GENERAL REMARKS

Future worldwide health effects of current smoking patterns

As a cause of human cancer, tobacco smoke is uniquely important. In some populations it has, in recent decades, caused about half of all cancer deaths in men, plus a smaller, but increasing proportion of cancer deaths in women. Worldwide, it causes more cancer deaths than can be attributed to all other known causes of the disease and, in addition, it causes even more deaths from vascular and respiratory diseases than from cancer (US DHHS, 1989; Peto *et al*., 1994; Parkin *et al.*, 2000).

The fact that prolonged cigarette smoking is a cause — and the major cause — of lung cancer was reliably established during the 1950s, as was the fact that it can also cause several other types of cancer and various other diseases (for a historical review, see Doll, 1998). In the previous IARC *Monograph* on tobacco smoking (IARC, 1986), it was concluded that there was *sufficient evidence* that the habit could cause not only lung cancer, but also cancers of the upper aerodigestive tract, pancreas and lower urinary tract. Section 2 of the present monograph on tobacco smoke reviews and confirms these qualitative conclusions about particular types of cancer. It also reviews epidemiological studies on other types of cancer, which provide good evidence for some cancers (e.g. of the breast, endometrium and prostate) that smoking is of little or no causal relevance. Findings for other cancers (of the stomach, liver and cervix, renal-cell carcinoma and myeloid leukaemia) provide *sufficient evidence* that they can be caused by smoking, i.e. that smoking can increase their age-specific incidence rates. Other sections review the changing patterns of exposure, and the experimental evidence that tobacco smoke contains many chemicals that can, under certain circumstances, induce DNA damage or cancer in experimental animals. These qualitative conclusions about the many different chemicals in smoke and the many different types of cancer caused in humans do not, however, adequately reflect the real magnitude of the overall effects of smoking on mortality. This general introduction therefore summarizes the net effects of smoking on mortality from all cancers and overall mortality (for individuals and for populations), and indicates the extent to which individuals or populations who have already smoked for some years or decades can still limit these risks by cessation of the habit. Smoking lowers the risk for a few diseases and for one cancer (endometrial carcinoma), but this reduced risk is inconsequential, when compared with the net detriment of smoking to health.

Persistent cigarette smoking throughout adult life

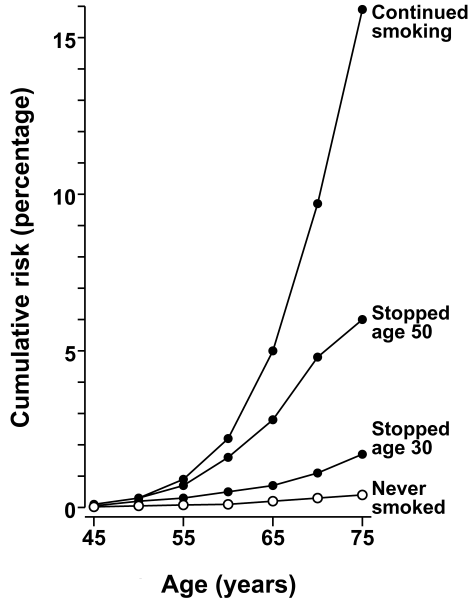
Two observations are of particular relevance to assessing the current and future hazards of smoking. First, cigarettes, as commonly smoked during the twentieth century, have proved to be substantially more hazardous than other forms of tobacco that were commonly smoked in the nineteenth century. Second, the earlier in life that cigarette smoking is fully established, the greater are the hazards among persistent smokers in middle and old age. These differences in hazard can be substantial: for example, a difference of only a few years in the age at which smoking was established may lead to an approximately twofold difference in hazard many years later (Doll & Peto, 1981). Thus, national rates for lung cancer in people of around 70 years of age depend strongly on the intensity of pulmonary exposure to cigarette smoke half a century ago, when they were about 20 years of age. Retrospective assessment of smoking behaviour in previous decades, however, is subject to error; this limits the ability of epidemiological data to identify the ensuing consequences of earlier smoking. Current disease rates also depend strongly on current smoking patterns; even after a few decades of smoking, people who stop smoking before they develop lung cancer (or some other serious disease) decrease their risk of death from the habit: see Figure 1.

This dependence of current disease rates (not only on current smoking patterns but also on cigarette smoking patterns many decades earlier) implies a delay of about half a century between an upsurge in cigarette use by young adults in a particular population and the main upsurge in cases of lung cancer, and of some of the other smoking-related diseases, that eventually results. In contrast with this extremely long delay between increases in smoking and increases in risk, population-wide decreases in tobacco smoking can produce substantial benefits within just one or two decades.

