

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 $0.2 \mu\text{m}$ ([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 $910\text{--}920^\circ\text{C}$ 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'-Nitrosoornicotine (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](#)).

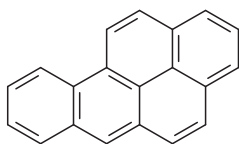
In summary, cigarette smoke is an exceedingly complex mixture which contains over 5300

compounds including multiple toxicants and carcinogens.

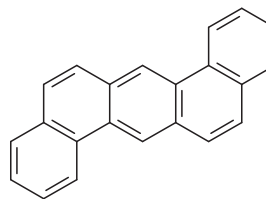
1.2.2 Smoke from other tobacco products

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](#)).

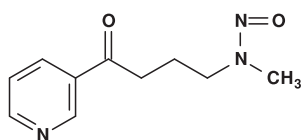
Fig. 1.1 Structures of some representative tobacco smoke carcinogens



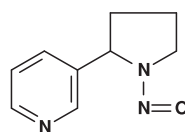
benzo[a]pyrene (BaP)



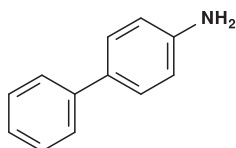
dibenz[a,h]anthracene



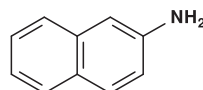
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)



N'-nitrososornicotine (NNN)



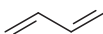
4-aminobiphenyl



2-naphtylamine



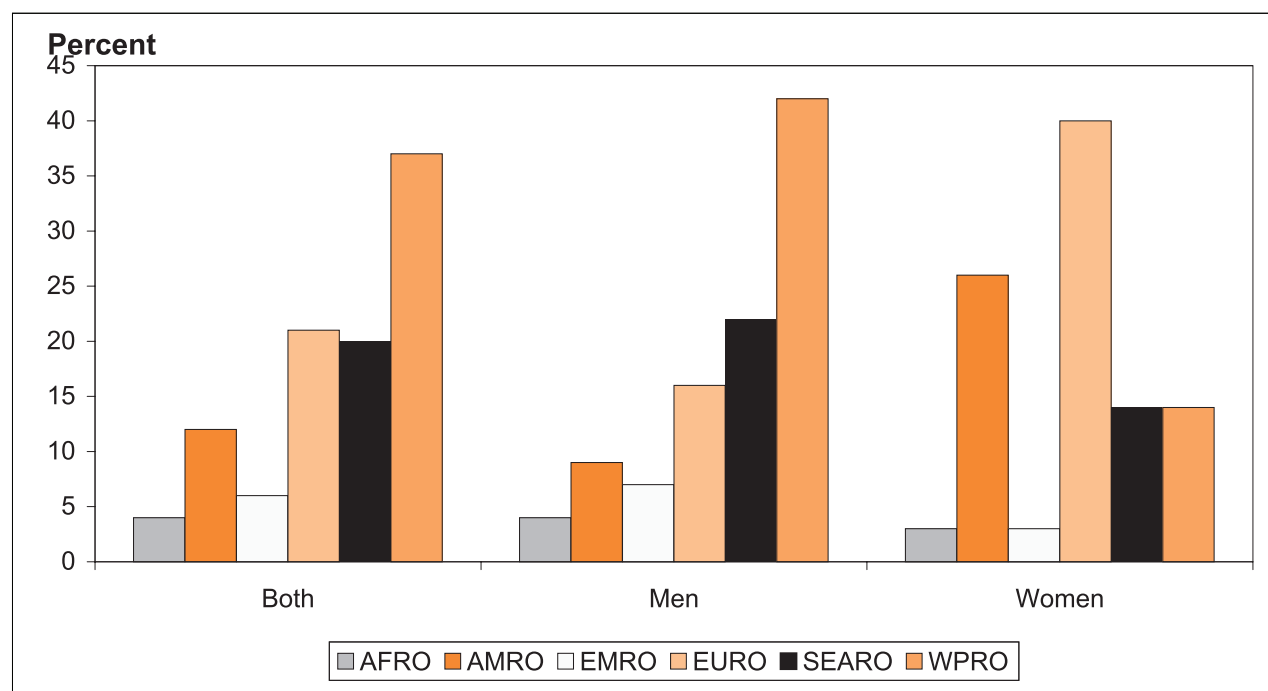
benzene



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](http://www.who.int/2011)). The six WHO regions are: EMRO, Eastern Mediterranean Region; EURO, European

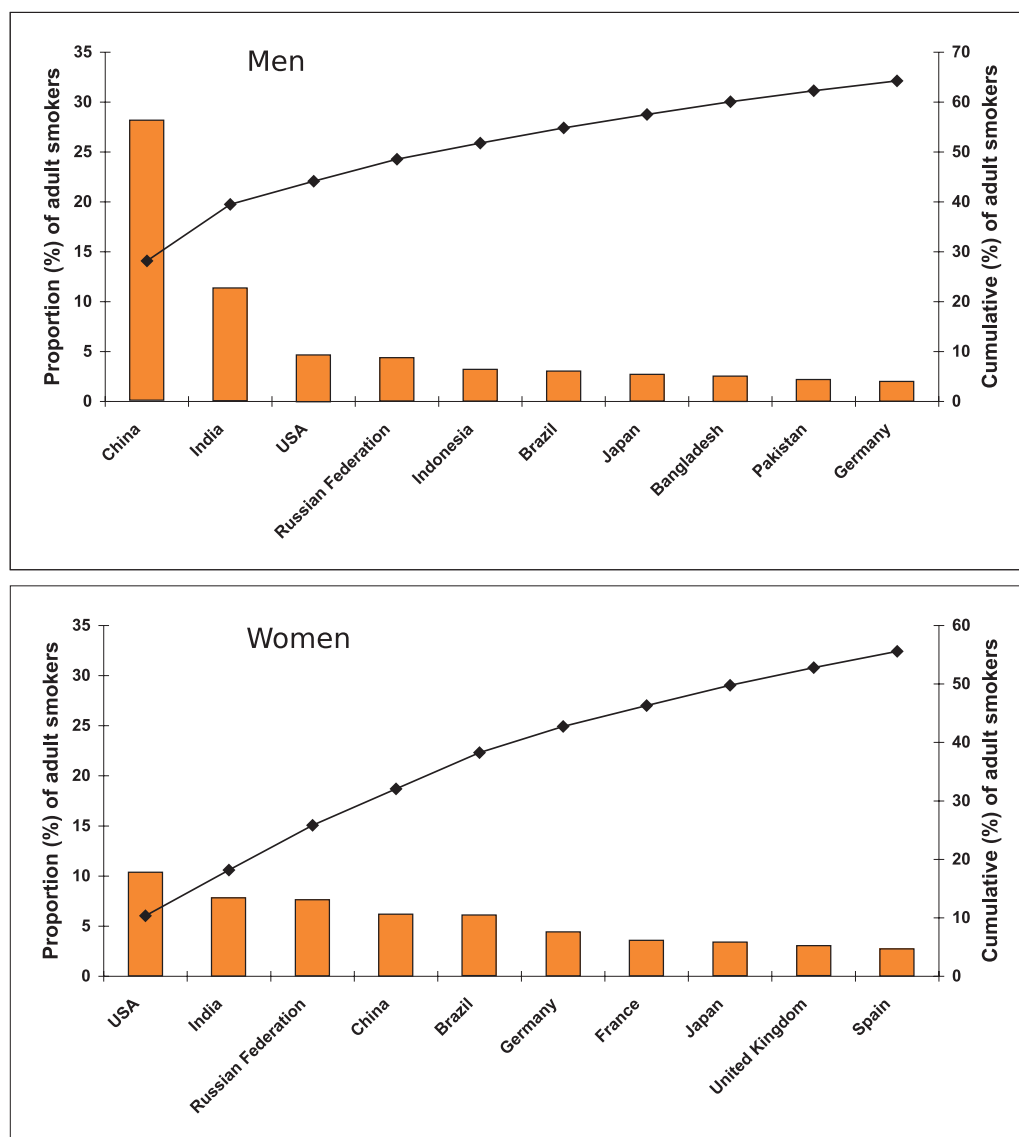
Region; AFRO, African Region; WPRO, Western Pacific Region; SEARO, South East Asian Region; AMRO, Region of the Americas. A listing of the countries in each region can be viewed at <http://www.who.int/about/structure/en/index.html>.

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).

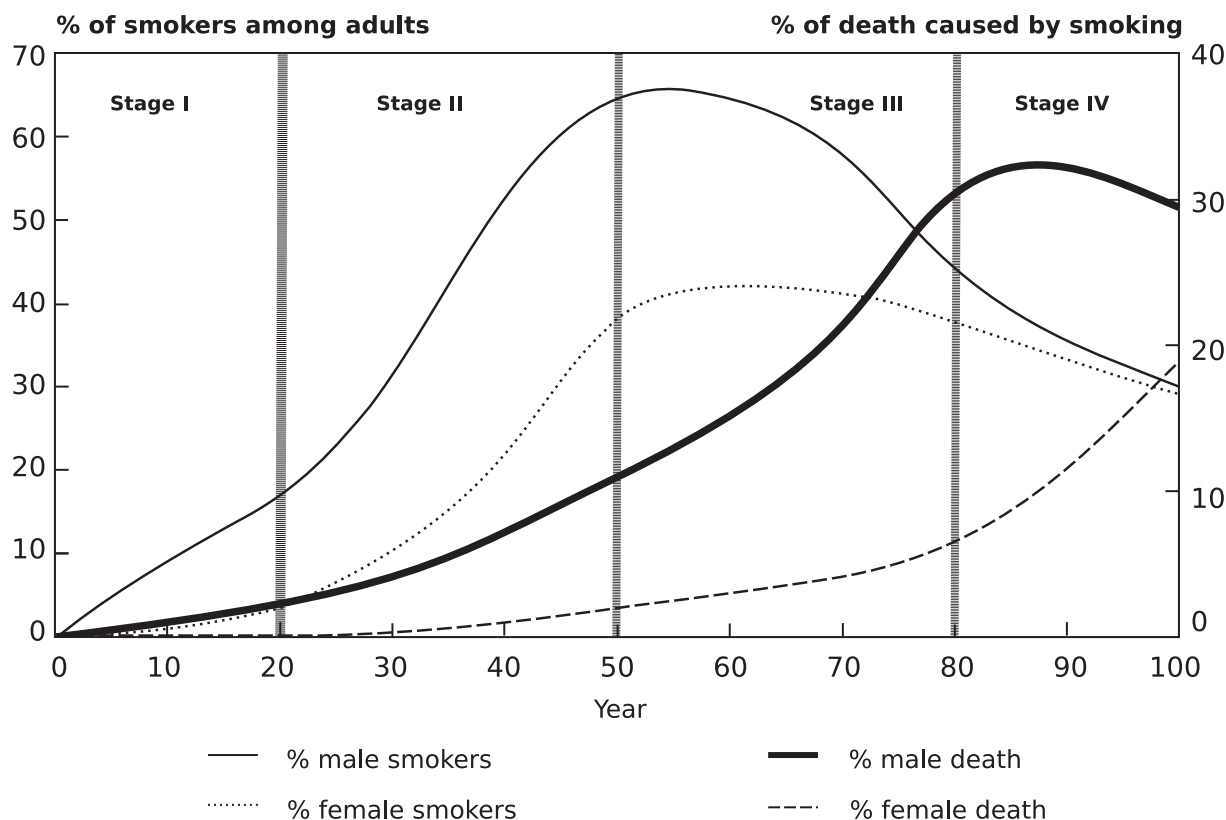
Stage 1 is characterized by low smoking prevalence in men (less than 15%) and very low in women (less than 10%). Death and disease from smoking are not apparent in this phase, as nearly all health effects from smoking are related to past smoking habits and their cumulative effects rather than current 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

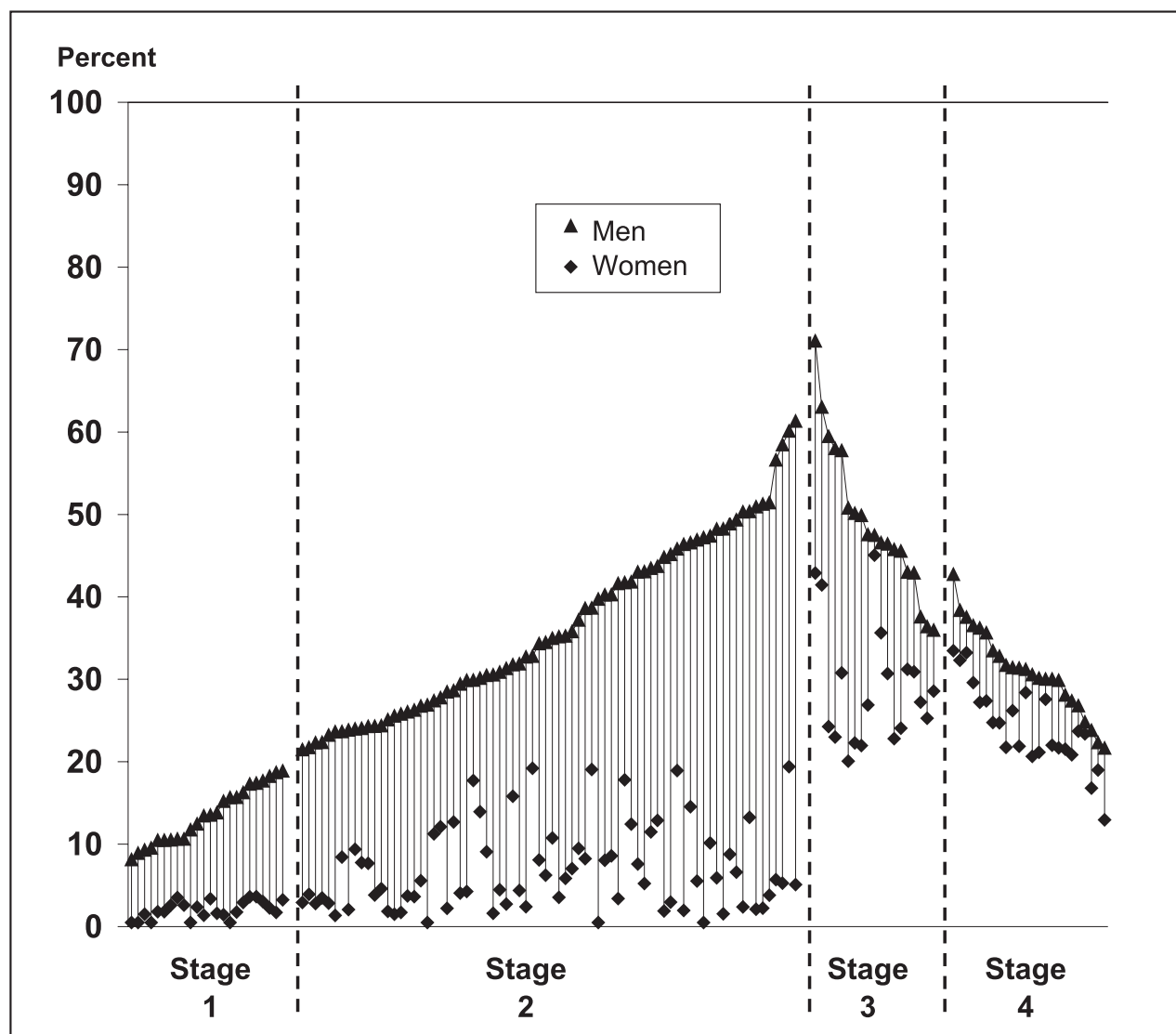
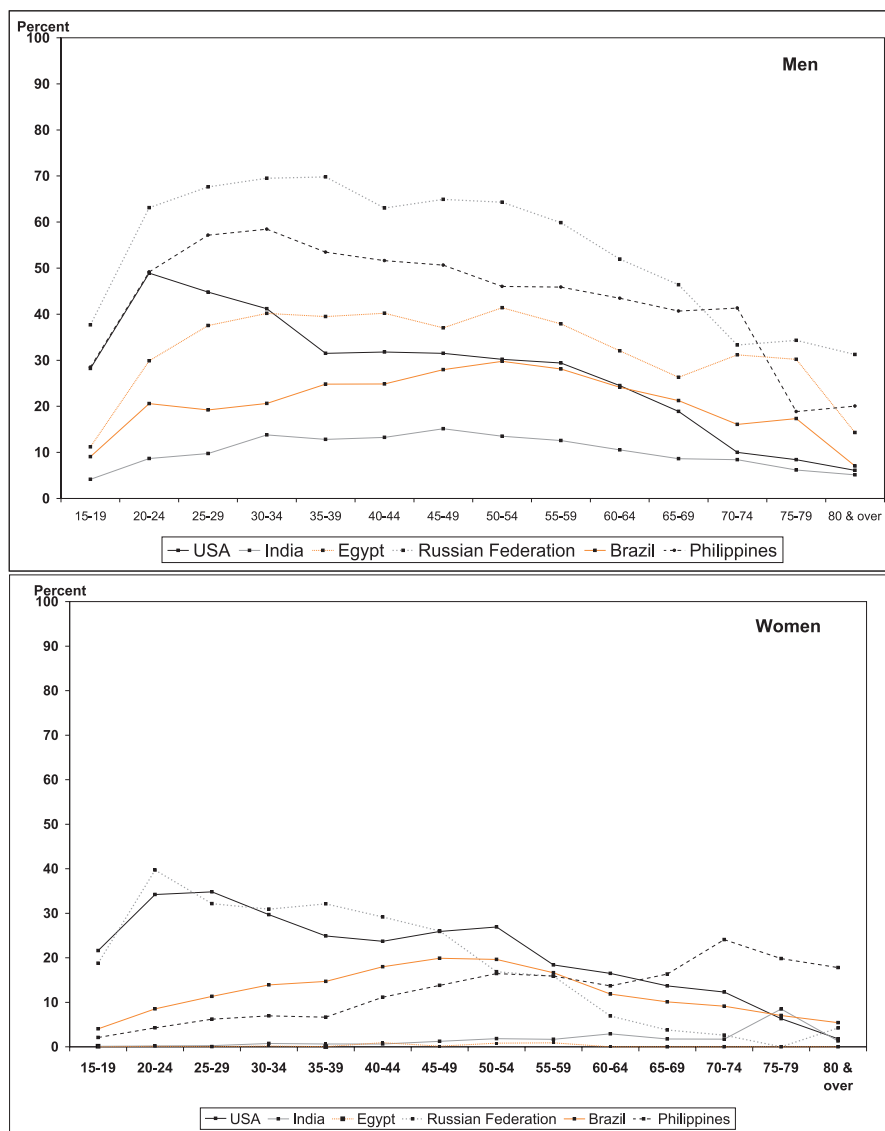


Fig. 1.6 Age-specific rates of smoking prevalence, in men and women in 2009

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 multi-lateral evidence-based treaty on tobacco control

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

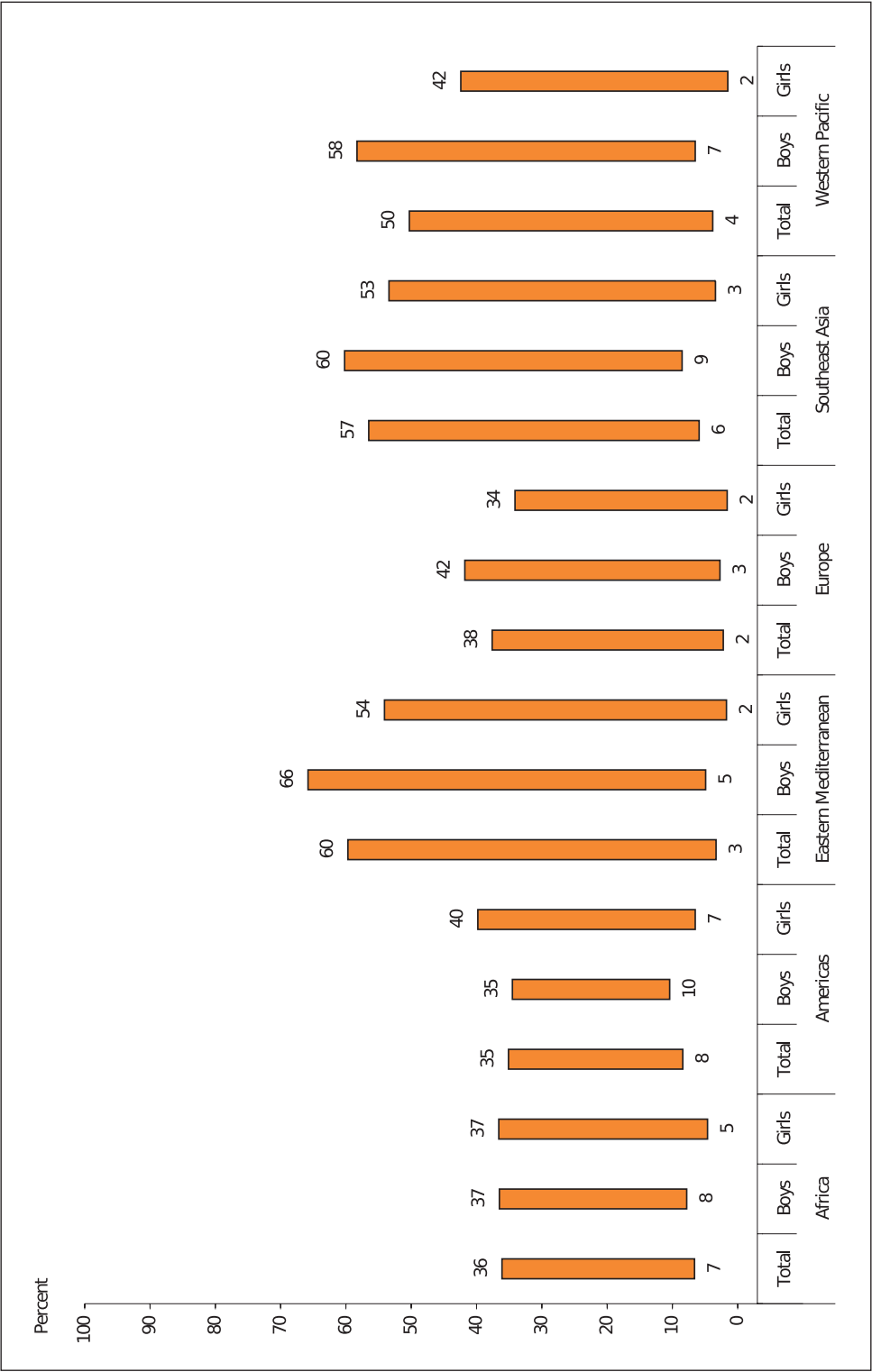
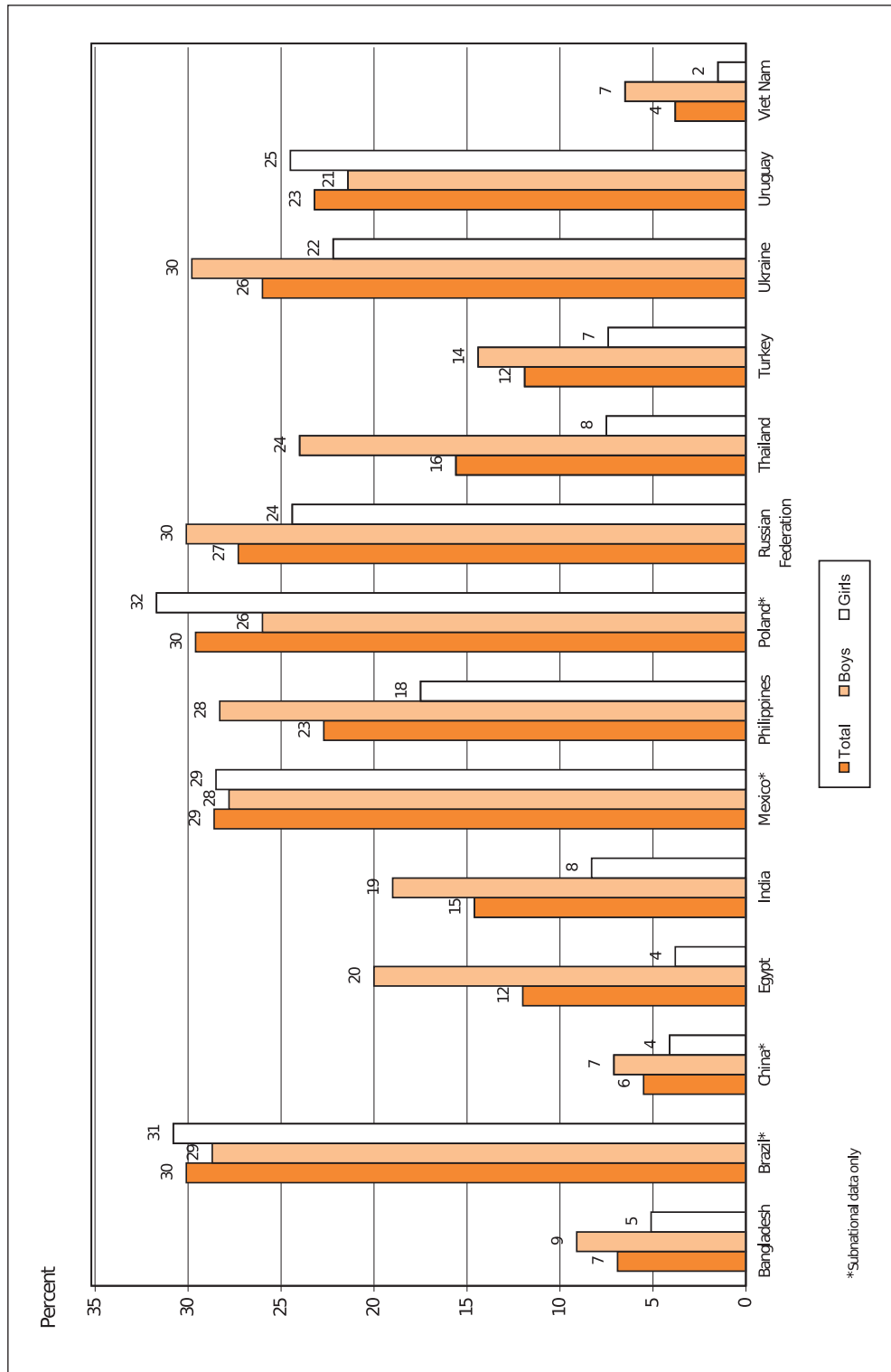


Fig. 1.8 Range of prevalence of current tobacco use in youth, 2005–2009, by WHO region



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 polycyclic 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

Ile⁴⁶²Val was associated with lung cancer susceptibility among Caucasians or African Americans. Among Caucasians, however, CYP1B1 Leu⁴³² 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 Leu⁴³² 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 (rs2909430), 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/m³. The absolute risks of lung cancer by age 75 years at radon concentrations of 0, 100, and 400 Bq/m³ 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 CYP1A1*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 ($\alpha(1)$ ATD) is one of the most common genetic disorders, especially among European descendants. Recent results suggest that $\alpha(1)$ 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/mm³), 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 sino-nasal 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. Friberg *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; Friberg *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 under-report 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 hepatitis 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 ([Kiemenev 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 ([Linnet 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 ([McDivitt 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 Malmö, 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 progesterone 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 or 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](#); [Loerbroeks 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 (Ile¹⁴³Val) 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) reviewed 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 life-style 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, socio-economic 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 aerodigestive 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 B6C3F₁

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/m³ 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	Alveolar adenocarcinomas: M–4/100 (alveolar adenocarcinoma) Controls–0/100 F–4/100 (alveolar adenocarcinoma) 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) _{F₁} (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	
			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	
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 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 <i>et al.</i> (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 Lung AdC: 7/38 (18%) Controls–0/38 Kidney A: 6/16 (16%) (F only) Controls–0/21 Liver carcinomas: 2/16 (5%) (F only) Controls–0/21	$P < 0.001$ $P < 0.01$ $P < 0.01$	
Rats, Wistar (F) Davis <i>et al.</i> (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 <i>et al.</i> (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 alveolar C) Controls–3/93 (3%) Subcutaneous sarcomas at forelimb ulceration sites: 21/80 (26%) Controls–0/93	$P < 0.05$ $P < 0.05$	
Rats, CDF (F344)/CrIBR (M, F) Finch <i>et al.</i> (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%) F: LCS–4/145 (3%) HCS–6/83 (7%) Filtered air–0/113	$P < 0.05$ $P < 0.05$	

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
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%) Lung AdC– LCS 1/178 (1%) HCS 5/82 (6%) Controls 3/118 (3%) All lung tumours– LCS 4/178 (2%) HCS 7/82 (8%) Controls 4/118 Nasal cavity (all tumour types)– LCS 1/178 (1%) HCS 5/82 (6%) Controls 1/118 (1%) F: Lung A– LCS 7/175 (6%) HCS 7/81 (9%) Sham-exposed controls 0/119 AdC– LCS 4/175 (2%) HCS 4/81 (5%) Controls 0/119 All lung tumours– LCS 10/175 (6%) HCS 11/81 (13%) Controls 0/119 Nasal cavity (all tumour types)– LCS 0/175 HCS 3/81 Controls 0/119	NS NS NS; trend, $P = 0.055$ $P = 0.032$ (HCS); trend, $P = 0.010$ NS (LCS); $P < 0.001$ (HCS) NS $P = 0.023$ (LCS); $P = 0.001$ (HCS) $P = 0.020$ (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. (1972)	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. (1972)	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%		
	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) Bernfield 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 ₂ O 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)/CrIBR (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 <i>et al.</i> (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 <i>et al.</i> (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)	<i>P</i> < 0.01 <i>P</i> < 0.01
Syrian golden (M) Harada <i>et al.</i> (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)	<i>P</i> < 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/m³ (LCS and HCS groups, respectively). At 12 weeks, rats were removed from smoke chambers and exposed nose-only to plutonium oxide (²³⁹PuO₂) 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 ²³⁹PuO₂ were higher than those in animals exposed to ²³⁹PuO₂, 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 IR4F 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: 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 IR4F 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

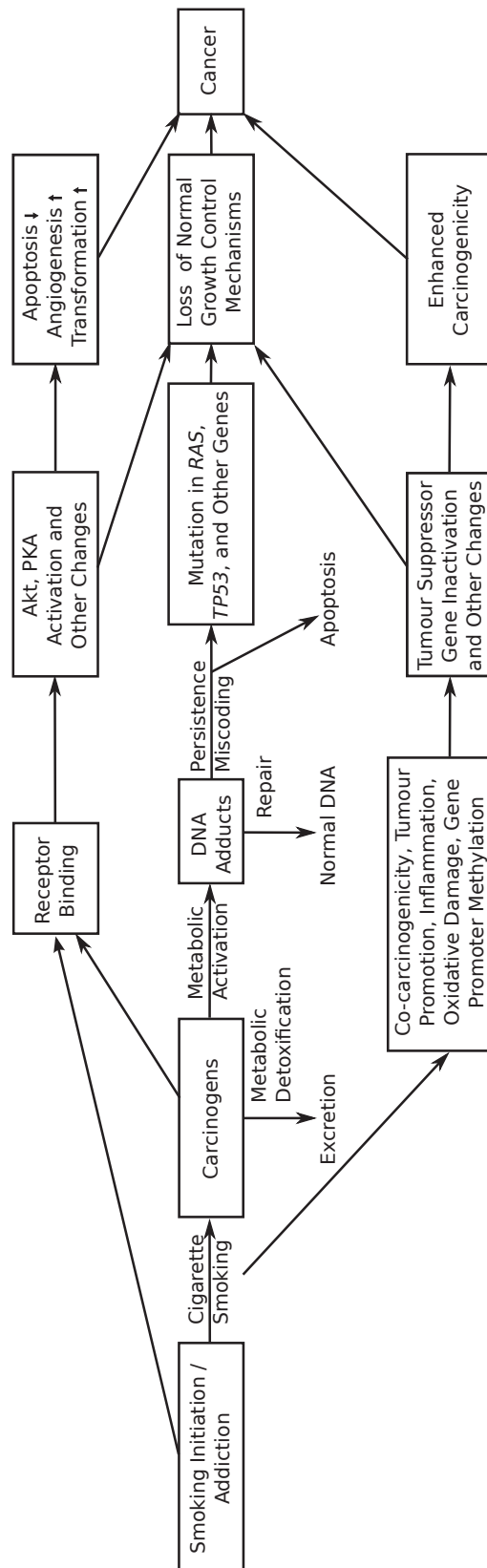
A conceptual model for understanding mechanisms by which tobacco smoke causes cancer is shown in Fig. 4.1 ([Hecht, 1999, 2003](#)). This model also applies to smokeless tobacco and other forms of smoked tobacco and, in theory, to second-hand tobacco smoke since it contains all of the same carcinogens 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.

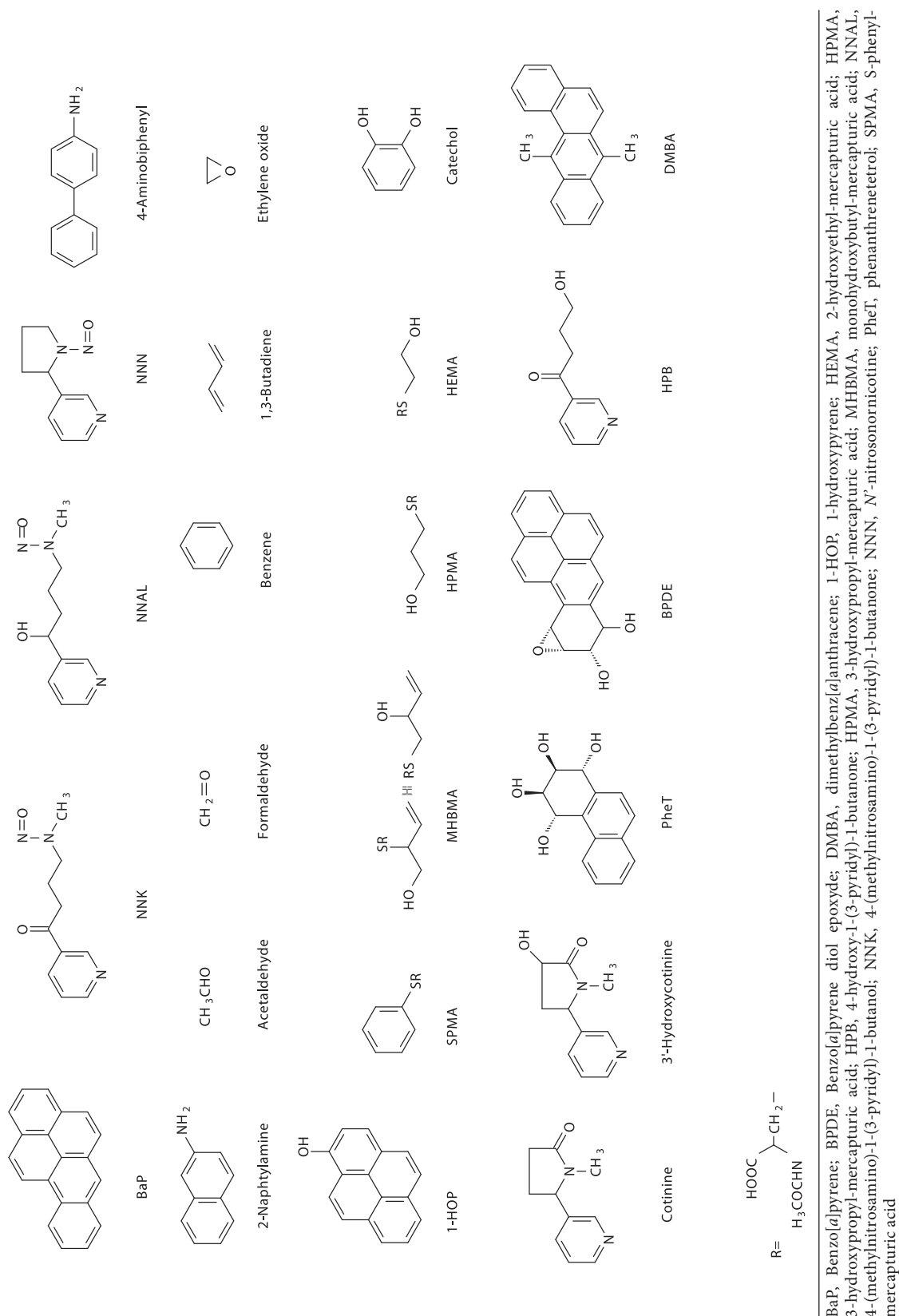
Numerous studies demonstrate the uptake of tobacco smoke carcinogens and toxicants by smokers, and showed higher levels of their metabolites in urine and blood of smokers than non-smokers (Sections 4.1.1 and 4.1.2). There are substantial differences in carcinogen exposure among people because of the 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



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'''- P¹, P³-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

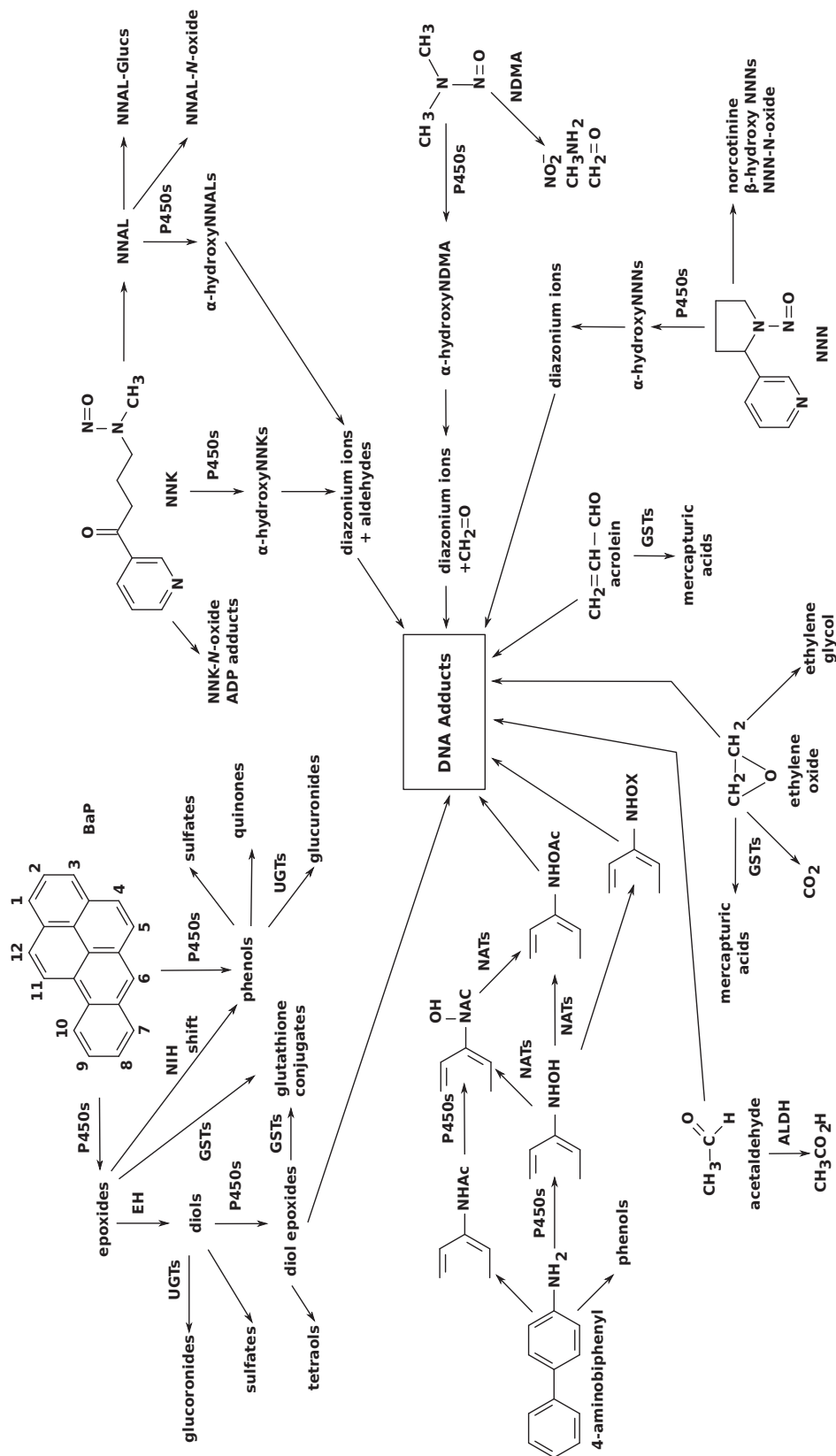
Serum and saliva metabolites have been used as biomarkers much less often than urine metabolites. The most frequently measured tobacco smoke toxicant in serum and saliva is cotinine, documented as a useful biomarker of cigarette smoking in many studies (Lee, 1999; Hukkanen *et al.*, 2005). Total NNAL 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.

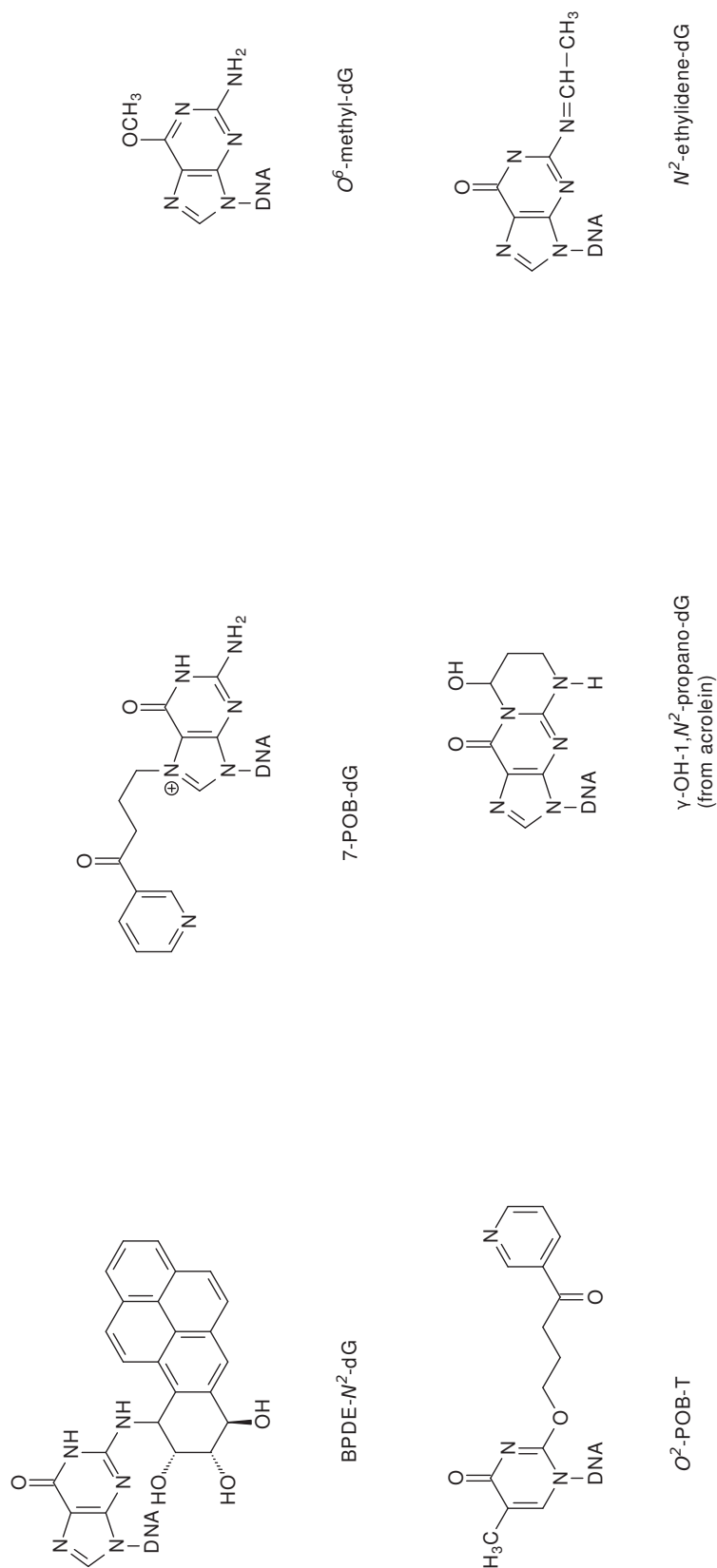
The structures of DNA adducts of tobacco smoke carcinogens have been characterized in detail, but a complete description of these structures is beyond the scope of this section. Selected DNA adduct structures are shown in Fig. 4.4. A major DNA adduct of BaP results from *trans*- addition of the benzo[*a*]pyrene 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-butanone; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosomethyl-1-butanone; 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, 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 ofamol 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

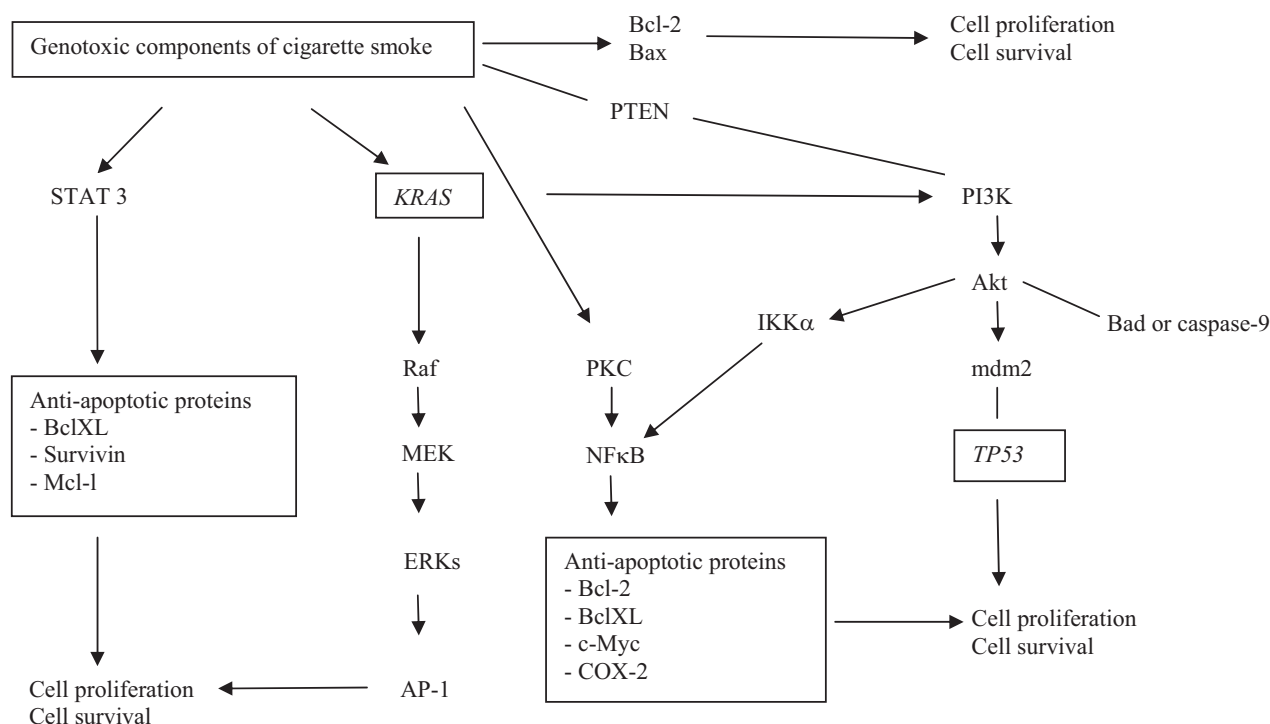
proteins, superoxide dismutase, glutathione transferase, heme oxygenase, *CYP* genes (*1A2*, *1A1* and *1B1*), interleukins and chemokines.

[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- κ B*, 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 (PGE₂) 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; Ile⁴⁶²Val). 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; Thr⁴⁶¹Asn) ([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*; *Ile¹⁰⁵Val*), in exon 6 (*Ala¹¹⁴Val*), 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 Ile¹⁰⁵Val* polymorphism; but the pooled analysis suggested an overall statistically significant mild association between lung cancer and homozygosity or heterozygosity for the *Val¹⁰⁵* 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 polymorphisms 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 biomarkers 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](#); [Kuljucka-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](#); [Kuljukkka-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* Ile⁴⁶²Val 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 ([Kuljukkka-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 (Viezzler *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* (Ile⁴⁶²Val) 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 ³²P-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, genotoxins, 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 haemoglobin 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 etiological 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 (*Thr⁴⁶¹Asn, 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) Asp¹⁴⁸Glu, 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 *PI6^{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

haematopoietic 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 (16 α -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 16 α -OHE1 or to 2-OHE1 or to 4-OHE1. 16 α -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 16 α -hydroxylation pathway. However, the ratio of urinary 2-OHE1:16 α -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 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 (*K_m*) 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 ([Tuyens 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 O⁶-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 accessory 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).

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Harm reduction in nicotine addiction

Helping people who can't quit

A report by the Tobacco Advisory Group of the Royal College
of Physicians, October 2007



Royal College
of Physicians

Setting higher medical standards

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Foreword

I am proud that the Royal College of Physicians remains at the forefront of policy development in the field of smoking 45 years after our influential intervention of 1962. John Britton and his team have produced another stimulating and radical report that faces up to the issue of nicotine addiction and challenges the current position on alternative nicotine products. I congratulate them on this comprehensive, carefully argued report and commend it to you.

October 2007

Ian Gilmore
President, Royal College of Physicians

Preface

Cigarette smoking is powerfully addictive, and caused 100 million deaths in the 20th century. In the 21st century, if smoking trends persist as expected, one billion people will die from smoking tobacco. All of these deaths are preventable.

Current national and international tobacco control policies focus, quite rightly, on measures that help to prevent people from starting smoking, and help existing smokers to quit. However, once established, smoking is a very difficult addiction to break, and millions of people smoking today will never succeed. At present rates of progress it will take over two decades for the prevalence of smoking in the UK to halve from current levels, such that by 2025 there will probably still be over five million smokers in the UK. Preventing harm to the health of these smokers is a vital priority in this country, and in all countries where the smoking epidemic is established.

The Royal College of Physicians first called for radical policies to reduce the prevalence of smoking in 1962. Several of the policies we recommended then have since become established international practice. However, those measures, then and now, do not address the problem of smokers who cannot quit. The majority of the 150 million deaths from smoking expected worldwide in the next 20 years will occur in people who are smoking today. These people need help.

In this report we make the case for harm reduction strategies to protect smokers. We demonstrate that smokers smoke predominantly for nicotine, that nicotine itself is not especially hazardous, and that if nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives could be saved. We also argue that the regulatory systems that currently govern nicotine products in most countries, including the UK, actively discourage the development, marketing and promotion of significantly safer nicotine products to smokers.

Harm reduction is a fundamental component of many aspects of medicine and, indeed, everyday life, yet for some reason effective harm reduction principles have not been applied to tobacco smoking. This report makes the case for radical reform of the way that nicotine products are regulated and used in society. The ideas we present are controversial, and challenge many current and entrenched views in medicine and public health. They also have the potential to save millions of lives. They deserve serious consideration.

October 2007

John Britton
Chair, Tobacco Advisory Group of the Royal College of Physicians

1 | Use of tobacco in society

- 1.1 Introduction
- 1.2 The history of tobacco use
- 1.3 The smoking epidemic
- 1.4 The health impacts of tobacco smoking
- 1.5 Conclusions

1.1 Introduction

An estimated 1.3 billion people worldwide currently smoke tobacco, mostly in the form of cigarettes.¹ The number of smokers is growing, particularly in middle- and low-income countries where cigarettes are marketed aggressively by some of the world's most powerful companies, and is expected to reach 1.6 billion by 2025.² The health impacts of this inexorable spread in smoking are daunting. Smoking is already the leading cause of premature death in the developed world and is rapidly reaching that status in the developing world.³

Historically, tobacco has been used in a wider variety of forms, including smokeless tobacco. Use of smokeless tobacco has remained widespread in parts of the world and, in some countries, particularly Sweden and the United States, is once again increasing. This chapter reviews the history and diversity of tobacco use over time and place, examines the global spread of the cigarette epidemic, and reviews briefly the health impacts of different forms of tobacco use.

1.2 The history of tobacco use

1.2.1 Origins

Although historical accounts of tobacco use vary,^{4–6} the fact that tobacco is considered so powerful in native American culture that it is thought to play a part in creation itself suggests that tobacco use is an ancient activity in the Americas.⁷ The tobacco plant is indigenous to the American continent. By 15000 BC humans there may have begun to pick and use wild tobacco species, and smoked tobacco as part of ceremonial practices. By 5000 BC it is likely that

tobacco cultivation began simultaneously with maize-based agriculture in central Mexico.⁵ Thence, tobacco use and cultivation spread northwards – the first archaeological evidence for tobacco use, found in New Mexico, dates to 1400 BC – and smoking, originally limited to medicinal and ceremonial rituals, became adopted by wider society.^{5,6}

By the time the Europeans arrived on the continent, tobacco use among indigenous Americans throughout North and South America was widespread and a core element of virtually all Native American cultures.^{5,8} Christopher Columbus was presented with tobacco leaves on his arrival in October 1492 and he and his fellow explorers provide the first written documentation of tobacco use.⁵ Records suggest that tobacco was being used in a variety of forms: it was smoked, chewed, inhaled as a powder, drunk as a tea, inserted as a liquid enema and consumed as a jelly. The natives of North America, for example, smoked tobacco with a pipe, while the Mayas mainly used crude cigars and cigarettes.^{4,7}

1.2.2 The global spread of tobacco use begins

A few years after Columbus' arrival in America, tobacco leaf and seeds were brought back to Spain and Portugal. Tobacco use then gradually spread throughout Europe, Russia and the Middle East.^{4,9} In 1560, Jean Nicot, the French ambassador to the Portuguese court (after whom nicotine was named), introduced tobacco and smoking to the French court as a medicine. Between 1530 and 1600, Spanish and Portuguese traders introduced tobacco to China, Japan, the Philippines, India and Africa.¹⁰ Oceania was the last continent reached by tobacco – Captain Cook arrived smoking a pipe in 1769 and was promptly doused with water lest he be a demon.¹⁰

The predominant mode of tobacco use has changed considerably over time. In Europe, for example, pipe use predominated throughout the 17th century, to be replaced by snuff at the turn of the 18th century.¹¹ By the end of the 18th century, snuff taking was in decline and a revival in smoking, initially in the form of cigars, occurred, although largely among the wealthier classes.^{8,11} Spain became a centre for cigar manufacture in the 1600s, and the European cigarette probably originated in the practice of beggars who rolled fragments of tobacco from used cigars in paper to make *papaletes*.⁴ Philip Morris, which is now the world's largest privately run cigarette company, began life in 1847 as a tobacconist on Bond Street in London, selling hand-rolled Turkish cigarettes. The Crimean War (1853–6) popularised cigarette smoking among British soldiers who copied the art of hand-rolling tobacco from their Turkish allies. The first factories making hand-rolled cigarettes opened in the UK in the 1850s.

In the USA also, cigars, snuff and chewing tobacco were popular before cigarettes, which were first made from scraps left over after the production of other tobacco products. Cigarettes did not gain widespread popularity until after the American Civil War (1861–5). The origins of the US tobacco companies reflect this pattern. Lorillard was established in 1760 to process tobacco, cigars, and snuff. The Liggett & Myers Tobacco Company developed from a family snuff business established in the early 1800s. Twelve years after its official formation in 1873, it became the largest manufacturer of plug chewing tobacco in the world. The RJ Reynolds Tobacco Company was established in 1875 to produce chewing tobacco.

Elsewhere, the traditional form of tobacco use, until cigarettes were introduced, was often pipe smoking.⁵ In Japan, although cigar smoking was introduced first via the Portuguese, smoking in long thin pipes (*kiseru*), probably introduced by the Dutch, became far more popular and came to accompany the tea ceremony.⁵ Cigarettes were only introduced after the Meiji Restoration of 1868.¹² In China, tobacco pipe smoking was also traditional and, although initially seen as taboo (with various unsuccessful prohibitions ordered), it became so widely accepted by the 18th century that even women and children smoked.⁵

1.2.3 Mass production of cigarettes and the launch of the smoking epidemic

The nature and scale of tobacco use changed irrevocably in the early 1880s with the introduction of the Bonsack machine (a cigarette-rolling machine to replace hand rolling) and the mass manufacture of cigarettes.¹¹ Compared with traditional smoking methods, manufactured cigarettes were relatively clean, easy to use and increasingly affordable.¹³ From that point on, cigarettes, and white cigarettes in particular, became the dominant form of tobacco used, and cigarette smoking spread globally on a massive scale.² The mass manufacture of cigarettes stimulated cigarette marketing, initially to overcome resistance to machine-made goods but subsequently to create demand for the vastly increased production.¹⁴ Competition between the tobacco companies in the US and UK markets escalated, prompting the first series of tobacco company mergers and the launch of the global cigarette manufacturers, known today as the transnational tobacco companies.¹⁵ The smoking epidemic had begun.

1.2.4 Continuing diversity in tobacco use

By the end of the 19th century, manufactured cigarettes and various types of hand-rolled cigarette accounted for up to 85% of all tobacco consumed worldwide.²

However, in contrast to the almost exclusive use of white cigarettes in the West, tobacco was, and continues to be, smoked in many different ways elsewhere. Bidis, which comprise tobacco hand-rolled in a non-tobacco leaf, are commonly used across much of South East Asia, and in India outsell cigarettes by seven to one. The Indonesian market is dominated by kreteks, cigarettes in which tobacco is blended with cloves, producing an anaesthetic agent (eugenol) which leads to deeper inhalation and high tar yields.¹⁶ The water pipe (shisha, hookah or hubbly bubbly) is commonly used to smoke tobacco in many countries of North Africa, the Mediterranean and parts of Asia, and clay pipes (suipa, chilum or hookli) are used in South East Asia.^{10,16} These and other methods of tobacco use are discussed in more detail in Chapter 5. Even manufactured cigarettes vary widely in design, for example in the use of filters, paper and additives. They also vary in the kind of tobacco used and how it is processed – factors that in turn influence the physiochemical nature of the smoke. In the United Kingdom, for example, flue-cured tobacco is preferred, while elsewhere in Europe a mixture of air-cured and flue-cured tobacco predominates.¹⁷

Traditional forms of smokeless tobacco use do persist, leading to considerable national and regional variation in tobacco habits. Smokeless tobacco use is widespread across much of South, South East and Central Asia, North Africa and the Middle East. In Mumbai, India, for example, 56% of women chew tobacco.¹⁰ There is a wide variation in the type of tobacco used and in the ingredients added (see Box 1.1).^{10,18,19}

In developed countries, use of smokeless tobacco is far less common. In the UK, for example, smokeless tobacco is used almost exclusively by minority groups of South Asian origin, among whom usage is thought to vary according to community and gender from 27% to 98%.²⁰ In the United States, an estimated 3% of adults use smokeless tobacco (including chewing tobacco and snuff) compared with about 20% who smoke cigarettes,^{21,22} though use of smokeless tobacco has increased over recent years.²³

An exception to the dominance of the cigarette in developed countries is Sweden where snus, a moist snuff that can be rolled by the user or bought in soft porous packs which are put under the upper lip, is used widely. Snus has been used in Sweden since 1637, and Sweden has the highest rate of per capita consumption of snuff in the world.²⁴ The high rates of snus use among Swedish men, combined with the fact that male smoking and tobacco-related mortality rates in Sweden are the lowest in the world and have been for some time,²⁵ has led to a growing interest in the role that less harmful smokeless tobacco products could play in smoking cessation and harm reduction as part of a broad approach to the provision and regulation of alternative sources of nicotine.^{26,27} However,

Box 1.1 Forms of tobacco use.

Smoking tobacco

Manufactured cigarettes Machine-manufactured cigarettes containing shredded or reconstituted tobacco processed with hundreds of chemicals and wrapped in paper, usually with a filter.

Bidis Small, thin, hand-rolled cigarettes containing small volumes of tobacco hand-wrapped in non-tobacco leaves, usually dried temburni leaves. Common in South Asia, particularly India.

Kreteks Clove-flavoured cigarettes commonly consumed in Indonesia.

Cigars Air-cured and fermented tobaccos within a tobacco leaf wrapper. Vary in size from cigarette-sized cigarillos to much larger versions. Vary in form regionally, with some forms smoked with the ignited end placed inside the mouth.

Pipes Tobacco placed in the bowl of the pipe and inhaled through the stem, sometimes through water.

Smokeless tobacco

Often referred to as spit tobacco, spitting tobacco or swallow tobacco. Produced in two main forms – chewing tobacco and snuff:

Chewing tobacco Taken orally by placing a pinch of the mixture in the mouth between the gum and cheek and gently sucking and chewing. A wide variety of regional forms exists with use most common in Asia, the Middle East and the US (and migrant groups from these regions). Forms include: *gutkha*, *khaini*, *mawa*, *mishri*, *pan masala*, *qiwam*, *zarda* (Asia), *shammah* and *zarda* (Middle East), *loose-leaf*, *moist plug*, *plug and twist-roll* (US). The tobacco is often mixed with a variety of other compounds including spices or sweeteners, lime (calcium hydroxide) and other psychoactive substances such as areca nut.

Moist snuff Ground tobacco taken orally and held in the mouth between cheek and gum. Increasingly pre-packaged into small paper or cloth packets. Forms include *snus* (Sweden and Norway), *nass* or *naswa* (central Asia and the Middle East) and *toombak* (Sudan). A variety of brands are available in the US including *Skoal*, *Skoal Bandits* and *Timber Wolf*.

Dry snuff Powered tobacco inhaled through the nose or held between the lip and gum or cheek. Once popular, its use is now in decline.

Adapted from the *Tobacco atlas*,¹⁰ Smokeless tobacco factsheets,¹⁸ and CDC factsheet.¹⁹

the supply of snus or other oral tobacco products that are designed to be sucked was prohibited in the European Union in the early 1990s, so, with the exception of some minority use in Sweden's neighbouring countries, this product is not used appreciably elsewhere in Europe. Smokeless products that are designed to be chewed, including those used by the South Asian community, remain legal.

1.3 The smoking epidemic

1.3.1 A conceptual model

The onset of mass manufacture of cigarettes precipitated the smoking epidemic. A four-stage model of the epidemic has been described, based on observations of trends in cigarette consumption and tobacco-related diseases in western countries with the longest history of cigarette use, namely the United Kingdom and the United States (Fig 1.1; Table 1.1).²⁸ The model describes the typical sequence of uptake of smoking in men and women, and the subsequent occurrence of the harmful consequences of smoking. The epidemic begins with a rise in male smoking, followed by a period of stable high rates and then gradual decline. The onset of female smoking typically occurs later but then follows a similar pattern. Tobacco-related mortality among men and women follows the rise and fall of smoking prevalence, but with a lag of about 30–40 years.



Fig 1.1 The four-stage evolution of the smoking epidemic. Reproduced from Lopez AD, Collishaw NE, Piha T. A descriptive model of the cigarette epidemic in developed countries. *Tob Control* 1994;3:242–7, with permission from the BMJ Publishing Group.²⁸

The delay between the onset of smoking and its health impacts is a key feature of the epidemic, and one that explains why historically there has been confusion about the health impacts of tobacco. Smoking kills through causing a wide range of diseases, principally cancers, vascular disease and chronic lung disease (see Chapter 6 for further discussion). The delay between the onset of smoking and the occurrence of disease varies at individual and population level and from one disease to another. Death rates from lung cancer in a population do not reach

Table 1.1. The four stages of the smoking epidemic.

	Male		Female		Cigarette consumption (per capita)	Tobacco control
	Smoking prevalence	Deaths from tobacco	Smoking prevalence	Deaths from tobacco		
Stage 1 (1–2 decades)	Comparatively low <15%, but increasing.	At the start, deaths from tobacco similar to non-smoking populations. By the end of this phase some male deaths attributable to tobacco.	Rare: 0–10%.	As in non-smoking populations.	Low: <500/adult (most consumed by men).	Tobacco control underdeveloped. Smoking becomes socially acceptable.
Stage 2 (2–3 decades)	Continues to increase rapidly, peaks at 50–80%. Relatively few ex-smokers. Smoking rates similar in different social classes and may be higher in upper classes.	By the end of this phase ~10% male deaths due to tobacco. Male lung cancer rates increase approximately 10-fold from 5 to 50 per 100,000.	Increases rapidly, but lags behind men by 1–2 decades.	Rise in lung cancer rates much less. May reach 8–10 per 100,000.	1,000–3,000 (majority consumed by men). Men: 2,000–4,000.	Tobacco control not well developed.

continued over

Table 1.1. The four stages of the smoking epidemic – continued.

	Male		Female		Cigarette consumption (per capita)	Tobacco control
	Smoking prevalence	Deaths from tobacco	Smoking prevalence	Deaths from tobacco		
Stage 3 (3 decades)	Plateaus at a high level, then starts to decline. Lower in middle and older age men who give up. Male and female prevalence rates become more similar. Declines in prevalence greater among better educated.	Rapid rise in smoking-related mortality (to approximately 30% deaths) and higher in middle age. By the end of this phase lung cancer rates peak at around 110–120 per 100,000.	Plateaus at a lower level than in men (max 35–45%) and often for prolonged period, then declines late in this phase. Marked age gradient with higher rates in young women. Declines in prevalence greater among better educated.	Still relatively low (5%), but rising. By the end of this phase lung cancer rates reach approximately 23–40 per 100,000.	Men: 3,000–4,000. Women: 1,000–2,000.	Tobacco control improves. Smoking becomes less socially acceptable. Conditions for enacting tobacco control measures become more favourable.
Stage 4	Continues to decline but slowly. Male prevalence might be around 33–55%. Social class differences persist.	Peak in smoking-related mortality at 30–35% of all deaths (40–45% in middle age) during the early part of this stage. About one decade later, mortality from tobacco will start to decline.	Continues to decline but slowly. Social differences persist.	Rising rapidly. Will peak at ~20–25% of all deaths 2–3 decades into this phase (approximately 2 decades after the male peak) and decline thereafter.		Continued change in social climate. Smoke-free legislation becomes more feasible.

