pathol Med*, 21: 105–108. PMID:1583594

Suri K, Goldman HM, Wells H (1971). Carcinogenic effect of a dimethyl sulphoxide extract of betel nut on the mucosa of the hamster buccal pouch. *Nature*, 230: 383–384. PMID:4927728

Thomas G, Hashibe M, Jacob BJ *et al.* (2003). Risk factors for multiple oral premalignant lesions. *Int J Cancer*, 107: 285–291. PMID:12949809

Tomar SL (2002). Snuff use and smoking in U.S. men: implications for harm reduction. *Am J Prev Med*, 23: 143–149. PMID:12350445

Tomar SL, Winn DM, Swango PA *et al.* (1997). Oral mucosal smokeless tobacco lesions among adolescents in the United States. *J Dent Res*, 76: 1277–1286. PMID:9168861

Tricker AR & Preussmann R (1988). The occurrence of N-nitrosocompounds [corrected] in zarda tobacco. *Cancer Lett*, 42: 113–118. doi:10.1016/0304-3835(88)90247-9 PMID:3242503

Tyldesley WR (1971). Tobacco chewing in english coal miners. A preliminary report. *Br J Oral Surg*, 9: 21–28. PMID:5286076

Van Duuren BL, Sivak A, Segal A *et al.* (1966). The tumor-promoting agents of tobacco leaf and tobacco smoke condensate. *J Natl Cancer Inst*, 37: 519–526. PMID:5923502

Vincent RG & Marchetta F (1963). The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx or larynx. *Am J Surg*, 106: 501–505. PMID:14062955

Vogler WR, Lloyd JW, Milmore BK (1962). A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. *Cancer*, 15: 246–258. PMID:13926472

Wahi PN (1968). The epidemiology of oral anc oropharyngeal cancer. A report of the study in Mainpuri district, Uttar Pradesh, India. *Bull World Health Organ*, 38: 495–521. PMID:5302449

Wasnik KS, Ughade SN, Zodpey SP, Ingole DL (1998). Tobacco consumption practices and risk of oro-pharyngeal cancer: a case-control study in Central India. *Southeast Asian J Trop Med Public Health*, 29: 827–834. PMID:10772572

Weitkunat R, Sanders E, Lee PN (2007). Meta-analysis of the relation between European and American smokeless tobacco and oral cancer. *BMC Public Health*, 7: 334 PMID:18005437

Westbrook KC (1980) *Snuff dipper's carcinoma. Fact or Fiction? In: Prevention and Detection of Cancer.*, Nieburg HE (ed) New York: Marcel Dekker.

Williams RR & Horm JW (1977). Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst*, 58: 525–547. PMID:557114

Williams RR, Stegens NL, Horm JW (1977). Patient interview study from the Third National Cancer Survey: overview of problems and potentials of these data. *J Natl Cancer Inst*, 58: 519–524. PMID:839554

Winn DM (1986) *Smokeless tobacco and oral/pharynx cancer: The role of cofactors.* In*: Mechanisms in Tobacco Carcinogenesis.*, Hoffmann D, Harris CC (eds) Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, No. Banbury Report No. 23, 361–375.

Winn DM, Blot WJ, Shy CM *et al.* (1981a). Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med*, 304: 745–749. PMID:7193288

Winn DM, Blot WJ, Shy CM *et al.* (1981b). Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med*, 304: 745–749. doi:10.1056/NEJM198103263041301 PMID:7193288

Winn DM, Ziegler RG, Pickle LW *et al.* (1984). Diet in the etiology of oral and pharyngeal cancer among women from the southern United States. *Cancer Res*, 44: 1216–1222. PMID:6692405

Wolfe MD & Carlos JP (1987). Oral health effects of smokeless tobacco use in Navajo Indian adolescents. *Community Dent Oral Epidemiol*, 15: 230–235. PMID:3476250

Wynder EL & Bross IJ (1957). Aetiological factors in mouth cancer; an approach to its prevention. *Br Med J*, 1: 1137–1143. PMID:13426561

Wynder EL & Bross IJ (1961). A study of etiological factors in cancer of the esophagus. *Cancer*, 14: 389–413. doi:10.1002/1097-0142(196103/04)14:2<389::AID-CNCR2820140220>3.0.CO;2-E PMID:13786981

Wynder EL, Bross IJ, Feldman RM (1957a). A study of the etiological factors in cancer of the mouth. *Cancer*, 10: 1300–1323. PMID:13489682

Wynder EL, Hultberg S, Jacobsson F, Bross IJ (1957). Environmental factors in cancer of the upper alimentary tract; a Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. *Cancer*, 10: 470–487. doi:10.1002/1097-0142(195705/06)10:3<470::AID-CNCR2820100309>3.0.CO;2-7 PMID:13460941

Wynder EL, Hultberg S, Jacobsson F, Bross IJ (1957b). Environmental factors in cancer of the upper alimentary tract; a Swedish study with special reference to Plummer-Vinson (Paterson-Kelly) syndrome. *Cancer*, 10: 470–487. PMID:13460941

Wynder EL, Kabat G, Rosenberg S, Levenstein M (1983). Oral cancer and mouthwash use. *J Natl Cancer Inst*, 70: 255–260. PMID:6571934

Wynder EL & Stellman SD (1977). Comparative epidemiology of tobacco-related cancers. *Cancer Res*, 37: 4608–4622. PMID:562711

Wynder EL & Wright G (1957). A study of tobacco carcinogenesis. I. The primary fractions. *Cancer*, 10: 255–271. PMID:13426984

Ye W, Ekström AM, Hansson LE *et al.* (1999). Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. *Int J Cancer*, 83: 223–229. doi:10.1002/(SICI)1097-0215(19991008)83:2<223::AID-IJC13>3.0.CO;2-M PMID:10471531

Young TB, Ford CN, Brandenburg JH (1986). An epidemiologic study of oral cancer in a statewide network. *Am J Otolaryngol*, 7: 200–208. PMID:3728828

Zahm SH, Blair A, Holmes FF *et al.* (1989). A case-control study of soft-tissue sarcoma. *Am J Epidemiol*, 130: 665–674. PMID:2773915

Zahm SH, Heineman EF, Vaught JB (1992). Soft tissue sarcoma and tobacco use: data from a prospective cohort study of United States veterans. *Cancer Causes Control*, 3: 371–376. doi:10.1007/BF00146891 PMID:1617125

Zaridze DG, Blettner M, Matiakin EG *et al.* (1986). The effect of nass use and smoking on the risk of oral leukoplakia. *Cancer Detect Prev*, 9: 435–440. PMID:3779705

Zaridze DG, Kuvshinov JP, Matiakin E *et al.* (1985). Chemoprevention of oral and esophageal cancer in Uzbekistan, Union of Soviet Socialist Republics. *Natl Cancer Inst Monogr*, 69: 259–262. PMID:2939349

Zendehdel K, Nyrén O, Luo J *et al.* (2008). Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. *Int J Cancer*, 122: 1095–1099. doi:10.1002/ijc.23076 PMID:17973262

Zheng T, Cantor KP, Zhang Y *et al.* (2001). Risk of brain glioma not associated with cigarette smoking or use of other tobacco products in Iowa. *Cancer Epidemiol Biomarkers Prev*, 10: 413–414. PMID:11319186

Zheng W, McLaughlin JK, Gridley G *et al.* (1993). A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*, 4: 477–482. doi:10.1007/BF00050867 PMID:8218880

* Exceptionally, the most recent updates of well-established ongoing surveys and reports, published after the meeting, were included in this Monograph. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.

TOBACCO SMOKING

Tobacco smoking was considered by previous IARC Working Groups in 1986, 1987 and 2002 (IARC, 1986, 1987, 2004a). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Smoked tobacco products

Smoked forms of tobacco include various kinds of cigarettes (manufactured, hand-rolled, filtered, un-filtered and flavoured), cigars and pipes. While cigarette smoking, particularly manufactured cigarettes, is by far the main form of tobacco smoked globally, in some countries other forms of smoked tobacco are dominant (IARC, 2004a). In India, for example, bidis (made of coarse and uncured tobacco) account for about 60% of smoked tobacco products whereas cigarettes account for 20% (Ray & Gupta, 2009; IIPS, 2010). Water pipes, another form of smoked tobacco known by other various names such as gaza, hookah, narghile, shisha, hubble-bubble, are commonly smoked in the Eastern Mediterranean region, in some parts of Asia including India, and in North Africa (Asma *et al.*, 2009).

1.2 Chemical composition of tobacco smoke

1.2.1 Smoke from cigarettes

One cubic cm of fresh, un-aged cigarette mainstream smoke [the smoke emerging from the mouth end of a cigarette during smoking] has about 4×10^9 particles with a mean diameter of about 0.2 μm (Borgerding & Klus, 2005). The size of the particles increases as the smoke ages. Temperatures in the burning cone of the cigarette are about 800 °C during the smoulder period between puffs and increase to 910–920 °C at the periphery of the cone during puffing (Borgerding & Klus, 2005). Hydrogen is generated in the glowing cone, resulting in an oxygen deficient reducing atmosphere (Borgerding & Klus, 2005). The approximate composition of mainstream smoke of a plain cigarette is summarized in Table 1.1 (Borgerding & Klus, 2005). The total particulate matter, after subtraction of the amounts of nicotine and water, is referred to as 'tar'.

Over 5300 compounds have been identified in tobacco smoke (Rodgman & Perfetti, 2009). Classes of compounds include but are not limited to neutral gases, carbon and nitrogen oxides, amides, imides, lactams, carboxylic acids, lactones, esters, aldehydes, ketones,

Table 1.1 Approximate chemical composition of mainstream smoke generated by a plain cigarette

Compound or class of components	Relative amount w/w (%)
Nitrogen	58
Oxygen	12
Carbon dioxide	13
Carbon monoxide	3.5
Hydrogen, argon	0.5
Water	1
Volatile organic substances	5
Particulate phase	8

From Borgerding & Klus (2005)

alcohols, phenols, amines, *N*-nitrosamines, *N*-heterocyclics, aliphatic hydrocarbons, monocyclic and polycyclic aromatic hydrocarbons (PAHs), nitriles, anhydrides, carbohydrates, ethers, nitro compounds and metals (Rodgman & Perfetti, 2009).

The addictive properties of tobacco smoke are attributed to nicotine, the principal tobacco alkaloid in smoke (Hukkanen *et al.*, 2005). Minor tobacco alkaloids include nornicotine, anatabine and anabasine (Hukkanen *et al.*, 2005). The tobacco alkaloids are not generally considered carcinogenic, but are accompanied by carcinogens in each puff of smoke.

There are over 70 carcinogens in tobacco smoke that have been evaluated by the *IARC Monographs* programme as having sufficient evidence for carcinogenicity in either laboratory animals or humans (IARC, 2004a). The different chemical classes of carcinogens and representatives of each are presented in Table 1.2 (IARC, 2004a). Sixteen of these – benzo[*a*]pyrene (BaP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosonornicotine (NNN), 2-naphthylamine, 4-aminobiphenyl, formaldehyde, 1,3-butadiene, benzene, vinyl chloride, ethylene oxide, arsenic, beryllium, nickel compounds, chromium VI, cadmium, and polonium-210 – are classified as carcinogenic to humans (Group 1). Structures of some representative carcinogens in cigarette smoke are shown in Fig. 1.1. There are other likely carcinogens in cigarette smoke that have not been evaluated by the *IARC Monographs* programme. These include, for example, PAHs with incompletely characterized occurrence levels and carcinogenic activities; over 500 PAHs have been identified (Rodgman & Perfetti, 2006).

PAHs, tobacco-specific *N*-nitrosamines, aromatic amines, aldehydes and certain volatile organics likely contribute significantly to the carcinogenic activity of tobacco smoke (Hecht, 2003).

In the early part of the 20th century, PAHs were identified as carcinogenic constituents of coal tar (Phillips, 1983). They are products of incomplete combustion of all organic matter and occur, always as complex mixtures, in tars, soots, broiled foods, vehicle engine exhaust and tobacco smoke. PAHs are generally locally acting carcinogens, and some, such as the prototypic compound BaP, have strong carcinogenic activity on mouse skin and in rodent lung. Heterocyclic analogues of PAHs also occur in cigarette smoke. Concentrations of individual PAHs in mainstream cigarette smoke are generally in the range of 1–50 ng per cigarette (IARC, 2004a).

Among the carcinogenic *N*-nitrosamines in tobacco smoke are tobacco-specific *N*-nitrosamines, which are derived from, and structurally related to, the tobacco alkaloids. Two of the most important of these are NNK and NNN (Hecht & Hoffmann, 1988). Levels of NNK and NNN in cigarette smoke vary depending on tobacco type and other factors, but are frequently in the range of 50–200 ng per cigarette (IARC, 2004a).

Aromatic amines were first identified as human carcinogens from industrial exposures in the dye industry in the early part of the 20th century. They include the well known human bladder carcinogens 2-naphthylamine and 4-aminobiphenyl which, along with other

Table 1.2 Tobacco smoke carcinogens evaluated in the *IARC Monographs*

Chemical Class	Number of Carcinogens	Representative Carcinogens
Polycyclic aromatic hydrocarbons (PAHs) and their heterocyclic analogues	15	Benzo[*a*]pyrene (BaP) Dibenz[*a*,*h*]anthracene
N-Nitrosamines	8	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) *N*′-Nitrosonornicotine (NNN)
Aromatic amines	12	4-Aminobiphenyl 2-Naphthylamine
Aldehydes	2	Formaldehyde Acetaldehyde
Phenols	2	Catechol Caffeic acid
Volatile hydrocarbons	3	Benzene 1,3-Butadiene Isoprene
Other organics	12	Ethylene oxide Acrylonitrile
Inorganic compounds	8	Cadmium Polonium-210

There are many other carcinogens in cigarette smoke that have not been evaluated in an *IARC Monograph*.
From IARC (2004a)

isomers, are found in cigarette smoke, but their levels are generally quite low (1–20 ng per cigarette) (IARC, 2004a).

Aldehydes such as formaldehyde and acetaldehyde occur widely in the human environment and are also found in human blood. Concentrations of acetaldehyde and formaldehyde in cigarette smoke are far higher than those of PAHs, *N*-nitrosamines or aromatic amines but their carcinogenic activities are weak (Hecht, 2003). Cigarette mainstream smoke typically contains 10–30 µg formaldehyde/cigarette and 800–900 µg acetaldehyde/cigarette (IARC, 2004a).

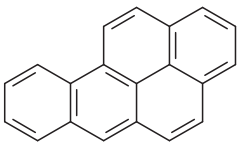
Volatile hydrocarbons in cigarette smoke include 1,3-butadiene, a powerful multi-organ carcinogen in the mouse, and benzene, a known human leukaemogen. 1,3-Butadiene (20–40 µg/cigarette) and benzene (12–50 µg/cigarette) are two of the most prevalent strong carcinogens in cigarette smoke (IARC, 2004a).

In summary, cigarette smoke is an exceedingly complex mixture which contains over 5300 compounds including multiple toxicants and carcinogens.

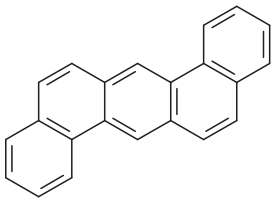
1.2.2 Smoke from other tobacco products

Some constituents have been measured in roll-your-own cigarettes, and their levels are comparable to or higher than those in commercial brands. Carcinogen and toxicant levels expressed per unit are higher in cigars than in cigarettes because of their larger size, and in some instances are also higher per litre of smoke. Levels of nicotine and tobacco-specific nitrosamines were comparable in bidis and commercial Indian cigarettes; bidis also contain high levels of eugenol, as do kreteks. Levels of NNK and NNN in chuttas were considerably higher than in standard cigarettes (IARC, 2004a).

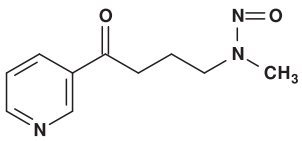
Fig. 1.1 Structures of some representative tobacco smoke carcinogens



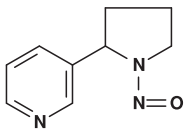
benzo[*a*]pyrene (BaP)



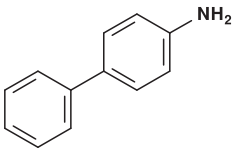
dibenz[*a,h*]anthracene



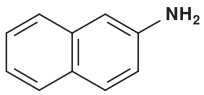
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)



N'-nitrosonornicotine (NNN)

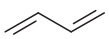


4-aminobiphenyl



2-naphtylamine

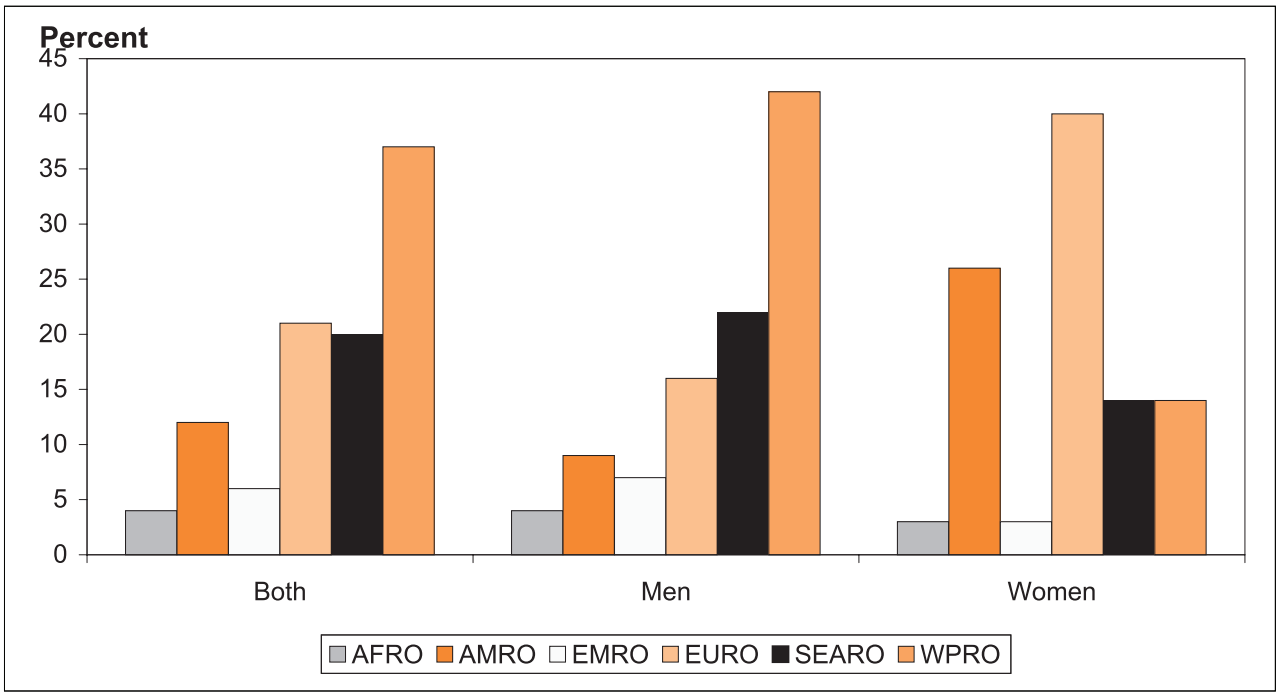
benzene



1,3-butadiene

ethylene oxide

Fig. 1.2 Proportion of adult smokers by WHO region in 2009



From WHO (2011)

1.3 Prevalence of tobacco smoking

1.3.1 Data collection and methods

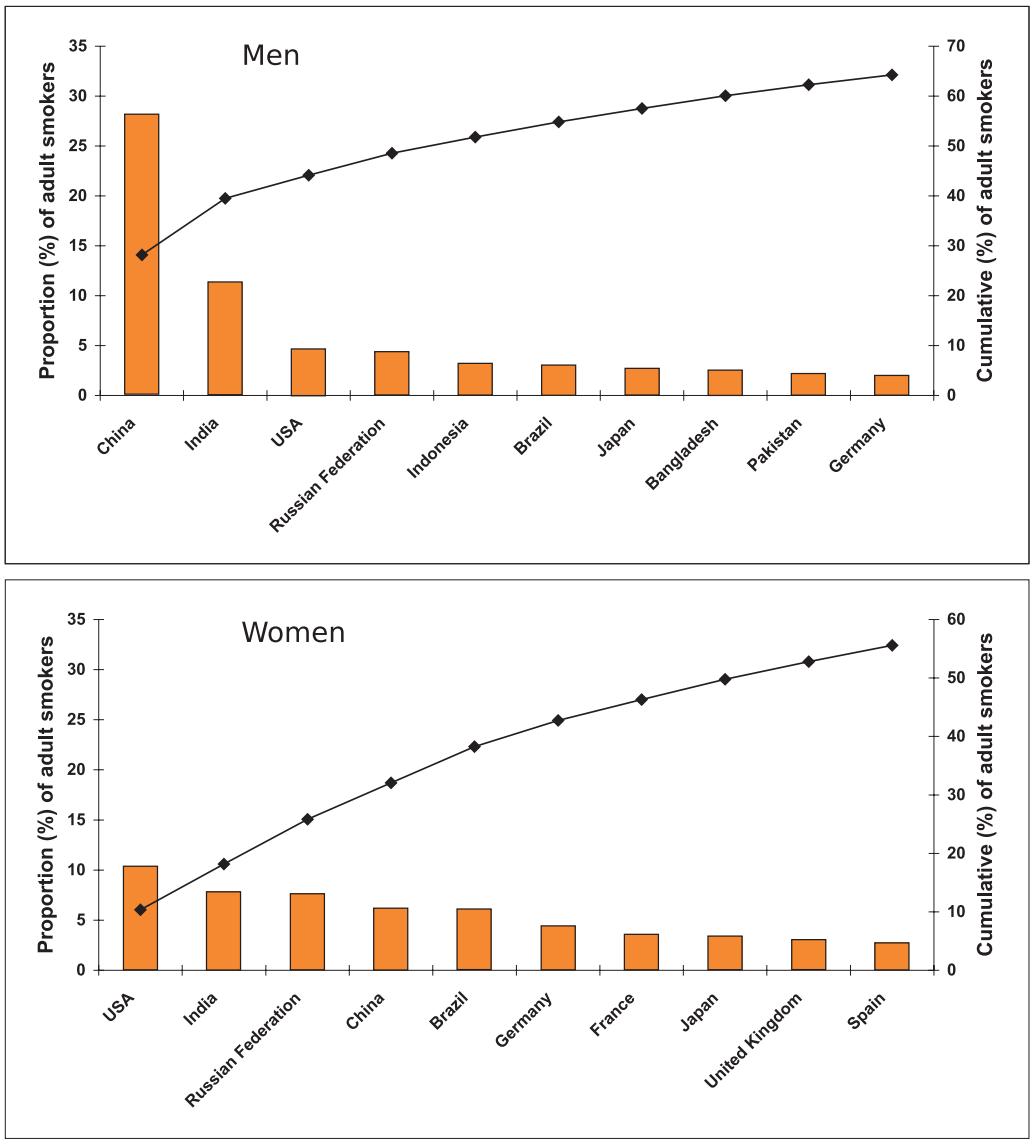
Data on smoking tobacco are available from WHO's Global Infobase (www.who.int/infobase) and the WHO Global Health Observatory (www.who.int/gho/en) – repositories of information on tobacco use and other risk factors in young people (13–15 years old) and adults (aged 15 years and over). The data span several years and are acquired from government reports, journals and unpublished sources. WHO has in the recent past used and modelled these data to produce estimates of tobacco smoking prevalence, published in the WHO Reports on the Global Tobacco Epidemic. For a complete explanation of methods used, the reader is referred to the Technical Note on Prevalence in the 3rd WHO Report on the Global Tobacco Epidemic (WHO, 2011). The six WHO regions are: EMRO, Eastern Mediterranean Region; EURO, European Region; AFRO, African Region; WPRO, Western Pacific Region; SEARO, South East Asian Region; AMRO, Region of the Americas. A listing of the countries in each region can be viewed at http://www.who.int/about/structure/en/index.html.

1.3.2 Distribution of smokers by WHO region and country

WHO estimates that in 2009, there was about 1.1 billion adult smokers worldwide, representing nearly a quarter (22%) of the global adult population (WHO, 2011). A disaggregation by the six WHO regions (Fig. 1.2) shows that over a third of smokers worldwide live in WPRO (highly influenced by the People's Republic of China), followed by SEARO, which has around a fifth of the world's smokers (influenced by India and Indonesia).

The number of smokers in any country is a function of both the prevalence of smoking and the size of the population. A further

Fig. 1.3 Proportion and cumulative percentage of smokers in high-burden countries, in men (A) and women (B) in 2009



From WHO (2011)

disaggregation of the regions by country shows that a few countries account for a large proportion of tobacco smokers. Ranked in descending order of the number of smokers, the five countries of China, India, United States of America (USA), Russian Federation and Indonesia account for about 52% of adult smokers in the world, with China and India alone accounting for 40% (Fig. 1.3). Furthermore, nearly two-thirds of the world's smokers live in only ten countries of the world.

1.3.3 Distribution of smokers by sex

With a global average smoking prevalence of 36%, men account for just over 80% of all smokers. The male adult prevalence is 4–5 times that for women, at 8%. This difference varies across WHO

regions. Smoking among men, concentrated in the five countries of China, India, Indonesia, Russian Federation and USA (Fig. 1.3), accounts for about 56% of global smoking among men. Women smokers are mostly concentrated in EURO and AMRO. These two regions account for 40% and 26% of all women smokers globally, respectively. The prevalences for women in these two regions are about half of those in men, whereas the difference is substantially greater in the other regions. Just as men smoke more than women everywhere, so too among young people, boys generally smoke more than girls. There is an increasing concern, however, that the gap may diminish, not because of a reduction in boys prevalence but because of an increase in the proportion of girls who are taking up smoking (Warren *et al.*, 2006).

1.3.4 The four stage smoking model

(a) The four stages of tobacco use

Lopez *et al.* (1994) used trend data on smoking prevalence and tobacco attributable mortality to show the evolution of tobacco use in a country. Four stages of smoking and attributable mortality have been identified to represent the growth and eventual decline of smoking among men and women (Fig. 1.4).

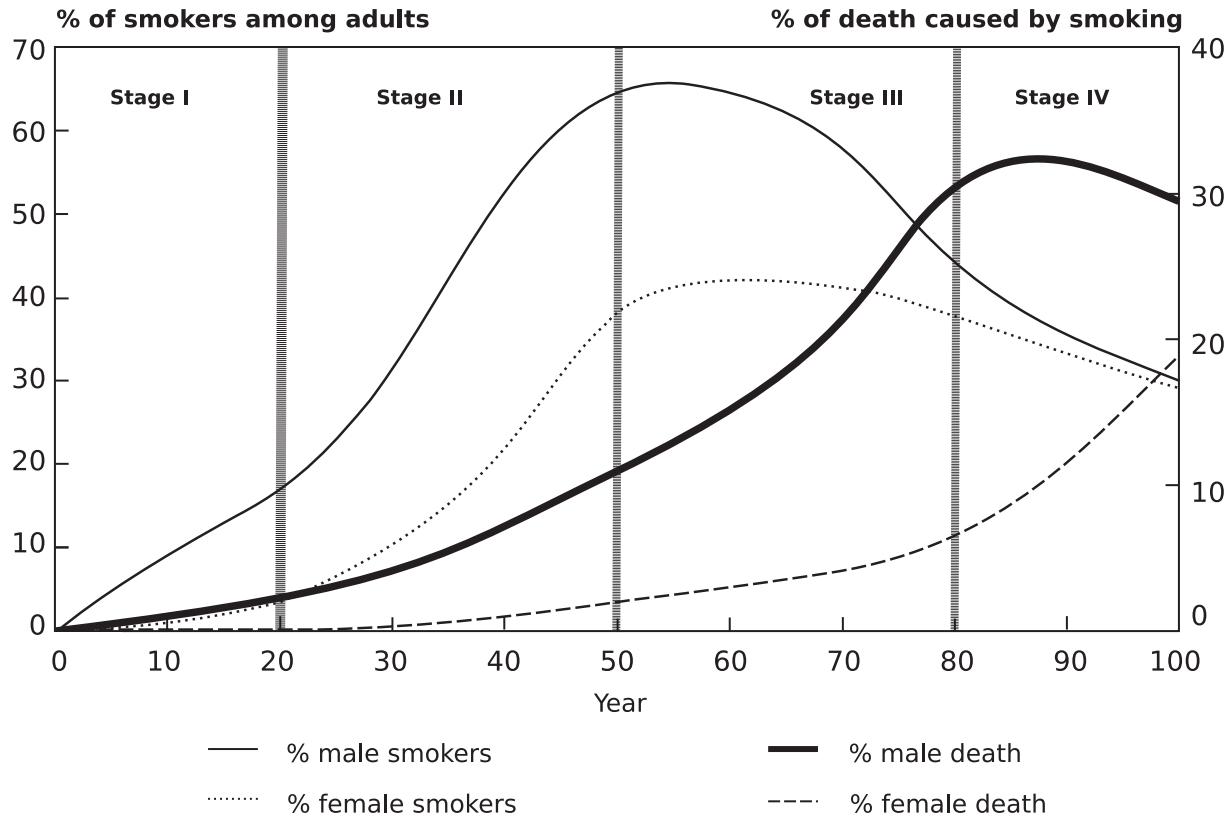
Stage 1 is characterized by low smoking prevalence in men (less than 15%) and very low in women (less than 10%). Death and disease from smoking are not apparent in this phase, as nearly all health effects from smoking are related to past smoking habits and their cumulative effects rather than current smoking. In Stage 2, smoking prevalence in men rapidly increases while it increases more slowly in women. Towards the end of this stage, smoking prevalence in men typically peaks to lie at 50–60%, with 10% of deaths in men attributable to smoking; deaths in women are comparatively fewer. After a protracted period of high smoking prevalence, Stage 3 shows a decline in smoking prevalence in men to around 40%. Smoking prevalence in women peaks and then begins to decline; towards the end of this stage the gap between men's and women's prevalence starts to narrow. However, smoking attributable deaths in men increase from around 10% to 25–30% within a span of three decades; in women the deaths are increasing but are still quite low. In the final Stage 4, smoking prevalences in both men and women continue to decline albeit relatively slowly in comparison with Stage 3, with the gap substantially narrowing to lie at around five percentage points, and as little as one percentage point in some countries. In Stage 4, smoking mortality in men peaks to between 30–35% and then declines to below 30% at the end of this period. In women, the health effects from past smoking persist, with increasing mortality, but remain lower than in men, and recently have begun to decline in some countries.

(b) Smoking prevalence worldwide

Using prevalence data for men and women collected in 2006 for 140 countries, WHO determined at which stage of the tobacco epidemic countries are in the model of Lopez *et al.* (1994). In Fig. 1.5, countries have been ranked by smoking prevalence in men in ascending order for Stages 1 and 2, and then in descending order for Stages 3 and 4. (Smoking prevalence in men is almost always higher than in women, with a few exceptions observed in the fourth stage.) While most countries fit the classification, there are a few exceptions, most of which in the last stage. Prevalence between Stage 3 and Stage 4 is discontinuous in both sexes. This is due to the classification followed, which puts countries with a relatively narrow difference in prevalence between men and women in Stage 4 even though their prevalence is largely comparable with those in Stage 3.

Most African countries fall in the first stage of the smoking model, characterized by low smoking prevalence in men and very low prevalence in women. Three of the five high burden

Fig. 1.4 The four stages of the tobacco epidemic



From Lopez *et al.* (1994)

countries fall in stage 2 (India, Indonesia and China), with the rest comprising a combination of countries from Africa, South East Asia, eastern Europe and the Middle East. At this stage smoking prevalences in women continue to remain very low, most countries having a prevalence in adult women of less than 10%.

Stage 3 includes the fourth high burden country (Russian Federation), along with countries in eastern Europe, South America and western Europe, which fall at the end of Stage 3. Stage 4 is populated entirely by the developed countries of western Europe, North America and Oceania. The USA, the fifth high burden country, fall in the last stage as a result of the relatively small difference in the smoking prevalence between men and women compared to the other intermediate stages. As mentioned before, Stage 4 includes countries where the smoking prevalence is higher in women than in men, with a small (< 8%) difference.

(c) Age-specific prevalence

Age-specific prevalence for men and women aged 15 years or older is presented for six representative countries for current smoking (Fig. 1.6). There are wide variations in age-specific prevalence between these countries. In men, prevalence varies from less than 10% to 75% in the 15–19 years age range to lie between 10% and 55% in the oldest age range. Prevalence among women varies from less than 1% to as high as 45% in young adults (15–19 years). Unlike men, prevalence in women tends to converge after age

Fig. 1.5 Prevalence of smoking in 140 countries in 2009, staged according to the model by Lopez

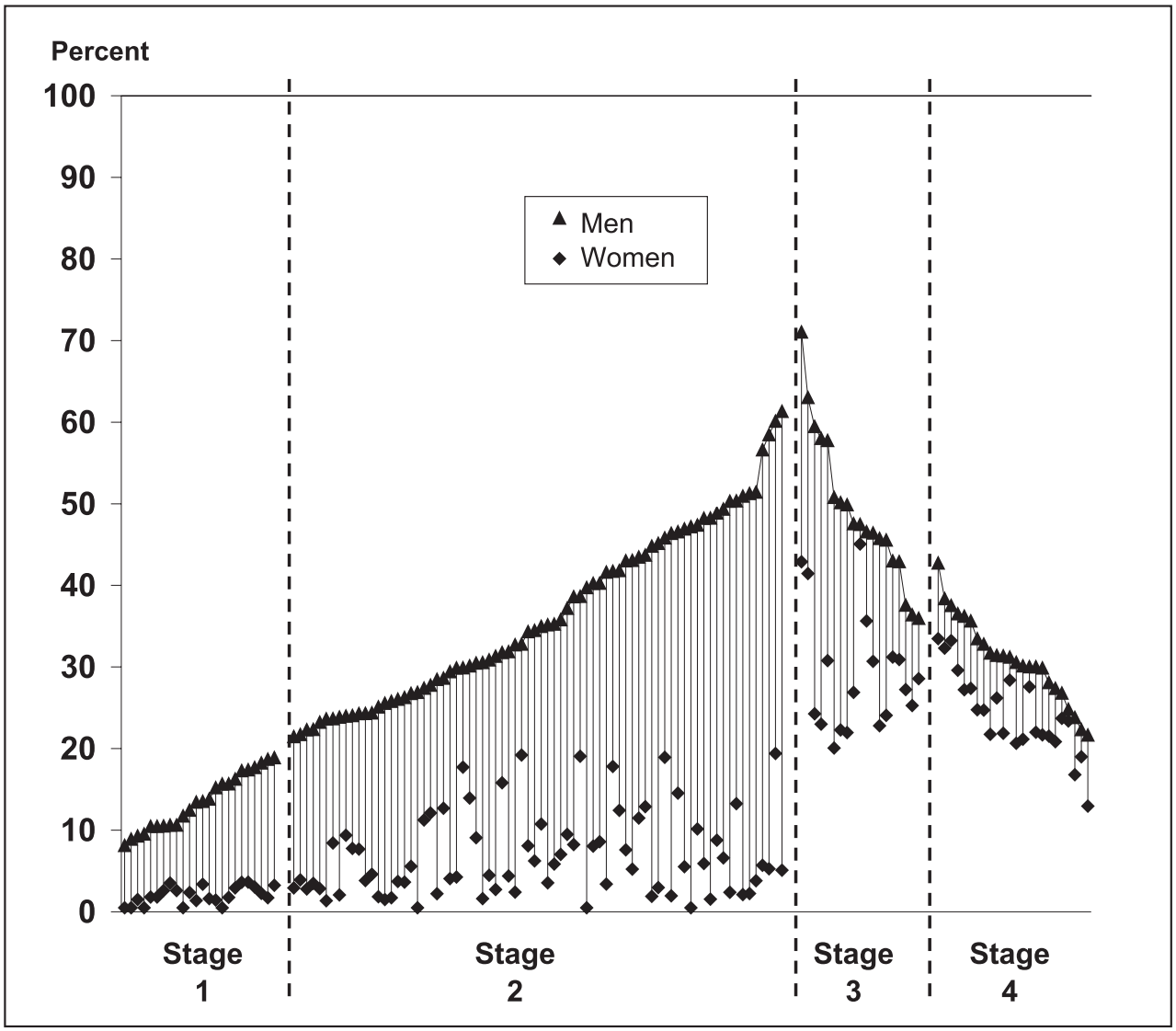
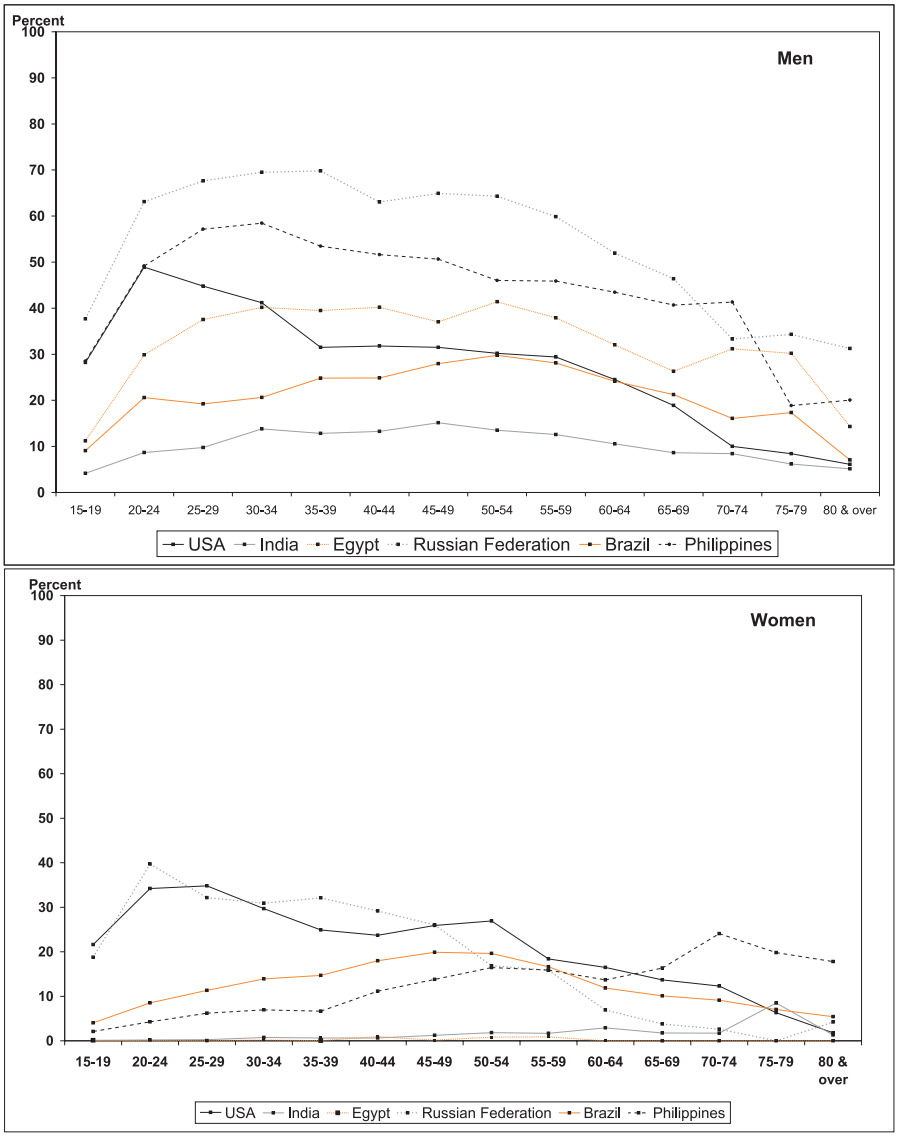


Fig. 1.6 Age-specific rates of smoking prevalence, in men and women in 2009



50, lying within 15 percentage points. Prevalence in women is almost always lower than in men in all age groups.

Initiation of smoking is shifting, and is taking place at earlier ages in both developed and developing countries. In developed countries, quitting smoking is also shifting to occur at a younger age, whereas in developing countries there is no such evidence.

(d) Smoking in youth

Information on smoking habits in youth are collected from a variety of youth surveys that include the Global Youth Tobacco Survey (GYTS), Global school-based Student Health Survey (GSHS) and Health Behaviour in School Aged Children (HBSC). Some countries have their own youth surveys, or have them as part of a general health or household survey, such as the Student Survey in Argentina, the Youth Smoking Survey in Canada, and New Zealand's Tobacco Survey.

The GYTS is a school-based survey designed to monitor tobacco use among youths aged 13 to 15 years. The GYTS uses a standard set of questions and sampling methods in over 160 countries. The survey has core questions that span seven thematic areas pertinent to tobacco. In addition to these, countries can include country-specific questions that allow assessment of tobacco use unique to the country. To assess prevalence of smoking, students are asked to report their smoking habits for both cigarettes and other tobacco products that they may have consumed over the past 30 days. Since its inception in 1999, the GYTS has covered over 2 million students. Although most GYTS are national surveys, in some countries they are limited to subnational locations. Further, countries conduct the GYTS in different years, rendering comparison for the same year difficult.

Prevalence of current tobacco use [including smokeless tobacco] in youth in 2004–09 for fourteen high burden low and middle income countries is shown in Fig. 1.7. The Russian Federation has the highest prevalence of current tobacco use among the high burden countries for which national data are available. Further, in the Americas and Europe the difference in prevalence between boys and girls is smaller than in other regions. In contrast, in Egypt, India and Thailand, prevalences in boys are significantly higher than in girls.

Fig. 1.8 shows the range of current tobacco use by WHO region for boys and for girls and for both sexes combined. There are wide variations in current tobacco use within each region. The largest variations are observed in EMRO and SEARO irrespective of sex, reflecting potentially disparate initiation rates in countries within the region. In AFRO, the range of current tobacco use between boys and girls is virtually the same. In some countries (e.g. Argentina, Peru, Sierra Leone, Bulgaria, Croatia, Cook Islands, New Zealand), tobacco use in girls exceeds that in boys; but overall boys and girls show remarkably similar propensity to take up tobacco use.

Warren *et al.* (2006) present global estimates and regional averages for current tobacco smoking in youth using GYTS data spanning 1999–2005. Their estimates show that one in five boys and one in seven girls currently smoke tobacco. Prevalence of current smoking for both boys and girls combined was highest in AMRO (22.2%) and lowest in WPRO (11.4%). AMRO have the highest average for current tobacco smoking for boys (24%) and for girls (20.4%) whereas the lowest prevalence was in WPRO among boys (15%) and in SEARO among girls (7.1%).

1.4 Regulations and policies: the WHO Framework Convention on Tobacco Control

The WHO Framework Convention on Tobacco Control (WHO FCTC) – the first multilateral evidence-based treaty on tobacco control

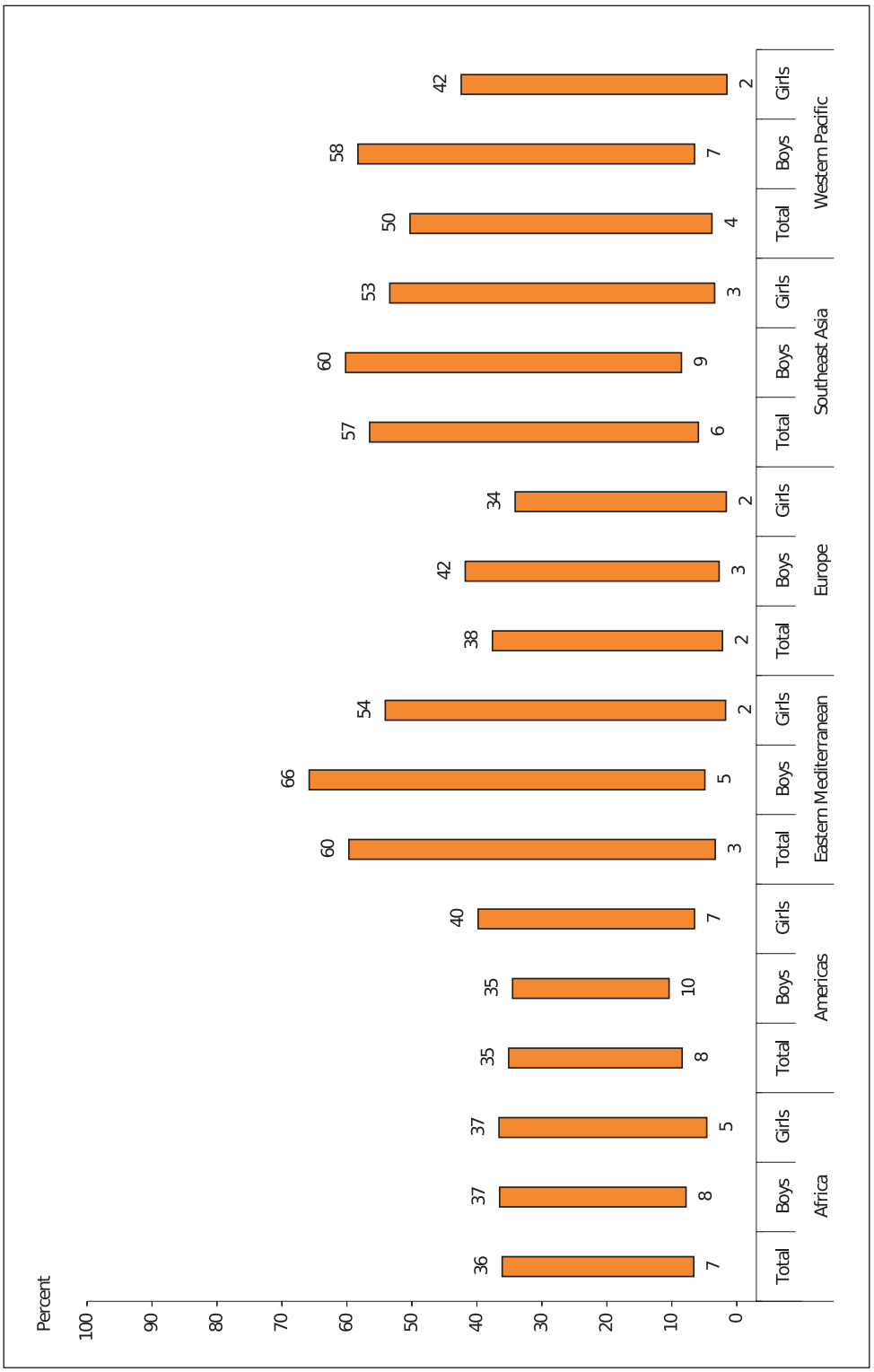
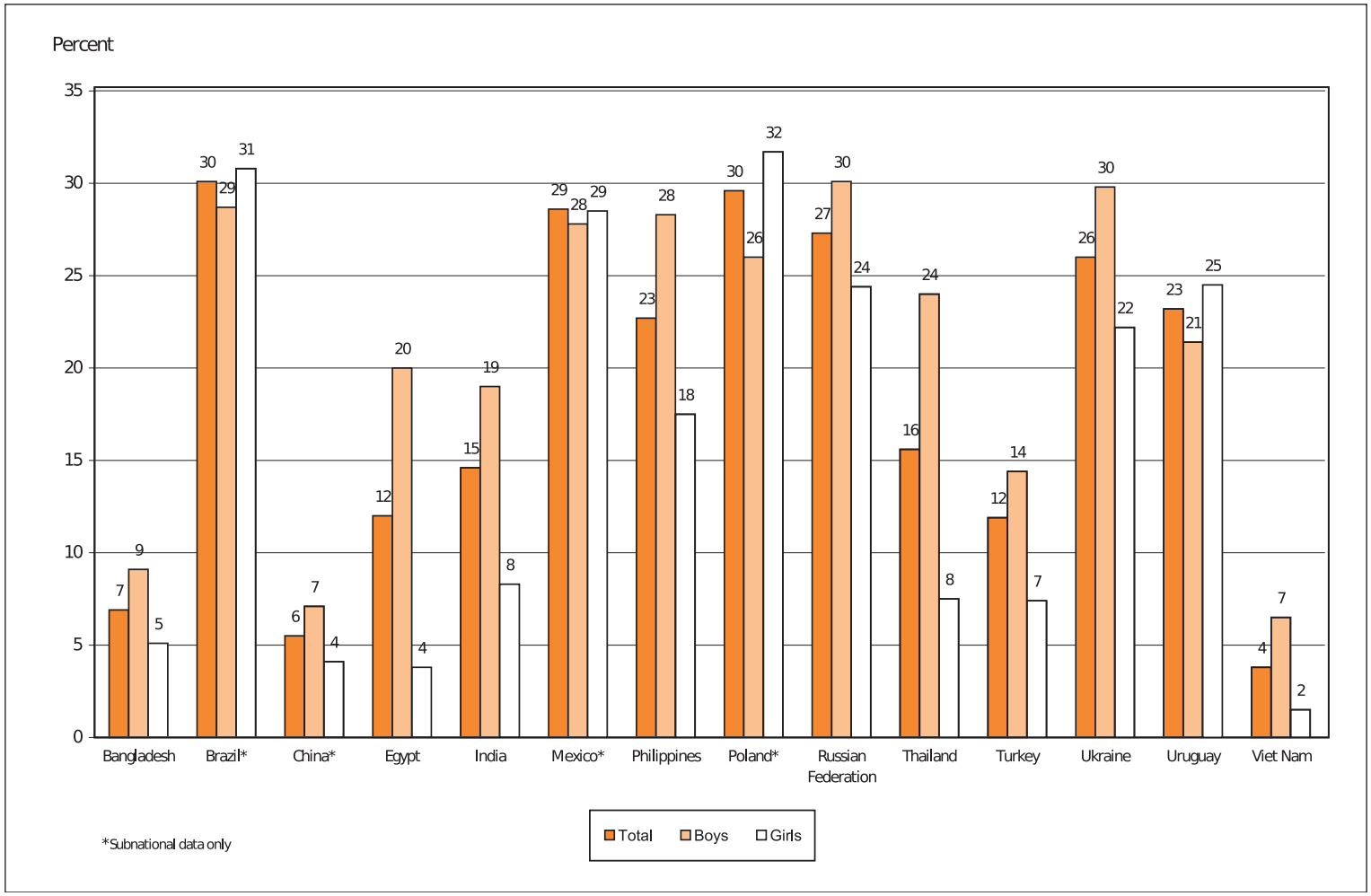


Fig. 1.7 Prevalence of current tobacco use in youth for selected countries, 2005–2009

Fig. 1.8 Range of prevalence of current tobacco use in youth, 2005–2009, by WHO region



Figures have been rounded off and show prevalences in countries with national and subnational jurisdiction.

– articulates tobacco control measures available to countries to counter the growing tobacco epidemic. This treaty, which entered into force in 2005, represents one of the most universal treaties in the United Nations history. In 2008, the WHO launched MPOWER, a technical assistance package comprised of six strategies that reflects one or more of the WHO FCTC measures and helps countries meet their commitments to the WHO FCTC.

2. Cancer in Humans

2.1 Introduction

The available knowledge on the relationship between tobacco smoking and a variety of human cancers is based primarily on epidemiological evidence. An immense amount of such evidence has been obtained, and only a small proportion can be referred to here. The cancers considered to be causally related to tobacco smoking in the previous *IARC Monograph* on tobacco smoking (IARC, 2004a) included lung, oral cavity, nasal cavity and paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, oesophagus (adenocarcinoma and squamous cell carcinoma), upper aerodigestive tract combined, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, cervix and myeloid leukaemia. In addition, it was concluded that there was evidence suggesting lack of carcinogenicity for cancers of the breast and of the endometrium.

Since 2002, there have been additional cohort and case–control studies on the relationship of tobacco smoking in different forms to these and other cancers in many countries. A large body of evidence has been obtained from cohort studies with respect to different cancer sites and types of tobacco product. These cohort studies are described briefly in Table 2.1 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.1.pdf), listed by country. Case–control studies are described in the sections pertaining to cancer sites. More studies are now available from countries and populations that are still at an early stage of the tobacco epidemic. These studies are prone to underestimate the true strengths of the association between tobacco smoking and any specific cancer as the full effect of duration of smoking cannot be evaluated.

2.2 Cancer of the lung

2.2.1 Overview of studies

The main cause of lung cancer in humans is tobacco smoking and most information establishing this fact comes from epidemiological studies in which the assessment of exposure was based on self-reported information on personal smoking habits via self-administered questionnaire or in-person interviews. Since the previous *IARC Monograph* (IARC, 2004a), numerous studies have been published on the issues of tobacco smoking and sex and racial/ethnic susceptibility, 'tar' yields as measured by machine smoking, the relationship between histological changes and the design of cigarettes, dose–response association, genetic susceptibilities and interactions.

2.2.2 Factors affecting risk

Recent epidemiological studies incorporating measures of smoking metabolites in serum or urine are helping to refine our understanding of exposure-response relationships with tobacco smoke. Dose–response evidence has been obtained from three cohort studies (Flanders *et al.*, 2003; Boffetta *et al.*, 2006; Yuan *et al.*, 2009; Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.2.pdf) and four pooled analyses (Lubin & Caporaso, 2006; Lubin *et al.*, 2007a, b, 2008; Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.3.pdf)

since the previous *IARC Monograph* (IARC, 2004a).

The US American Cancer Society Cancer Prevention Study-II (CPS-II) is the largest cohort study on smoking and lung cancer risk using questionnaire assessment of exposure (Flanders *et al.*, 2003). In this study cigarette smoking duration is a much stronger predictor of lung cancer mortality than is cigarette smoking intensity, regardless of age in both men and women. These results are qualitatively similar to those reported by Doll & Peto (1978) and are consistent with IARC (2004a).

In a questionnaire-based assessment of the association of tobacco smoking with lung cancer risk, smokers at higher smoking intensities seem to experience a "reduced potency" per pack such that for equal total exposure, the excess odds ratio per pack–year decreases with intensity (Lubin *et al.* 2008). Below 15–20 cigarettes/day, the excess odds ratio/pack–year increases with intensity (Lubin & Caporaso, 2006; Lubin *et al.*, 2007a) while above 20 cigarettes/day, there is an 'inverse-exposure-rate' effect (Lubin *et al.*, 2007a) suggesting a greater risk for total exposure delivered at lower intensity (or a longer duration) than the equivalent exposure delivered at a higher intensity. The intensity effects were also statistically homogeneous across diverse cancer types, indicating that after accounting for risk from total pack–years, intensity patterns were comparable for cancer of the lung, bladder, oral cavity, pancreas and oesophagus. These analyses suggest that the risk of lung cancer increases with increasing tobacco exposure at all dose levels, but there is some levelling-off effect at the highest intensity of tobacco smoking.

However, when serum cotinine was used as a measure of exposure to tobacco smoking, rather than questionnaire-based data, the odds ratio of lung cancer increased linearly over the full range of exposure from ≤ 5 ng/mL through ≥ 378 ng/mL, with an odds ratio of 55.1 (95% confidence interval (CI): 35.7–85.0) in the highest exposure group. These results suggest that the decreased rate of lung cancer risk at high intensity of tobacco smoke previously described is a statistical artefact. Such an effect may be due to an inaccurate assessment of total tobacco smoke exposure from questionnaire-based studies at high exposure levels (Boffetta *et al.*, 2006). Somewhat similar results were obtained when both 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and total cotinine in urine were measured in subjects of two large cohort studies from Shanghai men and Singapore men and women (Yuan *et al.*, 2009). Among smokers with comparable smoking histories (as noted in questionnaire data) there is a 9-fold variation in subsequent risk of lung cancer between those with high and those with low levels of total urinary NNAL and cotinine. Thus measurements of urinary cotinine and total NNAL at a single point in time in a smoker could substantially improve the predictive power of a lung cancer assessment model based solely on self-reported smoking history (number of cigarettes/day, number of years of regular smoking). A positive NNAL-lung cancer association of comparable magnitude was observed in both Shanghai and Singapore subjects despite differences in the NNK content of tobacco smoked. The independent association between total urinary cotinine and lung cancer risk, after adjustment for total urinary NNAL and smoking history, suggests that tobacco smoke compounds other than NNK play a role in lung cancer development in smokers. Further, a single measurement of urinary NNAL may closely predict the average level of NNAL measured over a much longer period of time.

2.2.3 Types of tobacco or of cigarette

(a) Tar levels

In a previous *IARC Monograph* (IARC, 1986), it was concluded on the basis of the case–control, cohort studies and ecological evaluations

available at the time that prolonged use of 'high-tar' and unfiltered cigarettes is associated with greater risks than prolonged use of filter-tipped and 'low-tar' cigarettes. More recently (IARC, 2004a), it has been recognized that the actual quantitative impact of reduced 'tar' and filter-tipped cigarettes is difficult to assess because of, respectively, the concomitant increase in tobacco-specific nitrosamines that accompanies the greater use of blend tobacco and the compensatory changes in smoking behaviour by smokers attempting to maintain their accustomed level of nicotine intake. Nevertheless, it was concluded that changes in cigarette types since the 1950s have probably tended to reduce the risk for lung cancer associated with tobacco smoking.

Additional refinement in assessing the health effects associated with smoking cigarettes of various tar content has been possible since the publication of the earlier reports. Compared with smokers of medium tar (15–21 mg) filtered cigarettes risk was higher among men and women who smoked high tar (≥ 22 mg) non-filtered brands but there was no difference in risk among men and women who smoked 'very low tar' or 'low tar' brands compared with those who smoked 'medium tar' brands (Harris *et al.*, 2004). Regardless of tar content of their cigarettes, all current smokers had a far greater risk for lung cancer than people who had stopped smoking or had never smoked (Harris *et al.*, 2004).

(b) Mentholated cigarettes

In the previous *IARC Monograph* (IARC, 2004a) the conclusion was drawn that there is no additional risk associated with smoking mentholated cigarettes when total consumption (pack–years) was controlled versus non-mentholated ones. Recent evidence supports that conclusion.

Mentholated cigarettes first appeared in the 1920s, but were not widely used until the mid-1950s (Bogen, 1929; Federal Trade Commission, 2001). Since the early 1970s, menthol varieties have accounted for 25–60% of all cigarettes sold in the USA (Federal Trade Commission, 2001). There are strong ethnic differences in the use of menthol cigarettes; more than 60% of Black smokers of both sexes use menthol brands compared to fewer than 25% of White smokers (Royce *et al.*, 1993; Hymowitz *et al.*, 1995). Studies have generally not demonstrated an increased risk of lung cancer for mentholated cigarettes versus non-mentholated cigarettes (Kabat & Hebert, 1994; Carpenter *et al.*, 1999; Brooks *et al.*, 2003; Stellman *et al.*, 2003). Recent evidence also suggests that users of mentholated cigarettes smoke fewer pack–years than those of non-mentholated cigarettes.

The higher incidence of lung cancer among Blacks is an important public health concern but the causes remain unclear. Mentholated cigarette use does not appear to explain the racial disparity observed in lung cancer risk among those having the same total tobacco consumption.

2.2.4 Histology

Compiled databases from IARC and other sources indicated that squamous cell carcinoma rates [per 100000 person-years] among men declined by 30% or more in North America and some European countries between 1980–82 and 1995–97, while changing less dramatically in other areas; small cell carcinoma rates decreased less rapidly. In contrast, the proportion of adenocarcinoma cases rose among men and women in virtually all areas, with the increases among men exceeding 50% in many areas of Europe (Devesa *et al.*, 2005).

Based on a comparison of two large cohort studies initiated by the American Cancer Society (ACS) (CPS-I and CPS-II) in 1960 and 1980, respectively, a stronger association between smoking and adenocarcinoma was observed in recent compared to earlier follow-up periods (Thun & Heath, 1997). Additionally, an association between cigarette smoking and bronchioloalveolar carcinoma was also found in several

studies (Falk *et al.*, 1992; Morabia & Wynder, 1992).

A meta-analysis of 8 cohort and 14 case–control studies conducted in Japan among active smokers indicated significant excess lung cancer risks among men for both squamous cell carcinoma (relative risk (RR), 11.7) and adenocarcinoma (RR, 2.30). Among women the risks were 11.3 for squamous cell carcinoma and 1.37 for adenocarcinoma (Wakai *et al.*, 2006).

2.2.5 Population characteristics

(a) Sex

Meta-analyses on sex-specific susceptibility to lung cancer associated with tobacco smoking are presented in Table 2.4 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.4.pdf) and cohort studies in Table 2.5 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.5.pdf).

In the 1990s, two case–control studies indicated that relative risks for lung cancer associated with specific amounts and duration of cigarette smoking may be higher among women than among men (Risch *et al.*, 1993; Zang & Wynder, 1996).

In the large NIH-AARP [National Institutes of Health-American Association of Retired People] cohort (Freedman *et al.*, 2008), smoking was associated with lung cancer risk in both men and women. Age-standardized incidence rates for lung cancer tended to be higher in men than in women with comparable smoking histories (for current smokers and for quitters of less than 10 years), and in cases with squamous cell tumours. However, lung cancer risk was generally similar between men and women.

In a joint analysis, results from the Nurses' Health Study of women and the Health Professionals Follow-up Study in men (Bain *et al.*, 2004) suggest little difference in lung cancer susceptibility between men and women given equal smoking exposure. The hazard ratio in women ever smokers compared with men was 1.11 (95%CI: 0.95–1.31).

Serum cotinine levels were analysed in lung cancer cases and controls (Boffetta *et al.*, 2006). The lung cancer odds ratios (ORs) estimated for men and women were very similar for those with comparable serum cotinine levels. Other studies that have carefully quantified tobacco exposure via self-administered questionnaire or interview provide additional evidence of a comparable increase in lung cancer risk in the two sexes (Kreuzer *et al.*, 2000; Flanders *et al.*, 2003; Bain *et al.*, 2004).

In a meta-analysis of observational studies on cigarette smoking and cancer from 1961–2003 (conducted on 177 case–control studies, 75 cohort studies and two nested case–control studies), dose–response estimates were available in 44 studies: 19 with estimates for men only, 11 with estimates for women only and 14 with separate estimates for men and women (Gandini *et al.*, 2008). Overall, the risk of lung cancer for men and women increased by 7% for each additional cigarette smoked per day (RR, 1.07; 95%CI: 1.06–1.08). The increased risk appears to be slightly higher in women (RR, 1.08; 95%CI: 1.07–1.10) than in men (RR, 1.07; 95%CI: 1.05–1.08) ($P < 0.001$; adjusting for study type).

(b) Ethnicity

It has been postulated that susceptibility to lung cancer from tobacco smoking may differ by race and ethnicity (Schwartz & Swanson, 1997; Peto *et al.*, 1999; Stellman *et al.*, 2001; Kiyohara *et al.*, 2004, 2005, 2006; Pinsky, 2006; Wakai *et al.*, 2006; Vineis *et al.*, 2007; Takahashi *et al.*, 2008; Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.6.pdf). Lung cancer incidence rates vary considerable across racial/ethnic groups in the USA and elsewhere. Black men have higher rates than white men, while Hispanics, Asians and American Indians of both sexes have lower rates than whites (Stellman *et al.*, 2003; SEER, 2004).

Nutritional habits, smoking patterns, type of tobacco smoked and genetic factors may play a role in such differences between racial and ethnic groups.

The association of tobacco smoking and lung cancer does not appear to be as strong among Japanese as among populations of North America or Europe (Wakai *et al.*, 2006). In a meta-analysis of 8 cohort studies and 14 case–control studies conducted in Japan, the excess lung cancer risks observed for both men (RR, 4.39; 95%CI: 3.92–4.92) and women (RR, 2.79; 95%CI: 2.44–3.20) in both case–control and cohort studies were lower than would have been expected from studies in North America and Europe. The lower lifetime consumption of cigarettes in Japanese, due in part to a later initiation of smoking and a lower consumption per day has been suggested to explain this. Other differences that may have etiological significance include tobacco ingredients, different filters on cigarettes, lifestyle factors including diet, and possibly differences in genetic susceptibility. [The Working Group noted that North American or European populations were not directly included in any of these studies.]

Data from the Asian Pacific Cohort Studies Collaboration, 31 studies involving 480125 persons, evaluated the risk of death from lung cancer associated with smoking habits in Australia, New Zealand and Asia (Huxley *et al.*, 2007b). Among Asian men the hazard ratio was 2.48 versus 9.87 in men in Australia and New Zealand. Among women, the corresponding estimates were 2.35 and 19.33, respectively. [In these studies, Asian populations smoked fewer cigarettes for a shorter period of time compared to those in Australia and New Zealand.]

Based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER), Chinese women residing in the USA have a fourfold increased risk of lung cancer, and Filipino women a twofold increased risk, compared to that expected based on rates in non-Hispanic whites in the USA with a similar amount of cigarettes smoked (Epplein *et al.*, 2005). Among Chinese women, the increased risk was largely restricted to adenocarcinoma and large cell undifferentiated carcinoma. Chinese females residents of the western US mainland have a much higher risk of lung cancer than would be expected from their tobacco use patterns, just as they do in Asia (Peto *et al.*, 1999; Epplein *et al.*, 2005), the reason for these difference have not been identified. [Controlling for potential confounding factors was limited using aggregate data from SEER.]

Age, sex and race-specific risks of lung cancer mortality among lifetime non-smokers were compared in the two large ACS Cancer Prevention Study cohorts (CPS-I; CPS-II). The mortality rate was higher among African American women than among white women in CPS-II (hazard ratio (HR), 1.43; 95%CI: 1.11–1.36) (Thun *et al.*, 2006). This suggests an inherent susceptibility difference between white and black women but it could also be explained by access to care, diet, or exposure to environmental carcinogens.

The risk for lung cancer associated with cigarette smoking in 183813 African-American, Japanese-American, Latino, native Hawaiian and white men and women was examined in the Multiethnic Cohort Study in the USA (Haiman *et al.*, 2006). Information on demographic factors, smoking status, cigarettes/day smoked, years of smoking, years since quitting, diet, occupations, educational level and racial and ethnic group were collected for all subjects through a self-administered questionnaire at enrolment. Information about age of smoking initiation and cessation rates were collected on a subgroup of 5090 study subjects. Incident lung cancer cases were identified by linkage to the SEER cancer registries covering California and Hawaii. Among those who smoked no more than 10 cigarettes/day and those who smoked 11–20 cigarettes/day, relative risks ranged from 0.21 to 0.39 ($P < 0.001$) among Japanese Americans and Latinos and from 0.45

to 0.57 ($P < 0.001$) among whites as compared with African Americans. However, at levels exceeding 30 cigarettes/day, differences between racial/ethnic groups were no longer significant. The differences in lung cancer risk by racial group associated with smoking were observed for both men and women and for all histological types of lung cancer. These findings could not be explained by differences between populations in other known or suspected risk factors, including diet, occupation, and education level or by age at starting smoking or cessation of smoking.

Polymorphisms in glutathione-*S*-transferase (GST), GSTM1, GSTT1 and GSTP1 genes in humans are associated with reduction of enzymatic activity towards several substrates, including those found in tobacco smoke. In a population based case–control study involving early-onset lung cancer, African Americans carrying at least one G allele at the GSTP1 locus were more likely to have lung cancer compared with African Americans without a G allele after adjustment for age, sex, pack–years of smoking and a history of lung cancer in a first degree relative (OR, 2.9; 95%CI: 1.29–6.20). African Americans with either one or two risk genotypes at the GSTM1 (i.e. null genotype) and GSTP1 loci were at increased risk of having lung cancer compared with those having fully functional GSTM1 and GSTP1 genes (one risk genotype: OR, 2.8; 95%CI: 1.1–7.2 and two risk genotypes: OR, 4.0; 95%CI: 1.3–12.2). No significant single gene associations between GSTM1, GSTT1 and GSTP1 and early-onset lung cancer were observed in Caucasians, after adjusting for age, sex, pack–years and a family history of lung cancer (Cote *et al.*, 2005).

The cytochrome P450 (CYP) superfamily of enzymes catalyses one of the first steps in the metabolism of carcinogens such as polycylic aromatic hydrocarbons, nitroaromatics and arylamines. A population-based case–control study of lung cancer in the metropolitan Detroit area found that neither CYP1A1 MspI nor CYP1A1 Ile^{462}Val was associated with lung cancer susceptibility among Caucasians or African Americans. Among Caucasians, however, CYP1B1 Leu^{432} Val was significantly associated with lung cancer susceptibility (OR for at least one Val allele, 2.87; 95%CI: 1.63–5.07). Individuals with both this polymorphism and exposure to second-hand tobacco smoke were at particularly high risk for lung cancer. Combinations of particular CYP1B1 polymorphisms appeared to increase risk, although no combination differed significantly from the risk associated with CYP1B1 Leu^{432} Val alone (Cote *et al.*, 2005; Wenzlaff *et al.*, 2005).

The hypothesis that polymorphisms in TP53 may modulate the risk for lung cancer associated with tobacco smoke was evaluated in a case–control study of lung cancer in Baltimore, Maryland. African-Americans with Pro-T-A-G-G haplotype (combining the polymorphisms TP53_01 (rs1042522), TP53_65 (rs9895829), TP53_66 (re2909430), TP53_16 (rs1625895), and TP_11 (rs12951053)) had both an increased risk for lung cancer (HR, 2.32; 95%CI: 1.38–4.10) and a worsened lung cancer prognosis (HR, 2.38; 95%CI: 0.38–4.10) compared with those having the Arg-T-A-G-T haplotype. No association of TP53 polymorphisms with lung cancer was observed in Caucasians (Mechanic *et al.*, 2007). Common genetic variation in TP53 could modulate lung cancer pathways in African Americans. Differences in lung cancer susceptibility may exist based on race, tobacco exposure and selected genetic polymorphisms (Mechanic *et al.*, 2007).

2.2.6 Interactions

(a) Diet and exercise

Antioxidant vitamins, carotenoids, isothiocyanates, total dietary vegetables and fruit, and physical exercise have been associated with a decreased risk for cancer in some studies but the overall protective effect of diet and exercise account for only a small fraction of the total risk associated with tobacco smoking.

The association of fruit and vegetable with lung cancer incidence among both smokers and non-smokers was evaluated in the European Prospective Investigation into Cancer and Nutrition (EPIC). In current smokers lung cancer risk was significantly decreased with higher vegetable consumption, the hazard ratio being 0.78 (95%CI: 0.62–0.98) per 100 g increase in daily vegetable consumption, and 0.90 (95%CI: 0.81–0.99) per 100 g fruit (Linseisen *et al.*, 2007). While overall consumption of fruits and vegetables was not found to be protective of lung cancer in the NIH-AARP Diet and Health Study, higher consumption of several botanical subgroups (i.e. rosaceae, convolvulaceae, and umbelliferae) was significantly inversely associated with risk, but only in men (Wright *et al.*, 2008).

Cruciferous vegetables (i.e. broccoli, cabbage, cauliflower, Brussels sprouts, kale) are rich in isothiocyanates and have been hypothesized to have anticancer properties that may contribute to reduced risk for lung cancer. Isothiocyanates may inhibit the bioactivation of procarcinogens found in tobacco smoke such as polycyclic aromatic hydrocarbons and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (Hecht, 2000). Isothiocyanates may also enhance excretion of carcinogenic metabolites before they can damage DNA (Gasper *et al.*, 2005). Furthermore, sulforaphane, a major isothiocyanate found in broccoli, can induce cell cycle arrest and apoptosis (Seow *et al.*, 2005). GSTM1 and GSTT1 encode isoenzymes that play an important role in xenobiotic metabolism (Hecht, 2000). Individuals with homozygous deletion of GSTM1 and GSTT1, or both may metabolize isothiocyanates less efficiently and may be more intensely exposed to isothiocyanates after consumption of cruciferous vegetables. Epidemiological evidence from 30 studies on the association between lung cancer and either total cruciferous vegetable consumption (6 cohort and 12 case–control studies) or specific cruciferous vegetables (1 cohort and 11 case–control studies) was recently evaluated (Lam *et al.*, 2009). The risk for lung cancer among those in the highest category of total cruciferous vegetable intake was 22% lower in case–control studies (pooled OR, 0.78; 95%CI: 0.70–0.88) and 17% lower in cohort studies (pooled RR, 0.83; 95%CI: 0.62–1.08). The strongest inverse association of total cruciferous vegetable intake with lung cancer was seen among individuals with GSTM1 and GSTT1 double null genotypes (OR, 0.41; 95%CI: 0.26–0.65; p for interaction = 0.01). The inverse association was observed in both smokers and non-smokers.

The potential role of vitamin A in the development of lung cancer attracted early research interest (Bjelke, 1975). Carotenoids were thought to have anti-cancer properties and early evidence from case–control studies tended to support an inverse association of lung cancer incidence with β-carotene intake and with serum concentrations of β-carotene. However, the case–control design is not ideal for assessing the effect of serum carotenoids as a risk factor for lung cancer risk since the disease is likely to effect serum levels. In a meta-analysis of six randomized clinical trials and 25 prospective observational studies, Gallicchio *et al.* (2008) computed a pooled relative risk for studies comparing β-carotene supplements with placebo of 1.10 (95%CI: 0.89–1.36). Among observational studies, the pooled relative risk for total carotenoid dietary intake from six studies was 0.86 (95%CI: 0.75–0.99) among current smokers. For dietary intake of β-cryptoxanthin, data from six studies gave a pooled relative risk among smokers of 0.75 (95%CI: 0.58–0.96). No other carotenoids significantly reduced the risk in current, former or never smokers.

Based on a review of the literature, antioxidant vitamins show no clear protective effect on lung cancer risk in smokers or non-smokers, although there was some, albeit inconsistent, evidence pointing to a protective role for vitamin C and E. No clear protective role was observed for vitamin A (Ruano-Ravina *et al.*, 2006).

Increased physical activity has been associated with a reduction in the incidence and mortality from all-site cancer and some site-specific cancers in studies of non-smokers, but less is known about whether physical activity is associated with similar risk reduction in smokers. Several early studies suggested that physical activity is associated with decreased risk of lung cancer in men and women after adjusting for smoking, with risk reductions estimated from 18% (Peterson *et al.*, 2001) to 62% (Kubík *et al.*, 2001). The effect of physical activity on lung cancer risk was assessed in a sample drawn from participants in the Beta-Carotene and Retinol Efficacy Trial. The results suggested that physical activity may play a small role in reducing cancer risk and mortality among those with significant tobacco exposure. The incidence of lung cancer and of all cancer sites combined seemed to be more attenuated by exercise in men than in women, while the attenuation in lung cancer mortality was greater in women than in men. These effects may be more pronounced for younger people and may differ inconsistently by pack–years of smoking (Alfano *et al.*, 2004).

(b) Radon

In a pooled analysis of data from 13 case–control studies of residential radon and lung cancer from nine European countries (7148 cases of lung cancer and 14208 controls), the dose–response relation seemed to be linear with no threshold and remained significant in analyses limited to individuals from homes with measured radon < 200 Bq/m^3. The absolute risks of lung cancer by age 75 years at radon concentrations of 0, 100, and 400 Bq/m^3 would be about 0.4%, 0.5% and 0.7%, respectively, for lifelong non-smokers, and about 25 times greater (10%, 12% and 16%) for cigarette smokers. These studies show appreciable hazards from residential radon, particularly for smokers and recent ex-smokers (Darby *et al.*, 2005). Similar risks were identified in a pooling project of North American case–control studies (Krewski *et al.*, 2005).

(c) Asbestos

Exposure to asbestos and tobacco smoking are both known causes of lung cancer in humans (Doll & Peto, 1978; de Klerk *et al.*, 1996). Some studies suggest a multiplicative effect [where the effect of asbestos exposure is a multiple of the effect of smoking] (Hammond *et al.*, 1979; Doll & Peto, 1985), and meta-analyses have suggested that the additive model [where asbestos exposure and smoking are independent of each other] is unsound (Lee, 2001; Liddell, 2001). In a recent study of 2935 asbestos miners, persons exposed to asbestos and tobacco who subsequently quit smoking remained at a 90% increased risk of lung cancer up to 20 years after smoking cessation, compared to never-smoker asbestos workers (Reid *et al.*, 2006a).

(d) Genetic polymorphisms

Lung cancer is plausibly caused by the interplay between environmental factors and several low-risk alleles. Attempts in identifying specific single nucleotide polymorphisms (SNPs) responsible for modulating lung cancer risk have yielded few conclusive results. Recent studies have focused on mechanistically plausible polymorphisms in genes coding for enzymes involved in the activation, detoxification and repair of chemical damage caused by tobacco smoke. Genetic association studies indicate that several inherited genetic polymorphisms may be associated with lung cancer risk, but the data from individual studies with low statistical power are conflicting. Evidence from pooled or meta-analyses, along with some individual studies, is briefly summarized below.

(i) Metabolic genes

Most of the 70 carcinogens in tobacco smoke are procarcinogens that must be activated by phase I enzymes and may then be deactivated by

phase II enzymes. Polymorphisms that alter the function of the genes involved in the activation or detoxification of tobacco smoke carcinogens can potentially influence an individual's risk of developing a tobacco-related cancer.

Meta and pooled analyses of 34 case–control, genotype-based studies were conducted to assess the effect of GSTT1 genotypes and smoking on lung cancer risk. No significant interaction was observed (Raimondi *et al.*, 2006). A pooled analysis of 21 case–control studies from the International Collaborative study of Genetic Susceptibility to Environmental Carcinogens showed no evidence of increased risk for lung cancer among carriers of the GSTM1 null genotype and there was no evidence of interaction between GSTM1 genotype and either smoking status or cumulative tobacco consumption (Benhamou *et al.*, 2002). Similarly, in another pooled analysis the summary OR indicated the slow acetylator genotype of N-acetyltransferase 2 (NAT2) detoxification enzyme was not associated with lung cancer risk among Caucasians (Borlak & Reamon-Buettner, 2006). In a pooled analysis to test the hypothesis of interaction among genetic variants in increasing the individual risk for cancer, the cumulative effect of variants in three metabolic genes, CYP1A1, GSTM1 and GSTT1 was assessed. The risk for lung cancer was increased with the combination of CYP1A1*2B or CYP1A1*4 alleles and the double deletion of both GSTM1 and GSTT1 up to an OR of 8.25 (95%CI: 2.29–29.77). The combination including CY1A1*4 among never smokers was associated with an OR of 16.19 (95%CI: 1.90–137). These estimates did not change after adjustment by the number of cigarettes smoked and duration of smoking. The results were consistent across ethnicities and were approximately the same for adenocarcinoma and squamous cell carcinoma (Vineis *et al.*, 2007).

Microsomal epoxide hydrolase 1 (EPHX1) plays an important role in both the activation and detoxification of tobacco-derived carcinogens. Polymorphisms at exons 3 and 4 of the EPHX1 gene have been reported to be associated with variations in EPHX1 activity. In a meta-analysis of 13 case–control studies the low-activity (variant) genotype of EPHX1 polymorphism at exon 3 was associated with decreased risk for lung cancer (OR, 0.65; 95%CI: 0.44–0.96) among whites. In white-populations, the high activity (variant) genotype of EPHX1 polymorphism at exon 4 was associated with a modest increased risk of lung cancer (OR, 1.22; 95%CI: 0.79–1.90) and the predicted low activity was associated with a modest decrease in risk (OR, 0.72; 95%CI: 0.43–1.22) (Kiyohara *et al.*, 2006).

(ii) DNA repair and cell cycle pathways

Data from 14 studies of lung cancer were used in a pooled analysis focusing on 18 sequence variants in 12 DNA repair genes, including APEX1, OGG1, XRCC1, XRCC2, XRCC3, ERCC1, XPD, XPF, XPG, XPA, MGMT and TP53 (Hung *et al.*, 2008a). None of the variants appeared to have a large effect on lung cancer risk. In a recent meta-analysis the X-ray repair cross-complementing protein group 3 (XRCC3) and the xeroderma pigmentosum group D (XPD)/excision repair cross-complementing group 2 (ERCC2) genes were evaluated (Manuguerra *et al.*, 2006). The authors found no association between these genes and the cancer sites investigated (skin, breast and lung). A significant association was identified for XPD/ERCC2 single nucleotide polymorphisms (codons 312 and 751) and lung cancer.

(iii) Nicotine acetylcholine receptor genes

A series of large genome-wide association studies for lung cancer have identified susceptibility loci for lung cancer in chromosome arms 5p, 6p and 15q (Landi *et al.*, 2009). In particular, the susceptibility locus at chromosome region 15q25 includes several genes, including three that encode nicotinic acetylcholine receptor subunits (CHRNA5, CHRNA3 and CHRNB4). Nicotinic acetylcholine receptor subunit genes

code for proteins that form receptors present in neuronal and other tissue, in particular alveolar epithelial cells, pulmonary neuroendocrine cells, and lung cancer cell lines (Wang *et al.*, 2001; Minna, 2003) and bind to nicotine and nicotine derivatives including NNN. An association of CHRNA3 and CHRNA5 variants with nicotine dependence has been reported (Saccone *et al.*, 2007; Berrettini *et al.*, 2008). These genes may act, at least partially, upon cigarette smoking. Current smokers with one or two copies of the susceptibility variant are likely to smoke between one and two cigarettes more a day (Spitz *et al.*, 2008). Evidence for an effect of the 15q25 locus among never smokers is conflicting, with an association found in one study in Europe (Hung *et al.*, 2008b) and one in Asia (Wu *et al.*, 2009a), but not in others. Whether genes in the 15q25 locus have an effect on lung cancer beyond their propensity to increase numbers of cigarettes smoked is unclear.

Three genome-wide association studies identified genetic factors that modified disease risk. The first was a genome-wide association analysis to identify genetic polymorphisms associated with lung cancer risk in 1154 lung cancer patients of European ancestry who were current or former smokers and 1137 control subjects who were frequency matched to the lung cancer patients by age, sex, race and smoking status. Two SNPs, rs105173 and rs803419, which mapped to a region of strong linkage disequilibrium within 15q25.1, were strongly associated with risk of lung cancer, with an odds ratio for rs105173 of 1.31 ($P = 9.84 \times 10^{-6}$). This finding was replicated with an additional 711 case subjects and 632 control subjects from Texas ($P = 0.00042$) and in 2013 case subjects and 3062 control subjects in the United Kingdom ($P = 2.33 \times 10^{-10}$). The region of interest encompasses the nicotinic acetylcholine receptor subunit genes CHRNA3 and CHRNA5 (as well as CHRNB4) (Spitz *et al.*, 2008). A second genome-wide association study conducted among 1989 lung cancer cases and 2625 controls from six central European countries confirm these results (Hung *et al.*, 2008a). In a third genome-wide association study of 665 Icelandic, 269 Spanish and 90 Dutch lung cancer cases and 32244 controls a common variant in the nicotinic acetylcholine receptor gene cluster [chromosome region 15q24] was significantly associated with lung cancer risk (OR, 1.31; 95%CI: 0.1.19–1.44). The variant was observed to have a significant effect on the number of cigarettes smoked per day (Thorgeirsson *et al.*, 2008). These studies have all shown a link between this variant and lung cancer risk either through a mechanism involving nicotine dependence or a direct role in downstream signalling pathways that promote carcinogens. Together these results provide compelling evidence of a locus at 15q25 and 15q24 predisposing to lung cancer.

(iv) Alpha(1)-antitrypsin

Alpha(1)-antitrypsin deficiency (α(1)ATD) is one of the most common genetic disorders, especially among European descendents. Recent results suggest that α(1)ATD carriers are at a 70–100% increased risk of lung cancer, accounting for 11% to 12% of patients with lung cancer (Yang *et al.*, 2008). [The specific effect by smoking status was not evaluated.]

(v) Other genes

Mutations in the checkpoint CHEK2 gene have been associated with increased risk of breast, prostate and colon cancer and a decreased risk of lung cancer among those with the I157T missense variant of the CHEK2 gene. In a large Polish case–control study CHEK2 mutations were protective against lung cancer (OR, 0.3; 95%CI: 0.2–0.5) (Cybulski *et al.*, 2008).

The Swedish Family-Cancer Database was used to compare the rate of lung cancers among persons without family history of lung cancer to those with a family history (Li & Hemminki, 2004). A high risk by family history in adenocarcinoma (standardized incidence ratio (SIR),

2.03) and large cell carcinoma (SIR, 2.14) was found, a slightly lower risk among patients with squamous cell carcinoma (SIR, 1.63) and small cell carcinoma (SIR, 1.55). Among siblings, an increased risk was shown for concordant adenocarcinoma and small cell carcinoma at all ages and for all histological types when cancer was diagnosed before age 50. At young age, risks between siblings were higher than those between offspring and parents. These data suggest that a large proportion of lung cancers before age 50 are heritable and due to a high-penetrant recessive gene or genes that predispose to tobacco carcinogen susceptibility.

(e) Viral infection

Data are limited regarding lung cancer risk in human immunodeficiency virus (HIV)-infected persons with modest immune suppression, before the onset of acquired immunodeficiency syndrome (AIDS). Among 57350 HIV-infected persons registered in the USA during 1991–2002 (median CD4 counts 491 cells/mm^3), 871 cancers occurred. Risk was elevated for several non-AIDS defining malignancies, including cancer of the lung (SIR, 2.6 [n = 109]) (Engels *et al.*, 2008). [Specific evaluation with smoking status was not performed.]

2.3 Cancers of the upper aerodigestive tract

Evidence relating to cancers of the upper aerodigestive tract obtained from relevant cohort and case–control studies on specific sites is described in Sections 2.3.1 to 2.3.6; studies that looked at several subsites combined are described in Section 2.3.7. The major potential confounders for the relationship between smoking and cancers of the upper aerodigestive tract are alcohol consumption and use of any form of smokeless tobacco, and for some sites infection with human papillomavirus (HPV) (especially HPV16). In general, the studies examined by the Working Group had adjusted for these two confounders when appropriate. Some studies also adjusted for dietary intake, especially of fruits and vegetables, although few reported stratified relative risks.

2.3.1 Cancer of the oral cavity

Tobacco smoking was found to be causally related to oral cancer (IARC, 1986, 2004a). New studies on the relationship between oral cancer and cigarette smoking published since the most recent *IARC Monograph* (IARC, 2004a) include four cohort studies (Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.7.pdf), and eight case–control studies (Tables 2.8–2.11 online; see below).

(a) Intensity and duration of smoking

Intensity of smoking was measured in almost all cohort (Table 2.7 online) and case–control studies (IARC 2004a; Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.8.pdf and Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.9.pdf). In addition to the number of cigarettes or amount of tobacco smoked daily, cumulative exposure to cigarette smoke was also measured in terms of pack–years, tobacco-years or lifetime tobacco consumption. The link between duration of cigarette consumption and oral cancer was examined in 15 case–control studies. Seven case–control studies also considered age at starting smoking.

One cohort study (McLaughlin *et al.*, 1995) and 14 case–control studies reported a dose-dependent increase in risk with increasing number of cigarettes smoked daily or increasing daily tobacco consumption (Franceschi *et al.*, 1990, 1992, 1999; Nandakumar *et al.*, 1990; Zheng *et al.*, 1990; Choi & Kahyo, 1991; Oreggia *et al.*, 1991; Bundgaard *et al.*, 1995; Zheng *et al.*, 1997; De Stefani *et al.*, 1998; Hayes *et al.*, 1999; De Stefani

et al., 2007; Subapriya et al., 2007; Muwonge et al. 2008). Whenever analysed, the trend was always statistically significant (Franceschi et al., 1990, 1992; Oreggia et al., 1991; Bundgaard et al., 1995; McLaughlin et al. 1995; Hayes et al., 1999; Subapriya et al., 2007), except in the study of Muwonge et al. (2008) which also included bidi smokers.

Bundgaard et al. (1995) used lifetime tobacco consumption divided into four categories and reported a positive, significant trend after adjustment for life-time consumption of alcohol and other risk factors. A positive trend was also found in all studies that have analysed consumption in pack–years or tobacco-years (Zheng et al., 1990; Maier et al., 1992a; Macfarlane et al., 1995; Hung et al., 1997; Zheng et al., 1997; De Stefani et al., 1998, 2007; Applebaum et al., 2007; Muwonge et al., 2008), except Muwonge et al. (2008).

Ten studies (Franceschi et al., 1990, 1992; Nandakumar et al., 1990; Zheng et al., 1990; Choi & Kahyo, 1991; Oreggia et al., 1991; Zheng et al., 1997; De Stefani et al., 1998, 2007; Znaor et al., 2003; Subapriya et al., 2007; Muwonge et al., 2008) classified the duration of smoking in up to four categories, and all but one (Nandakumar et al., 1990) reported increased relative risks and a positive trend.

Of six studies that considered age at start of smoking (Franceschi et al., 1990, 1992; Choi & Kahyo, 1991; Oreggia et al., 1991; Zheng et al., 1997; Balaram et al., 2002) two reported a statistically significant trend of increasing risk with decreasing age at starting (Franceschi et al., 1990, 1992).

(b) Cessation of smoking

Three cohort studies (McLaughlin et al., 1995; Freedman et al., 2007a; Friborg et al. 2007) and nine case–control studies (Zheng et al., 1990; Choi & Kahyo, 1991; Oreggia et al., 1991; Franceschi et al., 1992; Ko et al., 1995; Zheng et al., 1997; De Stefani et al., 1998, 2007; Schildt et al., 1998; Balaram et al., 2002; Pacella-Norman et al., 2002; Muwonge et al. 2008) estimated risks for former smokers which were always lower than those for current smokers and in five studies almost reached unity (Zheng et al., 1990; Choi & Kahyo, 1991; Zheng et al., 1997; Schildt et al., 1998; Muwonge et al., 2008). Twelve case–control studies examined the risk by years since quitting and all reported a negative trend, with relative risks compared with those in non-smokers decreasing to near unity after 10 or more years (Franceschi et al., 1990, 1992; De Stefani et al., 1998, 2007; Schlecht et al., 1999a; Table 2.7 online; Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.10.pdf).

(c) Type of cigarette

The effect of the type of cigarette smoked was examined in several case–control studies (Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.11.pdf). The characteristics of the cigarettes included the presence of a filter, the type of tobacco, the tar content and whether the product was manufactured or hand-rolled. Two studies reported a statistically significantly higher risk for black than for blond tobacco (Oreggia et al., 1991; De Stefani et al., 1998, 2007). Similarly, a much higher risk was found for hand-rolled cigarettes than for manufactured cigarettes, and plain cigarettes had a much higher risk than filter-tipped cigarettes (De Stefani et al., 1998, 2007). In one study the differences between black and blond tobacco and between hand-rolled and manufactured cigarettes persisted after stratification by duration of smoking (De Stefani et al., 1998). Smoking cigarettes with a high-tar content led to higher risks than smoking cigarettes with a low-tar content (Franceschi et al., 1992) and the same trend was observed for cigarettes without filter compared to cigarettes with filter (De Stefani et al., 2007).

(d) Sex

Sex-specific effects were examined in two case–control studies (Zheng *et al.*, 1990; Hayes *et al.*, 1999). In both studies, the relative risks for all categories of intensity, duration of smoking and pack–years were higher for women than for men. [The Working Group noted that the background risk of oral cancer is considerably lower in women than men. Thus, the higher relative risk estimates in women than men indicate a higher proportionate contribution from smoking in women than men, rather than higher absolute risk.]

2.3.2 Cancer of the pharynx

Tobacco smoking was considered to be an important cause of oropharyngeal and hypopharyngeal cancers in the previous *IARC Monographs* on tobacco smoking (IARC, 1986, 2004a). Since then, results available from three cohort (Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.12.pdf) and seven case–control studies (Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.13.pdf and Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.14.pdf) provide further support for the association. Many studies, however, combine cancers of the oral cavity and pharynx (see Section 2.3.7). This section summarizes the evidence from all eight cohort and 21 case–control studies that reported results specifically on oropharyngeal and hypopharyngeal cancer, or on pharyngeal cancer in general; the latter may include data on nasopharyngeal cancer.

The risk for pharyngeal cancer was significantly increased in smokers in four cohort studies (Doll *et al.*, 2005; McLaughlin *et al.*,1995; Freedman *et al.*, 2007a; Friborg *et al.*, 2007) and all but one of the case–control studies (Rao *et al.*, 1999). The trend of increasing risk associated with increasing daily or cumulative consumption of cigarettes was evident from all these studies, particularly those from Europe (Brugere *et al.*, 1986; Tuyns *et al.*, 1988; Franceschi *et al.*, 1990, 1999; Maier *et al.*, 1994; Escribano Uzcudun *et al.*, 2002; Vlajinac *et al.*, 2006), India (Znaor *et al.*, 2003; Sapkota *et al.*, 2007), Uruguay (De Stefani *et al.*, 1998, 2007) and the USA (McLaughlin *et al.*, 1995; Applebaum *et al.*, 2007), and less strongly so in studies from Canada (Elwood *et al.*, 1984) and the Republic of Korea (Choi & Kahyo, 1991). The multicentre study in Europe, North and South America of Hashibe *et al.* (2007c) showed increased risks according to frequency (cigarettes/day) and duration (years) in never drinkers. Applebaum *et al.* (2007) found a relationship between increasing risk of pharyngeal cancer and increased pack–years of smoking in subjects with negative HPV16 serology but not in those with positive HPV16 serology (p value for interaction = 0.007).

In two case–control studies the risk increased with decreasing age at starting smoking (Franceschi *et al.*, 1990; Choi & Kahyo, 1991,), but adjustment was not made for duration and intensity of smoking. In a case–control study from Spain (Escribano Uzcudun *et al.*, 2002) the risk increased with the age of starting smoking.

Former smokers had consistently lower relative risks than did current smokers in both cohort (McLaughlin *et al.*, 1995; Freedman *et al.*, 2007a) and case–control studies (Choi & Kahyo, 1991; De Stefani *et al.*, 1998; Vlajinac *et al.*, 2006). In comparison with non-smokers, the relative risks for former smokers who had quit smoking for more than 10 years were between 2 and 4 (Franceschi *et al.*, 1990; De Stefani *et al.*, 1998; La Vecchia *et al.*, 1999), whereas the relative risks for current smokers in these studies were 10–14. In one study in Brazil (Schlecht *et al.*, 1999a), relative risks for former smokers who had stopped smoking for more than 10 years approached 1, whereas that for current smokers was just below 6. Consumption of black tobacco, hand-rolled cigarettes or plain cigarettes resulted in a higher

risk for pharyngeal cancer than consumption of blond tobacco, manufactured cigarettes or filter-tipped cigarettes (De Stefani *et al.*, 1998; 2007).

2.3.3 Cancer of the nasal cavity and accessory sinuses

In the Life Span Study in Japan (Akiba, 1994) the association of tobacco use with sinonasal cancer was examined. A total of 26 cases of sinonasal cancer were identified among 61505 adults during follow-up. Relative risk estimates, adjusted for sex, location, population group, atomic bomb exposure, year of birth and attained age, were 2.9 (95%CI: 0.5–) and 4.0 (95%CI: 1.2–) for former and current smokers, respectively, when compared with non-smokers [upper confidence limits were not reported]. The cohort of 34439 British doctors followed up to 50 years (Doll *et al.*, 2005) showed increased risk for current smokers and smokers of more than 25 cigarettes per day, but only six deaths from nasal cavity and sinuses cancers were observed (Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.15.pdf).

A total of nine case–control studies of nasal cavity and sinus cancers have been conducted. When histological types were combined, all studies found an increased risk associated with cigarette smoking, but only one was statistically significant (Caplan *et al.*, 2000). In seven studies, dose–response in terms of intensity of smoking (cigarettes/day), duration of smoking or pack–years was considered. A positive significant trend was found in five studies (Brinton *et al.*, 1984; Hayes *et al.*, 1987; Fukuda & Shibata, 1990; Zheng *et al.*, 1993; Caplan *et al.*, 2000) and suggested in the other two (Strader *et al.*, 1988; Zheng *et al.*, 1992c).

One study (Zheng *et al.*, 1993a) found a significant decrease in risk for sinonasal cancer associated with increasing number of years since cessation of smoking. In a previous study, the same authors had found a negative, non-significant association (Zheng *et al.*, 1992c).

Five studies analysed squamous-cell carcinomas and adenocarcinomas separately (Brinton *et al.*, 1984; Hayes *et al.*, 1987; Strader *et al.*, 1988; Zheng *et al.*, 1992c; 't Mannetje *et al.*, 1999). In all studies, there was a significantly increased risk for squamous-cell carcinomas, whereas the risk was generally not increased for adenocarcinomas.

2.3.4 Cancer of the nasopharynx

(a) Cohort studies

The risk for nasopharyngeal carcinoma has been examined in relation to tobacco use in six cohort studies, three of them reported since the last evaluation (IARC 2004a; Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.16.pdf). In one study, conducted in a low-risk area (Chow *et al.*, 1993a), a significant increase in risk among smokers and suggestive positive dose–response relationships by duration of smoking and age at starting smoking were found. In another study, conducted in Province of Taiwan, China, an area in which nasopharyngeal cancer area is endemic, a similarly increased risk was found, but it was not statistically significant (Liaw & Chen, 1998). Doll *et al.* (2005) identified a risk only for smokers of more than 25 cigarettes per day, however, this result was based on only four deaths. Friborg *et al.* (2007) in Singapore found statistically significant increased risk of nasopharyngeal cancer only for those smoking for 40 years or more. Hsu *et al.* (2009) in Taiwan, China observed increased statistically significant risks only for those smoking for 30 years or more and those with cumulative exposure of 30 pack–years or more.

(b) Case–control studies

The study designs and the results of the case–control studies on the association of nasopharyngeal carcinoma with cigarette smoking

reported since the previous *IARC Monograph* (IARC, 2004a) are given in Table 2.17 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.17.pdf) and Table 2.18 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.18.pdf), one being a nested case–control analysis within a cohort study (Marsh *et al.*, 2007).

In total, 14 informative case–control studies were available. In almost all of these, the risk for nasopharyngeal carcinoma was higher in smokers than in non-smokers. In Taiwan, China (Cheng *et al.*, 1999) high risks were statistically significant only for duration of smoking of 20 years or more. In the five studies conducted in the USA (Mabuchi *et al.*, 1985; Nam *et al.*, 1992; Zhu *et al.*, 1995; Vaughan *et al.*, 1996; Marsh *et al.*, 2007), where the incidence of nasopharyngeal carcinoma is low, the relative risks for current smokers ranged between 2 and 4, but were not statistically significant in the two studies (Mabuchi *et al.*, 1985; Marsh *et al.*, 2007). In a study conducted in Shanghai, an area of China in which nasopharyngeal carcinoma is not endemic (Yuan *et al.*, 2000), the relative risk was just below 2. In one study from the Philippines there was a sevenfold increase in risk after more than 30 years of smoking (West *et al.*, 1993). The four studies (Lin *et al.*, 1973; Yu *et al.*, 1990; Ye *et al.*, 1995; Cao *et al.*, 2000) conducted in areas of China in which nasopharyngeal carcinoma is endemic (Taiwan, China, Guangzhou, and Sihui) found relative risks for ever smoking ranging between 2 and 5. In the study from the North of Africa (Feng *et al.*, 2009) the only statistically significant increased risk was found for differentiated nasopharyngeal cancer in those that had smoked more than 22 cigarettes/day. [The result, based only on three cases, is very unstable (RR, 313; 95%CI: 1.94–50336).]

A statistically significant dose–response relationship was detected in seven studies that evaluated the effects of daily or cumulative exposure to tobacco smoke (Yu *et al.*, 1990; Nam *et al.*, 1992; Zhu *et al.*, 1995; Vaughan *et al.*, 1996; Cao *et al.*, 2000; Yuan *et al.*, 2000; Feng *et al.*, 2009) and was suggestive in two others (Lin *et al.*, 1973; West *et al.*, 1993). In two studies the risk of nasopharyngeal carcinoma decreased with increasing time since quitting smoking (Nam *et al.*, 1992; Vaughan *et al.*, 1996).

In the remaining studies, six from areas in which nasopharyngeal carcinoma is endemic (Ng, 1986; Yu *et al.*, 1986; Sriamporn *et al.*, 1992; Zheng *et al.*, 1994; Cheng *et al.*, 1999; Feng *et al.*, 2009; Guo *et al.*, 2009) and seven from areas in which it was not endemic (Henderson *et al.*, 1976; Lanier *et al.*, 1980; Mabuchi *et al.*, 1985; Ning *et al.*, 1990; Armstrong *et al.*, 2000, Marsh *et al.*, 2007), the relative risks for nasopharyngeal carcinoma for ever smoking were not significantly increased (Lanier *et al.*, 1980; Mabuchi *et al.*, 1985; Cheng *et al.*, 1999) or were close to 1.0 (Henderson *et al.*, 1976; Ng, 1986; Yu *et al.*, 1986; Ning *et al.*, 1990; Sriamporn *et al.*, 1992; Zheng *et al.*, 1994; Guo *et al.*, 2009).

In the two studies that distinguished between different histological types, relative risks were higher for keratinized (squamous-cell) carcinoma than for unkeratinized carcinoma (Zhu *et al.*, 1995; Vaughan *et al.*, 1996).

In the three studies in which men and women were analysed separately (Lin *et al.*, 1973; Nam *et al.*, 1992; Yuan *et al.*, 2000), the relative risks were found to increase similarly in both sexes in two studies (Nam *et al.*, 1992; Yuan *et al.*, 2000) and were higher among women in the study of Lin *et al.* (1973).

2.3.5 Cancer of the oesophagus

In the previous *IARC Monograph* (IARC, 2004a), both histological subtypes of oesophageal cancer (squamous-cell carcinoma and adenocarcinoma) were considered to be causally related to cigarette smoking. Many more epidemiological studies have since been conducted, and results of these studies further support this conclusion.

(a) *Squamous cell carcinoma and unspecified cancer of the oesophagus*

Since the previous *IARC Monograph* (IARC, 2004a), there have been reports on 9 cohort studies (Table 2.19 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.19.pdf) and 22 case–control studies (Tables 2.20–2.23; see below), making 30 cohort and 55 case–control studies in all. All showed that the risk of oesophageal squamous cell carcinoma was associated with cigarette smoking. In one study (Li *et al.*, 1989), the elevated risk was observed only in an area with a relatively low incidence of oesophageal cancer. However, two later studies in the same area, Lin County, China, found a twofold increase in risk for oesophageal cancer among smokers (Gao *et al.*, 1994; Lu *et al.*, 2000).

In most cohort studies and in most case–control studies with relatively large sample sizes (IARC, 2004a; Table 2.19 online; Table 2.20 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.20.pdf; Table 2.21 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.21.pdf), the risk for oesophageal cancer was shown to increase with increasing duration of smoking (11 cohort and 32 case–control studies) or number of cigarettes smoked daily (18 cohort and 31 case–control studies), and to decrease with increasing age at starting smoking (12 case–control studies). In comparison with pharyngeal and laryngeal cancers, relative risks for oesophageal cancer estimated by duration and by intensity of smoking were somewhat lower (see Sections 2.3.2 and 2.3.6, respectively).

Ten cohort and 20 case–control studies (IARC, 2004a; Table 2.19 online; Table 2.22 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.22.pdf) investigated the effect of smoking cessation on risk of oesophageal cancer. Although not all studies analysed the trend, all found a decreasing relative risk with increasing number of years since quitting. In some studies, the risk first started to decrease after 10 years of cessation (Brown *et al.*, 1988; Rolón *et al.*, 1995; Gammon *et al.*, 1997; Castellsagué *et al.*, 1999; Freedman *et al.*, 2007b; Bosetti *et al.*, 2008) or after 30 years of cessation (Pandeya *et al.*, 2008).

When comparing the types of tobacco smoked (Table 2.23 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.23.pdf), consumption of black tobacco resulted in a higher risk for oesophageal cancer than did consumption of blond tobacco (De Stefani *et al.*, 1990; Rolón *et al.*, 1995; Castellsagué *et al.*, 1999; Launoy *et al.*, 2000; Vioque *et al.*, 2008). Similarly, smoking untipped cigarettes generally resulted in a higher risk than smoking filter-tipped cigarettes (Vaughan *et al.*, 1995; Gammon *et al.*, 1997; Castellsagué *et al.*, 1999).

Two studies from the USA reported risks separately for blacks and whites. After adjustment for alcohol consumption, age and income, risks were very similar for former and current smokers and for the number of cigarettes smoked per day and duration of smoking (Brown *et al.*, 1994a; Brown *et al.*, 2001).

(b) *Adenocarcinoma of the oesophagus*

Two decades ago it was noted that incidence rates for adenocarcinoma of the oesophagus and gastric cardia had increased steadily in the USA, whereas the incidence rate for squamous-cell carcinoma of the oesophagus had remained relatively stable (Blot *et al.*, 1991). An increase in the incidence of adenocarcinoma of the distal oesophagus and cardia was also noted in the United Kingdom (Powell & McConkey, 1990), and in several other countries. Since 1990, several studies have focused on the risk factors for adenocarcinoma of the oesophagus. Since the last evaluation (IARC, 2004a) one cohort study (Freedman *et al.*, 2007b) and three case–control studies (Table 2.24 available at http://monographs.iarc.fr/ENG/Monographs/

vol100E/100E-01-Table2.24.pdf; Table 2.25 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.25.pdf) have been reported, totaling 13 case–control studies on the association of cigarette smoking and adenocarcinoma of the oesophagus.

(i) Intensity and duration of smoking

Ten studies, three that included only cases of adenocarcinoma of the oesophagus (Menke-Pluymers *et al.*, 1993; Gammon *et al.*, 1997; Wu *et al.*, 2001), three that included cases of adenocarcinoma of the oesophagus, gastro-oesophageal junction and gastric cardia combined (Kabat *et al.*, 1993; Brown *et al.*, 1994b; Vaughan *et al.*, 1995), and four that stratified by histology (Lindblad *et al.*, 2005; Freedman *et al.*, 2007b; Hashibe *et al.*, 2007a; Pandeya *et al.*, 2008), showed a significant positive association of adenocarcinoma of the oesophagus with cigarette smoking. The relative risks were somewhat lower than those for squamous cell carcinoma of the oesophagus. Three studies, one in China (Gao *et al.*, 1994), one in Sweden (Lagergren *et al.*, 2000), and one in the USA (Zhang *et al.*, 1996), reported similarly elevated relative risks, but some of these risks were not statistically significant, probably because of relatively small numbers of cases.

Of those studies that reported risks adjusted for alcohol consumption, a positive, significant dose–response relationship was found with intensity of smoking (Kabat *et al.*, 1993; Brown *et al.*, 1994b; Gammon *et al.*, 1997; Hashibe *et al.*, 2007a), duration of smoking (Gammon *et al.*, 1997; Pandeya *et al.*, 2008) and/or pack–years (Vaughan *et al.*, 1995; Zhang *et al.*, 1996; Gammon *et al.*, 1997; Pandeya *et al.*, 2008).

(ii) Cessation of smoking

Ten studies provided point estimates for former smokers. In eight, relative risks were lower in former smokers than in current smokers, although they remained elevated (Kabat *et al.*, 1993; Gao *et al.*, 1994; Vaughan *et al.*, 1995; Gammon *et al.*, 1997; Wu *et al.*, 2001; Lindblad *et al.*, 2005; Freedman *et al.*, 2007b; Pandeya *et al.*, 2008), and were increased in the other studies (Lagergren *et al.*, 2000; Hashibe *et al.*, 2007a). The decrease in relative risk associated with years since cessation was weak, but a significant trend was found in two out of six studies (Gammon *et al.*, 1997; Wu *et al.*, 2001).

(iii) Confounding

With the exception of two studies (Levi *et al.*, 1990; Wu *et al.*, 2001), all studies adjusted for alcohol intake as a potential confounder. Three more recent studies also adjusted for fruit and vegetables intake (Freedman *et al.*, 2007b; Hashibe *et al.*, 2007a; Pandeya *et al.*, 2008). Ten of these studies were conducted in the USA (Kabat *et al.*, 1993; Brown *et al.*, 1994b; Vaughan *et al.*, 1995; Zhang *et al.*, 1996; Gammon *et al.*, 1997; Freedman *et al.*, 2007b) the Netherlands (Menke-Pluymers *et al.*, 1993), the United Kingdom (Lindblad *et al.*, 2005), central and eastern Europe (Hashibe *et al.*, 2007a) and Australia (Pandeya *et al.*, 2008), where chewing of betel quid with tobacco or use of other forms of smokeless tobacco are not likely confounders. One study conducted in Sweden was adjusted for snuff use (Lagergren *et al.*, 2000).

(iv) Sex

Kabat *et al.* (1993) examined risks for men and women separately and observed similar patterns in both sexes, although risks among current smokers and heavy smokers were somewhat higher for women than for men. Lindblad *et al.* (2005) also found higher risks in women than in men, but they were not statistically significant.

2.3.6 Cancer of the larynx

Laryngeal cancer is one of the cancers most strongly associated with cigarette smoking (IARC, 1986, 2004a). Since the previous *IARC*

Monograph, more epidemiological evidence has become available to strengthen this conclusion.

(a) Potential confounders

Other causes of laryngeal cancer include alcohol consumption, some occupational exposures (e.g. sulphuric acid; IARC, 2012a) and possibly some dietary habits. In investigating associations between smoking and laryngeal cancer, potential confounding by alcohol consumption has been considered in most of the studies.

(b) Intensity and duration of smoking

Cohort and case–control studies have been carried out in Asia, Europe, North and South America, and South Africa. In all, the risk for laryngeal cancer was consistently higher in smokers, and a positive significant trend was observed with increasing duration and intensity of smoking (IARC, 2004a; Table 2.26 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.26.pdf; Table 2.27 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.27.pdf; Table 2.28 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.28.pdf).

In most case–control studies, the relative risks for laryngeal cancer were near to or greater than 10 for smokers who had smoked for longer than 40 years (Falk *et al.*, 1989; Zheng *et al.*, 1992b) or had smoked more than 20 cigarettes per day (Tuyns *et al.*, 1988; Falk *et al.*, 1989; Choi & Kahyo, 1991; Zatonski *et al.*, 1991; Muscat & Wynder, 1992; Zheng *et al.*, 1992b; Hedberg *et al.*, 1994; Sokić *et al.*, 1994; Talamini *et al.*, 2002). Cancer of the larynx in non-smokers is so rare that several studies used as the reference category light smokers (Herity *et al.*, 1982; Olsen *et al.*, 1985a; De Stefani *et al.*, 1987; Zatonski *et al.*, 1991; López-Abente *et al.*, 1992; Maier & Tisch, 1997), or former smokers (Hashibe *et al.*, 2007b). Consequently, relative risks were lower in these studies, although the increases were still statistically significant.

Three case–control studies reported odds ratios for cancer of the larynx that increased with decreasing age of starting smoking (Franceschi *et al.*, 1990; Zatonski *et al.*, 1991; Talamini *et al.*, 2002).

(c) Cessation of smoking

The risk for cancer of the larynx declines rather rapidly after cessation of smoking (IARC, 2004a; Table 2.29 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.29.pdf). No detectable higher risk compared with never-smokers was seen among subjects who had quit smoking for at least 10 years (Franceschi *et al.*, 1990; Ahrens *et al.*, 1991; Schlecht *et al.*, 1999a, b; Bosetti *et al.*, 2006; Hashibe *et al.*, 2007b).

(d) Types of tobacco or of cigarette

Some investigators considered the role of type of tobacco (IARC, 2004a; Table 2.30 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.30.pdf). An average 2.5-fold higher risk was observed in smokers of black tobacco compared to smokers of blond tobacco (De Stefani *et al.*, 1987; Tuyns *et al.*, 1988; López-Abente *et al.*, 1992). Smoking untipped cigarettes also led to a higher risk than smoking filter-tipped cigarettes (Wynder & Stellman, 1979; Tuyns *et al.*, 1988; Falk *et al.*, 1989). Those that smoke cigarettes only had higher risks of larynx cancer than those that smoke cigars only (Hashibe *et al.*, 2007b).

(e) Subsites

Six studies investigated the risk for glottic and supraglottic cancer separately (Olsen *et al.*, 1985a; Tuyns *et al.*, 1988; López-Abente *et al.*, 1992; Maier *et al.*, 1992b; Muscat & Wynder, 1992; Sapkota *et al.*, 2007). The cancer risk increased with increasing amount smoked per

day and with cumulative exposure for both subsites (IARC, 2004a; Table 2.28 online). In addition, the observed relative risks were higher for supraglottic cancer than for glottic cancer (Maier *et al.*, 1992b; Sapkota *et al.*, 2007).