Emerging hazards

Tobacco has been used for many centuries, originally in America, then in the sixteenth and seventeenth centuries in Europe, and subsequently throughout the world. The reasons for its widespread use are still imperfectly understood, but there are both psychosocial and pharmacological factors involved. Nicotine is addictive for many smokers, but other components of the smoke from tobacco, or from flavourants or other chemicals added to tobacco, may also be important. At first tobacco was smoked in pipes or as cigars: later, ‘bidis’, consisting of a small amount of tobacco wrapped in the leaf of another plant, began to be smoked in South Asia. Cigarettes, which would eventually cause much greater harm than did pipe or cigar smoking in the nineteenth century, only began to be manufactured in the second half of the nineteenth century; even in the early years of the twentieth century, cigarette consumption still remained low. Thereafter, however, cigarette consumption by men increased rapidly in the United Kingdom, the USA and several other industrialized countries, followed (decades later) by increased cigarette consumption by women in developed countries and also by men in developing countries.

Figure 1. Cumulative risk (%) of death from lung cancer (in the absence of other causes of death) in men at ages 45–75 years: in continuing cigarette smokers, ex-cigarette smokers who stopped at age 50 or at age 30 and lifelong nonsmokers, based on lung cancer death rates for men in the United Kingdom in 1990



From Peto *et al.* (2000)

[a] Nonsmoker risks are taken from a US prospective study of mortality

(For example, although the main increase in cigarette consumption by men was eventually about as great in China as in the United Kingdom or the USA, it took place about 50 years later, i.e. in the last quarter of the twentieth century, and its full effects on the mortality rates for Chinese men may take several more decades to emerge.) At present, cigarette consumption by women in developing countries is still relatively low.

In some countries, the spread of cigarette smoking during the twentieth century was driven or maintained by extensive advertising and promotion by tobacco companies. More recently, substantial efforts have been made in some countries to discourage smoking, and over the past few decades, cigarette consumption has been halved in a few countries such as the USA and the United Kingdom. Worldwide, however, about a thousand million men and a quarter of a thousand million women now smoke, consuming 5.5 million million cigarettes a year (plus many other tobacco products), and about 30 million young adults take up the habit each year (see Section 1). The emergence of increasingly large multinational tobacco companies with global reach could result in even more tobacco use in the future.

Because the main hazards of cigarette smoking in middle age (35–69 years) take several decades to become substantial, it was not until the 1950s (several decades after cigarette smoking became widespread) that clear medical evidence emerged, particularly from the USA and the United Kingdom, that smoking was a major cause of many fatal diseases, and was responsible for almost half of all male mortality in middle age. The main hazards in old age (≥ 70 years) take even longer — at least half a century — to become substantial, so only in recent decades has it become apparent that, for men in developed countries, about half of all persistent cigarette smokers would eventually be killed by the habit (a quarter in middle age plus a quarter in old age) (Doll *et al*., 1994). In addition, during the past quarter of a century, it has become increasingly clear that, although the main hazard is to the individual who smokes, there is some cancer hazard to nonsmokers (including former smokers) from exposure to secondhand tobacco smoke (see monograph on involuntary smoking, this volume).

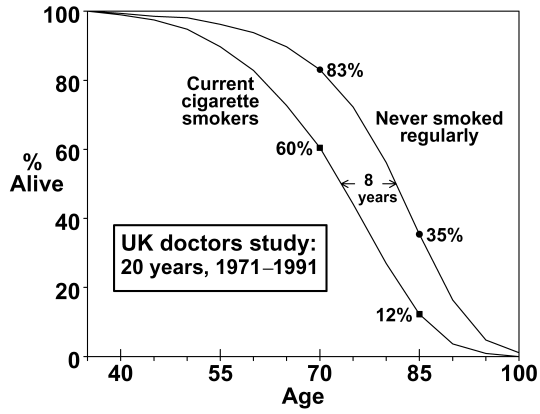
Figure 2 illustrates the effects of persistent cigarette smoking on mortality throughout adult life in male doctors in the United Kingdom: the difference in survival at age 70 years (i.e. 83% among nonsmokers versus 60% among smokers) reflects the fact that about one-quarter of the smokers had been killed by tobacco in middle age (35–69 years). Moreover, of those still alive at age 70 years, two-fifths of the nonsmokers and one-fifth of the smokers were still alive at 85 years of age. Among male doctors in the United Kingdom, many of those who had smoked substantial numbers of cigarettes for a long time gave up the habit permanently when clear evidence of its hazards emerged, and the extent to which cessation, even in middle age, eventually avoided hazard is illustrated in Figure 3.