Adapted from Lopez *et al* and reproduced with permission from the BMJ Publishing Group Ltd.²⁸

their maximum until 30–40 years after the peak in smoking prevalence, while deaths from vascular diseases will occur somewhat earlier.²⁸ Similarly, the excess risk of death from cardiovascular disease for an individual smoker declines quite quickly after quitting smoking, while the risk of lung cancer falls more slowly.^{28,29} The delayed occurrence of health impacts means that countries in the early stages of the epidemic may be able to prevent much of the future growth in tobacco-related disease if effective public health interventions are implemented immediately. However, in countries with long-established tobacco epidemics, or where prevalence has been growing for several decades, tobacco-related mortality can only be reduced in the short term if large numbers of current smokers quit.³⁰ Reducing uptake among young people will only reduce mortality many decades into the future.

Other trends suggested by the model include the one-to-two decade delay between the increase in male and female smoking and the changing social pattern of smoking. Smoking is initially more common among the upper classes – uptake of any ‘innovation’ being usually more rapid among wealthier people. However, as the better off quit in response to health promotion messages, this pattern reverses, resulting in considerable social inequalities in smoking habits and health in the later stages of the epidemic. This is discussed briefly below and described further in Chapter 10.

1.3.2 The smoking epidemic in the United Kingdom

In the UK, the smoking epidemic took hold from the start of the 20th century. Male smoking increased rapidly over the next 50 years,¹³ particularly during the two world wars, and by the late 1940s an estimated 65% of men were cigarette smokers. Male smoking prevalence then began to fall, and did so consistently until the early 1990s (Fig 1.2).³¹ Women began to smoke approximately 20 years after their male counterparts, once social barriers to female smoking had begun to be dismantled. The tobacco industry played a key role in this process by promoting smoking as a symbol of emancipation, assisted by social changes during the world wars.¹³ Female smoking then increased steadily, reaching a peak some 20 years later than male smoking in about the mid-1970s, and declined thereafter.

The UK is now in the later stages of the smoking epidemic model. Rates of smoking fell substantially through the 1970s and 1980s, particularly in men. Since the early 1990s, male and female smoking rates have been fairly similar. This pattern is typical of the late stages of the epidemic (though in some northern European countries female smoking is now more prevalent than male

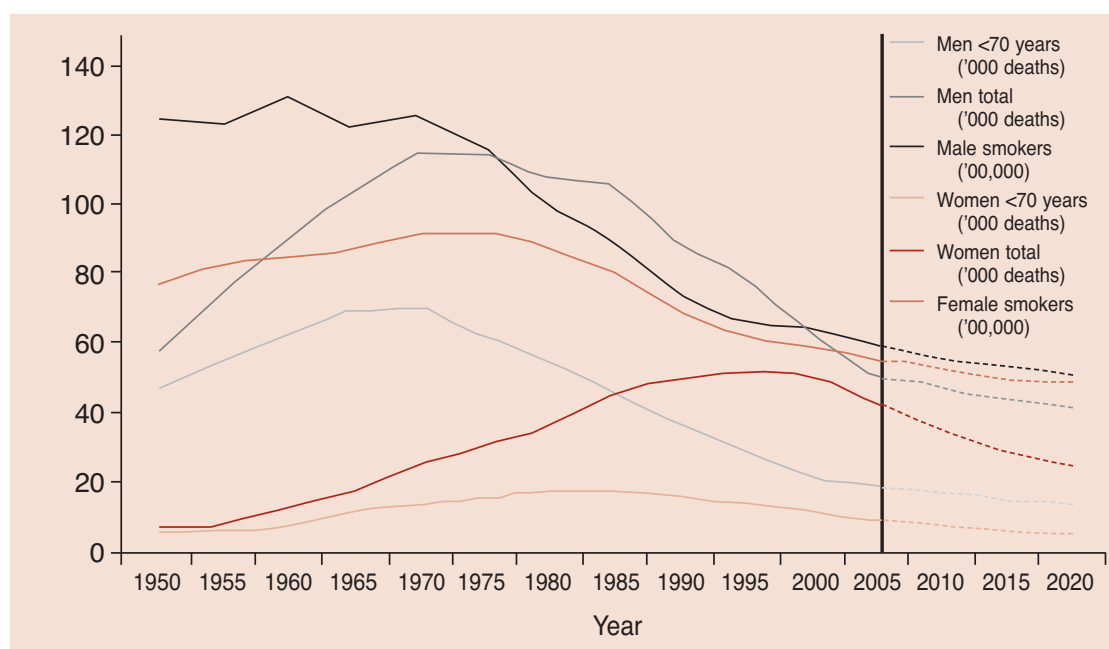


Fig 1.2 The UK smoking epidemic (projected data shown by dotted lines). Reproduced from West with permission.³¹

smoking). The rate of decline of smoking prevalence in the UK has since slowed considerably with little change through the 1990s.³² Detailed analysis shows that a significant decline of about 0.4% per year occurred between 1999 and 2002,³³ and the latest data (from the 2004/5 General Household Survey) again suggest a small decline in prevalence. Of adults in Britain aged 16 or over, 25% (26% men and 23% women) now smoke cigarettes (Fig 1.2).^{31,32}

Another key feature of this late stage of the epidemic is the social inequality in smoking and smoking-related health that emerges as smoking becomes increasingly entrenched among the least well off in society (see Chapter 10). In the UK, current smoking rates show an approximate two-fold variation between professional and working classes,^{33–35} though these figures hide a far greater disparity between the most and least deprived groups.³⁶ These gradients are among the largest in Europe.³⁷ Other differences in smoking behaviour between social groups include poorer smokers starting to smoke at a younger age, consuming more tobacco, and finding it harder to quit.^{36,38}

Mortality from tobacco, although still substantial (see Chapter 6), is also now declining in both men and women in the UK. Owing to the trends in smoking described above, the decline in male tobacco-related mortality occurred a few decades earlier than in women, in whom the decline has only recently begun.³⁶ Nevertheless, tobacco remains the leading cause of morbidity and mortality in the UK, recently estimated to cause 106,000 deaths each year, or about one in six of all deaths.^{38–42} Moreover, owing to the social gradients in smoking habits

described above, smoking is the leading cause of health inequalities, thought to account for half of the difference in survival to 70 years of age between the professional and unskilled manual social classes.³⁸

1.3.3 The smoking epidemic elsewhere

The smoking epidemic in other northern and western European countries, in North America and in Australasia is also relatively advanced, but elsewhere is typically at an earlier stage. Some countries in sub-Saharan Africa are still at stage one of the epidemic, with low rates of cigarette smoking limited largely to men, and with little or no increase in tobacco-related diseases yet evident.¹ Some countries in Asia, North Africa and Latin America fit stage two of the epidemic, characterised by higher rates of male smoking and an increase in tobacco-related diseases in men beginning to occur, while smoking among women remains a relatively new phenomenon. Other countries in these regions are moving towards stage three of the epidemic – also typical of some countries in southern and eastern Europe – where male smoking rates are very high but are starting to fall, female smoking rates are close to reaching their peak, but tobacco-related deaths continue to rise in both genders.¹

Not all countries fit the smoking epidemic model.¹ For example, in the countries of the former Soviet Union, tobacco smoking in men began around the end of the 19th century, at the same time as in the UK. However, the epidemic subsequently developed slightly differently, probably because cigarettes were produced and sold by a state monopoly rather than by the privately run transnational tobacco companies operating in the West. Thus, tobacco marketing was unknown, and smoking among women remained socially less acceptable and far less common. However, since the collapse of the Soviet system in the early 1990s, smoking rates in women have increased substantially; rates in women in Russia, for example, doubled between 1992 and 2003.⁴³ In men, the very high rates of smoking (between 50% and 65%)⁴⁴ have failed to decline as the model would predict. Instead, increases have been observed in Russia, the only former Soviet country in which longitudinal data have been analysed.⁴³ These increases can be attributed to the aggressive marketing by the transnational tobacco companies as they gained access to markets in the region and the absence of effective tobacco control measures.⁴⁴

1.3.4 The vector of the epidemic

Such patterns in the development of tobacco use within populations provide evidence of how the tobacco industry, particularly transnational tobacco

companies, acts as the vector for the epidemic. Patterns of smoking uptake can be explained largely by the presence and activity of the transnational tobacco companies, particularly from the 1950s onwards, when tobacco companies began to increase their international investments. During the 1970s, major investments were made in Latin America, in the 1980s in Asia, and in the 1990s in the former Eastern bloc countries.^{45,46,47} China, the world's largest tobacco market, remains the primary target for expansion, with companies jostling to establish the first substantial joint venture with the China National Tobacco Corporation.⁴⁸

This global expansion was first triggered by health scares in the West,^{14,49,50} which resulted in declining tobacco consumption, and subsequently by global political and economic change, including trade and investment liberalisation, and the opening of formerly closed markets. Trade and investment liberalisation has contributed significantly to increases in cigarette consumption, particularly in low- and middle-income countries.^{2,51} It is also notable that the most marked increases in smoking prevalence have occurred in markets newly targeted by the transnational tobacco companies, and particularly among women. As a result, and contrary to the view that could easily be formed by an affluent citizen in a developed country, the global smoking epidemic continues to grow. The consequences of this global expansion are startling. It has caused global cigarette consumption to continue to increase. Falling per capita consumption in industrialised countries (by 10% between 1970 and the mid-1990s) has been more than offset by rises in low- and middle-income countries (Fig 1.3).^{2,52} Over three quarters of the world's smokers (most recently estimated at 1.3 billion smokers) now live in low- and middle-income countries.^{1,53} While an estimated 35% of men in developed countries smoke, this compares with almost 50% of men in developing countries and almost two thirds of Chinese men.¹ As a result, the future global health burden from tobacco will continue to increase, particularly in women, and will shift sharply in geographical focus from high- to low- and middle-income countries as outlined further below.

1.4 The health impacts of tobacco smoking

Smoking is uniquely harmful: half of all long-term smokers will eventually be killed by their habit and, of these, half will die during middle age, losing 20–25 years of life.^{3,54,55} Smoking has now been positively associated with over 40 diseases and the list continues to grow (see Chapter 6).⁵⁶ For most diseases, the association with smoking is strong and viewed as causal. Specifically, the major associations between smoking and disease satisfy the commonly accepted criteria for causality. Thus, the associations are strong and consistent (having

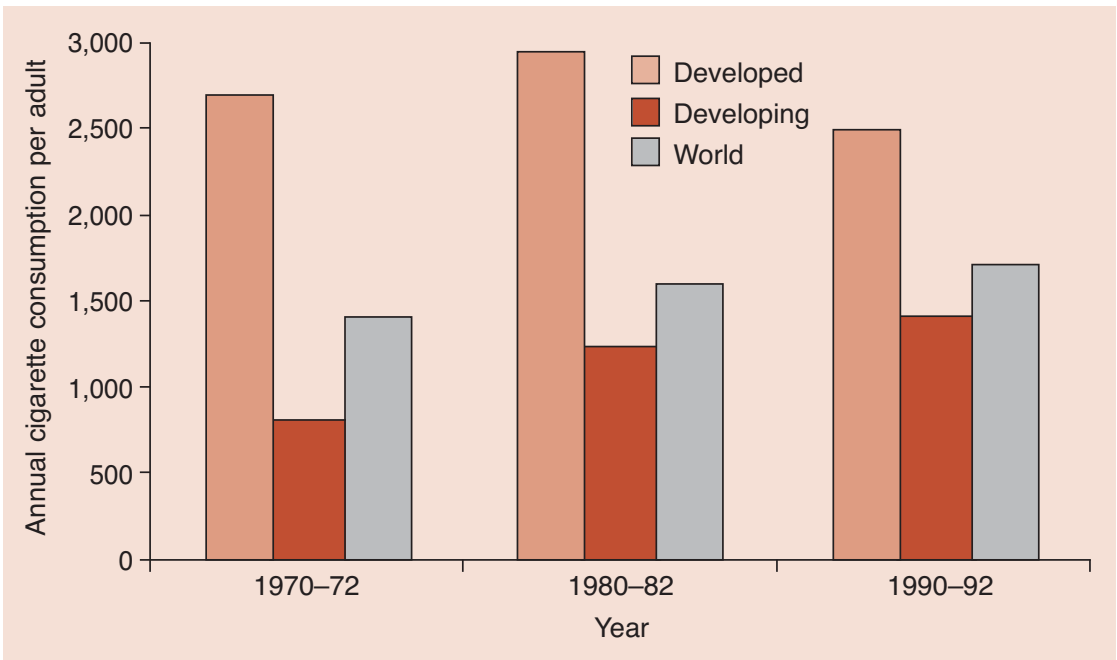


Fig 1.3 Trends in per capita adult cigarette consumption. Reproduced with permission from the International Bank for Reconstruction and Development/The World Bank.²

been found in numerous studies, using different designs, and in different populations), with evidence of a relation. The temporal relation between smoking and disease has been established and plausible biological mechanisms exist. The diseases fall into three main categories: cancer, vascular diseases and chronic lung diseases (Table 1.2).^{54,56-61}

Most of the evidence on the health impacts of smoking comes from high-income countries but more recent evidence is emerging from other countries including China and India.⁶²⁻⁶⁵ These studies suggest that the overall risks of smoking are about as great as in high-income countries and the diseases caused by smoking are similar. However, the specific patterns of smoking-related diseases may differ, reflecting the pre-existing distribution of underlying causes of death. In China, compared with the West, tobacco causes far more deaths from chronic lung diseases than from vascular disease. Smoking kills by making smoking-related diseases that are already present in the population much more common.

The components of cigarette smoke collectively explain its health impacts.^{66,67} Smoke contains over 4,000 chemicals, approximately 500 in the vapour phase (including carbon monoxide, ammonia, nitrogen oxides, hydrogen cyanide, and various hydrocarbons) and over 3,500 in the particulate phase (including ‘tars’ and most of the carcinogenic agents). Nicotine appears in both phases.¹⁷ Nicotine is the predominant addictive chemical and the reason why smokers continue to smoke (see Chapters 2, 3 and 4). However, cigarette smoke also contains carcinogenic agents in the particulate phase, including tobacco-specific

Table 1.2. Relative risks in current male smokers versus males who have never smoked (female data for cervical cancer) based on UK Doctors Study and the American Cancer Society Cancer Prevention Study II.		
Increased risk in smokers largely or entirely due to smoking	Increased risk among smokers partly due to smoking	Increased risk among smokers largely or partly due to confounding factors
Cancers		
Mouth, pharynx, larynx 24, 24.5	Oesophagus 7.5, 7.6	Liver 1.6
Lung 15, 22.4	Leukaemia (myeloid) 1.8,	Cervix 2.1
Bladder 2.3, 2.9	Kidney 2.1, 3	Large bowel
Pancreas 2.2, 2.1	Stomach 1.7	
Cardiovascular disease		
Ischaemic heart disease 1.6, 1.9	Cerebral vascular disease 1.5, 1.9	
Hypertension 1.4, 2.4		
Other heart disease 2.1		
Aortic aneurysm 4.1, 6.3		
Peripheral vascular disease 9.7		
Respiratory diseases		
Chronic obstructive pulmonary disease 12.7, 17.6	Pneumonia 1.9	
Asthma 2.2, 1.3		
Other diseases		
	Peptic ulcer	Cirrhosis
	Crohn's disease	Suicide
	Osteoporosis	Poisoning
	Periodontitis	
	Tobacco amblyopia	
	Age-related macular degeneration	
	Cataracts	
	Hip fracture	
Adapted from data in Doll, ⁵⁶ Boyle, ⁵⁷ Doll, ⁶⁰ and Wald and Hackshaw. ⁶¹		

N-nitrosamines (TSNAs), polynuclear aromatic hydrocarbons (PAH), and tobacco non-specific N-nitrosamines.¹⁷ The carbon monoxide, nitrogen oxides and other gaseous constituents of cigarette smoke have been shown to play a particular role in cardiovascular disease: they reduce oxygen transport, promote the atherosclerotic process, alter the serum lipid profile and increase platelet stickiness and tendency to aggregate.⁶⁸

The exact composition of tobacco smoke is primarily determined by the type of tobacco (including how it has been manufactured, cured and stored), although variations in cigarette design, including filtration, ventilation, paper and additives and the manner in which individuals smoke, also has an influence (see Chapter 5).^{17,67}

1.4.1 Impacts of smoking on global health status

The impacts of smoking on global health status are daunting. Smoking is the single largest cause of avoidable, premature death in economically developed countries, and is rapidly achieving this status outside the developed world.²⁸ Peto *et al* estimate that in 1995 smoking caused three million deaths globally and that by approximately 2025 this will increase to about 10 million deaths each year. Moreover, the global distribution of these deaths will change dramatically, reflecting the shift in the epidemic described above. In 1995, two thirds of deaths caused by tobacco occurred in the developed world and accounted for one in six deaths there; by 2025, three quarters of deaths caused by tobacco will be in the developing world.^{3,52}

1.4.2 The health impacts of smoking in context

Since the early 1990s, efforts have been made to assess the comparative importance of different risk factors on health, both globally and in regional population groups, in order to help determine policy and research priorities. Recently published analyses based on 2001 data compare smoking with 19 other risk factors.⁶⁹ These show that in high-income countries smoking is the leading cause of death, responsible for 18.5% (almost one in five) of all deaths. In low- and middle-income countries, estimates suggest that only high blood pressure and childhood underweight currently cause more deaths than smoking, and that smoking is responsible for 6.9% of the total (more than one in 15 deaths). Globally, smoking is estimated to have caused 4.8 million deaths in 2001; 8.5% of the total (approximately one in 12 deaths). This is in line with the estimates given above confirming the upward trajectory of the tobacco epidemic.

Tobacco also causes considerable long-term morbidity. Disability adjusted life years (DALYs) are a measure of healthy life lost as a result of individuals being in a state of poor health or disability. One DALY can be thought of as one lost year of healthy life. Estimates have been made using DALYs to quantify the impact of these risk factors on morbidity. Smoking was identified as the leading cause of disability in high-income countries, where it is responsible for 13% of DALYs

lost. In low- and middle-income countries it is responsible for 4% of DALYs lost (Fig 1.4).⁶⁹ Globally, smoking in 2001 was responsible for the loss of 72.9 million DALYs, almost 5% of the total. Along with mortality, the global burden of morbidity from tobacco is predicted to increase.^{69,70} The 2001 figures are almost double the estimated DALYs lost globally to tobacco use in 1990. A further rise to over 120 million DALYs lost to tobacco – just over 9% of the global total – is predicted by 2020.⁷⁰

1.4.3 The health impacts of other forms of tobacco use

Cigars, pipes and bidis

The data given above relate almost exclusively to cigarette smoking. The health consequences of smoking tobacco in other forms have been less thoroughly evaluated, but are thought to be broadly similar. The smoke from cigars, pipes and bidis has been shown to be carcinogenic and studies show an increased risk of cancers of the oral cavity, pharynx, larynx, oesophagus, lung and stomach – a subset of those already shown to be linked with cigarette smoking.⁷¹ Compared with cigarette smokers, cigar smokers appear to have similar risks of oral and oesophageal cancers, but lower risks of lung and laryngeal cancer, coronary heart disease and chronic obstructive pulmonary disease, probably because cigar smokers tend not to inhale and smoke less tobacco in total.⁷² Those who switch from cigarette smoking to cigar or pipe smoking reduce their risk of death over those that continue to smoke cigarettes, but have considerably higher risks of dying than those who quit altogether.^{72,73}

The changing cigarette

The form of the commercial cigarette has changed considerably since the 1950s, largely in response to health concerns. Filterless cigarettes have given way to filtered versions (virtually all cigarettes sold commercially in the UK are now filtered), the type and preparation of tobacco used in cigarettes has changed, various ingredients have been added, and machine-measured tar and nicotine yields (but not the actual tar and nicotine content or the tar and nicotine delivered in the process of normal smoking) have fallen considerably.^{17,67,74} Some studies suggest that the introduction of filters in the 1950s and initial reduction in tar yields from very high levels (over 25 mg) may have had some health benefits, particularly in reducing some cancer risks, but there has been little or no apparent effect on risk of vascular or chronic obstructive pulmonary disease.^{57,68,75} Any potential benefits have, however, largely been swamped by the introduction and

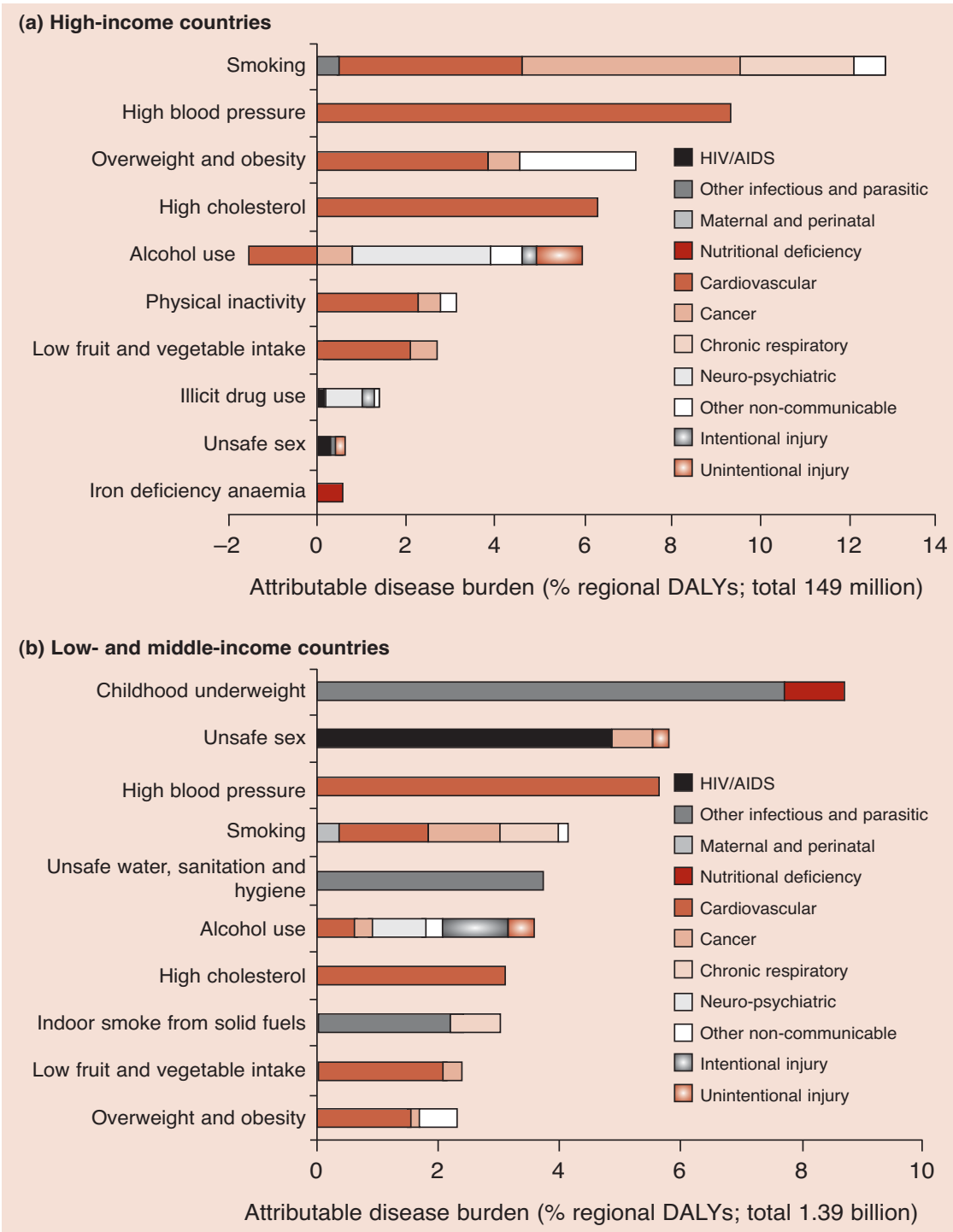


Fig 1.4 Burden of disease attributable in 2001 to 10 leading regional risk factors, by disease type in (a) high-income countries and (b) low- and middle-income countries. Reproduced from Lopez *et al* with permission of the World Bank.⁶⁹

marketing of so called ‘light’ cigarettes – a cynical attempt by the industry to encourage smokers concerned about health risks to switch to ‘lights’ rather than quit. Evidence suggests that although such cigarettes may have lower machine-measured nicotine and tar yields, the actual tar and nicotine delivered during smoking differs little from ‘full flavour’ cigarettes (see Chapter 5).⁷⁶

Smokeless products

The health risks of smokeless tobacco are considerably lower than those associated with combustible tobacco products as it is largely the combustion process that makes tobacco use so deadly.^{77,27} The evidence on the health effects of smokeless products is reviewed in Chapter 8. The major benefits of smokeless tobacco products over combustible products are the virtual absence of respiratory risks, and potentially lower cardiovascular risks due to the absence of the gaseous components in smoke. However, it is also clear that the risks of smokeless tobacco use vary between products and, although low in relation to cigarette smoking, are not inconsequential.

1.5 Conclusions

- ▶ Tobacco use originated in the American continent thousands of years ago and has spread to the rest of the world in the last 500 years.
- ▶ Tobacco continues to be used in many different ways, but the most common form of consumption is now the cigarette.
- ▶ The current global epidemic of cigarette smoking is a recent phenomenon, dating from around the turn of the 20th century.
- ▶ The onset of the smoking epidemic typically occurs in men before women, with epidemic increases in deaths caused by smoking occurring 20–30 years after the onset of smoking.
- ▶ In some developed countries, both smoking prevalence and mortality rates are now falling.
- ▶ Most countries are at an earlier stage of the epidemic, and globally both smoking rates and mortality are rising.
- ▶ Smoking is the biggest avoidable cause of premature death and disability in most developed countries, and with the evolution of the global smoking epidemic will be equally important in the future wherever smoking becomes prevalent.
- ▶ In 2001, smoking caused 4.8 million deaths, equivalent to about one in every 12 of all deaths, globally.
- ▶ By 2025, there will be an estimated 1.6 billion smokers in the world, and smoking will cause approximately 10 million deaths each year.
- ▶ Most of these deaths will occur in people who already smoke, rather than those who start smoking between now and 2025. Therefore, while preventing the uptake of smoking is crucially important to the prevention

of deaths in the longer term, promoting smoking cessation has a greater effect on mortality in the shorter term.

- It is, therefore, crucial to find ways of helping existing smokers to quit smoking, as well as preventing the uptake of smoking.

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2 | Nicotine and nicotinic receptors, and their role in smoking

- 2.1 Chemical and pharmacokinetic aspects of nicotine
- 2.2 The physiological functions of nicotinic receptors
- 2.3 Brain nicotinic receptors and cigarette smoking
- 2.4 Insights into nAChR activation, desensitisation and resensitisation from *in vivo* studies
- 2.5 Regulation of nicotinic receptor expression and function by chronic nicotine exposure
- 2.6 Acute actions of nicotine maintained in habitual cigarette smokers
- 2.7 Effects of nicotine on release of brain dopamine in smokers
- 2.8 Contribution of nicotinic receptor subtypes to the reinforcing effects of nicotine in animal models
- 2.9 Conclusions

2.1 Chemical and pharmacokinetic aspects of nicotine

Nicotine belongs to a large family of amine-containing chemicals called alkaloids. Most alkaloids are produced by plants. Although nicotine is particularly abundant in tobacco, detectable amounts are also found in some related plants, such as potato, aubergine and tomato. Nicotine in plants probably functions as an insecticide, and concentrated solutions of nicotine were once widely sold for this purpose, giving way in recent years to organophosphates.

The chemical name for nicotine is (S)-3-(1-Methyl-2-pyrroli-dinyl)pyridine, reflecting the existence of two nitrogen-containing carbon rings (Fig 2.1). In its pure form, nicotine is a colourless or pale yellow oily liquid. In chemical terms, pure nicotine is a base and is often referred to as nicotine free-base. It combines with acids to form stable, powdered salts which can be readily dissolved in water; this is the form of nicotine most commonly used by research scientists.

The absorption, distribution and fate of nicotine in the body has been studied extensively and reviewed recently.¹ Nicotine can be absorbed slowly or rapidly, depending on the route of administration and on the way the drug is formulated. Nicotine is most rapidly taken up after cigarette smoke inhalation, with arterial levels peaking approximately 20 seconds after each puff.² Although the kinetics

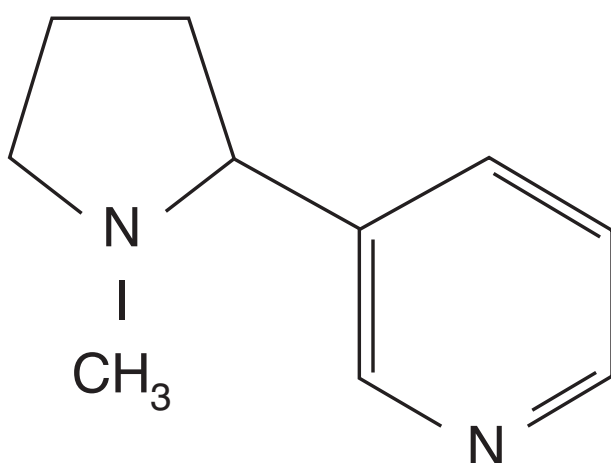


Fig 2.1 Chemical structure of nicotine.

of delivery of inhaled nicotine to the brain are still not fully understood, it is estimated that nicotine from smoked tobacco reaches the brain about 10 seconds faster than from the intravenously injected drug.² In contrast, the various forms of nicotine replacement therapy (patch, gum, nasal spray, inhaler etc) deliver nicotine much more slowly.¹

In body fluids such as blood, most nicotine molecules are positively charged and will not pass readily through cell membranes. This is because nicotine is a weak base, with a pKa of about 8.0.¹ Nevertheless, a significant proportion (approximately 30%) of nicotine in the circulation is uncharged, and in this form it distributes readily to tissues including the brain. The brain efficiently extracts nicotine from the circulation and releases it back to the blood over the course of many minutes.^{3,4} In abstinent smokers, nicotine levels in the blood initially decline with a half-life of about two hours. However, after a few hours of abstinence, nicotine disappears more slowly as the circulation continues to be replenished by nicotine stored in tissues.¹ Nicotine blood levels in smokers vary during the day,⁵ typically rising during the morning and reaching a plateau in the early afternoon which continues until late evening. During the night, nicotine levels decline to about one third of their daytime maximum. A pattern of peaks and troughs corresponding to individual cigarettes is superimposed on this circadian rhythm.

Nicotine undergoes extensive metabolism in the body, primarily in the liver, and six primary metabolites have been recognised in humans.¹ Cotinine, the most abundant metabolite, has a much longer plasma half-life than nicotine (16–20 hours).⁶ It is used in smoking cessation studies as a measure of tobacco smoke exposure and smoking to confirm self-reported abstinence. Animal experiments suggest that chronic nicotine exposure leads to an accumulation of cotinine and other metabolites in the brain.⁷ This is potentially significant because some metabolites are known to be pharmacologically active.^{1,8} For

example, both cotinine and nornicotine (another major metabolite) are able to enhance the *in vitro* release of dopamine in animal studies,^{9,10} and nornicotine is voluntarily self-administered by rats.¹¹ It is not known whether cotinine and nornicotine reach pharmacologically significant concentrations in the brains of smokers, but on present evidence it would certainly be premature to rule out a role for nicotine metabolites in the motivation to smoke. Any nicotine that is not metabolised is excreted, mainly by the kidney.

2.2 The physiological functions of nicotinic receptors

Nicotine produces pharmacological actions by targeting proteins whose natural role is to act as receptors for the neurotransmitter acetylcholine (ACh) (Fig 2.2). These receptors are commonly referred to as nicotinic cholinergic receptors or nAChRs. Acetylcholine also acts on a second type of receptor that is insensitive to nicotine but sensitive to a mushroom-derived drug, muscarine (termed muscarinic cholinergic receptors). Both ACh and nicotine activate nicotinic receptors, and they are therefore termed nicotinic agonists. Drugs which block these receptors are known as nicotinic antagonists.

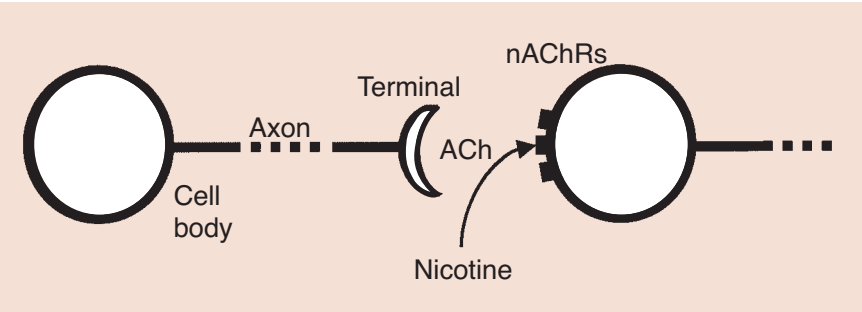


Fig 2.2 A cholinergic neuron (left) forming a synapse with a second neuron (right). The neurotransmitter acetylcholine (ACh) is released from a nerve terminal of the former and crosses the synapse to stimulate nicotinic receptors (nAChRs) located postsynaptically on the latter neuron. Nicotine, which is not naturally produced in the body, can gain access to the same nicotinic receptors as ACh. Once nicotine has bound to these receptors, it may stimulate or desensitise them, depending in part on the drug concentration and how long the drug is present. ACh = acetylcholine.

Acetylcholine performs a plethora of functions in the peripheral and central nervous systems, some mediated by nicotinic receptors and others by muscarinic receptors. The molecular structure of nicotinic receptors favours rapid communication between neurons. Thus, when nAChRs are activated by ACh or nicotine, they transmit a signal to the inside of the cell within milliseconds. In contrast, muscarinic ACh receptors tend to react within seconds to minutes. Rapid neurotransmission is obviously important at the junction between motor

nerve terminals and skeletal muscles, and it is therefore unsurprising that nAChRs mediate this function. Nicotinic receptors also play a key role in autonomic nervous system activity, thereby modulating processes as diverse as digestion, hormone secretion, blood pressure control, and pupil constriction.

In the brain and spinal cord, only a very small percentage of neurons use ACh as a neurotransmitter, yet these neurons ramify widely, so that virtually the entire central nervous system is supplied with ACh-releasing terminals. Nicotinic and muscarinic receptors are also widely distributed. These two receptor types are sometimes found at the same synapses, but can also occur independently. In anatomical terms, the brain can be subdivided into regions (cerebral cortex, hypothalamus, striatum etc) and into several hundred smaller structures known as nuclei. Most, if not all, brain nuclei express nicotinic receptors.^{12,13} Therefore, these anatomical considerations suggest that nicotine could exert a widespread influence on the brain through actions on nicotinic cholinergic receptors.

Nicotinic receptors are located on the outer surface of neurons and help to regulate their electrical activity. They do this principally by controlling the entry of electrically charged chemicals (ions, particularly sodium and calcium) into cells. Each nicotinic receptor is cylindrical in shape, and has a central channel through which ions can be permitted to pass into the cell (Fig 2.3). In the absence of an agonist, the nicotinic receptor assumes a ‘resting’ shape in which

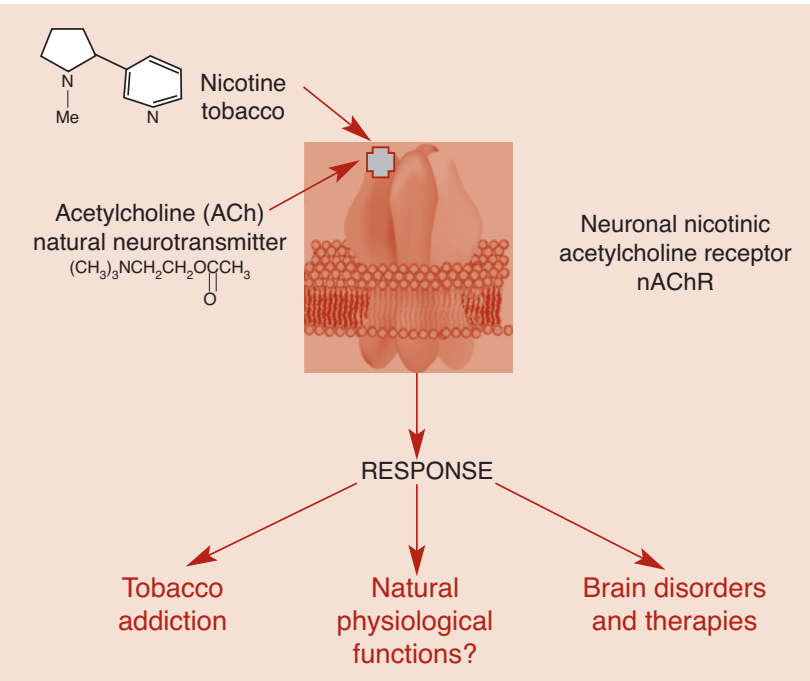


Fig 2.3 A nicotinic acetylcholine receptor located in the outer membrane of a neuron. The receptor comprises five subunits (shown in blue) surrounding a central channel, which can open to allow the passage of positively-charged ions (Na^+ and Ca^{++}) into the cell.

the ion channel is closed. When a nicotinic agonist is administered, some agonist molecules bind to the receptor and induce the receptor to change its shape so that the ion channel opens. The resultant flow of positively charged ions into the cell can have several consequences. First, the neuron becomes more electrically active, producing electrical impulses (action potentials) at a faster rate. When these impulses are conducted along the axon of the neuron to the nerve terminals, they result in increased release of the neurotransmitter. Second, some nicotinic receptors are capable of conducting calcium ions (Ca^{++}) into the neuron. Ca^{++} ions play a critical role as signalling molecules within the cell. By increasing Ca^{++} ion levels within the cell, nicotinic receptors can have a pronounced effect on many cell processes ranging from neurotransmitter release to gene expression.

Nicotinic receptors are composed of five subunits (Fig 2.3). Each subunit is encoded by a single gene and denoted by a Greek letter and Arabic number.¹⁴ All subunits expressed in the brain are either α or β (for example, $\alpha 4$, $\beta 2$). Nicotinic receptors, in turn, can be differentiated into subtypes, depending on the combination of subunits that they contain. Thus, according to current nomenclature,¹⁴ nAChRs that comprise only $\alpha 4\beta 2$ subunits are termed $\alpha 4\beta 2$ receptors; if additional types of subunits are suspected, a 'wild card' asterisk is added (hence $\alpha 4\beta 2^*$ receptors). In the brain, $\alpha 7^*$ and $\alpha 4\beta 2^*$ are particularly prevalent. It is not known how many nAChR subtypes are expressed in the mammalian brain, but pharmacological and molecular genetic studies have already identified about a dozen.¹⁵ Nicotinic receptor subtypes differ greatly in their anatomical location, in their sensitivity to nicotine, and in their propensity to desensitise (lose responsiveness to nicotine) and resensitise (become responsive to nicotine again) when exposed to this drug.^{15–17}

2.3 Brain nicotinic receptors and cigarette smoking

2.3.1 General issues

Nicotine is thought to play a critical role in tobacco dependence,¹⁸ and since nicotinic ACh receptors represent the main molecular target for this drug, they are likely to be heavily involved in the mechanisms of nicotine dependence. The receptor subtype or subtypes relevant to dependence are likely to be those located in neuronal systems mediating reinforcement, of which the ventral tegmental area (VTA) appears to be particularly important (see Chapter 3). However, on current evidence, it is likely that nAChRs in other brain areas also contribute to nicotine dependence.

To be involved in the development of dependence, the relevant nAChR subtypes have to be sensitive to smoking-relevant concentrations of nicotine. It is important to note that nicotine and other agonists not only activate nicotinic receptors; these drugs can also turn off (desensitise) receptor function. In the desensitised state, receptors are temporarily unreactive and their ion channels are closed. It used to be thought that nicotinic receptors only assume a desensitised state when exposed to high, near-lethal concentrations of nicotine. However, this conclusion was drawn from work on peripheral nicotinic receptors. In the brain, nicotinic receptors are generally much more prone to desensitisation, and some can even be turned off by levels of nicotine experienced on a daily basis by smokers.

The common assumption is that smokers seek nicotine to cause nAChR stimulation rather than desensitisation, or possibly a combination of the two. If nicotine receptor activation is indeed an important component of why smokers smoke, it is therefore evident that if receptors desensitise on exposure to nicotine, they should regain their sensitivity rapidly enough to ensure that a significant proportion of the receptors can be activated at any one time.

Daytime venous plasma nicotine concentrations in smokers tend to peak at around 30 ng/ml or 0.2 μM ,¹ and animal studies have shown that brain tissue sequesters nicotine, maintaining a 2.5–5-fold concentration gradient compared with levels in the blood.^{19,20} Brain nicotine concentrations in habitual smokers are, therefore, likely to fluctuate between about 0.1 μM and 1 μM , though these estimates do not allow for sequestration of brain nicotine in lipid and other cellular compartments where it may be unavailable to act on receptors.

2.3.2 Differential sensitivity of nicotinic receptor subtypes to activation by nicotine

Acute sensitivity of nAChRs to nicotine has been assessed *in vitro* in recombinant nAChR subtypes expressed in cultured cells or in frog egg cells (oocytes) and in native (naturally occurring) nAChRs also isolated from mammalian tissue, and also *in vivo* in laboratory animals. Recombinant receptors represent a useful research tool, but they frequently fail to match their native counterparts in pharmacological and other respects.²¹

In isolated brain tissue, brief submicromolar application of nicotine to native nAChRs exerts numerous actions, including neuronal excitation and increased release of several neurotransmitters.^{22,23} The use of isolated tissue permits greater control over the experimental conditions than is usually possible *in vivo*; consequently, one can be more confident that the observed effects of nicotine reflect direct actions of the drug on the neuronal population under study. The great

majority of these *in vitro* studies have been conducted in rat or mouse tissue. Neuronal excitation has been investigated using electrophysiological recording techniques mainly in brain areas and neuronal populations that are known to express nAChRs abundantly. These include the hippocampus, midbrain dopamine neurons, thalamus, and medial habenular nucleus.^{24–27} Electrophysiological approaches have also identified modulatory effects of nicotine on neurotransmitter release from defined neuronal projections in the brain, such as the thalamocortical and habenulo-interpeduncular pathways.^{28–32} In most cases, a stimulatory effect of nicotine was observed, but inhibition has also been reported.³³ In most of these studies, it has been possible to identify the neurotransmitter in question, such as glutamate or gamma-aminobutyric acid (GABA).^{28,29,32} Nicotine-evoked neurotransmitter release can also be studied from isolated synaptosomes (pinched-off nerve terminals) or tissue slices.^{15,23} This approach is more versatile than electrophysiological recording in that it can detect the release of a wider range of neurotransmitters, notably dopamine, ACh, noradrenaline and serotonin, in addition to glutamate and GABA.^{15,23}

The above effects of nicotine on neuronal excitability and neurotransmitter release are mediated by a variety of nAChR subtypes. For example, glutamate release is commonly regulated by nAChRs comprised of $\alpha 7$ subunits, whereas release of other neurotransmitters tends to be controlled by multiple receptor subtypes.¹⁵ This diverse pharmacology is seen at nicotine concentrations that are relevant to smoking. Several nicotine-sensitive nAChR subtypes have been identified in isolated rodent tissue using pharmacological and genetic knockout approaches.^{15,34–36} These include $\alpha 4\beta 2^*$ nAChRs (see section 2.2 for explanation of nomenclature), which are widely and abundantly expressed in the brains of all mammalian species examined, including the human brain.²¹ Other subtypes are distributed more discretely, such as $\alpha 6\beta 3^*$ isoforms associated with dopamine releasing terminals.³⁴ In contrast, the $\alpha 7^*$ nAChR subtype, although abundant in humans and other mammals, is only weakly activated by nicotine when applied acutely in concentrations likely to occur during smoking.²¹

2.3.3 Modulation of nicotinic receptor function by desensitisation and resensitisation

Experiments in animals have shown that nicotinic receptors in the brain typically become at least partially unresponsive to nicotine (desensitised) when the drug is applied continuously for a few seconds or minutes. The speed at which this happens, referred to as desensitisation kinetics, helps to determine which potentially active nAChR subtypes predominate in cigarette smokers. Perhaps surprisingly,

many receptors can be desensitised by concentrations of nicotine lower than those required for receptor activation.¹⁷ Potentially, then, a proportion of brain nAChRs may be desensitised even before the first cigarette is smoked in the morning. *In vitro* studies have shown profound differences between nAChR subtypes in terms of the rapidity and extent to which they desensitise when acutely exposed to nicotine.¹⁷ For example, $\alpha 7$ nAChRs desensitise in less than a second, but require high concentrations to do so, whereas $\alpha 4\beta 2$ receptors can desensitise at much lower (nanomolar) concentrations of nicotine, albeit much more slowly.

Pharmacological studies have tended to focus on the acute activating and desensitising actions of nicotine. Nicotine AChR subtypes differ markedly in their propensity to desensitise to subchronic *in vitro* exposure to nicotine over hours or days. Based on a substantial literature, nicotine administered in concentrations of 0.1–0.3 μM has been estimated to reduce nAChR function by approximately 50% for $\alpha 3\beta 2$ -nAChR; by 10–50% for $\alpha 3\beta 4$ -nAChR; by 50–100% for $\alpha 4\beta 2$ -nAChR; by 20–50% for $\alpha 4\beta 4$ -nAChR; and by 50–100% for $\alpha 7$ -nAChR.³⁷ Although not all of these receptor subtypes have yet been identified in the human brain, their existence seems likely, based on the anatomical distribution of messenger RNA (mRNA) that would encode them.^{21,38} Accordingly, it has been suggested that, in smokers, $\alpha 3^*$ -nAChRs, being less apt to desensitise, may predominate functionally over $\alpha 4^*$ and $\alpha 7^*$ -nAChRs.³⁹ Such a conclusion must be viewed with caution, however, not least because it is based on the use of recombinant nAChRs, which quite frequently behave differently from their native counterparts.³⁷ In this context, one should also note that native $\alpha 7$ receptors have been identified in the embryonic rat brain that do not inactivate with subchronic nicotine exposure.⁴⁰

While our knowledge of nAChR desensitisation kinetics is incomplete, even less is known about how rapidly different nAChR subtypes recover their function (resensitise) after brief nicotine exposure. Recombinant nAChRs have shown substantial recovery within minutes or hours of rapid nicotine removal in *in vitro* experiments, at least for the few receptor subtypes that have been tested thus far.^{37,41} In human neuroblastoma cells, which possess native $\alpha 3^*$ and $\alpha 7^*$ subtypes, the full nicotinic response was regained within five minutes, even after 48 hours exposure to nicotine.⁴² In isolated brain tissue, where multiple nAChR subtypes contribute to the response, some recovery of sensitivity has been observed within several minutes following brief application of nicotine,^{43,44} but an additional persistent insensitivity lasting several hours has also been detected, even after acute administration.⁴⁵

2.4 Insights into nAChR activation, desensitisation and resensitisation from *in vivo* studies

In vitro characterisation of nAChR functioning – activation, desensitisation and resensitisation – provides a starting point, but ultimately may tell us little about habitual smokers. One reason for this is that some potent nicotine actions observed *in vitro* have not been found to be significant when the drug is given acutely *in vivo*. This is illustrated by many dopaminergic neurons in the brain. These neurons express well-characterised nAChRs on their cell bodies and dendrites, which modulate cell firing.³⁶ In addition, dopaminergic neurons possess presynaptic receptors which promote transmitter release.³⁴ However, in laboratory rodents, systemic administration of nicotine stimulates dopamine release mainly or entirely by stimulating nAChRs in the dopamine cell body region.^{46,47} Brain noradrenergic neurons provide a second example of this phenomenon.⁴⁸ *In vitro* studies are also subject to the caveat that they cannot readily reproduce the longer-term changes in nAChRs that result from prolonged *in vivo* exposure to nicotine. Such alterations are discussed in the next section.

2.5 Regulation of nicotinic receptor expression and function by chronic nicotine exposure

2.5.1 Differential regulation of nicotinic receptor subtypes

Chronic and continuous exposure to nicotine can markedly alter the expression and function of brain nAChRs *in vivo*. In terms of nAChR expression, post-mortem analysis has shown that cigarette smokers possess more nicotinic receptors than non-smokers and ex-smokers.^{49–51} This high level of nAChR numbers was found in a number of brain regions, to somewhat differing degrees. Conceivably, individuals who ultimately become highly addicted smokers may possess more brain nicotinic receptors even before they take up cigarette smoking, or smoking may result in up-regulation of nicotinic receptors. The question of what is the main cause of the observed increase in nicotinic receptors in smokers could be examined best through longitudinal studies using brain imaging techniques. Animal studies strongly suggest that increased expression of nicotinic receptors stems at least in part from up-regulation following chronic nicotine administration.³⁷ Animal studies have also shown that nAChR subtypes differ in their propensity to proliferate in response to nicotine; for example, $\alpha 4\beta 2^*$ -nAChRs up-regulate more readily than $\alpha 7$ -nAChRs and $\alpha 3/\alpha 6\beta 2^*$ -nAChRs.^{37,52,53} Much less is known in this regard about the human brain, although, consistent with the animal literature, post-mortem analysis has revealed an increased density of $\alpha 4\beta 2^*$ -nAChRs but not $\alpha 7$ -nAChRs in

smokers.⁵⁰ The occurrence of agonist-induced receptor proliferation may appear paradoxical, but it is not always accompanied by increased receptor function.³⁷

In the animal literature, there are numerous reports of either functional down- or up-regulation of receptors following chronic nicotine exposure.³⁷ Unfortunately, most studies of this sort have had to rely on post-mortem analysis of brain tissue, and some of the mixed results in this field may be attributable to differences in the way that brain tissue is prepared. Nevertheless, when tissue preparation is standardised, it becomes apparent that nicotinic receptors located on different neuronal populations can regulate in opposite directions. For example, in one study, chronic nicotine administration led to an increase in nicotine-evoked release of dopamine and 5-HT from rat striatal slices, whereas ACh release was reduced in the same tissue.⁵⁴ In another more recent study, chronic nicotine administration greatly attenuated the ability of an acute nicotine challenge to promote *ex vivo* hippocampal ACh release, whereas nicotine-evoked noradrenaline release was increased.⁵⁵

These diverse findings presumably reflect anatomical differences in receptor subtype expression. This is suggested by studies in cultured cells, where extended nicotine exposure alters nAChR expression and function in a highly subtype-dependent manner.³⁷ Hence, it seems likely that chronic nicotine exposure in smokers promotes the function of certain nAChR subtypes at the expense of others, but the literature from animal studies gives little indication of which subtypes may be favoured in this way. For example, while radioligand binding studies in rats have reported a selective proliferation of $\alpha 4\beta 2^*$ or $\alpha 6^*$ receptors,^{56,57} it is not yet established whether increased receptor abundance translates into increased receptor function in these cases.

With *in vivo* nicotine exposure, more persistent forms of nAChR desensitisation ('receptor inactivation') are likely to come to the fore. Evidence for this comes from rodent studies where as few as one or two systemic injections of nicotine can induce nAChR-mediated tolerance for a few or even many hours, depending on the study.^{58–60} However, multiple injections of nicotine given over several days have been found to produce a much more prolonged nAChR inactivation, such that the prolactin release response to nicotine did not recover for more than a week after the last injection.⁵⁸

It is still largely a matter of speculation which of the many nAChR populations in the brain remain active during daytime smoking. Recently, however, it has been claimed that most $\alpha 4\beta 2$ receptors are desensitised by cigarette smoking.⁶¹ These authors used a positron emission tomography (PET) imaging radiotracer to estimate the degree of occupancy of $\alpha 4\beta 2$ -nAChRs in human smokers. Given that radio-labelled nicotine binds with high (nanomolar) affinity to $\alpha 4\beta 2$ receptors

in vitro, it was hypothesised that these receptors would be almost completely occupied by cigarette smoking. Subjects were screened to confirm that they had abstained from cigarettes for at least 48 hours when tested. Smoking exerted a remarkably profound effect on radiotracer binding, with effects apparent even after a single cigarette puff, and it was estimated that daytime smoking results in near-complete receptor occupancy (96% or more). It was further suggested that, across the day, most $\alpha 4\beta 2$ receptors shift to a high-affinity desensitised state, leaving very few that can still be activated by nicotine. However, this conclusion is tempered by the caveat that nAChR radiotracers are not capable of detecting receptors remaining in a lower-affinity state which would still be possible to activate by nicotine.

2.5.2 Effect of chronic exposure on acute *in vivo* effects of nicotine in animals

Nicotine exerts numerous acute neuropharmacological and behavioural effects in drug-naïve animals, but few studies have examined whether these effects can be obtained during chronic exposure to nicotine. This is surprising, since it is widely acknowledged that most cigarette smokers are continuously exposed to pharmacological concentrations of nicotine, even during the night and before the first cigarette of the day.¹ For various reasons, it has also proved difficult to emulate the pronounced diurnal pattern of nicotine exposure experienced by smokers in laboratory animals. Most investigators have employed subcutaneous osmotic mini-pumps that deliver nicotine at a constant rate over several days up to a few weeks. Against a background of continuous nicotine exposure, acute nicotine administration lost its ability to increase detectably dopamine overflow in the nucleus accumbens, measured by the microdialysis sampling method in rats.^{62,63} This finding may be highly significant, given the importance currently attributed to the mesolimbic dopamine system in mediating the reinforcing effects of nicotine (see Chapter 3). Importantly, the observed insensitivity to nicotine was associated with plasma concentrations mimicking daytime smoking levels. The loss of nicotine-induced mesolimbic dopamine overflow persisted for at least one or two days after withdrawal of chronic nicotine in rats.⁶⁴

By no means are all of nicotine's acute effects lost during chronic drug exposure, however. For example, in the above-mentioned microdialysis experiments, chronic drug infusion that was sufficient to abolish the mesolimbic dopamine response had little if any effect on dopamine overflow in the neighbouring nigrostriatal dopamine pathway.⁶² Clearly, then, at least some acute actions of nicotine can persist despite continuous nicotine dosing. This fact has also been demonstrated using immunohistochemical mapping of fos, a protein marker for neuronal activation.^{65,66}

In drug-naïve animals, a single systemic nicotine injection increased fos expression in several brain areas, as expected from previous studies. This acute response was affected variably by continuous chronic nicotine delivered by osmotic mini-pump; in some brain areas (the nucleus accumbens and parts of the hypothalamus, for example) it was reduced or abolished, whereas in another area (the central nucleus of the amygdala) it was unaffected.^{65,66} It is not known why tolerance to nicotine should develop in some neuronal populations but not in others, but differences in nicotinic receptor subtype expression almost certainly contribute to these differences.

The persistence of functional brain nAChRs in fos expression studies is remarkable, considering that chronic plasma nicotine levels in these studies were well in excess of those found in typical smokers. However, at least two other types of study provide corroborating evidence. In the first, administration of a nAChR antagonist to rodents receiving chronic nicotine readily precipitates withdrawal signs, some of which are mediated by brain nAChRs;⁶⁷ such a result would not be expected if all nAChRs were already inactivated. Second, nicotine-induced stimulation of brain nAChRs provides a signal that rats can learn to recognise in order to make the correct response to obtain a food reward. This acute effect of nicotine persists undiminished when superimposed on a background of chronic continuous nicotine.⁶⁸

2.6 Acute actions of nicotine maintained in habitual cigarette smokers

The evidence from animal studies reviewed above suggests, therefore, that, in the continued presence of nicotine, some brain nAChRs lose their ability to function while others remain sensitive to nicotine. But is this also the case in human cigarette smokers, and what happens to the key receptors which may modulate neurobiological processes underlying addiction to nicotine? These are harder questions to answer and few published studies have addressed this issue. It is well established that cigarette smokers become partially tolerant to a number of nicotine's subjective and behavioural effects, most notably nausea and other aversive effects.⁶⁹ As in animal studies, short-term tolerance can be demonstrated within minutes or hours of acute drug administration, and more prolonged drug exposure results in chronic tolerance. It is likely that at least some of the tolerance observed is mediated by desensitisation of nAChRs in the brain.

The animal evidence reviewed above suggests that profound tolerance to the actions of nicotine develops in some brain areas but not in others. In human subjects, it is possible to visualise the anatomical pattern of nicotinic activation

using functional magnetic resonance imaging (fMRI). Such a study has revealed widespread effects of intravenous nicotine in cigarette smokers.⁷⁰ However, the nicotine doses used in that study were extremely high, equivalent to the nicotine yield from one to two cigarettes infused in a single minute.¹ Hence, it is possible that nicotine was able to stimulate nAChR subtypes that would not normally be activated during smoking.

Human brain imaging has also been used to estimate the proportion of $\alpha 4\beta 2$ brain nicotinic receptors that are occupied by circulating levels of nicotine.⁶¹ The investigators concluded that, across the day, cigarette smoking causes most $\alpha 4\beta 2$ receptors to become desensitised, leaving very few that can still be activated by nicotine. As mentioned above, this conclusion should perhaps be viewed with caution, but, if true, these findings are potentially important given the high prevalence of this receptor subtype in the brain and in dopaminergic pathways in particular.

Perhaps surprisingly, administration of the nAChR blocker mecamylamine does not produce significant signs of nicotine withdrawal in human smokers, even when they are actively smoking.^{71,72} Since mecamylamine is centrally active, the absence of withdrawal effects might suggest that few nAChRs are still functional in these individuals. However, mecamylamine can precipitate mild withdrawal in human subjects wearing a nicotine patch instead of smoking.⁷³ Administration of mecamylamine also increases acutely cigarette smoking in a consistent manner, as if smokers are attempting to overcome the effects of nAChR blockade.^{71,73,74} Unfortunately, mecamylamine antagonises both central and peripheral nAChRs, both of which contribute to the short-term regulation of smoking behaviour.⁷⁵ Hence, human studies with mecamylamine do not unequivocally demonstrate the presence of functional nAChRs in the brain of active smokers.

2.7 Effects of nicotine on release of brain dopamine in smokers

It is widely thought that cigarette smokers seek nicotine because it releases dopamine in the mesolimbic system of the brain. Most of the evidence derives from laboratory studies in rodents. Thus, systemic injection of nicotine reliably increases mesolimbic dopamine release (see Chapter 3), and the same phenomenon has been observed in animals actively working to obtain the drug.⁷⁶ In addition, laboratory animals self-administer nicotine less if dopaminergic transmission is disrupted surgically or with drugs.^{77,78}

This sort of evidence may appear compelling, but it is important to consider the limitations of such studies, apart from the obvious possibility of species

differences. First, animals were typically drug-free when given nicotine, so brain nAChRs were minimally desensitised. Second, most of these studies were of only a few days' duration, reducing the possibility of compensatory receptor up- or down-regulation of nAChR density. Third, rats self-administering the drug were offered only limited daily access, insufficient to produce dependence.⁷⁹ Fourth, self-administered nicotine was delivered in multiple doses, each equivalent to the yield from one whole cigarette, potentially producing actions in the brain that would not be encountered by human smokers. Finally, intravenous nicotine was injected almost instantaneously, whereas nicotine from cigarette smoke is released into the bloodstream over the course of a minute or so.² This difference could be critical because recent evidence suggests that such differences in infusion speed can have a great effect on the impact that nicotine has on the brain in animal models.⁸⁰

What then is the evidence that cigarette smoking increases mesolimbic dopamine release (in human subjects)? This question has been addressed principally with PET imaging, using radiotracers that bind to dopamine receptors; the extent of dopamine release is inferred indirectly from a decline in radiotracer labelling. Results to date have been somewhat mixed. A first study, targeting the D1 subtype of dopamine receptor, provided no evidence for smoking-induced dopamine release.⁸¹ However, in this study, the control subjects were expecting a cigarette immediately after the scan, so it is possible that expectation-induced dopamine release obscured any effect of active smoking.

Subsequent studies have focused on the D2 dopamine receptor subtype. In one report,⁸² dopamine release did not consistently increase during cigarette smoking in subjects who were at least 12 hours abstinent. However, the degree of pleasure experienced during smoking was correlated with dopamine release. Unexpectedly, this correlation occurred not in the mesolimbic system, but instead in a dopamine terminal area (caudate-putamen) more usually associated with motor control than with emotion. In contrast, another group observed an apparent increase in mesolimbic dopamine release in subjects smoking after only three hours of deprivation.⁸³ This effect was surprisingly large, more akin to that seen previously with amphetamine and cocaine. However, a much smaller effect of smoking has now been reported in a new group of subjects.⁸⁴

Taken together, these PET imaging studies suggest that in humans cigarette smoke can increase dopamine release, even if the location and extent of this effect appears somewhat unpredictable. All subjects in the studies were at least three hours abstinent from smoking, and such an interval could conceivably allow many desensitised nAChRs to regain their function prior to the test session. Perhaps, then, the test cigarette resembled most closely that of the first

cigarette in a normal smoker's day. What remains entirely unknown is whether subsequent cigarettes are also capable of releasing brain dopamine. Instead, smoking-associated cues may well play a key role in maintaining cigarette smoking behaviour (see Chapter 3).

A further limitation of brain imaging studies is that they cannot tell us directly how much of an impact any dopamine release would have on smoking behaviour or subjective responses to smoking. One way to address this question is to attenuate dopaminergic transmission experimentally by giving a dopamine receptor blocker. This approach has yielded mixed results, with both increases and decreases in smoking behaviour reported in different studies.^{85–87} Here, interpretation is further complicated by the possibility of non-selective drug effects unrelated to dopamine receptor blockade. Dopaminergic transmission can also be reduced temporarily in human subjects by administering an experimental meal lacking the chemical precursors for this neurotransmitter. This dietary manipulation has previously been found to decrease the stimulant effects of amphetamine and cocaine – drugs which normally increase dopaminergic transmission. However, the dopamine-depleting diet failed to change smoking behaviour, the urge to smoke or various subjective effects of smoking.⁸⁸

2.8 Contribution of nicotinic receptor subtypes to the reinforcing effects of nicotine in animal models

Nicotinic receptors are distributed widely in the brain, and their natural function is to mediate the effects of the neurotransmitter ACh. Since nAChRs may be physiologically important, smoking cessation drugs that target multiple nAChRs indiscriminately are likely to have unwanted effects. With a view to developing more selective drugs, much effort has been expended trying to identify subtypes of nAChR that contribute to the reinforcing effects of nicotine in animal models.⁸⁹ Behavioural tests have focused largely on conditioned place preference (CPP) and intravenous nicotine self-administration (IVSA), with rats and mice being the animals of choice. The CPP procedure relies on the tendency of animals to prefer an environment where they previously received a rewarding stimulus. This type of conditioning is usually carried out using a two-compartment box: the animal is repeatedly confined to one side after drug injection and to the other side after a control injection of saline. On the test day, both sides are accessible and the time spent in each is recorded. The IVSA procedure, in contrast, makes use of a Skinner box equipped with levers, and here the animal must work in order to obtain the drug. Attention has also been paid to the mesolimbic dopamine system, in the expectation that this neuronal population

mediates the drug's reinforcing effects. Since nicotinic drugs tend to have limited selectivity for a given receptor subtype, much of this research has relied on the use of genetically modified (especially 'knockout') mice that fail to express a particular nAChR subunit.⁹⁰

Several conclusions can be drawn from these studies. First, CPP associated with systemic nicotine administration requires the expression of $\alpha 4$ and $\beta 2$ but not $\alpha 7$ subunits.^{91,92} Second, dopamine release evoked by acute systemic injection of nicotine also requires the presence of $\alpha 4$ and $\beta 2$ nAChR subunits,^{93,94} probably located in the dopamine cell body area.^{34,36,95} Third, nicotine IVSA relies to an important extent on nAChRs containing the $\beta 2$ subunit^{93,96} and possibly depends on $\alpha 7$ subunits as well, although here results are mixed.^{97,98} The participation of $\alpha 4$ -containing receptors in nicotine IVSA has not been established but seems likely, since this behaviour is dependent on mesolimbic dopamine transmission.⁷⁷ Finally, the possible participation of other nAChR subunits has not yet been reported.

Signs of nicotine withdrawal have also been studied in mice lacking specific nAChR subunits. In one study, mice were chronically treated with oral nicotine so as to achieve plasma levels in the low smoking range.⁹⁹ Spontaneous withdrawal subsequently elicited several behavioural signs, some being dependent on the expression of $\alpha 7$ subunits. Other studies have examined withdrawal precipitated by acute administration of the antagonist mecamylamine during chronic nicotine administration.^{100,101} Here, $\beta 4$ but not $\alpha 2$ receptors appeared critical, but circulating levels of nicotine were not measured to see whether they were in the smoking range.

Thus, it is still not clear which nAChR subtype or subtypes contribute to tobacco dependence, but animal models suggest that nicotinic receptors containing $\alpha 4$ and $\beta 2$ subunits are the most likely candidates. This conclusion appears consistent with the recently reported success of the $\alpha 4\beta 2$ -selective agonist varenicline in smoking cessation trials, although it should be borne in mind that varenicline has additional pharmacological actions.¹⁰² Finally, it is important to emphasise that existing animal testing paradigms model, at best, only certain aspects of cigarette smoking.

2.9 Conclusions

- ▶ Nicotine targets receptors whose natural function is to interact with the neurotransmitter acetylcholine (ACh).
- ▶ By activating these nicotinic receptors, nicotine increases the firing rate of neurons and increases the release of various neurotransmitters.