(f) Sex

Few studies investigated sex-specific effects. In one cohort study (Raitiola & Pukander, 1997) similar risks were found for men and women, whereas in two case–control studies (Zheng *et al.*, 1992b; Tavani *et al.*, 1994), the relative risks for women were up to 10-fold higher than for the corresponding categories in men, though a small number of cases were involved. However, Freedman *et al.* (2007a) observed higher relative risks in men than women (Table 2.26 online). One study looked at women only and found higher risks of laryngeal cancer in former and current smokers relative to non-smokers, and also according to the number of cigarettes per day with a clear dose–response effect ($P < 0.001$) (Gallus *et al.*, 2003b).

2.3.7 Cancer of the upper aerodigestive tract combined

In epidemiological studies, especially in cohort studies in which there are few cases at some sites, investigators often combine cancers of the oral cavity, pharynx, larynx and oesophagus and term these 'cancer of the upper aerodigestive tract'. This section summarizes the data from 19 cohort studies (IARC, 2004a; Table 2.31 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.31.pdf), and 40 case–control studies (IARC, 2004a; Tables 2.32–2.35; see below).

(a) Intensity and duration of smoking

In all but two cohort studies from Japan (Kono *et al.*, 1987; Akiba, 1994), the risk for cancer of the upper aerodigestive tract was strongly associated with cigarette smoking. Relative risks increased with increasing daily cigarette consumption (Hammond & Horn, 1958; Doll *et al.*, 1980, 1994; Akiba & Hirayama, 1990; Kuller *et al.*, 1991; Chyou *et al.*, 1995; Engeland *et al.*, 1996; Murata *et al.*, 1996; Yuan *et al.*, 1996; Kjaerheim *et al.*, 1998; Liaw & Chen, 1998; Yun *et al.*, 2005; Freedman *et al.*, 2007a), duration of smoking (Chyou *et al.*, 1995; Yun *et al.* 2005; Friborg *et al.*, 2007) or pack–years (Liaw & Chen, 1998; Freedman *et al.*, 2007a).

The main characteristics and results of the case–control studies are presented in IARC (2004a), and in Table 2.32 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.32.pdf) and Table 2.33 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.33.pdf), respectively. Intensity of smoking was measured in most of these studies. The link between duration of smoking and cancer of the upper aerodigestive tract was examined in 20 case–control studies (Blot *et al.*, 1988; Merletti *et al.*, 1989; Barra *et al.*, 1991; De Stefani *et al.*, 1992, 2007; Franceschi *et al.*, 1992; Day *et al.*, 1993; Mashberg *et al.*, 1993; Kabat *et al.*, 1994; Lewin *et al.*, 1998; Bosetti *et al.*, 2000a; Garrote *et al.*, 2001; Gallus *et al.*, 2003a; Lissowska *et al.*, 2003; Znaor *et al.*, 2003; Castellsagué *et al.*, 2004; Menvielle *et al.*, 2004a, b; Rodriguez *et al.*, 2004; Hashibe *et al.*, 2007c; Sapkota *et al.*, 2007). Nine also considered age at starting smoking (Blot *et al.*, 1988; Merletti *et al.*, 1989; Barra *et al.*, 1991; Franceschi *et al.*, 1992; Day *et al.*, 1993; Lewin *et al.*, 1998; Garrote *et al.* 2001; Lissowska *et al.* 2003; Menvielle *et al.* 2004a).

In all but one study (Rao *et al.*, 1999) there was an increased risk for cancer of the upper aerodigestive tract associated with cigarette smoking. A clear dose–response relationship was seen with increasing daily tobacco consumption and duration of smoking as well as with decreasing age at starting smoking in most of the studies examined.

(b) Cessation of smoking

Twelve cohort studies (Doll *et al.*, 1980, 1994; Tomita *et al.*, 1991; Akiba, 1994; Chyou *et al.*, 1995; Engeland *et al.*, 1996; Nordlund *et al.*, 1997; Kjaerheim *et al.*, 1998; Yun *et al.*, 2005; Freedman *et al.*, 2007a; Friborg *et al.*, 2007; Ide *et al.*, 2008) provided point estimates for former smokers (IARC 2004a; Table 2.31 online). The relative risks for former smokers were always lower than those for current smokers.

In 16 case–control studies the relative risk by years since quitting was examined and generally a statistically significant negative trend was found (Table 2.34 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.34.pdf).

(c) Types of cigarette

The characteristics studied in several case–control studies included the use of a filter, the type of tobacco, the tar content and whether the product was manufactured or hand-rolled (IARC, 2004a; Table 2.35 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.35.pdf). Consumption of black tobacco, cigars, untipped cigarettes, hand-rolled cigarettes, or cigarettes with a high-tar yield generally resulted in a higher risk than consumption of blond tobacco (Merletti *et al.*, 1989; Castellsagué *et al.*, 2004; De Stefani *et al.*, 2007), filter-tipped cigarettes (Merletti *et al.*, 1989; Mashberg *et al.*, 1993; Kabat *et al.*, 1994; Lissowska *et al.*, 2003; De Stefani *et al.*, 2007), manufactured cigarettes (De Stefani *et al.*, 1992, 2007) or low-tar cigarettes (Franceschi *et al.*, 1992). Two studies from India (Znaor *et al.*, 2003; Sapkota *et al.* 2007) revealed higher risks of *bidi* smoking related to cigarettes smoking.

(d) Sex

Sex-specific effects were analysed in four cohort studies (IARC 2004a; Table 2.31 online). In three cohort studies (Hammond & Seidman, 1980; Akiba & Hirayama, 1990; Freedman *et al.*, 2007a) a higher relative risk was found for male smokers than for female smokers; however, Ide *et al.* (2008) detected a higher risk among women in a study with a small number of cases.

In three case–control studies (Blot *et al.*, 1988; Kabat *et al.*, 1994; Muscat *et al.*, 1996) the relative risks were higher for women than for men in all categories of intensity of smoking (number of cigarettes per day), cumulative exposure (cumulative tar consumption, pack–years, duration of smoking) and age at starting smoking, as well as for former smokers. However, the trends in men were always in the same direction and of the same order of magnitude. An exception to the pattern was that in one study (Merletti *et al.*, 1989) the relative risk for smoking filter-tipped cigarettes was higher than that for smoking untipped cigarettes for women.

Overall, the strength of association by sex was generally similar, especially when taking into account the fact that women generally underreport levels of smoking and that most studies included many fewer women than men.

(e) Ethnicity

Relative risks were reported separately for blacks and whites in a large case–control study from the USA (Day *et al.*, 1993). Relative risks adjusted for alcohol consumption, sex and other relevant variables were very similar for the number of cigarettes smoked per day, years of cigarette smoking, age at starting smoking and number of years since stopping smoking.

2.4 Cancer of the stomach

2.4.1 Overview of studies

In the previous *IARC Monograph* (IARC, 2004a) it was concluded that there was *sufficient evidence* that tobacco smoking causes cancer of the stomach. Three meta-analyses have since examined the evidence for gastric cancer in 42

independent cohort studies published between 1958 and July 2007 (Ladeiras-Lopes *et al.*, 2008), in 46 case–control studies published between 1997 and June 2006 (La Torre *et al.*, 2009), and in 10 cohort and 16 case–control studies conducted in Japanese populations published between 1966 and March 2005 (Nishino *et al.*, 2006; Table 2.36 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.36.pdf). For current smokers compared to never smokers, the risk for stomach cancer was found to be statistically significantly increased by 53% (Ladeiras-Lopes *et al.*, 2008), 56% (Nishino *et al.*, 2006), and 57% when considering high quality case–control studies (La Torre *et al.*, 2009), with moderate to high heterogeneity.

Since the previous *IARC Monograph* (IARC, 2004a), the association between cigarette smoking and stomach cancer risk (15 studies) and mortality (4 studies) has been examined in 19 cohort studies (Table 2.37 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.37.pdf). Eleven of these were conducted in Asia (Sasazuki *et al.*, 2002; Jee *et al.*, 2004; Koizumi *et al.*, 2004; Wen *et al.*, 2004; Fujino *et al.*, 2005; Sauvaget *et al.*, 2005; Tran *et al.*, 2005; Kurosawa *et al.*, 2006; Kim *et al.*, 2007; Sung *et al.*, 2007; Shikata *et al.*, 2008), seven in Europe (Simán *et al.*, 2001; González *et al.*, 2003; Doll *et al.*, 2005; Lindblad *et al.*, 2005; Sjödahl *et al.*, 2007; Batty *et al.*, 2008; Zendehdel *et al.*, 2008) and one in the USA (Freedman *et al.*, 2007a). Only the updated British Doctors' study (Doll *et al.*, 2005) and the most recent studies (Shikata *et al.*, 2008; Zendehdel *et al.*, 2008) were not included in the meta-analysis of cohort studies (Ladeiras-Lopes *et al.*, 2008). Elevated risks in current smokers were found in all studies. The reported association of current smoking with mortality in the four cohort studies conducted in Taiwan, China (Wen *et al.*, 2004), Japan (Kurosawa *et al.*, 2006) and the United Kingdom (Doll *et al.*, 2005; Batty *et al.*, 2008) was comparable to that with incidence.

In addition, the association between smoking and stomach cancer risk has been reported in 37 case–control studies since the previous *IARC Monograph*, of which 22 are hospital-based and 15 population-based. With the exception of three studies (Campos *et al.*, 2006; García-González *et al.*, 2007; Suwanrungruang *et al.*, 2008; Table 2.38 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.38.pdf), all these studies were included in the meta-analysis conducted by (La Torre *et al.*, 2009).

2.4.2 Factors affecting risk

(a) Intensity and duration

Clear evidence has been provided by the meta-analyses as well as by the additional cohort studies that the risk for stomach cancer increases significantly with increasing daily cigarette consumption, duration or pack–years of smoking, although individual studies did not always find statistically significant dose–response relationships. In one meta-analysis based on 21 cohort studies, the risk for stomach cancer increased statistically significantly by 53% with consumption of approximately 20 cigarettes per day (Ladeiras-Lopes *et al.*, 2008). Using trend estimation analysis as proposed by Greenland & Longnecker (1992), the authors found an increase in relative risk from 1.3 for the lowest consumption to 1.7 for smoking 30 cigarettes per day.

(b) Cessation of smoking

Risk for stomach cancer has been generally found to be lower in former smokers than in current smokers. In six of the cohort studies decreasing risk with increasing years since stopping smoking was found although none found statistically significant dose–response relationships (González *et al.*, 2003; Koizumi *et al.*, 2004; Sauvaget *et al.*, 2005; Freedman *et al.*, 2007a; Kim *et al.*, 2007; Zendehdel *et al.*, 2008). Risk in former smokers was comparable to never smokers after quitting for 5 years (Kim *et al.*,

2007), 10 years (González *et al.*, 2003; Sauvaget *et al.*, 2005; Freedman *et al.*, 2007a) or 15 years (Koizumi *et al.*, 2004).

2.4.3 Subsites

The effect of current smoking on the risk for stomach cancer by subsite was assessed in ten cohort studies. Elevated risks were found for both cardia and non-cardia cancers. In six studies higher risks were found for cancer of the gastric cardia than for cancer of the distal stomach (Simán *et al.* 2001; González *et al.*, 2003; Freedman *et al.*, 2007a; Sung *et al.*, 2007; Shikata *et al.*, 2008; Zendehdel *et al.*, 2008), three studies found no difference (Sasazuki *et al.*, 2002; Lindblad *et al.*, 2005; Tran *et al.*, 2005), and in one study higher risk for cancer in the antrum rather than the body or the cardia was found (Koizumi *et al.*, 2004). A meta-analysis yielded statistically significant summary relative risks of 1.87 for cardia cancers and 1.60 for non-cardia cancers based on nine cohort studies (Ladeiras-Lopes *et al.*, 2008). However, there was substantial heterogeneity across studies for cardia cancers. For case–controls studies, the corresponding odds ratios were 2.05 (95%CI: 1.50–2.81) and 2.04 (95%CI: 1.66–2.50), respectively, with greater heterogeneity for non-cardia cancers. Criteria for the classification by subsite were not always described (Simán *et al.*, 2001; Koizumi *et al.*, 2004; Lindblad *et al.*, 2005; Tran *et al.*, 2005) and some studies included tumours located in the upper third of the stomach in the group of cardia cancer (Sasazuki *et al.*, 2002; Sung *et al.*, 2007; Shikata *et al.* 2008).

In three studies risk estimates for smoking associated stomach cancer were estimated by histological type (Sasazuki *et al.*, 2002; Koizumi *et al.*, 2004; Shikata *et al.*, 2008). The relative risks were 2.1 (95%CI: 1.2–3.6), 1.6 (95%CI: 1.1–2.3) and 2.3 (95%CI: 1.3–4.1) for the differentiated type, respectively, and 0.6 (95%CI: 0.3–1.1), 2.1 (95%CI: 1.1–4.1), and 1.3 (95%CI: 0.5–3.5) for the non-differentiated type, respectively.

2.4.4 Population characteristics

In four of the additional cohort studies risk was reported separately for men and women (González *et al.*, 2003; Jee *et al.*, 2004; Fujino *et al.*, 2005; Kim *et al.*, 2007), in three studies only for men (Koizumi *et al.*, 2004; Tran *et al.*, 2005; Sung *et al.*, 2007) and in one mortality study for men as well as for women (Wen *et al.*, 2004). Generally, the relative risks were smaller in women than in men. For all stomach cancers, risk in current smokers compared to never smokers was found to be significantly increased by 62% in men (based on 18 studies) and by 20% in women (based on nine studies) in the meta-analysis of cohort studies (Ladeiras-Lopes *et al.*, 2008). The men–women differences were independent of exposure level but could be explained by the sex difference in the distribution by histological type and other factors associated with socioeconomic status.

Ethnicity does not appear to modify the effect of smoking on stomach cancer risk. In the meta-analysis of case–control studies risk in current smokers was increased by 78% in Caucasians and by 48% in Asians (La Torre *et al.*, 2009). The summary risk based on the cohort studies increased by 46% and 47% in Caucasian and Asian studies, respectively. In a meta-regression analysis including the variables sex, population, and fruit and vegetable consumption, sex but not origin of the population showed significant differences in risk estimates (Ladeiras-Lopes *et al.*, 2008).

2.4.5 Bias and confounding

Generally, most cohort studies have relied on baseline information and did not update the exposure information, possibly leading to misclassification of smoking status. Most of

the recent cohort studies have accounted for confounding by alcohol consumption (Fujino *et al.*, 2005; Lindblad *et al.*, 2005; Sjödahl *et al.*, 2007; Sung *et al.*, 2007) as well as fruit and vegetable consumption (González *et al.*, 2003; Koizumi *et al.*, 2004; Freedman *et al.* 2007a) and still observed significantly increased risk of stomach cancer in current smokers.

2.4.6 Helicobacter pylori infection

The association between tobacco smoking and stomach cancer could be confounded or modified by the effect of *H. pylori* infection, an established risk factor for stomach cancer. In three case–control studies (Zaridze *et al.*, 2000; Brenner *et al.*, 2002; Wu *et al.* 2003), and two cohort studies (Simán *et al.*, 2001; Shikata *et al.*, 2008) the joint effects and possible interaction between *H. pylori* status and smoking in relation to risk for stomach cancer was investigated. Among subjects who had *H. pylori* infection, the risk for stomach cancer was higher in current smokers than in non-smokers by 1.6 to 2.7 fold, providing evidence for a causal effect of tobacco smoking independently of *H. pylori* infection. Smoking was associated with risk elevations of the same order of magnitude among subjects without *H. pylori* infection. Smoking and *H. pylori* therefore may act synergistically, leading to very high risks in current smokers with *H. pylori* infection compared to non-smokers without *H. pylori* infection. In one study that examined risk by subsite an effect of smoking independent of *H. pylori* infection for gastric cardia as well as distal gastric cancer was found (Wu *et al.*, 2003). In none of the studies was there statistically significant evidence for interaction.

2.5 Cancer of the pancreas

2.5.1 Overview of studies

Previous *IARC Monographs* (IARC, 1986, 2004a) concluded that exposure to tobacco smoke caused cancer of the pancreas. Additional evidence has come from a pooled analysis of eight cohort studies with almost 1500 incident cases of pancreatic cancer and an equal number of controls (Lynch *et al.*, 2009) as well as a meta-analysis of 82 independent studies (42 case–control studies, 40 cohort studies) published between 1950 and 2007 (Iodice *et al.*, 2008; Table 2.39 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.39.pdf). In the meta-analysis 74% and 20% significant increased risks for current and former smokers, respectively, were found with significant heterogeneity of effect regarding current smoking across studies. Adjustment for confounders explained some of the heterogeneity (Iodice *et al.*, 2008). A similar significant risk elevation of 77% for current smokers was found in the pooled analysis, without study heterogeneity (Lynch *et al.*, 2009). For former smokers, risk was increased non-significantly by 9%.

Since the previous *IARC Monograph* (IARC, 2004a), a total of 15 cohort studies have reported on the association between cigarette smoking and pancreatic cancer incidence (8 studies) and mortality (5 studies) or both (one study) (Table 2.40 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.40.pdf), two of which were included in the pooled analysis (Coughlin *et al.*, 2000; Vrieling *et al.*, 2009). Excluding case–control studies that did not report odds ratios for current smokers, there were three additional case–control studies (Duell *et al.*, 2002; Inoue *et al.*, 2003; Alguacil & Silverman, 2004; Table 2.41 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.41.pdf). The effect of cigar and pipe smoking on pancreatic cancer was

also examined in the ACS Cancer Prevention Study II regarding mortality (Shapiro *et al.*, 2000; Henley *et al.*, 2004) and in the Kaiser Permanente Medical Care Program regarding incidence (Iribarren *et al.*, 1999). All the additional studies showed an increased risk for pancreatic cancer associated with tobacco smoking, generally higher in current than in former smokers. The reported risk estimates were not always statistically significant, predominantly due to the small size of some studies and therefore lack of statistical precision.

2.5.2 Factors affecting risks

(a) Intensity and duration

Clear evidence has been provided by the meta-analysis, the pooled analysis as well as the additional studies that the risk for cancer of the pancreas increases significantly with increasing daily cigarette consumption, duration and pack–years of smoking (Coughlin *et al.*, 2000; Gapstur *et al.*, 2000; Nilsen & Vatten, 2000; Nilsson *et al.*, 2001; Isaksson *et al.*, 2002; Doll *et al.*, 2005; Yun *et al.*, 2005; Ansary-Moghaddam *et al.*, 2006; Gallicchio *et al.*, 2006; Vrieling *et al.*, 2009). In the meta-analysis risk of pancreatic cancer increased significantly by 62% with an increase of 20 cigarettes per day (based on 45 studies) and by 16% with a 10-year increase in smoking duration (based on 16 studies), but with significant study heterogeneity. In the pooled analysis, the excess odds ratio per pack–years generally declined with increasing smoking intensity (Lynch *et al.*, 2009).

(b) Cessation of smoking

A reduction in risk in former smokers who had stopped smoking for at least 10 years was found in the meta-analysis (Iodice *et al.*, 2008) and the pooled study (Lynch *et al.*, 2009). In some cohort studies risk was already comparable to never smokers five years after quitting (Boyle *et al.*, 1996; Fuchs *et al.*, 1996; Nilsen & Vatten, 2000; Vrieling *et al.*, 2009).

(c) Types of tobacco

In non–cigarette smokers, mortality from pancreatic cancer was increased although not statistically significantly so in cigar smokers in the CPS-II cohort study (Shapiro *et al.*, 2000) as well as a large case–control study (Alguacil & Silverman, 2004) but was less clearly elevated in the smaller Kaiser Permanente cohort study (Iribarren *et al.*, 1999). There was a significantly increased mortality for current cigar smokers who reported inhaling cigar smoke (Shapiro *et al.*, 2000). Pipe smoking was also found to be associated with an increased risk of cancer of the pancreas, which was stronger in those who reported that they inhaled the smoke (Henley *et al.*, 2004). A limitation of the cohort studies is that smoking habits were reported only at baseline, misclassification of smoking exposure is likely to underestimate the associated risks. In the meta-analysis there was a significant increase in risk of 47% associated with current cigar and/or pipe smoking (18 studies) and a non-significant risk elevation of 29% with former cigar and/or pipe smoking (5 studies) (Iodice *et al.*, 2008).

2.5.3 Population characteristics

The effect of sex on pancreatic cancer risk was investigated in two cohort studies (Nilsen & Vatten, 2000; Larsson *et al.*, 2005) and on pancreatic cancer mortality in four cohort studies (Coughlin *et al.*, 2000; Gapstur *et al.*, 2000; Nilsson *et al.*, 2001; Lin *et al.*, 2002a). The relative risks were comparable between men and women and no consistent evidence for an effect modification by sex was observed.

Ethnicity does not appear to modify the association of smoking with pancreatic cancer risk. The roughly twofold elevated risk in current smokers compared to never smokers was observed both in studies of Caucasians (Lynch *et al.*, 2009) and of Asians (Lin *et al.*, 2002a; Jee *et al.*, 2004; Yun *et al.*, 2005; Li *et al.*, 2006). In populations of the Asia-Pacific Region, there

was also no difference in the strength of association between Asia and Australia/New Zealand (Ansary-Moghaddam *et al.*, 2006).

2.5.4 Confounding factors

In two large cohort studies the risk estimates for pancreatic cancer associated with cigarette smoking were not substantially influenced by adjustment for further potential confounding factors, including diabetes, body mass index (BMI), alcohol and dietary intake (Coughlin *et al.*, 2000; Vrieling *et al.*, 2009).

2.6 Cancer of the colorectum

2.6.1 Overview of studies

In the previous *IARC Monograph* (IARC, 2004a) it was not possible to conclude that the association between tobacco smoking and colorectal cancer is casual, principally because of concern about confounding by other risk factors. That evaluation was based on a total of 60 epidemiologic studies, although only few were specifically designed to study the effects of smoking. Studies have however shown consistently that cigarette smoking is a risk factor for colorectal adenomatous polyps, which are recognized precursor lesions of colorectal cancer (Hill, 1978). To explain this discrepancy, Giovannucci *et al.* (1994) hypothesized that a long induction period is required for tobacco to play a role in colorectal carcinogenesis, which would not be captured by studies with shorter follow-up time.

Four recent meta-analyses consistently showed a strong association between cigarette smoking and colorectal cancer (Botteri *et al.*, 2008a; Liang *et al.*, 2009; Huxley *et al.*, 2009; Tsoi *et al.*, 2009).

2.6.2 Cohort studies

Since the previous *IARC Monograph* (IARC, 2004a), 22 additional cohort studies have investigated the association between tobacco smoke and colorectal cancer (Table 2.42 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.42.pdf). [Studies that did not provide point estimates of risk (Andersen *et al.*, 2009; Hansen *et al.*, 2009; Murphy *et al.*, 2009) and included prevalent colorectal cancer in patients with other diagnosis (Chan *et al.*, 2007) are excluded from this review]. Seven of the studies were conducted in Europe, nine in Asia and five in the USA. In eleven studies, risk estimates were reported solely for colorectal cancer (Tiemersma *et al.*, 2002a; Limburg *et al.*, 2003; Otani *et al.*, 2003; Colangelo *et al.*, 2004; Sanjoaquin *et al.*, 2004; Lüchtenborg *et al.*, 2005a; Kim *et al.*, 2006; Akhter *et al.*, 2007; Huxley, 2007a; Kenfield *et al.*, 2008; Hannan *et al.*, 2009), five studies separately for colon cancer and rectal cancer (Shimizu *et al.*, 2003; Wakai *et al.*, 2003; Jee *et al.*, 2004; Yun *et al.*, 2005; Batty *et al.*, 2008) and five studies both for colorectal cancer as well as for colon and rectal cancers (Terry *et al.*, 2002a; van der Hel *et al.*, 2003a; Doll *et al.*, 2005; Paskett *et al.*, 2007; Tsong *et al.*, 2007; Gram *et al.*, 2009). Six studies were restricted to women (Terry *et al.*, 2002a; Limburg *et al.*, 2003; van der Hel *et al.*, 2003a; Paskett *et al.*, 2007; Kenfield *et al.*, 2008; Gram *et al.*, 2009), and two studies to men (Doll *et al.*, 2005; Yun *et al.*, 2005; Akhter *et al.*, 2007). One study reported both colorectal incidence and mortality (Limburg *et al.*, 2003) and three studies only reported colorectal cancer mortality (Doll *et al.*, 2005; Huxley, 2007a; Batty *et al.*, 2008; Kenfield *et al.*, 2008).

(a) Smoking status

Virtually all studies reported elevated risk associated with smoking, although results were not always statistically significant. The largest meta-analysis based on 36 prospective studies

with data from a total of 3007002 subjects found that compared to never smokers, current smokers had a 15% significantly higher risk of developing colorectal cancer and 27% significantly higher risk of colorectal cancer mortality (Liang *et al.*, 2009; Table 2.43 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.43.pdf). In former smokers, colorectal cancer risk was also significantly elevated by 20% whereas colorectal cancer mortality was non-significantly increased by 20%. The risk estimates were not significantly different between colon and rectal cancer for current smokers (RR, 1.10 versus 1.19) and for former smokers (RR, 1.10 versus 1.20). There was no heterogeneity among colorectal cancer studies and no evidence for publication bias. Comparable risk elevations in current and former smokers were found in the other meta-analyses. For current smokers, the risk for colorectal cancer increased significantly by 16% when using data from 22 cohort studies (Huxley *et al.*, 2009), by 20% based on 28 cohort studies (Tsoi *et al.*, 2009), and by 7% based on data from 45 cohort and case–control studies (Botteri *et al.*, 2008a). In the latter meta-analysis a 17% significantly higher risk of colorectal cancer in former smokers was found.

(b) *Intensity of smoking*

All but three of the recent 21 cohort studies (van der Hel *et al.*, 2003a; Jee *et al.*, 2004; Sanjoaquin *et al.*, 2004) investigated dose–response relationships, using at least one of number of cigarettes smoked, duration of smoking, pack–years of smoking, age at smoking initiation, time since smoking cessation. In two further studies (Tiemersma *et al.*, 2002a; Batty *et al.*, 2008) these parameters were examined separately in current and former smokers, as by Chao *et al.* (2000). Statistically significant dose–response trends with amount smoked daily were reported for colorectal cancer (Lüchtenborg *et al.*, 2005a; Akhter *et al.*, 2007; Paskett *et al.*, 2007; Kenfield *et al.*, 2008), for colon cancer (Paskett *et al.*, 2007), and for rectal cancer (Paskett *et al.*, 2007; Tsong *et al.*, 2007). The dose–response of daily cigarette consumption and colorectal cancer was assessed in two meta-analyses (Liang *et al.*, 2009; Tsoi *et al.*, 2009) and both found statistically significant relationships. Based on eleven studies, Liang *et al.* (2009) found that risk for colorectal cancer increased significantly by 17% with an increase of 20 cigarettes/day and by 38% with an increase of 40 cigarettes/day, while colorectal cancer mortality increased by 41% and 98%, respectively (Table 2.43 online). The risk elevation associated with an increase of 20 cigarettes/day was greater for rectal than for colon cancer (13% versus 3%) but this difference was not statistically significant.

(c) *Duration of smoking*

In addition to two previously reported studies (Hsing *et al.*, 1998; Chao *et al.*, 2000), thirteen studies have examined duration of smoking and colorectal cancer risk. A statistically significant trend of increasing risk with increasing duration was found for colorectal (Limburg *et al.*, 2003; Kim *et al.*, 2006; Paskett *et al.*, 2007; Gram *et al.*, 2009), for colon cancer (Paskett *et al.*, 2007) and for rectal cancer (Terry *et al.*, 2002a; Paskett *et al.*, 2007; Tsong *et al.*, 2007). In one study, increasing duration of smoking was significantly associated with risk for colorectal cancer solely in former smokers (Tiemersma *et al.*, 2002a). Based on eight studies (Terry *et al.*, 2002a; Tiemersma *et al.*, 2002a; Limburg *et al.*, 2003; Lüchtenborg *et al.*, 2005a; Kim *et al.*, 2006; Akhter *et al.*, 2007; Paskett *et al.*, 2007; Tsong *et al.*, 2007), a meta-analysis for duration of smoking and colorectal cancer incidence yielded highly significant results (Liang *et al.*, 2009). Risk was increased by 9.4% with a 20-year increase in smoking duration and 19.7% with a 40-year increase. Smoking duration was also significantly associated with risk for rectal cancer but not for colon cancer. In another meta-analysis where dose–response relationship was modelled, a nonlinear increase in risk with

increasing duration was observed (Botteri *et al.*, 2008a). The risk started to increase after approximately 10 years of smoking and reached statistical significance after 30 years.

(d) Pack–years

Since the previous *IARC Monograph*, the association of colorectal cancer with pack–years of cigarette smoking has been evaluated in six studies (Limburg *et al.*, 2003; Otani *et al.*, 2003; Shimizu *et al.*, 2003; Wakai *et al.*, 2003; Kim *et al.*, 2006; Gram *et al.*, 2009). In addition to the previously reported significant results (Giovannucci *et al.*, 1994; Heineman *et al.*, 1994; Chao *et al.*, 2000; Stürmer *et al.*, 2000), a statistically significant trend of increasing risk with increasing pack–years was found for colorectal cancer in two studies (Limburg *et al.*, 2003; Gram *et al.*, 2009), and for colon cancer in one study (Gram *et al.*, 2009). In their dose–response analysis of pack–years and colorectal incidence, Liang *et al.* (2009) included five studies (Giovannucci *et al.*, 1994; Stürmer *et al.*, 2000; Limburg *et al.*, 2003; Otani *et al.*, 2003; Kim *et al.*, 2006) and found a statistically significant trend of increasing risk with increasing pack–years of smoking for colorectal cancer but not specifically for colon or rectal cancer. Risk for colorectal cancer increased by 27% for an increase of 35 pack–years and by 50% for an increase of 60 pack–years.

(e) Age at initiation

In nine of the cohort studies the age at smoking initiation in relation to colorectal cancer (eight studies) or colon and rectal cancer (four studies) was investigated. In four studies a statistically significant trend of increasing risk with decreasing age at initiation of smoking for colorectal cancer was found (Limburg *et al.*, 2003; Kim *et al.*, 2006; Akhter *et al.*, 2007; Gram *et al.*, 2009) and for colon cancer (Gram *et al.*, 2009) and rectal cancer (Tsong *et al.*, 2007). In one meta-analysis (Liang *et al.*, 2009), a highly significant association was found for age at smoking initiation and colorectal cancer incidence based on six studies (Limburg *et al.*, 2003; Kim *et al.*, 2006; Akhter *et al.*, 2007; Paskett *et al.*, 2007; Tsong *et al.*, 2007; Gram *et al.*, 2009). Risk for colorectal cancer was reduced by 2.2% for a 5-year delay in smoking initiation and by 4.4% for a 10-year delay.

(f) Smoking cessation

The effect of smoking cessation by years since stopping was assessed in seven studies, six for colorectal cancer (Tiemersma *et al.*, 2002a; Lüchtenborg *et al.*, 2005a, 2007; Paskett *et al.*, 2007; Kenfield *et al.*, 2008; Gram *et al.*, 2009; Hannan *et al.*, 2009) and three for colon and/or rectal cancer (Wakai *et al.*, 2003; Paskett *et al.*, 2007; Gram *et al.*, 2009). In one study a statistically significant trend in risk reduction with years since quitting was found both overall as well as separately for men and for women (Hannan *et al.*, 2009).

(g) Population characteristics

It has been suggested that the association between smoking and colorectal cancer may be stronger in men than in women. In the three recent cohort studies reporting sex–specific results (Shimizu *et al.*, 2003; Wakai *et al.*, 2003; Colangelo *et al.*, 2004), this was only observed in studies in Japan (Shimizu *et al.*, 2003; Wakai *et al.*, 2003), but could be attributed to the very low prevalence of smoking in women. The studies restricted to women have generally shown associations with cigarette smoking that were of comparable magnitude to those observed in men (Terry *et al.*, 2002a; Limburg *et al.*, 2003; van der Hel *et al.*, 2003a; Paskett *et al.*, 2007; Kenfield *et al.*, 2008; Gram *et al.*, 2009).

Recent studies have been carried out either in Europe and in USA, with predominantly Caucasian study subjects, or in Asia, mostly in Japan and in the Republic of Korea. The results from these studies suggest no differences in the association between tobacco smoking and

colorectal cancer between different ethnic groups.

(h) Subsites

Smoking and risks for colon cancer and for rectal cancer were investigated in eleven of the 21 additional studies. Risk patterns are generally consistent between colon and rectal cancer (Otani *et al.*, 2003; van der Hel *et al.*, 2003a; Wakai *et al.*, 2003; Jee *et al.*, 2004; Yun *et al.*, 2005; Batty *et al.*, 2008). In some studies, dose–response relationships were stronger for rectal cancer than for colon cancer (Terry *et al.*, 2002a; Paskett *et al.*, 2007) or were statistically significant only for rectal cancer (Shimizu *et al.*, 2003; Doll *et al.*, 2005; Tsong *et al.*, 2007). In a meta-analysis (Liang *et al.*, 2009) the association was stronger for rectal cancer than for colon cancer in the subset of cohort studies that differentiated cancer by site. Most dose–response variables were not associated with colon cancer incidence whereas associations were stronger for rectal cancer incidence and statistically significant with longer duration of smoking, albeit based only on a small number of studies. In one cohort study the increased risk associated with smoking was more apparent for proximal than for distal colon cancer (Lüchtenborg *et al.*, 2005a), which was not found in an earlier study (Heineman *et al.*, 1994).

(i) Confounding and effect modification

Smokers have been shown to be more likely than non-smokers to be physically inactive, to use alcohol, to have lower consumption of fruits and vegetables and higher consumption of fat and meat, and they are less likely to be screened for colorectal cancer (Le Marchand *et al.*, 1997; Ghadirian *et al.*, 1998; Nkondjock & Ghadirian, 2004; Reid *et al.*, 2006b; Mutch *et al.*, 2009).

Few potential confounders were considered in the cohort studies evaluated in the previous *IARC Monograph* (IARC, 2004a). Of the cohort studies published since, all except three (van der Hel *et al.*, 2003a; Jee *et al.*, 2004; Doll *et al.*, 2005) considered two or more potential confounders. In eleven of the recent studies adjustments were made for physical activity, alcohol consumption, overweight/obesity (Terry *et al.*, 2002a; Limburg *et al.*, 2003; Otani *et al.*, 2003; Wakai *et al.*, 2003; Yun *et al.*, 2005; Akhter *et al.*, 2007; Ashktorab *et al.*, 2007; Paskett *et al.*, 2007; Tsong *et al.*, 2007; Kenfield *et al.*, 2008; Hannan *et al.*, 2009), and seven also adjusted for dietary habits (e.g. intake of fruits and vegetables, dietary fibres, fat, red meat). Among the studies with the latter adjustments, eight (Giovannucci *et al.*, 1994; Chao *et al.*, 2000; Stürmer *et al.*, 2000; Limburg *et al.*, 2003; Yun *et al.*, 2005; Akhter *et al.*, 2007; Paskett *et al.*, 2007; Hannan *et al.*, 2009) found significant dose–response relationships with at least one of the smoking variables. In two studies a significant association of smoking with colorectal cancer risk was observed after accounting for history of colonoscopy (Paskett *et al.*, 2007; Hannan *et al.*, 2009). Risk factors in multivariable analyses in several studies were level of education, use of menopausal hormone therapy, family history and regular aspirin use. The association between smoking and colorectal cancer was not modified by these other characteristics, or by alcohol consumption in two studies (Otani *et al.*, 2003; Tsong *et al.*, 2007). Therefore, confounding factors do not seem to affect the observed significant increase in risk for colorectal cancer associated with tobacco smoking and the dose–response relationships with smoking variables.

When considering other types of smoking, it is generally found that cigar and pipe smoking are less associated with socioeconomic class and other life-style habits than cigarette smoking. Therefore, it is logical to assume that, for these types of smoking, risk associations derived from epidemiologic studies may be less prone to potential confounding. In all the cohort studies reviewed in the previous *IARC Monograph* (IARC, 2004a) an elevated, though not always statistically significant, risk was consistently reported for cancers of the colon and the rectum

associated with exclusive pipe and/or cigar smoking.

Infection with JC virus has been proposed as a potential risk factor for colon cancer (Rollison *et al.*, 2009) but results still need further validation.

Three cohort studies assessed possible modifying effects by genetic susceptibility. Rapid acetylator phenotype (as determined by polymorphisms of the *NAT2* gene involved in metabolism of heterocyclic aromatic amines) was found to increase the risk for colorectal cancer in smokers, in one (van der Hel *et al.*, 2003a) but not in another study (Tiemersma *et al.*, 2002a). For genes involved in the metabolism of polycyclic aromatic hydrocarbons such as *GSTM1* or *GSTT1,* no statistical contribution to the risk of colorectal cancer associated with smoking was observed (Tiemersma *et al.*, 2002a; Lüchtenborg *et al.*, 2005a).

2.6.3 Case–control studies

Thirty-one case–control studies were included in the previous *IARC Monograph* (IARC, 2004a). Although results were inconsistent with respect to risk association in ever versus former and current smokers, a dose–response relationship with smoking variables was found in some studies. Since then, seventeen case–control studies investigating the association between tobacco smoke and colorectal cancer risk have been published, seven carried out in Asia, four in Europe, five in North America and one in Hawaii (Table 2.44 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.44.pdf). Six studies reported solely for colorectal cancer (Ateş *et al.*, 2005; Chia *et al.*, 2006; Verla-Tebit *et al.*, 2006; Lüchtenborg *et al.*, 2007; Steinmetz *et al.*, 2007; Wu *et al.*, 2009b), four separately for colon and rectal cancer (Ji *et al.*, 2002; Sharpe *et al.*, 2002; Minami & Tateno, 2003; Goy *et al.*, 2008), two for colorectal cancer as well as for colon and rectal cancer (Ho *et al.*, 2004; Gao *et al.*, 2007; Wei *et al.*, 2009), three for colon cancer only (Diergaarde *et al.*, 2003; Kim *et al.*, 2003; Hu *et al.*, 2007) and one for rectal cancer only (Slattery *et al.*, 2003). Nine of the studies reported risk estimates separately for men and for women.

(a) Smoking status

Most case–control studies considered the effects of current and former smoking separately. A positive association between smoking and colorectal cancer was found in virtually all the studies, although the results were generally not statistically significant. Statistically significant increased risk was reported in current smokers for colorectal cancer (Chia *et al.*, 2006; Wu *et al.*, 2009b), for rectal cancer (Slattery *et al.*, 2003; Ho *et al.*, 2004), and in former smokers for colorectal cancer both in men and women combined (Chia *et al.*, 2006) and in women only (Lüchtenborg *et al.*, 2007). Five studies, which did not focus on the main effects of smoking, only evaluated risks for ever smoking (Diergaarde *et al.*, 2003; Kim *et al.*, 2003; Ateş *et al.*, 2005; Gao *et al.*, 2007; Hu *et al.*, 2007); none of these reported significant risk estimates.

(b) Intensity of smoking

Nine case–control studies investigated dose–response relationships considering at least one smoking variable. Number of cigarettes smoked daily was evaluated in seven studies, three for colorectal cancer (Verla-Tebit *et al.*, 2006; Lüchtenborg *et al.*, 2007; Wu *et al.*, 2009b), two for colon and rectal cancer (Ji *et al.*, 2002; Minami & Tateno, 2003), one for rectal cancer (Slattery *et al.*, 2003) and one for colorectal cancer and both subsites (Ho *et al.*, 2004). Statistically significant positive trends of increasing risk with increasing number of cigarettes smoked daily were found for colorectal cancer in only one study (Wu *et al.*, 2009b).

(c) *Duration of smoking, pack–years, age at initiation, smoking cessation*

Duration of smoking was examined in several studies in relation to colorectal cancer (Ho *et al.*, 2004; Chia *et al.*, 2006; Verla-Tebit *et al.*, 2006; Lüchtenborg *et al.*, 2007; Wu *et al.*, 2009b) and/or to colorectal cancer by subsite (Ji *et al.*, 2002; Minami & Tateno, 2003; Ho *et al.*, 2004). A statistically significant trend with increasing number of years smoked was found in two of the five studies of colorectal cancer (Chia *et al.*, 2006; Wu *et al.*, 2009b). In one study, increasing duration of smoking was significantly associated with risk for rectal cancer in ever smokers but not in current smokers (Ho *et al.*, 2004). In only one earlier case–control study was a significant association in ever smokers with increasing number of years of smoking for colon as well as rectal cancer found (Newcomb *et al.*, 1995).

Duration of smoking exposure was assessed by pack–years of smoking in seven studies (Ji *et al.*, 2002; Slattery *et al.*, 2003; Chia *et al.*, 2006; Verla-Tebit *et al.*, 2006; Lüchtenborg *et al.*, 2007; Goy *et al.*, 2008; Wu *et al.*, 2009b) and by age at smoking initiation in three studies (Ji *et al.*, 2002; Slattery *et al.*, 2003; Wu *et al.*, 2009b). All four studies that evaluated pack–years of smoking with respect to colorectal cancer risk found statistically significant associations. Two studies found a significant association with increasing pack–years in men and women combined; when investigated separately, the increasing trend was statistically significant only in women (Verla-Tebit *et al.*, 2006) or only in men (Wu *et al.*, 2009b). In one study a statistically significant trend with pack–years of smoking in both men and women was found only with non-filtered cigarettes (Lüchtenborg *et al.*, 2007); the relative risk was significant for colon as well as rectal cancer and was greater for rectal cancer.

In two studies a non-significant trend of decreasing risk with increasing time since stopped smoking was found (Verla-Tebit *et al.*, 2006; Lüchtenborg *et al.*, 2007).

(d) *Subsites and molecular subtypes*

A stronger association between tobacco smoking and rectal cancer compared with colon cancer has generally been observed in the studies that reported risk estimates by cancer site. In a recent meta-analysis including both cohort and case–control studies, higher smoking-related risk estimates for rectal cancer were found than for proximal and distal colon cancer (Botteri *et al.*, 2008a). Stronger relative risk in ever smokers, but not in current smokers, was found for proximal compared to distal tumours in one recent study (Hu *et al.*, 2007).

Colorectal cancer is a multipathway disease. A molecular approach to its classification utilizes: (1) the type of genetic instability, specifically microsatellite instability, and (2) the presence of DNA methylation or the CpG island methylator phenotype (CIMP) (Jass, 2007). Smoking has been associated with microsatellite instability in sporadic colon cancer. Higher risk for microsatellite-unstable than for microsatellite-stable tumours was found in four studies (Slattery *et al.*, 2000; Yang *et al.*, 2000; Chia *et al.*, 2006; Campbell *et al.*, 2009). The observed twofold risk elevation for colorectal cancer showing microsatellite instability is similar in order of magnitude to that found for colorectal polyps. In only one small study similar risk estimates for stable and unstable tumours were found (Diergaarde *et al.*, 2003). Microsatellite instability is characteristic of hereditary nonpolyposis colorectal cancer syndrome and smoking has been associated with colorectal cancer in patients with this syndrome (Watson *et al.*, 2004; Diergaarde *et al.*, 2007). Among sporadic colorectal tumours with microsatellite instability, about 11–28% carry somatic genetic mutations. In addition, the association of colon cancer with smoking was increased two to threefold when widespread CIMP and/or *BRAF* mutation, irrespective of microsatellite instability

status, was present (Samowitz *et al.*, 2006). These data indicate that the association with MSI-high tumours may be attributed to the association of smoking with CIMP and *BRAF* mutation.

(e) Effect modification

Effect modification by genetic polymorphisms in enzymes metabolizing tobacco smoke constituents could provide further evidence for a causal association between smoking and colorectal cancer. Most studies that have investigated modification of colorectal cancer risk associated with smoking by genetic polymorphisms of xenobiotic enzymes were too small to be informative (Inoue *et al.*, 2000; Smits *et al.*, 2003; Jin *et al.*, 2005; Tranah *et al.*, 2005; van den Donk *et al.*, 2005; Tijhuis *et al.*, 2008). Studies on the possible differential effect by acetylation status have reported stronger association of tobacco smoking (in terms of pack–years) with colorectal cancer risk in slow acetylators phenotypes (Lilla *et al.*, 2006), and with rectal cancer in rapid acetylators phenotypes (Curtin *et al.*, 2009). Furthermore, *CYP1A1* and *GSTM1* variant alleles were found to greatly affect colon cancer or rectal cancer risk in smokers (Slattery *et al.*, 2004).

2.6.4 Colorectal polyps

Colorectal adenomas and possibly some hyperplastic polyps are considered precursors of colorectal cancer. The epidemiologic evidence on the relationship between cigarette smoking and colorectal polyps has been generally consistent. Since the previous *IARC Monograph* (IARC, 2004a), twelve further independent studies have investigated this association (Table 2.45 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.45.pdf). All studies found a significantly increased risk for polyps in association with one or more smoking variables. A recent meta-analysis including 42 studies reported a statistically significant positive association between smoking and colorectal adenomas (Botteri *et al.*, 2008b). The meta-analysis, which included several studies that did not explicitly report relative risks for tobacco smoking (Cardoso *et al.*, 2002; Voskuil *et al.*, 2002; Sparks *et al.*, 2004; Gong *et al.*, 2005; Jiang *et al.*, 2005; Kim *et al.*, 2005; Mitrou *et al.*, 2006; Otani *et al.*, 2006; Skjelbred *et al.*, 2006), found a twofold risk elevation for colorectal adenomas in current smokers and a 50% increase in former smokers. The association had been previously found to be equally strong in men and women. In one of two recent studies, there was no difference in the results for men and women separately (Tranah *et al.*, 2004) but significantly greater effects in women were found in the other (Hermann *et al.*, 2009).

Significant positive trends with number of cigarettes per day were found in four (Ji *et al.*, 2006; Larsen *et al.*, 2006; Stern *et al.*, 2006; Shrubsole *et al.*, 2008) of five studies (Tiemersma *et al.*, 2004). Dose–response with duration of smoking was assessed in four studies (Ji *et al.*, 2002; Tiemersma *et al.*, 2004; Stern *et al.*, 2006; Shrubsole *et al.*, 2008) and with pack–years of smoking in five studies (Hoshiyama *et al.*, 2000; Ulrich *et al.*, 2001; Tranah *et al.*, 2004; Ji *et al.*, 2006; Shrubsole *et al.*, 2008; Omata *et al.*, 2009). All nine studies found statistically significant trends, which were consistent with those for adenomas and hyperplastic polyps when reported separately (Ulrich *et al.*, 2001; Ji *et al.*, 2006; Shrubsole *et al.*, 2008). Ever smokers were estimated to have a 13% (95%CI: 9–18%) increasing risk of presenting with adenomatous polyps for every additional 10 pack–years smoked in comparison to never smokers, based on data from 19 studies (Botteri *et al.*, 2008b).

Decreasing risks with years since quitting smoking were found in four studies (Ulrich *et al.*, 2001; Tiemersma *et al.*, 2004; Ji *et al.*, 2006; Shrubsole *et al.*, 2008), statistically significant so in the latter three studies. In comparison to never smokers, former smokers retained moderately elevated risk for colorectal polyps even 20

years after quitting smoking. One study examined both dose metrics (cigarettes per day, duration, and pack–years) and recency of tobacco use: in subjects who had quit smoking for at least 20 years, only the heaviest users of tobacco still had modest excess risks (Ji *et al.*, 2006).

It has been proposed that the association between cigarette smoking and polyps may be stronger with non-progressing adenomas, such as those that are smaller and less villous but the hypothesis is not supported in most studies (Anderson *et al.*, 2003; Toyomura *et al.*, 2004; Ji *et al.*, 2006; Skjelbred *et al.*, 2006). In one study a clearly higher risk for large and multiple adenomas in every anatomic site of the colon was found in a dose–response manner (Toyomura *et al.*, 2004). A meta-analysis found that the combined risk estimate for high-risk adenomas associated with smoking was greater than that for low-risk adenomas and that the difference was statistically significant for current smokers but not former smokers (Botteri *et al.*, 2008b). In addition, a stronger association of smoking with hyperplastic polyps than with adenomas was found in some studies (Ulrich *et al.*, 2001; Ji *et al.*, 2006; Shrubsole *et al.*, 2008) but not in another (Erhardt *et al.*, 2002). The risk associated with smoking may be even higher in subjects presenting with concurrent benign hyperplastic and adenomatous polyps (Ji *et al.*, 2006; Shrubsole *et al.*, 2008).

Relative risk estimates for tobacco smoking and polyps generally range between 2 and 3 whereas those for colorectal cancer range between 1.2 and 1.4. One possible explanation is the effect dilution due to the inclusion of a high proportion of individuals with precursor lesions in the unscreened control groups in most colorectal cancer studies (Terry & Neugut, 1998). Some indirect evidence for this hypothesis is provided by the meta-analysis of colorectal adenomas, which showed that the smoking-associated risk for adenomas was significantly higher in studies including subjects who had undergone complete colonoscopy in comparison to those in which some or all controls had undergone incomplete examination (i.e. only sigmoidoscopy) (Abrams *et al.*, 2008; Botteri *et al.*, 2008b).

It is also possible that smoking is associated with a subset of colorectal cancers so that relative risk estimates for colorectal cancer as a whole are diluted. The pattern of risk observed for colorectal cancer by microsatellite instability status and for type of colorectal polyps suggests that the traditional (non-serrated) adenoma-carcinoma sequence may proceed through a hyperplastic polyps-mixed polyps-serrated adenoma progression and that smoking may be more strongly related to the development of these subtypes (Jass *et al.*, 2000; Hawkins & Ward, 2001). More recently, a *BRAF* mutation was shown to be a specific marker for the serrated polyp neoplasia pathway originating from a hyperplastic polyp, in which the CIMP-high develops early and the microsatellite instability carcinoma develops late (O'Brien *et al.*, 2006). The findings of strong associations between smoking and colon cancer with CIMP and/or BRAF mutation, irrespective of microsatellite status, are compatible with this observation (Samowitz *et al.*, 2006).

2.7 Hepatocellular carcinoma

2.7.1 Overview of studies

In the previous *IARC Monograph* (IARC, 2004a), a causal relationship between liver cancer (hepatocellular carcinoma) and smoking was established. Two case–control and one cohort studies have been published since (Table 2.46 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.46.pdf). Overall, most cohort studies and the largest case–control studies, most notably those that included community controls, showed a moderate association between tobacco smoking and risk for hepatocellular carcinoma.

Confounding from alcohol has been addressed in the best studies. The association between alcohol drinking and hepatocellular carcinoma is strong, and alcohol intake is frequently misclassified, leading to potential residual confounding. However an association with smoking has been demonstrated also among non-drinkers.

A meta-analysis was based on 38 cohort studies and 58 case–control studies (Lee *et al.*, 2009). Compared to never smokers, the meta-relative risks adjusted for appropriate confounders were 1.51 (95%CI: 1.37–1.67) for current smokers and 1.12 (0.78–1.60) for former smokers. The increased liver cancer risk among current smokers appeared to be consistent in strata of different regions, study designs, study sample sizes, and publication periods. The association with smoking was observed in non-alcohol-drinkers (RR, 1.34; 95%CI: 0.92–1.94 in men and 1.31; 95%CI: 0.70–2.44 in women). Further supportive evidence is provided by the association between smoking and liver cancer observed among Chinese women and Japanese women, in whom alcohol drinking is extremely rare (Li *et al.*, 2011). One difficulty is that sometimes studies do not specify the histology of liver cancer (hepatocellular versus intra-hepatic biliary tract).

In the update of the Whitehall study (Batty *et al.*, 2008) (a cohort of 17363 government employees in London, followed-up for 38 years), the hazard ratio for death from liver cancer was 1.03 (0.49–2.16) in former smokers and 1.43 (0.69–2.95) in current smokers (based on 57 deaths). In the 50-year follow-up of the British doctors cohort (Doll *et al.*, 2005), there were 74 deaths from liver cancer. Death rates per 100000 per year were 4.4 in never smokers, 10.7 in smokers of 1–14 cigarettes/day, 2.6 in smokers of 15–24 cigarettes/day, and 31.3 in smokers of ≥ 25 cigarettes/day.

2.7.2 Factors affecting risks

(a) Dose–response relationship

Most studies, including the recent ones (Table 2.46 online), show a dose–response relationship with the number of cigarettes smoked and with smoking duration, with exceptions such as Franceschi *et al.* (2006) and some older studies from Asia. Relative risk estimates increased to 2.0 after 20 years of smoking.

(b) Cessation

Though former smokers tend to have lower relative risks than current smokers, there were no consistent patterns of risks after cessation, including in the recent studies (Table 2.46 online).

2.7.3 Interaction with hepatitis B or C

Infection with hepatitis B virus (HBV) is one of the major causes of liver cancer worldwide, whereas hepatis C virus (HCV) infection causes a large fraction of liver cancer in Japan, Northern Africa and southern Europe. While many studies, most notably from Asia, have found no attenuation of the association between smoking and liver cancer after adjustment/stratification for markers of HBV or HCV infection, an apparent interaction between smoking and HBV or HCV infection has been reported. The increase in risk for liver cancer associated with cigarette smoking appears to be greater among HBV carriers than among uninfected persons in some studies (Tu *et al.*, 1985), but not in others (Kuper *et al.*, 2000a). Two recent reports (Franceschi *et al.*, 2006; Hassan *et al.*, 2008a) studied possible interactions between smoking and hepatitis virus infection and both reported an apparent interaction between smoking and hepatitis C infection. Interactions between smoking and hepatitis B infection were not found among men in one study (Hassan *et al.*, 2008a) and the rarity of HBsAg prevented the evaluation of HBV and smoking in the other (Franceschi *et al.*, 2006;

Table 2.46 online). In the meta-analysis by Lee *et al.* (2009) adjustment for HBV reduced the relative risks in both men and women, while adjustment for HCV did not change the risk in women and increased it in men.

2.8 Renal cell carcinoma

2.8.1 Overview of studies

The previous *IARC Monograph* (IARC, 2004a) concluded that renal-cell carcinoma is associated with tobacco smoking in both men and women. Four case–control studies and no cohort studies have become available since then (Table 2.47 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.47.pdf). Overall these confirm the previous evidence, though with some conflicting results. In particular, both the study by Hu *et al.* (2005) in Canada and the multicentre European study by Brennan *et al.* (2008) do not show a clear effect of smoking. In contrast, the study by Theis *et al.* (2008) shows an increased risk with smoking duration (irregular, levelling-off after 40 years) and a statistically significant dose–response relationship with pack–years.

In the update of the Whitehall study (Batty *et al.*, 2008) (a cohort of 17363 government employees in London, followed for 38 years), the hazard ratio for deaths from kidney cancer was 0.64 (0.32–1.26) for former smokers, and 1.29 (0.69–2.41) for current smokers (based on 68 deaths). In the 50-year follow-up of the British doctor cohort (Doll *et al.*, 2005) there were 140 deaths from kidney cancer. Mortality rates per 100000 per year were 9.3 in never smokers, 16.4 in smokers of 1–14 cigarettes/day, 16.6 in smokers of 15–24 cigarettes/day, and 15.5 in smokers of ≥ 25 cigarettes/day (age-adjusted).

Hunt *et al.* (2005) performed a meta-analysis based on 19 case–control studies and 5 cohort studies (total 8032 cases in case–control and 1326 in cohort studies). The relative risk for smoking men was 1.54 (1.42–1.68), and for smoking women was 1.22 (1.09–1.36). A dose–response relationship was found in both men and women. The association observed was more convincing in population-based compared to hospital-based studies.

2.8.2 Confounding

Hypertension is a well established risk factor for kidney cancer but the association with smoking is only indirect. Potential confounding from hypertension was considered only by Brennan *et al.* (2008).

Other potential confounders such as BMI have been appropriately addressed in most studies.

2.8.3 Cessation

Most studies reviewed in the previous *Monograph* showed a lower risk for former smokers compared to current smokers, with a significant negative trend with increasing number of years since quitting (IARC, 2004a). In case–control study on smoking cessation and renal-cell carcinoma, the decrease in risk became significant only after 30 years of quitting (Parker *et al.*, 2003). In the meta-analysis (Hunt *et al.*, 2005), former smokers were at reduced risk after 10 years or more of quitting. A clear decline in risk after cessation was also reported by Theis *et al.* (2008). [The Working Group noted the poor quality of the study, considering the low response rate among controls.]

2.9 Cancer of the lower urinary tract (including cancer of the bladder, ureter, and renal pelvis)

2.9.1 Overview of studies

The previous *IARC Monograph* (IARC, 2004a) clearly identified a causal relationship of smoking with transitional-cell carcinomas and squamous-cell carcinomas of the bladder, ureter and renal pelvis both in men and women. Two new case–control studies (Cao *et al.*, 2005; Samanic *et al.*, 2006; Table 2.48 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.48.pdf) and two cohort studies (Bjerregaard *et al.*, 2006; Alberg *et al.*, 2007; Table 2.49 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.49.pdf) have been reported since then in addition to updates of cohort studies with longer follow-up.

In the update of the Whitehall study (Batty *et al.*, 2008) (a cohort of 17363 government employees in London, followed-up for 38 years), the hazard ratio for death from bladder cancer was 0.98 (0.62–1.54) in former smokers and 1.66 (1.06–2.59) in current smokers (based on 164 deaths). In the 50-year follow-up of the British doctors cohort (Doll *et al.*, 2005), there were 220 deaths from bladder cancer. Death rates per 100000 per year were 13.7 in never smokers, 37.7 in smokers of 1–14 cigarettes/day, 31.8 in smokers of 15–24 cigarettes/day, and 51.4 in smokers of ≥ 25 cigarettes/day. All the new studies confirm the existence of a dose–response relationship with the number of cigarettes smoked and with duration, and a decline in relative risk with time since quitting smoking, compared to non-quitters.

2.9.2 Types of tobacco

The risk of lower urinary tract cancer was more strongly associated with smoking air-cured (black) tobacco than smoking flue-cured (blond) tobacco in several studies (IARC, 2004a). The stronger association with air-cured (black) than blond tobacco among current smokers has not been clearly confirmed in a re-analysis of the Spanish multicentre case–control study (Samanic *et al.*, 2006). Relative risks in current smokers were 7.3 (4.9–10.9) in black tobacco smokers and 5.8 (3.4–10.0) in blond tobacco smokers; in former smokers, 4.2 (2.9–6.0) for black tobacco and 1.8 (1.0–3.2) for blond tobacco (Table 2.48 online). The effect of cessation was more pronounced in blond tobacco smokers than in black tobacco smokers, suggesting potentially different mechanisms of action of the two types of tobacco. Air-cured (black) tobacco is richer in arylamines.

2.9.3 Gene–environment interactions

A large number of studies have considered gene–environment interactions between tobacco smoking and genetic polymorphisms, including DNA repair genes (Vineis *et al.*, 2009) and genes involved in carcinogen metabolism (Malats, 2008; Dong *et al.*, 2008). Overall, there is evidence that the slow acetylator variant of the *NAT2* gene is involved in bladder carcinogenesis and may interact with smoking. The meta-relative risk for *NAT2* slow acetylator and bladder cancer was 1.46 (95%CI: 1.26–1.68; $P = 2.5 \times 10^{-7}$), based on 36 studies and 5747 cases (Dong *et al.*, 2008). Similar but weaker evidence has been provided for *GSTM1* (Malats, 2008).

The extent of interaction between *NAT2* variants and smoking is still unclear. In one study the *NAT2* acetylation status was found to modulate the association of bladder cancer and cigarette smoking through smoking intensity and not smoking duration (Lubin *et al.*, 2007). Studies are not consistent concerning the three-way association between smoking intensity, *NAT2* and bladder cancer. Some studies found greater effects at a lower level of exposure and others the opposite (Malats, 2008). Genome-wide

association studies have indicated 8q24 as a region that may confer high risk for bladder cancer (Kiemeney *et al.*, 2008).

2.10 Myeloid leukaemia (acute and chronic)

Myeloid leukaemia in adults was observed to be causally related to cigarette smoking in the previous *IARC Monograph* (IARC, 2004a). Risk increased with amount of tobacco smoked in a substantial number of adequate studies, with evidence of a dose–response relationship. Biological plausibility for a causal relationship of smoking with myeloid leukaemia is provided by the finding of known leukaemogens in tobacco smoke, one of which (benzene) is present in relatively large amounts. No evidence was found for an association with acute lymphocytic leukaemia.

One recently published cohort study included information on acute and chronic myeloid leukaemias (Fernberg *et al.*., 2007), based on 372 incident cases. A weak association was found between acute myeloid leukaemia and intensity of smoking, and a statistically significant association with current smoking (RR, 1.5; 95%CI: 1.06–2.11). No association was found with chronic myeloid leukaemia.

In the update of the Whitehall study (Batty *et al.*., 2008) (a cohort of 17363 government employees in London, followed-up for 38 years), the hazard ratio for mortality from myeloid leukaemias (acute plus chronic) was 5.08 (95%CI: 1.78–14.5) for current smokers, and 3.84 (95%CI: 1.35–11.0) for former smokers (based on 66 deaths). In the 50-year follow-up of the British doctors cohort (Doll *et al.*., 2005), there were 100 deaths from myeloid leukaemias. The mortality rates per 100000 per year were 6.3 in never smokers, 2.8 in smokers of 1–14 cigarettes/day, 14.0 in smokers of 15–24, and 18.3 in smokers of ≥ 25 cigarettes/day (age-adjusted).

2.11 Other leukaemias and lymphomas

2.11.1 Non-Hodgkin lymphoma

Six cohort studies have been published on the association between non-Hodgkin lymphoma and smoking, all reviewed in the previous *IARC Monograph* (IARC, 2004a). In five of these, no increased risk among smokers was evident (Doll *et al.*, 1994; McLaughlin *et al.*, 1995; Adami *et al.*, 1998; Herrinton & Friedman, 1998; Parker *et al.*, 2000). However, in one study, men who had ever smoked cigarettes had a twofold increase in risk for non-Hodgkin lymphoma, and the risk was still higher among the heaviest smokers (Linet *et al.*, 1992). Data from case–control studies generally also fail to support an effect of smoking on the incidence of non-Hodgkin lymphoma (Peach & Barnett, 2001; Stagnaro *et al.*, 2001; Schöllkopf *et al.*, 2005; Bracci & Holly, 2005; Table 2.50 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.50.pdf). Reanalysis of data of an Italian study (Stagnaro *et al.*, 2004) found a statistically significant association (OR, 1.4; 95%CI: 1.1–1.7) for blond tobacco exposure and non-Hodgkin lymphoma risk.

Three studies and a pooled analysis have examined histological subtypes of non-Hodgkin lymphoma. In one cohort study in women, smoking was associated with increased risk for follicular non-Hodgkin lymphoma (Parker *et al.*, 2000). Similarly, two other studies reported a weak positive association between smoking and risk for follicular lymphoma, but no effect for other histological types (Herrinton & Friedman, 1998; Stagnaro *et al.*, 2001). A large pooled analysis based on nine North-American and European case–control studies found an overall odds ratio of 1.07 (95%CI: 1.0–1.15) for smokers; the association was particularly strong for follicular lymphoma (OR, 1.31; 95%CI: 1.12–1.52) (Morton *et al.*, 2005).

2.11.2 Hodgkin lymphoma

In the previous *IARC Monograph* (IARC, 2004a) seven studies on the association between Hodgkin lymphoma and smoking were examined and null or weakly positive associations were noted. Among studies published since, a positive association was observed in two case–control (Willett *et al.*, 2007; Kanda *et al.*, 2009) and three cohort studies (Nieters *et al.*, 2006; Lim *et al.*, 2007; Nieters *et al.*, 2008), while one study found no clear association (Monnereau *et al.*, 2008). Several other recent studies also reported a positive association, but with some internal inconsistencies. In a European multicentre case–control study, no association was observed between tobacco and Hodgkin lymphoma for subjects below age 35 years, whereas for older subjects, ever-smokers experienced a doubled risk of Hodgkin lymphoma as compared to never smokers (Besson *et al.*, 2006). In contrast, a positive association was observed in young adults participating in the International Twin Study (Cozen *et al.*, 2009). A positive association was observed in a Scandinavian case–control study, but without a clear dose–response (Hjalgrim *et al.*, 2007). In a case–control study addressing infectious precursors, particularly Epstein-Barr virus (EBV), an increased risk for EBV-positive Hodgkin lymphoma was found among current smokers (Glaser *et al.*, 2004; Table 2.50 online).

Several of the above studies found positive associations for Hodgkin lymphoma while also demonstrating null or inverse associations with non-Hodgkin lymphoma (Nieters *et al.*, 2006; Lim *et al.*, 2007; Nieters *et al.*, 2008; Kanda *et al.*, 2009).

2.11.3 Multiple myeloma

In the previous *IARC Monograph* (IARC, 2004a), the large majority of studies on tobacco smoking and risk for multiple myeloma evaluated showed no clear association. More recently, two case–control studies found a positive association (Vlajinac *et al.*, 2003; Nieters *et al.*, 2006), whereas no clear association was observed in another case–control study (Monnereau *et al.*, 2008) or in a cohort study in Sweden (Fernberg *et al.*, 2007; Table 2.51 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.51.pdf).

2.12 Cancer of the breast

Approximately 150 epidemiological studies have been published on the relationship between breast cancer and active and passive smoking. The results from these studies have been comprehensively examined in peer-reviewed literature (Palmer & Rosenberg, 1993; Terry *et al.*, 2002a; Johnson *et al.*, 2002; Johnson, 2005; Terry & Goodman, 2006; Miller *et al.*, 2007). The previous *IARC Monograph* (IARC, 2004a) considered studies conducted through June 2002 and concluded that there is evidence suggesting lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast.

Other consensus reviews have drawn different conclusions, based partly on the availability of new data, and partly on differences in interpretation:

- The 2001 US Surgeon General Report on Women and Smoking (Department of Health & Human Services, 2001) concluded that tobacco smoking does not appear to appreciably affect breast cancer risk overall. However, several issues were not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether exposure to second-hand smoke affects risk.
- The 2004 US Surgeon General report on "The Health Consequences of Smoking" (Department of Health & Human

Services, 2004) concluded the evidence is suggestive of no causal relationship between tobacco smoking and breast cancer.

- The 2009 Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (Collishaw *et al.*, 2009) concludes that based on the weight of evidence from epidemiological and toxicological studies and understanding of biological mechanisms, the associations between tobacco smoking and both pre- and post-menopausal breast cancer are consistent with causality.

The lack of agreement in the conclusions from these groups is not surprising, given that the observed associations are weaker and less consistent for breast cancer than for other tobacco-related cancers. Furthermore, several methodological considerations could either obscure a small increase in risk caused by tobacco smoking, or alternatively introduce a spurious association where no causal relationship exists.

2.12.1 Methodological and related issues

The principal concerns about studies of tobacco smoking and breast cancer are the following: timing of exposure, the relevant disease endpoint, the potential for confounding by factors associated with both smoking and the occurrence/detection of breast cancer, the hypothesis that tobacco smoking may have opposing effects on breast cancer risk (protective and detrimental), and the hypothesis that some women may be genetically more susceptible to develop breast cancer from smoking, and that increased risk in these subgroups may be obscured in analyses of average risk in the population.

(a) Misclassification of exposure

Self-reported information on tobacco smoking is generally considered more reliable than questionnaire information on exposure to second-hand tobacco smoke. However, studies of tobacco smoking have not uniformly considered the duration of smoking (years), the average amount smoked (cigarettes/day), or the timing of initiation in relation to first full-term pregnancy. Only one (Al-Delaimy *et al.*, 2004) of the seven available cohort studies updated the information on smoking behaviour during follow-up. Whereas some exposure variables, such as age at initiation and age at first full-term pregnancy remain constant over time, others, such as smoking status, duration and age at cessation do not. Furthermore, the average age at initiation and duration of smoking are highly correlated with birth cohort and attained age. While the number of years of smoking before first full term pregnancy has been proposed as a potentially relevant measure of exposure, the range of this variable is constrained except among women whose first pregnancy occurs at an older age, which is itself an independent risk factor for breast cancer.

(b) Specificity of disease endpoints

Breast cancer is not a single disease. Accordingly, some researchers have postulated that exposure to tobacco smoke (from tobacco smoking or second-hand tobacco smoke) could differentially affect certain clinical subtypes of breast such as pre- or post-menopausal cancers or tumours with or without hormonal receptors. It is also possible that smoking might affect the survival of women with breast cancer, whether or not it affects incidence rates. Most published studies have measured incidence rates as the endpoint, although some have measured mortality rates or effects on survival.

(c) Confounding

Alcohol consumption is positively correlated with tobacco smoking (Marshall *et al.*, 1999) and is an established cause of breast cancer (IARC, 2010a; *Monograph* on Consumption of Alcoholic Beverages in this Volume). Most epidemiologic studies attempt to control for alcohol consumption using questionnaire information on usual drinking patterns. This approach is vulnerable to residual confounding, because self-reported data on lifetime alcohol consumption leave room for misclassification. Potential confounding by alcohol consumption is of greater concern for current than for former smokers, since, on average, current smokers drink more than former smokers (Reynolds *et al.*, 2004a, b). One study by the Collaborative Group on Hormonal Factors and Breast Cancer (Hamajima *et al.*, 2002) controlled rigorously for alcohol consumption by restricting the analysis of smoking and breast cancer to women who reported drinking no alcohol.

Conversely, mammography screening can be a negative confounder in studies of tobacco smoking and breast cancer incidence. Few studies of tobacco smoking in relation to breast cancer have controlled for mammography screening. Current smokers report a lower frequency of mammographic screening than never-smokers, whereas health conscious former smokers report higher screening rates (Gross *et al.*, 2006). Mammography screening affects the detection rather than the occurrence of breast cancer; it detects some tumours that might otherwise never have been recognized and allows earlier diagnosis of others, thereby increasing breast cancer incidence in the short-term. The consequence of uncontrolled confounding by mammography screening would be to underestimate an association between current smoking and breast cancer incidence, and to overestimate the association in former smokers. Confounding by screening would be expected to have the opposite effect in studies of breast cancer mortality.

Other correlates of tobacco smoking might also confound a potential association between tobacco smoking and breast cancer, although their net effect is likely to be smaller and harder to predict than confounding by alcohol and mammography screening. Women who smoke undergo menopause about two to three years earlier than never-smokers (Baron *et al.*, 1990). The effect of this may be partly or wholly offset by the greater likelihood of girls who experience early menarche to initiate smoking in early adolescence (Jean *et al.*, 2011). There is no documentation that smokers and never-smokers differ with respect to average years of ovulation. Tobacco smoking also has a complex relationship to body mass index. Post-menopausal women who smoke are less likely to be overweight or obese than former or never smokers, but overweight adolescent girls are more likely to begin smoking for weight control (Fine *et al.*, 2004). Similarly complex relationships exist between smoking and physical activity. Current smokers report less physical activity than either former or never smokers (Kaczynski *et al.*, 2008; Trost *et al.*, 2002), but only a small proportion of the population engages in the vigorous physical activity that is needed to protect against breast cancer. The socioeconomic correlates of smoking have changed over time. Women who attended college during the 1960s and 1970s were more likely to initiate smoking than less educated women, but subsequently college-educated women have been more likely to quit. Thus, the potential for confounding by reproductive patterns and use of post-menopausal hormone treatment varies by birth cohort and differs for current and former smokers.

Most epidemiological studies have attempted to control for factors that might confound the relationship between breast cancer and tobacco smoking using questionnaire information collected on these factors. None of the published

studies have been able to control for all of the potential confounders, however. Most studies lack data on screening behaviour and have limited information on alcohol consumption, use of post-menopausal hormones, and physical activity.

(d) Potential anti-estrogenic effects of tobacco smoking

Indirect evidence suggests that tobacco smoking may have anti-estrogenic effects that might offset the adverse effects of tobacco smoke carcinogens on breast cancer risk. Baron *et al.* (1990) pointed to observations suggesting lower estrogen activity levels in women who smoke compared to those who do not. Smokers have lower risk of endometrial cancer (Department of Health & Human Services, 2004), higher risk of osteoporosis (Jensen *et al.*, 1985; Jensen & Christiansen, 1988), earlier age at natural menopause (Baron *et al.*, 1990) and lower mammography density (Roubidoux *et al.*, 2003) than women who do not smoke. Smoking also attenuates the effects of hormone replacement therapy (HRT) on lipid profiles (Jensen & Christiansen, 1988) and serum estrone (McDivit *et al.*, 2008). No difference in serum concentrations of estradiol and estrone between post-menopausal smokers and non-smokers have been reported in several studies (Cassidenti *et al.*, 1992; Khaw *et al.*, 1988; Berta *et al.*, 1991; Longcope *et al.*, 1986; Berta *et al.*, 1992; Cauley *et al.*, 1989; Friedman *et al.*, 1987; Key *et al.*, 1991). However, smokers have been observed to have higher levels of androgens (Cassidenti *et al.*, 1992) (specifically androstenedione) (Khaw *et al.*, 1988; Cauley *et al.*, 1989; Friedman *et al.*, 1987; Key *et al.*, 1991), prolactin (Berta *et al.*, 1991), and unbound serum estradiol (Cassidenti *et al.*, 1992).

(e) Genetically susceptible subgroups

Certain subgroups of women may have greater risk of breast cancer when exposed to tobacco smoke because of genetic or other factors affecting cancer susceptibility. Potential interactions between inherited polymorphisms and tobacco smoking have been studied for selected candidate genes that affect carcinogen metabolism, modulation of oxidative damage, immune responses, and DNA repair (see Sections 2.12.4b and 4.2).

2.12.2 Analytical studies

Over 130 epidemiological studies on tobacco smoking and breast cancer were reviewed.

(a) Incidence in current and former smokers

Since the previous *IARC Monograph* (IARC, 2004a), seven reports on cohort studies (Al-Delaimy *et al.*, 2004; Reynolds *et al.*, 2004a; Gram *et al.*, 2005; Hanaoka *et al.*, 2005; Olson *et al.*, 2005; Cui *et al.*, 2006; Ha *et al.*, 2007) have been published on breast cancer incidence in relation to tobacco smoking (Table 2.52 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.52.pdf). Breast cancer incidence was significantly associated with current tobacco smoking in three studies (Reynolds *et al.*, 2004a; Olson *et al.*, 2005; Cui *et al.*, 2006), with relative risk estimates among the larger studies ranging from 1.12 (95%CI: 0.92–1.37) (Al-Delaimy *et al.*, 2004) to 1.32 (95%CI:1.10–1.57) (Reynolds *et al.*, 2004a). Former smoking was significantly associated with risk in only one cohort (Al-Delaimy *et al.*, 2004), with relative risk estimates across all of the cohorts ranging from 1.00 (95%CI: 0.93–1.08) (Cui *et al.*, 2006) to 1.18 (95%CI: 1.02–1.36) (Al-Delaimy *et al.*, 2004). The association with breast cancer is stronger in current than in former smokers in four of the seven cohort studies (Reynolds *et al.*, 2004a; Hanaoka *et al.*, 2005; Olson *et al.*, 2005; Cui *et al.*, 2006), although the confidence intervals overlap widely in all but one (Cui *et al.*, 2006). [The Working group noted that three cohort studies (Gram *et al.*, 2005; Hanaoka *et al.*, 2005; Olson *et al.*, 2005) provided data on both

the age-adjusted and the multivariate-adjusted risk estimates for current and former smoking. None of these showed attenuation of the estimate associated with current smoking, and two (Hanaoka *et al.*, 2005; Olson *et al.*, 2005) reported somewhat stronger estimates when adjusted for established risk factors besides age. None of the studies adjusted for the frequency of mammography screening. Residual confounding by screening and incomplete control for other risk factors would be expected to cause underestimation of the association with current smoking, and overestimation of the association with former smoking.]

Since the previous *IARC Monograph* (IARC, 2004a), a total of 12 case–control studies on tobacco smoking and breast cancer incidence have been published (Table 2.53 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.53.pdf). Results from the case–control studies are less consistent than those from the cohort studies. Six studies (Li *et al.*, 2004; Mechanic *et al.*, 2006; Magnusson *et al.*, 2007; Prescott *et al.*, 2007; Roddam *et al.*, 2007; Slattery *et al.*, 2008) differentiated between current and former smokers, while the six other reports (Band *et al.*, 2002; Lash & Aschengrau, 2002; Gammon *et al.*, 2004; Rollison *et al.*, 2008; Ahern *et al.*, 2009; Young *et al.*, 2009) specify only ever or never smokers. Only one study (Li *et al.*, 2004) reported a borderline significant increase in risk associated with current smoking, and two studies (Band *et al.*, 2002; Rollison *et al.*, 2008) with ever smoking.

None of the six case–control studies that presented data on breast cancer incidence separately for current and former smokers found a significant difference in risk between the two smoking categories; the relative risk estimates were higher for former than for current smokers in four of the studies (Mechanic *et al.*, 2006; Prescott *et al.*, 2007; Roddam *et al.*, 2007; Slattery *et al.*, 2008) and identical in the fifth (Magnusson *et al.*, 2007).

(b) Years of cessation

When the relative risk for breast cancer incidence in former smokers is examined by years since cessation in cohort studies (Table 2.54 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.54.pdf), the point estimates do not consistently decrease with longer time since cessation. In none of the four cohort studies (London *et al.*, 1989b; Egan *et al.*, 2002; Reynolds *et al.*, 2004a; Cui *et al.*, 2006) and in only one (Li *et al.*, 2005) of the five case–control studies (Chu *et al.*, 1990; Gammon *et al.*, 1998; Johnson *et al.*, 2000; Kropp & Chang-Claude, 2002; Li *et al.*, 2005) that formally tested for trend (Table 2.55 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.55.pdf) was there a statistically significant decrease in relative risk observed with longer time since cessation. Only one study has reported data on breast cancer mortality in relation to years since quitting or age at cessation (Calle *et al.*, 1994). A statistically significant inverse trend in the relative risk estimates was reported with both years since quitting (p trend = 0.04) and younger age at cessation (p trend = 0.02). [The Working Group noted that the inverse trends in the relative risk of dying from breast cancer observed in this study are weaker than those observed with most other cancers designated as causally associated with smoking.]

(c) Duration of smoking and age at initiation

Tables 2.56–2.61 (see below for links) list the published epidemiologic studies that relate breast cancer incidence to duration of tobacco smoking, age at initiation and/or timing relative to first full term pregnancy.

Longer duration of smoking is associated with higher breast cancer incidence in five of seven cohort studies (Table 2.56 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.56.pdf). A similar trend is seen inconsistently among the 33 case–control

studies that report relative risk estimates by duration of smoking (Table 2.57 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.57.pdf). Among the 18 studies that reported a formal test of trend, eight studies (Gammon *et al.*, 1998; Johnson *et al.*, 2000; Reynolds *et al.*, 2004a; Gram *et al.*, 2005; Li *et al.*, 2005; van der Hel *et al.*, 2005; Cui *et al.*, 2006; Mechanic *et al.*, 2006) reported a statistically significant or borderline increase in the relative risk of incident breast cancer with the duration of smoking; seven studies (Ewertz, 1990; Palmer *et al.*, 1991; Egan *et al.*, 2002; Al-Delaimy *et al.*, 2004; Lissowska *et al.*, 2006; Magnusson *et al.*, 2007; Prescott *et al.*, 2007) reported no trend, and one study (Brinton *et al.*, 1986) reported an inverse relationship.

Thirty studies, including cohort (Tables 2.58 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.58.pdf) and case–control studies (Table 2.59 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.59.pdf) related breast cancer incidence to age at smoking initiation. Fifteen of these (Chu *et al.*, 1990; Ewertz, 1990; Palmer *et al.*, 1991; Nordlund *et al.*, 1997; Gammon *et al.*, 1998; Johnson *et al.*, 2000; Egan *et al.*, 2002; Kropp & Chang-Claude, 2002; Gram *et al.*, 2005; Cui *et al.*, 2006; Lissowska *et al.*, 2006; Ha *et al.*, 2007; Lissowska *et al.*, 2007; Magnusson *et al.*, 2007; Prescott *et al.*, 2007; Slattery *et al.*, 2008) reported a formal test of trend. Among these, only two (Gram *et al.*, 2005; Ha *et al.*, 2007) found a statistically significant or borderline significantly higher risk in women who began smoking at a younger ages; twelve studies (Chu *et al.*, 1990; Ewertz, 1990; Palmer *et al.*, 1991; Nordlund *et al.*, 1997; Gammon *et al.*, 1998; Johnson *et al.*, 2000; Egan *et al.*, 2002; Cui *et al.*, 2006; Lissowska *et al.*, 2006; Magnusson *et al.*, 2007; Prescott *et al.*, 2007; Slattery *et al.*, 2008) found no relationship with age at initiation, and one (Kropp & Chang-Claude, 2002) reported higher risk among women who began smoking later. [The Working Group noted that at least two studies (Cui *et al.*, 2006; Slattery *et al.*, 2008) appear to have included never-smokers in the tests of trend and that the categories that define age at initiation differ across studies.]

The relative risk of incident breast cancer according to the timing of smoking initiation relative to first full-term pregnancy was reported in 21 studies, of cohort (Table 2.60 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.60.pdf) and case–control (Table 2.61 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.61.pdf) design. For nine studies (Hunter *et al.*, 1997; Egan *et al.*, 2002; Al-Delaimy *et al.*, 2004; Reynolds *et al.*, 2004a; Li *et al.*, 2005; Cui *et al.*, 2006; Prescott *et al.*, 2007; Rollison *et al.*, 2008; Young *et al.*, 2009) categorical data on years of smoking before first pregnancy are presented, whereas for 12 (Lash & Aschengrau, 1999; Innes & Byers, 2001; Band *et al.*, 2002; Kropp & Chang-Claude, 2002; Lash & Aschengrau, 2002; Fink & Lash, 2003; Lawlor *et al.*, 2004; Gram *et al.*, 2005; Olson *et al.*, 2005; Lissowska *et al.*, 2006; Magnusson *et al.*, 2007; Slattery *et al.*, 2008) whether smoking was initiated before or after the initial pregnancy was considered. Breast cancer incidence is consistently higher when smoking began before or during first pregnancy in most (Hunter *et al.*, 1997; Lash & Aschengrau, 1999; Innes & Byers, 2001; Band *et al.*, 2002; Egan *et al.*, 2002; Al-Delaimy *et al.*, 2004; Reynolds *et al.*, 2004a; Gram *et al.*, 2005; Li *et al.*, 2005; Olson *et al.*, 2005; Cui *et al.*, 2006; Slattery *et al.*, 2008; Young *et al.*, 2009) but not all (Kropp & Chang-Claude, 2002; Lash & Aschengrau, 2002; Fink & Lash, 2003; Prescott *et al.*, 2007) studies that tested this. [The Working Group noted that the number of years of smoking before first pregnancy is highly correlated with age at first full-term pregnancy, which is itself an independent risk factor for breast cancer.]

It has been argued that some studies, and especially cohort studies, may underestimate

the true association between tobacco smoking and breast cancer risk by ignoring or underestimating lifetime exposure to second-hand tobacco smoke of those in the referent group (California Environmental Protection Agency, 2005; Johnson, 2005; Collishaw *et al.*, 2009). This criticism is based on the hypothesis that exposure to second-hand smoke may confer almost the same degree of breast cancer risk as tobacco smoking. Under this hypothesis, the inclusion of women exposed to second-hand smoke in the referent group dilutes the contrast between exposed and unexposed women in studies of tobacco smoking, and causes underestimation of the association between tobacco smoking and breast cancer. In several case–control studies the association between breast cancer and tobacco smoking strengthened when the referent group was defined as women with "never active, never-passive" exposure to tobacco smoke (Morabia *et al.*, 1996; Lash & Aschengrau, 1999; Johnson *et al.*, 2000; Kropp & Chang-Claude, 2002). In contrast, a stronger association between tobacco smoking and breast cancer risk, when women exposed only to second-hand smoke are excluded from the referent group, has not been observed in cohort studies (Egan *et al.*, 2002; Reynolds *et al.*, 2004a). Debate continues over whether the case–control studies should be considered "of highest quality" because they provide "lifetime exposure assessment" (Collishaw *et al.*, 2009) or whether the cohort studies are more credible, because prospectively-collected exposure data are not susceptible to the recall bias that can affect retrospective studies.

(d) Survival and mortality from breast cancer

The relationship between smoking and the natural history of breast cancer has been examined in several studies (Daniell, 1988; Ewertz *et al.*, 1991; Daniell *et al.*, 1993; Scanlon *et al.*, 1995; Yu *et al.*, 1997; Manjer *et al.*, 2000; Murin & Inciardi, 2001; Holmes *et al.*, 2007). In cross-sectional analyses, Daniell *et al.* (1993) found that smokers with breast cancer had more and larger lymph node metastases than non-smokers, after controlling for primary tumour size and other variables. Further, a case–control study (Murin & Inciardi, 2001) and a retrospective cohort study (Scanlon *et al.*, 1995) found smoking to be associated with an increased risk of developing pulmonary metastases from breast cancer. However, these studies could not definitively distinguish lung metastases from primary lung cancers.

Five cohort studies have focused specifically upon the association of tobacco smoking with either breast cancer survival (Ewertz *et al.*, 1991; Yu *et al.*, 1997; Manjer *et al.*, 2000; Holmes *et al.*, 2007) or breast cancer death rates (Calle *et al.*, 1994). A study of 1774 Danish women showed no association between smoking and breast cancer survival (Ewertz *et al.*, 1991), as did a study of 5056 women with breast cancer in the Nurse's Health Study (Holmes *et al.*, 2007). In contrast, follow-up of 792 women with in situ or invasive breast cancer detected in a screening study in Malmø, Sweden found a crude relative risk for smokers and ex-smokers, compared to never smokers, of 1.44 (95%CI: 1.01–2.06) and of 1.13 (95%CI: 0.66–1.94), respectively (Manjer *et al.*, 2000). The relative risk associated with smoking remained significant after adjustment for age and stage at diagnosis (RR, 2.14; 95%CI: 1.47–3.10). A study based on the ACS Cancer Prevention Study II reported an association between current smoking and increased breast cancer death rates after six years of follow-up (Table 2.56 online; Calle *et al.*, 1994). Risk of death attributed to breast cancer was positively and significantly related to the duration of current smoking reported at the time of enrolment. However, the authors acknowledge that mortality studies cannot exclude biases arising from the effect of smoking on overall death rates, which could increase the potential for prevalent breast cancer to be coded as the underlying cause of death on the death certificate (Calle *et al.*, 1994).

2.12.3 Subtypes

(a) Pre- versus post-menopausal

Since the previous *IARC Monograph* (IARC, 2004a), 19 case–control studies have published data on tobacco smoking in relation to pre- and post-menopausal breast cancer (Table 2.62 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.62.pdf). The results are inconsistent. Of the 12 studies that provide information separately for current smokers (Schechter *et al.*, 1985; Brinton *et al.*, 1986; Rohan & Baron, 1989; Ewertz, 1990; Baron *et al.*, 1996; Gammon *et al.*, 1998; Millikan *et al.*, 1998; Johnson *et al.*, 2000; Zheng *et al.*, 2002; Magnusson *et al.*, 2007; Slattery *et al.*, 2008), only five (Schechter *et al.*, 1985; Johnson *et al.*, 2000; Magnusson *et al.*, 2007; Slattery *et al.*, 2008) found a stronger association with pre- than with post-menopausal breast cancer. The other analyses show either similar associations (Brinton *et al.*, 1986; Ewertz, 1990; Baron *et al.*, 1996; Gammon *et al.*, 1998; Millikan *et al.*, 1998; Zheng *et al.*, 2002) or a stronger association with post-menopausal breast cancer (Rohan & Baron, 1989; Millikan *et al.*, 1998; Johnson *et al.*, 2000; Zheng *et al.*, 2002).

(b) Hormone receptor status

Two cohort studies (London *et al.*, 1989a; Manjer *et al.*, 2001), one case–control study (Morabia *et al.*, 1998) and a case series (Yoo *et al.*, 1997) have examined the association between quantitative measures of cigarette smoking and breast cancer risk according to estrogen receptor (ER) status. In one of the cohort studies (Manjer *et al.*, 2001), a statistically significant increased risk (RR, 1.6) of ER negative tumours associated with current smoking was found but no clear association between smoking and ER positive tumours, and no difference in the association with progestogen receptor (PR)-positive and PR-negative tumours. In the other three studies there was no clear difference in the association related to ER or PR receptor status.

2.12.4 Susceptible populations

More than 30 studies and meta-analyses (Alberg *et al.*, 2004; Terry & Goodman, 2006; Ambrosone *et al.*, 2008; Collishaw *et al.*, 2009) have evaluated whether a family history of breast cancer and/or inherited polymorphisms in various genes may confer greater susceptibility to develop breast cancer from exposure to tobacco smoke. These are described below in relation to the measure indicating potential susceptibility.

(a) Family history

In two studies, whether a family history of breast cancer modifies susceptibility to develop breast cancer from tobacco smoking has been examined. Couch *et al.* (2001) measured breast cancer incidence among female family members in a cohort of breast cancer cases diagnosed between 1944 and 1952 at the University of Minnesota. Sisters and daughters in families with at least three breast and/or ovarian cancers were at 2.4 fold higher risk for breast cancer (95%CI: 1.2–5.1) if they smoked compared to never-smokers. No dose–response was observed in relation to pack–years of smoking.

Suzuki *et al.* (2007) reported a statistically significant interaction between family history of breast cancer and smoking history in a hospital-based case–control study of 3861 breast cancer cases treated at a large cancer centre in Japan between 1988 and 2000. A family history of breast cancer in the absence of smoking was associated with a relative risk of 1.44 (95%CI: 1.21–1.71); the relative risk estimate was 1.95 (95%CI: 1.36–2.81) in women who reported < 30 pack–years of tobacco smoking, and 4.33 (95%CI: 1.65–11.40) in women who reported > 30 pack–years of smoking.

[The Working group noted that Japanese women who smoked during this time period

may have differed from never-smokers in other characteristics related to breast cancer. Besides its strong correlation with female smoking, "Westernization" might be associated with delayed childbearing, smaller families, higher body mass index, and greater use of post-menopausal hormones.]

(b) Genetic polymorphisms

Studies of breast cancer, smoking and low penetrance genetic polymorphisms are summarized in Table 2.63 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.63.pdf). The candidate genes in these studies are involved in carcinogen metabolism [*N*-acetyltransferases (*NAT1, NAT2*), cytochrome P450s (*CYP1A1, CYP1B1, CYP2E2*), GSTs], host responses to oxidative stress (superoxide dismutase) or to infectious organisms (myeloperoxidase and immunoglobulin binding protein) and DNA repair (O^6-methylguanine DNA methyltransferase, nucleotide excision repair).

The most consistent associations with breast cancer risk have been observed among long-term smokers with the *NAT2* slow acetylation genotype (Terry & Goodman, 2006). *NAT2* slow acetylation genotype is thought to confer less capability to detoxify tobacco smoke carcinogens and is associated with an increase in breast cancer risk (Ambrosone *et al.*, 1996, 2008). Approximately 50–60% of Caucasian women are reported to be slow acetylators.

Table 2.63 (online) lists 15 studies of polymorphisms in *NAT2*, of which 9 were included in a pooled analysis and 13 in a meta-analysis (Ambrosone *et al.*, 2008). [The study by Delfino *et al.* (2000) was excluded from these analyses because cases included women with benign breast disease; the study by Lilla *et al.* (2005) was not considered because it is based on the same population as that by Chang-Claude *et al.* (2002).] The meta-analysis found a statistically significant association between ever tobacco smoking and breast cancer risk among women with the *NAT2* slow acetylator genotype (meta-RR, 1.27; 95%CI: 1.16–1.40) but not in those with rapid acetylator genotype (meta-RR, 1.05; 95%CI: 0.95–1.17). Pack–years of tobacco smoking was significantly associated with increasing breast cancer risk among women with *NAT2* slow acetylator genotype (meta-RR for ever smokers, 1.44; 95%CI: 1.23–1.68, for > 20 pack–years versus never smokers), but not among rapid acetylators (Ambrosone *et al.*, 2008). No main effect was seen between *NAT2* status and breast cancer risk (meta-RR, 1.0; 95%CI: 0.93–1.07). In contrast to an earlier meta-analysis (Alberg *et al.*, 2004), this study observed no difference in risk for pre- or post-menopausal breast cancer. The pooled analysis of nine studies (Ambrosone *et al.*, 2008) reported pooled risk estimates for pre- and post-menopausal women of 1.49 (95%CI: 1.08–2.04) and 1.42 (95%CI: 1.16–1.74), respectively, among women with slow *NAT2* genotype and at least 20 pack–years of smoking compared to never-smokers. The corresponding values for women with rapid acetylator genotype were 1.29 (95%CI: 0.89–1.86) and 0.88 (95%CI: 0.69–1.13). A statistically significant interaction was observed between pack–years of smoking as a continuous variable and *NAT2* genotype (p interaction = 0.03).

A population-based case–control study published after the meta-analysis by Ambrosone *et al.* compared the prevalence of the *NAT2* genotypes and their joint effect with smoking on breast cancer risk in Hispanic and non-Hispanic white women (Baumgartner *et al.*, 2009). Non-Hispanic white women were more likely ($P < 0.001$) than Hispanics to have a slow (41.7% versus 33.5%) or very slow (19.0% versus 11.1%) *NAT2* acetylator status. Breast cancer risk was significantly increased in non-Hispanic smoking white women with a very slow acetylator genotype (RR, 2.46; 95%CI: 1.07–5.65 for current versus never).

[The Working Group noted that publication bias remains a concern in the studies of *NAT2* published to date. All of the studies included in the meta-analysis by Ambrosone *et al.* were published between 1996 and 2006; some among them (Morabia *et al.*, 2000; Sillanpää *et al.*, 2007) reported very strong associations that seem inconsistent with the rest of the data. Because genetic studies often examine multiple genes, it is plausible that studies that find no main effect with *NAT2* have not examined this association or that null results for smoking have not been published.]

Fewer studies with less consistent findings have been published on polymorphisms in other genes such as *NAT1*, *CYP1A1*, *GST*, *NOS3*, *MPO*, *MnSOD2* and various DNA repair genes (Table 2.63 online).

2.12.5 High penetrance genes & prognosis

At least seven studies have examined the hypothesis that tobacco smoking may modify breast cancer risk among women who carry *BRCA1* and *BRCA2* mutations (Brunet *et al.*, 1998; Ghadirian *et al.*, 2004; Colilla *et al.*, 2006; Gronwald *et al.*, 2006; Nkondjock *et al.*, 2006; Breast Cancer Family Registry, 2008; Ginsburg *et al.*, 2009). The results have been inconsistent. A recent case–control study of women under age 50 years who were carriers of mutations in *BRCA1* or *BRCA2* reported increased risk for breast cancer associated with as little as five pack–years of smoking. Compared to non-smokers, the risk associated with five or more pack–years of smoking was 2.3 (95%CI: 1.6–3.5) for *BRCA1* mutation carriers and 2.6 (95%CI: 1.8–3.9) for *BRCA2* mutation carriers (Breast Cancer Family Registry, 2008). In contrast, six other studies reported no increased risk among *BRCA1* or *BRCA2* carriers who smoke. The Canadian Panel review (Collishaw *et al.*, 2009) postulated that the five previous studies (Brunet *et al.*, 1998; Ghadirian *et al.*, 2004; Colilla *et al.*, 2006; Gronwald *et al.*, 2006; Nkondjock *et al.*, 2006) may have failed to observe a relationship because they included prevalent cases. However, a sixth study published since the Canadian panel review is also negative (Ginsburg *et al.*, 2009).

2.13 Cancer of the cervix

The association between smoking and cervical cancer has been examined in many epidemiological studies over the past few decades.

Since the previous *IARC Monograph* (IARC, 2004a), additional epidemiological studies have been published. Study design and results of the case–control studies restricted to HPV positive women or that adjusted for HPV status are presented in Table 2.64 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.64.pdf) and Table 2.65 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.65.pdf). Cohort studies and pooled analyses are presented in Table 2.66 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.66.pdf) and Table 2.67 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.67.pdf), respectively. Table 2.68 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.68.pdf) and Table 2.69 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.69.pdf) present additional cohort studies and pooled analyses on tobacco smoking and cervical, cervical intraepithelia neoplasia and carcinoma in situ, with our without controlling for HPV status, respectively.

2.13.1 Dose–response relationship

A positive association between smoking and incidence of cervical squamous-cell carcinoma, which account for approximately 90% of all cervical cancers, has been shown consistently over several decades in many epidemiological studies

of various designs conducted across different geographic regions. Dose–response associations with smoking intensity and duration were noted in many of the studies where such associations were examined (Berrington de González *et al.*, 2004; Appleby *et al.*, 2006). Conversely, no clear association was found among former smokers. For adenocarcinoma of the cervix, which usually account for less than 10% of the total of all types of cervical cancer, there appears to be no clear association with smoking (Berrington de González *et al.*, 2004).

2.13.2 Interaction with HPV positivity

Epidemiological studies of smoking and cervical cancer increasingly have considered the effects of HPV infection, which is recognized as the main etiological factor for invasive and pre-invasive cervical neoplasia worldwide (IARC, 1995, 2012b). HPV infection has been considered not only with respect to possible effect modification (Hellberg & Stendahl, 2005; Gunnell *et al.*, 2006), but also to confounding, as both HPV infection and smoking habits are directly associated with number of sexual partners and other indications of high-risk sexual behaviours (Sikström *et al.*, 1995; Wang *et al.* 2004; Hellberg & Stendahl, 2005; McIntyre-Seltman *et al.*, 2005; Syrjänen *et al.*, 2007). Although there have been exceptions (Syrjänen *et al.*, 2007), recent studies have generally continued to show that statistical adjustment for the potential confounding effects of HPV infection, or restricting studies to women with high risk HPV infection (Plummer *et al.*, 2003), does not appreciably alter the finding of a positive association or its magnitude (McIntyre-Seltman *et al.*, 2005; Appleby *et al.*, 2006; Tolstrup *et al.*, 2006; Tsai *et al.*, 2007; Nishino *et al.*, 2008; Kapeu *et al.*, 2009).

Statistical adjustment for the potentially confounding effect of HPV infection was usually based on the measured presence of HPV DNA in cervical cells or anti-HPV serum antibodies in multivariate analytical models; as noted above, studies have also restricted their analyses to HPV-positive cases and controls. As there is currently no reliable marker of persistent HPV infection, case–control studies based on a cross-sectional measurement of HPV cannot distinguish between transient and persistent infections (Franco *et al.*, 1999). Tobacco smoking is suspected to facilitate acquisition or persistence of an HPV infection through a reduced number of Langerhans cells and CD4 lymphocytes, which are markers of local immune response in the cervix (Vaccarella *et al.*, 2008). In addition, smoking may affect innate immunity (Ferson *et al.*, 1979). Current smokers have been shown to have a slightly higher HPV prevalence than non-smokers in a broad range of world populations after adjustment for life-time number of sexual partners (OR, 1.18; 95%CI: 1.01–1.39) (Vaccarella *et al.*, 2008). Studies have evaluated the effect of smoking on HPV persistence. One study shows lower probability of HPV clearance among ever smokers (Giuliano *et al.*, 2002) but a few others found no relationship (Molano *et al.*, 2003; Richardson *et al.*, 2005).

2.14 Cancer of the endometrium

2.14.1 Overview of studies

To date, at least 42 epidemiological studies have examined the association between smoking and endometrial cancer, 25 reviewed in the previous *IARC Monograph* (IARC, 2004a) and 17 published since then (Petridou *et al.*, 2002; Folsom *et al.*, 2003; Furberg & Thune, 2003; Newcomb & Trentham-Dietz, 2003; Beral *et al.*, 2005; Matthews *et al.*, 2005; Viswanathan *et al.*, 2005; Okamura *et al.*, 2006; Strom *et al.*, 2006; Trentham-Dietz *et al.*, 2006; Weiss *et al.*, 2006a; Al-Zoughool *et al.*, 2007; Bjørge *et al.*, 2007; Lacey *et al.*, 2007; Loerbroks *et al.*, 2007; Setiawan *et al.*, 2007; Lindemann *et al.*, 2008). Study design and results of the additional studies

are presented separately for the case–control studies (Table 2.70 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.70.pdf and Table 2.71 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.71.pdf, respectively) and for the cohort studies (Table 2.72 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.72.pdf and Table 2.73 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.73.pdf, respectively).

(a) Cohort studies

The majority of the 13 cohort studies (Engeland *et al.*, 1996; Terry *et al.*, 1999, 2002b; Folsom *et al.*, 2003; Furberg & Thune 2003; Beral *et al.*, 2005; Viswanathan *et al.*, 2005; Al-Zoughool *et al.*, 2007; Bjørge *et al.*, 2007; Lacey *et al.*, 2007; Loerbroks *et al.*, 2007; Setiawan *et al.*, 2007; Lindemann *et al.*, 2008) suggest a decreased risk among current smokers, including the largest study with over 9000 cases (Bjørge *et al.*, 2007). In five of these studies quantitative smoking measures have been examined in relation to endometrial cancer risk (Terry *et al.*, 1999, 2002b; Viswanathan *et al.*, 2005; Al-Zoughool *et al.*, 2007; Loerbroks *et al.*, 2007). Of these, one (Terry *et al.*, 1999) found a 50% reduced risk among current smokers in the highest level of intensity (11 cigarettes per day or more) compared with non-smokers, but the number of cases was low and the confidence intervals correspondingly wide. A more recent and larger cohort study (Terry *et al.*, 2002b) found a statistically significant 40% reduced risk among current smokers of more than 20 cigarettes per day, but showed somewhat weaker and statistically non-significant reductions in risk with smoking of long duration or high cumulative consumption (i.e. pack–years). In contrast, the risk among former smokers was similar to that among never smokers. The largest of these studies generally showed decreasing risk of endometrial cancer with increasing smoking intensity, duration, and pack–years of consumption (Viswanathan *et al.*, 2005). Three studies examined the association between time since smoking cessation and endometrial cancer risk. Two of these studies suggested a positive association with time since quitting (compared with non-smokers) (Viswanathan *et al.*, 2005; Loerbroks *et al.*, 2007), whereas one found no association (Terry *et al.*, 2002b).

(b) Case–control studies

The results of 17 population-based case–control studies (Smith *et al.*, 1984; Tyler *et al.*, 1985; Franks *et al.*, 1987; Elliott *et al.*, 1990; Rubin *et al.*, 1990; Brinton *et al.*, 1993; Goodman *et al.*, 1997; Shields *et al.*, 1999; Jain *et al.*, 2000; McCann *et al.*, 2000; Newcomer *et al.*, 2001; Weiderpass & Baron, 2001; Newcomb & Trentham-Dietz, 2003; Matthews *et al.*, 2005; Strom *et al.*, 2006; Trentham-Dietz *et al.*, 2006; Weiss *et al.*, 2006a), that have included between 46 and 1304 endometrial cancer cases, generally have shown reductions in risk among current smokers compared with never smokers (although the magnitude of the reduction in risk has varied somewhat); results among former smokers compared with never smokers were equally variable, albeit somewhat weaker overall. The results of eight hospital-based case–control studies (Kelsey *et al.*, 1982; Lesko *et al.*, 1985; Levi *et al.*, 1987; Stockwell & Lyman, 1987; Koumantaki *et al.*, 1989; Austin *et al.*, 1993; Petridou *et al.*, 2002; Okamura *et al.*, 2006), which included between 83 and 1374 endometrial cancer cases, are somewhat consistent with those of population-based studies. They showed moderate (e.g. 30–40%) reduction in risks among current compared with never smokers, and unaltered risks (or perhaps a small 10–20% reduction in risk) in former compared with never smokers. The largest of the hospital-based studies (Stockwell & Lyman, 1987), with 1374 cases and 3921 controls, found both former and current smokers to be at moderately (approximately 30%) reduced risk

of endometrial cancer. To date, six population-based case–control studies (Tyler *et al.*, 1985; Lawrence *et al.*, 1987, 1989; Brinton *et al.*, 1993; Newcomer *et al.*, 2001; Weiderpass & Baron, 2001) have examined quantitative measures of smoking in relation to endometrial cancer risk, generally showing inverse associations to be strongest among current smokers of high intensity or long duration.

2.14.2 Confounders

Whereas the majority of these studies adjusted their relative risk estimates for potentially confounding variables, such as BMI, HRT, parity, diabetes, and age at menopause, studies that did not adjust for these variables tended to show similar inverse associations. Within individual studies, statistical adjustment for the effects of BMI and other covariates often made little difference, although some attenuation of relative risk estimates has been noted (Weiderpass & Baron, 2001; Terry *et al.*, 2002c).

2.14.3 Effect modification

The association between smoking and endometrial cancer risk according to factors that are known determinants of endogenous hormone concentrations, and which may counteract or augment possible tobacco-related hormonal changes, have been examined in several studies. These factors include menopausal status, HRT and BMI. Effect modification can reflect true underlying differences in the association across strata (for example, if cigarette smoking acts to reduce or modify estrogen concentrations differently in one group compared with another), but can also reflect methodological factors, such as differences that occur by chance or through the varying prevalence of confounding variables.

(a) Menopausal status

Although endometrial cancer is rare among pre-menopausal women, several studies have examined the association between cigarette smoking and endometrial cancer risk according to menopausal status, because the effect of smoking (if any) might vary according to the underlying hormonal milieu. The studies have included two cohort studies (Terry *et al.*, 2002b; Al-Zoughool *et al.*, 2007), five population-based case–control studies (Smith *et al.*, 1984; Franks *et al.*, 1987; Lawrence *et al.*, 1987; Brinton *et al.*, 1993; Weiderpass & Baron, 2001), and four hospital-based case–control studies (Lesko *et al.*, 1985; Levi *et al.*, 1987; Stockwell & Lyman, 1987; Koumantaki *et al.*, 1989). In all but one of these studies, a study of early stage endometrial cancer (Lawrence *et al.*, 1987), the inverse association was (to varying degrees) stronger among post-menopausal than pre-menopausal women. Among pre-menopausal women, the relative risk estimates for cigarette smoking have been inconsistent, sometimes showing increased risks with certain measures of cigarette smoking (Smith *et al.*, 1984; Stockwell & Lyman, 1987; Koumantaki *et al.*, 1989; Brinton *et al.*, 1993; Al-Zoughool *et al.*, 2007), sometimes showing decreased risks (Lawrence *et al.*, 1987; Levi *et al.*, 1987; Brinton *et al.*, 1993; Terry *et al.*, 2002b), and sometimes showing practically no association (Lesko *et al.*, 1985; Weiderpass & Baron, 2001; Al-Zoughool *et al.*, 2007). In analyses limited to post-menopausal women, on the other hand, all showed between 10% and 80% reduced risks of endometrial cancer with the various smoking measures.

(b) Hormone replacement therapy

Given the possibility that cigarette smoking affects hormone concentrations mostly among women who are taking HRT (Jensen *et al.*, 1985; Jensen & Christiansen, 1988; Cassidenti *et al.*, 1990), the inverse association between tobacco

smoking and endometrial cancer risk might be stronger among HRT users than among non-users. However, the results of studies that have examined the association between smoking and endometrial cancer risk according to HRT use have been equivocal (Weiss *et al.*, 1980; Franks *et al.*, 1987; Lawrence *et al.*, 1987; Levi *et al.*, 1987; Terry *et al.*, 2002b; Beral *et al.*, 2005). Whereas in two studies (Franks *et al.*, 1987; Levi *et al.*, 1987) a larger reduction in risk among smokers taking HRT than among smokers not taking HRT was observed, in two other studies (Lawrence *et al.*, 1987; Terry *et al.*, 2002b) there was no difference in the association according to HRT status. A cohort study that examined associations only among women using HRT showed no clear association among users of continuous combined HRT and cyclic combined HRT, but some suggestion of increased risk among smokers who used tibolone (perhaps more clearly among former smokers) (Beral *et al.*, 2005). Thus, although effect modification by HRT status is biologically plausible, the available epidemiological evidence is equivocal.

(c) Relative body weight

Obesity is an established risk factor for endometrial cancer (IARC, 2002). Smokers tend to have a lower BMI than non-smokers, although former smokers tend to have a higher BMI than current or never smokers (Baron *et al.*, 1990). Two case–control studies have examined the association between cigarette smoking and endometrial cancer risk according to BMI, one population-based (Elliott *et al.*, 1990) and one hospital-based (Levi *et al.*, 1987). Neither of these studies found clear differences in the association between smoking and endometrial cancer risk according to BMI. In a population-based case–control study of early stage endometrial cancer (Lawrence *et al.*, 1987), the inverse association with cigarette smoking tended to become stronger with increasing absolute rather than relative body weight.

2.14.4 Gene polymorphisms

Cigarette smoking and estrogen are both thought to influence cancer risk through pathways that are under the control of specific genes, such as those involved in the formation of bulky DNA adducts by estrogen metabolites (Cavalieri *et al.*, 2000) and both bulky and non-bulky adducts formed by carcinogens in tobacco smoke (Terry & Rohan, 2002). Therefore, studies have been conducted to examine the association between smoking and endometrial cancer risk according to genes that repair these types of DNA damage. In a moderately-sized population-based case–control study no clear effect modification according to certain polymorphisms in the *XPA* and *XPC* genes, both of which are involved in the nucleotide excision repair of bulky DNA adducts and may influence endometrial cancer risk, were found (Weiss *et al.*, 2005, 2006b). A nested case–control study also showed no clear effect modification according to three polymorphisms in *CYP1A1* (McGrath *et al.*, 2007), a gene that encodes microsomal CYP1A1, which contributes to aryl hydrocarbon hydroxylase activity, catalysing the metabolism of PAHs and other carcinogens found in tobacco smoke (Masson *et al.*, 2005). In another nested case–control study some evidence was found that the association between smoking and endometrial cancer may vary according to a polymorphism (Ile^{143}Val) in O^6-methylguanine DNA methyltransferase (*MGMT*). Overall, studies that address the association between smoking and endometrial cancer risk according to genotype are scarce.

2.15 Cancer of the prostate

Many epidemiological studies have examined the association between cigarette smoking and prostate cancer risk, and most have shown no consistent association (Hickey *et al.*, 2001; Levi & La Vecchia, 2001; Batty *et al.*, 2008; Butler

et al., 2009; Huncharek *et al.*, 2010; Table 2.74 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.74.pdf; Table 2.75 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.75.pdf). However, questions remain regarding whether smoking may alter risk in various population subgroups, for example, those defined by certain genotypes, and whether any association with smoking may be stronger for, or limited to, advanced tumours or prostate cancer mortality. Regarding this latter issue, the majority of epidemiological studies, including several large, long-term cohort studies, have reported a positive association between smoking and prostate cancer mortality (Rohrmann *et al.*, 2007; Zu & Giovannucci, 2009). Several studies that examined smoking in relation to both prostate cancer incidence and mortality tend to show positive results only for the latter (Rohrmann *et al.*, 2007; Zu & Giovannucci, 2009). Given the largely null results with respect to prostate cancer incidence, the latter findings suggest that smoking is less likely to be a causal agent in prostate cancer initiation than an agent that acts on existing tumours to promote their progression (Zu & Giovannucci, 2009).

A recent review of smoking and prostate cancer that focused specifically on aggressive and fatal tumours, considered the findings from 14 cohort studies (Zu & Giovannucci, 2009). Nine of these studies showed statistically significant increased risk with at least one smoking measure, and five showed increased risks that were not statistically significant for any measure. Only one study showed no association with any measure of tobacco consumption. Seven studies of various designs examined smoking with respect to indicators of cancer aggressive behaviour at the time of diagnosis. In these studies smoking was associated positively with tumour grade, risk of regional, distant, extraprostatic or metastatic disease, Gleason score, and biochemical outcome (failure) after prostate brachytherapy and in several dose–response associations with the respective endpoint were demonstrated. In one study smoking cessation was associated with a decline in risk compared with that among current smokers.