Trends in tobacco-attributed mortality in the United Kingdom and the USA, 1950–99

Cigarette smoking first became widespread among both men and women in the United Kingdom and the USA, and large epidemiological studies by the American Cancer Society yield indirect estimates of the overall cancer mortality attributed (and, by subtraction, that not attributed) to smoking over the past half century (1950–99) in those two countries (Figures 4 and 5). In the 1960s, men in the United Kingdom were probably the worst-affected major population in the world, but in recent decades male mortality from tobacco has declined substantially in the United Kingdom (Figure 4). In the USA, however, the mortality rate among men is only just beginning to decline substantially, whereas that among women in the USA has increased. In 1990, 34% of all cancer deaths in the USA were attributed to smoking (90% of the lung cancer deaths and 13% of the deaths from other, or unspecified, types of cancer; Table 1). Of the cancer deaths in the USA in 1990 that were attributed to smoking, three-quarters involved lung cancer (72% specified as such, plus one-third of the few deaths from cancer of an unspecified site). In people aged 35–69 years, the proportion of all cancer deaths in the USA in 1990 that were attributed to smoking was 40% (52% male, 27% female); at older ages, it was 31%. Relatively few deaths from cancer occur at younger ages. The rise in tobacco-attributed cancer

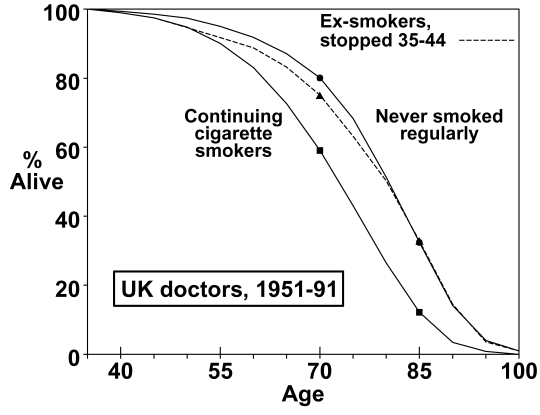
mortality in the USA during the second half of the twentieth century, first among men and then among women, is chiefly the inevitable but delayed effect of the rise in cigarette consumption during the first half of the twentieth century.

Figure 2. Effects of persistent cigarette smoking on the probability of surviving from 35 years to various ages