- ▶ The effect of nicotine on different nicotinic receptors is dose dependent and is also modified by sustained exposure, which causes some receptors to become desensitised.
- ▶ Long-term exposure to nicotine also causes an increase in the number of nicotinic receptors in the brain, but it is not clear how many of these receptors are functional.
- ▶ In animal studies, the acute reinforcing effects of nicotine appear to be dependent on dopamine release in the brain. However, nicotine-induced dopamine release is curtailed markedly or even disappears when animals are chronically exposed to the drug.
- ▶ Although cigarette smoking in humans promotes dopamine release, the contribution of this effect to sustained smoking behaviour in humans is still not fully understood (see Chapter 3).
- ▶ It is also not clear which nicotinic receptor subtypes are responsible for reinforcing effects of this drug in humans.

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3 | The neurobiological mechanisms underlying nicotine dependence

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3.1 Introduction

It is now widely accepted that nicotine is the primary addictive component of tobacco smoke. In recent years, however, it has become clear that the psychological mechanisms which mediate the addiction are more complex than they first appeared. This chapter will highlight the ways in which studies with experimental animals have contributed to our understanding of the psychobiological mechanisms which mediate addiction to nicotine and tobacco. The studies provide convincing evidence that nicotine exhibits the principal psychopharmacological properties of a drug of dependence, namely the ability to exhibit reinforcing or rewarding properties and to elicit an abstinence syndrome when the drug is withdrawn precipitously following a period of chronic administration. However, the experimental animal data also indicate that, when compared with many other drugs of dependence, the reinforcing properties of nicotine appear relatively weak. Thus, it may be that nicotine alone does not have the powerful addictive properties necessary to account for the highly addictive nature of tobacco smoking, and that addiction to tobacco reflects complex interactions between nicotine, other stimuli associated with the inhalation of tobacco smoke, and possibly other environmental, social or behavioural stimuli associated with smoking.

3.2 Nicotine self-administration in experimental animals

Many of the studies designed to investigate the psychological and neurobiological factors underlying the rewarding or reinforcing properties of nicotine have employed an intravenous self-administration (IVSA) model in which animals are trained to make a response, commonly to press a lever, to receive a small intravenous dose of nicotine. Thus, in this paradigm, the delivery of nicotine is under the control of the animal and is contingent upon the animal making the appropriate lever-pressing response (Fig 3.1).¹ Although this method of self-administration appears to be very different from the inhalation of nicotine in tobacco smoke, it models the need for the animal to learn and express a specific behaviour in order to receive the drug. The protocol is widely used to explore the reinforcing properties of addictive drugs, and the compounds which serve as reinforcers in this type of protocol (such as cocaine, amphetamine and heroin) are invariably addictive in human beings. Experimental animals do not learn to self-administer saline or non-reinforcing drugs. Furthermore, if saline is substituted for reinforcing drugs, such as nicotine, over a period of three to five sessions the animals stop responding because they learn that the behaviour no longer delivers a rewarding drug. Corrigall and Coen were amongst the first to report that nicotine could serve as a reinforcer in this paradigm in experimental rats, although it has since emerged that De Noble and Mele demonstrated this effect some years previously while working for Philip Morris.^{2,3} Subsequent studies have confirmed that the procedure provides a robust means of exploring nicotine-seeking behaviour and the

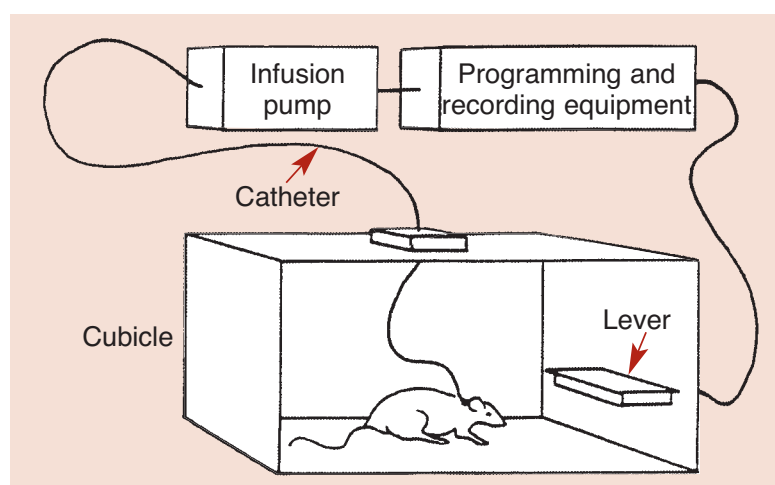


Fig 3.1 Apparatus that can be used to investigate the intravenous self-administration of nicotine in experimental rats. The nicotine is delivered from a syringe pump that is connected via a cannula to a catheter located in the jugular vein. The animals are trained to perform a task (depress a lever in this example) to receive small intravenous injections of nicotine. Reproduced from Stolerman *et al* with permission; copyright Elsevier 1991.¹

psychological and neurobiological mechanisms which mediate the reinforcing properties of nicotine that are considered pivotal to its ability to cause addiction in humans.⁴⁻⁶

3.3 Neurobiology underlying the reinforcing properties of nicotine

Most studies that have sought to establish the neurobiological mechanisms which mediate the reinforcing properties of nicotine have focused on the role of the mesolimbic dopamine (DA) neurons which project to the nucleus accumbens from the ventral tegmental area (VTA) of the midbrain (Fig 3.2). It is widely held that these neurons play a central role in the rewarding or reinforcing properties of drugs of dependence.⁷⁻¹⁰ The results reported by Corrigall and colleagues, which showed that selective lesions of the DA-secreting neurons that project to the nucleus accumbens attenuate responding for nicotine by experimental animals, emphasise the importance of these pathways to the reinforcing properties of nicotine.⁴ Subsequent studies showed that microinjections of a nicotinic receptor antagonist into the VTA of experimental animals has the same effect. These results

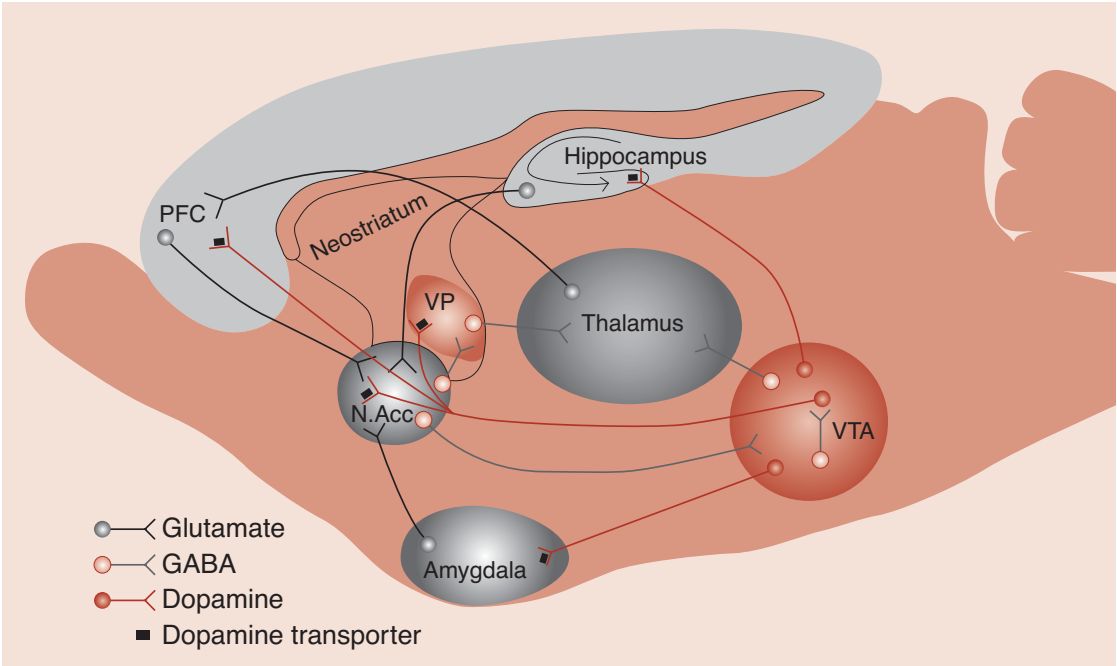


Fig 3.2 Mesolimbic dopamine pathways in the rat brain which project to the forebrain from the ventral tegmental area. The principal pathways project to the nucleus accumbens and prefrontal cortex (PFC). Other neurons project to the amygdala and hippocampus. Other areas of the brain, principally the PFC, amygdala and hippocampus, also send glutamatergic (excitatory) and GABA (inhibitory) projections to the nucleus accumbens. These projections may also exert significant control over dopamine release in the accumbens. Note also the inhibitory GABA feedback loop from the accumbens to the VTA. VTA = ventral tegmental area; N. Acc = nucleus accumbens; PFC = prefrontal cortex.

support the conclusion that the reinforcing properties of nicotine in this paradigm depend upon the stimulation of neuronal nicotine receptors located on or close to the DA cell bodies in the VTA that stimulate the activity (that is, the firing rate or firing pattern) of the DA neurons which innervate the nucleus accumbens.¹¹

For the past 20 years or so the effects of treatments which influence the activity of mesolimbic DA neurons have been explored in conscious freely-moving animals using techniques such as *in vivo* microdialysis. Although microdialysis probes are too large to sample DA release directly into the synaptic cleft, they can be used to measure changes in the concentration of DA in the interstitial space between the cells, often referred to as DA overflow. Experiments employing this technique have shown that non-contingent injections of nicotine (injections administered by an experimenter, over which the animal has no control) stimulate mesolimbic DA neurons in a way that results in substantial and sustained increases in the overflow of DA in the interstitial spaces between the cells in the nucleus accumbens.^{12,13} More recent imaging studies employing positron emission tomography (PET) have shown that exposure to cigarette smoke also increases DA release in the human nucleus accumbens.¹⁴ This observation supports conclusions drawn from an earlier study with human subjects which suggested that the reinforcing properties of tobacco smoke depend upon the stimulation of DA receptors in the brain.¹⁵ The results imply that studies with experimental animals are able to model changes in DA release in the nucleus accumbens that may be of relevance to our understanding of the neurobiology underlying the dependence upon tobacco in humans.

3.4 The role of the accumbal shell

The nucleus accumbens is composed of two subdivisions: the accumbal core and the accumbal shell, which are anatomically distinct and are thought to have different psychophysiological roles.^{16,17} Anatomically, the accumbal shell seems to form an extension of a clearly limbic structure, the amygdala, and is thought to mediate the rewarding properties of drugs of dependence. This conclusion is strongly supported by the results of a study with another psychostimulant drug of dependence, cocaine, which showed that rats can be trained to self-administer microinjections of the drug directly into the medial shell of the structure whereas they will not learn to self-administer the drug through cannulae targeted at the accumbal core.¹⁸ These results imply that increased DA release in the accumbal shell mediates the reinforcing properties of cocaine.

Sellings and Clarke showed that selective lesions of the DA terminals in the medial shell of the accumbens also attenuate the rewarding properties of

amphetamine.¹⁹ These results, when taken together, suggest that the rewarding properties of psychostimulant drugs of dependence, and the acquisition of a response to them, depends specifically upon increased DA overflow in the shell subdivision of the nucleus accumbens. By contrast, selective lesions of the DA projections to accumbal core diminish the increase in locomotion evoked by an injection of amphetamine.¹⁹ This observation supports the anatomical evidence that the accumbal core forms part of the motor systems of the brain and mediates the locomotor stimulant properties of drugs of abuse.

Acute injections of nicotine to nicotine-naïve animals increase DA overflow in the medial shell of the accumbens, but have little or no effect in the accumbal core.^{20,21} Di Chiara has summarised the evidence that stimulation of DA overflow in the accumbal shell is pivotally important to the development of nicotine-seeking behaviour, and is thus an essential component of the neurobiology underlying the reinforcing properties of the drug.^{9,22} In this important sense, it seems to resemble closely the mechanisms which are thought to mediate the reinforcing properties of other psychostimulant drugs of abuse.

Experiments performed some years ago showed that the self-administration of small intravenous injections of cocaine, which were contingent on a response, elicited greater increases in DA overflow in the nucleus accumbens, measured using microdialysis, than that evoked by the non-contingent infusion of matched intravenous doses of cocaine.^{23,24} This was a surprising finding because the effect could not be attributed to a simple pharmacological difference in the response between the two groups of rats in the experiment. Recently, Lecca and colleagues have reported that the self-administration of nicotine also results in greater DA overflow in the shell subdivision of the nucleus accumbens than non-contingent administration.²⁵ Other studies from the same laboratory have shown that the self-administration of cocaine also enhances its effects on DA overflow in the shell subdivision of the nucleus accumbens.²⁶ These findings highlight an important aspect of the effects of drugs of dependence on this pathway. When the animal has no control over the delivery of an addictive drug (non-contingent drug delivery), the increase in extracellular DA (DA overflow) evoked in the accumbal shell does not exhibit any sensitisation. Indeed, it may exhibit tolerance,²⁰ resulting in a reduced response to the drug when it is given repetitively as daily injections. However, when an addictive drug is self-administered (that is, when drug delivery is contingent upon the animal making the appropriate response), an enhanced or sensitised DA response to the drug may be observed in the accumbal shell.

Thus, it would appear that the neurobiological mechanisms underlying behavioural conditioning of the response influence the effects that these drugs exert on the DA neurons which innervate the accumbal shell, and that their

reinforcing properties are enhanced by the process of self-administration.^{25,26} This sensitised response is thought to be important to the development of dependence on drugs such as nicotine, although the neurobiological mechanisms which mediate the effect remain to be established.

3.5 The role of the accumbal core

The acute administration of nicotine to drug-naïve rats has little or no effect on DA overflow in the accumbal core. However, if the drug is given repetitively in the form of daily injections, the DA projections become sensitised to the drug and injections of nicotine elicit substantial and sustained increases in DA overflow in this subdivision of the structure.^{20,21} Neurons within the accumbal core send major projections to areas of the brain which mediate motor responses and, therefore, it has been proposed that this subdivision of the nucleus accumbens is likely to be involved in the control of locomotion.¹⁶ Because of this, it has been suggested that increased DA overflow in the accumbal core may mediate the locomotor stimulant properties of nicotine,^{13,20} which can be measured in animals as an increase in locomotion in a simple activity box. This conclusion is consistent with the evidence that the repetitive administration of nicotine to experimental rats not only results in sensitisation of its effects on DA overflow in the accumbal core, but also in sensitisation of its effects on locomotor activity. This is further supported indirectly by experiments with another psychostimulant, amphetamine, which have shown that selective destruction of DA terminals in the accumbal core of rats attenuate the locomotor stimulant properties of the drug.¹⁹

Other experiments, however, have shown that expression of the sensitised DA response to nicotine in the core of the accumbens of experimental rats is attenuated or abolished by the prior administration of drugs which block N-methyl-D-aspartic acid (NMDA) receptors for glutamate in the brain.^{27,28} Since the microdialysis studies which generated these data could be performed in conscious freely moving animals, it was also possible to test the effects of the antagonists on the sensitised locomotor response to nicotine in the same animals. The experiments showed that the antagonists had no effect on the sensitised locomotor response to nicotine, demonstrating a clear dissociation between the sensitised neural and the behavioural responses to the drug.^{27,28} The location of the NMDA receptors remains controversial, although it seems reasonable to suggest that they are located on the DA neurons in the VTA which project to the accumbens (Fig 3.3).²⁹

These and other results have led to the suggestion that the sensitised DA responses to nicotine observed in the accumbal core are more likely to be

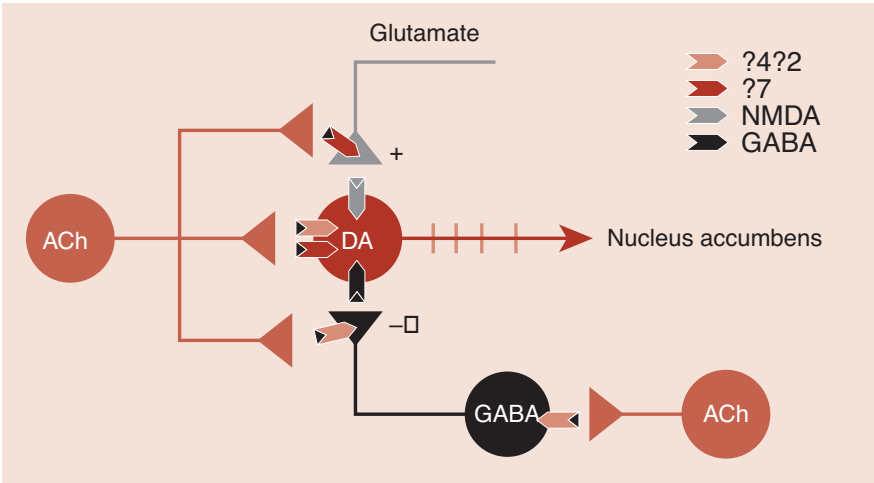


Fig 3.3 Neuronal regulation of mesoaccumbens dopamine neurons within the ventral tegmental area. The neurons shown are thought to synapse with the DA-secreting neurons in the ventral tegmental area (VTA). The ACh (cholinergic neurons) probably project, predominantly, from the pedunculopontine tegmentum (PPTg) in the midbrain. Some of the glutamate-secreting neurons may also project from project from the PPTg, although glutamate neurons in the prefrontal cortex also innervate this structure. The GABA-secreting neurons are located on projections from the nucleus accumbens and on inter-neurons located within the VTA. DA = dopamine; VTA = ventral tegmental area; ACh = acetylcholine.

implicated in the neurobiology underlying nicotine dependence than a simple neurobiological correlate of the locomotor stimulant properties of the drug.^{30,31} Interestingly, sensitisation of the DA projections to the accumbal core, evoked by nicotine, appear to be a response which predominates when the drug is given non-contingently by an experimenter rather than when the drug is self-administered. This fact led Lecca and colleagues to argue that the DA projections to the accumbal core do not play a major role in the neurobiology underlying nicotine addiction.²⁵ This conclusion, however, is controversial. Others have suggested that the sensitised DA responses in the accumbal core, evoked by repetitive administration of the drugs, is fundamentally important to their ability to cause dependence, particularly with regard to the role that conditioned stimuli play in the development of the addiction.^{32,33,39} This important issue is considered in the following section.

3.6 The role of conditioned stimuli in nicotine reinforcement

Most of the experiments which have explored nicotine self-administration in experimental animals have incorporated a conditioned stimulus into the experimental design. Indeed, it often proves difficult to demonstrate nicotine self-administration in experimental animals when nicotine is the sole reinforcer.^{33,35} In these paradigms, the presentation of nicotine is associated with the presentation of

another stimulus (such as a light or a tone which itself has little or no reinforcing properties), and both the acquisition and maintenance of responding for nicotine is facilitated.^{35,36} Furthermore, the cues can acquire the properties of a conditioned stimulus which maintains nicotine-seeking behaviour even when the primary reinforcer (nicotine) is absent.³⁵ Studies with other reinforcers, such as food or cocaine, have shown that the effects of conditioned stimuli on reward-seeking behaviour depend upon increased activity of neurons located within the core of the nucleus accumbens.^{37,38} Robinson and Berridge have long argued that the sensitised responses to drugs of abuse mediate the attribution of 'incentive salience' (the capacity to motivate animals to seek the drug) to conditioned stimuli paired with delivery of the drug.^{32,33} They argue that these paired stimuli or cues are, therefore, pivotally important to the transition to dependence.

Other animal studies, in which a conditioned stimulus has been paired with intravenous injections of cocaine rather than nicotine, have shown that in the absence of the primary reinforcer (cocaine) the non-contingent presentation of a conditioned stimulus evokes a regionally selective increase in DA overflow in the core of the nucleus accumbens.³⁹ The presentation of a conditioned stimulus in this way is thought to model the way such stimuli provoke drug-seeking behaviour in abstinent individuals. Thus, the data taken together provide strong support for the conclusion that increased DA overflow in the core subdivision of the nucleus accumbens promotes the compulsive drug-seeking behaviour that characterises the transition to addiction,³⁴ and that the addicted animal experiences reward from both the drug itself and from the paired stimulus.

3.7 Desensitisation and the neurobiology of addiction

The data summarised in the preceding paragraphs have provided strong support for the conclusion that the reinforcing properties of nicotine, which underpin addiction to the drug, depend upon stimulation of the nicotinic receptors located on the mesolimbic DA projections to the nucleus accumbens. However, if animals are given a second injection of nicotine within 60–90 minutes of the first, the DA response to the drug in the nucleus accumbens is either abolished or attenuated substantially.⁴⁰ Also, if nicotine is delivered by continuous infusion using a protocol which maintains the blood nicotine concentration at a level commonly found in the plasma of habitual smokers, the DA response to nicotine injection is blocked.^{40,41} Furthermore, the blood nicotine concentration in experimental animals allowed to self-administer nicotine intravenously rises quickly to concentrations that could be expected to desensitise the neuronal nicotinic receptors which mediate its effects on DA overflow in the nucleus accumbens.^{34,42} These

results, which are supported by other electrophysiological data,⁴³ suggest that exposure to nicotine not only stimulates the nicotinic receptors in the brain which mediate its effects on DA release in the accumbens, but can also desensitise the receptors if exposure to the drug is sustained even for a relatively short period of time. Many regular smokers smoke in a way that is likely to result in the accumulation of nicotine to a concentration that causes desensitisation of these receptors. Nevertheless, they continue to smoke, and to find the habit reinforcing, when it is unlikely that the nicotine they inhale has any significant effects on DA overflow in the accumbens.^{39,44} Thus, hypotheses which seek to explain the addiction to nicotine and tobacco need to explain why self-administration continues at a time when the drug no longer stimulates DA overflow.

3.8 The effects of nicotine withdrawal

There is abundant evidence that many regular smokers experience significant withdrawal effects when they first quit smoking, and that these symptoms can be relieved by nicotine replacement.^{45–48} Studies with experimental animals have shown that the abrupt withdrawal of nicotine, following a period of chronic treatment, elicits behavioural changes which are thought to model some of the symptoms of the tobacco abstinence syndrome experienced by abstinent smokers.^{49,50} Other behavioural results, using an experimental approach in which rats are trained to stimulate reward pathways within the brain directly through indwelling electrodes, suggest that nicotine withdrawal from experimental animals increases the threshold at which animals find stimuli sufficiently rewarding to elicit a behavioural response.^{51,52} This latter response to nicotine withdrawal has been putatively associated with decreased DA overflow in the accumbal shell.⁵³ The neural responses to nicotine withdrawal are thought to model the neurobiological changes within the brain which mediate the anhedonia (the diminished ability to experience pleasure) experienced by many smokers when they first quit the habit. This symptom may also be experienced following relatively short periods of overnight abstinence. All these behavioural consequences of nicotine withdrawal can be reversed by the administration of nicotine and some non-nicotinic therapies for tobacco dependence such as bupropion.^{54,55} Thus, these studies are thought to provide a behavioural model which can be used to explore novel treatments which might be used to alleviate the effects of nicotine withdrawal in humans.

It seems reasonable to suggest that many smokers will seek to maintain their blood nicotine concentrations at levels which prevent the symptoms of withdrawal. This explanation provides one potential reason why smokers may continue to

smoke at times when they are unlikely to experience any positive reinforcement derived directly from increased DA overflow in the nucleus accumbens. However, it does not account for the fact that nicotine replacement therapy, although a valuable aid to smoking cessation, is not as efficacious as would be anticipated if tobacco dependence reflected a 'simple' addiction to nicotine.⁵⁶ It is important, therefore, to consider more carefully other mechanisms that might be involved, including the putative role of the nicotine delivery vehicle, and of behavioural and other social factors and cues associated with smoking.

When given to animals that have not been preloaded with the drug, a single injection of nicotine results in a sustained increase in DA overflow that persists for 60–120 minutes.^{20,21} Mansvelder and colleagues have suggested that the sustained response reflects complex effects on the nicotinic receptors located on the DA neurons themselves and the terminals of GABA and glutamate neurons which innervate the VTA (see Fig 3.3).^{57,58} Balfour and colleagues have argued that the sustained DA response to nicotine is related to stimulation of NMDA glutamatergic receptors located on DA-secreting neurons in the VTA, resulting in an increased proportion of the cells which exhibit burst firing.^{34,40} Balfour and colleagues also suggest that burst-firing of DA neurons results in DA release from varicosities directly into the interstitial space sampled by the dialysis probes that are commonly used to measure DA overflow in the brain.⁴⁰ Common to the hypotheses of both groups is the concept that a single injection of nicotine elicits a sustained increase in extra-cellular DA, which plays a central role in the development of nicotine dependence. Significantly, a study by Lecca and colleagues has shown that the self-administration of nicotine also elicits a sustained increase in DA overflow in the accumbal shell and core which persists for at least 90 minutes into the experimental session.²⁵

3.9 The putative role of paracrine dopamine

The presentation of natural rewards, such as food to a hungry rat, also increases DA overflow in the nucleus accumbens. Recent studies, however, suggest that increased DA overflow in the nucleus accumbens is not essential for animals to learn to respond to obtain rewards of this type, although it does facilitate the acquisition of responding and increase its intensity.⁵⁰ Thus, increased DA overflow does not seem to mediate the reinforcing properties of natural rewards directly, but to enhance their effects on behaviour. Balfour has argued that the data are consistent with the hypothesis that extracellular DA in the interstitial space between the cells functions as a local hormone which influences the probability that an individual learns the behaviours associated with the delivery of rewards,

and also promotes reward-seeking behaviour in response to cues associated with the presentation of the reward (Fig 3.4).^{34,40} When compared with natural rewards, the effects of drugs of dependence on the concentration of DA in this extracellular space are large and sustained, and according to this theory it is this property of the drugs which confers on them their addictive potential. The hypothesis, summarised in Fig 3.4, proposes that increased DA overflow in the accumbal shell following nicotine administration confers reinforcing pleasurable properties on behaviours (lever-pressing in rats or smoking in humans), which result in delivery of the drug. It also confers reinforcing properties on the stimuli associated with its delivery, such as the irritation in the mouth, throat and bronchi, the taste of the tobacco smoke, or perhaps even the anticipation of smoking.

It is estimated that a smoker takes eight to 10 puffs on each cigarette which may be inhaled during periods when extracellular DA in the accumbal shell has been elevated by the nicotine boli in the first two or three puffs. Thus, the repetitive nature of cigarette smoking lends itself particularly well to rapid

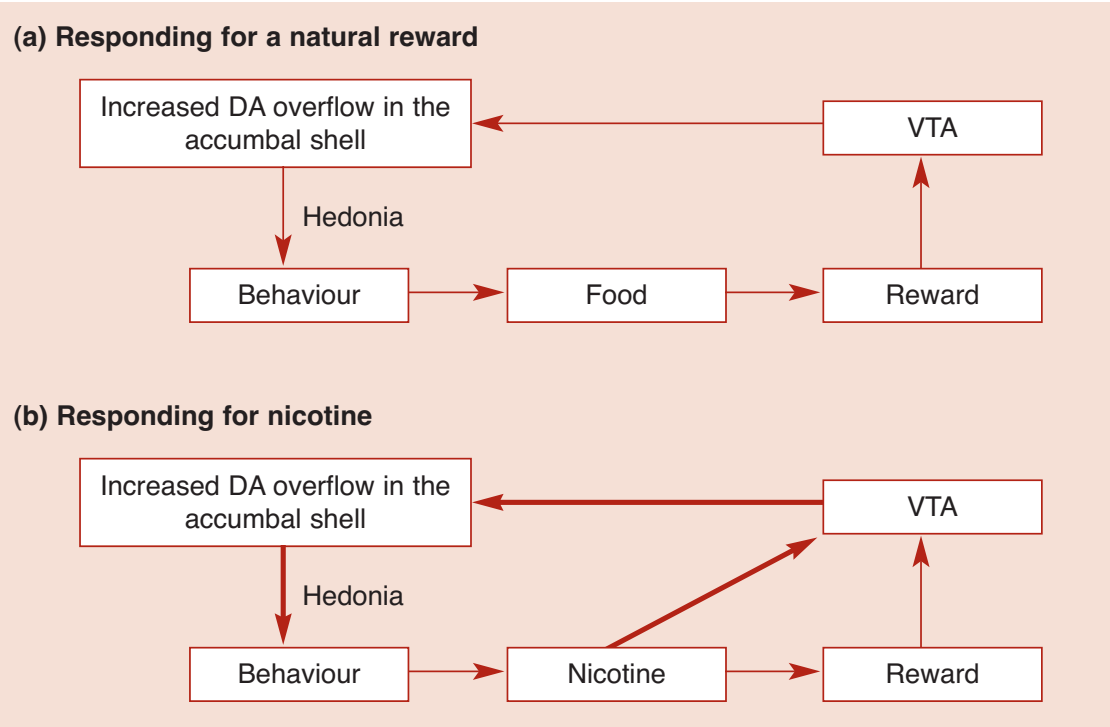


Fig 3.4 The role of increased dopamine overflow in the accumbal medial shell on responding for a reward. **(a)** The proposed circuitry by which a natural reward, such as food, increases DA overflow in the accumbal medial shell. It is hypothesised that this increased DA overflow confers rewarding or hedonic characteristics on a behaviour, such as a lever-pressing response, that results in presentation of the reward. **(b)** Nicotine may greatly enhance the hedonia associated with the behaviour by directly increasing extracellular DA in the accumbal shell, bypassing the need for the drug itself to exhibit rewarding properties. DA = dopamine. Reproduced from Balfour *et al* with permission; copyright Elsevier 2000.⁴⁰

acquisition of the addiction of tobacco. The hypothesis summarised in Fig 3.4 relates specifically to conditioned stimuli closely associated with the inhalation of tobacco smoke. However, it is also possible that increased DA overflow in the accumbal shell mediates the 'pleasure' smokers derive from environmental stimuli, such as specific locations or activities like taking a break from looking after the children, having a drink in a pub or relaxing after a meal, which they associate with smoking.

The hypothesis also proposes that extracellular DA in the accumbal core acts as a local hormone. It is proposed that its role in this subdivision of the nucleus accumbens is to increase the probability that the stimuli associated with smoking promote the desire or craving to smoke. Thus, when nicotine itself increases DA overflow in this part of the accumbens, it may serve to increase the craving to continue smoking. If a smoker experiences this effect by smoking following a period of abstinence, the hypothesis predicts that it will provide one of the powerful drivers which promote relapse. Furthermore, it seems reasonable to suggest that the regionally selective increases in DA overflow in the accumbal core, evoked by non-contingent exposure to conditioned stimuli or cues associated with delivery of an addictive drug, also contribute significantly to the cravings which commonly result in relapse.^{34,39,60}

As indicated earlier in this review, nicotine alone is a relatively weak reinforcer in a self-administration paradigm, and robust self-administration of the drug is best achieved using protocols which incorporate a conditioned reinforcer.^{35,36} The initial studies which demonstrated the facilitatory role of conditioned stimuli employed small intravenous injections of nicotine that were contingent upon the animal making a response (pressing a lever) in order to receive the injections of nicotine. It was assumed that for nicotine to confer reinforcing properties on a conditioned stimulus, such as a simple light, it was necessary for the nicotine injections paired with the stimulus to be contingent upon a response; that is, self-administered in a manner which could be controlled by the experimental animal. More recent studies suggest that this may not be true. Donny and colleagues have shown that non-contingent injections of nicotine, which are not under the control of the animals, also have the ability to confer significant reinforcing properties on a light stimulus which are equal in magnitude to those seen in animals which self-administer the drug.⁶¹

This observation may be profoundly significant because it suggests that, in the self-administration paradigms employing animal models, responding is reinforced to a significant extent by the conditioned stimulus rather than the drug directly.^{60,61} In this theory, an important role of nicotine in developing dependence is to greatly enhance the reinforcing or rewarding properties of stimuli

paired with delivery of the drug. If this observation translates to tobacco smoke, it implies that people may smoke, predominantly, for conditioned stimuli associated with inhaling tobacco smoke, rather than a simple dependence on the bolus of nicotine present in each puff. This conclusion gains much support from the studies of Rose and colleagues who have shown that sensory stimuli, such as the taste of the tobacco smoke or the irritation of the mouth and bronchi experienced by a smoker when they inhale tobacco smoke, play a pivotal role in regulating smoking behaviour and the craving to smoke.⁶² Furthermore, these stimuli seem to be particularly important for more highly addicted smokers.⁶³ Balfour has argued that these sensory stimuli serve as powerful conditioned reinforcers for smokers.^{34,60} The evidence that nicotine also plays a pivotal role in the addiction to tobacco is, nevertheless, compelling. Thus, if the hypothesis that sensory stimuli present in tobacco smoke are central to development of addiction to tobacco smoke is correct, it remains necessary to explain the role of nicotine. Balfour has sought to explain this paradox by suggesting that nicotine evokes changes in the brain which confer or magnify the reinforcing properties of sensory stimuli such as a light in animal studies or the sensory stimuli in tobacco smoke which would otherwise lack significant efficacy as a reinforcer.^{34,60}

3.10 A unifying hypothesis

There is growing consensus that increases in extracellular DA in the accumbal shell and core, evoked by nicotine, play complementary roles in the development of addiction to tobacco. This hypothesis proposes that the primary role of extracellular DA in the medial shell of the nucleus accumbens is to influence the probability that an individual exhibits a particular behaviour (Fig 3.5).⁴⁰ Increased extracellular DA in the accumbal shell is posited to enhance the 'rewarding' or hedonic properties of a behaviour, thereby increasing the probability that it is repeated. The result of this effect is to facilitate the acquisition and maintenance of behaviours that generate rewards so that they are learned efficiently. Responding for conditioned stimuli, associated with the presentation of either natural or drug rewards, seems to depend upon increased neural activity within the accumbal core.^{38,64} Non-contingent presentation of a conditioned stimulus, previously paired with an addictive drug, causes a regionally selective increase in DA overflow in the accumbal core.³⁹ The hypothesis predicts that increased DA overflow in this subdivision of the accumbens serves to increase the probability that exposure to a conditioned stimulus, associated with delivery of a reward, elicits Pavlovian reward-seeking behaviour. When this phylogenetically old, and relatively primitive, mechanism is stimulated

in its ability to act directly upon pathways within the brain which mediate behaviour and to evoke in these pathways unphysiologically large and sustained increases in extracellular DA. As a result, this learned or conditioned behaviour comes to dominate the behavioural repertoire of the individual.

For much of the day, the nicotine in tobacco smoke may not elicit the increases in DA overflow which the studies cited above imply mediate the dependence upon tobacco because receptors which mediate the responses are desensitised.⁴⁰ During these periods, it seems likely that smoking is reinforced solely by the conditioned stimuli present in tobacco smoke experienced by the smoker.^{34,40} Most smokers, however, experience times of abstinence each day, when they are asleep, for example, during which the receptors are resensitised. Thus, each day, there will also be occasions when the nicotine present in tobacco smoke again elicits the increases in DA overflow which are thought to be fundamentally important to its ability to confer potent reinforcing properties on stimuli present in the smoke, thereby maintaining the powerful addictive nature of the habit. In essence, therefore, tobacco smoking could be seen as a form of second order schedule of reinforcement in which responding is only occasionally reinforced by the direct effects of nicotine in the brain. Importantly, and perhaps surprisingly, the hypothesis does not require that the drug itself has euphoriant or rewarding properties in its own right. Indeed, there is some evidence that nicotine can have aversive properties which also depend upon its ability to stimulate DA neurons in the ventral tegmental area.^{65,66} These authors suggest that the data currently available support the conclusion that increased DA release in the nucleus accumbens may not mediate directly a rewarding property of nicotine itself, but has an important role in facilitating the acquisition and maintenance of specific goal-directed behaviours (lever-pressing in rats, smoking in humans) that result in presentation of the drug or stimuli.^{65,66} This conclusion is entirely consistent with the working hypothesis presented here, in which increased DA overflow in the accumbal shell and core play complementary roles in the promotion of behaviours that deliver nicotine and, especially, the conditioned stimuli associated with delivery of nicotine.

3.11 Inhibition of monoamine oxidase

It is also important to consider the possibility that tobacco smoke may contain other compounds that are reinforcing in their own right or which could potentiate the addictive properties of nicotine through a pharmacological interaction, rather than a psychological or behavioural mechanism. Fowler and colleagues have reported that tobacco smoke contains a compound, not nicotine itself, which inhibits the enzyme, monoamine oxidase (MAO).^{67,68} This is the main enzyme

responsible for the metabolism of DA in the human brain. They have argued that one of the primary consequences of this enzyme inhibition will be the potentiation of the effects of nicotine on monoamine, particularly DA, release in the brain, thereby enhancing the addictive potential of the nicotine inhaled in tobacco smoke. This conclusion is supported by the results of studies with experimental rats which have shown that pharmacological inhibition of MAO in the brain does enhance the reinforcing properties of nicotine when they are assessed using a self-administration paradigm.⁶⁹

3.12 Conclusions

- ▶ Drug dependence has commonly been perceived primarily as a ‘drug-seeking’ behaviour in which an addicted individual exhibits a powerful desire or craving for the drug, and that on each occasion the addicted individual takes the drug, he or she experiences a powerful rewarding effect which is mediated directly by the drug itself.
- ▶ However, evidence from both animal and human studies indicates that addiction to tobacco smoking is more complex. It also seems to depend critically upon the ability of nicotine to confer powerful rewarding properties on other sensory cues arising from the process of smoking, or possibly also the circumstances in which smoking occurs.
- ▶ The direct reinforcing properties of nicotine are experienced predominantly only after periods of temporary abstinence – after sleep, for example. For much of the remainder of the smoking day, nicotinic receptors are desensitised and the nicotine inhaled by the smoker probably does not cause stimulation of the pathways, particularly the mesolimbic DA system, implicated in the development of dependence. During these periods, smoking is probably reinforced primarily by conditioned stimuli (sensory cues) present in the smoke.
- ▶ By smoking in this way, smokers can maintain their blood nicotine level at a concentration sufficient to prevent the aversive consequences of withdrawal, while continuing to derive some positive reinforcement from the conditioned stimuli present in the smoke, and possibly other behavioural cues associated with smoking.
- ▶ Hypotheses concerning the neurobiological mechanisms have been derived predominantly from studies with experimental animals. As far as it has been possible to test them, the pharmacological responses to nicotine inhaled by humans in tobacco smoke elicit similar effects in the human

brain to those observed in experimental animals. It is important to acknowledge, however, that the rats and mice commonly used for experimental studies lack the complex cognitive skills and social behaviour of humans. It is also important to acknowledge that the interplay between the pharmacological properties of nicotine inhaled in tobacco smoke and the cues and conditioned stimuli associated with human tobacco dependence are likely to be even more complex than those revealed by animal studies. Future studies which seek to establish better treatments for tobacco addiction might usefully focus on this aspect of the problem.

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4 | Mechanisms of tobacco addiction in humans

- 4.1 Background and perspective
- 4.2 The addictiveness of tobacco products
- 4.3 The role of nicotine as the addictive drug in tobacco
- 4.4 The cycle of human tobacco use and addiction
- 4.5 Developments in imaging and cognitive assessment
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- 4.7 Conclusions

4.1 Background and perspective

As outlined in the previous chapter, research into the mechanisms of addiction in animal models in recent years has advanced understanding of the likely process and course of tobacco addiction in humans, and has implications for tobacco disease control and policy. It is now well established that nicotine is the drug in tobacco that is predominantly, but not entirely, responsible for the strength and course of addiction in tobacco smokers and the maintenance of tobacco smoking in the population. A report published by the Royal College of Physicians in 2000 described the reasons why cigarettes are an especially addictive form of nicotine delivery, and how nicotine addiction from tobacco smoking compared with other forms of drug addiction.¹ The report also described the biological mechanisms of addiction in humans, and how tobacco products are designed, manufactured and marketed to increase addiction risk.¹ Since then, the evidence base supporting understanding of nicotine as an addictive drug has continued to expand. Additionally, the importance of the cigarette as a vehicle to enhance the addictive effects of nicotine, and of neural mechanisms and genetic modulators of nicotine addiction, is becoming increasingly well documented.

4.2 The addictiveness of tobacco products

All leading medical authorities that have reviewed the evidence, including the Royal College of Physicians, the US Surgeon General, the US Food and Drug Administration (FDA), and the World Health Organization,^{1–4} have concluded

that tobacco products are highly addictive. In comparison with addiction to opioids, stimulants, sedatives, alcohol or other so-called ‘classic’ addicting substances, the risk of the development of addiction following initial use, the severity of the addiction, the risk of adverse health consequences and persistence of use even in the face of harm are all especially high with tobacco.^{1–3} Tobacco products optimise the delivery to the user of addictive doses of nicotine. The speed of absorption and addictive impact of nicotine is manipulated and optimised by the designs and ingredients used to make tobacco products.^{4,5} Compared with other addicting substances (including cocaine and heroin), initial use of nicotine is more likely to lead to addictive use, and the prevalence of addiction among all users is higher than that observed for other addictive substances. However, physiological dependence, intoxication and withdrawal are less pronounced than is the case with opioids and sedatives.^{1,2,6} In contrast with sedatives such as alcohol, nicotine intoxication occurs rarely in regular tobacco users.^{1,2}

4.3 The role of nicotine as the addictive drug in tobacco

Tobacco contains hundreds of substances; tobacco smoke contains more than 4,000, including several with potential behavioural effects. Nicotine is common to all tobacco products – smoked and smokeless.^{2,7,8} The addiction potential of nicotine is enhanced by the deliberate engineering of tobacco products as vehicles for nicotine delivery, among which cigarettes are recognised as the most addictive of all nicotine delivery systems.¹ These facts have long been recognised by the tobacco industry,^{2–4,9–11} as illustrated in a summary conclusion by a lead Philip Morris nicotine researcher, William L Dunn:

*The cigarette should be conceived not as a product but as a package. The product is nicotine Think of the cigarette pack as a storage container for a day's supply of nicotine Think of the cigarette as a dispenser of a dose unit of nicotine Think of a puff of smoke as the vehicle of nicotine Smoke is beyond question the most optimized vehicle of nicotine and the cigarette the most optimized dispenser of smoke.*¹⁰

The chemistry and pharmacology of nicotine alone qualify it as a potent and powerfully addicting drug.^{1,2} Specifically, nicotine meets all established criteria for a drug that produces addiction or, more technically, dependence and withdrawal (upon its abrupt abstinence) in the animal models used for making such determinations and investigating the mechanisms of addicting effects (see Chapter 3). Tobacco products are designed to enable nicotine to be readily and rapidly extracted, absorbed, and distributed to the central nervous system. The drug is five to

ten times more potent than cocaine or morphine in producing behavioural and psychic effects associated with addiction potential in humans, including measures of pleasure and liking.² Nicotine administration modulates levels of dopamine and other neurotransmitters that mediate addictive drug effects and primary biological drives such as reinforcement by food and other factors. Animal models demonstrate that nicotine produces reinforcing effects, tolerance, physical dependence and withdrawal, and suggest that some effects can be long lasting, including receptor up-regulation and a propensity to relapse to use following abstinence.^{1,2}

Some effects of nicotine, such as dose-related activation and inactivation of receptors and reversible tolerance were studied more than a century ago by pioneering researchers such as Langley and Dixon, while effects on specific nicotinic receptor subpopulations such as the $\alpha 7$ that appear to mediate reinforcement were not conclusively demonstrated until the 1990s.^{12–14} It has been recognised for centuries, and highlighted in the 1988 US Surgeon General's report on nicotine addiction, that nicotine can also contribute to the regulation of mood, cognition, attention, body weight and other functions that undoubtedly contribute to the power of the addiction and difficulty in giving up all forms of nicotine. An apparent genetic vulnerability to tobacco addiction and genetically conferred differences in nicotine addiction liability have been suspected, but not well understood, since at least the late 20th century.^{2,15,16}

4.4 The cycle of human tobacco use and addiction

4.4.1 Dependence and withdrawal

Dependence and withdrawal are separate disorders related to tobacco use. Each can be diagnosed by criteria issued by the World Health Organization in its International Classification of Diseases (ICD 10) and according to generally similar criteria by the American Psychiatric Association in its Diagnostic and Statistical Manual (DSM-IV).^{17,18} Essentially, dependence is the disorder of repetitive and compulsive use of a drug, whereas withdrawal is a syndrome of signs and symptoms that is precipitated when a regular user of a drug abruptly abstains. The more general term 'addiction' is often used synonymously with dependence by these same organisations, but is more variably defined. In this report, the term addiction is used interchangeably with dependence.

Dependence

The specific criteria for drug dependence used by both ICD 10 and DSM-IV are broadly similar, including phenomena such as the development of tolerance to

the effect of the drug, the occurrence of withdrawal symptoms on discontinuing use, increased drug use over time, compulsive use despite efforts to reduce or control ('out-of-control') drug use, and use in the face of adverse consequences. Whether the drug in question is cocaine, heroin, alcohol or nicotine, the criteria are the same, although drugs differ somewhat in their profiles of these phenomena. Intoxication is not a criterion of dependence, but is a frequent consequence of the use of many addictive drugs, and this too varies widely between drugs, occurring most prominently with alcohol and sedatives, and least commonly with stimulants and nicotine.¹

It is possible to use tobacco products occasionally without developing addiction, though even very low levels of tobacco exposure can be harmful to health. For example, second-hand smoke significantly increases the risk of lung cancer and many other diseases.^{1,19,20} With respect to most addictive drugs, most people who try the drug do not become addicted. For example, although cocaine is widely accepted as a highly addictive drug, several studies have shown that only about 5–6% of people who try cocaine develop dependence within two years of first use.²¹ The cigarette form of tobacco appears to be the most likely to lead to regular use and addiction in Britain and many other countries.^{1,20} Among young people who try smoking cigarettes, between one third and one half are currently likely to become regular smokers within two to three years. Many of these will try and fail to quit during their youth, but their addiction will drive them to persist in their use for many years, with drastic consequences to their health and life expectancy, and costs to healthcare, families and employers.^{1,22} The escalation from initial use to dependence is variable between individuals and is modulated by a variety of factors including opportunities to use tobacco, cost of the product, perception of harmfulness, social attitudes, and smoking behaviour of peers and family members. Several studies have found that the transition from initial use to regular use (variably defined as 'daily', 'five times per week', or '100 cigarettes') takes two to three years among adolescents.²³ Fewer studies are available in which measures of dependence have been collected from youth to determine the trajectory of development of dependence. However, the evidence suggests that at least some measures (trying and failing to quit, having strong cravings and having difficulty concentrating without cigarettes, for example) can emerge within weeks of initial use.²⁴

The most important determinant of the initial brand of cigarettes used appears to be the marketing and imagery associated with it, and many people remain loyal to that same brand for many years. While it appears that nicotine dosing characteristics can be manipulated by altering the ease of extraction of nicotine and the fraction of nicotine that is in the more bioavailable free-base (unprotonated) form, virtually any cigarette can be smoked to deliver a range of doses of nicotine.

Manipulation of the free-base fraction of nicotine with ammonia compounds and other ingredients may also alter the addictiveness of the products, but because most inhaled nicotine is absorbed, the extent to which such manipulation affects the graduation from initial use to addiction is unclear.^{1,3,25}

However, nicotine dosing characteristics are not the only factors in attracting new smokers and facilitating the graduation to regular use and addiction. Ingredients and design features that make cigarettes more palatable and attractive to target new smokers include a wide range of flavourings, smoke modifiers, burn accelerants and filter ventilation techniques.^{4,7,11,26–29}

Control of the fraction of free-base nicotine seems to be more important for oral smokeless tobacco products (chewing tobacco, moist snuff and snus), in making the product attractive to particular populations, than for cigarettes, because the speed and dose of nicotine delivered by these products depends more strongly on the free-base fraction of nicotine.^{3,30–32} This is because absorption of nicotine from oral smokeless tobacco products occurs predominantly in the mouth. Free-base nicotine is rapidly absorbed orally into systemic circulation by transfer across the buccal mucosa into the oral capillary bed, whereas protonated nicotine is much more slowly absorbed.^{3,30–32} Thus, to facilitate the development of addiction and minimise effects such as nausea that might discourage repeated use, smokeless tobacco companies have developed and marketed products that vary widely in their nicotine delivery characteristics. Products aimed at new tobacco users (termed ‘starter’ products within the industry) are designed to deliver their nicotine more slowly and in smaller amounts than products marketed to experienced, and presumed addicted and tolerant, tobacco users.^{3,23,30,32,33}

In addition to manipulating nicotine dosing characteristics to promote and maintain addiction, factors such as palatability and attractiveness also increase the likelihood that target populations will try, and continue to use, smokeless products.³ For example, in recent years, there has been a proliferation of smokeless tobacco products designed to be more convenient to use and to minimise the necessity of spitting, with unit doses of tobacco prepared in small sachets and lozenge forms, and in more user-friendly packaging such as pop-open containers (see Chapter 5).³⁴

Comparing the risk of escalation from initial use to addiction across different tobacco product types is difficult. Although there is an extensive base of epidemiological and laboratory evidence for cigarette smoking, the epidemiology and natural history of patterns of use of pipes, cigars, and smokeless tobacco is much less well documented. Moreover, daily intake for these products is less well defined than for cigarettes. Nonetheless, it appears likely that the risk of developing addiction following any smokeless use is lower than for cigarettes.^{30,35}

Medicinal nicotine products are intended for short-term use to support quitting smoking and are not designed to be attractive to non-tobacco users or to promote chronic use. The design, dosing and flavour (in the case of oral gum and lozenges) are intended to provide acceptable means of medicinal delivery to motivated smokers. Their nicotine dosing characteristics do not appear to facilitate the development of addiction and, although it is possible in principle, there is no documented evidence that initiation of tobacco addiction through the use of medicinal nicotine products has occurred.

The results of laboratory studies of the abuse liability of nicotine replacement medications are consistent with these conclusions, revealing the medications to be of low abuse liability compared with cigarettes.^{36–39} The nicotine nasal spray is the only medicinal form of nicotine replacement that readily enables the user to achieve doses of nicotine more closely approximating those provided by cigarette smoking or oral tobacco use. In fact, the nasal spray is capable of delivering nicotine rapidly enough to produce a transient two-fold nicotine boost in arterial blood relative to venous blood, and although its abuse liability is low compared with cigarettes, it does produce effects beyond those of other marketed medicinal nicotine products.^{40,41} These effects led the US Drug Enforcement Administration and the FDA to consider regulating the nasal spray as a controlled substance. Ultimately, the agencies decided against this, in part because the sensory properties of the nasal spray were considered unattractive enough to discourage use or abuse by persons not motivated to quit smoking.^{3,31}

Withdrawal

Although separate entities, withdrawal and dependence are closely related in that persons who show signs of dependence are also more likely, if they discontinue smoking, to experience withdrawal symptoms. Furthermore, withdrawal severity is related to the number of cigarettes smoked per day.^{1,2} Nonetheless, although withdrawal is associated with dependence, withdrawal is neither necessary nor sufficient for the development of dependence.^{17,18} For example, persons maintained on opioids for pain, sedatives for epilepsy and nicotine replacement for tobacco dependence may show signs of withdrawal if the drug is discontinued abruptly, but most such persons do not use the medicine in a manner considered ‘out of control’ or meeting criteria for ‘dependence’.⁴² Conversely, some opioid abusers do not use opioids daily, and show little or no withdrawal when abstinent from the drug. Many stimulant dependent people also display little or no withdrawal when not using.^{6,18,43}

Withdrawal is generally defined in terms of rebound-like symptoms that are

usually the opposite of those produced by administration of the drug. For example, opioid-associated pupillary dilation is replaced by constriction, sedative-associated muscle relaxation by tremors, and nicotine-associated calming by anxiety and irritation.^{6,43} Withdrawal syndromes are diagnosed according to specific criteria for each drug class.^{17,18} Criteria for tobacco or nicotine withdrawal include dysphoria or depressed mood state, irritability, anger, difficulty concentrating, anxiety and restlessness. Strong and recurrent cravings are also common and are associated with relapse to tobacco use.

The onset of withdrawal symptoms can contribute to the dependence process because resumption of tobacco use quickly relieves the symptoms. For example, a brain imaging study showed that the first three puffs on a cigarette could deliver sufficient nicotine to occupy 70% of $\alpha 4\beta 2$ nicotine receptors in the brain, and that smoking one cigarette resulted in 88% occupation, thus reducing withdrawal-associated cravings and perpetuating the addiction cycle.⁴⁴ It is not clear whether slower delivering forms of nicotine, such as uninhaled cigar smoke or oral smokeless tobacco, can saturate brain nicotine receptors so fully or rapidly, and this potential characteristic of inhaled cigarette smoke may help to explain why the cigarette appears to be the most addictive nicotine delivery system. Nicotine replacement medications can reverse withdrawal associated brain function deficits,^{13,33,45} but it is unlikely that current dosage formulations provide as rapid or as complete receptor satiation as is achieved by cigarettes.

Most cigarette smokers in Britain and many other developed countries begin smoking in adolescence and graduate to daily use and dependence, smoking between 10 and 30 cigarettes each day by the time they are around 18 years old. Most of these individuals also show signs of withdrawal on abrupt discontinuation of use. In contrast, intermittent smokers (smokers of fewer than five cigarettes per day) and non-daily cigarette smokers may still meet criteria for dependence, but many do not meet criteria for the withdrawal disorder. Withdrawal from smokeless tobacco use is qualitatively similar to that from cigarette smoking, but the magnitude of the symptoms is generally somewhat less than observed in cigarette smokers. This is consistent with the more gradually onsetting and offsetting effects of oral nicotine delivery compared with smoked tobacco.^{30,35}

4.4.2 Environmental determinants of tobacco use and addiction

The high risk of addiction that accompanies tobacco use is not a simple consequence of the intrinsic addictiveness of nicotine or even of the cigarette. Marketing and other social influences (for example, product use by social icons and in the media) affect the likelihood of smoking initiation, continuation and quitting,

as well as cigarette brand preferences of specific populations (such as targeted minorities, women and youth).^{3,46} Social influences and marketing using athletic and health-associated imagery were important factors in reversing the mid-20th century decline in smokeless tobacco use in the United States.^{3,47}

The risk of use of any addictive drug, of progression to regular use and addiction, and the probability of cessation, are all influenced by environmental factors.^{2,46} Factors important in initiation of drug use include the image of the drug, social forces (particularly the social acceptability of use and perceived prevalence of use in society and among peers), portrayed use in media, access, cost, and the effectiveness of ongoing drug education and prevention programmes.² Similarly, cessation can be precipitated and sustained outside treatment (sometimes referred to as 'spontaneous remission'), by social sanctions, access, cost, peers, and legal consequences.² For example, the risk of alcohol addiction is heightened in communities with ready access and greater social tolerance for use, and to opioids in anaesthetists and other medical professionals who have easy access to such drugs. Furthermore, environmental factors can strongly influence the prevalence of use and addiction of various forms of a given drug. This is evident in the dramatic shifts in preferred forms of tobacco over the course of the 20th century in England, the United States and Sweden.^{20,48} It is also true of other drugs. For example, the relative preference for beer, spirits, red versus white wine, and so on, have shifted in recent decades probably as a function of marketing campaigns and also by reports that moderate drinking of some alcoholic beverages may have health benefits.⁴⁹ The opioid analgesic OxyContin® became the preferred form of oxycodone among drug abusers in many countries, in part due to its formulation and in part due to environmental factors including extensive media reporting which implied more addictive effects than were explained by its pharmacology.^{50,51} Medicinal nicotine formulations are designed to be less attractive than products used for initiation of nicotine dependence or any use other than to quit smoking and sustain abstinence. However, it is plausible that patterns of abuse could emerge if these products were marketed more aggressively with, for example, messages implying weight control or attention improvement, or with campaigns similar to those used in the past to give cigarettes a highly desirable image through the use of various cultural icons as role models.

Although the risk of addiction is high following any smoking, and is present with all kinds of tobacco use,^{52,53} the fact that not all who try smoking escalate to addiction, and that many people who become daily and addicted smokers are able to quit, is encouraging from a public health perspective. In fact, the situation today in which one third to one half of initial users become regular smokers is

much more hopeful than in the 1970s, when Michael Russell observed what Jean Cocteau had said of opium in the 1930s, that, ‘He who has smoked will smoke’, was then true of tobacco smoking.²² Specifically, relying upon a 1960s survey of UK adults, Russell observed that persons who had smoked only four cigarettes had a 94% chance of smoking for another 30–40 years.⁵⁴ This perspective is important because it illustrates the importance of environmental determinants in the natural history of tobacco use. Environmental interventions that reduce the prevalence of tobacco use and the risk of progression to addiction, and stimulate cessation among users, are now increasingly understood and have been discussed in detail elsewhere.^{55–58} They include measures such as increasing price, smoke-free policies, tobacco advertising and promotion bans, health warnings and media campaigns, and individual smoking cessation treatment services. Although restricting access to procurement of cigarettes is supported by many tobacco control leaders to reduce use by youth, the practical difficulties in enforcement have lessened but not negated the importance of the seemingly obvious strong strategy.⁵⁹ Cessation of smoking by parents appears to support abstinence and motivate cessation by their children.⁶⁰ For established cigarette smokers, the marketing of and improved access to treatment for dependence and withdrawal to aid cessation are important in promoting cessation efforts as well as improving the chances of maintaining abstinence.^{61–63}

4.4.3 Role of tobacco product design in promoting addiction to smoking

For nicotine, as for other addictive drugs including opioids, cocaine, sedatives and alcohol, the pharmacological effects and liability of developing addiction depend in part on the formulation or vehicle of delivery, which also influences how the drug is used.^{64–66} For example, intravenous and smoked preparations of opioids and stimulants produce stronger and more desirable effects (to drug abusers) than oral preparations because the impact is quicker and stronger. Among oral formulations such as tablets, crushable forms that have a faster, stronger effect are generally the most attractive and addictive.⁶⁶ Smokable forms of opioids and cocaine, such as crack cocaine, essentially did for these drugs what cigarettes did for tobacco – they made it convenient to repeatedly self-administer desired doses, producing rapid and powerful effects that are extremely addictive.^{64,67}

The ingredients and design of tobacco products are intended to facilitate the rapid delivery of nicotine and consequently enhance the development of addiction in several ways.^{3–5} Tobacco leaf contains extractable nicotine that can readily lead to addiction by a variety of means of ingestion, though the degradation of

nicotine that occurs in the liver following its oral ingestion makes this a relatively unattractive route. Over thousands of years in the Americas, and over centuries throughout the rest of the world, tobacco-utilising vehicles for nicotine delivery have evolved to enhance the addictiveness of the drug to suit many different cultures, needs and interests.^{7,68} Furthermore, tobacco companies have researched and developed cigarettes to increase the likelihood that they will induce addiction quickly and strongly.^{3-5,9-11} Similarly, smokeless tobacco products have been engineered by many companies to facilitate the probability of repeated use and escalation to addiction. This includes physical design factors to control nicotine as well as to reduce unattractive product features, buffering chemicals to control nicotine dose and speed of absorption, and flavouring to appeal to various target populations (such as cherry flavour for youth).^{3,32,47}

A recent report by the Tobacco Regulation Study Group of the World Health Organization concluded that tobacco product modifications including ‘candy-like’ flavouring have been used to target youth for initiation.²⁹ Other published reports based on tobacco industry document analysis came to similar conclusions.²⁶⁻²⁹ In addition to making cigarettes more attractive to youth through flavour modification, cigarettes have been designed to provide smoother, less irritant smoke, using various chemical additives and physical design features to ease youth initiation.²⁶ Menthol has been used to cool and smooth the smoking experience, as well as to provide a distinct sensory feature incorporated in branding efforts targeted at various ethnic or other populations.^{69,70} Tobacco companies have targeted women with cigarettes, employing designs and ingredients to make them more physically attractive.^{71,72} Moreover, as documented by the US FDA, and through more recent evaluations of tobacco industry documents, the industry conducted extensive and sophisticated research on the neurobiology of tobacco dependence and the importance of nicotine dosing through control of free-base nicotine levels.^{3,31,73,74}

The concept of modifying the delivery system to affect addictiveness and attractiveness is neither new nor unique to tobacco. Flavoured alcoholic beverages – so called ‘alcopops’ – make alcohol more palatable, particularly for young people. Flavouring and other product modifications have been employed in youth-targeted alcohol marketing, according to the National Research Council and Institute of Medicine.^{49,75} The drug addiction researcher and editor of *Drug and Alcohol Dependence*, Robert Balster, made the following conclusion in his report to the World Health Organization:

It is well known that formulations and routes of administration play significant roles in the abuse of many drugs, including nicotine. Drug abuse scientists have begun to use this knowledge to suggest changes in the formulations of pharmaceuticals to reduce their risk for abuse and dependence. It is a perversion of

*science that the tobacco industry would apply these same principles to increase the use and abuse of their products.*⁷⁶

Tobacco industry documents confirm that the industry has used ammonia compounds to increase the fraction of rapidly absorbable free-base nicotine in smoke; acetaldehyde to interact with nicotine and to produce stronger ‘synergistic’ effects; menthol, glycerin, leuvenilic acid and chocolate in cigarettes to enable deeper absorption of smoke by masking the noxious constituents including nicotine; and extensive use of flavouring and physical design features to increase attractiveness and facilitate the development of addiction.

4.4.4 Genetic influences on tobacco addiction

Evidence that genetic factors play a role in the vulnerability to developing tobacco addiction as well as difficulty in achieving and sustaining abstinence originates in twin studies in the 1990s.^{77–79} These studies support the conclusion that the heritability index, namely the relative contribution of genetic factors or the ‘heritability’ of cigarette smoking compared with environmental factors, appears to be greater than 50%, with more recent studies suggesting heritability closer to 70%.⁸⁰ This is in the range of what is also estimated for alcoholism.⁸¹

Since then, a number of potential genetic mechanisms have been implicated in the development of tobacco use in youth, in addition to known environmental and family influences, and also in influencing the maintenance of addiction to smoking, including the serotonin transporter promoter polymorphism, various hepatic enzymes, dopamine receptor genotypes and brain-derived neurotrophic factor.^{82–88} Several reviews of the contribution of genetic factors to tobacco addiction are available, and this rapidly expanding area of research will not be recapitulated in detail in this report.^{89,90} Understanding of these effects on the addiction process is, however, still far from clear, and it seems that influences on the development of addiction may be very different from those that affect the maintenance of smoking behaviour in adults.

For example, the Ten Towns Heart Health Study assessed the relation between various measures of cigarette smoking, nicotine intake, genetically determined enzymes that influence nicotine metabolism and the effects of nicotine and dopamine in young smokers.⁸⁸ The study found that persons who metabolised nicotine more slowly due to diminished function of the CYP2A6 liver enzyme were more likely to progress to dependence than those who more rapidly metabolised nicotine. This contrasted with results of studies on adult smokers, which report lower dependence and increased cessation among persons with the

CYP2A6 allele.^{88,91,92} Also, whereas studies of adults have found that dopaminergic regulating genotypes affect the propensity to nicotine dependence, no such relation was found in young people in the Ten Towns study.^{93–95}

There are also some genetically conferred differences in nicotine metabolism and patterns of use across ethnic groups and, potentially, between males and females.^{92,96–102} It appears increasingly likely that some polymorphisms alter the vulnerability to tobacco addiction, possibly by modulation of the neurochemical mechanisms of nicotine reinforcement.^{90,103} Preliminary research also suggests that there are genetically conferred differences in beneficial response to medications for treating nicotine dependence.^{15,104,105} Such research may ultimately lead to the use of genetic testing to match treatment to individuals more effectively, though ethical and practical challenges to implementation will need to be considered and overcome,^{106,107} and the practical applicability and cost effectiveness of this approach are still far from proven.¹⁰⁸

4.5 Developments in imaging and cognitive assessment

In recent years, growth in understanding has come from more extensive evaluation of tobacco and nicotine effects in humans using brain imaging techniques and increasingly sophisticated cognitive assessment. Brain imaging techniques used in diagnostic medicine and for unravelling the pathogenesis of disease and cognitive function have evolved rapidly since the 1970s. The two most frequently used approaches for evaluating tobacco and nicotine in humans are positron emission tomography (PET) and magnetic resonance imaging (MRI), as well as its variant, functional MRI (fMRI). Electroencephalography (EEG) is not referred to as often as imaging, but modern EEG mapping may also be considered along with other approaches that provide a three-dimensional assessment of brain structure and function. These have been reviewed elsewhere.^{109–115} This chapter will highlight some recent findings that have implications for understanding addiction as well as potential implications for addressing tobacco addiction through treatment and policy.

4.5.1 Tobacco and nicotine effects on brain structure and function

Among the most important findings of clinical research utilising brain imaging techniques is that the human brain is changed structurally by tobacco exposure, with the change apparently explicable largely by the effects of nicotine. The key structural change is increased density of nicotine receptor binding sites. This has been demonstrated in studies comparing smokers with non-smokers, in post-

mortem studies of smokers, and in the direct relationship between amount of smoking and receptor up-regulation.^{116–118} Furthermore, another human autopsy study found a direct positive relationship between daily smoking and density of nicotine receptor binding sites in the hippocampus and thalamus.¹¹⁶ These findings are generally consistent with those reported in animal studies described in Chapter 3.