The association between smoking and prostate cancer risk according to genotype and other potentially effect-modifying factors have been examined in several studies. For example, in a population-based case–control study tobacco use was a risk factor for prostate cancer primarily among men with high BMI (Sharpe & Siemiatycki, 2001). The results of a cohort study in Switzerland suggest that risk of prostate cancer mortality is increased in smokers, particularly those with low plasma vitamin E levels (Eichholzer *et al.*, 1999). These latter associations, as well as those regarding several genotypes that may modify the association (Mao *et al.*, 2004; Nock *et al.*, 2006; Quiñones *et al.*, 2006; Yang *et al.*, 2006; Iguchi *et al.*, 2009; Kesarwani *et al.*, 2009), have yet to be fully clarified.

[The Working Group noted that several of the studies of smoking and prostate cancer mortality did not demonstrate clear dose–response associations with risk, and noted the possibility of bias due to confounding by screening behaviour. However, in the Health Professionals Follow-up Study, screening behaviour was not found to differ appreciably between smokers and non-smokers. In an analysis limited to men with a negative digital rectal examination in the prior two years, stronger associations were found between smoking and metastatic prostate cancer risk among high intensity smokers (RR, 4.2; 95%CI: 1.6–10.9) (Zu & Giovannucci, 2009). This finding was evidence against bias from screening behaviour.]

2.16 Cancer of the ovary

2.16.1 Overview of studies

A total of over 30 epidemiological studies have investigated the association between tobacco smoking and ovarian cancer risk. Of these, 24 were case–control studies (IARC, 2004a; Table 2.76 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.76.pdf; Table 2.77 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.77.pdf) and six were cohort studies (IARC, 2004a; Table 2.78 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.78.pdf; Table 2.79 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.79.pdf). Most studies showed no statistically significant association between a measure of smoking and risk for ovarian cancer overall (Newhouse *et al.*, 1977; Smith *et al.*, 1984; Tzonou *et al.*, 1984; Baron *et al.*, 1986; Stockwell & Lyman, 1987; Whittemore *et al.*, 1988; Hartge *et al.*, 1989; Polychronopoulou *et al.*, 1993; Engeland *et al.*, 1996; Goodman *et al.*, 2001; Goodman & Tung, 2003; Pan *et al.*, 2004; Zhang *et al.*, 2004; Kurian *et al.*, 2005; Niwa *et al.*, 2005; Baker *et al.*, 2006; Huusom *et al.*, 2006; Fujita *et al.*, 2008; Lurie *et al.*, 2008; Nagle *et al.*, 2008; Tworoger *et al.*, 2008); some showed positive associations (Doll *et al.*, 1980; Tverdal *et al.*, 1993; Kuper *et al.*, 2000b; Marchbanks *et al.*, 2000; Green *et al.*, 2001; Modugno *et al.*, 2002; Gram *et al.*, 2008; Rossing *et al.*, 2008) and one (Riman *et al.*, 2004) showed an inverse association.

2.16.2 Histological subtypes

Differences in ovarian cancer risk factor profiles have been observed according to histological type, on the basis of which it has been suggested that mucinous and non-mucinous tumours are etiologically distinct diseases (Risch *et al.*, 1996). Epidemiological studies that have considered histological type tend to support a positive association primarily between cigarette smoking and mucinous ovarian tumours (Kuper *et al.*, 2000b; Marchbanks *et al.*, 2000; Green *et al.*, 2001; Modugno *et al.*, 2002; Pan *et al.*, 2004; Zhang *et al.*, 2004; Kurian *et al.*, 2005; Tworoger *et al.*, 2008). In contrast, two studies showed no clear association between smoking and risk of mucinous or non-mucinous ovarian tumours (Riman *et al.*, 2004; Baker *et al.*, 2006). In addition, one early case–control study (Newhouse *et al.*, 1977), with 300 ovarian cancer cases and with both population and hospital controls, found no clear association with "ever" compared with "never" smoking, and reported no differences according to histological type.

A pooled analysis of 10 case–control studies (Kurian *et al.*, 2005) with 254 cases of mucinous and 1580 non-mucinous tumours found an increased risk of mucinous tumours among current smokers (RR, 2.4; 95%CI: 1.5–3.8), a positive association that was not observed with other histological types. Former smokers in that analysis did not have an increased risk of any histological type of ovarian cancer. This type of dose–response, whereby current smokers have a higher risk than former smokers, was observed in most, but not all, studies of mucinous ovarian cancer (Tables 2.77 and 2.79 online). Overall, the positive association between cigarette smoking and risk of mucinous ovarian tumours is generally consistent across both case–control and cohort studies conducted among various populations. In contrast, associations with smoking have been mostly null with respect to non-mucinous ovarian tumours, suggesting that recall bias is unlikely to explain the association with mucinous tumours.

[The Working Group considered the possibility that women who smoke may come to medical attention more frequently. This raises the possibility of detection bias, because mucinous tumours, benign or malignant, tend to be quite large and could be more easily detected on routine physical exam or testing. However, the

Working Group felt that detection bias would not account for the association entirely.

2.17 Cancer of the thyroid

The previous *IARC Monograph* (IARC, 2004a) noted inconsistent associations between smoking and thyroid cancer risk. In 2003, a pooled analysis of 14 case–control studies showed that smoking was inversely associated with thyroid cancer risk (Mack *et al.*, 2003; Table 2.80 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.80.pdf; Table 2.81 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.81.pdf). The sample consisted of 2725 thyroid cancer cases (2247 women, 478 men) and 4776 controls (3699 women, 1077 men). The inverse association was stronger among current smokers (RR, 0.6; 9% CI: 0.6–0.7) than former smokers (RR, 0.9; 9% CI: 0.8–1.1) and were similar in both men and women, for both papillary and follicular thyroid cancers, as well as by age and region. An inverse association between smoking and thyroid cancer risk was also found in a subsequent case–control study (Nagano *et al.*, 2007). In contrast, two case–control studies (Zivaljevic *et al.*, 2004; Bufalo *et al.*, 2006) reported no clear association between smoking and thyroid cancer risk (no risk ratio estimates were reported; hence, data are not shown in the tables) and a cohort study with 169 incident cases of thyroid cancer, also found no clear association with any qualitative or quantitative smoking measure (Navarro Silvera *et al.*, 2005; Table 2.82 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.82.pdf; Table 2.83 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.83.pdf).

2.18 Other cancers

The cancers reviewed in this section generally have low incidence and mortality rates and are not considered to be strongly associated with cigarette smoking. This raises the possibility of preferential reporting of positive associations in epidemiological studies.

2.18.1 Cancer of the salivary gland

Studies of smoking and cancers of the salivary gland reviewed in the previous *IARC Monograph* (IARC, 2004a) were sparse and their results were inconsistent (Spitz *et al.*, 1990; Swanson & Burns, 1997; Hayes *et al.*, 1999). A few additional studies also show inconsistent results (Kotwall, 1992; Pinkston & Cole, 1996; Horn-Ross *et al.*, 1997; Vories & Ramirez, 1997; Muscat & Wynder, 1998). Studies that focused specifically on Warthin's tumour [papillary cystadenoma lymphomatosum or adenolymphoma, a benign tumour of the parotid gland] tend to show strong positive associations with smoking (Kotwall, 1992; Pinkston & Cole, 1996; Vories & Ramirez, 1997). One study (Pinkston & Cole, 1996) compared the risk for Warthin's tumour with that for other salivary gland tumours and found that smoking increased risk significantly only for Warthin's tumour.

2.18.2 Cancer of the small intestine

Epidemiological studies (all of case–control design) reviewd in the previous *IARC Monograph* (IARC, 2004a) have been inconsistent in showing a positive association between smoking and cancers of the small intestine (Chow *et al.*, 1993b; Chen *et al.*, 1994; Wu *et al.*, 1997; Negri *et al.*, 1999; Kaerlev *et al.*, 2002). A more recent study showed no clear association (Hassan *et al.*, 2008b).

2.18.3 Cancers of the gallbladder and extra-hepatic bile ducts

Epidemiological studies of smoking and risk of cancers of the gallbladder and extra-hepatic bile ducts reviewed in the previous *IARC Monograph* (IARC, 2004a) tended to show null, weak, or moderately strong positive associations. More recent studies also tend to show either no clear association with biliary tract carcinoma/extra-hepatic cholangiocarcinoma (Shaib *et al.*, 2007; Welzel *et al.*, 2007) or suggest positive associations with gallbladder/biliary cancers (Pandey & Shukla, 2003; Yagyu *et al.*, 2008; Grainge *et al.*, 2009). Attention should be paid to potential confounders, especially BMI, when considering the results of epidemiological studies of risk of cancers of the gallbladder and extra-hepatic bile ducts. Recent studies that statistically adjusted for BMI, on gallbladder disease risk (Grainge *et al.*, 2009) or on extrahepatic biliary tract carcinoma risk (Ahrens *et al.*, 2007), showed a positive and null association with smoking, respectively. To date, there are too few studies with adequate control for potentially confounding factors to determine any clear pattern.

2.18.4 Soft-tissue sarcoma

As reported in the previous *IARC Monograph* (IARC, 2004a), one cohort study found an association between cigarette smoking and mortality from soft-tissue sarcoma after 26 years of follow-up but no dose–response relationship with the number of cigarettes/day, duration of smoking or pack–years (Zahm *et al.*, 1992). No effect of cigarette smoking was detected in an Italian hospital-based case–control study (Franceschi & Serraino, 1992).

2.18.5 Cancer of the skin

(a) Melanoma

Several case–control studies found no difference in the prevalence of tobacco smoking between patients with malignant melanoma and controls, and one study found an inverse association (IARC, 2004a). An inverse association with smoking was also found in the US Radiologic Technologists cohort Study (Freedman *et al.*, 2003a). In that study, smoking for at least 30 years compared with never smoking was inversely related to melanoma risk (RR, 0.6; 95%CI: 0.3–1.3), though risk was not associated with number of cigarettes/day. An inverse association was also observed in a cohort of Swedish construction workers (Odenbro *et al.*, 2007). In this study, the risk for malignant melanoma was reduced in a dose-dependant manner for both cigarette and pipe smokers. The possibility that smoking may reduce the risk for melanoma should, therefore, be considered.

(b) Non-melanoma skin cancer

Four studies showed a positive association between smoking and non-melanoma skin cancer risk (De Stefani *et al.*, 1995; Wojno, 1999; Smith & Randle, 2001; Boyd *et al.*, 2002), and two found no clear association (van Dam *et al.*, 1999; Corona *et al.*, 2001). When distinguishing between histological subtypes, tobacco smoking was linked to the incidence of squamous-cell carcinoma of the skin in most studies, whereas the results for basal cell carcinoma remain inconsistent (Zak-Prelich *et al.*, 2004). No clear association between smoking and risk for basal cell carcinoma was found in a cohort study (Freedman *et al.*, 2003b).

2.18.6 Cancer of the penis

Case–control studies of smoking and penile cancer (Hellberg *et al.*, 1987; Daling *et al.*, 1992, 2005; Maden *et al.*, 1993; Harish & Ravi, 1995;

Table 2.84 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.84.pdf; Table 2.85 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.85.pdf) and reviews of studies of smoking and penile cancer and population surveys (Dillner *et al.*, 2000; Favorito *et al.*, 2008; Bleeker *et al.*, 2009; Table 2.86 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.86.pdf; Table 2.87 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.87.pdf) consistently showed a positive association. In most studies there was a dose–response relationship, with higher risks among those with increased smoking intensity and/or duration. A study in Brazil showed a positive correlation with penile tumour grade (Favorito *et al.*, 2008). Based on the two reviews (Dillner *et al.*, 2000; Bleeker *et al.*, 2009), relative risks were generally increased twofold to fivefold among smokers.

Most studies did not adjust for HPV infection. In one case–control study (Daling *et al.*, 2005), current smoking was associated with a 160% increased risk of HPV-positive penile cancer (n = 75), and a 180% increased risk of HPV-negative penile cancer (n = 19), suggesting no important effect modification.

2.18.7 Cancer of the testis

Studies reviewed in the previous *IARC Monograph* (IARC, 2004a) showed no association between cigarette smoking and risk for testicular cancer. More recently, two case–control studies showed positive associations with smoking, one in Canada (Srivastava & Kreiger, 2004) and one in the Czech Republic (Dusek *et al.*, 2008).

2.18.8 Cancer of the central nervous system

A recent meta-analysis was conducted on smoking in relation to glioma risk (Mandelzweig *et al.*, 2009), which included 17 epidemiological studies (6 cohort and 11 case–control). It was concluded that smoking is not associated with risk of glioma, despite a small significant increased risk seen in cohort studies. A recent cohort study found no association between smoking and carcinoma of the brain (Batty *et al.*, 2008). There have been no consistent associations of smoking with other CNS tumours (IARC, 2004a). In a population-based case–control study in the USA, smoking was associated with increased risk of intracranial meningioma in men (OR, 2.1; 95%CI: 1.1–4.2) but not in women (Phillips *et al.*, 2005).

2.18.9 Cancer of the adrenal gland

Data on risk factors for adrenal carcinoma are sparse. In the US Veterans' Study there was a fivefold increase in risk among current cigarette smokers during 26 years of follow-up, with risk being particularly high among those who smoked most intensely (Chow *et al.*, 1996). Other forms of tobacco use were associated with a statistically non-significant increase in risk. A case–control study in the USA found a twofold increase in risk for adrenal cancer among heavy smokers in men, but not in women (Hsing *et al.*, 1996).

2.19 Bidi smoking

2.19.1 Cancer of the oral cavity

(a) Overview of studies

The association between cancers of oral cavity and bidi smoking has been examined in 10 case–control studies conducted in India (Sankaranarayanan *et al.*, 1989a, b, 1990a; Rao *et al.*, 1994; Rao & Desai, 1998; Dikshit & Kanhere, 2000; Balaram *et al.*, 2002; Znaor *et al.*, 2003; Subapriya *et al.*, 2007; Muwonge *et al.*, 2008; Table 2.88 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.88.pdf). In these studies both cases and controls were interviewed and analyses were restricted

to men, except for the studies by Balaram *et al.* (2002) and Subapriya *et al.* (2007), because very few women smoked among study subjects.

Three hospital-based case–control studies considered cancers of subsites of the oral cavity (gingiva, tongue and floor of the mouth, buccal and labial mucosa) (Sankaranarayanan *et al.*, 1989a, b, 1990a). All three studies showed a higher oral cancer risk for bidi smoking. In one early study an unadjusted relative risk of 1.6 (95%CI: 1.3–2.0) for oral cancer in bidi smokers was reported (Rao *et al.*, 1994). [The Working Group noted that the study had several deficiencies, particularly in the selection of controls that resulted in cigarette smoking apparently being protective for oral cancer.] In another early study (Rao & Desai, 1998) relative risks were estimated after stratification by age and place of residence. Bidi smoking was a significant risk factor for cancer of the base of the tongue (RR, 5.9; 95%CI: 4.2–8.2) but not significant for cancer of the anterior tongue. Relative risk for bidi smoking adjusted for alcohol drinking, illiteracy, non-vegetarian diet and tobacco chewing showed significant risk for cancer of the base of the tongue (RR, 4.7; 95%CI: 3.5–6.3) but not for cancer of the anterior tongue. In a population-based case–control study a relative risk of 1.5 (95%CI: 0.9–2.4), adjusted for age and tobacco quid chewing for smokers (bidis and/or cigarettes), was found (Dikshit & Kanhere, 2000).

Two hospital-based multi centre case–control studies on cancer of the oral cavity were conducted in southern India. One included 309 cases and 292 controls (Balaram *et al.*, 2002). The risk for oral cavity cancer among those who smoked < 20 bidis per day was 2.0 (95%CI: 1.1–3.8) and 2.5 (95%CI: 1.4–4.4) for ≥ 20 per day. The second study included 1563 cases and 3638 controls and found a risk for bidi smoking only of 2.2 (95%CI: 1.75–2.63) compared to never smokers, adjusted for age, centre, level of education, alcohol consumption and chewing (Znaor *et al.*, 2003).

In a hospital-based case–control study with 388 oral squamous cell carcinoma cases (202 men and 186 women) and an equal number of age and sex-matched controls the effect of lifestyle factors (tobacco chewing, smoking and alcohol drinking, diet and dental care) on the risk of oral cancer was evaluated (Subapriya *et al.*, 2007). Both cases and controls were interviewed using a structured questionnaire. The risk estimate for bidi smoking based on 22 cases (84 cases included in the model) and 22 controls was 4.6 (95%CI not given).

Data from a randomized control trial conducted between 1996 and 2004 in Trivandrum, southern India were used in a nested case–control analysis with 282 (163 men and 119 women) incident oral cancer cases and 1410 matched population controls aged 35 years and over (Muwonge *et al.*, 2008). Oral cancer risk among men, adjusted for education and religion, was 1.9 (95%CI: 1.1–3.2) for bidi smokers only compared to never smokers. No association was found between mixed smoking of bidi and cigarette and risk of oral cancer.

Rahman *et al.* (2003) performed a meta-analysis to investigate the relationship between bidi smoking and oral cancer. They identified 12 case–control studies published in English during 1996–2002 with quantitative information on bidi smoking and oral cancer. Of these, ten studies were conducted in India, one in Sri Lanka and one in Pakistan. All cases were confirmed histologically and exposure data were collected by direct interview. In these studies ORs were not adjusted for tobacco chewing or alcohol drinking. The OR for bidi smokers compared to never smokers based on random effects model was 3.1 (95%CI: 2.0 –5.0). The ORs ranged from 2.0 to 3.6 in different regions of India: studies conducted in Mumbai had an OR of 3.6 (95%CI: 1.6 –7.9), in central India 2.7 (95%CI: 1.6–4.6), in Kerala 2.0 (95%CI: 1.5–2.9) and in Bangalore 2.0 (95%CI: 1.1–3.7).

(b) Dose–response evidence

The trends in relative risks by intensity and duration of bidi smoking were both statistically significant in two studies (Rao *et al.*, 1994; Rao & Desai, 1998). A meta-analysis based on three studies on duration of bidi smoking and on five studies on number of bidi sticks per day, showed a dose–response relationship for duration of bidi smoking but not for number of sticks used per day (Rahman *et al.*, 2003).

In a nested case–control analysis (Muwonge *et al.*, 2008) a dose–response relationship was observed for duration of bidi smoking ($P = 0.045$). [It is not clear if the analysis was restricted to bidi smokers only (n = 40 men) and if smokers with combined smoking habits (bidi and cigarette) were excluded. Moreover, ORs for the dose–response analysis were not reported.]

2.19.2 Cancer of the pharynx

Five case–control studies, two hospital-based (Wasnik *et al.*, 1998; Rao *et al.*, 1999), one population-based (Dikshit & Kanhere, 2000) and two multicentric studies (Znaor *et al.*, 2003; Sapkota *et al.*, 2007) were conducted on cancers of oropharynx and hypopharynx in India (Table 2.88 online). In all these studies, analyses were restricted to men because very few women smoked among study subjects.

Wasnik *et al.* (1998) conducted a case–control study on oropharyngeal cancers with cases and controls were matched on age and sex. Odds ratios for tobacco smoking, predominantly in the form of bidi and/or chillum, were 2.3 (95%CI: 1.2–3.7) after adjustment for tobacco chewing and outdoor occupation. [The Working Group noted some problems with the data analysis.]

Rao *et al.* (1999) reported a relative risk for bidi smoking adjusted for alcohol, illiteracy, diet and tobacco chewing of 4.7 (3.6–6.3) for oropharyngeal cancer and of 2.8 (2.1–3.7) for cancer of the hypopharynx. Dikshit & Kanhere (2000) found an odds ratio for oropharyngeal cancer among bidi smokers only of 7.9 (95%CI: 5.1–12.4).

Znaor *et al.* (2003) reported a risk for bidi smoking only for pharyngeal cancer of 4.7 (95%CI: 3.5–6.3) and for combined bidi and cigarette smoking of 3.6 (95%CI: 2.55–4.98). Sapkota *et al.* (2007) reported an odds ratio for hypopharyngeal cancer of 6.8 (95%CI: 4.6–10.0) for bidi smokers compared to never smokers.

A dose–response relationship was observed for intensity and duration of bidi smoking for both cancers of oropharynx and hypopharynx (Rao *et al.*, 1999; Dikshit & Kanhere, 2000; Sapkota *et al.*, 2007).

2.19.3 Cancer of the lung

One cohort study (Jayalekshmy *et al.*, 2008), one population-based case–control study (Dikshit & Kanhere, 2000) and two hospital-based case–control studies (Gupta *et al.*, 2001; Gajalakshmi *et al.*, 2003) in India (Table 2.88 online) have investigated the relationship between bidi smoking and lung cancer. In all these studies both cases and controls were interviewed and analyses were restricted to men because very few women smoked among study subjects. One hospital-based case–control study in Chiang Mai, Thailand, looked at the association between lung cancer and *khii yoo*, hand-rolled cigars. The risk for lung cancer for *khii yoo* smoking was 1.2 in men and 1.5 in women, $P > 0.05$ (Simarak *et al.*, 1977).

In the population based case–control study by Dikshit & Kanhere (2000) the age-adjusted relative risk for lung cancer among bidi smokers only was 11.6 (95%CI: 6.4–21.3).

Gupta *et al.* (2001) reported an odds ratio for bidi smoking of 5.8 (95%CI: 3.4–9.7) from a hospital-based case–control study of lung cancer conducted in Chandigarh. Gajalakshmi *et al.* (2003) conducted a case–control study in two centres in which all subjects were interviewed by trained social investigators with standard

questionnaires. Odds ratios were adjusted for age, educational level, centre, chewing and alcohol habit. The odds ratios of lung cancer for former and current bidi smokers were 3.4 (95%CI: 2.1–5.4) and 5.3 (95%CI: 3.8–7.3), respectively. Odds ratios for former and current smokers of cigarette and bidi combined were 4.0 (95%CI: 2.5–6.6) and 9.1 (95%CI: 6.2–13.2), respectively.

Baseline data of a cohort of 359 619 residents in Kerala, India was collected by direct interview using standardized questionnaires during 1990–97 (Jayalekshmy *et al.*, 2008). After excluding rare earth workers, those who died, were diagnosed with cancer before 1997 or died within three years of interview, there were 65 829 bidi-smoking men aged 30–84 years old. Two hundred and twelve lung cancer cases were identified by the Karunagappally Cancer Registry between 1997 and 2004. The relative risk for lung cancer for current compared to never bidi smokers calculated by Poisson regression analysis and adjusted for age, religion and education was 3.9 (95%CI: 2.6–6.0; $P < 0.001$). The risk was lower among former than among current smokers.

(a) Dose–response evidence

Lung cancer risks increased with increasing bidi smoking intensities. The highest odds ratio was found for 9 pack–years (3.9; 95%CI: 2.1–7.1) (Gupta *et al.*, 2001). In a cohort study Jayalekshmy *et al.* (2008) found increased lung cancer incidence with increasing number of bidi sticks smoked per day ($P < 0.001$) and with increasing duration of bidi smoking ($P < 0.001$). [The number of lung cancer cases was small in each category, resulting in wide confidence intervals.] Gajalakshmi *et al.* (2003) also reported increased risk with duration and intensity of bidi smoking.

(b) Cessation of smoking

In two case–control studies (Gupta *et al.*, 2001; Gajalakshmi *et al.*, 2003) there was a clear decreasing trend in risk for years since quitting. Gajalakshmi *et al.* (2003) reported that lung cancer risk of former bidi smokers fell to 0.4 (0.1–1.2) after quitting for more than 15 years. The cohort study conducted in Kerala did not have the power to assess the risk associated with stopping bidi smoking (Jayalekshmy *et al.*, 2008).

2.19.4 Cancer of the larynx

Two hospital based case–control studies (Sankaranarayanan *et al.*, 1990b; Rao *et al.*, 1999) showed a higher risk for bidi smokers (Table 2.88 online). The relative risk was adjusted for age and religion in Sankaranarayanan *et al.* (1990b) study and for alcohol use, illiteracy, vegetarian/non-vegetarian diet and tobacco chewing in Rao *et al.* (1999) study. A multicentre case–control study on laryngeal cancer was conducted in four Indian centres using standardized questionnaires adjusting risks for centre, age, socioeconomic status, alcohol consumption, tobacco snuffing and tobacco chewing (Sapkota *et al.*, 2007). Compared to never smokers bidi smokers had a higher risk for cancers of the supraglottis (OR, 7.5; 95%CI: 3.8–14.7), glottis (OR, 5.3; 95%CI: 3.2–8.9) and rest of larynx (OR, 9.6; 95%CI: 5.6–16.4).

All levels of intensity and duration of bidi smoking were associated with significant relative risk estimates and dose–response for laryngeal cancer (Sankaranarayanan *et al.*, 1990b; Rao *et al.*, 1999). A strong dose–response relationship was observed for duration and frequency of bidi smoking for cancers of supraglottis, glottis and rest of larynx (Sapkota *et al.*, 2007).

2.19.5 Cancer of the oesophagus

Three hospital-based case–control studies and one multicentre study (Sankaranarayanan *et al.*, 1991; Nandakumar *et al.*, 1996; Nayar *et al.*, 2000; Znaor *et al.* 2003) showed increased risk for oesophageal cancer among bidi smokers in India (Table 2.88 online). A significantly elevated

risk for all three segments of the oesophagus was reported (Nandakumar *et al.*, 1996). One study (Nayar *et al.*, 2000) adjusted for chewing of betel leaf with tobacco and low consumption of vegetables other than leafy vegetables. The multicentre case–control study conducted in two centres in South India found an increased risk for oesophageal cancer for bidi smoking only (OR, 3.3; 95%CI: 2.45–4.39) (Znaor *et al.*, 2003). Odds ratios were adjusted for age, centre, level of education, alcohol consumption and chewing. Only men were analysed in all the above studies.

Significant effects were noted in men for all levels of intensity and for duration of more than 20 years of bidi smoking (Sankaranarayanan *et al.*, 1991).

2.19.6 Cancer of the stomach

In a hospital-based case–control study the association between stomach cancer and bidi smoking was analysed as part of a multicentre study (Gajalakshmi & Shanta, 1996). Cases and controls were matched on age, sex, religion and mother tongue. The odds ratio for stomach cancer for current bidi smokers only was 3.2 (95%CI: 1.8–5.7) and for current smokers of any type of tobacco was 2.7 (95%CI: 1.8–4.1).

Table 2.88 (online) summarizes the studies published since the last *IARC Monograph* (IARC, 2004a). A hospital-based case–control study of stomach cancer included 170 stomach cancer cases (121 men and 49 women) and 2184 controls (1309 men and 875 women) aged 30–75 years (Rao *et al.*, 2002). The association between bidi smoking and stomach cancer was not significant (RR, 0.8; 95%CI: 0.5–1.2) in a univariate analysis. The risk increased with increase in lifetime exposure to bidi smoking and was highly significant ($P < 0.001$).

One study investigated stomach cancer risk in association with smoking of *meiziol*, a local cigarette in Mizoram, India (Phukan *et al.*, 2005). Statistically significant higher risks were seen for smokers of combined users of tobacco (cigarette and *meiziol*), with an odds ratio of 3.1 (95%CI: 2.0–11.1). Among users of a single type of tobacco, higher risks were seen for *meiziol* smokers (OR, 2.2; 95%CI: 1.3–9.3) in the multivariate model in comparison to cigarette smokers. Overall, the excess risk was limited to smokers of > 10 *meiziols* per day.

2.20 Synergistic effects of tobacco smoking and alcohol drinking

This section addresses the combined effects of smoking and alcohol consumption on cancers of oral cavity, pharynx, larynx and oesophagus, which have been examined extensively. For the purposes of this report interdependence of effects is termed *effect modification*, and *synergism* and *antagonism* are used to describe the consequences of the interdependence of disease risk when both risk factors are present (Rothman & Greenland, 1998). The studies varied in their methods and in the approaches used to assess effect modification, which ranged from descriptive to formal estimation of interaction terms in multivariate models. Study designs of the case–control and cohort studies are presented in Table 2.89 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.89.pdf) and Table 2.90 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.90.pdf), respectively; and the results for both study designs are presented in Table 2.91 (available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-01-Table2.91.pdf).

2.20.1 Cancers of the upper aerodigestive tract

It was noted in the previous *IARC Monograph* (IARC, 2004a) with relatively large numbers of cases and controls that the pattern of increasing cancer risk with increasing alcohol consumption is strong (Mashberg *et al.*, 1993; Kabat *et al.*, 1994).

For cancers of the oral cavity, recent evidence comes from seven case–control studies and one cohort study. The pattern of odds ratios for smoking, across categories of alcohol consumption, is consistent with synergism. In four case–control studies with relatively large numbers of cases and controls (more than 200 cases and equivalent number of controls), the pattern of increasing cancer risks with increasing alcohol consumption was strong (Schlecht *et al.*, 1999b; Znaor *et al.*, 2003; Castellsagué *et al.*, 2004; Hashibe *et al.*, 2009). In the cohort study from Taiwan, China (Yen *et al.*, 2008) similar strong risks were also observed. In all four case–control studies in which the estimate of formal statistical interaction was examined, the tests were statistically significant (Schlecht *et al.*, 1999b; Znaor *et al.*, 2003; Castellsagué *et al.*, 2004; Hashibe *et al.*, 2009). In two case–control studies from India (Znaor *et al.*, 2003; Muwonge *et al.*, 2008) and in the cohort study from Taiwan, China (Yen *et al.*, 2008) the interaction of tobacco smoking, alcohol and betel quid chewing was examined. In general, the results suggested increasing risks when betel quid chewing was included in the model.

Five case–control studies and one cohort study examined the effect of interaction between tobacco and alcohol in pharyngeal cancer. The results from case–control studies were similar to those observed for oral cancer (Olsen *et al.*, 1985b; Choi & Kahyo, 1991; Schlecht *et al.*, 1999b; Znaor *et al.*, 2003; Hashibe *et al.*, 2009). In a Singapore cohort study (Friborg *et al.*, 2007) the pattern of odds ratios for smoking across categories of alcohol consumption was consistent with synergism for oropharyngeal but not for nasopharyngeal cancer.

Two cohort and fourteen case–control studies reported on joint effects of tobacco smoking and alcohol drinking on the risk for oesophageal cancer. Since multiple logistic regression models were used for analysing most of these studies, some of them tested likelihood ratio test for departure from multiplicativity of the individual effects of tobacco and alcohol. Generally, the positive results were stronger for squamous cell carcinoma. However, these tests for interaction are inadequate to assess synergy. Four studies from India and Taiwan, China, included betel quid chewing to the joint effect analysis of tobacco smoking and alcohol consumption and the results suggested increasing risks of oesophageal cancer.

Most of the twenty case–control studies of laryngeal cancer provided strong evidence for synergism of tobacco smoking and alcohol consumption. Only Zheng *et al.* (1992) did not find consistent evidence with synergism. In several studies, tests for interaction were carried out and reported to be 'non significant.' These were tests for departure from the multiplicative models, typically multiple logistic regression models, used to analyse the case–control data, and not tests for departure from additive model.

Several studies (14 case–control, 3 cohort) reported on cancer of the 'mixed upper aerodigestive tract', comprising studies on squamous cell carcinomas, regardless of specific sites. These studies also provided strong evidence for synergism.

The Working Group considers that there is strong evidence of tobacco smoking and alcohol consumption interaction on the incidence of upper aerodigestive tract cancers, as well as with regard to cancer of specific subsites of this anatomical region.

2.21 Synthesis

2.21.1 Lung

Tobacco smoking is the major cause of lung cancer, primarily from cigarettes. Duration of smoking is the strongest determinant of lung cancer in smokers. Risk also increases in proportion to the number of cigarettes smoked. The strong dose– and duration–response

relationships between lung cancer and tobacco smoking have been confirmed more recently in both questionnaire-based and biomarker-based studies. Tobacco smoking increases the risk of all histological types of lung cancer.

Differences in the intensity and/or duration of tobacco smoking may explain, in part, the lower lung cancer risks in Asian populations relative to whites. However, several studies of genetic polymorphisms among African-American and Caucasian populations provide some preliminary evidence supporting the hypothesis of a racial/ethnic disparity in susceptibility.

The results from observational studies do not provide strong support that a higher intake or a greater circulating concentration of carotenoids reduce lung cancer risk, particular in light of the elevated risk of lung cancer observed in the randomized trials of β-carotene supplementation. Residual confounding from smoking and the possibility that carotenoid measurements are serving as markers for a diet rich in total fruit and vegetables mitigate the likelihood of any protective role for total carotenoids or β-cryptoxanthins.

The specific genes that are responsible for enhanced lung cancer risk remain poorly understood, in spite of hundreds of candidate gene studies. Single-gene studies conducted to date have several limitations which contribute to inconclusive results, including small sample size and associated low power to detect moderate risks when allele frequencies are low.

2.21.2 Upper areodigestive tract

(a) Oral cavity

Tobacco smoking is causally associated with cancer of the oral cavity in both men and women. Since the previous *Monograph*, additional evidence has accumulated that further confirms the association. Risk increases with duration and intensity of smoking, and decreases after quitting.

(b) Pharynx

Tobacco smoking is an important cause of oropharyngeal and hypopharyngeal cancers. The risk increases with increasing duration and intensity of smoking and decreases with increasing time since quitting.

(c) Nasal cavity and accessory sinuses

The evidence of an association between tobacco smoking and sinonasal cancer is based on the results from case–control studies, each of which may be subject to different sources of bias. However, presence of a dose–response relationship in most studies, the decrease in risk associated with time since quitting, the consistently higher risks for squamous-cell carcinoma than for adenocarcinoma and the lack of potential confounders support the existence of a causal association.

(d) Nasopharynx

Although the interpretation of the results is complicated by small sample sizes in several studies, by different criteria used for the selection of controls and by the control groups in some studies including smoking-related diseases, the combined evidence shows an association between tobacco smoking and nasopharyngeal carcinoma in both endemic and non-endemic areas. Most studies that adjusted for known and suspected causes of nasopharyngeal carcinoma such as intake of Chinese-style salted fish, other dietary factors, alcohol drinking and family history of nasopharyngeal carcinoma, suggested only a limited confounding effect of these factors. Adjustment for infection with Epstein–Barr virus (human herpes virus 4), a major cause of nasopharyngeal carcinoma worldwide, was possible in just one of the available studies. However, it is unlikely that confounding by infection with Epstein–Barr virus would explain the observed association between tobacco smoking and risk for nasopharyngeal carcinoma.

(e) Oesophagus

Several well conducted case–control studies found a statistically significant higher risk for adenocarcinoma of the oesophagus in smokers than in nonsmokers. Positive dose–response relationships obtained using various indicators of amount smoked support a causal association, which is further corroborated by the findings of decreasing risks after smoking cessation. Several of these studies reported relative risks adjusted for alcohol consumption and other potential confounders. Further risk factors, such as chewing betel quid with tobacco or use of other forms of smokeless tobacco, have not been considered in these populations, but are not likely to be strong confounders. Studies from Australia, China and Europe also found increased risks for smokers.

(f) Larynx

Laryngeal cancer is one of the cancers most strongly associated with cigarette smoking. Recent epidemiological evidence strengthens this conclusion.

2.21.3 Stomach

The additional epidemiologic data showing a consistent association of stomach cancer with tobacco smoking in both men and women greatly strengthens the previous conclusion of a causal association. There was insufficient evidence for differential risks between cardia and non-cardia stomach cancer. Confounding and effect modification by H. pylori has not been found.

2.21.4 Pancreas

The additional data supports the previous evaluation that cancer of the pancreas is causally associated with tobacco smoking. The risk increases with increasing daily consumption levels and duration of smoking and decreases with increasing time since cessation of smoking. The risk remains elevated after accounting for potential confounding factors.

2.21.5 Colorectum

At the previous evaluation, there was already some evidence from prospective cohort and case–control studies that the risk of colorectal cancer is increased among tobacco smokers. However, inadequate adjustment for various potential confounders was considered to possibly account for some of the small increase in risk that appears to be associated with smoking. Since then, an appreciable amount of data has accumulated to support a causal association with smoking. In virtually all the cohort studies published since elevated risk associated with smoking was found, although not always statistically significant. More than half of the cohort studies that assessed dose–response relationships found statistically significant increasing risks with increasing daily cigarette consumption, duration of smoking and/or pack–years of smoking. Risk of colorectal cancer decreased with increasing delay in smoking initiation and years since cessation of smoking. A meta-analysis based on 36 cohort studies with data from a total of 3 million subjects found a significantly 15% increased risk of colorectal cancer and 27% higher risk of colorectal cancer mortality in current smokers compared to never smokers. A stronger association with smoking for rectal cancer than for colon cancer was found in the meta-analysis of the subset of cohort studies that differentiated colorectal cancer by site. Risk for colorectal cancer increased significantly by 17% and by 38% with 20 cigarettes and 40 cigarettes/day, respectively, and was elevated by 9.4% and by 19.7% with a 20-year and a 40-year duration of smoking, respectively. While these results are persuasive, this meta-analysis could not correct for the potential confounders in the individual studies. Convincing evidence has been provided by three large cohort studies that adjusted for at

least four important potential confounders (i.e. physical activity, alcohol consumption, body mass index and dietary intake of fruits and vegetables and/or meat); two studies also adjusted for history of colonoscopy. Significant dose–response relationships were found with one or more of the smoking variables, for risk of colorectal cancer and/or colon cancer and/or rectal cancer. Earlier cohort studies may not have been able to establish the association because of insufficient follow-up time and a limited number of cases. Updated results of several large cohort studies, which now show clearly significant increased risk of colorectal cancer associated with smoking, provide support for the lag-time hypothesis for smoking and colorectal risk.

Recent evidence suggests that smoking may be associated with the subtype of colorectal cancer characterized by microsatellite instability, and by CIMP status and BRAF mutation. For this subtype, the magnitude of risk associated with smoking reaches the twofold risk elevation consistently observed for colorectal adenomas and supported by a recent meta-analysis. Smoking has been associated with a stronger risk for hyperplastic polyps than for adenomas. Also, CIMP positivity and BRAF mutations have been associated with hyperplastic polyps, particularly serrated polyps. These data suggest that smoking may be associated primarily with a subtype of colorectal cancer that develops through a hyperplastic (serrated) polyp progression. The association with smoking may therefore be diluted when considering colon cancers overall.

2.21.6 Liver

Recent studies on smoking and hepatocellular carcinoma supports the established causal relationship. Supporting evidence comes from the consistency of the findings across regions (with the best evidence coming from Asian studies), and the observations of an association among non-drinkers and after controlling for hepatitis B or C virus infection.

2.21.7 Kidney

Recent evidence supports a causal association between kidney cancer and smoking. After adjustment for body mass index and hypertension, current and former smokers still had a greater risk for renal-cell cancer. A dose–response relationship with the number of cigarettes smoked has been noted in most studies, and a few also noted a reduction in risk after cessation.

2.21.8 Urinary bladder

Tobacco smoking is causally associated to bladder cancer, based on a large number of case–control and cohort studies that showed statistically significant associations not explained by confounding or bias. Risk increased with the duration of smoking and the number of cigarettes smoked. Also, stopping smoking at any age avoids the further increase in risk incurred by continued smoking. The evidence supporting a modulating role by *NAT2* polymorphisms is convincing.

2.21.9 Myeloid leukaemia

There is evidence for a causal association of tobacco smoking with myeloid leukaemia.

2.21.10 Breast

New evidence from cohort and case–control studies and from meta-analyses of genetic polymorphisms has become available since the previous *IARC Monograph* (IARC, 2004a). Results from seven new cohort studies consistently show a small overall association between current smoking and breast cancer incidence, with relative risk estimates ranging from 1.1–1.3 in studies with at least 100 exposed cases. The overall association is weaker than that observed with other cancers that have been designated as causally related to smoking, and the dose–response relationships (with years of smoking,

cigarettes smoked per day, age at initiation) are correspondingly small.

Emerging evidence from case–control studies suggests that inherited polymorphisms in the *NAT2* gene, which encode the slow acetylator phenotype, may modify (increase) the association between smoking and breast cancer. The p-value for interaction with pack–years of smoking as a continuous variable is statistically significant (P = 0.03) and another small study published since this meta-analysis supports the conclusion. The potential for publication bias remains of concern.

It is biologically plausible that tobacco smoke could be causally related to breast cancer risk. There are multiple chemicals in tobacco smoke that are known to cause mammary cancer in rodents. These substances reach the breast in humans; some are stored in adipose tissue, and some can be detected in nipple aspirate and DNA adducts.

Hypotheses have been proposed to explain why numerous well conducted epidemiological studies have generally not observed strong or consistent associations between tobacco smoking and breast cancer. Underlying all of these is the theory that tobacco smoking may have both protective and detrimental effects on breast cancer risk, which cancel each other out and which could explain the atypical dose–response relationship that has been reported between tobacco smoke and breast cancer from some studies.

2.21.11 Cervix

The largely positive findings observed in studies of cohort design, the relatively high consistency of positive associations found for squamous-cell carcinoma of the cervix (but not adenocarcinomas) across all epidemiological studies, including those with adjustment for a wide range of potentially confounding variables, and the positive associations observed in studies restricted to HPV-positive individuals, all argue against the observed positive association being due to recall or selection bias or confounding.

2.21.12 Endometrium

The results of epidemiological studies to date, including recent studies, largely show inverse associations of smoking with risk of postmenopausal endometrial cancer. However, the Working Group noted the few studies of premenopausal cancer that were less consistent, as well as indications of an increased risk among smokers in a recent multicentre European study.

2.21.13 Prostate

Many epidemiological studies have examined the association between cigarette smoking and prostate cancer risk, and most have shown no consistent association. The question remains whether smoking may alter risk in various population subgroups.

2.21.14 Ovary

A causal association between cigarette smoking and risk for mucinous ovarian tumours is indicated by 1) the consistency of the positive association across the large majority of ten pooled case–control studies and ten additional independent epidemiological studies of both case–control and cohort design, 2) the relatively strong magnitude of the association (typically greater than a doubling of risk among current smokers), 3) the tendency to show dose–response associations with risk, such that current smokers generally have higher risk than former smokers and the dose–response observed with measures of smoking intensity in some (but not all) studies, and 4) the specificity of the positive association with the mucinous histological type, which argues against recall bias as an explanation of the findings.

2.21.15 Thyroid

A pooled analysis of 14 case–control studies showed that smoking was inversely associated with thyroid cancer risk. Similar inverse associations were also observed in two subsequent case–control studies.

2.21.16 Other sites

There is inconsistent or sparse evidence for an association between tobacco smoking and other cancer sites that were considered by the Working Group.

2.21.17 Bidi smoking

Overall, bidi smoking increases the risk for cancers of the oral cavity, oropharynx, hypopharynx, larynx, lung, oesophagus and stomach.

3. Cancer in Experimental Animals

3.1 Mainstream tobacco smoke

3.1.1 Mouse

There have been multiple studies of the carcinogenic potential of tobacco smoke in mice (Table 3.1). Lifetime exposure of several mouse strains to cigarette smoke failed to result in the production of lung tumours (Harris & Negroni, 1967; Otto & Elmenhorst, 1967; Henry & Kouri, 1986). However, studies involving lifetime exposure of C57BL mice to a mixture of flue-cured or air-cured cigarette smoke or to the gas phase of flue-cured cigarette smoke led to significant increases in the number of lung tumours (adenomas) (Harris *et al.*, 1974). Similarly, lifetime exposure of Snell's mice to the gas phase of cigarette smoke led to an increased incidence of lung adenocarcinomas (Leuchtenberger & Leuchtenberger, 1970). Exposure of $B6C3F_1$ female mice to smoke for lifetime led to increased incidence of lung adenomas, bronchiolar papillomas and lung adenocarcinomas in smoke-exposed mice. In addition, the occurrence of squamous cell carcinomas of the nasal cavity in smoke-exposed mice was increased (Hutt *et al.*, 2005). In a recent study, Swiss mice were exposed whole-body to cigarette smoke for 120 days, starting within 12 hours of the birth. Smoke-exposed mice developed microscopic lung tumours beginning only 75 days after birth and reaching an overall incidence of 78.3% after 181–230 days. The mean lung tumour multiplicity was 6.1 and 13.6 tumours per mouse in males and females, respectively. In addition, malignant tumours, some of which may have had a metastatic origin, were detected in the urinary tract of smoke-exposed mice (Balansky *et al.*, 2007).

3.1.2 Rat

Several studies have evaluated the carcinogenic potential of mainstream tobacco smoke in rats (Table 3.1). Exposure of Wistar rats to cigarette smoke for lifetime did not increase the lung tumour incidence (Davis *et al.*, 1975). In contrast, exposure of Fischer 344 rats to a mixture of non-filter cigarette smoke for 128 weeks resulted in an increased incidence of nasal and lung tumours. There was also an increase in subcutaneous sarcomas at forelimb ulceration sites (Dalbey *et al.*, 1980). CDF rats were exposed to low-dose cigarette smoke (LCS) or high-dose cigarette smoke (HCS) for 126 weeks. The incidence of lung tumours was significantly higher only in female rats that received HCS (Finch *et al.*, 1995). In a recent study, Fischer 344 rats received whole body exposure to smoke containing either 100 mg (LCS) or 250 mg (HCS) total particulate matter/m^3 for 30 months. This led to significant increases in the incidence of lung and nasal cavity tumours in male rats treated with HCS but not with LCS. In female rats, there were significant increases in the incidence of lung adenomas

in animals treated with HCS and of all lung tumours in animals treated with both LCS and HCS. There was also a significant increase in the occurrence of nasal cavity tumours in female rats treated with HCS (Mauderly *et al.*, 2004).

3.1.3 Hamster

Four studies have evaluated the ability of mainstream tobacco smoke to induce tumours in hamsters (Table 3.1). Syrian golden hamsters were exposed to either a mixture of German reference cigarette smoke or of dark air-cured cigarette smoke for lifetime. There were increases in the incidence of laryngeal carcinomas in hamsters exposed to both smoke preparations (Dontenwill *et al.*, 1973). In a subsequent study, hamsters were exposed to a mixture of German reference cigarette smoke containing 1.5 mg nicotine, 0.173 mg phenol and 12.7 mL carbon monoxide/cigarette for lifetime. The incidence of laryngeal tumours in smoke-exposed hamsters was higher than in controls (Dontenwill *et al.*, 1977). BIO male hamsters exposed to a mixture of US reference smoke for 100 weeks developed laryngeal and nasopharyngeal tumours (Bernfeld *et al.*, 1974). In a subsequent study, male BIO hamsters exposed to smoke from commercial British filter cigarettes developed higher incidence of laryngeal tumours than controls (Bernfeld *et al.*, 1979).

3.2 Co-administration of tobacco smoke with known carcinogens and other agents

Study design and results of the studies on co-administration of tobacco smoke with known carcinogens and other agents are summarized in Table 3.2.

3.2.1 Rat

(a) Benzo[a]pyrene

Wistar rats received a single intratracheal instillation of 2 mg benzo[*a*]pyrene followed by lifetime exposure to cigarette smoke. This treatment led to a low incidence of lung tumours that was not significantly higher than in controls (Davis *et al.*, 1975). In another study Wistar rats were given intratracheal instillations of benzo[*a*]pyrene mixed with ferric oxide and exposed to cigarette smoke either during initiation and post-initiation or only after treatment with benzo[*a*]pyrene/ferric oxide (post-initiation). Inhalation of cigarette smoke during the initiation and post-initiation phases of carcinogenesis resulted in a higher lung tumour (squamous-cell carcinoma) multiplicity than that seen in rats exposed during the post-initiation phase only (Gupta *et al.*, 1990).

(b) Radon progeny

Sprague-Dawley rats were exposed to radon progeny at cumulative doses of 4000, 500 or 100 work-level-months (WLM), with or without concurrent exposure to cigarette smoke by inhalation for one year. Rats exposed to 4000 WLM radon progeny, without exposure to smoke, developed lung carcinomas (17/50). Thirty four carcinomas were seen in 50 rats exposed to radon and cigarette smoke. The 500 WLM radon progeny group exposed to radon only had 2/28 lung carcinomas as compared with 8/30 rats exposed to radon and cigarette smoke. No tumours were observed in rats treated with 100 WLM radon and one carcinoma was seen among 30 rats exposed to 100 WLM radon and cigarette smoke. Seventy five percent of the lung tumours were squamous-cell carcinomas, 20% were adenocarcinomas, and the remainder were undifferentiated carcinomas (Chameaud *et al.*, 1982).

Table 3.1 Carcinogenicity in response to mainstream tobacco smoke in animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, C57BL (M, F) Harris & Negroni (1967)	100 animals/sex/group Nose-only, mixture of fresh non-filter cigarette smoke/air (1/39, v/v), nicotine, 0.1 mg/mL; CO, 0.064% (v/v), 12 min/every other d; lifetime	Nicotine, 14–17 µg	Alveologenic adenocarcinomas: M–4/100 (alveologenic AdC) Controls–0/100 F–4/100 (alveologenic AdC) Controls–0/100	 $P = 0.06$ $P = 0.06$	
Mice, C57BL and BLH (sex, NR) Otto & Elmenhorst (1967)	126 animals/group Whole-body, gas phase of 12 cigarettes puffed 2 sec/min, concentration (NR), 90 min/d; lifetime (~27 mo)	NR	Lung (adenomas): C57BL–7/126 (5.5%) Controls–3/90 (3%) BLH–40/126 (32%) Controls–19/60 (32%)	 NS NS	
Mice, (C57BL/Cum × C3H/Anf Cum)F_1 (F) Henry & Kouri (1986)	2053, 1 014 sham Nose-only, 10% smoke from US reference cigarettes, concentration (NR), smoke 20 sec/min, 6–8 min/d, 5 d/wk for 110 wk; 116 wk	Particulate deposition, 125–200 µg	Alveolar adenocarcinomas: 19/978 (2%) Sham-exposed controls–7/651 (1%)	 $P = 0.10$	Shorter latency of tumour occurrence in smoke-exposed group suggested
Mice, C57BL (M, F) Harris *et al.* (1974)	100 animals/sex/group Nose-only, mixture of fresh flue-cured or air-cured cigarette smoke/air (1/39, v/v), concentration (NR), 12 min/d on alternate d; lifetime	NR	M: 9/162[a] (5%, flue-cured), 7/189[a] (4%, air-cured) Controls–3/160[a] (2%) F: 7/164[a] (4%, flue-cured), 0/173 (air-cured) Controls–1/159[a] (1%)	$P = 0.07$, flue-cured $P > 0.05$, air-cured $P = 0.04$, flue-cured	
	Nose-only, gas phase of flue-cured cigarette smoke, concentration (NR), 12 min/d on alternate d; lifetime	NR	M: 3/8[a] (37%) Controls–3/160[a] (2%) F: 2/88[a] (2%) Controls–1/159[a] (1%)	$P > 0.05$ $P > 0.05$	

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, Snell (M, F) Leuchtenberger & Leuchtenberger (1970)	160 M, 118 F Whole-body, whole fresh cigarette smoke, concentration (NR), 2 puffs, 1 × /d, lifetime (26 mo)	Nicotine, 5 µg	M: Lung A–7/107 (6.5%) Controls–8/106 (7.5%)	NS	
			Lung AdC–11/107 (10%) Controls–5/106 (4.7%)	$P = 0.15$	
			F: Lung A–2/65 (3%) Controls–1/78 (1.2%)	$P = 0.475$	
			Lung AdC–5/65 (7.7%) Controls–3/78 (3.8%)	$P = 0.035$	
	100 M, 89 F Whole-body, gas phase of fresh cigarette smoke, concentration (NR), 2 puffs, 1 × /d, lifetime (26 mo)	NR	M: Lung A–1/44 (2%) Controls–8/106 (7%)	NS	
			Lung AdC–10/44 (23%) Controls–5/106 (5%)	$P = 0.005$	
			F: Lung A–3/44 (7%) Controls–1/78 (1%)	$P = 0.15$	
			Lung AdC–5/44 (11%) Controls–3/78 (4%)	$P = 0.15$	
Mice, B6C3F1 (F) Hutt *et al.* (2005)	330, 326 controls Whole-body, smoke from Kentucky 2R1 unfiltered reference cigarettes, 250 mg total particulate matter/m^3, 6 h/d, 5 d/wk for 30 mo; 30 mo or lifetime	NR	Lung A: 93/330 (28%) Sham-exposed controls–22/326 (7%)	$P < 0.001$ $P < 0.007$	
			Bronchiolar papillomas: 15/330 (4%) Controls–0/326	$P < 0.001$	
			Lung AdC: 67/330 (20%) Controls–9/326	$P < 0.001$	
			All lung tumours: 148/330 (45%) Controls–31/326	$P < 0.001$[b]	
			Nasal cavity tumours: 20/330 (6%) Controls–0/326	$P = 0.002$, one-tailed Fisher	
			Squamous-cell carcinomas: 9/330 (3%) Controls–0/326		

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, Swiss (M, F) Balansky *et al.* (2007)	38, 36 controls (neonatal mice, 21 h of age) Whole-body, cigarette smoke/air, 818 mg total particulate matter/m^3, 65 min/d for 120 d	NR	Lung A: 15/38(19%) Sham-exposed controls–0/36	$P < 0.001$	
			Lung AdC: 7/38 (18%) Controls–0/38	$P < 0.01$	
			Kidney A: 6/16 (16%) (F only) Controls–0/21	$P < 0.01$	
			Liver carcinomas: 2/16 (5%) (F only) Controls–0/21		
Rats, Wistar (F) Davis *et al.* (1975)	408, 102 untreated, 102 sham Nose-only, mixture of cigarette smoke/air (1/5), concentration (NR), 15 sec/min, 2 × 11 min/d, 5 d/wk, lifetime	NR	4/408 (1%) (1 lung C and 3 lung neoplasms of uncertain malignancy) Controls–0/102 Sham treated controls–0/102	NS	
Rats, F344 (F) Dalbey *et al.* (1980)	80, 63 untreated, 30 sham Nose-only, mixture of non-filter cigarette smoke/air (1/10), 18.4 mg smoke particulate and 0.89 mg nicotine/cigarette, 1 cigarette/h, 7 cigarettes/d, 5 d/wk for 128 wk; 160 wk	Particulate deposition, 1.75 mg/d	10/80 (12%) (1 nasal AdC, 1 nasal C, 5 pulmonary A, 1 pulmonary C, 2 alveologenic C) Controls–3/93 (3%)	$P < 0.05$	
			Subcutaneous sarcomas at forelimb ulceration sites: 21/80 (26%) Controls–0/93	$P < 0.05$	
Rats, CDF® (F344)/CrlBR (M, F) Finch *et al.* (1995)	2165 animals Whole-body, cigarette smoke/air, 100 mg (LCS) or 250 mg (HCS) total particulate matter/m^3, 6 h/d, 5 d/wk for 30 mo; lifetime	NR	Lung tumours: M: LCS 3/173 (2%) HCS 7/78 (9%) Filtered air 3/119 (2%)	$P < 0.05$	
			F: LCS–4/145 (3%) HCS–6/83 (7%) Filtered air–0/113	$P < 0.05$	

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Rats, F344 (M, F) Mauderly *et al.* (2004)	M: 178 LCS, 82 HCS F: 175 LCS, 81 HCS Whole-body, smoke from Kentucky 1R3 unfiltered reference cigarettes, 100 mg (LCS) or 250 mg (HCS) total particulate matter/m^3, 6 h/d, 5 d/wk for 30 mo; lifetime	NR	M: Lung A– LCS 4/178 (2%) HCS 2/82 (2%) Sham-exposed controls 1/118 (1%)	NS	
			Lung AdC– LCS 1/178 (1%) HCS 5/82 (6%) Controls 3/118 (3%)	NS	
			All lung tumours– LCS 4/178 (2%) HCS 7/82 (8%) Controls 4/118	NS; trend, $P = 0.055$	
			Nasal cavity (all tumour types)– LCS 1/178 (1%) HCS 5/82 (6%) Controls 1/118 (1%)	$P = 0.032$ (HCS); trend, $P = 0.010$	
			F: Lung A– LCS 7/175 (6%) HCS 7/81 (9%) Sham-exposed controls 0/119	NS (LCS); $P < 0.001$ (HCS)	
			AdC– LCS 4/175 (2%) HCS 4/81 (5%) Controls 0/119	NS	
			All lung tumours– LCS 10/175 (6%) HCS 11/81 (13%) Controls 0/119	$P = 0.023$ (LCS); $P = 0.001$ (HCS)	
			Nasal cavity (all tumour types)– LCS 0/175 HCS 3/81 Controls 0/119	$P = 0.020$ (HCS); trend, $P = 0.003$	

Table 3.1 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Lung burden	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Hamsters, Syrian golden (M, F) Dontenwill *et al.* (1973)	80 animals/sex/group Whole-body, mixture of German reference cigarette smoke/air (1/15), concentration (NR), smoke of 30 cigarettes for 7–10 min; 1, 2 or 3 × /d, 5 d/wk, lifetime	NR	Laryngeal carcinomas: 1/160 (1%), 17/160 (11%) and 11/160 (7%) Controls–0/80		
	Whole-body, mixture of dark air-cured cigarette smoke/air (1/15), concentration (NR), Smoke of 30 cigarettes for 7–10 min: twice/d, 5 d/wk, lifetime	NR	Laryngeal carcinomas: 2/160 (1%) Controls–0/80		
Hamsters, Syrian golden (M, F) Dontenwill *et al.* (1977)	80 animals/group Whole-body, mixture of German reference cigarette smoke/air (1/15), 1.5 mg nicotine, 0.173 mg phenol and 12.7 mL CO/cigarette, smoke of 30 cigarettes for 7–10 min; 1, 2 or 3 × /d, 5 d/wk, lifetime	NR	M: Laryngeal C–0, 4, 6 and 11%, Controls–0% F: Laryngeal C–0, 1, 2 and 7% Controls–0%		
Rats, Inbred BIO 15.16 & Inbred BIO 87.20 (M) Bernfeld *et al.* (1974)	102 animals/group Whole-body, mixture of US reference cigarette smoke/air (1/5), concentration (NR), duration (NR)		Inbred BIO 15.16: Laryngeal tumours–9/84 (10%) Nasopharyngeal tumours–2/84 (2%) Sham-exposed controls 0/42 Controls 0/40 Inbred BIO 87.20: Laryngeal tumours–2/87 (2%) Sham-exposed controls 0/44 Controls 0/48		
Rats, Inbred BIO 15.16 (M) Bernfeld *et al.* (1979)	Number at start (NR) Whole-body, 11 or 22% smoke from commercial British filter cigarettes, concentration (NR), 2 × 12 min/d, 7 d/wk for 35–42 wk; up to 74–80 wk	NR	Laryngeal carcinomas: 11% smoke–3/44 (7%) 22% smoke–27/57 (47%) Sham-exposed controls 0/36; Controls 0/50		

[a] Most of these lung tumours are adenomas

[b] Nasal cavity tumours included 14 squamous cell carcinomas (5 in situ), 5 hemangiomas, and 1 respiratory papilloma

A, adenoma; AdC, adenocarcinoma; C, carcinoma; CO, carbon monoxide; d, day or days; F, female; h, hour or hours; HCS, high cigarette smoke; LCS, low cigarette smoke; M, male; min, minute or minutes; mo, month or months; NR, not reported; NS, not significant; sec, second or seconds; wk, week or weeks; yr, year or years

Table 3.2 Carcinogenicity in response to exposure to mainstream tobacco smoke in conjunction with exposure to known carcinogens or other agents in animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Rats, Wistar (F) Davis *et al.* (1975)	84 or 408 animals/group A single intratracheal instillation of benzo[*a*]pyrene (2 mg) + infusine + carbon black followed by British reference cigarette smoke/air (1/5); 1 cigarette, twice/d, 5 d/wk, lifetime	3/84 (4%, lung C), 1/84 (1%, lung C; benzo[*a*]pyrene alone), 4/408 (1%, 3 A + 1 malignant neoplasm; cigarette smoke only), 0/204 (controls + sham-exposed controls)	NS
Rats, Wistar (M) Gupta *et al.* (1990)	35 animals/group Cigarette smoke; 5 cigarettes/8.2 L air; 1 h/d during 2nd–24th wk or 10th–24th wk of the study Benzo[*a*]pyrene (20 mg) + Fe_2O_3; intratracheally (3 weekly doses) during 6th–8th wk of the study; 24 wk	Conventional diet: 2nd–24th wk, 2.14 lung C/animal; 10th–24th wk, 1.33 lung C/animal; benzo[*a*]pyrene control, 1.22 lung C/animal. Vitamin A-deficient diet: 2nd–24th wk, 2.86 lung C/animal; 10th–24th wk, 1.67 lung C/animal; benzo[*a*]pyrene control, 1.83 lung C/animal	
Rats, Sprague-Dawley, sex NR) Chameaud *et al.* (1982)	28–50 animals/group French reference cigarette smoke (9 cigarettes/500 L air); 10–15 min session, 4 d/wk for 1 yr Radon progeny (4 000, 500 or 100 WLM) Lifetime	4000 WLM: 34/50 (68%, lung C); 17/50 (34%, lung C; radon progeny alone) 500 WLM: 8/30 (27%, lung C); 2/28 (7%, lung C; radon progeny alone) 100 WLM: 1/30 (3%, lung C); 0/50 (radon progeny alone)	$P = 0.0015$
CDF*(F344)/CrlBR (M, F) Finch *et al.* (1995)	Number at start (NR) Cigarette smoke/air, 100 mg (LCS) or 250 mg (HCS) total particulate matter/m^3; 6 h/d, 5 d/wk for 126 wk $^{239}PuO_2$ aerosol, 1 wk (6th wk of the study); > 52 wk	49–61% (lung tumours, LCS + $^{239}PuO_2$) 72–74% (HCS + $^{239}PuO_2$) 20–33% ($^{239}PuO_2$) 2–3% (LCS) 7–8% (HCS)	
Syrian golden (M, F) Dontenwill *et al.* (1973)	80 animals/sex/group German reference cigarette smoke/air (1/15); Smoke of 30 cigarettes for 7–10 min; twice/d, 5 d/wk, lifetime DMBA (0.5 mg); intratracheally 10 d before the beginning of smoke exposure	32/160 (20%, laryngeal C), 17/160 (11%, laryngeal C; smoke only), 0/160 (DMBA alone)	

Table 3.2 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Syrian golden, (sex NR) Hoffmann *et al.* (1979)	20 or 40 animals/group Cigarette smoke/air (1/7); Cigarette smoke 2 × 10 min/d, 5 d/wk, 48 wk DMBA (0.24 mg); intralaryngeally	3/40 (7%, laryngeal C), 0/20 (smoke only), 0/20 (DMBA alone)	
Syrian golden (M) Takahashi *et al.* (1992)	10 or 30 animals/group Cigarette smoke/air (1/7); Smoke of 30 cigarettes for 9 min; twice/d, 5 d/wk, 12 wk NDEA (100 mg/kg bw); subcutaneously	Non-filter cigarettes (2.10 ± 1.74 P+H/animal) and filter cigarettes (1.93 ± 1.55 P + H/animal) versus sham-exposed (0.97 ± 1.03 P + H/animal)	$P < 0.01$ $P < 0.01$
Syrian golden (M) Harada *et al.* (1985)	30 animals/group Non-filter cigarette smoke/air (1/7); Smoke of 30 cigarettes for 6 min: twice/d, 5 d/wk, 58 wk NDEA (10 mg/hamster); subcutaneously (12 weekly doses)	Nasal cavity tumours 14/30 (47%, smoke + NDEA), 5/30 (17%, NDEA alone)	$P < 0.05$

A, adenoma; bw, body weight; C, carcinoma; d, day or days; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; h, hour or hours; HCS, high cigarette smoke; LCS, low cigarette smoke; M, male; min, minute or minutes; mo, month or months; NDEA, *N*-nitrosodiethylamine; NR, not reported; NS, not significant; P + H, epithelial hyperplasias and papillomas; sec, second or seconds; wk, week or weeks; WLM, work-level-months; yr, year or years

(c) Plutonium oxide

CDF®/CrlBR rats were exposed to either filtered air or mainstream cigarette smoke at concentrations of either 100 or 250 mg total particulate matter/m^3 (LCS and HCS groups, respectively). At 12 weeks, rats were removed from smoke chambers and exposed nose-only to plutonium oxide ($^{239}PuO_2$) then returned to the smoke chambers one week later for 30 months of continuous exposure to either filtered air or cigarette smoke. The incidence and multiplicity of lung tumours (adenocarcinomas, squamous-cell carcinomas, adenosquamous carcinomas) in animals exposed to both concentrations of cigarette smoke and $^{239}PuO_2$ were higher than those in animals exposed to $^{239}PuO_2$, LCS or HCS alone (Finch *et al.*, 1995).

3.2.2 Hamster

(a) 7,12-Dimethylbenz[a]anthracene

Groups of 160 Syrian golden hamsters received 7,12-dimethylbenz[*a*]anthracene (DMBA) intratracheally, followed by cigarette smoke for life, or treated with cigarette smoke or DMBA only. A total of 32 squamous-cell carcinomas of the larynx were observed in animals treated with both DMBA and cigarette smoke, in comparison with 17 in hamsters exposed to cigarette smoke only and none in hamsters treated with DMBA alone (Dontenwill *et al.*, 1973). Similar results were reported from other experiments in which Syrian golden hamsters were exposed to DMBA and cigarette smoke (Hoffmann *et al.*, 1979).

(b) N-Nitrosodiethylamine

Groups of hamsters received a single subcutaneous injection of *N*-nitrosodiethylamine (NDEA) and then were exposed to smoke from unfiltered cigarettes, filtered cigarettes and sham smoke. Controls were exposed to either unfiltered cigarette smoke, filtered cigarette smoke or sham smoke. In the NDEA-smoke-treated groups, epithelial hyperplasias and/or papillomas of the larynx were induced at higher frequency than in controls (Takahashi *et al.*, 1992). Hamsters exposed to cigarette smoke in air also received 12 weekly subcutaneous injections of NDEA (total dose, 10 mg/hamster). Treatment with NDEA only resulted in both benign and malignant tumours of the respiratory tract, and co-exposure to cigarette smoke potentiated the development of tumours in the nasal cavity (Harada *et al.*, 1985).

3.3 Smoke condensates

Study design and results of the studies on administration of tobacco smoke condensates are summarized in Table 3.3.

3.3.1 Skin application

(a) Mouse

Cigarette-smoke condensate produces both benign and malignant tumours on mouse skin. The carcinogenic potency of the cigarette-smoke condensate depends upon tobacco variety, composition of cigarette paper and the presence of additives (Wynder *et al.*, 1957; Gargus *et al.*, 1976; Gori, 1976).

(b) Rabbit

Cigarette-smoke condensate induced skin papillomas and carcinomas when applied to the ears of rabbits for lifetime (Graham *et al.*, 1957).

3.3.2 Intrapulmonary administration

Injection of 24 mg cigarette-smoke condensate into the lungs of female Osborne Mendel rats led to the development of squamous cell carcinomas (Stanton *et al.*, 1972). These observations were confirmed by Dagle *et al.* (1978) who observed a dose-dependent incidence of lung carcinomas when cigarette-smoke condensate prepared from two types of cigarettes were given.

Table 3.3 Carcinogenicity in response to exposure to cigarette-smoke condensate in animals

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mice CAF1 (M, F) Wynder *et al.* (1953)	112, 44 controls Skin painting (dorsal) of CSC, CSC/acetone solution (40 mg CSC/ application), 3 × /wk, lifetime	36/81 (44%, skin epidermoid C), 0/30 (acetone controls)	
Mice ICR Swiss (F) Gargus *et al.* (1976)	5200 Skin painting (dorsal) of CSC, CSC/acetone solution (150 mg or 300 mg CSC/wk), 6 × /wk, 78 wk	482/5200 (9%, skin C), 3/800 (0.4%, acetone controls)[a]	
Mice ICR Swiss (F) Gori (1976)	4900 Skin painting (dorsal) of CSC, CSC/acetone solution (25 mg or 50 mg CSC/application), 6 × /wk, 78 wk	1157/4900 (24%, skin C), 0/800 (acetone controls)	
Mice, ICR/Ha Swiss (F) Hoffmann & Wynder (1971)	30 animals/group Skin painting (dorsal) with CSC active fraction with or without subsequent painting of the skin with croton oil, CSC active fraction/acetone (2.5 mg of 0.6% CSC/application), 10 times on alternate d Croton oil (2.5%), 3 × /wk, up to 12 mo, 10 d after last CSC active fraction application; 15 mo	After 12 and 15 mo: 4/30 (13%, skin C), 0/65 (croton oil controls)	
Mice, Swiss (F) Wynder & Hoffmann (1961)	30–50 animals/group Skin painting (dorsal) of CSC with or without initiation by DMBA application; DMBA (75 µg); CSC/acetone (75 mg CSC/application, start: 1 wk after DMBA application), 2–3 × /wk, 12 mo; 15 mo	DMBA: 2/30 (7%, skin C) 2 × CSC: 1/40 (3%, skin C) DMBA + 2 × CSC: 8/30 (27%, skin C) 3 × CSC: 11/50 (22%, skin C) DMBA + 3 × CSC: 11/30 (37%, skin C)	
Mice, SENCAR (F) Meckley *et al.* (2004a)	40 animals/group Skin painting (dorsal) of CSC from Kentucky 1R4F reference cigarettes, with or without initiation by DMBA application; DMBA (75 µg) or acetone, 1x. Then starting 1 wk after DMBA or acetone: CSC in acetone, 0, 10, 20 or 40 mg/application, 3 × /wk, 29 wk; 31 wk	Mean mice with tumours/mice per group at 31 wk[e]: No DMBA: 0/40 acetone-acetone, 9/40 (22%) acetone-CSC 40 mg/treatment DMBA/CSC: 0/40, 3/40 (1.0), 16/40 (75 tumours/16 mice = 4.7), 32/40 (200 tumours/32 mice = 6.3)	
Mice, SENCAR (F) Meckley *et al.* (2004b)	40 animals/group Skin painting (dorsal) of CSC from Kentucky 1R4F reference cigarettes or ECLIPSE (non-burned) cigarettes, with or without initiation by DMBA application; DMBA (75 µg) or acetone, 1 × . Then starting 1 wk after DMBA or acetone: CSC in acetone, 0, 10, 20 or 40 mg/application, 3 × /wk, 29 wk; 31 wk	No DMBA: acetone/acetone 0/40 (0); acetone/1R4F CSC 40 mg, 9/40 (1.8); acetone/ECLIPSE CSC 40 mg, 0/40 (0) DMBA/CSC: acetone, 0/40 (0); 1R4F CSC 10 mg, 6/40 (1.8); 1R4F CSC 12 mg, 28/40 (6.6); 1R4F CSC 40 mg, 36/40 (6.8); ECLIPSE CSC, 0/40 (0); ECLIPSE CSC 10 mg, 1/40 (1); ECLIPSE CSC 20 mg, 2/40 (5.5); ECLIPSE CSC 40 mg, 12/40 (2.6)	

Table 3.3 (continued)

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance
Mice, SENCAR (F) Hayes *et al.* (2007)	40 or 50 animals/group Skin painting (dorsal) of CSC from heat-exchanged flue cured tobacco (HE; low TSNA) or direct-fire (DF) cured tobacco, with or without initiation by DMBA application; DMBA (75 µg) or acetone, 1 × . Then starting 1 wk after DMBA or acetone: CSC/acetone, 0, 9, 18, or 36 mg/application, 3 × /wk, 29 wk; 31 wk	No DMBA: acetone/acetone 0/40; acetone/DF CSC 36 mg, 5/50 (1.4); acetone/HE CSC 36 mg, 8/50 (1.3) DMBA/CSC: DF CSC, 0/40, DF CSC 9 mg, 15/40 (5.5); DF CSC 18 mg, 30/40 (10.0); DF CSC 36 mg, 43/50 (8.2); HE CSC, 0/40, HE CSC 9 mg, 17/40 (4.8); HE CSC 18 mg, 32/40 (7.3); HE CSC 36 mg, 42/50 (8.5)	$P < 0.05$ $P < 0.05$ $P < 0.05$
Mice, Swiss albino (M) Pakhale *et al.* (1988)	20 animals/group Oral gavage of Indian bidi smoke condensate; 1 mg bidi smoke condensate/0.1 mg DMSO, 5 d/wk, 55 wk; 90 wk	4/15 (27%, hepatic haemangiomas); 1/15 (7%, stomach papilloma); 1/15 (7%, stomach carcinoma); 1/15 (7%, oesophageal carcinoma); 0/15 (untreated or DMSO-treated controls)	
Rats, Osborne Mendel (F) Stanton *et al.* (1972)	Number/group at start (NR) Intrapulmonary administration of CSC pellet; CSC/beeswax:tricaprylin (24 mg CSC/injection), up to 107 wk after implantation	14/40[c] (35%, lung squamous-cell C), 0/63[c] (beeswax:tricaprylin controls)	
Rats, OM/NCR (F) Dagle *et al.* (1978)	120[d] Intrapulmonary administration of CSC pellet; CSC/beeswax:tricaprylin (5, 10, 20 or 67 mg CSC/injection), 120 wk after implantation	4, 10, 20 and 42% pulmonary C prevalence; 0% C prevalence for 3 control groups of about 190 rats each	
Rabbits, Albino New Zealand (M, F) Graham *et al.* (1957)	38, 7 controls Skin painting of CSC (both ears); CSC/acetone solution (100 mg CSC/application/ear), 5 × /wk, lifetime (4–6 yr)	4/38 (11%, 2 skin C + 1 skin liposarcoma + 1 skin fibrosarcoma), 0/7 (acetone controls)	

[a] Skin papillomas
[b] Mostly adenomas
[c] Incidence in animals that died 43–107 weeks after injection
[d] 4 × 10 rats/group terminated before 120 weeks
[e] Total visually identified and histologically confirmed skin tumours included mostly squamous papillomas and carcinomas [Tumour incidences and multiplicities estimated from graphs]
C, carcinoma; CSC, cigarette-smoke condensate; d, day or days; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMSO, dimethyl sulfoxide; F, female; M, male; NR, not reported; TSNA, tobacco-specific *N*-nitrosamines; wk, week or weeks

3.3.3 Initiation-promotion skin painting studies

Cigarette-smoke condensate and its fractions can act as skin co-carcinogens in Swiss and SENCAR mice when tested in conjunction with croton oil (Hoffmann & Wynder, 1971) or DMBA (Wynder & Hoffmann, 1961; Meckley *et al.*, 2004a, b; Hayes *et al.*, 2007).

3.3.4 Bidi smoke

Swiss albino mice administered 1 mg bidi smoke condensate in dimethyl sulfoxide (DMSO) by oral gavage developed haemangiomas (4/15), stomach carcinoma (1/15), and esophageal carcinoma (1/15), whereas no tumours were observed in controls (Pakhale *et al.*, 1988).

3.4 Synthesis

Mainstream tobacco smoke induced lung tumours in mice, lung and nasal cavity tumours in rats and laryngeal carcinomas in hamsters.

Co-administration of tobacco smoke with benzo[*a*]pyrene, radon progeny and plutonium resulted in higher lung tumour responses in rats than administration of either agent alone. Hamsters exposed to cigarette smoke and either DMBA or NDEA had higher lung tumour responses compared to cigarette smoke, DMBA or NDEA alone.

Topical application of cigarette-smoke condensate led to the development of skin tumours in mice and rabbits; intrapulmonary administration of cigarette-smoke condensate induced squamous cell carcinomas in rat lung.

4. Other Relevant Data

4.1 Overview of the mechanistic evidence for the carcinogenicity of tobacco

4.1.1 Conceptual model of the carcinogenesis of tobacco and tobacco smoke

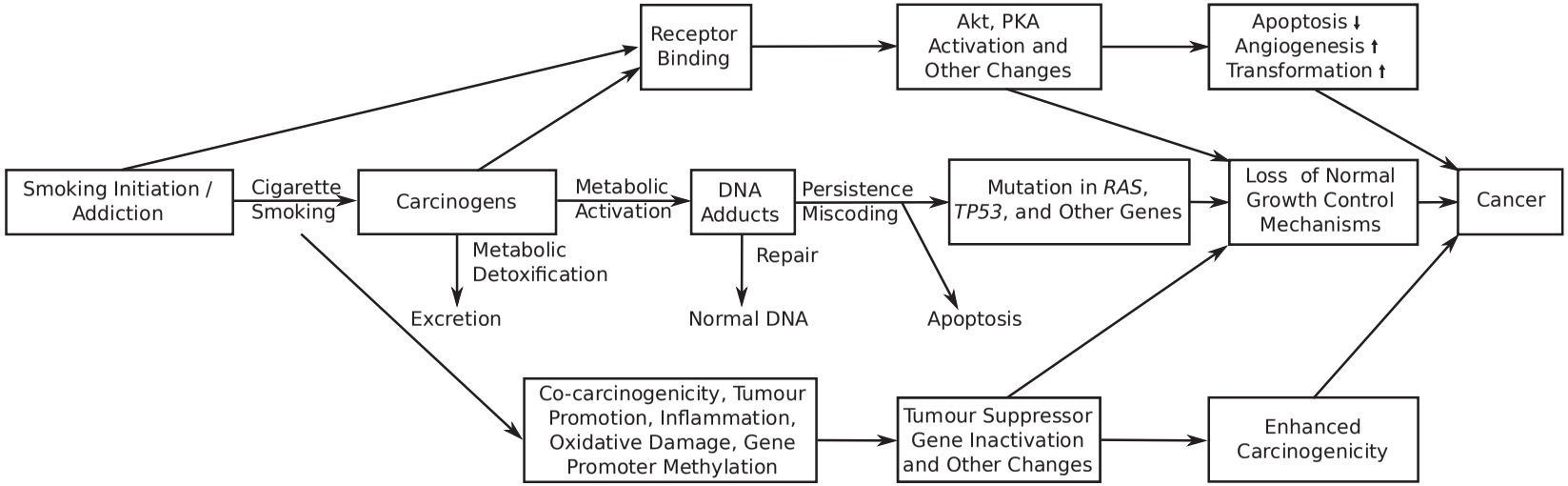
A conceptual model for understanding mechanisms by which tobacco smoke causes cancer is shown in Fig. 4.1 (Hecht, 1999, 2003). This model also applies to smokeless tobacco and other forms of smoked tobacco and, in theory, to second-hand tobacco smoke since it contains all of the same carcinogens and toxicants as mainstream cigarette smoke, although at lower doses.

The major accepted mechanistic pathway is summarized in the central track of Fig. 4.1. Smokers inhale carcinogens which, either directly or after metabolism, covalently bind to DNA, forming DNA adducts. DNA adducts are central to chemical carcinogenesis because they can cause miscoding and permanent mutations. If these mutations occur in critical regions of oncogenes and tumour suppressor genes, which are essential in growth control, the result can be loss of normal cellular proliferation mechanisms, genomic instability, and cancer. A study that sequenced 623 cancer-related genes in 188 human lung adenocarcinomas validated this premise by finding multiple somatic mutations in critical growth control genes, consistent with the chronic bombardment of cellular DNA by tobacco smoke carcinogens and their metabolically activated forms (Ding *et al.*, 2008).

Each step of this conceptual model is considered in detail below.

Most people begin smoking cigarettes when they are teenagers, and become addicted to nicotine. Nicotine is not generally considered to be a carcinogen (Schuller, 2009), but it is accompanied in each puff of each cigarette by a complex

Fig. 4.1 Conceptual model for understanding mechanisms of tobacco carcinogenesis



There may be overlap between these three tracks: e.g. mutation in *TP53* leading to tumour suppressor gene inactivation.

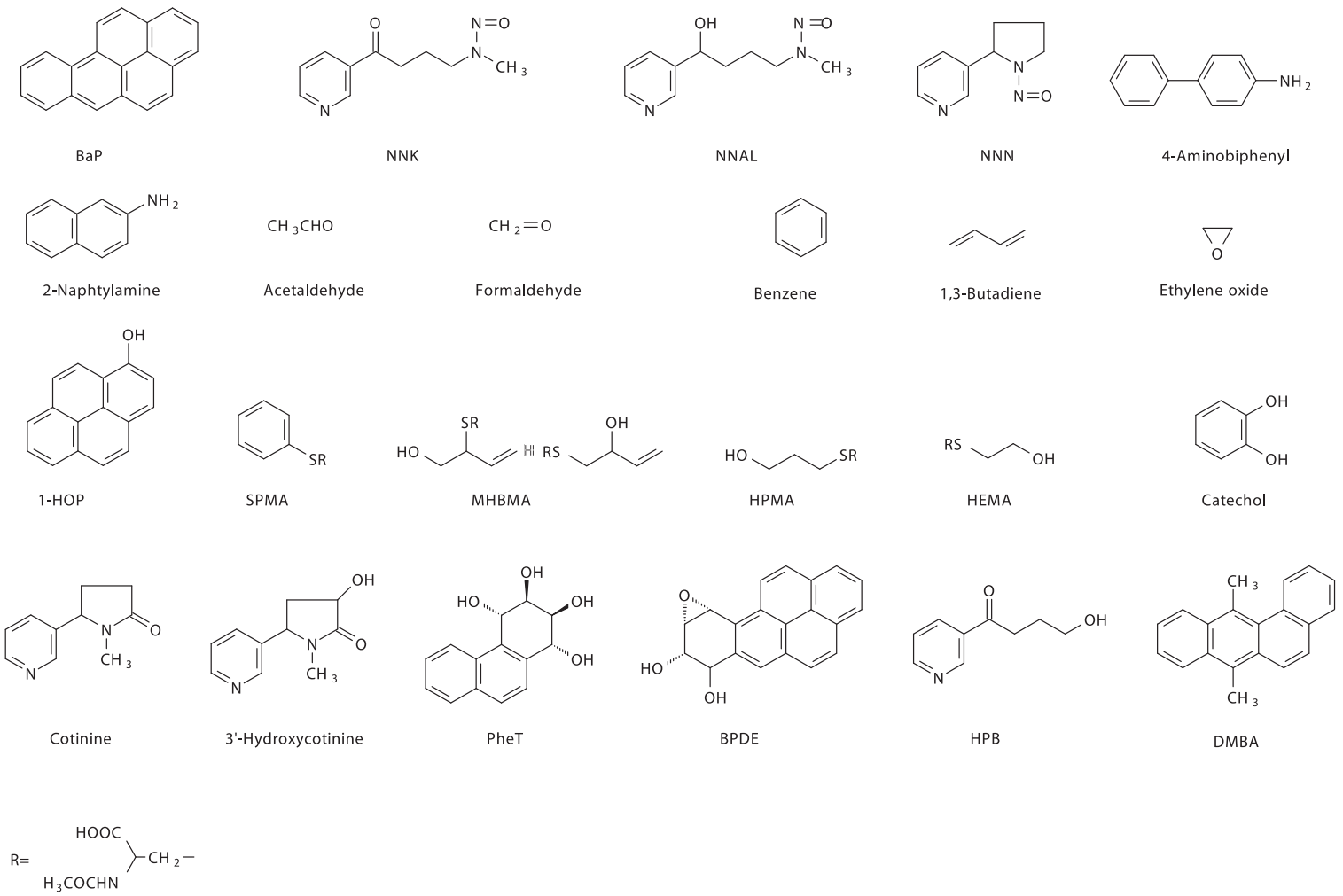
mixture of carcinogens and toxicants. There are over 60 carcinogens in cigarette smoke that have been evaluated in the previous *IARC Monograph* as having *sufficient evidence* for carcinogenicity in laboratory animals (IARC, 2004a), sixteen of which are considered to be *carcinogenic to humans (Group 1)*. There are also many other carcinogens and potential carcinogens in cigarette smoke that have not been evaluated (Rodgman & Perfetti, 2006; see Section 1.1). Structures of tobacco smoke constituents and biomarkers discussed here are presented in Fig. 4.2.

Numerous studies demonstrate the uptake of tobacco smoke carcinogens and toxicants by smokers, and showed higher levels of their metabolites in urine and blood of smokers than non-smokers (Sections 4.1.1 and 4.1.2). There are substantial differences in carcinogen exposure among people because of the number and types of cigarettes they smoke and the ways in which they smoke them. These differences can be monitored in part by biomarkers of exposure such as urinary metabolites or haemoglobin adducts (Section 4.1.2). Haemoglobin adducts of multiple aromatic amines and volatile carcinogens have been demonstrably related to tobacco (Hatsukami *et al.*, 2006a). There may also be differences in carcinogen exposure due to genetic variations (Section 4.2).

The body's response to cigarette smoke constituents is similar to its response to pharmaceutical agents and other foreign compounds. Drug metabolizing enzymes, most frequently CYPs, convert these compounds to more water soluble forms, facilitating excretion. During this natural protective attempt, some reactive intermediates are formed. These intermediates are frequently electrophilic (electron seeking, or bearing a partial or full positive charge). Electrophilic intermediates may react with water, generally resulting in detoxification, or may covalently bind to nucleophilic (electron rich) sites in DNA, forming DNA adducts (Guengerich, 2001; Jalas *et al.*, 2005), which are critical in the carcinogenic process (see Section 4.1.3c). CYP1A1 and CYP1B1, repeatedly shown to be inducible by cigarette smoke via interactions of smoke compounds with the aryl hydrocarbon receptor (AhR), are particularly important in the metabolic activation of PAHs, while CYP2A13 is critical for the metabolism of NNK (Nebert *et al.*, 2004; Jalas *et al.*, 2005). The inducibility of certain CYPs may be a critical aspect of cancer susceptibility in smokers (Nebert *et al.*, 2004). CYP1A2, CYP2A6, CYP2E1 and CYP3A4 are also important in the metabolism of cigarette smoke carcinogens to DNA binding intermediates (Jalas *et al.*, 2005), and aldo-keto reductase enzymes, also induced by tobacco smoke (Quinn *et al.*, 2008), are involved in the metabolism of NNK, BaP and other tobacco smoke carcinogens. Competing with this process of "metabolic activation" resulting in DNA binding is the intended metabolic detoxification, which leads to harmless excretion of carcinogen metabolites, and is also catalysed by CYPs and a variety of other enzymes including GSTs, uridine diphosphate-glucuronosyl transferases (UGTs), and arylsulfatases. The relative amounts of carcinogen metabolic activation and detoxification differ among individuals. It is widely hypothesized that this balance will affect cancer risk with those having higher activation and lower detoxification capacity being the most susceptible. This premise is supported in part by molecular epidemiologic studies of polymorphisms, or variants in more than 1% of the population, in certain genes coding for these enzymes (Vineis *et al.*, 2003; Carlsten *et al.*, 2008).

DNA adducts are thought to be a critical lesion in carcinogenesis. Many investigations demonstrate the presence of DNA adducts in human tissues, and some of these are summarized in Section 4.1.2c. There is massive evidence, particularly from studies which use relatively non-specific DNA adduct measurement methods, that DNA adduct levels in the lung and other tissues of smokers are higher than in non-smokers, and some epidemiologic data link

Fig. 4.2 Structures of compounds discussed in the text



BaP, Benzo[*a*]pyrene; BPDE, Benzo[*a*]pyrene diol epoxyde; DMBA, dimethylbenz[*a*]anthracene; 1-HOP, 1-hydroxypyrene; HEMA, 2-hydroxyethyl-mercapturic acid; HPMA, 3-hydroxypropyl-mercapturic acid; HPB, 4-hydroxy-1-(3-pyridyl)-1-butanone; HPMA, 3-hydroxypropyl-mercapturic acid; MHBMA, monohydroxybutyl-mercapturic acid; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N*'-nitrosonornicotine; PheT, phenanthrenetetrol; SPMA, S-phenyl-mercapturic acid

these higher adduct levels to increased cancer risk (IARC, 2004b; Veglia *et al.*, 2008). However, there is much more limited evidence from studies using specific carcinogen-derived DNA adducts as biomarkers (Pfeifer *et al.*, 2002). Oxidative DNA damage has also been observed, and this may result partially from exposure to metals in cigarette smoke (Stavrides, 2006).

Cellular DNA repair systems can excise DNA adducts and restore normal DNA structure (Christmann *et al.*, 2003). These complex multiple systems include direct base repair by alkyltransferases, removal of DNA damage by base and nucleotide excision repair, mismatch repair, and double strand repair. If these DNA repair systems are unsuccessful in fixing the damage, then the DNA adducts can persist, increasing the probability of a permanent mutation. There are polymorphisms in genes coding for some DNA repair enzymes. If these variants lead to deficient DNA repair, the probability of cancer development can increase (Vineis *et al.*, 2009).

DNA adducts can cause miscoding during replication when DNA polymerase enzymes misread the DNA adduct and consequently insert the wrong base opposite to it. There is some specificity in the relationship between specific DNA adducts formed from cigarette smoke carcinogens and the types of mutations which they cause. G to T and G to A mutations have often been observed (Section 4.1.3) (Hecht, 1999). Extensive studies have characterized the mutations which occur because of specific carcinogen-DNA adducts (Delaney & Essigmann, 2008). Mutations have been reported in the *KRAS* oncogene in lung cancer and in the *TP53* tumour suppressor gene in a variety of cigarette smoke-induced cancers (Ahrendt *et al.*, 2001; Pfeifer *et al.*, 2002; Ding *et al.*, 2008). The cancer causing role of these genes has been firmly established in animal studies (Lubet *et al.*, 2000; Johnson *et al.*, 2001). A selection and promotion process may also play a role in the final mutation spectrum seen in genes in smoking-associated tumours (Rodin & Rodin, 2005; Sudo *et al.*, 2008).

Urinary mutagenicity, sister chromatid exchanges, micronuclei in buccal cells, and other genetic effects have been consistently observed in smokers at higher levels than in non-smokers (IARC, 2004a; Proia *et al.*, 2006). In addition to mutations, numerous cytogenetic changes are observed in lung cancer, and chromosome damage throughout the field of the aerodigestive tract is strongly associated with cigarette smoke exposure. Mutations resulting from DNA adducts can cause loss of normal cellular growth control functions, via a complex process of signal transduction pathways, ultimately resulting in genomic instability, cellular proliferation and cancer (Ding *et al.*, 2008). Apoptosis, or programmed cell death, is a protective process, and can remove cells which have DNA damage, thus serving as a counterbalance to these mutational events. The balance between apoptotic mechanisms and those suppressing apoptosis will have a major impact on tumour growth.

While the central track of Fig. 4.1 is the major pathway by which tobacco smoke carcinogens cause cancer, other mechanisms also contribute, as indicated in the top and bottom tracks (Hecht, 2003). Nicotine, NNK, and NNN bind to nicotinic and other cellular receptors, resulting in activation of serine/threonine kinase Akt (also known as protein kinase B), protein kinase A, and other changes. Nicotine and NNK increase expression of survivin, an inhibitor of apoptosis in normal human bronchial epithelial cells, and survivin mRNA is detected in bronchial brush samples from heavy smokers (Jin *et al.*, 2008). This can cause decreased apoptosis, increased angiogenesis, and increased transformation (Heeschen *et al.*, 2001; West *et al.*, 2003). Thus, although nicotine is not carcinogenic, it may enhance carcinogenicity in various ways (Schuller, 2009). Cigarette smoke also contains well established oxidants, co-carcinogens, tumour promoting fractions, and inflammatory agents, as well as

cilia-toxic compounds such as acrolein, which impede clearance. Many studies demonstrate the co-carcinogenic and cytotoxic effects of catechol, an important constituent of cigarette smoke. An epigenetic pathway frequently observed in tobacco-induced cancers is enzymatic methylation of promoter regions of genes such as *p16* and *FHIT* [fragile histidine triad gene, a gene coding for a dinucleoside 5′, 5‴- P^1, P^3-triphosphate hydrolase, a putative tumour suppressor protein] resulting in gene silencing, which are also strongly implicated in tobacco-induced lung cancer (D'Agostini *et al.*, 2006; Bhutani *et al.*, 2008). When this occurs in tumour suppressor genes, the result can be unregulated proliferation (Belinsky, 2005). Inflammation due to smoking is associated with tumour promotion and activation of factors such as NFκB. Inflammation also plays a role in chronic obstructive pulmonary disease (COPD), which in turn is an independent risk factor for lung cancer (Smith *et al.*, 2006; Turner *et al.*, 2007; Lee *et al.*, 2008a).

This conceptual model can be applied to smokeless tobacco products. Smokeless tobacco products have much lower levels of carcinogens and toxicants that result from combustion, so the effects of these agents are not seen to a significant extent. The most prevalent strong carcinogens in smokeless tobacco are the tobacco-specific nitrosamines; other nitrosamines, PAHs, aldehydes and metals are also present, and there are large amounts of some inorganic salts that may contribute to inflammation (IARC, 2007a; Stepanov *et al.*, 2008). An additional factor in carcinogenesis by betel quid with tobacco is the basic pH resulting from addition of slaked lime to the quid, leading to oxidative damage and inflammation (IARC, 2004b).

Multiple studies demonstrate that tobacco-specific nitrosamines are absorbed and metabolised in smokeless tobacco users (IARC, 2007a).

There is evidence for DNA adduct formation in oral tissues of smokeless tobacco users, and sister chromatid exchanges, chromosomal aberrations, and micronuclei – consequences of DNA adduct formation – have been reported (Proia *et al.*, 2006; Warnakulasuriya & Ralhan, 2007). Many studies have demonstrated *RAS* and *TP53* mutations in smokeless tobacco users (Warnakulasuriya & Ralhan, 2007) consistent with the conceptual framework.

Oxidative stress and reactive oxygen species could play a significant role in cancer induction in smokeless tobacco users, particularly at high pH (Boffetta *et al.*, 2008). Chronic local inflammation and irritation induced by smokeless tobacco and its constituents could have a tumour promoting or co-carcinogenic effect (Boffetta *et al.*, 2008). Upregulation of cyclooxygenase-2, involved in prostaglandin synthesis and inflammation, has been observed in animal studies upon exposure to smokeless tobacco (Boffetta *et al.*, 2008). Smokeless tobacco products have relatively high levels of sodium chloride (NaCl), which could contribute to inflammation, tumour promotion, and co-carcinogenesis. Cancer of the oral cavity is strongly associated with tobacco smoking (IARC, 2004a) or chewing (IARC, 2007a) and alcoholic beverage drinking (IARC, 2010a) However only a fraction of exposed subjects develop tumours, which suggests that other exposures such as HPV may be independently involved or act as cofactors. HPV is known to infect the oral cavity of healthy individuals and several HPV-related lesions have been characterized (IARC, 2007b). Herpes simplex virus has also been shown to enhance the carcinogenicity of smokeless tobacco products in animal studies (Park *et al.*, 1986). These factors may contribute significantly to the local carcinogenic effects characteristic of smokeless tobacco use.

4.1.2 *Absorption, distribution, metabolism and excretion*

There are examples of toxicant and carcinogen metabolism and excretion for representatives of virtually every major class of compounds;

some of these are summarized in Table 4.1. Nicotine and five of its urinary metabolites – cotinine, 3′-hydroxycotinine and their glucuronides, and nicotine glucuronide – comprise about 73–96% of the nicotine dose (Hukkanen *et al.*, 2005), and are found in blood, sweat, hair and toenails (Al Delaimy, 2002; Hukkanen *et al.*, 2005; Stepanov *et al.*, 2007; Al Delaimy & Willett, 2008). Metabolites of various polycyclic aromatic hydrocarbons including pyrene, phenanthrene, fluorene, and benzo[*a*]pyrene have been quantified in human urine and are higher in smokers than in non-smokers (Hecht, 2002; Hecht *et al.*, 2005a; Jacob *et al.*, 2007; Hansen *et al.*, 2008). Metabolites of tobacco-specific nitrosamines – NNAL and its glucuronides (total NNAL) from NNK; and NNN and its glucuronides (total NNN) from NNN – are present in human urine (Hecht, 2002; Stepanov & Hecht, 2005; Hecht *et al.*, 2008a; Stepanov *et al.*, 2008). Total NNAL has also been quantified in blood and toenails (Hecht *et al.*, 2002; Stepanov *et al.*, 2007). Aromatic amine-haemoglobin adducts have been frequently measured in human blood, and their levels increase with smoking (Hecht, 2002; Hatsukami *et al.*, 2006a). Mercapturic acids of several tobacco smoke compounds such as benzene, 1,3-butadiene, acrolein, and ethylene oxide are present in human urine and are related to smoking (Carmella *et al.*, 2009). Haemoglobin adducts of acrylonitrile and related compounds are elevated in smokers' blood, and levels of metals such as Cd are increased in smokers' urine (Carmella *et al.*, 2002; IARC, 2004b).

All of the metabolites listed in Table 4.1 are elevated in cigarette smokers; in studies of second-hand smoke exposure, only nicotine metabolites and urinary total NNAL are consistently increased in exposed versus non-exposed subjects, although one very large study also observed an increase in PAH metabolites (Pirkle *et al.*, 2006; Hecht, 2008; Suwan-ampai *et al.*, 2009). Smokeless tobacco users have significantly raised levels of nicotine metabolites and tobacco-specific nitrosamine metabolites compared to non-tobacco users (Hecht *et al.*, 2007).

4.1.3 Biomarkers

Tobacco carcinogen biomarkers are quantifiable entities that can be *specifically* related to tobacco carcinogens. Specificity to a given carcinogen is critical because tobacco carcinogens vary widely in their potency and target organs.

Considering the mechanistic framework outlined in Fig. 4.1, one could visualize various types of biomarkers. Currently, biomarkers of carcinogen/toxicant dose, reflecting the second box of the central track of Fig. 4.1, are by far the most extensively used and validated. The second most common are measurements of DNA adducts (or protein adducts as their surrogates), but fewer of these have both practical utility and validation with respect to tobacco carcinogen specificity.

The use of tobacco carcinogen biomarkers bypasses many uncertainties in estimation of dose. The most commonly used estimation of dose is self-reported number of cigarettes/day, but this is not a very good marker. It may not be reported accurately and it provides no information on the way in which the cigarettes were smoked, which is critical when one considers the common phenomenon of smoker's compensation. Brand information together with machine smoking measurements of specific components is another way of obtaining a measure of dose. However, machine smoking measurements are known to have limitations and the application of a given machine smoking protocol to a given smoker requires smoking topography measurements for that smoker. A disadvantage of tobacco carcinogen biomarkers is that they are affected to some extent by individual differences in metabolism, which may complicate interpretation of dose.

Table 4.1 Examples of toxicant or carcinogen metabolites in tobacco users

Toxicant or carcinogen	Examples of metabolites in tobacco users	References
Nicotine	Cotinine, 3′-hydroxycotinine and their glucuronides in urine, blood or saliva; nicotine and cotinine in toenails	Al Delaimy (2002), Hukkanen *et al.* (2005), Al Delaimy & Willett (2008), Stepanov *et al.* (2007)
Polycyclic Aromatic Hydrocarbons (PAHs)	1-hydroxypyrene, phenanthrols, phenanthrene tetraols, fluorenols, benzo[*a*]pyrenols, benzo[*a*]pyrene tetraols in urine	Hecht (2002), Hecht *et al.* (2005a), Hansen *et al.* (2008), Jacob *et al.* (2007)
Tobacco-specific nitrosamines	NNAL and its glucuronides (total NNAL) in urine or blood, total NNN in urine; NNAL and NNN in toenails	Hecht (2002), Hecht *et al.* (2002, 2008a), Stepanov & Hecht (2005), Stepanov *et al.*, (2007, 2008)
Aromatic amines	Parent amines in urine and haemoglobin adducts in blood	Hecht (2002), Hatsukami *et al.* (2006a)
Volatile hydrocarbons		
Benzene 1,3-Butadiene	Muconic acid and S-phenyl-mercapturic acid (SPMA) in urine; Monohydroxybutyl-mercapturic acid (MHBMA) in urine	Hecht (2002), Carmella *et al.* (2009)
Acrolein	3-hydroxypropyl-mercapturic acid (HPMA) in urine	Carmella *et al.* (2009)
Ethylene oxide	2-hydroxyethyl-mercapturic acid (HEMA) in urine, haemoglobin adducts in blood	Bono *et al.* (2002), Carmella *et al.* (2009)
Acrylonitrile	Haemoglobin adducts in blood	Carmella *et al.* (2002)
Metals	Cadmium in urine	IARC (2004a)

(a) Urinary biomarkers

Probably the most practical and, to date, the most extensively applied tobacco carcinogen biomarkers are urinary metabolites of tobacco carcinogens, and these have been comprehensively reviewed (Hecht, 2002; IARC, 2004a). Advantages include the ready availability of samples, and concentrations in urine that are easily quantifiable using modern analytical chemistry methods, most frequently liquid chromatography-tandem mass spectrometry (LC-MS/MS). The urinary metabolites listed in Table 4.1 have all been used as biomarkers and all are validated with respect to exposure in cigarette smokers (Carmella *et al.*, 2009). Total nicotine equivalents (the sum of nicotine and the five metabolites in Table 4.1) is a particularly effective way of estimating nicotine dose from tobacco products.

Total NNAL, the sum of NNAL and its glucuronides, is a highly useful biomarker of NNK exposure (Hecht, 2002, 2003; Hatsukami *et al.*, 2006a). The tobacco-specificity of NNK, and therefore total NNAL, is a key feature of this biomarker because studies in which it is applied are not confounded by other environmental or dietary exposures. It also has a considerably longer half-life than cotinine and several other urinary biomarkers. Total NNAL has been used in numerous studies that estimated uptake of NNK in smokers under varying circumstances. In one example, smokers reduced their number of cigarettes smoked per day, but there was not a corresponding decrease in NNK uptake due to compensation (Hecht *et al.*, 2004). In another study, NNK and PAH uptake, estimated by total NNAL and 1-hydroxypyrene, respectively, were compared in smokers of regular, light, and ultra-light cigarettes, and found to be similar, consistent with epidemiologic studies that

demonstrate no protection against lung cancer in smokers of light compared to regular cigarettes (Hecht *et al.*, 2005b). Other studies evaluated NNK uptake in smokers who switched from their current cigarette brand to products advertised as being less hazardous, but the results generally did not support these claims (Hatsukami *et al.*, 2004). One of the most useful applications of total NNAL has been in studies of non-smokers exposed to second-hand tobacco smoke (Hecht, 2003). The sensitivity and specificity of this biomarker are ideal for such studies, and it is the most commonly elevated tobacco carcinogen biomarker in non-smokers exposed to second-hand smoke. Total NNAL has also found utility in establishing NNK uptake in smokeless tobacco users (Hecht *et al.*, 2002, 2007, 2008a, b; Hecht, 2008)

The relationship of urinary total NNAL to lung cancer was demonstrated in a study of stored urine samples collected years before diagnosis of lung cancer from smokers in Shanghai, China and Singapore (Yuan *et al.*, 2009). There was a significant relationship between total NNAL and lung cancer incidence, after correction for numbers of cigarettes smoked per day and duration of smoking. An 8.5 fold increased risk for lung cancer was observed for those smokers in the highest tertile of total NNAL and cotinine, relative to smokers with the same smoking history but in the lowest tertiles of total NNAL and cotinine. Urinary biomarkers were also used to demonstrate higher uptake of nicotine and NNK per cigarette in smokers with polymorphisms in the nicotinic acetylcholine genes associated with lung cancer in genome-wide association studies (see Section 4.2; Le Marchand *et al.*, 2008). Collectively, these results indicate that urinary total NNAL is not only a biomarker of exposure, but also a biomarker of risk for lung cancer.

(b) Serum and saliva metabolites

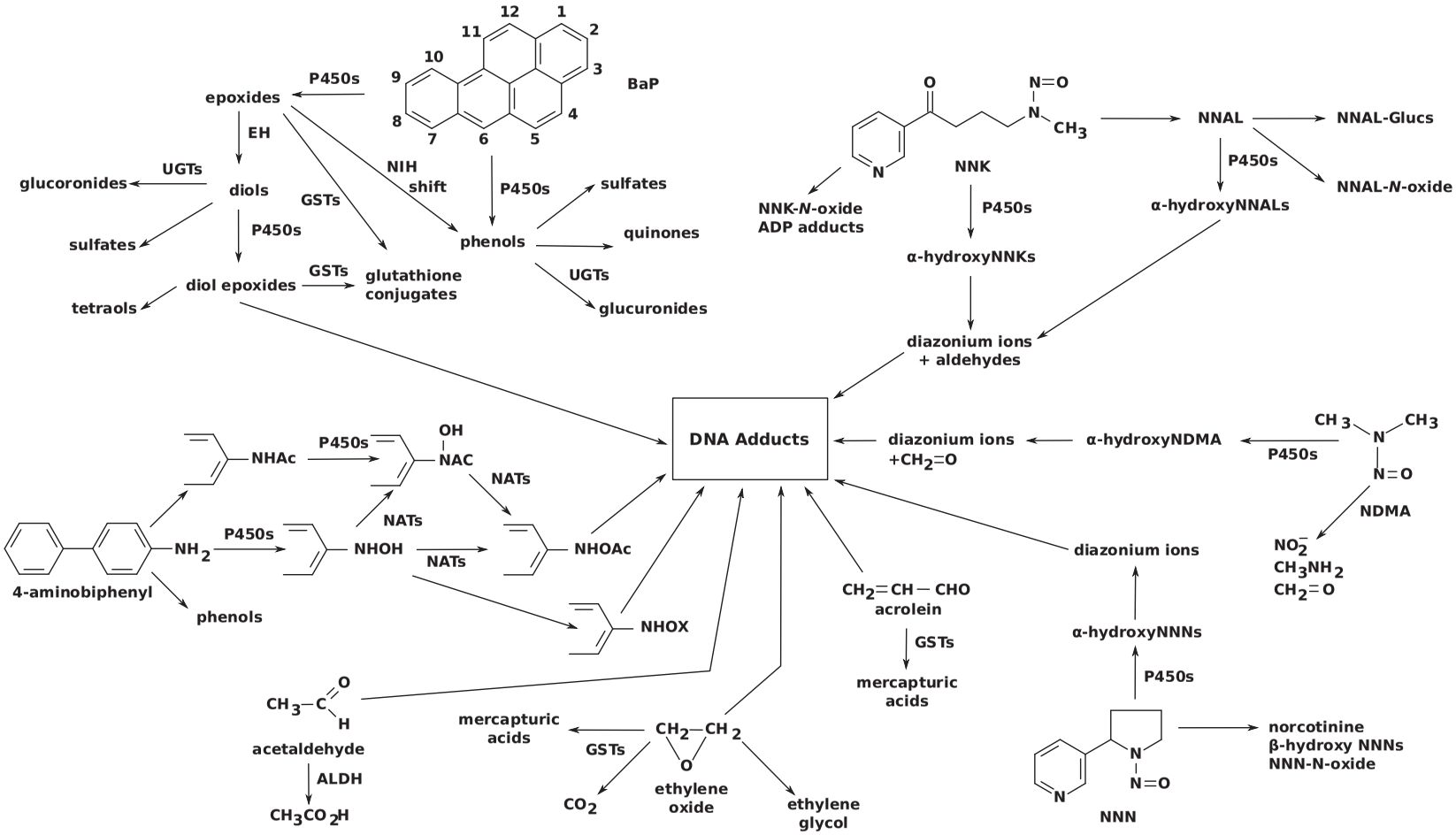
Serum and saliva metabolites have been used as biomarkers much less often than urine metabolites. The most frequently measured tobacco smoke toxicant in serum and saliva is cotinine, documented as a useful biomarker of cigarette smoking in many studies (Lee, 1999; Hukkanen *et al.*, 2005). Total NNAL can be readily quantified in serum and its levels remain relatively constant in a given smoker sampled at bimonthly intervals over a one year period. Consistent with the results described above, one study showed a significant relationship between total NNAL in prospectively collected serum samples from smokers and lung cancer risk (Church *et al.*, 2009). Other biomarkers that have been measured in serum include cadmium, benzene, styrene and *r*-1,*t*-2,3,*c*-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT) (IARC, 2004a; Church *et al.*, 2009).

(c) DNA adducts

Fig. 4.3 presents an overview of metabolism and DNA adduct formation from eight tobacco smoke compounds (clockwise from top left): BaP, NNK, *N*-nitrosodimethylamine (NDMA), NNN, acrolein, ethylene oxide, acetaldehyde and 4-aminobiphenyl. Evidence exists for DNA adduct formation from each of these carcinogens in smokers, based on studies carried out with tissues or blood cells. DNA adduct biomarkers have been applied mainly in studies of smokers, and there is far less evidence from studies of second-hand tobacco smoke or smokeless tobacco use.

The structures of DNA adducts of tobacco smoke carcinogens have been characterized in detail, but a complete description of these structures is beyond the scope of this section. Selected DNA adduct structures are shown in Fig. 4.4. A major DNA adduct of BaP results from *trans*- addition of the benzo[*a*]pyrene diol epoxide (BPDE) to the N^2-position of dG (Szeliga

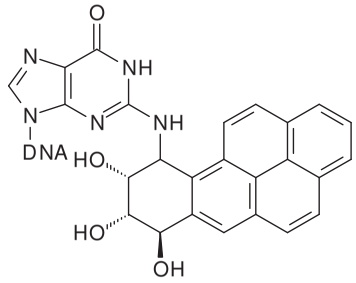
Fig. 4.3 Overview of metabolism and DNA adduct formation from eight tobacco smoke constituents



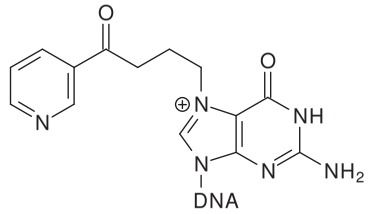
4-ABP, 4-aminobiphenyl; AC, acetyl; ADP, adenosine diphosphate; ALDH, aldehyde dehydrogenase; AKR, aldo-ketoreductase; B[*a*]P, benzo[*a*]pyrene; EH, epoxide hydrolase; Gluc, glucuronide; GSTs, glutathione *S*-transferases; NATs, *N*-acetyltransferases; NDMA, *N*-nitrosodimethylamine; NIH shift, phenomenon of hydroxylation-induced intramolecular migration; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, *N*'-nitrosonornicotine; P450s, cytochrome P450 enzymes; UGTs, uridine-5′-diphosphate-glucuronosyl transferases

Adapted from Cooper *et al.* (1983); Preussmann & Stewart (1984); Kadlubar & Beland (1985); Hecht (1998, 1999); Penning & Drury (2007); IARC (2008, 2010b).

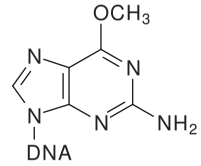
Fig. 4.4 Structures of some DNA adducts of tobacco smoke constituents



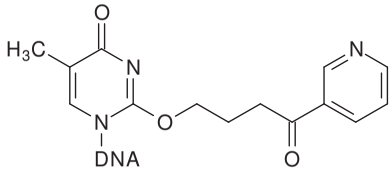
BPDE-N^2-dG



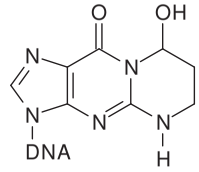
7-POB-dG



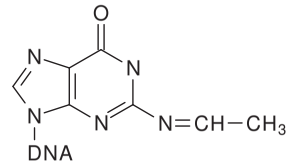
O^6-methyl-dG



O^2-POB-T



γ-OH-1,N^2-propano-dG
(from acrolein)



N^2-ethylidene-dG

BPDE-N^2-dG, benzo[*a*]pyrene diol epoxide-N^2-deoxyguanosine; 7-POB-dG, pyridyloxobutyl-deoxyguanosine; O^2-POB-T, O^2-pyridyloxobutyl-thymidine

& Dipple, 1998). Pyridyloxobutyl (POB)-DNA adducts of NNK and NNN are formed at the 7- and O^6-positions of deoxyguanosine dG, the O^2-position of thymidine, and the O^2-position of deoxycytidine (Hecht, 2008). They can be measured in part as 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB) released upon hydrolysis. Metabolic activation of NNK also leads to 7-methyl-dG and O^6-methyl-dG, identical to the DNA adducts formed from NDMA and other DNA methylating agents (Hecht, 2008). Ethylating agents and ethylene oxide in cigarette smoke also alkylate dG (Zhao *et al.*, 1999; Singh *et al.*, 2005). Acrolein and crotonaldehyde react with DNA to produce exocyclic 1,N^2-dG adducts, while acetaldehyde forms a Schiff base adduct with the exocyclic N^2 amino group of dG. There is evidence for the presence of all these DNA adducts in tissues or blood cells of smokers, but there are also many studies in which these specific adducts have been sought but not found (Boysen & Hecht, 2003).