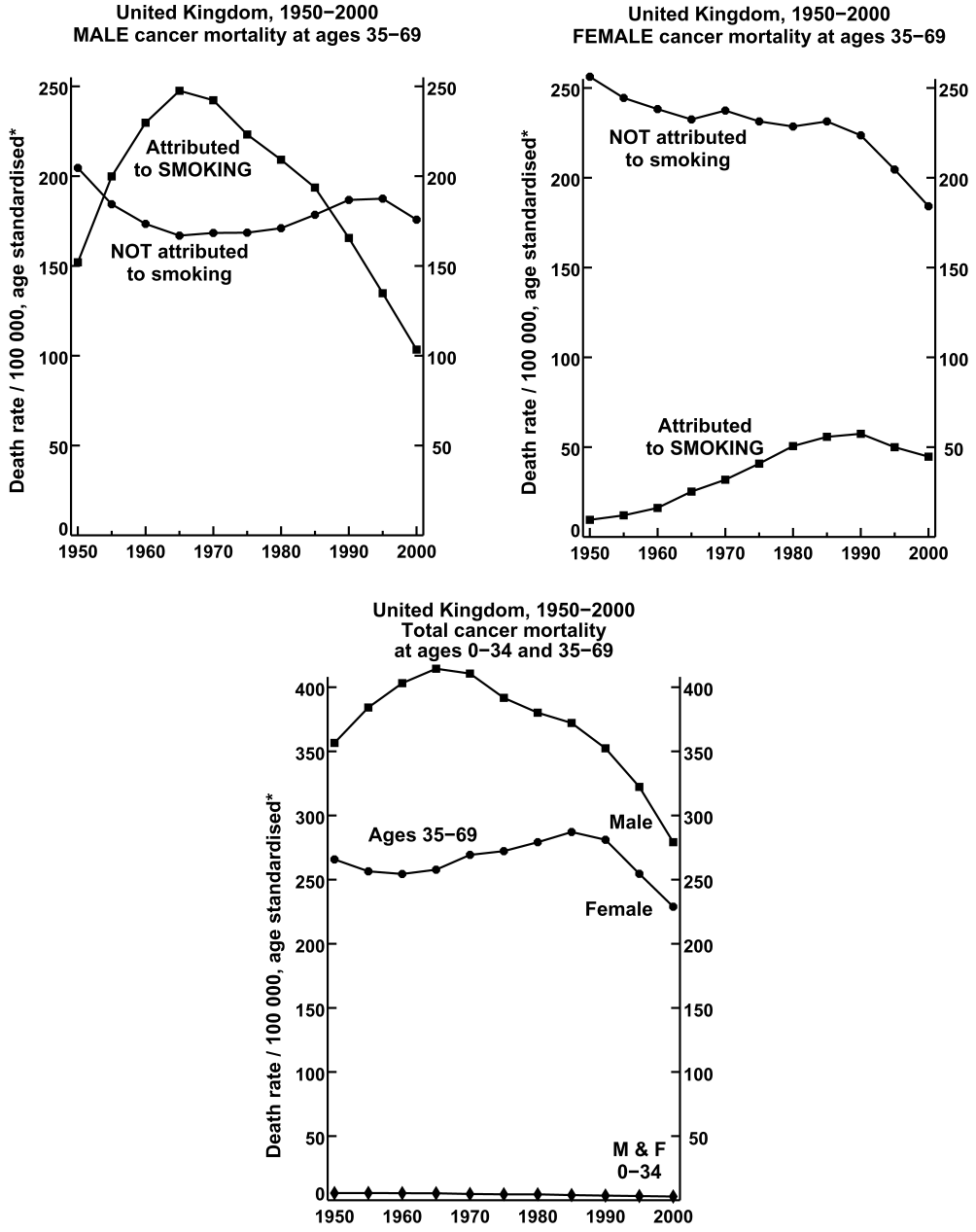
From Doll *et al.* (1994)

Figure 3. Effects of smoking cessation at ages 35–44 (broken line) on survival from age 35



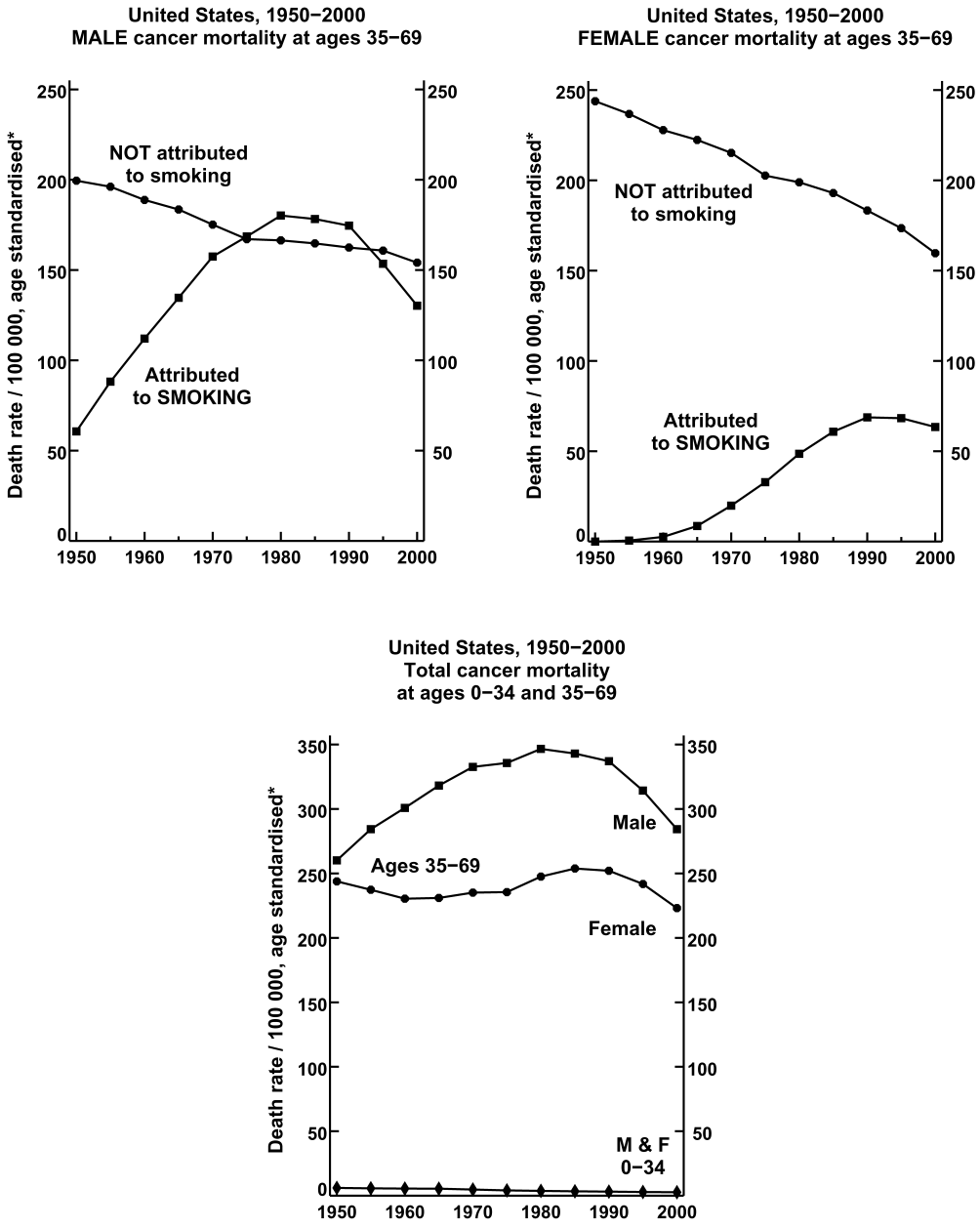
From Doll *et al.* (1994)
Even in middle age, those who stop before they have incurable cancer, or some other serious disease, avoid most of their subsequent risk of death from tobacco; stopping earlier is even more effective.

Figure 4. Cancer mortality rates in the United Kingdom, 1950–2000, subdivided into the parts attributed, and not attributed to smoking



From Peto *et al.* (1994)
*Mean of annual rates per 100 000 in component 5-year age groups

Figure 5. Cancer mortality rates in the USA, 1950–2000, subdivided into the parts attributed, and not attributed to smoking



From Peto *et al.* (1994)
*Mean of annual rates per 100 000 in component 5-year age groups

Table 1. Deaths in the USA based on the Cancer Prevention Study II in 1990 attributed to smoking/total number of deaths (thousands)

		0–34	35–69	≥ 70	All ages
Lung cancer	Male	–	45/48	39/43	84/91
	Female	–	22/26	20/24	43/50
	Both	–	68/75 (91%)	59/66 (89%)	127/141 (90%)
All cancers	Male	–/5	64/123	56/140	120/268
	Female	–/4	28/104	26/129	54/237
	Both	–/9	92/228 (40%)	83/269 (31%)	174/505 (34%)
All causes	Male	–/103	150/415	136/595	286/1113
	Female	–/48	73/257	102/730	175/1035
	Both	–/151	223/672 (33%)	238/1325 (18%)	461/2148 (21%)

From Peto *et al*. (1994)
–, not available

Table 1 also indicates that tobacco smoking caused substantially more deaths from vascular, respiratory and other non-neoplastic causes than from cancer. The proportion of all deaths in the USA (neoplastic, vascular, respiratory or other causes) at ages 35–69 years that were attributed to tobacco was 33% in 1990, compared with only 12% in 1950.

Trends in tobacco-attributed mortality in developed and developing countries

In the aggregate of all developed countries, the epidemic of death from tobacco of men in middle age may have reached its peak by about 1990, and was by then almost as great as that in the USA (Table 2). In 1990, the epidemic in women, however, although still increasing, was less than half as great in the aggregate of all developed countries as it was in the USA. If current smoking patterns persist, the main increases in tobacco deaths over the next few decades are likely to be among women in developed countries and, in particular, among men in developing countries. In some of the developing countries, the populations are large and cigarette consumption by men in these countries has increased substantially in recent decades (Table 3).

Worldwide, the only major causes of mortality that are currently increasing rapidly are HIV, tobacco and, probably, obesity (Doll *et al*., 1994; Peto *et al*., 1994; Ad Hoc Committee on Health Research, 1996; Murray & Lopez, 1996; WHO, 1997; Peto *et al*., 1999). If current smoking patterns persist, there will be about one thousand million deaths from tobacco during the twenty-first century, as against ‘only’ about 0.1 thousand million

Table 2. All developed countries: deaths based on the Cancer Prevention Study II in 1990 attributed to smoking/total number of deaths (thousands)

		0–34	35–69	≥ 70	All ages
Lung cancer	Male	–/1	231/246	141/156	372/402
	Female	–/1	44/64	42/61	86/125
	Both	–/2	275/310 (89%)	183/217 (84%)	458/529 (87%)
All cancers	Male	–/27	360/736	212/600	572/1362
	Female	–/23	56/500	56/564	112/1087
	Both	–/50	416/1236 (34%)	268/1164 (23%)	684/2449 (28%)
All causes	Male	–/504	865/2458	554/2851	1419/5813
	Female	–/244	160/1376	236/3998	396/5618
	Both	–/748	1025/3834 (27%)	790/6849 (12%)	1815/11431 (16%)

From Peto *et al*. (1994)
–, not available

(100 million) during the whole of the twentieth century (Table 4). About half of these deaths will be of people in middle age (35–69 years) rather than old age — and those killed by tobacco in middle age lose, on average, more than 20 years of life expectancy when compared with nonsmokers.

There are two main reasons for expecting this large increase in tobacco deaths. First, the population of middle-aged and old people worldwide is expected to increase. Second, the proportion of deaths in middle and old age that are caused by tobacco is expected to increase over the next few decades as a result of the delayed effects of the large increase in cigarette smoking among young adults over the past few decades (Doll *et al*., 1994; Peto *et al*., 1994; Ad Hoc Committee on Health Research, 1996; Murray & Lopez, 1996; WHO, 1997; Peto *et al*., 1999). Among persistent cigarette smokers, the risk of death from tobacco-related diseases in middle or old age is particularly great (about 1 in 2) only for those who start smoking in early adult life (Doll & Peto, 1981; Peto, 1986; Doll *et al*., 1994; Peto *et al*., 1994). Hence, the numbers of deaths from tobacco around the year 2000 were strongly influenced by the numbers of young adults who took up smoking around 1950, whereas the numbers of young adults who took up smoking around the year 2000 will strongly influence the numbers of deaths from tobacco around and beyond the year 2050.

In China, which is the largest and best studied of the developing countries (Liu *et al*., 1998; Niu *et al*., 1998; Peto *et al*., 1999), the increase in cigarette consumption by men and the increase in tobacco-related deaths both lag almost exactly 40 years behind the

Table 3. Forty-year delay between cigarette smoking and mortality from tobacco-related diseases in US adults and Chinese men

Cigarettes per day, by year			
US adults		Chinese men	
1910	1	1952	1
1930	4	1972	4
1950	10	1992	10
Proportion of overall mortality at ages 35–69 years attributed to tobacco			
US adults		Chinese men	
1950	12%	1990	12%
1990	33%	2030	33%[a]

From Peto *et al*. (1999)

[a] Projection if current smoking patterns persist, i.e. two-thirds of the young men in mainland China start smoking cigarettes, and few give up the habit. In Hong Kong, where cigarette consumption by men reached its peak in the early 1970s, the proportion of deaths that was attributed to tobacco in men aged 35–69 years was one-third in 1998 (Lam *et al.*, 2001).

Table 4. Projected numbers of deaths from tobacco during the twenty-first century, if current smoking patterns persist[a]

Period	Tobacco deaths (millions)
2000–24	~150
2025–49	~300
2050–99	> 500
Total, twenty-first century	~1000
(Twentieth century: for comparison)	(~100)

[a] Of 100 million people per year now reaching adulthood, ~30 million become smokers. If most persist, and about half of those who do are eventually killed by smoking, then the annual number of tobacco-related deaths will eventually be 10–15 million.

USA (Table 3). At present, few young women in China become smokers (Liu *et al*., 1998). Cigarette consumption by Chinese men averaged 1, 4 and 10 per day in 1952, 1972 and 1992, respectively, with no further increase occurring during the past few years. The proportion of deaths attributed to tobacco in Chinese men at ages 35–69 years was measured to be 12% in 1990, and is projected to be about 33% in 2030 (Liu *et al*., 1998; Niu *et al*., 1998). Two-thirds of the young men become persistent smokers, and about half of those who do so will eventually be killed by the habit: therefore, about one-third of all the young men in China will eventually be killed by tobacco if current smoking patterns persist. China, which has 20% of the world's population, produces and consumes about 30% of the world's cigarettes, and a large nationwide study has shown that China already suffers almost a million deaths a year from tobacco-related diseases, a figure that is likely to double at least by 2025.

Worldwide, about 4 million deaths a year are currently caused by tobacco; 2 million of these occur in developed and 2 million in developing countries. However, these current numbers reflect smoking patterns decades ago, and worldwide cigarette consumption has increased substantially over the past half century (WHO, 1997). At present, about 30% of young adults become persistent smokers and relatively few quit (except in selected populations, such as educated adults living in parts of western Europe and North America). The main diseases by which smoking kills people differ substantially between different populations, but there is no good reason to expect the overall 50% risk of death from persistent cigarette smoking to differ greatly between different populations.

There are already well over one thousand million smokers, and by the 2030s about another thousand million young adults will, at current uptake rates, have started to smoke. Based on current smoking patterns, worldwide annual mortality from tobacco is likely to rise from about 4 million around the year 2000 to about 10 million around the year 2030 (i.e. 100 million per decade) (Peto *et al*., 1994), and will rise somewhat further in later decades. Tobacco is therefore expected to cause about 150 million deaths in the first quarter of the twenty-first century and 300 million in the second quarter. Predictions for the third and, particularly, the fourth quarter of the century are inevitably more speculative. However, if over the next few decades about 20–30 million young adults a year become persistent smokers and about half are eventually killed by their habit, then about 10–15% of adult mortality in the second half of the century will be due to tobacco smoking (probably implying more than 500 million deaths due to tobacco for 2050–99; Table 4).

The numbers of tobacco deaths predicted to occur before 2050 cannot be greatly reduced unless a substantial proportion of the adults who have already been smoking for some time give up the habit. A decrease over the next decade or two in the proportion of children who become smokers will not have its main effects on mortality until the third quarter of this century.

The effects on tobacco deaths of adult smokers quitting before 2050 and of young people not starting to smoke after 2050 will probably be as follows:

- *Quitting*: If many of the adults who now smoke were to give up over the next decade or two, thus halving global cigarette consumption per adult by the year 2020, this would prevent about one-third of tobacco-related deaths in 2020 and would almost halve tobacco-related deaths in the second quarter of the century. Such changes would avoid about 20 or 30 million tobacco-related deaths in the first quarter of the century and would avoid about 100 or 150 million in the second quarter.
- *Not starting*: If, by progressive reduction over the next decade or two in the global uptake rate of smoking by young people, the proportion of young adults who become smokers were to be halved by 2020, this would avoid hundreds of millions of deaths from tobacco after 2050. It would, however, avoid almost none of the 150 million deaths from tobacco in the first quarter of the century, and would probably avoid 'only' about 10 or 20 million of the 300 million deaths from tobacco in the second quarter of the century.

Thus, using widely practicable ways of helping large numbers of young people not to become smokers could avoid hundreds of millions of tobacco-related deaths in the middle and second half of the twenty-first century, but not before. In contrast, widely practicable ways of helping large numbers of adult smokers to quit (preferably before middle age, but also in middle age) might avoid one or two hundred million tobacco-related deaths in the first half of this century. Large numbers of deaths during the second half of the century could also be avoided if many of those who, despite warnings, still start to smoke in future years could be helped to stop before they are killed by the habit. Such calculations suggest that the effects of quitting could be more rapidly appreciated on a population scale than the effects of prevention of starting smoking. However, a more thorough evaluation of different strategies, in particular on a worldwide scale, and consideration of the specificities of developed and developing countries, respectively, is outside the scope of the present monograph.

Methodological considerations in interpreting epidemiological evidence on smoking and disease

The epidemiological evidence on smoking and risk for disease comes largely from observational studies that compare the risk for disease in smokers with that in people who have never smoked. Evidence from such studies may be affected by bias and confounding, and chance may also explain the observed associations of smoking with risk for disease. Most of the evidence comes from case–control and cohort studies; both types of study are potentially subject to particular forms of bias. For case–control studies, comparability of cases and controls and success in their recruitment are particularly critical. For cohort studies, the degree of success in recruiting and retaining participants are important considerations in interpreting data.

In studies of smoking, as for studies of any agent, information bias and confounding are of concern. Information bias may affect the classification of both active and involun-

tary smoking and extend to the classification of disease. The potential for error in classifying active and involuntary smoking is well recognized and the potential magnitude of any resulting bias has been considered both qualitatively and quantitatively. The Working Group does not regard information bias as an important consideration in interpreting the evidence on active smoking. For involuntary smoking, several analyses on information bias were considered by the Working Group. This is discussed in detail in the monograph on involuntary smoking.

Confounding arises when the effect of active or involuntary smoking is artificially increased or decreased by a factor that is associated with exposure to smoke in a particular data set and is a risk factor on its own. Confounding becomes more plausible as an alternative to causality as the magnitude of risk decreases. There are various causes, other than smoking, of the cancers considered in this monograph and hence there is potential for confounding. However, these other agents produce confounding only if associated with smoking in specific data sets. Control may be incomplete, leaving the possibility of residual confounding. The Working Group considered the potential for confounding and noted the approach used to control for such.

Active smoking and involuntary smoking have been reported to be associated with the development of many forms of cancer, with a wide range of relative risks ranging from about 1.2 to 20 and higher. When the apparent relative risk is high (for example 10), confounding is unlikely to explain all the excess risk; it has seldom been difficult to recognize such an association and, in most instances, to deduce that it is causal. However, if the apparent relative risk approaches unity, the data need to be interpreted more carefully and subtle sources of bias and confounding must be taken into account. Under these circumstances, the findings from case–control studies may be difficult to interpret, because they may be distorted by the inclusion of controls who are not truly representative of the population from which the cases are drawn. When controls are selected from hospital patients, care has to be taken to exclude those with tobacco-related diseases because the relative risk of the condition being studied will be underestimated. When controls are drawn from the general population, it is important to know what proportion of the selected controls responded. Even if the proportion is known and the compliance rate is reasonably high, ensuring that the results are not biased to some extent by the inclusion of a disproportionate number of people who are interested in questions of health and are therefore unusually health conscious may be difficult. Such people may be less likely to smoke, causing the relative risk to be overestimated.

Cohort studies have their own problems and their results also require careful interpretation. One problem is that the reports do not always cover the same types of cancers. The findings for common cancers (e.g. cancers of the lung, stomach and large bowel) are nearly always reported, but those for rare cancers (e.g. cancers of the nasal sinuses and testis and leukaemia) may be reported only when the numbers observed are unexpectedly high. It may be necessary to limit the data used to those from cohort studies that have reported on many types of cancer (say 20 or more), although selection bias in reporting may still not be excluded for some of the less common cancers.

A second problem, which particularly affects cancers that may grow slowly, such as prostate cancer, is that many patients may die with the disease and not necessarily because of it. This, however, may not be adequately reflected on death certificates because death may be attributed to the cancer when the patient had actually died of an independent broncho-pneumonia, myocardial infarction or another of the many conditions that are made more common by cigarette smoking, thus creating an artefactual positive relationship between smoking and the cancer (Adami *et al*., 1996).

A third problem is that observations may continue to be made for many years after the characteristics of the individual members of the cohort have been recorded and, during this period, these characteristics may have changed. Some smokers may have stopped smoking and, as benefit is commonly obtained within a few years of stopping, this may result in an underestimation of the harmful effects of smoking.

Although cohort studies allow repeated assessments of smoking behaviour to capture any changes, in some studies (e.g. CPS-II, US Veterans), smoking was assessed only at the start of follow-up and cessation after enrolment was not recorded.

During their evaluation of smoking and disease, the Working Group had substantial evidence available for many cancer sites. These data were summarized in tables for qualitative evaluation as to the consistency of findings, strength of association and dose–response. Such evaluation of large bodies of data can also be accomplished through a collaborative, combined analysis of the original data from multiple studies or by pooling the summary results of individual studies, an approach referred to as meta-analysis.

In a collaborative re-analysis, the relevant investigators contribute the raw data for a pooled analysis and give detailed accounts of their procedures for reconciliation of differences. It is often possible to check the results obtained in case–control studies by comparing them with those obtained in cohort studies. Under these circumstances, the data from all the different types of study may prove sufficiently comparable to allow them to be combined.

When collaborative re-analyses are not possible or feasible, the next best approach to interpreting the data from multiple studies is to perform a meta-analysis of the results reported in the published literature. However, aspects of study design and other issues that may affect the results may not be fully allowed for because only summary findings are used. Meta-analysis can be used to evaluate heterogeneity between study findings. It is particularly informative when the results of individual studies lack precision.

An example of a collaborative re-analysis of data is the one relating the risk for breast cancer and active smoking described in Section 2 of this monograph. This type of analysis has not been undertaken in the study of cancers weakly related to smoking and, under these circumstances, reliable estimates of risk are most likely to be obtained from the results of cohort studies. Consequently, in considering such diseases as prostate cancer and leukaemia, which are certainly not strongly related to smoking and for which many sets of data are available, the results of case–control studies are less important.

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