In addition to changes in brain structure, there are changes in function that appear to mediate reinforcing, cognitive and other effects of nicotine. These include changes in electrical activity identified through electroencephalography, in regional cerebral glucose metabolism and regional blood flow, and release of dopamine in the ventral striatum section of the brain.^{113,119–125}

4.5.2 Brain correlates of craving and withdrawal

Although craving is often considered a purely behavioural or psychological effect, it is, in fact, a reliable correlate of physiological withdrawal signs and it can be experimentally elicited and studied.^{126–129} Brain imaging studies now make it clear that these responses are physiologically mediated, thus blurring the distinction between so-called physical and psychological effects. Specifically, overnight abstinence-associated craving for cigarettes and cue-elicited cravings are associated with changes in regional cerebral blood flow and metabolism in studies utilising PET methodology.^{130–132} Studies employing fMRI techniques have also demonstrated changes in cerebral blood flow associated with cue-elicited craving.^{133–137}

4.5.3 Tobacco and nicotine effects on cognitive functioning and attention

It has long been understood that tobacco abstinence among smokers was associated with impaired cognitive function and attention abilities in particular, and that resumption of smoking or nicotine administration could restore performance.^{2,138} Imaging studies support the conclusions that the altered brain functioning associated with withdrawal can be reversed by nicotine administration in a variety of forms, and further that, even in non-smokers, the small benefits of increased attention are present and are associated with observable changes in brain function.^{13,139–144}

4.5.4 Reversibility of effects: treatment implications

Although acute functional changes such as cue-elicited craving and associated changes in regional cerebral blood flow are reversible, some changes may be long

lasting. For example, a study of 67 female cigarette smokers (mean age 25.5 years) found acutely diminished cognitive function and associated electroencephalographic activation and heart rate, with extended evaluation over 31 days revealing little or no recovery.¹⁴⁵ Although animal studies suggest that effects of nicotine on brain structure and function are probably reversible over time, they are of little help at this point in determining the time course of reversal in persons with many years of exposure to nicotine and other smoke constituents. Moreover, insofar as smoke exposure began during the neuroplastic period of adolescence, the concept of reversing to a baseline level may not be appropriate because the brain was changed by nicotine during its own development.

An implication of these findings is that it appears increasingly probable that some smokers may experience very long-term, perhaps lifelong, disruption of brain function, mood and/or cognitive ability following smoking cessation. Such individuals may require similarly long-term treatment support or nicotine maintenance, and this may account for the sustained use of nicotine medications by some ex-smokers, many of whom report that their use is to enable them to maintain abstinence.^{146,147} It is also consistent with the conceptualisation of tobacco dependence as a chronic disorder. It is at odds, however, with the strong guidance on the labelling of tobacco dependence treatment products to discontinue use after a certain period (three or six months) and with limitations in duration of reimbursement of product use.

4.6 Insights from new pharmacological developments

Two new medicines and a new category of medicines have been evaluated in human studies of smoking tobacco dependence. The results of these studies, along with the earlier animal studies, contribute further to our understanding of the mechanisms of tobacco addiction.^{148,149} Varenicline is a nicotinic acting drug, but its primary actions are on a subset of the family of receptors that are responsive to nicotine. Specifically, it acts as a full agonist on the $\alpha 7$ nicotinic receptor, which is involved in nicotine reinforcement as well as cognitive functioning such as memory. It has more limited, partial agonist effects at the $\alpha 4\beta 7$ nicotinic receptor, which is also involved in reinforcement memory and other cognitive functioning. It is not clear that these receptors are critical in the withdrawal process and clinical data are not yet available to permit full comparison of the efficacy of varenicline with that of medicinal nicotine as withdrawal treatment. The efficacy of varenicline provides additional support for the key role of nicotine in the tobacco dependence process. It also shows that not all actions of nicotine are required for treatment efficacy, implying that not all actions of

nicotine are relevant to the dependence process. This concept is not novel, but the data, from preclinical study to human efficacy trials, shed additional light on the receptor level mechanisms of dependence in humans.

The development of the CB1 cannabinoid receptor antagonist rimonabant, and the demonstration in animal models and preliminary human data that it has some effect as a smoking cessation therapy,¹⁵⁰ is a further interesting development. The CB1 receptor mediates the reinforcing and other effects of marijuana through dopamine release. Whereas activation of this receptor by cannabis use is known to increase appetite, blockade of the receptor by rimonabant reduces appetite and supports smoking cessation.¹⁵⁰ These findings are consistent with animal data demonstrating that nicotine potentiates several physiological and behavioural effects of marijuana extract, delta-9-tetrahydrocannabinol, which acts at the CB1 receptor. Whether the CB1 receptor is vital in the production of nicotine dependence or rather is simply another means by which dopamine release is modulated by nicotine is not clear. Medicinal nicotine reduces appetite and body weight as well as urges to smoke.¹⁵¹ The apparent linkage of tobacco dependence and/or treatment to cannabis dependence also contributes to the understanding that drug dependence disorders and perhaps appetite disorders have common mechanisms that may lead to better common treatments.

4.7 Conclusions

- ▶ Addiction to nicotine arises from a combination of genetic, environmental and pharmacological factors, but the characteristics of the nicotine delivery system are also crucially important.
- ▶ Cigarettes are the most addictive tobacco product.
- ▶ Cigarettes and many other tobacco products have been specifically designed, engineered and marketed to enhance both development and maintenance of addiction.
- ▶ Medicinal nicotine products are designed and marketed to minimise their addiction potential.
- ▶ The development of addiction includes changes in brain structure and function that result in cessation-associated withdrawal effects that typically persist for many weeks or longer in some individuals, thereby impairing the ability to achieve and sustain abstinence.
- ▶ Treatment of dependence and withdrawal can restore brain function, mood, and cognitive abilities, and thereby support cessation, but individuals appear to vary widely in how long they may require treatment, and probably in what forms of treatment are acceptable and effective.

- ▶ However, some of the changes in brain structure and function in smokers, particularly in those who began smoking when very young, may not be entirely reversible.
- ▶ Some smokers may never fully overcome their addiction, or even ever be able to quit all nicotine use.

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5 | Sources of nicotine for human use

- 5.1 Available sources of nicotine for human use
- 5.2 Dose and delivery kinetics of nicotine from different sources
- 5.3 Contaminants and additives
- 5.4 Addiction potential of alternative nicotine products
- 5.5 Use of alternative nicotine sources as substitutes for cigarettes
- 5.6 Conclusions

5.1 Available sources of nicotine for human use

Nicotine is available to people in the form of conventional tobacco products, nicotine medications and, more recently, in cigarette-like smoking devices that are intended to reduce exposure to some tobacco toxins, also called potential reduced exposure products (PREPs).

5.1.1 Tobacco

Tobacco generally refers to the leaves and other parts of plants that have been domesticated and used to obtain the alkaloid nicotine. Tobacco plants are a species of the genus *Nicotiana*, belonging to the Solanaceae (nightshade) family. There are 64 *Nicotiana* species; the two that are cultivated for tobacco are *Nicotiana tabacum* and *Nicotiana rustica*, the latter containing higher levels of nicotine.

Nicotiana tabacum is the major source of commercial tobacco. Tobacco is consumed in a variety of forms, including cigarettes, cigars, cigarillos, bidis, kreteks, pipe tobacco, snuff (oral and nasal) and chewing tobacco, but the great majority of tobacco consumed around the world is in the form of cigarettes (Fig 5.1).

Cigarettes are composed of shredded tobacco leaves and other parts of tobacco plants, with flavourings and other ingredients added, encased in paper and often attached to a filter through which the smoke is puffed. Most cigarettes are made of blond tobacco, while some European and Middle Eastern cigarettes are made of dark tobacco. Cigars contain dark tobacco leaves that are rolled and coupled with a wrapper that may be tobacco leaf or reconstituted tobacco sheet. Cigarillos are small, narrow cigars with no cigarette paper or filter. Pipe tobacco consists of a

(a) Cigarettes



(e) Oral moist tobacco (snus)



(b) Cigar



(f) Oral compressed tobacco



(c) Nasal snuff



(g) Bidis



(d) Oral loose tobacco



(h) Alternative smoking devices (PREPs)



Fig 5.1 Examples of tobacco products.

blend of a variety of leaf types and is often heavily flavoured to give particular aromas and tastes. Bidis (used particularly in India and South East Asia) and kreteks (Indonesia) are described in Chapter 1.

Smokeless tobacco includes oral snuff, loose leaf tobacco, plug tobacco, twist or rope chewing tobacco and dry snuff. Loose leaf tobacco consists of tobacco leaf that has been heavily treated with liquorice and sugars. Plug tobacco is produced from leaves that are immersed in a mixture of liquorice and sugar and then pressed into a plug (usually a square). Twist or rope tobacco is made from leaves flavoured and twisted to resemble a rope.

Moist snuff consists of fine particles of tobacco that contain considerable moisture. Many are treated with flavouring such as wintergreen or mint. Moist snuff is used orally in a technique known as ‘snuff dipping’, which involves placing a pinch of tobacco between the cheek or lips and the gum, or beneath the tongue. Moist snuff is also available prepared in small porous packets containing a single dose, for use in the same way. Dry snuff is powdered tobacco that usually contains flavour and aroma additives, and is taken by sniffing into the nose. Recently, oral tobacco preparations consisting of tablets of ground and compressed tobacco for buccal administration have been developed (Fig 5.1).

5.1.2 Nicotine medications

Nicotine medications have been developed for use as an aid to smoking cessation. They consist of nicotine chewing gum, nicotine patches, nicotine inhaler, nicotine spray and nicotine lozenges. Nicotine Polacrilex (nicotine gum) was the first of these products to be developed and has been available in a range of doses for well over 20 years. Nicotine transdermal patches became available in the early 1990s and deliver nicotine through the skin over 16- or 24-hour periods. The nicotine inhalator is designed to resemble a cigarette, and delivers nicotine from a cartridge by sucking through a plastic mouthpiece. The nicotine nasal spray is an aqueous solution of nicotine, buffered to be alkaline to facilitate rapid absorption when sprayed into the nose. Nicotine lozenges are small tablets that are placed in the buccal cavity, from which nicotine is absorbed slowly (Fig 5.2).

5.1.3 Potential reduced exposure products

Two tobacco companies in the United States have test-marketed cigarette-like products that deliver nicotine but are reported to deliver less tar and some other tobacco toxins. RJ Reynolds introduced the ‘Premier’ device, which heats tobacco and tobacco flavour beads using a charcoal ignition system. This results in vapor-

(a) Gum



(d) Lozenge



(b) Transdermal patch



(e) Microtab



(c) Nasal spray



(f) Inhaler



Fig 5.2 Medicinal nicotine products (UK branded examples).

isation of liquid and then condensation into an aerosol. A second generation of this product, ‘Eclipse’, uses a carbon tip to heat a mixture of tobacco and glycerin which then passes through a charcoal filter.¹ Eclipse differs from Premier in that it does not have flavour beads or an aluminium cylinder. These changes modify the smoke aerosol so that it more closely resembles that of traditional cigarette products.

Philip Morris has test-marketed a device called ‘Accord’. This comprises a heating device called a ‘puff-activated lighter’ which fits special Accord cigarettes. A puff on the cigarette activates a microchip which produces a controlled two-second burn and delivers smoke to the user.²

Some cigarettes have been marketed as PREPs based on lower levels of some tobacco smoke carcinogens (Omni and Advance were marketed in the US as low nitrosamine cigarettes),^{3,4} and some smokeless tobacco products are marketed as PREPs based on low nitrosamine levels (such as Ariva, a compressed tobacco tablet) (Fig 5.1).⁵

5.2 Dose and delivery kinetics of nicotine from different sources

In considering the dose of nicotine from tobacco and other products, it is important to understand the difference between the nicotine content of the product and the systemic dose of nicotine delivery to the user. The nicotine content refers to how much nicotine is contained in the product either by weight of tobacco or in a unit of use (such as a cigarette). Delivery, or systemic dose, refers to the absolute amount of nicotine absorbed into the body of the user. The term 'bioavailability' will be used to indicate the fraction of the nicotine content of a single dosing unit that is absorbed into the circulation.

5.2.1 Cigarettes

Most cigarettes used by smokers are commercially manufactured products, but there is also considerable use of hand-rolled cigarettes. Most of the data on nicotine delivery come from manufactured cigarettes. Manufactured cigarettes typically contain about 0.7 g of tobacco, but this varies widely according to the size of the cigarette and the nature of the processing (whether expanded or 'puffed' tobacco is used). There is wide variation in the nicotine content of the tobacco in cigarettes, ranging from 7 mg/g to 23 mg/g in tobacco sampled from cigarettes from several countries.^{6,7} Typical US and UK cigarettes contain about 15–18 mg nicotine per gram of tobacco, or an average of 10–12 mg nicotine per cigarette.

The amount of nicotine absorbed from the cigarette depends on the intensity and volume of puffing, how much smoke is inhaled, and how many puffs are taken from the cigarette. The amount of smoke taken in may also be greatly influenced by whether ventilation holes in the filter are blocked by fingers or lips. Typically, between 1 mg and 2 mg of nicotine enters the systemic circulation from a cigarette, but the delivery of different products varies between 0.5 mg and over 3 mg of nicotine per cigarette.⁸

Cigarettes are routinely tested for 'yield' using the International Organization for Standardization (ISO) or US Federal Trade Commission (FTC) test procedures. These procedures involve the use of machines to smoke cigarettes according to a standard protocol, drawing 35 ml of smoke over two seconds every 60 seconds, until the cigarette is smoked to a 23 mm butt length. Machine test yields have been

the basis for marketing of light or mild (low-yield) cigarettes. These cigarettes are engineered to produce low levels of nicotine and tar when tested in smoking machines by ensuring that the smoke drawn into the machine is diluted by ambient air. This is achieved by using more porous cigarette paper and/or introducing ventilation holes in the filter (Fig 5.3), by increasing the burn rate of the cigarette, so the machine takes fewer puffs, and by the use of expanded tobacco.⁹ The nicotine content of the tobacco in the cigarette, however, is similar in low yield and regular cigarettes. Thus, the smoker can easily obtain the same dose of nicotine from low yield as from regular cigarettes by taking bigger and more frequent puffs, or by blocking ventilation holes in the filter with fingers or lips.



Fig 5.3 Ventilation holes in the cigarette filter reduce machine-measured nicotine and tar yield.

When a smoker puffs a cigarette, combustion is incomplete, and the smoke produced contains a mixture of tar, water and gases. Particulates form when nicotine vaporises, cools and condenses along with other combustion products. Tobacco smoke is inhaled into the lung, where nicotine is absorbed rapidly into the pulmonary circulation and hence directly into the arterial supply, reaching the brain within a few seconds. As a result of the inhaled route of delivery, nicotine concentrations in arterial blood after inhaling from a cigarette are several times higher than in venous blood, and much higher than those achieved by other nicotine delivery devices.^{10,11} This rapid absorption enhances the addictiveness of the delivery system.

5.2.2 Cigars

Cigars vary considerably in size and weight. Typical cigars weigh between 5 and 17 g, but small cigars can weigh as little as 0.5 g and the largest as much as 22 g.^{12,13}

The nicotine content of cigars shows similar variation, from around 5 mg to more than 400 mg per cigar. There is also variability in the pH of cigar smoke: small cigars tend to produce acidic pH similar to cigarettes whereas large cigar smoke is more alkaline. Alkaline smoke facilitates absorption of nicotine through the buccal mucosa, while substantial absorption of acidic smoke requires inhalation into the lungs.

Tests of cigars using standard smoking machine parameters defined by the International Committee for Cigar Smoke Study (20 ml puffs taken over 1.5 seconds once every minute until the cigar is burned to a specified butt-length) show that the yields of nicotine and tar for regular cigars are several-fold higher than cigarettes. Nicotine yields average 3.8 mg, 9.8 mg and 13.3 mg for small cigars, cigars and premium cigars, respectively.¹² However, the delivery of nicotine to the smoker depends strongly on whether the smoke is inhaled. Many cigar smokers, particularly those who have never smoked cigarettes, hold the smoke in the mouth without further inhalation, in which case the amount of nicotine absorbed may be relatively small.¹⁴ On the other hand, smokers of small cigars, and particularly those who have been regular cigarette smokers, often inhale the smoke, resulting in high levels of nicotine and smoke toxin exposure.

5.2.3 Pipes

A typical dose of tobacco to fill a pipe bowl is 3–4 g. Pipe smokers and cigarette smokers have similar levels of serum cotinine (the principal metabolite of nicotine) and urine nicotine, indicating that daily nicotine intake is similar for the two forms of tobacco use.¹⁵

Waterpipes, also known as hookah, narghile, shisha and hubble bubble, are widely used to smoke tobacco in the Middle East and parts of Asia, and increasingly in recent years in Western nations.¹⁶ Tobacco, often flavoured with fruit, mint or cappuccino, is burnt by charcoal and the smoke is drawn through water and then inhaled via a hose with a mouthpiece. An average amount of tobacco per pipe smoked is 20 g. Plasma nicotine levels after smoking for 45 minutes are reported to be higher than those seen after smoking a cigarette.¹⁷ Urinary cotinine levels in regular waterpipe users are similar to those of smokers.^{18,19}

5.2.4 Bidis

Typically, each bidi cigarette contains about 0.2 g of tobacco. The nicotine content of the tobacco ranges from 10 mg/g to 17 mg/g and differs in different countries.^{6,20} Yields by machine testing of Indian bidis range from 1.9 mg to 2.8 mg nicotine, and

26 mg to 41 mg tar per bidi. Plasma nicotine concentration in people smoking bidis is similar to those seen in people smoking regular cigarettes.²⁰

5.2.5 Kreteks

Kreteks are small cigars containing about 60% tobacco, 40% cloves and cocoa. Little data are available on nicotine content and nicotine blood concentrations while smoking kreteks. Machine yields for kreteks range from 2.2 mg to 4.5 mg nicotine and from 48 mg to 113 mg tar per kretek.²¹

5.2.6 Smokeless tobacco

Smokeless tobacco products vary considerably in nicotine content, pH and levels of various carcinogens. The highest concentrations of nicotine are in dry snuff (average 16.8 mg/g), followed by moist snuff (12.6 mg/g) and chewing tobacco (9.9 mg/g).²² The pH of smokeless tobacco products also varies widely, which is important because pH determines the proportion of nicotine that is in the un-ionized or free-base form, which in turn determines the ease with which nicotine crosses the buccal mucosa and is absorbed into the circulation. In one study of six popular brands of moist snuff from the US, nicotine content ranged from 3.4 mg/g to 11.5 mg/g, while pH ranged from 5.24 to 8.35.²³

A typical dose of moist tobacco is about 2 g.²⁴ In one study, the systemic dose of nicotine delivered by 2.5 g of moist snuff held in the mouth for 30 minutes averaged 3.6 mg, and the dose from an average of 7.9 g of chewing tobacco (a typical self-selected dose) chewed for 30 minutes averaged 4.5 mg nicotine.²⁵ With smokeless tobacco use for 30 minutes, plasma nicotine concentrations rise progressively over the period of use, followed by a slow decline over the next 90 minutes.^{25,26} There is evidence that nicotine continues to be absorbed through either the buccal mucosa or from the gastrointestinal tract after the product is removed from the mouth.²⁵ Studies measuring urine cotinine indicate that regular users of Swedish snus (oral moist snuff) absorb similar total daily doses of nicotine to regular cigarette smokers.²⁷

In addition to the traditional smokeless tobacco products, compressed tobacco tablets, such as Ariva and Stonewall, have recently been marketed as alternative oral nicotine products. Ariva contains 2.4 mg nicotine per gram, or approximately 0.7 mg per tablet.²⁸

5.2.7 Nicotine medications

Nicotine Polacrilex gum contains 2 mg or 4 mg nicotine. The systemic bioavailability of nicotine from gum averages about 50%, such that the systemic dose is

about 1 mg or 2 mg from the 2 mg and 4 mg gum respectively.²⁹ Systemic bioavailability is less than 100% because not all of the nicotine is extracted from the gum and because a considerable fraction of the nicotine is swallowed. Much of the nicotine absorbed after swallowing is metabolised during the first pass through the liver.

Nicotine patches contain different quantities of nicotine depending on their design. While the nominal dose of nicotine from patches is typically 15 mg for 16 hours or 21 mg for 24 hours, there are differences in actual plasma nicotine concentrations achieved from different brands of patches with the same nominal yields. The absorption of nicotine from patches is gradual with peak concentration times varying from one manufactured patch to another.³⁰ The rate and extent of the absorption of nicotine from patches may be affected by ambient temperature and by skin blood flow; for example, the rate of absorption may be accelerated by exercise.

Nicotine nasal sprays contain 0.5 mg nicotine per 0.5 ml spray. The recommended dose is one spray in each nostril (total of 1 mg). The bioavailability of nicotine nasal spray averages about 50%, but varies considerably from person to person. Nicotine is absorbed into the systemic circulation faster from nicotine nasal spray than from any other currently available medicinal nicotine preparations (see Chapter 7).¹¹

A nicotine inhalator cartridge contains 10 mg nicotine. Each puff delivers about 13 µg of nicotine, which is comparable to approximately one tenth of the dose of nicotine from a puff of a cigarette. The average systemic dose of nicotine delivered by each cartridge is 2 mg.³¹

Nicotine lozenges contain 2 mg or 4 mg nicotine. The bioavailability is slightly greater than that of nicotine gum but the time course of absorption is similar to that of the gum.³²

5.2.8 Potential reduced exposure products

The Eclipse device, when tested under FTC smoking conditions, generates a yield of 0.18 mg nicotine and 3.2 mg tar. Studies of individuals smoking Eclipse show similar plasma nicotine concentrations to those smoking the usual brand of cigarettes, although carbon monoxide levels are higher than in those using the usual brand.³³ The Accord device yields 0.2 mg nicotine and 3 mg tar by standardised machine testing. Smokers who switch to Accord have lower blood nicotine concentrations than when smoking cigarettes.³⁴

5.3 Contaminants and additives

5.3.1 Additives and tobacco

Besides tobacco, numerous other ingredients are used in the production of cigarettes. These include humectants such as glycerol that retain moisture; sugars added to casings so that the cigarette smoke is not too alkaline or harsh; inorganic salts to alter the burning characteristics of the cigarettes; and numerous flavourants. Commonly used flavourants include liquorice, cocoa, vanillin, fruit extracts and menthol. Tobacco additives have generally been judged to be acceptable as food additives, but it is unclear whether these additives become potentially toxic in the combustion process. For example, the combustion of glycerol leads to formation of acrolein, a reactive aldehyde and respiratory irritant.³⁵

Menthol has local anaesthetic qualities and is widely used as a flavourant in cigarettes, particularly in the United States. Menthol has a cooling effect on the throat. It has been speculated that menthol allows deeper inhalation and greater intake of tobacco smoke, although the evidence on this is conflicting. Mentholated cigarettes typically contain about 3 mg menthol.³⁶ Menthol may make cigarettes more addictive, owing to its intense sensory qualities (see Chapter 3).³⁷

A number of alkylbenzene flavourants that are pulmonary irritants or are carcinogens or genotoxins have been measured in cigarettes.³⁸ The most common are anethole, myristicin, safrole, pulegone, piperonal and methyleugenol.

Ammonia compounds are added in significant amounts to cigarettes, up to 1.5% by weight. Ammonia in sufficient amounts can increase the pH of smoke. At higher smoke pHs, a greater proportion of nicotine in the smoke is in the un-ionized or free-base form.³⁹ The free-base form is more volatile than ionized nicotine, and because it is un-ionized passes through cell membranes relatively easily. The result is greater sensory impact on the throat and upper airway and potentially more rapid systemic absorption of nicotine. Recent studies of smoke pH reported values ranging from 6.0 to 7.8 for popular American cigarettes, indicating that considerable nicotine is in the free-base form in cigarette smoke.⁴⁰

Smokeless tobacco also contains many flavourants as well as alkaline salts to facilitate buccal absorption of nicotine. Liquorice is widely used in tobacco products and can aggravate hypertension due to its mineralocorticoid actions. Users of some smokeless tobaccos consume large amounts of sodium, as much as 30–45 mmol per day, which could aggravate salt-sensitive conditions such as hypertension or heart failure.⁴¹

5.3.2 Carcinogens in tobacco

More than 4,500 compounds, including 69 carcinogens, have been identified in tobacco smoke, most of which are formed in the combustion process. However, there are several that are present in the tobacco before combustion, of which the tobacco-specific nitrosamines (TSNAs), N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are especially potent. TSNAs are formed from nicotine and nitrites in the curing process by microbial reduction of nitrate to nitrite. Further TSNAs are produced during combustion. NNN and NNK are present in cigarette tobacco, but the levels are quite variable, with concentrations up to 58,000 ng/g tobacco for NNN and up to 10,745 ng/g tobacco for NNK.⁴² The levels of TSNAs vary by country of origin of cigarettes, with particularly high levels measured in cigarettes from India and Italy. Higher levels of TSNAs are found in dark tobacco cigarettes and cigarettes with higher nitrate content in the tobacco. New curing processes have been shown to reduce or eliminate TSNAs from cigarette tobacco.⁴² Other carcinogenic volatile nitrosamines, including N-nitrosodimethylamine (NDMA), N-nitrosethylmethylamine (NEMA) and N-nitrosopyrrolidine (NPYR), are also found in cigarette tobacco.

In addition to nitrosamines, tobacco contains potential carcinogenic inorganic chemicals including arsenic, beryllium, nickel, chromium, cadmium, lead and polonium-210.

In the combustion process several potentially carcinogenic aldehydes are formed, including formaldehyde, acetaldehyde and crotonaldehyde.

Preformed NNN and NNK have been identified in cigars and bidi tobacco. Kreteks contain large amounts of eugenol, a constituent of cloves. Eugenol is a local anaesthetic but it is also cytotoxic and may contribute to pulmonary injury.

Smokeless tobacco products also contain TSNAs and other nitrosamines, as well as traces of polycyclic aromatic hydrocarbons, metals, polonium-210 and aldehydes.³⁵ The TSA levels in smokeless products vary widely around the world. TSA levels have declined in recent years in Sweden and in the US, with some products containing extremely low levels;²⁸ however, in some countries (such as India) levels are extremely high.⁴³

5.4 Addiction potential of alternative nicotine products

As described earlier, the rate of absorption of nicotine varies considerably between the many available nicotine sources. Inhalation of cigarette smoke results in the most rapid absorption of nicotine and the highest nicotine concentrations in arterial blood compared with other nicotine sources. Rapid absorption makes the

product more addictive for several reasons.⁴⁴ First, high concentrations in arterial blood are delivered to the brain quickly, and these high levels produce a greater intensity of brain stimulation. Rapid delivery of high levels also allows a smoker to overcome the effects of short-term tolerance to the actions of nicotine. Since nicotine effects are perceived quickly, rapid delivery also allows the smoker to titrate the dose of nicotine to optimise effects on arousal and mood. Finally, the temporal proximity of reinforcement to drug taking is known to promote the self-administration of drugs in general. Thus the cigarette is an optimal device for promoting and sustaining nicotine addiction.

Smokeless tobacco products deliver similar daily doses of nicotine to cigarettes, but the rate of absorption is slower and the peak concentrations achieved are lower than from cigarette smoking.²⁵ Therefore, the intensity of positive reinforcement from a particular dose of nicotine is likely to be less from smokeless tobacco than that experienced from cigarette smoking, although physical dependence on smokeless tobacco certainly can develop. Many smokeless tobacco users become dependent and have great difficulty quitting, although some, such as professional baseball players in the US, use smokeless tobacco for putative athletic enhancement reasons.

Nicotine replacement therapies vary in the rate of nicotine absorption. Nicotine nasal spray achieves the fastest absorption, and concerns have been raised that it is likely to be the most addictive of the medicinal formulations. Nicotine gum, inhaler and lozenge have similar pharmacokinetic profiles and also provide some degree of positive reinforcement, although much less than a cigarette. Nicotine gum does have some dependence liability and some gum users have difficulty stopping gum use. Clinical trials of nicotine gum show prolonged use at 12 months after smoking cessation in 9–22% of users, and for nicotine nasal spray in 32–43% of individuals,⁴⁵ though sustained use from self-purchased products is much lower (see Chapter 4). Nicotine patches release nicotine slowly, producing little or no positive reinforcement. Dependence does not appear to be a problem with the use of nicotine patches.

There are little data on PREPs and dependence because the use of these products has been limited to small numbers of smokers.

5.5 Use of alternative nicotine sources as substitutes for cigarettes

Two questions arise in considering nicotine sources as substitutes for cigarette smoking. The first is whether these sources will be satisfying to smokers and prove to be acceptable substitutes for cigarettes. The second is whether the safety profiles are acceptable. This latter question is discussed in more detail in later

chapters, though, on purely theoretical grounds, the absence of other toxins found in tobacco and particularly in its combustion products suggests strongly that these products will be far safer.

Several studies have looked at the question of whether nicotine replacements are useful for the purpose of reducing cigarette use. Some smokers are able to reduce their cigarette consumption and exposure to carbon monoxide and some other tobacco smoke toxins by using various nicotine products. Smoking reduction studies have examined the use of nicotine gum, nicotine patches, nicotine spray and nicotine oral tablets.^{3,46} In general, the extent of reduction of levels of biomarkers of tobacco smoke response is less than the change expected from the magnitude of change in the self-reporting number of cigarettes smoked per day.^{47,48} This may be due to misreporting of cigarette consumption, and/or to compensation by smoking each cigarette more intensively. The number of smokers who are able to substantially reduce their smoking tends to decrease over time during clinical trials, and questions remain as to whether this approach has long-term viability.

The use of smokeless tobacco as a substitute for cigarette smoking has been of considerable recent interest.⁴⁹ Smokeless tobacco does not generate combustion products, which are thought to be responsible for most of the injurious effects of cigarette smoking. The safety of smokeless tobacco products is discussed elsewhere. Smokeless tobacco has been suggested as a way to help people quit smoking, and some smokeless products have been marketed specifically for use when a person cannot smoke cigarettes. However, the long-term use of smokeless tobacco as an alternative to cigarette smoking has not yet been experimentally evaluated.

5.6 Conclusions

- ▶ A wide variety of nicotine products are available, delivering a range of nicotine doses. The cigarette is the most widely used product.
- ▶ Cigarettes deliver high doses of nicotine into the lungs, where it is absorbed rapidly and transported directly in the systemic circulation to the brain.
- ▶ The nicotine from cigarettes is carried in smoke which contains thousands of other chemicals, including many that are carcinogenic or otherwise toxic.
- ▶ Some of these toxins are present in tobacco before combustion. Most are combustion products.
- ▶ Smokeless tobacco also contains toxins and carcinogens, but delivers high doses of nicotine without most of the toxic components in smoke.
- ▶ Medicinal nicotine products deliver pure nicotine but in relatively low doses and, particularly for nicotine transdermal patches, very slowly. They do not deliver other toxic chemicals.

- ▶ The available alternative nicotine products all deliver nicotine more slowly than cigarettes, and are therefore probably less addictive.
- ▶ It is possible that alternative nicotine products could provide a safer long-term substitute for cigarette smoking. If so, this could benefit individual and public health.

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6 | The risk profile of smoked tobacco

- 6.1 Introduction
- 6.2 Population trends in smoking prevalence in the United Kingdom
- 6.3 Trends in prevalence in other countries
- 6.4 Health risks associated with active smoking
- 6.5 Health risks associated with passive smoking
- 6.6 Effects of smoking cessation
- 6.7 Conclusions

6.1 Introduction

Cigarette smoking is established as a significant cause of death and morbidity. It is the largest identified avoidable cause of ill-health and premature death. Despite a vast accumulation of evidence since the first research studies were published in the 1950s, and public awareness of the adverse health effects, many people continue to smoke. Furthermore, smoking is emerging as a significant public health hazard in developing countries where there is potential for a large number of premature deaths.

6.2 Population trends in smoking prevalence in the United Kingdom

At the height of the smoking epidemic in England in the 1950s, as many as 80% of men and 40% of women were current smokers.¹ Since then, there has been a clear decline in the prevalence of smoking. Over the 30-year period between 1974 and 2004 the percentage of the adult population of Great Britain who smoked cigarettes almost halved (Fig 6.1). However, the rate of decline has been slower in recent years, suggesting a levelling off in prevalence.

Most people start smoking in adolescence. In Britain, more than 40% of male smokers started smoking before the age of 16 years and this has hardly changed between 1992 and 2004 (Fig 6.2).² The proportion of females starting to smoke before the age of 16 was smaller but has been increasing, from 28% in 1992 to 35% in 2004. This has been mirrored by a decrease in the proportion of females starting to smoke at the age of 20 or over (Fig 6.2).² Furthermore, the younger a person is

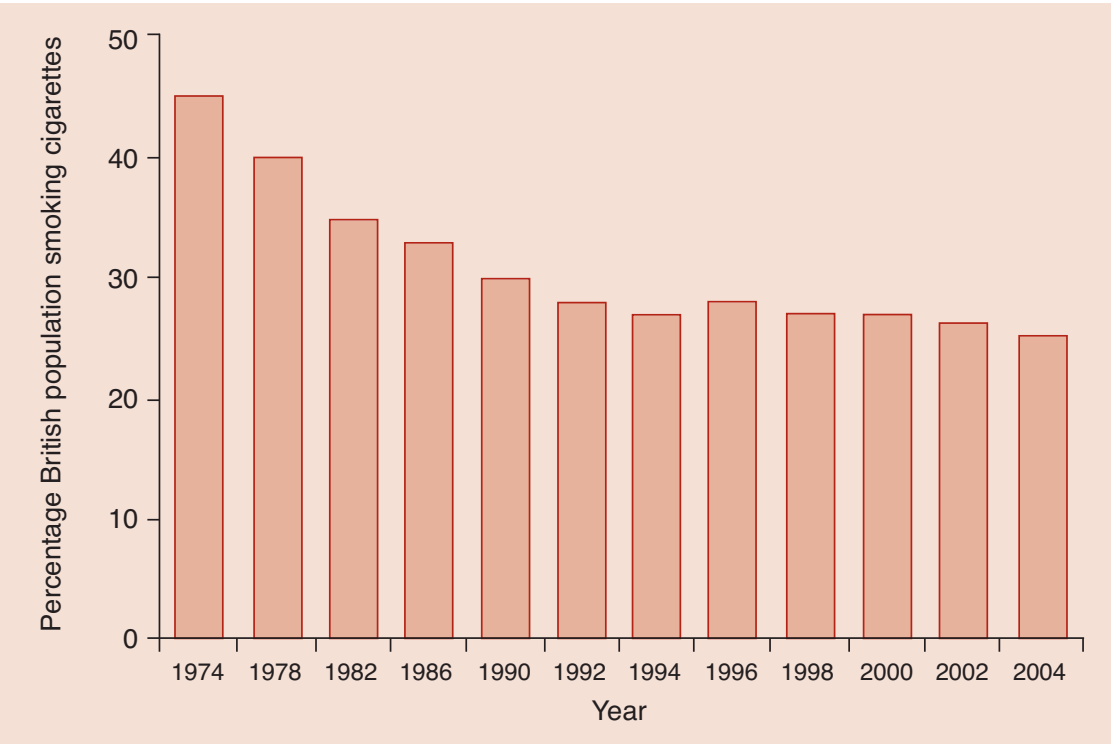


Fig 6.1 The percentage of the population of Great Britain that smoked cigarettes between 1974 and 2004. Source: General Household Survey.² Reproduced under the terms of the Click-Use Licence.

when they start smoking, the more cigarettes they tend to consume. Fifty-five percent of males who smoke 20 or more cigarettes each day started smoking before the age of 16 compared with 28% who smoke one to nine cigarettes each day.²

The prevalence of smoking in children varies significantly with age and is correlated with parental smoking. In England, the proportion of children who smoke regularly increases sharply from 1% among those aged 11 years to 20% of those aged 15 years,³ with a greater proportion of female smokers (25% of girls compared with 16% of boys). In other countries, for example Bulgaria and the Ukraine, as many as 30% or more males aged 15 years smoke.⁴ In China, an estimated 8.6% of male and 0.4% of female adolescents are current smokers, though this may reflect later uptake of smoking.⁵ Children who start smoking by 15 years are likely to continue smoking well into middle age.

6.3 Trends in prevalence in other countries

While the prevalence of smoking is decreasing or stabilising in many developed countries, it is high and increasing in many countries in the developing world. Table 6.1 shows the prevalence and number of smokers in developed, developing and transitional countries (such as those in eastern Europe). In 2000, there were 1.2 billion smokers worldwide (82% male) and an estimated 1.3 billion in 2003.⁶

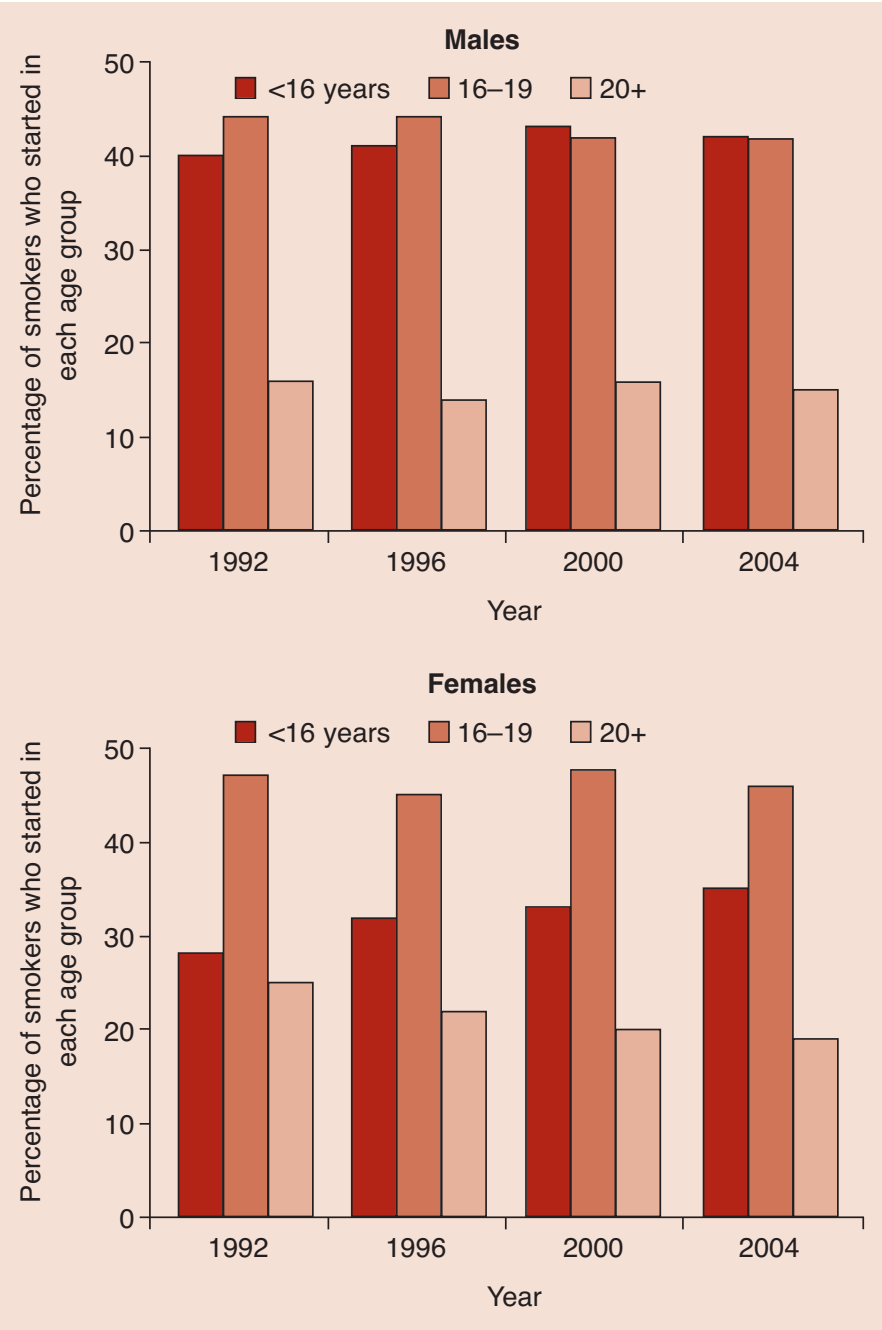


Fig 6.2 The proportion of smokers who started their habit age <16 years, 16–19 or 20 or over. Source: General Household Survey.² Reproduced under the terms of the Click-Use Licence.

Assuming there will be no change in prevalence, there are expected to be 1.45 billion smokers in the world in 2010, rising to 1.7 billion in 2025. As a result, the burden of morbidity and mortality, and consequent economic and healthcare costs, will increasingly be concentrated in developing countries, which have the least resources to cope with the smoking epidemic.

As described in Chapter 1, the smoking prevalence in a particular country can be modelled according to distinct stages of the smoking epidemic.⁷ It may take

Table 6.1. Estimated worldwide prevalence and numbers of smokers in 2000.

Level of development	Prevalence of smoking in people aged ≥15 years (%)			Numbers of smokers (millions)*		
	Male	Female	Total	Male	Female	Total
Developed	34	21	27	115	76	191
Developing	50	7	29	810	115	924
Transitional	54	14	33	83	24	107
World	48	10	29	1,006	218	1,224

*there is some rounding. Source: Guindon *et al.*⁶

40 to 50 years for the prevalence to peak in men before smoking prevalence begins to decline. The peak and decline in women occurs several decades later than in men. Many economically developed countries are in a similar situation to the UK, but countries such as China are perhaps only beginning to reach the peak of male smoking. In 2002, there were 300 million smokers in China, with a prevalence of 66% of men and 3% of women.⁸ The potential for growth in smoking among women in China and other countries predicted by the smoking epidemic model has profound implications for future public health.

6.4 Health risks associated with active smoking

Tobacco smoke contains over 3,000 chemicals, many of them toxic and/or carcinogenic, so it is not surprising that smoking has been associated with an increased risk of a wide range of diseases. Two reports on smoking in 2004 – the US Surgeon General’s report and the International Agency for Research on Cancer monograph – concluded that the following disorders are caused by smoking:^{9,10}

- ▶ cancer of the lung, oral cavity, pancreas, stomach, bladder, cervix, oesophagus, kidney, liver, larynx, myeloid leukaemia
- ▶ cardiovascular disease: abdominal aortic aneurysm, atherosclerosis, cerebrovascular disease, ischaemic heart disease
- ▶ respiratory disease: chronic obstructive pulmonary disease (chronic bronchitis and emphysema), pneumonia, respiratory symptoms such as cough, phlegm, wheeze and breathlessness
- ▶ reproductive effects: miscarriage and stillbirths, reduced fertility, low birth weight, complications in pregnancy such as preterm birth and premature rupture of membranes
- ▶ other effects: cataracts, hip fracture, osteoporosis, peptic ulcer.

The disorders cover a wide spectrum of illness in humans including cancer, vascular disease and respiratory disease. The link with lung cancer is well established, but it is now accepted that there are several other cancers caused by smoking.^{9,10} In the UK, smoking accounts for about 30% of all cancer deaths. Table 6.2 shows the relative risks of selected fatal disorders and an estimate of the number of deaths each year in England caused by smoking.¹¹ Smoking also causes a range of other disorders, many that are chronic and require continuous treatment, such as diabetes and Crohn’s disease. Selected non-fatal disorders, the relative risk in current smokers, and an estimate of the burden in every 100,000 adults who smoke are given in Table 6.3.¹²

The less well known effects of smoking include sight-threatening disorders such as age-related macula degeneration (AMD), cataracts and thyroid eye disease.^{13–15}

Table 6.2. Estimated number of annual deaths in England caused by smoking for selected disorders.				
Disorder		Relative risk in current smokers compared to never-smokers		Number of deaths due to smoking
		Men	Women	
Cancer	Lung	26.6	13.6	23,700
	Upper respiratory	10.6	6.1	600
	Oesophagus	5.3	9.3	4,000
	Bladder	2.9	1.6	1,600
	Kidney	2.8	1.3	700
	Stomach	2.1	1.2	1,500
	Pancreas	2.2	2.3	1,600
	Myeloid leukaemia	1.4	1.2	300
	Unspecified site	4.4	2.1	1,800
Respiratory	Chronic obstructive pulmonary disease	14.1	14.0	17,400
	Pneumonia	1.9 to 2.3*	2.0 to 4.6*	3,300
Circulatory	Ischaemic heart disease	1.4 to 4.2*	1.4 to 5.2*	17,700
	Stroke	1.4 to 5.1*	1.2 to 4.5*	4,500
	Aortic aneurysm	5.3	8.2	5,600
	Myocardial degeneration	2.1	1.7	200
	Atherosclerosis	1.9	2.2	200
Digestive	Stomach/duodenal ulcer	4.5	6.4	1,800
Total		—	—	86,500
* The relative risk decreases with increasing age.				
Sources: adapted from two tables from the Health Development Agency (HDA) with permission. ¹¹				
Available from National Institute for Health and Clinical Excellence website: www.nice.org.uk				

Table 6.3. Summary of selected common non-fatal disorders associated with smoking.

Disorder		Gender (age if not all ages)	Approximate relative risk in current smokers compared to never-smokers	Estimate of the number of individuals developing the condition due to smoking among 100,000 smokers per year#
Gastrointestinal	Peptic ulcer	Women	2	440
		Men	2	800
	Crohn's disease	Women	4.5	190
		Men	2	80
	Gallbladder disease	Men and women	1.3	100
Skin	Psoriasis	Women	2.5	2,180
		Men	1.4	730
Neurological	Alzheimer's disease+	Men and women (≥65)	1.1	120
Eyes	Cataract extraction	Women (≥45)	1.5	70
		Men (≥45)	1.5	135
	Age-related maculopathy	Women (≥50)	2	55
		Men (≥40)	2	85
Bones	Hip fracture	Women (55–64)	1.2	10
		Women (≥85)	2.1	2,420

continued over

Table 6.3. Summary of selected common non-fatal disorders associated with smoking – *continued*.

Disorder		Gender (age if not all ages)	Approximate relative risk in current smokers compared to never-smokers	Estimate of the number of individuals developing the condition due to smoking among 100,000 smokers per year [#]
Fertility and pregnancy	Infertility	Women	1.4	9,500
	Miscarriage	Women	1.25	4,700
	Low birth weight (<2,500 grams)	Women	1.8	3,330
	Limb reduction defect	Women	1.5	30
Hormonal	Type II diabetes mellitus	Women (30–55)	1.2	35
		Men (≥40)	2	240
Teeth	Periodontitis	Men and women	4	17,140

[#] Risk difference between smokers and non-smokers. Based on the incidence of the disorder (per 100,000 per year), except psoriasis and periodontitis (based on the prevalence) and miscarriage, limb reduction defects and birth weight (based on 100,000 births).

+ Included for interest, since although there is a suggestion of an association there may not be one at all.

Reproduced from Hackshaw.¹²

Age-related macular degeneration is the most common cause of blindness in most developed countries. In the UK, an estimated 17,800 people are blind because of smoking.¹⁶

In the UK, about 115,000 people died from smoking in 2000, compared with 512,000 in the USA (Table 6.4).¹⁷ This represents about a fifth of all deaths in each of those two countries. There could be more than one billion deaths from smoking in the 21st century if current trends continue.¹⁸

Table 6.4. Number and percentage of deaths caused by smoking in selected developed countries in 2000.			
Country	Total number of deaths ('000)	Number attributable to smoking ('000)	Percentage of all deaths attributable to smoking
Canada	218	44	20
France	531	60	11
Germany	839	109	13
Italy	560	80	14
Japan	962	113	12
Spain	360	451	13
UK	608	115	19
USA	2,403	512	21

Reproduced from Peto *et al.*¹⁷

Worldwide, smoking is responsible for a massive 4.8 million deaths each year (range 3.9 to 5.9 million), and more than half of these occur in developing countries (Table 6.5).¹⁹ This is equivalent to about one death every seven seconds. As smoking declines in developed countries over the forthcoming years, the burden of smoking-related illness will shift to the poorer countries. The full burden of smoking-related disease and death in large countries such as China and India will not arise until several decades from now.

The full effects of smoking on mortality can be seen in long-term studies of smokers, including one study of British doctors.²⁰ This study established that about half of continuing smokers die prematurely from their habit, though it may be that as many as two thirds of all smokers die early.²⁰ A quarter of these deaths occur in middle age (35–69 years) and life expectancy is reduced, on average, by about 10 years (Fig 6.3).²⁰ It is only recently that the scale of the risk to smokers has been fully realised and quantified. Many smokers may be unaware of the magnitude of this effect.

Smoking is one of the main causes of social inequalities in health, especially in developed countries. Smoking accounts for about half the number of deaths in the

Table 6.5. Estimated worldwide mortality (in thousands) attributable to smoking by cause of death in 2000.

Cause	Men		Women		Total
	30–69 yrs	70+ yrs	30–69 yrs	70+ yrs	
Lung cancer	398	294	77	79	848
Cancer of mouth, oropharynx or oesophagus	152	66	17	15	250
Other cancer	195	135	17	24	371
Chronic obstructive pulmonary disease	269	433	86	178	966
Other respiratory disease	274	93	34	32	433
Cardiovascular disease	848	476	143	223	1,690
Other causes	145	57	36	35	273
Total deaths	2,280	1,556	410	587	4,831

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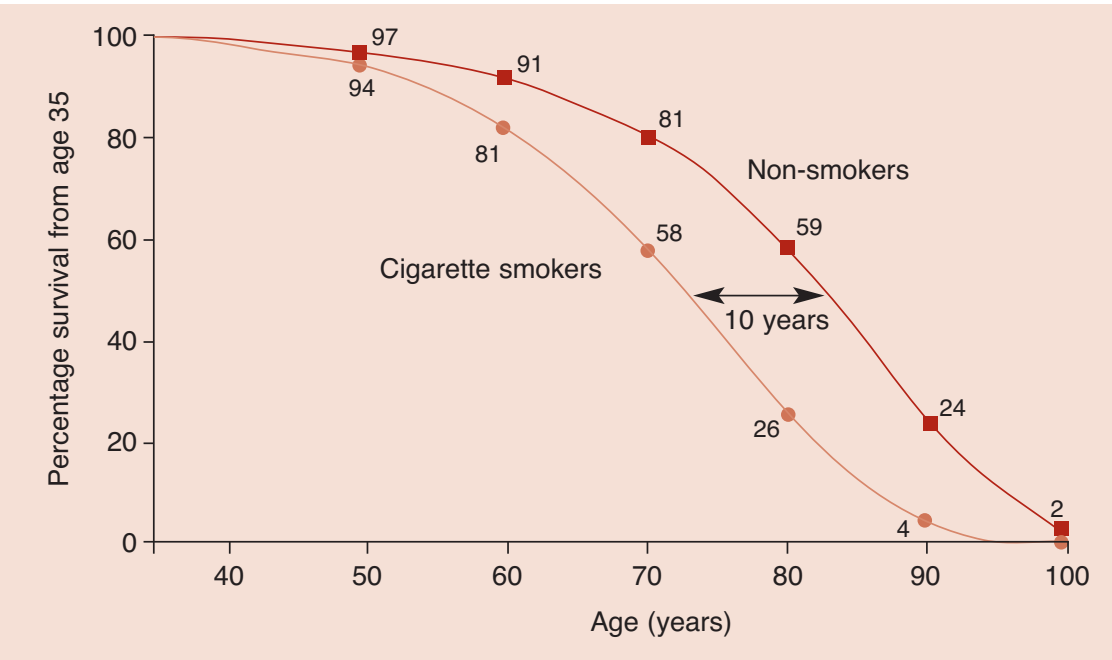


Fig 6.3 Survival from age 35 for continuing cigarette smokers and lifelong non-smokers among UK male physicians born 1900–1930. Reproduced from Doll *et al* with permission from the BMJ Publishing Group.²⁰

lowest socio-economic group (Fig 6.4).²¹ In England and Wales, there is a five-fold increase in smoking-related deaths among people in the lowest socio-economic group compared with those in the highest. Most of those who died aged 35–69 would have survived to 70 years and above if they had not smoked. The effect is similar in other countries. The effects of smoking on social inequalities in health are discussed in more detail in Chapter 10.

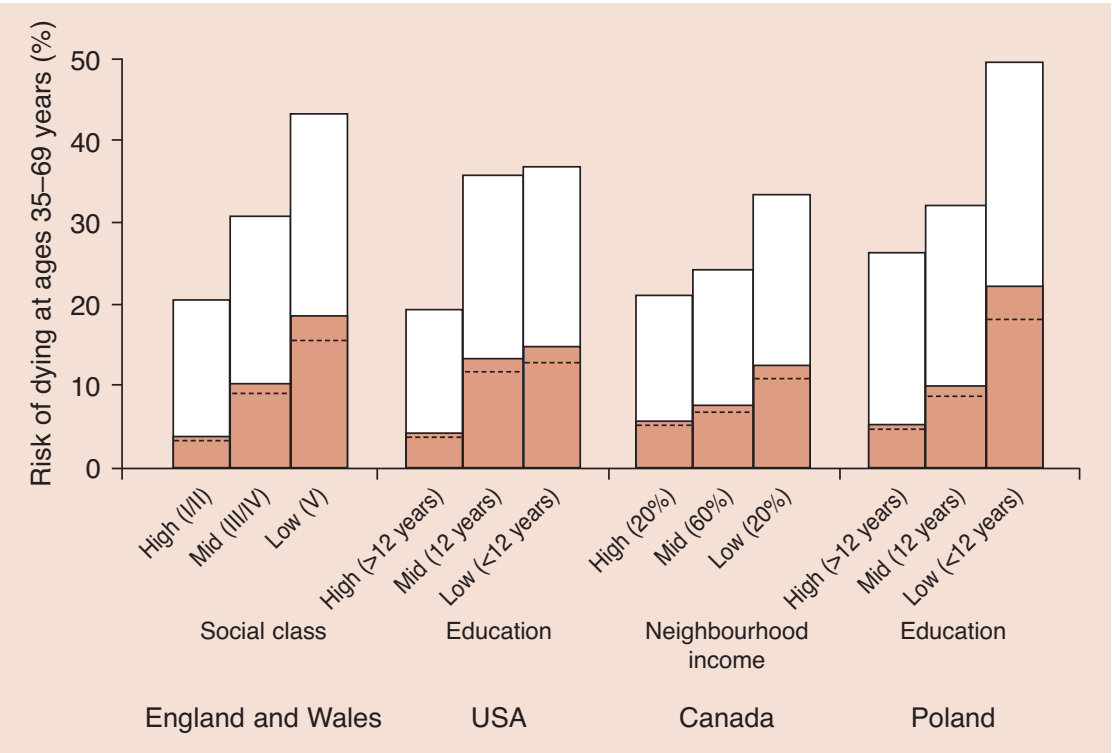


Fig 6.4 Bar chart showing social inequalities in male mortality. Each bar shows the risk of a man aged 35 years old in 1996 dying from any cause between the age of 35 and 69 years. The shaded section indicates how much of this risk is due to smoking. The shaded part of the bar up to the dashed lines represents the proportion who would have lived beyond 70 years had they not smoked.

6.5 Health risks associated with passive smoking

The evidence for harm caused by passive smoking (exposure to environmental tobacco smoke, involuntary smoking or second-hand smoking) emerged in the 1970s. The smoke breathed in by a non-smoker contains the same range of toxic substances as that inhaled by active smokers, and typically delivers about 1% of the quantity of these substances inhaled by active smokers.²² It is, therefore, plausible that passive smoking causes the same disorders that affect smokers, but at a lower risk. There is direct evidence from observational studies of adult non-smokers that passive smoking increases the risk of developing lung cancer, ischaemic heart disease, chronic obstructive pulmonary disease (COPD) and

stroke, with percentage increases in risk of 24%, 30%, 25% and 45% respectively.^{22,23} These represent important increases in risk, particularly in countries where the smoking prevalence is high such as China, and one in eight non-smoking men and half of non-smoking women are exposed to passive smoke at home, and about a quarter are exposed at work.²⁴ There is, therefore, the potential for a large number of non-smokers, as well as smokers, in China to develop lung cancer, heart disease and COPD in the future due to passive smoking exposure, as a consequence of the high prevalence of smoking.

Health concerns about passive smoking tend to focus on lung cancer because this disease is largely specific to smoking. However, ischaemic heart disease (IHD) is much more common in non-smokers, so although the effect of passive smoking on IHD risk is much weaker than on lung cancer, the number of individuals affected by IHD is much greater. This fact is often overlooked.

In the European Union, there are over six times more IHD deaths than lung cancer deaths because of passive smoking (Table 6.6).²³ Strokes caused by smoking are estimated to account for several thousand premature deaths each year. In total, an estimated 19,242 non-smokers in the EU die each year from these four causes by breathing other people’s tobacco smoke – equivalent to one death every 27 minutes

Table 6.6. Estimated number of deaths in 2002 among non-smokers due to passive smoking in 24 EU countries.#

Cause of death	Exposure at home, adults			Exposure at work		Total (home plus workplaces)*
	24<65	65+	All	All work-places	Hospitality industry	
Lung cancer	403	629	1,032	521	16	1,553
Ischaemic heart disease	1,781	6,977	8,758	1,481	48	10,239
Stroke	729	4,954	5,683	596	19	6,279
Chronic obstructive pulmonary disease	155	815	970	201	6	1,171
Total*	3,068	13,375	16,443	2,799	89	19,242

* there is some rounding

Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and UK.

Reproduced from Jamrozik with permission from the European Respiratory Society Journals Ltd.²³

6.6 Effects of smoking cessation

In the same way that the effects of smoking were not fully realised until a large number of smokers had been followed for many years, the effect of giving up has also only recently been fully quantified. In the British Doctors Study, a large proportion of participants were long-term smokers but then quit in the 1950s and 1960s.²⁰ From this, it is possible to quantify accurately the benefits of stopping in a group of people in whom the risk of dying because of smoking was substantial before they had quit. People who give up smoking can benefit from a significant reduction in risk for all fatal disorders, though the risk does not decrease to the same level in never-smokers (Table 6.7).²⁰

There is a clear relationship between the age when a smoker quits and the risk of dying prematurely (Fig 6.5).²⁰ If a smoker quits when aged about 30 years, they avoid almost all the risk of premature death from smoking. Someone aged 50 years could halve the chance of premature death, and even quitting at 60 years could reduce a smoker’s risk and gain them, on average, three years of life expectancy.

While stopping smoking undoubtedly has benefits on overall mortality, the degree of benefit varies for different disorders. It may take 20–30 years before the risk of lung cancer in an ex-smoker is about 80% lower than the risk in continuing smokers.¹ After about 15 years, the risk could be halved. In contrast, an

Table 6.7. Average percentage change in risk among all ex-smokers compared to that in current smokers or never-smokers.*		
Cause of death	Percentage increase in risk in ex-smokers compared to never-smokers (%)	Percentage decrease in risk in ex-smokers compared to current smokers (%)
Lung cancer	300	73
Cancer of the mouth, pharynx, larynx or oesophagus	189	57
All other cancers	11	21
Chronic obstructive pulmonary disease	482	59
Other respiratory disease	34	29
Ischaemic heart disease	23	24
Cerebrovascular disease	16	26
Other vascular disease	24	32
Other medical conditions	9	29
All causes	25	32

* based on the age-standardised death rate per 1,000 men/year.
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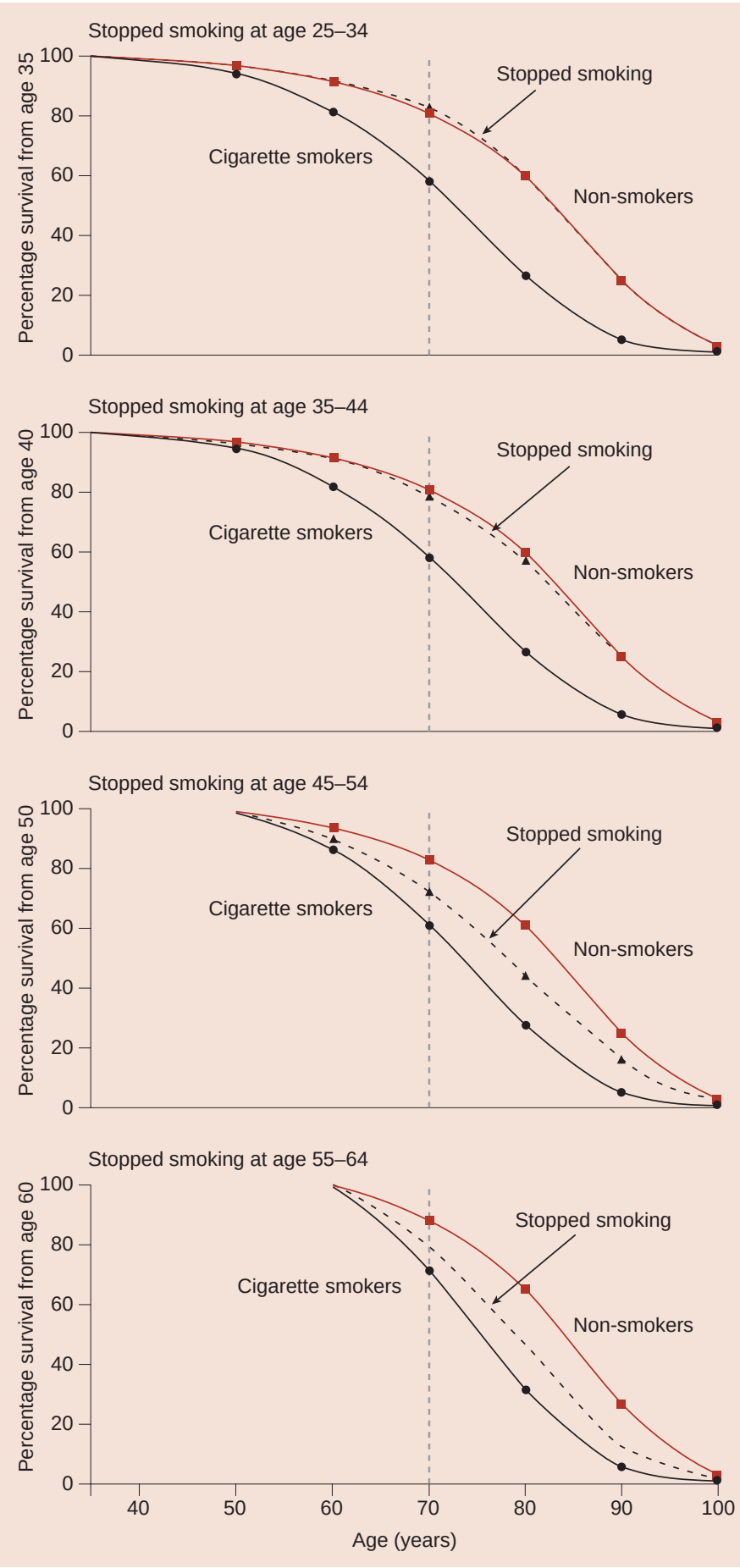


Fig 6.5 The effect on survival of stopping smoking cigarettes at age 25–34 (effect from age 35), age 35–44 (effect from age 40), age 45–54 (effect from age 50), and age 55–64 (effect from age 60). Reproduced from Doll *et al* with permission from the BMJ Publishing Group.²⁰

estimated third of the risk of developing coronary heart disease could be avoided after only two years of cessation and almost all of the risk is eliminated after 10 years.²⁵ Similarly, there is evidence that most of the risk of having a stroke disappears between two and four years after quitting.²⁶ Smoking cessation is also of benefit to people who have already developed disease. Smokers with coronary heart disease who quit can reduce their risk of dying prematurely by 36%, compared with continuing smokers.²⁷

6.7 Conclusions

- ▶ Smoking currently kills 5 million people each year.
- ▶ In the 20th century there were an estimated 100 million premature deaths attributable to smoking. If current smoking patterns continue there could be more than 1 billion deaths in the 21st century.
- ▶ A large proportion of the population in many countries still take up smoking when young and continue their habit into middle and old age. Of all those who die from smoking worldwide, half are in developing countries, but this proportion is likely to increase unless the smoking epidemic can be halted.
- ▶ Passive smoking is also a major avoidable cause of death and disability.
- ▶ Stopping smoking is highly effective, even in older smokers, and generates immediate benefits to health.
- ▶ To avoid a greater public health disaster in the current century more efforts should be made to prevent non-smokers from starting to smoke, and to encourage smokers to quit.

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7 | The risks of medicinal nicotine

- 7.1 Introduction
- 7.2 Local effects
- 7.3 Systemic adverse effects of nicotine replacement therapy
- 7.4 Conclusions

7.1 Introduction

Medicinal nicotine, commonly referred to as nicotine replacement therapy or NRT, has been available as a therapy for smokers trying to quit smoking for over 20 years. Nicotine replacement therapy has been used extensively in the UK, particularly since the relaxation of general sales restrictions in 1999 and 2001 and since all NRT products became available on reimbursable National Health Service prescriptions in 2001 (Fig 7.1).¹ Clinical experience with NRT is extensive and provides strong evidence that NRT is a safe and well tolerated treatment.² Nicotine replacement therapy may have adverse effects, however, including local effects occurring at the point of nicotine absorption, which are relatively specific to the mode of delivery, and systemic effects that probably apply to all products. In general, the local effects tend to be mild and transient, and information about these is readily available from the large number of clinical trials of NRT products. In contrast, information on potentially important systemic effects, such as precipitation of acute cardiovascular events, is generally less easily available because these events are rare and their risk is difficult to assess in clinical trials. However, observational data have been helpful in assessing the likely magnitude of these risks.

7.2 Local effects

The frequency and severity of local adverse effects varies with the route of administration and the dose of NRT used.