Measurement of these DNA adducts as biomarkers potentially can provide the most direct link between cellular exposure and cancer, because DNA adducts are so critical in carcinogenesis. However, it is challenging because their levels are extremely low, frequently ranging from 1 per 10^6 to 1 per 10^8 normal bases, and the tissue or blood samples containing them are usually available in only small quantities. Fortunately, the routine detection of amol levels [attomole, equivalent to 10 moles] of DNA adducts by conventional LC-MS/MS techniques is now feasible (Singh & Farmer, 2006). There are still relatively few examples of quantitation of *specific* DNA adducts of tobacco carcinogens in tissues of smokers using mass spectrometry, high pressure liquid chromatography (HPLC)-fluorescence, HPLC with electrochemical detection, or postlabelling techniques (Pfeifer *et al.*, 2002). A much larger body of work has used the highly sensitive, but relatively non-specific ^{32}P-postlabelling and immunoassay methods of DNA adduct detection. Although the adducts detected using ^{32}P-postlabelling are often referred to as "aromatic DNA adducts," there is strong evidence that they are not related to PAHs (Arif *et al.*, 2006). Adduct levels are generally higher in lung tissues of smokers than non-smokers while studies using blood DNA have produced varied results. Adducts have also been detected in the larynx, oral and nasal mucosa, bladder, cervix, breast, pancreas, stomach, placenta, foetal tissue, cardiovascular tissues, sputum, and sperm of smokers (IARC, 2004a). A meta-analysis of the relationship of DNA adduct levels in smokers to cancer, as determined by ^{32}P-postlabelling in the majority of studies or enzyme linked immunosorbent assay (ELISA), demonstrated a positive relationship in current smokers (Veglia *et al.*, 2003; 2008).

(d) Protein adducts

Carcinogen-haemoglobin (Hb) and serum albumin adducts are regarded as surrogates for DNA adduct measurements. Although these proteins are not targets for carcinogenesis, virtually all carcinogens that react with DNA will also react with protein. Advantages of haemoglobin adducts include the ready availability of haemoglobin from blood and the relatively long lifetime of the erythrocyte in humans – 120 days –,which provides an opportunity for adducts to accumulate. Studies on protein adducts in smokers have been comprehensively reviewed (IARC, 2004a).

Haemoglobin adducts of aromatic amines are a highly informative type of carcinogen biomarker, with levels that are consistently higher in smokers than non-smokers, particularly for 3-aminobiphenyl and 4-aminobiphenyl-Hb adducts. Haemoglobin binds aromatic amines efficiently because heme accelerates the rate of nitrosoarene formation from the hydroxylamine, which is produced metabolically from the aromatic amine by CYP1A2 (Fig. 4.3; Skipper & Tannenbaum, 1990). Binding of the nitrosoarene occurs at the β-93 cysteine residue of human

haemoglobin; the adduct is hydrolysed releasing the free amine, which is quantified by GC-MS (Skipper & Tannenbaum, 1990). Adduct levels are clearly related to cigarette smoking (Skipper & Tannenbaum, 1990). Adducts that form at the terminal valine of haemoglobin are also useful biomarkers: examples include those derived from ethylene oxide, acrylonitrile and acrylamide (Bergmark, 1997; Fennell *et al.*, 2000). Ethylated N-terminal valine of haemoglobin is also higher in smokers than in non-smokers (Carmella *et al.*, 2002).

HPB-releasing Hb adducts of NNK and NNN have been quantified in studies of smokers and smokeless tobacco users (IARC, 2004a, 2007a). These adducts are thought to be tobacco-specific, but some studies report their presence in non-smokers (Falter *et al.*, 1994; Schlöbe *et al.*, 2008).

4.1.4 Genetic and related effects

(a) Mutagenicity and cytogenetic effects

Tobacco smoke and its condensates are mutagenic in a wide variety of test systems from bacteria to mammalian cells in culture to rodents and humans (DeMarini, 2004; IARC, 2004a; Husgafvel-Pursiainen, 2004). In bacterial systems, the heterocyclic amines and aromatic amines in condensates account for much of the frameshift mutagenicity, whereas the PAHs and nitrosamines may account for some of the base-substitution mutagenicity (DeMarini *et al.*, 1995). G to T is the predominant class of base-substitution mutation induced by condensates in experimental systems and found in oncogenes and tumour-suppressor genes in smoking-associated lung tumours (IARC, 2004a). The genotoxic potencies of a variety of condensates in several genotoxicity assays likely have only qualitative value with regard to health risk assessment (DeMarini *et al.*, 2008). This is consistent with findings that smokers of low- or high-tar cigarettes have similar urinary levels of lung carcinogens (Hecht *et al.*, 2005b; Hatsukami *et al.*, 2006b) and similar risks for lung cancer (Harris *et al.*, 2004).

In rodents, cigarette smoke induces sister chromatid exchange and micronuclei in bone marrow and lung cells. Human newborns of smoking mothers have increased frequencies of *HPRT* mutations, chromosomal translocations, and DNA strand breaks. Sperm of smokers has increased frequencies of aneuploidy, DNA adducts, strand breaks, and oxidative damage. Cigarette smoke also causes germ-cell mutations in mice (Yauk *et al.*, 2007). Collectively, these data suggest that smoking is likely a germ-cell mutagen in humans. Smoking produces mutagenic urine and somatic-cell mutations in humans, including *HPRT* mutations, sister chromatid exchange, microsatellite instability and DNA damage in a variety of tissues. Genotoxic effects have been found in eight organ sites at which tobacco smoke causes cancer in humans (DeMarini, 2004; IARC, 2004a).

(b) Mutations in TP53, KRAS and related genes

Gene mutation data from a variety of databases, including the IARC Cancer *TP53* Mutation Database (http://www-p53.iarc.fr/), have been collated in the Genetic Alterations in Cancer (GAC) database (http://dir-apps.niehs.nih.gov/gac/) so that mutations in a variety of genes in various cancerous tissues can be compared. An assessment of the Gene Alterations in Cancer database showed that at least three genes were mutated more frequently in lung tumours from smokers than non-smokers (Lea *et al.*, 2007): *TP53* (39 versus 26%), *K-RAS* (20 versus 3%), and loss of heterozygosity at *FHIT* (57 versus 27%). Thus, genes in the cell cycle (*TP53*), cell signalling (*KRAS*) and apoptotic (*FHIT*) pathways are mutated more frequently in smoking- rather than in nonsmoking-associated lung tumours. Genomic sequencing of lung tumours has identified other mutated genes that are associated with smoking; ten times more genes are mutated in

lung tumours from smokers compared to non-smokers (Ding *et al.*, 2008).

GC to TA transversions were the predominant class of base-substitution mutation found in *TP53* and *KRAS* genes in lung tumours from smokers, with the frequency of this mutation in *TP53* being 30% in smokers versus 22% in non-smokers. In smoking-associated oral cancers, the percentage of GC to TA mutations in *TP53* was 15% versus 2%, respectively. This mutation spectrum is consistent with that produced by a variety of known carcinogens present in tobacco smoke (IARC, 2004a). At the codon level, the most frequently mutated codons in *TP53* in lung tumours of smokers were 157, 175, 245, 248, and 273, all of which occur in the DNA-binding domain of the protein; among these codons, only 273 was mutated in lung tumours from non-smokers. Only three of these codons (157, 245 and 273) were mutated in smoking-associated larynx tumours, and only codon 157 was mutated in smoking-associated oral tumours. Thus, the mutational specificity at *TP53* is different among smoking- and nonsmoking-associated tumours and among smoking-associated tumours at various organs (Lea *et al.*, 2007). Thus, different pathways are involved in the development of different types of tumours (Le Calvez *et al.*, 2005; Mounawar *et al.*, 2007; Subramanian & Govindan, 2008).

4.1.5 Effects on gene expression profile

As indicated in a review by Sen *et al.* (2007) involving microarray analysis of 18 studies in human smokers, 7 in smoke-exposed rodents, and 3 in condensate-exposed mammalian cells, smoking generally upregulated a wide variety of genes, especially those involved in the stress response, phase I metabolism, and immune response. Genes that were consistently expressed differentially in smokers (as assessed in alveolar macrophages, lung cells or peripheral lymphocytes) included metallothioneins, heat-shock proteins, superoxide dismutase, glutathione transferase, heme oxygenase, *CYP* genes (*1A2*, *1A1* and *1B1*), interleukins and chemokines.

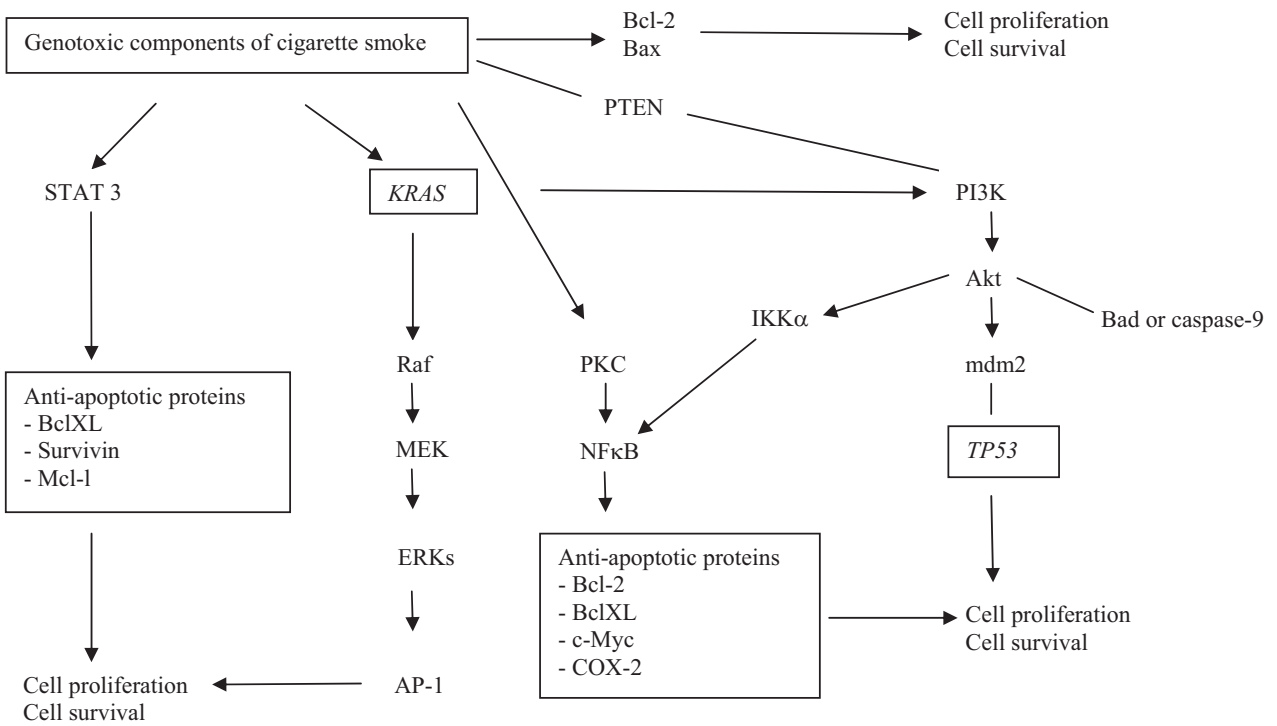
Spira *et al.* (2004) analysed global gene expression in bronchial epithelial cells and found that the expression levels of metabolizing and antioxidant genes had reverted to control levels after two years of smoking cessation. However, expression of potential oncogenes and tumour-suppressor genes never reverted to never-smoker levels even after years of smoking cessation. Consistently, expression of microRNAs is generally downregulated by cigarette smoke (Izzotti *et al.*, 2009). As discussed below, smoking also altered methylation patterns and gene expression in smoking-associated tumours.

4.1.6 Other effects associated with carcinogenesis

(a) Proliferation, differentiation, apoptosis, and inflammation

As noted above, the signal-transduction pathways in lung tumours from smokers are distinctly different from those of non-smokers (Mountzios *et al.*, 2008). Fig 4.5 shows details of signalling pathways that are deregulated by tobacco smoke. The involvement of high frequencies of mutated *K-RAS* and *TP53* genes in smoking-associated lung tumours results in altered regulation of cell proliferation, differentiation, cytoskeletal organization and protein trafficking. Cigarette smoking activates *NF-κB*, which induces pro-inflammatory cytokine expression and induces growth factors and proliferative signals (Mountzios *et al.*, 2008). This gene also influences the expression of the anti-apoptotic gene *BCL2* and pro-apoptotic gene *BAX*. Smoking produces chronic inflammation, which promotes cancer (Walser *et al.*, 2008). Smoking results in high levels of reactive oxygen species, which damage epithelial and endothelial cells and impair their function. In smoking-associated lung cancer, elevated levels of cyclooxygenase-2 (COX-2) and

Fig. 4.5 General scheme of some cell-signalling pathways that are deregulated by tobacco smoke in lung carcinogenesis



Akt, serine/threonine protein kinase; ERKs, extracellular regulated kinases; MEK, mitogen-activated protein kinase; Bad, Bcl2-associated agonist of cell death; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; NF-κB, nuclear factor κB; IKKα, inhibitor of nuclear factor κ-B kinase; PTEN, phosphatase and tensin homologue; STAT3, signal transducer and activator of transcription, COX-2, cyclooxygenase-2

prostaglandin (PGE_2) indicate apoptosis resistance, proliferation, immunosuppression, angiogenesis, invasion, and epithelial-mesenchymal transition (Walser *et al.*, 2008).

(b) Endogenous nitrosation

Intragastric formation of *N*-nitroso compounds, measured using urinary nitrosamino acids excreted in urine, was increased in smokers compared to non-smokers (Hoffmann & Brunnemann, 1983). Two recent studies demonstrated that NNN forms endogenously in some users of nicotine replacement therapy products (Stepanov *et al.*, 2009a, b).

(c) Hormonal changes

These are described in Section 4.3.2a.

4.2 Polymorphisms in carcinogen-metabolizing genes

4.2.1 Introduction

It has been long proposed that the known variation among individuals in their capacity to activate and detoxify carcinogens may be associated with increased susceptibility to cancer, and that polymorphisms of carcinogen-metabolising genes may play a significant role. The most intensively studied genes involved in the metabolism of carcinogens include the various *CYP* genes, the *GST* genes and the *NAT* genes. Other relevant xenobiotic-metabolising genes, such as *EPHX*, sulfotransferase (*SULT*), *UGT*, myeloperoxidase (*MPO*), and NAD(P)H quinone oxidoreductase-1 (*NQO1*) genes, have also been studied. Recently, extensive pooled studies and

reviews have been published on polymorphisms of carcinogen-metabolising genes and their role in cancer susceptibility, especially in tobacco-related lung cancer and cancers at other sites. Similarly, various biomarkers of exposure and genotoxicity that are presumed to provide a mechanistic basis for such associations have been comprehensively investigated in relation to these polymorphisms. A brief overview based largely on reviews and the meta- and pooled analyses is presented here.

4.2.2 Genetic polymorphisms of carcinogen metabolism: some central genes

(a) CYP genes

CYPs comprise the principal enzyme system catalysing various phase I oxidation reactions, including metabolic activation and detoxification of many carcinogenic substances in tobacco smoke such as PAHs. Of the various CYP enzymes expressed in humans, many of those belonging to CYP1 to CYP3 families play a role in carcinogen metabolism, producing highly reactive DNA-damaging metabolites as well as detoxified metabolites (Guengerich & Shimada, 1998; Lang & Pelkonen, 1999; Ingelman-Sundberg, 2004). CYPs have evolved into a wide superfamily with close to 60 different active genes currently identified; most of these genes exhibit polymorphism (www.cypalleles.ki.se).

(i) *CYP1A1*

Several allelic variants of the human *CYP1A1* gene are currently known (www.cypalleles.ki.se). The major variant forms of the *CYP1A1* gene (wildtype allele *CYP1A1*1*) mostly frequently studied for association to cancer susceptibility include the following two alleles: (i) *CYP1A1*2A* allele (m1 allele; *Msp* I) and (ii) *CYP1A1*2B* (Cascorbi *et al.*, 1996) or *CYP1A1*2C* (www.cypalleles.ki.se) allele (m2 allele; Ile^{462}Val). Importantly, the *CYP1A1* m1 allele and m2 allele are in complete linkage disequilibrium in Caucasians (Kawajiri, 1999; Bartsch *et al.*, 2000). In addition, *CYP1A1*4* allele (m4; Thr^{461}Asn) (Cascorbi *et al.*, 1996), and *CYP1A1*3* (m3) allele found in African-Americans but not in Caucasians or Asians (Crofts *et al.*, 1993) are included in some studies (Bartsch *et al.*, 2000).

In smoking-related lung cancer, the various *CYP1A1* polymorphisms as well as the differences in the frequencies of the rare variant alleles between ethnicities contribute to the differences in findings. There are collective analyses of data predominantly indicating an overall mild to moderate effect of *CYP1A1* polymorphisms on lung cancer risk (Kawajiri, 1999; Bartsch *et al.*, 2000; Houlston, 2000; Le Marchand *et al.*, 2003; Vineis *et al.*, 2003; Vineis *et al.*, 2004; Lee *et al.*, 2008a; Shi *et al.*, 2008). In many reviews and meta- or pooled analyses the increased risk associated with *CYP1A1* polymorphism has most clearly been seen in Asian populations (Kawajiri, 1999; Le Marchand *et al.*, 2003; Vineis *et al.*, 2003; Lee *et al.*, 2008a; Shi *et al.*, 2008).

Multiple studies have also analysed the gene-gene interactions between *CYP1A1*, *GSTM1* and *GSTT1* polymorphisms and lung cancer (d'Errico *et al.*, 1999; Houlston, 1999; Benhamou *et al.*, 2002; Bolt & Thier, 2006; Raimondi *et al.*, 2006; Ye *et al.*, 2006; Carlsten *et al.*, 2008). Some of the analyses have indicated that the elevated risk for lung cancer may be more pronounced for some *CYP1A1/GSTM1* null genotype combinations (Le Marchand *et al.*, 1998; Bartsch *et al.*, 2000; Vineis *et al.*, 2004, 2007; Lee *et al.*, 2008a; Shi *et al.*, 2008).

(ii) *CYP1A2*

CYP1A2 is highly inducible and metabolises, including deacetylation reactions, many tobacco smoke carcinogens such as aromatic and heterocyclic amines and nitro-aromatic compounds, and tobacco-specific nitrosamines such as NNK (Nebert *et al.*, 2004; Jalas *et al.*, 2005; IARC, 2007a). A few major variant alleles have been described (www.cypalleles.ki.se), some of which

may have been reported to influence inducibility (Nakajima *et al.*, 1999; Ingelman-Sundberg *et al.*, 2007). Overall, the phenotype-genotype relations have not been well established for *CYP1A2*, although current evidence points towards contribution of genetic variation (Murayama *et al.*, 2004; Ingelman-Sundberg *et al.*, 2007); data on possible associations with tobacco related cancer are sparse (Agundez, 2004; Nebert & Dalton, 2006).

(iii) CYP2A6

Several aspects of smoking behaviour are likely to be influenced by *CYP2A6* genetic variation, which influences nicotine metabolism (Malaiyandi *et al.*, 2005; Mwenifumbo & Tyndale, 2007). The most important functionally altered allele is *CYP2A6*4* (gene deletion), which confers a poor-metabolizer phenotype in homozygous individuals (Malaiyandi *et al.*, 2005; Ingelman-Sundberg *et al.*, 2007; Mwenifumbo & Tyndale, 2007). In some studies, polymorphic variants of *CYP2A6* gene have been implicated in susceptibility to smoking-related cancers (Gambier *et al.*, 2005; Malaiyandi *et al.*, 2005; Nakajima, 2007). In line with this, the accumulated data have suggested that *CYP2A6* polymorphism may affect cancer risk in smokers but not in non-smokers (Tan *et al.*, 2001; Kamataki *et al.*, 2005; Malaiyandi *et al.*, 2005; Canova *et al.*, 2009).

(iv) CYP2A13

From human CYPs, CYP2A13 is the primary form involved in the metabolic activation of the tobacco-specific nitrosamines NNK and NNN (Jalas *et al.*, 2005; IARC, 2007a). The *CYP2A13* gene exhibits polymorphism in humans (Zhang *et al.*, 2002; Jalas *et al.*, 2005), and experimental studies suggest that some of the polymorphisms may affect the hydroxylation of NNN and NNK (Jalas *et al.*, 2005; Schlicht *et al.*, 2007). However, the data on possible effects of these polymorphisms on the risk of tobacco-related cancers in humans are still limited (Wang *et al.*, 2003; Song *et al.*, 2009; Timofeeva *et al.*, 2009).

(v) CYP2D6

The *CYP2D6* gene shows high variability in expression. The enzyme is not inducible, and therefore genetic variation largely contributes to the interindividual variation in enzyme activity. Currently, more than 100 different functional CYP2D6 gene variants have been described, and these are divided into alleles causing abolished, decreased, normal, and ultrarapid enzyme activity (Ingelman-Sundberg, 2005; Ingelman-Sundberg *et al.*, 2007). The most important null alleles leading to poor-metabolizer phenotype are *CYP2D6*4* (splice defect) and *CYP2D6*5* (gene deletion) (Ingelman-Sundberg, 2005; Ingelman-Sundberg *et al.*, 2007).

A large series of studies have been carried out over the past 20 years on the association between *CYP2D6* polymorphism and susceptibility to lung cancer and to some other tobacco-related cancers (Wolf & Smith, 1999). Despite some indication of an association between CYP2D6 poor-metabolizer and decreased risk for lung cancer, no major role for CYP2D6 in carcinogen metabolism or a molecular basis for such an association have been discovered (Wolf & Smith, 1999; Ingelman-Sundberg, 2005).

(vi) Other CYP genes

CYP1B1 allelic variants that affect the catalytic activity have been described but they have been studied to a lesser extent for the association with susceptibility to smoking-related cancers (Thier *et al.*, 2003). Some positive findings have been reported on head and neck cancer (Ko *et al.*, 2001), and lung cancer (Zienolddiny *et al.*, 2008).

Several polymorphisms have been characterized in the *CYP2E1* gene and several positive associations with the risk of different cancers have been reported, in particular for cancers of the upper aerodigestive tract, lung and gastrointestinal tract (Section 2.19). *CYP2E1* may also

play an important role in the interaction of the carcinogenic effects of alcohol and tobacco (Section 4.4).

From the human *CYP3A* locus (*CYP3A4*, *CYP3A5* and *CYP3A7*), the *CYP3A4*1B* allele has been associated with lung cancer and prostate cancer in some studies but not in all (Dally *et al.*, 2003; Rodriguez-Antona & Ingelman-Sundberg, 2006). However, the role of these variants in relation to tobacco smoking is unknown.

(b) GSTM1 and other GST genes

Polymorphic *GST* genes have long been proposed to modify susceptibility to lung cancer (Seidegård *et al.*, 1986; Ketterer *et al.*, 1992). The polymorphic genes encoding the various classes of cytosolic GST enzymes include the *GSTM1* and *GSTM3* genes (mu class), the *GSTP1* gene (pi class), and the *GSTT1* gene (theta class). The gene deletion (null) allele of the *GSTM1* gene (*GSTM1*0*) and of the *GSTT1* gene (*GSTT1*0*) have been the most intensively studied polymorphisms in relation to increased susceptibility to cancer (Strange *et al.*, 2001; Bolt & Thier, 2006; McIlwain *et al.*, 2006). For the *GSTP1* gene, the form most abundantly present in lung tissue, genetic variation in exon 5 (*GSTP1*2*; $Ile^{105}Val$), in exon 6 ($Ala^{114}Val$), as well as a combination of these, are the variations most frequently studied for cancer susceptibility (Watson *et al.*, 1998; Cote *et al.*, 2009).

Numerous reviews, meta- and pooled analyses have been published over the past 15 years or so for the *GST* genes with systematic assessments covering altogether tens of thousands of cases and controls. For the *GSTM1* null genotype, such analyses have largely provided negative, suggestive or at most moderately positive results for an association with an increased risk for lung cancer (d'Errico *et al.*, 1999; Houlston, 1999; Benhamou *et al.*, 2002; Ye *et al.*, 2006; Carlsten *et al.*, 2008). The larger the studies, the less significant the estimates for the role of *GSTM1* emerge in systematic analysis (Ye *et al.*, 2006; Carlsten *et al.*, 2008). Also the varying allele frequencies related to ethnic background affect the findings for *GSTM1* as well as for many other genes (Garte *et al.*, 2001; Ye *et al.*, 2006; Carlsten *et al.*, 2008; Lee *et al.*, 2008a).

In a meta-analysis of the association between the *GSTT1* gene polymorphism and lung cancer no association between *GSTT1* null genotype and risk for lung cancer in Caucasians was observed, but a positive association was found for Asians (Raimondi *et al.*, 2006). A significant association for either Caucasians or Asians was also not found in a pooled analysis (Raimondi *et al.*, 2006). A meta-analysis found no significant association between lung cancer risk and the *GSTP1* $Ile^{105}Val$ polymorphism; but the pooled analysis suggested an overall statistically significant mild association between lung cancer and homozygosity or heterozygosity for the Val^{105} allele (Cote *et al.*, 2009).

A recent body of epidemiologic data suggests an inverse association between cruciferous vegetables/isothiocyanates intake and cancers of the colorectum, lung and breast; the studies also provide evidence that this protective effect is greater among individuals who possess the *GSTM1* or *T1* null genotype, who would be expected to accumulate higher levels of isothiocyanates at the target tissue level, a pre-requisite for their enzyme-inducing effects (Seow *et al.*, 2005). The association between isothiocyanates and cancer, and its modification by *GSTM1* and *GSTT1* status, is most consistent for lung cancer and appears to be strongest among current smokers who possess the combined *GSTM1* and *GSTT1* null genotypes (London *et al.*, 2000a; Spitz *et al.*, 2000; Zhao *et al.*, 2001; Brennan *et al.*, 2005; Seow *et al.*, 2005).

(c) NAT1 and NAT2 genes

The pooled and meta-analyses carried out on *NAT1* and *NAT2* polymorphisms and bladder cancer risk have consistently reported significantly increased risk for *NAT2* slow acetylators

(Dong *et al.*, 2008; Malats, 2008; see also Section 2.9). Data on *NAT1* fast acetylators are inconsistent, as are the studies suggesting an increased risk for *NAT2* rapid acetylator status. Additionally, genotypes for other genes, specially *GSTM1*, have also been implicated (Vineis *et al.* 2001; García-Closas *et al.*, 2005; Hein, 2006; Sanderson *et al.*, 2007; Dong *et al.*, 2008; Malats, 2008).

In a recent large study on tobacco-related lung cancer and upper aerodigestive cancers, the *NAT* genes, in particular *NAT*10* haplotype, emerged from a set of 16 genes as involved in the risk (McKay *et al.*, 2008). When more than one hundred single nucleotide polymorphisms for 31 genes involved in phase I or phase II metabolism or in antioxidant defence were investigated, only four of the previously reported polymorphisms of the *GSTP1*, *EPHX1* and superoxide dismutase *SOD2* genes and the *NAT1* fast acetylator phenotype remained significantly associated with risk of non-small cell lung cancer after correction for multiple testing (Zienolddiny *et al.*, 2008).

In breast cancer, several recent meta-analyses of epidemiological studies have suggested increased risk among smokers with the *NAT2* slow acetylator genotype; such an association has been observed especially among long-term smokers and post-menopausal women (Terry & Goodman, 2006; Ambrosone *et al.*, 2008; Ochs-Balcom *et al.*, 2007; Baumgartner *et al.*, 2009).

In all, the role of the *NAT* gene polymorphisms in tobacco-related cancers, with the exceptions of increased risk of bladder cancer and possibly breast cancer in *NAT2* slow acetylators, remains largely open due to the incomplete understanding of phenotype-genotype relationships, and the interplay between these two genes and their polymorphisms (Hein, 2002, 2006).

(d) Others

Genes coding for EPHX, UGT and SULT enzymes, mainly but not exclusively involved in detoxification reactions, exhibit polymophisms with numerous gene variants discovered (Mackenzie *et al.*, 1997; London *et al.*, 2000b; Glatt *et al.*, 2001; Burchell, 2003). Additional polymorphic genes studied for their significance in cancer susceptibility are the *NQO1* and *MPO* genes, with NQO1 playing a dual role in the detoxification and activation of procarcinogens, and MPO converting lipophilic carcinogens into hydrophilic forms (Nebert *et al.*, 2002). All these genes have been studied for their possible association with tobacco-related cancer risk to a varying extent and with variable outcomes (London *et al.*, 2000b; Bamber *et al.*, 2001; Garte, 2001; To-Figueras *et al.*, 2001; Tiemersma *et al.*, 2002b; Guillemette, 2003; Wells *et al.*, 2004; Kiyohara *et al.*, 2005; Moreno *et al.*, 2005; Nagar & Remmel, 2006; Gallagher *et al.*, 2007).

4.2.3 Biomarkers of tobacco carcinogenesis and polymorphic genes of carcinogen metabolism

A myriad of studies have investigated association between various biomarkers of tobacco-related carcinogenesis and genetic variation of genes involved in carcinogen metabolism. For involvement in increased cancer susceptibility, a large variety of intermediate biomarker have been studied, including PAH metabolites in urine, urinary mutagenicity, DNA and protein adducts, cytogenetic alterations, *HPRT* mutant lymphocytes, as well as somatic mutations of the tumour suppressor gene *TP53* and *KRAS* oncogene occurring in cancer tissue.

(a) PAH metabolites and mutagenicity in urine

(i) PAH metabolites in urine

Increased excretion of 1-hydroxypyrene in urine in association with the *GSTM1* null genotype has been reported in many studies on individuals with occupational or environmental exposure to PAHs (Yang *et al.*, 1999; Alexandrie *et al.*, 2000; Lee *et al.*, 2001; Kuljukka-Rabb *et al.*, 2002; Kato *et al.*, 2004). The associations seen between *GSTT1* polymorphism and the

PAH metabolites are somewhat more variable. Similarly, the joint effect of *GSTM1* and *GSTT1* null genotypes, as well as the effects of some other genes of xenobiotic metabolism, such as *EPHX*, *CYP1A1*, *CYP1A2* and the aryl hydrocarbon receptor (*AhR*) gene have been either positive or negative (Yang *et al.*, 1999; Alexandrie *et al.*, 2000; Lee *et al.*, 2001; Zhang *et al.*, 2001; Kuljukka-Rabb *et al.*, 2002; Yang *et al.*, 2003; Chen *et al.*, 2007; Cocco *et al.*, 2007; Bin *et al.*, 2008).

Another PAH metabolite studied in this context is phenanthrene, the simplest PAHs with a bay region, a feature closely associated with carcinogenicity. A study quantified ratios of urinary products of metabolic activation (such as PheT) and detoxification (such as phenanthrols, HOPhe) of phenanthrene in 346 smokers, who were also genotyped for 11 polymorphisms in genes involved in PAHs metabolism, including the *CYP1A1* and *GSTM1* genes. A significant association between the presence of the *CYP1A1* $Ile^{462}Val$ polymorphism and high PheT/3-HOPhe ratios was found, particularly in combination with the *GSTM1* null polymorphism (Hecht *et al.*, 2006).

Overall, the data on the influence of genetic variation in PAHs metabolism on the levels of the urinary metabolite biomarkers are variable, and currently inconclusive.

(ii) Urinary mutagenicity

One relatively early line of research investigated the relationship between urinary mutagenicity and genetic variation in activation or detoxification genes. These studies, however, have seldom been focused on smokers only but rather on other sources of exposure (Pavanello & Clonfero, 2000).

In some studies, *NAT2* slow acetylator genotype either alone or in combination with *GSTM1* null genotype has been associated with increased urinary mutagenicity in the *Salmonella* test in individuals with occupational, environmental or medicinal PAH-related exposure, or in smokers (Vineis & Malats, 1999; Pavanello & Clonfero, 2000). In another study, CYP1A2 activity, but not *NAT2*, *GSTM1* or *GSTT1* genotypes influenced urinary mutagen excretion in smokers (Pavanello *et al.*, 2002). A further study also suggested contribution of the *CYP1A2* gene variation to increased urinary mutagenicity in heavy smokers (Pavanello *et al.*, 2005). Associations with variants of other xenobiotic-metabolising genes (such as *EPHX1*) have also been reported, with somewhat complex results (Kuljukka-Rabb *et al.*, 2002).

(b) DNA adducts

The relationship between the variants of polymorphic genes of carcinogen metabolism and tobacco smoke-related DNA adduct formation has been addressed in an abundant number of studies among smokers, occupationally exposed groups, and patients with smoking-related cancer. In addition, multiple *in vitro* studies on this relationship have been carried out (Bartsch *et al.*, 2000; Pavanello & Clonfero, 2000; Alexandrov *et al.*, 2002; Wiencke, 2002).

The intensive efforts to study the relationship between *CYP1A1* and *GSTM1* gene polymorphism and the level of aromatic-hydrophobic/bulky PAH-DNA adducts in human lungs have so far provided little evidence for a role of a single metabolic genotype or their combinations on DNA adduct formation, with largely weak, non-significant or contradictory results. However, a trend of increasing adduct levels in subjects with the *CYP1A1*2-GSTM1*0* genotype combination has been observed, which was reinforced when BPDE-DNA adducts were specifically assessed. These results suggest a gene-gene interaction, supported by biological data from other studies (Bartsch *et al.*, 2000; Alexandrov *et al.*, 2002; Wiencke, 2002). Such gene-gene interaction lends support to the increased risk for lung cancer found in carriers of these genotypes in Japanese, among whom the frequency of the

variant *CYP1A1* allele is much higher (Bartsch *et al.*, 2000; Alexandrov *et al.*, 2002).

A wide selection of genes and genotypes included in the various studies have made it difficult to assess the overall role of the polymorphisms of *GSTM1* and other genes alone or in combination. Differences between the studies in the types of adducts determined, the various tissues, cell types and cancers studied, detection methods, variation in sources and types of exposure, sample size, gender differences, and sometimes poor knowledge regarding the alleles, genotypes and haplotypes under study also contribute to the large variability seen in these studies (d'Errico *et al.*, 1999; Hemminki *et al.*, 2001; Alexandrov *et al.*, 2002; Wiencke, 2002).

(c) Cytogenetic biomarkers of genotoxicity

(i) Chromosome aberrations and sister chromatid exchanges

Early studies investigating whether homozygosity for the *GSTM1* null allele affects prevalence of cytogenetic changes in lymphocytes of smokers reported positive results (Seidegård *et al.*, 1990; van Poppel *et al.*, 1992; Cheng *et al.*, 1995). Since then, studies have investigated the association between genetic polymorphisms of xenobiotic-metabolising genes and cytogenetic biomarkers in smokers and in some occupational groups (Rebbeck, 1997; Autrup, 2000; Pavanello & Clonfero, 2000; Norppa, 2003, 2004).

Collectively, the reported findings are in support of increased susceptibility of smokers to chromosomal effects in association with *GSTM1* and *GSTT1* null variants deficient in detoxification of tobacco smoke carcinogens. Exposure to genotoxicants generated from other environmental sources (e.g. polluted air, diet, endogenous sources such as reactive oxygen species) may contribute to the observed associations, and it is likely that other polymorphic metabolic genes such as *NAT2* may be involved (Pavanello & Clonfero, 2000; Norppa, 2001, 2003).

(ii) Micronucleus induction

The relationship between formation of micronuclei and genetic polymorphisms of carcinogen metabolism has been addressed in a wide range of human population studies (Norppa, 2003, 2004). Induction of micronuclei in smokers may be little, if at all, affected by *GSTM1*, *GSTT1* or *NAT2* genotypes. In contrast, the *NAT1* rapid genotype appears to show an association with increased susceptibility to smoking-related micronuclei (Norppa, 2004).

A recent review evaluated more than seventy human studies on genetic polymorphisms and micronucleus frequency detected either in peripheral blood lymphocytes or exfoliated cells in populations exposed to various genotoxic agents. There were no significant genotype effects involved in micronucleus induction in smokers (Iarmarcovai *et al.*, 2008). The relationship between genetic polymorphisms and micronucleus formation is complex, and is influenced to a variable extent by several genes of xenobiotic metabolism and DNA repair, as well as the variety of chromosomal alterations known to contribute to micronucleus formation (Iarmarcovai *et al.*, 2008).

(iii) Chromosomal damage induced in vitro

The effects of genotypes or genotype combinations *in vitro* on the induction of various cytogenetic endpoints by tobacco-smoke carcinogens and their metabolites have been studied, initially focused on the *GSTM1* and *GSTT1* null genotypes (Norppa, 2001, 2004). In a study investigating NNK *in vitro*, lymphocytes from *GSTM1* null donors were more sensitive to induction of chromosomal aberrations and sister chromatid exchanges by NNK than lymphocytes from *GSTM1* positive donors (Salama *et al.*, 1999).

(d) Gene mutations

(i) HPRT mutant lymphocytes

Associations between the frequencies of *HPRT* mutant T-lymphocytes in populations exposed to genotoxic agents, such as smokers, and the polymorphism of xenobiotic-metabolising genes have been studied. In the early studies, positive, weak, or negative associations were reported for *GSTM1* null genotype, and negative findings were published for *NAT2* slow acetylator genotype in occupationally exposed or non-exposed subjects (Rebbeck, 1997; Vineis & Malats, 1999). When healthy, non-smoking and occupationally non-exposed young adults were studied for HPRT mutant frequency and polymorphisms in *CYP1A1*, *GSTM1* and *NAT2* genes, none of these polymorphisms, analysed individually, were found to influence the *HPRT* mutant frequency (Davies *et al.*, 1999). A significant interaction between the *GSTM1* null genotype and *NAT2* slow acetylator was associated with higher mutant frequency, but no other genotype combinations (Davies *et al.*, 1999). Some later studies have reported variable associations between *HPRT* mutant frequency and polymorphisms for either individual genes (*GSTM1*, *GSTT1* or *EPHX1*) or some of the genotypes in combination among exposed (Viezzer *et al.*, 1999; Abdel-Rahman *et al.*, 2001, 2003).

(ii) Mutations of the TP53 gene and other cancer-related genes

Whether the frequency of somatic mutations detected in tumour tissue in cancer-related genes, primarily the *TP53* tumour suppressor gene and *KRAS* oncogene, may be modified by polymorphisms in carcinogen metabolizing genes was first investigated assessing the effects of the *GSTM1* genotype, alone or in combination with other genetic polymorphisms. Several, but not all, such studies showed significant association between *GSTM1* null genotype and either the frequency or type of *TP53* mutations in smoking-induced lung cancer or other cancer type (Rebbeck, 1997; Vineis & Malats, 1999; Autrup, 2000). Fewer studies examined the association between *TP53* mutations and *GSTT1* polymorphism, and some results suggested the involvement of both null genotypes (Vineis & Malats, 1999; Autrup, 2000).

In smokers with non-small cell lung cancer, the risk of mutation was found to be the highest among the homozygous carriers of the *CYP1A1* rare allele *CYP1A1 MspI* (*Ile*^{462}*Val*) who also exhibited the *GSTM1* null genotype (Kawajiri *et al.*, 1996). Similarly, positive associations between *K-RAS* mutations and homozygosity for the *CYP1A1* rare allele were observed; the risk of mutation was enhanced when the *CYP1A1* susceptible genotype was combined with *GSTM1* null genotype (Kawajiri *et al.*, 1996). In another study, also carried out in a Japanese study population, *K-RAS* mutations occurred with greater frequency in lung adenocarcinoma smoking patients and of the *GSTM1* null genotype as compared with the *GSTM1* positive genotype (Noda *et al.*, 2004).

Many of the studies that assessed *NAT2* acetylator genotypes have found non-significant associations with the frequency or type of *TP53* mutation in bladder, lung, or other cancers (Vineis & Malats, 1999; Autrup, 2000). A study on bladder cancer did not find an overall association between *TP53* mutation frequency and *GSTM1*, *GSTT1*, *GSTP1* or *NAT2* genotypes. However, among patients with *TP53* mutations, transversion mutations were more frequent in those with *GSTM1* null genotype as compared to those with GSTM1 positive genotype; no significant associations were found for the *NAT2* gene (Ryk *et al.*, 2005).

In rectal cancer, overall negative results for an association between *TP53* or *KRAS* mutations and *GSTM1* and *NAT2* polymorphisms among smokers and non-smokers exposed to tobacco smoke were found (Curtin *et al.*, 2009). An interaction of second-hand tobacco smoke and *NAT2*

was found in *TP53* mutation positive tumours but not in smokers (Curtin *et al.*, 2009). Earlier, an increased risk of *TP53* transversion mutations among *GSTM1* positive individuals who smoked cigarettes was found in colon cancer (Slattery *et al.*, 2002).

A statistically significant association was observed between the *GSTT1* null genotype and *TP53* mutation status of breast tumour in one study (Gudmundsdottir *et al.*, 2001), while in another larger study none of the genotypes for *CYP1B1*, *GSTM1*, *GSTT1* and *GSTP1* genes alone were associated with somatic *TP53* mutations (Van Emburgh *et al.*, 2008).

In summary, data from various cancer types on the association between genetic polymorphisms of carcinogen-metabolizing genes and somatic mutations of the *TP53* and *K-RAS* genes vary widely and do not permit to conclude (Rebbeck, 1997; Vineis & Malats, 1999; Autrup, 2000).

4.3 Site-specific mechanisms of carcinogenicity of tobacco smoke

4.3.1 Sites with sufficient evidence of carcinogenicity of tobacco smoking

(a) Lung

The conceptual model presented in Section 4.1 (Fig. 4.1) depicts the main mechanistic steps by which cigarette smoke causes cancer. Smokers inhale into their lungs carcinogens which, either directly or after metabolism, covalently bind to DNA, forming DNA adducts (see Section 4.1, Fig. 4.3). Tobacco smoke contains multiple strong lung carcinogens such as NNN, NNK, PAHs, 1,3-butadiene and cadmium. Levels of tobacco smoke-related DNA adducts, mainly ^{32}P-postlabelled aromatic-hydrophobic/PAH-related bulky DNA adducts, in the lung are higher in smokers than in non-smokers (Phillips, 2002; IARC, 2004a; Hecht, 2008). Higher levels of DNA adducts have further been linked to increased risk for cancer in pooled and meta-analyses (IARC, 2004a; Veglia *et al.*, 2008).

Mutations in *TP53* and *K-RAS* genes, two central genes of human carcinogenesis, are more frequently mutated in smokers' lung cancer as compared to lung cancer from non-smokers (DeMarini, 2004; IARC, 2004a; Lea *et al.*, 2007; Ding *et al.*, 2008; see Section 4.1.3). In particular, *TP53* but also to some extent *K-RAS* mutations found in smoking-associated lung tumours exhibit mutational specificity that is consistent with the pattern produced by PAH diol epoxides in experimental studies and different from that observed in non-smokers' lung cancer (Pfeifer *et al.*, 2002; DeMarini, 2004; IARC, 2004a; Le Calvez *et al.*, 2005; Section 4.1.3). Keeping with such exposure-specific mutation profile, lung cancer in non-smokers exposed to second-hand tobacco smoke shows mutational similarity to smokers' lung cancer, although less data are available (Husgafvel-Pursiainen, 2004; IARC, 2004a; Le Calvez *et al.*, 2005; Subramanian & Govindan, 2008). The different pathways of lung carcinogenesis for smokers and non-smokers are likely to involve somatic mutations and other genetic alterations in a larger set of genes that are critical in controlling normal cellular growth via signal transduction (Bode & Dong, 2005; Lea *et al.*, 2007; Ding *et al.*, 2008).

Smoking-related lung carcinogenesis also involves a multitude of other alterations influencing the complex pathogenic pathways involved in lung cancer development, such as increased inflammation, aberrant apoptosis, increased angiogenesis, tumour progression and tumour metastasis (Wolff *et al.*, 1998; Heeschen *et al.*, 2001; Schuller, 2002; West *et al.*, 2003; Smith *et al.*, 2006; Lee *et al.*, 2008b; Section 4.1.5). Continued exposure to toxicants, genotoxicants, carcinogens, co-carcinogens and tumour promoters present in tobacco smoke has major effects on biological processes at all steps of multistep tumourigenesis of human lung (Hecht,

2003, 2008; Section 4.1). For example, nicotine in tobacco smoke is currently not described as a full carcinogen, but it exerts its biological effects via binding to nicotinic and other cellular receptors and likely enhances cell transformation and carcinogenicity through mechanisms not yet defined (Heeschen *et al.*, 2001; West *et al.*, 2003).

Numerous studies have provided evidence that the human genome may contain one or several loci that confer susceptibility to lung cancer. There are low-penetrance genes involved in the metabolism of tobacco smoke carcinogens, DNA repair and cell cycle control that may influence individual susceptibility to lung cancer (Spitz *et al.*, 2006). The role of the polymorphisms of these various classes of genes in lung carcinogenesis requires a systematic evaluation of the genetic evidence with stringent criteria (Ioannidis, 2008; Risch & Plass, 2008; Vineis *et al.*, 2009; Sections 4.1 and 4.2). Recently, genome-wide association studies have identified a susceptibility locus at chromosome 15q25.1 (Amos *et al.*, 2008; Hung *et al.*, 2008; Thorgeirsson *et al.*, 2008). The identity or function of the gene is not yet known, nor is the mechanism through which it may predispose to lung cancer. It is however likely that lung cancer susceptibility is related to the nicotine receptor gene residing at 15q25.1, and there is some evidence suggesting that it may be related to increased uptake of nicotine and NNK per cigarette (Le Marchand *et al.*, 2008).

In addition to genetic alterations, a growing body of evidence shows that epigenetic mechanisms, such as aberrant DNA methylation, histone modifications and RNA-mediated gene silencing are involved in cancer development (Jones & Baylin, 2007; Cortez & Jones, 2008). In lung carcinogenesis, gene promoter-associated (CpG island-specific) hypermethylation is an early and frequent event causing transcriptional inactivation of genes involved in regulation of cellular growth and differentiation (Belinsky, 2004). For example, several studies have indicated that the tumour suppressor gene *p16* ($p16^{INK4a/CDKN2A}$), a cell cycle regulator, is among the genes most frequently inactivated by aberrant methylation in lung cancer from smokers (Belinsky, 2004), with differences seen between smokers and never-smokers (Toyooka *et al.*, 2006). Significant associations have been established between smoking and promoter hypermethylation of tumour suppressor genes in lung tumours from smokers, and in plasma, serum or sputum DNA from cancer-free smokers (Belinsky, 2004; Belinsky *et al.*, 2005, 2006; Toyooka *et al.*, 2006).

(b) Oral cavity

PAHs can be carcinogenic at the site of application, which could include the human oral cavity. DMBA, a highly carcinogenic PAH not present in tobacco or tobacco smoke, is a standard model compound for induction of oral tumours in the hamster cheek pouch; less is known about the effects on the oral cavity of PAHs that do occur in tobacco products (Shklar, 1972; Rao, 1984; Vairaktaris *et al.*, 2008). A mixture of NNN and NNK induced oral tumours in rats when applied locally (Hecht *et al.*, 1986), and DNA adduct formation from NNN, NNK and NNAL has been observed in the rat oral cavity (Zhang *et al.*, 2009a, b). HPB-releasing DNA adducts from NNK and/or NNN have been reported in exfoliated oral cells from smokers and smokeless tobacco users (Heling *et al.*, 2008) and HPB-releasing heamoglobin adducts are elevated in smokeless tobacco users (IARC, 2007a). Unidentified DNA adduct levels are consistently elevated in oral cells and tissues from smokers compared to non-smokers (IARC, 2004a). Mutations in the *TP53* gene have been observed in oral tumours from smokers and smokeless tobacco users (IARC, 2006b, 2007a; Warnakulasuriya & Ralhan, 2007). Tobacco-associated genetic mutations including micronuclei, gene mutations, DNA polymorphisms, and chromosomal abnormalities have been reported in studies of buccal cells from smokers and smokeless tobacco users (Proia *et al.*, 2006). The use of lime by betel quid chewers is associated

with enhanced oxidative damage that could play a role in inflammation or tumour promotion (IARC, 2004b).

(c) Larynx and nasopharynx

Hamsters exposed to cigarette smoke by inhalation consistently developed benign and malignant tumours of the larynx; tumours were produced by inhalation of the particulate phase, but not the gas phase of cigarette smoke (IARC, 1986). In related studies in which hamsters were treated with DMBA by intratracheal instillation followed by exposure to cigarette smoke, a significantly higher incidence of laryngeal tumours was observed than in hamsters exposed only to cigarette smoke or to DMBA (IARC, 1986). Collectively, these results indicate an initiation-promotion mechanism for the production of laryngeal tumours, and are consistent with the results of experiments in which tobacco smoke condensate is applied to mouse skin (IARC, 1986). The combined data implicate PAHs and tumour promoters in tobacco smoke as potential etiologic agents for cancer of the larynx in hamsters. Levels of DNA adducts measured by non-specific methods were higher in larynx tissue from smokers than from non-smokers (IARC, 2004a). Analyses of mutations in the *TP53* gene from tumours of the larynx in smokers show a pattern similar to that observed in lung tumours, and both are consistent with the pattern produced by PAH diol epoxides (IARC, 2006b). The available data are consistent with the conceptual framework illustrated in Fig. 4.1 (Szyfter *et al.*, 1999).

Formaldehyde, a constituent of cigarette smoke, causes nasopharyngeal cancer in humans (IARC, 2006a). A recent study demonstrates a 10-fold higher level of the formaldehyde-DNA adduct N^6-hydroxymethyldeoxyadenosine in leukocytes of smokers compared to non-smokers, suggesting its possible involvement in nasopharyngeal cancer in smokers (Wang *et al.*, 2009). Acetaldehyde, another carcinogenic constituent of tobacco smoke, which also forms genotoxic adducts (Section 4.1), may also contribute to the development of these forms of head and neck cancer.

(d) Oesophagus

Nitrosamines are probably the most effective oesophageal carcinogens known, with particularly strong activity in the rat (Lijinsky, 1992). NNN and NDEA are both present in cigarette smoke, and levels of NNN greatly exceed those of NDEA (IARC, 2004a). NNN is also present in considerable quantities in smokeless tobacco and betel quid containing tobacco (IARC, 2004a, 2007a). Thus, NNN is a likely candidate as a causative agent for esophageal cancer in smokers, smokeless tobacco users, and chewers of betel-quid with tobacco. While considerable mechanistic data are available from studies of NNN in laboratory animals (Hecht, 1998; Wong *et al.*, 2005; Lao *et al.*, 2007; Zhang *et al.*, 2009a), there are little comparable data in humans.

Increased acetaldehyde production derived both from tobacco smoke and from microbial alcohol oxidation may play a role in the synergistic carcinogenic action of alcohol and smoking on oesophagus, as well as on other upper aerodigestive locations (Homann *et al.*, 2000; Salaspuro & Salaspuro, 2004; Lee *et al.*, 2007a).

(e) Stomach

Hypermethylation of the E-cadherin 1 gene (*CDH1*) was observed preferentially in gastric tumours from smokers rather than non-smokers (Poplawski *et al.*, 2008). *CDH1* can act as a tumour-suppressor gene, preventing cells from growing and dividing in an uncontrolled way to form a cancerous tumour. Because the protein encoded by this gene helps cells stick together, altered regulation may lead to metastasis.

Boccia *et al.* (2007) found an increased risk for stomach cancer among smokers who had the *SULT1A1 His* genotype, and Lee *et al.* (2006) found an increased risk for those who had the *m2* allelic variant of *CYP1A1*. A nested case–control

study found that smokers had an increased risk of gastric cancer if they carried at least one variant allele A in Ex7+129 C > A (*Thr*^{461}*Asn*, *m4*) of *CYP1A1* (Agudo *et al.*, 2006). Stomach cancer tissue from smokers had higher levels of stable DNA adducts than did those from non-smokers; however, the number of non-smokers was quite small (Dyke *et al.*, 1992).

(f) Pancreas

NNK and its metabolite NNAL are the only pancreatic carcinogens known to be present in tobacco and tobacco smoke. NNK was detected in the pancreatic juice of 15 of 18 samples from smokers, at levels significantly higher than in non-smokers; NNAL and NNN were also detected in some samples (Prokopczyk *et al.*, 2002). DNA adducts of NNK and NNAL were present in pancreatic tissue of rats treated with these nitrosamines (Zhang *et al.*, 2009b), but were not detected in most human pancreatic tissue samples (Prokopczyk *et al.*, 2005).

(g) Colorectum

Tobacco smoke contains heterocyclic amines, such as 2-amino-1-methyl-6-phenylimidazo[4,5,6]pyridine (PhIP), which are intestinal carcinogens in rats and mutate the adenomatous polyposis coli (*Apc*) gene in mice (Møllersen *et al.*, 2004). The *APC* gene is frequently mutated and has altered expression in human colon cancer (Samowitz *et al.*, 2007; Samowitz, 2008). A recent model of colon cancer by Sweeney *et al.* (2009) suggests that this disease can develop via at least three independent mechanistic pathways. One pathway is initiated by methylation of *MINT* (methylation in tumour) markers that proceeds down a pathway predisposing to microsatellite instability, followed by methylation of the mismatch repair gene mutL homologue 1 (*MHL1*) and the tumour-suppressor gene *TP16,* followed by mutation in *BRAF* (a homologue of a viral raf oncogen). A second independent pathway is initiated with a mutation in the *APC* gene, followed by a mutation in the *TP53* gene. A third independent pathway involves only *KRAS2* mutations. One study found BPDE-DNA adducts at a higher frequency in colon DNA from smokers than from non-smokers (Alexandrov *et al.*, 1996). Mutations or epigenetic changes in some or all of these genes have been found in smoking-associated colon or colorectal tumours.

Microsatellite instability, which is the expansion or contraction of short nucleotide repeats, occurs in approximately 10–15% of sporadic colorectal cancer, and is usually associated with smoking and hypermethylation of the promoter of the mismatch repair gene *MLH1* (Samowitz, 2008). Smoking-associated colorectal tumours also have high frequencies of methylation at CpG islands (Samowitz, 2008).

In a case–control study of colorectal cancer, Kasahara *et al.* (2008) found that the genetic polymorphism *APEX1/APE1* (apurinic/apyrimidinic endonuclease-1) Asp^{148}Glu, which is a gene involved in DNA repair, was associated with risk for colorectal cancer among smokers but not non-smokers. Other studies have also found associations between polymorphisms in the DNA repair genes *XRCC1* and smoking and risk for colorectal cancer (Stern *et al.*, 2007; Campbell *et al.*, 2009).

(h) Liver

Tobacco smoke contains liver carcinogens such as furan and certain nitrosamines. Liver tumours exhibit increased expression of *C-MYC, P16*^{INK4A}, epidermal growth factor receptor (*EGFR*), telomerase, transforming growth factor-*α* (*TGF-α*), insulin-like growth factor-2 (*IGF-2*) and *RAF* oncogene (Abou-Alfa, 2006). Smokers show altered expression of some of these genes or of genes in the same or similar pathways (Sen *et al.*, 2007). A genome-wide association study found that SNP rs1447295 in the 8q24 chromosome was positively associated with liver cancer among ever-smokers (Park *et al.*, 2008). Thus, tobacco smoke appears to have epigenetic

effects on the liver that may contribute to hepatocellular carcinoma.

(i) Urinary bladder

Tobacco smoke contains aromatic amines such as 4-aminobiphenyl and 2-naphthylamine, which are human bladder carcinogens (see IARC, 2012a). In bladder tumours, smoking was associated with a more than twofold increase risk of methylation of the promoter region of the *P16*^{INK4A} gene and of the soluble Frizzled receptor protein (*SFRP*) gene (Marsit *et al.*, 2006). In addition, Tang *et al.* (2009) suggested that epigenetic silencing of *Wnt* antagonists through hypermethylation may play a role in smoking-related invasive bladder cancer (Tang *et al.*, 2009). SNP rs6983267 of the 8q24 chromosome was inversely associated with bladder cancer among ever-smokers (Park *et al.*, 2008). Smokers generally have mutagenic urine and smoking is associated with specific cytogenetic changes and DNA breaks in bladder tumours (DeMarini, 2004). Smoking-associated stable DNA adducts have been found in bladder tissue or exfoliated urothelial cells, supporting a role for DNA damage in smoking-associated bladder cancer (Phillips, 2002).

(j) Cervix

The cervical mucus of smokers is more mutagenic than that of non-smokers, and cervical epithelia of smokers have higher frequencies of micronuclei than those of non-smokers (DeMarini, 2004). Several studies have found increased levels of DNA adducts in cervical tissue from smokers relative to non-smokers, suggesting a role for smoking-associated DNA damage in cervical cancer (Phillips, 2002).

(k) Ovary

It has been observed that the inverse associations reported for serous and endometrioid tumours with respect to parity and oral contraceptives did not hold for the mucinous tumours. Based on these observations, Risch *et al.* (1996) suggested that mucinous ovarian tumours may be etiologically unrelated to the other types of epithelial tumours. Whereas mucinous elements such as gastric or intestinal type glands may be seen in mature teratomas, a form of germ cell neoplasia, overall mucinous tumours are classified as surface epithelial tumours because transitions among the subtypes may be observed. The major difference between mucinous and serous tumours is their biologic behaviour. Mucinous carcinomas of the ovary are slow growing tumours that appear to develop from their benign counterparts. The fact that the transitions between the benign, borderline, and malignant form of the disease can be seen in the same tumour suggests that over time, there is a progression from benign to malignant (Riopel *et al.*, 1999). *K-ras* mutational analysis, for example, demonstrates a heterogeneous distribution of the mutation within different parts of the same neoplasm, suggesting that acquisition of the *K-ras* mutation occurs in malignant transformation (Mandai *et al.*, 1998). Serous carcinomas seem to develop de novo rather than from a benign pre-existing lesion; alternatively, the rate of progression is rapid and the precursor lesion is obliterated before the detection of the tumour. In some data, current smoking is associated with a shorter interval to detection of mucinous than non-mucinous tumours. Because the mucinous tumour is slow growing, smoking could contribute to the malignant progression of the adenoma-carcinoma sequence, as the benign form of the tumour may have been present for some time.

(l) Leukaemia

Tobacco smoke contains known leukaemogens such as benzene, 1,3-butadiene and formaldehyde (IARC, 2012a). The mechanisms of leukaemogenesis are currently not well understood. Data indicate that leukaemogenic agents, such as benzene, cause toxicity to the

haemotopoietic system, as well as genotoxicity at low levels, and that genetic polymorphisms may be involved in these processes (Aksoy, 1989; Lan *et al.*, 2004; Garte *et al.*, 2008; Hosgood *et al.*, 2009; Lau *et al.*, 2009; Rappaport *et al.*, 2009). Recent studies suggest the importance in carcinogen-related leukaemogenesis of damage to haematopoietic stem/progenitor cells circulating in the peripheral blood, or, alternatively, damage to primitive pluripotent progenitor cells present in other tissues (Zhang *et al.*, 2009c). In these two models, damaged stem/progenitor cells would then travel to the bone marrow and become initiated leukaemic stem cells. Mechanisms considered central in these models are: disruption of bone marrow DNA, through e.g. formation of DNA adducts, DNA–protein crosslinks, the action of free radicals or active states of oxygen; intercalation of metals within the DNA structure; or inhibition of enzymes involved in cell division (Zhang *et al.*, 2007, 2009c).

4.3.2 Sites with limited evidence of carcinogenicity or evidence suggesting lack of carcinogenicity

(a) Breast

(i) Carcinogenic pathway

Carcinogens found in tobacco smoke pass through the alveolar membrane and into the blood stream, by means of which they can be transported to the breast via plasma lipoproteins (Yamasaki & Ames, 1977; Shu & Bymun, 1983; Plant *et al.*, 1985). Tobacco smoke contains known rodent mammary carcinogens, including PAHs and aromatic amines (IARC, 1986, 2004a; el-Bayoumy, 1992; Ambrosone & Shields, 1999; Ambrosone, 2001; Hoffmann *et al.*, 2001) which, due to their lipophilicity, can be stored in breast adipose tissue (Obana *et al.*, 1981; Morris & Seifter, 1992) and then metabolized and activated by human mammary epithelial cells (MacNicoll *et al.*, 1980). Tobacco smoke constituents reach the breast as demonstrated by the detection of cotinine in breast fluid (Petrakis *et al.*, 1978). There is evidence suggesting the presence of mutagenic arylamines (Thompson *et al.*, 2002) and PAHs (Zanieri *et al.*, 2007) in human breast milk. Cigarette smoke condensate has been shown to transform normal human breast epithelial cells *in vitro* (Narayan *et al.*, 2004), perhaps by blocking long-patch base excision repair (Kundu *et al.*, 2007). Transformation and cytogenetic effects have been observed in human mammary epithelial cells after exposure to chemical carcinogens such as PAHs or arylamine (Mane *et al.*, 1990; Eldridge *et al.*, 1992; Calaf & Russo, 1993).

The formation of specific adducts from PAHs and aromatic amines has been observed in human breast epithelial cells *in vitro*, and unspecified-DNA adducts have been found in exfoliated ductal epithelial cells in human breast milk (Gorlewska-Roberts *et al.*, 2002; Thompson *et al.*, 2002).

Mutations in the *TP53* tumour suppressor gene have been found in 15–30% of breast cancers (Goldman & Shields, 1998; Olivier & Hainaut, 2001). An increased prevalence and altered spectrum of *TP53* mutations in breast tumours have been observed among current smokers compared with never smokers (Conway *et al.*, 2002). The breast tumours with the most pronounced smoking-related mutational pattern (for example, a greater number of G:C→T:A transversions) were from women who had smoked for more than 20 years, although total *TP53* mutations were not associated with smoking duration (Conway *et al.*, 2002). This increased frequency of G to T transversions in smokers versus non-smokers is also observed in the IARC TP53 database (IARC, 2006b; Van Emburgh *et al.*, 2008).

Recent meta-analyses of epidemiological studies tend to show positive associations of breast cancer with long-term smoking among *NAT2* slow acetylators, especially among post-menopausal women (who are more likely than pre-menopausal women to be very long-term

smokers). Firozi *et al.* (2002) showed that breast tissue from *NAT2* slow acetylators had significantly higher levels of the diagonal radioactive zone (smoking-related) DNA adduct pattern than that from fast acetylators.

High rates of breast cancer in women exposed to ionizing radiation during adolescence (aged 10–19 years at exposure) (Tokunaga *et al.*, 1987) suggested that the adolescent breast may also be sensitive to the DNA-damaging effects of other exposures. This might also be true for the genotoxic compounds contained in tobacco smoke. Although some studies have supported such association, the results have been sparse and mixed. In addition, it is difficult to separate the effects of early life exposure to tobacco and smoking duration (Terry & Rohan, 2002).

Early age at first full-term pregnancy has been associated with reduced breast cancer risk (Kelsey *et al.*, 1993), hypothetically due to terminal differentiation of the breast epithelium that occurs late in the first trimester. It has been suggested that in the early stages of pregnancy, when growth-promoting hormone levels are high, but before terminal differentiation (Montelongo *et al.*, 1992), the breast may be particularly susceptible to the cancer-promoting chemicals in tobacco smoke. Several epidemiological studies compared measures of smoking before and after a first full-term pregnancy. Although suggestive, the data did not consistently show an increased risk for breast cancer among women who smoked before a first full-term pregnancy (Adami *et al.*, 1988; Hunter *et al.*, 1997; Band *et al.*, 2002; Egan *et al.*, 2003; Gram *et al.*, 2005; Li *et al.*, 2005; Olson *et al.*, 2005; Cui *et al.*, 2006). Smoking was associated with a 50% increased risk among women with slow *NAT2* acetylation genotype (Egan *et al.*, 2003). Overall, studies of risk in association with the timing of smoking relative to a first pregnancy are inconclusive; nevertheless, the breast tissue appears to have a greater susceptibility to the carcinogenic chemicals in tobacco smoke before compared to after terminal differentiation of breast epithelium.

(ii) Estrogenic pathway

The "anti-estrogenic" mechanism through which tobacco smoking may inhibit breast cancer progression is unclear. Estrogen is a known risk factor for breast cancer and several hypotheses have been proposed: earlier age at menopause among smokers, a reduction in the gastrointestinal absorption or distribution of estrogen, enhanced metabolism of estradiol to inactive catechol estrogens, increased binding of estrogens by serum sex hormone-binding globulin, lowered levels of estrogen derived from adipose tissue (Baron, 1984; Baron *et al.*, 1990; Terry & Rohan, 2002). Several studies of cigarette smoking and mammographically-defined breast density showed lower measures of breast density in current smokers than in non-smokers (Sala *et al.*, 2000; Vachon *et al.*, 2000; Warwick *et al.*, 2003; Jeffreys *et al.*, 2004; Modugno *et al.*, 2006; Bremnes *et al.*, 2007; Butler *et al.*, 2008). Since exposure to estrogen has been associated positively with breast density, a strong risk factor for breast cancer (McCormack & dos Santos Silva, 2006), the results of these studies are consistent with an anti-estrogenic effect of cigarette smoking. Although smokers and non-smokers may have the same concentrations of estrogens overall, it may be the type rather than the absolute levels of circulating estrogens that is important. Smokers might have a lower concentration of more biologically active estrogens, primarily 16-α-hydroxyestrone (16α-OHE1) (Michnovicz *et al.*, 1986, 1988; Berta *et al.*, 1992; Berstein *et al.*, 2000; Terry *et al.*, 2002b). Estrogen can be metabolized along three pathways, to 16α-OHE1 or to 2-OHE1 or to 4-OHE1. 16α-OHE1 and 4-OHE1 have been observed to increase mammary epithelial cell proliferation rates in experimental studies (Schütze *et al.*, 1993, 1994; IARC, 2007c). In contrast, 2-OHE1 might decrease epithelial cell proliferation rates (Bradlow *et al.*, 1996;

Muti *et al.*, 2000). If cigarette smoking increases estradiol 2-hydroxylation, as has been suggested (Michnovicz *et al.*, 1986), thereby increasing the ratio of 2-OHE1:16-α-OHE1, an inverse association between smoking and breast cancer risk might be observed. However, only one study has directly examined 2-hydroxylation in relation to cigarette smoking (Michnovicz *et al.*, 1986). Using injected radiolabelled estradiol, a 50% increased estradiol 2-hydroxylation was found in premenopausal women who smoked at least 15 cigarettes/day compared with non-smokers. Two studies of urinary estrogens found increased excretion of 2-OHE1 and decreased excretion of estriol among smokers (Michnovicz *et al.*, 1988; Berstein *et al.*, 2000), which may also support the hypothesis that smoking decreases the formation of active estrogen metabolites along the 16α-hydroxylation pathway. However, the ratio of urinary 2-OHE1:16α-OHE1 was not related to breast cancer risk in the one case–control study that examined the association (Ursin *et al.*, 1999). The 4-hydroxylation of estrogens is catalysed by CYP1B1, which is induced by tobacco smoke (Nebert *et al.*, 2004). This has been postulated as an additional pathway that could lead to formation of DNA adducts via catechol estrogen-quinones (Gaikwad *et al.*, 2008) and oxidative/DNA damage via redox-cycling (Zhu & Conney, 1998). The ratio of 2-OHE1:4-OHE1 has been studied in relation to breast cancer risk and smoking in one study (Berstein *et al.*, 2000). Smokers carrying the *CYP1B1 Val* allele [associated with high hydroxylation activity] had a significantly higher risk for breast cancer compared to never smokers with the *Leu/Leu* [wildtype] genotype (Saintot *et al.*, 2003).

(b) Endometrium

Exogenous estrogens unopposed by progesterone have been shown to increase the risk for endometrial cancer through increased mitotic activity of endometrial cells, increased number of DNA replication errors, and somatic mutations resulting in the malignant phenotype (IARC, 2007c, 2012c). Hence, factors associated with estrogen absorption or metabolism may alter the risk of this malignancy. Several investigators have hypothesized that cigarette smoking might be have anti-estrogenic effects, and through this mechanism reduce the risk of endometrial cancer (Baron, 1984; Baron *et al.*, 1990; Terry *et al.*, 2002b, 2004a).

Whether mediated through changes in the amount of adipose tissue, altered age at menopause, or anti-estrogenic effects, blood hormone concentrations might be an important link between smoking and the reduced risk of endometrial cancer observed in most epidemiological studies. The estrogens that have typically been studied in relation to cigarette smoking include estrone, sex hormone binding globulin (SHBG)-bound estradiol, and estriol. Blood concentrations of androgens, typically androstenedione and dehydroepiandrosterone sulfate (DHEAS), have also been studied, because these are biological precursors of estrone. Studies that have examined blood concentrations of SHBG are less common, and studies of unbound (free) estradiol are scarce.

Studies of cigarette smoking and blood hormone concentrations have been conducted mostly among post-menopausal women who were not taking HRT. Of these studies, nine examined serum (Friedman *et al.*, 1987; Cauley *et al.*, 1989; Slemenda *et al.*, 1989; Schlemmer *et al.*, 1990; Cassidenti *et al.*, 1992; Austin *et al.*, 1993; Law *et al.*, 1997) or plasma (Khaw *et al.*, 1988; Longcope & Johnston, 1988) estrone, ten examined serum (Friedman *et al.*, 1987; Cauley *et al.*, 1989; Slemenda *et al.*, 1989; Schlemmer *et al.*, 1990; Key *et al.*, 1991; Cassidenti *et al.*, 1992; Austin *et al.*, 1993; Law *et al.*, 1997) or plasma (Khaw *et al.*, 1988; Longcope & Johnston, 1988) estradiol, and two examined serum (Cassidenti *et al.*, 1992) or plasma (Longcope & Johnston, 1988) free estradiol. These studies consistently showed little or no association between smoking

and blood estrogen concentrations among post-menopausal women who were not taking hormone replacement therapy. Among pre-menopausal women, three studies (Longcope & Johnston, 1988; Key *et al.*, 1991; Berta *et al.*, 1992) found no clear association between cigarette smoking and estrogen concentrations. Studies that adjusted hormone measurements for the effects of BMI (and other covariates) showed similar results to those that did not, suggesting that BMI is not a strong confounder of this association.

In two studies the association between cigarette smoking and blood estrogen concentrations after randomization of women to groups receiving either estradiol or placebo were examined (Jensen & Christiansen, 1988; Cassidenti *et al.*, 1990). In a small study of 25 post-menopausal women, unbound estradiol was significantly lower among smokers than non-smokers both at baseline and shortly after taking micronized estradiol orally (Cassidenti *et al.*, 1990). No important differences were observed between smokers and non-smokers in serum concentrations of either estrone or bound estradiol. In contrast, in a study in which 110 post-menopausal women were randomized to take hormones (either orally or percutaneously) or a placebo (Jensen & Christiansen, 1988), smokers had lower concentrations of both estrone and bound estradiol than non-smokers after oral (but not percutaneous) hormone treatment for at least one year (concentrations of free estrogens were not examined). These results indicate that smoking might affect the absorption or metabolism of hormones used in replacement therapy.

Of the five studies that have examined the association between cigarette smoking and serum (Lapidus *et al.*, 1986; Cassidenti *et al.*, 1992; Law *et al.*, 1997) or plasma (Khaw *et al.*, 1988; Longcope & Johnston, 1988) SHBG, none found any clear association. However, one of these studies (Khaw *et al.*, 1988) found an inverse association between smoking and the ratio of bound estradiol to SHBG, a measure of estrogen activity. In this context, Cassidenti *et al.* (1990) found unbound (but not SHBG-bound) estradiol was significantly lower among smokers than non-smokers both at baseline and after taking oral estradiol, suggesting an increased SHBG-binding capacity in the women who smoked.

In post-menopausal women, androgens are the major source of estrone, converted through aromatization in fat deposits. Thus, adiposity is positively correlated with estrogen concentrations in post-menopausal women. Of the nine studies in which blood concentrations of androstenedione were examined in smokers (Friedman *et al.*, 1987; Khaw *et al.*, 1988; Longcope & Johnston, 1988; Cauley *et al.*, 1989; Slemenda *et al.*, 1989; Schlemmer *et al.*, 1990; Cassidenti *et al.*, 1992; Austin *et al.*, 1993; Law *et al.*, 1997), higher circulating concentrations were found among current than among never or former smokers in all studies. However, there was no clear variation in blood estrone concentrations by smoking status, suggesting a reduced conversion of androstenedione to estrone among smokers. Of the five studies where cigarette smoking and DHEAS concentrations were examined, three (Khaw *et al.*, 1988; Cassidenti *et al.*, 1992; Law *et al.*, 1997) found increased blood concentrations among current smokers, one (Friedman *et al.*, 1987) found also an increase that was not statistically significant, whereas another (Key *et al.*, 1991) found no clear differences according to smoking status.

Cigarette smoking and urinary estrogen concentrations have been examined in seven studies (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986; Trichopoulos *et al.*, 1987; Michnovicz *et al.*, 1988; Berta *et al.*, 1992; Key *et al.*, 1996; Berstein *et al.*, 2000). Of these, three found no major differences according to smoking status (Trichopoulos *et al.*, 1987; Michnovicz *et al.*, 1988; Berta *et al.*, 1992). The remaining four studies all showed lower urinary estriol concentrations among smokers than among non-smokers, but mixed results for urinary estrone and estradiol.

Two of these studies (Michnovicz *et al.*, 1988; Berstein *et al.*, 2000) showed higher concentrations of 2-hydroxyestrone among smokers, than non-smokers but only after estrogen treatment in Berstein *et al.* (2000).

Age at natural menopause varies substantially under the influence of genetic and environmental factors (McKinlay, 1996). A relatively early age at menopause has been associated with reduced risk of endometrial cancer (Kelsey *et al.*, 1982; Baron, 1984; Baron *et al.*, 1990; Akhmedkhanov *et al.*, 2001). A one year decrease in age at menopause has been associated approximately with a 7% decrease in risk (Kelsey *et al.*, 1982). It has been proposed that cigarette smoking decreases the age at natural menopause (Baron *et al.*, 1990), more clearly with qualitative than quantitative smoking measures (Parente *et al.*, 2008), and thus might reduce endometrial cancer risk through reduced exposure to endogenous estrogens. On average, smokers have menopause approximately 1 to 1.5 years earlier than non-smokers (Terry *et al.*, 2002b, 2004a). Adjustment for obesity and other covariates did not alter the results (Terry *et al.*, 2002b).

4.4 Mechanistic considerations of the interaction of ethanol and tobacco carcinogens

The combined effects of alcoholic beverages and tobacco on the risk for cancer incidence and mortality have been widely studied in human populations. When tested for multiplicative and additive interactions, synergistic effects of alcoholic beverages and tobacco have been found, especially for oropharyngeal and oesophageal cancers (Homann *et al.*, 2000; Castellsagué *et al.*, 2004; Salaspuro & Salaspuro, 2004; Lee *et al.*, 2005a; Lee *et al.*, 2007b).

Data support at least four possible mechanisms for the modifying effects of alcoholic beverages on cancer risk due to tobacco.

1. Alcohol may have a local permeabilizing effect on penetration of the oral mucosa by tobacco carcinogens (Du *et al.*, 2000), particularly important in the case of oropharyngeal and oesophageal cancer.
2. CYP2E1 and other CYPs may both activate and detoxify carcinogens present in tobacco smoke, including NDMA, NDEA, NNK, benzene and other tobacco-derived carcinogens in two ways: CYP induction increases metabolic activation of tobacco carcinogens leading to enhanced formation of proximate reactive chemical species at target sites; and alteration of phase II conjugation/detoxification enzymes by ethanol may also occur, changing the effective dose at the target site.
3. Competitive inhibition of CYP metabolism leads to reduced central hepatic and gastrointestinal clearance thus increasing dose delivery of carcinogens to peripheral target tissues (reviewed in Meskar *et al.*, 2001).
4. Effects of acetaldehyde derived by microbial alcohol oxidation and from the tobacco smoke (Homann *et al.*, 2000; Salaspuro & Salaspuro, 2004).

Supportive evidence for ii) and iii) is briefly presented below.

4.4.1 Effects of induction of CYPs by ethanol

(a) CYP2E1

Ethanol induces CYP2E1 in the human liver and in all species tested. Over 70 substrates of CYP2E1 have been compiled (Raucy & Carpenter, 1993; Guengerich *et al.*, 1994; Djordjević *et al.*, 1998; Klotz & Ammon, 1998; Cederbaum, 2006). Among those are tobacco carcinogens such as benzene, vinyl chloride, NDMA, NDEA and *N*-nitrosopyrrolidine, as well as many low-molecular-weight compounds. Induction of CYP2E1 by ethanol generated increased levels of toxic metabolites from the metabolism of many of these chemicals (Novak & Woodcroft, 2000). Pyridine, a constituent of tobacco smoke and

substrate of CYP2E1, generates DNA damaging products by redox-cycling (Kim & Novak, 1990).

In humans, in addition to the prominent CYP2E1 expression in the centrilobular regions of the liver, the enzyme is also detectable in the kidney cortex and, at lower levels, in organs such as the oropharynx, nasal mucosa, ovary, testis, small intestine, colon and pancreas (Ingelman-Sundberg *et al.*, 1994; Lieber, 1999, 2004).

In rats, ethanol induced CYP2E1 in epithelia of the cheek, tongue and oesophagus (Shimizu *et al.*, 1990). As a result of CYP2E1 induction by ethanol in the upper respiratory tract and possibly of inhibition of carcinogen clearance, hamsters had a significant increase of nasal cavity and tracheal tumours after intraperitoneal injection of *N*-nitrosopyrrolidine (McCoy *et al.*, 1981). Thus, induction of CYP2E1 by ethanol may participate in the genesis of cancers at several sites via metabolic activation of tobacco carcinogens into reactive species in target tissues.

(b) Other xenobiotic-activating CYPs

In addition to CYP2E1, several CYPs, including CYP3A4 and probably CYP1A2 in humans, and CYP1A1, 2B1 and 3A in rat liver, may be induced by ethanol. Of particular interest are members of the CYP3A family, which have wide substrate specificity and have been implicated in the activation of several known or suspected human carcinogens, including those derived from tobacco (Wojnowski & Kamdem, 2006). Both CYP3A4 and CYP1A2 metabolize NNK (Jalas *et al.*, 2005). Based on the Michaelis constant (Km) data (IARC, 2007a), the relative efficiencies in NNK metabolism by human CYP are (from greatest catalyst to least): 2A13 > 2B6 > 2A6 > 1A2 ~1A1 > 2D6 ~2E1 ~3A4. As the amount of CYP enzymes with overlapping substrate specificity that participate in nitrosamine metabolism varies according to organ and species, it is difficult to determine their individual contribution at target sites.

4.4.2 Effects of inhibition of CYPs by ethanol

Ethanol is a competitive inhibitor of CYP2E1 (reviewed in Anderson, 1992). It also inhibits the activities of CYP1A1, 2B6 and 2C19 but not those of CYP1A2.

Direct inhibition of CYPs by ethanol in target tissues may reduce metabolic activation of xenobiotics and hence local toxic and tumorigenic effects. Thus CYP inhibition in the liver could increase extrahepatic exposure to genotoxic metabolites from tobacco carcinogens that are substrates for these CYP enzymes. This mechanism is supported by several studies.

Ethanol caused a fivefold increase in oesophageal DNA adducts in rats induced by NDEA (Swann, 1984). In monkeys, O^6-methylguanine-DNA adducts after an oral dose of NDMA with or without ethanol were increased by co-exposure to ethanol in all tissues except the liver (Anderson *et al.*, 1996). Effects were seen in the oesophagus (17-fold increase), colonic mucosa (12-fold), pancreas (sixfold), urinary bladder (11-fold), ovary (ninefold), uterus (eightfold), brain (ninefold), spleen (13-fold) and nasal mucosa (fivefold). In these studies, ethanol treatment was acute, so that enzyme induction was improbable, and the oesophagus was not directly exposed to either ethanol or carcinogen. This indicates that a systemic interaction, most likely inhibition of hepatic carcinogen clearance, was responsible for the observed effects in the oesophagus and other extrahepatic tissues. The 17-fold increase in DNA adducts in the monkey oesophagus is similar to the 18-fold increased risk for human oesophageal cancers in tobacco smokers combined with heavy alcohol drinking (Tuyns *et al.*, 1977).

The relevance of increased genotoxic effects in extrahepatic target sites by ethanol is confirmed by many rodent experiments. Oral dosing of mice with NDMA in ethanol resulted in nasal cavity tumours (olfactory neuroblastoma) that were not seen with NDMA or ethanol alone (Griciute

et al., 1981). Ethanol in the drinking-water led to a ninefold increase in oesophageal tumours in rats induced by NDEA (Aze *et al.*, 1993). Ethanol given by gavage to nursing dams together with NDMA or NNK (Chhabra *et al.*, 2000) increased O^6-methylguanine-DNA adducts in maternal mammary glands, by 10-fold with NDMA and to a lesser extent with NNK. In the suckling infants, DNA adducts were detected in the lungs and kidneys after maternal exposure to NDMA and increased about fourfold after maternal co-treatment with ethanol. In mice, ethanol given with NDMA in the drinking-water resulted in a fourfold increase in lung tumours, but had no significant effect when NDMA was given intragastrically, intraperitoneally, subcutaneously or intravenously (Anderson, 1992). These negative findings support that direct inhibition of hepatic carcinogen clearance by ethanol is the main operative mechanism.

There is indirect evidence that ethanol can inhibit the *in vivo* clearance of the carcinogen NDMA in humans: individuals with chronic renal failure showed detectable blood and urine levels of NDMA, which were increased by consumption of ethanol (Dunn *et al.*, 1990). Other studies that involved sources of NDMA from tobacco smoke, diet or pharmaceuticals are consistent with ethanol reducing its clearance rate in humans (Anderson, 1992).

Other possible modifying effects of ethanol in tobacco-related tumorigenesis are presented in Section 4 of the *Monograph* on Consumption of Alcoholic Beverages in this Volume.

4.5 Synthesis

4.5.1 Mechanisms of tobacco-related carcinogenesis

The pathways by which tobacco products cause cancer essentially recapitulate established mechanisms of carcinogenesis by individual compounds, which were elaborated by landmark studies during the second half of the 20th century. These studies demonstrate that most carcinogens, either directly or after metabolism catalyzed by multiple cytochrome P450 enzymes, react with nucleophilic sites in DNA to form covalent binding products called adducts (a contraction for "addition products"). These DNA adducts, if left unrepaired by cellular DNA repair enzymes, persist and cause mistakes during DNA replication leading to incorporation of the wrong base in a DNA strand and consequent permanent mutations. If these permanent mutations occur in important regions of critical growth control genes such as the oncogene *KRAS* or the tumor suppressor gene *p53*, cellular growth processes can become severely unregulated and cancer can result. Multiple studies of mutations in *KRAS*, *p53*, and other growth control genes in lung tumours from smokers, some of which report thousands of mutations, are fully consistent with this overall concept.

It is the complexity of tobacco carcinogenesis which challenges investigators to identify specific mechanisms that fully explain the ways in which tobacco products cause each type of cancer. There are over 70 established carcinogens in cigarette smoke, and analyses of smokers' urine and blood clearly demonstrate higher uptake of these compounds in smokers than in non-smokers. The urine of smokers is consistently mutagenic. Similar considerations apply to smokeless tobacco users, although there are fewer identified carcinogens. Multiple DNA adducts are present in the lungs and other tissues of smokers, and sister chromatid exchanges as well as other genetic effects are consistently observed. But much less is known about the specifics of the process. Only relatively few DNA adducts in smokers' lungs have been structurally characterized and the relationship between specific adducts and the consequent mutations in critical genes is still somewhat unsettled.

There are other processes which contribute to cancer induction by tobacco products, based on

multiple studies in both laboratory animals and humans. These include inflammation, tumor promotion, oxidative damage, co-carcinogenesis, and direct activation of cellular growth pathways by constituents of smoke. Many studies demonstrate the involvement of these processes in tobacco carcinogenesis but the details by which they interact with the DNA damage pathways and their roles in specific cancers caused by tobacco products are still not fully understood.

4.5.2 Genetic polymorphisms

Multiple studies have been carried out on the role of genetic polymorphisms of xenobiotic metabolism in smoking-related carcinogenesis in humans. These studies have covered various cancer types, with lung cancer representing one of the most intensively studied. The polymorphic genes, their variant forms, and the genotype combinations investigated in these studies have similarly been numerous. In addition to the associations with increased risk of cancer, much data have accumulated on relationships between the polymorphisms and the various biomarkers of tobacco carcinogenesis in non-cancer control populations, whether smokers or non-smokers, in subjects with work-related exposure or in patients with other cancers.

Despite the massive body of research, many observations remain ambiguous. Some associations between genetic polymorphism and increased risk for cancer, such as for the *GSTM1* null genotype, alone or in combination with *CYP1A1* polymorphism, in lung cancer, or the *NAT2* slow acetylator genotype in bladder cancer and breast cancer appear stronger and more consistent, but not without controversies. Similarly, the data on the various biomarkers of tobacco-related carcinogenesis exhibit inconsistencies.

The variability in the data is at least partially likely due to differences between the studies in the genes and gene variants included (many of which are still of unknown functional or regulatory consequence), in the types of cancer studied, in levels and sources of exposure, in ethnic backgrounds, in sex, in histological types and in the features of the genome such as haplotype blocks and copy number variation resulting in linkage disequilibrium. In addition, gene-gene interactions and gene-environment interactions are likely to contribute to the discrepancies in current data. Mechanisms of tobacco-related carcinogenesis also involve genes from numerous other classes, such as those encoding for DNA repair proteins and many other regulators of cell cycle and growth. In addition; there are well described mechanistic pathways of carcinogenesis mediated via epigenetic alterations and genetic instability, to mention a few.

4.5.3 Site-specific mechanisms

The Working Group reviewed the mechanistic evidence relative to specific target sites for which there is sufficient evidence of carcinogenicity in humans, i.e. lung, oral cavity, oesophagus, larynx and nasopharynx, pancreas, stomach, liver, urinary bladder, leukaemia, cervix and ovary. Genotoxic effects have been found in eight organ sites at which tobacco smoke causes cancer in humans (DeMarini, 2004).

Sites with limited evidence of carcinogenicity or evidence suggesting lack of carcinogenicity in humans include the breast and the endothelium and relevant mechanisms are presented below.

Breast — There are several plausible mechanisms by which smoking may increase breast cancer risk, and some data support such an effect, including the increased risk among long-term smokers with *NAT2* slow genotype. Despite the overall lack of clear association in epidemiological studies, and the potential anti-estrogenic effects of smoking, the possibility that smoking increases breast cancer risk is biologically plausible.

Endothelium — The mechanisms by which cigarette smoking reduces the risk for endometrial cancer among current smokers, mainly among postmenopausal, remain unclear.

4.5.4 Interaction of ethanol and tobacco carcinogens

Data in rodents and non-human primates on the relationships between a) inhibition of hepatic clearance of nitrosamines by ethanol, b) the formation of promutagenic DNA adducts and c) tumours in extra-hepatic targets, likely also pertain in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of tobacco smoking.

Tobacco smoking causes cancers of the lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and accesory sinuses, larynx, oesophagus, stomach, pancreas, colorectum, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and ovary (mucinous), and myeloid leukaemia. Also, a positive association has been observed between tobacco smoking and cancer of the female breast. For cancers of the endometrium (post-menopausal) and of the thyroid, there is *evidence suggesting lack of carcinogenicity*.

There is *sufficient evidence* in humans for the carcinogenicity of parental smoking. Parental smoking causes hepatoblastoma in children. Also, a positive association has been observed between parental smoking and childhood leukaemia (particularly acute lymphocytic leukaemia).

There is *sufficient evidence* in experimental animals for the carcinogenicity of tobacco smoke and of tobacco smoke condensates.

Tobacco smoking is *carcinogenic to humans (Group 1)*.

References

Abdel-Rahman SZ, Ammenheuser MM, Ward JB Jr (2001). Human sensitivity to 1,3-butadiene: role of microsomal epoxide hydrolase polymorphisms. *Carcinogenesis*, 22: 415–423. doi:10.1093/carcin/22.3.415 PMID:11238181

Abdel-Rahman SZ, El-Zein RA, Ammenheuser MM *et al.* (2003). Variability in human sensitivity to 1,3-butadiene: Influence of the allelic variants of the microsomal epoxide hydrolase gene. *Environ Mol Mutagen*, 41: 140–146. doi:10.1002/em.10142 PMID:12605384

Abou-Alfa GK (2006). Hepatocellular carcinoma: molecular biology and therapy. *Semin Oncol*, 33: Suppl 11S79–S83. doi:10.1053/j.seminoncol.2006.10.015 PMID:17178294

Abrams JA, Terry MB, Neugut AI (2008). Cigarette smoking and the colorectal adenoma-carcinoma sequence. *Gastroenterology*, 134: 617–619. doi:10.1053/j.gastro.2007.12.015 PMID:18242224

Adami HO, Lund E, Bergström R, Meirik O (1988). Cigarette smoking, alcohol consumption and risk of breast cancer in young women. *Br J Cancer*, 58: 832–837. PMID:3224085

Adami J, Nyrén O, Bergström R *et al.* (1998). Smoking and the risk of leukemia, lymphoma, and multiple myeloma (Sweden). *Cancer Causes Control*, 9: 49–56. doi:10.1023/A:1008897203337 PMID:9486463

Agudo A, Sala N, Pera G *et al.* (2006). Polymorphisms in metabolic genes related to tobacco smoke and the risk of gastric cancer in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*, 15: 2427–2434. doi:10.1158/1055-9965.EPI-06-0072 PMID:17164366

Agundez JA (2004). Cytochrome P450 gene polymorphism and cancer. *Curr Drug Metab*, 5: 211–224. doi:10.2174/1389200043335621 PMID:15180491

Ahern TP, Lash TL, Egan KM, Baron JA (2009). Lifetime tobacco smoke exposure and breast cancer incidence. *Cancer Causes Control*, 20: 1837–1844. doi:10.1007/s10552-009-9376-1 PMID:19533391

Ahrendt SA, Decker PA, Alawi EA *et al.* (2001). Cigarette smoking is strongly associated with mutation of the *K-ras* gene in patients with primary adenocarcinoma of the lung. *Cancer*, 92: 1525–1530. doi:10.1002/1097-0142(20010915)92:6<1525::AID-CNCR1478>3.0.CO;2-H PMID:11745231

Ahrens W, Jöckel KH, Patzak W, Elsner G (1991). Alcohol, smoking, and occupational factors in cancer of the larynx: a case-control study. *Am J Ind Med*, 20: 477–493. doi:10.1002/ajim.4700200404 PMID:1785612

Ahrens W, Timmer A, Vyberg M *et al.* (2007). Risk factors for extrahepatic biliary tract carcinoma in men: medical conditions and lifestyle: results from a European multicentre case-control study. *Eur J Gastroenterol Hepatol*,

19: 623–630. doi:10.1097/01.meg.0000243876.79325.a1 PMID:17625430

Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P (2001). Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. *Ann N Y Acad Sci*, 943: 296–315. PMID:11594550

Akhter M, Nishino Y, Nakaya N *et al.* (2007). Cigarette smoking and the risk of colorectal cancer among men: a prospective study in Japan. *Eur J Cancer Prev*, 16: 102–107. doi:10.1097/01.cej.0000228412.98847.bc PMID:17297385

Akiba S (1994). Analysis of cancer risk related to longitudinal information on smoking habits. *Environ Health Perspect*, 102: Suppl 815–19. PMID:7851325

Akiba S & Hirayama T (1990). Cigarette smoking and cancer mortality risk in Japanese men and women–results from reanalysis of the six-prefecture cohort study data. *Environ Health Perspect*, 87: 19–26. doi:10.2307/3431001 PMID:2269225

Aksoy M (1989). Hematotoxicity and carcinogenicity of benzene. *Environ Health Perspect*, 82: 193–197. doi:10.2307/3430775 PMID:2676498

Al-Delaimy WK (2002). Hair as a biomarker for exposure to tobacco smoke. *Tob Control*, 11: 176–182. doi:10.1136/tc.11.3.176 PMID:12198265

Al-Delaimy WK, Cho E, Chen WY *et al.* (2004). A prospective study of smoking and risk of breast cancer in young adult women. *Cancer Epidemiol Biomarkers Prev*, 13: 398–404. PMID:15006915

Al-Delaimy WK & Willett WC (2008). Measurement of tobacco smoke exposure: comparison of toenail nicotine biomarkers and self-reports. *Cancer Epidemiol Biomarkers Prev*, 17: 1255–1261. doi:10.1158/1055-9965.EPI-07-2695 PMID:18483348

Al-Zoughool M, Dossus L, Kaaks R *et al.* (2007). Risk of endometrial cancer in relationship to cigarette smoking: results from the EPIC study. *Int J Cancer*, 121: 2741–2747. doi:10.1002/ijc.22990 PMID:17657712

Alberg AJ, Daudt A, Huang HY *et al.* (2004). N-acetyltransferase 2 (*NAT2*) genotypes, cigarette smoking, and the risk of breast cancer. *Cancer Detect Prev*, 28: 187–193. doi:10.1016/j.cdp.2004.04.001 PMID:15225898

Alberg AJ, Kouzis A, Genkinger JM *et al.* (2007). A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol*, 165: 660–666. doi:10.1093/aje/kwk047 PMID:17204516

Alexandrie AK, Warholm M, Carstensen U *et al.* (2000). CYP1A1 and GSTM1 polymorphisms affect urinary 1-hydroxypyrene levels after PAH exposure. *Carcinogenesis*, 21: 669–676. doi:10.1093/carcin/21.4.669 PMID:10753202

Alexandrov K, Cascorbi I, Rojas M *et al.* (2002). CYP1A1 and GSTM1 genotypes affect benzo[a]pyrene DNA adducts in smokers' lung: comparison with aromatic/hydrophobic adduct formation. *Carcinogenesis*, 23: 1969–1977. doi:10.1093/carcin/23.12.1969 PMID:12507920

Alexandrov K, Rojas M, Kadlubar FF *et al.* (1996). Evidence of *anti*-benzo[*a*]pyrene diolepoxide-DNA adduct formation in human colon mucosa. *Carcinogenesis*, 17: 2081–2083. doi:10.1093/carcin/17.9.2081 PMID:8824539

Alfano CM, Klesges RC, Murray DM *et al.* (2004). Physical activity in relation to all-site and lung cancer incidence and mortality in current and former smokers. *Cancer Epidemiology, Biomarkers & Prevention*, 13: 2233–2241.

Alguacil J & Silverman DT (2004). Smokeless and other noncigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews. *Cancer Epidemiol Biomarkers Prev*, 13: 55–58. doi:10.1158/1055-9965.EPI-03-0033 PMID:14744733

Ambrosone CB (2001). Impact of genetics on the relationship between smoking and breast cancer risk. *Journal of Women's Cancer*, 3: 17–22.

Ambrosone CB, Freudenheim JL, Graham S *et al.* (1996). Cigarette smoking, N-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. *JAMA*, 276: 1494–1501. doi:10.1001/jama.276.18.1494 PMID:8903261

Ambrosone CB, Kropp S, Yang J *et al.* (2008). Cigarette smoking, *N-acetyltransferase 2* genotypes, and breast cancer risk: pooled analysis and meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 17: 15–26. doi:10.1158/1055-9965.EPI-07-0598 PMID:18187392

Ambrosone CB, Shields PG (1999). *Smoking as a risk factor for breast cancer.* In: *Breast cancer: molecular genetics, pathogenesis, and therapeutics*. Bowcock AM, editor. Tetowa, NJ: Humana Press, pp. 519–536,.

Amos CI, Wu X, Broderick P *et al.* (2008). Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet*, 40: 616–622. doi:10.1038/ng.109 PMID:18385676

Andersen V, Agerstjerne L, Jensen D *et al.* (2009). The multidrug resistance 1 (MDR1) gene polymorphism G-rs3789243-A is not associated with disease susceptibility in Norwegian patients with colorectal adenoma and colorectal cancer; a case control study. *BMC Med Genet*, 10: 18 doi:10.1186/1471-2350-10-18 PMID:19250544

Anderson JC, Attam R, Alpern Z *et al.* (2003). Prevalence of colorectal neoplasia in smokers. *Am J Gastroenterol*, 98: 2777–2783. doi:10.1111/j.1572-0241.2003.08671.x PMID:14687832

Anderson LM (1992). *Modulation of nitrosamine metabolism by ethanol: implications for cancer risk*. In: *Alcohol and Cancer*. Watson RR, editor. Boca Raton, FL: CRC Press, pp. 17–54.

Anderson LM, Souliotis VL, Chhabra SK *et al.* (1996). *N*-nitrosodimethylamine-derived O^6-methylguanine in DNA of monkey gastrointestinal and urogenital organs

and enhancement by ethanol. *Int J Cancer*, 66: 130–134. doi:10.1002/(SICI)1097-0215(19960328)66:1<130::AID-IJC22>3.0.CO;2-G PMID:8608956

Ansary-Moghaddam A, Huxley R, Barzi F *et al.*Asia Pacific Cohort Studies Collaboration (2006). The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. *Cancer Epidemiol Biomarkers Prev*, 15: 2435–2440. doi:10.1158/1055-9965.EPI-06-0368 PMID:17164367

Applebaum KM, Furniss CS, Zeka A *et al.* (2007). Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst*, 99: 1801–1810. doi:10.1093/jnci/djm233 PMID:18042931

Appleby P, Beral V, Berrington de González A *et al.* International Collaboration of Epidemiological Studies of Cervical Cancer (2006). Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *Int J Cancer*, 118: 1481–1495. doi:10.1002/ijc.21493 PMID:16206285

Arif JM, Dresler C, Clapper ML *et al.* (2006). Lung DNA adducts detected in human smokers are unrelated to typical polyaromatic carcinogens. *Chem Res Toxicol*, 19: 295–299. doi:10.1021/tx0502443 PMID:16485906

Armstrong RW, Imrey PB, Lye MS *et al.* (2000). Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. *Int J Epidemiol*, 29: 991–998. doi:10.1093/ije/29.6.991 PMID:11101539

Ashktorab H, Begum R, Akhgar A *et al.* (2007). Folate status and risk of colorectal polyps in African Americans. *Dig Dis Sci*, 52: 1462–1470. doi:10.1007/s10620-006-9236-8 PMID:17372834

Asma S, Bettcher DW, Samet J *et al.* (2009). *Tobacco*. In: *Oxford Textbook Of Public Health*. Detels R, editor. Oxford: Oxford University Press.

Ateş NA, Tamer L, Ateş C *et al.* (2005). Glutathione S-transferase M1, T1, P1 genotypes and risk for development of colorectal cancer. *Biochem Genet*, 43: 149–163. doi:10.1007/s10528-005-1508-z PMID:15932063

Austin H, Drews C, Partridge EE (1993). A case-control study of endometrial cancer in relation to cigarette smoking, serum estrogen levels, and alcohol use. *Am J Obstet Gynecol*, 169: 1086–1091. PMID:8238164

Autrup H (2000). Genetic polymorphisms in human xenobiotica metabolizing enzymes as susceptibility factors in toxic response. *Mutat Res*, 464: 65–76. PMID:10633178

Aze Y, Toyoda K, Furukawa F *et al.* (1993). Enhancing effect of ethanol on esophageal tumor development in rats by initiation of diethylnitrosamine. *Carcinogenesis*, 14: 37–40. doi:10.1093/carcin/14.1.37 PMID:8425269

Bain C, Feskanich D, Speizer FE *et al.* (2004). Lung cancer rates in men and women with comparable histories of smoking. *J Natl Cancer Inst*, 96: 826–834. PMID:15173266

Baker JA, Odunuga OO, Rodabaugh KJ *et al.* (2006). Active and passive smoking and risk of ovarian cancer. *Int J Gynecol Cancer*, 16: Suppl 1211–218. doi:10.1111/j.1525-1438.2006.00473.x PMID:16515593

Balansky R, Ganchev G, Iltcheva M *et al.* (2007). Potent carcinogenicity of cigarette smoke in mice exposed early in life. *Carcinogenesis*, 28: 2236–2243. doi:10.1093/carcin/bgm122 PMID:17522065

Balaram P, Sridhar H, Rajkumar T *et al.* (2002). Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *Int J Cancer*, 98: 440–445. doi:10.1002/ijc.10200 PMID:11920597

Bamber DE, Fryer AA, Strange RC *et al.* (2001). Phenol sulphotransferase *SULT1A1*1* genotype is associated with reduced risk of colorectal cancer. *Pharmacogenetics*, 11: 679–685. doi:10.1097/00008571-200111000-00006 PMID:11692076

Band PR, Le ND, Fang R, Deschamps M (2002). Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. *Lancet*, 360: 1044–1049. doi:10.1016/S0140-6736(02)11140-8 PMID:12383984

Baron JA (1984). Smoking and estrogen-related disease. *Am J Epidemiol*, 119: 9–22. PMID:6362403

Baron JA, Byers T, Greenberg ER *et al.* (1986). Cigarette smoking in women with cancers of the breast and reproductive organs. *J Natl Cancer Inst*, 77: 677–680. PMID:3462409

Baron JA, La Vecchia C, Levi F (1990). The antiestrogenic effect of cigarette smoking in women. *Am J Obstet Gynecol*, 162: 502–514. PMID:2178432

Baron JA, Newcomb PA, Longnecker MP *et al.* (1996). Cigarette smoking and breast cancer. *Cancer Epidemiol Biomarkers Prev*, 5: 399–403. PMID:9162307

Barra S, Barón AE, Franceschi S *et al.* (1991). Cancer and non-cancer controls in studies on the effect of tobacco and alcohol consumption. *Int J Epidemiol*, 20: 845–851. doi:10.1093/ije/20.4.845 PMID:1800421

Bartsch H, Nair U, Risch A *et al.* (2000). Genetic polymorphism of *CYP* genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol Biomarkers Prev*, 9: 3–28. PMID:10667460

Batty GD, Kivimaki M, Gray L *et al.* (2008). Cigarette smoking and site-specific cancer mortality: testing uncertain associations using extended follow-up of the original Whitehall study. *Ann Oncol*, 19: 996–1002. doi:10.1093/annonc/mdm578 PMID:18212091

Baumgartner KB, Schlierf TJ, Yang D *et al.* (2009). N-acetyltransferase 2 genotype modification of active cigarette smoking on breast cancer risk among hispanic and non-hispanic white women. *Toxicol Sci*, 112: 211–220. PMID:19692670

Belinsky SA (2004). Gene-promoter hypermethylation as a biomarker in lung cancer. *Nat Rev Cancer*, 4: 707–717. PMID:15343277

Belinsky SA (2005). Silencing of genes by promoter hypermethylation: key event in rodent and human lung cancer. *Carcinogenesis*, 26: 1481–1487. doi:10.1093/carcin/bgi020 PMID:15661809

Belinsky SA, Klinge DM, Dekker JD *et al.* (2005). Gene promoter methylation in plasma and sputum increases with lung cancer risk. *Clin Cancer Res*, 11: 6505–6511. PMID:16166426

Belinsky SA, Liechty KC, Gentry FD *et al.* (2006). Promoter hypermethylation of multiple genes in sputum precedes lung cancer incidence in a high-risk cohort. *Cancer Res*, 66: 3338–3344. PMID:16540689

Benhamou S, Lee WJ, Alexandrie AK *et al.* (2002). Meta- and pooled analyses of the effects of glutathione *S*-transferase M1 polymorphisms and smoking on lung cancer risk. *Carcinogenesis*, 23: 1343–1350. doi:10.1093/carcin/23.8.1343 PMID:12151353

Beral V, Bull D, Reeves GMillion Women Study Collaborators (2005). Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, 365: 1543–1551. doi:10.1016/S0140-6736(05)66455-0 PMID:15866308

Bergmark E (1997). Hemoglobin adducts of acrylamide and acrylonitrile in laboratory workers, smokers and nonsmokers. *Chem Res Toxicol*, 10: 78–84. doi:10.1021/tx960113p PMID:9074806

Bernfeld P, Homburger F, Russfield AB (1974). Strain differences in the response of inbred Syrian hamsters to cigarette smoke inhalation. *J Natl Cancer Inst*, 53: 1141–1157. PMID:4279301

Bernfeld P, Homburger F, Soto E, Pai KJ (1979). Cigarette smoke inhalation studies in inbred Syrian golden hamsters. *J Natl Cancer Inst*, 63: 675–689. PMID:288930

Berrettini W, Yuan X, Tozzi F *et al.* (2008). Alpha-5/alpha-3 nicotinic receptor subunit alleles increase risk for heavy smoking. *Mol Psychiatry*, 13: 368–373. doi:10.1038/sj.mp.4002154 PMID:18227835

Berrington de González A, Sweetland S, Green J (2004). Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a meta-analysis. *Br J Cancer*, 90: 1787–1791. PMID:15150591

Berstein LM, Tsyrlina EV, Kolesnik OS *et al.* (2000). Catecholestrogens excretion in smoking and non-smoking postmenopausal women receiving estrogen replacement therapy. *J Steroid Biochem Mol Biol*, 72: 143–147. doi:10.1016/S0960-0760(00)00038-8 PMID:10775805

Berta L, Fortunati N, Gennari P *et al.* (1991). Influence of cigarette smoking on pituitary and sex hormone balance in healthy premenopausal women. *Fertil Steril*, 56: 788–789. PMID:1915961

Berta L, Frairia R, Fortunati N *et al.* (1992). Smoking effects on the hormonal balance of fertile women. *Horm Res*, 37: 45–48. doi:10.1159/000182280 PMID:1398476

Besson H, Brennan P, Becker N *et al.* (2006). Tobacco smoking, alcohol drinking and Hodgkin's lymphoma: A European multicenter case-control study (Epilymph). *Br J Cancer*, 95: 378–384.

Bhutani M, Pathak AK, Fan YH *et al.* (2008). Oral epithelium as a surrogate tissue for assessing smoking-induced molecular alterations in the lungs. *Cancer Prev Res (Phila)*, 1: 39–44. PMID:19138934

Bin P, Leng S, Cheng J *et al.* (2008). Association of aryl hydrocarbon receptor gene polymorphisms and urinary 1-hydroxypyrene in polycyclic aromatic hydrocarbon-exposed workers. *Cancer Epidemiol Biomarkers Prev*, 17: 1702–1708. doi:10.1158/1055-9965.EPI-07-2812 PMID:18628420

Bjelke E (1975). Dietary vitamin A and human lung cancer. *Int J Cancer*, 15: 561–565. doi:10.1002/ijc.2910150405 PMID:1140863

Bjerregaard BK, Raaschou-Nielsen O, Sørensen M *et al.* (2006). Tobacco smoke and bladder cancer–in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, 119: 2412–2416. doi:10.1002/ijc.22169 PMID:16894557

Bjørge T, Engeland A, Tretli S, Weiderpass E (2007). Body size in relation to cancer of the uterine corpus in 1 million Norwegian women. *Int J Cancer*, 120: 378–383. doi:10.1002/ijc.22260 PMID:17066451

Bleeker MC, Heideman DA, Snijders PJ *et al.* (2009). Penile cancer: epidemiology, pathogenesis and prevention. *World J Urol*, 27: 141–150. doi:10.1007/s00345-008-0302-z PMID:18607597

Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr (1991). Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA*, 265: 1287–1289. doi:10.1001/jama.265.10.1287 PMID:1995976

Blot WJ, McLaughlin JK, Winn DM *et al.* (1988). Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res*, 48: 3282–3287. PMID:3365707

Boccia S, Sayed-Tabatabaei FA, Persiani R *et al.* (2007). Polymorphisms in metabolic genes, their combination and interaction with tobacco smoke and alcohol consumption and risk of gastric cancer: a case-control study in an Italian population. *BMC Cancer*, 7: 206 PMID:17996038

Bode AM & Dong Z (2005). Signal transduction pathways in cancer development and as targets for cancer prevention. *Prog Nucleic Acid Res Mol Biol*, 79: 237–297. PMID:16096030

Boffetta P, Clark S, Shen M *et al.* (2006). Serum cotinine level as predictor of lung cancer risk. *Cancer Epidemiol Biomarkers Prev*, 15: 1184–1188. doi:10.1158/1055-9965.EPI-06-0032 PMID:16775179

Boffetta P, Hecht SS, Gray N *et al.* (2008). Smokeless tobacco and cancer. *Lancet Oncol*, 9: 667–675. doi:10.1016/S1470-2045(08)70173-6 PMID:18598931

Bogen E (1929). The composition of cigarets and cigaret smoke. *Journal of the American Medical Association*, 93: 1110–1114.

Bolt HM & Thier R (2006). Relevance of the deletion polymorphisms of the glutathione *S*-transferases *GSTT1* and *GSTM1* in pharmacology and toxicology. *Curr Drug Metab*, 7: 613–628. doi:10.2174/138920006778017786 PMID:16918316

Bono R, Vincenti M, Saglia U *et al.* (2002). Tobacco smoke and formation of *N*-(2-hydroxyethyl)valine in human hemoglobin. *Arch Environ Health*, 57: 416–421. doi:10.1080/00039890209601430 PMID:12641182

Borgerding M & Klus H (2005). Analysis of complex mixtures–cigarette smoke. *Exp Toxicol Pathol*, 57: Suppl 143–73. doi:10.1016/j.etp.2005.05.010 PMID:16092717

Borlak J & Reamon-Buettner SM (2006). N-acetyltransferase 2 (NAT2) gene polymorphisms in colon and lung cancer patients. *BMC Med Genet*, 7: 58 doi:10.1186/1471-2350-7-58 PMID:16827944

Bosetti C, Gallus S, Peto R *et al.* (2008). Tobacco smoking, smoking cessation, and cumulative risk of upper aerodigestive tract cancers. *Am J Epidemiol*, 167: 468–473. doi:10.1093/aje/kwm318 PMID:18056925

Bosetti C, Garavello W, Gallus S, La Vecchia C (2006). Effects of smoking cessation on the risk of laryngeal cancer: an overview of published studies. *Oral Oncol*, 42: 866–872. doi:10.1016/j.oraloncology.2006.02.008 PMID:16931120

Bosetti C, Negri E, Franceschi S *et al.* (2000a). Risk factors for oral and pharyngeal cancer in women: a study from Italy and Switzerland. *Br J Cancer*, 82: 204–207. PMID:10638990

Botteri E, Iodice S, Bagnardi V *et al.* (2008a). Smoking and colorectal cancer: a meta-analysis. *JAMA*, 300: 2765–2778. doi:10.1001/jama.2008.839 PMID:19088354

Botteri E, Iodice S, Raimondi S *et al.* (2008b). Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology*, 134: 388–395. doi:10.1053/j.gastro.2007.11.007 PMID:18242207

Boyd AS, Shyr Y, King LE Jr (2002). Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. *J Am Acad Dermatol*, 46: 706–709. doi:10.1067/mjd.2002.120467 PMID:12004311

Boyle P, Maisonneuve P, Bueno de Mesquita B *et al.* (1996). Cigarette smoking and pancreas cancer: a case control study of the search programme of the IARC. *Int J Cancer*, 67: 63–71. doi:10.1002/(SICI)1097-0215(19960703)67:1<63::AID-IJC12>3.0.CO;2-D PMID:8690527

Boysen G & Hecht SS (2003). Analysis of DNA and protein adducts of benzo[a]pyrene in human tissues using structure-specific methods. *Mutat Res*, 543: 17–30. doi:10.1016/S1383-5742(02)00068-6 PMID:12510015

Bracci PM & Holly EA (2005). Tobacco use and non-Hodgkin lymphoma: results from a population-based case-control study in the San Francisco Bay Area, California. *Cancer Causes Control*, 16: 333–346.

Bradlow HL, Telang NT, Sepkovic DW, Osborne MP (1996). 2-hydroxyestrone: the 'good' estrogen. *J Endocrinol*, 150: SupplS259–S265. PMID:8943806

Breast Cancer Family Registry; Kathleen Cuningham Consortium for Research into Familial Breast Cancer (Australasia) Ontario Cancer Genetics Network (Canada) (2008). Smoking and risk of breast cancer in carriers of mutations in BRCA1 or BRCA2 aged less than 50 years. *Breast Cancer Res Treat*, 109: 67–75. doi:10.1007/s10549-007-9621-9 PMID:17972172

Bremnes Y, Ursin G, Bjurstam N, Gram IT (2007). Different measures of smoking exposure and mammographic density in postmenopausal Norwegian women: a cross-sectional study. *Breast Cancer Res*, 9: R73 doi:10.1186/bcr1782 PMID:17963507

Brennan P, Hsu CC, Moullan N *et al.* (2005). Effect of cruciferous vegetables on lung cancer in patients stratified by genetic status: a mendelian randomisation approach. *Lancet*, 366: 1558–1560. PMID:16257343

Brennan P, van der Hel O, Moore LE *et al.* (2008). Tobacco smoking, body mass index, hypertension, and kidney cancer risk in central and eastern Europe. *Br J Cancer*, 99: 1912–1915. doi:10.1038/sj.bjc.6604761 PMID:19034282

Brenner H, Arndt V, Bode G *et al.* (2002). Risk of gastric cancer among smokers infected with Helicobacter pylori. *Int J Cancer*, 98: 446–449. doi:10.1002/ijc.10201 PMID:11920598

Brinton LA, Barrett RJ, Berman ML *et al.* (1993). Cigarette smoking and the risk of endometrial cancer. *Am J Epidemiol*, 137: 281–291. PMID:8452136

Brinton LA, Blot WJ, Becker JA *et al.* (1984). A case-control study of cancers of the nasal cavity and paranasal sinuses. *Am J Epidemiol*, 119: 896–906. PMID:6731431

Brinton LA, Schairer C, Stanford JL, Hoover RN (1986). Cigarette smoking and breast cancer. *Am J Epidemiol*, 123: 614–622. PMID:3953540

Brooks DR, Palmer JR, Strom BL, Rosenberg L (2003). Menthol cigarettes and risk of lung cancer. *Am J Epidemiol*, 158: 609–616, discussion 617–620. doi:10.1093/aje/kwg182 PMID:14507595

Brown LM, Blot WJ, Schuman SH *et al.* (1988). Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *J Natl Cancer Inst*, 80: 1620–1625. doi:10.1093/jnci/80.20.1620 PMID:3193480

Brown LM, Hoover R, Silverman D *et al.* (2001). Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors.

Am J Epidemiol, 153: 114–122. doi:10.1093/aje/153.2.114 PMID:11159155

Brown LM, Hoover RN, Greenberg RS *et al.* (1994a). Are racial differences in squamous cell esophageal cancer explained by alcohol and tobacco use? *J Natl Cancer Inst*, 86: 1340–1345. doi:10.1093/jnci/86.17.1340 PMID:8064893

Brown LM, Silverman DT, Pottern LM *et al.* (1994b). Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. *Cancer Causes Control*, 5: 333–340. doi:10.1007/BF01804984 PMID:8080945

Brugere J, Guenel P, Leclerc A, Rodriguez J (1986). Differential effects of tobacco and alcohol in cancer of the larynx, pharynx, and mouth. *Cancer*, 57: 391–395. doi:10.1002/1097-0142(19860115)57:2<391::AID-CNCR2820570235>3.0.CO;2-Q PMID:3942973

Brunet JS, Ghadirian P, Rebbeck TR *et al.* (1998). Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes. *J Natl Cancer Inst*, 90: 761–766. doi:10.1093/jnci/90.10.761 PMID:9605646

Bufalo NE, Leite JL, Guilhen ACT *et al.* (2006). Smoking and susceptibility to thyroid cancer: an inverse association with CYP1A1 allelic variants. *Endocr Relat Cancer*, 13: 1185–1193. doi:10.1677/ERC-06-0002 PMID:17158763

Bundgaard T, Wildt J, Frydenberg M *et al.* (1995). Case-control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control*, 6: 57–67. doi:10.1007/BF00051681 PMID:7718736

Burchell B (2003). Genetic variation of human UDP-glucuronosyltransferase: implications in disease and drug glucuronidation. *Am J Pharmacogenomics*, 3: 37–52. PMID:12562215

Butler LM, Gold EB, Greendale GA *et al.* (2008). Menstrual and reproductive factors in relation to mammographic density: the Study of Women's Health Across the Nation (SWAN). *Breast Cancer Res Treat*, 112: 165–174. doi:10.1007/s10549-007-9840-0 PMID:18066689

Butler LM, Wang R, Wong AS *et al.* (2009). Cigarette smoking and risk of prostate cancer among Singapore Chinese. *Cancer Causes Control*, 20: 1967–1974.

Calaf G & Russo J (1993). Transformation of human breast epithelial cells by chemical carcinogens. *Carcinogenesis*, 14:483–492.doi:10.1093/carcin/14.3.483PMID:8453725

California Environmental Protection Agency (2005). *Health effects assessment for ETS: final*. Sacramento, CA: California Environmental Protection Agency, Office of Environmental Health Hazard Assesment.

Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr (1994). Cigarette smoking and risk of fatal breast cancer. *Am J Epidemiol*, 139: 1001–1007. PMID:8178779

Campbell PT, Curtin K, Ulrich CM *et al.* (2009). Mismatch repair polymorphisms and risk of colon cancer, tumour microsatellite instability and interactions with lifestyle factors. *Gut*, 58: 661–667. doi:10.1136/gut.2007.144220 PMID:18523027

Campos F, Carrasquilla G, Koriyama C *et al.* (2006). Risk factors of gastric cancer specific for tumor location and histology in Cali, Colombia. *World J Gastroenterol*, 12: 5772–5779. PMID:17007041

Canova C, Hashibe M, Simonato L *et al.* (2009). Genetic associations of 115 polymorphisms with cancers of the upper aerodigestive tract across 10 European countries: the ARCAGE project. *Cancer Res*, 69: 2956–2965. doi:10.1158/0008-5472.CAN-08-2604 PMID:19339270

Cao SM, Liu Q, Huang TB (2000). Analysis for risk factors of nasopharyngeal carcinoma in Sihui city. [chinese] *Cancer*, 19: 987–989.

Cao W, Cai L, Rao JY *et al.* (2005). Tobacco smoking, GSTP1 polymorphism, and bladder carcinoma. *Cancer*, 104: 2400–2408. doi:10.1002/cncr.21446 PMID:16240451

Caplan LS, Hall HI, Levine RS, Zhu K (2000). Preventable risk factors for nasal cancer. *Ann Epidemiol*, 10: 186–191. doi:10.1016/S1047-2797(99)00049-6 PMID:10813512

Cardoso MA, Maruta LM, Kida AA *et al.* (2002). Micronutrients and the risk of colorectal adenomas: a case-control study in São Paulo, Brazil. *IARC Sci Publ*, 156: 361–363. PMID:12484206

Carlsten C, Sagoo GS, Frodsham AJ *et al.* (2008). Glutathione *S*-transferase M1 (*GSTM1*) polymorphisms and lung cancer: a literature-based systematic HuGE review and meta-analysis. *Am J Epidemiol*, 167: 759–774. doi:10.1093/aje/kwm383 PMID:18270371

Carmella SG, Chen M, Han S *et al.* (2009). Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. *Chem Res Toxicol*, 22: 734–741. doi:10.1021/tx800479s PMID:19317515

Carmella SG, Chen M, Villalta PW *et al.* (2002). Ethylation and methylation of hemoglobin in smokers and nonsmokers. *Carcinogenesis*, 23: 1903–1910. doi:10.1093/carcin/23.11.1903 PMID:12419839

Carpenter CL, Jarvik ME, Morgenstern H *et al.* (1999). Mentholated cigarette smoking and lung-cancer risk. *Ann Epidemiol*, 9: 114–120. doi:10.1016/S1047-2797(98)00042-8 PMID:10037555

Cascorbi I, Brockmöller J, Roots I (1996). A C4887A polymorphism in exon 7 of human *CYP1A1*: population frequency, mutation linkages, and impact on lung cancer susceptibility. *Cancer Res*, 56: 4965–4969. PMID:8895751

Cassidenti DL, Pike MC, Vijod AG *et al.* (1992). A reevaluation of estrogen status in postmenopausal women who smoke. *Am J Obstet Gynecol*, 166: 1444–1448. PMID:1534446

Cassidenti DL, Vijod AG, Vijod MA *et al.* (1990). Short-term effects of smoking on the pharmacokinetic profiles of micronized estradiol in postmenopausal women. *Am J Obstet Gynecol*, 163: 1953–1960. PMID:2256508

Castellsagué X, Muñoz N, De Stefani E *et al.* (1999). Independent and joint effects of tobacco smoking and

alcohol drinking on the risk of esophageal cancer in men and women. *Int J Cancer*, 82: 657–664. doi:10.1002/(SICI)1097-0215(19990827)82:5<657::AID-IJC7>3.0.CO;2-C PMID:10417762

Castellsagué X, Quintana MJ, Martínez MC *et al.* (2004). The role of type of tobacco and type of alcoholic beverage in oral carcinogenesis. *Int J Cancer*, 108: 741–749. doi:10.1002/ijc.11627 PMID:14696101

Cauley JA, Gutai JP, Kuller LH *et al.* (1989). The epidemiology of serum sex hormones in postmenopausal women. *Am J Epidemiol*, 129: 1120–1131. PMID:2729251

Cavalieri E, Frenkel K, Liehr JG *et al.* (2000). Estrogens as endogenous genotoxic agents–DNA adducts and mutations. *J Natl Cancer Inst Monogr*, 2775–93. PMID:10963621

Cederbaum AI (2006). CYP2E1–biochemical and toxicological aspects and role in alcohol-induced liver injury. *Mt Sinai J Med*, 73: 657–672. PMID:16878272

Chameaud J, Perraud R, Chrétien J *et al.* (1982). Lung carcinogenesis during in vivo cigarette smoking and radon daughter exposure in rats. *Recent Results Cancer Res*, 82: 11–20. PMID:7111833

Chan AO, Jim MH, Lam KF *et al.* (2007). Prevalence of colorectal neoplasm among patients with newly diagnosed coronary artery disease. *JAMA*, 298: 1412–1419. PMID:17895457

Chang-Claude J, Kropp S, Jäger B *et al.* (2002). Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 11: 698–704. PMID:12163321

Chao A, Thun MJ, Jacobs EJ *et al.* (2000). Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. *J Natl Cancer Inst*, 92: 1888–1896. doi:10.1093/jnci/92.23.1888 PMID:11106680

Chen B, Hu Y, Jin T *et al.* (2007). The influence of metabolic gene polymorphisms on urinary 1-hydroxypyrene concentrations in Chinese coke oven workers. *Sci Total Environ*, 381: 38–46. doi:10.1016/j.scitotenv.2007.02.021 PMID:17498780

Chen CC, Neugut AI, Rotterdam H (1994). Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. *Cancer Epidemiol Biomarkers Prev*, 3: 205–207. PMID:8019367

Cheng TJ, Christiani DC, Xu X *et al.* (1995). Glutathione *S*-transferase *mu* genotype, diet, and smoking as determinants of sister chromatid exchange frequency in lymphocytes. *Cancer Epidemiol Biomarkers Prev*, 4: 535–542. PMID:7549811

Cheng YJ, Hildesheim A, Hsu MM *et al.* (1999). Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan. *Cancer Causes Control*, 10: 201–207. doi:10.1023/A:1008893109257 PMID:10454065

Chhabra SK, Anderson LM, Perella C *et al.* (2000). Coexposure to ethanol with N-nitrosodimethylamine or 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone during lactation of rats: marked increase in O^6-methylguanine-DNA adducts in maternal mammary gland and in suckling lung and kidney. *Toxicol Appl Pharmacol*, 169: 191–200. doi:10.1006/taap.2000.9068 PMID:11097872

Chia VM, Newcomb PA, Bigler J *et al.* (2006). Risk of microsatellite-unstable colorectal cancer is associated jointly with smoking and nonsteroidal anti-inflammatory drug use. *Cancer Res*, 66: 6877–6883. doi:10.1158/0008-5472.CAN-06-1535 PMID:16818666

Choi SY & Kahyo H (1991). Effect of cigarette smoking and alcohol consumption in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int J Epidemiol*, 20: 878–885. doi:10.1093/ije/20.4.878 PMID:1800426

Chow WH, Hsing AW, McLaughlin JK, Fraumeni JF Jr (1996). Smoking and adrenal cancer mortality among United States veterans. *Cancer Epidemiol Biomarkers Prev*, 5: 79–80. PMID:8850265

Chow WH, Linet MS, McLaughlin JK *et al.* (1993b). Risk factors for small intestine cancer. *Cancer Causes Control*, 4: 163–169. doi:10.1007/BF00053158 PMID:8481495

Chow WH, McLaughlin JK, Hrubec Z *et al.* (1993a). Tobacco use and nasopharyngeal carcinoma in a cohort of US veterans. *Int J Cancer*, 55: 538–540. doi:10.1002/ijc.2910550403 PMID:8406978

Christmann M, Tomicic MT, Roos WP, Kaina B (2003). Mechanisms of human DNA repair: an update. *Toxicology*, 193: 3–34. doi:10.1016/S0300-483X(03)00287-7 PMID:14599765

Chu SY, Stroup NE, Wingo PA *et al.* (1990). Cigarette smoking and the risk of breast cancer. *Am J Epidemiol*, 131: 244–253. PMID:2404408

Church TR, Anderson KE, Caporaso NE *et al.* (2009). A prospectively measured serum biomarker for a tobacco-specific carcinogen and lung cancer in smokers. *Cancer Epidemiol Biomarkers Prev*, 18: 260–266. doi:10.1158/1055-9965.EPI-08-0718 PMID:19124507

Chyou PH, Nomura AM, Stemmermann GN (1995). Diet, alcohol, smoking and cancer of the upper aerodigestive tract: a prospective study among Hawaii Japanese men. *Int J Cancer*, 60: 616–621. doi:10.1002/ijc.2910600508 PMID:7860134

Cocco P, Moore PS, Ennas MG *et al.* (2007). Effect of urban traffic, individual habits, and genetic polymorphisms on background urinary 1-hydroxypyrene excretion. *Ann Epidemiol*, 17: 1–8. doi:10.1016/j.annepidem.2005.11.001 PMID:16406813

Colangelo LA, Gapstur SM, Gann PH, Dyer AR (2004). Cigarette smoking and colorectal carcinoma mortality in a cohort with long-term follow-up. *Cancer*, 100: 288–293. doi:10.1002/cncr.11923 PMID:14716762

Colilla S, Kantoff PW, Neuhausen SL *et al.* (2006). The joint effect of smoking and AIB1 on breast cancer risk in BRCA1 mutation carriers. *Carcinogenesis*, 27: 599–605. doi:10.1093/carcin/bgi246 PMID:16244359

Collishaw NE, Boyd NF, Cantor KP *et al.* (2009). *Canadian expert panel on tobacco smoke and breast cancer risk*. Toronto: Ontario Tobacco Research Unit.

Conway K, Edmiston SN, Cui L *et al.* (2002). Prevalence and spectrum of p53 mutations associated with smoking in breast cancer. *Cancer Res*, 62: 1987–1995. PMID:11929815

Cooper CS, Grover PL, Sims P (1983). *The metabolism and activation of benzo[a]pyrene*. In: *Progress in Drug Metabolism*, Vol. 7. Bridges JW, Chasseaud LF, editors. London: Wiley & Sons, pp. 295–396

Corona R, Dogliotti E, D'Errico M *et al.* (2001). Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. *Arch Dermatol*, 137: 1162–1168. PMID:11559211

Cortez CC & Jones PA (2008). Chromatin, cancer and drug therapies. *Mutat Res*, 647: 44–51. PMID:18691602

Cote ML, Chen W, Smith DW *et al.* (2009). Meta- and pooled analysis of *GSTP1* polymorphism and lung cancer: a HuGE-GSEC review. *Am J Epidemiol*, 169: 802–814. doi:10.1093/aje/kwn417 PMID:19240225

Cote ML, Kardia SL, Wenzlaff AS *et al.* (2005). Combinations of glutathione S-transferase genotypes and risk of early-onset lung cancer in Caucasians and African Americans: a population-based study. *Carcinogenesis*, 26: 811–819. doi:10.1093/carcin/bgi023 PMID:15661806

Couch FJ, Cerhan JR, Vierkant RA *et al.* (2001). Cigarette smoking increases risk for breast cancer in high-risk breast cancer families. *Cancer Epidemiol Biomarkers Prev*, 10: 327–332. PMID:11319172

Coughlin SS, Calle EE, Patel AV, Thun MJ (2000). Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control*, 11: 915–923. doi:10.1023/A:1026580131793 PMID:11142526

Cozen W, Hamilton AS, Zhao P *et al.* (2009). A protective role for early oral exposures in the etiology of young adult Hodgkin lymphoma. *Blood*, 114: 4014–4020.

Crofts F, Cosma GN, Currie D *et al.* (1993). A novel CYP1A1 gene polymorphism in African-Americans. *Carcinogenesis*, 14: 1729–1731. doi:10.1093/carcin/14.9.1729 PMID:8104732

Cui Y, Miller AB, Rohan TE (2006). Cigarette smoking and breast cancer risk: update of a prospective cohort study. *Breast Cancer Res Treat*, 100: 293–299. doi:10.1007/s10549-006-9255-3 PMID:16773435

Curtin K, Samowitz WS, Wolff RK *et al.* (2009). Somatic alterations, metabolizing genes and smoking in rectal cancer. *Int J Cancer*, 125: 158–164. doi:10.1002/ijc.24338 PMID:19358278

Cybulski C, Masojc B, Oszutowska D *et al.* (2008). Constitutional CHEK2 mutations are associated with a decreased risk of lung and laryngeal cancers. *Carcinogenesis*, 29: 762–765. doi:10.1093/carcin/bgn044 PMID:18281249

D'Agostini F, Izzotti A, Balansky R *et al.* (2006). Early loss of Fhit in the respiratory tract of rodents exposed to environmental cigarette smoke. *Cancer Res*, 66: 3936–3941. doi:10.1158/0008-5472.CAN-05-3666 PMID:16585223

d'Errico A, Malats N, Vineis P, Boffetta P (1999). Review of studies of selected metabolic polymorphisms and cancer. *IARC Sci Publ*, 148: 323–393. PMID:10493265

Dagle GE, McDonald KE, Smith LG, Stevens DL Jr (1978). Pulmonary carcinogenesis in rats given implants of cigarette smoke condensate in beeswax pellets. *J Natl Cancer Inst*, 61: 905–910. PMID:278868

Dalbey WE, Nettesheim P, Griesemer R *et al.* (1980). Chronic inhalation of cigarette smoke by F344 rats. *J Natl Cancer Inst*, 64: 383–390. PMID:6928229

Daling JR, Madeleine MM, Johnson LG *et al.* (2005). Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *Int J Cancer*, 116: 606–616. doi:10.1002/ijc.21009 PMID:15825185

Daling JR, Sherman KJ, Hislop TG *et al.* (1992). Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol*, 135: 180–189. PMID:1311142

Dally H, Edler L, Jäger B *et al.* (2003). The *CYP3A4*1B* allele increases risk for small cell lung cancer: effect of gender and smoking dose. *Pharmacogenetics*, 13: 607–618. doi:10.1097/00008571-200310000-00004 PMID:14515059

Daniell HW (1988). Increased lymph node metastases at mastectomy for breast cancer associated with host obesity, cigarette smoking, age, and large tumor size. *Cancer*, 62: 429–435. doi:10.1002/1097-0142(19880715)62:2<429::AID-CNCR2820620230>3.0.CO;2-4 PMID:3383142

Daniell HW, Tam E, Filice A (1993). Larger axillary metastases in obese women and smokers with breast cancer–an influence by host factors on early tumor behavior. *Breast Cancer Res Treat*, 25: 193–201. doi:10.1007/BF00689833 PMID:8369520

Darby S, Hill D, Auvinen A *et al.* (2005). Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ*, 330: 223 doi:10.1136/bmj.38308.477650.63 PMID:15613366

Davies MJ, Turner JG, Vives-Bauza C, Rumsby PC (1999). Investigation of mutant frequency at the *HPRT* locus and changes in microsatellite sequences in healthy young adults. *Mutat Res*, 431: 317–323. PMID:10635997

Davis BR, Whitehead JK, Gill ME *et al.* (1975). Response of rat lung to inhaled tobacco smoke with or without prior exposure to 3,4-benzpyrene (BP) given by intratracheal instillation. *Br J Cancer*, 31: 469–484. PMID:1156528

Day GL, Blot WJ, Austin DF *et al.* (1993). Racial differences in risk of oral and pharyngeal cancer: alcohol, tobacco, and other determinants. *J Natl Cancer Inst*, 85: 465–473. doi:10.1093/jnci/85.6.465 PMID:8445674

de Klerk NH, Musk AW, Eccles JL *et al.* (1996). Exposure to crocidolite and the incidence of different histological types of lung cancer. *Occup Environ Med*, 53: 157–159. doi:10.1136/oem.53.3.157 PMID:8704855

De Stefani E, Boffetta P, Deneo-Pellegrini H *et al.* (2007). The effect of smoking and drinking in oral and pharyngeal cancers: a case-control study in Uruguay. *Cancer Lett*, 246: 282–289. doi:10.1016/j.canlet.2006.03.008 PMID:16624486

De Stefani E, Boffetta P, Oreggia F *et al.* (1998). Smoking patterns and cancer of the oral cavity and pharynx: a case-control study in Uruguay. *Oral Oncol*, 34: 340–346. doi:10.1016/S1368-8375(98)00014-1 PMID:9861338

De Stefani E, Correa P, Oreggia F *et al.* (1987). Risk factors for laryngeal cancer. *Cancer*, 60: 3087–3091. doi:10.1002/1097-0142(19871215)60:12<3087::AID-CNCR2820601238>3.0.CO;2-6 PMID:3677031

De Stefani E, Espasandin J, Ronco A *et al.* (1995). Tobacco smoking and the risk of non-melanoma skin cancer. *Tob Control*, 4(2): 175–179. PMCID: PMC1759430 doi:10.1136/tc.4.2.175

De Stefani E, Muñoz N, Estève J *et al.* (1990). Mate drinking, alcohol, tobacco, diet, and esophageal cancer in Uruguay. *Cancer Res*, 50: 426–431. PMID:2295081

De Stefani E, Oreggia F, Rivero S, Fierro L (1992). Hand-rolled cigarette smoking and risk of cancer of the mouth, pharynx, and larynx. *Cancer*, 70: 679–682. doi:10.1002/1097-0142(19920801)70:3<679::AID-CNCR2820700323>3.0.CO;2-Z PMID:1623483

Delaney JC & Essigmann JM (2008). Biological properties of single chemical-DNA adducts: a twenty year perspective. *Chem Res Toxicol*, 21: 232–252. doi:10.1021/tx700292a PMID:18072751

Delfino RJ, Smith C, West JG *et al.* (2000). Breast cancer, passive and active cigarette smoking and N-acetyltransferase 2 genotype. *Pharmacogenetics*, 10: 461–469. doi:10.1097/00008571-200007000-00009 PMID:10898115

DeMarini DM (2004). Genotoxicity of tobacco smoke and tobacco smoke condensate: a review. *Mutat Res*, 567: 447–474. doi:10.1016/j.mrrev.2004.02.001 PMID:15572290

DeMarini DM, Gudi R, Szkudlinska A *et al.* (2008). Genotoxicity of 10 cigarette smoke condensates in four test systems: comparisons between assays and condensates. *Mutat Res*, 650: 15–29. PMID:18006367

DeMarini DM, Shelton ML, Levine JG (1995). Mutation spectrum of cigarette smoke condensate in Salmonella: comparison to mutations in smoking-associated tumors. *Carcinogenesis*, 16: 2535–2542. doi:10.1093/carcin/16.10.2535 PMID:7586163

Department of Health and Human Services (2001). *Women and Smoking: A Report of the Surgeon General.* Washington: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Department of Health and Human Services (2004). *The Health Consequences of Smoking: A Report of the Surgeon General.* Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Devesa SS, Bray F, Vizcaino AP, Parkin DM (2005). International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer*, 117: 294–299. doi:10.1002/ijc.21183 PMID:15900604

Diergaarde B, Braam H, Vasen HF *et al.* (2007). Environmental factors and colorectal tumor risk in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol*, 5: 736–742. PMID:17544999

Diergaarde B, Vrieling A, van Kraats AA *et al.* (2003). Cigarette smoking and genetic alterations in sporadic colon carcinomas. *Carcinogenesis*, 24: 565–571. doi:10.1093/carcin/24.3.565 PMID:12663519

Dikshit RP & Kanhere S (2000). Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. *Int J Epidemiol*, 29: 609–614. doi:10.1093/ije/29.4.609 PMID:10922335

Dillner J, von Krogh G, Horenblas S, Meijer CJLM (2000). Etiology of squamous cell carcinoma of the penis. *Scand J Urol Nephrol Suppl*, 34: 189–193. doi:10.1080/00365590050509913 PMID:11144896

Ding L, Getz G, Wheeler DA *et al.* (2008). Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*, 455: 1069–1075. doi:10.1038/nature07423 PMID:18948947

Djordjević D, Nikolić J, Stefanović V (1998). Ethanol interactions with other cytochrome P450 substrates including drugs, xenobiotics, and carcinogens. *Pathol Biol (Paris)*, 46: 760–770. PMID:9922992

Doll R, Gray R, Hafner B, Peto R (1980). Mortality in relation to smoking: 22 years' observations on female British doctors. *Br Med J*, 280: 967–971. doi:10.1136/bmj.280.6219.967 PMID:7417764

Doll R & Peto R (1978). Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Community Health*, 32: 303–313. doi:10.1136/jech.32.4.303 PMID:744822

Doll R, Peto R (1985). *Effects on health of exposure to asbestos*. London: Health and Safety Commission.

Doll R, Peto R, Boreham J, Sutherland I (2005). Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer*, 92: 426–429. PMID:15668706

Doll R, Peto R, Wheatley K *et al.* (1994). Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*, 309: 901–911. PMID:7755693

Dong LM, Potter JD, White E *et al.* (2008). Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. *JAMA*, 299: 2423–2436. doi:10.1001/jama.299.20.2423 PMID:18505952

Dontenwill W, Chevalier HJ, Harke HP *et al.* (1973). Investigations on the effects of chronic cigarette-smoke inhalation in Syrian golden hamsters. *J Natl Cancer Inst*, 51: 1781–1832. PMID:4765388

Dontenwill W, Chevalier HJ, Harke HP *et al.* (1977). Untersuchungen über den Effekt der chronischen Zigarettenrauchinhalation beim syrischen Goldhamster und über die Bedeutung des Vitamin A auf die bei Berauchung gefundenen Organveränderungen *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol*, 89: 153–180. doi:10.1007/BF00308516 PMID:143143

Du X, Squier CA, Kremer MJ, Wertz PW (2000). Penetration of N-nitrosonornicotine (NNN) across oral mucosa in the presence of ethanol and nicotine. *J Oral Pathol Med*, 29: 80–85. doi:10.1034/j.1600-0714.2000.290205.x PMID:10718403

Duell EJ, Holly EA, Bracci PM *et al.* (2002). A population-based, case-control study of polymorphisms in carcinogen-metabolizing genes, smoking, and pancreatic adenocarcinoma risk. *J Natl Cancer Inst*, 94: 297–306. PMID:11854392

Dunn SR, Simenhoff ML, Lele PS *et al.* (1990). *N*-nitrosodimethylamine blood levels in patients with chronic renal failure: modulation of levels by ethanol and ascorbic acid. *J Natl Cancer Inst*, 82: 783–787. doi:10.1093/jnci/82.9.783 PMID:2325149

Dusek L, Abrahamova J, Lakomy R *et al.* (2008). Multivariate analysis of risk factors for testicular cancer: a hospital-based case-control study in the Czech Republic. *Neoplasma*, 55: 356–368. PMID:18505349

Dyke GW, Craven JL, Hall R, Garner RC (1992). Smoking-related DNA adducts in human gastric cancers. *Int J Cancer*, 52: 847–850. doi:10.1002/ijc.2910520602 PMID:1459723

Egan KM, Newcomb PA, Titus-Ernstoff L *et al.* (2003). Association of NAT2 and smoking in relation to breast cancer incidence in a population-based case-control study (United States). *Cancer Causes Control*, 14: 43–51. doi:10.1023/A:1022517506689 PMID:12708724

Egan KM, Stampfer MJ, Hunter D *et al.*Nurses' Health Study (2002). Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study.*Epidemiology*,13:138–145.doi:10.1097/00001648-200203000-00007 PMID:11880753

Eichholzer M, Stähelin HB, Lüdin E, Bernasconi F (1999). Smoking, plasma vitamins C, E, retinol, and carotene, and fatal prostate cancer: seventeen-year follow-up of the prospective basel study. *Prostate*, 38: 189–198. doi:10.1002/(SICI)1097-0045(19990215)38:3<189::AID-PROS3>3.0.CO;2-N PMID:10068343

el-Bayoumy K (1992). Environmental carcinogens that may be involved in human breast cancer etiology. *Chem Res Toxicol*, 5: 585–590. doi:10.1021/tx00029a001 PMID:1445997

Eldridge SR, Gould MN, Butterworth BE (1992). Genotoxicity of environmental agents in human mammary epithelial cells. *Cancer Res*, 52: 5617–5621. PMID:1394185

Elliott EA, Matanoski GM, Rosenshein NB *et al.* (1990). Body fat patterning in women with endometrial cancer. *Gynecol Oncol*, 39: 253–258. doi:10.1016/0090-8258(90)90247-I PMID:2258066

Elwood JM, Pearson JC, Skippen DH, Jackson SM (1984). Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int J Cancer*, 34: 603–612. doi:10.1002/ijc.2910340504 PMID:6500740

Engeland A, Andersen A, Haldorsen T, Tretli S (1996). Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. *Cancer Causes Control*, 7: 497–506. doi:10.1007/BF00051881 PMID:8877046

Engels EA, Biggar RJ, Hall HI *et al.* (2008). Cancer risk in people infected with human immunodeficiency virus in the United States. *International Journal of Cancer*, 123: 187–194. doi:10.1002/ijc.23487

Epplein M, Schwartz SM, Potter JD, Weiss NS (2005). Smoking-adjusted lung cancer incidence among Asian-Americans (United States). *Cancer Causes Control*, 16: 1085–1090. doi:10.1007/s10552-005-0330-6 PMID:16184474

Erhardt JG, Kreichgauer HP, Meisner C *et al.* (2002). Alcohol, cigarette smoking, dietary factors and the risk of colorectal adenomas and hyperplastic polyps–a case control study. *Eur J Nutr*, 41: 35–43. doi:10.1007/s003940200004 PMID:11990006

Escribano Uzcudun A, Rabanal Retolaza I, García Grande A *et al.* (2002). Pharyngeal cancer prevention: evidence from a case–control study involving 232 consecutive patients. *J Laryngol Otol*, 116: 523–531. PMID:12238672

Ewertz M (1990). Smoking and breast cancer risk in Denmark. *Cancer Causes Control*, 1: 31–37. doi:10.1007/BF00053181 PMID:2102274

Ewertz M, Gillanders S, Meyer L, Zedeler K (1991). Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. *Int J Cancer*, 49: 526–530. doi:10.1002/ijc.2910490409 PMID:1917153

Falk RT, Pickle LW, Brown LM *et al.* (1989). Effect of smoking and alcohol consumption on laryngeal cancer risk in coastal Texas. *Cancer Res*, 49: 4024–4029. PMID:2736543

Falk RT, Pickle LW, Fontham ET *et al.* (1992). Epidemiology of bronchioloalveolar carcinoma. *Cancer Epidemiology, Biomarkers & Prevention*, 1: 339–344.

Falter B, Kutzer C, Richter E (1994). Biomonitoring of hemoglobin adducts: aromatic amines and tobacco-specific nitrosamines. *Clin Investig*, 72: 364–371. doi:10.1007/BF00252829 PMID:8086771

Favorito LA, Nardi AC, Ronalsa M *et al.* (2008). Epidemiologic study on penile cancer in Brazil. *Int Braz J Urol*, 34: 587–591, discussion 591–593. doi:10.1590/S1677-55382008000500007 PMID:18986562

Federal Trade Commission (2001). *Cigarette report for 1999*. C. Department. Washington D.C.

Feng BJ, Khyatti M, Ben-Ayoub W *et al.* (2009). Cannabis, tobacco and domestic fumes intake are associated with nasopharyngeal carcinoma in North Africa. *Br J Cancer*, 101: 1207–1212. doi:10.1038/sj.bjc.6605281 PMID:19724280

Fennell TR, MacNeela JP, Morris RW *et al.* (2000). Hemoglobin adducts from acrylonitrile and ethylene oxide in cigarette smokers: effects of *glutathione S-transferase T1*-null and *M1*-null genotypes. *Cancer Epidemiol Biomarkers Prev*, 9: 705–712. PMID:10919741

Fernberg P, Odenbro A, Bellocco R *et al.* (2007). Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: a nationwide cohort study in Sweden. *Cancer Res*, 67: 5983–5986. doi:10.1158/0008-5472.CAN-07-0274 PMID:17575169

Ferson M, Edwards A, Lind A *et al.* (1979). Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. *Int J Cancer*, 23: 603–609. doi:10.1002/ijc.2910230504 PMID:457307

Finch GL, Nikula KJ, Barr EB *et al.* (1995). *Effects of combined exposure of F344 rats to radiation and chronically inhaled cigarette smoke*. In: *Annual Report of the Inhalation Toxicology Research Institute. ITRI-149.* Bice DE, Hahn FF, Hoover R *et al.*,editors

Fine LJ, Philogene GS, Gramling R *et al.* (2004). Prevalence of multiple chronic disease risk factors. 2001 National Health Interview Survey. *Am J Prev Med*, 27: Suppl18–24. doi:10.1016/j.amepre.2004.04.017 PMID:15275670

Fink AK & Lash TL (2003). A null association between smoking during pregnancy and breast cancer using Massachusetts registry data (United States). *Cancer Causes Control*, 14: 497–503. doi:10.1023/A:1024922824237 PMID:12946045

Firozi PF, Bondy ML, Sahin AA *et al.* (2002). Aromatic DNA adducts and polymorphisms of *CYP1A1*, *NAT2*, and *GSTM1* in breast cancer. *Carcinogenesis*, 23: 301–306. doi:10.1093/carcin/23.2.301 PMID:11872636

Flanders WD, Lally CA, Zhu BP *et al.* (2003). Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption: results from Cancer Prevention Study II. *Cancer Res*, 63: 6556–6562. PMID:14559851

Folsom AR, Demissie Z, Harnack LIowa Women's Health Study (2003). Glycemic index, glycemic load, and incidence of endometrial cancer: the Iowa women's health study. *Nutr Cancer*, 46: 119–124. doi:10.1207/S15327914NC4602_03 PMID:14690786

Franceschi S, Barra S, La Vecchia C *et al.* (1992). Risk factors for cancer of the tongue and the mouth. A case-control study from northern Italy. *Cancer*, 70: 2227–2233. doi:10.1002/1097-0142(19921101)70:9<2227::AID-CNCR2820700902>3.0.CO;2-Z PMID:1394055

Franceschi S, Levi F, La Vecchia C *et al.* (1999). Comparison of the effect of smoking and alcohol drinking between oral and pharyngeal cancer. *Int J Cancer*, 83: 1–4. doi:10.1002/(SICI)1097-0215(19990924)83:1<1::AID-IJC1>3.0.CO;2-8 PMID:10449598

Franceschi S, Montella M, Polesel J *et al.* (2006). Hepatitis viruses, alcohol, and tobacco in the etiology of hepatocellular carcinoma in Italy. *Cancer Epidemiol Biomarkers Prev*, 15: 683–689. doi:10.1158/1055-9965.EPI-05-0702 PMID:16614109

Franceschi S & Serraino D (1992). Risk factors for adult soft tissue sarcoma in northern Italy. *Ann Oncol*, 3: Suppl 2S85–S88. PMID:1622876

Franceschi S, Talamini R, Barra S *et al.* (1990). Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx, and esophagus in northern Italy. *Cancer Res*, 50: 6502–6507. PMID:2208109

Franco EL, Villa LL, Sobrinho JP *et al.* (1999). Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis*, 180: 1415–1423. doi:10.1086/315086 PMID:10515798

Franks AL, Kendrick JS, Tyler CW Jr (1987). Postmenopausal smoking, estrogen replacement therapy, and the risk of endometrial cancer. *Am J Obstet Gynecol*, 156: 20–23. PMID:3799753

Freedman DM, Sigurdson A, Doody MM *et al.* (2003a). Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. *Cancer Causes Control*, 14: 847–857. doi:10.1023/B:CACO.0000003839.56954.73 PMID:14682442

Freedman DM, Sigurdson A, Doody MM *et al.* (2003b). Risk of basal cell carcinoma in relation to alcohol intake and smoking. *Cancer Epidemiol Biomarkers Prev*, 12: 1540–1543. PMID:14693751

Freedman ND, Abnet CC, Leitzmann MF *et al.* (2007a). Prospective investigation of the cigarette smoking-head and neck cancer association by sex. *Cancer*, 110: 1593–1601. doi:10.1002/cncr.22957 PMID:17724671

Freedman ND, Abnet CC, Leitzmann MF *et al.* (2007b). A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol*, 165: 1424–1433. doi:10.1093/aje/kwm051 PMID:17420181

Freedman ND, Leitzmann MF, Hollenbeck AR *et al.* (2008). Cigarette smoking and subsequent risk of lung

cancer in men and women: analysis of a prospective cohort study. *Lancet Oncol*, 9: 649–656. doi:10.1016/S1470-2045(08)70154-2 PMID:18556244

Friborg JT, Yuan JM, Wang R *et al.* (2007). A prospective study of tobacco and alcohol use as risk factors for pharyngeal carcinomas in Singapore Chinese. *Cancer*, 109: 1183–1191.

Friedman AJ, Ravnikar VA, Barbieri RL (1987). Serum steroid hormone profiles in postmenopausal smokers and nonsmokers. *Fertil Steril*, 47: 398–401. PMID:2951278

Fuchs CS, Colditz GA, Stampfer MJ *et al.* (1996). A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med*, 156: 2255–2260. doi:10.1001/archinte.156.19.2255 PMID:8885826

Fujino Y, Mizoue T, Tokui N *et al.*JACC Study Group (2005). Cigarette smoking and mortality due to stomach cancer: findings from the JACC Study. *J Epidemiol*, 15: Suppl 2S113–S119. doi:10.2188/jea.15.S113 PMID:16127222

Fujita M, Tase T, Kakugawa Y *et al.* (2008). Smoking, earlier menarche and low parity as independent risk factors for gynecologic cancers in Japanese: a case-control study. *Tohoku J Exp Med*, 216: 297–307. doi:10.1620/tjem.216.297 PMID:19060444

Fukuda K & Shibata A (1990). Exposure-response relationships between woodworking, smoking or passive smoking, and squamous cell neoplasms of the maxillary sinus. *Cancer Causes Control*, 1: 165–168. doi:10.1007/BF00053168 PMID:2102286

Furberg AS & Thune I (2003). Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. *Int J Cancer*, 104: 669–676. doi:10.1002/ijc.10974 PMID:12640672

Gaikwad NW, Yang L, Muti P *et al.* (2008). The molecular etiology of breast cancer: evidence from biomarkers of risk. *Int J Cancer*, 122: 1949–1957. PMID:18098283

Gajalakshmi CK & Shanta V (1996). Lifestyle and risk of stomach cancer: a hospital-based case-control study. *Int J Epidemiol*, 25: 1146–1153. doi:10.1093/ije/25.6.1146 PMID:9027518

Gajalakshmi V, Hung RJ, Mathew A *et al.* (2003). Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India. *Int J Cancer*, 107: 441–447. doi:10.1002/ijc.11377 PMID:14506745

Gallagher CJ, Muscat JE, Hicks AN *et al.* (2007). The UDP-glucuronosyltransferase 2B17 gene deletion polymorphism: sex-specific association with urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol glucuronidation phenotype and risk for lung cancer. *Cancer Epidemiol Biomarkers Prev*, 16: 823–828. doi:10.1158/1055-9965.EPI-06-0823 PMID:17416778

Gallicchio L, Boyd K, Matanoski G *et al.* (2008). Carotenoids and the risk of developing lung cancer: a systematic review. *Am J Clin Nutr*, 88: 372–383. PMID:18689373

Gallicchio L, Kouzis A, Genkinger JM *et al.* (2006). Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. *Prev Med*, 42: 200–205. doi:10.1016/j.ypmed.2005.12.014 PMID:16458957

Gallus S, Altieri A, Bosetti C *et al.* (2003a). Cigarette tar yield and risk of upper digestive tract cancers: case-control studies from Italy and Switzerland. *Ann Oncol*, 14: 209–213. doi:10.1093/annonc/mdg074 PMID:12562646

Gallus S, Bosetti C, Franceschi S *et al.* (2003b). Laryngeal cancer in women: tobacco, alcohol, nutritional, and hormonal factors. *Cancer Epidemiol Biomarkers Prev*, 12: 514–517. PMID:12814996

Gambier N, Batt AM, Marie B *et al.* (2005). Association of *CYP2A6*1B* genetic variant with the amount of smoking in French adults from the Stanislas cohort. *Pharmacogenomics J*, 5: 271–275. doi:10.1038/sj.tpj.6500314 PMID:15940289

Gammon MD, Eng SM, Teitelbaum SL *et al.* (2004). Environmental tobacco smoke and breast cancer incidence. *Environ Res*, 96: 176–185. doi:10.1016/j.envres.2003.08.009 PMID:15325878

Gammon MD, Schoenberg JB, Ahsan H *et al.* (1997). Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst*, 89: 1277–1284. doi:10.1093/jnci/89.17.1277 PMID:9293918

Gammon MD, Schoenberg JB, Teitelbaum SL *et al.* (1998). Cigarette smoking and breast cancer risk among young women (United States). *Cancer Causes Control*, 9: 583–590. doi:10.1023/A:1008868922799 PMID:10189043

Gandini S, Botteri E, Iodice S *et al.* (2008). Tobacco smoking and cancer: a meta-analysis. *International Journal of Cancer*, 122: 155–164. doi:10.1002/ijc.23033

Gao CM, Takezaki T, Wu JZ *et al.* (2007). CYP2E1 Rsa I polymorphism impacts on risk of colorectal cancer association with smoking and alcohol drinking. *World J Gastroenterol*, 13: 5725–5730. PMID:17963298

Gao YT, McLaughlin JK, Blot WJ *et al.* (1994). Risk factors for esophageal cancer in Shanghai, China. I. Role of cigarette smoking and alcohol drinking. *Int J Cancer*, 58: 192–196. doi:10.1002/ijc.2910580208 PMID:8026880

Gapstur SM, Gann PH, Lowe W *et al.* (2000). Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA*, 283: 2552–2558. doi:10.1001/jama.283.19.2552 PMID:10815119

García-Closas M, Malats N, Silverman D *et al.* (2005). NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet*, 366: 649–659. doi:10.1016/S0140-6736(05)67137-1 PMID:16112301

García-González MA, Lanas A, Quintero E *et al.*Spanish Gastroenterological Association AEG (2007). Gastric cancer susceptibility is not linked to pro-and anti-inflammatory cytokine gene polymorphisms in whites: a Nationwide Multicenter Study in Spain. *Am J Gastroenterol*, 102: 1878–1892. doi:10.1111/j.1572-0241.2007.01423.x PMID:17640324

Gargus JL, Powers MB, Habermann RT *et al.* (1976). *Mouse dermal bioassays of cigarette smoke condensates*. In: *Report No. 1. Toward Less Hazardous Cigarettes. The First Set of Experimental Cigarettes (DHEW Publ. No. (NIH)76–905).* Washington DC: Public Health Service, National Institutes of Health, National Cancer Institute, pp. 85–94.

Garrote LF, Herrero R, Reyes RM *et al.* (2001). Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. *Br J Cancer*, 85: 46–54. doi:10.1054/bjoc.2000.1825 PMID:11437401

Garte S (2001). Metabolic susceptibility genes as cancer risk factors: time for a reassessment? *Cancer Epidemiol Biomarkers Prev*, 10: 1233–1237. PMID:11751439

Garte S, Gaspari L, Alexandrie AK *et al.* (2001). Metabolic gene polymorphism frequencies in control populations. *Cancer Epidemiol Biomarkers Prev*, 10: 1239–1248. PMID:11751440

Garte S, Taioli E, Popov T *et al.* (2008). Genetic susceptibility to benzene toxicity in humans. *J Toxicol Environ Health A*, 71: 1482–1489. PMID:18836923

Gasper AV, Al-Janobi A, Smith JA *et al.* (2005). Glutathione S-transferase M1 polymorphism and metabolism of sulforaphane from standard and high-glucosinolate broccoli. *Am J Clin Nutr*, 82: 1283–1291. PMID:16332662

Ghadirian P, Lubinski J, Lynch H *et al.* (2004). Smoking and the risk of breast cancer among carriers of BRCA mutations. *Int J Cancer*, 110: 413–416. doi:10.1002/ijc.20106 PMID:15095307

Ghadirian P, Maisonneuve P, Perret C *et al.* (1998). Epidemiology of sociodemographic characteristics, lifestyle, medical history, and colon cancer: a case-control study among French Canadians in Montreal. *Cancer Detect Prev*, 22: 396–404. doi:10.1046/j.1525-1500.1998.00058.x PMID:9727620

Ginsburg O, Ghadirian P, Lubinski J *et al.*Hereditary Breast Cancer Clinical Study Group (2009). Smoking and the risk of breast cancer in BRCA1 and BRCA2 carriers: an update. *Breast Cancer Res Treat*, 114: 127–135. doi:10.1007/s10549-008-9977-5 PMID:18483851

Giovannucci E, Rimm EB, Stampfer MJ *et al.* (1994). A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. *J Natl Cancer Inst*, 86: 183–191. PMID:8283490

Giuliano AR, Sedjo RL, Roe DJ *et al.* (2002). Clearance of oncogenic human papillomavirus (HPV) infection: effect of smoking (United States). *Cancer Causes Control*, 13: 839–846. doi:10.1023/A:1020668232219 PMID:12462549

Glaser SL, Keegan TH, Clarke CA *et al.* (2004). Smoking and Hodgkin lymphoma risk in women United States. *Cancer Causes Control*, 15: 387–397.

Glatt H, Boeing H, Engelke CE *et al.* (2001). Human cytosolic sulphotransferases: genetics, characteristics, toxicological aspects. *Mutat Res*, 482: 27–40. PMID:11535246

Goldman R & Shields PG (1998). Molecular epidemiology of breast cancer. *In Vivo*, 12: 43–48. PMID:9575425

Gong Z, Xie D, Deng Z *et al.* (2005). The PPARgamma Pro12Ala polymorphism and risk for incident sporadic colorectal adenomas. *Carcinogenesis*, 26: 579–585. doi:10.1093/carcin/bgh343 PMID:15564289

González CA, Pera G, Agudo A *et al.* (2003). Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer*, 107: 629–634. doi:10.1002/ijc.11426 PMID:14520702

Goodman MT, Hankin JH, Wilkens LR *et al.* (1997). Diet, body size, physical activity, and the risk of endometrial cancer. *Cancer Res*, 57: 5077–5085. PMID:9371506

Goodman MT, McDuffie K, Kolonel LN *et al.* (2001). Case-control study of ovarian cancer and polymorphisms in genes involved in catecholestrogen formation and metabolism. *Cancer Epidemiol Biomarkers Prev*, 10: 209–216. PMID:11303589

Goodman MT & Tung KH (2003). Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States). *Cancer Causes Control*, 14: 569–577. doi:10.1023/A:1024828309874 PMID:12948288

Gori GB (1976). *Report on the second set of experimental cigarettes*. In: *Report No. 2. Toward Less Hazardous Cigarettes. The Second Set of Experimental Cigarettes (DHEW Publ. No. (NIH) 76–1111).* Washington DC: Public Health Service, National Institutes of Health, National Cancer Institute.

Gorlewska-Roberts K, Green B, Fares M *et al.* (2002). Carcinogen-DNA adducts in human breast epithelial cells. *Environ Mol Mutagen*, 39: 184–192. doi:10.1002/em.10060 PMID:11921188

Goy J, Rosenberg MW, King WD (2008). Health risk behaviors: examining social inequalities in bladder and colorectal cancers. *Ann Epidemiol*, 18: 156–162. PMID:18191762

Graham EA, Croninger AB, Wynder EL (1957). Experimental production of carcinoma with cigarette tar. IV. Successful experiments with rabbits. *Cancer Res*, 17: 1058–1066. PMID:13489709

Grainge MJ, West J, Solaymani-Dodaran M *et al.* (2009). The antecedents of biliary cancer: a primary care case-control study in the United Kingdom. *Br J Cancer*, 100: 178–180. doi:10.1038/sj.bjc.6604765 PMID:19018260

Gram IT, Braaten T, Adami HO *et al.* (2008). Cigarette smoking and risk of borderline and invasive epithelial ovarian cancer. *Int J Cancer*, 122: 647–652.

Gram IT, Braaten T, Lund E *et al.* (2009). Cigarette smoking and risk of colorectal cancer among Norwegian women. *Cancer Causes Control*, 20: 895–903. doi:10.1007/s10552-009-9327-x PMID:19274482

Gram IT, Braaten T, Terry PD *et al.* (2005). Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiol Biomarkers Prev*, 14: 61–66. PMID:15668477

Green A, Purdie D, Bain C *et al.* (2001). Cigarette smoking and risk of epithelial ovarian cancer (Australia). *Cancer Causes Control*, 12: 713–719. doi:10.1023/A:1011297403819 PMID:11562111

Greenland S & Longnecker MP (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol*, 135: 1301–1309. PMID:1626547

Griciute L, Castegnaro M, Bereziat JC (1981). Influence of ethyl alcohol on carcinogenesis with *N*-nitrosodimethylamine. *Cancer Lett*, 13: 345–352. doi:10.1016/0304-3835(81)90063-X PMID:7306961

Gronwald J, Byrski T, Huzarski T *et al.* (2006). Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. *Breast Cancer Res Treat*, 95: 105–109. doi:10.1007/s10549-005-9051-5 PMID:16261399

Gross CP, Filardo G, Singh HS *et al.* (2006). The relation between projected breast cancer risk, perceived cancer risk, and mammography use. Results from the National Health Interview Survey. *J Gen Intern Med*, 21: 158–164. PMID:16390511

Gudmundsdottir K, Tryggvadottir L, Eyfjord JE (2001). *GSTM1*, *GSTT1*, and *GSTP1* genotypes in relation to breast cancer risk and frequency of mutations in the *p53* gene. *Cancer Epidemiol Biomarkers Prev*, 10: 1169–1173. PMID:11700265

Guengerich FP (2001). Common and uncommon cytochrome P450 reactions related to metabolism and chemical toxicity. *Chem Res Toxicol*, 14: 611–650. doi:10.1021/tx0002583 PMID:11409933

Guengerich FP & Shimada T (1998). Activation of procarcinogens by human cytochrome P450 enzymes. *Mutat Res*, 400: 201–213. PMID:9685642

Guengerich FP, Shimada T, Yun CH *et al.* (1994). Interactions of ingested food, beverage, and tobacco components involving human cytochrome P4501A2, 2A6, 2E1, and 3A4 enzymes. *Environ Health Perspect*, 102: Suppl 949–53. PMID:7698084

Guillemette C (2003). Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. *Pharmacogenomics J*, 3: 136–158. doi:10.1038/sj.tpj.6500171 PMID:12815363

Gunnell AS, Tran TN, Torrång A *et al.* (2006). Synergy between cigarette smoking and human papillomavirus type 16 in cervical cancer in situ development. *Cancer Epidemiol Biomarkers Prev*, 15: 2141–2147. doi:10.1158/1055-9965.EPI-06-0399 PMID:17057029

Guo X, Johnson RC, Deng H *et al.* (2009). Evaluation of nonviral risk factors for nasopharyngeal carcinoma in a high-risk population of Southern China. *Int J Cancer*, 124: 2942–2947. doi:10.1002/ijc.24293 PMID:19296536

Gupta D, Boffetta P, Gaborieau V, Jindal SK (2001). Risk factors of lung cancer in Chandigarh, India. *Indian J Med Res*, 113: 142–150. PMID:11558323

Gupta MP, Khanduja KL, Koul IB, Sharma RR (1990). Effect of cigarette smoke inhalation on benzo[a]pyrene-induced lung carcinogenesis in vitamin A deficiency in the rat. *Cancer Lett*, 55: 83–88. doi:10.1016/0304-3835(90)90015-P PMID:2265418

Ha M, Mabuchi K, Sigurdson AJ *et al.* (2007). Smoking cigarettes before first childbirth and risk of breast cancer. *Am J Epidemiol*, 166: 55–61. doi:10.1093/aje/kwm045 PMID:17426039

Haiman CA, Stram DO, Wilkens LR *et al.* (2006). Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med*, 354: 333–342.

Hamajima N, Hirose K, Tajima K *et al.*Collaborative Group on Hormonal Factors in Breast Cancer (2002). Alcohol, tobacco and breast cancer–collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*, 87: 1234–1245. doi:10.1038/sj.bjc.6600596 PMID:12439712

Hammond EC & Horn D (1958). Smoking and death rates: report on forty-four months of follow-up of 187,783 men. 2. Death rates by cause. *J Am Med Assoc*, 166: 1294–1308. PMID:12308037

Hammond EC & Seidman H (1980). Smoking and cancer in the United States. *Prev Med*, 9: 169–174. doi:10.1016/0091-7435(80)90071-7 PMID:7383981

Hammond EC, Selikoff IJ, Seidman H (1979). Asbestos exposure, cigarette smoking and death rates. *Ann N Y Acad Sci*, 330: 1 Health Hazard473–490. doi:10.1111/j.1749-6632.1979.tb18749.x PMID:294198

Hanaoka T, Yamamoto S, Sobue T *et al.*Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Study Group (2005). Active and passive smoking and breast cancer risk in middle-aged Japanese women. *Int J Cancer*, 114: 317–322. doi:10.1002/ijc.20709 PMID:15540214

Hannan LM, Jacobs EJ, Thun MJ (2009). The association between cigarette smoking and risk of colorectal cancer in a large prospective cohort from the United States. *Cancer Epidemiol Biomarkers Prev*, 18: 3362–3367. doi:10.1158/1055-9965.EPI-09-0661 PMID:19959683

Hansen AM, Mathiesen L, Pedersen M, Knudsen LE (2008). Urinary 1-hydroxypyrene (1-HP) in environmental and occupational studies–a review. *Int J Hyg Environ Health*, 211: 471–503. doi:10.1016/j.ijheh.2007.09.012 PMID:18222724

Hansen RD, Krath BN, Frederiksen K *et al.* (2009). GPX1 Pro(198)Leu polymorphism, erythrocyte GPX activity, interaction with alcohol consumption and smoking,

and risk of colorectal cancer. *Mutat Res*, 664: 13–19. PMID:19428376

Harada T, Kitazawa T, Maita K, Shirasu Y (1985). Effects of vitamin C on tumor induction by diethylnitrosamine in the respiratory tract of hamsters exposed to cigarette smoke. *Cancer Lett*, 26: 163–169. doi:10.1016/0304-3835(85)90022-9 PMID:3978606

Harish K & Ravi R (1995). The role of tobacco in penile carcinoma. *Br J Urol*, 75: 375–377.

Harris JE, Thun MJ, Mondul AM, Calle EE (2004). Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982–1998. *BMJ (Clinical Research Ed.)*, 328: 72–78. doi:10.1136/bmj.37936.585382.44

Harris RJ & Negroni G (1967). Production of lung carcinomas in C57BL mice exposed to a cigarette smoke and air mixture. *Br Med J*, 4: 637–641. doi:10.1136/bmj.4.5580.637 PMID:4293822

Harris RJ, Negroni G, Ludgate S *et al.* (1974). The incidence of lung tumours in c57bl mice exposed to cigarette smoke: air mixtures for prolonged periods. *Int J Cancer*, 14: 130–136. doi:10.1002/ijc.2910140116 PMID:4617705

Hartge P, Schiffman MH, Hoover R *et al.* (1989). A case-control study of epithelial ovarian cancer. *Am J Obstet Gynecol*, 161: 10–16. PMID:2750791

Hashibe M, Boffetta P, Janout V *et al.* (2007a). Esophageal cancer in Central and Eastern Europe: tobacco and alcohol. *Int J Cancer*, 120: 1518–1522. doi:10.1002/ijc.22507 PMID:17205526

Hashibe M, Boffetta P, Zaridze D *et al.* (2007b). Contribution of tobacco and alcohol to the high rates of squamous cell carcinoma of the supraglottis and glottis in Central Europe. *Am J Epidemiol*, 165: 814–820. doi:10.1093/aje/kwk066 PMID:17244634

Hashibe M, Brennan P, Benhamou S *et al.* (2007c). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst*, 99: 777–789. doi:10.1093/jnci/djk179 PMID:17505073

Hashibe M, Brennan P, Chuang SC *et al.* (2009). Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev*, 18: 541–550. doi:10.1158/1055-9965.EPI-08-0347 PMID:19190158

Hassan MM, Phan A, Li D *et al.* (2008b). Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study. *Int J Cancer*, 123: 867–873. doi:10.1002/ijc.23529 PMID:18491401

Hassan MM, Spitz MR, Thomas MB *et al.* (2008a). Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *Int J Cancer*, 123: 1883–1891. doi:10.1002/ijc.23730 PMID:18688864

Hatsukami DK, Benowitz NL, Rennard SI *et al.* (2006a). Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine Tob Res*, 8: 600–622. PMID:16920658

Hatsukami DK, Le CT, Zhang Y *et al.* (2006b). Toxicant exposure in cigarette reducers versus light smokers. *Cancer Epidemiol Biomarkers Prev*, 15: 2355–2358. doi:10.1158/1055-9965.EPI-06-0240 PMID:17164356

Hatsukami DK, Lemmonds C, Zhang Y *et al.* (2004). Evaluation of carcinogen exposure in people who used "reduced exposure" tobacco products. *J Natl Cancer Inst*, 96: 844–852. PMID:15173268

Hawkins NJ & Ward RL (2001). Sporadic colorectal cancers with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. *J Natl Cancer Inst*, 93: 1307–1313. PMID:11535705

Hayes JR, Meckley DR, Stavanja MS *et al.* (2007). Effect of a flue-curing process that reduces tobacco specific nitrosamines on the tumor promotion in SENCAR mice by cigarette smoke condensate. *Food Chem Toxicol*, 45: 419–430. doi:10.1016/j.fct.2006.08.024 PMID:17070977

Hayes RB, Bravo-Otero E, Kleinman DV *et al.* (1999). Tobacco and alcohol use and oral cancer in Puerto Rico. *Cancer Causes Control*, 10: 27–33. doi:10.1023/A:1008876115797 PMID:10334639

Hayes RB, Kardaun JW, de Bruyn A (1987). Tobacco use and sinonasal cancer: a case-control study. *Br J Cancer*, 56: 843–846. PMID:3435710

Hecht SS (1998). Biochemistry, biology, and carcinogenicity of tobacco-specific *N*-nitrosamines. *Chem Res Toxicol*, 11: 559–603. doi:10.1021/tx980005y PMID:9625726

Hecht SS (1999). Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst*, 91: 1194–1210. doi:10.1093/jnci/91.14.1194 PMID:10413421

Hecht SS (2000). Inhibition of carcinogenesis by isothiocyanates. *Drug Metab Rev*, 32: 395–411. doi:10.1081/DMR-100102342 PMID:11139137

Hecht SS (2002). Human urinary carcinogen metabolites: biomarkers for investigating tobacco and cancer. *Carcinogenesis*, 23: 907–922. doi:10.1093/carcin/23.6.907 PMID:12082012

Hecht SS (2003). Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nat Rev Cancer*, 3: 733–744. doi:10.1038/nrc1190 PMID:14570033

Hecht SS (2008). Progress and challenges in selected areas of tobacco carcinogenesis. *Chem Res Toxicol*, 21: 160–171. doi:10.1021/tx7002068 PMID:18052103

Hecht SS, Carmella SG, Edmonds A *et al.* (2008b). Exposure to nicotine and a tobacco-specific carcinogen increase with duration of use of smokeless tobacco. *Tob Control*, 17: 128–131. doi:10.1136/tc.2007.023242 PMID:18375734

Hecht SS, Carmella SG, Murphy SE *et al.* (2007). Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers. *Cancer Epidemiol*

Biomarkers Prev, 16: 1567–1572. doi:10.1158/1055-9965.EPI-07-0227 PMID:17684130

Hecht SS, Carmella SG, Stepanov I *et al.* (2008a). Metabolism of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone to its biomarker total NNAL in smokeless tobacco users. *Cancer Epidemiol Biomarkers Prev*, 17: 732–735. doi:10.1158/1055-9965.EPI-07-2843 PMID:18349296

Hecht SS, Carmella SG, Ye M *et al.* (2002). Quantitation of metabolites of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone after cessation of smokeless tobacco use. *Cancer Res*, 62: 129–134. PMID:11782369

Hecht SS, Carmella SG, Yoder A *et al.* (2006). Comparison of polymorphisms in genes involved in polycyclic aromatic hydrocarbon metabolism with urinary phenanthrene metabolite ratios in smokers. *Cancer Epidemiol Biomarkers Prev*, 15: 1805–1811. doi:10.1158/1055-9965.EPI-06-0173 PMID:17035385

Hecht SS, Chen M, Yoder A *et al.* (2005a). Longitudinal study of urinary phenanthrene metabolite ratios: effect of smoking on the diol epoxide pathway. *Cancer Epidemiol Biomarkers Prev*, 14: 2969–2974. doi:10.1158/1055-9965.EPI-05-0396 PMID:16365018

Hecht SS & Hoffmann D (1988). Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. *Carcinogenesis*, 9: 875–884. doi:10.1093/carcin/9.6.875 PMID:3286030

Hecht SS, Murphy SE, Carmella SG *et al.* (2004). Effects of reduced cigarette smoking on the uptake of a tobacco-specific lung carcinogen. *J Natl Cancer Inst*, 96: 107–115. PMID:14734700

Hecht SS, Murphy SE, Carmella SG *et al.* (2005b). Similar uptake of lung carcinogens by smokers of regular, light, and ultralight cigarettes. *Cancer Epidemiol Biomarkers Prev*, 14: 693–698. doi:10.1158/1055-9965.EPI-04-0542 PMID:15767351

Hecht SS, Rivenson A, Braley J *et al.* (1986). Induction of oral cavity tumors in F344 rats by tobacco-specific nitrosamines and snuff. *Cancer Res*, 46: 4162–4166. PMID:3731083

Hedberg K, Vaughan TL, White E *et al.* (1994). Alcoholism and cancer of the larynx: a case-control study in western Washington (United States). *Cancer Causes Control*, 5: 3–8. doi:10.1007/BF01830720 PMID:8123776

Heeschen C, Jang JJ, Weis M *et al.* (2001). Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. *Nat Med*, 7: 833–839. doi:10.1038/89961 PMID:11433349

Hein DW (2002). Molecular genetics and function of NAT1 and NAT2: role in aromatic amine metabolism and carcinogenesis. *Mutat Res*, 506–507: 65–77. PMID:12351146

Hein DW (2006). *N*-acetyltransferase 2 genetic polymorphism: effects of carcinogen and haplotype on urinary bladder cancer risk. *Oncogene*, 25: 1649–1658. doi:10.1038/sj.onc.1209374 PMID:16550165

Heineman EF, Zahm SH, McLaughlin JK, Vaught JB (1994). Increased risk of colorectal cancer among smokers: results of a 26-year follow-up of US veterans and a review. *Int J Cancer*, 59: 728–738. doi:10.1002/ijc.2910590603 PMID:7989109

Heling A-K, Schutte-Borkovec K, Heppel C *et al.* (2008). *Pyridyloxobutylated DNA adducts in oral mucosa of nonsmokers, smokers and snuff dippers in relation to other biomarkers of exposure*. AACR Meeting Abstracts, April 2008, Abstract 1883

Hellberg D & Stendahl U (2005). The biological role of smoking, oral contraceptive use and endogenous sexual steroid hormones in invasive squamous epithelial cervical cancer. *Anticancer Res*, 25: 3041–3046. PMID:16080563

Hellberg D, Valentin J, Eklund T, Nilsson S (1987). Penile cancer: is there an epidemiological role for smoking and sexual behaviour? *Br Med J (Clin Res Ed)*, 295: 1306–1308. doi:10.1136/bmj.295.6609.1306 PMID:3120988

Hemminki K, Koskinen M, Zhao C (2001). DNA adducts as a marker for cancer risk? *Int J Cancer*, 92: 923–925. doi:10.1002/ijc.1273 PMID:11351318

Henderson BE, Louie E, SooHoo Jing J *et al.* (1976). Risk factors associated with nasopharyngeal carcinoma. *N Engl J Med*, 295: 1101–1106. PMID:980005

Henley SJ, Thun MJ, Chao A, Calle EE (2004). Association between exclusive pipe smoking and mortality from cancer and other diseases. *J Natl Cancer Inst*, 96: 853–861. doi:10.1093/jnci/djh144 PMID:15173269

Henry CJ & Kouri RE (1986). Chronic inhalation studies in mice. II. Effects of long-term exposure to 2R1 cigarette smoke on (C57BL/Cum x C3H/AnfCum)F1 mice. *J Natl Cancer Inst*, 77: 203–212. PMID:3459913

Herity B, Moriarty M, Daly L *et al.* (1982). The role of tobacco and alcohol in the aetiology of lung and larynx cancer. *Br J Cancer*, 46: 961–964. PMID:7150489

Hermann S, Rohrmann S, Linseisen J (2009). *Lifestyle factors, obesity and the risk of colorectal adenomas in EPIC-Heidelberg*. Cancer Causes Control.

Herrinton LJ & Friedman GD (1998). Cigarette smoking and risk of non-Hodgkin's lymphoma subtypes. *Cancer Epidemiol Biomarkers Prev*, 7: 25–28. PMID:9456239

Hickey K, Do KA, Green A (2001). Smoking and prostate cancer. *Epidemiol Rev*, 23: 115–125. PMID:11588835

Hill M (1978). Etiology of the adenoma-carcinoma sequence. *Major Probl Pathol*, 10: 153–162. PMID:616868

Hjalgrim H, Ekström-Smedby K, Rostgaard K *et al.* (2007). Cigarette smoking and risk of Hodgkin lymphoma: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*, 16: 1561–1566.

Ho JW, Lam TH, Tse CW *et al.* (2004). Smoking, drinking and colorectal cancer in Hong Kong Chinese: a case-control study. *Int J Cancer*, 109: 587–597. doi:10.1002/ijc.20018 PMID:14991582

Hoffmann D & Brunnemann KD (1983). Endogenous formation of *N*-nitrosoproline in cigarette smokers. *Cancer Res*, 43: 5570–5574. PMID:6616484

Hoffmann D, Hoffmann I, El-Bayoumy K (2001). The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. *Chem Res Toxicol*, 14: 767–790. doi:10.1021/tx000260u PMID:11453723

Hoffmann D, Rivenson A, Hecht SS *et al.* (1979). Model studies in tobacco carcinogenesis with the Syrian golden hamster. *Prog Exp Tumor Res*, 24: 370–390. PMID:395571

Hoffmann D & Wynder EL (1971). A study of tobacco carcinogenesis. XI. Tumor initiators, tumor accelerators, and tumor promoting activity of condensate fractions. *Cancer*, 27: 848–864. doi:10.1002/1097-0142(197104)27:4<848::AID-CNCR2820270415>3.0.CO;2-4 PMID:5574075

Holmes MD, Murin S, Chen WY *et al.* (2007). Smoking and survival after breast cancer diagnosis. *Int J Cancer*, 120: 2672–2677. doi:10.1002/ijc.22575 PMID:17278091

Homann N, Tillonen J, Meurman JH *et al.* (2000). Increased salivary acetaldehyde levels in heavy drinkers and smokers: a microbiological approach to oral cavity cancer. *Carcinogenesis*, 21: 663–668. doi:10.1093/carcin/21.4.663 PMID:10753201

Horn-Ross PL, Ljung BM, Morrow M (1997). Environmental factors and the risk of salivary gland cancer. *Epidemiology*, 8: 414–419. doi:10.1097/00001648-199707000-00011 PMID:9209856

Hosgood HD 3rd, Zhang L, Shen M *et al.* (2009). Association between genetic variants in *VEGF*, *ERCC3* and occupational benzene haematotoxicity. *Occup Environ Med*, 66: 848–853. PMID:19773279

Hoshiyama Y, Kono S, Sasaba T *et al.* (2000). Relation of Cigarette Smoking, Alcohol Use, and Dietary Habits to Colon Adenomas: A Case-Control Study in Saitama, Japan. *Asian Pac J Cancer Prev*, 1: 139–146. PMID:12718681

Houlston RS (1999). Glutathione *S*-transferase M1 status and lung cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 8: 675–682. PMID:10744127

Houlston RS (2000). *CYP1A1* polymorphisms and lung cancer risk: a meta-analysis. *Pharmacogenetics*, 10: 105–114. doi:10.1097/00008571-200003000-00002 PMID:10761998

Hsing AW, McLaughlin JK, Chow WH *et al.* (1998). Risk factors for colorectal cancer in a prospective study among U.S. white men. *Int J Cancer*, 77: 549–553. doi:10.1002/(SICI)1097-0215(19980812)77:4<549::AID-IJC13>3.0.CO;2-1 PMID:9679757

Hsing AW, Nam JM, Co Chien HT *et al.* (1996). Risk factors for adrenal cancer: an exploratory study. *Int J Cancer*, 65: 432–436. doi:10.1002/(SICI)1097-0215(19960208)65:4<432::AID-IJC6>3.0.CO;2-Y PMID:8621222

Hsu WL, Chen JY, Chien YC *et al.* (2009). Independent effect of EBV and cigarette smoking on nasopharyngeal carcinoma: a 20-year follow-up study on 9,622 males without family history in Taiwan. *Cancer Epidemiol Biomarkers Prev*, 18: 1218–1226. doi:10.1158/1055-9965.EPI-08-1175 PMID:19336547

Hu J, Morrison H, Mery L *et al.*Canadian Cancer Registries Epidemiology Research Group (2007). Diet and vitamin or mineral supplementation and risk of colon cancer by subsite in Canada. *Eur J Cancer Prev*, 16: 275–291. doi:10.1097/01.cej.0000228411.21719.25 PMID:17554200

Hu J & Ugnat AMCanadian Cancer Registries Epidemiology Research Group (2005). Active and passive smoking and risk of renal cell carcinoma in Canada. *Eur J Cancer*, 41: 770–778. doi:10.1016/j.ejca.2005.01.003 PMID:15763654

Hukkanen J, Jacob P 3rd, Benowitz NL (2005). Metabolism and disposition kinetics of nicotine. *Pharmacol Rev*, 57: 79–115. doi:10.1124/pr.57.1.3 PMID:15734728

Huncharek M, Haddock KS, Reid R, Kupelnick B (2010). Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health*, 100: 693–701. doi:10.2105/AJPH.2008.150508 PMID:19608952

Hung HC, Chuang J, Chien YC *et al.* (1997). Genetic polymorphisms of CYP2E1, GSTM1, and GSTT1; environmental factors and risk of oral cancer. *Cancer Epidemiol Biomarkers Prev*, 6: 901–905.

Hung RJ, Christiani DC, Risch A *et al.* (2008a). International lung cancer consortium: pooled analysis of sequence variants in DNA repair and cell cycle pathways. *Cancer Epidemiology, Biomarkers & Prevention*, 17: 3081–3089. doi:10.1158/1055-9965.EPI-08-0411

Hung RJ, McKay JD, Gaborieau V *et al.* (2008). A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature*, 452: 633–637. doi:10.1038/nature06885 PMID:18385738

Hung RJ, McKay JD, Gaborieau V *et al.* (2008b). A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature*, 452: 633–637. doi:10.1038/nature06885 PMID:18385738

Hunt JD, van der Hel OL, McMillan GP *et al.* (2005). Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. *Int J Cancer*, 114: 101–108. doi:10.1002/ijc.20618 PMID:15523697

Hunter DJ, Hankinson SE, Hough H *et al.* (1997). A prospective study of *NAT2* acetylation genotype, cigarette smoking, and risk of breast cancer. *Carcinogenesis*, 18: 2127–2132. doi:10.1093/carcin/18.11.2127 PMID:9395212

Husgafvel-Pursiainen K (2004). Genotoxicity of environmental tobacco smoke: a review. *Mutat Res*, 567: 427–445. doi:10.1016/j.mrrev.2004.06.004 PMID:15572289

Hutt JA, Vuillemenot BR, Barr EB *et al.* (2005). Life-span inhalation exposure to mainstream cigarette smoke

induces lung cancer in B6C3F1 mice through genetic and epigenetic pathways. *Carcinogenesis*, 26: 1999–2009. doi:10.1093/carcin/bgi150 PMID:15944214

Huusom LD, Frederiksen K, Høgdall EV *et al.* (2006). Association of reproductive factors, oral contraceptive use and selected lifestyle factors with the risk of ovarian borderline tumors: a Danish case-control study. *Cancer Causes Control*, 17: 821–829. doi:10.1007/s10552-006-0022-x PMID:16783610

Huxley R; Asia Pacific Cohort Studies Collaboration (2007a). The role of lifestyle risk factors on mortality from colorectal cancer in populations of the Asia-Pacific region. *Asian Pac J Cancer Prev*, 8: 191–198. PMID:17696730

Huxley R, Jamrozik K, Lam TH *et al.*Asia Pacific Cohort Studies Collaboration (2007b). Impact of smoking and smoking cessation on lung cancer mortality in the Asia-Pacific region. *Am J Epidemiol*, 165: 1280–1286. doi:10.1093/aje/kwm002 PMID:17369610

Huxley RR, Ansary-Moghaddam A, Clifton P *et al.* (2009). The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. *Int J Cancer*, 125: 171–180. doi:10.1002/ijc.24343 PMID:19350627

Hymowitz N, Corle D, Royce J *et al.* (1995). Smokers' baseline characteristics in the COMMIT trial. *Prev Med*, 24: 503–508. doi:10.1006/pmed.1995.1080 PMID:8524726

IARC (1986). Tobacco smoking. *IARC Monogr Eval Carcinog Risk Chem Hum*, 38: 1–421.

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203

IARC (1995). Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum*, 64: 1–378. PMID:16755705

IARC (2002). *IARC handbook of cancer prevention, vol. 6. Weight control and physical activity*. IARC Press, Lyon: International Agency for Research on Cancer

IARC (2004a). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, 83: 1–1438. PMID:15285078

IARC (2004b). Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. *IARC Monogr Eval Carcinog Risks Hum*, 85: 1–334. PMID:15635762

IARC (2006a). Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. *IARC Monogr Eval Carcinog Risks Hum*, 88: 1–478. PMID:17366697

IARC (2006b). *TP53 mutation database*. http://www.p53.iarc.fr/index.htlm.

IARC (2007a). Smokeless tobacco and some tobacco-specific N-nitrosamines. *IARC Monogr Eval Carcinog Risks Hum*, 89: 1–592. PMID:18335640

IARC (2007b). Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum*, 90: 1–636. PMID:18354839

IARC (2007c). Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. *IARC Monogr Eval Carcinog Risks Hum*, 91: 1–528. PMID:18756632

IARC (2008). 1,3-Butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). *IARC Monogr Eval Carcinog Risks Hum*, 97: 1–510.

IARC (2010a). Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum*, 96: 1–1428.

IARC (2010b). Some Aromatic Amines, Organic Dyes, and Related Exposures *IARC Monogr Eval Carcinog Risks Hum*, 99: 1–692.

IARC (2012c). Pharmaceuticals. *IARC Monogr Eval Carcinog Risks Hum*, 100A: 1–437. PMID:18335640

IARC (2012b). Biological agents. *IARC Monogr Eval Carcinog Risks Hum*, 100B: 1–475. PMID:18335640

IARC (2012a). Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum*, 100F: PMID:18335640

Iarmarcovai G, Bonassi S, Botta A *et al.* (2008). Genetic polymorphisms and micronucleus formation: a review of the literature. *Mutat Res*, 658: 215–233. doi:10.1016/j.mrrev.2007.10.001 PMID:18037339

Ide R, Mizoue T, Fujino Y *et al.*JACC Study Group (2008). Cigarette smoking, alcohol drinking, and oral and pharyngeal cancer mortality in Japan. *Oral Dis*, 14: 314–319. doi:10.1111/j.1601-0825.2007.01378.x PMID:18449960

Iguchi T, Sugita S, Wang CY *et al.* (2009). MnSOD genotype and prostate cancer risk as a function of NAT genotype and smoking status. *In Vivo*, 23: 7–12. PMID:19368118

IIPS; International Institute for Population Sciences (2010).* *Mumbai and Ministry of Health and Family Welfare, Government of India. Global Adult Tobacco Survey India (GATS India)*. New Delhi, India: Ministry of Health and Family Welfare, Government of India

Ingelman-Sundberg M (2004). Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms. *Naunyn Schmiedebergs Arch Pharmacol*, 369: 89–104. doi:10.1007/s00210-003-0819-z PMID:14574440

Ingelman-Sundberg M (2005). Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J*, 5: 6–13. doi:10.1038/sj.tpj.6500285 PMID:15492763

Ingelman-Sundberg M, Ronis MJ, Lindros KO *et al.* (1994). Ethanol-inducible cytochrome P4502E1: regulation, enzymology and molecular biology. *Alcohol Alcohol Suppl*, 2: 131–139. PMID:8974327

Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C (2007). Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther*, 116: 496–526. doi:10.1016/j.pharmthera.2007.09.004 PMID:18001838

Innes KE & Byers TE (2001). Smoking during pregnancy and breast cancer risk in very young women (United States). *Cancer Causes Control*, 12: 179–185. doi:10.1023/A:1008961512841 PMID:11246847

Inoue H, Kiyohara C, Marugame T *et al.* (2000). Cigarette smoking, CYP1A1 MspI and GSTM1 genotypes, and colorectal adenomas. *Cancer Res*, 60: 3749–3752. PMID:10919645

Inoue M, Tajima K, Takezaki T *et al.* (2003). Epidemiology of pancreatic cancer in Japan: a nested case-control study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). *Int J Epidemiol*, 32: 257–262. doi:10.1093/ije/dyg062 PMID:12714546

Ioannidis JP (2008). Calibration of credibility of agnostic genome-wide associations. *Am J Med Genet B Neuropsychiatr Genet*, 147B: 964–972. PMID:18361430

Iodice S, Gandini S, Maisonneuve P, Lowenfels AB (2008). Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg*, 393: 535–545. doi:10.1007/s00423-007-0266-2 PMID:18193270

Iribarren C, Tekawa IS, Sidney S, Friedman GD (1999). Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. *N Engl J Med*, 340: 1773–1780. doi:10.1056/NEJM199906103402301 PMID:10362820

Isaksson B, Jonsson F, Pedersen NL *et al.* (2002). Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*, 98: 480–482. doi:10.1002/ijc.10256 PMID:11920604

Izzotti A, Calin GA, Arrigo P *et al.* (2009). Downregulation of microRNA expression in the lungs of rats exposed to cigarette smoke. *FASEB J*, 23: 806–812. doi:10.1096/fj.08-121384 PMID:18952709

Jacob P 3rd, Wilson M, Benowitz NL (2007). Determination of phenolic metabolites of polycyclic aromatic hydrocarbons in human urine as their pentafluorobenzyl ether derivatives using liquid chromatography-tandem mass spectrometry. *Anal Chem*, 79: 587–598. doi:10.1021/ac060920l PMID:17222024

Jain MG, Howe GR, Rohan TE (2000). Nutritional factors and endometrial cancer in Ontario, Canada. *Cancer Control*, 7: 288–296. PMID:10832115

Jalas JR, Hecht SS, Murphy SE (2005). Cytochrome P450 enzymes as catalysts of metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco specific carcinogen. *Chem Res Toxicol*, 18: 95–110. doi:10.1021/tx049847p PMID:15720112

Jass JR (2007). Molecular heterogeneity of colorectal cancer: Implications for cancer control. *Surg Oncol*, 16: Suppl 1S7–S9. doi:10.1016/j.suronc.2007.10.039 PMID:18023574

Jass JR, Young J, Leggett BA (2000). Hyperplastic polyps and DNA microsatellite unstable cancers of the colorectum. *Histopathology*, 37: 295–301. PMID:11012735

Jayalekshmy PA, Akiba S, Nair MK *et al.* (2008). Bidi smoking and lung cancer incidence among males in Karunagappally cohort in Kerala, India. *Int J Cancer*, 123: 1390–1397. doi:10.1002/ijc.23618 PMID:18623085

Jean RT, Wilkinson AV, Spitz MR *et al.* (2011). Psychosocial risk and correlates of early menarche in Mexican-American girls. *Am J Epidemiol*, 173: 1203–1210. Epub 2011 Mar 31.

Jee SH, Samet JM, Ohrr H *et al.* (2004). Smoking and cancer risk in Korean men and women. *Cancer Causes Control*, 15:341–348.doi:10.1023/B:CACO.0000027481.48153.97 PMID:15141135

Jeffreys M, Warren R, Gunnell D *et al.* (2004). Life course breast cancer risk factors and adult breast density (United Kingdom). *Cancer Causes Control*, 15: 947–955. PMID:15577297

Jensen J & Christiansen C (1988). Effects of smoking on serum lipoproteins and bone mineral content during postmenopausal hormone replacement therapy. *Am J Obstet Gynecol*, 159: 820–825. PMID:2972209

Jensen J, Christiansen C, Rødbro P (1985). Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. *N Engl J Med*, 313: 973–975. doi:10.1056/NEJM198510173131602 PMID:4047104

Ji BT, Dai Q, Gao YT *et al.* (2002). Cigarette and alcohol consumption and the risk of colorectal cancer in Shanghai, China. *Eur J Cancer Prev*, 11: 237–244. doi:10.1097/00008469-200206000-00007 PMID:12131657

Ji BT, Weissfeld JL, Chow WH *et al.* (2006). Tobacco smoking and colorectal hyperplastic and adenomatous polyps. *Cancer Epidemiol Biomarkers Prev*, 15: 897–901. doi:10.1158/1055-9965.EPI-05-0883 PMID:16702367

Jiang J, Suzuki S, Xiang J *et al.* (2005). Plasma carotenoid, alpha-tocopherol and retinol concentrations and risk of colorectal adenomas: A case-control study in Japan. *Cancer Lett*, 226: 133–141. doi:10.1016/j.canlet.2005.03.040 PMID:15885891

Jin MJ, Chen K, Song L *et al.* (2005). The association of the DNA repair gene XRCC3 Thr241Met polymorphism with susceptibility to colorectal cancer in a Chinese population. *Cancer Genet Cytogenet*, 163: 38–43. doi:10.1016/j.cancergencyto.2005.05.001 PMID:16271954

Jin Q, Menter DG, Mao L *et al.* (2008). Survivin expression in normal human bronchial epithelial cells: an early and critical step in tumorigenesis induced by tobacco exposure. *Carcinogenesis*, 29: 1614–1622. doi:10.1093/carcin/bgm234 PMID:18635526

Johnson KC (2005). Accumulating evidence on passive and active smoking and breast cancer risk. *Int J Cancer*, 117: 619–628. doi:10.1002/ijc.21150 PMID:15929073

Johnson KC, Goodman M, Kelsh M *et al.* (2002). Passive and active smoking as possible confounders in studies of breast cancer risk. *Epidemiology*, 13: 610–611, author

reply 610–611. doi:10.1097/00001648-200209000-00029 PMID:12192238

Johnson KC, Hu J, Mao YCanadian Cancer Registries Epidemiology Research Group (2000). Passive and active smoking and breast cancer risk in Canada, 1994–97. *Cancer Causes Control*, 11: 211–221. doi:10.1023/A:1008906105790 PMID:10782655

Johnson L, Mercer K, Greenbaum D *et al.* (2001). Somatic activation of the K-ras oncogene causes early onset lung cancer in mice. *Nature*, 410: 1111–1116. doi:10.1038/35074129 PMID:11323676

Jones PA & Baylin SB (2007). The epigenomics of cancer. *Cell*, 128: 683–692. doi:10.1016/j.cell.2007.01.029 PMID:17320506

Kabat GC, Chang CJ, Wynder EL (1994). The role of tobacco, alcohol use, and body mass index in oral and pharyngeal cancer. *Int J Epidemiol*, 23: 1137–1144. doi:10.1093/ije/23.6.1137 PMID:7721514

Kabat GC & Hebert JR (1994). Use of mentholated cigarettes and oropharyngeal cancer. *Epidemiology*, 5: 183–188. PMID:8172993

Kabat GC, Ng SKC, Wynder EL (1993). Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. *Cancer Causes Control*, 4: 123–132.

Kaczynski AT, Manske SR, Mannell RC, Grewal K (2008). Smoking and physical activity: a systematic review. *Am J Health Behav*, 32: 93–110. PMID:18021037

Kadlubar FF, Beland FA (1985). *Chemical properties of ultimate carcinogenic metabolites of arylamines and arylamides.* In: *Polycyclic Hydrocarbons and Carcinogenesis.* Harvey RG, editor. Washington, D.C.: American Chemical Society.

Kaerlev L, Teglbjaerg PS, Sabroe S *et al.* (2002). The importance of smoking and medical history for development of small bowel carcinoid tumor: a European population-based case-control study. *Cancer Causes Control*, 13: 27–34.

Kamataki T, Fujieda M, Kiyotani K *et al.* (2005). Genetic polymorphism of CYP2A6 as one of the potential determinants of tobacco-related cancer risk. *Biochem Biophys Res Commun*, 338: 306–310. doi:10.1016/j.bbrc.2005.08.268 PMID:16176798

Kanda J, Matsuo K, Kawase T *et al.* (2009). Association of alcohol intake and smoking with malignant lymphoma risk in Japanese: a hospital-based case-control study at Aichi Cancer Center. *Cancer Epidemiol Biomarkers Prev*, 18: 2436–2441. Epub 2009 Sep 1.

Kapeu AS, Luostarinen T, Jellum E *et al.* (2009). Is smoking an independent risk factor for invasive cervical cancer? A nested case-control study within Nordic biobanks. *Am J Epidemiol*, 169: 480–488. doi:10.1093/aje/kwn354 PMID:19074773

Kasahara M, Osawa K, Yoshida K *et al.* (2008). Association of *MUTYH Gln324His* and *APEX1 Asp148Glu* with colorectal cancer and smoking in a Japanese population. *J Exp Clin Cancer Res*, 27: 49 doi:10.1186/1756-9966-27-49 PMID:18823566

Kato M, Loomis D, Brooks LM *et al.* (2004). Urinary biomarkers in charcoal workers exposed to wood smoke in Bahia State, Brazil. *Cancer Epidemiol Biomarkers Prev*, 13: 1005–1012. PMID:15184257

Kawajiri K (1999). CYP1A1. *IARC Sci Publ*, 148: 159–172. PMID:10493257

Kawajiri K, Eguchi H, Nakachi K *et al.* (1996). Association of *CYP1A1* germ line polymorphisms with mutations of the *p53* gene in lung cancer. *Cancer Res*, 56: 72–76. PMID:8548778

Kelsey JL, Gammon MD, John EM (1993). Reproductive factors and breast cancer. *Epidemiol Rev*, 15: 36–47. PMID:8405211

Kelsey JL, LiVolsi VA, Holford TR *et al.* (1982). A case-control study of cancer of the endometrium. *Am J Epidemiol*, 116: 333–342. PMID:7114042

Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA (2008). Smoking and smoking cessation in relation to mortality in women. *JAMA*, 299: 2037–2047. doi:10.1001/jama.299.17.2037 PMID:18460664

Kesarwani P, Singh R, Mittal RD (2009). Association of GSTM3 intron 6 variant with cigarette smoking, tobacco chewing and alcohol as modifier factors for prostate cancer risk. *Arch Toxicol*, 83: 351–356. doi:10.1007/s00204-008-0343-5 PMID:18668224

Ketterer B, Harris JM, Talaska G *et al.* (1992). The human glutathione *S*-transferase supergene family, its polymorphism, and its effects on susceptibility to lung cancer. *Environ Health Perspect*, 98: 87–94. doi:10.2307/3431252 PMID:1486868

Key TJ, Pike MC, Baron JA *et al.* (1991). Cigarette smoking and steroid hormones in women. *J Steroid Biochem Mol Biol*, 39: 4A529–534. doi:10.1016/0960-0760(91)90247-3 PMID:1832941

Key TJ, Pike MC, Brown JB *et al.* (1996). Cigarette smoking and urinary oestrogen excretion in premenopausal and post-menopausal women. *Br J Cancer*, 74: 1313–1316. PMID:8883424

Khaw KT, Tazuke S, Barrett-Connor E (1988). Cigarette smoking and levels of adrenal androgens in postmenopausal women. *N Engl J Med*, 318: 1705–1709. doi:10.1056/NEJM198806303182601 PMID:2967432

Kiemeney LA, Thorlacius S, Sulem P *et al.* (2008). Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nat Genet*, 40: 1307–1312. doi:10.1038/ng.229 PMID:18794855

Kim CS, Kim MC, Cheong HK *et al.* (2005[The association of obesity and left colonic adenomatous polyps in Korean adult men]). *J Prev Med Pub Health*, 38: 415–419. PMID:16358826.

Kim HJ, Lee SM, Choi NK *et al.* (2006). [Smoking and colorectal cancer risk in the Korean elderly][Article in Korean]*J Prev Med Pub Health*, 39: 123–129.

Kim JI, Park YJ, Kim KH *et al.* (2003). hOGG1 Ser326Cys polymorphism modifies the significance of the environmental risk factor for colon cancer. *World J Gastroenterol*, 9: 956–960. PMID:12717837

Kim SG & Novak RF (1990). Role of P450IIE1 in the metabolism of 3-hydroxypyridine, a constituent of tobacco smoke: redox cycling and DNA strand scission by the metabolite 2,5-dihydroxypyridine. *Cancer Res*, 50: 5333–5339. PMID:2167153

Kim Y, Shin A, Gwack J *et al.* (2007). Cigarette smoking and gastric cancer risk in a community-based cohort study in Korea *J Prev Med Public Health*, 40: 467–474. doi:10.3961/jpmph.2007.40.6.467 PMID:18063902

Kiyohara C, Yoshimasu K, Shirakawa T, Hopkin JM (2004). Genetic polymorphisms and environmental risk of lung cancer: a review. *Rev Environ Health*, 19: 15–38. PMID:15186038

Kiyohara C, Yoshimasu K, Takayama K, Nakanishi Y (2005). NQO1, MPO, and the risk of lung cancer: a HuGE review. *Genet Med*, 7: 463–478. doi:10.1097/01.gim.0000177530.55043.c1 PMID:16170238

Kiyohara C, Yoshimasu K, Takayama K, Nakanishi Y (2006). EPHX1 polymorphisms and the risk of lung cancer: a HuGE review. *Epidemiology*, 17: 89–99. PMID:16357600

Kjaerheim K, Gaard M, Andersen A (1998). The role of alcohol, tobacco, and dietary factors in upper aerogastric tract cancers: a prospective study of 10,900 Norwegian men. *Cancer Causes Control*, 9: 99–108. doi:10.1023/A:1008809706062 PMID:9486469

Klotz U & Ammon E (1998). Clinical and toxicological consequences of the inductive potential of ethanol. *Eur J Clin Pharmacol*, 54: 7–12. doi:10.1007/s002280050412 PMID:9591923

Ko Y, Abel J, Harth V *et al.* (2001). Association of CYP1B1 codon 432 mutant allele in head and neck squamous cell cancer is reflected by somatic mutations of p53 in tumor tissue. *Cancer Res*, 61: 4398–4404. PMID:11389067

Ko YC, Huang YL, Lee CH *et al.* (1995). Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. *J Oral Pathol Med*, 24: 450–453. doi:10.1111/j.1600-0714.1995.tb01132.x PMID:8600280

Koizumi Y, Tsubono Y, Nakaya N *et al.* (2004). Cigarette smoking and the risk of gastric cancer: a pooled analysis of two prospective studies in Japan. *Int J Cancer*, 112: 1049–1055. doi:10.1002/ijc.20518 PMID:15386347

Kono S, Ikeda M, Tokudome S *et al.* (1987). Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. *Jpn J Cancer Res*, 78: 1323–1328. PMID:3123436

Kotwall CA (1992). Smoking as an etiologic factor in the development of Warthin's tumor of the parotid gland. *Am J Surg*, 164: 646–647. doi:10.1016/S0002-9610(05)80725-1 PMID:1334381

Koumantaki Y, Tzonou A, Koumantakis E *et al.* (1989). A case-control study of cancer of endometrium in Athens. *Int J Cancer*, 43: 795–799. doi:10.1002/ijc.2910430509 PMID:2714884

Kreuzer M, Boffetta P, Whitley E *et al.* (2000). Gender differences in lung cancer risk by smoking: a multicentre case-control study in Germany and Italy. *Br J Cancer*, 82: 227–233. PMID:10638994

Krewski D, Lubin JH, Zielinski JM *et al.* (2005). Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology*, 16: 137–145. PMID:15703527

Kropp S & Chang-Claude J (2002). Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am J Epidemiol*, 156: 616–626. doi:10.1093/aje/kwf093 PMID:12244030

Kubík A, Zatloukal P, Boyle P *et al.* (2001). A case-control study of lung cancer among Czech women. *Lung Cancer*, 31: 111–122. PMID:11165390

Kuljukka-Rabb T, Nylund L, Vaaranrinta R *et al.* (2002). The effect of relevant genotypes on PAH exposure-related biomarkers. *J Expo Anal Environ Epidemiol*, 12: 81–91. doi:10.1038/sj.jea.7500204 PMID:11859435

Kuller LH, Ockene JK, Meilahn E *et al.*MRFIT Research Group (1991). Cigarette smoking and mortality. *Prev Med*, 20: 638–654. doi:10.1016/0091-7435(91)90060-H PMID:1758843

Kundu CN, Balusu R, Jaiswal AS *et al.* (2007). Cigarette smoke condensate-induced level of adenomatous polyposis coli blocks long-patch base excision repair in breast epithelial cells. *Oncogene*, 26: 1428–1438. doi:10.1038/sj.onc.1209925 PMID:16924228

Kuper H, Titus-Ernstoff L, Harlow BL, Cramer DW (2000b). Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer. *Int J Cancer*, 88: 313–318. doi:10.1002/1097-0215(20001015)88:2<313::AID-IJC26>3.0.CO;2-5 PMID:11004686

Kuper H, Tzonou A, Kaklamani E *et al.* (2000a). Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer*, 85: 498–502. doi:10.1002/(SICI)1097-0215(20000215)85:4<498::AID-IJC9>3.0.CO;2-F PMID:10699921

Kurian AW, Balise RR, McGuire V, Whittemore AS (2005). Histologic types of epithelial ovarian cancer: have they different risk factors? *Gynecol Oncol*, 96: 520–530. doi:10.1016/j.ygyno.2004.10.037 PMID:15661246

Kurosawa M, Kikuchi S, Xu J, Inaba Y (2006). Highly salted food and mountain herbs elevate the risk for stomach cancer death in a rural area of Japan. *J Gastroenterol Hepatol*, 21: 1681–1686. doi:10.1111/j.1440-1746.2006.04290.x PMID:16984589

La Torre G, Chiaradia G, Gianfagna F *et al.* (2009). Smoking status and gastric cancer risk: an updated meta-analysis of case-control studies published in the past ten years. *Tumori*, 95: 13–22. PMID:19366050

La Vecchia C, Franceschi S, Bosetti C *et al.* (1999). Time since stopping smoking and the risk of oral and

pharyngeal cancers. *J Natl Cancer Inst*, 91: 726–728. doi:10.1093/jnci/91.8.726a PMID:10218516

Lacey JV Jr, Leitzmann MF, Chang SC *et al.* (2007). Endometrial cancer and menopausal hormone therapy in the National Institutes of Health-AARP Diet and Health Study cohort. *Cancer*, 109: 1303–1311. doi:10.1002/cncr.22525 PMID:17315161

Ladeiras-Lopes R, Pereira AK, Nogueira A *et al.* (2008). Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control*, 19: 689–701. doi:10.1007/s10552-008-9132-y PMID:18293090

Lagergren J, Bergström R, Lindgren A, Nyrén O (2000). The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer*, 85: 340–346. doi:10.1002/(SICI)1097-0215(20000201)85:3<340::AID-IJC8>3.0.CO;2-N PMID:10652424

Lam TK, Gallicchio L, Lindsley K *et al.* (2009). Cruciferous vegetable consumption and lung cancer risk: a systematic review. *Cancer Epidemiol Biomarkers Prev*, 18: 184–195. doi:10.1158/1055-9965.EPI-08-0710 PMID:19124497

Lan Q, Zhang L, Li G *et al.* (2004). Hematotoxicity in workers exposed to low levels of benzene. *Science*, 306: 1774–1776. doi:10.1126/science.1102443 PMID:15576619

Landi MT, Chatterjee N, Yu K *et al.* (2009). A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. *Am J Hum Genet*, 85: 679–691. doi:10.1016/j.ajhg.2009.09.012 PMID:19836008

Lang M & Pelkonen O (1999). Metabolism of xenobiotics and chemical carcinogenesis. *IARC Sci Publ*, 14813–22. PMID:10493245

Lanier A, Bender T, Talbot M *et al.* (1980). Nasopharyngeal carcinoma in Alaskan Eskimos Indians, and Aleuts: a review of cases and study of Epstein-Barr virus, HLA, and environmental risk factors. *Cancer*, 46: 2100–2106. doi:10.1002/1097-0142(19801101)46:9<2100::AID-CNCR2820460932>3.0.CO;2-G PMID:6253051

Lao Y, Yu N, Kassie F *et al.* (2007). Analysis of pyridyloxobutyl DNA adducts in F344 rats chronically treated with (*R*)- and (*S*)-*N*'-nitrosonornicotine. *Chem Res Toxicol*, 20: 246–256. doi:10.1021/tx060208j PMID:17305408

Lapidus L, Lindstedt G, Lundberg PA *et al.* (1986). Concentrations of sex-hormone binding globulin and corticosteroid binding globulin in serum in relation to cardiovascular risk factors and to 12-year incidence of cardiovascular disease and overall mortality in postmenopausal women. *Clin Chem*, 32: 146–152. PMID:3940696

Larsen IK, Grotmol T, Almendingen K, Hoff G (2006). Lifestyle as a predictor for colonic neoplasia in asymptomatic individuals. *BMC Gastroenterol*, 6: 5 doi:10.1186/1471-230X-6-5 PMID:16412216

Larsson SC, Permert J, Håkansson N *et al.* (2005). Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. *Br J Cancer*, 93: 1310–1315. doi:10.1038/sj.bjc.6602868 PMID:16288300

Lash TL & Aschengrau A (1999). Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol*, 149: 5–12. PMID:9883788

Lash TL & Aschengrau A (2002). A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Res Treat*, 75: 181–184. doi:10.1023/A:1019625102365 PMID:12243511

Lau A, Belanger CL, Winn LM (2009). *In utero* and acute exposure to benzene: investigation of DNA double-strand breaks and DNA recombination in mice. *Mutat Res*, 676: 74–82. PMID:19486867

Launoy G, Milan C, Faivre J *et al.* (2000). Tobacco type and risk of squamous cell cancer of the oesophagus in males: a French multicentre case-control study. *Int J Epidemiol*, 29: 36–42. doi:10.1093/ije/29.1.36 PMID:10750601

Law MR, Cheng R, Hackshaw AK *et al.* (1997). Cigarette smoking, sex hormones and bone density in women. *Eur J Epidemiol*, 13: 553–558. doi:10.1023/A:1007389712487 PMID:9258568

Lawlor DA, Ebrahim S, Smith GD (2004). Smoking before the birth of a first child is not associated with increased risk of breast cancer: findings from the British Women's Heart and Health Cohort Study and a meta-analysis. *Br J Cancer*, 91: 512–518. doi:10.1038/sj.bjc.6601916 PMID:15226777

Lawrence C, Tessaro I, Durgerian S *et al.* (1987). Smoking, body weight, and early-stage endometrial cancer. *Cancer*, 59: 1665–1669. doi:10.1002/1097-0142(19870501)59:9<1665::AID-CNCR2820590924>3.0.CO;2-2 PMID:3828966

Lawrence C, Tessaro I, Durgerian S *et al.* (1989). Advanced-stage endometrial cancer: contributions of estrogen use, smoking, and other risk factors. *Gynecol Oncol*, 32: 41–45. doi:10.1016/0090-8258(89)90847-0 PMID:2909447

Le Calvez F, Mukeria A, Hunt JD *et al.* (2005). *TP53* and *KRAS* mutation load and types in lung cancers in relation to tobacco smoke: distinct patterns in never, former, and current smokers. *Cancer Res*, 65: 5076–5083. doi:10.1158/0008-5472.CAN-05-0551 PMID:15958551

Le Marchand L, Derby KS, Murphy SE *et al.* (2008). Smokers with the *CHRNA* lung cancer-associated variants are exposed to higher levels of nicotine equivalents and a carcinogenic tobacco-specific nitrosamine. *Cancer Res*, 68: 9137–9140. doi:10.1158/0008-5472.CAN-08-2271 PMID:19010884

Le Marchand L, Guo C, Benhamou S *et al.* (2003). Pooled analysis of the *CYP1A1* exon 7 polymorphism

and lung cancer (United States). *Cancer Causes Control*, 14: 339–346. doi:10.1023/A:1023956201228 PMID:12846365

Le Marchand L, Sivaraman L, Pierce L *et al.* (1998). Associations of *CYP1A1*, GSTM1, and *CYP2E1* polymorphisms with lung cancer suggest cell type specificities to tobacco carcinogens. *Cancer Res*, 58: 4858–4863. PMID:9809991

Le Marchand L, Wilkens LR, Kolonel LN *et al.* (1997). Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res*, 57: 4787–4794. PMID:9354440

Lea IA, Jackson MA, Li X *et al.* (2007). Genetic pathways and mutation profiles of human cancers: site- and exposure-specific patterns. *Carcinogenesis*, 28: 1851–1858. doi:10.1093/carcin/bgm176 PMID:17693665

Lee CH, Wu DC, Lee JM *et al.* (2007a). Carcinogenetic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking. *Eur J Cancer*, 43: 1188–1199. doi:10.1016/j.ejca.2007.01.039 PMID:17383866

Lee CH, Wu DC, Lee JM *et al.* (2007b). Anatomical subsite discrepancy in relation to the impact of the consumption of alcohol, tobacco and betel quid on esophageal cancer. *Int J Cancer*, 120: 1755–1762. doi:10.1002/ijc.22324 PMID:17230518

Lee CY, Lee JY, Kang JW, Kim H (2001). Effects of genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and GSTT1 on the urinary levels of 1-hydroxypyrene and 2-naphthol in aircraft maintenance workers. *Toxicol Lett*, 123: 115–124. doi:10.1016/S0378-4274(01)00374-5 PMID:11641039

Lee JM, Yanagawa J, Peebles KA *et al.* (2008b). Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. *Crit Rev Oncol Hematol*, 66: 208–217. doi:10.1016/j.critrevonc.2008.01.004 PMID:18304833

Lee K, Cáceres D, Varela N *et al.* (2006). Allelic variants of cytochrome P4501A1 (CYP1A1), glutathione S transferase M1 (GSTM1) polymorphisms and their association with smoking and alcohol consumption as gastric cancer susceptibility biomarkers *Rev Med Chil*, 134: 1107–1115. PMID:17171211

Lee KM, Kang D, Clapper ML *et al.* (2008a). *CYP1A1*, *GSTM1*, and *GSTT1* polymorphisms, smoking, and lung cancer risk in a pooled analysis among Asian populations. *Cancer Epidemiol Biomarkers Prev*, 17: 1120–1126. doi:10.1158/1055-9965.EPI-07-2786 PMID:18463401

Lee KW, Kuo WR, Tsai SM *et al.* (2005a). Different impact from betel quid, alcohol and cigarette: risk factors for pharyngeal and laryngeal cancer. *Int J Cancer*, 117: 831–836. doi:10.1002/ijc.21237 PMID:15957167

Lee PN (1999). *Uses and abuses of cotinine as a marker of tobacco smoke exposure*. In: *Analytical Determination of Nicotine and Related Compounds and Their Metabolites*. Gorrod JW, Jacob P III, editors. Amsterdam: Elsevier, pp. 669–719

Lee PN (2001). Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. *Occup Environ Med*, 58: 145–153. doi:10.1136/oem.58.3.145 PMID:11171926

Lee YCA, Cohet C, Yang YC *et al.* (2009). Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. *Int J Epidemiol*, 38: 1497–1511. doi:10.1093/ije/dyp280 PMID:19720726

Lesko SM, Rosenberg L, Kaufman DW *et al.* (1985). Cigarette smoking and the risk of endometrial cancer. *N Engl J Med*, 313: 593–596. doi:10.1056/NEJM198509053131001 PMID:4022045

Leuchtenberger C, Leuchtenberger R (1970). *Effects of chronic inhalation of whole fresh cigarette smoke and of its gas phase on pulmonary tumorigenesis in Snell's mice*. In: *Morphology of Experimental Respiratory Carcinogenesis. Proceedings of a Biology Division.* Nettesheim P, Hanna MGJ, Deathevage JWJ, editors. Oak Ridge National Laboratory Conference, US Atomic Energy Commission, pp. 329–346.

Levi F & La Vecchia C (2001). Tobacco smoking and prostate cancer: time for an appraisal. *Ann Oncol*, 12: 733–738. doi:10.1023/A:1011124523984 PMID:11484946

Levi F, la Vecchia C, Decarli A (1987). Cigarette smoking and the risk of endometrial cancer. *Eur J Cancer Clin Oncol*, 23: 1025–1029. doi:10.1016/0277-5379(87)90353-1 PMID:3665988

Levi F, Ollyo JB, La Vecchia C *et al.* (1990). The consumption of tobacco, alcohol and the risk of adenocarcinoma in Barrett's oesophagus. *Int J Cancer*, 45: 852–854. doi:10.1002/ijc.2910450511 PMID:2335388

Lewin F, Norell SE, Johansson H *et al.* (1998). Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. *Cancer*, 82: 1367–1375.

Li CI, Malone KE, Daling JR (2005). The relationship between various measures of cigarette smoking and risk of breast cancer among older women 65–79 years of age (United States). *Cancer Causes Control*, 16: 975–985. doi:10.1007/s10552-005-2906-6 PMID:16132806

Li JY, Ershow AG, Chen ZJ *et al.* (1989). A case-control study of cancer of the esophagus and gastric cardia in Linxian. *Int J Cancer*, 43: 755–761. doi:10.1002/ijc.2910430502 PMID:2714880

Li W, Ray RM, Gao DL *et al.* (2006). Occupational risk factors for pancreatic cancer among female textile workers in Shanghai, China. *Occup Environ Med*, 63: 788–793. doi:10.1136/oem.2005.026229 PMID:16847032

Li X & Hemminki K (2004). Inherited predisposition to early onset lung cancer according to histological type. *International Journal of Cancer*, 112: 451–457. doi:10.1002/ijc.20436

Li Y, Jiang Y, Zhang M *et al.* (2011). Drinking behaviour among men and women in China: the 2007 China Chronic Disease and Risk Factor Surveillance. *Addiction*, 106: 1946–1956.

Li Y, Millikan RC, Bell DA *et al.* (2004). Cigarette smoking, cytochrome P4501A1 polymorphisms, and breast cancer among African-American and white women. *Breast Cancer Res*, 6: R460–R473. doi:10.1186/bcr814 PMID:15217514

Liang PS, Chen TY, Giovannucci E (2009). Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer*, 124: 2406–2415. doi:10.1002/ijc.24191 PMID:19142968

Liaw KM & Chen CJ (1998). Mortality attributable to cigarette smoking in Taiwan: a 12-year follow-up study. *Tob Control*, 7: 141–148. doi:10.1136/tc.7.2.141 PMID:9789932

Liddell FD (2001). The interaction of asbestos and smoking in lung cancer. *Ann Occup Hyg*, 45: 341–356. PMID:11418084

Lieber CS (1999). Microsomal ethanol-oxidizing system (MEOS): the first 30 years (1968–1998)–a review. *Alcohol Clin Exp Res*, 23: 991–1007. doi:10.1111/j.1530-0277.1999.tb04217.x PMID:10397283

Lieber CS (2004). The discovery of the microsomal ethanol oxidizing system and its physiologic and pathologic role. *Drug Metab Rev*, 36: 511–529. doi:10.1081/DMR-200033441 PMID:15554233

Lijinsky W (1992). *Chemistry and biology of N-Nitroso compounds*. Monographs on Cancer Research. Cambridge University Press

Lilla C, Risch A, Kropp S, Chang-Claude J (2005). SULT1A1 genotype, active and passive smoking, and breast cancer risk by age 50 years in a German case-control study. *Breast Cancer Res*, 7: R229–R237. doi:10.1186/bcr976 PMID:15743503

Lilla C, Verla-Tebit E, Risch A *et al.* (2006). Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev*, 15: 99–107. PMID:16434594

Lim U, Morton LM, Subar AF *et al.* (2007). Alcohol, smoking, and body size in relation to incident Hodgkin's and non-Hodgkin's lymphoma risk. *Am J Epidemiol*, 166: 697–708.