7.2.1 Nicotine transdermal patches

Local skin reactions to nicotine transdermal patches, including itching and skin irritation, are common. For example, in one trial of 3,575 smokers, skin itching

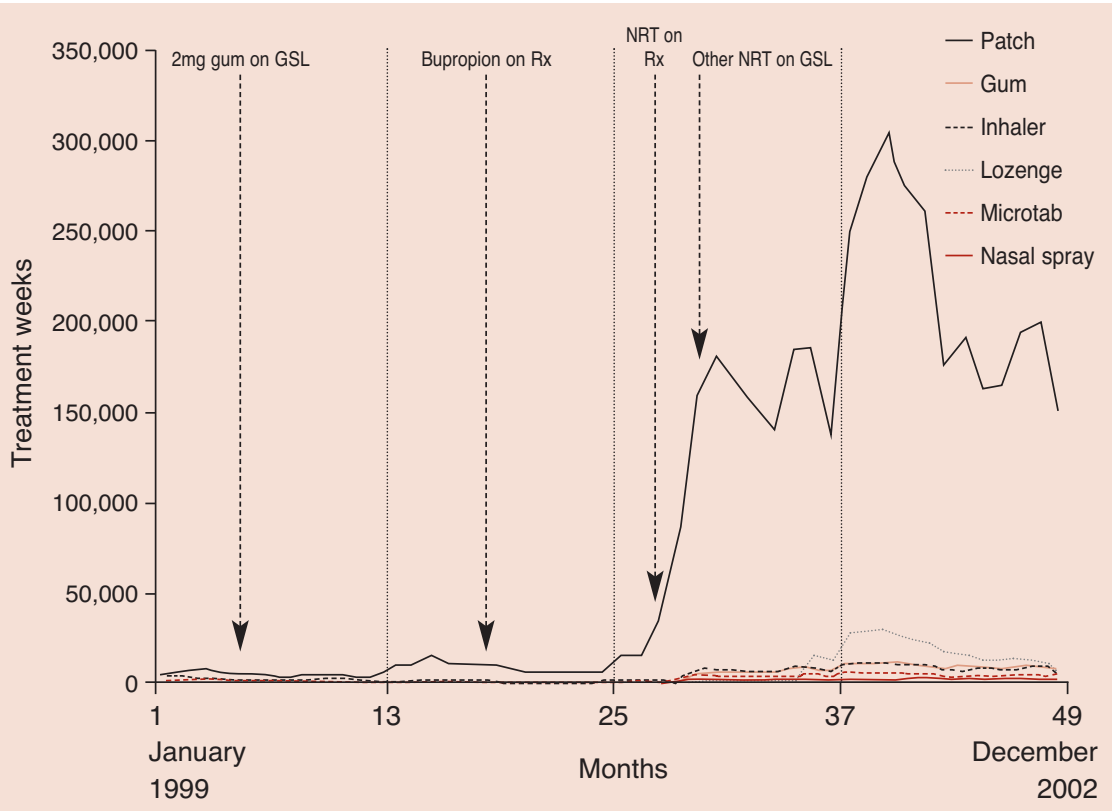


Fig 7.1 Monthly prescriptions of nicotine replacement therapy used for smoking cessation in the UK 1999 to 2002 (month 1 being January 1999). Arrows indicate introduction of policy. GSL = general sale list (available over-the-counter); Rx = on prescription. Reproduced from West *et al* with permission from the BMJ Publishing Group.¹

occurred in 14.4% of users of a 25 mg patch; in 12.9% with a 15 mg patch; and in 5% of users with a placebo.³ In a trial using a 21 mg patch, adverse skin reactions occurred in 18.5% in the active treatment group and in 6.9% in the placebo group.⁴ In most cases skin reactions are short-lived and the risk can be reduced by varying the site used for patch application. Further evidence of the transient nature of this response is provided by an observational survey of patch users two weeks after treatment, in which only 9.5% of users recalled a skin reaction.⁵

7.2.2 Gum, lingual tablets and lozenges

Nicotine gum and other oral nicotine products can cause dyspepsia and gastrointestinal discomfort. For example, in a clinical trial of 4 mg gum involving 364 people, 16% of people using gum reported dyspepsia compared with 2% in the placebo group.⁶ Similar figures have been published in other trials.² In one head-to-head comparison between 4 mg gum and 4 mg lozenge, the risk of dyspepsia or nausea was similar for the two preparations.⁷ Gum has also been reported to cause gingival pain, toothache and hiccups.^{2,8}

7.2.3 Inhalators and nasal spray

The main local adverse effects of nicotine inhalators and nasal sprays are throat or nose irritation and cough.² In one placebo-controlled trial of 400 participants, throat irritation occurred in 7% of nicotine inhalator users, compared with 2% with a placebo.⁹ The equivalent figures for cough were similar at 6.5% and 2% respectively. Other trials involving inhalators have reported lower adverse event rates.¹⁰ Nasal sprays are generally well tolerated. For example, in a trial of 227 smokers randomised to receive four weeks of treatment with a nasal spray or a matched placebo, only two subjects (one in the active arm and one in the placebo arm) were advised to stop using their spray because of local side effects.¹¹

7.3 Systemic adverse effects of nicotine replacement therapy

Most users and healthcare workers are not greatly worried by transient local effects of NRT, but would be concerned if NRT was found to have more serious systemic adverse effects. Particular concerns include a possible increase in incidence of cardiovascular events and effects during pregnancy on fetal development and the risk of congenital abnormalities.

7.3.1 Cardiovascular risk and sudden death

Nicotine causes catecholamine release and vasoconstriction and, therefore, an increase in blood pressure and heart rate. It is therefore plausible that NRT could precipitate acute cardiovascular events, particularly in susceptible people. However, the peak venous levels of nicotine occurring with NRT are typically 30–50% lower than those from cigarettes, and around five times lower than the peak arterial levels that cigarettes deliver, suggesting that NRT should be safer than continuing to smoke (Fig 7.2).¹² Furthermore, in one study of 12 healthy smokers, doses of NRT of up to 63 mg per day (that is, around two to three times higher than the typical daily dose) combined with smoking did not affect heart rate or blood pressure.¹³

Concerns about cardiovascular side effects grew following case reports of acute myocardial infarction in people using NRT.¹⁴ However, such studies provide little evidence about causation, and the observed events may have been coincidental. Data from observational epidemiological studies and controlled trials are required to test the hypothesis that NRT causes cardiovascular side effects.

In general, clinical trials using healthy people have insufficient statistical power to detect an adverse impact of NRT on the risk of having an acute cardiovascular event. For example, in the CEASE study (one of the largest clinical

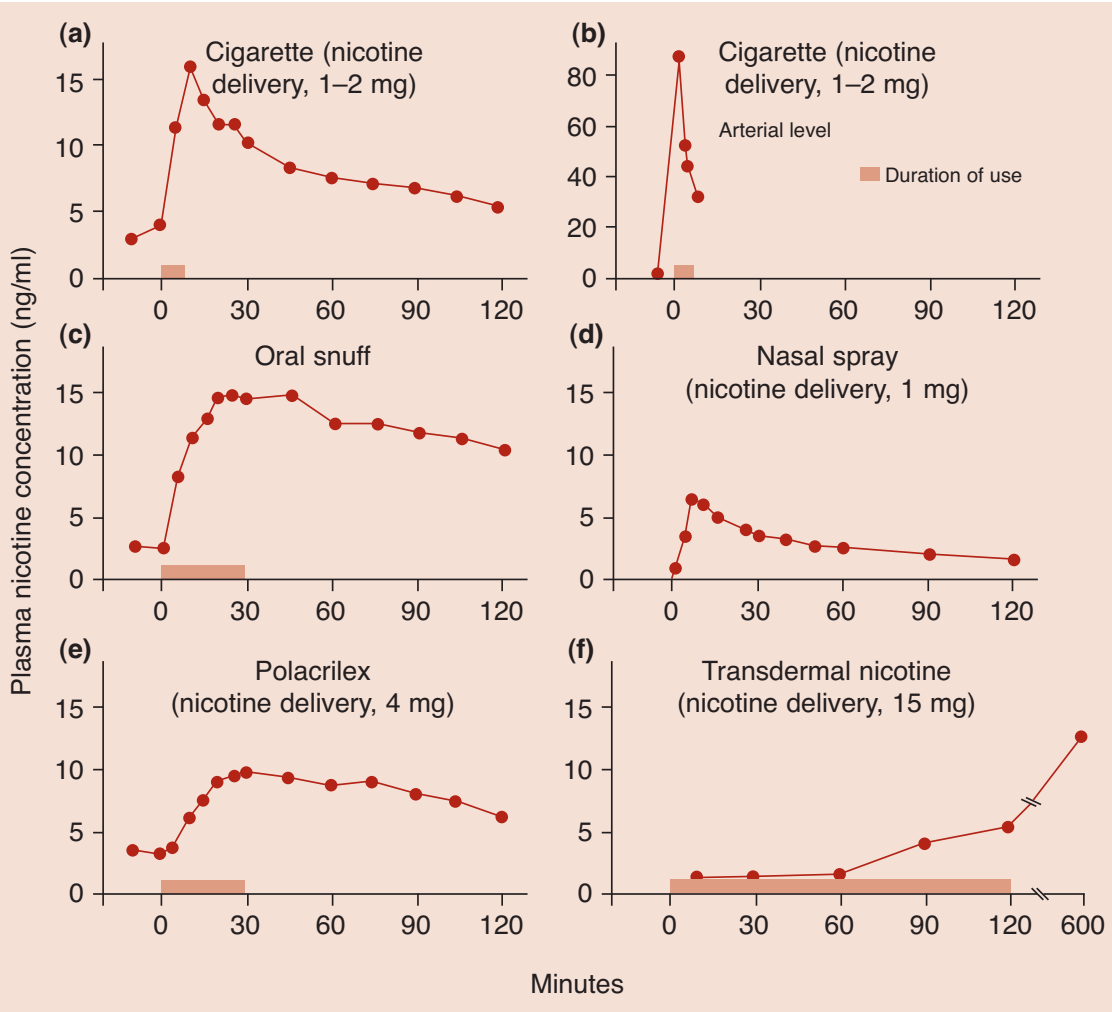


Fig 7.2 Plasma nicotine concentrations from different sources. Reproduced from Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med* 1995;333:1196–203.¹² Copyright1995 © Massachusetts Medical Society. All rights reserved.

trials) 3,575 smokers were randomised to receive a placebo, a 15 mg patch or a 25 mg patch for eight or 22 weeks.³ Four myocardial infarctions occurred, but only one of these took place during active NRT treatment. Two of the other cases occurred after participants had completed their course of NRT, and one in a participant in the placebo group. Most other clinical trials involving NRT involve considerably smaller numbers of participants. However, a meta-analysis of 35 clinical trials involving more than 9,000 participants found no evidence of an increase in the incidence of acute cardiovascular events with the use of NRT.¹⁵

The cardiovascular effects of NRT have been investigated in studies of individuals with established ischaemic heart disease. Such individuals could be at increased risk of cardiovascular side effects due to the presence of pre-existing heart disease. In one study of 36 patients with known ischaemic heart disease, the use of nicotine patches (14 mg and 21 mg) reduced the extent of exercise-induced myocardial ischaemia assessed by thallium scanning.¹⁶ The authors

suggested that the mechanism for this unexpected beneficial effect may be reduced cigarette consumption. A larger study assessed the effect of NRT on a composite endpoint comprising death, myocardial infarction, cardiac arrest, worsening angina requiring hospital admission, arrhythmia, or congestive heart failure in 584 smokers with a past history of cardiovascular disease randomised to receive patches (21 mg for six weeks, then 14 mg for two weeks, then 7 mg for two weeks) or a placebo. By week 14, this composite outcome occurred in 5.4% of those who had received NRT, and 7.9% of those who received a placebo. In addition, there was no significant increase in other cardiovascular adverse effects in the actively treated group.¹⁷ Similar reassurance comes from trials in people with coronary artery disease which have included 24-hour ECG monitoring and/or exercise testing and which demonstrate that NRT does increase the risk of having sub-clinical ST segment depression/ischaemic episodes.^{18,19}

Data on the risks of NRT use in the general population are available from an analysis of observational data from 33,247 UK primary care patients on the Health Improvement Network (a primary care consultation record database) who were prescribed NRT between June 1985 and November 2003. The study compared the risk of events in subjects in the 56 days before and after the first NRT prescription, using the remaining available person-time as the baseline. There was no evidence of an increased risk of acute myocardial infarction, acute stroke or death in the 56 days after the first prescription for NRT (Figs 7.3 and 7.4).²⁰ The estimated risk of cardiac or cerebrovascular events was actually higher than average in the few weeks before prescription, suggesting that general practitioners may have tended to prescribe NRT to people shortly after acute cardiovascular events, when the risk of further events would be expected to be particularly high (Figs 7.3 and 7.4). Alternatively or additionally, the reduced risk may simply be attributable to smoking cessation. The death rate during the first 56 days after starting treatment with NRT was, if anything, slightly lower than that during subsequent follow-up (hazard ratio 0.86; 95% confidence interval 0.60 to 1.23).

Overall, therefore, the clinical trial and observational data indicate that, in relation to cardiovascular outcomes, NRT is safe and specifically does not increase the incidence of acute cardiovascular events or of sudden death in healthy volunteers, the general population or patients with pre-existing cardiovascular disease.

7.3.2 Effects on the fetus

There is abundant evidence that smoking during pregnancy is associated with higher levels of miscarriage, intrauterine growth retardation, preterm birth and perinatal mortality.²¹ Despite this, there have been few studies of the use of NRT

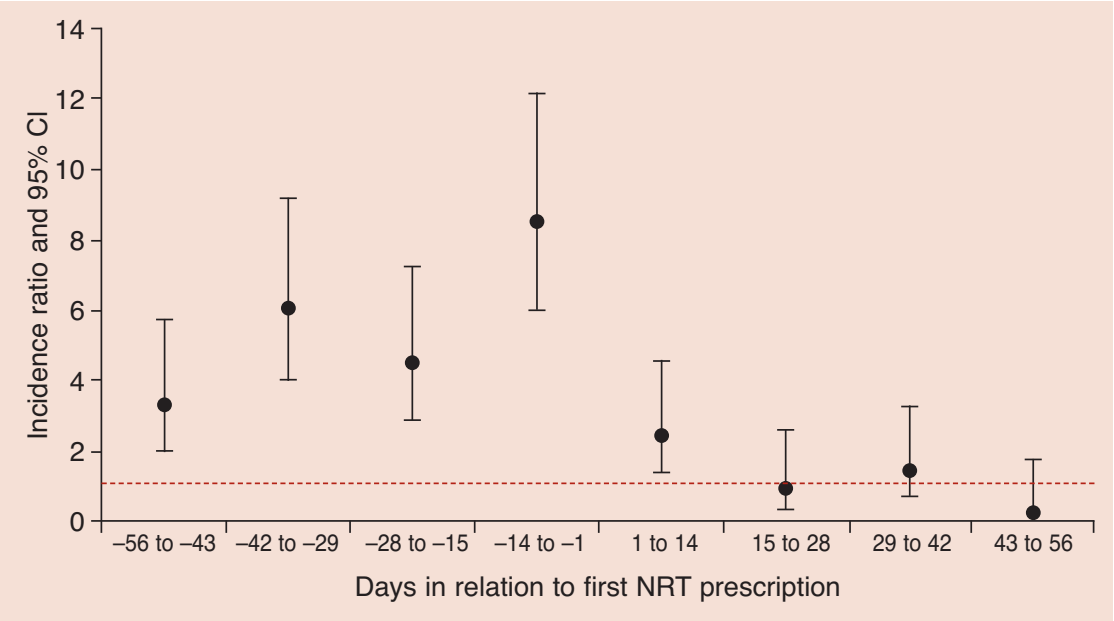


Fig 7.3 Temporal relation between relative incidence of acute myocardial infarction and first prescription for NRT in UK primary care data. Dotted line indicates an incidence ratio of 1 (no effect). Reproduced from Hubbard *et al* with permission from the BMJ Publishing Group Ltd.²⁰

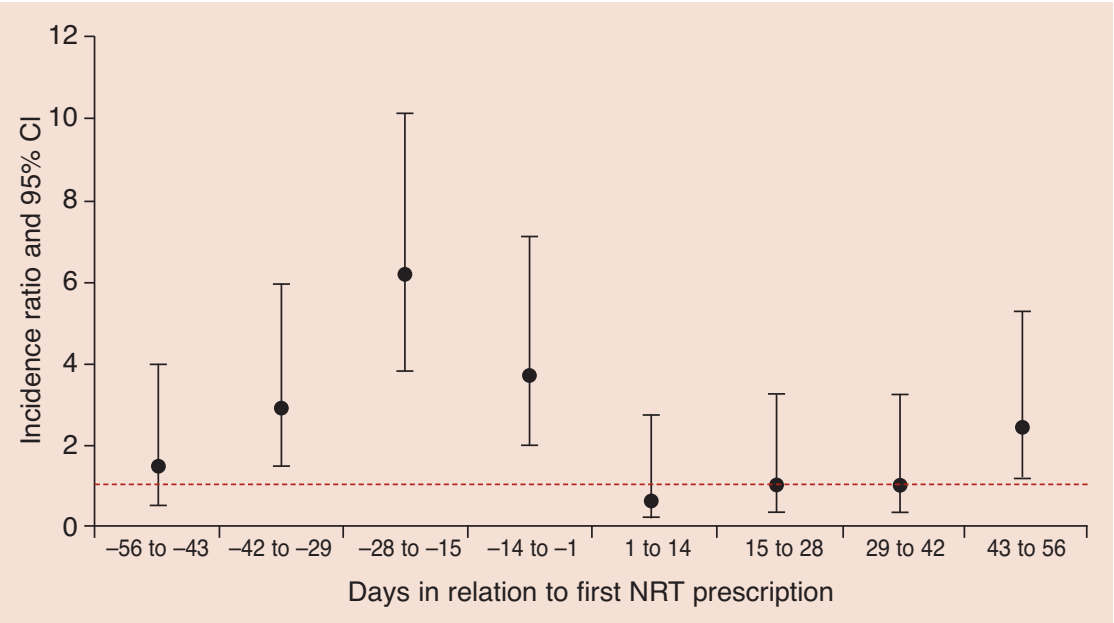


Fig 7.4 Temporal relation between relative incidence of acute stroke and first prescription for NRT in UK primary care data. Dotted line indicates an incidence ratio of 1 (no effect). Reproduced from Hubbard *et al* with permission from the BMJ Publishing Group Ltd.²⁰

during pregnancy, mainly because of the logistical difficulties of undertaking drug intervention trials in pregnant women. In the only published trial of NRT in pregnant women, 250 healthy pregnant smokers were randomised to receive either a nicotine patch (15 mg patch for eight weeks followed by 10 mg patch for three

weeks) or a matched placebo.²² Adherence to the trial medications was low in this study, but no serious adverse events were recorded, and the mean birth weight of children born to women who were given NRT, in an intention-to-treat analysis, was 186 g higher than that in the placebo group. An observational study has looked at the safety of NRT using data from the Danish Nation Birth Cohort,²³ which contains information for 76,768 first born singletons born between January 1997 and December 2003. The proportion of women smoking during pregnancy was 27%, and overall the risk of congenital malformations was no different for children born to either smokers or non-smokers. A total of 231 women used NRT during the first trimester of pregnancy, and among the children born to these women there were 19 congenital malformations. This represented an increase in risk in comparison with non-smokers on the borderline of statistical significance (prevalence ratio 1.61; 95% confidence interval 1.01 to 2.58). Among these 19 congenital malformations, 14 were musculoskeletal (including seven cases of hip dislocation) and, on the basis of EUROCAT definitions (www.eurocat.ulster.ac.uk), six were classified as major abnormalities. The risk of major abnormalities was not increased in relation to the unexposed people (prevalence ratio 1.13, 95% confidence interval 0.62 to 2.07).

Overall, the available data on the safety of NRT during pregnancy are limited, and more clinical trials and post-marketing surveillance studies are needed.²⁴ However, the data available suggest that nicotine does not reduce birth weight, and is not a cause of serious developmental abnormalities. The unexpected finding of an increase in the incidence of non-major musculoskeletal abnormalities is based on a small number of events in a single study. However, it requires further investigation.

7.3.3 Breastfeeding

Nicotine enters breast milk,²⁵ and in a study of 15 breastfeeding mothers who smoked an average of 17 cigarettes per day, the nicotine level in breast milk during periods of smoking was similar to that during the use of a 21 mg patch.²⁶ When the mothers were given 14 mg or 7 mg patches, the nicotine levels in breast milk were below the levels during normal smoking. The impact of breast milk nicotine exposure on the infant is not known, but is clearly likely to be no greater than that arising from active smoking by the mother.

7.3.4 Other potential health effects

At present there are no data from either clinical trials or from observational studies to suggest that the use of NRT causes or exacerbates any of the other

major health problems caused by cigarette smoking, such as chronic obstructive pulmonary disease, lung cancer, pneumonia or peripheral vascular disease. There are theoretical concerns arising from experiments in mice that suggest that when nicotine comes into contact with tumours implanted in mucosal surfaces, it may promote tumour growth.²⁷ Recent work to assess effects on angiogenesis in animals also raises the possibility that nicotine could promote tumour growth and atherosclerosis. Such effects may be more relevant in association with sustained long-term use of NRT.^{28,29} However, there is no evidence that this theoretical risk derived from animal studies translates into an increase in cancer risk or tumour growth in humans.

7.4 Conclusions

- ▶ Extensive experience with nicotine replacement therapy in clinical trial and observational study settings demonstrates that medicinal nicotine is a very safe drug.
- ▶ Adverse effects are primarily local and specific to the mode of delivery used.
- ▶ NRT does not appear to provoke acute cardiovascular events, even in people with pre-existing cardiovascular disease.
- ▶ There is no direct evidence that NRT therapy is carcinogenic or influences the risk of other common smoking-related diseases in humans.
- ▶ Evidence on the safety of NRT during pregnancy is limited, but suggests that NRT does not increase the risk of major developmental anomalies or reduce birth weight. However, NRT may increase the risk of minor musculoskeletal anomalies. Further evidence on these effects is needed.
- ▶ Evidence on the safety of long-term use of NRT is lacking, but there are no grounds to suspect appreciable long-term adverse effects on health.
- ▶ In any circumstance, the use of NRT is many orders of magnitude safer than smoking.

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8 | The risk profile of smokeless tobaccos

- 8.1 Introduction
- 8.2 Common types of smokeless tobacco used around the world
- 8.3 Potentially harmful constituents
- 8.4 Overview of health effects of smokeless tobacco products
- 8.5 Health effects of smokeless tobacco compared with cigarettes
- 8.6 Conclusions

8.1 Introduction

In the context of the history of tobacco use, as outlined in Chapter 1, cigarette smoking is a recent phenomenon. Tobacco has been used in human societies for at least 2,000 years, but the epidemic of cigarette smoking, which at the end of the 20th century involved over one billion people (47% of all adult men and 12% of all adult women in the world),¹ originated little more than a century ago.

Before the emergence of cigarette smoking in ‘mature’ tobacco markets such as northern Europe, North America and Australia, smokeless tobacco products (which in Europe included nasal snuff) were initially the most widely used, while pipe and cigar smoking became popular in the 19th century. However, in the latter half of the 20th century, tobacco consumption in these populations reduced steadily, largely as a result of increasing awareness of the harmful effects of smoking on health.² The pattern of consumption of these different products in the United States during the past 120 years illustrates these trends (Fig 8.1) and is typical of experience in many mature tobacco market countries.³

Today, manufactured cigarettes are the dominant nicotine product consumed in the European Union and most other parts of the world. Other forms of smoked tobacco (cigars, pipes, roll-your-own, bidis and kreteks) are also used in many countries. The combustion of tobacco and inhalation of the resulting smoke causes the rapid absorption of nicotine along with thousands of other toxins in the lungs. This high delivery of toxins to the lungs of tobacco smokers has caused a global epidemic of lung disease, primarily lung cancer and chronic obstructive pulmonary disease (COPD).

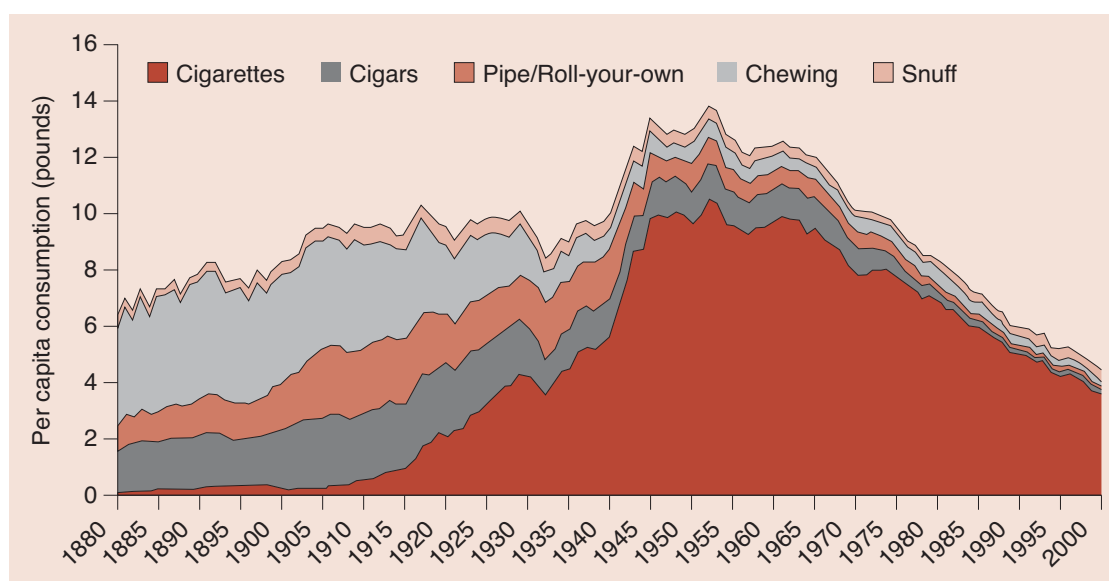


Fig 8.1 Per capita consumption of various tobacco products (in pounds) in the United States, 1880–2000. Census note: among persons >18 years old. Beginning in 1982, fine-cut chewing tobacco was reclassified as snuff. Reproduced from *Tobacco situation and outlook report* with permission from the Nature Publishing Group.³ Figure courtesy of Gary Giovino.

However, as recently as the beginning of the 20th century, forms of smokeless tobacco (tobacco products that are chewed, sucked or sniffed) were the dominant form of tobacco use (Fig 8.1). The earliest of these products, a dry snuff typically used nasally, is now rarely used even in countries where it is still freely available (including Germany, India, USA and some parts of Africa). In some countries, however, including India and Sweden, other smokeless tobacco products continue to compete with cigarettes as the most widely used products.^{4,5} The use of smokeless tobacco in its various forms is, in fact, common throughout the world: chewing tobacco and oral snuff (tobacco that is sucked rather than chewed) are used in North America; snus (a moist oral snuff) is widely used in Sweden and to a lesser extent Norway; and paan and gutka (both oral tobacco products) are used in South East Asia.

All of these varieties deliver pharmacologically active doses of nicotine by direct absorption through the lining of the mouth. These different products vary as much as 130-fold in their content and delivery of tobacco toxins.⁶ Some have very high concentrations of tobacco-specific nitrosamines (TSNAs) and are a significant cause of oral cancer,⁷ while others, including the snus used in Sweden, have relatively low concentrations of TSNAs and appear either to not cause cancer, or to present a much lower level of risk.^{8–10} Given the harmful effects of nicotine on the fetus, all of these products are potentially harmful in pregnancy. It has been suggested that the variety used in Sweden (snus) is around 90% less

harmful to health than smoking,¹¹ and has had a net beneficial effect on the health of men in Sweden by acting to reduce the number of daily smokers.⁴

Awareness that smokeless tobacco can compete with cigarettes for market share, and that some forms of smokeless tobacco may be markedly less harmful to health than smoked tobacco, has led to a renewed interest within the public health community in the role of smokeless tobacco in reducing mortality and morbidity caused by smoking. This issue has caught the attention of some of the major cigarette manufacturers, who have begun to test-market new smokeless tobacco products around the world. However, before forming a reaction to such developments, it is important to understand the nature of these different types of smokeless tobaccos and their associated health risks. This chapter will describe the most commonly used forms of smokeless tobacco, the toxin constituents and nicotine deliveries of smokeless tobacco products, and summarise the epidemiological evidence on the known health effects of different forms of smokeless tobacco.

8.2 Common types of smokeless tobacco used around the world

There is a diverse range of smokeless tobacco products in use in different parts of the world, and a comprehensive review of all individual products is beyond the scope of this report. A useful summary guide, with photographs, is available from the US National Cancer Institute and Centers for Disease Control,¹² and online at: www.cancercontrol.cancer.gov/tcrb/stfact_sheet_combined10-23-02.pdf

8.2.1 South East Asia: paan, gutka and other products

Paan is a South Asian snack, which consists of mineral or slaked lime (calcium hydroxide), spices, sweeteners and the areca nut (which is sometimes inaccurately called ‘betel nut’) wrapped in a triangular package using betel leaves, and often held together with a toothpick. It is intended to be chewed. In India and other parts of South East Asia (Pakistan, Vietnam, Sri Lanka), tobacco is often added. In other countries (Taiwan, for example) the product is consumed without tobacco. The lime acts to keep the main psychoactive ingredients in the free-base or alkaline form, thus enhancing buccal absorption into the bloodstream. The areca nut contains the alkaloid arecoline, which promotes salivation (the saliva is stained red) and is itself a psychoactive stimulant with effects similar to those of nicotine.¹³ This combination, known as a ‘betel quid’, has been used for several thousand years in many South Asian countries, often in association with important cultural ceremonies. Areca nut is also available combined with spices in ready-to-eat commercially produced pouches called paan masala. When tobacco is included, the product is called gutka.

Several other types of smokeless tobacco products commonly used in South East Asia include mishri, a pyrolysed tobacco product often used as dentifrice by women; zarda, a moist or dry chewing tobacco mixed with colourings, spices and perfumes, dried whole and chopped tobacco leaves; and nass, which comprises tobacco mixed with lime, ash and cotton oil. Many other forms are also available.

A representative, cross-sectional national family health survey of 301,984 adults aged 18 and older, from 92,447 households in 26 Indian states in 1998–9, found that 18% of Indian adults smoke tobacco and 21% chew tobacco.¹⁴ Smokeless tobacco use was found to be more common than smoking among women (13% and 3% respectively), whereas smoking was more common than chewing in men (33% and 29% respectively). Previous studies in India showed a broadly similar pattern.¹⁵ This suggests that, with an adult population of over 760 million people, there are over 160 million users of smokeless tobacco in India alone (114 million men and 48 million women).

8.2.2 North America: moist snuff, dry snuff and chewing tobacco

The two main types of smokeless tobacco used in North America are moist snuff and chewing tobacco. North American moist snuff contains tobacco with relatively high concentrations of nitrates and is allowed to ferment both before and after packaging, resulting in the formation of carcinogenic tobacco-specific nitrosamines (TSNAs). American moist snuff also tends to be made from dark fire-cured tobacco, resulting in raised concentrations of the carcinogen benzo(a)pyrene. American snuff is sold in cans either as loose tobacco varying in consistency from that similar to tea-leaves to ground coffee, or as ‘portion packed’ in sachets like small tea-bags. Moist snuff is typically used by placing a loose or packaged portion of tobacco in the space between the gum and the cheek or lip. It is not usually chewed.

Chewing tobacco is sold in a variety of forms (primarily ‘plug’ or ‘looseleaf’), is typically combined with syrup or other sweeteners and has a more dense texture allowing it to be chewed.

Dry snuff is made typically from fire-cured tobacco that has been fermented and ground into a powder. It was originally intended for nasal use, but women in the southern states of America have used dry snuff as an oral tobacco since the early 1800s.¹⁶ Dry snuff is the oldest form of tobacco used in Europe. Winn *et al* studied elderly (mean age 69) female participants who used dry snuff orally.¹⁷ Beyond this study, epidemiological evidence on the effects of dry snuff is very sparse.^{18,19}

Use of smokeless tobacco by adults in the United States has now declined to around 5% of men and has remained at less than 1% of women. Use in the

previous month by high school seniors has also declined from 20% in the mid-1980s to around 14% in 2003.²⁰ Within this general downward trend, however, use of moist snuff has increased by 66% over the past 15 years.^{21,22}

8.2.3 Scandinavia: snus

The moist snuff traditionally used in Sweden is called ‘snus’. The tobacco is air- and sun-cured, ground and processed by steam treatment (a process similar to pasteurisation) rather than fermentation. It is believed that the heat treatment prevents microbial fermentation and consequent nitrosamine formation.⁴ Selection of air-cured tobaccos also minimises the content of polycyclic aromatic hydrocarbons (for example, benzo(a)pyrene). Snus is sold either loose or portion-packed, and the tins are typically kept refrigerated in stores. The product is placed between the gum and upper lip and does not typically result in increased salivation requiring spitting (as is common with North American ‘spit tobacco’). The largest manufacturer of Swedish snus has introduced a manufacturing standard for its snus products, called the ‘Gothiateg Standard’, which specifies maximum permissible limits for toxins in the product (see Table 8.1).⁴ The prevalence of daily snus use in Sweden has increased between 1976 and 2004, from approximately 9% to 22% in men and from 0% to 4% in women.

Table 8.1. The Gothiatek Standard, a voluntary market-based toxicity standard used for snus products by Swedish Match Tobacco Company.	
Toxin	Maximum permissible limit
Nitrate	3.5 mg/kg
Tobacco-specific nitrosamines (TSNA)	5 mg/kg
N-Nitrosodimethylamine (NDMA)	5 µg/kg
Benzo(a)pyrene (BaP)	10 µg/kg
Cadmium	0.5 mg/kg
Lead	1.0 mg/kg
Arsenic	0.25 mg/kg
Nickel	2.25 mg/kg
Chromium	1.5 mg/kg

µg = microgram or 10⁻⁶g. mg/kg ~ parts per million (ppm); µg/kg is equivalent to parts per billion (ppb). Limits based on 50% water content – double the limits for dry weight equivalents.

8.2.4 Sudan: toombak

Loose snuff, known locally as ‘toombak’, was introduced in Sudan over 400 years ago.⁷ Toombak is produced from the *Nicotiana rustica* species of tobacco, and the

fermented ground powder is mixed with an aqueous solution of sodium bicarbonate. The resultant product is moist with a strong aroma, and its use is widespread in Sudan, particularly among men (around 35% of men compared with 3% of women).

8.2.5 New smokeless tobacco products

Particularly in the past 15 years or so, various novel smokeless tobacco products have been developed and marketed. One example is a compressed nicotine lozenge made from powdered tobacco that dissolves in the mouth (marketed as Ariva). The manufacturer claims that it is low in tobacco toxins such as TSNAs. This product has been available in US pharmacies for several years but has not sold in significant volume. Other new products include a dissolvable, low-TSNA preparation called Stonewall Hard Snuff. In the United Kingdom a variety of unlicensed tobacco/nicotine lozenges (including Stoppers and Stubit) have been marketed through pharmacies as unlicensed smoking cessation aids.²³

A number of new brands of smokeless tobacco claiming to differ from traditional brands have recently been launched in the United States. Revel, for example, is a portion-packed snuff tobacco that appears to be targeted at cigarette smokers for use when they cannot smoke. Other products, including Camel Snus and Taboka are also being test-marketed, but have not to date gained significant market share.

8.3 Potentially harmful constituents

Aside from nicotine, the main constituents of smokeless tobacco suspected of harming health are those included in the Gothiatek Standard (see Table 8.1). Smokeless tobacco is capable of delivering sufficient quantities of nicotine with sufficient speed to have reinforcing psychoactive effects and, as discussed in Chapter 5, is potentially dependence-forming in many users. Fig 8.2 shows the blood nicotine profile of one brand of Swedish snus in comparison with cigarettes and nicotine replacement therapies.⁴

Of the other constituent toxins, most attention has focused on four tobacco-specific nitrosamines (TSNAs): N-Nitrosornicotine (NNN), N-Nitrosoanatabine (NAT), N-nitrosoanabasine (NAB), and 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The International Agency for Research on Cancer (IARC) has concluded that NNN and NNK are carcinogenic to humans,²⁴ and some studies have focused on measuring concentrations of these TSNAs. However, other toxins, such as the known carcinogen benzo(a)pyrene, are also present in some forms of smokeless tobacco and could potentially cause harmful effects.

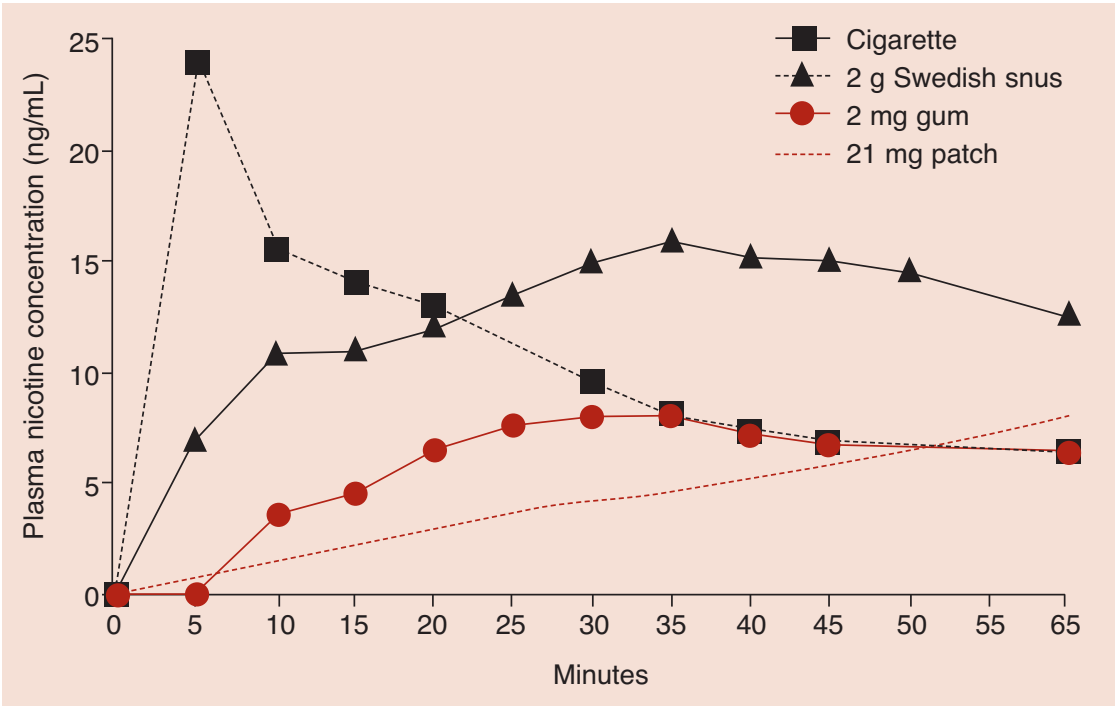


Fig 8.2 Venous blood concentrations (ng/ml) of nicotine in plasma, as a function of time for various nicotine delivery systems. All plasma nicotine concentrations have been reconfigured such that the pre-absorption level starts at 0 ng/ml (to take out baseline differences). Reproduced from Foulds *et al* with permission from the BMJ Publishing Group.⁴

The types of toxins measured and the method of reporting toxin concentrations have varied across studies, sometimes making comparisons difficult. Table 8.2 summarises the results of studies of concentrations of TSNA in moist snuff products, conducted from 1990 to 2000. Note that these analyses are based on dry weight. Much higher concentrations of NNN and NNK are found in Sudanese toombak than North American smokeless tobacco, which in turn has higher concentrations than Swedish snus (Table 8.2).

Since 2000, a number of studies have compared toxin content in a variety of smokeless products. Osterdahl *et al* reported on analyses of samples of Swedish snus from eight manufacturers (including seven small-scale manufacturers).²⁹ They reported that the mean level of the total TSNA contained in moist snus was around 1.0 µg/g (based on wet weight), and suggested that the level of TSNA in moist snuff on the Swedish market has been reduced greatly since the middle of the 1980s.

Rodu and Jansson reported on TSNA levels in a variety of tobacco products available in 2003.³⁰ The main results of this study show negligible TSNA content in Ariva, very low TSNA levels in Revel, Exalt, Swedish snus and North American chewing tobacco, moderate levels in US moist snuff, and very high levels in some brands of US dry snuff (Table 8.3).³⁰

Table 8.2. Mean tobacco-specific nitrosamine content (and range) of moist snuff products from various sources based on dry weight.					
Country and brand (year sampled)	Manufac-turer	Nicotine (mg/g)	NNK (µg/g)	NNN (µg/g)	Total TSNA (µg/g)
Sweden					
Three brands* (1990–91) ²⁵	Swed. Match		1.4–2.1	5.2–5.7	9.2–11.2
Ettan Snus (2000) ²⁶	Swed. Match		0.5	1.1	2.8
Sudan (toombak) ²⁷					
5 samples* (1990)		32.2–102.4	630–7,870	830–3,805	
5 samples* (1990)		8.4– 26.0	1,140–2,790	420–1,550	
3 samples* (1993)			188–362	241–369	
United States					
2 samples* (1991) ²⁵		18.6 – 20.6	0.5–0.8	4.8–8.0	
1 sample* (1992) ²⁵		16.7	0.6	5.6	
Copenhagen (1994) ²⁸	USSTC	12 (11.3–12.7)	1.9 (1.3–2.5)	8.7 (7.3–10.1)	17.2 (14.2–20.2)
Skoal, Original fine cut (1994) ²⁸	USSTC	11.9 (10.7–13.4)	1.3 (1.2–1.4)	8.2 (6.9–9.5)	14.9 (12.4–17.4)
Skoal Bandts Straight (1994) ²⁸	USSTC	10.1 (9.3–10.9)	0.9 (0.6–1.2)	5.1 (4.1–6.1)	8.2 (6.5–9.9)
Kodiak Wintergreen (1994) ²⁸	Conwood	10.9 (10.1–11.7)	0.6 (0.4–0.8)	6.3 (5.2–7.4)	11.0 (8.6–13.4)
Hawken Wintergreen (1994) ²⁸	Conwood	3.2 (3.0–3.4)	0.2 (.16–.24)	3.1 (2.8–3.4)	4.1 (3.7–4.5)
Skoal (2000) ²⁶	USSTC		4.3	20.8	64.0
Copenhagen(2000) ²⁶	USSTC		3.4	14.3	41.1
Timber Wolf(2000) ²⁶	Swed. Match		0.95	3.0	7.5
Silver Creek(2000) ²⁶	Swisher		17.8	41.4	127.9
NNK = 4(Methylnitrosamino)-1-(3-pyridyl)-1- butanone; NNN = N-Nitrosonornicotine; TSNA = tobacco-specific nitrosamines.					
* Brand not specified in study.					

Stepanov *et al* reported on the concentrations of TSNAs in smokeless tobacco and related products sold in India,³¹ and also in new smokeless products sold in the United States and Sweden (2006).³² The main results (based on wet weight) demonstrate a wide variation in TSNA concentrations across products, from <0.05 µg/g NNN in Ariva, and Stonewall hard tobaccos, to >35 µg/g NNN in two brands of Indian Khani (Table 8.4).^{31,32} There was some overlap in TSNA concentrations found in Swedish snus and different brands of traditional American smokeless products, but the new Revel brand had lower concentrations than both of those

Table 8.3. TSNA levels^a in American and Swedish tobacco products, 2003.

				Total		
Tobacco type/ brand name	Dry matter (%)	NNN	NNK	NAT	NAB	TSNAs
Cigarettes						
Camel	91	3.4	0.8	2.2	0.1	6.5
Marlboro	91	3.5	1.5	1.9	0.1	7.0
Chewing tobacco						
Beech Nut	78	3.0	0.8	0.8	0.1	4.7
Red Man	76	1.0	0.3	0.5	0.0	1.8
Oliver Twist – Tropical	81	0.9	0.1	0.5	0.0	1.5
Oliver Twist – Senior	80	1.7	0.3	1.3	0.1	3.4
Moist snuff, US						
Skoal Straight Long Cut	46	5.2	1.6	3.8	0.3	10.9
Skoal Bandits Straight	51	4.2	0.7	1.8	0.1	6.8
Skoal Wintergreen	44	2.7	0.6	1.4	0.1	4.8
Copenhagen	46	5.5	1.3	5.0	0.3	12.1
Copenhagen pouches	46	2.4	0.4	1.5	0.1	4.5
Hawken Wintergreen	74	4.8	1.1	1.1	0.3	7.3
Kodiak Wintergreen	48	6.4	0.7	4.8	0.4	12.3
Moist snuff, Sweden						
General	45	1.1	0.4	0.6	0.1	2.1
Ettan	47	1.1	0.3	0.6	0.1	2.0
Catch Licorice	52	1.0	0.4	0.6	0.0	2.0
Goteborgs Rape	44	1.1	0.4	0.6	0.0	2.2
Grovsnus	45	1.1	0.5	0.6	0.1	2.2
Dry snuff						
Bruton	94	287	922	77	31	1,219
Red Seal	94	210	280	210	32	1,096
Dental Sweet	93	19	6.5	14	1.2	41
Scotch	93	21	22	20	2.1	65
New products						
Revel	95	1.3	0.2	0.7	0.1	2.3
Ariva	97	0.0	<0.1	0.0	0.0	<0.1
Exalt	91	3.1	1.1	1.5	0.2	5.8

^a All concentrations in parts per million based on dry weight.

NNN = N-Nitrosornicotine; NAT = N-Nitrosoanatabine; NAB = N-Nitrosoanabasine; NNK = 4-(Methylnitrosamino)-1-(3-pyridyl) – butanone; TSNA = tobacco-specific nitrosamines.

Data from Rodu *et al.*³⁰ Reproduced with permission from *Critical Reviews in Oral Biology and Medicine*.

Table 8.4. Tobacco-specific nitrosamines, nitrate, nitrite and nicotine in Indian, US and Swedish smokeless tobacco and related products.

Product	Tobacco-specific nitrosamines (µg/g)						
	NNN	NAT	NAB	NNK	NO ₃ ⁻ (µg/g)	NO ₂ ⁻ (µg/g)	Nicotine (mg/g)
Khani							
Raja	76.9	13.8	8.83	28.4	705	1,020	21.3
Hans Chhap	39.3	4.83	3.78	2.34	1,090	1,410	19.6
Zarda							
Goa 1000	8.36	1.98	0.48	3.09	966	2.20	14.6
Moolchand Super	6.47	0.64	0.46	1.64	1,320	ND	15.0
Sanket 999	7.77	1.51	0.36	1.99	1,910	2.08	65.0
Baba 120	4.81	1.40	0.19	1.07	1,700	1.63	44.2
Shimla	19.9	1.53	1.19	2.61	1,360	2.53	13.8
Other tobacco							
Hathi Chhap	2.75	1.53	0.23	0.85	2,760	1.97	39.5
Gai Chhap	19.2	11.9	1.57	2.61	2,950	8.40	47.8
Miraj	1.74	0.35	0.12	0.08	1,420	13.6	15.6
Mishri							
Shahin	4.21	2.55	0.15	0.87	1,720	5.18	21.0
Gutka							
Star 555	0.47	0.07	0.02	0.13	417	1.61	6.77
Manikchand	0.38	0.05	0.01	0.12	43.9	2.00	3.22
Zee	0.32	0.05	0.01	0.08	62.3	3.42	3.31
Tulsi Mix	0.69	0.07	0.02	0.31	184	2.58	5.67

continued

Table 8.4. Tobacco-specific nitrosamines, nitrate, nitrite and nicotine in Indian, US and Swedish smokeless tobacco and related products – continued.

Product	Tobacco-specific nitrosamines (µg/g)						
	NNN	NAT	NAB	NNK	NO ₃ ⁻ (µg/g)	NO ₂ ⁻ (µg/g)	Nicotine (mg/g)
<i>Gutka – continued</i>							
Wiz	0.31	0.04	0.02	0.13	215	2.82	1.67
Kuber	0.32	0.03	0.01	0.13	47.3	4.50	1.23
Pan Parag	0.44	0.06	0.02	0.12	332	2.84	2.67
Zatpat	1.09	0.08	0.05	0.43	171	1.99	5.48
Vimal	0.09	0.01	ND	0.04	268	1.58	6.82
Josh	0.49	0.08	0.03	0.20	252	1.74	11.4
<i>Supari</i>							
Goa	ND	ND	ND	ND	7.5	4.71	NA
Moolchand	ND	ND	ND	ND	8.5	2.48	NA
Rajanigandha	ND	ND	ND	ND	8.8	3.34	NA
Sanket	ND	ND	ND	ND	8.5	4.27	NA
Shimla	ND	ND	ND	ND	8.0	6.56	NA
<i>Creamy snuff/toothpaste</i>							
IPCO	3.32	0.53	0.11	1.31	580	ND	4.71
Dentobac	2.52	1.49	0.07	2.16	232	ND	7.71
<i>Snuff</i>							
Click	0.56	0.38	0.02	0.24	2.260	ND	71.4

continued

Table 8.4. Tobacco-specific nitrosamines, nitrate, nitrite and nicotine in Indian, US and Swedish smokeless tobacco and related products – continued.

Product	Tobacco-specific nitrosamines (µg/g)						
	NNN	NAT	NAB	NNK	NO ₃ ⁻ (µg/g)	NO ₂ ⁻ (µg/g)	Nicotine (mg/g)
Tooth powder							
Baidyanath	0.04	ND	ND	ND	48.6	ND	0.72
New Roshanjyot	ND	ND	ND	ND	11.6	1.25	0.25
Dabur	0.04	ND	ND	ND	27.6	ND	0.58
Reference snuff							
Kentucky IS3	3.39	3.15	0.25	0.94	3.86	6.35	36.2
New tobacco products							
Hard snuff							
Ariva	0.019	0.12	0.008	0.037			
Stonewall	0.056	0.17	0.007	0.043			
Swedish snus							
General	0.98	0.79	0.06	0.18			
Exalt							
Purchased in Sweden	2.3	0.98	0.13	0.27			
Purchased in the US	2.1	0.68	0.05	0.24			
Revel							
Mint flavored	0.62	0.32	0.018	0.033			
Wintergreen flavored	0.64	0.31	0.017	0.032			

continued

Table 8.4. Tobacco-specific nitrosamines, nitrate, nitrite and nicotine in Indian, US and Swedish smokeless tobacco and related products – continued.

Product	Tobacco-specific nitrosamines (µg/g)						
	NNN	NAT	NAB	NNK	NO ₃ ⁻ (µg/g)	NO ₂ ⁻ (µg/g)	Nicotine (mg/g)
Tobacco-free snuff							
Smokey Mountain	ND	ND	ND	ND			
Nicotine replacement therapy products							
NicoDerm CQ (patch, 4-mg nicotine) ^f	ND	ND	ND	0.008			
Nicorete (gum, 4-mg nicotine) ^f	0.002	ND	ND	ND			
Commit (lozenge, 2-mg nicotine) ^f	ND	ND	ND	ND			
Conventional tobacco products							
US snuff							
Copenhagen							
Snuff	2.2	1.8	0.12	0.75			
Long Cut	3.9	1.9	0.13	1.6			
Skoal							
Long Cut Straight	4.5	4.1	0.22	0.47			
Bandits	0.9	0.24	0.014	0.17			
Kodiak							
Ice	2.0	0.72	0.063	0.29			
Wintergreen	2.2	1.8	0.15	0.41#			

ND = none detected; NNN = N-Nitrosanornicotine; NAT = N-Nitrosoanatabine; NAB = N-Nitrosoanabasine; NNK = 4(Methylnitrosamino)-1-(3-pyridyl) – butanone. Data from Stepanov *et al.*^{31,32}

categories (though slightly higher than the new ‘hard tobacco’ brands). All the TSNA levels found in smokeless tobacco were higher than those found in nicotine replacement products, which contained only trace levels of TSNA.

McNeill *et al* reported on a variety of toxin concentrations (based on dry weight) in Asian smokeless tobacco products purchased in the UK, as well as select products from other countries (Table 8.5).⁶ This study found Ariva (hard tobacco) to have undetectable levels of TSNA, and over 100-fold variations in toxin concentrations across other products. One Asian zarda product (Hakim Pury) had particularly high TSNA levels, and the leading US snuff product (Copenhagen) had notably higher concentrations of benzo(a)pyrene.

The implications of the data from these various sources are that there are very large differences in toxin concentrations between different smokeless tobacco products, and that development and production of new smokeless products with very low toxin concentrations is commercially feasible. It is therefore possible that some of these products might offer substantially less harmful alternatives to smoked tobacco or to some existing forms of smokeless tobacco.

8.4 Overview of health effects of smokeless tobacco products

Over the past decade, studies have examined the effects of paan/areca nut use with and without tobacco added, and have confirmed that the paan use without tobacco is highly carcinogenic.^{33–36} Merchant *et al* found that people using paan without tobacco were 9.9 times more likely to develop oral cancer and those using paan with tobacco were 8.4 times more likely to develop oral cancer, compared with non-users after adjustment for other covariates.³³ This study and others identified an independent effect of paan without tobacco in the causation of oral cancer, and a role of areca-specific nitrosamine as a causative carcinogen has been suggested.³⁷ When discussing the potentially harmful constituents of smokeless tobacco products it is therefore important to distinguish the constituents intrinsic to the smokeless tobacco, as opposed to the constituents that are sometimes added to or taken along with tobacco. The most important example of the latter category is areca nut. Areca nut is clearly carcinogenic when consumed without tobacco,³⁶ and so studies purporting to provide evidence on the effects of smokeless tobacco that include or fail to distinguish those users also using areca nut (or smoked tobacco) cannot provide clear evidence on the role of smokeless tobacco *per se*. Given that areca nut also affects cardiovascular function (albeit in a manner that has been insufficiently studied),¹³ this point also applies to studies of the effects of smokeless tobacco on heart disease that do not distinguish users who mix tobacco with areca nut.

Table 8.5. Content of smokeless tobacco products.^a

Brand	Moisture (% w/w)	TSNA (µg/g)	BaP (ng/g)	NDMA (ng/g)	Nitrite (µg/g)	Chromium (mg/kg)	Nickel (mg/kg)	Arsenic (mg/kg)	Lead (mg/kg)	Nicotine (mg/g)	Average pH	Free nicotine (mg/g)
UK purchased products												
Gutkha products												
Manikchard	1.68	0.289	0.40	ND	ND	0.26	1.22	0.04	0.15	3.1	9.19	3.0
Tulsi Mix	1.25	1.436	1.28	ND	ND	0.33	1.43	0.06	0.19	8.2	9.52	8.0
Zarda products												
Hakim Pury	4.91	29.705	0.32	ND	ND	2.15	5.35	0.29	1.36	42.7	6.00	0.4
Dalal Misti	8.96	1.574	8.89	ND	ND	0.87	2.09	0.11	1.14	8.6	6.15	0.1
Zarda												
Baba Zarda (GP)	7.88	0.716	2.04	ND	ND	2.34	5.88	0.24	1.18	48.4	5.32	0.1
Tooth cleaning powder												
A. Quardir Gull	3.35	5.117	5.98	7	ND	3.56	5.31	0.46	1.39	64.0	9.94	63.2
Dried tobacco leaves												
Tobacco Leaf	5.16	0.223	0.11	ND	ND	2.34	4.37	0.20	1.06	83.5	5.52	0.3

continued

Table 8.5. Content of smokeless tobacco products^a – continued.

Brand	Moisture (% w/w)	TSNA (µg/g)	BaP (ng/g)	NDMA (ng/g)	Nitrite (µg/g)	Chromium (mg/kg)	Nickel (mg/kg)	Arsenic (mg/kg)	Lead (mg/kg)	Nicotine (mg/g)	Average pH	Free nicotine (mg/g)
Products purchased outside UK												
Baba 120 (India)	13.18	2.361	2.83	ND	ND	2.08	2.94	0.40	1.56	55.0	4.88	0.04
Snus (Sweden)	45.84	0.478	1.99	ND	ND	1.54	2.59	0.30	0.50	15.2	7.86	6.3
Ariva (US)	2.40	ND	0.40	ND	ND	1.40	2.19	0.12	0.28	9.2	7.57	2.4
Copenhagen (US)	48.10	3.509	19.33	ND	6.7	1.69	2.64	0.23	0.45	25.8	7.39	4.9
Detection Limits		0.025 for each		5	0.2							

^a All figures are averages of two measurements, except for pH which gives the average of three measurements. On average, measurements agreed by less than 10%. Total TSNA = total tobacco-specific N-nitrosamines (NNK+NNN+NAB); BaP = Benzo(a)pyrene; NDMA = N-nitrosodimethylamine. Data from McNeill *et al.*⁶

Over recent years, a number of reviews of health effects of smokeless tobacco or specific types of smokeless tobacco have been published. A systematic review by Critchley and Unal concluded that chewing betel quid (including areca nut) with tobacco is associated with a substantial risk of oral cancer, but that most studies based in the United States or Scandinavia did not find statistically significant effects, though moderate positive associations could not be ruled out as many studies were too small to be conclusive.³⁸ Critchley and Unal also concluded that there may be an association between smokeless tobacco use and cardiovascular disease, but that further studies with adequate sample sizes are required.³⁹ The rest of this section will examine the evidence for an association between smokeless tobacco and specific types of disease.

8.4.1 Oral cancer

One of the biggest concerns about the use of smokeless tobacco stems from the large body of evidence from a number of countries showing that people who use smokeless tobacco have a higher risk of developing cancer of the mouth. A 2001 US Institute of Medicine (IOM) report stated that, 'A large number of studies in India, including cohort, case-control, and intervention studies, support an association between oral cancer and smokeless tobacco, and these studies are consistent, strong, coherent and temporally plausible.'⁴⁰ The IOM report stated that toombak users in Sudan also have a much higher risk of oral cancer than non-users and that, 'In spite of conflicting US data, it can be concluded that snuff use in the United States also increases the risk of oropharyngeal cancers.'

Some of the best evidence for a carcinogenic effect of smokeless tobacco in the United States comes from a study by Winn and colleagues.¹⁷ This case-control study focused on women in North Carolina, USA and found that white never smoking women who used oral dry snuff powder had a relative risk of over 4.2 (2.6–6.7) for developing oral and pharyngeal cancer. Women who had used dry snuff for 50 years had a 50-fold increase in risk for some oral cancers. It should be noted that only a tiny minority of smokeless users use this type of tobacco in the United States. The data in Table 8.3 also suggest that some forms of dry snuff have much higher concentrations of carcinogens than any other smokeless products.

It is difficult to separate out the effects of areca nut, smoking and smokeless tobacco in South East Asian studies as these habits are typically highly correlated. Since the publication of the IOM report, additional large studies of the relationship between smokeless tobacco use and oral cancer have been published. In one of the largest studies, Henley *et al* examined the association between exclusive use of oral tobacco (compared with never tobacco users) and mortality from various causes in

the Cancer Prevention Studies (CPS-I and II) conducted by the American Cancer Society.⁴¹ The CPS-I analysis included 7,745 exclusive smokeless tobacco users (median age 62) and almost 70,000 never tobacco users recruited in 1959 and followed up to determine cause of death by 1971. CPS-II analyses included 2,488 smokeless users (median age 57) and over 110,000 never tobacco users recruited in 1982 and followed up to determine cause of death by 2000. The studies both ascertained tobacco use at the outset of the study and assumed that use did not change throughout the follow-up period (Table 8.6).⁴¹

Neither analysis found evidence of a statistically significant increase in the risk of death from oral cancer. The adjusted hazard ratio estimate in CPS-I was 2.02 and 0.9 in CPS-II. The confidence intervals on both of these estimates were wide. The CPS-I estimate is derived from a larger number of smokeless tobacco users but with shorter follow-up and included only 13 deaths from oral cancer. The CPS-II population of 2,488 smokeless users with a median age of 57 at enrolment and followed for 18 years generated only one death from oral cancer in exclusive smokeless tobacco users and none in former users. Together, these findings suggest that any effect, if present, is very small. Five-year survival from oral cancer has been around 50% for the past 30 years,⁴² and so it is unlikely that the lack of effect was due to a large number of incident cases occurring but not causing death.

Accortt *et al* analysed the National Health and Nutrition Examination Survey (NHANES-1) in the United States, comparing the incidence of oral cancer in 414 smokeless tobacco users and 2,979 never tobacco users.⁴³ The participants were aged 45–75 at enrolment in the mid-1970s and were followed up around 10 years later. No cases of oral cancer were observed among the smokeless users, and it was concluded that the standardised incidence rate was not increased among smokeless users.

Rosenquist *et al* conducted a case-control study in southern Sweden to examine the risk of oral cancer in snus users, and found that while both alcohol consumption (odds ratio = 2.6) and smoked tobacco consumption (odds ratio = 4.7) were associated with oral cancer, there was no increased risk of oral cancer among snus users in southern Sweden (odds ratio 1.1).⁹

Roosaar *et al* conducted a record-linkage 20-year follow-up study of 267 Swedish snus users who presented originally with snus-related oral lesions.⁸ They found three cases of oral cancer, none of which was at the original lesion site (that is, none was at the spot where the participant originally placed his smokeless tobacco), and the original snus-induced lesions had disappeared among the 62 individuals who had quit using snus. They concluded that the incidence of oral cancer in this cohort of individuals with snus-induced lesions was slightly higher than expected, but that cancers rarely occur at the site of lesions observed in the distant past.

Table 8.6. Adjusted mortality hazard ratios (and 95% confidence intervals) associated with the use of smokeless tobacco, relative to never tobacco use among men who never used other tobacco products, CPS-I (1959–1972) and CPS-II (1982–2000), in the United States.

Cause of death (ICD-7 code)	Multivariate-adjusted hazard ratio, CPS-I	Multivariate-adjusted hazard ratio, CPS-II
All causes	1.17 (1.11–1.23)	1.18 (1.08–1.29)
All cancers (140–239)	1.07 (0.95–1.20)	1.19 (1.02–1.40)
Oropharynx cancer (140–148)	2.02 (0.53–7.74)	0.90 (0.12–6.71)
Digestive system cancer (150–159)	1.26 (1.05–1.52)	1.04 (0.77–1.38)
Lung cancer (162–163)	1.08 (0.64–1.83)	2.00 (1.23–3.24)
Genitourinary system cancer (177–181)	0.97 (0.77–1.22)	1.15 (0.85–1.56)
Other cancers (160–161, 163–175, 190–205)	0.90 (0.71–1.14)	1.49 (1.04–2.14)
Hematopoietic cancers (200–208)		0.95 (0.60–1.51)
Cardiovascular disease (330–468)	1.18 (1.11–1.26)	1.23 (1.09–1.39)
Coronary heart disease (420)	1.12 (1.03–1.21)	1.26 (1.08–1.47)
Cerebrovascular disease (330–334)	1.46 (1.31–1.64)	1.40 (1.10–1.79)
Other cardiovascular (335–398, 400–419, 421–468)	1.05 (0.91–1.22)	1.07 (0.82–1.39)
Other causes (001–138, 206–289, 470–E999)	1.17 (1.06–1.30)	1.11 (0.97–1.25)
Diabetes (260)	0.88 (0.53–1.47)	1.12 (0.55–2.29)
Respiratory system diseases (470–527)	1.28 (1.03–1.59)	1.11 (0.84–1.45)
Influenza, pneumonia (480–493)	1.16 (0.88–1.51)	0.85 (0.56–1.29)
Chronic obstructive pulmonary disease (480–493)	1.86 (1.12–3.06)	1.28 (0.71–2.32)
Digestive system disease (530–587)	1.49 (1.14–1.93)	1.38 (0.92–2.07)
Colitis and other intestinal (570–578)	1.42 (0.94–2.12)	1.12 (0.65–1.92)
Cirrhosis (581)	1.49 (0.87–2.56)	3.02 (1.60–5.69)
Genitourinary system diseases (590–637)	1.34 (1.00–1.80)	1.02 (0.62–1.69)
Nephritis and other kidney disease (590–603)	1.37 (0.98–1.92)	1.01 (0.53–1.93)
External causes (E800–E999)	1.05 (0.84–1.32)	1.26 (0.93–1.70)

CPS-I and CPS-II = Cancer Prevention Studies conducted by the American Cancer Society; ICD = World Health Organization International Classification of Diseases.

Data from Henley *et al.*⁴¹ Reproduced with kind permission from Springer Science and Business Media.

Rodu and colleagues reviewed the relationship between oral cancer and smokeless tobacco.³⁰ They found no evidence of increased risk of oral cancer from chewing tobacco or most types of moist snuff typically available in North America, but did find a significantly increased risk of oral cancer from use of some types of dry snuff (Fig 8.3). Most recently, Luo *et al* reported on the risk for oral cancer among a cohort of almost 280,000 Swedish male construction workers followed up for 20 years.⁴⁴ As in the studies mentioned above,^{4,8,9} they found that snus use did not increase risks of oral cancer (rates were in fact slightly lower in snus users than in non-tobacco users), whereas smoking more than doubled the risk (Fig 8.4).⁴⁴

Overall, therefore, it seems clear that some forms of smokeless tobacco, primarily those with the highest concentrations of carcinogens, cause oral cancer. However, it is also clear that the risk of oral cancer associated with use of low-TSNA

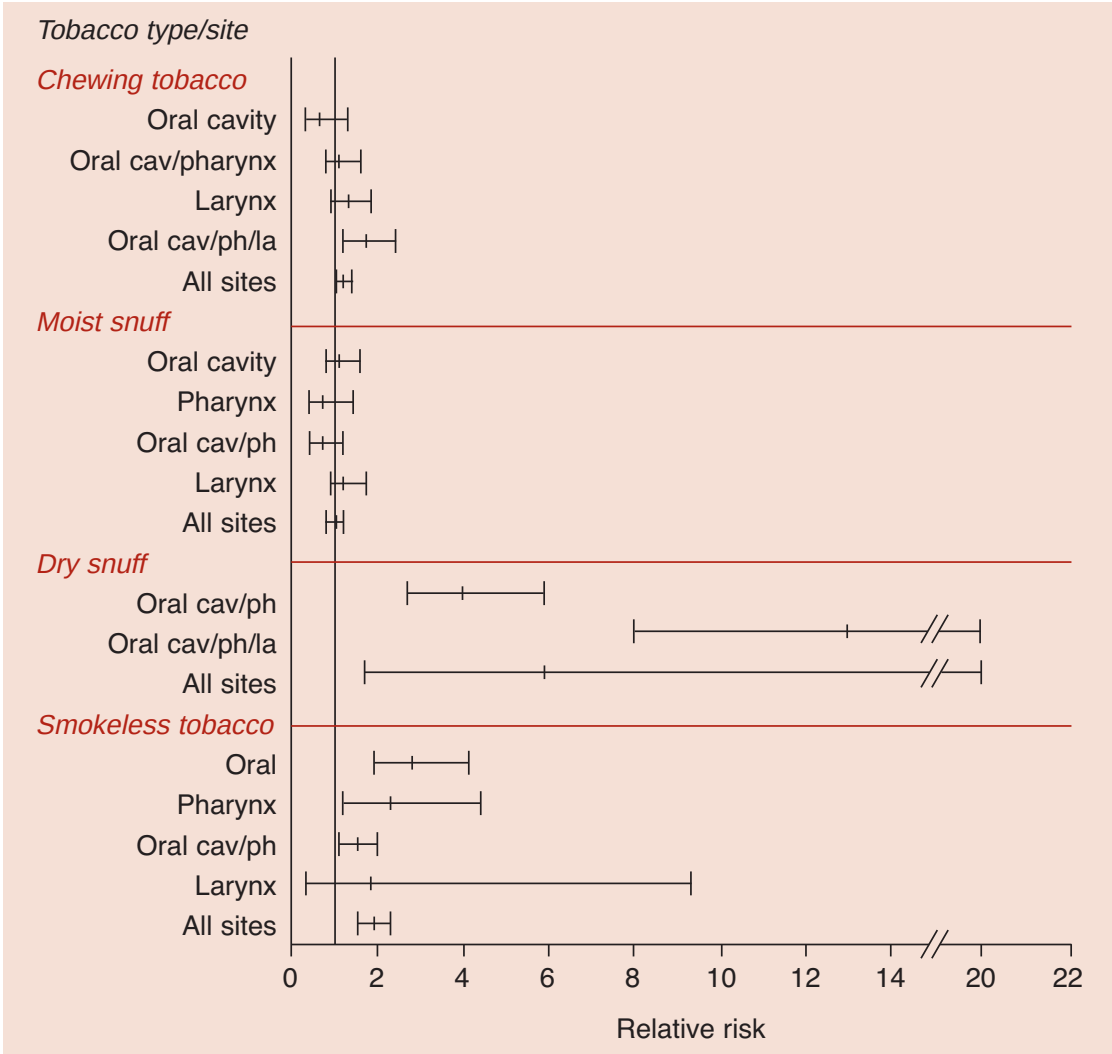


Fig 8.3 Summary relative risks (where 1 = identical risk to never tobacco user) for oral cancer and related sites according to SLT product type. Oral Cav = Oral Cavity; Ph = Pharynx; La = Larynx. Adapted from Rodu *et al*.³⁰ Reproduced with permission from *Critical Reviews in Oral Biology and Medicine*.

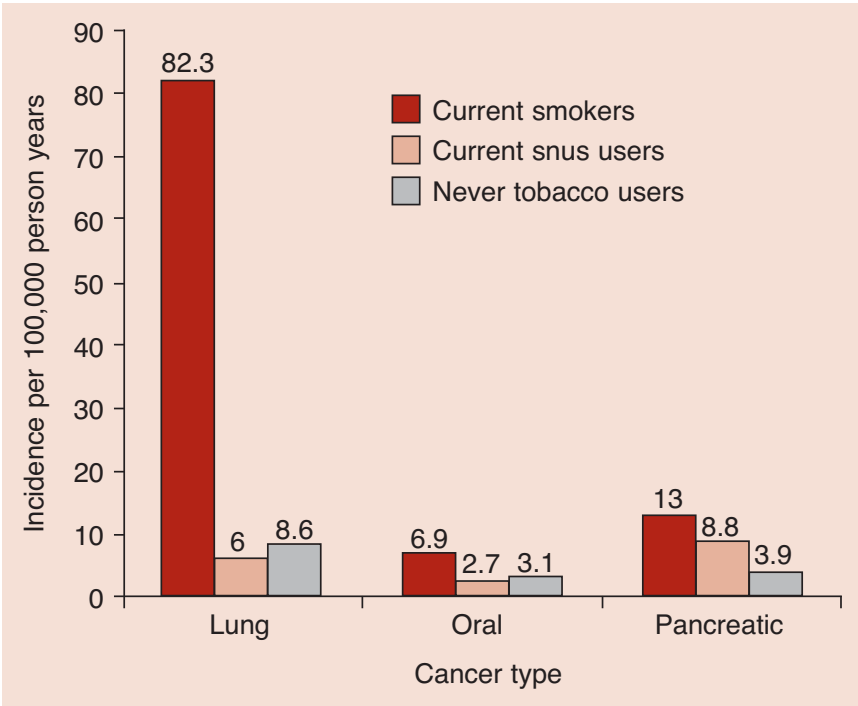


Fig 8.4 Incidence rate for three types of cancer (by 2004) as a function of tobacco use status in male Swedish construction workers at recruitment (1978–92). Adapted from data in Luo *et al.*⁴⁴

tobacco products such as Swedish snus is small, and possibly non-existent. The main evidence associating smokeless tobacco with oral cancer comes predominantly from studies in populations combining smokeless tobacco with other toxins (such as areca nut) or from populations using products that contain higher concentrations of carcinogenic compounds than are present in current moist snuff or new smokeless tobacco products available in the United States or Scandinavia.

8.4.2 Pancreatic cancer

It has also been suggested that smokeless tobacco may increase risks of pancreatic cancer, and there are plausible mechanisms for such effects. Smoking is a known cause of pancreatic cancer and TSNAs have been identified in pancreatic secretions of smokers.⁴⁵ Recently, Stepanov and Hecht found higher levels of some TSNAs in the urine of smokeless tobacco users compared with smokers, so it is plausible that levels will pass through the pancreas in smokeless tobacco users.⁴⁶

Bofetta *et al* reported a prospective cohort study of 10,136 Norwegian men who were enrolled in 1966 and followed to diagnosis by 2001, and of whom 32% used smokeless tobacco at some stage.⁴⁷ This study reported relative risks of eight types of cancer in current, former, and ever smokeless users. Overall, there was little consistent evidence of increased cancer risk among smokeless users. Among

ever or current users, relative risks greater than one were reported for cancer at four different sites (oral/pharyngeal, oesophagus, stomach, pancreas) and four below one (lung cancer, lung adenocarcinoma, kidney and bladder). The effect on pancreatic cancer was significant in ever users (relative risk 1.67; 95% confidence interval 1.12 to 2.50) and borderline significant in current users (relative risk 1.60; 95% CI 1.00 to 2.55). This effect was restricted, however, to analyses including snus users who were also current or former smokers. Among non-smoking snus users the relative risk was 0.85 (95% CI 0.24 to 3.07).

A case-control study from the United States of the effects of smokeless tobacco use on risk for pancreatic cancer compared 154 lifelong non-smokers newly diagnosed with pancreatic cancer and 844 controls aged 30–79.⁴⁸ Estimated odds ratios for pancreatic cancer were all increased, though non-significantly, in users of cigars, pipes or smokeless tobacco. In ever users of smokeless tobacco the odds ratio was 1.4 (95% CI 0.5 to 3.6) and in current users it was 1.1 (95% CI 0.4 to 3.1). This effect was dose related, with an adjusted odds ratio of 3.5 (95% CI 1.1 to 11) in those defined as heavy users (more than 2.5 ounces of smokeless tobacco per week) compared with 0.3 (95% CI 0.04 to 2.5) in light users (less than 2.5 ounces per week).

The findings of the first of these studies have been challenged on numerous grounds, including that the observed effect of smokeless tobacco was restricted to current smokers, and that the analysis did not correct for potentially important confounding by alcohol intake.⁴⁷ However, the recent study by Luo *et al* also found a significantly increased rate of pancreatic cancer among snus users versus never tobacco users (about a doubling of risk), and both of these groups had lower risks than smokers.⁴⁴ The implication of these findings is that smokeless tobacco, including the snus consumed in Sweden over the past half century, appears to be associated with an increased risk of pancreatic cancer.

8.4.3 Lung cancer

In the CPS-II study described above there was a significantly increased risk of death from lung cancer in smokeless tobacco users (hazard ratio 2.0; 95% CI 1.23 to 3.24).⁴¹ This effect was not seen in the CPS-I study (hazard ratio 1.08; 95% CI 0.64 to 1.83), and was surprising since the mechanism whereby use of smokeless tobacco in the mouth may cause cancer of the lung is not clear. It has been suggested that increased systemic exposure to NNK, a powerful systemic lung carcinogen, could be involved,⁴⁹ though other explanations for the finding, particularly bias arising from increased passive smoke exposure among smokeless tobacco users, have also been suggested.⁵⁰ This latter interpretation is sup-

ported by the fact that the raised age-adjusted hazard ratio for death from COPD, which is strongly related to smoke exposure, was 1.8 (95% CI 1.01 to 3.23) among smokeless users in CPS-II. To our knowledge, the observation of a raised risk of lung cancer in smokeless tobacco users has not been made in any other study, whereas a number have reported no increase in lung cancer risk among smokeless users.^{44,47,51,52} In the Luo *et al* study, snus users had a slightly lower risk of lung cancer than never tobacco users, whereas smokers' risks were increased by approximately 10-fold.⁴⁴ Similarly, in the study by Bolinder *et al*, the relative risk for lung cancer among snus users compared with never tobacco users was 0.8 among men aged 55–65, whereas the relative risk was 30.6 (95% CI 14.6 to 64.1) for smokers of at least 15 cigarettes per day (again compared with never tobacco users).⁵¹

8.4.4 Smokeless tobacco and all cancer mortality

Bolinder and colleagues found a non-significant relative risk of death from cancer of 1.1 for snus users compared with never tobacco users (95% CI 0.9 to 1.4) in a prospective study of Swedish construction workers that included a relatively large sample, many of whom had used snus for over 40 years.⁵¹ In the 1,734 snus users aged 55–65, most of whom would presumably have used snus for over 35 years, the relative risk for cancer death compared with non tobacco users was 1.0. This study found significantly increased all-cause mortality in snus users compared with never tobacco users, largely due to elevated cardiovascular mortality.

Overall, the numerous studies examining the effect of Swedish snus on cancer risk are fairly consistent in finding no increase in all-cause cancer among snus users.^{51,53–55} Many of the Swedish studies of the relation between snus and cancer were robust enough to detect significant effects for tobacco smoking,^{51,53,56} or alcohol use,^{54,56} though these effects were generally much larger than those related to snus. Lagergen *et al* reported that combined smoking and alcohol use was strongly associated with oesophageal squamous cell carcinoma, with an odds ratio of over 23 for heavy users compared to never users.⁵⁶ The main exception has been the Luo study that found no increased risk of lung or oral cancer, but an increased risk of pancreatic cancer in snus users.⁴⁴ The relative magnitude of these risks is shown in Fig 8.4. It is particularly noteworthy that in the analyses by Luo *et al* of the whole male cohort, men who had ever used snus were significantly less likely to develop lung or oral cancer, and non-significantly less likely to develop pancreatic cancer, as compared with men who had never used snus (presumably because snus use reduced smoking).⁴⁴ Thus, it appears that, despite finding an association between snus use and pancreatic cancer, this study

demonstrates that snus availability and use instead of cigarettes may have produced a large reduction in cancer incidence – primarily via reduced rates of lung cancer among smokers who switched. The majority of the snus users who developed pancreatic cancer in the study by Luo *et al* had used snus before the 1980s. Since that time, the level of carcinogens in snus has reduced.²⁹

8.4.5 Smokeless tobacco and cardiovascular risk

Early studies of smokeless tobacco and cardiovascular diseases were primarily carried out in Sweden, and produced inconsistent results. Bolinder *et al* reported on a 12-year follow up of 135,000 Swedish construction workers, and found an increased risk of death from myocardial infarction in snus users compared with never tobacco users (relative risk 1.4; 96% CI 1.2 to 1.6).⁵¹ Huhtasaari *et al* reported on two studies, neither of which found significantly increased cardiovascular risks for snus users, and one of which reported a significantly reduced risk of non-fatal myocardial infarction in snus users when compared with never regular tobacco users (odds ratio 0.58; 95% CI 0.35 to 0.94).^{57,58} Each of these studies reported significantly increased risks for smokers, with larger effect sizes than those for snus users. Much of this evidence has been synthesised in previous reviews, which have concluded that, while most of the evidence was not supportive of a significant relationship, the inconsistencies in the study outcomes mean that a moderate effect of smokeless tobacco use on cardiovascular disease cannot be excluded.^{4,39,58,59}

Since those reviews were published, five further studies have been reported.^{41,60–63} Hergens *et al* reported a case-control study in 1,432 Swedish men who had a myocardial infarction in 1992–4, and 1,810 controls.⁶⁰ After adjustment for age, area and smoking, the relative risk for a first myocardial infarction was 1.1 (95% CI 0.8 to 1.5) for former snus users, and 1.0 (95% CI 0.8 to 1.3) for current snus users. The hypothesis that smokeless tobacco increases the risk of myocardial infarction was therefore not supported by these findings. Johansson *et al* conducted a 12-year follow-up study in 3,120 healthy Swedish men to establish risk factors for coronary heart disease.⁶¹ The adjusted hazard ratio for never smoking snus users compared with never tobacco users was 1.41 (95% CI 0.61 to 3.28), whereas both smokers and former smokers had higher and significantly increased risks.

The recent analyses of the effects of smokeless use in the CPS-I and CPS-II studies found consistently raised hazard ratios for cardiovascular disease as a whole, coronary heart disease as a specific diagnosis, and for cerebrovascular disease as a specific diagnosis in particular, in both cohorts (Table 8.6).⁴¹ The potential for confounding by passive smoke exposure in this study is outlined above, but the more recent INTERHEART case-control study, involving 12,133 cases and 14,435 con-

trols across 52 countries, provides further evidence.⁶² This study controlled for a number of potential confounding variables, including exposure to second-hand smoke, and estimated an adjusted odds ratio of 1.57 (95% CI 1.24 to 2.00) for tobacco chewers, adjusted for smoking status. In analysis of exclusive tobacco chewers (excluding smokers), the odds ratio for myocardial infarction was significantly increased at 2.23 (95% CI 1.41 to 3.52) compared with never tobacco users. Adjustment for other potential confounding variables such as diabetes, obesity, hypertension, exercise, and diet had little effect. The risks of acute myocardial infarction associated with smokeless and other types of tobacco use from the INTERHEART study are shown in Fig 8.5.⁶² There were insufficient numbers of users included in the study to draw conclusions about the product-specific effects of snuff or paan use.

A prospective incident case-control study of the cardiovascular risks from snus in Sweden compared 525 male cases of myocardial infarction and 1,798 matched controls.⁶³ This study found no increased risk of myocardial infarction or sudden cardiac death among exclusive snuff users, whereas smokers' risks were two to three times those of never smokers.

The authors of the INTERHEART study hypothesised that the mechanisms whereby oral tobacco may increase the risk of myocardial infarction could involve

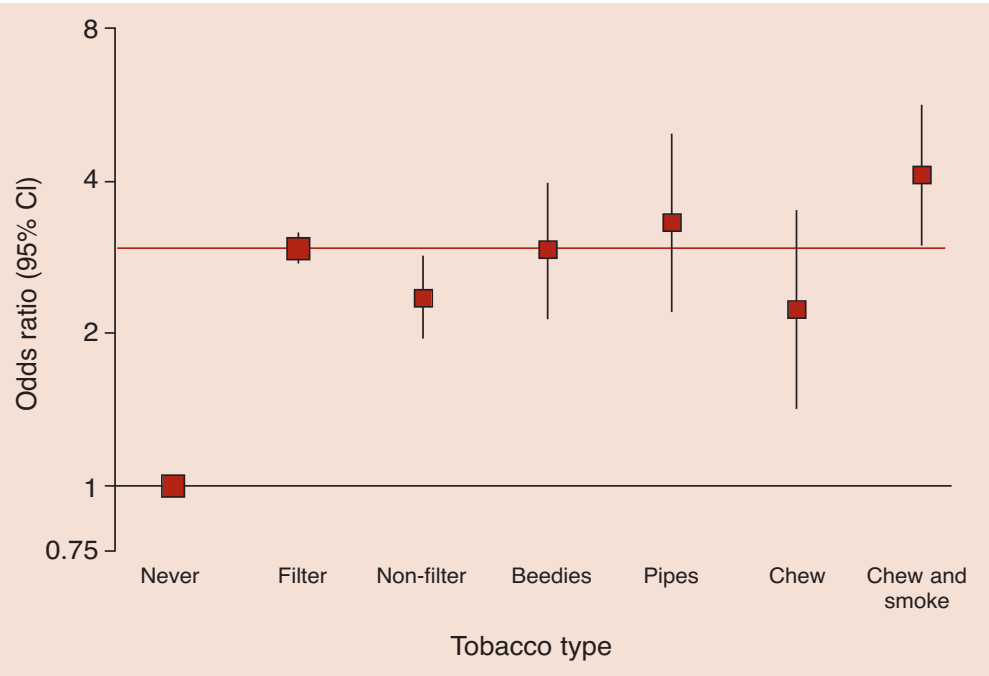


Fig 8.5 Risk of acute myocardial infarction associated with type of tobacco used. Odds ratio for current smokers = 2.95 (95% CI 2.77–3.14) indicated by broken horizontal line. Never = never smokers; Filter = filter cigarettes; Non-filter = non-filter cigarettes; Beedies = smoking beedies alone; Pipes = smoking pipes/cigars; Chew = chewing tobacco alone; Chew and smoke = both chewing and smoking tobacco. Reproduced from Teo *et al* with permission from Elsevier, copyright 2006.⁶²

arterial damage and short-term increases in blood pressure caused by nicotine.^{64,65} If the mechanism is mediated largely via nicotine effects, then these findings would be likely to apply to all forms of smokeless tobacco, as well as to long-term use of nicotine replacement therapy. The main weakness of the INTERHEART study's analysis of smokeless tobacco use was that many of those included in the analyses were likely to also chew areca nut and other additives along with their tobacco. Given the known cardiovascular effects of areca nut, it is unclear how much of the excess risk in the INTERHEART study can be attributed to tobacco.¹³

In conclusion, the evidence remains mixed but three large studies have found increased risks of cardiovascular disease in smokeless tobacco users, as compared with never tobacco users.^{41,51,62} Where these studies reported the cardiovascular risks associated with smoking, these were always greater than those associated with smokeless tobacco use. The possibility remains that a part of these effects of smokeless tobacco use is due to confounding variables (such as passive smoke exposure) or to concomitant use of areca nut. However, the most plausible interpretation is that long-term smokeless tobacco use is associated with a modest increased risk of serious cardiovascular events (and specifically myocardial infarction). It is also plausible that this elevated risk is due to the effects of nicotine,^{64,65} though the potential contributions of other components of smokeless tobacco have not, to date, been investigated. However, of six studies of risks of myocardial infarction in long-term Swedish snus users, only one found an increased risk,⁵¹ and five did not detect any increased risk over never tobacco users,^{57,58,60–63} despite the fact that these snus users were typically absorbing high doses of nicotine over decades.

8.4.6 Pregnancy

Animal studies have implicated nicotine as a cause of some of the widely known adverse effects of tobacco smoking on the healthy development of the fetus during pregnancy. It follows that smokeless tobacco use during pregnancy is likely to incur some of the risks associated with smoking during pregnancy.⁶⁶ A small number of studies have been published recently which shed some light on the effects of smokeless tobacco on pregnancy.

England *et al* examined data from the Swedish Birth Register for women who delivered babies during 1999–2000.⁶⁷ The study compared 789 snus users with 11,240 cigarette smokers and 11,495 women not using any tobacco. Compared with non-users, adjusted mean birth weight was reduced in snuff users by 39 g (95% CI 6 g to 72 g) and in smokers by 190 g (95% CI 178 g to 202 g). Preterm delivery was increased in snuff users (adjusted odds ratio 1.98; 95% CI 1.46 to

2.68) and smokers (adjusted odds ratio 1.57; 95% CI 1.38 to 1.80). Pre-eclampsia was reduced in smokers (adjusted odds ratio 0.63; 95% CI 0.53 to 0.75), but increased in snuff users (adjusted odds ratio 1.58; 95% CI 1.09 to 2.27).

Steyn *et al* studied the patterns and effects of maternal snuff use, cigarette smoking and exposure to environmental tobacco smoke during pregnancy on birth weight and gestational age in women living in Johannesburg and Soweto in 1990.⁶⁸ A cohort of 1,593 women provided information about their own and household members' use of tobacco products during pregnancy. Women who smoked cigarettes or used snuff during pregnancy accounted for 6.1% and 7.5% of the study population respectively. The birth weight reduction adjusted for possible confounders was 137 g (95% CI 26.6 g to 247.3 g) for cigarette smokers and 17.1 g (95% CI -69.5 to 102.7 g) for snuff users, when compared with the birth weight of non-tobacco users. They concluded that snuff use was not associated with low birth weight.

Gupta and Subramoney conducted a population-based prospective cohort study to investigate whether smokeless tobacco use was associated with increased risks for stillbirth in India.⁶⁹ The adjusted risk for stillbirth in users was 2.6 (95% CI 1.4 to 4.8). Most women used mishri (a pyrolysed tobacco product often used as dentifrice), and there was a dose-response relationship between the daily frequency of use and stillbirth risk.

Overall, these epidemiological studies are consistent with the evidence from animal studies that exposure to nicotine via smokeless tobacco in pregnancy is harmful to the fetus, causing a reduction in birth weight of about 20% of that caused by smoking, and increasing risks of pre-eclampsia and stillbirth.

8.4.7 Periodontal disease

There is clear evidence that smokeless tobacco use causes smokeless tobacco keratosis, gum erosion and increases the risk of periodontal disease, although typically to a lesser extent than cigarette smoking.^{16,70–72}

8.5 Health effects of smokeless tobacco compared with cigarettes

Very few studies have directly compared the health risks of smokeless tobacco use with those of cigarette smoking. Roth *et al* reviewed studies comparing the risks of smoking with those of Swedish snus.⁷³ They found only seven studies in which direct comparisons were made. Although few in number, these studies do provide quantitative evidence that, for certain health outcomes, the health risks associated with snus are lower than those associated with smoking. Specifically, this is true

for lung cancer (based on one study), for oral cancer (based on one study), for gastric cancer (based on one study), for cardiovascular disease (based on three of four studies), and for all-cause mortality (based on one study).

Another way of indirectly assessing the magnitude of risks is to compare the published hazard ratios for specific diseases in smokeless users and smokers in the CPS-II study in the United States. Here we find that smokers have relative risks of death from oral cancers of 10.9 to 14.6, relative risks of lung cancer death of 23.3, and relative risk of death from COPD of 10.6,⁷⁴ as compared with adjusted hazard ratios of 0.9, 2.0, and 1.3 respectively for the most directly comparable diagnostic categories in smokeless tobacco users (all of these relative to never tobacco users).⁴¹

Quantification of the magnitude of the difference in risks could be aided by direct comparison using the same diagnostic categories and risk measure, but it is very clear that, for most of the major health effects of tobacco, smoking is many times more dangerous than smokeless tobacco use. Perhaps the main exceptions are pre-eclampsia, because other components in tobacco smoke appear to have a mild preventive effect,⁶⁷ and cardiovascular disease, in which the risks from smoking, although certainly greater than those from smokeless use, may be in a similar range of risk. As discussed in section 8.4.5, cardiovascular risk estimates vary widely, but are typically slightly greater than those of never tobacco users and consistently less than those of smokers. For example, in the CPS studies in the United States, relative risks for smokers compared with never smokers ranged from 1.5 for ischaemic heart disease in men over 65 to 7.1 for aortic aneurysm in women.⁷⁴ As shown in Table 8.6, the adjusted hazard ratios for male smokeless users compared with never tobacco users ranged from 1.12 for coronary heart disease to 1.46 for cerebrovascular disease.

In an exercise carried out to estimate the relative hazards of snus use and smoking, a panel of nine experts was asked to determine expert opinions of mortality risks associated with use of low-nitrosamine smokeless tobacco (LN-SLT) marketed for oral use.¹¹ They concluded that, in comparison with smoking, there is at least a 90% reduction in the relative risk of LN-SLT use. In reporting the results of a subsequent study using a similar design, the authors concluded that the introduction of a new LN-SLT product in the United States under strict regulations would increase SLT use, but reduce overall smoking prevalence. They said, ‘This reduction would likely yield substantial health benefits but uncertainties surround the role of marketing and other tobacco control policies.’⁷⁵ Much of the evidence for this conclusion is based on the experience in Sweden of snus becoming more popular than smoking in Swedish men, and being used by a significant proportion of Swedish smokers in the process of quitting smoking.^{4,76,77}

One study found that among men who made attempts to quit smoking, snus was the most commonly used cessation aid, being used by 24% on their latest quit attempt (meaning it is used more frequently as a cessation aid than the total use of all the nicotine replacement products).⁷⁷ Importantly, the data from Sweden also suggest that rather than snus acting as a gateway to smoking for young people, those people who take up snus use are actually significantly less likely to become regular smokers.^{77–79} In the northern part of Sweden, where snus use is particularly popular, the effects on reducing smoking have been particularly marked. One recent study reported that the prevalence of daily smoking among men in northern Sweden fell from 19% in 1986 to only 9% (CI 7.0% to 11%) in 1999, and to only 3% (CI 0.1% to 5.4%) in men age 25–34 years; while the prevalence of exclusive snus use increased to 27% (95% CI 24 to 30%) and 34% (95% CI 27 to 42%) respectively.⁸⁰

8.5.1 Health effects in ex-smokers who switch to smokeless tobacco

One recent study using the CPS-II cohort compared tobacco-related disease mortality among 4,443 men who switched from cigarettes to smokeless tobacco ('switchers'), with those of 111,952 men who quit smoking completely without using any other tobacco ('quitters').⁸¹ After 20 years of follow-up, switchers had a higher rate of death from any cause (hazard ratio 1.08; 95% CI 1.01 to 1.15), lung cancer (hazard ratio 1.46; CI 1.24 to 1.73), coronary heart disease (hazard ratio 1.15; 1.00 to 1.29), cancer of the oral cavity and pharynx (hazard ratio 2.5; CI 1.2 to 5.7 based on only seven deaths in switchers) and stroke (hazard ratio 1.24; 1.01 to 1.53), compared with those who quit tobacco entirely. Interestingly, this study also found almost significantly increased risk of death from COPD in switchers (hazard ratio 1.32; CI 0.96 to 1.78). The analyses were also separated into chew and snuff users. For snuff users (27% of switchers), the adjusted hazard ratios for all cause mortality (1.11), coronary heart disease (1.12) and stroke (0.89) were not significantly elevated, and were lower than those for lung cancer (hazard ratio 1.75; CI 1.2 to 2.5) and COPD (hazard ratio 1.68; CI 0.9 to 3.3).

The switchers and quitters differed significantly in some important baseline characteristics (for example, 30% of the switchers had less than a high school education compared with 13% of quitters), but the results summarised above were adjusted for a range of relevant demographic and behavioural factors, including previous smoking rate, years of smoking, fruit intake, body mass index and other factors recorded at recruitment in 1982. The authors acknowledged the possibility that residual confounding (for example, exposure to second-hand smoke or subsequent relapse to smoking) could account for some or all of the increased risk in

switchers. However, they concluded that this study, together with the other CPS-II data, suggests that using smokeless tobacco compares unfavourably with both complete tobacco cessation and never use of tobacco products. Unfortunately, neither this nor the other papers from the CPS studies have reported a comparison of relative risks in smokeless users and smokers. This would be informative for smokers who feel they either cannot, or do not want to, quit tobacco, but would like to significantly reduce their risks from tobacco use.

8.5.2 Smokeless tobacco: a gateway to smoking or a means of quitting smoking?

Given that smokeless tobacco is much less harmful than smoking, the issue of how smokeless tobacco may influence smoking rates is relevant to judging its overall health impact. If people who start using smokeless tobacco are at a higher risk of starting smoking or a lower risk of quitting smoking (all other things being equal), this would add significantly to the health impact of smokeless tobacco use. Conversely, if smokeless tobacco use reduces risk of smoking or helps smokers to quit, that should also be considered in weighing its harmfulness, both for the individual and for public health.

Unfortunately, there is very little available information on patterns of use of smokeless tobacco and effects on smoking prevalence outside Sweden. Rodu and Godshall have reviewed the evidence from national surveys in the United States.²¹ They reported that the 1986 US Adult Use of Tobacco Survey found that 7% (1.7 million) of male ex-smokers had used smokeless tobacco to help them quit smoking cigarettes, as compared with 1.7% of male ex-smokers (405,000) who had used organised smoking cessation programmes to help them quit smoking. The 1991 US National Health Interview (NHI) Survey revealed that a third of adult smokeless tobacco users were former cigarette smokers (around 1.8 million). The 1998 NHI Survey revealed that 5.8% of daily snuff users reported quitting smoking cigarettes within the past year; that daily snuffers were three times more likely to report being former smokers than were never snuff users; and that daily snuff users were four times more likely to have quit smoking in the past year than never snuff users.

The question of whether smokeless tobacco use acts as a gateway to smoking in the United States has been the subject of heated debate. Kozlowski *et al* reported that a maximum of 23% of US young smokeless tobacco users progressed into smoking, based on the finding that 35% of 23–34-year-old smokeless users had never smoked, and 42% smoked before they used smokeless tobacco.⁸² They also found that those who used cigarettes before moist snuff were 2.1 times more likely

to have quit smoking (95% CI 1.21 to 6.39) than cigarette-only users. They concluded that the large majority of US smokeless users do not in fact progress to smoking. However, a study of recruits to the US Army by Haddock *et al* and a longitudinal study of almost 4,000 US male adolescents by Tomar both found that young men who started using smokeless tobacco were approximately twice and 3.5 times respectively more likely to smoke subsequently.^{83,84} While these findings must be interpreted cautiously since use of smokeless tobacco and progression to smoking are likely to be biased by a range of cultural and other factors, there is evidently some uncertainty over the extent of gateway use in these and other US studies.

Recent studies in Sweden, however, appear to be consistent in finding that Swedes who start using snus are less likely to become smokers and Swedish smokers who start using snus are more likely to quit smoking.^{77–80} The study by Ramström *et al* found that the odds of initiating daily smoking were significantly lower for men who had started using snus than for those who had not (odds ratio 0.28; 95% CI 0.22 to 0.36) (Fig 8.6).⁷⁷ Among male primary smokers, 28% started secondary daily snus use and 73% did not. Of those secondary snus users, 88% had ceased daily smoking completely by the time of the survey compared with 56% of those primary daily smokers who never became daily snus users, (odds ratio 5.7; 95% CI 4.9 to 8.1). Among men who made attempts to quit smoking, snus was the most commonly used cessation aid, being used by 24% on their latest quit attempt.

One potential reason why more people have switched from smoking to smokeless tobacco in Sweden than the United States is that in Sweden the public health authorities have updated their information on health risks according to the latest scientific evidence,⁸⁵ whereas in the United States the public have been informed that smokeless tobacco is just as harmful as smoking cigarettes.^{86,87} In an environment in which smokers are informed and believe that smokeless tobacco is just as harmful to health as smoking, one would not expect many to switch for health reasons.

A recent comprehensive systematic review and meta-analysis of the health effects of snus concluded that:

*The evidence suggests that the harm of using snus relative to non-tobacco is significantly less than found for smoking with regard to cancer of the head, neck and gastrointestinal region, and cardiovascular disease events.*⁸⁸

Snus is currently banned in Australia. Gartner *et al* used the best available data and expert reviews to estimate the likely health impact of snus in Australia.⁸⁹ They conclude that snus is likely to produce a net benefit to population health, with the size of the benefit dependent on how many inveterate smokers switch to snus.

Pathways of initiation and progression of tobacco use among men in Sweden.

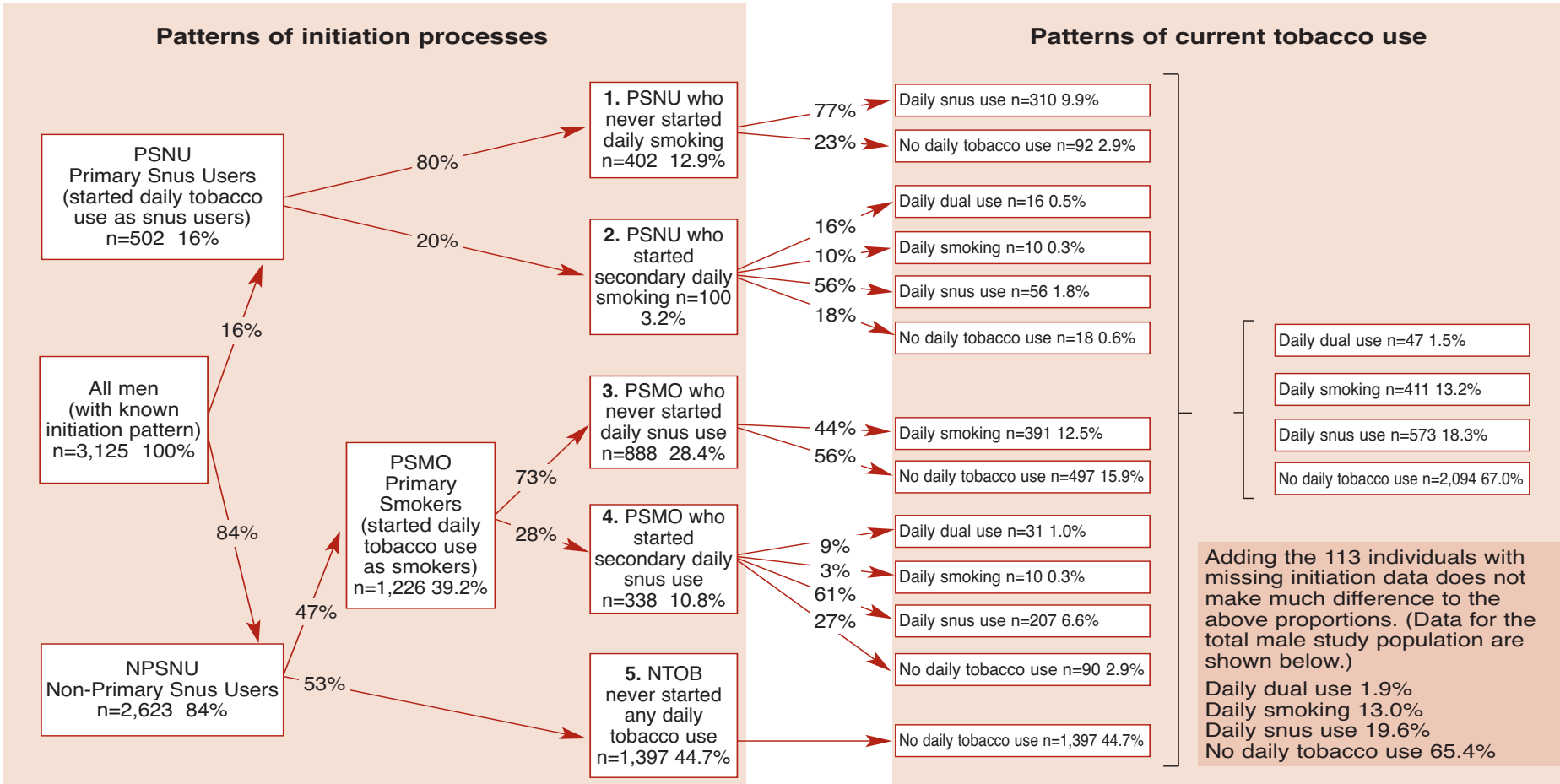


Fig 8.6 Pathways of male tobacco use in Sweden (percentages in boxes based on all men ages 16–79). The left section shows the proportions of men who started daily snus use, smoking, both (and if so, in what order) or no tobacco use. The central section shows, for each initiation category, the proportions of men who continued or quit each type of tobacco use that was initiated. The right section shows the proportions of men following 13 different pathways to current tobacco use. NPSNU = non-primary snus users; NTOB = never tobacco users; PSMO = primary smokers; PSNU = primary snus users. From Ramstrom and Foulds;⁷⁷ reproduced with permission from the BMJ Publishing Group Ltd.

The epidemiology of tobacco use in Sweden suggests that if the public is offered a substantially less harmful smokeless tobacco product along with access to accurate information on relative risks, a substantial proportion can switch to the less harmful product. This has clear implications for public health.⁹⁰

8.6 Conclusions

- ▶ Smokeless tobacco is not a single product, but rather a summary term for a range of different tobacco products which deliver nicotine without combustion.
- ▶ Smokeless tobacco products differ substantially in their risk profile in approximate relation to the content of toxins in the tobacco.
- ▶ In some parts of the world (particularly Asia), smokeless tobacco is commonly mixed with other products that are themselves harmful.
- ▶ On toxicological and epidemiological grounds, some of the Swedish smokeless products appear to be associated with the lowest potential for harm to health.
- ▶ These Swedish smokeless products appear to increase the risk of pancreatic cancer, and possibly of cardiovascular disease, particularly myocardial infarction.
- ▶ Some smokeless tobacco products also increase the risk of oral cancer, but if true of Swedish smokeless tobacco, the magnitude of this effect is small.
- ▶ All of the above hazards are of a lower magnitude than those associated with cigarette smoking.
- ▶ Smokeless tobacco products have little or no effect on the risk of chronic obstructive pulmonary disease or lung cancer.
- ▶ Therefore, in relation to cigarette smoking, the hazard profile of the lower risk smokeless products is very favourable.
- ▶ Smokeless tobacco use by pregnant women is harmful to the unborn fetus, but the hazard of smokeless use relative to maternal cigarette smoking is not clearly established.
- ▶ In Sweden, the available low-harm smokeless products have been shown to be an acceptable substitute for cigarettes to many smokers, while 'gateway' progression from smokeless to smoking is relatively uncommon.
- ▶ Smokeless tobacco, therefore, has potential application as a lower hazard alternative to cigarette smoking.
- ▶ The applicability of smokeless tobacco as a substitute for cigarette smoking if made available to populations with no tradition of smokeless use is not known.

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9 | Current nicotine product regulation

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9.1 Introduction

The range of nicotine and tobacco products available in most countries is extensive, and includes pure medicinal nicotine products; chewing tobacco, snuff and other smokeless tobacco products; raw tobacco for smoking in hand-rolled cigarettes or pipes; and cigarettes and cigars (see Chapter 5). Currently, there is no overarching regulatory framework for these products in the UK or any other country. In addition, there is no systematic regulatory process applied across the production of tobacco products from manufacturers to distributors, wholesalers, retailers and marketers, although some recent attempts have been made to control the supply chain through government initiatives to control smuggling. In recent years, the UK and other countries have implemented a broad range of tobacco control strategies,^{1,2} but regulation of the product itself has received relatively little attention or resource. This may be partly due to a lack of clarity as to whether it is possible to make cigarettes less harmful and, if so, how best to do this. It is also unclear what role other tobacco and nicotine products can play in reducing the health burden caused by tobacco use in the UK.

Cigarettes were developed and marketed in the UK and elsewhere decades before the dangers of smoking were known, and were therefore widely used long before a regulatory response proportionate to their risk could be developed. As a result, cigarettes have remained largely exempt from consumer protection legislation, and

tobacco product regulations were introduced gradually in a piecemeal way over the years by various regulatory bodies or government departments with responsibility for different aspects and categories of the product. For example, at present some tobacco product regulations, such as machine-measured tar, nicotine and carbon monoxide yields of cigarettes and the supply of oral tobacco, are decided at EU level by European Directives and apply across the UK and other EU countries. Some, such as taxation, smuggling and advertising controls other than those with cross border effects, are decided at UK level. Others, such as smoke-free legislation, are regulated by the devolved administrations in Scotland, Wales and Northern Ireland. Medicinal nicotine products are regulated by the Medicines and Healthcare products Regulatory Agency (MHRA), which has a UK-wide remit.

For the purposes of this chapter we have divided the range of nicotine and tobacco products into four categories: smoked tobacco, smokeless tobacco, new tobacco product formulations and potential reduced exposure products (PREPs), and ‘clean’ (typically medicinal) nicotine products. Brief details follow on the main types of regulations that apply to these different product categories, grouped largely according to product, price, promotion and place (illustrated in Table 9.1). The chapter then explores the options for improving and optimising the regulatory framework for these products, predominantly from a UK (and EU) perspective.

9.2 Smoked tobacco products

Smoked tobacco products include cigarettes, hand-rolling tobacco, pipes and cigars. Before the emergence of evidence of a link between smoking and lung cancer³ and

Table 9.1. Range of potential regulations governing tobacco and other nicotine products.		
Product	Mode of use	How product is used, for example, smoked or chewed
	Content	Tobacco content, such as nitrosamines and additives
	Design	A range of features such as filters, pressure drop, ventilation, way the tobacco is processed
	Yields	What comes out of the product when used
	Delivery and exposure	The amount of nicotine and other constituents reaching the human body, and the speed of delivery and absorption
Price		Tax structure and price, non-monetary costs, incentives
Promotion		Advertising, sponsorship and marketing
Place		Retail outlet restrictions and accessibility
		Age restrictions
		Packet size restrictions

the Royal College of Physicians (RCP) 1962 report⁴ on smoking and health, there was very little regulation of any tobacco product. Aside from tax/duty rules only the sale of tobacco to children was regulated, dating from legislation passed in 1908.

The RCP report set out the need for a comprehensive strategy to reduce smoking, including advertising restrictions, price rises, education about the dangers of smoking, and support for smokers when they attempted to stop smoking. For the most part, however, these were not implemented through legislation. Instead the government entered into an increasingly complex series of 'voluntary agreements' negotiated in private with the tobacco industry. These agreements proved difficult to enforce, left loopholes that were exploited by the industry, and have now been largely discredited as ineffective.⁵ From the 1990s, these voluntary agreements were gradually superseded by legislative approaches, often driven by directives from the European Commission.

In 1998, nearly 50 years after the first UK report linking smoking to lung cancer,³ the UK government published a comprehensive strategy to reduce smoking in England in the form of a White Paper, *Smoking kills*.¹ The stated aim of the strategy was to reduce smoking among children and young people, and help adult smokers – particularly pregnant women and smokers from socioeconomically disadvantaged groups – to quit. The White Paper also recognised that smoking was an addiction. As discussed below, however, despite this progress, the tobacco product itself has remained virtually unregulated. The key regulations applying to smoked tobacco products are as follows.

9.2.1 Price

The retail price of cigarettes reflects the sum of the manufacturers' price, duty and tax, and the retail margin. Increasing the cost of tobacco products through taxation has been widely used as a tobacco control measure in the UK because it both reduces smoking and generates revenue for central government.

The level of duty and taxes on tobacco products (specifically cigarettes, cigars, pipe tobacco, hand-rolling tobacco and chewing tobacco) are set by the Treasury. Initially, excise duty was based only on the tobacco content of cigarettes, but a more complex system was introduced in 1978, when duties on additives and substitutes used in the manufacture of tobacco products were also introduced. Tobacco products in Europe are now subject to both excise tax (levied either as a specific tax or an ad valorem tax) and value added tax (VAT). Specific tax is a fixed sum per cigarette regardless of the value of the product. Ad valorem tax varies in proportion to the value of the goods levied, and thus keeps pace with price inflation. Currently, specific and ad valorem taxes account for approximately equal shares of the excise tax on cigarettes, and total taxation for about 76% of the retail price of cigarettes in

the UK. Tax in the UK is now high relative to other European countries (see Fig 9.1),² having risen above rates of inflation particularly during the 1990s.

Smuggling and illegal sale of cigarettes has been a significant problem in the UK, and since 2000 a range of policy and regulatory measures have been introduced to reduce the market share⁶ of smuggled and counterfeit cigarettes, and hand-rolling tobacco. The Finance Act 2006 included legislation placing obligations on all manufacturers to ensure that cigarettes and hand-rolled tobacco do not evade tobacco duties.⁷

The potential for a taxation strategy to alter consumption has been clearly demonstrated in the UK. In 1978 a supplementary tax was introduced for cigarettes with the highest tar yields (over 20 mg tar) for a period, and resulted in and the near elimination of brands with over 20 mg tar yields from the market.⁸ Duties on hand-rolling tobacco were frozen in the UK for a period in the 1990s, because the illicit market share for hand-rolled tobacco had become particularly high. The resulting increase in the price differential between hand-rolling tobacco and manufactured cigarettes only served to exacerbate the problem and there was an

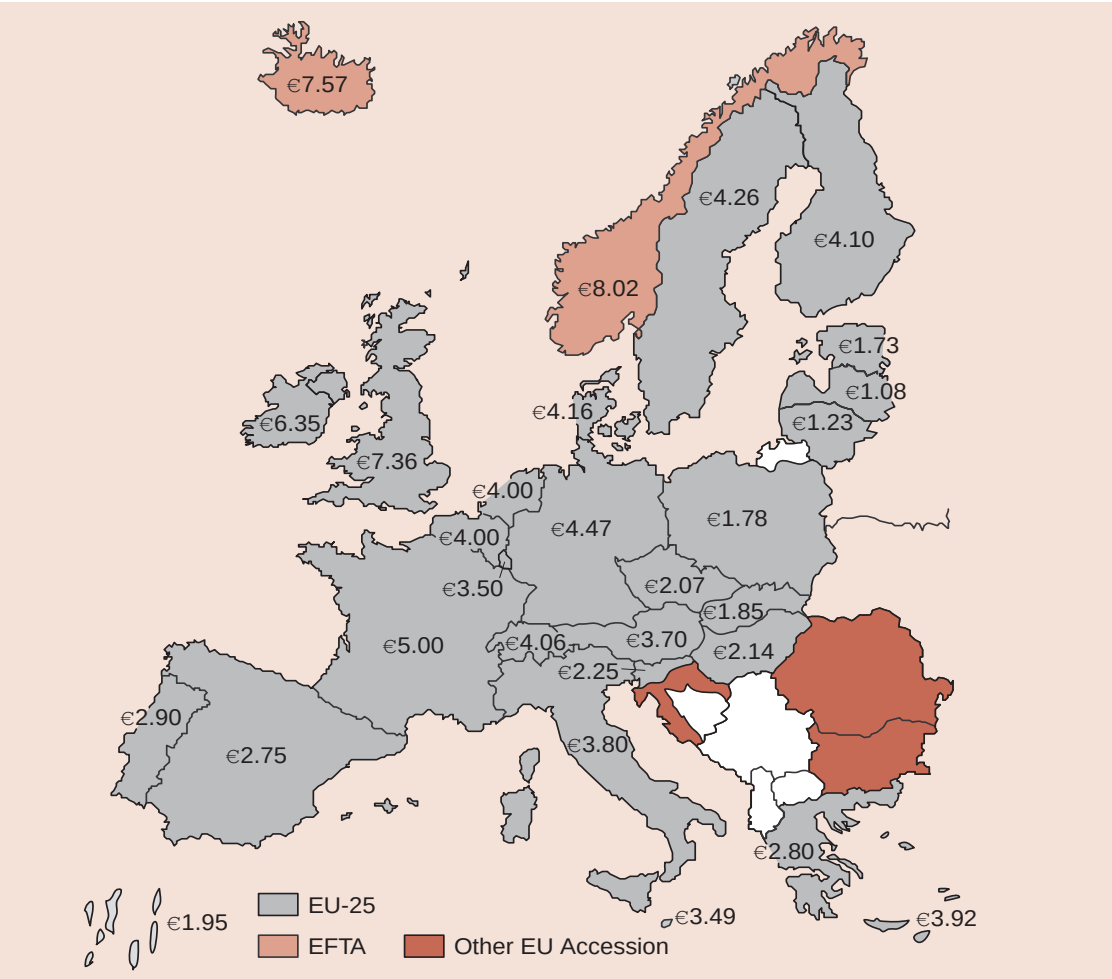


Fig 9.1 Retail price (in Euros) of 20 Marlboro cigarettes in EU countries on 1 January 2006. Adapted from Joosens and Raw, 2006.²

increase in the proportion of smokers using hand-rolled tobacco from 10% in 1984 to 25% in 2006.⁹ Hand-rolling tobacco in the UK is still taxed at a lower rate compared to cigarettes, only about 66% of the total price being tax.¹⁰

9.2.2 Promotion

Advertising of tobacco products, defined as ‘a product consisting wholly or partly of tobacco and intended to be smoked, sniffed, sucked or chewed’, is now banned throughout the UK by law. The Tobacco Advertising and Promotion Act 2002¹¹ prohibits tobacco advertising on billboards, in print media, by direct mail and through sponsorship. Point of sale advertising is allowed but limited to one A5-sized advertisement, a third of which must be a health warning. The government also has the power under this Act,¹¹ as yet unused, to introduce further regulations on point of sale displays, such as controlling the number of displays and packets on display, the proximity of tobacco products to children’s products like sweets, or potentially by banning all displays of tobacco products at the point of sale.

9.2.3 Product

Regulation of the tobacco product itself is the responsibility of the UK Department of Health, and is currently limited to additives and machine measured yields (see below). A full explanation of how tobacco products are designed, what goes into them and what comes out of them, is not currently required by regulatory authorities in the UK. Articles concerning product regulation are included in the Framework Convention on Tobacco Control,¹² which the UK government has ratified and is thus committed to implement. At present, however, the yields, content and other characteristics of tobacco products in the UK are regulated as follows.

Yields

Since the 1970s, the main regulatory strategy for reducing the harmfulness of cigarettes has been to reduce the machine-smoked tar and nicotine yields they deliver. This process began with a series of voluntary agreements and subsequently through EU regulations, and has been accompanied by introduction of ‘low tar’ brands with names suggesting reduced harm to the user such as ‘light’ or ‘mild’. The most recent EU directive,^{13,14} set maximum yields of tar, nicotine and carbon monoxide for cigarettes.

This approach to regulating cigarettes and its effects on reducing health effects has been extensively reviewed.^{15,16} There is now broad recognition that machine-smoked yields do not reflect the exposures sustained in practice by smokers

using the product, and that there are minimal, if any, health benefits realised by smoking lower tar and nicotine yield cigarettes. This approach is now recognised as wholly inappropriate as a basis for regulating the harm done by cigarettes,¹⁵ but the regulations remain in force. The European Commission, in their review of the directive in 2005,¹⁷ commented that it did not propose to revise the standards ‘until solid evidence shows that better methods exist to replace them’.

There are no regulations concerning the yields of hand-rolling tobacco. An ISO emissions standard has been developed for hand-rolled cigarettes made in a consistent manner and the industry displays this on packs in a number of EU countries such as the Netherlands. The UK has declined to support this because it may be misleading to consumers about the actual real-life yields to smokers. The same argument should be used against displaying yields on packs of manufactured cigarettes, although this is required by European legislation rather than a voluntary arrangement (see below).

Content

Another approach has been to control the use of additives. Until 1970, few ingredients other than tobacco and paper were used in cigarettes, largely because their use was proscribed. Following the revision of the tax system in 1978, statutory controls on additives became subject to a voluntary agreement with the tobacco industry. The government stated at the time¹⁸ that ‘... it will amend the Medicines Act 1968 in order to control the use of tobacco substitutes and additives in smoking products in the UK, if the need arises at any time’. This option has not been invoked, and an updated voluntary agreement still applies.

In 2001 a European directive¹⁴ required the disclosure of ingredients for all tobacco products (defined in this legislation as meaning ‘products for the purposes of smoking, sniffing, sucking or chewing, inasmuch as they are, even partly, made of tobacco, whether genetically modified or not’). Ingredients added to the products and cigarette papers must now be disclosed by brand name to include the type, quantity and function for each ingredient, and toxicological data. The latter should include effects on health either alone or in combination with other ingredients and addictive effects, for ingredients both in the burnt and unburnt forms. The directive required all member states to ensure that the list of ingredients for each product was made public, though this was qualified by a reference to trade secrecy. How this should be done and by when was not specified. To date, despite the requirements of the European directive to do so, no information on additives in tobacco products has been made public in the UK or in most other European countries. Efforts are currently ongoing with EU member states to create a uniform reporting and publishing standard that would allow consistent public reporting.

Concerns have also been raised as to whether the definition of ingredients and additives is sufficiently comprehensive to pick up all products added to the raw tobacco in the manufacture of cigarettes, and over the manner in which the information is reported.¹⁹ The European Commission has also commented on the incomplete nature of the data it receives on ingredients from member states¹⁷ and is developing harmonised data collection methods based on a common format and improved definitions. Nevertheless, concerns remain about the lack of capacity to assess the data, and further research and analysis has been recommended to create scientifically sound criteria before approval or prohibition of ingredients can be progressed.¹⁹

There are no regulatory controls on the raw tobacco itself (such as the levels of known carcinogens like nitrosamines) used in combustible products.

Design

There are no regulations concerning the design of tobacco products in the UK. Canada and some US States have regulated the propensity of cigarettes to cause fires by mandating the sale of only fire safe cigarettes. There is currently a campaign for reduced ignition propensity (RIP) legislation to be adopted in the UK, and the Department for Trade and Industry, the Department of Health and the Department for Communities and Local Government have supported setting such a standard.²⁰

Product information and health warnings

In response to evidence that machine-smoked tar yields are not valid measures of exposure to the smoker, the European Commission has now required that labels such as 'light' or 'mild' on low tar cigarettes be removed.¹⁴ However, manufacturers are still required to list tar, nicotine and CO yields on cigarette packs,¹⁴ and continue to use other names such as 'smooth', that imply less harm.²¹ Health warnings have been required on cigarette packs in the UK since 1971 and were introduced for hand-rolling tobacco (and chewing tobacco products) in 1988. The warning is now required to cover 30% of the front and 40% of the back of cigarette packs.¹⁴ Parties to the FCTC are required to put in place health warnings that are at least 30% but preferably more than 50% of the principal display area of the pack or package within three years of the Treaty coming into force.

In 2003 the European Commission produced rules for the use of graphic warnings on the back of tobacco packs, and subsequently a library of colour photographs for use by member states, but member states could choose whether they

required these warnings. To date only Belgium has introduced these, and only on cigarettes. However, the UK government has announced that graphic warnings will be phased in for all tobacco products beginning in the autumn of 2008.

Aside from the above requirements (plus the need for duty paid markings on cigarettes and hand-rolled tobacco and product identification and traceability markings for all tobacco products), the remainder of the tobacco product pack can be used as the industry sees fit. In the wake of advertising bans, the pack remains a key marketing tool for the industry,²² and can be used to reinforce and maximise positive imagery and associations with a brand and with cigarettes, through careful choice of logos, layout and use of colour.

9.2.4 Place of sale

Regulation of the place of sale is also a responsibility of the Department of Health. No licence is required to sell or distribute tobacco products, which can therefore be distributed and sold from any retail outlet that is VAT registered. In the UK, sale to persons under 16 years of age is prohibited, though there is consistent evidence that children under 16 years have no difficulty in practice in purchasing cigarettes from shops.²³ In England, Scotland and Wales this minimum age will increase to 18 years from 1 October 2007. It is illegal to sell cigarettes singly or in packets of fewer than 10. An age of sale warning should be displayed wherever tobacco products are sold.

9.3 Smokeless tobacco products

9.3.1 Oral snuff

The supply and sale of oral snuff were first banned by the UK Government under the Consumer Protection Act in 1988 in response to plans by US Tobacco (a leading US manufacturer of smokeless tobacco) to build a factory manufacturing oral snuff products (Skoal Bandits) in Scotland. The law hinged on evidence of the carcinogenicity of the products in the USA, and a concern that US Tobacco was specifically marketing its products at young people.⁵ The law was invoked for oral snuff products because, unlike smoked tobacco, they did not yet have an established market. Chewing tobacco was also excluded from the ban because it was in common use among South Asians in the UK.

In July 1992 a European Council Directive²⁴ prohibited member states from marketing tobacco products for oral use, except those intended to be smoked or chewed. When Sweden subsequently joined the EU it negotiated a special exemption for snus, because there was an established tradition of oral snuff (snus) use in Sweden, going back several decades. In response to this Directive, new

regulations to this effect came into force in the UK on 1 January 1993.²⁵ When the EU Directive was recast in 2001,¹⁴ the ban on oral snuff was retained and the UK regulations cited above remain in force. The ban was challenged in the European Court of Justice by Swedish Match, who manufacture snus, along with a German tobacco wholesaler, contending that snus was a much safer product than cigarettes. However, the European Court of Justice rejected the challenge on the basis that at the time of the passing of the Directive, some scientists believed that such smokeless tobacco products could cause cancer and that they were also addictive.²⁶

The regulations¹⁴ define oral snuff as:

any product made wholly or partly of tobacco which is intended for oral use, unless it is intended to be smoked or chewed and is either in powder or particulate form or any combination of these forms, whether presented in sachet portions or porous sachets or in any other way, or presented in a form resembling a food product.

The distinction between what is legal and what is not is therefore somewhat arbitrary and based on whether the product is chewed or sucked. For example, a Danish smokeless tobacco product, Oliver Twist, which resembles moist oral snuff, is not banned because the packaging refers to chewing.

In 2005, in its first report on the application of the Tobacco Products Directive,¹⁷ the Commission commented that separate sections were not included on tobacco products for oral use or hand-rolled tobacco because

the replies from the Member States [to a questionnaire on the Directive] did not provide any new information as there was not enough new scientific information on tobacco products that may have the potential to reduce harm. However, the Commission continues to follow closely scientific developments as regards different aspects of tobacco products and their health effects, including carcinogenic, cardiotoxic and dependence producing effects, and will cover any findings in detail in the next report.

The next report is due in 2007.

9.3.2 Chewing tobacco

As chewing tobacco is recognised within the definition of tobacco products used in the various regulations described in the section on combustible tobacco above, these regulations also apply to chewing tobacco. However, the voluntary agreement on control of additives was only signed by the manufacturers and importers of combustible tobacco products and so does not apply to smokeless tobacco products. Similar to combustible products, there are no regulatory controls on the raw tobacco itself. If therapeutic claims are made for the product, they must be

licensed by the Medicines and Healthcare products Regulatory Authority (see below). Chewing tobacco packs are required to carry a health warning: 'This tobacco product can damage your health and is addictive'. Duty on chewing tobacco has been increasing in line with combustible tobacco but duty-paid markings are not required for chewing tobacco products.

9.3.2 Nasal snuff

Duty is not payable on nasal snuff products in the UK. However, advertising of nasal snuff products is not permitted and nasal snuff does fall within the definition of tobacco products within the EU product regulation directive¹⁴ and so these regulations do apply. Nasal snuff is required to show the same health warning as chewing tobacco products.

9.4 New tobacco product formulations and potential reduced exposure products

Tobacco companies are free to bring new brands of cigarette, hand-rolling tobacco or chewing tobacco (other than oral snuff intended to be sucked) to the market without reporting to any regulatory authorities. Under UK regulations,¹⁴ producers of cigarettes do, however, need to supply to the Secretary of State the names of brands to be produced and brands to be discontinued; tar, nicotine and carbon monoxide machine based yields of all these brands; and to provide product samples to be tested. Producers of every kind of tobacco product must also provide details of ingredients as described above, though this seems to have been ignored for new chewing tobacco products and combustible products to date. All new tobacco (oral or smoked) products must carry a health warning. There is no post marketing surveillance system for new tobacco products in place or required of manufacturers.

There is a proliferation of new tobacco products, some of which are not clearly conventional cigarettes or smokeless tobacco products, being launched in various countries. Those that resemble cigarettes are commonly referred to as potential reduced exposure products (PREPs). Some of these are conventional cigarettes containing tobacco with a reduced carcinogen content, or incorporating a filter device that removes a greater proportion of toxins from the cigarette. Others resemble cigarettes but are in fact novel devices that deliver nicotine by heating rather than burning tobacco or a tobacco derivative (see Chapter 5). It is not clear how these products will be regulated, or who will be responsible for their regulation, if and when such products are launched in the UK. The same applies for other novel tobacco-based products such as Nicogel, which is described as a tobacco gel, designed for topical use,²⁷ and is available for purchase in the UK.

9.5 Medicinal nicotine products

Nicotine replacement therapies (NRT) are regulated in the UK within the medicines regulatory framework, which is a comprehensive system first established in the Medicines Act of 1968. The system is currently implemented by the Medicines and Healthcare products Regulatory Agency (MHRA; formerly the Medicines Control Agency, MCA) with assistance from the Commission for Human Medicines. The MHRA has a UK-wide remit and is responsible to the Department of Health for regulating all medicines and medical devices by ensuring their efficacy and safety. The MHRA considers that any product claiming, or implying, that it can assist in the cessation of using nicotine products and smoking, is a medicine, and therefore comes within its regulatory framework.²⁸ Although weaknesses and failings within the MHRA and the medicines regulatory framework have been highlighted,²⁹ in comparison with tobacco products, regulatory oversight of NRT is very comprehensive.

9.5.1 Product

Nicotine gum was developed by Pharmacia in 1967, registered as a pharmaceutical and made available in Sweden in 1978, and introduced in the UK in 1981. The manufacturers demonstrated that NRT was effective at relieving withdrawal effects and increasing the chances of successful quitting, leading to the licensing of NRT as a medicine by the then MCA, for the relief of withdrawal symptoms as an aid to smoking cessation. As is standard practice, the potential risks and adverse effects of nicotine gum and the NRT products that followed (see Chapter 5) were assessed in relation to placebo, and as a consequence various contraindications and cautions were placed on the use of NRT.

Most of the regulation of smoking cessation medications is carried out by the Licensing Division within the MHRA, responsible for assessing and approving applications for product licences known as ‘marketing authorisations’ which set out conditions for use. Authorisations are required for new medicinal products or variations for medicines already licensed, such as new routes of administration, new formulations, or new uses. Hence a new nicotine product cannot be launched on the market without having been through the authorisation process. All applications are assessed by medical, pharmaceutical and scientific staff at the MHRA and often also involve independent expert advice outside of the MHRA through advisory bodies. Unlike cigarettes, licences are also needed for companies involved in all the stages of the manufacture and distribution of the product and this requires an inspection by the Medicines Inspectorate. The Licensing Division also has responsibility for authorising clinical trials of potential medicines. The MHRA also runs a post-marketing surveillance system for all medicines involving

the reporting of adverse events (both through the pharmaceutical companies and health professionals through the Yellow Card reporting system), testing of medicines, inspection and enforcement.

Pharmaceutical companies are required to give a detailed description and composition of medicine products including the function and rationale for inclusion of each ingredient in the product, a detailed description of the manufacturing process and data on the stability of the product. This includes flavouring. The content of the active substances must be expressed quantitatively per dosage unit. The results of biological and toxicity testing are also required.

When the MHRA was formed in 2003 it adopted new objectives including 'making an effective contribution to public health'. Following representations from health organisations, in 2005 the Committee on Safety of Medicines (an advisory committee for the MHRA) set up a working group on NRT which examined the current evidence on efficacy and safety and made recommendations to relax the controls on the use of NRT products.³⁰ The key change was to accept that users of medicinal nicotine would otherwise be smoking tobacco, which is many times more harmful than medicinal nicotine. As a result, a number of changes to the licence were made, to extend the period of use to up to nine months, and to widen accessibility to the products to smokers with stable cardiovascular disease, pregnant smokers and to young smokers (from 12 years of age). In addition, two NRT products (Nicorette gum and Nicorette inhalator) were allowed to be used as part of a controlled strategy for quitting by cutting down on cigarette smoking in parallel with NRT use.

9.5.2 Place

There has been a progressive relaxation of initially strong restrictions on where and how NRT is available over the years since the products were introduced. Having first been excluded ('blacklisted') from availability on reimbursable NHS prescriptions, NRT products became reimbursable in April 2001. Three of the NRT products available on the UK market (gums, patches and lozenges) can now be sold on general sale (that is, through non-pharmacy retail outlets provided they are lockable and the product supplied in an unopened manufacturer's pack); the others (tablets, inhalators and nasal spray) are available only through pharmacies. The products on general sale are mainly sold in supermarket chains. The lack of NRT in the convenience market (in contrast to tobacco products which are available ubiquitously) is probably due to the stringent conditions regarding their accessibility as described above, their high prices (see below), and consequent low rates of sale relative to cigarettes.³¹ NRT is most commonly packaged in weekly supplies but some smaller pack sizes (such as a two-day supply) are also available.

9.5.3 Promotion

Promotion of product information for drugs is under strict regulatory control via the Patient Information Quality Unit of the MHRA. Information to consumers is provided on the label or in patient information leaflets, which have to be approved in line with a European Council directive.³² There are requirements to take patients' views into account in how this information is presented and received. Advertising to the public is permitted for medicines legally classified for pharmacy or general sale (prescription-only medicines may only be promoted to healthcare professionals). The advertising of all medicines is controlled through a combination of statutory measures (with criminal and civil sanctions) and self-regulation through codes of practice.

The restrictions applied by the MHRA on advertising are much stronger than those applied to other consumer products. For example, all parts of the advertising must comply with the particulars outlined in the Summary of Product Characteristics (SPC) and should encourage the rational use of the product by presenting it objectively and without exaggerating its properties. Advertising to the general public must contain a legible invitation to read carefully the instructions on the leaflet or packaging. The MHRA can require a viewing of the advertising before it is released.

9.5.4 Price

The price of NRT products to the NHS is controlled through the Pharmaceutical Price Regulation Scheme (PPRS), which determines the profit made by the pharmaceutical companies through the sale of their medicines to the NHS. When dispensed on prescription, NRT costs the smoker a relatively small fixed charge. Many smokers qualify for free prescriptions.

The price of NRT sold over the counter and in general sale is controlled by the pharmaceutical companies. For many years, NRT prices in the UK were broadly similar to the cost of regular smoking, though more recently the relative price of NRT has fallen. NRT is typically sold in packs containing a week's supply, which greatly adds to the purchase cost and may discourage purchase, particularly among lower income smokers. In the 2007 Budget, VAT on NRT was reduced from 17.5% to 5%, with effect from 1 July 2007 for one year.