Limburg PJ, Vierkant RA, Cerhan JR *et al.* (2003). Cigarette smoking and colorectal cancer: long-term, subsite-specific risks in a cohort study of postmenopausal women. *Clin Gastroenterol Hepatol*, 1: 202–210. PMID:15017492

Lin TM, Chen KP, Lin CC *et al.* (1973). Retrospective study on nasopharyngeal carcinoma. *J Natl Cancer Inst*, 51: 1403–1408. PMID:4762926

Lin Y, Tamakoshi A, Kawamura T *et al.*JACC Study Group. Japan Collaborative Cohort (2002a). A prospective cohort study of cigarette smoking and pancreatic cancer in Japan. *Cancer Causes Control*, 13: 249–254. doi:10.1023/A:1015052710213 PMID:12020106

Lindblad M, Rodríguez LA, Lagergren J (2005). Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control*, 16: 285–294. doi:10.1007/s10552-004-3485-7 PMID:15947880

Lindemann K, Vatten LJ, Ellstrøm-Engh M, Eskild A (2008). Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. *Br J Cancer*, 98: 1582–1585. doi:10.1038/sj.bjc.6604313 PMID:18362938

Linet MS, McLaughlin JK, Hsing AW *et al.* (1992). Is cigarette smoking a risk factor for non-Hodgkin's lymphoma or multiple myeloma? Results from the Lutheran Brotherhood Cohort Study. *Leuk Res*, 16: 621–624. doi:10.1016/0145-2126(92)90011-U PMID:1635380

Linseisen J, Rohrmann S, Miller AB *et al.* (2007). Fruit and vegetable consumption and lung cancer risk: updated information from the European Prospective Investigation into Cancer and Nutrition (EPIC). *International Journal of Cancer*, 121: 1103–1114. doi:10.1002/ijc.22807

Lissowska J, Brinton LA, Garcia-Closas M (2007). Re: more data regarding the effects of passive smoking on breast cancer risk among younger women. *Int J Cancer*, 120: 2517–2518. doi:10.1002/ijc.22610 PMID:17290385

Lissowska J, Brinton LA, Zatonski W *et al.* (2006). Tobacco smoking, NAT2 acetylation genotype and breast cancer risk. *Int J Cancer*, 119: 1961–1969. doi:10.1002/ijc.22044 PMID:16721725

Lissowska J, Pilarska A, Pilarski P *et al.* (2003). Smoking, alcohol, diet, dentition and sexual practices in the epidemiology of oral cancer in Poland. *Eur J Cancer Prev*, 12: 25–33. doi:10.1097/00008469-200302000-00005 PMID:12548107

Loerbroks A, Schouten LJ, Goldbohm RA, van den Brandt PA (2007). Alcohol consumption, cigarette smoking, and endometrial cancer risk: results from the Netherlands Cohort Study. *Cancer Causes Control*, 18: 551–560. doi:10.1007/s10552-007-0127-x PMID:17437180

London SJ, Colditz GA, Stampfer MJ *et al.* (1989a). Prospective study of relative weight, height, and risk of breast cancer. *JAMA*, 262: 2853–2858. doi:10.1001/jama.262.20.2853 PMID:2810620

London SJ, Colditz GA, Stampfer MJ *et al.* (1989b). Prospective study of smoking and the risk of breast cancer. *J Natl Cancer Inst*, 81: 1625–1631. doi:10.1093/jnci/81.21.1625 PMID:2795691

London SJ, Smart J, Daly AK (2000b). Lung cancer risk in relation to genetic polymorphisms of microsomal epoxide hydrolase among African-Americans and Caucasians in Los Angeles County. *Lung Cancer*, 28: 147–155. doi:10.1016/S0169-5002(99)00130-0 PMID:10717332

London SJ, Yuan JM, Chung FL *et al.* (2000a). Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms, and lung-cancer risk: a prospective study of men in Shanghai, China. *Lancet*, 356: 724–729. doi:10.1016/S0140-6736(00)02631-3 PMID:11085692

Longcope C, Baker R, Johnston CC Jr (1986). Androgen and estrogen metabolism: relationship to obesity. *Metabolism*, 35: 235–237. doi:10.1016/0026-0495(86)90206-4 PMID:3456482

Longcope C & Johnston CC Jr (1988). Androgen and estrogen dynamics in pre- and postmenopausal women: a comparison between smokers and nonsmokers. *J Clin Endocrinol Metab*, 67: 379–383. doi:10.1210/jcem-67-2-379 PMID:3392163

Lopez AD, Collishaw N, Piha T (1994). A descriptive model of the cigarette epidemic in developed countries. *Tobacco Control*, 3: 242–247. doi:10.1136/tc.3.3.242

López-Abente G, Pollán M, Monge V, Martínez-Vidal A (1992). Tobacco smoking, alcohol consumption, and laryngeal cancer in Madrid. *Cancer Detect Prev*, 16: 265–271. PMID:1473116

Lu J, Lian S, Sun X *et al.* (2000). A case-control study on the risk factors of esophageal cancer in Linzhou *Zhonghua Liu Xing Bing Xue Za Zhi*, 21: 434–436. PMID:11860829

Lubet RA, Zhang Z, Wiseman RW, You M (2000). Use of p53 transgenic mice in the development of cancer models for multiple purposes. *Exp Lung Res*, 26: 581–593. doi:10.1080/01902140150216684 PMID:11195457

Lubin JH, Alavanja MC, Caporaso N *et al.* (2007a). Cigarette smoking and cancer risk: modeling total exposure and intensity. *Am J Epidemiol*, 166: 479–489. doi:10.1093/aje/kwm089 PMID:17548786

Lubin JH, Caporaso N, Hatsukami DK *et al.* (2007b). The association of a tobacco-specific biomarker and cigarette consumption and its dependence on host characteristics. *Cancer Epidemiology, Biomarkers & Prevention*, 16: 1852–1857. doi:10.1158/1055-9965.EPI-07-0018

Lubin JH & Caporaso NE (2006). Cigarette smoking and lung cancer: modeling total exposure and intensity. *Cancer Epidemiology, Biomarkers & Prevention*, 15: 517–523. doi:10.1158/1055-9965.EPI-05-0863

Lubin JH, Kogevinas M, Silverman D *et al.* (2007). Evidence for an intensity-dependent interaction of NAT2 acetylation genotype and cigarette smoking in the Spanish Bladder Cancer Study. *Int J Epidemiol*, 36: 236–241. doi:10.1093/ije/dym043 PMID:17510079

Lubin JH, Virtamo J, Weinstein SJ, Albanes D (2008). Cigarette smoking and cancer: intensity patterns in the alpha-tocopherol, beta-carotene cancer prevention study in Finnish men. *Am J Epidemiol*, 167: 970–975. doi:10.1093/aje/kwm392 PMID:18250081

Lüchtenborg M, Weijenberg MP, Kampman E *et al.* (2005a). Cigarette smoking and colorectal cancer: APC mutations, hMLH1 expression, and GSTM1 and GSTT1 polymorphisms. *Am J Epidemiol*, 161: 806–815. doi:10.1093/aje/kwi114 PMID:15840612

Lüchtenborg M, White KK, Wilkens L *et al.* (2007). Smoking and colorectal cancer: different effects by type of cigarettes? *Cancer Epidemiol Biomarkers Prev*, 16: 1341–1347. doi:10.1158/1055-9965.EPI-06-0519 PMID:17626999

Lurie G, Wilkens LR, Thompson PJ *et al.* (2008). Genetic polymorphisms in the Paraoxonase 1 gene and risk of ovarian epithelial carcinoma. *Cancer Epidemiol Biomarkers Prev*, 17: 2070–2077. doi:10.1158/1055-9965.EPI-08-0145 PMID:18708400

Lynch SM, Vrieling A, Lubin JH *et al.* (2009). Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Am J Epidemiol*, 170: 403–413. doi:10.1093/aje/kwp134 PMID:19561064

Mabuchi K, Bross DS, Kessler II (1985). Cigarette smoking and nasopharyngeal carcinoma. *Cancer*, 55: 2874–2876. doi:10.1002/1097-0142(19850615)55:12<2874::AID-CNCR2820551228>3.0.CO;2-4 PMID:3995493

Macfarlane GJ, Zheng T, Marshall JR *et al.* (1995). Alcohol, tobacco, diet and the risk of oral cancer: a pooled analysis of three case-control studies. *Eur J Cancer B Oral Oncol*, 31B: 181–187. doi:10.1016/0964-1955(95)00005-3 PMID:7549758

Mack WJ, Preston-Martin S, Dal Maso L *et al.* (2003). A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. *Cancer Causes Control*, 14: 773–785. doi:10.1023/A:1026349702909 PMID:14674742

Mackenzie PI, Owens IS, Burchell B *et al.* (1997). The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. *Pharmacogenetics*, 7: 255–269. PMID:9295054

MacMahon B, Trichopoulos D, Cole P, Brown J (1982). Cigarette smoking and urinary estrogens. *N Engl J Med*, 307: 1062–1065. PMID:7121516

MacNicoll AD, Easty GC, Neville AM *et al.* (1980). Metabolism and activation of carcinogenic polycyclic hydrocarbons by human mammary cells. *Biochem Biophys Res Commun*, 95: 1599–1606. doi:10.1016/S0006-291X(80)80081-7 PMID:6774726

Maden C, Sherman KJ, Beckmann AM *et al.* (1993). History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *J Natl Cancer Inst*, 85: 19–24. doi:10.1093/jnci/85.1.19 PMID:8380060

Magnusson C, Wedrén S, Rosenberg LU (2007). Cigarette smoking and breast cancer risk: a population-based study in Sweden. *Br J Cancer*, 97: 1287–1290. doi:10.1038/sj.bjc.6604007 PMID:17912245

Maier H, Dietz A, Gewelke U *et al.* (1992a). Tobacco and alcohol and the risk of head and neck cancer. *Clin Investig*, 70: 320–327. doi:10.1007/BF00184668 PMID:1521046

Maier H, Gewelke U, Dietz A *et al.* (1992b[). Laryngeal cancer and occupation — results of the Heidelberg laryngeal cancer study]*HNO*, 40: 44–51.

Maier H, Sennewald E, Heller GF, Weidauer H (1994). Chronic alcohol consumption–the key risk factor for pharyngeal cancer. *Otolaryngol Head Neck Surg*, 110: 168–173. PMID:7906410

Maier H & Tisch M (1997). Epidemiology of laryngeal cancer: results of the Heidelberg case-control study. *Acta Otolaryngol Suppl*, 527: 160–164. doi:10.3109/00016489709124063 PMID:9197510

Malaiyandi V, Sellers EM, Tyndale RF (2005). Implications of *CYP2A6* genetic variation for smoking behaviors and nicotine dependence. *Clin Pharmacol Ther*, 77: 145–158. doi:10.1016/j.clpt.2004.10.011 PMID:15735609

Malats N (2008). Genetic epidemiology of bladder cancer: scaling up in the identification of low-penetrance genetic markers of bladder cancer risk and progression. *Scand J Urol Nephrol Suppl*, 42: 131–140. doi:10.1080/03008880802285172 PMID:18815927

Mandai M, Konishi I, Kuroda H *et al.* (1998). Heterogeneous distribution of K-ras-mutated epithelia in mucinous ovarian tumors with special reference to histopathology. *Hum Pathol*, 29: 34–40. doi:10.1016/S0046-8177(98)90387-2 PMID:9445131

Mandelzweig L, Novikov I, Sadetzki S (2009). *Smoking and risk of glioma: a meta-analysis*. Cancer Causes Control.

Mane SS, Purnell DM, Hsu IC (1990). Genotoxic effects of five polycyclic aromatic hydrocarbons in human and rat mammary epithelial cells. *Environ Mol Mutagen*, 15: 78–82. doi:10.1002/em.2850150204 PMID:2307152

Manjer J, Andersson I, Berglund G *et al.* (2000). Survival of women with breast cancer in relation to smoking. *Eur J Surg*, 166: 852–858. doi:10.1080/110241500447227 PMID:11097150

Manjer J, Malina J, Berglund G *et al.* (2001). Smoking associated with hormone receptor negative breast cancer. *Int J Cancer*, 91: 580–584. doi:10.1002/1097-0215(200002)9999:9999<::AID-IJC1091>3.0.CO;2-V PMID:11251985

Manuguerra M, Saletta F, Karagas MR *et al.* (2006). XRCC3 and XPD/ERCC2 single nucleotide polymorphisms and the risk of cancer: a HuGE review. *Am J Epidemiol*, 164: 297–302. doi:10.1093/aje/kwj189 PMID:16707649

Mao GE, Morris G, Lu QY *et al.* (2004). Glutathione S-transferase P1 Ile105Val polymorphism, cigarette smoking and prostate cancer. *Cancer Detect Prev*, 28: 368–374. doi:10.1016/j.cdp.2004.07.003 PMID:15542263

Marchbanks PA, Wilson H, Bastos E *et al.* (2000). Cigarette smoking and epithelial ovarian cancer by histologic type. *Obstet Gynecol*, 95: 255–260. doi:10.1016/S0029-7844(99)00531-1 PMID:10674590

Marsh GM, Youk AO, Buchanich JM *et al.* (2007). Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers. *Regul Toxicol Pharmacol*, 48: 308–319. doi:10.1016/j.yrtph.2007.04.006 PMID:17544557

Marshall JR, Hastrup JL, Ross JS (1999). Mismeasurement and the resonance of strong confounders: correlated errors. *Am J Epidemiol*, 150: 88–96. PMID:10400558

Marsit CJ, Karagas MR, Schned A, Kelsey KT (2006). Carcinogen exposure and epigenetic silencing in bladder cancer. *Ann N Y Acad Sci*, 1076: 810–821. doi:10.1196/annals.1371.031 PMID:17119258

Mashberg A, Boffetta P, Winkelman R, Garfinkel L (1993). Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans. *Cancer*, 72: 1369–1375. doi:10.1002/1097-0142(19930815)72:4<1369::AID-CNCR2820720436>3.0.CO;2-L PMID:8339227

Masson LF, Sharp L, Cotton SC, Little J (2005). Cytochrome P-450 1A1 gene polymorphisms and risk of breast cancer: a HuGE review. *Am J Epidemiol*, 161: 901–915. doi:10.1093/aje/kwi121 PMID:15870154

Matthews CE, Xu WH, Zheng W *et al.* (2005). Physical activity and risk of endometrial cancer: a report from the Shanghai endometrial cancer study. *Cancer Epidemiol Biomarkers Prev*, 14: 779–785. doi:10.1158/1055-9965.EPI-04-0665 PMID:15824143

Mauderly JL, Gigliotti AP, Barr EB *et al.* (2004). Chronic inhalation exposure to mainstream cigarette smoke increases lung and nasal tumor incidence in rats. *Toxicol Sci*, 81: 280–292. doi:10.1093/toxsci/kfh203 PMID:15213336

McCann SE, Freudenheim JL, Marshall JR *et al.* (2000). Diet in the epidemiology of endometrial cancer in western New York (United States). *Cancer Causes Control*, 11: 965–974. doi:10.1023/A:1026551309873 PMID:11142531

McCormack VA & dos Santos Silva I (2006). Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 15: 1159–1169. doi:10.1158/1055-9965.EPI-06-0034 PMID:16775176

McCoy GD, Hecht SS, Katayama S, Wynder EL (1981). Differential effect of chronic ethanol consumption on the carcinogenicity of *N*-nitrosopyrrolidine and *N*'-nitrosonornicotine in male Syrian golden hamsters. *Cancer Res*, 41: 2849–2854. PMID:7248945

McDivit AM, Greendale GA, Stanczyk FZ, Huang M-H (2008). Effects of alcohol and cigarette smoking on change in serum estrone levels in postmenopausal women randomly assigned to fixed doses of conjugated equine estrogens with or without a progestin. *Menopause*, 15: 382–385. doi:10.1097/gme.0b013e3181407cb2 PMID:18000469

McGrath M, Hankinson SE, De Vivo I (2007). Cytochrome P450 1A1, cigarette smoking, and risk of endometrial cancer (United States). *Cancer Causes Control*, 18: 1123–1130. doi:10.1007/s10552-007-9051-3 PMID:17717632

McIlwain CC, Townsend DM, Tew KD (2006). Glutathione *S*-transferase polymorphisms: cancer incidence and therapy. *Oncogene*, 25: 1639–1648. doi:10.1038/sj.onc.1209373 PMID:16550164

McIntyre-Seltman K, Castle PE, Guido R *et al.* ALTS Group (2005). Smoking is a risk factor for cervical intraepithelial neoplasia grade 3 among oncogenic human papillomavirus DNA-positive women with equivocal or mildly abnormal cytology. *Cancer Epidemiol Biomarkers Prev*, 14: 1165–1170. doi:10.1158/1055-9965.EPI-04-0918 PMID:15894667

McKay JD, Hashibe M, Hung RJ *et al.* (2008). Sequence variants of *NAT1* and *NAT2* and other xenometabolic genes and risk of lung and aerodigestive tract cancers in Central Europe. *Cancer Epidemiol Biomarkers Prev*, 17: 141–147. doi:10.1158/1055-9965.EPI-07-0553 PMID:18199719

McKinlay SM (1996). The normal menopause transition: an overview. *Maturitas*, 23: 137–145. doi:10.1016/0378-5122(95)00985-X PMID:8735352

McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr (1995). Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. *Int J Cancer*, 60: 190–193. doi:10.1002/ijc.2910600210 PMID:7829214

Mechanic LE, Bowman ED, Welsh JA *et al.* (2007). Common genetic variation in TP53 is associated with lung cancer risk and prognosis in African Americans and somatic mutations in lung tumors. *Cancer Epidemiology, Biomarkers & Prevention*, 16: 214–222. doi:10.1158/1055-9965.EPI-06-0790

Mechanic LE, Millikan RC, Player J *et al.* (2006). Polymorphisms in nucleotide excision repair genes, smoking and breast cancer in African Americans and whites: a population-based case-control study. *Carcinogenesis*, 27: 1377–1385. doi:10.1093/carcin/bgi330 PMID:16399771

Meckley D, Hayes JR, Van Kampen KR *et al.* (2004a). A responsive, sensitive, and reproducible dermal tumor promotion assay for the comparative evaluation of cigarette smoke condensates. *Regul Toxicol Pharmacol*, 39: 135–149. doi:10.1016/j.yrtph.2003.12.003 PMID:15041145

Meckley DR, Hayes JR, Van Kampen KR *et al.* (2004b). Comparative study of smoke condensates from 1R4F cigarettes that burn tobacco versus ECLIPSE cigarettes that primarily heat tobacco in the SENCAR mouse dermal tumor promotion assay. *Food Chem Toxicol*, 42: 851–863. doi:10.1016/j.fct.2004.01.009 PMID:15046832

Menke-Pluymers MB, Hop WC, Dees J *et al.* The Rotterdam Esophageal Tumor Study Group (1993). Risk factors for the development of an adenocarcinoma in columnar-lined (Barrett) esophagus. *Cancer*, 72: 1155–1158. doi:10.1002/1097-0142(19930815)72:4<1155::AID-CNCR2820720404>3.0.CO;2-C PMID:8339208

Menvielle G, Luce D, Goldberg P *et al.* (2004a). Smoking, alcohol drinking and cancer risk for various sites of the larynx and hypopharynx. A case-control study in France. *Eur J Cancer Prev*, 13: 165–172. doi:10.1097/01.cej.0000130017.93310.76 PMID:15167214

Menvielle G, Luce D, Goldberg P, Leclerc A (2004b). Smoking, alcohol drinking, occupational exposures and social inequalities in hypopharyngeal and laryngeal cancer. *Int J Epidemiol*, 33: 799–806. doi:10.1093/ije/dyh090 PMID:15155704

Merletti F, Boffetta P, Ciccone G *et al.* (1989). Role of tobacco and alcoholic beverages in the etiology of cancer of the oral cavity/oropharynx in Torino, Italy. *Cancer Res*, 49: 4919–4924. PMID:2758421

Meskar A, Plee-Gautier E, Amet Y *et al.* (2001). Alcohol-xenobiotic interactions. Role of cytochrome P450 2E1 *Pathol Biol (Paris)*, 49: 696–702. doi:10.1016/S0369-8114(01)00235-8 PMID:11762131

Michnovicz JJ, Hershcopf RJ, Naganuma H *et al.* (1986). Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *N Engl J Med*, 315: 1305–1309. PMID:3773953

Michnovicz JJ, Naganuma H, Hershcopf RJ *et al.* (1988). Increased urinary catechol estrogen excretion in female smokers. *Steroids*, 52: 69–83. doi:10.1016/0039-128X(88)90218-8 PMID:2854668

Miller MD, Marty MA, Broadwin R *et al.* California Environmental Protection Agency (2007). The association between exposure to environmental tobacco smoke and breast cancer: a review by the California Environmental Protection Agency. *Prev Med*, 44: 93–106. doi:10.1016/j.ypmed.2006.08.015 PMID:17027075

Millikan RC, Pittman GS, Newman B *et al.* (1998). Cigarette smoking, N-acetyltransferases 1 and 2, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 7: 371–378. PMID:9610785

Minami Y & Tateno H (2003). Associations between cigarette smoking and the risk of four leading cancers in Miyagi Prefecture, Japan: a multi-site case-control study. *Cancer Sci*, 94: 540–547. doi:10.1111/j.1349-7006.2003.tb01480.x PMID:14529588

Minna JD (2003). Nicotine exposure and bronchial epithelial cell nicotinic acetylcholine receptor expression in the pathogenesis of lung cancer. *J Clin Invest*, 111: 31–33. PMID:12511585

Mitrou PN, Watson MA, Loktionov AS *et al.* (2006). MTHFR (C677T and A1298C) polymorphisms and risk of sporadic distal colorectal adenoma in the UK Flexible Sigmoidoscopy Screening Trial (United Kingdom). *Cancer Causes Control*, 17: 793–801. doi:10.1007/s10552-006-0016-8 PMID:16783607

Modugno F, Ness RB, Cottreau CM (2002). Cigarette smoking and the risk of mucinous and nonmucinous epithelial ovarian cancer. *Epidemiology*, 13: 467–471. doi:10.1097/00001648-200207000-00016 PMID:12094103

Modugno F, Ngo DL, Allen GO *et al.* (2006). Breast cancer risk factors and mammographic breast density in women over age 70. *Breast Cancer Res Treat*, 97: 157–166. doi:10.1007/s10549-005-9105-8 PMID:16362132

Molano M, Van den Brule A, Plummer M *et al.* (2003). Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. *Am J Epidemiol*, 158: 486–494.

Møllersen L, Vikse R, Andreassen A *et al.* (2004). Adenomatous polyposis coli truncation mutations in 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-induced intestinal tumours of multiple intestinal neoplasia mice. *Mutat Res*, 557: 29–40. PMID:14706516

Monnereau A, Orsi L, Troussard X *et al.* (2008). Cigarette smoking, alcohol drinking, and risk of lymphoid neoplasms: results of a French case-control study. *Cancer Causes Control*, 19: 1147–1160.

Montelongo A, Lasunción MA, Pallardo LF, Herrera E (1992). Longitudinal study of plasma lipoproteins and hormones during pregnancy in normal and diabetic women. *Diabetes*, 41: 1651–1659. doi:10.2337/diabetes.41.12.1651 PMID:1446807

Morabia A, Bernstein M, Héritier S, Khatchatrian N (1996). Relation of breast cancer with passive and active exposure to tobacco smoke. *Am J Epidemiol*, 143: 918–928. PMID:8610705

Morabia A, Bernstein M, Ruiz J *et al.* (1998). Relation of smoking to breast cancer by estrogen receptor status. *Int J Cancer*, 75: 339–342. doi:10.1002/(SICI)1097-0215(19980130)75:3<339::AID-IJC2>3.0.CO;2-3 PMID:9455790

Morabia A, Bernstein MS, Bouchardy I *et al.* (2000). Breast cancer and active and passive smoking: the role of the N-acetyltransferase 2 genotype. *Am J Epidemiol*, 152: 226–232. doi:10.1093/aje/152.3.226 PMID:10933269

Morabia A & Wynder EL (1992). Relation of bronchioloalveolar carcinoma to tobacco. *BMJ*, 304: 541–543. doi:10.1136/bmj.304.6826.541 PMID:1313719

Moreno V, Glatt H, Guino E *et al.*Bellvitge Colorectal Cancer Study Group (2005). Polymorphisms in sulfotransferases *SULT1A1* and *SULT1A2* are not related to colorectal cancer. *Int J Cancer*, 113: 683–686. doi:10.1002/ijc.20613 PMID:15455379

Morris JJ & Seifter E (1992). The role of aromatic hydrocarbons in the genesis of breast cancer. *Med Hypotheses*, 38: 177–184. doi:10.1016/0306-9877(92)90090-Y PMID:1513270

Morton LM, Hartge P, Holford TR *et al.* (2005). Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). *Cancer Epidemiol Biomarkers Prev*, 14: 925–933.

Mounawar M, Mukeria A, Le Calvez F *et al.* (2007). Patterns of *EGFR*, *HER2*, *TP53*, and *KRAS* mutations of *p14^{arf}* expression in non-small cell lung cancers in relation to smoking history. *Cancer Res*, 67: 5667–5672. doi:10.1158/0008-5472.CAN-06-4229 PMID:17575133

Mountzios G, Fouret P, Soria J-C (2008). Mechanisms of Disease: signal transduction in lung carcinogenesis – a comparison of smokers and never-smokers. *Nat Clin Pract Oncol*, 5: 610–618. doi:10.1038/ncponc1181 PMID:18628738

Murata M, Takayama K, Choi BCK, Pak AWP (1996). A nested case-control study on alcohol drinking, tobacco smoking, and cancer. *Cancer Detect Prev*, 20: 557–565. PMID:8939341

Murayama N, Soyama A, Saito Y *et al.* (2004). Six novel nonsynonymous *CYP1A2* gene polymorphisms: catalytic activities of the naturally occurring variant enzymes. *J Pharmacol Exp Ther*, 308: 300–306. doi:10.1124/jpet.103.055798 PMID:14563787

Murin S & Inciardi J (2001). Cigarette smoking and the risk of pulmonary metastasis from breast cancer. *Chest*, 119: 1635–1640. doi:10.1378/chest.119.6.1635 PMID:11399684

Murphy G, Shu XO, Gao YT *et al.* (2009). *Family cancer history affecting risk of colorectal cancer in a prospective cohort of Chinese women*. Cancer Causes Control.

Muscat JE, Richie JP Jr, Thompson S, Wynder EL (1996). Gender differences in smoking and risk for oral cancer. *Cancer Res*, 56: 5192–5197. PMID:8912856

Muscat JE & Wynder EL (1992). Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. *Cancer*, 69: 2244–2251. doi:10.1002/1097-0142(19920501)69:9<2244::AID-CNCR2820690906>3.0.CO;2-O PMID:1562970

Muscat JE & Wynder EL (1998). A case/control study of risk factors for major salivary gland cancer. *Otolaryngol Head Neck Surg*, 118: 195–198. doi:10.1016/S0194-5998(98)80013-2 PMID:9482552

Mutch MG, Schoen RE, Fleshman JW *et al.* (2009). A multicenter study of prevalence and risk factors for aberrant crypt foci. *Clin Gastroenterol Hepatol*, 7: 568–574. doi:10.1016/j.cgh.2009.01.016 PMID:19418605

Muti P, Bradlow HL, Micheli A *et al.* (2000). Estrogen metabolism and risk of breast cancer: a prospective study of the 2:16alpha-hydroxyestrone ratio in premenopausal and postmenopausal women. *Epidemiology*, 11: 635–640. doi:10.1097/00001648-200011000-00004 PMID:11055622

Muwonge R, Ramadas K, Sankila R *et al.* (2008). Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. *Oral Oncol*, 44: 446–454. doi:10.1016/j.oraloncology.2007.06.002 PMID:17933578

Mwenifumbo JC & Tyndale RF (2007). Genetic variability in CYP2A6 and the pharmacokinetics of nicotine. *Pharmacogenomics*, 8: 1385–1402. doi:10.2217/14622416.8.10.1385 PMID:17979512

Nagano J, Mabuchi K, Yoshimoto Y *et al.* (2007). A case-control study in Hiroshima and Nagasaki examining non-radiation risk factors for thyroid cancer. *J Epidemiol*, 17: 76–85. doi:10.2188/jea.17.76 PMID:17545694

Nagar S & Remmel RP (2006). Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene*, 25: 1659–1672. doi:10.1038/sj.onc.1209375 PMID:16550166

Nagle CM, Olsen CM, Webb PM *et al.* Australian Cancer Study Group; Australian Ovarian Cancer Study Group (2008). Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors. *Eur J Cancer*, 44: 2477–2484. doi:10.1016/j.ejca.2008.07.009 PMID:18707869

Nakajima M (2007). Smoking behavior and related cancers: the role of *CYP2A6* polymorphisms. *Curr Opin Mol Ther*, 9: 538–544. PMID:18041664

Nakajima M, Yokoi T, Mizutani M *et al.* (1999). Genetic polymorphism in the 5′ -flanking region of human *CYP1A2* gene: effect on the CYP1A2 inducibility in humans. *J Biochem*, 125: 803–808. PMID:10101295

Nam JM, McLaughlin JK, Blot WJ (1992). Cigarette smoking, alcohol, and nasopharyngeal carcinoma: a case-control study among U.S. whites. *J Natl Cancer Inst*, 84: 619–622. doi:10.1093/jnci/84.8.619 PMID:1556772

Nandakumar A, Anantha N, Pattabhiraman V *et al.* (1996). Importance of anatomical subsite in correlating risk factors in cancer of the oesophagus–report of a case–control study. *Br J Cancer*, 73: 1306–1311. PMID:8630297

Nandakumar A, Thimmasetty KT, Sreeramareddy NM *et al.* (1990). A population-based case-control investigation on cancers of the oral cavity in Bangalore, India. *Br J Cancer*, 62: 847–851. PMID:2245179

Narayan S, Jaiswal AS, Kang D *et al.* (2004). Cigarette smoke condensate-induced transformation of normal human breast epithelial cells in vitro. *Oncogene*, 23: 5880–5889. doi:10.1038/sj.onc.1207792 PMID:15208684

Navarro Silvera SA, Miller AB, Rohan TE (2005). Risk factors for thyroid cancer: a prospective cohort study. *Int J Cancer*, 116: 433–438. doi:10.1002/ijc.21079 PMID:15818623

Nayar D, Kapil U, Joshi YK *et al.* (2000). Nutritional risk factors in esophageal cancer. *J Assoc Physicians India*, 48: 781–787. PMID:11273469

Nebert DW & Dalton TP (2006). The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. *Nat Rev Cancer*, 6: 947–960. doi:10.1038/nrc2015 PMID:17128211

Nebert DW, Dalton TP, Okey AB, Gonzalez FJ (2004). Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. *J Biol Chem*, 279: 23847–23850. doi:10.1074/jbc.R400004200 PMID:15028720

Nebert DW, Roe AL, Vandale SE *et al.* (2002). NAD(P)H:quinone oxidoreductase (*NQO1*) polymorphism, exposure to benzene, and predisposition to disease: a HuGEreview. *Genet Med*, 4:62–70. doi:10.1097/00125817-200203000-00003 PMID:11882782

Negri E, Bosetti C, La Vecchia C *et al.* (1999). Risk factors for adenocarcinoma of the small intestine. *Int J Cancer*, 82: 171–174. doi:10.1002/(SICI)1097-0215(19990719)82:2<171::AID-IJC3>3.0.CO;2-T PMID:10389747

Newcomb PA, Storer BE, Marcus PM (1995). Cigarette smoking in relation to risk of large bowel cancer in women. *Cancer Res*, 55: 4906–4909. PMID:7585528

Newcomb PA & Trentham-Dietz A (2003). Patterns of postmenopausal progestin use with estrogen in relation to endometrial cancer (United States). *Cancer Causes Control*, 14: 195–201. doi:10.1023/A:1023066304473 PMID:12749724

Newcomer LM, Newcomb PA, Trentham-Dietz A, Storer BE (2001). Hormonal risk factors for endometrial cancer: modification by cigarette smoking (United States). *Cancer Causes Control*, 12: 829–835. doi:10.1023/A:1012297905601 PMID:11714111

Newhouse ML, Pearson RM, Fullerton JM *et al.* (1977). A case control study of carcinoma of the ovary. *Br J Prev Soc Med*, 31: 148–153. PMID:588853

Ng TP (1986). A case-referent study of cancer of the nasal cavity and sinuses in Hong Kong. *Int J Epidemiol*, 15: 171–175. doi:10.1093/ije/15.2.171 PMID:3721678

Nieters A, Deeg E, Becker N (2006). Tobacco and alcohol consumption and risk of lymphoma: results of a population-based case-control study in Germany. *Int J Cancer*, 118: 422–430.

Nieters A, Rohrmann S, Becker N *et al.* (2008). Smoking and lymphoma risk in the European prospective investigation into cancer and nutrition. *Am J Epidemiol*, 167: 1081–1089.

Nilsen TI & Vatten LJ (2000). A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trøndelag, Norway. *Cancer Causes Control*, 11: 645–652. doi:10.1023/A:1008916123357 PMID:10977109

Nilsson S, Carstensen JM, Pershagen G (2001). Mortality among male and female smokers in Sweden: a 33 year follow up. *J Epidemiol Community Health*, 55: 825–830. doi:10.1136/jech.55.11.825 PMID:11604439

Ning JP, Yu MC, Wang QS, Henderson BE (1990). Consumption of salted fish and other risk factors for nasopharyngeal carcinoma (NPC) in Tianjin, a low-risk region for NPC in the People's Republic of China. *J Natl Cancer Inst*, 82: 291–296. doi:10.1093/jnci/82.4.291 PMID:2299678

Nishino K, Sekine M, Kodama S *et al.* (2008). Cigarette smoking and glutathione S-transferase M1 polymorphism associated with risk for uterine cervical cancer. *J Obstet Gynaecol Res*, 34: 994–1001.

Nishino Y, Inoue M, Tsuji I *et al.*Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan (2006). Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*, 36: 800–807. doi:10.1093/jjco/hyl112 PMID:17210611

Niwa Y, Wakai K, Suzuki S *et al.*JACC Study Group (2005). Cigarette smoking and the risk of ovarian cancer in the Japanese population: findings from the Japanese Collaborate Cohort study. *J Obstet Gynaecol Res*, 31: 144–151. doi:10.1111/j.1447-0756.2005.00261.x PMID:15771641

Nkondjock A & Ghadirian P (2004). Dietary carotenoids and risk of colon cancer: case-control study. *Int J Cancer*, 110: 110–116. doi:10.1002/ijc.20066 PMID:15054875

Nkondjock A, Robidoux A, Paredes Y *et al.* (2006). Diet, lifestyle and BRCA-related breast cancer risk among French-Canadians. *Breast Cancer Res Treat*, 98: 285–294. doi:10.1007/s10549-006-9161-8 PMID:16541324

Nock NL, Liu X, Cicek MS *et al.* (2006). Polymorphisms in polycyclic aromatic hydrocarbon metabolism and conjugation genes, interactions with smoking and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*, 15: 756–761. doi:10.1158/1055-9965.EPI-05-0826 PMID:16614120

Noda N, Matsuzoe D, Konno T *et al.* (2004). Risk for K-ras gene mutations in smoking-induced lung cancer is associated with cytochrome P4501A1 and glutathione S-transferase micro1 polymorphisms. *Oncol Rep*, 12: 773–779. PMID:15375499

Nordlund LA, Carstensen JM, Pershagen G (1997). Cancer incidence in female smokers: a 26-year follow-up. *Int J Cancer*, 73: 625–628. doi:10.1002/(SICI)1097-0215(19971127)73:5<625::AID-IJC2>3.0.CO;2-Z PMID:9398036

Norppa H (2001). Genetic polymorphisms and chromosome damage. *Int J Hyg Environ Health*, 204: 31–38. doi:10.1078/1438-4639-00069 PMID:11725342

Norppa H (2003). Genetic susceptibility, biomarker respones, and cancer. *Mutat Res*, 544: 339–348. doi:10.1016/j.mrrev.2003.09.006 PMID:14644336

Norppa H (2004). Cytogenetic biomarkers and genetic polymorphisms. *Toxicol Lett*, 149: 309–334. doi:10.1016/j.toxlet.2003.12.042 PMID:15093278

Novak RF & Woodcroft KJ (2000). The alcohol-inducible form of cytochrome P450 (CYP 2E1): role in toxicology and regulation of expression. *Arch Pharm Res*, 23: 267–282. doi:10.1007/BF02975435 PMID:10976571

O'Brien MJ, Yang S, Mack C *et al.* (2006). Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. *Am J Surg Pathol*, 30: 1491–1501.

Obana H, Hori S, Kashimoto T, Kunita N (1981). Polycyclic aromatic hydrocarbons in human fat and liver. *Bull Environ Contam Toxicol*, 27: 23–27. doi:10.1007/BF01610981 PMID:7296033

Ochs-Balcom HM, Wiesner G, Elston RC (2007). A meta-analysis of the association of *N*-acetyltransferase 2 gene (*NAT2*) variants with breast cancer. *Am J Epidemiol*, 166: 246–254. PMID:17535831

Odenbro A, Gillgren P, Bellocco R *et al.* (2007). The risk for cutaneous malignant melanoma, melanoma in situ and intraocular malignant melanoma in relation to tobacco use and body mass index. *Br J Dermatol*, 156: 99–105. doi:10.1111/j.1365-2133.2006.07537.x PMID:17199574

Okamura C, Tsubono Y, Ito K *et al.* (2006). Lactation and risk of endometrial cancer in Japan: a case-control study. *Tohoku J Exp Med*, 208: 109–115. doi:10.1620/tjem.208.109 PMID:16434833

Olivier M & Hainaut P (2001). TP53 mutation patterns in breast cancers: searching for clues of environmental carcinogenesis. *Semin Cancer Biol*, 11: 353–360. doi:10.1006/scbi.2001.0390 PMID:11562177

Olsen J, Sabreo S, Fasting U (1985a). Interaction of alcohol and tobacco as risk factors in cancer of the laryngeal region. *J Epidemiol Community Health*, 39: 165–168. doi:10.1136/jech.39.2.165 PMID:4009100

Olsen J, Sabroe S, Ipsen J (1985b). Effect of combined alcohol and tobacco exposure on risk of cancer of the hypopharynx. *J Epidemiol Community Health*, 39: 304–307. doi:10.1136/jech.39.4.304 PMID:4086960

Olson JE, Vachon CM, Vierkant RA *et al.* (2005). Prepregnancy exposure to cigarette smoking and subsequent risk of postmenopausal breast cancer. *Mayo Clin Proc*, 80: 1423–1428. doi:10.4065/80.11.1423 PMID:16295021

Omata F, Brown WR, Tokuda Y *et al.* (2009). Modifiable risk factors for colorectal neoplasms and hyperplastic polyps. *Intern Med*, 48: 123–128. doi:10.2169/internalmedicine.48.1562 PMID:19182421

Oreggia F, De Stefani E, Correa P, Fierro L (1991). Risk factors for cancer of the tongue in Uruguay. *Cancer*, 67: 180–183. doi:10.1002/1097-0142(19910101)67:1<180::AID-CNCR2820670130>3.0.CO;2-R PMID:1985715

Otani T, Iwasaki M, Ikeda S *et al.* (2006). Serum triglycerides and colorectal adenoma in a case-control study among cancer screening examinees (Japan). *Cancer Causes Control*, 17: 1245–1252. doi:10.1007/s10552-006-0065-z PMID:17111255

Otani T, Iwasaki M, Yamamoto S *et al.*Japan Public Health Center-based Prospective Study Group (2003). Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. *Cancer Epidemiol Biomarkers Prev*, 12: 1492–1500. PMID:14693743

Otto H & Elmenhorst H (1967). Experimental studies on tumour induction with the gas phase of cigarette smoke.] *Z Krebsforsch*, 70: 45–47. doi:10.1007/BF00524450

Pacella-Norman R, Urban MI, Sitas F *et al.* (2002). Risk factors for oesophageal, lung, oral and laryngeal cancers in black South Africans. *Br J Cancer*, 86: 1751–1756. doi:10.1038/sj.bjc.6600338 PMID:12087462

Pakhale SS, Sarkar S, Jayant K, Bhide SV (1988). Carcinogenicity of Indian bidi and cigarette smoke condensate in Swiss albino mice. *J Cancer Res Clin Oncol*, 114: 647–649. doi:10.1007/BF00398193 PMID:3204112

Palmer JR & Rosenberg L (1993). Cigarette smoking and the risk of breast cancer. *Epidemiol Rev*, 15: 145–156. PMID:8405197

Palmer JR, Rosenberg L, Clarke EA *et al.* (1991). Breast cancer and cigarette smoking: a hypothesis. *Am J Epidemiol*, 134: 1–13. PMID:1853854

Pan SY, Ugnat AM, Mao Y *et al.*Canadian Cancer Registries Epidemiology Research Group (2004). Association of cigarette smoking with the risk of ovarian cancer. *Int J Cancer*, 111: 124–130. doi:10.1002/ijc.20242 PMID:15185353

Pandey M & Shukla VK (2003). Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. *Eur J Cancer Prev*, 12: 269–272. doi:10.1097/00008469-200308000-00005 PMID:12883378

Pandeya N, Williams GM, Sadhegi S *et al.* (2008). Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. *Am J Epidemiol*, 168: 105–114. doi:10.1093/aje/kwn091 PMID:18483122

Parente RC, Faerstein E, Celeste RK, Werneck GL (2008). The relationship between smoking and age at the menopause: A systematic review. *Maturitas*, 61: 287–298. doi:10.1016/j.maturitas.2008.09.021 PMID:19019585

Park NH, Sapp JP, Herbosa EG (1986). Oral cancer induced in hamsters with herpes simplex infection and simulated snuff dipping. *Oral Surg Oral Med Oral Pathol*, 62: 164–168. doi:10.1016/0030-4220(86)90039-3 PMID:3462612

Park SL, Chang S-C, Cai L *et al.* (2008). Associations between variants of the 8q24 chromosome and nine smoking-related cancer sites. *Cancer Epidemiol Biomarkers Prev*, 17: 3193–3202. doi:10.1158/1055-9965.EPI-08-0523 PMID:18990762

Parker AS, Cerhan JR, Dick F *et al.* (2000). Smoking and risk of non-Hodgkin lymphoma subtypes in a cohort of older women. *Leuk Lymphoma*, 37: 341–349. PMID:10752985

Parker AS, Cerhan JR, Janney CA *et al.* (2003). Smoking cessation and renal cell carcinoma. *Ann Epidemiol*, 13: 245–251. doi:10.1016/S1047-2797(02)00271-5 PMID:12684190

Paskett ED, Reeves KW, Rohan TE *et al.* (2007). Association between cigarette smoking and colorectal cancer in the Women's Health Initiative. *J Natl Cancer Inst*, 99: 1729–1735. doi:10.1093/jnci/djm176 PMID:18000222

Pavanello S & Clonfero E (2000). Biological indicators of genotoxic risk and metabolic polymorphisms. *Mutat Res*, 463: 285–308. doi:10.1016/S1383-5742(00)00051-X PMID:11018745

Pavanello S, Pulliero A, Lupi S *et al.* (2005). Influence of the genetic polymorphism in the 5′ -noncoding region of the *CYP1A2* gene on *CYP1A2* phenotype and urinary mutagenicity in smokers. *Mutat Res*, 587: 59–66. PMID:16188490

Pavanello S, Simioli P, Lupi S *et al.* (2002). Exposure levels and cytochrome P450 1A2 activity, but not *N*-acetyltransferase, glutathione *S*-transferase (GST) *M1* and *T1*, influence urinary mutagen excretion in smokers. *Cancer Epidemiol Biomarkers Prev*, 11: 998–1003. PMID:12376499

Peach HG & Barnett NE (2001). Critical review of epidemiological studies of the association between smoking and non-Hodgkin's lymphoma. *Hematol Oncol*, 19: 67–80. doi:10.1002/hon.677 PMID:11438976

Penning TM & Drury JE (2007). Human aldo-keto reductases: Function, gene regulation, and single nucleotide polymorphisms. *Arch Biochem Biophys*, 464: 241–250. doi:10.1016/j.abb.2007.04.024 PMID:17537398

Peterson GM, Schmitz K *et al.* (2001). *Physical activity among smokers is inversely associated with lung cancer incidence in Iowa Women's Health Study*. 25th Annual Meeting of the American Society of Preventive Oncology

Peto R, Chen ZM, Boreham J (1999). Tobacco–the growing epidemic. *Nat Med*, 5: 15–17. doi:10.1038/4691 PMID:9883828

Petrakis NL, Gruenke LD, Beelen TC *et al.* (1978). Nicotine in breast fluid of nonlactating women. *Science*, 199: 303–305. doi:10.1126/science.619458 PMID:619458

Petridou E, Koukoulomatis P, Dessypris N *et al.* (2002). Why is endometrial cancer less common in Greece than in other European Union countries? *Eur J Cancer Prev*, 11: 427–432. doi:10.1097/00008469-200210000-00004 PMID:12394239

Pfeifer GP, Denissenko MF, Olivier M *et al.* (2002). Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene*, 21: 7435–7451. doi:10.1038/sj.onc.1205803 PMID:12379884

Phillips DH (1983). Fifty years of benzo(a)pyrene. *Nature*, 303: 468–472. doi:10.1038/303468a0 PMID:6304528

Phillips DH (2002). Smoking-related DNA and protein adducts in human tissues. *Carcinogenesis*, 23: 1979–2004. doi:10.1093/carcin/23.12.1979 PMID:12507921

Phillips LE, Longstreth WT Jr, Koepsell T *et al.* (2005). Active and passive cigarette smoking and risk of intracranial meningioma. *Neuroepidemiology*, 24: 117–122. Epub 2004 Dec 30.

Phukan RK, Zomawia E, Narain K *et al.* (2005). Tobacco use and stomach cancer in Mizoram, India. *Cancer Epidemiol Biomarkers Prev*, 14: 1892–1896.

Pinkston JA & Cole P (1996). Cigarette smoking and Warthin's tumor. *Am J Epidemiol*, 144: 183–187. PMID:8678050

Pinsky PF (2006). Racial and ethnic differences in lung cancer incidence: how much is explained by differences in smoking patterns? (United States). *Cancer Causes Control*, 17: 1017–1024. doi:10.1007/s10552-006-0038-2 PMID:16933052

Pirkle JL, Bernert JT, Caudill SP *et al.* (2006). Trends in the exposure of nonsmokers in the U.S. population to secondhand smoke: 1988–2002. *Environ Health Perspect*, 114: 853–858. PMID:16759984

Plant AL, Benson DM, Smith LC (1985). Cellular uptake and intracellular localization of benzo(a)pyrene by digital fluorescence imaging microscopy. *J Cell Biol*, 100: 1295–1308. doi:10.1083/jcb.100.4.1295 PMID:3980583

Plummer M, Herrero R, Franceschi S *et al.*IARC Multicentre Cervical Cancer Study Group (2003). Smoking and cervical cancer: pooled analysis of the IARC multicentric case–control study. *Cancer Causes Control*, 14: 805–814. doi:10.1023/B:CACO.0000003811.98261.3e PMID:14682438

Polychronopoulou A, Tzonou A, Hsieh CC *et al.* (1993). Reproductive variables, tobacco, ethanol, coffee and somatometry as risk factors for ovarian cancer. *Int J Cancer*, 55: 402–407. doi:10.1002/ijc.2910550312 PMID:8375923

Poplawski T, Tomaszewska K, Galicki M *et al.* (2008). Promoter methylation of cancer-related genes in gastric carcinoma. *Exp Oncol*, 30: 112–116. PMID:18566573

Powell J & McConkey CC (1990). Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer*, 62: 440–443. PMID:2206952

Prescott J, Ma H, Bernstein L, Ursin G (2007). Cigarette smoking is not associated with breast cancer risk in young women. *Cancer Epidemiol Biomarkers Prev*, 16: 620–622. doi:10.1158/1055-9965.EPI-06-0873 PMID:17372262

Preussmann R, Stewart BW (1984). *N-Nitroso Carcinogens.* In: *Chemical Carcinogens, Second Edition, ACS Monograph 182.* Searle CE, editor. Washington, DC: American Chemical Society.

Proia NK, Paszkiewicz GM, Nasca MA *et al.* (2006). Smoking and smokeless tobacco-associated human buccal cell mutations and their association with oral cancer–a review. *Cancer Epidemiol Biomarkers Prev*, 15: 1061–1077. doi:10.1158/1055-9965.EPI-05-0983 PMID:16775162

Prokopczyk B, Hoffmann D, Bologna M *et al.* (2002). Identification of tobacco-derived compounds in human pancreatic juice. *Chem Res Toxicol*, 15: 677–685. doi:10.1021/tx0101088 PMID:12018989

Prokopczyk B, Leder G, Trushin N *et al.* (2005). 4-Hydroxy-1-(3-pyridyl)-1-butanone, an indicator for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced DNA damage, is not detected in human pancreatic tissue. *Cancer Epidemiol Biomarkers Prev*, 14: 540–541. doi:10.1158/1055-9965.EPI-04-0626 PMID:15734986

Quinn AM, Harvey RG, Penning TM (2008). Oxidation of PAH *trans*-dihydrodiols by human aldo-keto reductase AKR1B10. *Chem Res Toxicol*, 21: 2207–2215. doi:10.1021/tx8002005 PMID:18788756

Quiñones LA, Irarrázabal CE, Rojas CR *et al.* (2006). Joint effect among p53, CYP1A1, GSTM1 polymorphism combinations and smoking on prostate cancer risk: an exploratory genotype-environment interaction study. *Asian J Androl*, 8: 349–355. doi:10.1111/j.1745-7262.2006.00135.x PMID:16625286

Rahman M, Sakamoto J, Fukui T (2003). Bidi smoking and oral cancer: a meta-analysis. *Int J Cancer*, 106: 600–604. doi:10.1002/ijc.11265 PMID:12845659

Raimondi S, Paracchini V, Autrup H *et al.* (2006). Meta- and pooled analysis of GSTT1 and lung cancer: a HuGE-GSEC review. *Am J Epidemiol*, 164: 1027–1042. doi:10.1093/aje/kwj321 PMID:17000715

Raitiola HS & Pukander JS (1997). Etiological factors of laryngeal cancer. *Acta Otolaryngol Suppl*, 529: 215–217. doi:10.3109/00016489709124126 PMID:9288314

Rao AR (1984). Modifying influences of betel quid ingredients on B(a)P-induced carcinogenesis in the buccal pouch of hamster. *Int J Cancer*, 33: 581–586. doi:10.1002/ijc.2910330506 PMID:6327538

Rao DN & Desai PB (1998). Risk assessment of tobacco, alcohol and diet in cancers of base tongue and oral tongue–a case control study. *Indian J Cancer*, 35: 65–72. PMID:9849026

Rao DN, Desai PB, Ganesh B (1999). Alcohol as an additional risk factor in laryngopharyngeal cancer in Mumbai–a case-control study. *Cancer Detect Prev*, 23: 37–44. doi:10.1046/j.1525-1500.1999.09906.x PMID:9892989

Rao DN, Ganesh B, Dinshaw KA, Mohandas KM (2002). A case-control study of stomach cancer in Mumbai, India. *Int J Cancer*, 99: 727–731. doi:10.1002/ijc.10339 PMID:12115507

Rao DN, Ganesh B, Rao RS, Desai PB (1994). Risk assessment of tobacco, alcohol and diet in oral cancer–a case-control study. *Int J Cancer*, 58: 469–473. doi:10.1002/ijc.2910580402 PMID:8056441

Rappaport SM, Kim S, Lan Q *et al.* (2009). Evidence that humans metabolize benzene via two pathways. *Environ Health Perspect*, 117: 946–952. PMID:19590688

Raucy JL & Carpenter SJ (1993). The expression of xenobiotic-metabolizing cytochromes P450 in fetal tissues. *J Pharmacol Toxicol Methods*, 29: 121–128. doi:10.1016/1056-8719(93)90062-J PMID:8364226

Ray CS & Gupta P (2009). Bidis and Smokeless Tobacco. *Current Science*, 96: 1324–1334.

Rebbeck TR (1997). Molecular epidemiology of the human glutathione *S*-transferase genotypes *GSTM1* and *GSTT1* in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev*, 6: 733–743. PMID:9298582

Reid A, de Klerk NH, Ambrosini GL *et al.* (2006a). The risk of lung cancer with increasing time since ceasing exposure to asbestos and quitting smoking. *Occup Environ Med*, 63: 509–512. doi:10.1136/oem.2005.025379 PMID:16849527

Reid ME, Duffield-Lillico AJ, Sunga A *et al.* (2006b). Selenium supplementation and colorectal adenomas: an analysis of the nutritional prevention of cancer trial. *Int J Cancer*, 118: 1777–1781. doi:10.1002/ijc.21529 PMID:16217756

Reynolds P, Hurley S, Goldberg DE *et al.* (2004a). Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J Natl Cancer Inst*, 96: 29–37. doi:10.1093/jnci/djh002 PMID:14709736

Reynolds P, Hurley SE, Hoggatt K *et al.* (2004b). Correlates of active and passive smoking in the California Teachers Study cohort. *J Womens Health (Larchmt)*, 13: 778–790. doi:10.1089/jwh.2004.13.778 PMID:15385072

Richardson H, Abrahamowicz M, Tellier PP *et al.* (2005). Modifiable risk factors associated with clearance of type-specific cervical human papillomavirus infections in a cohort of university students. *Cancer Epidemiol Biomarkers Prev*, 14: 1149–1156. doi:10.1158/1055-9965. EPI-04-0230 PMID:15894665

Riman T, Dickman PW, Nilsson S *et al.* (2004). Some lifestyle factors and the risk of invasive epithelial ovarian cancer in Swedish women. *Eur J Epidemiol*, 19: 1011–1019. doi:10.1007/s10654-004-1633-8 PMID:15648594

Riopel MA, Ronnett BM, Kurman RJ (1999). Evaluation of diagnostic criteria and behavior of ovarian intestinal-type mucinous tumors: atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive, and metastatic carcinomas. *Am J Surg Pathol*, 23: 617–635. doi:10.1097/00000478-199906000-00001 PMID:10366144

Risch A & Plass C (2008). Lung cancer epigenetics and genetics. *Int J Cancer*, 123: 1–7. PMID:18425819

Risch HA, Howe GR, Jain M *et al.* (1993). Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. *Am J Epidemiol*, 138: 281–293. PMID:8395141

Risch HA, Marrett LD, Jain M, Howe GR (1996). Differences in risk factors for epithelial ovarian cancer by histologic type. Results of a case-control study. *Am J Epidemiol*, 144: 363–372. PMID:8712193

Roddam AW, Pirie K, Pike MC *et al.* (2007). Active and passive smoking and the risk of breast cancer in women aged 36–45 years: a population based case-control study in the UK. *Br J Cancer*, 97: 434–439. doi:10.1038/sj.bjc.6603859 PMID:17579618

Rodgman A & Perfetti TA (2006). The composition of cigarette smoke: a catalogue of the polycyclic aromatic hydrocarbons. *Beitr. Tabakforschung Inti.*, 22: 13–69.

Rodgman A, Perfetti TA (2009). *Alphabetical Component Index*. In: *The Chemical Components of Tobacco and Tobacco Smoke*. Rodgman A, Perfetti TA, editors. Boca Raton, FL: CRC Press, pp. 1483–1784.

Rodin SN & Rodin AS (2005). Origins and selection of p53 mutations in lung carcinogenesis. *Semin Cancer Biol*, 15: 103–112. doi:10.1016/j.semcancer.2004.08.005 PMID:15652455

Rodriguez T, Altieri A, Chatenoud L *et al.* (2004). Risk factors for oral and pharyngeal cancer in young adults. *Oral Oncol*, 40: 207–213. doi:10.1016/j.oraloncology.2003.08.014 PMID:14693246

Rodriguez-Antona C & Ingelman-Sundberg M (2006). Cytochrome *P450* pharmacogenetics and cancer. *Oncogene*, 25: 1679–1691. doi:10.1038/sj.onc.1209377 PMID:16550168

Rohan TE & Baron JA (1989). Cigarette smoking and breast cancer. *Am J Epidemiol*, 129: 36–42. PMID:2910070

Rohrmann S, Genkinger JM, Burke A *et al.* (2007). Smoking and risk of fatal prostate cancer in a prospective U.S. study. *Urology*, 69: 721–725. doi:10.1016/j.urology.2006.12.020 PMID:17445658

Rollison DE, Brownson RC, Hathcock HL, Newschaffer CJ (2008). Case-control study of tobacco smoke exposure and breast cancer risk in Delaware. *BMC Cancer*, 8: 157 doi:10.1186/1471-2407-8-157 PMID:18518960

Rollison DE, Helzlsouer KJ, Lee JH *et al.* (2009). Prospective study of JC virus seroreactivity and the development of colorectal cancers and adenomas. *Cancer Epidemiol Biomarkers Prev*, 18: 1515–1523. doi:10.1158/1055-9965. EPI-08-1119 PMID:19383887

Rolón PA, Castellsagué X, Benz M, Muñoz N (1995). Hot and cold mate drinking and esophageal cancer in Paraguay. *Cancer Epidemiol Biomarkers Prev*, 4: 595–605. PMID:8547825

Rossing MA, Cushing-Haugen KL, Wicklund KG, Weiss NS (2008). Cigarette smoking and risk of epithelial ovarian cancer. *Cancer Causes Control*, 19: 413–420. doi:10.1007/s10552-007-9103-8 PMID:18080774

Rothman KJ, Greenland S (1998). *Modern Epidemiology*, 2nd ed. Philadelphia, USA: Lippincott-Raven Publishers.

Roubidoux MA, Kaur JS, Griffith KA *et al.* (2003). Relationship of mammographic parenchymal patterns to breast cancer risk factors and smoking in Alaska Native women. *Cancer Epidemiol Biomarkers Prev*, 12: 1081–1086. PMID:14578146

Royce JM, Hymowitz N, Corbett K *et al.*COMMIT Research Group (1993). Smoking cessation factors among African Americans and whites. *Am J Public Health*, 83: 220–226. doi:10.2105/AJPH.83.2.220 PMID:8427327

Ruano-Ravina A, Figueiras A, Freire-Garabal M, Barros-Dios JM (2006). Antioxidant vitamins and risk of lung cancer. *Curr Pharm Des*, 12: 599–613. doi:10.2174/138161206775474396 PMID:16472151

Rubin GL, Peterson HB, Lee NC *et al.* (1990). Estrogen replacement therapy and the risk of endometrial cancer: remaining controversies. *Am J Obstet Gynecol*, 162: 148–154. PMID:2301483

Ryk C, Berggren P, Kumar R *et al.* (2005). Influence of *GSTM1*, *GSTT1*, *GSTP1* and *NAT2* genotypes on the *p53* mutational spectrum in bladder tumours. *Int J Cancer*, 113: 761–768. doi:10.1002/ijc.20650 PMID:15499621

Saccone SF, Hinrichs AL, Saccone NL *et al.* (2007). Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Hum Mol Genet*, 16: 36–49. doi:10.1093/hmg/ddl438 PMID:17135278

Saintot M, Malaveille C, Hautefeuille A, Gerber M (2003). Interactions between genetic polymorphism of cytochrome P450–1B1, sulfotransferase 1A1, catechol-o-methyltransferase and tobacco exposure in breast cancer risk. *Int J Cancer*, 107: 652–657. doi:10.1002/ijc.11432 PMID:14520706

Sala E, Warren R, McCann J *et al.* (2000). Smoking and high-risk mammographic parenchymal patterns: a case-control study. *Breast Cancer Res*, 2: 59–63. doi:10.1186/bcr29 PMID:11056684

Salama SA, Abdel-Rahman SZ, Sierra-Torres CH *et al.* (1999). Role of polymorphic *GSTM1* and *GSTT1* genotypes on NNK-induced genotoxicity. *Pharmacogenetics*, 9: 735–743. doi:10.1097/00008571-199912000-00008 PMID:10634136

Salaspuro V & Salaspuro M (2004). Synergistic effect of alcohol drinking and smoking on *in vivo* acetaldehyde concentration in saliva. *Int J Cancer*, 111: 480–483. doi:10.1002/ijc.20293 PMID:15239123

Samanic C, Kogevinas M, Dosemeci M *et al.* (2006). Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev*, 15: 1348–1354. doi:10.1158/1055-9965.EPI-06-0021 PMID:16835335

Samowitz WS (2008). Genetic and epigenetic changes in colon cancer. *Exp Mol Pathol*, 85: 64–67. doi:10.1016/j.yexmp.2008.03.008 PMID:18482722

Samowitz WS, Albertsen H, Sweeney C *et al.* (2006). Association of smoking, CpG island methylator phenotype, and V600E BRAF mutations in colon cancer. *J Natl Cancer Inst*, 98: 1731–1738. doi:10.1093/jnci/djj468 PMID:17148775

Samowitz WS, Slattery ML, Sweeney C *et al.* (2007). *APC* mutations and other genetic and epigenetic changes in colon cancer. *Mol Cancer Res*, 5: 165–170. doi:10.1158/1541-7786.MCR-06-0398 PMID:17293392

Sanderson S, Salanti G, Higgins J (2007). Joint effects of the *N*-acetyltransferase 1 and 2 (*NAT1* and *NAT2*) genes and smoking on bladder carcinogenesis: a literature-based systematic HuGE review and evidence synthesis. *Am J Epidemiol*, 166: 741–751. doi:10.1093/aje/kwm167 PMID:17675654

Sanjoaquin MA, Appleby PN, Thorogood M *et al.* (2004). Nutrition, lifestyle and colorectal cancer incidence: a prospective investigation of 10998 vegetarians and non-vegetarians in the United Kingdom. *Br J Cancer*, 90: 118–121. doi:10.1038/sj.bjc.6601441 PMID:14710217

Sankaranarayanan R, Duffy SW, Day NE *et al.* (1989b). A case-control investigation of cancer of the oral tongue and the floor of the mouth in southern India. *Int J Cancer*, 44: 617–621. doi:10.1002/ijc.2910440410 PMID:2793234

Sankaranarayanan R, Duffy SW, Nair MK *et al.* (1990b). Tobacco and alcohol as risk factors in cancer of the larynx in Kerala, India. *Int J Cancer*, 45: 879–882. doi:10.1002/ijc.2910450517 PMID:2335391

Sankaranarayanan R, Duffy SW, Padmakumary G *et al.* (1989a). Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India. *Br J Cancer*, 60: 638–643. PMID:2803939

Sankaranarayanan R, Duffy SW, Padmakumary G *et al.* (1990a). Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. *J Epidemiol Community Health*, 44: 286–292. doi:10.1136/jech.44.4.286 PMID:2277249

Sankaranarayanan R, Duffy SW, Padmakumary G *et al.* (1991). Risk factors for cancer of the oesophagus in Kerala, India. *Int J Cancer*, 49: 485–489. doi:10.1002/ijc.2910490402 PMID:1917146

Sapkota A, Gajalakshmi V, Jetly DH *et al.* (2007). Smokeless tobacco and increased risk of hypopharyngeal and laryngeal cancers: a multicentric case-control study from India. *Int J Cancer*, 121: 1793–1798. doi:10.1002/ijc.22832 PMID:17583577

Sasazuki S, Sasaki S, Tsugane SJapan Public Health Center Study Group (2002). Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer*, 101: 560–566. doi:10.1002/ijc.10649 PMID:12237898

Sauvaget C, Lagarde F, Nagano J *et al.* (2005). Lifestyle factors, radiation and gastric cancer in atomic-bomb survivors (Japan). *Cancer Causes Control*, 16: 773–780. doi:10.1007/s10552-005-5385-x PMID:16132787

Scanlon EF, Suh O, Murthy SM *et al.* (1995). Influence of smoking on the development of lung metastases from breast cancer. *Cancer*, 75: 2693–2699. doi:10.1002/1097-0142(19950601)75:11<2693::AID-CNCR2820751109>3.0.CO;2-E PMID:7743472

Schechter MT, Miller AB, Howe GR (1985). Cigarette smoking and breast cancer: a case-control study of screening program participants. *Am J Epidemiol*, 121: 479–487. PMID:4014139

Schildt EB, Eriksson M, Hardell L, Magnuson A (1998). Oral snuff, smoking habits and alcohol consumption in

relation to oral cancer in a Swedish case-control study. *Int J Cancer*, 77: 341–346. doi:10.1002/(SICI)1097-0215(19980729)77:3<341::AID-IJC6>3.0.CO;2-O PMID:9663593

Schlecht NF, Franco EL, Pintos J *et al.* (1999b). Interaction between tobacco and alcohol consumption and the risk of cancers of the upper aero-digestive tract in Brazil. *Am J Epidemiol*, 150: 1129–1137. PMID:10588073

Schlecht NF, Franco EL, Pintos J, Kowalski LP (1999a). Effect of smoking cessation and tobacco type on the risk of cancers of the upper aero-digestive tract in Brazil. *Epidemiology*, 10: 412–418. doi:10.1097/00001648-199907000-00012 PMID:10401876

Schlemmer A, Jensen J, Riis BJ, Christiansen C (1990). Smoking induces increased androgen levels in early post-menopausal women. *Maturitas*, 12: 99–104. doi:10.1016/0378-5122(90)90087-M PMID:2123959

Schlicht KE, Michno N, Smith BD *et al.* (2007). Functional characterization of CYP2A13 polymorphisms. *Xenobiotica*, 37: 1439–1449. PMID:17922361

Schlöbe D, Hölzle D, Hatz D *et al.* (2008). 4-Hydroxy-1-(3-pyridyl)-1-butanone-releasing DNA adducts in lung, lower esophagus and cardia of sudden death victims. *Toxicology*, 245: 154–161. doi:10.1016/j.tox.2007.12.021 PMID:18243467

Schöllkopf C, Smedby KE, Hjalgrim H *et al.* (2005). Cigarette smoking and risk of non-Hodgkin's lymphoma — a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*, 14: 1791–1796.

Schuller HM (2002). Mechanisms of smoking-related lung and pancreatic adenocarcinoma development. *Nat Rev Cancer*, 2: 455–463. PMID:12189387

Schuller HM (2009). Is cancer triggered by altered signalling of nicotinic acetylcholine receptors? *Nat Rev Cancer*, 9: 195–205. doi:10.1038/nrc2590 PMID:19194381

Schütze N, Vollmer G, Knuppen R (1994). Catecholestrogens are agonists of estrogen receptor dependent gene expression in MCF-7 cells. *J Steroid Biochem Mol Biol*, 48: 453–461. doi:10.1016/0960-0760(94)90193-7 PMID:8180106

Schütze N, Vollmer G, Tiemann I *et al.* (1993). Catecholestrogens are MCF-7 cell estrogen receptor agonists. *J Steroid Biochem Mol Biol*, 46: 781–789. doi:10.1016/0960-0760(93)90319-R PMID:8274412

Schwartz AG & Swanson GM (1997). Lung carcinoma in African Americans and whites. A population-based study in metropolitan Detroit, Michigan. *Cancer*, 79: 45–52. doi:10.1002/(SICI)1097-0142(19970101)79:1<45::AID-CNCR7>3.0.CO;2-L PMID:8988725

SEER (2004). *Surveillance research Program, Cancer Statistics Branch*. http://www.seer.cancer.gov/publications/csr.html

Seidegård J, Pero RW, Markowitz MM *et al.* (1990). Isoenzyme(s) of glutathione transferase (class Mu) as a marker for the susceptibility to lung cancer: a follow up study. *Carcinogenesis*, 11: 33–36. doi:10.1093/carcin/11.1.33 PMID:2295125

Seidegård J, Pero RW, Miller DG, Beattie EJ (1986). A glutathione transferase in human leukocytes as a marker for the susceptibility to lung cancer. *Carcinogenesis*, 7: 751–753. doi:10.1093/carcin/7.5.751 PMID:3698203

Sen B, Mahadevan B, DeMarini DM (2007). Transcriptional responses to complex mixtures: a review. *Mutat Res*, 636: 144–177. doi:10.1016/j.mrrev.2007.08.002 PMID:17888717

Seow A, Vainio H, Yu MC (2005). Effect of glutathione-S-transferase polymorphisms on the cancer preventive potential of isothiocyanates: an epidemiological perspective. *Mutat Res*, 592: 58–67. doi:10.1016/j.mrfmmm.2005.06.004 PMID:16019037

Setiawan VW, Pike MC, Kolonel LN *et al.* (2007). Racial/ethnic differences in endometrial cancer risk: the multiethnic cohort study. *Am J Epidemiol*, 165: 262–270. doi:10.1093/aje/kwk010 PMID:17090617

Shaib YH, El-Serag HB, Nooka AK *et al.* (2007). Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a hospital-based case-control study. *Am J Gastroenterol*, 102: 1016–1021. doi:10.1111/j.1572-0241.2007.01104.x PMID:17324130

Shapiro JA, Jacobs EJ, Thun MJ (2000). Cigar smoking in men and risk of death from tobacco-related cancers. *J Natl Cancer Inst*, 92: 333–337. doi:10.1093/jnci/92.4.333 PMID:10675383

Sharpe CR & Siemiatycki J (2001). Joint effects of smoking and body mass index on prostate cancer risk. *Epidemiology*, 12: 546–551. doi:10.1097/00001648-200109000-00014 PMID:11505174

Sharpe CR, Siemiatycki JA, Rachet BP (2002). The effects of smoking on the risk of colorectal cancer. *Dis Colon Rectum*, 45: 1041–1050. PMID:12195188

Shi X, Zhou S, Wang Z *et al.* (2008). *CYP1A1* and *GSTM1* polymorphisms and lung cancer risk in Chinese populations: a meta-analysis. *Lung Cancer*, 59: 155–163. doi:10.1016/j.lungcan.2007.08.004 PMID:17900751

Shields TS, Weiss NS, Voigt LF, Beresford SA (1999). The additional risk of endometrial cancer associated with unopposed estrogen use in women with other risk factors. *Epidemiology*, 10: 733–738. doi:10.1097/00001648-199911000-00014 PMID:10535788

Shikata K, Doi Y, Yonemoto K *et al.* (2008). Population-based prospective study of the combined influence of cigarette smoking and Helicobacter pylori infection on gastric cancer incidence: the Hisayama Study. *Am J Epidemiol*, 168: 1409–1415. doi:10.1093/aje/kwn276 PMID:18945691

Shimizu M, Lasker JM, Tsutsumi M, Lieber CS (1990). Immunohistochemical localization of ethanol-inducible P450IIE1 in the rat alimentary tract. *Gastroenterology*, 99: 1044–1053. PMID:2203661

Shimizu N, Nagata C, Shimizu H *et al.* (2003). Height, weight, and alcohol consumption in relation to the

risk of colorectal cancer in Japan: a prospective study. *Br J Cancer*, 88: 1038–1043. doi:10.1038/sj.bjc.6600845 PMID:12671701

Shklar G (1972). Experimental oral pathology in the Syrian hamster. *Prog Exp Tumor Res*, 16: 518–538. PMID:4557243

Shrubsole MJ, Wu H, Ness RM *et al.* (2008). Alcohol drinking, cigarette smoking, and risk of colorectal adenomatous and hyperplastic polyps. *Am J Epidemiol*, 167: 1050–1058. doi:10.1093/aje/kwm400 PMID:18304959

Shu HP & Bymun EN (1983). Systemic excretion of benzo(a)pyrene in the control and microsomally induced rat: the influence of plasma lipoproteins and albumin as carrier molecules. *Cancer Res*, 43: 485–490. PMID:6293698

Sikström B, Hellberg D, Nilsson S, Mårdh PA (1995). Smoking, alcohol, sexual behaviour and drug use in women with cervical human papillomavirus infection. *Arch Gynecol Obstet*, 256: 131–137. doi:10.1007/BF01314641 PMID:7574905

Sillanpää P, Heikinheimo L, Kataja V *et al.* (2007). CYP1A1 and CYP1B1 genetic polymorphisms, smoking and breast cancer risk in a Finnish Caucasian population. *Breast Cancer Res Treat*, 104: 287–297. doi:10.1007/s10549-006-9414-6 PMID:17063266

Simán JH, Forsgren A, Berglund G, Florén C-H (2001). Tobacco smoking increases the risk for gastric adenocarcinoma among Helicobacter pylori-infected individuals. *Scand J Gastroenterol*, 36: 208–213. doi:10.1080/003655201750065988 PMID:11252415

Simarak S, de Jong UW, Breslow N *et al.* (1977). Cancer of the oral cavity, pharynx/larynx and lung in North Thailand: case-control study and analysis of cigar smoke. *Br J Cancer*, 36: 130–140. PMID:19028

Singh R & Farmer PB (2006). Liquid chromatography-electrospray ionization-mass spectrometry: the future of DNA adduct detection. *Carcinogenesis*, 27: 178–196. doi:10.1093/carcin/bgi260 PMID:16272169

Singh R, Kaur B, Farmer PB (2005). Detection of DNA damage derived from a direct acting ethylating agent present in cigarette smoke by use of liquid chromatography-tandem mass spectrometry. *Chem Res Toxicol*, 18: 249–256. doi:10.1021/tx049793j PMID:15720129

Sjödahl K, Lu Y, Nilsen TI *et al.* (2007). Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study. *Int J Cancer*, 120: 128–132. doi:10.1002/ijc.22157 PMID:17036324

Skipper PL & Tannenbaum SR (1990). Protein adducts in the molecular dosimetry of chemical carcinogens. *Carcinogenesis*, 11: 507–518. doi:10.1093/carcin/11.4.507 PMID:2182215

Skjelbred CF, Saebø M, Wallin H *et al.* (2006). Polymorphisms of the XRCC1, XRCC3 and XPD genes and risk of colorectal adenoma and carcinoma, in a Norwegian cohort: a case control study. *BMC Cancer*, 6: 67 doi:10.1186/1471-2407-6-67 PMID:16542436

Slattery ML, Curtin K, Anderson K *et al.* (2000). Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. *J Natl Cancer Inst*, 92: 1831–1836. doi:10.1093/jnci/92.22.1831 PMID:11078760

Slattery ML, Curtin K, Giuliano AR *et al.* (2008). Active and passive smoking, IL6, ESR1, and breast cancer risk. *Breast Cancer Res Treat*, 109: 101–111. doi:10.1007/s10549-007-9629-1 PMID:17594514

Slattery ML, Curtin K, Ma K *et al.* (2002). *GSTM*-1 and *NAT2* and genetic alterations in colon tumors. *Cancer Causes Control*, 13: 527–534. doi:10.1023/A:1016376016716 PMID:12195642

Slattery ML, Edwards S, Curtin K *et al.* (2003). Associations between smoking, passive smoking, GSTM-1, NAT2, and rectal cancer. *Cancer Epidemiol Biomarkers Prev*, 12: 882–889. PMID:14504199

Slattery ML, Samowtiz W, Ma K *et al.* (2004). CYP1A1, cigarette smoking, and colon and rectal cancer. *Am J Epidemiol*, 160: 842–852. doi:10.1093/aje/kwh298 PMID:15496536

Slemenda CW, Hui SL, Longcope C, Johnston CC Jr (1989). Cigarette smoking, obesity, and bone mass. *J Bone Miner Res*, 4: 737–741. PMID:2816518

Smith CJ, Perfetti TA, King JA (2006). Perspectives on pulmonary inflammation and lung cancer risk in cigarette smokers. *Inhal Toxicol*, 18: 667–677. doi:10.1080/08958370600742821 PMID:16864557

Smith EM, Sowers MF, Burns TL (1984). Effects of smoking on the development of female reproductive cancers. *J Natl Cancer Inst*, 73: 371–376. PMID:6589429

Smith JB & Randle HW (2001). Giant basal cell carcinoma and cigarette smoking. *Cutis*, 67: 73–76. PMID:11204609

Smits KM, Gaspari L, Weijenberg MP *et al.* (2003). Interaction between smoking, GSTM1 deletion and colorectal cancer: results from the GSEC study. *Biomarkers*, 8: 299–310. doi:10.1080/1354750031000121467 PMID:12944179

Sokić SI, Adanja BJ, Marinković JP, Vlajinac HD (1994). Case-control study of risk factors in laryngeal cancer. *Neoplasma*, 41: 43–47. PMID:8202195

Song DK, Xing DL, Zhang LR *et al.* (2009). Association of *NAT2*, *GSTM1*, *GSTT1*, *CYP2A6*, and *CYP2A13* gene polymorphisms with susceptibility and clinicopathologic characteristics of bladder cancer in Central China. *Cancer Detect Prev*, 32: 416–423. PMID:19303722

Sparks R, Bigler J, Sibert JG *et al.* (2004). TGFbeta1 polymorphism (L10P) and risk of colorectal adenomatous and hyperplastic polyps. *Int J Epidemiol*, 33: 955–961. doi:10.1093/ije/dyh102 PMID:15020570

Spira A, Beane J, Shah V *et al.* (2004). Effects of cigarette smoke on the human airway epithelial cell transcriptome. *Proc Natl Acad Sci U S A*, 101: 10143–10148. doi:10.1073/pnas.0401422101 PMID:15210990

Spitz MR, Amos CI, Dong Q *et al.* (2008). The CHRNA5–A3 region on chromosome 15q24–25.1 is a risk factor both for nicotine dependence and for lung cancer. *J Natl Cancer Inst*, 100: 1552–1556. doi:10.1093/jnci/djn363 PMID:18957677

Spitz MR, Duphorne CM, Detry MA *et al.* (2000). Dietary intake of isothiocyanates: evidence of a joint effect with glutathione *S*-transferase polymorphisms in lung cancer risk. *Cancer Epidemiol Biomarkers Prev*, 9: 1017–1020. PMID:11045782

Spitz MR, Fueger JJ, Goepfert H, Newell GR (1990). Salivary gland cancer. A case-control investigation of risk factors. *Arch Otolaryngol Head Neck Surg*, 116: 1163–1166. PMID:2206501

Spitz MR, Wu X, Wilkinson A, Wei D (2006). *Cancer of the Lung*. In: *Cancer Epidemiology and Prevention*. Schottenfeld D, Fraumeni JF, editors. New York: Oxford University Press, Chap 33, pp. 638–658.

Sriamporn S, Vatanasapt V, Pisani P *et al.* (1992). Environmental risk factors for nasopharyngeal carcinoma: a case-control study in northeastern Thailand. *Cancer Epidemiol Biomarkers Prev*, 1: 345–348. PMID:1305465

Srivastava A & Kreiger N (2004). Cigarette smoking and testicular cancer. *Cancer Epidemiol Biomarkers Prev*, 13: 49–54. doi:10.1158/1055-9965.EPI-03-0133 PMID:14744732

Stagnaro E, Ramazzotti V, Crosignani P *et al.* (2001). Smoking and hematolymphopoietic malignancies. *Cancer Causes Control*, 12: 325–334. doi:10.1023/A:1011216102871 PMID:11456228

Stagnaro E, Tumino R, Parodi S *et al.* (2004). Non-Hodgkin's lymphoma and type of tobacco smoke. *Cancer Epidemiol Biomarkers Prev*, 13: 431–437.

Stanton MF, Miller E, Wrench C, Blackwell R (1972). Experimental induction of epidermoid carcinoma in the lungs of rats by cigarette smoke condensate. *J Natl Cancer Inst*, 49: 867–877. PMID:4647499

Stavrides JC (2006). Lung carcinogenesis: pivotal role of metals in tobacco smoke. *Free Radic Biol Med*, 41: 1017–1030. doi:10.1016/j.freeradbiomed.2006.06.024 PMID:16962926

Steinmetz J, Spyckerelle Y, Guéguen R, Dupré C (2007). Alcohol, tobacco and colorectal adenomas and cancer. Case-control study in a population with positive fecal occult blood tests *Presse Med*, 36: 1174–1182. PMID:17350789

Stellman SD, Chen Y, Muscat JE *et al.* (2003). Lung cancer risk in white and black Americans. *Ann Epidemiol*, 13: 294–302. doi:10.1016/S1047-2797(02)00420-9 PMID:12684197

Stellman SD, Takezaki T, Wang L *et al.* (2001). Smoking and lung cancer risk in American and Japanese men: an international case-control study. *Cancer Epidemiol Biomarkers Prev*, 10: 1193–1199. PMID:11700268

Stepanov I, Carmella SG, Briggs A *et al.* (2009a). Presence of the carcinogen *N*'-nitrosonornicotine in the urine of some users of oral nicotine replacement therapy products. *Cancer Res*, 69: 8236–8240. PMID:19843845

Stepanov I, Carmella SG, Han S *et al.* (2009b). Evidence for endogenous formation of *N*'-nitrosonornicotine in some long-term nicotine patch users. *Nicotine Tob Res*, 11: 99–105. PMID:19246447

Stepanov I & Hecht SS (2005). Tobacco-specific nitrosamines and their pyridine-*N*-glucuronides in the urine of smokers and smokeless tobacco users. *Cancer Epidemiol Biomarkers Prev*, 14: 885–891. doi:10.1158/1055-9965.EPI-04-0753 PMID:15824160

Stepanov I, Hecht SS, Lindgren B *et al.* (2007). Relationship of human toenail nicotine, cotinine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol to levels of these biomarkers in plasma and urine. *Cancer Epidemiol Biomarkers Prev*, 16: 1382–1386. doi:10.1158/1055-9965.EPI-07-0145 PMID:17627002

Stepanov I, Upadhyaya P, Carmella SG *et al.* (2008). Extensive metabolic activation of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in smokers. *Cancer Epidemiol Biomarkers Prev*, 17: 1764–1773. doi:10.1158/1055-9965.EPI-07-2844 PMID:18628430

Stern MC, Conti DV, Siegmund KD *et al.* (2007). DNA repair single-nucleotide polymorphisms in colorectal cancer and their role as modifiers of the effect of cigarette smoking and alcohol in the Singapore Chinese Health Study. *Cancer Epidemiol Biomarkers Prev*, 16: 2363–2372. doi:10.1158/1055-9965.EPI-07-0268 PMID:18006925

Stern MC, Siegmund KD, Conti DV *et al.* (2006). XRCC1, XRCC3, and XPD polymorphisms as modifiers of the effect of smoking and alcohol on colorectal adenoma risk. *Cancer Epidemiol Biomarkers Prev*, 15: 2384–2390. doi:10.1158/1055-9965.EPI-06-0381 PMID:17164360

Stockwell HG & Lyman GH (1987). Cigarette smoking and the risk of female reproductive cancer. *Am J Obstet Gynecol*, 157: 35–40. PMID:3605266

Strader CH, Vaughan TL, Stergachis A (1988). Use of nasal preparations and the incidence of sinonasal cancer. *J Epidemiol Community Health*, 42: 243–248. doi:10.1136/jech.42.3.243 PMID:2471766

Strange RC, Spiteri MA, Ramachandran S, Fryer AA (2001). Glutathione-*S*-transferase family of enzymes. *Mutat Res*, 482: 21–26. PMID:11535245

Strom BL, Schinnar R, Weber AL *et al.* (2006). Case-control study of postmenopausal hormone replacement therapy and endometrial cancer. *Am J Epidemiol*, 164: 775–786. doi:10.1093/aje/kwj316 PMID:16997897

Stürmer T, Glynn RJ, Lee IM *et al.* (2000). Lifetime cigarette smoking and colorectal cancer incidence in the Physicians' Health Study I. *J Natl Cancer Inst*, 92: 1178–1181. doi:10.1093/jnci/92.14.1178 PMID:10904092

Subapriya R, Thangavelu A, Mathavan B *et al.* (2007). Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. *Eur J Cancer Prev*, 16: 251–256. doi:10.1097/01.cej.0000228402.53106.9e PMID:17415096

Subramanian J & Govindan R (2008). Molecular genetics of lung cancer in people who have never smoked. *Lancet Oncol*, 9: 676–682. doi:10.1016/S1470-2045(08)70174-8 PMID:18598932

Sudo H, Li-Sucholeiki X-C, Marcelino LA *et al.* (2008). Fetal-juvenile origins of point mutations in the adult human tracheal-bronchial epithelium: absence of detectable effects of age, gender or smoking status. *Mutat Res*, 646: 25–40. PMID:18824180

Sung NY, Choi KS, Park EC *et al.* (2007). Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. *Br J Cancer*, 97: 700–704. doi:10.1038/sj.bjc.6603893 PMID:17637680

Suwan-ampai P, Navas-Acien A, Strickland PT, Agnew J (2009). Involuntary tobacco smoke exposure and urinary levels of polycyclic aromatic hydrocarbons in the United States, 1999 to 2002. *Cancer Epidemiol Biomarkers Prev*, 18: 884–893. doi:10.1158/1055-9965.EPI-08-0939 PMID:19258471

Suwanrungruang K, Sriamporn S, Wiangnon S *et al.* (2008). Lifestyle-related risk factors for stomach cancer in northeast Thailand. *Asian Pac J Cancer Prev*, 9: 71–75. PMID:18439078

Suzuki T, Matsuo K, Wakai K *et al.* (2007). Effect of familial history and smoking on common cancer risks in Japan. *Cancer*, 109: 2116–2123. doi:10.1002/cncr.22685 PMID:17410537

Swann PF (1984). Effect of ethanol on nitrosamine metabolism and distribution. Implications for the role of nitrosamines in human cancer and for the influence of alcohol consumption on cancer incidence. *IARC Sci Publ*, 57501–512. PMID:6533040

Swanson GM & Burns PB (1997). Cancers of the salivary gland: workplace risks among women and men. *Ann Epidemiol*, 7: 369–374. doi:10.1016/S1047-2797(97)00041-0 PMID:9279445

Sweeney C, Boucher KM, Samowitz WS *et al.* (2009). Oncogenetic tree model of somatic mutations and DNA methylation in colon tumors. *Genes Chromosomes Cancer*, 48: 1–9. doi:10.1002/gcc.20614 PMID:18767147

Syrjänen K, Shabalova I, Petrovichev N *et al.* (2007). Smoking is an independent risk factor for oncogenic human papillomavirus (HPV) infections but not for high-grade CIN. *Eur J Epidemiol*, 22: 723–735. doi:10.1007/s10654-007-9180-8 PMID:17828436

Szeliga J & Dipple A (1998). DNA adduct formation by polycyclic aromatic hydrocarbon dihydrodiol epoxides. *Chem Res Toxicol*, 11: 1–11. doi:10.1021/tx970142f PMID:9477220

Szyfter K, Szmeja Z, Szyfter W *et al.* (1999). Molecular and cellular alterations in tobacco smoke-associated larynx cancer. *Mutat Res*, 445: 259–274. PMID:10575435

't Mannetje A, Kogevinas M, Luce D *et al.* (1999). Sinonasal cancer, occupation, and tobacco smoking in European women and men. *Am J Ind Med*, 36: 101–107. doi:10.1002/(SICI)1097-0274(199907)36:1<101::AID-AJIM14>3.0.CO;2-A PMID:10361593

Takahashi I, Matsuzaka M, Umeda T *et al.* (2008). Differences in the influence of tobacco smoking on lung cancer between Japan and the USA: possible explanations for the 'smoking paradox' in Japan. *Public Health*, 122: 891–896. doi:10.1016/j.puhe.2007.10.004 PMID:18420238

Takahashi M, Imaida K, Mitsumori K *et al.* (1992). Promoting effects of cigarette smoke on the respiratory tract carcinogenesis of Syrian golden hamsters treated with diethylnitrosamine. *Carcinogenesis*, 13: 569–572. doi:10.1093/carcin/13.4.569 PMID:1576708

Talamini R, Bosetti C, La Vecchia C *et al.* (2002). Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. *Cancer Causes Control*, 13: 957–964. doi:10.1023/A:1021944123914 PMID:12588092

Tan W, Chen GF, Xing DY *et al.* (2001). Frequency of *CYP2A6* gene deletion and its relation to risk of lung and esophageal cancer in the Chinese population. *Int J Cancer*, 95: 96–101. doi:10.1002/1097-0215(20010320)95:2<96::AID-IJC1017>3.0.CO;2-2 PMID:11241319

Tang Y, Simoneau AR, Liao WX *et al.* (2009). WIF1, a Wnt pathway inhibitor, regulates SKP2 and c-myc expression leading to G1 arrest and growth inhibition of human invasive urinary bladder cancer cells. *Mol Cancer Ther*, 8: 458–468. doi:10.1158/1535-7163.MCT-08-0885 PMID:19174556

Tavani A, Negri E, Franceschi S *et al.* (1994). Attributable risk for laryngeal cancer in northern Italy. *Cancer Epidemiol Biomarkers Prev*, 3: 121–125. PMID:8049633

Terry MB & Neugut AI (1998). Cigarette smoking and the colorectal adenoma-carcinoma sequence: a hypothesis to explain the paradox. *Am J Epidemiol*, 147: 903–910. PMID:9596467

Terry P, Baron JA, Weiderpass E *et al.* (1999). Lifestyle and endometrial cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*, 82: 38–42. doi:10.1002/(SICI)1097-0215(19990702)82:1<38::AID-IJC8>3.0.CO;2-Q PMID:10360818

Terry P, Rohan TE, Franceschi S *et al.* (2004a). *Endometrial cancer.* In: *Tobacco: Science, Policy and Public Health*. Boyle P, Gray N, Henningfield J *et al.*, editors. Oxford University Press.

Terry PD & Goodman M (2006). Is the association between cigarette smoking and breast cancer modified by genotype? A review of epidemiologic studies and meta-analysis. *Cancer Epidemiol Biomarkers*

Prev, 15: 602–611. doi:10.1158/1055-9965.EPI-05-0853 PMID:16614098

Terry PD, Miller AB, Rohan TE (2002a). Prospective cohort study of cigarette smoking and colorectal cancer risk in women. *Int J Cancer*, 99: 480–483. doi:10.1002/ijc.10364 PMID:11992421

Terry PD, Miller AB, Rohan TE (2002b). A prospective cohort study of cigarette smoking and the risk of endometrial cancer. *Br J Cancer*, 86: 1430–1435. PMID:11986776

Terry PD & Rohan TE (2002). Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol Biomarkers Prev*, 11: 953–971. PMID:12376493

Terry PD, Rohan TE, Franceschi S, Weiderpass E (2002c). Cigarette smoking and the risk of endometrial cancer. *Lancet Oncol*, 3: 470–480. doi:10.1016/S1470-2045(02)00816-1 PMID:12147433

Theis RP, Dolwick Grieb SM, Burr D *et al.* (2008). Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study. *BMC Cancer*, 8: 387 doi:10.1186/1471-2407-8-387 PMID:19108730

Thier R, Brüning T, Roos PH *et al.* (2003). Markers of genetic susceptibility in human environmental hygiene and toxicology: the role of selected CYP, NAT and GST genes. *Int J Hyg Environ Health*, 206: 149–171. doi:10.1078/1438-4639-00209 PMID:12872524

Thompson PA, DeMarini DM, Kadlubar FF *et al.* (2002). Evidence for the presence of mutagenic arylamines in human breast milk and DNA adducts in exfoliated breast ductal epithelial cells. *Environ Mol Mutagen*, 39: 134–142. doi:10.1002/em.10067 PMID:11921181

Thorgeirsson TE, Geller F, Sulem P *et al.* (2008). A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature*, 452: 638–642. doi:10.1038/nature06846 PMID:18385739

Thun MJ & Heath CW Jr (1997). Changes in mortality from smoking in two American Cancer Society prospective studies since 1959. *Prev Med*, 26: 422–426. doi:10.1006/pmed.1997.0182 PMID:9245660

Thun MJ, Henley SJ, Burns D *et al.* (2006). Lung cancer death rates in lifelong nonsmokers. *J Natl Cancer Inst*, 98: 691–699. PMID:16705123

Tiemersma EW, Bunschoten A, Kok FJ *et al.* (2004). Effect of SULT1A1 and NAT2 genetic polymorphism on the association between cigarette smoking and colorectal adenomas. *Int J Cancer*, 108: 97–103. doi:10.1002/ijc.11533 PMID:14618622

Tiemersma EW, Kampman E, Bueno de Mesquita HB *et al.* (2002a). Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control*, 13: 383–393. doi:10.1023/A:1015236701054 PMID:12074508

Tiemersma EW, Kloosterman J, Bunschoten A *et al.* (2002b). Role of EPHX genotype in the associations of smoking and diet with colorectal adenomas. *IARC Sci Publ*, 156: 491–493. PMID:12484240

Tijhuis MJ, Visker MH, Aarts JM *et al.* (2008). NQO1 and NFE2L2 polymorphisms, fruit and vegetable intake and smoking and the risk of colorectal adenomas in an endoscopy-based population. *Int J Cancer*, 122: 1842–1848. doi:10.1002/ijc.23246 PMID:18074351

Timofeeva MN, Kropp S, Sauter W *et al.*LUCY-Consortium (2009). CYP450 polymorphisms as risk factors for early-onset lung cancer: gender-specific differences. *Carcinogenesis*, 30: 1161–1169. doi:10.1093/carcin/bgp102 PMID:19414505

To-Figueras J, Gené M, Gómez-Catalán J *et al.* (2001). Lung cancer susceptibility in relation to combined polymorphisms of microsomal epoxide hydrolase and glutathione *S*-transferase P1. *Cancer Lett*, 173: 155–162. doi:10.1016/S0304-3835(01)00626-7 PMID:11597790

Tokunaga M, Land CE, Yamamoto T *et al.* (1987). Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1980. *Radiat Res*, 112: 243–272. doi:10.2307/3577254 PMID:3685255

Tolstrup J, Munk C, Thomsen BL *et al.* (2006). The role of smoking and alcohol intake in the development of high-grade squamous intraepithelial lesions among high-risk HPV-positive women. *Acta Obstet Gynecol Scand*, 85: 1114–1119. doi:10.1080/00016340600677027 PMID:16929418

Tomita M, Odaka M, Matsumoto M *et al.* (1991). Cigarette smoking and mortality among Japanese males in a prospective cohort study *Nippon Koshu Eisei Zasshi*, 38: 492–497. PMID:1747539

Toyomura K, Yamaguchi K, Kawamoto H *et al.* (2004). Relation of cigarette smoking and alcohol use to colorectal adenomas by subsite: the self-defense forces health study. *Cancer Sci*, 95: 72–76. doi:10.1111/j.1349-7006.2004.tb03173.x PMID:14720330

Toyooka S, Tokumo M, Shigematsu H *et al.* (2006). Mutational and epigenetic evidence for independent pathways for lung adenocarcinomas arising in smokers and never smokers. *Cancer Res*, 66: 1371–1375. PMID:16452191

Tran GD, Sun XD, Abnet CC *et al.* (2005). Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*, 113: 456–463. doi:10.1002/ijc.20616 PMID:15455378

Tranah GJ, Giovannucci E, Ma J *et al.* (2004). Epoxide hydrolase polymorphisms, cigarette smoking and risk of colorectal adenoma in the Nurses' Health Study and the Health Professionals Follow-up Study. *Carcinogenesis*, 25: 1211–1218. doi:10.1093/carcin/bgh126 PMID:14988221

Tranah GJ, Giovannucci E, Ma J *et al.* (2005). APC Asp1822Val and Gly2502Ser polymorphisms and risk

of colorectal cancer and adenoma. *Cancer Epidemiol Biomarkers Prev*, 14: 863–870. doi:10.1158/1055-9965.EPI-04-0687 PMID:15824157

Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA (2006). Weight change and risk of endometrial cancer. *Int J Epidemiol*, 35: 151–158. doi:10.1093/ije/dyi226 PMID:16278243

Trichopoulos D, Brown J, MacMahon B (1987). Urine estrogens and breast cancer risk factors among post-menopausal women. *Int J Cancer*, 40: 721–725. doi:10.1002/ijc.2910400602 PMID:3692620

Trost SG, Owen N, Bauman AE *et al.* (2002). Correlates of adults' participation in physical activity: review and update. *Med Sci Sports Exerc*, 34: 1996–2001. doi:10.1097/00005768-200212000-00020 PMID:12471307

Tsai HT, Tsai YM, Yang SF *et al.* (2007). Lifetime cigarette smoke and second-hand smoke and cervical intraepithelial neoplasm — a community-based case-control study. *Gynecol Oncol*, 105: 181–188. Epub 2007 Jan 3.

Tsoi KK, Pau CY, Wu WK *et al.* (2009). Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol*, 7: 682–688, e1–e5. PMID:19245853

Tsong WH, Koh WP, Yuan JM *et al.* (2007). Cigarettes and alcohol in relation to colorectal cancer: the Singapore Chinese Health Study. *Br J Cancer*, 96: 821–827. PMID:17311023

Tu JT, Gao RN, Zhang DH, Gu BC (1985). Hepatitis B virus and primary liver cancer on Chongming Island, People's Republic of China. *Natl Cancer Inst Monogr*, 69: 213–215. PMID:3834335

Turner MC, Chen Y, Krewski D *et al.* (2007). Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med*, 176: 285–290. doi:10.1164/rccm.200612-1792OC PMID:17478615

Tuyns AJ, Estève J, Raymond L *et al.* (1988). Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). *Int J Cancer*, 41: 483–491. doi:10.1002/ijc.2910410403 PMID:3356483

Tuyns AJ, Péquignot G, Jensen OM (1977). [Esophageal cancer in Ille-et-Vilaine in relation to levels of alcohol and tobacco consumption. Risks are multiplying] *Bull Cancer*, 64: 45–60. PMID:861389

Tverdal A, Thelle D, Stensvold I *et al.* (1993). Mortality in relation to smoking history: 13 years' follow-up of 68,000 Norwegian men and women 35–49 years. *J Clin Epidemiol*, 46: 475–487. doi:10.1016/0895-4356(93)90025-V PMID:8501474

Tworoger SS, Gertig DM, Gates MA *et al.* (2008). Caffeine, alcohol, smoking, and the risk of incident epithelial ovarian cancer. *Cancer*, 112: 1169–1177. doi:10.1002/cncr.23275 PMID:18213613

Tyler CW Jr, Webster LA, Ory HW, Rubin GL (1985). Endometrial cancer: how does cigarette smoking influence the risk of women under age 55 years having this tumor? *Am J Obstet Gynecol*, 151: 899–905. PMID:3985056

Tzonou A, Day NE, Trichopoulos D *et al.* (1984). The epidemiology of ovarian cancer in Greece: a case-control study. *Eur J Cancer Clin Oncol*, 20: 1045–1052. doi:10.1016/0277-5379(84)90107-X PMID:6540687

Ulrich CM, Bigler J, Whitton JA *et al.* (2001). Epoxide hydrolase Tyr113His polymorphism is associated with elevated risk of colorectal polyps in the presence of smoking and high meat intake. *Cancer Epidemiol Biomarkers Prev*, 10: 875–882. PMID:11489754

Ursin G, London S, Stanczyk FZ *et al.* (1999). Urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*, 91: 1067–1072. doi:10.1093/jnci/91.12.1067 PMID:10379970

Vaccarella S, Herrero R, Snijders PJ *et al.*IARC HPV Prevalence Surveys (IHPS) Study Group (2008). Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys. *Int J Epidemiol*, 37: 536–546. doi:10.1093/ije/dyn033 PMID:18316350

Vachon CM, Kuni CC, Anderson K *et al.* (2000). Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control*, 11: 653–662. doi:10.1023/A:1008926607428 PMID:10977110

Vairaktaris E, Spyridonidou S, Papakosta V *et al.* (2008). The hamster model of sequential oral oncogenesis. *Oral Oncol*, 44: 315–324. doi:10.1016/j.oraloncology.2007.08.015 PMID:18061531

van Dam RM, Huang Z, Rimm EB *et al.* (1999). Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. *Am J Epidemiol*, 150: 459–468. PMID:10472945

van den Donk M, Buijsse B, van den Berg SW *et al.* (2005). Dietary intake of folate and riboflavin, MTHFR C677T genotype, and colorectal adenoma risk: a Dutch case-control study. *Cancer Epidemiol Biomarkers Prev*, 14: 1562–1566. doi:10.1158/1055-9965.EPI-04-0419 PMID:15941973

van der Hel OL, Bueno de Mesquita HB, Sandkuijl L *et al.* (2003a). Rapid N-acetyltransferase 2 imputed phenotype and smoking may increase risk of colorectal cancer in women (Netherlands). *Cancer Causes Control*, 14: 293–298. doi:10.1023/A:1023601922106 PMID:12814209

van der Hel OL, Bueno-de-Mesquita HB, van Gils CH *et al.* (2005). Cumulative genetic defects in carcinogen metabolism may increase breast cancer risk (The Netherlands). *Cancer Causes Control*, 16: 675–681. doi:10.1007/s10552-005-1227-0 PMID:16049806

Van Emburgh BO, Hu JJ, Levine EA *et al.* (2008). Polymorphisms in drug metabolism genes, smoking, and *p53* mutations in breast cancer. *Mol Carcinog*, 47: 88–99. doi:10.1002/mc.20365 PMID:17683074

van Poppel G, de Vogel N, van Balderen PJ, Kok FJ (1992). Increased cytogenetic damage in smokers deficient in glutathione S-transferase isozyme *mu*. *Carcinogenesis*, 13:303–305.doi:10.1093/carcin/13.2.303PMID:1740022

Vaughan TL, Davis S, Kristal A, Thomas DB (1995). Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*, 4: 85–92. PMID:7742727

Vaughan TL, Shapiro JA, Burt RD *et al.* (1996). Nasopharyngeal cancer in a low-risk population: defining risk factors by histological type. *Cancer Epidemiol Biomarkers Prev*, 5: 587–593. PMID:8824359

Veglia F, Loft S, Matullo G *et al.*Genair-EPIC Investigators (2008). DNA adducts and cancer risk in prospective studies: a pooled analysis and a meta-analysis. *Carcinogenesis*, 29: 932–936. doi:10.1093/carcin/bgm286 PMID:18343884

Veglia F, Matullo G, Vineis P (2003). Bulky DNA adducts and risk of cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 12: 157–160. PMID:12582026

Verla-Tebit E, Lilla C, Hoffmeister M *et al.* (2006). Cigarette smoking and colorectal cancer risk in Germany: a population-based case-control study. *Int J Cancer*, 119: 630–635. doi:10.1002/ijc.21875 PMID:16496385

Viezzer C, Norppa H, Clonfero E *et al.* (1999). Influence of *GSTM1*, *GSTT1*, *GSTP1*, and *EPHX* gene polymorphisms on DNA adduct level and *HPRT* mutant frequency in coke-oven workers. *Mutat Res*, 431: 259–269. PMID:10635992

Vineis P, Anttila S, Benhamou S *et al.* (2007). Evidence of gene gene interactions in lung carcinogenesis in a large pooled analysis. *Carcinogenesis*, 28: 1902–1905. doi:10.1093/carcin/bgm039 PMID:17307802

Vineis P & Malats N (1999). Strategic issues in the design and interpretation of studies on metabolic polymorphisms and cancer. *IARC Sci Publ*, 148: 51–61. PMID:10493248

Vineis P, Manuguerra M, Kavvoura FK *et al.* (2009). A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility. *J Natl Cancer Inst*, 101: 24–36. PMID:19116388

Vineis P, Marinelli D, Autrup H *et al.* (2001). Current smoking, occupation, *N*-acetyltransferase-2 and bladder cancer: a pooled analysis of genotype-based studies. *Cancer Epidemiol Biomarkers Prev*, 10: 1249–1252. PMID:11751441

Vineis P, Veglia F, Anttila S *et al.* (2004). CYP1A1, GSTM1 and GSTT1 polymorphisms and lung cancer: a pooled analysis of gene-gene interactions. *Biomarkers*, 9: 298–305. doi:10.1080/13547500400011070 PMID:15764294

Vineis P, Veglia F, Benhamou S *et al.* (2003). CYP1A1 T^{3801}C polymorphism and lung cancer: a pooled analysis of 2451 cases and 3358 controls. *Int J Cancer*, 104: 650–657. doi:10.1002/ijc.10995 PMID:12594823

Vioque J, Barber X, Bolumar F *et al.*PANESOES Study Group (2008). Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. *BMC Cancer*, 8: 221 doi:10.1186/1471-2407-8-221 PMID:18673563

Viswanathan AN, Feskanich D, De Vivo I *et al.* (2005). Smoking and the risk of endometrial cancer: results from the Nurses' Health Study. *Int J Cancer*, 114: 996–1001. doi:10.1002/ijc.20821 PMID:15645490

Vlajinac HD, Marinkovic JM, Sipetic SB *et al.* (2006). Case-control study of oropharyngeal cancer. *Cancer Detect Prev*, 30: 152–157. doi:10.1016/j.cdp.2006.02.001 PMID:16647226

Vlajinac HD, Pekmezović TD, Adanja BJ *et al.* (2003). Case-control study of multiple myeloma with special reference to diet as risk factor. *Neoplasma*, 50: 79–83.

Vories AA & Ramirez SG (1997). Warthin's tumor and cigarette smoking. *South Med J*, 90: 416–418. PMID:9114834

Voskuil DW, Kampman E, Grubben MJ *et al.* (2002). Meat consumption and meat preparation in relation to colorectal adenomas among sporadic and HNPCC family patients in The Netherlands. *Eur J Cancer*, 38: 2300–2308. doi:10.1016/S0959-8049(02)00455-0 PMID:12441267

Vrieling A, Bueno-De-Mesquita B, Boshuizen HC *et al.* (2009). Fruit and vegetable consumption and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, 124: 1926–1934. PMID:19107929

Wakai K, Hayakawa N, Kojima M *et al.*JACC Study Group (2003). Smoking and colorectal cancer in a non-Western population: a prospective cohort study in Japan. *J Epidemiol*, 13: 323–332. PMID:14674660

Wakai K, Inoue M, Mizoue T *et al.*Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan (2006). Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol*, 36: 309–324. doi:10.1093/jjco/hyl025 PMID:16735374

Walser T, Cui X, Yanagawa J *et al.* (2008). Smoking and lung cancer: the role of inflammation. *Proc Am Thorac Soc*, 5: 811–815. doi:10.1513/pats.200809-100TH PMID:19017734

Wang H, Tan W, Hao B *et al.* (2003). Substantial reduction in risk of lung adenocarcinoma associated with genetic polymorphism in CYP2A13, the most active cytochrome P450 for the metabolic activation of tobacco-specific carcinogen NNK. *Cancer Res*, 63: 8057–8061. PMID:14633739

Wang M, Cheng G, Balbo S *et al.* (2009). Clear differences in levels of a formaldehyde-DNA adduct in leukocytes of smokers and non-smokers. *Cancer Research*, 69:7170–7174.

Wang SS, Schiffman M, Herrero R *et al.* (2004). Determinants of human papillomavirus 16 serological conversion and persistence in a population-based cohort of 10 000 women in Costa Rica. *Br J Cancer*, 91: 1269–1274. doi:10.1038/sj.bjc.6602088 PMID:15292929

Wang Y, Pereira EF, Maus AD *et al.* (2001). Human bronchial epithelial and endothelial cells express alpha7 nicotinic acetylcholine receptors. *Mol Pharmacol*, 60: 1201–1209. PMID:11723227

Warnakulasuriya KA & Ralhan R (2007). Clinical, pathological, cellular and molecular lesions caused by oral smokeless tobacco–a review. *J Oral Pathol Med*, 36: 63–77. PMID:17238967

Warren CW, Jones NR, Eriksen MP, Asma SGlobal Tobacco Surveillance System (GTSS) collaborative group (2006). Patterns of global tobacco use in young people and implications for future chronic disease burden in adults. *Lancet*, 367: 749–753. doi:10.1016/S0140-6736(06)68192-0 PMID:16517275

Warwick J, Pinney E, Warren RM *et al.* (2003). Breast density and breast cancer risk factors in a high-risk population. *Breast*, 12: 10–16. doi:10.1016/S0960-9776(02)00212-6 PMID:14659350

Wasnik KS, Ughade SN, Zodpey SP, Ingole DL (1998). Tobacco consumption practices and risk of oropharyngeal cancer: a case-control study in Central India. *Southeast Asian J Trop Med Public Health*, 29: 827–834. PMID:10772572

Watson MA, Stewart RK, Smith GB *et al.* (1998). Human glutathione *S*-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. *Carcinogenesis*, 19: 275–280. doi:10.1093/carcin/19.2.275 PMID:9498276

Watson P, Ashwathnarayan R, Lynch HT, Roy HK (2004). Tobacco use and increased colorectal cancer risk in patients with hereditary nonpolyposis colorectal cancer (Lynch syndrome). *Arch Intern Med*, 164: 2429–2431. PMID:15596632

Wei YS, Lu JC, Wang L *et al.* (2009). Risk factors for sporadic colorectal cancer in southern Chinese. *World J Gastroenterol*, 15: 2526–2530. PMID:19469004

Weiderpass E & Baron JA (2001). Cigarette smoking, alcohol consumption, and endometrial cancer risk: a population-based study in Sweden. *Cancer Causes Control*, 12: 239–247. doi:10.1023/A:1011201911664 PMID:11405329

Weiss JM, Saltzman BS, Doherty JA *et al.* (2006a). Risk factors for the incidence of endometrial cancer according to the aggressiveness of disease. *Am J Epidemiol*, 164: 56–62. doi:10.1093/aje/kwj152 PMID:16675538

Weiss JM, Weiss NS, Ulrich CM *et al.* (2005). Interindividual variation in nucleotide excision repair genes and risk of endometrial cancer. *Cancer Epidemiol Biomarkers Prev*, 14: 2524–2530. doi:10.1158/1055-9965.EPI-05-0414 PMID:16284373

Weiss JM, Weiss NS, Ulrich CM *et al.* (2006b). Nucleotide excision repair genotype and the incidence of endometrial cancer: effect of other risk factors on the association. *Gynecol Oncol*, 103: 891–896. doi:10.1016/j.ygyno.2006.05.020 PMID:16806437

Weiss NS, Farewall VT, Szekely DR *et al.* (1980). Oestrogens and endometrial cancer: effect of other risk factors on the association. *Maturitas*, 2: 185–190. doi:10.1016/0378-5122(80)90003-1 PMID:7442552

Wells PG, Mackenzie PI, Chowdhury JR *et al.* (2004). Glucuronidation and the UDP-glucuronosyltransferases in health and disease. *Drug Metab Dispos*, 32: 281–290. doi:10.1124/dmd.32.3.281 PMID:14977861

Welzel TM, Graubard BI, El-Serag HB *et al.* (2007). Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin Gastroenterol Hepatol*, 5: 1221–1228. doi:10.1016/j.cgh.2007.05.020 PMID:17689296

Wen CP, Tsai SP, Chen CJ, Cheng TY (2004). The mortality risks of smokers in Taiwan: Part I: cause-specific mortality. *Prev Med*, 39: 528–535. doi:10.1016/j.ypmed.2004.02.010 PMID:15313092

Wenzlaff AS, Cote ML, Bock CH *et al.* (2005). CYP1A1 and CYP1B1 polymorphisms and risk of lung cancer among never smokers: a population-based study. *Carcinogenesis*, 26: 2207–2212. doi:10.1093/carcin/bgi191 PMID:16051642

West KA, Brognard J, Clark AS *et al.* (2003). Rapid Akt activation by nicotine and a tobacco carcinogen modulates the phenotype of normal human airway epithelial cells. *J Clin Invest*, 111: 81–90. PMID:12511591

West S, Hildesheim A, Dosemeci M (1993). Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case-control study. *Int J Cancer*, 55: 722–727. doi:10.1002/ijc.2910550504 PMID:7503957

Whittemore AS, Wu ML, Paffenbarger RS Jr *et al.* (1988). Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol*, 128: 1228–1240. PMID:3195564

WHO (2011).* *Third WHO Report on the Global Tobacco Epidemic*. World Health Organization. http://www.who.int/tobacco/global_report/2011/en/index.html

Wiencke JK (2002). DNA adduct burden and tobacco carcinogenesis. *Oncogene*, 21: 7376–7391. doi:10.1038/sj.onc.1205799 PMID:12379880

Willett EV, O'Connor S, Smith AG, Roman E (2007). Does smoking and alcohol modify the risk of Epstein-Barr virus-positive or -negative Hodgkin lymphoma. *Epidemiology*, 18: 130–136.

Wojno TH (1999). The association between cigarette smoking and basal cell carcinoma of the eyelids in women. *Ophthal Plast Reconstr Surg*, 15: 390–392. doi:10.1097/00002341-199911000-00004 PMID:10588245

Wojnowski L & Kamdem LK (2006). Clinical implications of *CYP3A* polymorphisms. *Expert Opin Drug Metab Toxicol*, 2: 171–182. doi:10.1517/17425255.2.2.171 PMID:16866606

Wolf CR & Smith G (1999). Cytochrome P450 CYP2D6. *IARC Sci Publ*, 148: 209–229. PMID:10493260

Wolff H, Saukkonen K, Anttila S *et al.* (1998). Expression of cyclooxygenase-2 in human lung carcinoma. *Cancer Res*, 58: 4997–5001. PMID:9823297

Wong HL, Murphy SE, Hecht SS (2005). Cytochrome P450 2A-catalyzed metabolic activation of structurally similar carcinogenic nitrosamines: *N*'-nitrosonornicotine enantiomers, *N*-nitrosopiperidine, and *N*-nitrosopyrrolidine. *Chem Res Toxicol*, 18: 61–69. doi:10.1021/tx0497696 PMID:15651850

Wright ME, Park Y, Subar AF *et al.* (2008). Intakes of fruit, vegetables, and specific botanical groups in relation to lung cancer risk in the NIH-AARP Diet and Health Study. *Am J Epidemiol*, 168: 1024–1034. doi:10.1093/aje/kwn212 PMID:18791192

Wu AH, Crabtree JE, Bernstein L *et al.* (2003). Role of Helicobacter pylori CagA+ strains and risk of adenocarcinoma of the stomach and esophagus. *Int J Cancer*, 103: 815–821. doi:10.1002/ijc.10887 PMID:12516104

Wu AH, Wan P, Bernstein L (2001). A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). *Cancer Causes Control*, 12: 721–732. doi:10.1023/A:1011290704728 PMID:11562112

Wu AH, Yu MC, Mack TM (1997). Smoking, alcohol use, dietary factors and risk of small intestinal adenocarcinoma. *Int J Cancer*, 70: 512–517. doi:10.1002/(SICI)1097-0215(19970304)70:5<512::AID-IJC4>3.0.CO;2-0 PMID:9052748

Wu C, Hu Z, Yu D *et al.* (2009a). Genetic variants on chromosome 15q25 associated with lung cancer risk in Chinese populations. *Cancer Res*, 69: 5065–5072. doi:10.1158/0008-5472.CAN-09-0081 PMID:19491260

Wu IC, Lee CH, Kuo CH *et al.* (2009b). Consumption of cigarettes but not betel quid or alcohol increases colorectal cancer risk. *J Formos Med Assoc*, 108: 155–163. doi:10.1016/S0929-6646(09)60046-2 PMID:19251551

Wynder EL, Gottlieb S, Wright G (1957). A study of tobacco carcinogenesis. IV. Different tobacco types. *Cancer*, 10: 1206–1209. doi:10.1002/1097-0142(195711/12)10:6<1206::AID-CNCR2820100618>3.0.CO;2-P PMID:13489672

Wynder EL, Graham EA, Croninger AB (1953). Experimental production of carcinoma with cigarette tar. *Cancer Res*, 13: 855–864. PMID:13116124

Wynder EL & Hoffmann D (1961). A study of tobacco carcinogenesis. VIII. The role of the acidic fractions as promoters. *Cancer*, 14: 1306–1315. doi:10.1002/1097-0142(196111/12)14:6<1306::AID-CNCR2820140621>3.0.CO;2-T PMID:14008628

Wynder EL & Stellman SD (1979). Impact of long-term filter cigarette usage on lung and larynx cancer risk: a case-control study. *J Natl Cancer Inst*, 62: 471–477. PMID:283277

Yagyu K, Kikuchi S, Obata Y *et al.*JACC Study Group (2008). Cigarette smoking, alcohol drinking and the risk of gallbladder cancer death: a prospective cohort study in Japan. *Int J Cancer*, 122: 924–929. doi:10.1002/ijc.23159 PMID:17955487

Yamasaki E & Ames BN (1977). Concentration of mutagens from urine by absorption with the nonpolar resin XAD-2: cigarette smokers have mutagenic urine. *Proc Natl Acad Sci U S A*, 74: 3555–3559. doi:10.1073/pnas.74.8.3555 PMID:333441

Yang J, Qian LX, Wu HF *et al.* (2006). Genetic polymorphisms in the cytochrome P450 1A1 and 2E1 genes, smoking, drinking and prostate cancer susceptibility: a case-control study in a Han nationality population in Southern China. *Int J Urol*, 13: 773–780. doi:10.1111/j.1442-2042.2006.01401.x PMID:16834659

Yang M, Kim S, Lee E *et al.* (2003). Sources of polycyclic aromatic hydrocarbon exposure in non-occupationally exposed Koreans. *Environ Mol Mutagen*, 42: 250–257. doi:10.1002/em.10196 PMID:14673870

Yang M, Koga M, Katoh T, Kawamoto T (1999). A study for the proper application of urinary naphthols, new biomarkers for airborne polycyclic aromatic hydrocarbons. *Arch Environ Contam Toxicol*, 36: 99–108. doi:10.1007/s002449900447 PMID:9828267

Yang P, Cunningham JM, Halling KC *et al.* (2000). Higher risk of mismatch repair-deficient colorectal cancer in alpha(1)-antitrypsin deficiency carriers and cigarette smokers. *Mol Genet Metab*, 71: 639–645. doi:10.1006/mgme.2000.3089 PMID:11136557

Yang P, Sun Z, Krowka MJ *et al.* (2008). Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. *Arch Intern Med*, 168: 1097–1103. doi:10.1001/archinte.168.10.1097 PMID:18504338

Yauk CL, Berndt ML, Williams A *et al.* (2007). Mainstream tobacco smoke causes paternal germ-line DNA mutation. *Cancer Res*, 67: 5103–5106. doi:10.1158/0008-5472.CAN-07-0279 PMID:17545587

Ye WM, Ye YN, Lin RD *et al.* (1995). Case control study on nasopharyngeal cancer in southern region of Fujian province. *Chin J Prev Control Chronic Dis*, 3: 158–161.

Ye Z, Song H, Higgins JP *et al.* (2006). Five glutathione s-transferase gene variants in 23,452 cases of lung cancer and 30,397 controls: meta-analysis of 130 studies. *PLoS Med*, 3: 524–534 doi:10.1371/journal.pmed.0030091 PMID:16509765

Yen TT, Lin WD, Wang CP *et al.* (2008). The association of smoking, alcoholic consumption, betel quid chewing and oral cavity cancer: a cohort study. *Eur Arch Otorhinolaryngol*, 265: 1403–1407. doi:10.1007/s00405-008-0659-z PMID:18389268

Yoo KY, Tajima K, Miura S *et al.* (1997). Breast cancer risk factors according to combined estrogen and progesterone receptor status: a case-control analysis. *Am J Epidemiol*, 146: 307–314. PMID:9270409

Young E, Leatherdale S, Sloan M *et al.* (2009). Age of smoking initiation and risk of breast cancer in a sample of Ontario women. *Tob Induc Dis*, 5: 4 doi:10.1186/1617-9625-5-4 PMID:19222858

Yu GP, Ostroff JS, Zhang ZF *et al.* (1997). Smoking history and cancer patient survival: a hospital cancer registry study. *Cancer Detect Prev*, 21: 497–509. PMID:9398990

Yu MC, Garabrant DH, Huang TB, Henderson BE (1990). Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J Cancer*, 45: 1033–1039. doi:10.1002/ijc.2910450609 PMID:2351484

Yu MC, Ho JH, Lai SH, Henderson BE (1986). Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: report of a case-control study in Hong Kong. *Cancer Res*, 46: 956–961. PMID:3940655

Yuan JM, Koh WP, Murphy SE *et al.* (2009). Urinary levels of tobacco-specific nitrosamine metabolites in relation to lung cancer development in two prospective cohorts of cigarette smokers. *Cancer Res*, 69: 2990–2995. doi:10.1158/0008-5472.CAN-08-4330 PMID:19318550

Yuan JM, Ross RK, Wang XL *et al.* (1996). Morbidity and mortality in relation to cigarette smoking in Shanghai, China. A prospective male cohort study. *JAMA*, 275: 1646–1650. doi:10.1001/jama.275.21.1646 PMID:8637137

Yuan JM, Wang XL, Xiang YB *et al.* (2000). Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. *Int J Cancer*, 85: 364–369. doi:10.1002/(SICI)1097-0215(20000201)85:3<364::AID-IJC12>3.0.CO;2-C PMID:10652428

Yun YH, Jung KW, Bae JM *et al.* (2005). Cigarette smoking and cancer incidence risk in adult men: National Health Insurance Corporation Study. *Cancer Detect Prev*, 29: 15–24. doi:10.1016/j.cdp.2004.08.006 PMID:15734213

Zahm SH, Heineman EF, Vaught JB (1992). Soft tissue sarcoma and tobacco use: data from a prospective cohort study of United States veterans. *Cancer Causes Control*, 3: 371–376. doi:10.1007/BF00146891 PMID:1617125

Zak-Prelich M, Narbutt J, Sysa-Jedrzejowska A (2004). Environmental risk factors predisposing to the development of basal cell carcinoma. *Dermatol Surg*, 30: s2248–252. doi:10.1111/j.1524-4725.2004.30089.x PMID:14871217

Zang EA & Wynder EL (1996). Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst*, 88: 183–192. doi:10.1093/jnci/88.3-4.183 PMID:8632492

Zanieri L, Galvan P, Checchini L *et al.* (2007). Polycyclic aromatic hydrocarbons (PAHs) in human milk from Italian women: influence of cigarette smoking and residential area. *Chemosphere*, 67: 1265–1274. doi:10.1016/j.chemosphere.2006.12.011 PMID:17258279

Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V (2000). Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. *Cancer Causes Control*, 11: 363–371. doi:10.1023/A:1008907924938 PMID:10843447

Zatonski W, Becher H, Lissowska J, Wahrendorf J (1991). Tobacco, alcohol, and diet in the etiology of laryngeal cancer: a population-based case-control study. *Cancer Causes Control*, 2: 3–10. doi:10.1007/BF00052355 PMID:1873431

Zendehdel K, Nyrén O, Luo J *et al.* (2008). Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. *Int J Cancer*, 122: 1095–1099. doi:10.1002/ijc.23076 PMID:17973262

Zhang J, Ichiba M, Hara K *et al.* (2001). Urinary 1-hydroxypyrene in coke oven workers relative to exposure, alcohol consumption, and metabolic enzymes. *Occup Environ Med*, 58: 716–721. doi:10.1136/oem.58.11.716 PMID:11600727

Zhang L, Rothman N, Li G *et al.* (2007). Aberrations in chromosomes associated with lymphoma and therapy-related leukemia in benzene-exposed workers. *Environ Mol Mutagen*, 48: 467–474. doi:10.1002/em.20306 PMID:17584886

Zhang L, Steinmaus C, Eastmond DA *et al.* (2009c). Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. *Mutat Res*, 681: 150–168. doi:10.1016/j.mrrev.2008.07.002 PMID:18674636

Zhang S, Wang M, Villalta PW *et al.* (2009a). Quantitation of pyridyloxobutyl DNA adducts in nasal and oral mucosa of rats treated chronically with enantiomers of *N*'-nitrosonornicotine. *Chem Res Toxicol*, 22: 949–956. doi:10.1021/tx900040j PMID:19405515

Zhang S, Wang M, Villalta PW *et al.* (2009b). Analysis of pyridyloxobutyl and pyridylhydroxybutyl DNA adducts in extrahepatic tissues of F344 rats treated chronically with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and enantiomers of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Chem Res Toxicol*, 22: 926–936. doi:10.1021/tx900015d PMID:19358518

Zhang X, Su T, Zhang QY *et al.* (2002). Genetic polymorphisms of the human *CYP2A13* gene: identification of single-nucleotide polymorphisms and functional characterization of an Arg257Cys variant. *J Pharmacol Exp Ther*, 302: 416–423. PMID:12130698

Zhang Y, Coogan PF, Palmer JR *et al.* (2004). Cigarette smoking and increased risk of mucinous

epithelial ovarian cancer. *Am J Epidemiol*, 159: 133–139. doi:10.1093/aje/kwh015 PMID:14718214

Zhang ZF, Kurtz RC, Sun M *et al.* (1996). Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol, and socioeconomic factors. *Cancer Epidemiol Biomarkers Prev*, 5: 761–768. PMID:8896886

Zhao B, Seow A, Lee EJ *et al.* (2001). Dietary isothiocyanates, glutathione *S*-transferase -M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. *Cancer Epidemiol Biomarkers Prev*, 10: 1063–1067. PMID:11588132

Zhao C, Tyndyk M, Eide I, Hemminki K (1999). Endogenous and background DNA adducts by methylating and 2-hydroxyethylating agents. *Mutat Res*, 424: 117–125. PMID:10064855

Zheng T, Holford T, Chen Y *et al.* (1997). Risk of tongue cancer associated with tobacco smoking and alcohol consumption: a case-control study. *Oral Oncol*, 33: 82–85. doi:10.1016/S0964-1955(96)00056-5 PMID:9231164

Zheng T, Holford TR, Zahm SH *et al.* (2002). Cigarette smoking, glutathione-s-transferase M1 and t1 genetic polymorphisms, and breast cancer risk (United States). *Cancer Causes Control*, 13: 637–645. doi:10.1023/A:1019500109267 PMID:12296511

Zheng TZ, Boyle P, Hu HF *et al.* (1990). Tobacco smoking, alcohol consumption, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. *Cancer Causes Control*, 1: 173–179. doi:10.1007/BF00053170 PMID:2102288

Zheng W, Blot WJ, Shu XO *et al.* (1992). Diet and other risk factors for laryngeal cancer in Shanghai, China. *Am J Epidemiol*, 136: 178–191. PMID:1415140

Zheng W, Blot WJ, Shu XO *et al.* (1992b). Diet and other risk factors for laryngeal cancer in Shanghai, China. *Am J Epidemiol*, 136: 178–191. PMID:1415140

Zheng W, Blot WJ, Shu XO *et al.* (1992c). A population-based case-control study of cancers of the nasal cavity and paranasal sinuses in Shanghai. *Int J Cancer*, 52: 557–561. doi:10.1002/ijc.2910520410 PMID:1399136

Zheng W, McLaughlin JK, Chow WH *et al.* (1993a). Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. *Am J Epidemiol*, 138: 965–972. PMID:8256781

Zheng W, McLaughlin JK, Gridley G *et al.* (1993). A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*, 4: 477–482. doi:10.1007/BF00050867 PMID:8218880

Zheng YM, Tuppin P, Hubert A *et al.* (1994). Environmental and dietary risk factors for nasopharyngeal carcinoma: a case-control study in Zangwu County, Guangxi, China. *Br J Cancer*, 69: 508–514. PMID:8123482

Zhu BT & Conney AH (1998). Functional role of estrogen metabolism in target cells: review and perspectives. *Carcinogenesis*, 19: 1–27. doi:10.1093/carcin/19.1.1 PMID:9472688

Zhu K, Levine RS, Brann EA *et al.* (1995). A population-based case-control study of the relationship between cigarette smoking and nasopharyngeal cancer (United States). *Cancer Causes Control*, 6: 507–512. doi:10.1007/BF00054158 PMID:8580298

Zienolddiny S, Campa D, Lind H *et al.* (2008). A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of non-small cell lung cancer in smokers. *Carcinogenesis*, 29: 1164–1169. doi:10.1093/carcin/bgn020 PMID:18258609

Zivaljevic V, Vlajinac H, Marinkovic J *et al.* (2004). Cigarette smoking as a risk factor for cancer of the thyroid in women. *Tumori*, 90: 273–275. PMID:15315303

Znaor A, Brennan P, Gajalakshmi V *et al.* (2003). Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer*, 105: 681–686. doi:10.1002/ijc.11114 PMID:12740918

Zu K & Giovannucci E (2009). Smoking and aggressive prostate cancer: a review of the epidemiologic evidence. *Cancer Causes Control*, Epub ahead of printPMID: 19562492.

SECOND-HAND TOBACCO SMOKE

Second-hand tobacco smoke was considered by a previous IARC Working Group in 2002 as "involuntary smoking" (IARC, 2004). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Second-hand tobacco smoke comprises the smoke released from the burning tip of a cigarette (or other burned tobacco product) between puffs (called sidestream smoke (SM)) and the smoke exhaled by the smoker (exhaled mainstream smoke (MS)). Small additional amounts are contributed from the tip of the cigarette and through the cigarette paper during a puff, and through the paper and from the mouth end of the cigarette between puffs (Jenkins *et al.*, 2000).

Second-hand tobacco smoke is also referred as 'environmental tobacco smoke', 'passive smoking' or 'involuntary smoking' (IARC, 2004). The terms 'passive smoking' or 'involuntary smoking' suggest that while involuntary or passive smoking is not acceptable, voluntary or active smoking is acceptable. In this document, we use the term second-hand tobacco smoke (WHO, 2010).

1.1 Chemical composition

Many studies have examined the concentrations of cigarette smoke constituents in mainstream and sidestream smoke. The composition of mainstream and sidestream smoke is qualitatively similar but quantitatively different. The ratios of sidestream to mainstream smoke vary greatly depending on the constituent. Some representative SS:MS ratios are: nicotine, 7.1; carbon monoxide, 4.8; ammonia, 455; formaldehyde, 36.5; acrolein, 18.6; benzo[*a*]pyrene, 16.0; *N*′-nitrosonornicotine (NNN), 0.43; (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 0.40 (Jenkins *et al.*, 2000; IARC, 2004).

The physicochemical properties of second-hand tobacco smoke are different from those of mainstream smoke and sidestream smoke because of its rapid dilution and dispersion into the indoor environment (IARC, 2004). Concentrations of individual constituents in second-hand tobacco smoke can vary with time and environmental conditions. Field studies of these constituents and representative data have been extensively summarized (Jenkins *et al.*, 2000; IARC, 2004). Some representative data are presented in Table 1.1 (Jenkins *et al.*, 2000; IARC, 2004; US Department of Health and Human Services, 2006).

Table 1.1 Concentration of selected constituents in second-hand tobacco smoke

Constituent	Concentration
Nicotine	10–100 μg/m^3
Carbon monoxide	5–20 ppm
Benzene	15–30 μg/m^3
Formaldehyde	100–140 μg/m^3
Acetaldehyde	200–300 μg/m^3
1,3-Butadiene	20–40 μg/m^3
Benzo[*a*]pyrene	0.37–1.7 ng/m^3
NNK	0.2–29.3 ng/m^3
NNN	0.7–23 ng/m^3

1.2 Sources of exposure

Second-hand tobacco smoke is present in virtually all places where smoking takes place (Navas-Acien *et al.*, 2004): at home, in the workplace, in bars, restaurants, public buildings, hospitals, public transport and educational institutions. The setting that represents the most important source of exposure differs depending on the population. For example in children, the home environment may constitute a significant source of exposure, while other sources that may contribute are schools and public transportation. Likewise, for most women, the home environment is the primary source of second-hand tobacco smoke, which may be enhanced by exposure at the workplace.

Biomarker studies have evaluated carcinogen uptake in non-smokers to second-hand tobacco smoke. The NNK metabolites NNAL and its glucuronides (total NNAL) are consistently elevated in non-smokers exposed to second-hand tobacco smoke, in studies conducted in various living and occupational environments, and from infancy through adulthood (Hecht *et al.*, 2006; Hecht, 2008). Levels of the biomarker of PAHs, urinary 1-hydroxypyrene, were significantly elevated in a large study of non-smokers exposed to second-hand tobacco smoke (Suwan-ampai *et al.*, 2009).

1.3 Measures of exposure

A conceptual framework for considering exposure to second-hand tobacco smoke is the "microenvironmental model," which takes the weighted sum of the concentrations of second-hand tobacco smoke in the microenvironments where time is spent, with the weights the time spent in each, as a measure of personal exposure (Jaakkola & Jaakkola, 1997). Direct measures of exposure use concentrations of second-hand tobacco smoke components in the air in the home, workplace, or other environments, combined with information on the time spent in the microenvironments where exposure took place. Measurements of tobacco smoke biomarker(s) in biological specimens also represent a direct measure of exposure to second-hand smoke (Samet & Yang, 2001; Table 1.2). Indirect measures are generally obtained by survey questionnaires. These include self-reported exposure and descriptions of the source of second-hand tobacco smoke in relevant microenvironments, most often the home and workplace (Samet & Yang, 2001).

One useful surrogate measure, and the only available in many countries, is the prevalence of smoking among men and women. It provides a measure of the likelihood of exposure. In most countries in Asia and the Middle East,

Table 1.2 Types of indicators measuring exposure to second-hand tobacco smoke

Measure	Suggested indicators
Direct	Concentration of second-hand tobacco smoke components in the air: - Nicotine - Respirable particles - Other markers Biomarker concentrations: - Cotinine - Carboxyhaemoglobin
Indirect	Report of second-hand tobacco smoke exposure at: Home - Number of smokers - Smoking of parents - Intensity (number of cigarettes smoked) Workplace - Presence of second-hand tobacco smoke - Number of smokers
Surrogate	Pre Prevalence of smoking tobacco in men and in women Sel Self reported smoking habits of parents Nic Nicotine concentration in house dust

From Samet & Yang (2001) and Whitehead *et al.* (2009)

for example, the very high prevalence of smoking among men combined with the low prevalence among women would imply that most women are exposed to second-hand tobacco smoke at home (Samet & Yang, 2001).

To measure exposure to second-hand tobacco smoke in children, self-reported smoking habits of their parents are used as a surrogate (US Department of Health and Human Services, 2006). More recently, other surrogate measures such as nicotine concentrations in house dust have been considered less biased than parental smoking as they reflect cumulative smoking habits and long-term exposure rather than current patterns of smoking (Whitehead *et al.*, 2009).

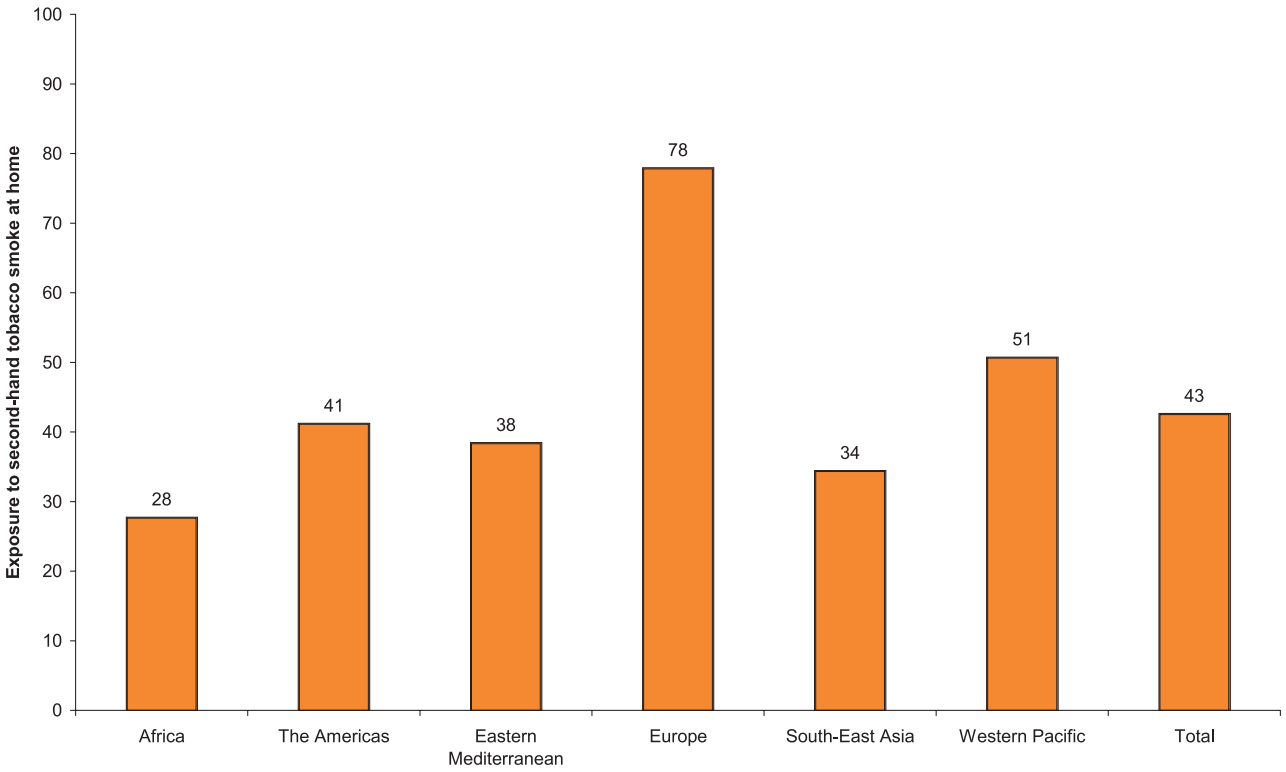
1.4 Prevalence of exposure

1.4.1 Exposure among children

(a) Overview

The most extensive population-based data on exposure to second-hand tobacco smoke among children are available through the Global Youth Tobacco Survey (GYTS) (CDC/WHO, 2009). GYTS is part of the Global Tobacco Surveillance System (GTSS), developed by the WHO and the United States' Centers for Disease Control and Prevention (CDC) in 1998. The GYTS is a school-based survey designed to measure tobacco use and some key tobacco control measures among youth (13–15 years) using a common methodology and core questionnaire. While most GYTS are national surveys, in some countries they are limited to subnational locations. Further, countries conduct the GYTS in different years, rendering comparison across countries for the same year difficult. The GYTS questionnaire

Fig. 1.1 Average prevalence (in%) of 13–15 year old children living in a home where others smoke, by WHO region, 2007



From CDC (2008)

asks about children's exposure to second-hand tobacco smoke in their home or in other places in the last 7 days preceding the survey. Since its inception in 1999, over 2 million students in 160 countries representing all six WHO regions have participated in the GYTS (WHO, 2008, 2009a).

Country-level estimates on second-hand tobacco smoke exposure at home and in public places among youth are available in the WHO Reports on the global tobacco epidemic (WHO, 2008, 2009a, 2011).

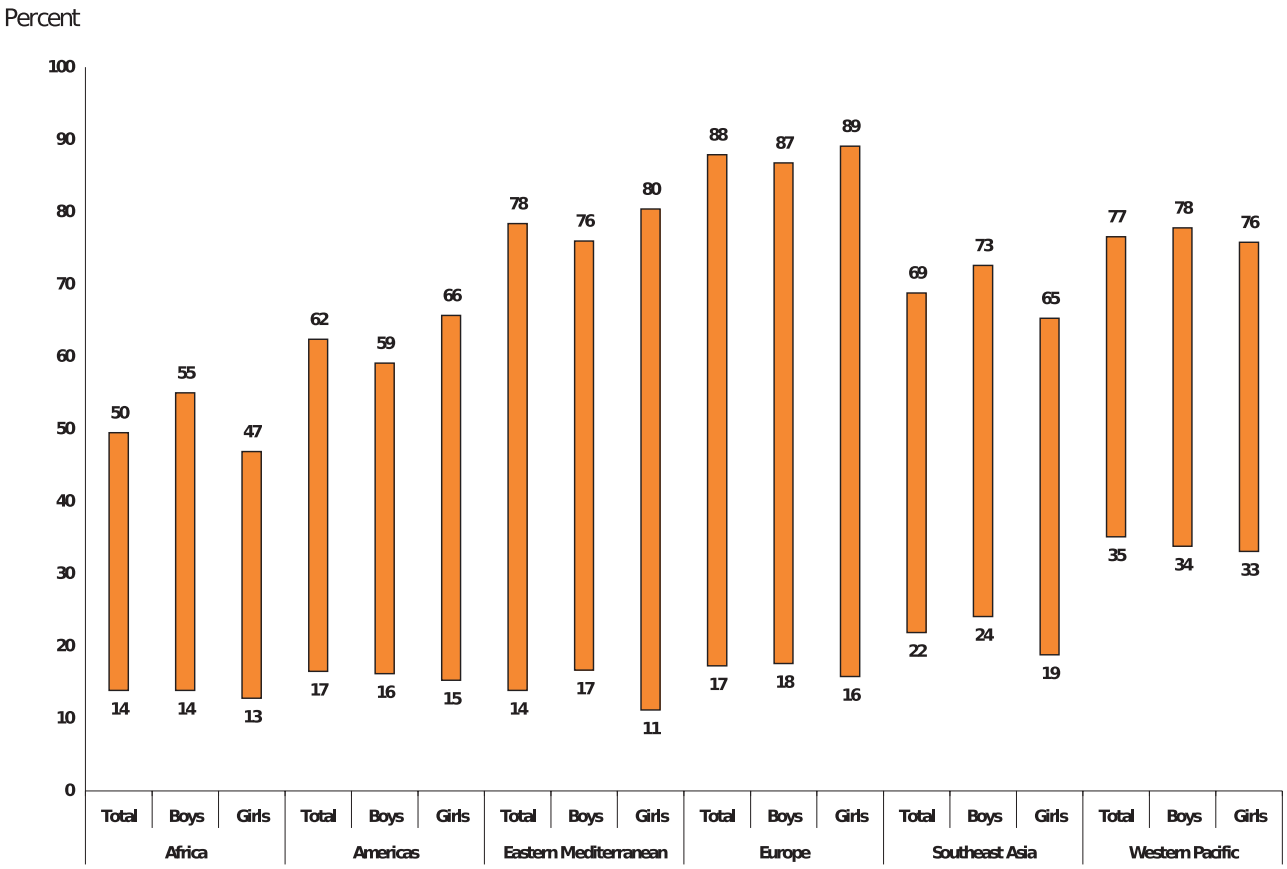
(b) Exposure at home

Nearly half of youth aged 13–15 years are exposed to second-hand tobacco smoke in their homes (Fig. 1.1; CDC, 2008). Among the six WHO regions, exposure to second-hand tobacco smoke at home was highest in the European Region (77.8%) and lowest in the African region (27.6%). In the other four regions, exposure to second-hand tobacco smoke at home ranged from 50.6% in the Western Pacific Region to 34.3% in the South East Asian Region.

Fig. 1.2 shows the range of exposure to second-hand tobacco smoke at home by WHO region for boys and girls and for both sexes combined. The largest variations are observed in the Eastern Mediterranean Region and the European Region irrespective of sex. These variations are predominantly due to differences in parental smoking prevalence between countries, as well as the impact of the smoke-free places campaigns in place in various countries.

Country-level estimates from the Global Youth Tobacco Survey (1999–2009) are presented in Table 1.3.

Fig. 1.2 Range of prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke at home, by WHO region, 2009



From CDC/WHO (2009)

Öberg and colleagues have estimated the worldwide exposure to second-hand tobacco smoke among children by using parent's current smoking status as an indicator of exposure among children (WHO, 2010). Four out of ten children (approximately 700 million children globally) have at least one parent who currently smokes, predisposing them to exposure to second-hand tobacco smoke at home (Table 1.4). Children in the Western Pacific Region had the highest level of potential exposure (68%) while Africa had the lowest, with about 13% of children having at least one parent who smoked. In the 2010 WHO Report on global estimate of the burden of disease from second-hand smoke (WHO, 2010), country-level estimates were collected or modelled from various sources. [Data partially overlap with those of the Global Youth Tobacco Survey].

(c) Exposure outside home

Similar to second-hand tobacco smoke exposure at home, almost half of the youth are exposed to second-hand tobacco smoke in public places, according to estimates from the Global Youth Tobacco Survey (Fig. 1.3; CDC, 2008). Exposure was highest in Europe (86.1%); for the other five regions, exposure to second-hand tobacco smoke in public places ranged from 64.1% in the Western Pacific to 43.7% in Africa.

Table 1.3 Prevalence of exposure to second-hand tobacco smoke at home and outside home among 13–15 year olds, by country and sex, from the Global Youth Tobacco Survey (participating countries only) — 1999–2009

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Afghanistan	EMRO	Kabul	2004	38.8	43.4	33.3	45.0	60.2	23.6
Albania	EURO	National	2009	49.7	48.6	50.9	64.5	65.3	63.9
Algeria	AFRO	Constantine	2007	38.7	39.8	37.9	60.2	66.0	56.2
Antigua and Barbuda	AMRO	National	2009	26.7	22.5	29.7	47.5	45.0	49.6
Argentina	AMRO	National	2007	54.7	51.7	57.7	68.6	66.4	70.7
Armenia	EURO	National	2009	70.6	69.2	71.6	78.3	80.7	76.4
Bahamas	AMRO	National	2009	25.1	23.4	27.0	51.0	50.8	52.7
Bahrain	EMRO	National	2002	38.7	37.2	39.5	45.3	49.7	40.9
Bangladesh	SEARO	National	2007	34.7	37.8	32.4	42.2	47.1	38.7
Barbados	AMRO	National	2007	25.9	25.9	26.0	59.6	59.7	59.6
Belize	AMRO	National	2008	25.7	26.2	25.1	50.4	52.1	48.6
Benin	AFRO	Atlantique Littoral	2003	21.5	23.7	18.3	38.0	41.3	33.5
Bhutan	SEARO	National	2009	29.5	29.2	29.5	59.4	58.6	59.7
The Plurinational State of Bolivia	AMRO	La Paz	2003	34.3	34.3	34.4	52.9	54.4	51.4
Bosnia and Herzegovina	EURO	National	2008	77.3	74.0	80.3	84.0	82.3	85.6
Botswana	AFRO	National	2008	38.5	38.2	38.6	62.1	60.0	63.7
Brazil	AMRO	São Paulo	2009	35.5	31.9	38.7	51.3	48.2	54.1
Bulgaria	EURO	National	2008	63.9	61.5	66.3	70.1	66.7	73.7
Burkina Faso	AFRO	Ouagadougou	2009	29.2	28.9	29.2	47.5	53.5	42.2
Burundi	AFRO	National	2008	33.9	35.2	31.7	49.3	54.0	45.3
Cambodia	WPRO	National	2003	47.0	48.9	44.5	58.5	60.6	56.5
Cameroon	AFRO	Yaounde	2008	21.7	25.0	19.1	45.8	49.3	42.4
Cape Verde	AFRO	National	2007	13.9	13.9	13.7	25.4	27.0	24.2
Central African Republic	AFRO	Bangui	2008	35.2	29.9	40.7	52.4	49.9	53.8
Chad	AFRO	National	2008	33.9	34.1	31.2	55.1	54.0	56.2
Chile	AMRO	Santiago	2008	51.7	48.9	54.4	68.3	63.4	73.0
China	WPRO	Shanghai	2005	47.0	46.6	47.4	35.2	34.2	36.2
Colombia	AMRO	Bogota	2007	26.2	25.3	27.0	56.1	55.1	56.9
Comoros	AFRO	National	2007	35.2	35.7	34.9	58.3	66.7	52.9
Congo	AFRO	National	2009	22.3	24.7	19.6	44.4	46.8	41.5
Cook Islands	WPRO	National	2008	61.9	58.8	64.5	73.8	70.3	76.8

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Costa Rica	AMRO	National	2008	21.6	20.8	22.1	41.5	40.0	42.8
Côte d'Ivoire	AFRO	National	2009	33.1	33.1	33.0	74.4	75.9	72.3
Croatia	EURO	National	2007	73.4	71.4	75.7	82.5	81.2	84.2
Cuba	AMRO	Havana	2004	62.4	59.1	65.7	65.0	64.6	65.8
Cyprus	EURO	National	2005	87.9	86.8	89.1	87.8	85.4	90.4
Czech Republic	EURO	National	2007	38.0	37.3	38.9	75.2	71.6	79.5
Democratic Republic of the Congo	AFRO	Kinshasa	2008	30.2	32.5	27.0	36.8	37.4	34.7
Djibouti	EMRO	National	2009	36.0	36.2	35.3	44.7	44.8	44.8
Dominica	AMRO	National	2009	26.9	25.2	27.4	62.3	61.4	62.5
Dominican Republic	AMRO	National	2004	33.1	31.1	34.5	41.9	38.5	44.9
Ecuador	AMRO	Quito	2007	28.9	27.5	30.2	52.5	49.5	54.6
Egypt	EMRO	National	2009	47.6	50.1	45.9	52.2	57.7	47.5
El Salvador	AMRO	National	2009	17.9	19.3	16.5	33.7	36.7	30.7
Equatorial Guinea	AFRO	National	2008	47.5	47.8	45.8	61.7	64.0	59.8
Eritrea	AFRO	National	2006	18.4	20.4	14.8	37.3	40.4	32.3
Estonia	EURO	National	2007	41.1	39.3	42.8	68.5	68.2	68.7
Ethiopia	AFRO	Addis Ababa	2003	14.9	15.5	12.8	41.2	45.1	37.4
Fiji	WPRO	National	2009	42.1	45.4	39.6	55.1	55.2	54.9
Gambia	AFRO	Banjul	2008	45.8	45.8	44.4	59.2	61.6	57.2
Georgia	EURO	National	2008	62.7	62.4	62.8	74.4	75.5	73.4
Ghana	AFRO	National	2009	19.1	19.6	17.9	32.3	33.9	30.4
Greece	EURO	National	2005	…	…	…	…	…	…
Grenada	AMRO	National	2009	27.3	24.9	29.7	53.1	50.5	55.7
Guatemala	AMRO	National	2008	23.1	23.9	22.1	40.8	43.8	37.9
Guinea	AFRO	National	2008	27.7	27.6	28.1	52.3	57.0	48.1
Guinea-Bissau	AFRO	Bissau	2008	31.0	32.1	29.7	35.3	36.6	34.1
Guyana	AMRO	National	2004	33.4	36.6	30.6	61.1	62.9	59.1
Haiti	AMRO	Port-au-Prince	2005	32.3	34.7	29.6	43.2	46.2	40.4
Honduras	AMRO	Tegucigalpa	2003	29.6	26.2	31.6	42.2	46.9	38.4
Hungary	EURO	National	2008	43.0	39.9	45.3	72.6	70.0	74.7
India	SEARO	National	2009	21.9	24.1	18.8	36.6	39.0	33.1
Indonesia	SEARO	National	2009	68.8	72.6	65.3	78.1	83.7	73.1

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Islamic Republic of Iran	EMRO	National	2007	35.4	38.1	32.7	44.8	49.8	39.6
Iraq	EMRO	Baghdad	2008	32.3	30.3	34.4	29.2	27.8	30.7
Jamaica	AMRO	National	2006	32.5	32.2	32.5	60.5	59.9	61.6
Jordan	EMRO	National	2009	53.6	50.6	55.5	50.5	50.6	49.7
Kenya	AFRO	National	2007	24.7	25.4	23.6	48.2	48.6	47.6
Kiribati	WPRO	National	2009	68.3	68.7	68.3	65.8	67.9	64.0
Kuwait	EMRO	National	2009	49.8	46.9	52.0	53.3	54.3	52.4
Kyrgyzstan	EURO	National	2008	33.4	35.1	31.9	57.7	58.7	56.8
Lao People's Democratic Republic	WPRO	Vientiane Capital	2007	40.3	41.2	39.5	55.4	57.7	53.2
Latvia	EURO	National	2007	55.2	55.1	55.1	72.7	73.2	72.3
Lebanon	EMRO	National	2005	78.4	76.0	80.4	74.4	73.9	74.7
Lesotho	AFRO	National	2008	36.9	34.2	37.3	52.6	50.2	53.2
Liberia	AFRO	Monrovia	2008	23.6	22.2	24.5	45.5	45.1	45.4
Lithuania	EURO	National	2009	38.3	34.1	42.6	64.9	66.5	63.3
Madagascar	AFRO	National	2008	49.5	55.0	44.9	62.9	69.5	57.5
Malawi	AFRO	National	2009	19.7	25.0	14.0	29.5	32.9	26.1
Malaysia	WPRO	National	2009	48.7	49.6	47.6	64.1	67.7	60.2
Maldives	SEARO	National	2007	48.3	49.4	47.1	68.0	70.6	65.4
Mali	AFRO	National	2008	48.5	50.1	46.9	81.4	83.1	79.2
Marshall Islands	WPRO	National	2009	52.1	54.7	50.5	59.7	60.5	60.6
Mauritania	AFRO	National	2009	37.5	39.8	35.0	50.9	55.4	47.1
Mauritius	AFRO	National	2008	36.1	38.5	34.1	73.6	77.2	70.7
Mexico	AMRO	Mexico City	2006	46.2	46.3	45.5	60.2	61.6	59.0
Federated States of Micronesia	WPRO	National	2007	60.7	60.4	59.6	71.3	73.3	68.7
Mongolia	WPRO	National	2007	54.4	53.7	54.3	55.5	60.7	50.7
Montenegro	EURO	National	2008	76.8	73.5	79.9	69.9	68.8	70.8
Morocco	EMRO	National	2006	27.1	24.7	29.2	41.1	41.1	40.9
Mozambique	AFRO	Maputo	2007	22.5	25.2	19.6	26.2	28.6	23.0
Myanmar	SEARO	National	2007	34.1	38.8	29.4	46.4	51.2	42.1
Namibia	AFRO	National	2008	38.1	38.0	37.9	49.9	47.7	51.5
Nepal	SEARO	National	2007	35.3	38.5	31.7	47.3	49.5	44.7
New Zealand	WPRO	National	2008	36.0	38.5	33.1	67.2	63.3	71.3

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Nicaragua	AMRO	Centro Managua	2003	43.7	43.9	43.2	54.1	56.4	51.9
Niger	AFRO	National	2009	24.1	28.1	20.4	54.3	58.8	50.2
Nigeria	AFRO	Abuja	2008	21.7	29.2	12.8	39.7	43.6	36.0
Oman	EMRO	National	2007	13.9	16.7	11.2	27.4	29.8	25.2
Pakistan	EMRO	Islamabad	2003	26.6	32.1	21.7	33.9	42.5	26.4
Palau	WPRO	National	2009	…	…	…	79.2	70.4	85.3
Panama	AMRO	National	2008	21.9	22.2	21.5	40.3	38.9	41.4
Papua New Guinea	WPRO	National	2007	73.9	75.4	72.2	86.4	87.0	85.6
Paraguay	AMRO	National	2008	32.5	35.1	30.1	55.3	57.3	53.4
Peru	AMRO	National	2007	25.5	26.2	24.2	46.8	46.9	46.4
Philippines	WPRO	National	2007	54.5	55.7	53.1	64.8	67.2	62.8
Poland	EURO	Warsaw	2009	49.1	42.8	54.6	76.8	75.5	77.8
Qatar	EMRO	National	2007	35.7	36.3	35.2	45.9	52.1	42.8
Republic of Korea	WPRO	National	2008	37.6	33.8	41.6	70.8	67.3	74.8
Republic of Moldova	EURO	National	2008	20.3	20.6	20.1	57.0	59.4	54.8
Romania	EURO	National	2009	52.8	50.0	55.4	59.1	57.1	61.3
Russian Federation	EURO	National	2004	76.4	74.3	78.5	89.4	89.0	89.9
Rwanda	AFRO	National	2008	19.2	19.9	18.0	…	…	…
Saint Kitts and Nevis	AMRO	National	2002	16.5	16.2	15.3	48.8	48.0	49.0
Saint Lucia	AMRO	National	2007	25.2	28.4	22.6	64.0	61.1	65.7
Saint Vincent and the Grenadines	AMRO	National	2007	31.5	31.7	30.9	59.7	56.5	61.8
Samoa	WPRO	National	2007	59.1	60.8	56.4	62.8	64.8	60.5
San Marino	EURO	National	2009	32.9	31.8	34.0	65.8	62.8	69.3
Saudi Arabia	EMRO	National	2007	27.9	28.9	26.4	38.2	45.1	31.6
Senegal	AFRO	National	2007	47.6	49.9	42.5	48.3	48.3	45.0
Serbia	EURO	National	2008	76.9	73.4	80.0	71.9	68.1	74.8
Seychelles	AFRO	National	2007	42.3	38.2	46.1	57.1	54.3	60.6
Sierra Leone	AFRO	National	2008	44.2	46.3	42.9	56.5	59.9	53.4
Singapore	WPRO	National	2000	35.1	34.8	35.2	65.1	64.0	66.0
Slovakia	EURO	National	2007	44.9	42.4	46.9	69.3	68.0	70.5
Somalia	EMRO	Somaliland	2007	29.1	30.8	21.9	48.7	50.2	41.8
South Africa	AFRO	National	2008	32.1	32.7	31.5	41.1	43.5	39.4

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Sri Lanka	SEARO	National	2007	35.4	37.6	33.4	65.9	66.5	65.1
Sudan	EMRO	National	2009	27.6	26.0	28.7	33.1	33.8	32.0
Suriname	AMRO	National	2009	46.6	44.2	47.7	53.3	51.4	53.8
Swaziland	AFRO	National	2009	23.3	21.8	24.3	55.6	52.1	58.0
Syrian Arab Republic	EMRO	National	2010	60.1	58.7	61.7	58.4	61.1	55.7
Thailand	SEARO	National	2009	45.7	46.6	44.7	67.6	68.0	67.1
The former Yugoslav Republic of Macedonia	EURO	National	2008	67.5	64.7	70.5	66.0	63.7	68.3
Timor-Leste	SEARO	National	2009	59.4	66.7	52.1	61.3	66.7	56.0
Togo	AFRO	National	2007	20.2	23.5	15.7	41.6	45.1	36.7
Trinidad and Tobago	AMRO	National	2007	40.1	36.3	43.6	64.2	62.8	65.9
Tunisia	EMRO	National	2007	51.9	53.1	50.6	65.2	69.7	61.0
Turkey	EURO	National	2009	48.6	43.8	53.0	79.9	80.1	79.6
Tuvalu	WPRO	National	2006	76.6	77.8	75.8	76.7	72.0	79.3
Uganda	AFRO	National	2007	20.0	20.7	18.8	45.6	46.1	45.2
United Arab Emirates	EMRO	National	2005	25.3	24.3	25.4	31.6	34.3	28.4
United Republic of Tanzania	AFRO	Arusha	2008	15.7	16.4	14.9	34.7	35.2	33.9
United States of America	AMRO	National	2009	35.7	35.3	36.1	42.8	38.2	47.6
Uruguay	AMRO	National	2007	50.5	47.6	52.5	68.6	64.0	72.1
Uzbekistan	EURO	Tashkent	2008	17.3	17.6	15.8	46.7	47.5	42.4
Vanuatu	WPRO	National	2007	59.3	62.8	56.7	75.9	78.7	73.9
Venezuela (Bolivarian Republic of)	AMRO	National	1999	43.5	40.7	45.3	47.8	47.0	48.4
Viet Nam	WPRO	National	2007	58.5	59.0	58.0	71.2	71.4	71.0
West Bank*	EMRO	West Bank	2009	63.0	61.6	64.4	61.6	67.6	55.8
Gaza Strip*	EMRO	Gaza Strip	2005	47.4	48.0	46.5	46.1	51.9	40.6
Yemen	EMRO	National	2008	44.9	48.2	37.8	42.7	49.8	30.7
Zambia	AFRO	Lusaka	2007	23.1	21.2	24.3	45.5	43.2	47.1
Zimbabwe	AFRO	Harare	2008	20.9	22.0	19.4	40.1	40.5	39.5

* Refers to a territory

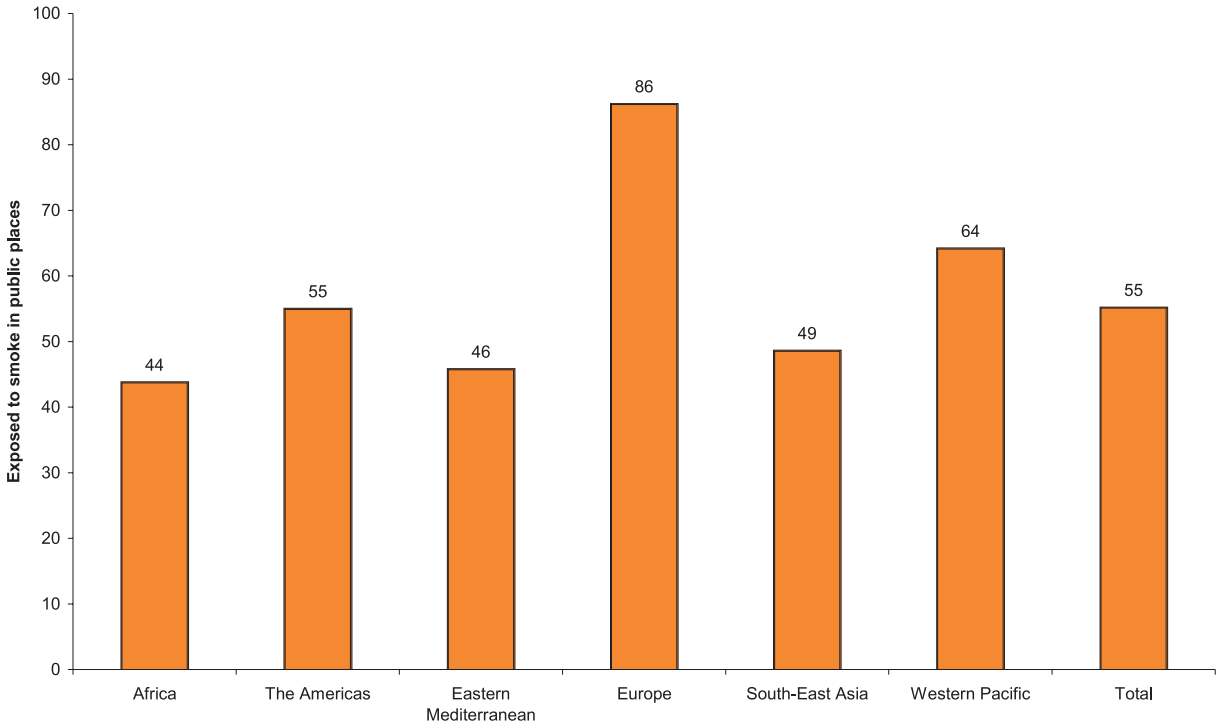
From WHO (2008, 2009a)

Table 1.4 Proportion of children under 15 years with one or more parent who smokes, by WHO subregion (based on survey data and modeling)

Subregion	Parental smoking (%)
Africa (D)	13
Africa (E)	13
The Americas (A)	25
The Americas (B)	29
The Americas (D)	22
Eastern Mediterranean (B)	37
Eastern Mediterranean (D)	34
Europe (A)	51
Europe (B)	61
Europe (C)	61
South-eastern Asia (B)	53
South-eastern Asia (D)	36
Western Pacific (A)	51
Western Pacific (B)	68
GLOBAL	41

WHO subregional country grouping (adapted from WHO, 2002):
Africa. ***Region D***: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo; ***Region E***: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
The Americas. ***Region A***: Canada, Cuba, USA; ***Region B***: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela; ***Region D***: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
Eastern Mediterranea. ***Region B***: Bahrain, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahirya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates; ***Region D***: Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
Europe. ***Region A***: Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom; ***Region B***: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Serbia and Montenegro, Slovakia, Tajikistan, Former Yugoslav Republic of The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan; ***Region C***: Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of the Republic of Moldova, Russian Federation, Ukraine
South-eastern Asia. ***Region B***: Indonesia, Sri Lanka, Thailand; ***Region D***: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar (Burma), Nepal, Timor-Leste
Western Pacific. ***Region A***: Australia, Brunei Darussalam, Japan, New Zealand, Singapore; ***Region B***: Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam
Regions are categorized as follows (WHO-approved classifications): A = very low child mortality and very low adult mortality; B = low child mortality and low adult mortality; C = low child mortality and high adult mortality; D = high child mortality and high adult mortality; E = high child mortality and very high adult mortality.

Fig. 1.3 Average prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke in public places, by WHO region, 2007



From CDC (2008)

Fig. 1.4 presents the range of exposure to second-hand tobacco smoke outside home by WHO region for boys and girls and for both sexes combined. There are wide variations in second-hand tobacco smoke exposure outside home within each region. The largest variations are observed in the African region and the Western Pacific region irrespective of sex. This is largely influenced by the presence of smoke-free legislation for public paces in the countries, as well as levels of enforcement and public's compliance with these laws.

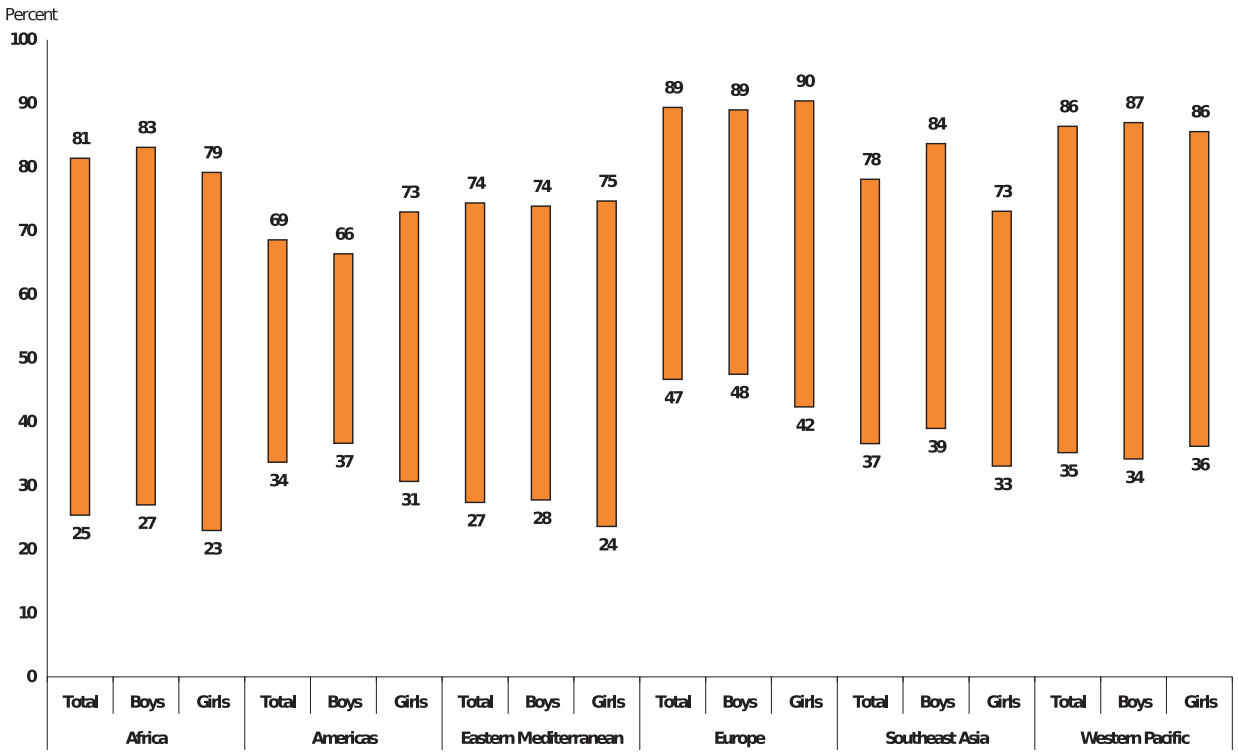
1.4.2. Exposure among adults

(a) Overview

While the GYTS offers a valuable global source for estimating exposure to second-hand tobacco smoke among children, there is no such extensive source of data for adults. Estimates of second-hand tobacco smoke exposure among adults have used the definitions of exposure based on having a spouse who smokes or exposure to tobacco smoke at work. For the countries lacking such data, exposure was estimated using a model based on smoking prevalence among men from the WHO Global InfoBase.

About one third of adults worldwide are regularly exposed to second-hand tobacco smoke (Table 1.5). The highest exposure was estimated in European Region C with 66% of the population

Fig. 1.4 Range of prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke outside their home, by WHO region, 2009



From CDC/WHO (2009)

being regularly exposed to second-hand tobacco smoke. The lowest regional exposure was estimated in the African region (4%). Differences between men and women were generally small, except in Eastern Mediterranean Region D and South East Asia Region B.

(b) Exposure at home

The Global Tobacco Surveillance System, through its adult household survey "Global Adult Tobacco Survey" (GATS), collects information on key tobacco control indicators including information on second-hand tobacco smoke exposure at home, at work and several public places (WHO, 2009b). GATS is a nationally representative survey conducted among persons aged ≥ 15 years using a standardized questionnaire, sample design, data collection method, and analysis protocol. GATS results are available from 14 countries with a high tobacco burden. Additionally since 2008, The WHO STEPwise approach to surveillance (STEPS) surveys have started to collect information on exposure to second-hand tobacco smoke at home and at work, now available for 7 countries (WHO, 2009c).

In the 21 countries that have reported data on exposure to second-hand tobacco smoke, large numbers of people are exposed at home (Fig. 1.5). Exposure was highest in Sierra Leone (74%) and lowest in the British Virgin Islands (3%). Overall, differences between men and women were relatively small in most countries; in China, Cambodia and Mongolia, more women reported being exposed to second-hand tobacco smoke

Table 1.5 Proportion of non-smoking adults exposed regularly to second-hand tobacco smoke, by WHO region (based on survey data and modeling)

	Exposure in men	Exposure in women
WHO Subregion	(%)	(%)
Africa (D)	7	11
Africa (E)	4	9
The Americas (A)	16	16
The Americas (B)	13	21
The Americas (D)	15	18
Eastern Mediterranean (B)	24	22
Eastern Mediterranean (D)	21	34
Europe (A)	34	32
Europe (B)	52	53
Europe (C)	66	66
South-eastern Asia (B)	58	41
South-eastern Asia (D)	23	18
Western Pacific (A)	50	54
Western Pacific (B)	53	51
GLOBAL	33	31

From WHO (2010)
For the WHO subregional country grouping, see footnote of Table 1.4.

in their homes then men. This lack of difference implies that even when prevalence of smoking among women is low, they are exposed to second-hand tobacco smoke at home as much as men.

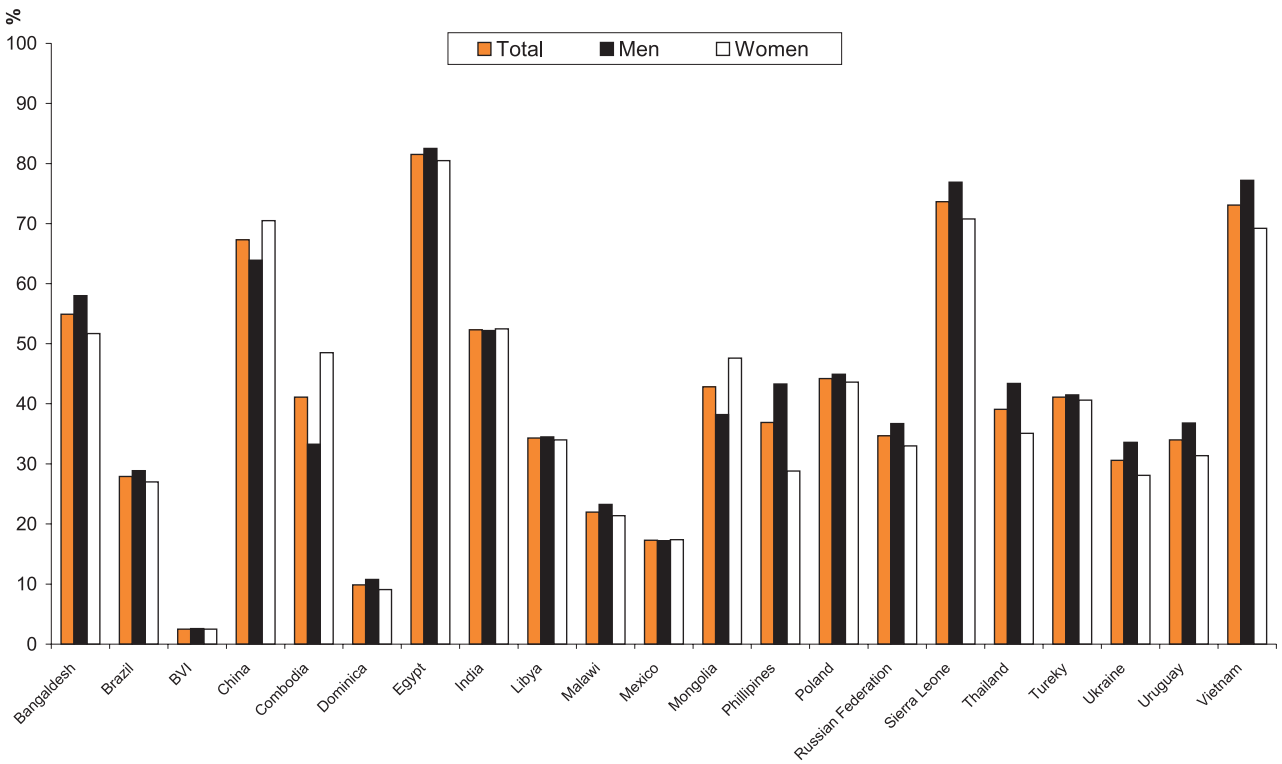
(c) Exposure at the workplace

The same magnitude of second-hand tobacco smoke exposure at the workplace was reported as at home (Fig. 1.6). Exposure to second-hand tobacco smoke at the workplace was highest in Sierra Leone (74%) and lowest in the British Virgin Islands (3%). However, more men reported being exposed to others' smoke at their workplace as compared to women in all countries. This difference was most significant in Libyan Arab Jamahirya and Bangladesh. These differences could be explained by the fact that women either tend to work in places where smoking is banned, such as education or health facilities, or work predominantly with other women.

1.5 Regulations

The World Health Organization's Framework Convention on Tobacco Control (WHO FCTC) is a multilateral treaty with legally binding obligations for its 174 Parties (as of November 2011) (WHO, 2003). This comprehensive treaty contains supply and demand reduction measures available to countries to counter the tobacco epidemic. Article 8 of the Treaty specifically addresses the need for protection from second-hand tobacco smoke, and articulates the "adoption and implementation of effective legislative, executive, administrative and /or other measures" by Parties to the Convention to this effect. Guidelines to Article 8 specify key elements needed in legislation to help countries meet the highest standards of protection from second-hand tobacco smoke and provide a clear timeline for Parties to adopt appropriate measures (within five years after entry into Force of the WHO FCTC) (WHO, 2007).

Fig. 1.5 Prevalence of adults exposed to second-hand tobacco smoke in their homes, in the countries that completed the Global Adult Tobacco Survey (GATS) and WHO STEPwise approach to surveillance (STEPS) surveys, 2008–2009



From WHO (2009b, c)
GATS defines second-hand tobacco smoke exposure at home as reporting that smoking inside their home occurs daily, weekly, or monthly.
STEPS defines second-hand tobacco smoke exposure at home as reporting exposure in the home on one or more days in the past 7 days.

All countries, regardless of their FCTC ratification status, are taking steps to reduce second-hand tobacco smoke in public places, through either planning the steps to or implementing national smoke-free laws for public places or workplaces. In 2008, approximately 5% of the world's population (354 million) had national smoke-free laws. Fig. 1.7 provides details on the number of public places with national smoke-free legislation for all WHO Member States.

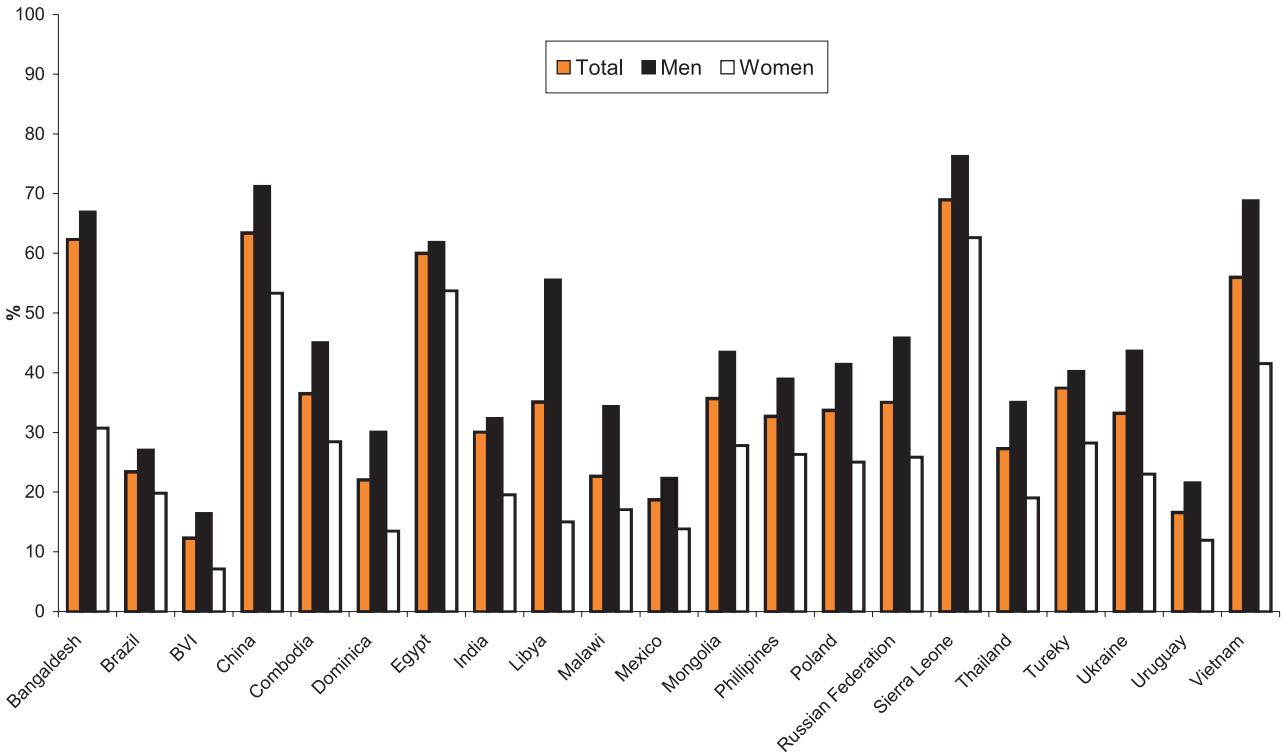
As of December 2008, fifteen countries across the globe have legislation that provide the highest level of protection against second-hand tobacco smoke exposure. These include: Albania, Australia, Bhutan, Canada, Colombia, Guatemala, Islamic Republic of Iran, Ireland, Marshall Islands, New Zealand, Panama, Turkey, Turkmenistan, United Kingdom of Great Britain and Northern Ireland and Uruguay.

2 Cancer in Humans

2.1 Cancer of the lung

More than 50 epidemiological studies since 1981 have examined the association between second-hand tobacco smoke and lung cancer resulting in the conclusion that exposure of non-smokers to second-hand tobacco smoke is causally associated with lung cancer risk (IARC, 2004). Many studies previously

Fig. 1.6 Prevalence of adults exposed to second-hand tobacco smoke in their workplaces, in the countries that completed the Global Adult Tobacco Survey and WHO STEPwise approach to surveillance (STEPS) surveys, 2008–2009

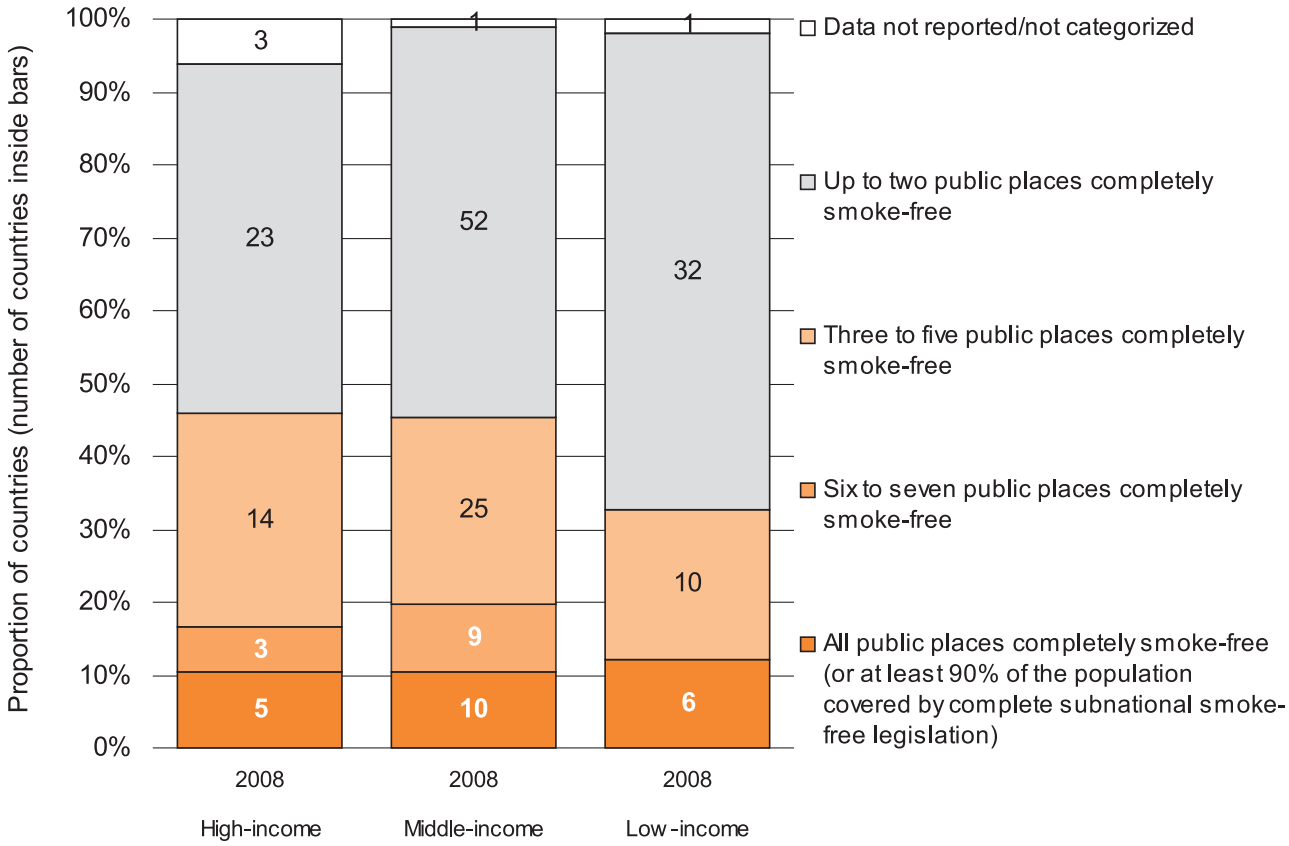


GATS defines second-hand tobacco smoke exposure at work as indoor workers who were exposed at work in the past 30 days.
STEPS defines second-hand tobacco smoke exposure at work as reporting exposure in the workplace on one or more days in the past 7 days
From WHO (2009b, c)

available assessed the lung cancer risk among the nonsmoking spouses of smokers since it is one of the sources of adult exposure to second-hand tobacco smoke that is less likely to be subject to exposure misclassification or other bias. Several important new, cohort, case–control studies and meta-analyses have been published since 2004 that provide additional evidence confirming the causal association (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.3.pdf). These new studies also expand our assessment of the effect of second-hand tobacco smoke in the workplace allowing for more refined estimates of lung cancer risk. Preliminary data also suggest significant interactions between several genetic polymorphisms, second-hand tobacco smoke and lung cancer risk.

In a meta-analysis of 55 studies, including 7 cohort, 25 population based case–control studies and 23 hospital based case–control studies the pooled relative risk (RR) for lung cancer for never smoking women exposed to second-hand tobacco smoke from spouses was 1.27 (95%CI: 1.17–1.37). The relative risk for studies in North America was 1.15 (95%CI: 1.03–1.28), in Asia 1.31 (95%CI: 1.16–1.48) and Europe 1.31 (1.24–1.52) (Taylor *et al.*, 2007).

Fig. 1.7 Number and percentage of countries with number of public places covered by smoke free legislations, by income status (as of 31 December 2008)



From WHO (2009a)

In a meta-analysis of 22 studies that assessed the effect of second-hand tobacco smoke exposures at work, the relative risk for lung cancer among exposed non-smokers was 1.24 (95%CI: 1.18–1.29) and among those workers classified as highly exposed to second-hand tobacco smoke at work 2.01 (95%CI: 1.33–2.60) compared to those with no exposure at work (Stayner *et al.*, 2007).

In a large cohort study conducted in 10 European countries (European Prospective Investigation into Cancer and Nutrition, EPIC), it was estimated that the hazard ratio (HR) for lung cancer risk from second-hand tobacco smoke exposure at home and/or at work for never smokers and ex-smokers (at least 10 years) was 1.34 (0.85–2.13) (Vineis *et al.*, 2007a). The main component of this risk was attributable to exposure at the workplace, resulting in a hazard ratio of 1.65 (1.04–2.63). The overall hazard ratio between childhood exposure and the risk of lung cancer in adulthood was 2.00 (0.94–4.28); among children with daily exposure for many hours each day the hazard ratio was 3.63 (1.19–11.12). In a separate analysis of workplace exposure to second-hand tobacco smoke in this cohort women were observed to have a lung cancer hazard ratio of 2.13 (1.6–3.4) (Veglia *et al.*, 2007).

In a large population-based cohort study conducted in Japan, findings confirmed that exposure to second-hand tobacco smoke is

a risk factor for lung cancer among Japanese women (Kurahashi *et al.*, 2008). Compared with women married to never smokers, the hazard ratio for all lung cancer incidence was 1.34 (95%CI:0.81–2.21) and for adenocarcinoma 2.03 (95%CI:1.07–3.86). For adenocarcinoma dose–response relationships were seen for both intensity (*P* for trend = 0.02) and total amount (*P* for trend = 0.03) of the husband's smoking. Exposure to second-hand tobacco smoke at the workplace also increased the risk of lung cancer (HR, 1.32; 95%CI: 0.85–2.04).

Data from a cohort study of women from Shanghai, China also found that exposure to second-hand tobacco smoke is associated with lung cancer mortality. Exposure to second-hand tobacco smoke at work was associated with a significantly increased mortality to lung cancer (HR 1.79, 95%CI: 1.09–2.93) but the risk was not significant for exposure to husband's second-hand tobacco smoke (HR 1.09, 95%CI: 0.74–1.61) (Wen *et al.*, 2006). In a case–control study of lung cancer among lifetime non-smoking Chinese men living in Hong Kong Special Administrative Region a non-significant association between all lung cancer and ever being exposed to household and/or workplace second-hand tobacco smoke was observed (OR, 1.11, 95%CI: 0.74–1.67) but a significant increase was observed for adenocarcinoma (OR, 1.68, 95%CI: 1.00–2.38) (Tse *et al.*, 2009).

In a long-term case–control study of lung cancer cases at the Massachusetts General Hospital, study participants exposed to second-hand tobacco smoke at work and at leisure were at a significantly greater risk (OR, 1.30, 95%CI: 1.08–1.57) if the exposure occurred between birth and 25 years of age. If the exposures occurred after the age of 25 years the risk was not elevated (OR, 0.66, 95%CI: 0.21–1.57) but the confidence limits are wide for this subgroup analysis (Asomaning *et al.*, 2008).

In two other cohort studies, one conducted in California (Enstrom & Kabat, 2003) and another in New Zealand (Hill *et al.*, 2007) no excess risk was observed among lifelong non-smokers exposed to second-hand tobacco smoke. In the California study the relative risk was 0.99 (95%CI: 0.72–1.37) based on 126 lung cancer cases. [The confidence intervals in this study are relatively wide and they include the current IARC estimate of lung cancer risk from second-hand tobacco smoke exposure. In addition the opportunity for substantial misclassification of second-hand tobacco smoke exposure is great because exposures outside the home were not assessed and the second-hand tobacco smoke exposures were not re-evaluated after enrollment into the study.] Hill *et al.* (2007) observed no association between second-hand tobacco smoke exposure in a census enumeration of current second-hand tobacco smoke exposure at home and linkage to cancer registries three years later. The authors suggest that this may be a result of either the misclassification of total second-hand tobacco smoke exposure since exposures outside the home were not assessed and/or the fact that a 3-year follow-up after exposure ascertainment may have been too short to capture important exposures before the diagnosis of lung cancer.

One case–control study (Wenzlaff *et al.*, 2005) and one case-only study (Bonner *et al.*, 2006) assessed lung cancer risk associated with second-hand tobacco smoke exposure and several polymorphisms. In the case–control study, individuals were stratified by household second-hand tobacco smoke exposure (yes/no), those with *CYP1B1 Leu*^{432}*Val* genotype alone or in combination with Phase II enzyme polymorphisms were more strongly associated with lung cancer risk if they also were exposed to at least some household second-hand tobacco smoke exposure compared to those that had no exposure. In the case-only study a significant interaction was observed between lung cancer risk, second-hand tobacco smoke and a GSTM1 (null) genotype (OR, 2.28, 95%CI:1.15–4.51).

2.2 Cancer of the breast

2.2.1 Overview of studies

The relationship between exposure to second-hand tobacco smoke and breast cancer has been comprehensively reviewed in the peer reviewed literature (Johnson, 2005; Miller *et al.*, 2007) and in reports from national and international committees (IARC, 2004, 2009; California Environmental Protection Agency, 2005; US. Department of Health and Human Services, 2006; Collishaw *et al.*, 2009). These reviews have drawn different conclusions. IARC (2004) characterized the evidence as "inconsistent," based on studies published or in press by June, 2002. A US Surgeon General Report (2006) concluded that the evidence was "suggestive but not sufficient" to infer a causal relationship between second-hand tobacco smoke and breast cancer, whereas reviews by the California Environmental Protection Agency (CalEPA) in 2005 and by a panel of researchers in this area convened in Canada (Collishaw *et al.*, 2009) designated the evidence for second-hand tobacco smoke as "consistent with a causal association in younger primarily premenopausal women."

A total of 16 new studies have been published since the previous *IARC Monograph* (IARC, 2004). These include three cohort studies (Reynolds *et al.*, 2004; Hanaoka *et al.*, 2005; Pirie *et al.*, 2008) (Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.4.pdf), and 13 new case–control studies (Lash & Aschengrau, 2002; Alberg *et al.*, 2004; Gammon *et al.*, 2004; Shrubsole *et al.*, 2004; Bonner *et al.*, 2005; Sillanpää *et al.*, 2005; Lissowska *et al.*, 2006; Mechanic *et al.*, 2006; Roddam *et al.*, 2007; Rollison *et al.*, 2008; Slattery *et al.*, 2008; Ahern *et al.*, 2009; Young *et al.*, 2009) (Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.5.pdf). Table 2.5 also presents two case–control studies not discussed previously (Zhao *et al.*, 1999; Liu *et al.*, 2000). Several meta-analyses have also been published as new data became available (California Environmental Protection Agency, 2005; Johnson, 2005; US. Department of Health and Human Services, 2006; Pirie *et al.*, 2008; IARC, 2009).

The largest of the cohort studies, identified 2518 incident breast cancers among 224917 never smokers followed for an average of 3.5 years in the British Million Women Study (Pirie *et al.*, 2008). The cohort was drawn from women, age 50–64 years, participating in mammography screening programmes. Nearly all cases were post-menopausal and the overall analyses pertain to postmenopausal breast cancer. No relationship was observed between breast cancer risk and smoking by a parent at the time of birth and/or age 10 years (HR, 0.98; 95%CI: 0.88–1.08); the results were also null for smoking by a current partner (HR, 1.02; 95%CI: 0.89–1.16) or exposure to the combination of parental and spousal smoking (HR, 1.03; 95%CI: 0.90–1.19). Pirie *et al.* (2008) also present a meta-analysis of studies of second-hand smoke and breast cancer risk, separating studies by cohort or case–control design. No overall association was observed in the cohort studies. These largely represent post-menopausal breast cancer, so the analysis was not stratified by menopausal status. An overall association was seen in the case–control studies, similar to the findings of other meta-analyses (California Environmental Protection Agency, 2005; US. Department of Health and Human Services, 2006; IARC, 2009). [Pirie *et al.* (2008) focus on the discrepancy between the cohort and case–control results and propose that the associations observed in early case–control studies can likely be explained by recall bias. The study has been criticized for the lack of information on occupational exposures to second-hand smoke (Collishaw *et al.*, 2009).]

A second large cohort study (Reynolds *et al.*, 2004) identified 1998 women diagnosed with breast cancer during five years of follow-up of the

California Teachers Study. Analyses were based on 433 women with pre/peri-menopausal breast cancer and 1361 women with postmenopausal cancer. No association was observed between post-menopausal breast cancer and residential exposure to second-hand tobacco smoke in childhood or adulthood. No association was initially reported with pre/peri-menopausal breast cancer in analyses based on menopausal status at enrollment (RR 0.93, 95%CI: 0.71–1.22). When menopausal status was defined by age at diagnosis rather than by age at enrollment, the hazard ratio for premenopausal breast cancer among women exposed in both childhood and adulthood increased to 1.27 (95%CI: 0.84–1.92) (Reynolds *et al.*, 2006).

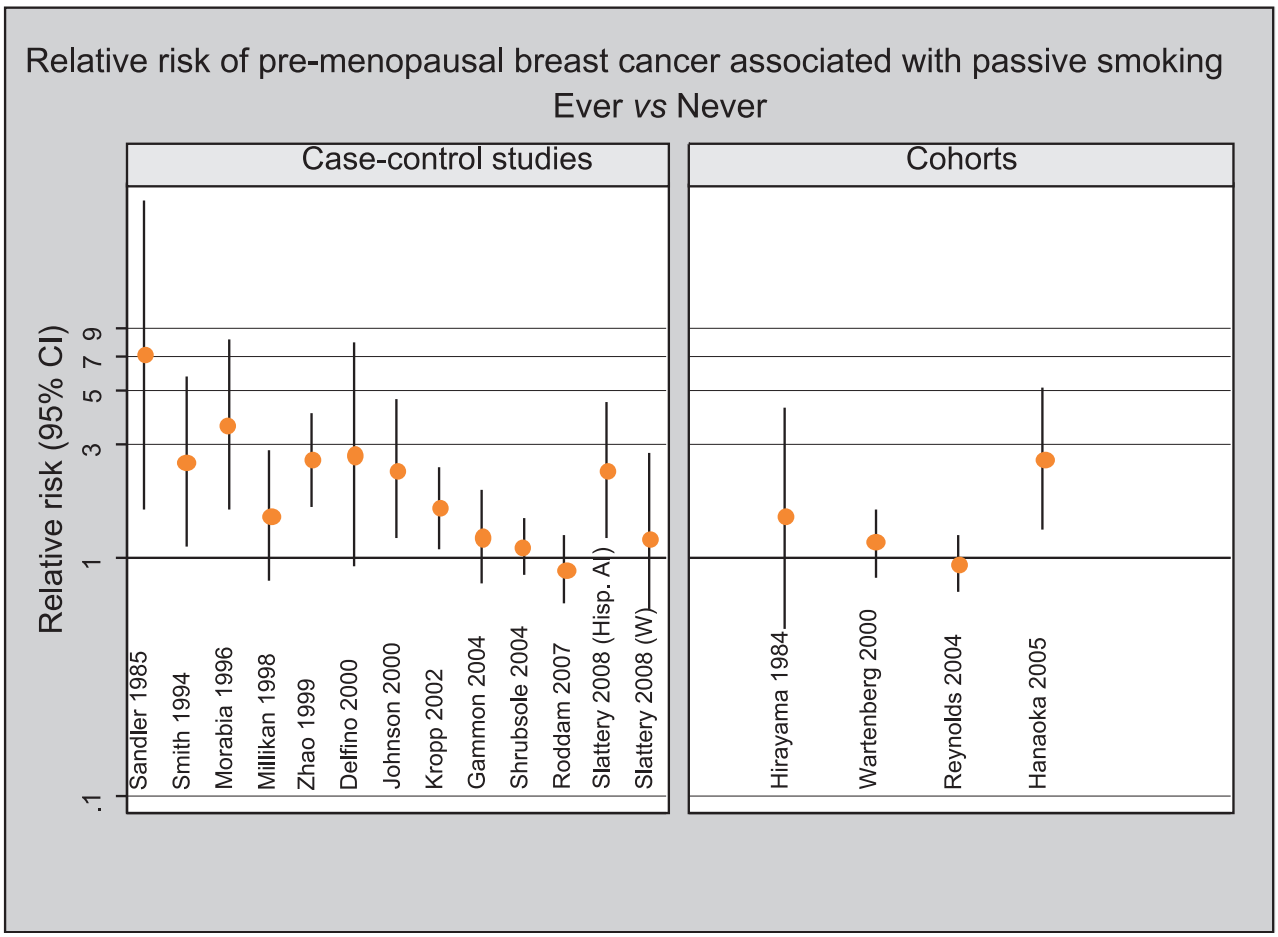
Hanaoka *et al.* (2005) identified 162 incident breast cancer cases during a nine-year follow-up of 20169 Japanese women, age 40–59 years, who reported no history of active smoking when enrolled in the Japan Public Health Center (JPHC) study in 1990. Nearly three quarters (72%) of the women reported exposure to second-hand tobacco smoke. About half of the women were premenopausal when enrolled in the study, although there were only nine unexposed cases among the pre-menopausal women. The multivariate-adjusted relative risk for breast cancer among all exposed women irrespective of menopausal status was 1.1 (95%CI: 0.8–1.6) compared to those classified as unexposed. The corresponding relative risks for women who were pre- or postmenopausal at baseline were 2.6 (95%CI: 1.3–5.2) and 0.7 (95%CI: 0.4–1.0), respectively.

Six of the 13 new population-based case–control studies included more than 1000 cases each (Shrubsole *et al.*, 2004; Bonner *et al.*, 2005; Lissowska *et al.*, 2006; Mechanic *et al.*, 2006; Slattery *et al.*, 2008; Young *et al.*, 2009; Table 2.5 on-line). None of these 13 studies showed an overall increase in breast cancer risk associated with second-hand tobacco smoke exposure in Caucasians. The incidence of premenopausal breast cancer was associated with one or more indices of second-hand tobacco smoke exposure in all four studies that stratified the results by menopausal status (Gammon *et al.*, 2004; Shrubsole *et al.*, 2004; Bonner *et al.*, 2005; Slattery *et al.*, 2008) although the association was not always statistically significant (Gammon *et al.*, 2004; Bonner *et al.*, 2005; Fig. 2.1). Associations were also reported between second-hand tobacco smoke exposure and overall breast cancer risk in African Americans (Mechanic *et al.*, 2006) and with premenopausal breast cancer in Hispanics/American Indians (Slattery *et al.*, 2008). The associations observed in these case–control studies are generally weaker than those reported in earlier case–control studies. Whereas the relative risk estimates reported in the earlier studies often equalled or exceeded 2.0 (Sandler *et al.*, 1985a; Lash & Aschengrau, 1999; Zhao *et al.*, 1999; Johnson & Repace, 2000; Liu *et al.*, 2000) or 3.0 (Smith *et al.*, 1984; Morabia *et al.*, 1996; Liu *et al.*, 2000; Morabia *et al.*, 2000), the estimates in the later studies were mostly under 1.5, even in studies that reported positive associations.

2.2.2 Issues affecting the interpretation of studies

One important consideration in evaluating these data has been the lack of a strong and convincing relationship between active smoking and breast cancer. Several theories have been advanced to explain why second-hand tobacco smoke might have a stronger effect on breast cancer than active smoking (California Environmental Protection Agency, 2005; Johnson, 2005; Collishaw *et al.*, 2009). Central to these is the hypothesis that active smoking may have counterbalancing protective and detrimental effects on breast cancer risk that, in combination, produce little or no overall association, whereas second-hand tobacco smoke may have only an adverse effect on risk. The weakness of this theory is that there is little direct evidence (see Section 4) identifying the

Fig. 2.1 Relative risk of pre-menopausal breast cancer associated with second-hand tobacco smoke. Ever versus never.



Study sorted by calendar year

mechanism by which active smoking may cause the proposed [protective] antiestrogenic effects. Without knowing the mechanism, it has been impossible to prove that active smoking has this effect but exposure to second-hand tobacco smoke does not. A second hypothesis that has been advanced is that second-hand tobacco smoke may have a greater effect on pre- than on postmenopausal breast cancer. This theory was proposed by CalEPA in 2005 (Johnson & Glantz, 2008) based on analyses of studies available at the time, and was subsequently questioned by some (US. Department of Health and Human Services, 2006) but not all (Collishaw *et al.*, 2009) subsequent reviews. [Because this arose as an a posteriori observation rather than as an a priori hypothesis, it must be confirmed by independent studies.] The strongest support for the hypothesis comes from a cohort study in Japan (Hanaoka *et al.*, 2005), which reported significantly increased risk (RR 2.6, 95%CI: 1.3–5.2) of premenopausal breast cancer in women who previously reported having ever lived with a regular smoker or ever being exposed to second-hand tobacco smoke for at least one hour per day in settings outside the home. However, the

referent group in this analysis included only nine unexposed cases. No associations were observed with post-menopausal breast cancer. A weak association between second-hand tobacco smoke exposure and premenopausal breast cancer was reported in the California Teachers cohort, when menopausal status was defined by age at diagnosis rather than age at entry into the study (Reynolds *et al.*, 2006). In case–control studies published since the CalEPA review (California Environmental Protection Agency, 2005) that reported results stratified by menopausal status, Bonner *et al.* (2005) and Slattery *et al.* (2008) reported stronger associations with pre- than with post-menopausal breast cancer, although the only statistically significant association with premenopausal breast cancer was in Hispanic or American Indian women who had second-hand tobacco smoke exposure of more than ten hours per week (OR, 2.3, 95%CI:1.2–4.5) (Slattery *et al.*, 2008). In a case–control study of breast cancer in women age 36–45 years Roddam *et al.* (2007) observed no increased risk in premenopausal women who, since age 16, were married to or lived with a boyfriend who smoked for at least one year.

Two other explanations for inconsistencies in the evidence relate to the fundamental design differences between cohort and case–control studies. A critical advantage of cohort studies is that they collect information on exposures before the disease of interest is diagnosed, thus preventing knowledge of disease status influencing how participants recall and/or report their exposures. Recall bias is especially challenging in case–control studies of exposures that are difficult to measure, when recollection of the frequency and intensity of exposure is necessarily subjective. In counterpart, an important advantage of case–control studies is that they can collect more detailed information on the exposure of interest than is usually possible in cohort studies. Together, these factors create what has been described as "a tension" between the potential for recall or selection bias in case–control studies, and the reduced possibility of collecting full "lifetime exposure histories" in cohort studies (Collishaw *et al.*, 2009). The discrepancy in the results from case–control and cohort studies is seen especially in the earlier case–control studies, which found much stronger associations than those observed in most recent studies. Five studies in particular (Smith *et al.*, 1984; Morabia *et al.*, 1996; Zhao *et al.*, 1999; Johnson & Repace, 2000; Kropp & Chang-Claude, 2002) were considered by Collishaw *et al.* (2009) as having the most complete information on lifetime exposure to second-hand tobacco smoke from all sources. At the same time, these studies are among the most susceptible to recall bias for two reasons. The first is a general problem of case–control studies, in that cases are more likely to remember and report potentially hazardous exposures than controls. Second, recall bias is potentially more problematic when subjective considerations can influence reporting. It is easier to report smoking by a parent or spouse than it is to remember exposures from other sources that possibly occurred many years ago in daily life. Exposure to second-hand tobacco smoke was highly prevalent in the decades following World War II in Europe and North America. It would be unusual for someone not to be exposed. The studies that the California Environmental Protection Agency (2005) considered to have the best information on exposure to second-hand tobacco smoke are also those which rely more heavily on recall of past exposures outside the home. Moreover, inclusion in the referent group in these studies is also vulnerable to recall bias. Previous reviews by IARC (2004) and the US Surgeon General (US. Department of Health and Human Services, 2006) have expressed concern about potential biases that may be introduced by relying on a small and unusual subgroup (the unexposed to active smoking and second-hand tobacco smoke) as the referent category in these studies. Recall bias remains a plausible explanation for why the

association with second-hand tobacco smoke is stronger in studies that collect "lifetime exposure histories" than in those that rely on parental or spousal smoking. In addition, publication bias cannot be ruled out because the reporting of association limited by subgroup (pre-menopausal) could have been selective.

[The Working Group noted that adjustment for potential confounders using the questionnaire data on other established risk factors for breast cancer did not eliminate the association with second-hand tobacco smoke in these studies. However, this does not resolve concerns about the possibility of recall or publication bias.]

Several meta-analyses have been published, largely showing similar results but leading to substantially different interpretations of the evidence (California Environmental Protection Agency, 2005; US Department of Health and Human Services, 2006; Johnson, 2007; IARC, 2009). The California Environmental Protection Agency (2005) calculated a pooled estimate for second-hand tobacco smoke and breast cancer risk of 1.11 (95%CI: 1.04–1.19) in all women and 1.38 (95%CI: 1.21–1.56) in premenopausal women, based on 19 studies and a fixed effects model. These estimates increased to 1.89 (95%CI: 1.57–2.27) for all women and 2.18 (95%CI: 1.70–2.79) in premenopausal women when the analysis was restricted to the subset of studies considered to have the best exposure data.

Based on these analyses, the California Environmental Protection Agency (2005) and Collishaw *et al.* (2009) emphasized the positive association with premenopausal breast cancer in their conclusion that the evidence is "consistent with a causal relationship" whereas the US Surgeon General (US Department of Health and Human Services, 2006) was more cautious in characterizing the evidence as "suggestive but not sufficient."

[The Working Group noted that the criterion used by IARC specifies "sufficient evidence of carcinogenicity in which chance, bias and confounding could be ruled out with reasonable confidence." This is a more stringent definition than "consistent with a causal relationship."]

2.3 Cancers of the upper aerodigestive tract

2.3.1 Upper areodigestive tract combined

Cancers of the upper aerodigestive tract traditionally comprise cancers of the oral cavity, pharynx, larynx and oesophagus. However, some epidemiological studies have examined only head and neck cancers restricted to tumours of the oral cavity, pharynx and larynx. Four case–control studies (Tan *et al.*, 1997; Zhang *et al.*, 2000; Lee *et al.*, 2008; Ramroth *et al.*, 2008) assessed the effects of second-hand tobacco smoke on head and neck cancers combined and separately for oral cavity, oropharynx or larynx cancers (Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.6.pdf).

In a hospital-based case–control study in the USA, including only non smoking cases and controls, Tan *et al.* (1997) detected high risk of head and neck cancer among those ever exposed to second-hand tobacco smoke at home or at work. Women presented higher risk at home (OR, 7.3; $P < 0.001$) than men (OR, 1.1; $P < 0.79$). On the other hand, men showed higher risk at work (OR, 11.6; $P < 0.001$) than women (OR, 8.9; $P < 0.002$). [The authors did not provide the percentages of the telephone interviews done with the spouses of cases and controls. Probably, this is the main weakness of this study and differential misclassification of exposure to second-hand tobacco smoke could not be excluded. The analysis was performed without adjustment for potential confounding variables.] In a study in the USA, Zhang *et al.* (2000) observed an increased risk (OR, 2.4; 95%CI: 0.9–6.8) with lifetime second-hand tobacco smoke exposure (ever/never) for head and neck cancers, adjusted for age, sex, ethnicity, education, alcohol drinking,

pack-years of cigarette smoking, and marijuana consumption.

Lee *et al.* (2008) pooled the data from several studies including cases of head and neck cancers and controls (population and hospital) from central Europe, Latin America and United States. Two groups were examined separately, never tobacco users and never tobacco and alcohol users. Among never tobacco users, no association was observed between ever exposure to second-hand tobacco smoke at home or at work and the risk for head and neck cancers. Among never tobacco and alcohol users, a non-statistically significant risk (or 1.30; 95%ci: 0.94–1.81) was observed. When considering specific anatomical sites, only laryngeal cancer risk was increased when ever exposed to second-hand tobacco smoke in a lifetime, detected among never tobacco users (OR, 1.71; 95%CI: 0.98–3.00) and among never tobacco and alcohol users (OR, 2.90; 95%CI: 1.09–7.73).

In Germany, in a population-based case–control study on laryngeal cancer, Ramroth *et al.* (2008) observed a non-statistically significant risk (OR, 2.0; 95%CI: 0.39–10.7) for exposure to second-hand tobacco smoke (ever/never) at home and in workplaces among nonsmokers.

(a) Evidence of a dose–response

Zhang *et al.* (2000) observed a dose–response relationship with the intensity of exposure to second-hand tobacco smoke (never, moderate and heavy) on head and neck cancers ($P = 0.025$); those at heavy level of exposure at home or at work showed highest risk for head and neck cancer (OR, 3.6; 95%CI: 1.1–11.5). However, the classification of exposure to second-hand tobacco smoke at work as never, occasionally or regularly did not show any dose–response effect; and the risk for the groups of occasionally or regularly exposed at home were similar and non statistically significant.

Lee *et al.* (2008) explored the intensity and duration of sexposure to second-hand tobacco smoke. For intensity the number of hours of exposure per day was considered at home (0–3 hours, > 3 hours) or at the workplace (never, 1–3 hours and > 3 hours). Among both groups of never tobacco users and never tobacco and alcohol users non-statistically significant risks of head and neck cancers were observed for those exposed for > 3 hours per day at home or at work. For duration the number of years of exposure at home and at work was considered (never, 1–15 years, and > 15 years). Among never tobacco users, there was a trend of increase in risk for head and neck cancers with greater number of years of exposure at home, but not at work. Among never tobacco and alcohol users, the duration of exposure showed a trend for exposure both at work or at home.

Considering specific anatomical sites, for cancer of the oral cavity no dose–response effect was observed with increasing number of years of exposure to second-hand tobacco smoke at home or at work. For cancer of the pharynx, a dose–response effect was observed with increasing number of years of exposure to second-hand tobacco smoke with only at home, in both never tobacco users and never tobacco and alcohol users. For cancer of the larynx, a dose–response effect was noted with increasing number of years of exposure to second-hand tobacco smoke at home among never tobacco users and at work among never tobacco and alcohol users. Among never tobacco and alcohol users, all the odd ratios (OR) were statistically significantly elevated for > 15 years of exposure at home or at work for head and neck cancers overall and separately for cancer of the pharynx, and only at work for cancer of the larynx.

2.3.2 Cancers of the nasopharynx, and nasal cavity and sinonasal cavity

The relationship between exposure to second-hand tobacco smoke and risk for these rare cancers of the upper respiratory tract has

been examined in one cohort study (Hirayama, 1984; Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.7.pdf) and five case–controls studies (Fukuda & Shibata, 1990; Yu *et al.*, 1990; Zheng *et al.*, 1993; Cheng *et al.*, 1999; Yuan *et al.*, 2000; Table 2.6 on-line). A positive association was found in most of these studies.

Hirayama (1984) found an increased risk of sinonasal cancer in women (histology not noted) associated with increasing numbers of cigarettes smoked by husbands of nonsmoking women. When compared with nonsmoking women married to nonsmokers, wives whose husbands smoked had a relative risk of 1.7 (95%CI: 0.7–4.2) for 1–14 cigarettes per day, 2.0 (95%CI: 0.6–6.3) for 15–19 cigarettes per day and 2.55 (95%CI: 1.0–6.3) for ≥ 20 cigarettes per day (*P* for trend = 0.03).

Fukuda & Shibata (1990) reported the results of a Japanese case–control study based on 169 cases of squamous-cell carcinoma of the maxillary sinus and 338 controls matched on sex, age and residence in Hokkaido, Japan. Among nonsmoking women, a relative risk of 5.4 ($P < 0.05$) was associated with exposure in the household to second-hand tobacco smoke from one or more smokers. Active smoking was associated with an increased risk for squamous-cell carcinoma of the maxillary sinus in men in the same study.

Zheng *et al.* (1993) used data from the 1986 US National Mortality Followback Survey to assess risk for cancer of the nasal cavity and sinuses in relation to exposure to second-hand tobacco smoke in white men. A total of 147 deaths from cancer of the nasal cavity and sinuses was compared to 449 controls who had died from other causes (excluding any causes strongly linked to alcohol and/or tobacco use). Data were obtained from postal questionnaires completed by next-of-kins. Among nonsmokers, patients with nasal cancer were more likely to have a spouse who smoked cigarettes (RR, 3.0; 95%CI: 1.0–8.9) after adjustment for age and alcohol use. When the analysis of cases was restricted to those with cancer of the maxillary sinus, the risk was somewhat higher (RR 4.8; 95%CI: 0.9–24.7). The risks reported for active smoking and exposure to second-hand tobacco smoke were of similar magnitude in this study.

Neither second-hand tobacco smoke exposure during childhood nor exposure during adulthood were positively associated with an increased risk for nasopharyngeal cancer in a study in Taiwan, China (Cheng *et al.*, 1999). Although histological type was not specified, all cases were histologically confirmed. Among never-smokers, the risk estimates for cumulative exposure to second-hand tobacco smoke (pack-person-years) in childhood declined as exposure increased (*P* for trend = 0.05); a similar but non-significant inverse relationship was found for exposure during adulthood. Significant elevations in risk for nasopharyngeal cancer were observed for active smokers in this study. [The Working Group noted that the exposure assessment was relatively detailed and that the estimates of relative risk were adjusted for age, sex, education and family history of nasopharyngeal cancer.]

A large population-based case–control study conducted in Shanghai, China, included 935 cases of nasopharyngeal carcinoma and 1032 population controls randomly selected from a population-registry and frequency-matched by sex and 5-year age group (Yuan *et al.*, 2000). All cases were histologically confirmed, but the cell type was not specified. The study subjects were interviewed face to face, and the response rates were 84% for cases and 99% for controls. In female never-smokers, a consistent increase in risk related to exposure to second-hand tobacco smoke during childhood was noted. The relative risk was 3.4 (95%CI: 1.4–8.1) if the mother smoked; 3.0 (95%CI: 1.4–6.2) if the father smoked; 2.7 (95%CI: 1.1–6.9) if another household member smoked and 3.0 (95%CI: 1.4–6.2)

if any household member smoked. Risks associated with exposure to second-hand tobacco smoke during adulthood in women were also statistically significantly increased. For male never-smokers, the associations were weaker and were not statistically significantly elevated for exposure during childhood and adulthood. [The Working Group noted that this was a large, well conducted study that included a detailed exposure assessment and adjustment for numerous potential confounders.]

2.4 Leukaemia and lymphomas

Kasim *et al.* (2005) analysed the risk of leukaemia in adults after exposure to second-hand tobacco smoke (Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.8.pdf). This case–control study was based on postal questionnaires. There was a slightly increased risk (*P* for trend = 0.001) with increasing duration of exposure to second-hand tobacco smoke. The association was limited to chronic lymphocytic leukaemia and was stronger for occupational exposures to second-hand tobacco smoke.

2.5 Other cancers in adults

2.5.1 All cancer combined

Hirayama (1984), Sandler *et al.* (1985b), and Miller (1990) observed a significant association between exposure to second-hand tobacco smoke and overall cancer incidence or mortality. Nishino *et al.* (2001) also studied all cancers combined and reported a relative risk of 1.1 (95%CI: 0.92–1.4) associated with husband's smoking.

2.5.2 Cancers of the gastrointestinal tract

In addition to the studies reviewed previously (Sandler *et al.* 1988; Gerhardsson de Verdier *et al.*, 1992; Mao et.al., 2002), ten new studies have been identified: two cohort (Nishino *et al.*, 2001; Hooker *et al.*, 2008; Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.13.pdf); seven case–control (Sandler *et al.*, 1985a, b; Slattery *et al.*, 2003; Lilla *et al.*, 2006; Wang *et al.*, 2006; Duan *et al.*, 2009; Verla-Tebit *et al.*, 2009; Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.14.pdf) and one case-only study (Peppone *et al.*, 2008; Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.15.pdf). Two studies (Sandler *et al.*, 1985a; Wang *et al.*, 2006) did not provide risk estimates of gastrointestinal cancers for never smokers and are not discussed further. [No data for these studies are included in the tables.]

Sandler *et al.* (1985b) observed a relative risk of 0.7 and 1.3 for cancer of the digestive system from exposure to maternal and paternal passive smoke, respectively. [No CIs were provided and the numbers of never smokers exposed were small.] Verla-Tebit *et al.* (2009) found no evidence of an increased risk for colorectal cancer associated with exposure to second-hand tobacco smoke overall.

(a) Cancer of the colorectum

Nishino *et al.* (2001) observed no association with husband's smoking for cancer of the colon (RR 1.3; CI: 0.65–2.4) or of the rectum (RR 1.8; 0.85–3.9).

Four studies investigated risk for cancer or the colon and/or rectum by sex. Sandler *et al.* (1988) reported an increased risk for colorectal cancer in men (RR 3.0; 95%CI: 1.8–5.0) but a protective effect in women (RR 0.7; 95%CI: 0.6–1.0). Slattery *et al.* (2003) noted that rectal cancer was significantly associated with exposure to second-hand tobacco smoke in men (OR, 1.5; 95%CI: 1.1–2.2 for never smokers) but not in women. Hooker *et al.* (2008) reported an effect among men only, with a significantly increased risk for rectal cancer in the 1963 cohort (RR 5.8, 95%CI: 1.8–18.4) but not

the 1975 cohort. Gerhardsson de Verdier *et al.* (1992) found an increased risk for rectal cancer in men (RR 1.9; 95%CI: 1.0–3) and for colon cancer in women (RR 1.8; 95%CI: 1.2–2.8). [The Working Group noted that it is unclear whether the analysis was restricted to never-smokers.]

When analysing different sources of exposure to second-hand tobacco smoke, Verla-Tebit *et al.* (2009) found no evidence of an increased risk for cancer of the colorectum associated with exposure to second-hand tobacco smoke specifically during childhood or at work, but observed a significant increase in risk associated with spousal exposure.

Peppone *et al.* (2008) noted that considerable exposure to second-hand tobacco smoke, especially during childhood, was more likely to lead to an earlier-age diagnosis of cancer of the colorectum.

In exploring the association of cancer of the colorectum with exposure to second-hand tobacco smoke and NAT1 and NAT2 status, Lilla *et al.* (2006) noted that risk may only be relevant among genetically susceptible (NAT1 and NAT2 status) individuals.

(b) Cancer of the stomach

Nishino *et al.* (2001) observed no association with husband's smoking for cancer of the stomach (RR, 0.95; 95%CI: 0.58–1.6).

The two studies on the association of exposure to second-hand tobacco smoke with stomach cancer by subsite (cardia versus distal) gave contradictory results. In one study (Mao *et al.*, 2002) a positive trend ($P = 0.03$) in risk for cancer of the gastric cardia was associated with lifetime exposure to second-hand tobacco smoke (residential plus occupational) in never smoking men, with a relative risk of 5.8 (95%CI: 1.2–27.5) at the highest level of exposure (≥ 43 years); no increased risks or trends were observed for distal gastric cancer. In the other study, Duan *et al.* (2009) an increased risk for distal gastric cancer was found, but not for gastric cardia [Data were not analysed by sex due to small sample size].

2.5.3 Cancer of the pancreas

Six studies have been identified on the association of exposure to second-hand tobacco smoke with cancer of the pancreas: three cohort (Nishino *et al.*, 2001; Gallicchio *et al.*, 2006; Bao *et al.*, 2009; the latter two are summarized in Table 2.17 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.17.pdf) and three case–control (Villeneuve *et al.*, 2004; Hassan *et al.*, 2007; Lo *et al.*, 2007; the former two studies are summarized in Table 2.18 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.18.pdf).

(a) Exposure in adulthood

Data from the majority of the studies (Nishino *et al.*, 2001; Villeneuve *et al.*, 2004; Gallicchio *et al.*, 2006; Hassan *et al.*, 2007; Bao *et al.*, 2009) suggested lack of an association of cancer of the pancreas with never smokers exposed to second-hand tobacco smoke in adulthood at home or at work. (RR 1.2 (95%CI: 0.45–3.1) and 1.21 (95%CI: 0.60–2.44) respectively).

Lo *et al.* (2007) reported an odd ratio of 6.0 (95%CI: 2.4 –14.8) for never smokers (both sexes combined) exposed to second-hand tobacco smoke in Egypt. [The Working Group noted the small numbers of cases, the use of hospital controls and the small proportion of the cases (35%) with histopathological confirmation. Data are not included in Table 2.18 on-line].

(b) Exposure during childhood

In the Nurses' Health Study, Bao *et al.* (2009) noted an increased risk for cancer of the pancreas (RR 1.42; 95%CI: 1.07–1.89) for maternal but not for paternal smoking (RR 0.97; 95%CI: 0.77–1.21) during childhood.

2.5.4 Cancer of the kidney (renal cell carcinoma)

Two case–control studies have been published on the association of exposure to second-hand tobacco smoke with cancer of the kidney (specifically renal cell carcinoma) since IARC (2004) (Hu *et al.*, 2005; Theis *et al.*, 2008; Table 2.19 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.19.pdf). In both studies a significantly increased risk associated with exposure to second-hand tobacco smoke among never smokers was reported.

2.5.5 Cancer of the urinary bladder

A total of seven studies and one meta-analysis have considered the association between exposure to second-hand tobacco smoke and cancer of the urinary bladder: three cohort studies (Zeegers *et al.*, 2002; Bjerregaard *et al.*, 2006; Alberg *et al.*, 2007; Table 2.9, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.9.pdf), four case–control studies (Burch *et al.*, 1989; Chen *et al.*, 2005a; Samanic *et al.*, 2006; Jiang *et al.*, 2007; Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.10.pdf), and one meta-analysis (Van Hemelrijck *et al.*, 2009).

(a) Population-based exposure-response relationship

Burch *et al.* (1989) and Zeegers *et al.* (2002) reported no increased risk for cancer of the urinary bladder [Data are not included in the Tables]. Van Hemelrijck *et al.* (2009) reported a meta-relative risk of 0.99 (95%CI: 0.86–1.14) for never smokers exposed to second-hand tobacco smoke. [Data not included in Table. The Working Group noted the marked variation in risk in the analyses by sex and by timing of exposure to second-hand tobacco smoke during adulthood or childhood].

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Bjerregaard *et al.* (2006) compared ever versus never exposed to second-hand tobacco smoke as an adult or a child: the risk for cancer of the urinary bladder increased for exposures during childhood (OR, 1.38; 95%CI: 1.00–1.90), and was stronger for never-smokers (OR, 2.02; 95%CI: 0.94–4.35).

Alberg *et al.* (2007) analysed data from two cohorts of non-smoking women in the USA exposed to second-hand smoke at home. An association with exposure to second-hand tobacco smoke was found in the 1963 cohort (RR, 2.3; 95%CI: 1.0–5.4) but not in the 1975 cohort (RR, 0.9; 95%CI: 0.4–2.3). [The Working Group noted the small number of cases available for some of the risk estimates.]

In a study assessing occupational exposure to second-hand tobacco smoke (Samanic *et al.*, 2006), the risk for cancer of the urinary bladder was increased in the highest exposure category among women (RR, 3.3; 95%CI: 1.1–9.5) but not among men (RR, 0.6; 95%CI: 0.2–1.4).

(b) Molecular-based exposure-response relationship

4-aminobiphenyl (4-ABP) can form DNA adducts and induce mutations, and cigarette smoke is the most prominent source of exposure to 4-aminobiphenyl in humans (see Section 4). Jiang *et al.* (2007) used variation in 4-ABP-haemoglobin adducts levels to assess exposure to second-hand tobacco smoke and reported a significantly increased risk with increasing lifetime exposure among never-smoking women exposed in adulthood or childhood.

Chen *et al.* (2005a) hypothesized that the ability to detoxify arsenic (a risk factor urinary bladder cancer) through methylation may modify risk related to second-hand tobacco smoke exposure. Results of the adjusted analyses show that a high primary methylation index associates with lower risk of cancer of the urinary bladder (OR, 0.37; 95%CI: 0.14–0.96, p interaction = 0.11) in second-hand tobacco smoke exposed subjects

compared to unexposed. In endemic area the ability to methylate arsenic may play a role in reducing the risk of cancer of the urinary bladder associated with second-hand tobacco smoke exposure. [The Working Group noted that the small number of cases and the use of hospital controls limit the validity of inferences from this study].

Using case–control data for never and former smokers nested within the EPIC study Vineis *et al.* (2007b) examined susceptibility in genes involved in oxidative stress (such as *NQO1*, *MPO*, *COMT*, *MnSOD*), in phase I (such as *CYP1A1* and *CYP1B1*) and phase II (such as *GSTM1*, and *GSTT1*) metabolizing genes, and in methylene-tetrahydrofolate (*MTHFR*). *GSTM1* deletion was strongly associated with risk for urinary bladder cancer in never smokers (OR, 1.75; 95%CI: 0.89–3.43), and a similar association was noted for former smokers and for men.

2.5.6 Cancer of the cervix

The cohort studies evaluated previously (Hirayama, 1984; Jee *et al.*, 1999; Nishino *et al.*, 2001) consistently indicated the lack of association between exposure to second-hand tobacco smoke and cancer of the uterine cervix, while the informative case–control studies (Sandler *et al.*, 1985b; Slattery *et al.*, 1989; Scholes *et al.*, 1999) suggested a non-statistically significant increase in risk.

A total of 10 new studies have been identified: one cohort study (Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.11.pdf) and nine case–control studies (Buckley *et al.*, 1981; Brown *et al.*, 1982; Hellberg *et al.*, 1986; Hirose *et al.*, 1996; Coker *et al.*, 2002; Wu *et al.*, 2003; Tay & Tay, 2004; Sobti *et al.*, 2006; Tsai *et al.*, 2007; Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.12.pdf). Three early case–control studies (Buckley *et al.*, 1981; Brown *et al.*, 1982; Hellberg *et al.*, 1986) did not look at risk of exposure to second-hand tobacco smoke in never smoking women, and are not further discussed.

(a) Squamous cell carcinoma of the cervix

A significant increase risk for invasive cancer of the uterine cervix associated with exposure to second-hand tobacco smoke during adulthood was found in three case–control studies (Hirose *et al.*, 1996; Wu *et al.*, 2003; Tay & Tay, 2004) and one cohort study (Trimble *et al.*, 2005).

(b) Cervical intraepithelial lesions and neoplasia

An earlier case–control study (Coker *et al.*, 1992) found no statistically significant association between exposure to second-hand tobacco smoke and CIN II/III in non-smokers, after adjustment for age, race, education, number of partners, contraceptive use, history of sexually transmitted disease and history of Pap smear. A later study (Coker *et al.*, 2002) looked at risk of low grade and high grade cervical squamous intraepithelial lesions (LSIL and HSIL, respectively) in HPV positive never-smokers and reported a significant association with exposure to second-hand tobacco smoke. In a community-based case–control study, Tsai *et al.* (2007) observed a markedly increased risk for both CIN1 and CIN2 in both HPV-positive and HPV-negative women exposed to second-hand tobacco smoke. Only Coker *et al.* (2002) and Tsai *et al.* (2007) controlled for HPV status in women.

Sobti *et al.* (2006) reported that cervical cancer risk is increased in individuals exposed to second-hand tobacco smoke with *GSTM1* (null), *GSTT1* (null) and *GSTP1* ($Ile^{105}Val$) genotypes, with odd ratios ranging from 6.4 to 10.2.