9.5.5 New nicotine products

The recent government White Paper, *Choosing health*,³³ commented that the MHRA and pharmaceutical companies were discussing the development of new

and innovative nicotine replacement therapies. However, innovation by the pharmaceutical companies appears unlikely while concerns persist that the MHRA would impose strong restrictions on products which more closely mimicked cigarettes and posed a greater chance of addiction than the current range of NRT products.

Nicotine products that do not contain tobacco do not necessarily have to be classified as a medicine. The MHRA decides whether any new nicotine product should be classified as a medicine on the basis of consumer perceptions, and claims being made by the manufacturers. A medicinal product is defined as:

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;*
- (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.²⁸*

In the 1990s, Stoppers, lozenges containing nicotine, were sold unlicensed on general sale in the UK.³⁴ They were available for around 12 years before being withdrawn from the market.

9.6 Regulatory imbalance

The above discussion demonstrates the huge disparities and inconsistencies that exist between the tobacco and medicinal nicotine product regulations. Overall, combustible tobacco products are the least regulated and medicinal nicotine products are the most highly regulated. Given the huge differences in the proven or likely hazards of these products to individual and public health, this represents a substantial and illogical regulatory imbalance. The regulations in turn affect how the products are available to the public, with combustible tobacco products the most and medicinal nicotine products the least easily available, and also determine use. For example, the lack of access to NRT on a 24-hour basis in widely accessible outlets means that NRT purchases tend to be planned rather than made on impulse.

In addition to the imbalance between the regulations applying to the different nicotine products, there is a similar imbalance in the resources (human and financial) dedicated to the regulation of the products. In 2004/5, the MHRA had a budget of around £70m and 750 staff who can call on a number of advisory committees.³⁵ Whilst only a fraction of this resource is dedicated to NRT regulation, the available capacity is substantially higher than the budget and staff dedicated to tobacco regulation. Currently only one staff member in the UK (or English) Ministry of Health, a toxicologist, is dedicated to tobacco product

regulatory work, although a proportion of tobacco policy team time is also used for product regulation. The former UK government scientific advisory committee (the Scientific Committee on Tobacco and Health – SCOTH) has not been reconstituted since its last term of office came to an end in 2004.

This situation contrasts starkly with other similar areas of relevance to public health. For example, in 2005–6, the Food Standards Agency had a staff of over 2,400, and a budget of over £135m.³⁶ Similarly the Health Protection Agency in 2006 had a budget of £235m and 3,000 employees.³⁷ Although the Wanless 2004 review³⁸ recommended in the Department of Health’s review of arm’s length bodies that ‘Responsibilities should be assigned for:... the regulation of nicotine and tobacco’, this did not happen.

9.7 Approaches to nicotine and tobacco product regulation in different countries

In developed countries NRT products are typically regulated within the country’s medicines regulatory framework. To our knowledge, no country has co-regulated NRT and tobacco within the same regulatory system, although some, for example Canada, have the potential to do so as the same organisation regulates both products. The US has also made several attempts to have the same agency regulate the products. This section summarises the status of US tobacco product regulation, and then outlines a few examples from other countries where the regulatory structures or frameworks adopted differ from those in the UK.

9.7.1 Tobacco and nicotine product regulation in the United States

In the 1990s the Food and Drug Administration (FDA) in the US made an initial determination to regulate nicotine-containing cigarettes and smokeless tobacco products as combination drugs/devices within their jurisdiction. Following extensive public consultation, this culminated in a ‘Final Assertion of Jurisdiction’ being published in August 1996. As the FDA also regulated NRT products, there was a brief period of ‘coregulation’ of the nicotine market between 1996 and 2000. Legal challenges by the tobacco industry resulted in a decision by the Supreme Court in 2000 to overturn FDA’s assertion of jurisdiction. The only way the FDA could then regulate tobacco products was by the enactment of new legislation by the Congress.

In early 2007, two identical bipartisan bills were introduced in the Senate and House of Representatives to grant the US FDA regulation of tobacco products by reinstating the 1996 FDA rule and also extending the provisions. The new provisions included the requirement from the FDA for detailed disclosure of ingredients, nicotine and harmful smoke constituents. They also empower the

FDA to require changes to current and future tobacco products to protect public health, and to regulate reduced harm products. FDA activity was to be funded through a fee on tobacco manufacturers allocated by market share.

These new bills have received support from various leading health organisations in the US and at least one tobacco company. However, there are concerns that the bar for reduced risk products entering the market is so high as to make it very difficult for the industry to introduce a reduced-risk product to the US market. For example, claims of reduced risk would need to be proven both at the individual and population level, and doing so could require comprehensive studies of non-smokers, ex-smokers, and smokers, of adults and children, carried out over several decades. This would be impossible in practice before bringing a product to market.

9.7.2 Canada tobacco and nicotine product regulatory framework

Including the regional offices, there are about 150 people working in the Tobacco Control Programme at Health Canada. The annual budget for tobacco control is about \$60m Canadian dollars. The Canadian government has implemented legislation which requires comprehensive disclosure of tobacco products from tobacco manufacturers,³⁹ but has not yet regulated any aspect of product content or delivery. In Canada NRT products are also regulated by Health Canada, so there is the potential for co-regulation but this has not happened to date.

9.7.3 Regulation of snus in Sweden

In Sweden, snus is regulated as a food product under the Swedish Food Act. This is because the product is taken into the mouth and partly ingested. Regulating snus as a food means that only flavourings and ingredients that are accepted for food products are allowed in snus. As snus is regulated as a foodstuff the excise duties are comparatively lower than on cigarettes and other forms of tobacco.

9.7.4 Irish Office of Tobacco Control

In Ireland in 2002 a specific body, the Office of Tobacco Control (OTC), was set up to build capacity for tobacco control measures. The OTC manages all aspects of tobacco control. The implementation of the smoke-free policy in Ireland, which was the first national comprehensive smoke-free policy in the EU, heralded the way for several other countries to bring in similar policies following Ireland's example. The remit of the OTC also includes the potential to regulate the product, but this power has not yet been implemented due to a tobacco industry challenge on the Irish tobacco control legislation, and other tobacco control policies taking priority. Nicotine replacement therapies are regulated by the Irish Medicines Board.

9.8 Future regulatory options

The above sections have identified how nicotine and tobacco regulation in the UK and many other countries is currently weakest for the most harmful form of nicotine delivery, the cigarette. The inconsistencies and shortages in regulatory capacity for nicotine and tobacco product regulation have also been demonstrated. Restricting the choices available to smokers as to how they get their nicotine, and favouring smoked over non-combustible nicotine delivery systems, clearly works against public health. If the development of new and improved nicotine delivery systems is to be encouraged in the future, it is imperative to have a clear regulatory framework within which all nicotine products can be assessed in relation to their health impact. The aim of such a framework should be to reduce the health effects of tobacco use by minimising the use of nicotine-containing products overall but among regular users to maximise the use of safer nicotine products and minimise the use of combustible products. Having access to a comprehensive surveillance system would be critical in order to be able to respond quickly to any untoward changes in nicotine use. This section discusses the structural options for developing a coherent nicotine regulatory framework and steps that can be taken in the interim while such a framework is being developed.

9.8.1 Options for structural change

9.8.1.1 Regulate all nicotine products in the Medicines Regulatory Framework

In the 1970s the then Health Minister, Dr David Owen, proposed bringing cigarettes under the Medicines Act (a ‘levelling up’ option; see Chapter 11) but was moved from his post before the change was implemented. Although this proposition has not been formally raised since, and the definition of a medicine was subsequently changed, the fact that nicotine exerts a pharmacological action and modifies physiological functions could enable tobacco products to be regulated in this way. The MHRA, however, has not declared any interest in taking over tobacco regulation.

9.8.1.2 Take medicinal nicotine out of the Medicines Regulatory Framework

To correct the regulatory imbalance between medicinal nicotine and tobacco regulation, one solution would be to take clean nicotine products out of the Medicines Regulatory Framework and apply similar regulations to those currently

used for tobacco (a ‘levelling down’ option; see Chapter 11). Given the weaknesses of, and piecemeal approach to, tobacco product regulation, there would be concerns about this among public health advocates. It is also likely to be an unattractive option to the pharmaceutical companies who would be left to compete with tobacco companies on the open market.

9.8.1.3 The establishment of a new nicotine and tobacco regulatory authority

A further option is to take tobacco and medicinal nicotine out of their existing regulatory frameworks and into a new structure. Current civil service structures mean staff turnover is frequent and greater capacity for tobacco regulation has not been forthcoming despite repeated calls over recent years. Creating a new institution to manage regulation has been the approach favoured in the UK for the regulation of drugs and food, and has been the preferred approach at least for tobacco regulation in other countries (such as Ireland). Establishing a single institution with a combined remit of tobacco and nicotine regulation would probably be the most efficient and coordinated way to enable a comprehensive approach to co-regulation of nicotine and tobacco products. A new institution would mean that a permanently staffed agency would be created with adequate authority to create an appropriate regulatory framework for tobacco and nicotine. Calls have been made for a nationalised tobacco industry or a state-owned monopoly for tobacco regulation.⁴⁰ These suggestions could be considered as the structure and the remit of the new authority is developed. As discussed in more detail in Chapter 12, the Royal College of Physicians believes that developing a new institution is the optimum approach to nicotine and tobacco products commensurate with the scale of the problem and the complexities of the regulatory responses needed.⁴¹

This issue was addressed in *Choosing health* in which the Government commented, without further justification of this statement, that ‘we do not think that there is a case for setting up a brand new UK agency to regulate tobacco, as some have called for...’. The result is that the current piecemeal, inconsistent and irrational regulation of nicotine products continues to prevail.

9.8.2 Interim steps towards more coherent nicotine regulation

Whilst the establishment of a dedicated nicotine regulatory authority is likely to be the best means of delivering a rational and comprehensive nicotine regulatory framework that can maximise benefits to public health, there are steps that could

be taken relatively easily in the interim to increase the accessibility of smokers to a wider range of medicinal nicotine products and to decrease accessibility to the most dangerous, smoked nicotine products.

The White Paper, *Choosing health*, outlined ways in which the MHRA and the pharmaceutical industry could work together to look at widening access and promoting use of NRT, including: ‘developing new and innovative therapies’, ‘promotion of therapies through a wider choice of outlets’, and ‘encouraging retailers to allocate more space for stop smoking therapy products and space alongside cigarettes’. There has been little if any progress towards these objectives since the publication of the White Paper. More could be done within the existing regulatory system to encourage the improvement, development and promotion of medicinal nicotine products for smokers, by removing some of the real or perceived restrictions on nicotine product development, marketing and use. In particular, the current real or perceived likely restrictions on retail sale and display, and on marketing of nicotine products imposed by the MHRA could be relaxed substantially to increase accessibility to smokers, and to encourage the development and test marketing of more acceptable, more effective, and more affordable products. Current licence restrictions on long-term use of medicinal nicotine could be relaxed, and use as a means of cutting down on smoking and temporary abstinence from smoking encouraged more widely. Wider general availability of NRT in retail outlets could be encouraged, possibly in conjunction with a licensing system for tobacco retailers that requires them to provide alternative products could also be considered. All point of sale displays promoting cigarettes could be banned, and tobacco products required to be placed out of sight of customers. Consideration should also be given to any changes that can be made to reduce the harmfulness of cigarettes. One such current promising proposal is to reduce the ignition propensity of cigarettes, and a requirement to do this should be introduced without delay.

9.9 Conclusions

- ▶ Nicotine product regulation has developed in a largely reactive and piecemeal fashion over the years.
- ▶ Smoked tobacco products remained free from regulation for many years, and are now subject to minimal controls on content, delivery and safety.
- ▶ Some smokeless tobacco products are regulated very strictly (that is, they are prohibited) whilst others are subject to even less regulation than cigarettes.
- ▶ Medicinal nicotine products are regulated very strictly, as medicines.

- ▶ The lax regulation of most tobacco products affords considerable market freedom for tobacco companies to innovate and develop their products.
- ▶ The tight regulation of medicinal nicotine imposes very strict restrictions on new product development.
- ▶ Some newly launched tobacco products, including the PREPs, seem to lie completely outside of the current regulations.
- ▶ This clear and unjustifiable regulatory imbalance works against public health.
- ▶ UK government resources dedicated to tobacco product regulation are very small.
- ▶ History demonstrates that regulatory change can achieve substantial changes in consumption of different tobacco products.
- ▶ The regulation of nicotine products needs to be radically overhauled to encourage the use of less harmful products, and reduce the use of the more harmful sources of nicotine.
- ▶ Whilst some progress can be made in this regard through the existing regulatory systems, the establishment of a nicotine and tobacco regulatory authority is the preferred way of bringing comprehensive and rational controls on the nicotine product market that will minimise the harm caused by nicotine use.

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10 | Current nicotine product use and socioeconomic deprivation

- 10.1 Introduction
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- 10.4 Costs of smoking
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10.1 Introduction

The use of tobacco products, and their consequent impact on health, varies substantially across society in relation to socioeconomic factors. Jarvis and Wardle identified what they called a general law of Western industrialised society that, 'Any marker of disadvantage that can be envisaged and measured, whether personal, material or cultural, is likely to have an independent association with cigarette smoking.'¹ They specify Western industrialised society as it is clear that their statement does not apply to countries in the earlier stages of the smoking epidemic. Their general law can also be extended to cover smoking cessation, in that any marker of disadvantage that can be measured is also likely to have an independent association with difficulty in giving up smoking. This chapter explores some of these effects in relation to smoked tobacco use in the United Kingdom.

10.2 Tobacco use among disadvantaged groups

There is a clear social gradient in smoking such that smoking rates are considerably higher among poorer people than among those who are better off. In 2005, 18% of men in professional and managerial occupations smoked, compared with 32% in routine and manual occupations (Fig 10.1).² Despite a reduction in the

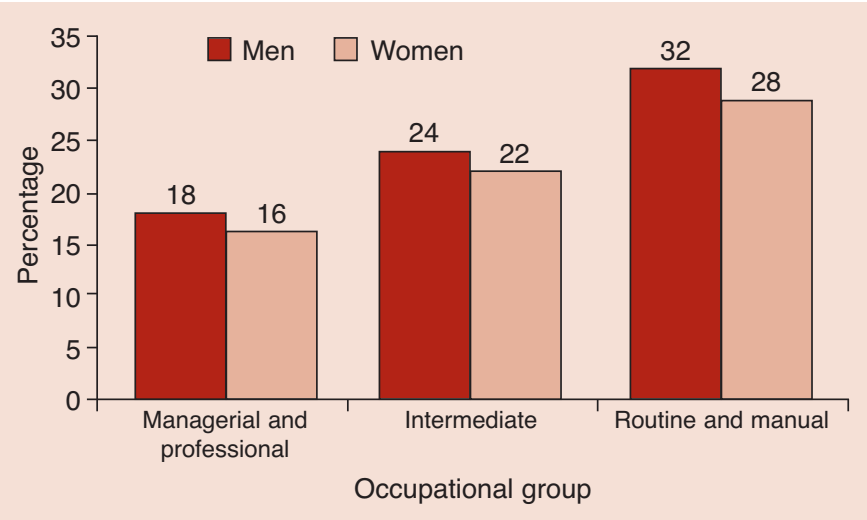


Fig 10.1 Prevalence of cigarette smoking among adults by sex and occupational group in Great Britain in 2005. Source: General Household Survey, 2005.² Reproduced under the terms of the Click-Use Licence.

overall prevalence of tobacco smoking in the UK over the past 30 years, smoking rates among lower income groups have remained significantly higher, maintaining the differential, and there has been little change at all in all occupational groups over the past decade (Fig 10.2).²

Furthermore, traditional measures of socioeconomic status tend to underplay the extent to which smoking has become concentrated in the poorest sections of society. Studies which have separated out the poorest in society, such as lone parents in receipt of social security benefits, have found smoking rates in excess

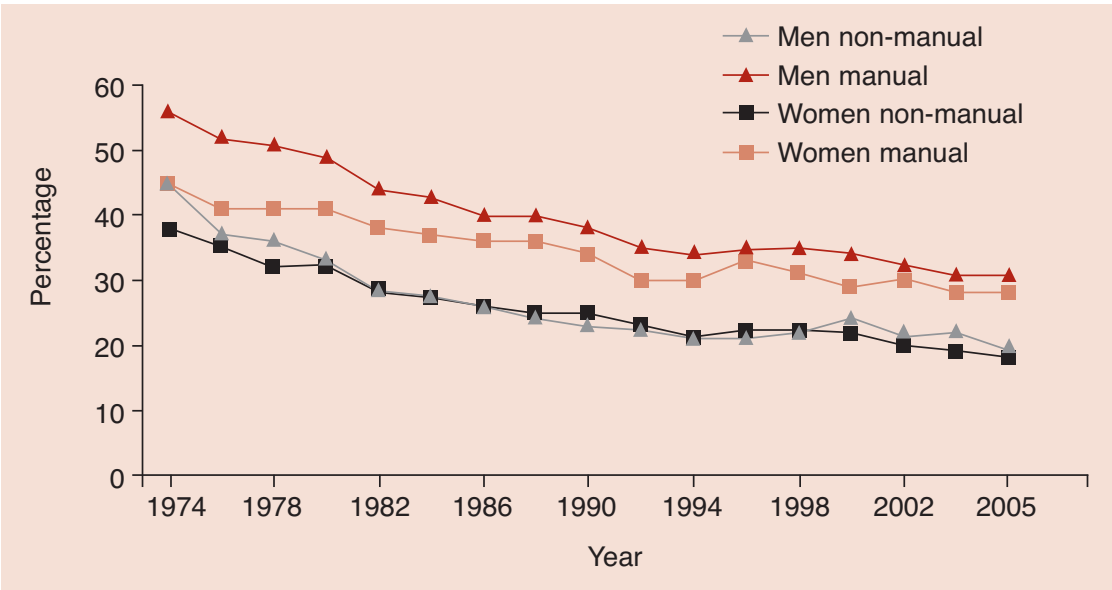


Fig 10.2 Smoking prevalence by sex and socioeconomic group in Great Britain in 1974–2005. Source: General Household Survey, 2005.² Reproduced under the terms of the Click-Use Licence.

of 75%.³ Among the most affluent in the UK, smoking prevalence halved in the 30 years from 1973 to 2003, to only 16%. Among the most deprived, however, smoking rates have stayed the same: 70% were smokers in 1973 and 70% still smoked 30 years later in 2003.¹

There are many other indicators of disadvantage that are linked to higher rates of smoking. For example, the odds of being a smoker are substantially increased in individuals without access to a car, who live in rented housing or in crowded accommodation, or who have no academic qualifications. Single mothers, including those who are divorced or separated, are also more likely to smoke. The following definable populations also have especially high smoking prevalence.

10.2.1 People with mental health problems

Smoking is significantly more prevalent among people with mental health problems than among the general population, and particularly among those with a diagnosis of a psychotic disorder. Smoking rates are as high as 80% among people with schizophrenia,⁴ while over 70% of people with psychotic disorders who live in institutions smoke. Of these smokers, over half smoke more than 20 cigarettes per day.⁵

A national survey of psychiatric morbidity in over 8,000 people in the general population found that people with neurotic disorders such as depressive episodes, phobias or obsessive compulsive disorders were twice as likely as those with no neurotic disorder to smoke. Having more than one neurotic disorder was associated with heavy smoking.⁶ Smoking has also been associated with adult attention deficit disorder,⁷ eating disorders and substance abuse disorders.⁸

10.2.2 Prisoners

There were around 76,200 people in prison in England and Wales in 2005, and this number continues to rise.⁹ Government estimates are that at least 80% of people in prison smoke.¹⁰ The prison population is made up predominantly of young men, most of whom spend relatively short periods – weeks or months rather than years – in prison.

10.2.3 Black and minority ethnic groups

The Health Survey for England in 1999 found that smoking rates in many minority ethnic groups are lower than those in the rest of the population (Fig 10.3).¹¹ An exception was the smoking rate among Bangladeshi men, of whom 44% smoked.



Fig 10.3 Prevalence of cigarette smoking among adults by ethnicity and sex. Reproduced from Erens *et al* with permission of the Stationery Office.¹¹ Reproduced under the terms of the Click-Use Licence.

The survey also found that the proportion of ‘heavy smokers’ (those smoking 20 or more cigarettes per day) in all minority groups was lower than the proportion of heavy smokers in the rest of the population (37%). The lower smoking rates among some groups reflect cultural and religious differences, particularly among some Muslim women. However, rates of chewing tobacco – almost unknown in the wider population – are a health concern among some minority ethnic groups, particularly in people from South Asia.¹¹

The higher smoking rates among some minority ethnic groups may be attributable to the socioeconomic position of these groups. The Office for National Statistics reported that minority ethnic groups were more likely than white groups to live in low income households in 2000–01, although this varied by ethnic group.¹² The highest rate was among Pakistanis and Bangladeshis of whom 60% were living in low income households compared with 16% of the white population. Nearly a half of black non-Caribbean households also lived on low incomes.

10.3 Consumption of tobacco and levels of nicotine dependence

Poorer smokers also tend to consume more tobacco than more affluent smokers, which is in turn a strong indicator of higher levels of nicotine dependence. Smokers in routine and manual groups consume on average 15 cigarettes per day, compared with smokers in managerial and professional groups who consume 12 cigarettes per day.² There is also evidence that poorer smokers take in more nicotine, and consequently more of the toxic emissions, from each cigarette

smoked – either by smoking cigarettes with a higher yield, by leaving a shorter stub, or by drawing harder on the cigarette. Data from the Health Survey for England show that the average level of saliva cotinine (a measure of nicotine intake) among the most deprived is 30% higher than among the most affluent (Fig 10.4).¹ The more deprived smokers are thus likely to experience greater harm from their smoking.

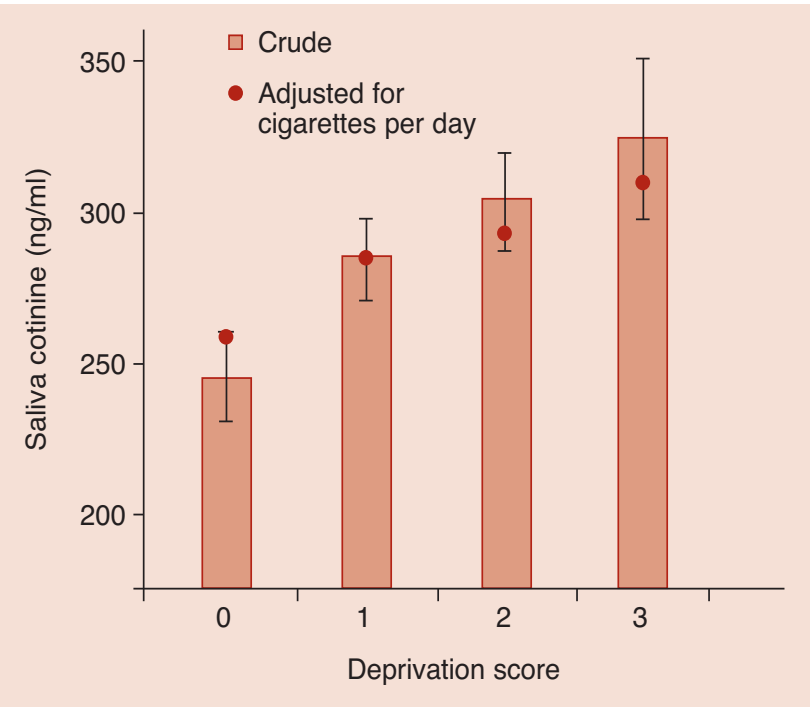


Fig 10.4 Saliva cotinine levels by deprivation in adult smokers in Britain in 2001. Reproduced from Jarvis *et al* under the terms of the Click-Use Licence.¹

Indications of increased nicotine dependence among deprived groups in the UK are shown not just by quantitative differences in the amount smoked and nicotine metabolite levels, but also by factors such as time of first cigarette smoked and perceived difficulty of not smoking for a whole day.² Smokers in routine and manual occupations are more likely to report that they would find it difficult to go without smoking for a whole day (61% compared with 55% in intermediate and 50% in managerial and professional occupational groups) and were also more likely to have their first cigarette of the day within five minutes of waking up (18% in routine and manual groups, compared with only 10% in managerial and professional groups).² Since smoking-related disease is dose related, the fact that disadvantaged smokers tend to smoke more will directly increase their risk of mortality and morbidity. Also, since nicotine dependence is a critical indicator of ease of quitting smoking, this also indicates that disadvantaged smokers are also less likely to succeed in quitting smoking (see Section 10.7).

10.4 Costs of smoking

A smoking habit of 20 cigarettes per day at typical current UK retail prices costs about £1,900 per year. Poorer smokers spend a disproportionately large share of their income on cigarettes compared with more affluent smokers. In 2003, the poorest 10% of households spent 2.43% of their income on cigarettes each week, while the richest 10% of households spent 0.52% of their income.¹³ In 1994, a study of the most deprived groups – including lone parents in receipt of state benefits – found that three out of four families had one or more smokers and that these smoking families spent one seventh of their disposable income on cigarettes, thus further exacerbating the impact of poverty on the family.³ A more recent study in the north of England found that female heavy smokers were four times more likely, and male heavy smokers two times more likely, to report financial difficulties than non-smokers even after adjusting for age and quintile of deprivation.¹⁴

While price increases have been shown to be effective in reducing consumption, and some economists have argued that poor smokers respond more to price than do affluent smokers,¹⁵ this does not always appear to be the case. Among the most heavily addicted smokers, many of whom are in the most disadvantaged groups, the response to price increases does not appear to be cessation but alternative strategies, such as switching to cheaper brands,¹⁶ hand-rolled tobacco, smuggled cigarettes, cutting down on the number smoked, or a combination of these, rather than quitting altogether. However, as a result of compensatory smoking (maintaining nicotine intake by smoking fewer cigarettes more intensely) the health benefits achieved by cutting down the number of cigarettes smoked is likely to be minimised or even completely negated.¹⁷

10.5 Inequalities in the burden of ill health caused by smoking

One in two lifelong smokers is killed by smoking-related diseases.¹⁸ In the UK, over 100,000 smokers die every year as a result of their habit,¹⁸ and for every one who dies around another 20 are suffering from smoking-related diseases, many of whom will go on to die.^{19,20} Smoking-related disease is a major cause of mortality and morbidity in disadvantaged groups, which have higher rates of smoking and lower rates of cessation. Additional factors such as poorer diet, earlier onset of smoking and higher levels of smoke intake (see above) exacerbate the risks.

Smoking is the biggest identified cause of inequalities in mortality between rich and poor in the UK.²¹ It accounts for over half of the difference in risk of premature death across the range of socioeconomic status.¹ Death rates from tobacco are two to three times higher among disadvantaged social groups than among the

better off.²² Smokers in poorer social groups also tend to start to smoke at an earlier age: 48% of men and 40% of women in routine and manual occupations had become regular smokers by the age of 16 compared with 33% of men and 28% of women in managerial and professional occupations.²

Given the disproportionately high prevalence of smoking among people with serious mental health disorders, it is likely that a particularly high proportion of this population will die from a smoking-related disease. A 17-year prospective study in Finland, for example, found that having a mental disorder predicted an elevated risk of death from cardiovascular disease, respiratory disease and suicide.²³ The same study also demonstrated an association between schizophrenia and mortality from respiratory disease, which the authors suggest is also likely to be explained by smoking.

10.6 Disadvantage and smoking uptake

Children growing up in poverty and deprivation are more likely to live in homes where parents and/or siblings smoke,² so it is not surprising that they are themselves more likely to smoke. Parents and other family members are role models for the young and are a main source of primary socialisation. It has been shown that a significant reduction in the number of children taking up smoking is dependent on reducing smoking by adult role models.²⁴ Children are almost three times more likely to become regular smokers if both their parents smoke than if neither parent smokes.²⁵ Children growing up in an environment in which adult smoking prevalence is high are also more likely to experience adult smoking outside the home, which is also likely to increase the likelihood that they start smoking.²⁶

In the national cohort of babies born in one week in 1958, the prevalence of cigarette smoking at age 16 ranged from 24% among those from the most affluent homes to 48% from the most deprived homes.²⁷ This gradient at age 16 was much sharper when cohort members were defined retrospectively by their own achieved social status seven years later at age 23, rather than by the characteristics of the parental household. In other words, the factors that led to a higher risk of smoking at age 16, such as poor school record and lower self-esteem, also led to an increased likelihood of subsequent downward social mobility. Furthermore, by their 30s, half of the better off young smokers had stopped smoking while three quarters of smokers in the lowest income group were still smoking.²⁷

10.7 Smoking cessation in disadvantaged groups

The available evidence indicates that the desire to give up smoking is similar across social groups. Around two thirds of smokers, whatever their social groups,

want to stop smoking.²⁸ Studies have also shown that around half of all smokers with mental health problems also want to quit.⁵ The NHS Stop Smoking Services, set up over the past six years, represent a cost-effective and widely available source of help for smokers wishing to quit.²⁹ Recent research suggests that these NHS services have succeeded in attracting poorer smokers wishing to quit in areas of social deprivation. Nearly a third of all smokers in receipt of treatment services lived in the most disadvantaged quintile of areas while less than one in ten lived in the most advantaged quintile. An indicator of positive discrimination for each health authority area was calculated to quantify the extent to which the proportion of disadvantaged smokers being treated was greater than that in the population, and this ranged from just under 0% to 18%.³⁰ However, the overall contribution of the services to a fall in smoking prevalence is estimated to be only 0.1–0.3% per year.³¹ Around a fifth of smokers in all socioeconomic classifications have used nicotine replacement therapy (NRT). More smokers in managerial and professional classes bought NRT over the counter, and more smokers in routine and manual occupations obtained their NRT on prescription, either paid for or free.²⁸

However, even if poorer people are equally or more likely to make an attempt at quitting than more affluent people, higher levels of nicotine dependence make the likelihood of success lower. Rates of stopping smoking are three times lower among the least well off in society compared with the wealthiest (Fig 10.5).² The greater difficulties in quitting are exacerbated by fewer alternative diversionary or coping resources. Chances of success are reduced still further by a higher prevalence of peer group smoking and the greater likelihood of having a smoking partner.³²

10.8 Exposure to second-hand smoke at work

The introduction of comprehensive smoke-free workplace legislation will help to reduce health inequalities, as levels of exposure to second-hand smoke at work otherwise tend to be higher among the less affluent workers in society. In Britain in 2004, only 4% of those in managerial and professional occupations worked in buildings with no restrictions on smoking, whereas 12% of those in intermediate occupations and 10% of those in routine and manual occupations worked in buildings with no restrictions on smoking (see Fig 10.6).³³

Immediately before the implementation of smoke-free legislation in the UK began, 2.3 million UK workers were exposed to cigarette smoke throughout their workplace,³⁴ with hospitality workers particularly heavily exposed. About 10.4 million people worked in places where smoking was permitted in designated areas and were therefore also likely to have been exposed to tobacco smoke.³⁴

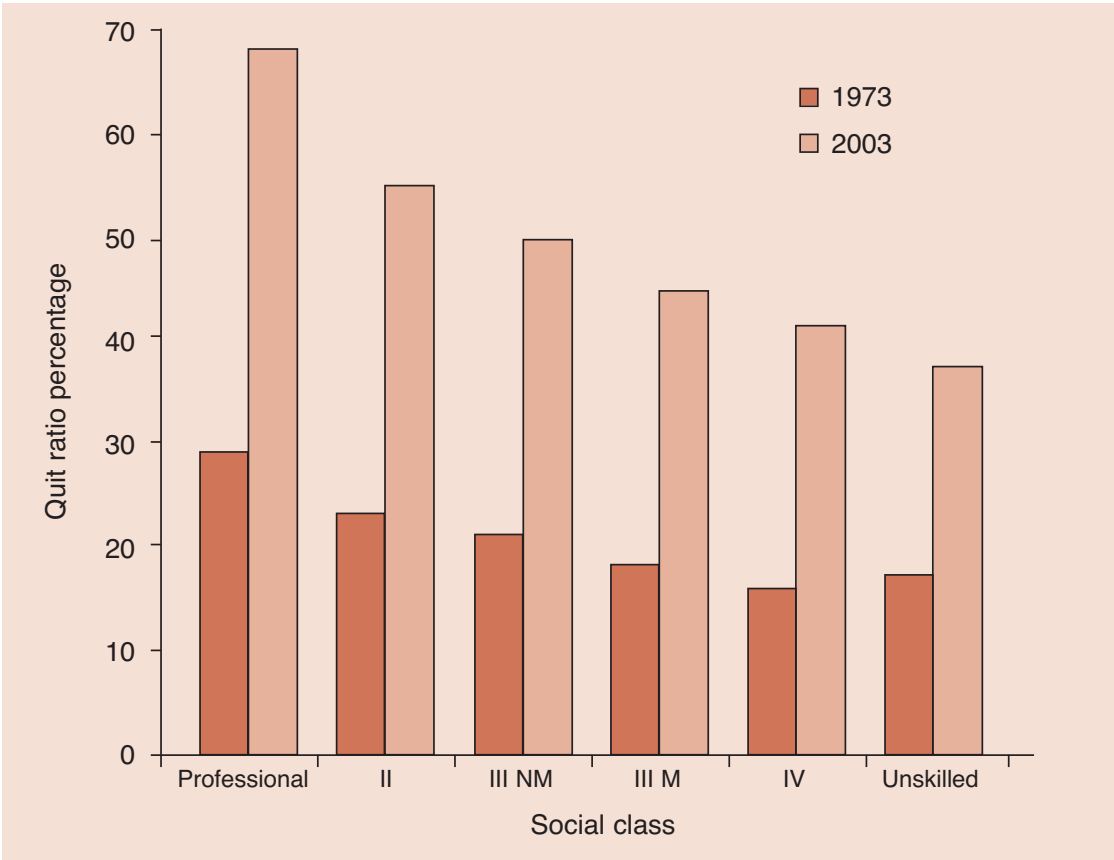


Fig 10.5 Smoking cessation by occupational social group in Great Britain in 1973–2003. I = Professional; II = managerial and technical intermediate; III NM = non-manual skilled; III M = manual skilled; IV = partly skilled; V = unskilled. Source: General Household Survey, 2005.² Reproduced under the terms of the Click-Use Licence.

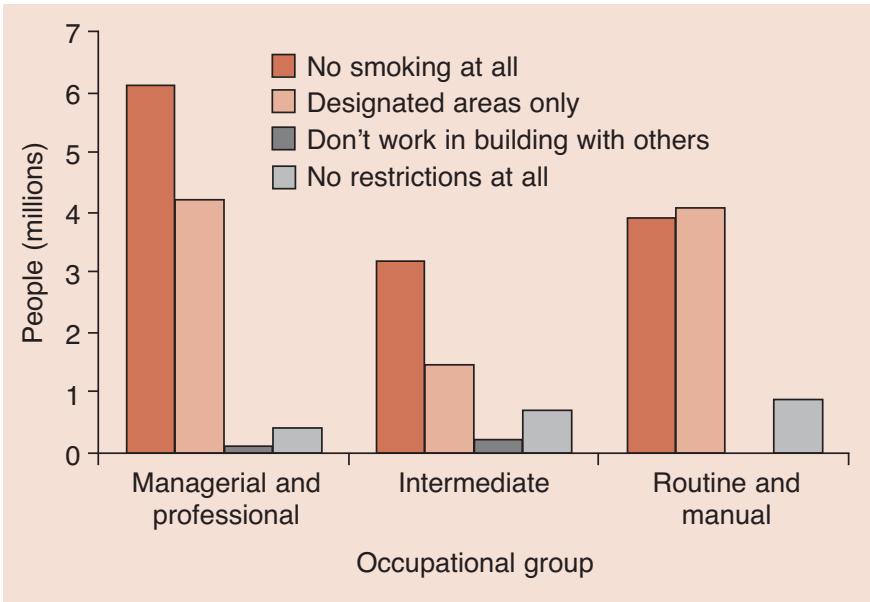


Fig 10.6 Exposure to smoke at work by occupational group in Great Britain in 2004. Source: Labour Force Survey and Office for National Statistics Omnibus Survey 2004.³³

Exposure to tobacco smoke at work in the UK in 2003 was estimated to be responsible for the deaths of more than two employed people per working day (617 deaths per year), including 54 deaths in the hospitality industry each year.³⁵ These inequalities should now be largely eradicated by the comprehensive smoke-free legislation enforcing smoke-free enclosed public places throughout the UK in place since July 2007.

10.9 Exposure to second-hand smoke in the home

The majority of exposure to second-hand smoke occurs in the home, where legislation cannot be brought to bear. The health impacts are substantial, accounting for an estimated 2,700 deaths in adults aged 20–64 years, and 8,000 deaths among people aged over 65 in the UK in 2003.³⁵ Estimates of the proportion of children exposed to tobacco smoke at home vary from 32% to 42%.^{36,37} Children of unskilled manual workers are substantially more likely to be exposed than those of professional people (54% and 18% exposed respectively),³⁷ and their level of exposure is typically higher since more people in the household are likely to be smokers (Fig 10.7).²⁴ Children who grow up in homes where parents smoke are at substantially increased risk of a range of childhood illnesses, including respiratory infection, middle ear disease and asthma exacerbation.³⁸ They are also approximately three times more likely to get lung cancer than the children of non-smokers, even if they do not take up the habit themselves as adults.³⁹

10.10 Smoking and pregnancy

Smoking in pregnancy causes adverse outcomes, notably an increased risk of miscarriage, reduced birth weight and perinatal death.^{40,41} Exposure to passive smoking during pregnancy is also an independent risk factor for low birth weight.^{42–45} Babies exposed to their mother's tobacco smoke before birth grow up with reduced lung function.⁴⁶ Parental smoking is also a risk factor for sudden infant death syndrome (cot death).⁴⁷ The Infant Feeding Survey for 2000 found that 21% of non-smoking pregnant women were exposed to the smoke of someone else – usually a partner – who smoked in the home throughout their pregnancy. Living with a partner who smoked was highly correlated with low socioeconomic status.⁴⁸

The Infant Feeding Survey also found that, in the UK in 2000, 20% of mothers smoked throughout pregnancy. Of mothers classed as 'never worked', 36% smoked throughout pregnancy compared with only 8% of mothers in managerial and professional occupations.⁴⁸ Younger mothers were also more likely to smoke

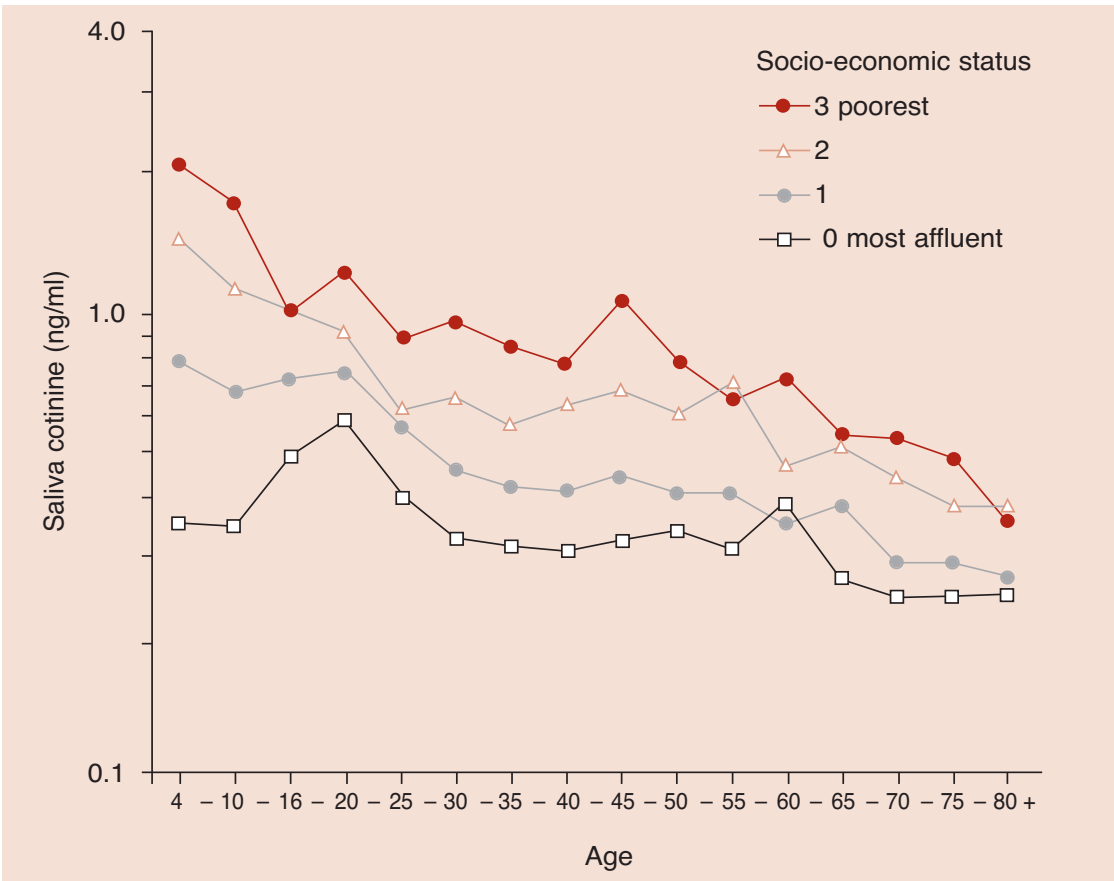


Fig 10.7 Geometric mean saliva cotinine in non-smokers by age and socioeconomic status, 1996–2003.²⁴

throughout pregnancy than older mothers: 40% of mothers less than 20 years of age smoked throughout pregnancy compared with 13% of mothers aged 35 and over (Fig 10.8).⁴⁸

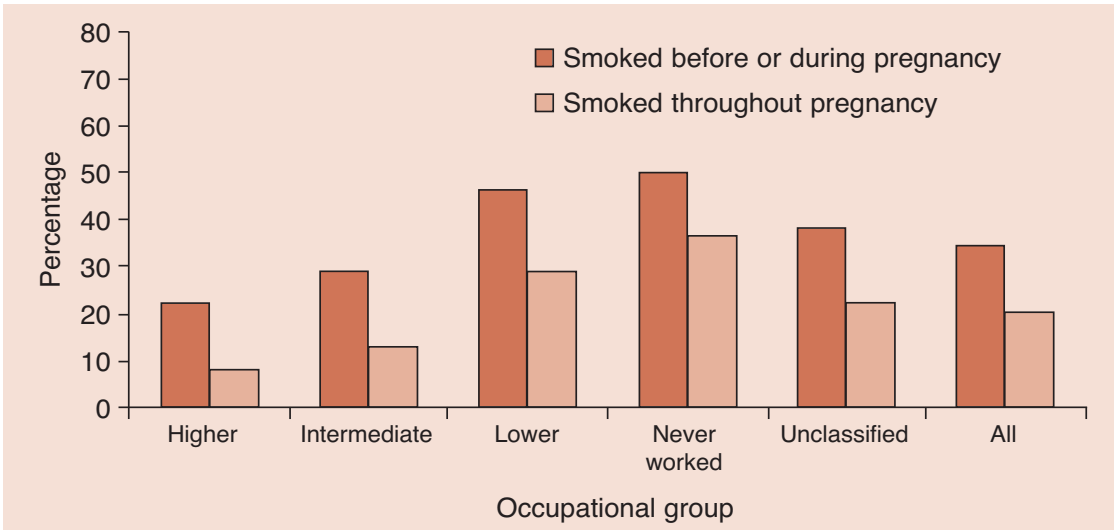


Fig 10.8 Prevalence of smoking before and throughout pregnancy by occupational group. Reproduced from Hamlyn *et al* with permission of the Stationery Office.⁴⁸ Reproduced under the terms of the Click-Use Licence.

10.11 Conclusions

- ▶ In Western industrial society, and particularly in the UK, cigarette smoking is strongly linked with socioeconomic disadvantage.
- ▶ People in disadvantaged socioeconomic groups are more likely to smoke, to smoke heavily, and to be more heavily addicted to smoking.
- ▶ This is also true of other disadvantaged groups, such as people with mental health problems or people in prison.
- ▶ Smokers in disadvantaged socioeconomic groups are just as likely to want to quit smoking, and more likely to use smoking cessation services, than relatively advantaged smokers.
- ▶ However, they are much less likely to succeed in quitting smoking.
- ▶ As a result, and in contrast to more advantaged groups, smoking prevalence has changed very little in recent years among the most disadvantaged in society.
- ▶ Smoking therefore causes even more death and disability in disadvantaged groups than in the rest of society, and is indeed the biggest cause of social inequalities in health.
- ▶ Children growing up in disadvantaged households are more likely to be exposed to cigarette smoke in the home, are more likely to start smoking, and to start when especially young.
- ▶ Disadvantaged smokers, and their children, therefore have the most to gain from harm reduction strategies for tobacco use.

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11 | Ethics, human rights and harm reduction for tobacco users

- 11.1 Background to the harm reduction approach
- 11.2 Components of the harm reduction argument
- 11.3 Harm reduction options for tobacco use
- 11.4 Approaches to rebalancing the nicotine product market
- 11.5 Conclusions

11.1 Background to the harm reduction approach

Smoking is dangerous to the health of the smoker and to others, including a fetus that is exposed to the smoke the smoker generates. Smoking is also highly addictive. Encouraging smokers to quit smoking, and developing better ways of helping them to do so, is a recognised public health priority. There is, however, a complementary approach, which is to reduce the harm caused by tobacco smoking by making effective but less hazardous substitute products available to the smoker.

An outline to this approach is as follows. The smoker who wishes to give up smoking faces many obstacles, particularly the psychological and physiological components of addiction. Different smokers use different routes to quitting, and may try several methods before finding one that works for them. However, many smokers continue to smoke in spite of a desire to quit, and even those who do not want to quit may wish to lessen the impact their smoking has on themselves and others. Since nicotine is the primary addictive constituent of tobacco smoke, the harm reduction approach for those who cannot otherwise quit smoking tobacco or who want to reduce the impact their smoking has on themselves and others is to substitute cigarettes with less hazardous alternatives. Even though smoking-related harms may be merely reduced rather than removed by this approach, many lives could also be saved and much morbidity prevented. For the purposes of discussion in this chapter we will consider the two broad groups of less hazardous alternatives discussed in Chapter 7 and Chapter 8: products based on medicinal nicotine, which we will assume to be the least hazardous alternative, and smokeless tobacco products, which we will assume to be more hazardous than medicinal nicotine, but much less hazardous than smoked tobacco products.

11.2 Components of the harm reduction argument

There are a number of objections to the harm reduction argument, just as there are for harm reduction approaches in relation to use of alcohol and psychoactive drugs. Doctors and public health experts are concerned with the empirical question: does making less hazardous products available and attractive to smokers actually, on balance, save lives, reduce tobacco-related morbidity and help smokers to quit smoking? There are many reasons why they may not: the existence of 'safer' products might cause some people who had previously been put off by the unitary 'smoking is dangerous' message to take up smoking or other tobacco product use; smokers might take longer to stop using tobacco with these products available than would otherwise be the case; the risks to health of the alternative products may be lower than cigarettes but are still a lot worse than not using nicotine products at all; and so on. But, as an empirical question, it is open to scientific study, and the harm reductionist and strict tobacco control theorist should be able to agree that such research is worth carrying out, and also that regulations which prevent this research are unhelpful.

A further objection to the harm reduction approach is an ethical one. The basis of this objection is that smoking is bad, as harm reducers allow, but promoting less harmful nicotine products as a substitute for smoking merely perpetuates the use of a drug in society. By this argument, harm reduction approaches dilute the message that smoking and indeed all nicotine or tobacco product use is or is potentially dangerous and undesirable. Furthermore, the consideration of smokeless tobacco products in this harm reduction strategy might allow the tobacco industry to promulgate an image of good corporate citizenship, while simultaneously continuing to market (and globalise) its highly dangerous cigarette products and promoting smokeless products as a vehicle to extend tobacco use. As former US Surgeon General, C Everett Koop, recently wrote:

The problem with harm reduction approaches is that they may pose theoretical benefits to a few individuals, along with real and theoretical risks to many others. This was the experience with smokeless tobacco products in the United States, in which relatively few recalcitrant cigarette smokers may have switched from cigarettes to snuff, incurring theoretical (but as yet uncertain) disease reduction, while, at the same time, a new epidemic of smokeless tobacco was observed in young boys, who happened to be athletes.¹

The force of this argument is both empirical and moral: the moral point is that the good intention of the harm reduction initiative induced a group of individuals otherwise rather unlikely to smoke to take up tobacco consumption. In essence, they had been 'corrupted'.

Arguments against harm reduction in the cases of heroin injecting, gambling or prostitution may focus on the immorality of the behaviour being regulated, whereas it is unlikely that many people think that smoking as such is immoral in present-day society. The moral force of these arguments in relation to tobacco use is directed instead at three parties: the tobacco industry in its ceaseless quest for new custom and profits; the harm reduction school of thought for abetting the industry in the sort of scenario Koop describes; and the wider community of people who see smoking as intrinsically morally unproblematic. In the cases of drug taking, smoking, alcohol consumption, gambling or prostitution, there are some who find these activities morally unproblematic so far as they represent conscious choices by consenting adults. There are also those who may find in these activities something to criticise morally, but would not see this as amounting to a case for legal prohibition or discouraging regulation.

Hence, critics of harm reductionist approaches to these activities see harm reduction as giving tacit support, in practice if not in theory, to these morally or legally permissive positions. And insofar as the critics of harm reduction see these kinds of activity as both wrong and to be legally prohibited, they reject harm reduction as failing to concede the moral wrongness of the activities involving harm. What critics of harm reduction are willing to accept, however, is that while taking this hard line will encourage some to desist from these activities completely, it will also leave others exposed to greater risk than they would be under a harm reduction approach, and that this may lead to greater aggregate harm than the harm reduction approach. They are willing to accept this on the basis that abstinence is morally preferable to ‘moderated’ consumption, and that moderated consumption is no better than unmoderated consumption. In a comparative example, they would see no difference between paying for sex in the context of a licensed brothel or in the context of unlicensed kerb crawling, even if the prostitutes and their clients may be safer in the former case. In the case of tobacco control, if you think that selling tobacco products involves a moral wrong, by deliberately exposing people to something that is harmful and addictive, then the moral wrong is hardly affected by the form in which the tobacco is sold.

It is not the view of the Royal College of Physicians that smoking is intrinsically immoral. Some consequences of smoking (such as non-consensual harm to others) may be morally wrong, and there are certainly morally difficult questions to ask about both the selling and consumption of highly addictive products which are dangerous to health. As with alcohol, however, these issues are sufficiently complex that no definitive position on the morality of smoking, insofar as it relates to the behaviour of individual smokers, has been reached. For the purposes of this report, therefore, we give no further consideration to the

objections to harm reduction which focus on the morality or otherwise of smoking as such. Our focus is on a consideration of the harms to health posed by smoking and of proposals for policy to limit these harms.

11.3 Harm reduction options for tobacco use

In relation to tobacco use there are three basic harm reduction strategies available. The first is simply to maintain the status quo, in which efforts to prevent the harm caused by smoking are based entirely on strategies to achieve complete abstinence from nicotine use. In the second, nicotine products that represent an acceptable alternative to smoked tobacco (specifically cigarette smoking) to the smoker, but at substantially reduced relative risk, are made as available as cigarettes to adults. In the third, these alternative nicotine products are made relatively more available than cigarettes to adults. By 'more available' we include making them more affordable and more widely retailed. In the remainder of this chapter, the ethical arguments for and against each of these three options are summarised.

The ethical framework of analysis is a straightforward one. We consider in turn autonomy and individual rights, beneficence and paternalism, justice, and consequence-based arguments. Autonomy is the power each competent person has for making decisions about his or her own welfare and best interests. Beneficence is the moral obligation to benefit others. It is often argued that some public health or policy activity is justified on the grounds that it protects or promotes the good of those affected. Where this conflicts with the autonomous choices of competent people, or where they are not consulted (even if they might implicitly agree), imposition of the policy is termed 'paternalistic'. In reality, many public policy decisions are paternalistic in practice, and sometimes in principle, and such decisions require a moral justification in light of this. There has to be a good reason why the objective cannot be achieved through the autonomous choices of people themselves, and why the good of the objective outweighs the wrong done by overriding people's autonomy. Justice, for present purposes, concerns the fairness of the distribution of benefits and harms in society, such as health or costs of compliance with regulations. Autonomy, beneficence and paternalism, and justice-based arguments will generally be advanced in terms of rights (either legal, moral or human). Sometimes arguments are made which concentrate purely on weighing up the outcomes of different decisions and actions, without consideration of rights; these are consequentialist arguments.

Debates about public health issues such as tobacco regulation illustrate the ways that different kinds of moral principles interact. Public health concerns can override individual rights in specific circumstances in which an individual could

cause harm to society as a whole. When there is low cost to the individual and high benefit to society, public health interests should prevail.² Public health ethicists have argued that it is not enough to speculate that there is *some* chance of adverse effects to society if an individual is allowed to exercise rights, it is necessary to show that there is *clear and convincing* evidence that the risk to society is substantial. In judging whether public health interests should override individual health interests, one needs to evaluate both the ‘proportionality’ and the ‘probability’ of the problems for public health.^{3,4}

11.3.1 Model 1: the status quo

Autonomy and individual rights

Autonomy and individual rights are not given special priority in this model. No recognition is given to the right to exert autonomous choice over tobacco use by making choices from a range of acceptable and effective but substantially less hazardous products. It may be argued that promotion of autonomy does not imply making a wider range of tobacco products available. More choice need not mean more autonomy. Promotion of autonomy does mean realising the exercise of autonomy. Expanding the range of nicotine delivery products might actually impair autonomous choice by diverting choice from one harmful product to another, when what the smoker actually prefers is to give up smoking and to overcome the desire to smoke. Denying the smoker the means to realise this escape from addiction could be considered a constraint on autonomy. What is then at stake is whether alternative nicotine delivery products are an effective means of escaping tobacco addiction, and whether they help more people to stop smoking tobacco than more direct methods of quitting. Proponents of this model would argue that smokeless or novel nicotine delivery products should only be introduced into the market on the basis of good, clinical evidence that they are effective in aiding smoking cessation, and that they do not induce significant other harms from a public health point of view (such as being a gateway to active smoking). This would involve active regulation of such products on the model of medicinal products, as is indeed the case at present.

Beneficence/paternalism

It is considered wrong to release hazardous products into the market. Medicinal nicotine products are likely to be by far the least hazardous nicotine formulations, but if they are developed to become effective as cigarette substitutes they will

almost certainly also be highly addictive. Smokeless tobacco is certainly addictive and more hazardous than medicinal nicotine. Aside from inherent risks to health arising from nicotine use, those who become addicted to medicinal nicotine or smokeless tobacco products might also, because of their addiction, switch to the very dangerous cigarette. In other words, alternative nicotine products could be a causal or relapse 'gateway' to cigarette smoking. This is a 'slippery slope' argument: if the step is taken to make alternative nicotine products more readily available, this will be problematic because of what it leads to (increased uptake of smoking or greater relapse). A similar argument is that some who have given up nicotine use altogether may now start to use nicotine products again, thereby increasing risk to those individuals. Also, there is concern that a product that is safer for individual users could result in a net loss for public health or society because of an increased numbers of users. All of these issues support the position of taking away the choice of individuals for their own good.

Justice

For our purposes, justice can be considered as fair treatment. In particular, one could ask: why is smoking tobacco available, but some smokeless tobacco products banned? Doesn't this discriminate unfairly against those whose preference is for smokeless tobacco? Yet this conclusion may not follow. There is arguably no right to consume tobacco, and consequently no right to consume it in any particular form. That is, no reasonable system of rights would allocate a specific right to people to smoke tobacco, anymore than it would allocate a specific right to consume caviar or watch television. At most, it might allocate a right to non-interference in one's private life, so far as what one is doing harms no one else. That smoking tobacco is not banned may be inconsistent with the ban on smokeless products, but the consequence of identifying this anomaly should be (as per the beneficence argument) to ban smoking as soon as may be possible, rather than relaxing restrictions on smokeless products. What justice requires instead is that vulnerable people should be protected from avoidable risks of addiction, and that people should not be hindered from promoting their own vital interests. Since smokers, as all of us, have a vital interest in their health, policy should not introduce measures which inhibit smokers' pursuit of that interest. But this needs to be balanced against the protection and promotion of the vital interests of all. Thus, for example, suppose that making smokeless tobacco products more easily available helped some smokers to quit smoking, but also delayed complete cessation in others, and induced some non-tobacco-users to take up tobacco use. What justice requires here turns on the empirical facts about what happens when

smokeless, or indeed other nicotine products, are made available under different regulatory regimes.

Consequentialist perspectives

So far we have considered rights-based arguments. But, in practice, we need to consider the consequences of any policy proposed. To the extent that dangerous products are kept off the market, this should protect public health. The beneficence/paternalism arguments above can also be viewed as ‘consequentialist’ arguments; for example, the concern that lower risks to individuals distributed over more individuals could result in greater harm for society. The introduction of a ‘safer’ tobacco product could also create confusion as to the safety of any or all tobacco-based products. The adverse public health consequence might be that some current smokers continue to use harmful tobacco-based products (albeit in a different form) longer than they otherwise might, and some current non-smokers are initiated into tobacco use on the basis that they see the risk–benefit ratio of a smokeless tobacco product as being just favourable enough to make use attractive. Thus, it could be viewed as a strategic mistake, which might possibly be disastrous, to allow dilution of the central message.

11.3.2 Model 2: alternative nicotine products should be made as available as cigarettes to adults

In this model, traditional tobacco products remain available on the same basis as now, with similar tobacco control policies in place so far as these relate to smoked tobacco, but regulation of alternative nicotine products (including smokeless tobacco and medicinal nicotine products) is relaxed to make them as easily available in terms of quantity, price, availability for sale and number of outlets, as smoked tobacco products. There are many ways to do this, from making alternative nicotine products freely available, marketed in direct competition with cigarettes (for example, in low-cost, single day packs sold alongside cigarettes) at the most liberal end, to a position of restricting the distribution of tobacco products on the same basis as currently applies to nicotine replacement products. In other words, this model is about levelling the regulation of tobacco products for both smoked and smokeless products, be that levelling up or levelling down.

Autonomy and individual rights

The principles of autonomy and individual rights are that adults should have knowledge of and access to less hazardous forms of nicotine in case they want to

choose to use them. If significantly less hazardous means exist to satisfy a nicotine addiction, honest information and availability are ways to respect individual rights. The current nicotine addict in particular may be viewed as someone who has the right to this information, in that the nicotine addict has a challenge and a great need to quit smoking.

This right to information is not extensive: it is a right not to be deceived or misled. Other things being equal, it is not ethically justifiable to promote a public health message (for example, that smokeless tobacco products are as, or almost as, dangerous as cigarettes) which is false merely because telling the truth is too complicated or might confuse people. However, we can also claim a stronger right: it is arguable that consumers have a right to know salient information about the products they wish to use, and about products which they may wish to use but are prevented from using on public health or product safety grounds. They have a right as citizens to know the reasons for decisions taken in the name of their best interests. While there may occasionally be circumstances under which certain kinds of information are state secrets for reasons of national security, or under which people are temporarily misled in order to prevent a panic, these kinds of reason hardly seem to apply to tobacco control.

For those who aren't satisfied that a citizen has a 'right to know', consider that the principle of individual autonomy supports the view that there is a human right to fair information relevant to healthcare and to products that would improve health. The Nuremberg Code (1949) and the United Nations Universal Declaration of Human Rights (1948) acknowledge a basic human right of autonomy. From legal perspectives, there are now expectations about patient autonomy and patient rights to be informed about, and to consent to, medical treatment.⁵⁻⁷

In addition to autonomy-based rights to accurate information about the comparative risks and benefits of smokeless and medicinal nicotine products, one can argue that the smoker has a right to access products which would enable him or her to give up smoking tobacco. Since smoking is an addiction, and cessation is difficult for many smokers, smokers face a conflict between their desire to smoke and their desire not to smoke. The desire not to smoke has two components: a first order desire not to smoke, perhaps in response to social pressure, beliefs in the harmful effects of smoking on health or other similar reasons; and a second order desire not to want to smoke, that is, to overcome cravings. Reinforcing their autonomy means enabling them to allow this latter, second order desire to dominate the former, first order desire to smoke. Denying access to alternative nicotine products which could ease the transition from smoking to zero tobacco consumption inhibits their autonomy by making this reinforcement more difficult.⁸

Beneficence/paternalism

The beneficence/paternalism arguments raised above under Model 1 concerning possible ‘slippery slopes’ toward taking up tobacco smoking or making final tobacco-use cessation more remote remain salient, but they are now in conflict with the autonomy and individual rights arguments raised here. However, providing choice in nicotine products may benefit current smokers who wish to cease tobacco use in the context of a gradual ‘weaning’ off cigarettes, and will also benefit some of those affected by second-hand smoke by eliminating the source of that smoke in the case of smokers who switch to smokeless or medicinal nicotine products. This is not a paternalist argument save in the very weakest sense. On one reading, it is simply about extending choice, which is not paternalist in any sense. On a more plausible reading, it is about extending choice to promote or induce a move from a more to a less hazardous mode of consuming nicotine, with the hope that this will produce a move to cessation (which is mildly paternalist, but in an uncontroversial way). In other words, the beneficence/paternalism arguments may be consistent with the autonomy-based arguments used to support Model 2, provided there is good evidence that the balance of benefit in terms of smoking cessation is favourable with respect to any risk that smokeless tobacco products will encourage new smokers, or dissuade existing smokers, from achieving tobacco-use cessation.

Justice

From the point of view of consumers, it is unjust that they have ready access to particularly hazardous tobacco smoking products, but no legal access to some less hazardous smokeless products or to a more satisfactory medicinal product that could be used as a much less hazardous source of nicotine and arguably as a way to quit smoking entirely. Although, as argued under Model 1, there is no right to smoke (or otherwise consume) tobacco, there is a right to be protected from harms. Barring access to safer forms of the substance to which one is addicted could be seen as imposing avoidable harms if the tobacco user will be impelled by their addiction to use a more dangerous form in the absence of safer alternatives. From the point of view of manufacturers, it is unjust that one manufacturer should be allowed to market a very dangerous nicotine delivery system, while another manufacturer is not allowed to market, equally freely, much less dangerous nicotine delivery systems. This is especially the case when the basic justification for not marketing the product, as in the case of smokeless tobacco, is that they are dangerous. Manufacturer A, who sells cigarettes, is legally entitled to

market his or her product; manufacturer B, who sells a form of smokeless tobacco, is not, even though the risks of B's product are less than those of A's. If the grounds for restraining B's trade are purely those of safety, then it seems A is being unfairly favoured over B on the grounds of a formal inconsistency in application of the principle underlying the restraint of B's trade.

Consequentialist perspectives

In the consequentialist perspectives above in support of maintaining the status quo in terms of regulation of medicinal and smokeless tobacco product restrictions, the focus was on the various bad things that might happen if restrictions, particularly on the use of smokeless tobacco products, were lifted. But there is a flaw in this argument. What various good things might fail to happen if the prohibitions are not lifted? It is an empirical question whether the number of novice tobacco users drawn into tobacco use by more widespread availability of smokeless tobacco or medicinal nicotine products, and the number of current tobacco users who defer cessation by switching to use of a lower hazard smokeless product, is or is not outweighed by the number of tobacco users who find direction cessation impossible but find cessation via switching from smoking to smokeless product or medicinal nicotine use possible. From a narrow consequentialist point of view, whereby the ethical justification of a policy is fixed by the net number of lives (or quality adjusted life years) saved, it matters what the facts are here about the relative risks of different kinds of products, likely transition rates from non-use to use of smokeless products, from smokeless product to smoking, from smoking to smokeless products, and so on. It is inadequate to simply speculate on what might happen, for example, with the availability of smokeless products.

When risks from a product used as a substitute for a more hazardous one are relatively small, the level of additional use needed to maintain a public health equilibrium (no changes in population-level problems) becomes very high. The risk to individuals from medicinal nicotine seems to be so low that it is not possible for use to increase enough to cause a net public health loss. That is, if risks from over-the-counter medicinal nicotine are, for example, less than 0.1% of those from cigarette smoking, then use would have to increase over 1,000 times more than any reduction in smoking achieved by their availability to cause an equal public health problem. For smokeless products such as snus, if the risk is as much as 10% of that of cigarette smoking, use would have to increase by 10 times the number of smokers who switched from smoking to smokeless use to generate an equal public health problem.^{9,10} In relation to the theory that the availability of lower risk smokeless tobacco (or medicinal nicotine) may provide a causal gateway to cigarette smoking,

there is some evidence that smokeless tobacco is a gateway for some to cigarettes, but there is also evidence that, for the majority of users, smokeless tobacco is not a gateway and may even help prevent smoking.^{11–13} However, uptake of smokeless use by young people would still have to be very extensive to outweigh the public health benefits achieved in those smokers who switched to snus use. It is also important to appreciate that adolescent experimentation with cigarette smoking is the dominant gateway to a smoking habit in adulthood. A child at high risk of becoming a smoker would probably be better off using smokeless tobacco than cigarettes in this context, because the latter would greatly increase the odds of the child becoming an adult smoker, and whereas use of smokeless tobacco has a much reduced risk of leading to cigarette smoking. The above analysis takes no account of the additional benefits realised by switching from smoked to an alternative nicotine product on the ‘third party costs’ of smoking, such as the effects of smoking on non-smokers through passive smoking-related illness, fires, and so on.

11.3.3 Model 3: smokeless tobacco products should made more available than cigarettes to adults

Essentially, the arguments for this model combine the arguments for Model 2 with the general principle that the availability of smoking tobacco should be reduced, or the less radical alternative that smoking tobacco be driven down or out of the competitive market by greatly increasing the availability of smokeless tobacco and other nicotine delivery products.

Autonomy and individual rights

Current approaches to smoking tobacco do impose restrictions on its availability through restrictions on where, how and to whom it may be sold. These could be intensified in various ways: for instance, by raising the legal age at which one may purchase tobacco, requiring sellers to be licensed and issuing licenses very sparingly, or making tobacco a prescription-only product. This would clearly reduce autonomy in trying to block or restrict smokers’ access to smoking tobacco rather than merely encouraging cessation through persuasion, education or the choice of safer alternatives. Price controls are arguably easier to defend than point of sale restrictions, since they operate through the autonomous choice to purchase smoking rather than alternative products. Thus, an expansion in the range of safer alternatives, which would tip the balance away from smoking tobacco and towards smokeless or nicotine replacement products, would be more consistent with autonomy and individual rights.

Beneficence/paternalism

Either approach (restriction of access to smoking tobacco or expansion of access to alternatives) can be seen as a beneficent/paternalist approach to alteration in smokers' behaviour. The argument here is essentially the same as that for Model 2. The difference is purely empirical: which approach has the better consequences in terms of the safety of tobacco users and in terms of eventual cessation, cultural change in the direction of disapproval of smoking, or other objectives of tobacco control?

Justice

It can be argued that restriction of access to smoking tobacco would be unfair, because it would impose disproportionate burdens on smokers who are addicted, though not if access restrictions leave smoked tobacco products available but less ubiquitously so (for example, through licensing a limited number of retail outlets). It may be that many of these individuals would find it easier to use alternative products, or to give up smoking, and this would be a good outcome. But not all smokers would be able to do this, and some might find the costs of alternatives excessive in relation to the costs of smoking tobacco (especially where the price of tobacco in black markets is taken into account) unless prices of alternatives were regulated with a view to promoting public health. Hence, from the point of view of justice, restriction of access to tobacco alone would need to be supplemented by expanded access to alternative products which are safer and no more expensive than smoking tobacco.

Consequentialist perspectives

The main issue here is whether adopting a restrictive access to smoking tobacco policy, with or without an expanded access to alternatives policy, would actually succeed in helping people avoid the harms of smoking. The obvious concern about a policy to restrict smoking tobacco would be that it might encourage illicit use of smoking tobacco and the associated illegal trade in smoked tobacco products. The obvious concern about an expanded access to alternatives policy would be that it might encourage continued use of products which remain harmful, rather than progression to cessation. The same arguments apply to Model 2, and the issue here is therefore an empirical one of what works best.

11.4 Approaches to rebalancing the nicotine product market

Changing the nicotine market, as outlined in sections 11.3.2 and 11.3.3 above, could be achieved through two different approaches: levelling down or levelling up. In the levelling down option, all alternative nicotine products that offer a clinically relevant reduction in risk could be deregulated to the same or greater extent than is currently the case for cigarettes and other smoked products, and market forces could then be left to determine whether existing and new less hazardous, more acceptable and more affordable nicotine products are promoted, brought to market and used by smokers. At the other extreme, it has been suggested that governments could take the tobacco industry into state control, either directly or through a third party organisation, and thus radically control promotion, distribution, branding and all other aspects of the tobacco market.¹⁴ Both approaches are paternalistic, in that they attempt to influence consumer preferences in the direction of safer products, but they are also both consistent with the current regulation of smoking tobacco through taxation. The ethical issues of these options, or other approaches, go beyond those raised above, in that they mainly concern the ethics of regulating or otherwise controlling privately owned businesses through direct government action on the suppliers of the products, in addition to altering the behaviour of the consumers.

11.5 Conclusions

- ▶ Although stopping tobacco use is the ideal outcome for individual and public health, this is often difficult to achieve. Making a wider range of safer products available would be a harm reduction approach to tobacco control.
- ▶ Harm reduction approaches in public health are sometimes criticised for condoning the activity they are trying to make safer. The Royal College of Physicians takes no position on the morality of smoking. However, since smoking is dangerous to health, and is hard to give up, the College wants to see a range of effective methods to help smokers quit or to reduce the harm they sustain.
- ▶ The present status quo, in which cigarettes are freely available, medicinal nicotine products are available but under regulations that restrict availability and effectiveness, and some smokeless tobacco products are prohibited, denies smokers the right to choose safer nicotine products.
- ▶ Balancing the nicotine market, so that all nicotine products are equally available and comparably priced, would provide smokers with choice but would not encourage change from high risk to lower risk products.

- ▶ Rebalancing the market in favour of the safest nicotine products would provide choice, encourage safer nicotine use, and reduce morbidity and mortality.
- ▶ The ethical aspects of regulating alternatives to smoking tobacco are complex, and three positions can be defended: maintaining the status quo, making alternatives to smoking tobacco as easily available as smoking tobacco now is, or making them more easily available than smoking tobacco now is.
- ▶ Each alternative represents a balance of consumer rights, consumer protection, fairness and general policy considerations.
- ▶ The Royal College of Physicians favours an approach which would make smoking easier to give up, while discouraging people from starting to smoke in the first place, by making alternatives to smoking tobacco more widely available and by regulating smoking products more tightly through pricing, marketing controls and formal regulation of the production and sale of tobacco products. It believes that this offers the best balance of the ethical considerations surveyed in this chapter.

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12 | Reducing the harm from nicotine use: implications for health policy and nicotine product regulation

- 12.1 Introduction
- 12.2 The importance of nicotine in smoking behaviour
- 12.3 The relative harm of different nicotine products
- 12.4 The effectiveness of medicinal nicotine products as an alternative to smoking
- 12.5 Smokeless tobacco products as an alternative to smoking
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- 12.9 The consequences of failure to act
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12.1 Introduction

Smoking is powerfully addictive and kills half of all regular smokers.¹ As outlined in Chapter 1, having caused 100 million deaths in the 20th century,² and currently causing about five million deaths each year,³ smoking is expected to result in a total of one billion deaths worldwide in the 21st century.² There are an estimated one billion smokers in the world, and this figure is expected to rise to 1.6 billion by 2025. Of all smoking products in current use, the cigarette is the most hazardous, the most addictive, and by far the most widely used.

Preventing people from ever starting to smoke is clearly the ideal means of preventing harm from smoking, but is only part of the solution for countries in which the smoking epidemic is already established. Preventing uptake of smoking will have minimal impact on deaths from smoking over the more immediate future because of the lead time of 20 years or more between starting smoking and the incidence of the main adverse effects on health. This means that the great majority of the global total of 150 million deaths from smoking expected in the next 20 years will occur in people who are smoking today. Preventing these deaths requires a focus on the needs of these individuals and helping as many as possible, as soon as possible, to stop smoking tobacco.

Current internationally endorsed tobacco control policies focus on both preventing the uptake of smoking and encouraging cessation by using taxation to increase the price of tobacco products, making workplaces and public places smoke-free, implementing effective health promotion campaigns, prohibiting tobacco advertising, providing cessation services, and other measures.^{4,5} These policies are of proven effectiveness,⁶ but even if fully implemented the magnitude of their effect on prevalence is modest. For example, in Massachusetts and California active tobacco control policy implementation achieved additional reductions in prevalence of around half a percentage point per year,^{7,8} and in California this effect was not sustained in the longer term.⁷ Even with full implementation of all recognised effective tobacco control policies it will take many years for a marked reduction in smoking prevalence, and in the morbidity and mortality that smoking causes, to be realised.

In the nine years since the publication of the White Paper, *Smoking kills*,⁹ the UK government has taken a lead in implementing a wide range of tobacco control policies.¹⁰ Cigarette prices in the United Kingdom are among the highest in Europe,¹⁰ tobacco advertising is prohibited, smoking cessation services are available through the National Health Service to all smokers who want to quit, and comprehensive smoke-free policies have now been fully implemented. However, even if these measures succeed in maintaining or even increasing the recent rate of decline in UK smoking prevalence of about 0.4 percentage points per year for the longer term,¹¹ with 24% of British adults currently smoking it will take at least two decades for the prevalence of smoking in the UK to halve from current levels.¹² Even at that stage, there will be over five million smokers in the UK. These persistent smokers will include a high proportion who are heavily addicted and therefore find it especially difficult to quit despite many attempts to do so. There may also be a substantial number of 'hardcore' smokers who have no desire or intention to quit.¹³ These smokers and their families, who tend to be predominantly from the most socioeconomically deprived sectors of society,^{13,14} will bear a huge burden of potentially avoidable morbidity and mortality.

Current internationally recommended approaches to tobacco control are important, particularly in countries at an early stage of the smoking epidemic, and need to be maintained.^{4,5} However, in countries such as the UK with a substantial population of established current smokers, tobacco control measures will not significantly reduce the shorter-term and medium-term burden of the morbidity and mortality caused by smoking, particularly among the most disadvantaged in society. In short, current tobacco control policy will fail to protect smokers who are unable to quit. New approaches are urgently needed to prevent death and disease in these people. Since they are not otherwise likely to quit smoking, the obvious

alternative and public health priority is to find ways to reduce the harm caused by their habit.

12.2 The importance of nicotine in smoking behaviour

The evidence summarised in this report (Chapters 2, 3 and 4) demonstrates that nicotine in tobacco smoke is powerfully addictive. This addictiveness is probably enhanced by other components in the smoke, from physical stimuli arising from smoke inhalation, and possibly also by other related behavioural and environmental stimuli. Exposure to high levels of nicotine, and exposure from a relatively early age, may also result in neurodevelopmental changes that in turn influence the intensity of addiction. Once established, nicotine addiction is the principal underlying driver of sustained smoking behaviour.

12.3 The relative harm of different nicotine products

Nicotine is available in a wide range of products (see Chapter 5) in three broad categories: smoked tobacco, of which the cigarette is pre-eminent; medicinal nicotine, currently marketed as nicotine replacement therapy and intended for short-term use as a smoking cessation therapy; and smokeless tobacco products, of which oral tobacco is the most widely used.

Cigarettes and other smoked tobacco products are by far the most harmful of these nicotine sources (see Chapter 6). Cigarettes are designed to enhance the development and maintenance of addiction, and hence sustained use of the product. Cigarette smoke is harmful primarily because it delivers nicotine in conjunction with an extensive range of toxins and carcinogens.

By contrast, the safety record of medicinal nicotine products is extremely good (see Chapter 7). Although it is unlikely that medicinal nicotine (or any drug) is completely safe, there is no evidence that medicinal nicotine is carcinogenic, or that, in practice, its use increases appreciably the risk of acute cardiovascular events, or indeed that nicotine itself is responsible for much if any of the harm caused by cigarette smoking. To practical purposes, therefore, in comparison with smoking cigarettes, use of medicinal nicotine is extremely safe.

Smokeless tobacco products differ widely in their risk profile (see Chapter 8), largely in relation to the content of toxins in the tobacco. Of the more widely used products, Swedish oral tobacco (snus) appears to be the least hazardous. On current evidence it appears that snus use may increase the risk of cancer of the pancreas, and also of cardiovascular disease, but to a lesser extent than cigarette smoking. Snus use does not appear to be associated with an increased risk of oral

cancer, but increased risks are well documented in association with use of some other smokeless products.

Unlike cigarette smoking, snus use does not cause lung cancer, chronic obstructive pulmonary disease or many other major adverse health effects associated with smoking. Thus, while undoubtedly more hazardous than medicinal nicotine, smokeless tobacco products, and particularly the low nitrosamine products, are substantially less hazardous than smoked tobacco.

12.4 The effectiveness of medicinal nicotine products as an alternative to smoking

Since first becoming available around 20 years ago, medicinal nicotine products have been licensed for use in the UK and in most other countries as cessation therapy. Although some national regulators now approve use for temporary abstinence or ‘cutting down to quit’, the great majority of medicinal nicotine has been used as a temporary substitute for nicotine from cigarette smoke during a quit attempt. Although use of medicinal nicotine increases the likelihood of quitting smoking by a factor of around 80%,¹⁵ the overall effectiveness of medicinal nicotine is disappointing, since, in conjunction with best practice behavioural support, only about one in five smokers succeeds in quitting for six months or more.^{16,17} Only a very small minority of smokers continue to use medicinal nicotine products in the longer term, and the risk of relapse to smoking increases substantially when use of medicinal nicotine ceases.¹⁸ It is evident from the fact that relapse is so common among smokers quitting using medicinal nicotine products, and that long-term use of such products is so rare, that the available medicinal products are not strong substitutes for smoking. If these products were more effective they would be much more widely used, and probably more difficult to quit.

There are several likely reasons for this. Medicinal products are designed to minimise addiction potential by delivering nicotine more slowly and in lower doses than cigarettes. These characteristics also make them less effective as substitutes. Their packaging and pricing has tended to make them expensive at the point of sale to smokers, thus inhibiting impulse purchase or experimentation. This is likely to be especially so for less affluent smokers. They are marketed, packaged and promoted as cessation treatments, rather than as attractive and affordable competition to cigarettes. Although some are available for over-the-counter sale, their availability and display profile in retail outlets is substantially less than for cigarettes. Medicinal nicotine is also widely perceived by smokers to be harmful.¹⁹

12.5 Smokeless tobacco products as an alternative to smoking

Use of smokeless tobacco products predated cigarette smoking in many parts of the world, and continues to be widespread in many countries in which the smoking epidemic is still at an early stage. In countries at later stages of the smoking epidemic, the evidence on trends in use of smokeless tobacco, and on the gateway phenomenon by which smokeless products might encourage uptake of smoking or help existing smokers to stop smoking, is mixed.

In the United States, where smokeless tobacco has been used widely in the past, the prevalence of smokeless tobacco use has declined in recent years and is now low.²⁰ Smokeless products are not used widely in the USA as a smoking substitute by existing smokers, and the evidence relating to the concern that smokeless products might act as a 'gateway' into smoking is inconclusive (Chapter 8). In Europe, use of smokeless tobacco in the form of snus is prevalent in Sweden, where the evidence suggests that, in recent years, snus has been used among smokers predominantly as a substitute and/or cessation product. There has been relatively little gateway use by non-smokers into smoking. Snus is available in Norway but has not been used widely and does not appear to have had an appreciable effect on smoking behaviour. Use of smokeless tobacco elsewhere in the European Union, outside specific ethnic minority groups, is rare.

Thus, the Swedish data suggest that smokeless products, and particularly snus, may have the potential to act as effective substitutes for smoking, while experience elsewhere suggests that this effect may also be country or culture dependent, possibly arising from relative social acceptance of smokeless use, or from differences in perceived health risks among consumers. The Swedish data also indicate, however, that it may be useful to explore the possibility of harnessing some of the dose, delivery characteristics and associated stimuli provided by snus in the development of new medicinal products.

12.6 Harm reduction strategies

Harm reduction strategies are pragmatic approaches to reducing the harm arising from a hazardous behaviour. In broad terms, harm reduction is fundamentally embodied in the application of common sense and the widespread regulatory controls intended to minimise the inevitable hazards of everyday life. In relation to tobacco smoke exposure, legislation prohibiting smoking in enclosed public and workplaces is an example of a harm reduction strategy intended to protect workers from the adverse effects of passive smoke exposure.

Harm reduction strategies are used widely in public health to reduce the harm caused, for example, by illicit drug use and a range of other behaviours. The

rationale behind their application in this context is that while the best option for individuals and/or society would be to avoid harmful behaviours completely, the next best option, if avoidance is not a practical or realistic option, is to minimise the harm caused by the behaviour.

Cigarette smoking is a highly hazardous and addictive behaviour, and complete abstinence from smoking is the obvious best option for health. However, as argued in this report, this option is not realistically achievable in the short-term or medium-term future for a substantial proportion of smokers in populations in which smoking is already established. In this context, since tobacco smoking is driven primarily by addiction to nicotine, but the harm from smoking is caused by other smoke constituents, the rational next-best option is to reduce the harm arising from nicotine use by providing it in a form that does not involve inhaling smoke. The alternative sources of nicotine offered need to be acceptable to smokers as substitutes for cigarettes, and available at a price and with marketing and health messages necessary to encourage smokers to substitute them for tobacco smoking. They also need to be substantially less hazardous than smoking.

Effective harm reduction strategies have not, to date, been applied to any significant extent to tobacco smoking. Controls based on machine-measured cigarette yields have been ineffective. Attempts to restrict the toxicity of conventional cigarettes by altering the content of tobacco or other measures used in potential reduced exposure products (PREPs) (Chapter 9) have not been shown to deliver real reductions in risk, and will not have an appreciable effect on the risk of smoking unless they result in radical reductions in exposure to toxins and carcinogens. The option of providing nicotine without smoke, intended as a long-term or, if necessary, lifelong substitute for regular smoking, has not been explored. Medicinal nicotine products have been developed and used almost exclusively as temporary cessation aids. Use of smokeless tobacco products, although substantially less hazardous than smoking, is currently actively discouraged, and in relation to some products in the European Union, prohibited.

The fundamental argument of this report is that this current situation is perverse, unjust and acts against the rights and best interests of smokers and the public health. Harm reduction has the potential to play a major part in preventing death and disability in the millions of people who currently smoke and who, in the context of exposure to currently available drivers and supports to cessation, either cannot or will not otherwise quit smoking. These smokers have a right to be able to obtain and choose from a range of safer nicotine products (Chapter 11), and they have a right to accurate and unbiased information to guide that choice. In a recent study, it was estimated that if a product such as snus were introduced into the US market and promoted with a warning stating,

‘This product is addictive and may increase your risk of disease. This product is substantially less harmful than cigarettes, but abstaining from tobacco use altogether is the safest course of action’, the prevalence of smoking in the USA would decline by between 1.3 and 3.1 percentage points over five years.²¹ That is an annual decline of between 0.25 and 0.6 percentage points per year, or approximately 0.4 percentage points per year; sufficient to double the recent rate of decline in the UK.¹¹ A switch of only 0.4% of the population of smokers in the UK each year from smoking to less harmful nicotine sources – a conservative target – would save around 25,000 lives in only 10 years.²²

There are, however, a number of obstacles and barriers to the development of an effective harm reduction strategy for tobacco smoking. These include the moral concerns of health professionals and others outlined in Chapter 11, and reluctance by governments to engage in a difficult and controversial shift in policy. However, one of the main obstacles to progress is the current system of regulation that applies to nicotine products.

12.7 Current nicotine product regulation and health

Regulation of nicotine products varies between countries, but, as outlined in Chapter 9, has tended to evolve in piecemeal reactive legislation for tobacco products, while medicinal nicotine has been subject to the much stricter regulatory frameworks that most countries apply to medicines.

Cigarettes and other smoked tobacco products have enjoyed almost complete freedom from regulatory control in many countries for many years, and although now subject to a growing range of restrictions on machine-measured nicotine and tar yields, and on advertising and health warnings, smoked tobacco products remain remarkably free from any regulation likely to have an appreciable effect on the harm caused to the consumer. Indeed, a major reason why tobacco products have remained exempt from consumer protection regulation for so long is that their status as a legal product is so inconsistent with their risk profile that the proportionate application of the regulatory systems that control other consumer products would result in their immediate withdrawal from sale. As a consequence of this freedom from effective health, safety and consumer protection regulation, the most dangerous and addictive nicotine products remain regulated to a minimal degree and in extreme disproportion to their hazard, and are freely available and widely used. Under the current regulatory system, tobacco companies remain free to develop or modify, and bring to market, new smoked tobacco products, PREPs, and other tobacco derivatives with little by way of regulatory control.

Medicinal nicotine products, in contrast, are strongly regulated as drugs. This has resulted in the development and marketing of nicotine products that have low addiction potential, deliver low nicotine doses, and are promoted and marketed for short-term use as cessation aids. While this may be justified in the context of smoking cessation objectives, these characteristics are almost entirely the opposite of those needed if medicinal nicotine is to prove an effective and acceptable cigarette substitute. Thus the safest available nicotine products are currently subject to the highest level of regulation, and the most dangerous to the least. The restrictions that these regulations impose on the likely uptake and availability of medicinal nicotine products may have acted as a major disincentive to innovation and competition in the medicinal nicotine market.

In terms of relative hazard, smokeless tobacco products vary, but all are less hazardous than smoking and some are especially so. The regulations imposed on these products in the UK and most EU countries are entirely inconsistent, both within the range of smokeless tobacco products (since the least hazardous are the most regulated) and also in relation to medicinal or smoked nicotine. Some products, such as chewing tobacco or nasal snuff, are available and subject to minimal regulatory controls, yet are more hazardous by comparison with other smokeless products. Others, such as snus, appear to be the least hazardous yet are widely prohibited. In view of the low hazard associated with low-toxin oral products such as snus, and evidence of the potential of these products as smoking substitutes, their prohibition in the context of free availability of other smokeless and smoked tobacco products is irrational. The potential for existing or new smokeless products to provide an alternative source of nicotine for smokers, to complement medicinal products, merits further investigation. While rationalisation of smokeless product regulation by extending the prohibitions that apply to some products across the full range of smokeless tobacco would resolve the present inconsistency, the danger is that if smokeless products can help some smokers to quit who would not otherwise do so, without other marked adverse effects on public health, this potential benefit will be lost. At the other extreme, lifting the prohibition on low hazard products and in effect further extending the free hand currently enjoyed and exploited by the tobacco industry to a new product area is potentially disastrous. The market in smokeless tobacco, as for all nicotine products, needs consistent and rational monitoring and control.

12.8 How should nicotine products be regulated to improve public health?

Nicotine products need to be regulated pragmatically to reduce the overall harm caused by nicotine dependence and use. This will involve trying to reduce overall

levels of nicotine product use, and also reducing the proportion of nicotine users who use the most hazardous nicotine delivery devices, particularly cigarettes. Achieving this will require radical overhaul. The current nicotine regulatory framework needs to be changed so that it encourages as many smokers as possible to quit smoking and all nicotine use completely, and encourages those who cannot quit to switch to a safer source of nicotine, while minimising use by people who would not otherwise have used nicotine products. It should not encourage new users to start using any nicotine product. The framework also needs to encourage innovation, development and ultimately the use of new medicinal nicotine products at the less hazardous end of the spectrum, and to demand significant reductions in hazard, availability and affordability of products at the smoked tobacco extreme.

Overall, the framework should ensure that the market forces of affordability, promotion and availability to the consumer apply strongly and in direct inverse relation to the hazard of the product, thus creating the most favourable market environment for the least hazardous products, and discouraging the use of more hazardous products. The anomalies that inhibit new product development, in particular rapid delivery, user-friendly medicinal products and more widespread use of existing low-hazard products, need to be removed. The regulatory system for nicotine products must also be able to respond to and mitigate potentially counterproductive trends in marketing or use of nicotine products, and must therefore have access to regular, frequent surveillance data on patterns of use, marketing strategies and health claims by manufacturers. It must also ensure that alternative nicotine products, be they medicinal or tobacco-based, are marketed with appropriate health information.

Nicotine product regulation should also evolve so that smoked tobacco products are subject to progressively increased restrictions on availability and marketing, with the longer-term objective of minimising and, in due course, eradicating the use of smoked tobacco. A coherent and planned strategy to achieve these objectives would need to be pursued by government, the medicines regulators, the industry, and the medical and smoking cessation community.

The ideal outcome would be a coherent and consistent nicotine regulatory system that takes responsibility for all nicotine products. There are many potential ways of achieving this outcome, such as bringing all nicotine products under the responsibility of an existing agency (such as food or drug regulation agencies), or by creating an overarching coordinating body to oversee and complement the activities of the agencies currently involved in regulating nicotine products. However, our firm conclusion is that the special problems of regulating nicotine products, and providing market surveillance, clear consumer information and

monitoring industry activity, requires special skills and concentrated expertise that would be best established in a dedicated nicotine product regulatory authority. Some of the initial and continuing functions of the proposed authority are outlined in Box 12.1.

While working towards a nicotine regulatory authority, we believe that significant changes to the way that nicotine is regulated by the Medicines and Healthcare products Regulation Agency (MHRA) could easily be made in the more immediate future. This would enable the ‘new and innovative therapies’ envisaged in the White Paper, *Choosing health*, to be developed and promoted to smokers.²³ Some relaxation of the restrictions on use of medicinal nicotine have already been made by the MHRA, which now accepts that users of nicotine products would otherwise be smoking, and that the risks of use of nicotine products should be assessed in that context. However, we would like to see the MHRA extending this harm reduction model to other aspects of medicinal nicotine product development and use, in order to promote the availability of fast-acting, user-friendly products that are easily available, affordable, and likely (if effective) to be used for the longer term. Controls on advertising of medicinal nicotine products could be relaxed to allow manufacturers to promote medicinal products on a harm reduction platform, thus also helping to break down public misconceptions of the risks of nicotine use. Simplification of the licensing process and other measures that encourage competition in the medicinal nicotine market to generate better and more affordable products are likely to be beneficial to public health. The recent reduction of taxation on medicinal nicotine products by the UK government is a welcome example of a simple innovation that is likely to encourage greater use.

Implementing a strong harm reduction strategy for smokers would give smokers the choice, currently not available to them, to use products that are tens of times if not hundreds of times less hazardous than cigarettes, so saving lives and significantly reducing social inequality in health. It would also support the introduction of smoke-free legislation, help to denormalise smoking, significantly reduce exposure to passive smoke in the home (where children in particular are most heavily exposed) and help to reduce the number of smoking-related fires in both domestic and commercial settings. Such a strategy would be a market-based, low-cost public health intervention.

12.9 The consequences of a failure to act

The inevitable consequence of failing to address the special problems of nicotine product regulation will be the perpetuation of current smoking among millions

Box 12.1 Suggested roles and functions of a national nicotine regulatory authority.	
Functions at initiation ▶ Baseline measurement of all current nicotine product use ▶ Ensure full implementation of conventional tobacco control policies ▶ Permissive licensing of medicinal nicotine products for use as smoking substitutes ▶ Substantial relaxation of restrictions on marketing and sale of medicinal nicotine products ▶ Removal of tax on medicinal nicotine products ▶ Communication of objective health risk information for nicotine products and promotion of harm reduction principles to smokers and the public ▶ Establishment of ground rules for monitoring the use of health messages in promoting the use of lower hazard nicotine products as substitutes for smoking ▶ Imposition of generic packaging for all tobacco products ▶ Prohibition of retail display of smoked tobacco products ▶ Strong graphic health warnings on smoked tobacco products ▶ Setting of tax and consequently retail price of all nicotine products in relation to their likely relative risk to health ▶ Prohibit all sale of nicotine products to individuals aged under 18 ▶ Introduce licensing of retailers of all smoked tobacco products ▶ Assume responsibility for overseeing nicotine product delivery and toxicity monitoring ▶ Mandate the introduction of reduced ignition propensity cigarettes ▶ Take expert advice on how current restrictions on smokeless tobacco could be reformed to public health benefit	Continuing functions ▶ Regular monitoring of trends in nicotine product use, promotion and availability ▶ Monitoring impact of licensing and marketing relaxation on medicinal nicotine use, and revision as necessary to promote public health ▶ Progressive increases in tax on the most hazardous products ▶ Continued promotion of health information on different nicotine products and development and monitoring of mass communication strategies to prevent uptake, promote cessation, and reduce harm ▶ Progressive reduction in retail licences for smoked tobacco products ▶ Monitoring and policing of illicit and underage tobacco and nicotine trade ▶ Work with the commercial sector to promote competition and innovation in the medicinal nicotine market ▶ Monitoring and prevention of smoked product placement and new methods of marketing (eg internet, viral marketing) ▶ Act on expert advice to set framework for licensing of low-hazard smokeless products and possible test marketing ▶ Progressively incentivise minority, high risk smokeless tobacco users to quit or else migrate to safer products ▶ Identify and respond to new developments or threats to health from new or existing product development or promotion ▶ Control of expenditure on tobacco control interventions to ensure evidence-based and cost-effective interventions are used ▶ Support nicotine regulation and tobacco control approaches in resource-poor countries

of people, and a consequent continued epidemic of death and disability caused by tobacco smoking. Specifically, cigarettes and other smoked tobacco products will continue to be marketed with minimal restriction on their safety or content; smoking products alleged to present lower risks to the smoker, such as PREPs, will be freely marketed and their health claims unsubstantiated; the medicinal nicotine market will continue to focus on low-addiction, low-dose, low-effectiveness products while also stifling competition and innovation; the current piecemeal and inconsistent regulation of smokeless products will continue, preventing smokers in most EU countries from choosing to use a significantly less hazardous tobacco product than cigarettes; and the majority of smokers alive today will continue to smoke, and half will die as a result.

12.10 Conclusions

- ▶ Most of the deaths and disease caused by smoking in the near- and medium-term future will occur in people who are smoking now.
- ▶ Current conventional preventive measures focus entirely on preventing uptake of smoking and helping smokers to quit smoking.
- ▶ This approach will be ineffective for the millions of smokers who, despite best efforts to persuade and help them to quit, will carry on smoking. Half of these smokers, representing millions in the United Kingdom alone, will die as a result.
- ▶ This burden of mortality and morbidity will markedly exacerbate social inequality in health.
- ▶ Tobacco control policy needs to be radically extended to address the needs of these smokers, by implementing effective harm reduction strategies.
- ▶ Harm reduction in smoking can be achieved by providing smokers with safer sources of nicotine that are acceptable and effective cigarette substitutes.
- ▶ There is a moral and ethical duty to provide these products to addicted smokers.
- ▶ Current systems of regulation of nicotine products inhibit the development of innovative medicinal nicotine substitutes for cigarettes, and perpetuate the use of the most dangerous nicotine products. This is unjust, irrational and immoral.
- ▶ Nicotine product regulation must, therefore, be reformed.
- ▶ The unprecedented and unjustifiable market freedoms enjoyed by manufacturers of cigarettes and other smoked tobacco products must end.

- ▶ The development of new, more effective, more acceptable and user-friendly medicinal nicotine substitutes for smoking needs to be encouraged.
- ▶ A major step towards an effective harm reduction strategy could be taken by the implementation of simple changes to the regulation, promotion and taxation of medicinal nicotine.
- ▶ Low nitrosamine smokeless tobacco products may have a positive role to play in a coordinated and regulated harm reduction strategy which maximises public health benefit and protects against commercial market exploitation.
- ▶ The regulation of nicotine products, be they medicinal or tobacco-based, thus needs radical reform to ensure that the market forces of affordability, promotion and availability act in a strong and directly inverse relation to the hazard of the nicotine product, and that the marketing and use of nicotine products is carefully monitored to maximise public health benefit.
- ▶ While it may be possible to achieve this reform and consistency by a more rational application of existing regulatory frameworks, our conclusion is that the scale of the problem and the difficulties of achieving successful reform are such that the problem will be best addressed by the creation of a nicotine regulatory authority to take control of all aspects of regulation of all nicotine products.

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13 | Key conclusions and recommendations

Use of tobacco in society

- ▶ Tobacco use originated in the American continent thousands of years ago and has spread to the rest of the world in the past 500 years.
- ▶ Tobacco continues to be used in many different ways, but the most common form of consumption is now the cigarette.
- ▶ The current global epidemic of cigarette smoking is a recent phenomenon, dating from around the turn of the 20th century.
- ▶ The onset of the smoking epidemic typically occurs in men before women, with epidemic increases in deaths caused by smoking occurring 20–30 years after the onset of smoking.
- ▶ In some developed countries, both smoking prevalence and mortality rates are now falling.
- ▶ Most countries are at an earlier stage of the epidemic, and globally both smoking rates and mortality are rising.
- ▶ Smoking is the biggest avoidable cause of premature death and disability in most developed countries, and with the evolution of the global smoking epidemic will be equally important in the future wherever smoking becomes prevalent.
- ▶ In 2001, smoking caused 4.8 million deaths, equivalent to about one in every 12 of all deaths, globally.
- ▶ By 2025 there will be an estimated 1.6 billion smokers in the world, and smoking will cause approximately 10 million deaths each year.
- ▶ Most of these deaths will occur in people who already smoke, rather than those who start smoking between now and 2025. Therefore, whilst preventing the uptake of smoking is crucially important to the prevention of deaths in the longer term, promoting smoking cessation has a greater effect on mortality in the shorter term.
- ▶ It is, therefore, crucial to find ways of helping existing smokers to quit smoking, as well as preventing the uptake of smoking.

Mechanisms of action of nicotine in the brain

- ▶ Nicotine targets receptors whose natural function is to interact with the neurotransmitter acetylcholine.
- ▶ By activating these nicotinic receptors, nicotine increases the firing rate of neurons and increases the release of various neurotransmitters.
- ▶ The effect of nicotine on different nicotinic receptors is dose dependent and is also modified by sustained exposure, which causes some receptors to become desensitised.
- ▶ Long-term exposure to nicotine also causes an increase in the number of nicotinic receptors in the brain, but it is not clear how many of these receptors are functional.
- ▶ In animal studies, the acute reinforcing effects of nicotine appear to be dependent on dopamine release in the brain. However, nicotine-induced dopamine release is markedly curtailed or even disappears when animals are chronically exposed to the drug.
- ▶ Although cigarette smoking in humans promotes dopamine release, the contribution of this effect to sustained smoking behaviour is still not fully understood.
- ▶ It is also not clear which nicotinic receptor subtypes are responsible for the reinforcing effects of this drug in humans.

Experimental evidence on addiction to nicotine

- ▶ Drug dependence has commonly been perceived as being primarily a 'drug-seeking' behaviour in which an addicted individual exhibits a powerful desire or craving for the drug, and that on each occasion the addicted individual takes the drug, he or she experiences a powerful rewarding effect which is mediated directly by the drug itself.
- ▶ Evidence from both animal and human studies indicates that addiction to tobacco smoking is more complex. It also seems to depend critically upon the ability of nicotine to confer powerful rewarding properties on other sensory cues arising from the process of smoking, and possibly also on the circumstances in which smoking occurs.
- ▶ The direct reinforcing properties of nicotine are experienced

predominantly only after periods of temporary abstinence, after sleep for example. For much of the remainder of the smoking day, nicotinic receptors are desensitised and the nicotine inhaled by the smoker probably does not then cause stimulation of the pathways implicated in the development of dependence. During these periods, smoking is probably reinforced primarily by conditioned stimuli (sensory cues) present in the smoke.

- ▶ By smoking in this way, smokers maintain their blood nicotine level at a concentration sufficient to prevent the aversive consequences of withdrawal, while continuing to derive some positive reinforcement from the conditioned stimuli present in the smoke, and, possibly, other behavioural cues associated with smoking.
- ▶ Hypotheses concerning the neurobiological mechanisms have been derived predominantly from studies with experimental animals. As far as it has been possible to test them, the pharmacological responses to nicotine, inhaled by humans in tobacco smoke, elicit similar effects in the human brain to those observed in experimental animals.
- ▶ The interplay between the pharmacological properties of nicotine inhaled in tobacco smoke and the cues and conditioned stimuli associated with human tobacco dependence are likely to be even more complex than those revealed by animal studies. Future studies which seek to establish better treatments for tobacco addiction might usefully focus on this aspect of the problem.

Nicotine addiction in humans

- ▶ Addiction to nicotine arises from a combination of genetic, environmental and pharmacological factors, but the characteristics of the nicotine delivery system are also crucially important.
- ▶ Cigarettes are the most addictive tobacco product.
- ▶ Cigarettes and many other tobacco products have been specifically designed, engineered and marketed to enhance both development and maintenance of addiction.
- ▶ Medicinal nicotine products are designed and marketed to minimise their addiction potential.
- ▶ The development of addiction includes changes in brain structure

and function that result in cessation-associated withdrawal effects that typically persist for many weeks or longer in some individuals, thereby impairing the ability to achieve and sustain abstinence.

- ▶ Treatment of dependence and withdrawal can restore brain function, mood, and cognitive abilities, and thereby support cessation, but individuals appear to vary widely in how long they may require treatment, and probably in what forms of treatment are acceptable and effective.
- ▶ However, some of the changes in brain structure and function in smokers, particularly those who began smoking when very young, may not be entirely reversible.
- ▶ Hence, some smokers may never fully overcome their addiction, or even ever be able to quit all nicotine use.

Sources of nicotine

- ▶ There is a wide variety of nicotine products available for use, delivering a range of nicotine doses. The cigarette is the most widely used product.
- ▶ Cigarettes deliver high doses of nicotine into the lungs, where it is absorbed rapidly and transported directly in the systemic circulation to the brain.
- ▶ The nicotine from cigarettes is carried in smoke which contains thousands of other chemicals, including many that are carcinogenic or otherwise toxic.
- ▶ Some of these toxins are present in tobacco before combustion. Most are combustion products.
- ▶ Smokeless tobacco also contains toxins and carcinogens, but delivers high doses of nicotine without most of the toxic components in smoke.
- ▶ Medicinal nicotine products deliver pure nicotine, but in relatively low doses and, particularly for nicotine transdermal patches, very slowly. They do not deliver other toxic chemicals.
- ▶ The available alternative nicotine products all deliver nicotine more slowly than cigarettes, and are, therefore, probably less addictive.
- ▶ It is possible that alternative nicotine products could provide a safer long-term substitute for cigarette smoking. If so, this could benefit individual and public health.

The risks of smoking

- ▶ Smoking currently kills nearly 5 million people each year.
- ▶ In the 20th century, there were an estimated 100 million premature deaths attributable to smoking. If current smoking patterns continue, there could be more than 1 billion deaths in the 21st century.
- ▶ A large proportion of the population in many countries still take up smoking when young and continue their habit into middle and old age. Of all those who die from smoking worldwide, half are in developing countries, but this proportion is likely to increase unless the smoking epidemic can be halted.
- ▶ Passive smoking is also a major avoidable cause of death and disability.
- ▶ Stopping smoking is highly effective, even in older smokers, and generates immediate benefits to health.
- ▶ To avoid a greater public health disaster in the current century, more efforts should be made to prevent non-smokers from starting to smoke and to encourage smokers to quit.

The risks of medicinal nicotine

- ▶ Extensive experience with nicotine replacement therapy (NRT) in clinical trial and observational study settings demonstrates that medicinal nicotine is a very safe drug.
- ▶ Adverse effects are primarily local and specific to the mode of delivery used.
- ▶ NRT does not appear to provoke acute cardiovascular events, even in people with pre-existing cardiovascular disease.
- ▶ There is no direct evidence that NRT therapy is carcinogenic, or influences the risk of other common smoking-related diseases in humans.
- ▶ Evidence on the safety of NRT during pregnancy is limited, but suggests that NRT does not increase the risk of major developmental anomalies or reduce birth weight. However, NRT may increase the risk of minor musculoskeletal anomalies. Further evidence on these effects is needed.
- ▶ Evidence on the safety of long-term use of NRT is lacking, but

there are no grounds to suspect appreciable long-term adverse effects on health.

- ▶ In any circumstance, the use of NRT is many orders of magnitude safer than smoking.

The risks of smokeless tobacco

- ▶ Smokeless tobacco is not a single product, but rather a summary term for a range of different tobacco products which deliver nicotine without combustion.
- ▶ Smokeless tobacco products differ substantially in their risk profile in approximate relation to the content of toxins in the tobacco.
- ▶ In some parts of the world (particularly South Asia), smokeless tobacco is commonly mixed with other products that are themselves harmful.
- ▶ On toxicological and epidemiological grounds, some of the Swedish smokeless (snus) products appear to be associated with the lowest potential for harm to health.
- ▶ Swedish smokeless products appear to increase the risk of pancreatic cancer, and possibly cardiovascular disease, particularly myocardial infarction.
- ▶ Some smokeless tobacco products also increase the risk of oral cancer, but, if true of Swedish smokeless tobacco, the magnitude of this effect is small.
- ▶ All of the above hazards of smokeless tobacco are of a lower magnitude than those associated with cigarette smoking.
- ▶ Smokeless tobacco products have little or no effect on the risk of chronic obstructive pulmonary disease or lung cancer.
- ▶ Therefore, in relation to cigarette smoking, the hazard profile of the lower risk smokeless products is very favourable.
- ▶ Smokeless tobacco use by pregnant women is harmful to the unborn fetus, but the hazard of smokeless use relative to maternal cigarette smoking is not clearly established.
- ▶ In Sweden, the available low-harm smokeless products have been shown to be an acceptable substitute for cigarettes to many smokers, while 'gateway' progression from smokeless to smoking is relatively uncommon.

- ▶ Smokeless tobacco therefore has potential application as a lower hazard alternative to cigarette smoking.
- ▶ The applicability of smokeless tobacco as a substitute for cigarette smoking if made available to populations with no tradition of smokeless use is not known.

Current approaches to nicotine product regulation

- ▶ Nicotine product regulation has developed in a largely reactive and piecemeal fashion over the years.
- ▶ Smoked tobacco products remained free from regulation for many years, and are now subject to minimal controls on content, delivery and safety.
- ▶ Some smokeless tobacco products are regulated strictly (they are prohibited) whilst others are subject to even less regulation than cigarettes.
- ▶ Medicinal nicotine products are regulated strictly, as medicines.
- ▶ The lax regulation of most tobacco products affords considerable market freedom for tobacco companies to innovate and develop their products.
- ▶ The tight regulation of medicinal nicotine imposes very strict restrictions on new product development.
- ▶ Some newly launched tobacco products, including the potential reduced exposure products (PREPs), seem to lie completely outside the current regulations.
- ▶ This clear and unjustifiable regulatory imbalance works against public health.
- ▶ UK government resources dedicated to tobacco product regulation are very small.
- ▶ History demonstrates that regulatory change can achieve substantial changes in consumption of different tobacco products.
- ▶ The regulation of nicotine products needs to be radically overhauled to encourage the use of less harmful products and reduce the use of the more harmful sources of nicotine.
- ▶ Whilst some progress can be made in this regard through the existing regulatory systems, the establishment of a nicotine and tobacco regulatory authority is the preferred way of bringing

comprehensive and rational controls on the nicotine product market that will minimise the harm caused by nicotine use.

Current nicotine product use and socioeconomic deprivation

- ▶ In Western industrial society, and particularly in the UK, cigarette smoking is strongly linked with socioeconomic disadvantage.
- ▶ People in disadvantaged socioeconomic groups are more likely to smoke, to smoke heavily and to be more heavily addicted to smoking.
- ▶ This is also true of other disadvantaged groups, such as people with mental health problems and people in prison.
- ▶ Smokers in disadvantaged socioeconomic groups are just as likely to want to quit smoking, and more likely to use smoking cessation services, than relatively advantaged smokers.
- ▶ Smokers in disadvantaged socioeconomic groups are much less likely to succeed in quitting smoking.
- ▶ As a result, and in contrast to more advantaged groups, smoking prevalence has changed very little in recent years among the most disadvantaged in society.
- ▶ Smoking therefore causes even more death and disability in disadvantaged groups than in the rest of society, and is indeed the biggest cause of social inequalities in health.
- ▶ Children growing up in disadvantaged households are more likely to be exposed to cigarette smoke in the home, and are more likely to start smoking and to start when especially young.
- ▶ Disadvantaged smokers, and their children, have the most to gain from harm reduction strategies for tobacco use.

Ethics, human rights and harm reduction

- ▶ Although stopping tobacco use is the ideal outcome for individual and public health, this is often difficult to achieve. Making a wider range of safer products available would be a harm reduction approach to tobacco control.
- ▶ Harm reduction approaches in public health are sometimes criticised for condoning the activity they are trying to make safer.

The Royal College of Physicians takes no position on the morality of smoking. However, since smoking is dangerous to health and is hard to give up, the College wants to see a range of effective methods to help smokers quit or to reduce the harm they sustain.

- ▶ The present status quo, in which cigarettes are freely available, medicinal nicotine products are available but under regulations that restrict availability and effectiveness, and some smokeless tobacco products are prohibited, denies smokers the right to choose safer nicotine products.
- ▶ Balancing the nicotine market, so that all nicotine products are equally available and comparably priced, would provide smokers with choice but would not encourage change from high-risk to lower-risk products.
- ▶ Rebalancing the market in favour of the safest nicotine products would provide choice, encourage safer nicotine use, and reduce morbidity and mortality.
- ▶ The ethical aspects of regulating alternatives to smoking tobacco are complex, and three positions can be defended: maintaining the status quo; making alternatives to smoking tobacco as easily available as smoking tobacco now is; and making alternatives more easily available than smoking tobacco now is.
- ▶ Each approach represents a balance of consumer rights, consumer protection, fairness and general policy considerations.
- ▶ The College favours an approach which would make smoking easier to give up, while discouraging starting smoking in the first place, through making alternatives to smoking tobacco more widely available and through regulating smoking products more tightly by pricing, marketing controls, and formal regulation of the production and sale of tobacco products.

Implications for health policy and nicotine product regulation

- ▶ Most of the deaths and disease caused by smoking in the near- and medium-term future will occur in people who are smoking now.
- ▶ Current conventional preventive measures focus entirely on preventing uptake of smoking and helping smokers to quit smoking.

- ▶ This approach will be ineffective for the millions of smokers who, despite best efforts to persuade and help them to quit, will carry on smoking. Half of these smokers, representing millions in the UK alone, will die as a result.
- ▶ This burden of mortality and morbidity will markedly exacerbate social inequality in health.
- ▶ Tobacco control policy needs to be radically extended to address the needs of these smokers with implementation of effective harm reduction strategies.
- ▶ Harm reduction in smoking can be achieved by providing smokers with safer sources of nicotine that are acceptable and effective cigarette substitutes.
- ▶ There is a moral and ethical duty to provide these products to addicted smokers.
- ▶ Current systems of regulation of nicotine products inhibit the development of innovative medicinal nicotine substitutes for cigarettes and perpetuate the use of the most dangerous nicotine products. This is unjust, irrational and immoral.
- ▶ Nicotine product regulation must therefore be reformed.
- ▶ The unprecedented and unjustifiable market freedoms enjoyed by manufacturers of cigarettes and other smoked tobacco products must end.
- ▶ The development of new, more effective, more acceptable and user-friendly medicinal nicotine substitutes for smoking needs to be encouraged.
- ▶ A major step towards an effective harm reduction strategy could be taken by the implementation of simple changes to the regulation, promotion and taxation of medicinal nicotine.
- ▶ Low nitrosamine smokeless tobacco products may have a positive role to play in a coordinated and regulated harm reduction strategy which maximises public health benefit and protects against commercial market exploitation.
- ▶ The regulation of nicotine products, whether medicinal or tobacco-based, thus needs radical reform to ensure that the market forces of affordability, promotion and availability act in a strong and directly inverse relation to the hazard of the nicotine product, and that the marketing and use of nicotine products are carefully monitored to maximise public health benefit.

- ▶ While it may be possible to achieve this reform and consistency by more rational application of existing regulatory frameworks, our conclusion is that the scale of the problem, and the difficulties of achieving successful reform, are such that the problem will be best addressed by the creation of a nicotine regulatory authority to take control of all aspects of regulation of all nicotine products.

Ingredients and Emissions

Clearing the smoke, US Institute of Medicine, 2001

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For copyright reasons (see below) we are unable to provide the full reference.

However, we have attached a copy of the summary of the report (available at <https://www.iom.edu/~media/Files/Report%20Files/2003/Clearing-the-Smoke-The-Science-Base-for-Tobacco-Harm-Reduction/tobacco8pgfinal2.PDF>)

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Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction

Kathleen Stratton, Padma Shetty, Robert Wallace, and Stuart Bondurant, Editors, Committee to Assess the Science Base for Tobacco Harm Reduction, Board on Health Promotion and Disease Prevention

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INSTITUTE OF MEDICINE

Shaping the Future for Health

CLEARING THE SMOKE:

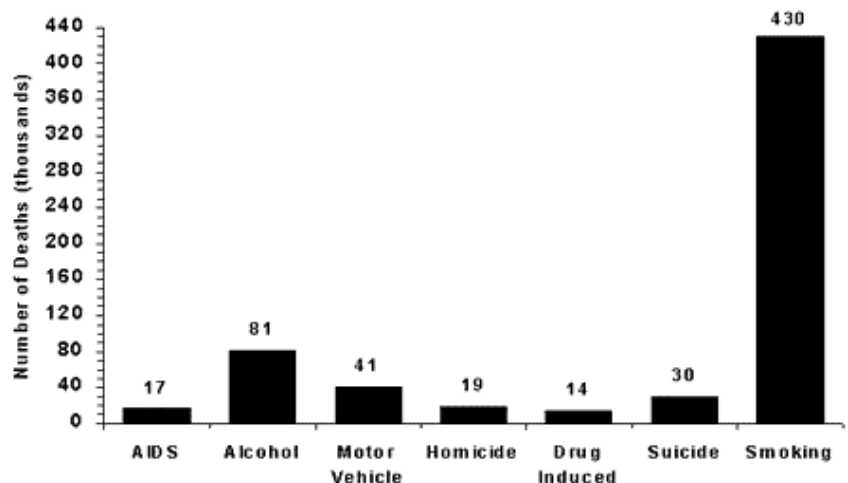
ASSESSING THE SCIENCE BASE FOR TOBACCO HARM REDUCTION

Tobacco use, especially cigarette smoking, is the single largest environmental cause of death and disease in the United States. Claiming more than 400,000 lives annually, smoking kills more people than do AIDS, alcohol, cocaine, heroin, homicide, suicide, motor vehicle crashes, and fires combined. The primary causes of death from tobacco each year are cardiovascular disease (approximately 180,000 deaths), cancer (approximately 150,000 deaths), and respiratory disease (approximately 85,000 deaths). The average reduction in life expectancy for smokers is 6.6 years.

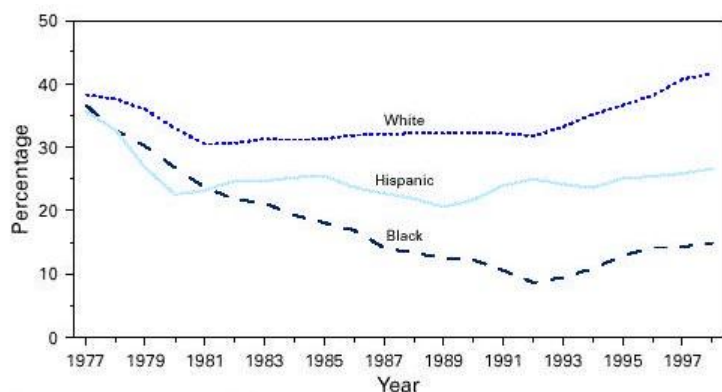
Even nonsmokers are threatened, facing exposure to the “environmental tobacco smoke” produced by smokers, as well as to other hazardous situations, especially fires, that arise from smoking. For example, approximately 30,000 nonsmokers die each year from cardiovascular disease caused by the inhalation of second-hand smoke. Also, the maternal and paternal smoker places the fetus and infant at risk for numerous growth and developmental impairments.

The dangers of smoking have been known for decades. Among the major early warnings, the first U.S. Surgeon General’s report on smoking and health, issued in 1964, concluded that “the use of tobacco, especially cigarette smoking, has been causally linked to several diseases,” including lung cancer, coronary artery disease, chronic bronchitis, and emphysema.

Yet today, roughly 48 million adults—nearly one-quarter of the adult population—smoke cigarettes. Although this rate is far lower than the 42 percent recorded in 1965, the decline in smoking among adults appears to have leveled off during much of the past decade. Many adolescents also are smoking regularly or are experimenting with tobacco use. In a recent survey, nearly 13 percent of middle-school students and 35 percent of high-school students reported smoking during the preceding month—a troubling



Comparative causes of annual deaths in the United States. SOURCE: CDC.



Trends in cigarette smoking* among 12th graders, by racial/ethnic group—United States, 1977–1998.[†]

*Smoking on 1 of the 30 days before the survey. [†]2-year moving averages are used to stabilize estimates.

SOURCE: CDC/University of Michigan, Monitoring the Future Project.

Thus, while 70 percent of smokers say they want to quit, and 34 percent of smokers attempt to quit each year, only 10 percent of those who try to quit actually break their addiction and remain tobacco-free for a year.

Numerous products that make explicit or implied claims to lower the health risks of cigarettes and other forms of tobacco have been introduced into the U.S. marketplace—and there is a strong likelihood of more products and increased marketing in the near future.

finding given that the vast majority of adult smokers begin during their youth.

A Role for Harm Reduction

Without doubt, the best way for people to avoid the health risks of smoking is to never begin smoking, and the best way for those who already smoke to minimize their health risks is to quit promptly. Even after years of smoking, quitting reduces risk both immediately and in the long-term for many tobacco-related conditions. Several types of smoking cessation programs, some aimed at individuals and some at communities, have been shown to

be modestly effective. For many smokers, however, quitting proves difficult. The simple fact is tobacco contains nicotine, which is both pleasurable to the user and highly addictive. Thus, while 70 percent of smokers say they want to quit, and 34 percent of smokers attempt to quit each year, only 10 percent of those who try to quit actually break their addiction and remain tobacco-free for a year.

Because many people cannot or will not stop using tobacco, and because many adolescents will continue to experiment with things “taboo,” there almost certainly will remain a significant population whose health is at risk from smoking. Indeed, it has been predicted that even with the most intensive application of the most effective programs for abstinence and cessation, at least 10 percent to 15 percent of adults in the United States would continue to smoke.

The huge personal and public toll of smoking has prompted the search for means to reduce the harm associated with tobacco use for those individuals who continue to smoke. Numerous products that make explicit or implied claims to lower the health risks of cigarettes and other forms of tobacco have been introduced into the U.S. marketplace—and there is a strong likelihood of more products and increased marketing in the near future.

In light of such developments, the U.S. Food and Drug Administration asked the Institute of Medicine, an arm of the National Academy of Sciences, to convene a committee of experts to lay out the scientific methods and standards by which these products and their effect on public health could be assessed. The committee issued its report, called *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*, in February 2001.

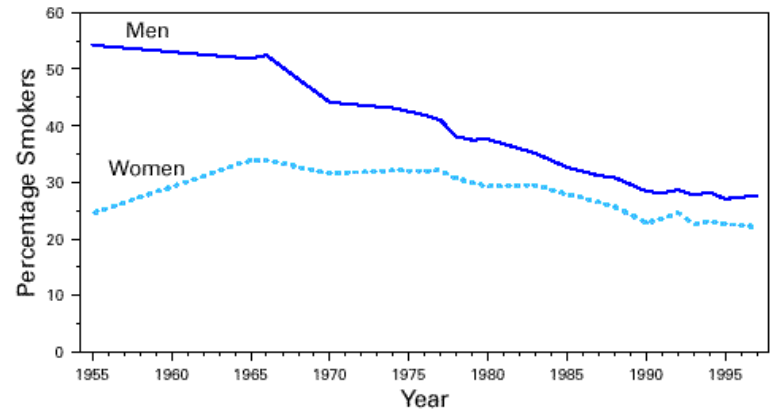
Products Aimed at Risk Reduction

The committee focused on two types of products, both of which are intended to reduce tobacco-related exposure and potentially reduce the risk of disease compared to conventional tobacco products.

The first type includes tobacco and cigarette-like products that result in potentially decreased emission of some toxicants. Some of these products are made with different types of tobacco or additives, or they are made using different methods of curing, blending, or processing the tobacco. Others use modified delivery systems that change the composition of the smoke that the user inhales by such means as reducing the burning temperature of the tobacco, diluting the smoke with air, or adding special “carriers” for smoke particles.

The second type includes several pharmaceutical agents, some of which are currently approved for short-term use in smoking cessation. These products might be used long-term to maintain cessation or concomitantly with continued but decreased consumption of cigarettes or other conventional forms of tobacco. Many of these products contain nicotine incorporated into patches, gums, oral inhalers, and nasal sprays. Others contain particular antidepressants that reduce the craving for tobacco.

Although both types of products could potentially result in *reduced exposure* to toxicants from a given instance of tobacco use, such reduced exposure does not necessarily assure *reduced risk* to the individual user or *reduced harm* to the larger population. At the population level, for example, the potential benefits might be reduced if some people, perceiving these products to be safer, begin using tobacco who otherwise would not have done so, if some smokers who might have quit do not, or if some former smokers resume smoking. Therefore, and in order to avoid any misinterpretation, the committee chose to use the generic term “potential reduced-exposure products,” or PREPs, to describe these products. Despite any potential harm reduction that PREPs may offer, the use of tobacco in any form poses greater risk than having no exposure to tobacco at all.



Trends in cigarette smoking* among persons aged ≥ 18 years, by sex—United States, 1955–1997.

SOURCE: CDC/1955 Current Population Survey; 1965–1997 National Health Review Survey.

At the population level, for example, the potential benefits might be reduced if some people, perceiving these products to be safer, begin using tobacco who otherwise would not have done so, if some smokers who might have quit do not, or if some former smokers resume smoking.

What We Know

In considering these products, the committee examined four basic questions: (1) Does use of a product decrease exposure to the harmful substances in tobacco? (2) Is this decreased exposure associated with decreased harm to health? (3) Since actual health effects associated with these products might not appear for many years, are there surrogate indicators of their effects that could be measured in a time frame sufficient for product evaluation? (4) What are the public health implications of tobacco harm-reduction products? Where answers could not be determined, the committee was asked to propose a broad strategy by which the knowledge base should be assembled.

The committee reached the following principal conclusions regarding these questions:

- There are sufficient data to suggest that, for many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is biologically and clinically feasible.
- No PREPs have yet been evaluated comprehensively enough (including for a sufficient time) to provide evidence for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use. Such impact likely will not be directly or conclusively demonstrated for many years.
- Surrogate measures of tobacco-related diseases exist that could be used to give guidance or to help predict whether or not PREPs are likely to be risk-reducing. Available candidate surrogate measures must be further validated and more must be developed in order to be useful for PREP evaluation and regulation.
- PREPs exist that have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products.
- Regulation of all tobacco products (as recommended in the 1994 IOM report *Growing up Tobacco Free: Preventing Nicotine Addiction in Children and Youths*), including all PREPs, is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected. Regulation could assure that adequate research, on everything from smoke chemistry and toxicology to long-term epidemiology, is conducted and that the public receives reliable information as to the risks and benefits of PREPs.
- The public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative.

A Comprehensive Approach to Tobacco Harm Reduction

...tobacco harm reductions efforts... necessarily rely on public health tools such as research, surveillance, and regulation aimed at improving education and communication directed to the consumer.

Following on these general conclusions, tobacco harm reduction efforts, if conducted properly, could lead to reduced tobacco-related morbidity and mortality for those people who cannot or will not give up tobacco. Such an effort necessarily relies on public health tools such as research, surveillance, and regulation aimed at improving education and communication directed to the consumer.

Research

In order to strengthen the evidence base for harm reduction, the committee presented a more specific research agenda for assessing harm-reduction products. The plan identified five general scientific areas that should be explored:

1. *Description of the dose-response relationship between tobacco smoke and/or constituent exposure and health outcomes.* There are more than 4,000 different chemicals in tobacco smoke, many of them toxic. For the most part, the data are insufficient to accurately describe the relationship of tobacco use and disease formation at the level of detail that would establish all casual agents or the exact dose-response relationship. Consequently, the confidence with which the potential benefits or risks of PREPs can be extrapolated, especially at low doses,

is uncertain.

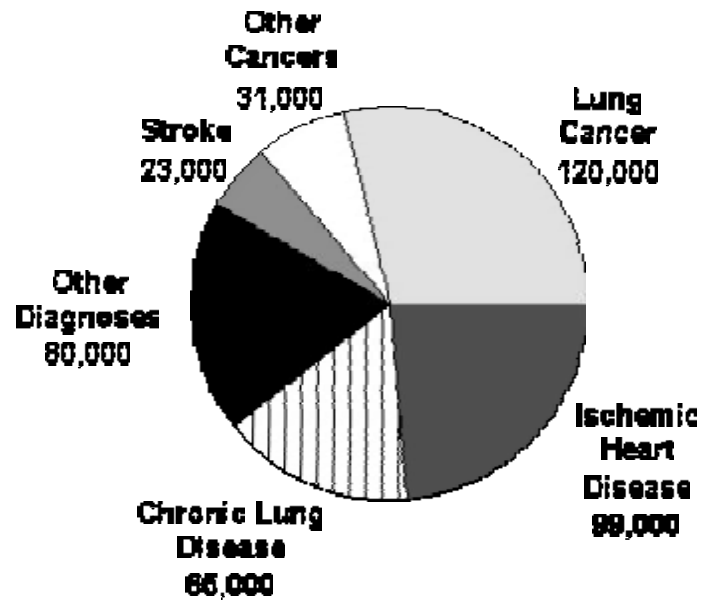
2. *Identification and development of surrogate markers for disease.* Possible markers include, for example, measures of inflammation and vascular activation, which may be related to measures of cardiovascular physiology and, ultimately, reflect the risk of clinical cardiovascular disease or lung disease. Biomarkers of genetic damage in blood, sputum, urine, and internal organs may indicate early carcinogenic processes and risk of cancer development. Ideally, a set of behavioral markers also might be developed to monitor such things as the substitution of PREPs for smoking cessation or the increase in initiation due to the availability of PREPs.

3. *Preclinical research.* Animal models and in vitro testing can contribute to the design and evaluation of PREPs. In particular, the new technologies of genomics and proteomics have great potential for evaluating and comparing the effects of tobacco exposure and use of PREPs on gene translation and expression in cancerous and noncancerous diseases.

4. *Short-term clinical and epidemiological studies.* Some effects of PREPs could be detected by epidemiological studies, by measurement of intermediate disease markers, or by clinical studies of smokers who are unwilling or unable to quit but are willing to use PREPs compared to a control group of users of conventional tobacco products. Validated biomarkers of disease, when available, should be developed in these studies in order to assess potential risk reduction within a practical time-frame. Human studies also are required for evaluating the relationship of such various factors as individual smoking history, environment, gender, race, and diet to disease risk and likelihood of harm reduction.

5. *The role of long-term epidemiological studies and surveillance.* Most tobacco-related diseases develop clinically over several years. Thus, the only direct and definitive way to assess the value of PREPs is to monitor the health outcomes of users compared to control groups over an extended period.

To help in organizing the scientific base for evaluation of PREPs, the committee made use of a risk assessment framework similar to that used to gauge the health risks for other environmental and occupational exposures. In particular, the committee turned to a 1983 National Research Council report called *Risk Assessment in the Federal Government*. Known as “The Red Book,” the report outlined several basic steps in risk assessment. These steps include hazard identification (Does the toxicant cause the adverse effect?), dose-response assessment (What is the relationship between toxicant dose and disease incidence in humans?), exposure assessment (What exposures are currently experienced or anticipated under different circumstances?), and risk characterization (What is the estimated incidence of the adverse effect in a given population?). The process also must take into account public health, social, economic, and political considerations.



Deaths attributable to Cigarette Smoking—United States, 1990.
SOURCE: CDC SAMMEC, MMWR 1993; 42:645–9.

Only a comprehensive program of surveillance and regulation focused to assure the public is accurately informed about the health effects of the new products and to assess the relative toxicity of all products offers a reasonable possibility of achieving a net gain in health from use of PREPs.

While fully addressing research needs will take years of concerted effort, immediate actions also are required to successfully achieve a goal of harm reduction. Today, there is little public authority over tobacco products of any type. Thus, the committee concluded that in order to obtain the best available scientific evaluation of current and emerging PREPs, and to provide the best advice on these products to the public, some national authority over PREPs is needed. Only a comprehensive program of surveillance and regulation focused to assure the public is accurately informed about the health effects of the new products and to assess the relative toxicity of all products offers a reasonable possibility of achieving a net gain in health from use of PREPs.

Surveillance

Toward this end, the committee recommended development of a national surveillance system to assess the relative contribution of PREPs to the health of the public. This system would collect information on a range of elements necessary to understand the population impact of tobacco products and PREPs, including consumer attitudes and beliefs, product characteristics and usage patterns, marketing messages, rates of people who start or quit using tobacco products, and the prevalence of major smoking-related diseases, population level biomarkers indicating actual degree of tobacco or tobacco smoke exposure, among other information. The tobacco industry would be required to provide data on the constituents of tobacco products as well as on product distribution and sales.

Implementation

In order to best implement the scientific and policy recommendations made, the committee further recommended development of a national regulatory system for all modified tobacco products with risk-reduction or exposure-reduction claims, explicit or implicit, and for any other products offered to the public to promote reduction or cessation of tobacco use. For this purpose, the regulatory framework outlined is narrow and focused exclusively on evidence supporting claims and any necessary powers required to assess PREPs, pharmaceutical or tobacco-related. This network would build on the foundation of existing food and drug laws, with adaptations to take into account the unique history and toxicity of tobacco products.

In sum, the committee determined that it is both feasible and desirable to implement a comprehensive, scientifically based program that promotes and assesses the use of PREPs. Such a system must be carefully implemented and must incorporate the following features:

- Manufacturers have incentive to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease.
- Consumers are accurately informed of all of the known, unknown, likely, and potential consequences of using these products.

- Promotion, advertising, and labeling of these products are firmly regulated to prevent false or misleading claims.
- Health effects of using PREPs are monitored on a continuing basis.
- Basic, clinical, and epidemiological research is conducted to establish the potential use of PREPs for reducing risks for disease in individuals and for reducing harm to the population as a whole.
- Harm reduction is implemented as a component of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

As outlined here, a comprehensive approach that utilizes scientific research, surveillance, and regulatory tools is necessary for the realization of the potential individual and societal benefits of tobacco harm reduction.

As outlined here, a comprehensive approach that utilizes scientific research, surveillance, and regulatory tools is necessary for the realization of the potential individual and societal benefits of tobacco harm reduction.



For More Information . . .

Copies of *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction* are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at www.nap.edu. The full text of the report is available on line at <http://books.nap.edu/catalog/10030.html>

Support for this project was provided by the Food and Drug Administration prior to the March 2000 decision by the Supreme Court denying the FDA comprehensive authority over tobacco products. The views presented in this report are those of the Institute of Medicine Committee to Assess the Science Base for Tobacco Harm Reduction and are not necessarily those of the funding agencies.

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