2.5.7 Cancer of the ovary

One cohort study (Nishino *et al.*, 2001) and two case–control studies (Goodman & Tung, 2003; Baker *et al.*, 2006; Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/

vol100E/100E-02-Table2.16.pdf) have been published on the association of exposure to second-hand tobacco smoke with cancer of the ovary. In all three studies a null or inverse association of cancer of the ovary for never smokers exposed to second-hand tobacco smoke was found. Nishino *et al.* (2001) observed no association with husband's smoking (RR 1.7; 95%CI: 0.6- 5.2). Goodman & Tung (2003) reported no association of exposure to second-hand tobacco smoke during childhood with risk of cancer of the ovary. Baker *et al.* (2006) reported a decreased risk of cancer of the ovary for never smokers exposed to second-hand tobacco smoke (OR, 0.68; 95%CI: 0.46–0.99), with similar findings for former and current smokers.

2.5.8 Tumours of the brain and CNS

A total of three case–control studies (Ryan *et al.*, 1992; Hurley *et al.*, 1996; Phillips *et al.*, 2005) have considered the association of second-hand tobacco smoke and cancers of the brain and central nervous system. Ryan *et al.* (1992) reported an increased risk of meningioma associated with spousal exposure, particularly among women (RR 2.7; 95%CI: 1.2–6.1). In a case–control study of gliomas in Australia no association was found for exposure to second-hand tobacco smoke in never smokers (RR 0.97, 95%CI: 0.61–1.53) (both sexes combined) (Hurley *et al.*, 1996). However Phillips *et al.* (2005) found that spousal smoking was associated with an increased risk for intracranial meningioma in both sexes combined (OR, 2.0; 95%CI: 1.1–3.5), the risk increased with increasing duration of exposure (*P* for trend = 0.02).

2.5.9 Other cancers

One case–control study on hepatocellular cancer (Hassan *et al.*, 2008) and one on cancer of the testis (McGlynn *et al.*, 2006) were published since IARC (2004). Hassan *et al.* (2008) did not find an association with exposure to second-hand tobacco smoke and hepatocellular cancer, while that of McGlynn *et al.* (2006) did not support the hypothesis that maternal smoking is related to the development of cancer of the testis (Table 2.20 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.20.pdf). However, these studies provide limited information on the association of exposure to second-hand tobacco smoke with the risk of these cancers.

2.6 Parental tobacco smoking and childhood cancers

2.6.1. Overview

A large number of studies have evaluated the association of cancer risk in childhood with exposure to parental smoking. However, childhood cancers are extremely heterogeneous, both between major cancer sites and within subtypes. In addition, given the rarity of childhood cancers, studies of specific cancer sites and subtypes that have adequate sample sizes and detailed exposure assessments are difficult to achieve.

(a) Smoking exposure assessment

Parental smoking before and during pregnancy exposes germ cells (spermatozoa and ova) and/or the fetus to the same chemical mixture and levels of tobacco smoke as during active smoking, while post-natal exposure to parental tobacco smoking exposes the offspring to second-hand tobacco smoke. Some studies distinguish whether exposure to parental smoking was preconceptional, *in utero* or postnatal. Even when a study reports only on one time period, exposure may have occurred at all three periods. Exposures to tobacco smoking during each of these periods tend to correlate, in particular, paternal smoking is less likely to change during and after pregnancy. In addition, paternal and

maternal smoking habits are highly correlated (Boffetta *et al.*, 2000).

Most studies assessed the number of cigarettes smoked per day (e.g. 0–10, 11–20, 20+) and, when data were available, some assessed continuous consumption of cigarettes per day. One study reported exposure in pack-years (Lee *et al.*, 2009). The SEARC international case–control study assessed polycyclic aromatic hydrocarbons (PAHs) as the main exposure of interest and obtained information on both tobacco smoke and occupational exposures (Cordier *et al.*, 2004).

(b) Bias and confounding

Whitehead *et al.* (2009) evaluated the adequacy of self-reported smoking histories on 469 homes of leukaemia cases and controls and found that nicotine concentrations derived from interview responses to a structured questionnaire strongly correlated to measured levels in dust samples.

The major confounders for the relationship between parental smoking and childhood cancers were markers of socioeconomic status, race or ethnicity, birth weight or gestational age, parental age, sex and age of the case child. In most studies matching or adjusting for these confounders was performed as appropriate. In some studies matching was performed for birth order and centre of diagnosis.

2.6.2 All childhood cancers combined

In addition to the four cohort and 10 case–control studies reviewed by IARC (2004), three case–control studies have examined the role of second-hand tobacco smoke in relation to risk for all childhood cancers combined (Sorahan *et al.*, 2001; Pang *et al.*, 2003; Sorahan & Lancashire, 2004; Table 2.21 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.21.pdf).

(a) Intensity and timing of parental smoking

In a follow-up of the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) by McKinney *et al.* (1987), a statistically significant positive trend with daily paternal smoking before pregnancy was observed when cases were compared with controls selected from General Practitioners' (GPs') lists, but not from hospitals; an inverse trend was noted for maternal smoking before pregnancy when cases were compared with hospital, but not with General Practitioners, controls (Sorahan *et al.*, 2001).

In the United Kingdom Childhood Cancer Study (UKCCS), Pang *et al.* (2003) observed a similar pattern of increasing risk with increasing intensity of paternal preconception smoking, and of decreasing risk for increasing maternal smoking before and during pregnancy for all diagnoses combined, and for most individual diagnostic groups.

In the most recent report from the Oxford Survey of Childhood Cancers (OSCC), the risk of death from all childhood cancers combined was not associated with maternal smoking, but was consistently associated with paternal smoking alone or in combination with maternal smoking, in both adjusted and unadjusted analyses [Ex-smokers of more than 2 years before birth of the survey child were assimilated to non-smokers] (Sorahan & Lancashire, 2004).

(b) Bias and confounding

The significant trends observed by Sorahan *et al.* (2001) and Pang & Birch (2003) did not diminish when adjusted for potential confounding covariates or with simultaneous analysis of parental smoking habits. The relationship between maternal smoking and birth weight reported by Sorahan *et al.* (2001) suggested that self-reported maternal smoking was equally reliable for cases and for controls. However, comparisons of smoking patterns with national data suggested that control parents in this study were heavier smokers.

2.6.3 Leukaemias and lymphomas

Since IARC (2004), one cohort study (Mucci *et al.*, 2004) (Table 2.22 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.22.pdf), eleven case–control studies (Table 2.23 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.23.pdf), and one meta-analysis (Lee *et al.*, 2009) (Table 2.24 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.24.pdf) have evaluated the association of parental tobacco smoking with the risk for lymphatic and haematopoietic cancers.

(a) Duration and intensity of exposure

From a meta-analysis of 30 studies published before 1999 Boffetta *et al.* (2000) reported no statistically significant association for all lymphatic and haematopoietic neoplasms and noted evidence of publication bias for the available data.

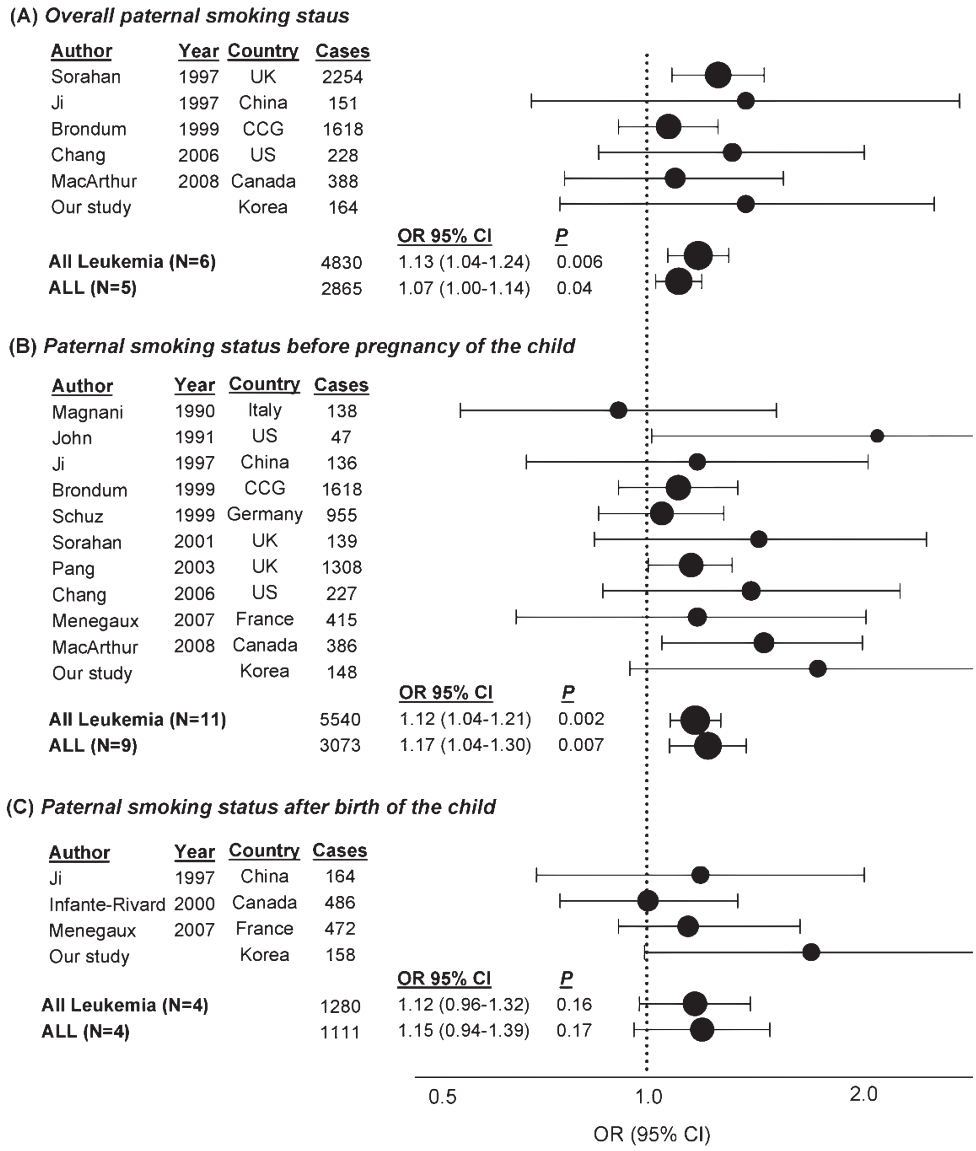
Lee *et al.* (2009) performed a meta-analysis of twelve studies on paternal smoking and risk of childhood leukaemia. Paternal smoking before conception of the index child was significantly associated with the risk for acute leukaemia (AL) and acute lymphoblastic leukaemia (ALL) (Fig. 2.2).

In a cohort study, maternal smoking was associated with a lower risk of acute lymphoblastic leukaemia, a higher risk of acute myeloid leukaemia (AML) particularly among heavy smokers, and a slight excess risk for non-Hodgkin lymphoma (NHL) (Mucci *et al.*, 2004).

Because of the diversity of types of exposure (paternal, maternal, parental), of timing of exposure (preconception, *in utero*, post-natally) and of the outcome, the case–control studies are briefly summarized individually.

Schüz *et al.* (1999) showed that the risk for acute childhood leukaemias was inversely related to maternal smoking during pregnancy. Paternal smoking before pregnancy showed no association with leukaemia risk for any smoking category. Sorahan *et al.* (2001) reported a non-significant positive association between risk for acute lymphoblastic leukaemia and daily cigarette smoking by fathers before pregnancy, and a non-significant inverse association between risk for acute lymphoblastic leukaemia and daily smoking by mothers before pregnancy. Down Syndrome children are highly susceptible to the development of acute leukaemia. In a case–control study of 27 children with acute leukaemia and Down Syndrome compared with 58 Down Syndrome children without acute leukaemia Mejía-Aranguré *et al.* (2003) found that paternal smoking of more than 10 cigarettes/day, both preconception and after birth of the index child was associated with acute leukaemia. In the UKCC case–control study (Pang *et al.*, 2003), paternal but not maternal preconception tobacco smoking of 1–19 cigarettes/day was associated with an increased risk of leukaemia, and a similar pattern was reported for lymphoma. Menegaux *et al.* (2005) reported no increased risk of acute lymphoblastic leukaemia or acute nonlymphocytic leukaemia (ANLL) associated with any category of post-natal exposure to tobacco smoking (i.e. maternal smoking during breastfeeding or after, paternal smoking after birth, other smokers at home), except for an increased risk of acute nonlymphocytic leukaemia with paternal smoking. In a later study, (Menegaux *et al.*, 2007) reported no association between acute and parental smoking, by subtype (acute myeloid leukaemia or acute lymphoblastic leukaemia) or by time of exposure, with the exception of an increased risk of acute lymphoblastic leukaemia associated with maternal smoking during pregnancy. Chang *et al.* (2006) reported no risk for acute leukaemia, acute lymphoblastic leukaemia or acute myeloid leukaemia associated with maternal smoking either by period of smoking (preconception, during pregnancy, post-natally) or by amount smoked. Paternal preconception smoking was strongly associated

Fig. 2.2 Meta-analysis of the association between paternal smoking and childhood leukaemia



with risk for acute myeloid leukaemia both by period and intensity of smoking. When both paternal preconception smoking and maternal postnatal smoking were considered, the risk for acute lymphoblastic leukaemia was stronger. Rudant *et al.* (2008) reported a significant positive association between paternal smoking and acute lymphoblastic leukaemia, acute myeloid leukaemia, Burkitt lymphoma, and anaplastic large cell non-Hodgkin lymphoma, with increasing relative risks (RR) with increasing number of cigarettes smoked. No associations with Hodgkin lymphoma or other types of non-Hodgkin lymphoma were observed. Non-significantly elevated risks were observed for maternal smoking during pregnancy for acute lymphoblastic leukaemia and non-Hodgkin lymphoma, but not in the highest category of 10 or more cigarettes/day. MacArthur *et al.* (2008) reported non-significantly elevated risk estimates for acute lymphoblastic leukaemia and acute myeloid leukaemia with maternal smoking, but

not with paternal smoking, before and during pregnancy. Lee *et al.* (2009) in Seoul, Republic of Korea, reported that paternal smoking was associated with a significantly increased risk of acute leukaemia and acute lymphoblastic leukaemia in a dose–response manner. The proportion of mothers who smoked was too low (6.1% in controls) to analyse risk in association with maternal smoking.

(b) Potential confounders

In the study of Down Syndrome children (Mejía-Aranguré *et al.*, 2003), the adjustment models did not show any interaction between paternal alcoholism and smoking. Menegaux *et al.* (2005) examined the association of parental smoking and maternal alcohol and coffee intake during pregnancy with the risk for childhood leukaemia. They found no association of acute lymphoblastic leukaemia or acute nonlymphocytic leukaemia with maternal smoking during pregnancy but an association with maternal alcohol and coffee consumption.

(c) Effect modification

Cigarette smoke is a known germ-cell mutagen in mice (Yauk *et al.*, 2007), a likely germ-cell mutagen in humans (see Section 4.1.3a) and alters gene expression (see Section 4.1.4). Infante-Rivard *et al.* (2000) first assessed the role of parental smoking and *CYP1A1* genetic polymorphisms with leukaemia and reported no statistically significant association with leukaemia overall. However, a case-only subanalysis suggested that the effect of parental smoking may be modified by variant alleles in the *CYP1A1* gene: *CYP1A1*2B* tended to decrease risks and *CYP1A1*2A* and *CYP1A1*4* increased the risks associated with smoking in the second and third trimesters of pregnancy. Clavel *et al.* (2005) examined the role of metabolic polymorphisms in the *CYP1A1*, *GSTM1*, *GSTP1*, *GSTT1* and *NQO1* genes. The slow *EPHX1* allele (exon 3 homozygous genotype) was negatively associated with leukaemia, in particular acute lymphoblastic leukaemia, whereas the fast *EPHX1* allele (exon 4 homozygous genotype) was positively associated with leukaemia overall. A non-significant association with acute lymphoblastic leukaemia was noted for the homozygous *NQO1*2* genotype. There was a significant interaction of the *CYP1A1*2A* allele with smoking in the case-only analysis and a not significant interaction, but similar in magnitude, in the case–control analysis. A significant interaction was also observed with the *GSTM1* deletion in the case-only analysis, but not in the case–control analysis. Lee *et al.* (2009) genotyped five single-nucleotide *CYP1A1* polymorphisms: acute lymphoblastic leukaemia risk was significantly increased for cases without the *CGACC* haplotype and with paternal smoking or the presence of at least one smoker in the home.

RAS is the second most mutated gene in smoking-associated lung tumours (Section 4.1.3b). *RAS* mutations have been consistently correlated with myeloid leukaemias in adults and children, in particular with occupationally-associated adult myeloid leukemias (Taylor *et al.*, 1992; Barletta *et al.*, 2004). Wiemels *et al.* (2005) studied the relationship of *RAS* mutations, hyperdiploidy (> 50 chromosomes) and smoking in a case series of 191 acute leukaemia. Smoking was negatively associated with hyperdiploidy (possibly due to the sensitivity of the hyperdiploid clone and consequent differential survival) and hyperdiploid acute leukaemia cases had the highest rates of *RAS* mutations. [Paternal smoking in the three months before pregnancy was less frequent among hyperdiploids than among non-hyperdiploids.]

2.6.4 Cancers of the brain and central nervous system

Since IARC (2004), the association of exposure to parental smoking and risk for childhood brain and central nervous system (CNS) tumours has been examined in one cohort study (Brooks

et al., 2004; Table 2.25 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.25.pdf), six case–control studies (Schüz *et al.*, 1999; Sorahan *et al.*, 2001; Filippini *et al.*, 2002; Pang *et al.*, 2003; Cordier *et al.*, 2004; Plichart *et al.*, 2008; Table 2.26 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.26.pdf), and one meta-analysis (Huncharek *et al.*, 2002; Table 2.27 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.27.pdf).

A meta-analysis of 30 studies published before 1999 indicated no significant increase in risk for CNS tumours associated with maternal smoking during pregnancy and an increased risk for brain tumours with paternal smoking (Boffetta *et al.*, 2000).

Huncharek *et al.* (2002) included one cohort and eleven case–control studies in a meta-analysis and found no clear association of maternal smoking during pregnancy with risk for childhood brain tumours, and a null risk estimate for all CNS tumours (even when the analysis was restricted to astrocytomas, the main brain tumour type). The results were comparable and consistently null for all sensitivity analyses conducted (Table 2.27 on-line).

Brooks *et al.* (2004) analysing the Swedish birth cohort study observed that children, in particular those aged 2–4 years, whose mother smoked during pregnancy, had an increased incidence of childhood brain tumours; the increase in risk was similar for benign and malignant brain tumours and most apparent for astrocytomas (Table 2.25 on-line).

Schüz *et al.* (1999) evaluated parental smoking and CNS tumour risk in children < 15 years from the German Childhood Cancer Registry (see Table 2.26 on-line). No association with risk of CNS tumours was observed for either maternal smoking during pregnancy or paternal smoking before pregnancy. Sorahan *et al.* (2001) found no significant association or trends of risk of CNS tumours with either paternal or maternal smoking, except for low level of maternal exposure [the latter analysis is based on only eleven exposed cases and one control, yielding a very wide confidence interval]. Filippini *et al.* (2002) observed no association between risk of childhood brain tumours and parental smoking before pregnancy, maternal smoking, regular maternal exposure to second-hand tobacco smoke during pregnancy, or exposure of the child to second-hand tobacco smoke during its first year of life. The results did not vary by child's age at diagnosis, type of CNS tumour or study centre. Plichart *et al.* (2008) reported no association for maternal smoking during pregnancy with CNS tumours, while paternal smoking preconception showed a significant association, especially for astrocytomas. When assessing parental exposure to PAHs, Cordier *et al.* (2004) observed an association of paternal exposure to occupational PAHs preconception with all childhood brain tumours and with astroglial tumours, but no trend of increasing risk with increased exposure. Paternal smoking alone was associated with a risk for astroglial tumours when compared with non-smoking, non-occupationally-exposed fathers. Pang *et al.* (2003) found a decreased CNS risk with maternal smoking of more than 20 cigarettes/day preconception, in both unadjusted and adjusted analyses. In the analyses by histological subgroups a statistically significant decreased risk was associated with maternal smoking during pregnancy for primitive neuroectodermal tumours.

2.6.5 Hepatoblastoma

Hepatoblastoma is an embryonal tumour presumably of fetal origin and prenatal exposures are likely more important than post-natal. In some children, a diagnosis of hepatoblastoma is evident at birth or shortly thereafter, with a median age at diagnosis of 12 months. The ability of hepatoblastoma tumour cells to synthesize α-fetoprotein (AFP), a major serum protein

synthesized by fetal liver cells, also suggests a fetal origin. Also, hepatoblastomas, like many other embryonal tumours, are associated with Beckwith-Wiedemann syndrome and hemihypertrophy, further suggesting a gestational oncogenic event (DeBaun & Tucker, 1998). Data were available for both maternal and paternal exposures from two studies (Pang *et al.*, 2003; Sorahan & Lancashire, 2004) while two other studies (McLaughlin *et al.*, 2006; Pu *et al.*, 2009) were limited to data on maternal smoking, available from birth certificates and medical records, respectively (Table 2.28). Most of these studies had limited sample sizes given the extreme rarity of these tumours.

(a) Parental smoking exposure

After adjustment for relevant covariates, Pang *et al.* (2003) observed a statistically significant increased risk of hepatoblastoma in association with maternal preconception smoking (OR, 2.68; 95%CI: 1.16–6.21, $P = 0.02$) in a somewhat dose-dependent manner ($P = 0.058$). The association with parental smoking was strongest (relative to neither parent smoking) when both parents smoked (OR, 4.74; 95%CI: 1.68–13.35, $P = 0.003$). Sorahan & Lancashire (2004) found no increased risk associated with maternal or paternal smoking alone compared to non-smokers, in both adjusted and unadjusted analyses. In contrast, parental smoking (paternal and maternal smoking combined) was strongly and consistently associated with an increased risk for hepatoblastoma in both adjusted and unadjusted analyses.

In a record-based case–cohort study only maternal smoking was examined (McLaughlin *et al.*, 2006). Extremely low birth weight (< 1000 g) was strongly associated with hepatoblastoma. After adjustement for birth weight, a statistically significant elevated risk for hepatoblastoma was found with maternal smoking (RR 2.1; 95%CI: 1.0–4.2). The increased risk was stronger for children diagnosed at the age of two years or older (RR 6.0 versus 1.4). Also, the relarive risk for maternal smoking and hepatoblastoma was stronger for children with normal birth weight [> 2500 g] than for low birth weight children. For cases of hepatoblastoma diagnosed after the age of two years, the relative risk for maternal smoking among children with normal birth weight was also stronger than that among children with low birth weight.

Another study on maternal smoking only was conducted in Chonquing, China (Pu *et al.*, 2009). After adjustment for birth weight, a significantly increased risk for hepatoblastoma was found for maternal smoking (RR 2.9; 95%CI: 1.1–4.2). Adjustments for maternal age, maternal body mass index and sex of the baby did not change the odd ratios. When analyses were stratified by birth weight, the odd ratio associated with maternal smoking for children with a birth weight greater than 2500 g was increased almost fourfold. Stratification by age at diagnosis showed that the risk increased almost fivefold with diagnosis at the age of two years or over. [The Working Group noted that since information regarding mother's smoking status for both cases and controls was obtained before diagnosis the potential for biased recall of maternal exposures during pregnancy is reduced].

(b) Bias and confounding

The known risk factors for hepatoblastoma include low and very low birth weights (< 2000 g and < 1000 g, respectively), maternal age and use of assisted reproductive technologies. All studies adjusted for maternal age, and low birth weight was addressed in three of them (Pang & Birch, 2003; McLaughlin *et al.*, 2006; Pu *et al.*, 2009). Assisted reproductive technologies were not considered to be an important potential confounder of these studies.

Spector & Ross (2003) argued that the association of hepatoblastoma with parental smoking observed by Pang *et al.* (2003) might be confounded by birth weight. In their response,

Table 2.28 Studies of parental tobacco smoking and childhood hepatoblastoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories (case/control)	(Cases/ controls)	OR (95% CI)* * $P < 0.05$ ** $P < 0.01$	Adjustment for potential confounders	Comments
Pang *et al.* (2003) United Kingdom	3838 childhood cancer cases, of which 28 hepatoblastoma; Hospital based; < 15 yr of age; 1991–94 in Scotland; 1992–94 in England and Wales	7581 controls; matched for sex, date of birth and geographical area of residence at diagnosis; randomly selected from Family Health Services Authorities in England and Wales and Health boards in Scotland	Face-to-face structured interviews; Computerized self-administered questionnaires to parents of index child	*Parental smoking*			Deprivation and parental age at birth of index child	Underreporting of smoking by case mothers
				Neither parent	(8/3142)	1.00 (ref)		
				Mother only	(2/574)	2.02 (0.40–10.2)		
				Father only	(3/1008)	1.86 (0.46–7.55)		
				Both parents	(10/1249) **	4.74 (1.68–13.35)		
				Paternal preconception smoking (cigarettes per d)				
				0	(11/3082)	1 (ref)		
				1–19	(6/1003)	1.88 (0.67–5.26)		
				20+	(7/1440)	1.65 (0.61–4.45)		
				Trend *P*	0.272			
				Maternal preconception smoking (cigarettes per d)				
				0	(10/3916)	1 (ref)		
				1–19	(9/1490)	2.99 (1.15–7.76)*		
				20+	(4/882)	2.17 (0.65–7.20)		
				P for trend	0.058			
Pang & Birch (2003) United Kingdom	Birch and Kelsey diagnostic subgroups, which group biologically similar tumours together (UKCCS Investigators, 2000) excluding diagnostic subgroups with less than 10 cases			*Maternal preconception smoking*	(28/7581)	2.68 (1.16–6.21)*	§ As above, additionally adjusted for birth weight	
				Both parents preconception smoking	(27/6987)	4.74**		
				§ *Maternal preconception smoking*		2.50*		
				§ *Both parents preconception smoking*		4.97**		

Table 2.28 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories (case/control)	(Cases/ controls)	OR (95% CI)* * $P < 0.05$ ** $P < 0.01$	Adjustment for potential confounders	Comments
Sorahan & Lancashire (2004) United Kingdom, 1953–84	43 deaths from hepatoblastoma < 16 yr of age	5777 matched controls, (analysed as unmatched series)	Parental smoking during yr 1953–55, 1971–76, 1977–81	*Maternal cigarette smoking*			Sex, age at death, yr of death, social class, sibship position, age of mother and father at birth of child, obstetric radiography	
				Non-smoker	(19/3191)	1 (ref)		
				Smoker	(24/2524)	1.73 (0.93–3.21)		
				Paternal cigarette smoking				
				Non-smoker	(12/2267)	1 (ref)		
				Smoker	(28/3359)	2.10 (1.03–4.25)*		
				Parental cigarette smoking				
				Neither parent	(9/1601)	1.0 (ref)		
				Mother only	(3/662)	0.85 (0.23–3.19)		
				Father only	(8/1545)	1.23 (0.46–3.28)		
				Both parents	(20/1800)	2.69 (1.18–6.13)*		
McLaughlin *et al.* (2006), New York, USA, 1985–2001	58 cases of hepatoblastoma, identified from New York State Cancer Registry	Matched on yr of birth, electronic birth records for 1985–2001 from New York State	Routinely recorded data on birth certificate	*Maternal smoking*			Birth yr and birth weight	Association of maternal smoking was stronger in children with birth weights over 2.5kg.
				Non-smoker	(36/3439)	1 (ref)		
				Smoker	(12/742)	2.1 (1.0–4.2)		
				Birth weight > 2500 g		2.7 (1.2–5.5)		
				Birth weight > 2500 g and age > 2 yr		5.8 (1.4–25.1)		
				Maternal smoking				
Pu *et al.* (2009), Chongquing China, 1990–97	58 cases	92 controls, appendicitis patients, matched on age, sex, yr	Medical record of mother or follow-up interviews as needed	Non-smoker	(43/84)	1 (ref)	Birth weight	
				Smoker	(15/8)	2.9 (1.1–4.2)		

d, day or days; yr, year or years

Pang & Birch (2003) showed evidence supporting their initial conclusion: the comparable results for maternal smoking, smoking by both parents and maternal smoking for cases diagnosed at an older age, i.e. one year or older, before and after adjustment for birth weight, appear to rule out low birth weight as an explanation for the association.

Also, both later studies (McLaughlin *et al.*, 2006; Pu *et al.*, 2009) reported higher relative risks for children with normal birth weight compared to those with low birth weight, particularly in cases diagnosed after the age of two years.

2.6.6 Other childhood cancers

Several other childhood cancers have been studied in relation to parental tobacco smoke exposures, namely neuroblastoma, nephroblastoma, bone tumours, Wilms tumour, soft tissue sarcomas, other neoplasms of the reticuloendothelial system, and childhood germ cell tumours. The data are few and inconsistent (Schüz *et al.*, 1999; Sorahan *et al.*, 2001; Chen *et al.*, 2005b; Table 2.28).

2.7 Synthesis

2.7.1 Lung

The totality of evidence available to date firmly establishes that exposure to second-hand tobacco smoke at home and at the workplace is causally associated with lung cancer risk in both men and women. This association has been observed in studies from North America, Europe, and Asia. Emerging evidence is also suggesting that exposure to second-hand tobacco smoke among children significantly enhances the risk of lung cancer in adulthood.

2.7.2 Breast

A large number of cohort studies, case–control studies and meta-analyses have assessed the association between exposure to second-hand tobacco smoke and breast cancer. Recent large cohort studies in Europe and North America showed no association between second-hand tobacco smoke and breast cancer. Positive associations in one or more subgroups were reported from some case–control studies; however, these associations were weaker in more recent studies compared with earlier studies.

Explorative analyses focusing on premenopausal breast cancer have suggested that second-hand tobacco smoke may preferentially cause premenopausal breast cancer. Positive associations were largely reported from case–control studies, in which both recall and publication bias cannot be ruled out. Case–control studies that collect a lifetime exposure history are particularly vulnerable to subjective and differential reporting of exposures that occurred long in the past from sources that are difficult to quantify. Overall, the results for an association with premenopausal breast cancer are also inconsistent.

2.7.3 Upper aerodigestive tract combined

Most evidence of the association between second-hand tobacco smoke and upper aerodigestive tract cancers, and the subsites of the oral cavity, pharynx and larynx, comes from a pooled analysis. Overall, the association between second-hand tobacco smoke exposure and cancers of the larynx and pharynx is less than causal.

2.7.4 Nasopharynx, and nasal cavity and accesory sinuses

There is some evidence from a cohort and case–control study that exposure to second-hand tobacco smoke increases the risk of sinonasal cancer; for cancer of the nasopharynx, the evidence is contradictory.

2.7.5 Others sites

Overall, data are conflicting and sparse for the association of exposure to second-hand tobacco smoke with all cancers combined, cancers of the gastrointestinal tract combined, and cancers of the stomach, colon, rectum, pancreas, liver (hepatocellular carcinoma), kidney (renal cell carcinoma), urinary bladder, cervix, ovary, testes, and brain and central nervous system.

2.7.6 Childhood cancers

(a) All childhood cancers combined

Four cohort studies, 13 case–control studies and one meta-analysis have assessed the association of parental tobacco smoking with childhood cancers, all sites combined, in offspring. Most of the early studies only assessed the contribution of maternal smoking, whereas recent studies generally assessed both paternal and maternal smoking, and at various time periods (preconception, during pregnancy, post-natally). Overall, the evidence for an association between parental smoking and childhood cancer (all sites combined) remains inconsistent and may be subject to bias. Nevertheless, a fairly consistent association of paternal tobacco smoking with childhood cancers is beginning to emerge, which is stronger in studies with more specific exposure assessments.

(b) Leukaemias and lymphomas

Two cohort studies, 27 case–control studies and 2 meta-analyses have examined the association of childhood haematopoietic malignancies (leukaemia and lymphoma) with exposure to parental smoking (paternal, maternal or both). All studies examined leukaemia, and a large number of these addressed non-Hodgkin lymphoma.

The body of evidence suggests a consistent association of leukaemia (and lymphoma) with paternal smoking preconception and with combined parental smoking, with risk ratios ranging from 1.5 to 4.0. Maternal tobacco smoking during pregnancy generally showed modest increases in risk, or null or inverse relationships. The combined effects of preconception and post-conception exposures to tobacco smoke were highly significant.

Several studies on lymphoma risk associated with parental smoking showed significantly elevated risks associated with paternal tobacco smoking preconception. The analyses had small samples sizes, and biases due to participation, recall and response, especially related to exposure, cannot be ruled out.

(c) Brain and central nervous system

The association of childhood tumours of the brain and central nervous system with parental smoking was assessed in two cohort studies, 21 case–control studies and 2 meta-analyses. Overall these studies do not show an association with either paternal smoking, largely preconception, or maternal smoking prior, during or after pregnancy, or by CNS types, gliomas and primitive neuroectodermal tumours. The strongly positive associations noted in some studies for paternal tobacco smoking with astrocytomas are offset by the lack of association with childhood brain tumours reported by the large UK Childhood Cancer Study.

(d) Hepatoblastoma

Four informative case–control studies provided data on the association between parental smoking and hepatoblastomas. Two studies reported on both maternal and paternal smoking, while the two others assessed only maternal smoking. In one study where a large number of categories of childhood cancers ($n = 25$) were assessed, the only childhood cancer that showed an association with parental smoking was hepatoblastoma. This original observation was confirmed in three later studies, with relative risks ranging from 2.0 to 5.5. Chance, bias and

confounding were adequately addressed in the data from the studies available. The evidence for the association of parental smoking with hepatoblastoma is convincing, with an emphasis on prenatal exposures.

(e) Other childhood cancers

Most of the associations reported for the other childhood cancers, notably soft tissue sarcomas, rhabdomyosarcomas, Ewing's sarcoma, neuroblastoma, Wilms tumour, reticuloendothelial sarcomas and germ cell tumours were null, with a few isolated and inconsistent positive observations.

3. Cancer in Experimental Animals

3.1 Simulated second-hand tobacco smoke

Simulated second-hand tobacco smoke, frequently a mixture of 89% sidestream and 11% mainstream smoke, generated from cigarettes by smoking machines (Teague *et al.*, 1994) has been tested for carcinogenicity in adult mice of strains that are genetically susceptible to induction of lung tumours (Malkinson, 1992). Mice were exposed in inhalation chambers. Several studies reported no increase in lung tumour incidence or multiplicity in mice exposed to simulated second-hand tobacco smoke for 5–9 months and killed immediately thereafter (Witschi *et al.*, 1995, 1997a; Finch *et al.*, 1996). It was suggested that the lack of tumour response in simulated second-hand tobacco smoke-exposed mice might be due to treatment-induced stress (as determined by the increased plasma corticosterone level) that has been shown to attenuate lung tumorigenesis (Stinn *et al.*, 2005a).

In subsequent studies from several laboratories (Table 3.1), an increased multiplicity and often increased incidence of lung tumours was reported in male and female A/J mice exposed for five months and kept in filtered air for another four months (Witschi *et al.*, 1997a, b, 1998, 1999; D'Agostini *et al.*, 2001) or longer (Witschi *et al.*, 2006) before the mice were killed. Similar results were obtained with Swiss albino mice (Witschi *et al.*, 2002). In these studies, no nasal tumours were observed in smoke-exposed mice.

In one study, male and female transgenic mice with a dominant negative *p53* mutation on an A/J background were exposed to simulated second-hand tobacco smoke for 9.5 continuous months or for 5 months followed by recovery in air for 4.5 months. Transgenic mice exposed by either regimen developed significantly higher incidence and multiplicity of lung tumours than sham-exposed control transgenic mice (DeFlora *et al.*, 2003). Neither lung tumour incidence nor multiplicity was increased in smoke-exposed wild-type control mice in this study.

In one study, male and female rats exposed to room-aged sidestream cigarette smoke by nose-only inhalation for 24 months and then killed had no increased incidence of lung or other tumours in comparison with fresh-air controls. Lung tumours were not significantly increased in rats exposed for 24 months and kept until 30 months of age (Stinn *et al.*, 2005b).

3.2 Sidestream smoke condensate

In one study, sidestream cigarette smoke condensate applied to the shaved skin of female NMRI mice lower back, at total weekly doses of 5, 10 and 15 mg, for 3 months caused benign and malignant skin tumours and mammary carcinomas in mice observed for their lifespan and was more potently carcinogenic in this assay than mainstream smoke condensate. No cutaneous or subcutaneous tumours developed in any of three control groups ($P < 0.001$) (Mohtashamipur *et al.*, 1990). In one study, fractionated sidestream cigarette smoke condensates were implanted into the lungs of female rats. The fraction containing

Table 3.1 Carcinogenicity studies of inhalation exposure to simulated second-hand tobacco smoke[a] in A/J mice, transgenic mice with a dominant negative *p53* mutation, and Wistar rats as a function of length of the post-exposure recovery period

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, A/J (M) Witschi *et al.* (1997a)	48 animals/group Chamber concentration, 0 or 87 mg/m^3 total suspended particulates; 6 h/d, 5 d/wk for 5 mo followed by 0 or 4 mo post-exposure recovery 9 mo	5 mo: 2/24 (8%, 0.1 ± 0.1); 6/24 (25%, 0.3 ± 0.1) 9 mo: 9/24 (38%, 0.5 ± 0.2); 20/24 (83%, 1.4 ± 0.2)	NS Incidence: $P < 0.05$ Multiplicity: $P < 0.05$	> 80% of tumours were adenomas; the rest were adenocarcinomas
Mice, A/J (F) D'Agostini *et al.* (2001)	20 animals/group Chamber concentration, 0 or 120 mg/m^3 total suspended particulates; 6 h/d, 5 d/wk, for 5 mo followed by 4 mo post-exposure recovery 9 mo	5/20 (25%, 0.25 ± 0.10); 15/20 (75%, 1.05 ± 0.17)	Incidence: $P < 0.01$ Multiplicity: $P < 0.01$	
A/J mice (sex NR) Witschi *et al.* (2006)	24, 25 controls (12 mo) 19, 17 controls (24 mo) Chamber concentration, 0 (control) or 158 mg/m^3 total suspended particulates; 6 h/d, 5 d/wk, for 6 mo followed by 4 or 16 mo post-exposure recovery 24 mo	12 mo: 13/24 (54%, 0.9 ± 0.2); 24/25 (96%, 1.8 ± 0.2) 24 mo: 8/9 (89%, 2.1 ± 0.5); 10/10 (100%, 4.3 ± 0.7)	Incidence: $P < 0.05$ Multiplicity: $P < 0.05$ Incidence: NS Multiplicity: $P < 0.05$	80% of tumours were adenomas
(UL53–3xA/J)F_1, Transgenic mice (M, F) De Flora *et al.* (2003)	222 (108; 114 controls) Chamber concentration, 0 (control) or 113 mg/m^3 total suspended particulates; 6 h/d for 5 mo or 9.5 mo followed by 0 or 4.5 mo post-exposure recovery 9.5 mo	No recovery: NR; 17/30 (57%, 0.93 ± 0.18) With recovery: 5/26 (19%, 0.27 ± 0.10); 15/23 (65%, 0.74 ± 0.11)	Incidence: $P < 0.01$ Multiplicity: $P < 0.01$ Incidence: $P < 0.01$ Multiplicity: $P < 0.01$	
Wistar rats (M, F) Stinn *et al.* (2005b)	99 rats/group Nose-only exposure; concentration, 0 (controls) or low dose 3 mg/m^3 or high dose 10 mg/m^3; 6 h/d, 7 d/wk, 24 mo followed by 0 or 6 mo post-exposure recovery 30 mo	24 mo: controls–0/16 Low dose–0/16 High dose–0/16 30 mo: controls–2/99 (2%) Low dose–4/98 (4%) High dose–5/94 (5%)	NS	

[a] Simulated second-hand tobacco smoke: 89% sidestream and 11% mainstream smoke from Kentucky 1R4F or 2R1 reference cigarettes

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

PAHs with four and more rings (dose, 1.06 mg/rat) induced 5 lung carcinomas in 35 treated rats; fractions containing no PAHs or PAHs with two or three rings (16 mg/rat) had little or no carcinogenic effect (Grimmer *et al.*, 1988).

3.3 Observational studies of companion animals

In one study, sinonasal cancers occurred more frequently in pet dogs of long-nosed breeds which lived in homes with at least one smoker (Reif *et al.*, 1998), but no such excess risk was seen in a second study (Bukowski *et al.*, 1998). A marginal excess risk of lung cancer was observed in dogs aged 10 years or less and exposed to household tobacco smoke in one study (Reif *et al.*, 1992). Risk of bladder cancer in dogs was not related to exposure to household cigarette smoke in another study (Glickman *et al.*, 1989).

Risk of malignant lymphoma was increased in pet cats exposed to household tobacco smoke in one study (Bertone *et al.*, 2002), but the conclusion that this association was causal has been questioned (Denson, 2003). In another study by the same group (Bertone *et al.*, 2003), exposure of pet cats to household tobacco smoke was also associated with a non-significant 2-fold increase in risk of oral squamous cell carcinoma.

3.4 Synthesis

Several studies showed consistent increases in lung tumour multiplicity and often lung tumour incidence in inbred strain A/J mice and in transgenic mice with a dominant negative *p53* tumour suppressor gene exposed by inhalation. In addition, in one report, skin and mammary tumours were induced in NMRI mice exposed to sidestream cigarette smoke condensate applied topically to the skin.

4. Other Relevant Data

See Section 4 of the *Monograph* on Tobacco Smoking in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of second-hand tobacco smoke. Second-hand tobacco smoke causes cancer of the lung. Also, a positive association has been observed between exposure to second-hand tobacco smoke and cancers of the larynx and the pharynx.

There is *sufficient* evidence in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke.

There is *sufficient* evidence in experimental animals for the carcinogenicity of sidestream tobacco smoke condensates.

Second-hand tobacco smoke is *carcinogenic to humans (Group 1).*

References

Ahern TP, Lash TL, Egan KM, Baron JA (2009). Lifetime tobacco smoke exposure and breast cancer incidence. *Cancer Causes Control*, 20: 1837–1844. doi:10.1007/s10552-009-9376-1 PMID:19533391

Alberg AJ, Daudt A, Huang HY *et al.* (2004). N-acetyltransferase 2 (NAT2) genotypes, cigarette smoking, and the risk of breast cancer. *Cancer Detect Prev*, 28: 187–193. doi:10.1016/j.cdp.2004.04.001 PMID:15225898

Alberg AJ, Kouzis A, Genkinger JM *et al.* (2007). A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke. *Am J Epidemiol*, 165: 660–666. doi:10.1093/aje/kwk047 PMID:17204516

Asomaning K, Miller DP, Liu G *et al.* (2008). Second hand smoke, age of exposure and lung cancer risk. *Lung Cancer*, 61: 13–20. doi:10.1016/j.lungcan.2007.11.013 PMID:18191495

Baker JA, Odunuga OO, Rodabaugh KJ *et al.* (2006). Active and passive smoking and risk of ovarian cancer. *Int J*

Gynecol Cancer, 16: Suppl 1211–218. doi:10.1111/j.1525-1438.2006.00473.x PMID:16515593

Bao Y, Giovannucci E, Fuchs CS, Michaud DS (2009). Passive smoking and pancreatic cancer in women: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev*, 18: 2292–2296. doi:10.1158/1055-9965.EPI-09-0352 PMID:19602702

Barletta E, Gorini G, Vineis P *et al.* (2004). Ras gene mutations in patients with acute myeloid leukaemia and exposure to chemical agents. *Carcinogenesis*, 25: 749–755. doi:10.1093/carcin/bgh057 PMID:14688017

Bertone ER, Snyder LA, Moore AS (2002). Environmental tobacco smoke and risk of malignant lymphoma in pet cats. *Am J Epidemiol*, 156: 268–273. doi:10.1093/aje/kwf044 PMID:12142262

Bertone ER, Snyder LA, Moore AS (2003). Environmental and lifestyle risk factors for oral squamous cell carcinoma in domestic cats. *J Vet Intern Med*, 17: 557–562. doi:10.1111/j.1939-1676.2003.tb02478.x PMID:12892308

Bjerregaard BK, Raaschou-Nielsen O, Sørensen M *et al.* (2006). Tobacco smoke and bladder cancer–in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, 119: 2412–2416. doi:10.1002/ijc.22169 PMID:16894557

Boffetta P, Trédaniel J, Greco A (2000). Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: A meta-analysis. *Environ Health Perspect*, 108: 73–82. doi:10.1289/ehp.0010873 PMID:10620527

Bonner MR, Bennett WP, Xiong W *et al.* (2006). Radon, secondhand smoke, glutathione-S-transferase M1 and lung cancer among women. *Int J Cancer*, 119: 1462–1467. doi:10.1002/ijc.22002 PMID:16642467

Bonner MR, Nie J, Han D *et al.* (2005). Secondhand smoke exposure in early life and the risk of breast cancer among never smokers (United States). *Cancer Causes Control*, 16: 683–689. doi:10.1007/s10552-005-1906-x PMID:16049807

Brooks DR, Mucci LA, Hatch EE, Cnattingius S (2004). Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births. *Cancer Causes Control*, 15: 997–1005. doi:10.1007/s10552-004-1123-z PMID:15801484

Brown DC, Pereira L, Garner JB (1982). Cancer of the cervix and the smoking husband. *Can Fam Physician*, 28: 499–502. PMID:21286079

Buckley JD, Harris RW, Doll R *et al.* (1981). Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet*, 2: 1010–1015. doi:10.1016/S0140-6736(81)91215-0 PMID:6118477

Bukowski JA, Wartenberg D, Goldschmidt MJohn A. Bukowski Daniel Wartenberg (1998). Environmental causes for sinonasal cancers in pet dogs, and their usefulness as sentinels of indoor cancer risk. *J Toxicol Environ Health A*, 54: 579–591. doi:10.1080/009841098158719 PMID:9726781

Burch JD, Rohan TE, Howe GR *et al.* (1989). Risk of bladder cancer by source and type of tobacco exposure: a case-control study. *Int J Cancer*, 44: 622–628. doi:10.1002/ijc.2910440411 PMID:2793235

California Environmental Protection Agency (2005). *Health Effects Assessment for ETS: Final.* California Environmental Protection Agency, Office of Environmental Health Hazard Assesment: Sacramento, CA.

CDC (2008). Centers for Disease Control and Prevention. Global Youth Tobacco Surveillance, 2000–2007. *Morbidity and Mortality Weekly Report.*, 57: 1–21. PMID:18185492

CDC/WHO (2009). Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO). Global Youth Tobacco Survey (GYTS). Atlanta GA. (http://www.cdc.gov/tobacco/global/gyts/index.htm, (accessed 27 November 2011).

Chang JS, Selvin S, Metayer C *et al.* (2006). Parental smoking and the risk of childhood leukemia. *Am J Epidemiol*, 163: 1091–1100. doi:10.1093/aje/kwj143 PMID:16597704

Chen YC, Su HJ, Guo Y-LL *et al.* (2005a). Interaction between environmental tobacco smoke and arsenic methylation ability on the risk of bladder cancer. *Cancer Causes Control*, 16: 75–81. doi:10.1007/s10552-004-2235-1 PMID:15868449

Chen Z, Robison L, Giller R *et al.* (2005b). Risk of childhood germ cell tumors in association with parental smoking and drinking. *Cancer*, 103: 1064–1071. doi:10.1002/cncr.20894 PMID:15685619

Cheng YJ, Hildesheim A, Hsu MM *et al.* (1999). Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan. *Cancer Causes Control*, 10: 201–207. doi:10.1023/A:1008893109257 PMID:10454065

Clavel J, Bellec S, Rebouissou S *et al.* (2005). Childhood leukaemia, polymorphisms of metabolism enzyme genes, and interactions with maternal tobacco, coffee and alcohol consumption during pregnancy. *Eur J Cancer Prev*, 14: 531–540. doi:10.1097/00008469-200512000-00007 PMID:16284498

Coker AL, Bond SM, Williams A *et al.* (2002). Active and passive smoking, high-risk human papillomaviruses and cervical neoplasia. *Cancer Detect Prev*, 26: 121–128. doi:10.1016/S0361-090X(02)00039-9 PMID:12102146

Coker AL, Rosenberg AJ, McCann MF, Hulka BS (1992). Active and passive cigarette smoke exposure and cervical intraepithelial neoplasia. *Cancer Epidemiol Biomarkers Prev*, 1: 349–356. PMID:1305466

Collishaw NE *et al.* (2009). *Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk*, in *OTRU Special Report Series.* Ontario Tobacco Research Unit: Toronto.

Cordier S, Monfort C, Filippini G *et al.* (2004). Parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors: The SEARCH International Childhood Brain Tumor Study. *Am J Epidemiol*, 159: 1109–1116. doi:10.1093/aje/kwh154 PMID:15191928

D'Agostini F, Balansky RM, Bennicelli C *et al.* (2001). Pilot studies evaluating the lung tumor yield in cigarette smoke-exposed mice. *Int J Oncol*, 18: 607–615. PMID:11179494

De Flora S, Balansky RM, D'Agostini F *et al.* (2003). Molecular alterations and lung tumors in p53 mutant mice exposed to cigarette smoke. *Cancer Res*, 63: 793–800. PMID:12591728

DeBaun MR & Tucker MA (1998). Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *J Pediatr*, 132: 398–400. doi:10.1016/S0022-3476(98)70008-3 PMID:9544889

Denson KW (2003). Re: Environmental tobacco smoke and risk of malignant lymphoma in pet cats. *Am J Epidemiol*, 158: 1227–1228, author reply 1227–1228. PMID:14692044

Duan L, Wu AH, Sullivan-Halley J, Bernstein L (2009). Passive smoking and risk of oesophageal and gastric adenocarcinomas. *Br J Cancer*, 100: 1483–1485. doi:10.1038/sj.bjc.6605023 PMID:19352383

Enstrom JE & Kabat GC (2003). Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960–98. *BMJ*, 326: 1057 doi:10.1136/bmj.326.7398.1057 PMID:12750205

Filippini G, Maisonneuve P, McCredie M *et al.* (2002). Relation of childhood brain tumors to exposure of parents and children to tobacco smoke: the SEARCH international case-control study. Surveillance of Environmental Aspects Related to Cancer in Humans. *Int J Cancer*, 100: 206–213. doi:10.1002/ijc.10465 PMID:12115571

Finch GL, Nikula KJ, Belinsky SA *et al.* (1996). Failure of cigarette smoke to induce or promote lung cancer in the A/J mouse. *Cancer Lett*, 99: 161–167. doi:10.1016/0304-3835(95)04059-5 PMID:8616820

Fukuda K & Shibata A (1990). Exposure-response relationships between woodworking, smoking or passive smoking, and squamous cell neoplasms of the maxillary sinus. *Cancer Causes Control*, 1: 165–168. doi:10.1007/BF00053168 PMID:2102286

Gallicchio L, Kouzis A, Genkinger JM *et al.* (2006). Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer. *Prev Med*, 42: 200–205. doi:10.1016/j.ypmed.2005.12.014 PMID:16458957

Gammon MD, Eng SM, Teitelbaum SL *et al.* (2004). Environmental tobacco smoke and breast cancer incidence. *Environ Res*, 96: 176–185. doi:10.1016/j.envres.2003.08.009 PMID:15325878

Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM (1992). Occupational exposures and cancer of the colon and rectum. *Am J Ind Med*, 22: 291–303. doi:10.1002/ajim.4700220303 PMID:1519614

Glickman LT, Schofer FS, McKee LJ *et al.* (1989). Epidemiologic study of insecticide exposures, obesity, and risk of bladder cancer in household dogs. *J Toxicol Environ Health*, 28: 407–414. doi:10.1080/15287398909531360 PMID:2593174

Goodman MT & Tung KH (2003). Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States). *Cancer Causes Control*, 14: 569–577. doi:10.1023/A:1024828309874 PMID:12948288

Grimmer G, Brune H, Dettbarn G *et al.* (1988). Contribution of polycyclic aromatic compounds to the carcinogenicity of sidestream smoke of cigarettes evaluated by implantation into the lungs of rats. *Cancer Lett*, 43: 173–177. doi:10.1016/0304-3835(88)90167-X PMID:3203336

Hanaoka T, Yamamoto S, Sobue T *et al.*Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Study Group (2005). Active and passive smoking and breast cancer risk in middle-aged Japanese women. *Int J Cancer*, 114: 317–322. doi:10.1002/ijc.20709 PMID:15540214

Hassan MM, Abbruzzese JL, Bondy ML *et al.* (2007). Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: a case-control study. *Cancer*, 109: 2547–2556. doi:10.1002/cncr.22724 PMID:17492688

Hassan MM, Spitz MR, Thomas MB *et al.* (2008). Effect of different types of smoking and synergism with hepatitis C virus on risk of hepatocellular carcinoma in American men and women: case-control study. *Int J Cancer*, 123: 1883–1891. doi:10.1002/ijc.23730 PMID:18688864

Hecht SS (2008). Progress and challenges in selected areas of tobacco carcinogenesis. *Chem Res Toxicol*, 21: 160–171. doi:10.1021/tx7002068 PMID:18052103

Hecht SS, Carmella SG, Le KA *et al.* (2006). 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides in the urine of infants exposed to environmental tobacco smoke. *Cancer Epidemiol Biomarkers Prev*, 15: 988–992. doi:10.1158/1055-9965.EPI-05-0596 PMID:16702381

Hellberg D, Valentin J, Nilsson S (1986). Smoking and cervical intraepithelial neoplasia. An association independent of sexual and other risk factors? *Acta Obstet Gynecol Scand*, 65: 625–631. doi:10.3109/00016348609158400 PMID:3799159

Hill SE, Blakely T, Kawachi I, Woodward A (2007). Mortality among lifelong nonsmokers exposed to secondhand smoke at home: cohort data and sensitivity analyses. *Am J Epidemiol*, 165: 530–540. doi:10.1093/aje/kwk043 PMID:17172631

Hirayama T (1984). Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev Med*, 13: 680–690. doi:10.1016/S0091-7435(84)80017-1 PMID:6536942

Hirose K, Tajima K, Hamajima N *et al.* (1996). Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. *Jpn J Cancer Res*, 87: 1001–1009. doi:10.1111/j.1349-7006.1996.tb02132.x PMID:8878465

Hooker CM, Gallicchio L, Genkinger JM *et al.* (2008). A prospective cohort study of rectal cancer risk in relation to active cigarette smoking and passive smoke exposure. *Ann Epidemiol*, 18: 28–35. doi:10.1016/j.annepidem.2007.06.010 PMID:17900927

Hu J & Ugnat AMCanadian Cancer Registries Epidemiology Research Group (2005). Active and passive smoking and risk of renal cell carcinoma in Canada. *Eur J Cancer*, 41: 770–778. doi:10.1016/j.ejca.2005.01.003 PMID:15763654

Huncharek M, Kupelnick B, Klassen H (2002). Maternal smoking during pregnancy and the risk of childhood brain tumors: a meta-analysis of 6566 subjects from twelve epidemiological studies. *J Neurooncol*, 57: 51–57. doi:10.1023/A:1015734921470 PMID:12125967

Hurley SF, McNeil JJ, Donnan GA *et al.* (1996). Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. *J Epidemiol Community Health*, 50: 442–446. doi:10.1136/jech.50.4.442 PMID:8882229

IARC (2009). *Evaluating the effectiveness of smoke-free policies*. IARC Handbook of Cancer Prevention. Vol. 13. Lyon: International Agency for Research on Cancer. http://www.iarc.fr/en/publications/pdfs-online/prev/index1.php

IARC (2004). Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*, 83: 1–1438. PMID:15285078

Infante-Rivard C, Krajinovic M, Labuda D, Sinnett D (2000). Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Québec, Canada). *Cancer Causes Control*, 11: 547–553. doi:10.1023/A:1008976116512 PMID:10880037

Jaakkola MS & Jaakkola JJK (1997). Assessment of exposure to environmental tobacco smoke. *Eur Respir J*, 10: 2384–2397. doi:10.1183/09031936.97.10102384 PMID:9387970

Jee SH, Ohrr H, Kim IS (1999). Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int J Epidemiol*, 28: 824–828. doi:10.1093/ije/28.5.824 PMID:10597977

Jenkins RA, Guerin MR, Tomkins BA (2000) *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement, Second Edition*., Jenkins RA, Guerin MR, Tomkins BA, editors. London: Lewis Boca Raton.

Jiang X, Yuan JM, Skipper PL *et al.* (2007). Environmental tobacco smoke and bladder cancer risk in never smokers of Los Angeles County. *Cancer Res*, 67: 7540–7545. doi:10.1158/0008-5472.CAN-07-0048 PMID:17671226

Johnson KC (2005). Accumulating evidence on passive and active smoking and breast cancer risk. *Int J Cancer*, 117: 619–628. doi:10.1002/ijc.21150 PMID:15929073

Johnson KC (2007). Re: more data regarding the effects of passive smoking on breast cancer risk among younger women. *Int J Cancer*, 120: 2519–2520. doi:10.1002/ijc.22611 PMID:17304510

Johnson KC & Glantz SA (2008). Evidence second-hand smoke causes breast cancer in 2005 stronger than for lung cancer in 1986. *Prev Med*, 46: 492–496. doi:10.1016/j.ypmed.2007.11.016 PMID:18182169

Johnson KC & Repace J (2000). Lung cancer and passive smoking. Turning over the wrong stone. *BMJ*, 321: 1221–, author reply 1222–1223. doi:10.1136/bmj.321.7270.1221 PMID:11073521

Kasim K, Levallois P, Abdous B *et al.*Canadian Cancer Registries Epidemiology Research Group (2005). Environmental tobacco smoke and risk of adult leukemia. *Epidemiology*, 16: 672–680. doi:10.1097/01.ede.0000173039.79207.80 PMID:16135944

Kropp S & Chang-Claude J (2002). Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am J Epidemiol*, 156: 616–626. doi:10.1093/aje/kwf093 PMID:12244030

Kurahashi N, Inoue M, Liu Y *et al.*JPHC Study Group (2008). Passive smoking and lung cancer in Japanese non-smoking women: a prospective study. *Int J Cancer*, 122: 653–657. doi:10.1002/ijc.23116 PMID:17935128

Lash TL & Aschengrau A (1999). Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol*, 149: 5–12. PMID:9883788

Lash TL & Aschengrau A (2002). A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Res Treat*, 75: 181–184. doi:10.1023/A:1019625102365 PMID:12243511

Lee KM, Ward MH, Han S *et al.* (2009). Paternal smoking, genetic polymorphisms in CYP1A1 and childhood leukemia risk. *Leuk Res*, 33: 250–258. doi:10.1016/j.leukres.2008.06.031 PMID:18691756

Lee YC, Boffetta P, Sturgis EM *et al.* (2008). Involuntary smoking and head and neck cancer risk: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev*, 17: 1974–1981. doi:10.1158/1055-9965.EPI-08-0047 PMID:18708387

Lilla C, Verla-Tebit E, Risch A *et al.* (2006). Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev*, 15: 99–107. doi:10.1158/1055-9965.EPI-05-0618 PMID:16434594

Lissowska J, Brinton LA, Zatonski W *et al.* (2006). Tobacco smoking, NAT2 acetylation genotype and breast cancer

risk. *Int J Cancer*, 119: 1961–1969. doi:10.1002/ijc.22044 PMID:16721725

Liu L, Wu K, Lin X *et al.* (2000). Passive Smoking and Other Factors at Different Periods of Life and Breast Cancer Risk in Chinese Women who have Never Smoked - A Case-control Study in Chongqing, People's Republic of China. *Asian Pac J Cancer Prev*, 1: 131–137. PMID:12718680

Lo AC, Soliman AS, El-Ghawalby N *et al.* (2007). Lifestyle, occupational, and reproductive factors in relation to pancreatic cancer risk. *Pancreas*, 35: 120–129. doi:10.1097/mpa.0b013e318053e7d3 PMID:17632317

MacArthur AC, McBride ML, Spinelli JJ *et al.* (2008). Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. *Cancer Causes Control*, 19: 283–295. doi:10.1007/s10552-007-9091-8 PMID:18283545

Malkinson AM (1992). Primary lung tumors in mice: an experimentally manipulable model of human adenocarcinoma. *Cancer Res*, 52: Suppl2670s–2676s. PMID:1562998

Mao Y, Hu J, Semenciw R, White KCanadian Cancer Registries Epidemiology Research Group (2002). Active and passive smoking and the risk of stomach cancer, by subsite, in Canada. *Eur J Cancer Prev*, 11: 27–38. doi:10.1097/00008469-200202000-00005 PMID:11917206

McGlynn KA, Zhang Y, Sakoda LC *et al.* (2006). Maternal smoking and testicular germ cell tumors. *Cancer Epidemiol Biomarkers Prev*, 15: 1820–1824. doi:10.1158/1055-9965.EPI-06-0389 PMID:17035387

McKinney PA, Cartwright RA, Saiu JM *et al.* (1987). The inter-regional epidemiological study of childhood cancer (IRESCC): a case control study of aetiological factors in leukaemia and lymphoma. *Arch Dis Child*, 62: 279–287. doi:10.1136/adc.62.3.279 PMID:3646026

McLaughlin CC, Baptiste MS, Schymura MJ *et al.* (2006). Maternal and infant birth characteristics and hepatoblastoma. *Am J Epidemiol*, 163: 818–828. doi:10.1093/aje/kwj104 PMID:16510543

Mechanic LE, Millikan RC, Player J *et al.* (2006). Polymorphisms in nucleotide excision repair genes, smoking and breast cancer in African Americans and whites: a population-based case-control study. *Carcinogenesis*, 27: 1377–1385. doi:10.1093/carcin/bgi330 PMID:16399771

Mejía-Aranguré JM, Fajardo-Gutiérrez A, Flores-Aguilar H *et al.* (2003). Environmental factors contributing to the development of childhood leukemia in children with Down's syndrome. *Leukemia*, 17: 1905–1907. doi:10.1038/sj.leu.2403047 PMID:12970794

Menegaux F, Ripert M, Hémon D, Clavel J (2007). Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study. *Paediatr Perinat Epidemiol*, 21: 293–299. doi:10.1111/j.1365-3016.2007.00824.x PMID:17564585

Menegaux F, Steffen C, Bellec S *et al.* (2005). Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. *Cancer Detect Prev*, 29: 487–493. doi:10.1016/j.cdp.2005.06.008 PMID:16289502

Miller GH (1990). The impact of passive smoking: cancer deaths among nonsmoking women. *Cancer Detect Prev*, 14: 497–503. PMID:2224913

Miller MD, Marty MA, Broadwin R *et al.*California Environmental Protection Agency (2007). The association between exposure to environmental tobacco smoke and breast cancer: a review by the California Environmental Protection Agency. *Prev Med*, 44: 93–106. doi:10.1016/j.ypmed.2006.08.015 PMID:17027075

Mohtashamipur E, Mohtashamipur A, Germann PG *et al.* (1990). Comparative carcinogenicity of cigarette mainstream and sidestream smoke condensates on the mouse skin. *J Cancer Res Clin Oncol*, 116: 604–608. doi:10.1007/BF01637081 PMID:2254379

Morabia A, Bernstein M, Héritier S, Khatchatrian N (1996). Relation of breast cancer with passive and active exposure to tobacco smoke. *Am J Epidemiol*, 143: 918–928. PMID:8610705

Morabia A, Bernstein MS, Bouchardy I *et al.* (2000). Breast cancer and active and passive smoking: the role of the N-acetyltransferase 2 genotype. *Am J Epidemiol*, 152: 226–232. doi:10.1093/aje/152.3.226 PMID:10933269

Mucci LA, Granath F, Cnattingius S (2004). Maternal smoking and childhood leukemia and lymphoma risk among 1,440,542 Swedish children. *Cancer Epidemiol Biomarkers Prev*, 13: 1528–1533. PMID:15342456

Navas-Acien A, Peruga A, Breysse P *et al.* (2004). Secondhand tobacco smoke in public places in Latin America, 2002–2003. *JAMA*, 291: 2741–2745. doi:10.1001/jama.291.22.2741 PMID:15187056

Nishino Y, Tsubono Y, Tsuji I *et al.* (2001). Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. *Cancer Causes Control*, 12: 797–802. doi:10.1023/A:1012273806199 PMID:11714107

Pang D & Birch JM (2003). Reply: smoking and hepatoblastoma:confounding by birth weight? *Br J Cancer*, 89: 603 doi:10.1038/sj.bjc.6601144

Pang D, McNally R, Birch JM (2003). Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. *Br J Cancer*, 88: 373–381. doi:10.1038/sj.bjc.6600774 PMID:12569379

Peppone LJ, Mahoney MC, Cummings KM *et al.* (2008). Colorectal cancer occurs earlier in those exposed to tobacco smoke: implications for screening. *J Cancer Res Clin Oncol*, 134: 743–751. doi:10.1007/s00432-007-0332-8 PMID:18264728

Phillips LE, Longstreth WT Jr, Koepsell T *et al.* (2005). Active and passive cigarette smoking and risk of intracranial meningioma. *Neuroepidemiology*, 24: 117–122. doi:10.1159/000082998 PMID:15637448

Pirie K, Beral V, Peto R *et al.*Million Women Study Collaborators (2008). Passive smoking and breast cancer in never smokers: prospective study and meta-analysis. *Int J Epidemiol*, 37: 1069–1079. doi:10.1093/ije/dyn110 PMID:18544575

Plichart M, Menegaux F, Lacour B *et al.* (2008). Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE). *Eur J Cancer Prev*, 17: 376–383. doi:10.1097/CEJ.0b013e3282f75e6f PMID:18562965

Pu CL, Guo CB, Jin XQ *et al.* (2009). [Retrospective analysis of maternal and infant birth features of hepatoblastoma patients] *Zhonghua Gan Zang Bing Za Zhi*, 17: 459–461. PMID:19567028

Ramroth H, Dietz A, Becher H (2008). Environmental tobacco smoke and laryngeal cancer: results from a population-based case-control study. *Eur Arch Otorhinolaryngol*, 265: 1367–1371. doi:10.1007/s00405-008-0651-7 PMID:18379814

Reif JS, Bruns C, Lower KS (1998). Cancer of the nasal cavity and paranasal sinuses and exposure to environmental tobacco smoke in pet dogs. *Am J Epidemiol*, 147: 488–492. PMID:9525536

Reif JS, Dunn K, Ogilvie GK, Harris CK (1992). Passive smoking and canine lung cancer risk. *Am J Epidemiol*, 135: 234–239. PMID:1546698

Reynolds P, Hurley S, Goldberg DCalifornia Teachers Study Steering Committee (2006). Accumulating evidence on passive and active smoking and breast cancer risk. *Int J Cancer*, 119: 239–1, author reply 240–241. doi:10.1002/ijc.21776 PMID:16432834

Reynolds P, Hurley S, Goldberg DE *et al.* (2004). Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J Natl Cancer Inst*, 96: 29–37. doi:10.1093/jnci/djh002 PMID:14709736

Roddam AW, Pirie K, Pike MC *et al.* (2007). Active and passive smoking and the risk of breast cancer in women aged 36–45 years: a population based case-control study in the UK. *Br J Cancer*, 97: 434–439. doi:10.1038/sj.bjc.6603859 PMID:17579618

Rollison DE, Brownson RC, Hathcock HL, Newschaffer CJ (2008). Case-control study of tobacco smoke exposure and breast cancer risk in Delaware. *BMC Cancer*, 8: 157 doi:10.1186/1471-2407-8-157 PMID:18518960

Rudant J, Menegaux F, Leverger G *et al.* (2008). Childhood hematopoietic malignancies and parental use of tobacco and alcohol: the ESCALE study (SFCE). *Cancer Causes Control*, 19: 1277–1290. doi:10.1007/s10552-008-9199-5 PMID:18618277

Ryan P, Lee MW, North B, McMichael AJ (1992). Risk factors for tumors of the brain and meninges: results from the Adelaide Adult Brain Tumor Study. *Int J Cancer*, 51: 20–27. doi:10.1002/ijc.2910510105 PMID:1563840

Samanic C, Kogevinas M, Dosemeci M *et al.* (2006). Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. *Cancer Epidemiol Biomarkers Prev*, 15: 1348–1354. doi:10.1158/1055-9965.EPI-06-0021 PMID:16835335

Samet J, Yang G (2001) *Passive smoking, women and children*. In: *Women and the Tobacco Epidemic, Challenges for the 21st Century,* Samet, J. and Yoon, S.-Y., editors. (WHO/NMH/TF1/ 01.1), Geneva: World Health Organization

Sandler DP, Everson RB, Wilcox AJ (1985a). Passive smoking in adulthood and cancer risk. *Am J Epidemiol*, 121: 37–48. PMID:3964991

Sandler DP, Everson RB, Wilcox AJ, Browder JP (1985b). Cancer risk in adulthood from early life exposure to parents' smoking. *Am J Public Health*, 75: 487–492. doi:10.2105/AJPH.75.5.487 PMID:3985235

Sandler RS, Sandler DP, Comstock GW *et al.* (1988). Cigarette smoking and the risk of colorectal cancer in women. *J Natl Cancer Inst*, 80: 1329–1333. doi:10.1093/jnci/80.16.1329 PMID:3172257

Scholes D, McBride C, Grothaus L *et al.* (1999). The association between cigarette smoking and low-grade cervical abnormalities in reproductive-age women. *Cancer Causes Control*, 10: 339–344. doi:10.1023/A:1008993619060 PMID:10530602

Schüz J, Kaatsch P, Kaletsch U *et al.* (1999). Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol*, 28: 631–639. doi:10.1093/ije/28.4.631 PMID:10480689

Shrubsole MJ, Gao YT, Dai Q *et al.* (2004). Passive smoking and breast cancer risk among non-smoking Chinese women. *Int J Cancer*, 110: 605–609. doi:10.1002/ijc.20168 PMID:15122595

Sillanpää P, Hirvonen A, Kataja V *et al.* (2005). NAT2 slow acetylator genotype as an important modifier of breast cancer risk. *Int J Cancer*, 114: 579–584. doi:10.1002/ijc.20677 PMID:15609332

Slattery ML, Curtin K, Giuliano AR *et al.* (2008). Active and passive smoking, IL6, ESR1, and breast cancer risk. *Breast Cancer Res Treat*, 109: 101–111. doi:10.1007/s10549-007-9629-1 PMID:17594514

Slattery ML, Edwards S, Curtin K *et al.* (2003). Associations between smoking, passive smoking, GSTM-1, NAT2, and rectal cancer. *Cancer Epidemiol Biomarkers Prev*, 12: 882–889. PMID:14504199

Slattery ML, Robison LM, Schuman KL *et al.* (1989). Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *JAMA*, 261: 1593–1598. doi:10.1001/jama.1989.03420110069026 PMID:2918652

Smith EM, Sowers MF, Burns TL (1984). Effects of smoking on the development of female reproductive cancers. *J Natl Cancer Inst*, 73: 371–376. PMID:6589429

Sobti RC, Kaur S, Kaur P *et al.* (2006). Interaction of passive smoking with GST (GSTM1, GSTT1, and GSTP1) genotypes in the risk of cervical cancer in India. *Cancer Genet Cytogenet*, 166: 117–123. doi:10.1016/j.cancergencyto.2005.10.001 PMID:16631467

Sorahan T & Lancashire RJ (2004). Parental cigarette smoking and childhood risks of hepatoblastoma: OSCC data. *Br J Cancer*, 90: 1016–1018. doi:10.1038/sj.bjc.6601651 PMID:14997199

Sorahan T, McKinney PA, Mann JR *et al.* (2001). Childhood cancer and parental use of tobacco: findings from the inter-regional epidemiological study of childhood cancer (IRESCC). *Br J Cancer*, 84: 141–146. doi:10.1054/bjoc.2000.1556 PMID:11139329

Spector LG & Ross JA (2003). Smoking and hepatoblastoma: confounding by birth weight? *Br J Cancer*, 89: 602–603, author reply 603. doi:10.1038/sj.bjc.6601143 PMID:12888836

Stayner L, Bena J, Sasco AJ *et al.* (2007). Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health*, 97: 545–551. doi:10.2105/AJPH.2004.061275 PMID:17267733

Stinn W, Teredesai A, Anskeit E *et al.* (2005b). Chronic nose-only inhalation study in rats, comparing room-aged sidestream cigarette smoke and diesel engine exhaust. *Inhal Toxicol*, 17: 549–576. doi:10.1080/08958370591000564 PMID:16033752

Stinn W, Teredesai A, Kuhl P *et al.* (2005a). Mechanisms involved in A/J mouse lung tumorigenesis induced by inhalation of an environmental tobacco smoke surrogate. *Inhal Toxicol*, 17: 263–276. doi:10.1080/08958370590922544 PMID:15814487

Suwan-ampai P, Navas-Acien A, Strickland PT, Agnew J (2009). Involuntary tobacco smoke exposure and urinary levels of polycyclic aromatic hydrocarbons in the United States, 1999 to 2002. *Cancer Epidemiol Biomarkers Prev*, 18: 884–893. doi:10.1158/1055-9965.EPI-08-0939 PMID:19258471

Tan EH, Adelstein DJ, Droughton ML *et al.* (1997). Squamous cell head and neck cancer in nonsmokers. *Am J Clin Oncol*, 20: 146–150. doi:10.1097/00000421-199704000-00008 PMID:9124188

Tay SK & Tay KJ (2004). Passive cigarette smoking is a risk factor in cervical neoplasia. *Gynecol Oncol*, 93: 116–120. doi:10.1016/j.ygyno.2003.12.032 PMID:15047223

Taylor JA, Sandler DP, Bloomfield CD *et al.* (1992). ras oncogene activation and occupational exposures in acute myeloid leukemia. *J Natl Cancer Inst*, 84: 1626–1632. doi:10.1093/jnci/84.21.1626 PMID:1433344

Taylor R, Najafi F, Dobson A (2007). Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *Int J Epidemiol*, 36: 1048–1059. doi:10.1093/ije/dym158 PMID:17690135

Teague SV, Pinkerton KE, Goldsmith M *et al.* (1994). Sidestream cigarette smoke generation and exposure system for environmental tobacco smoke studies. *Inhal Toxicol*, 6: 79–93. doi:10.3109/08958379409029697

Theis RP, Dolwick Grieb SM, Burr D *et al.* (2008). Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study. *BMC Cancer*, 8: 387 doi:10.1186/1471-2407-8-387 PMID:19108730

Trimble CL, Genkinger JM, Burke AE *et al.* (2005). Active and passive cigarette smoking and the risk of cervical neoplasia. *Obstet Gynecol*, 105: 174–181. doi:10.1097/01.AOG.0000148268.43584.03 PMID:15625160

Tsai HT, Tsai YM, Yang SF *et al.* (2007). Lifetime cigarette smoke and second-hand smoke and cervical intraepithelial neoplasm–a community-based case-control study. *Gynecol Oncol*, 105: 181–188. doi:10.1016/j.ygyno.2006.11.012 PMID:17204311

Tse LA, Yu IT, Au JS *et al.* (2009). Environmental tobacco smoke and lung cancer among Chinese nonsmoking males: might adenocarcinoma be the culprit? *Am J Epidemiol*, 169: 533–541. doi:10.1093/aje/kwn385 PMID:19126588

UKCCS Investigators; UK Childhood Cancer Study Investigators (2000). The United Kingdom Childhood Cancer Study: objectives, materials and methods. *Br J Cancer*, 82: 1073–1102. doi:10.1054/bjoc.1999.1045 PMID:10737392

US Department of Health and Human Services (2006). *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Van Hemelrijck MJ, Michaud DS, Connolly GN, Kabir Z (2009). Secondhand smoking, 4-aminobiphenyl, and bladder cancer: two meta-analyses. *Cancer Epidemiol Biomarkers Prev*, 18: 1312–1320. doi:10.1158/1055-9965.EPI-08-0613 PMID:19336562

Veglia F, Vineis P, Overvad K *et al.* (2007). Occupational exposures, environmental tobacco smoke, and lung cancer. *Epidemiology*, 18: 769–775. doi:10.1097/EDE.0b013e318142c8a1 PMID:18062064

Verla-Tebit E, Lilla C, Hoffmeister M *et al.* (2009). Exposure to environmental tobacco smoke and the risk of colorectal cancer in a case-control study from Germany. *Eur J Cancer Prev*, 18: 9–12. doi:10.1097/CEJ.0b013e3282f0c06c PMID:19077559

Villeneuve PJ, Johnson KC, Mao Y, Hanley AJCanadian Cancer Registries Research Group (2004). Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study. *Can J Public Health*, 95: 32–37. PMID:14768739

Vineis P, Hoek G, Krzyzanowski M *et al.* (2007a). Lung cancers attributible to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health*, 6: 100–112. doi:10.1186/1476-069X-6-7

Vineis P, Veglia F, Garte S *et al.* (2007b). Genetic susceptibility according to three metabolic pathways in cancers of the lung and bladder and in myeloid leukemias in nonsmokers. *Ann Oncol*, 18: 1230–1242. doi:10.1093/annonc/mdm109 PMID:17496311

Wang Z, Tang L, Sun G *et al.* (2006). Etiological study of esophageal squamous cell carcinoma in an endemic region: a population-based case control study in Huaian, China. *BMC Cancer*, 6: 287 doi:10.1186/1471-2407-6-287 PMID:17173682

Wen W, Shu XO, Gao YT *et al.* (2006). Environmental tobacco smoke and mortality in Chinese women who have never smoked: prospective cohort study. *BMJ*, 333: 376 doi:10.1136/bmj.38834.522894.2F PMID:16837487

Wenzlaff AS, Cote ML, Bock CH *et al.* (2005). CYP1A1 and CYP1B1 polymorphisms and risk of lung cancer among never smokers: a population-based study. *Carcinogenesis*, 26: 2207–2212. doi:10.1093/carcin/bgi191 PMID:16051642

Whitehead T, Metayer C, Ward MH *et al.* (2009). Is house-dust nicotine a good surrogate for household smoking? *Am J Epidemiol*, 169: 1113–1123. doi:10.1093/aje/kwp021 PMID:19299402

Wiemels JL, Zhang Y, Chang J *et al.* (2005). RAS mutation is associated with hyperdiploidy and parental characteristics in pediatric acute lymphoblastic leukemia. *Leukemia*, 19: 415–419. doi:10.1038/sj.leu.2403641 PMID:15674422

Witschi H, Espiritu I, Dance ST, Miller MS (2002). A mouse lung tumor model of tobacco smoke carcinogenesis. *Toxicol Sci*, 68: 322–330. doi:10.1093/toxsci/68.2.322 PMID:12151628

Witschi H, Espiritu I, Maronpot RR (2006). Lung tumors in 2 year old strain A/J mice exposed for 6 months to tobacco smoke. *Cancer Lett*, 241: 64–68. doi:10.1016/j.canlet.2005.10.002 PMID:16290922

Witschi H, Espiritu I, Maronpot RR *et al.* (1997a). The carcinogenic potential of the gas phase of environmental tobacco smoke. *Carcinogenesis*, 18: 2035–2042. doi:10.1093/carcin/18.11.2035 PMID:9395199

Witschi H, Espiritu I, Peake JL *et al.* (1997b). The carcinogenicity of environmental tobacco smoke. *Carcinogenesis*, 18: 575–586. doi:10.1093/carcin/18.3.575 PMID:9067559

Witschi H, Espiritu I, Uyeminami D (1999). Chemoprevention of tobacco smoke-induced lung tumors in A/J strain mice with dietary myo-inositol and dexamethasone. *Carcinogenesis*, 20: 1375–1378. doi:10.1093/carcin/20.7.1375 PMID:10383915

Witschi H, Espiritu I, Yu M, Willits NH (1998). The effects of phenethyl isothiocyanate, N-acetylcysteine and green tea on tobacco smoke-induced lung tumors in strain A/J mice. *Carcinogenesis*, 19: 1789–1794. doi:10.1093/carcin/19.10.1789 PMID:9806160

Witschi H, Oreffo VI, Pinkerton KE (1995). Six-month exposure of strain A/J mice to cigarette sidestream smoke: cell kinetics and lung tumor data. *Fundam Appl Toxicol*, 26: 32–40. doi:10.1006/faat.1995.1072 PMID:7657060

WHO; World Health Organization (2002) *The world health report 2002—reducing risks, promoting healthy life*. Geneva: World Health Organization. http://www.who.int/whr/2002/en/ index.html (accessed Feb 18, 2010).

WHO; World Health Organization (2003). *WHO Framework Convention on Tobacco Control*. Geneva: World Health Organization (updated 2004, 2005; http://www.who.int/tobacco/framework/WHO_FCTC_english.pdf, (accessed 01 November 2011).

WHO; World Health Organization (2007). *WHO Guidelines for implementation of Article 8 of the WHO Framework Convention on Tobacco Control (Protection from exposure to tobacco smoke),* Geneva. (http://www.who.int/fctc/guidelines/article_8/en/index.html, accessed 17 August 2011).

WHO; World Health Organization (2008). *WHO report on the global tobacco epidemic: the MPOWER package.* Geneva: World Health Organization.

WHO; World Health Organization (2009a). *WHO report on the global tobacco epidemic: Implementing smoke-free environments.* Geneva: World Health Organization.

WHO; World Health Organization (2009b). *Global Adult Tobacco Survey (GATS) reports and factsheets.* Geneva: World Health Organization (http://www.who.int/tobacco/surveillance/survey/gats/en/index.html, accessed 01 November 2011).

WHO; World Health Organization (2009c). *STEPwise approach to surveillance (STEPS) – STEPS country reports.* Geneva: World Health Organization (http://www.who.int/chp/steps/reports/en/index.html, accessed 01 November 2009).

WHO; World Health Organization (2010)*. *Global estimate of the burden of disease from second-hand smoke.* Öberg M, Woodward A, Jaakkola MS, Peruga A, Prüss-Ustün A. http://whqlibdoc.who.int/publications/2010/9789241564076_eng.pdf (accessed November 21, 2011).

WHO; World Health Organization (2011)*. *WHO report on the global tobacco epidemic: Warning about the dangers of tobacco.* Geneva: World Health Organization.

Wu MT, Lee LH, Ho CK *et al.* (2003). Lifetime exposure to environmental tobacco smoke and cervical intraepithelial neoplasms among nonsmoking Taiwanese women. *Arch Environ Health*, 58: 353–359. PMID:14992310

Yauk CL, Berndt ML, Williams A *et al.* (2007). Mainstream tobacco smoke causes paternal germ-line DNA

mutation. *Cancer Res*, 67: 5103–5106. doi:10.1158/0008-5472.CAN-07-0279 PMID:17545587

Young E, Leatherdale S, Sloan M *et al.* (2009). Age of smoking initiation and risk of breast cancer in a sample of Ontario women. *Tob Induc Dis*, 5: 4 doi:10.1186/1617-9625-5-4 PMID:19222858

Yu MC, Garabrant DH, Huang TB, Henderson BE (1990). Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J Cancer*, 45: 1033–1039. doi:10.1002/ijc.2910450609 PMID:2351484

Yuan JM, Wang XL, Xiang YB *et al.* (2000). Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. *Int J Cancer*, 85: 364–369. doi:10.1002/(SICI)1097-0215(20000201)85:3<364::AID-IJC12>3.0.CO;2-C PMID:10652428

Zeegers MP, Goldbohm RA, van den Brandt PA (2002). A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control*, 13: 83–90. doi:10.1023/A:1013954932343 PMID:11899922

Zhang ZF, Morgenstern H, Spitz MR *et al.* (2000). Environmental tobacco smoking, mutagen sensitivity, and head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*, 9: 1043–1049. PMID:11045786

Zhao Y, Shi Z, Liu L (1999). [Matched case-control study for detecting risk factors of breast cancer in women living in Chengdu] *Zhonghua Liu Xing Bing Xue Za Zhi*, 20: 91–94. PMID:10682541

Zheng W, McLaughlin JK, Chow WH *et al.* (1993). Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. *Am J Epidemiol*, 138: 965–972. PMID:8256781

* Exceptionally, the most recent updates of well-established ongoing surveys and reports, published after the meeting, were included in this Monograph. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 83

Tobacco Smoke and Involuntary Smoking

Summary of Data Reported and Evaluation

Last updated: 24 July 2002

TOBACCO SMOKING AND TOBACCO SMOKE
(Group 1)

5. Summary of Data Reported and Evaluation

For definition of groups, see Preamble.

VOL.: 83 (2002)

5.1 Exposure data

Smoking of tobacco is practised worldwide by over one thousand million people. However, while smoking prevalence has declined in many developed countries, it remains high in others and is increasing among women and in developing countries. Between one-fifth and two-thirds of men in most populations smoke. Women's smoking rates vary more widely but rarely equal male rates.

Tobacco is most commonly smoked as cigarettes, both manufactured — which are a highly sophisticated nicotine delivery system — and hand-rolled. Pipes, cigars, bidis and other products are used to a lesser extent or predominantly in particular regions. Cigarettes are made from fine-cut tobaccos which are wrapped in paper or a maize leaf. Cigars consist of cut tobacco filler formed in a binder leaf and with a wrapper leaf rolled spirally around the bunch. Bidis contain shredded tobacco wrapped in non-tobacco leaves, usually dried *temburni* leaves.

The chemical composition of tobacco smoke, although influenced by the specific manner in which individuals smoke, is primarily determined by the type of tobacco. It is also influenced by the design of the smoking device or product and, for cigarettes, by the presence or absence of filters, and by other factors including ventilation, paper porosity and types of additives. As a result, concentrations of individual chemicals in smoke vary. Analysis of the ways in which people smoke modern cigarettes shows that actual doses of nicotine, carcinogens and toxins depend on the intensity and method of smoking and have little relation to stated tar yields. The total volume of smoke drawn from cigarettes as a result of specific smoking patterns is the principal determinant of dose to the smoker. All presently available tobacco products that are smoked deliver substantial amounts of established carcinogens to their users.

The yields of tar, nicotine and carbon monoxide from cigarettes, as measured by standard machine-smoking tests, have fallen over recent decades in cigarettes sold in most parts of the world, but have remained higher in some countries. The tar and nicotine yields as currently measured are misleading and have only little value in the assessment of human exposure to carcinogens.

The regulation of smoking and smoke yields varies widely around the world in scope and degree of enforcement. Certain regulatory actions, such as taxes and workplace smoking bans, are effective in reducing smoking rates and protecting nonsmokers.

5.2 Human carcinogenicity data

In the previous 1986 *IARC Monograph* on tobacco smoking, cancers of the lung, oral cavity, pharynx, larynx, oesophagus (squamous-cell carcinoma), pancreas, urinary bladder and renal pelvis were identified as caused by cigarette smoking. Many more studies published since this earlier Monograph support these causal links. In addition, there is now sufficient evidence for a causal association between cigarette smoking and cancers of the nasal cavities and nasal sinuses, oesophagus (adenocarcinoma), stomach, liver, kidney (renal-cell carcinoma), uterine cervix and myeloid leukaemia.

In cancer sites that were causally linked to cigarette smoking in the previous *IARC Monograph* on tobacco smoking, the observed relative risks ranged generally from approximately 3 for pancreatic cancer to more than 20 for lung cancer. For those cancer sites that were now also linked to cigarette smoking in this Monograph,

generally two- to threefold increased risks were observed.

Cigarettes

Lung

Lung cancer is the most common cause of death from cancer in the world. The total number of cases is now estimated to be 1.2 million annually and is still increasing. The major cause of lung cancer is tobacco smoking, primarily of cigarettes. In populations with prolonged cigarette use, the proportion of lung cancer cases attributable to cigarette smoking has reached 90%.

The duration of smoking is the strongest determinant of lung cancer in smokers. Hence, the earlier the age of starting and the longer the continuation of smoking in adulthood, the greater the risk. Risk of lung cancer also increases in proportion to the numbers of cigarettes smoked.

Tobacco smoking increases the risk of all histological types of lung cancer including squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma (including bronchiolar/alveolar carcinoma) and large-cell carcinoma. The association between adenocarcinoma of the lung and smoking has become stronger over time. The carcinogenic effects of cigarette smoking appear similar in both women and men.

Stopping smoking at any age avoids the further increase in risk of lung cancer incurred by continued smoking. The younger the age at cessation, the greater the benefit.

Urinary tract

Tobacco smoking is a major cause of transitional-cell carcinomas of the bladder, ureter and renal pelvis. Risk increases with the duration of smoking and number of cigarettes smoked. As for lung cancer, stopping smoking at any age avoids the further increase in risk incurred by continued smoking.

Evidence from several cohort and case–control studies published since the previous *IARC Monograph* on tobacco smoking has indicated that renal-cell carcinoma is associated with tobacco smoking in both men and women. The association is not explained by confounding. A dose–response relationship with the number of cigarettes smoked has been noted in most studies, and a few also noted a reduction in risk after cessation.

Oral cavity

Tobacco smoking, including cigarette smoking, is causally associated with cancer of the oral cavity (including lip and tongue) in both men and women. Since the previous *IARC Monograph* on tobacco smoking, evidence from many more studies has accumulated that further confirms this association. Use of smokeless tobacco and/or alcohol in combination with tobacco smoking greatly increases the risk of oral cancer. Risk increases substantially with duration of smoking and number of cigarettes smoked. Risk among former smokers is consistently lower than among current smokers and there is a trend of decreasing risk with increasing number of years since quitting.

Nasal cavity and paranasal sinuses

An increased risk of sinonasal cancer among cigarette smokers has been reported in all nine case–control studies for which results are available. Of seven studies that have analysed dose–response relationships, a positive trend was found in five and was suggested in the other two. In all the five studies that have analysed squamous-cell carcinoma and adenocarcinoma separately, the relative risk was clearly increased for squamous-cell carcinoma.

Nasopharynx

An increased risk for nasopharyngeal cancer among cigarette smokers was reported in one cohort study and nine case–control studies. Increased relative risks were reported in both high- and low-risk geographical regions for nasopharyngeal cancer. A dose–response relationship was detected with either duration or amount of smoking. A reduction in risk after quitting was also detected. The potential confounding effect of infection with Epstein–Barr virus was not controlled for in these studies; however, such an effect was not considered to be plausible. No important role was shown for other potential confounders.

Oropharynx and hypopharynx

Oropharyngeal and hypopharyngeal cancer are causally associated with cigarette smoking. The risk increased with increased duration of smoking and daily cigarette consumption and decreased with increasing time since quitting.

Oesophagus

Tobacco smoking is causally associated with cancer of the oesophagus, particularly squamous-cell carcinoma. Tobacco smoking is also causally associated with adenocarcinoma of the oesophagus. In most of the epidemiological studies, the risk for all types of oesophageal cancer increased with numbers of cigarettes smoked daily and duration of smoking. However, risk for oesophageal cancer remains elevated many years after cessation of smoking.

Tobacco and alcohol in combination with tobacco smoking greatly increase the risk for squamous-cell carcinoma of the oesophagus. In India, use of smokeless tobacco in combination with smoking also greatly increases the risk.

Larynx

Laryngeal cancer is causally associated with cigarette smoking. The risk increases substantially with duration and number of cigarettes smoked. Use of alcohol in combination with tobacco smoking greatly increases the risk for laryngeal cancer. A few studies also reported that relative risks for cancer of the larynx increased with decreasing age at start of smoking. The relative risk decreased with increasing time since quitting smoking.

Pancreas

Cancer of the pancreas is causally associated with cigarette smoking. The risk increases with duration of smoking and number of cigarettes smoked daily. The risk remains elevated after allowing for potential confounding factors such as alcohol consumption. The relative risk decreased with increasing time since quitting smoking.

Stomach

The data available in 1986 did not permit the earlier IARC Working Group to conclude that the association between tobacco smoking and stomach cancer was causal. Since that time, further studies have shown a consistent association of cancer of the stomach with cigarette smoking in both men and women in many cohort and case–control studies conducted in various parts of the world. Confounding by other factors (e.g. alcohol consumption, *Helicobacter pylori* infection and dietary factors) can be reasonably ruled out. Risk increases with duration of smoking and number of cigarettes smoked, and decreases with increasing duration of successful quitting. In studies that had adequate numbers, the relative risks for men and women were similar.

Liver

In the previous *IARC Monograph* on tobacco smoking, a causal relationship between liver cancer and smoking could not be established, chiefly due to possible confounding from alcohol intake and hepatitis B and hepatitis C virus infections. Many cohort studies and case–control studies have provided additional information on smoking and liver cancer since then. Most of the cohort studies and the largest case–control studies (most notably those that included community controls) showed a moderate association between tobacco smoking and risk of liver cancer. In many studies, the risk for liver cancer increased with the duration of smoking or the number of cigarettes smoked daily. Former smokers who had stopped smoking for more than 10 years showed a decline in liver cancer risk. Confounding from alcohol can be ruled out, at least in the best case–control studies, by means of careful adjustment for drinking habits. An association with smoking has also been demonstrated among non-drinkers. Many studies, most notably from Asia, have shown no attenuation of the association between smoking and liver cancer after adjustment/stratification for markers of hepatitis B/hepatitis C virus infection. There is now sufficient evidence to judge the association between tobacco smoking and liver cancer as causal.

Cervix

An association of invasive cervical squamous-cell carcinoma with smoking has been observed in the large number of studies reviewed. The most recent studies have controlled for infection with human papillomavirus, a known cause of cervical cancer. The effect of smoking was not diminished by the adjustment for human papillomavirus infection, or analysis restricted to cases and controls both positive for human papillomavirus (as ascertained by human papillomavirus DNA or human papillomavirus serological methods). There is now sufficient evidence to establish a causal association of squamous-cell cervical carcinoma with smoking. In the small number of studies available for adeno- and adeno-squamous-cell carcinoma, no consistent association was observed.

Leukaemia

Myeloid leukaemia in adults was observed to be causally related to smoking. Risk increased with amount of tobacco smoked in a substantial number of adequate studies. No clear evidence of any risk was seen for lymphoid leukaemia/lymphoma.

Support for a causal relationship of smoking with myeloid leukaemia is provided by the finding of known leukaemogens in tobacco smoke, one of which (benzene) is present in sufficient amounts to account for up to half of the estimated excess of acute myeloid leukaemia.

Colorectal cancer

There is some evidence from prospective cohort studies and case–control studies that the risk of colorectal cancer is increased among tobacco smokers. However, it is not possible to conclude that the association between tobacco smoking and colorectal cancer is causal. Inadequate adjustment for various potential confounders could account for some of the small increase in risk that appears to be associated with smoking.

Female breast

Most epidemiological studies have found no association with active smoking, after controlling for established risk factors (e.g. age at time of first birth, parity, family history of breast cancer and alcohol). The large multicentre pooled analysis of the association of smoking with breast cancer in non-drinkers confirms the lack of an increased risk of breast cancer associated with smoking.

Endometrium

Cigarette smoking is not associated with an increased risk for endometrial cancer.

An inverse relationship of cigarette smoking with endometrial cancer is observed consistently in most case–control and cohort studies, after adjustment for major confounders. This pattern is stronger in post-menopausal women.

Prostate

No clear evidence of any risk for prostate cancer is seen in case–control studies or in studies of incident cases in cohort studies. The small excess observed in some analytical mortality studies can reasonably be explained by bias in the attribution of the underlying cause of death.

Other

There is inconsistent and/or sparse evidence for association between cigarette smoking and other cancer sites that were considered by the Working Group.

Cigars and pipes

Cigar and/or pipe smoking is strongly related to cancers of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus, the magnitude of risk being similar to that from cigarette smoking. These risks increase with the amount of cigar and/or pipe smoking and with the combination of alcohol and tobacco consumption. Cigar and/or pipe smoking is causally associated with cancer of the lung and there is evidence that cigar and/or pipe smoking are also causally associated with cancers of the pancreas, stomach and urinary bladder.

Bidi

Bidi smoking is the most common form of tobacco smoking in India and is also prevalent in other south-Asian countries and an emerging problem in the USA. Bidi smoke was considered as carcinogenic in the earlier *IARC Monograph* on tobacco smoking, and later studies have provided further evidence of causality. Case–control studies demonstrated a strong association at various sites: oral cavity (including subsites), pharynx, larynx, oesophagus, lung and stomach. Almost all studies show significant trends with duration of bidi smoking and number of bidis smoked.

Synergy

For public health purposes, synergy should be characterized as a positive departure from additivity. The epidemiological literature often inadequately describes combined effects of smoking with co-exposures to other carcinogenic agents and in many studies power is limited for characterizing combined effects. The issue of synergistic effects can be appropriately addressed by epidemiological studies that show stratified analysis and have sufficient power. The studies reviewed found evidence of synergy between smoking and several occupational causes of lung cancer (arsenic, asbestos and radon), and between smoking and alcohol consumption for cancers of the oral cavity, pharynx, larynx and oesophagus and between smoking and human papillomavirus infection for cancer of the cervix. Data were inadequate to evaluate the evidence for synergy between smoking and other known causes of cancer (e.g. hepatitis B and alcohol for liver cancer).

5.3 Animal carcinogenicity data

Cigarette smoke has been tested for carcinogenicity by inhalation studies in rodents, rabbits and dogs. The model systems for animal exposure to tobacco smoke do not fully simulate human exposure to tobacco smoke, and the tumours that develop in animals are not completely representative of human cancer. Nevertheless, the animal data provide valuable insights regarding the carcinogenic potential of tobacco smoke.

The most compelling evidence for a positive carcinogenic effect of tobacco smoke in animals is the

reproducible increase observed in several studies in the occurrence of laryngeal carcinomas in hamsters exposed to whole tobacco smoke or to its particulate phase. In four of five studies in rats, exposure to whole smoke led to modest increases in the occurrence of malignant and/or benign lung tumours. Similarly, in four of eight studies in mice of varying susceptibility to lung tumour development, exposure to whole smoke led to a modest increase in the frequency of lung adenomas. An increased incidence of lung 'tumours' has also been reported in dogs exposed to tobacco smoke, but it is uncertain whether the histopathological features of the lesions are consistent with malignancy. In hamsters exposed to both cigarette smoke and chemical carcinogens (*N*-nitrosodiethylamine and 7,12-dimethylbenz[*a*]anthracene), the tumour response in the respiratory tract was higher than in hamsters exposed to either agent alone. The same is true in rats exposed simultaneously to cigarette smoke and radionuclides (radon progeny and plutonium oxide).

Cigarette smoke condensate both initiates and promotes tumour development in animals. It reproducibly induces both benign and malignant skin tumours in mice following topical application. Similarly, it produces skin tumours in rabbits following topical application. Topical application to the oral mucosa also produced an increased incidence of lung tumours and lymphomas in mice. In rats, cigarette smoke condensate produced lung tumours after intrapulmonary injection. In initiation/promotion assays in mouse skin, a single topical application of cigarette smoke condensate followed by application of croton oil was sufficient to initiate both benign and malignant skin tumours. Smoke condensates of Indian bidi administered to mice by gavage were found to induce tumours in a number of organs. Collectively, these data provide evidence of the carcinogenic effect of mainstream tobacco smoke in experimental animals.

5.4 Other relevant data

Causal associations have been clearly established between active smoking and adverse reproductive outcomes and numerous non-neoplastic diseases, including chronic obstructive pulmonary disease and cardiovascular diseases.

Tobacco smoking is addictive, and nicotine has been established as the major addictive constituent of tobacco products. Measurement of the nicotine metabolite, cotinine, in human blood, urine or saliva provides a specific and sensitive test for exposure to tobacco smoke and can be used to distinguish active and passive smokers from nonsmokers.

Active smoking raises the concentrations of carbon monoxide, benzene and volatile organic compounds in exhaled air. The concentrations of urinary metabolites of some important tobacco smoke carcinogens and related compounds are consistently higher in smokers than in nonsmokers. These include metabolites of benzene, a known carcinogen in humans, as well as metabolites of several carcinogens that cause lung tumours in rodents. Covalent binding to blood proteins by carcinogens present in tobacco smoke has been demonstrated to occur at significantly higher levels in smokers than in nonsmokers. The adducts are derived from various compounds including aromatic amines (e.g. 4-aminobiphenyl), polycyclic aromatic hydrocarbons (e.g. benzo[*a*]pyrene), tobacco-specific nitrosamines (e.g. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), benzene, acrylamide and acrylonitrile.

Smoking-related DNA adducts have been detected by a variety of analytical methods in the respiratory tract, urinary bladder, cervix and other tissues. In many studies the levels of carcinogen-DNA adducts have been shown to be higher in tissues of smokers than in tissues of nonsmokers. Some but not all studies have demonstrated elevated levels of these adducts in the peripheral blood and in full-term placenta. Smoking-related adducts have also been detected in cardiovascular tissues. Collectively, the available biomarker data provide convincing evidence that carcinogen uptake, activation and binding to cellular macromolecules, including DNA, are higher in smokers than in nonsmokers.

The exposure of experimental animals, primarily rodents, to mainstream tobacco smoke results in a number of biological effects that include (i) increases or decreases in the activities of phase I and phase II enzymes involved in carcinogen metabolism, (ii) increases in the activation of antioxidant enzymes, (iii) increased expression of nitric oxide synthase and of various protein kinases and collagenase, (iv) the formation of tobacco smoke-related DNA adducts in several tissues and (v) reduced clearance of particulate material from the lung.

Smoking is known to have inhibitory or inducing effects on the activities of many enzymes in human tissues. These include xenobiotic metabolizing enzymes, which affect drug and carcinogen metabolism. Numerous studies have reported effects on enzymes in cells treated in culture with tobacco smoke or tobacco smoke condensates.

In humans, smoking produces gene mutations and chromosomal abnormalities. Urine from smokers is mutagenic. Relative to nonsmokers, lung tumours of smokers contain higher frequencies of *TP53* and *KRAS* mutations, and the spectrum of mutations has unique features. Most of the genetic effects seen in smokers are also observed in cultured cells or in experimental animals exposed to tobacco smoke or smoke condensate. Tobacco smoke is genotoxic in humans and in experimental animals.

5.5 Evaluation

There is *sufficient evidence* in humans that tobacco smoking causes cancer of the lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, oesophagus, stomach, pancreas, liver, kidney (body and pelvis), ureter, urinary bladder, uterine cervix and bone marrow (myeloid leukaemia).

There is *evidence suggesting lack of carcinogenicity* of tobacco smoking in humans for cancers of the female breast and endometrium.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tobacco smoke and tobacco smoke condensates.

Overall evaluation

Tobacco smoking and tobacco smoke *are carcinogenic to humans (Group 1).*

For definition of the italicized terms, see Preamble.

INVOLUNTARY SMOKING
(Group 1)

For definition of groups, see Preamble.

VOL.: 83 (2002)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Involuntary (or passive) smoking is exposure to secondhand tobacco smoke, which is a mixture of exhaled mainstream smoke and sidestream smoke released from the smouldering cigarette or other smoking device (cigar, pipe, bidi, etc.) and diluted with ambient air. Involuntary smoking involves inhaling carcinogens, as well as other toxic components, that are present in secondhand tobacco smoke. Secondhand tobacco smoke is sometimes referred to as 'environmental' tobacco smoke. Carcinogens that occur in secondhand tobacco smoke include benzene, 1,3-butadiene, benzo[*a*]pyrene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and many others.

Secondhand tobacco smoke consists of a gas phase and a particulate phase; it changes during its dilution and distribution in the environment and upon ageing. The concentrations of respirable particles may be elevated substantially in enclosed spaces containing secondhand tobacco smoke. The composition of tobacco smoke inhaled involuntarily is variable quantitatively and depends on the smoking patterns of the smokers who are producing the smoke as well as the composition and design of the cigarettes or other smoking devices. The secondhand tobacco smoke produced by smoking cigarettes has been most intensively studied.

Secondhand tobacco smoke contains nicotine as well as carcinogens and toxins. Nicotine concentrations in the air in homes of smokers and in workplaces where smoking is permitted typically range on average from 2 to 10 micrograms/m^3.

5.2 Human carcinogenicity data

Lung cancer

Involuntary smoking involves exposure to the same numerous carcinogens and toxic substances that are present in tobacco smoke produced by active smoking, which is the principal cause of lung cancer. As noted in the previous *IARC Monograph* on tobacco smoking, this implies that there will be some risk of lung cancer from exposure to secondhand tobacco smoke.

More than 50 studies of involuntary smoking and lung cancer risk in never-smokers, especially spouses of smokers, have been published during the last 25 years. These studies have been carried out in many countries. Most showed an increased risk, especially for persons with higher exposures. To evaluate the information collectively, in particular from those studies with a limited number of cases, meta-analyses have been conducted in which the relative risk estimates from the individual studies are pooled together. These meta-analyses show that there is a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from the spouse who smokes. The excess risk is of the order of 20% for women and 30% for men and remains after controlling for some potential sources of bias and confounding. The excess risk increases with increasing exposure. Furthermore, other published meta-analyses of lung cancer in never-smokers exposed to secondhand tobacco smoke at the workplace have found a statistically significant increase in risk of 12–19%. This evidence is sufficient to conclude that involuntary smoking is a cause of lung cancer in never-smokers. The magnitudes of the observed risks are reasonably consistent with predictions based on studies of active smoking in many populations.

Breast cancer

The collective evidence on breast cancer risk associated with involuntary exposure of never-smokers to tobacco smoke is inconsistent. Although four of the 10 case–control studies found statistically significant increases in risks, prospective cohort studies as a whole and, particularly, the two large cohort studies in the USA of nurses and of volunteers in the Cancer Prevention Study II provided no support for a causal relation between involuntary exposure to tobacco smoke and breast cancer in never-smokers. The lack of a positive dose–response also argues against a causal interpretation of these findings. Finally, the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking.

Childhood cancer

Overall, the findings from studies of childhood cancer and exposure to parental smoking are inconsistent and are likely to be affected by bias. There is a suggestion of a modest association between exposure to maternal tobacco smoke during pregnancy and childhood cancer for all cancer sites combined; however, this is in contrast with the null findings for individual sites. Studies on paternal tobacco smoking suggest a small increased risk for lymphomas, but bias and confounding cannot be ruled out.

Other cancer sites

Data are conflicting and sparse for associations between involuntary smoking and cancers of the nasopharynx, nasal cavity, paranasal sinuses, cervix, gastrointestinal tract and cancers at all sites combined. It is unlikely that any effects are produced in passive smokers that are not produced to a greater extent in active smokers or that types of effects that are not seen in active smokers will be seen in passive smokers.

5.3 Animal carcinogenicity data

Secondhand tobacco smoke for carcinogenicity studies in animals is produced by machines that simulate human active smoking patterns and combine mainstream and sidestream smoke in various proportions. Such mixtures have been tested for carcinogenicity by inhalation studies in rodents. The experimental model systems for exposure to secondhand tobacco smoke do not fully simulate human exposures, and the tumours that develop in animals are not completely representative of human cancer. Nevertheless, the animal data provide valuable insights regarding the carcinogenic potential of secondhand tobacco smoke.

A mixture of 89% sidestream smoke and 11% mainstream smoke has been tested for carcinogenic activity in mouse strains that are highly susceptible to lung tumours (strains A/J and Swiss). In strain A/J mice, this mixture consistently produces a significant, modest increase in lung tumour incidence and lung tumour multiplicity when the mice are exposed for 5 months followed by a 4-month recovery period. These lung tumours are predominantly adenomas. Continuous exposure of strain A/J mice to the above mixture of mainstream and sidestream tobacco smoke for 9 months with no recovery period did not increase the incidence of lung tumours. In Swiss strain mice, the same mixture induced lung tumours by both protocols, i.e. when the animals were exposed for 5 months followed by a 4-month recovery period and when they were exposed continuously for 9 months with no recovery period. In addition, exposure of Swiss mice to the tobacco smoke mixture for a shorter period was sufficient to induce lung tumours.

Condensates of sidestream and of mainstream cigarette smoke have been tested for carcinogenicity. Both kinds of condensates produced a spectrum of benign and malignant skin tumours in mice following topical application, and the sidestream condensate exhibited higher carcinogenic activity. Sidestream smoke condensate was shown to produce a dose-dependent increase in lung tumours in rats following implantation into the lungs.

Increased relative risks for lung and sinonasal cancer have been reported in companion animals

(dogs) exposed to secondhand tobacco smoke in homes.

5.4 Other relevant data

Involuntary smoking has been associated with a number of non-neoplastic diseases and adverse effects in never-smokers, including both children and adults. Epidemiological studies have demonstrated that exposure to secondhand tobacco smoke is causally associated with coronary heart disease. From the available meta-analyses, it has been estimated that involuntary smoking increases the risk of an acute coronary heart disease event by 25–35%. Adverse effects of involuntary smoking on the respiratory system have also been detected. In adults, the strongest evidence for a causal relation exists for chronic respiratory symptoms. Some effects on lung function have been detected, but their medical relevance is uncertain.

Data on the hormonal and metabolic effects of involuntary smoking are sparse. However, female involuntary smokers do not appear to weigh less than women who are not exposed to secondhand tobacco smoke, a pattern that contrasts with the findings for active smoking. No consistent association of maternal exposure to secondhand smoke with fertility or fecundity has been identified. There is no clear association of passive smoking with age at menopause.

Maternal cigarette smoking has repeatedly been associated with adverse effects on fetal growth; full-term infants born to women who smoke weigh about 200 g less than those born to nonsmokers. A smaller adverse effect has been attributed to maternal passive smoking.

Cotinine, and its parent compound nicotine, are highly specific for exposure to secondhand smoke. Because of its favourable biological half-life and the sensitivity of techniques for quantifying it, cotinine is currently the most suitable biomarker for assessing recent exposure to secondhand tobacco smoke uptake and metabolism in adults, children and newborns.

Several studies in humans have shown that concentrations of adducts of carcinogens to biological macromolecules, including haemoglobin adducts of aromatic amines and albumin adducts of polycyclic aromatic hydrocarbons, are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not exposed to secondhand tobacco smoke. Protein adduct concentrations in fetal cord blood correlate with those in maternal blood but are lower. Fewer studies have investigated DNA adduct levels in white blood cells of exposed and unexposed nonsmokers, and most studies have not shown clear differences.

In studies of urinary biomarkers, metabolites of the tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been found to be consistently elevated in involuntary smokers. Levels of these metabolites are 1–5% as great as those found in smokers. The data demonstrating uptake of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a lung carcinogen in rodents, by nonsmokers are supportive of a causal link between exposure to secondhand tobacco smoke and development of lung cancer.

The exposure of experimental animals, primarily rodents, to secondhand tobacco smoke has several biological effects that include (i) increases or decreases in the activity of phase I enzymes involved in carcinogen metabolism; (ii) increased expression of nitric oxide synthase, xanthine oxidase and various protein kinases; (iii) the formation of smoke-related DNA adducts in several tissues; and (iv) the presence of urinary biomarkers of exposure to tobacco smoke.

In adult experimental animals, sidestream tobacco smoke has been found to produce changes that are similar to those observed with exposure of humans to secondhand tobacco smoke. These include inflammatory changes in the airways and accelerated formation of arteriosclerotic plaques. Although the changes are often comparatively minor and require exposure to rather elevated concentrations of sidestream smoke, they support the results of human epidemiological studies. During pre- and postnatal exposure, sidestream smoke produces intrauterine growth retardation, changes the pattern of metabolic enzymes in the developing lung, and gives rise to hyperplasia of the pulmonary neuroendocrine cell population. In addition, it adversely affects pulmonary compliance and airway responsiveness to pharmacological challenges.

In humans, involuntary smoking is associated with increased concentrations of mutagens in urine. Some studies have shown a correlation of urinary mutagenicity with concentrations of urinary cotinine. Increased levels of sister chromatid exchanges have not been observed in involuntary smokers; however, there is some indication of elevated levels in exposed children. Lung tumours from nonsmokers exposed to tobacco smoke contain *TP53* and *KRAS* mutations that are similar to those found in tumours from smokers. The genotoxicity of sidestream smoke, 'environmental' tobacco smoke, sidestream smoke condensate or a mixture of sidestream and mainstream smoke condensates has been demonstrated in experimental systems *in vitro* and *in vivo*.

5.5 Evaluation

There is *sufficient evidence* that involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) causes lung cancer in humans.

There is *limited evidence* in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke.

There is *sufficient evidence* in experimental animals for the carcinogenicity of sidestream smoke condensates.

In addition, the Working Group noted that there are published reports on possible carcinogenic effects of secondhand tobacco smoke in household pet dogs.

Overall evaluation

Involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble.