
Chapter 11

SMOKING AND ORAL TOBACCO USE

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SUMMARY

Smoking has been causally associated with increased mortality from several diseases. This chapter provides global and regional estimates of premature mortality and disease burden in 2000 caused by tobacco use, including an analysis of uncertainty. It also describes a method for estimating the future burden of disease that could be avoided through smoking cessation or prevention.

Comparable data, especially age-specific data, on the prevalence of smoking are often unavailable or inaccurate. More importantly, current prevalence of smoking is a poor proxy for cumulative hazards of smoking, which depend on factors such as age at which smoking began, duration of smoking, the number of cigarettes smoked per day, cigarette characteristics such as tar and nicotine content or filter type, and smoking behaviour such as degree of inhalation. We used the smoking impact ratio (*SIR*) as a marker for accumulated smoking risk. *SIR* uses lung cancer mortality in excess of never-smokers as a biological marker for accumulated hazards of smoking. Lung cancer mortality data were from the Global Burden of Disease (GBD) mortality database. Never-smoker lung cancer mortality rates were estimated based on the household use of coal in unvented stoves for each subregion.¹ Age-sex-specific *SIR* was divided into three categories: zero, medium ($0 < SIR \leq 0.5$), and high ($0.5 < SIR \leq 1.0$).

Estimates of mortality and disease burden due to smoking were made for lung cancer, upper aerodigestive cancer, all other cancers, chronic obstructive pulmonary disease (COPD), other respiratory diseases, cardiovascular diseases and selected other medical causes. All diseases for which no plausible physio-biological causal mechanism is currently known were excluded from the analysis of the category “other medical causes”, as were the impacts of maternal smoking during pregnancy. No estimates were made for non-medical causes (injuries). Estimates were

limited to ages 30 years and above. The American Cancer Society Cancer Prevention Study, Phase II (CPS-II), with follow-up for the years 1982–88, was the reference population and provided data on exposure-disease relationships. For China, the exposure-disease relationship was estimated from the retrospective proportional mortality analysis of Liu et al. (1998). Relative risks were corrected for confounding and extrapolation to other regions using conservative correction factors for groups of diseases. For non-fatal outcomes, we assumed that the same attributable fraction as mortality applied to all cancers and COPD (i.e. smoking changes mortality by changing incidence) and used only one half of this value for other health outcomes (i.e. assumed smoking changes mortality by changing incidence and severity/case fatality).

Estimates of reduction in risk after smoking cessation were obtained from the re-analysis of CPS-II, with follow-up for the years 1982–98, for lung cancer, COPD and cardiovascular diseases. To obtain the estimates of exposure under a “business-as-usual” scenario, we assigned male and female populations of countries to one of the ten main or transitional stages of a descriptive model of the smoking epidemic based on available prevalence data. This model was used to divide per capita tobacco consumption data into age–sex-specific estimates. Historical consumption and mortality trends were used to project lung cancer mortality and *SIR* under the business-as-usual scenario.

Quantitative analysis of uncertainty was conducted for five input parameters: population lung cancer mortality, never-smoker lung cancer mortality, reference population smoker and never-smoker lung cancer mortality, relative risks and relative risk correction factors. Uncertainty in population lung cancer was based on a critical review of the quality of country mortality reporting. Uncertainty in never-smoker mortality rates was based on the likely presence of other risk factors for lung cancer, and uncertainty in reference population lung cancer mortality and in relative risk estimates was estimated from the statistical uncertainty in CPS-II data and data from the Chinese retrospective proportional mortality analysis of Liu et al. (1998). Uncertainty in the correction factor was based on the potential and measured confounding of smoking hazard estimates due to other risk factors. Three other sources of uncertainty were discussed qualitatively: uncertainty associated with the use of *SIR* as the exposure variable, uncertainty associated with exposure to environmental tobacco smoke (ETS), and uncertainty in the estimates of non-fatal conditions.

In the year 2000, there were an estimated 4.83 (95% CI 3.94–5.93) million deaths in the world attributable to smoking. Of these, 2.41 (95% CI 1.80–3.15) million deaths were in developing countries and 2.43 (95% CI 2.13–2.78) million deaths in industrialized countries. There were 3.84 million global smoking-attributable deaths among men (2.02 million in developing countries and 1.81 million in industrialized countries) and 1.00 million among women (0.38 million in developing

countries and 0.61 million in industrialized countries). The leading causes of death due to smoking were cardiovascular diseases with 1.69 million deaths, COPD with 0.97 million deaths and lung cancer with 0.85 million deaths. In addition to those cases shared with smokers, there were an estimated 60 000 deaths from oral tobacco use in SEAR-D.

Smoking and oral tobacco use accounted for 4.1% of healthy life years lost in the world in 2000. Given the demographic and epidemiological transitions and current smoking patterns in the developing world, the health loss from smoking will grow even larger unless effective interventions and policies that reduce smoking among males and prevent increases among females in developing countries are implemented.

1. INTRODUCTION

Tobacco is cultivated in many regions of the world and can be legally purchased in all countries. The dried leaf of the plant *nicotiana tabacum* is used for smoking, chewing or as snuff. Smoking has been causally associated with substantially increased risk of premature mortality from lung cancer as well as other medical causes (Doll et al. 1994; Liu et al. 1998; U.S. Department of Health and Human Services 1989; Zaridze and Peto 1986). As a result, in populations where smoking has been common for many decades, tobacco use accounts for a considerable proportion of premature mortality, as illustrated by estimates of smoking-attributable deaths in industrialized countries (Peto et al. 1992).

There have been large increases in smoking in developing countries, especially among males, over the last part of the twentieth century (Corrao et al. 2000; WHO 1997). The first estimates of the health consequences of smoking in China and India have also shown substantially increased risk of mortality and disease among smokers (Dikshit and Kanhere 2000; Gupta and Mehta 2000; Liu et al. 1998; Niu et al. 1998; Gajalakshmi et al. 2003). This chapter provides estimates of premature mortality and morbidity caused by smoking in all regions of the world, with complete description of methods and data sources, including quantitative estimates of uncertainty. It also describes a method for estimating the future burden of disease due to smoking that could be avoided through cessation or prevention.

It is well-known that the accumulated hazards of smoking depend on factors such as the age at which smoking began, the number of cigarettes smoked per day, cigarette characteristics such as tar and nicotine content or filter type, and smoking behaviour such as degree of inhalation (Fletcher and Peto 1977; Liu et al. 1998; Peto 1986). Current prevalence of smoking alone is therefore an insufficient indicator of accumulated risk from smoking. Although such pattern variables have been studied in a few industrialized countries (Nicolaidis-Bouman et al. 1993), few data are available elsewhere. This lack of knowledge about important parameters of smoking patterns and history, coupled with the fact that

smoking is currently increasing in many developing countries, motivates using an exposure variable that better describes accumulated risk in populations with varying smoking histories.

Peto et al. (1992) used data on absolute lung cancer mortality to obtain the proportions of mortality from lung cancer as well as various other diseases attributable to smoking. We extended this method for indirect estimation of excess mortality due to smoking to all regions of the world and also included analysis of morbidity and uncertainty. The large retrospective proportional mortality analysis in China (Liu et al. 1998) and newer studies from India provided a means for calibrating and verifying the method for developing countries using direct estimates from the world's largest countries.

1.1 EVIDENCE FOR CAUSALITY

Smoking has been one of the most extensively studied human health risks, with detailed epidemiological research dating back to the 1930s (Doll and Hill 1950; Levin et al. 1950; Mills and Porter 1950; Muller 1939; Schairer and Schoniger 1943; Schrek et al. 1950; Wassink 1948; Wynder and Graham 1950) (see Table 1 in Doll 1986 for a summary of early studies). The sample size and details of data and methods have grown in subsequent studies in a number of countries, leading to a growing list of more than 60 000 publications on the hazards of smoking (Lopez 1999). The evidence for the causal relationship between smoking and all-cause and cause-specific mortality, as well as the mechanisms of disease causation have been extensively reviewed (Doll 1986, 1998b; U.S. Department of Health and Human Services 1989). Added to these are a number of recent studies, especially from developing countries such as China and India (Doll et al. 1994; Gajalakshmi et al. 2003; Gupta and Mehta 2000; Lam et al. 2001; Liu et al. 1998; Niu et al. 1998). We provide a brief summary of this evidence.

Randomized controlled trials of smoking and health, with randomization of exposure to cigarette smoking, would be impossible for ethical and logistical reasons. Therefore, research on the health impacts of smoking has been based on observational epidemiology and statistical adjustment. The first evidence for the causal relationship between smoking and mortality was from case-control studies. After the initial evidence from case-control studies, numerous prospective cohort studies were initiated to establish the relationship between smoking and mortality. These included studies in the United Kingdom of Great Britain and Northern Ireland (Male British Doctors) (Doll and Peto 1976; Doll et al. 1994), the United States of America (Males in 25 States, Males in 9 States, U.S. Veterans, California Occupations, the American Cancer Society Cancer Prevention Study Phases I and II) (Dunn et al. 1960; Garfinkel 1985; Hammond 1966; Hammond and Horn 1958; Kahn 1966; Peto et al. 1992; Thun et al. 1997a, 1997b), Japan (Hirayama 1977), Canada (Canadian Veterans) (Best et al. 1961), Sweden (Cederlof et al. 1975),

and more recently India (Gupta and Mehta 2000) and a number of other countries. Evidence for the relationship between smoking and total mortality or cause-specific mortality has been consistent among the studies. The causes of mortality from smoking include lung cancer and cancer of various other sites, cardiovascular diseases, COPD and other respiratory diseases, gastric ulcer and a number of other causes.

In addition to establishing the basic causal relationship between smoking and mortality, the results from all these studies exhibit the features and criteria that have been considered important in establishing causality:

1. consistently large risks relative to life-long non-smokers—more than a 20-fold increase in risk for some diseases;
2. existence of a dose–response relationship that shows increasing risk with increasing number of cigarettes smoked and duration of smoking (Doll 1986; Peto 1986; Thun et al. 1997b; U.S. Department of Health and Human Services 1989);
3. consistency of mortality (in particular for lung cancer) with smoking characteristics and cigarette type (such as tar and nicotine yield) across sexes and populations (Doll 1986);
4. risk reduction with smoking cessation, and a decreasing risk gradient with increasing time since smoking cessation (Doll 1986; U.S. Department of Health and Human Services 1989); and
5. biological plausibility. Cigarette smoke contains a number of known human carcinogens and other toxics (Hecht 2003). The toxic (in particular carcinogenic) properties of cigarette smoke have also been established in studies with laboratory animals (U.S. Department of Health and Human Services 1989). More recently, the pathophysiological mechanisms for some non-cancer effects such as COPD and cardiovascular diseases have also been studied and established (see U.S. Department of Health and Human Services 1989 for a summary).

2. METHODS AND DATA

2.1 EXPOSURE VARIABLE

LUNG CANCER MORTALITY AS AN INDICATOR OF ACCUMULATED SMOKING HAZARD

Peto et al. (1992) observed that the level of lung cancer mortality compared with never-smokers is an indicator of the accumulated hazard of smoking and the “maturity” of the smoking epidemic in a population. The relationship between cumulative smoking and lung cancer from various populations confirm this relationship (Peto 1986; Yamaguchi

et al. 2000). Based on this observation, the smoking impact ratio (*SIR*) is defined as population lung cancer mortality in excess of never-smokers, relative to excess lung cancer mortality for a known reference group of smokers. Formally, the ratio in Equation 1 measures the *absolute* excess lung cancer mortality due to smoking in the study population, relative to the *absolute* excess lung cancer mortality in life-long smokers of the reference population.

$$SIR = \frac{C_{LC} - N_{LC}}{S_{LC}^* - N_{LC}^*} \quad (1)$$

C_{LC} : (age–sex-specific) lung cancer mortality rate in the study population (e.g. country of analysis)

N_{LC} : (age–sex-specific) lung cancer mortality rate of never-smokers in the same population

S_{LC}^* and N_{LC}^* : (age–sex-specific) lung cancer mortality rates for smokers and never-smokers in a reference population

Liu et al. (1998) found that in China, the relative risk of mortality from lung cancer as a result of smoking is approximately constant in different cities and villages whose non-smoker lung cancer mortality rates varied by a factor of 10 (see Figure 4 in Liu et al. 1998). A constant relative risk means that smoking results in a larger absolute excess mortality (i.e. the numerator of Equation 1) where never-smoker lung cancer mortality is higher (and smaller absolute excess mortality where never-smoker lung cancer mortality is lower). Therefore, to be converted to an indicator of the maturity of the smoking epidemic, the numerator and denominator of Equation 1 need to be normalized with the respective never-smoker lung cancer mortality rates. We defined the background-adjusted *SIR* by the following relationship:

$$SIR = \frac{C_{LC} - N_{LC}}{S_{LC}^* - N_{LC}^*} \times \frac{N_{LC}^*}{N_{LC}} \quad (2)$$

where C_{LC} , N_{LC} , S_{LC}^* , and N_{LC}^* are defined as above.

Following Peto et al. (1992), we used the CPS-II study population (described below) as the reference population. This is because, among the numerous studies of smoking and cause-specific mortality (U.S. Department of Health and Human Services 1989), CPS-II is one of the very few with follow-up conducted when the smoking epidemic was at its highest levels, especially for men. Therefore, the vast majority of (male) CPS-II current-smokers had been lifelong cigarette smokers. Further, the estimates of increased risk of mortality among smokers were available for both men and women and in smaller age groups than in other studies of smoking and mortality, such as the Male British Doctors cohort (Doll et al. 1994).

It is straightforward to show that SIR equals the proportion of reference-population (i.e. CPS-II) smokers in a mix of smokers and never-smokers, which has the same lung cancer mortality rate as the study population (Peto et al. 1992).² This provides a convenient interpretation of SIR : using excess lung cancer mortality over never-smokers, SIR captures the accumulated hazards of smoking by converting the smokers in the study population into equivalents of smokers in the reference population where hazards for other diseases have been measured (Peto et al. 1992).

SIR values were calculated for individual countries and then averaged (population-weighted) across the 14 reporting subregions by age group and sex. The age groups used in the analysis were 0–4, 5–14, 15–29, 30–44, 45–59, 60–69, 70–79, and ≥ 80 , which are the reporting age groups used in the GBD study. No deaths before the age of 30 years were attributed to smoking. Peto et al. (1992) used 35 as the lowest age for considering the impacts of smoking. Because of the GBD age grouping, we also included the 30–34 age group. The number of deaths attributed to smoking among people between 30 and 34 years of age is likely to be very small.

SIR values larger than 1.0 were set to 1.0. This occurred in the case of males in the 30–44 age group in 17 European countries and one Western Pacific island, and in the 45–59 age group in three countries in eastern Europe. Relatively low lung cancer mortality in younger ages can lead to unstable SIR values. This is particularly the case if the never-smoker rates are estimated with error, which is more likely in younger ages when lung cancer is relatively rare. Further, although a SIR larger than 1.0 may seem to imply that a population which consists of some smokers and some never-smokers had higher lung cancer mortality than CPS-II life-long smokers, factors such as the type and number of cigarettes or the age at which smoking began can result in such a pattern, especially where prevalence of smoking is high. The age of smoking initiation is particularly important for SIR values in earlier ages such as those affected in this analysis. For example, historical lung cancer mortality data show SIR larger than 1.0 among British males aged <60 years in some years between 1950 and 1970 and American males between 1968 and 1976. We nonetheless set the SIR for these groups to 1.0 to avoid any potential overestimation of risk.

EXPOSURE CATEGORIES

SIR is a measure of exposure in the population, vs the individual. In fact, since SIR is based on the lung cancer mortality rate, it cannot be defined at the level of an individual. It is nonetheless possible to divide a population into subgroups with different SIR s subject to the constraint that the overall population SIR should remain unchanged.

Suppose that a population with a specific SIR is divided into three subgroups with SIR_1 , SIR_2 and SIR_3 . Then

$$SIR = a_1SIR_1 + a_2SIR_2 + a_3SIR_3 \quad (3)$$

and

$$a_1 + a_2 + a_3 = 1.0 \quad (4)$$

where a_1 , a_2 , and a_3 are the fractions of the population in the three subgroups. The above system of equations is under-determined for any division of more than two subgroups. If one considers never-smokers as one of the subgroups (subgroup 1) then, by definition of the smoking impact ratio, $SIR_1 = 0$ and

$$SIR = a_2SIR_2 + a_3SIR_3 \quad (5)$$

If p denotes the fraction of the population who have been smokers at some stage of their lives: $a_1 = 1 - p$ and $a_2 + a_3 = p$.

After some manipulation, it can be shown that

$$a_2 = \frac{SIR - pSIR_3}{SIR_2 - SIR_3} \quad (6a)$$

and

$$a_3 = \frac{SIR - pSIR_2}{SIR_3 - SIR_2} \quad (6b)$$

But prevalence data (p) are often unavailable or inaccurate, because of both differences in the definition of “ever-smoker” (someone who has smoked at least one cigarette in their life) and data collection complexity. In this work, the additional requirement for age-specific information makes the existing prevalence data—which are often defined for youth and adults only—even less useful. Therefore, in dividing the population into subgroups, the calculation of the fraction of the population in each subgroup is subject to the constraint that the overall SIR remains unchanged.

The specific categories that were used correspond to $SIR_1 = 0$, $0 < SIR_1 \leq 0.5$, and $0.5 < SIR_3 \leq 1.0$. For the last two categories, the midpoints (0.25 and 0.75) were used in estimating the fraction of population in the two categories (a_2 and a_3), once again subject to the constraint that the overall SIR be equal to the original population SIR . The analysis was conducted to divide each age-sex-subregion SIR value into three categories.

THEORETICAL-MINIMUM-RISK EXPOSURE DISTRIBUTION

Because the harmful effects of smoking outweigh the potential health benefits for a small number of diseases (such as parkinsonism) by many

orders of magnitude (Doll 1986, 1998a), the dose–response relationships for smoking and overall mortality and burden of disease are monotonically increasing. Therefore, the minimum risk from smoking would occur in a population in which no one had ever smoked. Further, although such a population may not be achievable in practice, there are no physical limits to reduction of smoking. Therefore, the theoretical minimum exposure distribution was chosen as a population with a *SIR* of zero.

POPULATION AND LUNG CANCER MORTALITY STATISTICS

The age–sex-specific population estimates for the 191 WHO Member States were from the United Nations Population Division, and mortality statistics from WHO’s GBD database. GBD mortality statistics are divided by country, sex, age (five-year age groups up to 85 and then ≥ 85), and more than 150 causes of death. The sources of mortality data include vital registration and sample registration, population laboratories, and epidemiological studies. Details of mortality data and cause-of-death analysis methods are described elsewhere (Mathers et al. 2002) and are summarized below where relevant.

The reliability of the *SIR* is determined by the reliability of lung cancer mortality estimates. In countries with good vital registration and medical certification of deaths (approximately 75 countries), lung cancer mortality is diagnosed with a high degree of accuracy. For example, microscopic confirmation of diagnosis against the cause reported on death certificates has suggested a 95% or higher confirmation rate in these settings (Percy and Muir 1989; Percy et al. 1990). In approximately another 50 countries, vital registration of mortality is incomplete and medical certification of the cause much less reliable. Standard demographic techniques (Bennett and Horiuchi 1984; Hill 1981; Preston et al. 2000) are used in the GBD project to correct all-cause death rates by age for these populations, and lung cancer rates are adjusted accordingly. Finally, for countries without vital registration, overall age-specific death rates were first determined using model life-tables (Lopez et al. 2002). Total cancer death rates are then estimated based on regional information about proportionate cancer mortality. Within this death rate, the distribution by site is based on regional incidence patterns from cancer registries reporting to the International Agency for Research on Cancer, IARC (Parkin et al. 1992, 1997). This indirect procedure is likely to entail considerable uncertainty, as we describe below.

2.2 RISK FACTOR–DISEASE RELATIONSHIPS

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY (ACS CPS-II)

The American Cancer Society’s Cancer Prevention Study, phase II (CPS-II) is a prospective study of smoking and death in more than one million Americans aged >30 years when they completed a questionnaire in 1982,

with the latest follow-up in 1998. A complete description of the study is provided elsewhere and summarized below (Garfinkel 1985; Peto et al. 1992; Thun et al. 1995, 1997a, 1997b, 2000). In 1992, when the first six-year (1982–1988) results were obtained, mortality follow-up was virtually complete for the first two years, and about 98–99% complete for the next four. Because some conditions that cause death in the first two years may have affected smoking habits at entry (e.g. those diagnosed with lung cancer may have stopped smoking because of their disease or related symptoms), analysis was restricted to years 3–6 inclusive (1984–1988) (Peto et al. 1992). The analysis related deaths (subdivided by cause, sex and five-year age groups at the time of death) to person-years (with accounting for incompleteness) for those who in 1982 had never smoked regularly, and for those who were then current cigarette smokers (Peto et al. 1992). Most of the CPS-II current-smokers were life-long cigarette smokers with a mean consumption of about 20 cigarettes per day. Relative risks for cause-specific mortality among smokers in the CPS-II population are provided in Table 11.1.

RETROSPECTIVE PROPORTIONAL MORTALITY STUDY IN CHINA

In a retrospective study of one million deaths in 24 urban centres and 74 rural areas of China, Liu et al. (1998) used proportional mortality analysis to obtain relative risks for three groups of diseases (neoplastic, respiratory and cardiovascular diseases). As explained in Liu et al. (1998), proportional mortality analysis cannot estimate excess mortality for these causes of death in the reference group. Therefore, in this study (Liu et al. 1998) the attributable fraction for causes other than the above three groups was considered to be zero. At the same time, since a few of the deaths in the reference group were also due to smoking, this method would underestimate (as zero) the proportion of mortality due to the causes in the reference group. The relative risks and attributable fractions of cause-specific mortality from Liu et al. (1998) are summarized in Table 11.2.

DISEASE OUTCOMES AND HAZARD SIZE

Lung cancer mortality attributable to smoking was obtained as the difference between population lung cancer mortality and that of never-smokers (i.e. the numerator of Equation 1). For all other diseases, the relative risks from CPS-II (Table 11.1) were used. To obtain mortality from other causes, a “mixture” of CPS-II smokers and non-smokers was taken to give a *SIR* equal to that of the study population (as described above, the proportion of smokers in this mixture equals the *SIR* of the study population). This mixture was then used together with the cause-specific relative risks from CPS-II (Table 11.1) to estimate population attributable fractions (PAF) in the study population for different diseases.

Table 11.1 Selected relative risks for cause-specific mortality for years 3–6 inclusive of ACS CPS-II prospective study of one million American adults

Cause (ICD-9 code)	Male	Female
Lung cancer (162) ^a	24.22	12.50
Upper aerodigestive cancer (mouth, oropharynx or oesophagus) (140–150 and 161)	7.87	6.95
Other cancer (rest of 140–209)	1.69	1.20
Chronic obstructive pulmonary disease (490–492, 496)	13.82	14.21
Other respiratory diseases (460–466, 480–487, 381–382) ^b		
35–59	3.05	2.69
60–64	2.31	2.68
65–69	2.09	2.52
70–74	2.00	2.00
≥75	1.54	1.44
Infectious and parasitic diseases (001–139, 320–323, 614–616 with the exception of those above), maternal and perinatal conditions (630–676, 760–779), neuro-psychiatric conditions (290–319, 324–359), cirrhosis of the liver (571), congenital anomalies (740–759), and non-medical causes (injuries) (E800–999) ^c	NA	NA
Other medical causes (rest of 000–799)		
35–59	3.05	2.69
60–64	2.31	2.68
65–69	2.09	2.52
70–74	2.00	2.00
≥75	1.54	1.44

NA Not applicable.

^a For lung cancer, the population attributable fraction was obtained by direct subtraction of population lung cancer mortality from that of non-smokers.

^b This category also includes tuberculosis (010–018, 137) for which there are separate estimates of relative risk in China.

^c Peto et al. (1992) included medical (non-injury) causes of death in this category with the category “other medical causes”. We assumed that none of the deaths in this category were attributable to smoking because of lack of established causal pathways.

Source: Peto et al. (1992).

The use of relative risk models in estimating tobacco-attributable mortality has been criticized in the past (Lee 1996). While both additive and multiplicative risk models have been used in epidemiology (Moolgavkar and Venzon 1987), the use of a relative risk approach for common risk factors for common diseases is standard in epidemiological literature based on its ability to capture the “risk magnification” role of most risk factors. In the particular case of smoking, Liu et al. (1998) found that in China, the relative risks for mortality from lung cancer and other major diseases are approximately constant in different cities and

Table 11.2 Selected relative risks and attributable fractions of mortality from the retrospective mortality analysis of one million deaths in China

Cause (ICD-9 code)	Ages 35–69 years		Ages ≥70 years	
	Weighted mean relative risks (SE)	% deaths attributable to smoking	Weighted mean relative risks (SE)	% deaths attributable to smoking
Male				
<i>Malignant neoplasm (140–208)</i>	1.51 (0.02)	24.4	1.39 (0.03)	18.7
Lung cancer (162)	2.72 (0.05)	52.3	2.47 (0.07)	46.6
Oesophageal cancer (150)	1.61 (0.04)	27.9	—	18.2
Stomach cancer (151)	1.35 (0.03)	18.1	—	9.1
Liver cancer (155)	1.40 (0.03)	20.2	—	14.7
Mouth, pharynx, larynx, pancreas or bladder (140–9, 161, 157, 188)	1.51 (0.05)	24.6	—	19.1
Other malignant neoplasm	1.24 (0.03)	13.1	—	—
<i>Respiratory</i>	1.31 (0.02)	17.2	1.54 (0.02)	24.6
Chronic obstructive pulmonary disease (ICD 490–492, 496, 416–417)	1.43 (0.03)	22.6	1.63 (0.03)	27.4
Respiratory tuberculosis (011, 012, 018)	1.20 (0.04)	11.3	—	24.5
Other respiratory (rest of 460–519)	1.07 (0.05)	4.2	—	—
<i>Cardiovascular (390–415, 418–459)</i>	1.15 (0.02)	8.5	1.06 (0.02)	3.4
Stroke (430–439)	1.17 (0.02)	10.0	—	4.2
Ischaemic heart disease (410–414)	1.28 (0.03)	14.7	—	2.8
Other cardiovascular diseases (all cardiovascular except 430–439, 410–414, 416–417)	0.94 (0.03)	NA	—	—
Other causes (reference group)	1.00	NA	1.00	NA
Female				
<i>Malignant Neoplasm (140–208)</i>	1.37 (0.04)	4.0	1.37 (0.03)	4.7
Lung cancer (162)	2.64 (0.08)	19.4	2.50 (0.09)	20.1
Oesophageal cancer (150)	1.34 (0.08)	2.8	—	4.3
Stomach cancer (151)	1.17 (0.06)	1.7	—	2.3
Liver cancer (155)	1.22 (0.06)	2.4	—	4.2
Mouth, pharynx, larynx, pancreas, or bladder (140–9, 161, 157, 188)	1.53 (0.09)	6.4	—	9.1
Other malignant neoplasm	1.04 (0.04)	0.5	—	—
<i>Respiratory</i>	1.61 (0.05)	7.5	1.59 (0.03)	7.4
Chronic obstructive pulmonary disease (ICD 490–492, 496, 416–417)	1.72 (0.05)	9.3	1.70 (0.03)	8.6
Respiratory tuberculosis (011, 012, 018)	1.29 (0.08)	2.8	—	6.7
Other respiratory (rest of 460–519)	1.14 (0.09)	1.5	—	—

continued

Table 11.2 Selected relative risks and attributable fractions of mortality from the retrospective mortality analysis of one million deaths in China (*continued*)

Cause (ICD-9 code)	Ages 35–69 years		Ages ≥70 years	
	Weighted mean relative risks (SE)	% deaths attributable to smoking	Weighted mean relative risks (SE)	% deaths attributable to smoking
Cardiovascular (390–415, 418–459)	1.01 (0.03)	0.2	1.02 (0.02)	0.2
Stroke (430–439)	0.97 (0.03)	NA	—	—
Ischaemic heart disease (410–414)	1.30 (0.05)	4.1	—	2.0
Other cardiovascular diseases (all cardiovascular except 439–439, 410–414, 416–417)	0.94 (0.05)	NA	—	—
Other causes (reference group)	1.00	NA	1.00	NA

— Values not reported in Liu et al. (1998).
NA Not applicable.
Source: Liu et al. (1998), Tables 1 and 5.

villages where background (non-smoker) mortality rates for the same disease varied significantly. This finding also has been confirmed in studies which stratified on serum cholesterol for cardiovascular diseases (Jee et al. 1999).

The exception to the use of CPS-II relative risks was tobacco-attributable mortality in China, for which direct estimates of the fraction of cause-specific mortality due to smoking from 1990 were available. For China, attributable fractions for diseases other than lung cancer were obtained using relative risks from Liu et al. (1998). Since smoking has been increasing in China over the past few decades, we used *SIR* estimates to capture the impact of this trend. The relative risks for each smoker from Liu et al. (1998) were converted to relative risks for each unit of *SIR* (i.e. equivalent to life-long CPS-II smoker) by back-calculation in 1990 and used with 2000 *SIR* estimates. The upper aerodigestive cancer category was constructed from oesophageal cancer and cancers of five minor sites (mouth, pharynx, larynx, pancreas and bladder) by using weights based on the number of deaths in each disease category. Relative risks per unit of *SIR* for China (which correspond to the same level of accumulated smoking hazard as Table 11.1 for CPS-II life-long smokers), are provided in Table 11.3.

Although smokers are found to have increased mortality due to causes other than those in Table 11.1, none of the deaths from non-medical causes (injuries) and the following medical causes (for which there are no known pathways of causality) were attributed to smoking: infectious and parasitic diseases (with the exception of those in the category “other respiratory disease” for which there were estimates of hazard), maternal

Table 11.3 Relative risks for each unit of *SIR*^a for China obtained by back-calculation from 1990 estimates of attributable mortality from Table 11.2

Cause	Male		Female ^b	
	35–69 years	≥70 years	35–69 years	≥70 years
Lung cancer	20.97	35.76	14.19	15.06
Upper aerodigestive cancer	7.71	9.90	2.78	3.89
Other cancer	4.39	5.12	1.56	2.30
Chronic obstructive pulmonary disease	6.32	16.03	6.62	6.26
Tuberculosis	3.32	7.32	2.58	2.49
Other respiratory diseases	1.80	3.14	1.83	1.79
Cardiovascular diseases	2.69	2.40	1.11	1.11
Other causes (reference category) ^c	1.00	1.00	1.00	1.00

^a Equivalent to a CPS-II life-long smoker in Table 11.1.

^b Relative risks for females are likely to be unstable due to low prevalence of female smoking in China.

^c Since the proportional mortality method used by Liu et al. (1998) does not allow obtaining attributable mortality for causes in the reference group, the relative risks were estimated as one. At the same time, since some deaths in this category are also due to smoking the relative risks from CPS-II were used for these causes.

and perinatal conditions (see below for discussion), neuro-psychiatric conditions, cirrhosis of the liver and congenital anomalies.

There is increasing evidence of an association between smoking and tuberculosis (Dhillon et al. 2000; Gajalakshmi et al. 2003; Lam et al. 2001; Liu et al. 1998). The role of air pollutants in increased risk of infectious pulmonary disease has also been suspected to be through weakening of lung function and defence mechanisms (Thomas and Zelikoff 1999). At the same time tuberculosis is a highly communicable disease whose transmission dynamics are affected by a number of factors. Further, progress from infection to disease and mortality is highly dependent on control and treatment mechanisms. Because of this crucial role of cofactors in tuberculosis incidence and mortality, and their concentration in specific sectors of society, we did not extrapolate relative risks for this disease from one setting to another. We considered tuberculosis as a separate cause of mortality due to smoking only in China where published direct estimates on the relationship were available. We grouped tuberculosis with the category “other respiratory diseases”, which have a lower relative risk, in all other countries. Not including tuberculosis as a separate cause of death for the rest of the world is a conservative assumption. This is particularly true in the case of India where recent evidence indicates risks larger than those in China (Dhillon et al. 2000; Gajalakshmi et al. 2003).

Many deaths from burns and other injuries due to fires are also attributable to smoking. For example, pooled studies from Australia, the

United Kingdom and the United States show an attributable fraction of 0.23 for fire-related injuries due to smoking (English et al. 1995). The number of fire-related deaths and injuries are highly dependent on local circumstances including population density, housing, the availability of emergency services, etc. A relative risk approach would, therefore, be unsuitable for their analysis, which is better conducted using injury registries. Given the large burden of injuries due to fires, excluding non-medical causes undoubtedly results in an underestimation of the health impacts of tobacco.

There has also been growing evidence of the impact of maternal smoking on maternal and child health. Specific outcomes include still births and neonatal deaths, perinatal mortality, low birth weight, primary and secondary infertility, ectopic pregnancy and spontaneous abortion and a number of other child and maternal conditions (U.S. Department of Health and Human Services 1989, 2001). Despite the evidence for the relationship, there has been little quantification of the impact of maternal exposure on child disease and mortality, especially in settings with high background levels of child and maternal mortality. Further, these estimates would require estimating what fraction of female smokers continues to smoke during pregnancy. Not including quantitative estimates of the health hazards for maternal and child health also underestimates the burden of disease due to smoking.

Before using the relative risks from CPS-II, we reduced the excess risk attributed to smoking using constant correction factors as described below. As explained by Peto et al. (1992), a constant correction factor, although arbitrary, avoids overestimating mortality due to confounding in the ACS CPS-II relative risk estimates (which were adjusted for age and sex only) as well as extrapolation of relative risk values from this population to other populations, where exposure to other risk factors that could modify the effects of smoking in a non-multiplicative way may be different. The issue of the confounding of the CPS-II risk estimates used by Peto et al. (1992) and the arbitrary nature of the correction factor were used to challenge the indirect estimates of mortality due to this risk factor (Lee 1996; Sterling et al. 1993).

In studies other than CPS-II, the overall impact of confounding due to diet on the estimates of excess risk of mortality from smoking has been found to be considerably less than half of the excess risk for cardiovascular diseases (such as those studies reviewed as a part of the meta-analysis of ETS and ischaemic heart disease [IHD] by Law et al. 1997 or in analysis of multiple cardiovascular disease risk factors in Japan Hirayama 1990). Alcohol consumption and smoking are correlated in many populations, including in the United States where the ACS CPS-II, which was used to obtain relative risks, was conducted. Alcohol may affect cardiovascular disease (in particular IHD) in both beneficial and harmful ways depending on the patterns of consumption (Britton and McKee 2000; Puddey et al. 1999; chapter 12 in this book). Alcohol

was associated with a reduction in cardiovascular disease mortality risk in CPS-II (Thun et al. 1997c). But the overall death rates were lowest among men and women reporting about one drink daily and increased with heavier drinking, particularly among adults aged <60 years with lower risk of cardiovascular disease (Thun et al. 1997c). It may also have been the case that CPS-II smokers had more harmful drinking patterns, which would confound the relative risk estimates for cardiovascular disease. At the same time, given that the beneficial impacts of alcohol in this cohort persisted even at higher consumption levels, any possible confounding effect on estimates of smoking hazard size is likely to be considerably less than one half of the excess risk. In the Nurses' Health Study, Kawachi et al. (1997) found that the relative risk for cardiovascular diseases as a result of smoking after adjustment for multiple covariates (3.74) was larger than the unadjusted relative risk (3.47); the change was not statistically significant. The reduction in cardiovascular disease excess risk due to adjustment for age, community, history of hypertension and diabetes, consumption of alcohol, systolic blood pressure, and frequency of walking in a study of the relationship between smoking and mortality in three United States communities was 20% for men (2.0 to 1.8). Adjustment resulted in an increase in female relative risk (from 1.7 to 1.8) (LaCroix et al. 1991); neither change was statistically significant.

Among cancers, upper aerodigestive cancers are the diseases for which confounding due to alcohol consumption may be most important. There is evidence from studies in different parts of the world on the interaction (excess over multiplicative) between alcohol and tobacco for various upper aerodigestive cancers (Flanders and Rothman 1982; Kinjo et al. 1998). As described by Flanders and Rothman (1982), this interactive effect as well as the correlation between exposure to these two risk factors, would imply larger risks from smoking than would be the case in the absence of interaction and correlation. Therefore, reduction of risk by one half is likely to not only account for potential confounding but also result in conservative estimates.

In response to the criticism about the lack of empirical evidence for confounding correction, CPS-II data were re-analysed together with adjustment for potential confounders (Malarcher et al. 2000; Thun et al. 2000). Malarcher et al. (2000) found that adjusting for multiple covariates (age, education, alcohol use, hypertension status and diabetes status) only marginally changed the fraction of mortality attributable to smoking in the United States, as shown in Table 11.4. As seen in the table, except for cerebrovascular disease (CVD) among men, adjustment for confounding had no or little effect, or even resulted in a slight increase, on the smoking-attributable mortality.

In a more detailed re-analysis of CPS-II data, Thun et al. (2000) adjusted for age, race, education, marital status, occupation ("blue collar" worker) and total weekly consumption of citrus fruits and vegetables in estimat-

Table 11.4 Effect of adjustment for confounding on the fraction of cause-specific mortality attributable to smoking

	Male		Female	
	Age-adjusted	Fully-adjusted	Age-adjusted	Fully-adjusted
Lung cancer	0.91 (0.89–0.92)	0.89 (0.87–0.91)	0.71 (0.68–0.74)	0.77 (0.71–0.80)
COPD	0.85 (0.82–0.88)	0.88 (0.83–0.92)	0.70 (0.65–0.74)	0.68 (0.61–0.76)
IHD	0.23 (0.20–0.26)	0.24 (0.21–0.27)	0.08 (0.06–0.10)	0.10 (0.06–0.13)
CVD	0.16 (0.09–0.22)	0.10 (0.02–0.19)	0.10 (0.07–0.12)	0.09 (0.05–0.12)

Source: Malarcher et al. (2000).

ing the relative risk of mortality due to a range of neoplasms, cardiovascular diseases and respiratory diseases. In addition, the analysis for cardiovascular diseases adjusted for current aspirin use or alcohol consumption, body mass index (BMI), physical activity at work or leisure and weekly consumption of fatty foods. For lung cancer and COPD, the analysis also adjusted for occupational exposure to asbestos. Similar to the analysis of Malarcher et al. (2000), with the exception of stroke among men, whose relative risk declined from 2.9 (95% CI 2.3–3.7) to 2.4 (95% CI 1.8–3.0) for the 35–64-year age group and from 1.8 (95% CI 1.6–2.2) to 1.5 (95% CI 1.2–1.8) for those aged >64 years, excess risks increased, stayed unchanged or decreased by small amounts. As in the case of Malarcher et al. (2000), the largest decrease was in the case of stroke for males (17% decrease in excess risk for the 35–64-year age group and 38% for those aged ≥ 65 years). Overall, Thun et al. (2000) concluded that adjustment for confounding reduced their estimates of mortality attributable to smoking in the United States by approximately 1%.

Finally, the Chinese retrospective study provides some evidence that background disease rates do not change the proportion of mortality attributable to smoking (Figures 4 and 5 in Liu et al. 1998). In extrapolating hazard size from industrialized to developing countries, one would have to deal with availability of health services (such as medical care for cardiovascular disease patients) if extrapolation were based on absolute risk (i.e. number of deaths) because the number of fatal cases would vary based on available treatment. If extrapolation is made based on risk of mortality for smokers *relative* to non-smokers, however, availability of health services would not bias the estimates if smokers and non-smokers have similar access to these services.

Based on this evidence of the robustness of CPS-II relative risk estimates to adjustment for confounding and extrapolation across settings with different background mortality rates, we modified the choice of correction factor from that used by Peto et al. (1992). We used a correction factor of 30%, approximately equal to the largest reduction in excess risk due to confounding seen in the re-analysis of CPS-II data, to reduce

the excess risk for all cause-specific relative risks (see also discussion of uncertainty). This choice continues to be conservative to account for any potential residual confounding or any other potential sources of overestimation arising from extrapolation across regions. For the category, “other medical causes”, where the extent of confounding is still not known, we continued to attribute only one half of the excess mortality estimated by CPS-II.

The excess risk for China was reduced by 5%. Confounding due to other risk factors is likely to have been negligible in China because of the more homogenous level of exposure to other risk factors (e.g. diet, alcohol, and indoor air pollution from coal) in the population compared to the CPS-II population (R. Peto, personal communication, 2001). The proportional mortality method used by Liu et al. (1998) also is not affected by confounding due to any risk factor that increases mortality in the study and reference disease categories (such as effects of alcohol on cancer and liver cirrhosis). Finally, since the relative risks are used for China only, effect modification due to other risk factors is not a concern. The 5% reduction of excess risk was used to account for the potential small level of residual confounding.

ASSESSMENT OF MORBIDITY

Virtually all causes of mortality (diseases) that are affected by smoking are chronic diseases due to long-term exposure. Therefore, a reasonable assumption would be that smoking increases mortality by increasing disease incidence, rather than modifying case fatality among those who would already be affected by the disease. Since the non-fatal component of disability-adjusted life years (DALYs) (i.e. years lived with disability or YLD) is based on incidence, this assumption would imply that the relative risks for mortality and incidence are equal. Among the causes of mortality considered, the most obvious exception to this assumption may be asthma and respiratory infections, where smoking may affect incidence, case fatality or both. For these diseases we assumed that one half of the morbidity obtained from the above approach is due to smoking. To provide conservative estimates, we also considered that for those diseases where medical interventions may reduce case fatality (such as some cardiovascular diseases) and those for which smokers have a smaller excess risk compared to non-smokers (such as the “other medical conditions” category), the increased risk of mortality may be partially due to increased case fatality. Therefore, for these diseases also, we assumed that one half of the above attributable fraction was due to smoking. In summary, the attributable fraction of morbidity due to smoking was assumed to be the same as mortality for all cancers and COPD, and one half of the latter for all other causes.

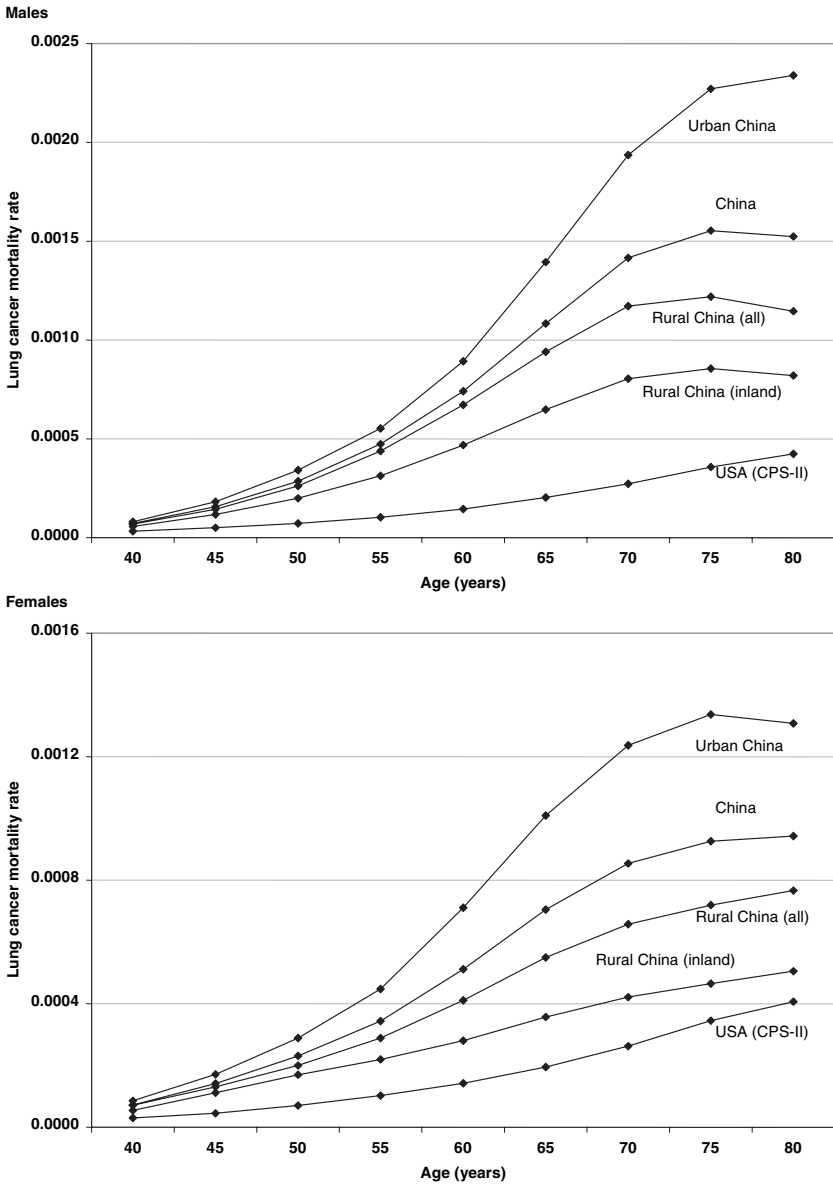
2.3 CHOICE OF NEVER-SMOKER LUNG CANCER MORTALITY IN THE STUDY POPULATION

In Equation 2, C_{LC} is from the GBD mortality database and S_{LC}^* and N_{LC}^* directly from CPS-II. The only parameter to be estimated indirectly is N_{LC} , since direct estimates of never-smoker lung cancer mortality are known for very few countries. Figure 11.1 shows non-smoker lung cancer mortality for the United States (from CPS-II) and China (from Liu et al. 1998). The detailed data in Liu et al. (1998) further allow dividing the Chinese rates into urban and rural areas, and the latter into coastal and inland rural.

As seen in Figure 11.1, age-specific non-smoker lung cancer mortality is considerably higher in China than in the United States for both males and females. In China itself, there are also marked differences between different parts of the country with urban areas having the highest non-smoker lung cancer mortality rates and inland rural areas the lowest (also seen in Figure 4 in Liu et al. 1998). The difference between the non-smoker lung cancer mortality rates for the United States and China, and between urban and rural regions of China is explained by the Chinese patterns of household energy use over the past few decades. Coal is a common household fuel in China, often burned in stoves and buildings without adequate ventilation (Du et al. 1996; Liu et al. 1998; Smith et al. 1993; Wang et al. 1996). Exposure to coal smoke and cooking fumes has been associated with increased lung cancer incidence in China (Du et al. 1996; He et al. 1991; Wang et al. 1996). In inland rural regions of China, where incomes are the lowest, biomass (including crop residues and wood) has been the dominant household fuel compared with coastal villages and cities where coal has been more commonly used.

The relationship between biomass fuels and lung cancer has been absent or considerably smaller than that between coal and lung cancer (Bruce et al. 2000; Ko et al. 1997; Smith and Liu 1993; Sobue 1990) as seen also in chapter 18. Although urban air pollution has been linked to increased lung cancer mortality in some studies, the size of the risk is considerably smaller than the effects of smoking or direct exposure to coal smoke (Doll 1978; Jedrychowski et al. 1990; Nyberg et al. 2000; Pope et al. 2002; Vena 1982). Further, the impact of ambient air pollution on lung cancer has been found to be smaller among non-smokers than among smokers, with one study finding increased risk of lung cancer as a result of urban air pollution among smokers only (Jedrychowski et al. 1990; Vena 1982). For example, exposure to high levels of urban air pollution, even in regions where coal was used extensively, was found to increase the risk of mortality from lung cancer by approximately 14% among non-smokers (vs 40% among smokers) (Jedrychowski et al. 1990). Coupled with the fact that only small fractions of national populations live in the most polluted urban areas,

Figure 11.1 Non-smoker mortality from lung cancer in different populations



Note: Chinese rates correspond to 1990. Note that the scales on the female and male charts are different to maintain the resolution for females.

Source: Ezzati and Lopez (2003).

overall population lung cancer mortality is not expected to be greatly affected by urban air pollution. For example, the lung cancer mortality rate among non-smoking American women remained constant at approximately 12 per 100 000 between 1960 and 1986 despite changes in exposure to urban air pollution (U.S. Department of Health and Human Services 1989).

Based on the pattern of background lung cancer mortality rates, and the underlying risk factors for increased lung cancer mortality in China and its various regions, background (never-smoker) lung cancer rates for the different subregions were based on the estimated use of coal for domestic energy in unvented stores as provided in chapter 18. We used Chinese non-smoker rates for China, a weighted average of Chinese and CPS-II non-smoker for SEAR-D where coal is also used for household fuel (with weights for Chinese rates equal to the prevalence of coal use), and CPS-II non-smoker rates for the remaining countries of the world where domestic coal use in unvented stoves is negligible. The remaining risk factors with potential effects on lung cancer mortality (ambient air pollution, occupational hazards, indoor air pollution from radon or biomass smoke, etc.) affect all populations in varying degrees. The net impacts of these other risk factors are considered as sources of uncertainty in extrapolating never-smoker lung cancer mortality from one setting to another.

2.4 RISK REVERSIBILITY

Estimating the burden of disease that might be avoidable as a result of exposure removal requires knowledge of risk reversibility (the decline in risk after exposure is removed) for those who are current smokers.³ For those who never begin to smoke, of course, the entire disease burden as a result of smoking is avoided. The benefits of smoking cessation for reduction of mortality risk have been reported in a number of studies (Best et al. 1961; Doll and Hill 1956; Doll and Peto 1976; Doll et al. 1994; Dunn et al. 1960; Hammond 1966; Kahn 1966; U.S. Department of Health and Human Services 1990c). Many studies have also considered the reduction in risk with time since cessation. Most of these studies have focused on the reduction in the risk of lung cancer and cardiovascular causes since cessation. Although the estimates of risk reduction time have varied among different studies, possibly due to different smoking histories and other differences (such as age at which cessation occurred) among the study populations, the benefits of cessation have been consistently demonstrated.

To capture the history and accumulated hazards of smoking, we continued to use smoking impact ratio (*SIR*) as the exposure variable in considering risk reversibility. We first estimated risk reversibility for lung cancer to obtain estimates of reduction in *SIR* values after cessation. For diseases other than lung cancer, we estimated the reduction in disease risk per unit of *SIR*—our exposure variable—using the studies on risk

reversibility. Together with the *SIR* estimates after cessation, these provided estimates of avoidable mortality for causes other than lung cancer, which also took into consideration the full history of smoking before cessation.

LUNG CANCER

The reduction in lung cancer risk with smoking cessation has been demonstrated in a number of studies (Alderson et al. 1985; Higgins et al. 1988; Kahn 1966; Lubin et al. 1984; Pathak et al. 1986; Peto and Doll 1984; Peto et al. 2000; Sobue et al. 1991; U.S. Department of Health and Human Services 1990a). Peto et al. (2000) provided an analysis of risk reduction for those who would have been life-long smokers but stopped smoking at various ages using two case-control studies for lung cancer, and national lung cancer mortality statistics in 1950 and 1990 (see Figure 3 in Peto et al. 2000). Table 11.5 shows the reduction in risk, relative to those who continue to smoke, as a function of time since cessation. The results are presented for all ages to increase statistical stability (S. Darby, personal communication, 2001). The large difference between male and female estimates of reversibility in this study is because female estimates were based on relatively few cases of ex-smokers with lung cancer (S. Darby, personal communication, 2001). Also, because the smoking epidemic for females lagged the male epidemic in the United Kingdom, as elsewhere, the comparison of 1950 and 1990 lung cancer mortality rates was likely to have included few females who had stopped smoking after the peak of the epidemic.

These estimates of decline in risk are consistent with those from a number of prospective cohort studies (summarized in Table 3 in U.S. Department of Health and Human Services 1990a) including Male British Doctors, United States Veterans, and American Cancer Society CPS-I and CPS-II. When all subjects are considered, these prospective

Table 11.5 Decline in the risk of lung cancer mortality with time since smoking cessation

<i>Smoking status</i>	<i>Male</i>	<i>Female</i>
Current smoker	1.00	1.00
<i>Years since cessation among former smokers</i>		
0–9	0.66	0.69
10–19	0.42	0.21
20–29	0.18	0.05
≥30	0.08	—

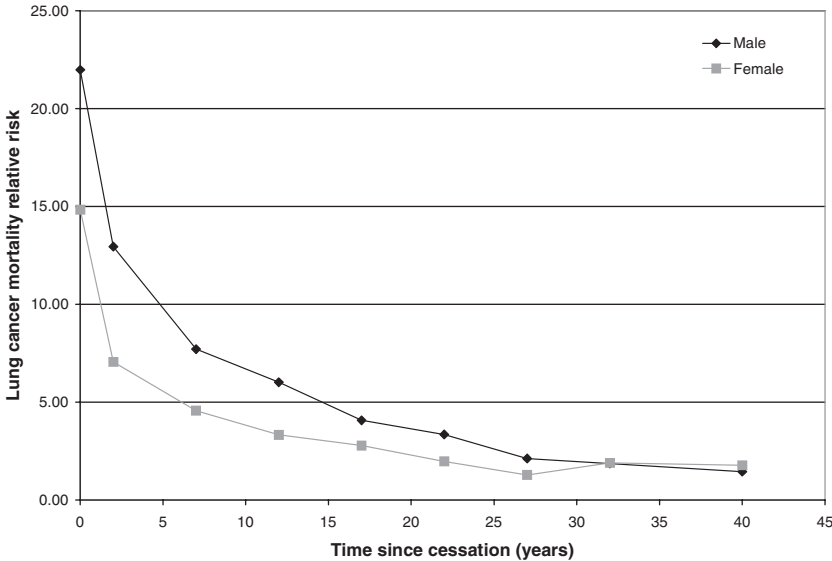
— Value not reported.

Source: Peto et al. (2000).

studies show a consistent increase in relative risk in the first five years from the date of cessation (U.S. Department of Health and Human Services 1990a). This can be attributed to selection bias, as those who die in the first few years after cessation are likely to have stopped smoking because they had been diagnosed with a disease. This is confirmed in the separate analysis of those with and without history of chronic disease in CPS-II. In this analysis, those without a history of chronic disease have a consistent declining trend in lung cancer mortality risk compared to all respondents (Figure 11.2). To estimate lung cancer risk reversibility with cessation, we used a re-analysis of CPS-II data (1998 follow-up) excluding those subjects with a history of chronic disease (lung cancer, COPD, cardiovascular diseases) (Figure 11.2).

Despite some remaining differences, the male and female reversibility estimates in Figure 11.2 are much more similar than those in Table 11.5. With better estimates of reversibility among females, we took sex-specific estimates of reversibility to be consistent with the sex-specific smoker and non-smoker lung cancer mortality rates used in the definition of *SIR*. For the last two cessation periods (30–34 and ≥ 35 years)

Figure 11.2 Relative risk of lung cancer among former smokers (compared with lifelong non-smokers) with time since cessation



Note: Zero years represent current smokers. The estimates at 40 years represent cessation of more than 35 years in the subjects. Data are from ACS CPS-II 1998 follow-up.

Source: American Cancer Society, unpublished data, 2002.

female estimates show a slight increase in risk compared to the 25–29 year cessation period. This anomaly, which is not statistically significant, is probably due to a small number of events in these groups, itself caused by the more recent maturity of the female smoking epidemic in the United States compared to men. Too few women would have stopped smoking so long ago to have had more than 35 years of cessation and a large number of lung cancer events. For these two cessation periods, we simply assumed that the declining trend observed between the 20–24 and 25–29 year periods would continue.

Avoidable lung cancer mortality can be estimated from the difference between lung cancer risk as it would have been without cessation and the risk that results from cessation. If, as above, we denote smoker and non-smoker lung cancer mortality rates in the reference cohort as S_{LC}^* and N_{LC}^* , and lung cancer mortality rates for those who stopped smoking x years ago as $S_{LC,x}^*$, then for this cohort of former smokers $S_{LC,x}^* - N_{LC}^*$ is the mortality attributable to past smoking, and $S_{LC}^* - S_{LC,x}^*$ is the mortality avoidable because they stopped smoking x years ago. If RR and RR_x are the relative risks for life-long smokers without and with cessation respectively, then $S_{LC}^* = RR \times N_{LC}^*$ and $S_{LC,x}^* = RR_x \times N_{LC}^*$. Attributable and avoidable mortality x years after cessation is then $N_{LC}^* \times (RR_x - 1)$ and $N_{LC}^* \times (RR - RR_x)$. Of course, for those who never begin to smoke, $S_{LC,x}^* = N_{LC}^*$ and no mortality is attributed to this risk factor and $S_{LC,x}^* - N_{LC}^*$ (i.e. the whole excess mortality due to smoking) is avoidable. In Table 11.5, for example, for males who stop smoking, 34%, 58% and 82% of lung cancer mortality would be avoided within 10, 20 and 30 years from cessation, respectively, compared to what would have happened had they continued to smoke. The remaining 66%, 42% and 18% of mortality in these time periods is still attributable to their past smoking, despite cessation.

So far, by using CPS-II estimates of risk reversibility, we have implicitly addressed risk reversibility among those who have smoked since youth and stop smoking at a given age (because ACS smokers were life-long smokers, including at cessation time). We argued earlier, however, that such information is rare and unreliable, and that the only measure of accumulated history of smoking is the *SIR*. We also showed earlier that for each population, *SIR* is the equivalent prevalence of life-long smokers. Therefore, to obtain estimates of avoidable burden in each cohort, a fraction of whom have smoked for some period, the estimates of attributable and avoidable mortality x years after cessation are given by $SIR \times (S_{LC,x}^* - N_{LC}^*) = SIR \times N_{LC}^* \times (RR_x - 1)$ and $SIR \times (S_{LC}^* - S_{LC,x}^*) = SIR \times N_{LC}^* \times (RR - RR_x)$ respectively where, *SIR* is measured at the time of cessation (say in 2000 for estimates of avoidable burden as a result of cessation in 2000). We emphasize that this estimation, like all other uses of *SIR*, is based on the assumption that the equivalence of *SIR* with life-long smokers holds in estimating the benefits of cessation.

Finally, to apply this information to populations with different background (non-smoker) mortality rates, we used the results of Liu et al. (1998) who found that in China the relative risk for mortality from lung cancer was approximately constant in different cities where the non-smoker lung cancer mortality varies by a factor of 10. Therefore for populations whose background mortality is N_{LC} , the attributable burden due to past smoking x years after cessation is given by $SIR \times N_{LC} \times (RR_x - 1)$ and the avoidable burden as a result of cessation by $SIR \times N_{LC} \times (RR - RR_x)$.

SIR AFTER CESSATION

To estimate the decline in risk for other diseases, while accounting for the pre-cessation history of smoking, we needed to also estimate the value of SIR after cessation. Once again noting that SIR is the equivalent of life-long smokers in the population, the lung cancer mortality rate in the population as a whole, C_{LC} , can be re-written as:

$$C_{LC} = SIR \times RR \times N_{LC} + (1 - SIR) \times N_{LC}$$

If the same number of life-long smokers continue to smoke, SIR will remain more or less constant for the cohort and in each time period their new SIR will be given by the same relationship, with RR referring to the age-specific relative risk. On the other hand, if the smokers stop smoking, after x years their relative risk will decrease to RR_x a value less than RR at any time after cessation (Table 11.5). In this case, the new (post-cessation) lung cancer mortality rate, $C_{LC,x}$, is given by:

$$C_{LC,x} = SIR \times RR_x \times N_{LC} + (1 - SIR) \times N_{LC}$$

Replacing this value for $C_{LC,x}$ in Equation 2 to obtain the post-cessation smoking impact ratio, SIR_x , gives:

$$SIR_x = \frac{SIR \times RR_x \times N_{LC} + (1 - SIR) \times N_{LC} - N_{LC}}{S_{LC}^* - N_{LC}^*} \times \frac{N_{LC}^*}{N_{LC}}$$

with some algebraic simplification and noting that $S_{LC,x}^* = RR \times N_{LC}^*$,

$$SIR_x = SIR \frac{RR_x \times N_{LC} - N_{LC}}{RR \times S_{LC}^* - N_{LC}^*} \times \frac{N_{LC}^*}{N_{LC}}$$

or

$$SIR_x = SIR \times \frac{RR_x - 1}{RR - 1}$$

In other words, smoking cessation after x years results in scaling down the population SIR values relative to what they would be if smoking continued, with the scaling factor equal to the ratio of excess lung cancer risk after cessation to excess lung cancer risk if cessation did not occur.⁴

DISEASES OTHER THAN LUNG CANCER

The decline of relative risk for cardiovascular diseases as a function of time since cessation has been estimated in a number of studies, resulting in a range of estimates for the rate of decline (Cook et al. 1986; Dobson et al. 1991; Kawachi et al. 1997; LaCroix et al. 1991; Rogot and Murray 1980; Rosenberg et al. 1985, 1990; U.S. Department of Health and Human Services 1990c). Kawachi et al. (1997) also considered the decline in the risk of other causes of mortality, including all cancers and external causes.

To convert the estimates of relative risk reduction from the time of cessation for diseases other than lung cancer to the estimates of relative risk per unit of SIR we used the following notation: Let RR and RR' be the age-specific risks of lung cancer and disease A respectively for life-long smokers in the absence of cessation; RR_x and RR'_x the age-specific relative risks at some specific time, x , after cessation; and RR'_{SIR} and $RR'_{SIR,x}$ the relative risks of disease A per unit of SIR without and with cessation respectively. In all cases, $RR'_{SIR} = RR'$ since in the absence of cessation, the relative risks for life-long smokers (from CPS-II for example) would apply. It is $RR'_{SIR,x}$ that we are interested in, which, with the decline in SIR as outlined above, is now the risk of disease A "per unit of former life-long smoker". Four scenarios are possible.

1. If the rate of decline in relative risk for cause A is the same as the rate of decline in relative risk for lung cancer, then the relative risk per unit of SIR would stay constant at the pre-cessation level (except for age effects). This is because, in this case, all the benefits of cessation for both disease A and lung cancer (which move together) would be captured in the decline of SIR (to SIR_x). Therefore, in this case $RR'_{SIR,x} = RR'$.
2. If there had been no decline in lung cancer risk (i.e. $RR_x = RR$ and $SIR_x = SIR$) but there was a decline in the risk of disease A (i.e. $RR'_x < RR'$), then the relative risk per unit of SIR would decline at the same rate as the decline in relative risk for disease A after cessation. This is because, in this case, none of the benefits of cessation would be captured by decline in SIR , and therefore they need to be included in the estimates of relative risk per unit of SIR . In this case $RR'_{SIR,x} = RR'_x$.
3. If disease A is an acute condition, such as an injury or death (or possibly an acute respiratory infection) due to smoking-caused fires then cessation would result in complete removal of the risk for A , and $RR'_{SIR,x} = 1$.

4. If cessation results in lowering of the risk for both lung cancer and disease *A*, but at different rates, then the relative risk of disease *A* per unit of *SIR* after cessation, is given by the following relationship:

$$RR'_{SIR,x} = 1 + (RR'_x - 1) \times \frac{RR'_x - 1}{RR' - 1} \times \frac{RR - 1}{RR_x - 1}$$

The product of the terms $\frac{RR'_x - 1}{RR' - 1}$ and $\frac{RR - 1}{RR_x - 1}$ captures the relative drop in excess risk for disease *A* (first term) compared to lung cancer (second term). If the risk of disease *A* declines faster than lung cancer, then the relative risk per unit of *SIR* will decline to capture the additional benefits of cessation for disease *A*, compared to lung cancer. On the other hand, if the risk of disease *A* declines more slowly than lung cancer, then the relative risk per unit of *SIR* will rise to capture the reduced benefits of cessation for disease *A*, compared to lung cancer.⁵ Scenarios 1–3 above are special cases of this general relationship.

The estimates of *RR* and *RR_x* (for lung cancer) can be obtained from Figure 11.2 for different times since cessation. To estimate *RR'* and *RR'_x* for COPD and cardiovascular diseases, we used CPS-II data. In the analysis of risk reversibility for cardiovascular diseases for the first six-year follow up (1988), the estimates for those who had quit for less than one year showed inconsistent patterns (Table 11.6) even though subjects with cancer, heart disease and stroke were excluded at baseline (U.S. Department of Health and Human Services 1990b). This has been attributed to both high incidence of smoking resumption and the possible inclusion of subjects who stopped smoking as a result of symptoms from undiagnosed illness (U.S. Department of Health and Human Services 1990b).

Table 11.6 Decline in the risk of cardiovascular disease mortality with time since smoking cessation

Smoking status	RR (Male)		RR (Female)	
	≤20 cig/day	>20 cig/day	≤20 cig/day	>20 cig/day
Current smoker	1.93	2.02	1.76	2.27
Years since cessation among former smokers				
<1	1.43	2.56	2.13	1.41
1–2	1.61	1.57	0.87	1.16
3–5	1.49	1.41	1.31	0.96
6–10	1.28	1.63	0.74	1.88
11–15	0.99	1.16	1.2	1.37
≥16	0.88	1.09	1.17	1.12

Source: U.S. Department of Health and Human Services (1990b).

The rate of decline in relative risk and the unstable behaviour in the early years since cessation were nonetheless consistent with other studies (see Table 2 in U.S. Department of Health and Human Services 1990b and the estimates [Kawachi et al. 1997] from the Nurses' Health Study).

Re-analysis of ACS CPS-II data (1998 follow up) with more stringent exclusion of subjects with a history of chronic disease (lung cancer, COPD, vascular diseases) shows a more consistent pattern of risk reversibility, especially if the first cessation period is considered as 2 years, which reduces the likelihood of high smoking resumption rates. Figure 11.3 shows the estimates of relative risk for COPD and cardiovascular disease with time since cessation for males and females using this re-analysis. To apply risk reversibility with cessation to the CPS-II and Chinese baseline relative risk estimates in Tables 11.1 and 11.3, we estimated the *relative* decline in relative risks after x years of cessation (i.e. the ratio of relative risk x years after cessation to current smokers in Figure 11.3) and applied this to CPS-II or Chinese relative risks (i.e. RR') to obtain RR'_x .

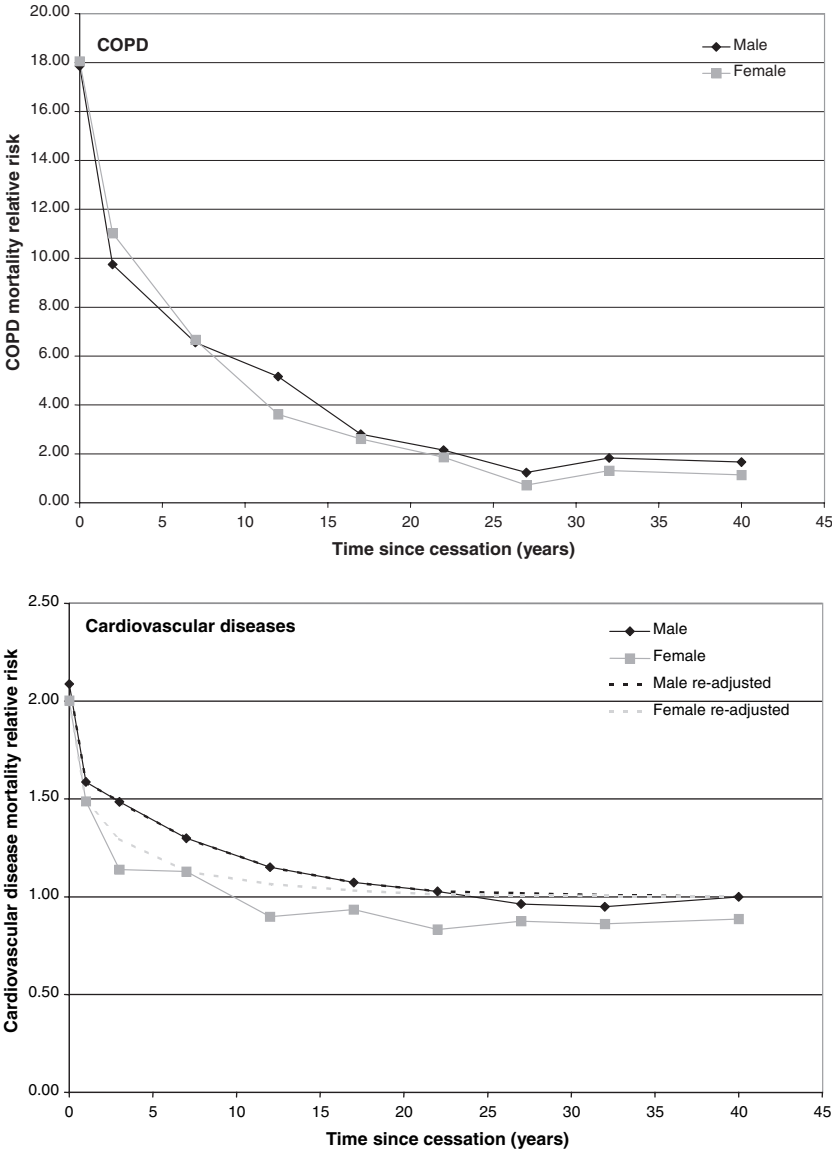
For cardiovascular disease among men, former smokers with long cessation periods have lower risk than never-smokers (statistically not significant). This pattern, however, is implausible and is likely to be due to unobserved confounders that have affected the behaviour of former smokers (e.g. the same factor may have motivated cessation and change in diet or physical activity) and hence, lowered their risk. To account for this, we re-adjusted the values for the 25–29 and 30–34-year cessation periods based on the trends between the 20–24 and ≥ 35 periods. For females, the estimates for cessation beyond 10 years were re-adjusted based on the male trends to asymptotically reach 1 for the longest cessation periods. The re-adjusted values are shown as dotted lines in Figure 11.3.

Given the potentially similar biological mechanisms of carcinogenesis, we assumed that all other cancers had the same rate of decline in relative risk as lung cancer. This is also seen in estimates of relative risk since smoking cessation for cancers including and excluding lung cancer analysed by Kawachi et al. (1997). Therefore, as described in scenario 1 above, the relative risk per unit of SIR remains constant for these diseases and the benefits of cessation in terms of avoidable mortality are fully captured by the decline in SIR . For all other disease categories, we used scenario 4 to estimate the risk per unit of SIR after cessation. We assumed that these diseases, for which reversibility data were not available, followed the same time pattern of decline as cardiovascular diseases, which decline more rapidly than lung cancer.

2.5 ANALYSIS OF UNCERTAINTY

In one taxonomy, uncertainty in quantitative risk assessment can be divided into *parameter uncertainty* and *model uncertainty* (Finkel 1990; National Research Council 1994). Parameter uncertainty includes the

Figure 11.3 Relative risk of chronic obstructive pulmonary disease (COPD) and cardiovascular diseases among former smokers



Note: Zero years represent current smokers. The estimates at 40 years represent cessation of more than 35 years in the subjects. Data are from ACS CPS-II 1998 follow up.

Source: American Cancer Society, unpublished data, 2003.

uncertainty quantifiable using random-variable methods such as that in a risk factor distribution, the magnitude of the risk factor–disease relationship, and burden of disease estimates. Model uncertainty is defined as uncertainty due to gaps in scientific theory (Finkel 1990; National Research Council 1994). In other words, model uncertainty occurs in those aspects of the analysis which are not currently quantifiable using a random-variable statistical methodology. In risk assessment, model uncertainty, broadly defined, also includes cases where exposure distributions or exposure–response relationships for populations are not known and are extrapolated from others. The uncertainty reported here is the 95% range of the combined distribution. In the following sections we describe the sources of uncertainty and the approach for quantifying parameter uncertainty.

PARAMETER UNCERTAINTY

Uncertainty for each of the variables and parameters in the analysis was estimated separately. These include population lung cancer mortality and never-smoker lung cancer mortality for each subregion, lung cancer mortality for smokers and never-smokers in the reference population, and relative risks. The first four parameters are those needed for the estimation of *SIR* which, when combined with the relative risk of mortality, gives the fraction of cause-specific mortality due to smoking. Estimates of uncertainty for individual parameters were combined in a simulation using Latin hypercube sampling to obtain overall uncertainty for *SIR* and relative risk values, and eventually the fraction of mortality or morbidity due to smoking. The parameter-specific uncertainty estimates were obtained as follows:

1. *Population lung cancer mortality*: The GBD estimates of mortality do not currently include complete analysis of uncertainty. To obtain uncertainty estimates for population lung cancer mortality, we assigned each country into one of four uncertainty categories based on the quality of available mortality data, as we described earlier. Lung cancer mortality information for the four country categories were assigned uncertainty ranges equal to 10%, 20%, 40% and 80% of the best-estimate, with a triangular distribution. Since for countries with good vital registration, 95% or higher confirmation rates of the cause reported on death certificates have been found (Percy et al. 1990; Percy and Muir 1989), 10% is more than double the observed uncertainty and a conservative estimate of true uncertainty. Eighty per cent uncertainty for the least certain countries, i.e. those with no established mortality reporting, implies that we have allowed nearly all of lung cancer mortality to be due to misclassification. Given that zero lung cancer mortality is implausible, higher levels of uncertainty could occur only on the upper side of these estimates, making this a conservative assumption for lung cancer mortality and *SIR*. Countries with less complete and/or less reliable data were

Table 11.7 Uncertainty (as % of best-estimate) assigned to reported or estimated country level lung cancer mortality

Uncertainty	Country ^a
10%	AMR-A – all; AMR-B – Chile, Costa Rica, Dominica, Uruguay; EMR-B – Bahrain; EUR-A – all except Croatia; EUR-B – Poland, Slovakia; EUR-C – Estonia, Hungary, Latvia, Lithuania, Russian Federation; WPR-A – all except Brunei Darussalam
20%	AMR-B – Argentina, Bahamas, Barbados, Colombia, Mexico, Panama, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and Grenadines, Trinidad and Tobago, Venezuela; EMR-B – Kuwait; EUR-A – Croatia; EUR-B – Armenia, Bosnia and Herzegovina, Bulgaria, Romania, The former Yugoslav Republic of Macedonia, Serbia and Montenegro; EUR-C – Belarus, Republic of Moldova, Ukraine; WPR-A – Brunei Darussalam; WPR-B – China
40%	AFR-D – Mauritius; AFR-E – South Africa; AMR-B – Antigua and Barbuda, Belize, Brazil, Grenada, Jamaica, Suriname; EMR-D – Egypt; EUR-B – Albania, Georgia, Kyrgyzstan, Tajikistan, Uzbekistan; EUR-C – Kazakhstan; SEAR-B – Thailand; WPR-B – Fiji, Malaysia, Marshall Islands, Republic of Korea
80%	AFR-D – all except Mauritius; AFR-E – all except South Africa; AMR-B – Dominican Republic, El Salvador, Guyana, Honduras, Paraguay; AMR-D – all; EMR-B – all except Bahrain and Kuwait; EMR-D – all except Egypt; SEAR-B – Indonesia, Sri Lanka; SEAR-D – all; WPR-B – all except China, Fiji, Malaysia, Marshall Islands, Republic of Korea

^a By subregion.

assumed to have 20% or 40% uncertainty around the best-estimate of lung cancer mortality. Table 11.7 shows the countries assigned to each uncertainty category.

2. Never-smoker lung cancer mortality: For China, estimates of the uncertainty for never-smoker lung cancer mortality rates from the proportional mortality study were used (Liu et al. 1998). For all other countries, where non-smoker lung cancer mortality rates were assumed to be those of CPS-II, we assumed an uncertainty of 15% around CPS-II estimates plus the statistical uncertainty of the CPS-II estimates themselves. Fifteen per cent is approximately equivalent to the whole (non-smoker) population being exposed to the highest levels of air pollution, such as that in the centre of the industrial city of Cracow, Poland, which resulted in a 14% increase in lung cancer mortality over the period 1980–1985 (Jedrychowski et al. 1990) or the whole (never-smoker) population being exposed to more than $10 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ (particulates below 2.5 microns in diameter) (Pope et al. 2002). Because the net difference between accumulated exposure to additional lung cancer risk factors (radon, urban air pollution, biomass smoke) in any two countries is less than the whole population, 15% is a relatively large uncertainty range for never-smoker lung cancer mortality.

3. *Reference population smoker and never-smoker lung cancer mortality*: We used statistical uncertainty of the CPS-II population since the reference population is constant in all regions of the world and the excess mortality of the reference population of smokers is simply a normalizing factor.

4. *Relative risk*: Uncertainties in relative risks were obtained directly from the CPS-II and Chinese mortality studies as well as the decline in risk due to cessation.

5. *Confounding and extrapolation of relative risk and correction factor*: To avoid overestimation of risk as a result of confounding in CPS-II relative risks, as well as from the extrapolation of relative risk to other regions, we have reduced the relative risk values by 30% to 50% for various diseases. To account for uncertainty in the level of the correction factor, we assumed that the 30% correction factor could vary between 10% and 50% with a triangular distribution. The lower end of this range corresponds to the typical amount of reduction in excess risk seen after adjustment for covariates in the re-analysis of CPS-II data (Thun et al. 2000) and seen in other studies such as the magnitude of confounding due to diet found by Law et al. (1997). The upper end is the conservative correction used by Peto et al. (1992) before the level of confounding was known and larger than those in the CPS-II re-analysis (Thun et al. 2000). The 50% correction factor used for the “other medical causes” group was assumed to be highly uncertain and in the range of 10% to 90% with a triangular distribution. We also assumed that the 5% correction factor for estimates of relative risk for China were in the range of 0–10% with a triangular distribution.

MODEL UNCERTAINTY

Although lung cancer mortality provides a biological marker for accumulated exposure to the hazards of smoking in general, the question remains whether it equally represents the accumulated hazards for each of the diseases considered in this analysis. Two factors may reduce the accuracy of excess lung cancer and *SIR* as markers of accumulated hazard:

1. *If the cigarette smoke characteristics that cause lung cancer are not fully correlated with those that cause the other hazard*: While the carcinogens in cigarette smoke are the cause of cancer, the concentration or size distribution of respirable particles or other pollutants may be a better indicator of some of the other health effects. The validity of the *SIR* method compared to direct estimates in the United States was estimated by Peto et al. (1992). Comparisons with other (largely direct) methods for other countries also show consistent results (Bronnum-Hansen and Juel 2000; Valkonen and van Poppel 1997).

2. *If the time-to-hazard (or hazard accumulation function as described in chapter 1) is different for lung cancer and other diseases caused by smoking:* Lung cancer is caused by exposure and hazard accumulated over an extended period of time spent smoking. This property may be shared by some other outcomes of smoking, such as other cancers and COPD. Some of the other health effects of smoking, such as acute respiratory diseases, may occur after immediate exposure, and others, such as cardiovascular disease, are determined by a period of exposure that may be somewhat shorter than that of lung cancer. With these differences, when smoking is on the rise, an indicator based on excess lung cancer—which generally occurs later—would underestimate the impacts of those diseases that occur earlier. On the other hand some time after smoking begins to decline, an indicator based on excess lung cancer would overestimate the impacts of those diseases, where risk declines faster with cessation than lung cancer.⁶ Since smoking has been increasing in most regions of the world over the past two or three decades, the net effect of this would be an underestimation of current global mortality due to cardiovascular and some other diseases in our analysis.

In addition to the uncertainty in the use of *SIR* as exposure variable, the following other sources of uncertainty have not been quantified:

3. *The impact of environmental tobacco smoke on SIR estimates:* The carcinogenic effects of cancer agents are likely to apply at low levels without a threshold (Peto 1978). Therefore exposure to environmental tobacco smoke (ETS) is a likely cause of lung cancer. This relationship, as well as the impact of ETS on cardiovascular disease, has also been established in epidemiological studies (Australia National Health and Medical Research Council 1997; Environmental Protection Agency 1992; Hackshaw et al. 1997; Law et al. 1997; UK Department of Health Scientific Committee on Tobacco and Health 1998). Although we did not conduct a separate analysis of the burden of disease due to ETS, because of its relationship to lung cancer, ETS exposure affects *SIR* estimates.

Of the four variables in the *SIR* relationship (C_{LC} , N_{LC} , S_{LC}^* , and N_{LC}^* in Equation 2), the effects of ETS are smallest on life-long smokers (S_{LC}^*) who are almost completely affected by direct smoking. The lung cancer mortality of the population as a whole (C_{LC}) is also affected more by direct smoking but nonetheless captures the effects of both direct and indirect exposure to tobacco smoke. The effects of ETS are largest on never-smokers (N_{LC} and N_{LC}^*) who would otherwise not be exposed to tobacco smoke. Therefore, both N_{LC} and N_{LC}^* are larger in the presence of ETS than they would be in its absence. Since C_{LC} is almost always smaller than S_{LC}^* , increasing non-smoker lung cancer rates will result in

a larger relative reduction (through subtraction) in the numerator of Equation 1 compared to the denominator, and therefore an underestimation of *SIR* values.

4. *Estimates of non-fatal health outcomes:* To obtain relative risks for non-fatal effects of these diseases, we have assumed that smoking increases mortality by increasing disease incidence (rather than modifying case fatality) for cancers and COPD. We have assumed a potential change in either the incidence or the severity/case fatality for all other causes. Given that most of the diseases affected by smoking are chronic diseases as a result of chronic exposure, this is a conservative assumption and requires further investigation using epidemiological studies on the relationship between smoking and disease incidence.

5. *Future exposure and risk reversibility:* Estimates of avoidable burden are possibly the most uncertain component of a risk assessment exercise because of the number of assumptions that, by definition, are needed for estimates of future burden. These include estimates of the “business-as-usual” trends of smoking and lung cancer and estimates of risk reversibility (reduction in relative risk) for those current smokers who stop smoking.

The future estimates of lung cancer mortality and *SIR* (see below) are based on a number of assumptions. These include the descriptive model of the tobacco epidemic and its parameters, the estimates of total tobacco consumption, and the statistical model used for estimating lung cancer based on consumption. As we discussed under risk reversibility, the estimates of decline in the relative risk for lung cancer, and more importantly for other diseases, after smoking cessation are derived from a limited number of studies and extrapolated to people of different ages, sexes and smoking histories. At the same time it may be possible that the benefits of cessation are more dependent on the specific history of smoking such as duration of smoking and age at cessation, than the current accumulated risk (which is captured by *SIR*) as also seen in the comparison between male and female reductions in lung cancer risk in Table 11.5. In this case, the use of *SIR* as the indicator of pre-cessation history would create an additional source of uncertainty. At the same time, after a few decades, the potential health benefits of smoking reduction occur among those who would be prevented from smoking altogether. In this case, the longer-term estimates of avoidable burden would be less dependent on the specifics of risk reversibility and depend only on the estimates of risk among life-long smokers, which are known with much greater certainty.

2.6 ADDITIONAL ORAL CANCER MORTALITY DUE TO ORAL TOBACCO USE

Oral tobacco use, in the form of chewing of betel-quinid with tobacco, is common in many parts of south Asia, and in particular in the Indian sub-continent (Bhonsle et al. 1992). Although oral tobacco use has been associated with increased risk of all-cause mortality (Gupta and Mehta 2000), we focus here on the risk of oral cancer which is the most-widely known and studied outcome of this risk behaviour (Gupta et al. 1982; International Agency for Research on Cancer (IARC) 1984; U.S. Department of Health and Human Services 1986), and a leading form of cancer mortality in the region (Parkin et al. 1997). Smoking in India is much more common among men than women whereas the prevalence of tobacco chewing is of comparable magnitude, although still higher among men (Corrao et al. 2000; Gupta 1996; WHO 1997). Given the correlation between smoking and oral tobacco use, many cases of oral cancer are likely to be affected by both habits. To report the total burden of disease due to both forms of tobacco use, we made estimates of only those cases of oral cancer that are caused by tobacco chewing *in addition* to smoking. The estimates were applied to SEAR-D only. Oral tobacco use is common throughout the region, whose mortality estimates are nonetheless dominated by those from India.

We obtained estimates of the fraction of total chewers who do not smoke (p_c) and the fraction of total smokers who do not chew (p_s) using a survey of tobacco habits in various ethnic and religious groups in India (Gupta 1996). The estimates of oral cancer for smokers who do not chew (p_s) are included in those from the application of the *SIR* method. Those who both smoke and chew (p_{sc} as a fraction of total smokers), have a higher risk than smokers-only, by a factor $RR_{(chewing+smoking)/smoking}$, because of their additional chewing habit. We used $RR_{(chewing+smoking)/smoking}$ to increase the CPS-II relative risk estimates for the upper-aerodigestive cancer category for this group,⁷ and applied these increased risk estimates to oral cancer mortality. The difference between these new estimates of oral cancer (using increased relative risk) and those using the CPS-II risk estimate, are the *additional* deaths due to oral tobacco use over and above those accounted for by smoking, among those who both chew and smoke. Finally, for those who chew only (p_c), we used the corresponding relative risk, $RR_{(chewing\ and\ not\ smoking)}$, to obtain estimates of oral cancer mortality, which are independent from those obtained using the *SIR* method. For this group, we directly used the estimated prevalence of chewing. Although oral cancer as a result of tobacco chewing is also dependent on accumulated exposure, the relative risk estimates from recent literature are directly applicable because they were used in the same time period and region where epidemiological studies took place.

For males, we used the estimate that 20% of all smokers also chew (WHO 1997), which is close to the largest overlap of any ethnic or reli-

gious group found in a study of socio-demographic characteristics of tobacco users (Gupta 1996). Assuming a 40% prevalence of smoking and a 65% prevalence of total tobacco use, this implies that 32% of adult males smoke only, 8% of adult males both smoke and chew, and another 25% chew only, consistent with other estimates (WHO 1997). For females, we used a 33% prevalence of total tobacco use and a 3% prevalence of smoking (Corrao et al. 2000; WHO 1997). We also assumed that all female smokers also chew tobacco (Gupta 1996), hence 30% of adult females are chewers-only.

A review of studies prior to 1982 that estimated the relative risk of oral cancer due to tobacco chewing is provided by Gupta et al. (1982). We did not use these estimates since the definitions of cancer sites or control for covariates were not consistent with more recent studies. All these studies nonetheless show statistically significant increased risk of oral cancer due to tobacco chewing. A number of recent studies have estimated the relative risks for oral cancer (or one of its sub-types) based on stratification by smoking and tobacco chewing, all finding a significant increase in the risk of oral cancer among chewers regardless of their smoking habits (Balaram et al. 2002; Dikshit and Kanhere 2000; Rao et al. 1994; Sankaranarayanan et al. 1989a, 1989b, 1990). A description of recent studies and their estimates of relative risk (or odds ratio) of oral cancer due to chewing tobacco among smokers and non-smokers is provided in Table 11.8. Those studies that provided separate analysis according to the frequency of chewing also consistently show an increasing dose-response relationship. Note that in some of the studies, those who both chew and smoke tobacco had lower risk than those who used oral tobacco only. This may be because smokers chewed less tobacco than those whose only habit was tobacco chewing. We used a relative risk of 3.64 for chewing only and 1.7 for those who both chew and smoke relative to smokers. These values, which are lower than almost all other studies, are from non-drinkers in the study of Rao et al. (1994) to avoid confounding due to alcohol consumption, an important risk factor for oral cancer.

3. RESULTS

3.1 EXPOSURE (*SIR*) ESTIMATES

Figure 11.4 shows *SIR* estimates for females and males in developing and industrialized countries. We have also shown in the figure legend the best estimate of adult smoking prevalence for each subregion. As discussed above, prevalence estimates are uncertain and based on data from a limited number of countries. At the same time, as discussed by Jha et al. (2002), despite uncertainties in country-level and age-specific estimates, they provide a reasonable indication of current smoking status among adults in each subregion. The subregion WPR-B includes China.

Table 11.8 Summary of studies on the relationship between tobacco chewing, smoking and oral cancer^a

Study location (reference)	Cancer site (ICD code)	Number of cases and control choice	Covariate adjustment	Effect size
Kerala (Sankaranarayanan et al. 1989a)	Oral tongue and the floor of the mouth (ICD 141.1–141.4 and 144)	228 cases; 453 hospital-based controls matched for age, sex and religion	Age	$RR_{\text{chewing}} = 6.13$; $RR_{\text{smoking}} = 4.98$; $RR_{\text{chewing+smoking}} = 7.02^b$
Kerala (Sankaranarayanan et al. 1989b)	Gingiva (ICD 143.0 and 143.1)	187 cases; 895 hospital-based controls with respiratory, intestinal, and genito-urinary infections, excluding malignancy in sites other than head and neck	Age	$RR_{\text{chewing}} = 11.76$; $RR_{\text{smoking}} = 4.21$; $RR_{\text{chewing+smoking}} = 16.48^b$
Kerala (Sankaranarayanan et al. 1990)	Buccal and labial mucosa (ICD 145.0, 145.1, and 145.6–140.3 and 140.4)	414 cases; 895 hospital-based controls with non-malignant conditions	Age, religion	$RR_{\text{chewing}} = 14.28$; $RR_{\text{smoking}} = 4.21$; $RR_{\text{chewing+smoking}} = 21.46^b$
Bangalore (Nandakumar et al. 1990)	Oral cavity (140–141 and 143–145 excluding 141.0)	348 cases; 348 hospital-based controls with non-malignant conditions matched for age, sex and residence	Age, sex, religion and diet	$RR_{\text{chewing}} = 10.2$; $RR_{\text{smoking}} = 3.5$; $RR_{\text{chewing+smoking}} = 9.2^b$

continued

Table 11.8 Summary of studies on the relationship between tobacco chewing, smoking and oral cancer^a (continued)

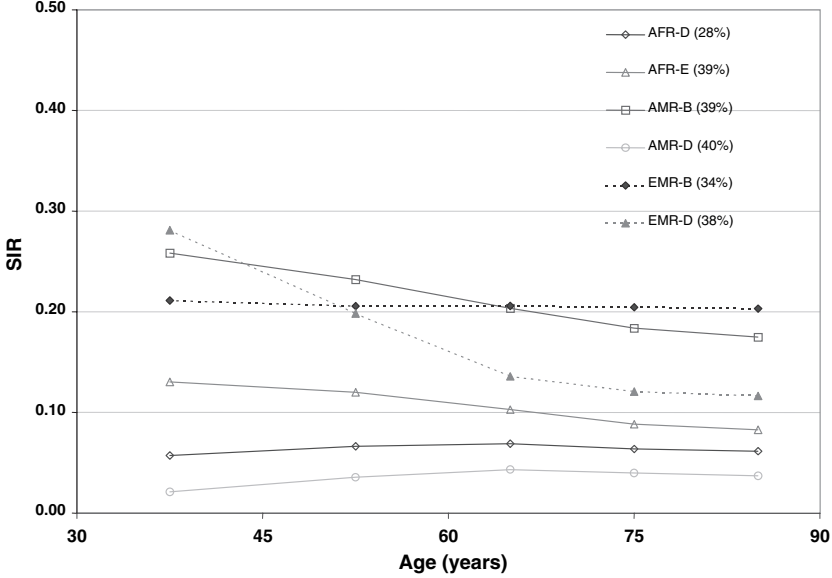
Study location (reference)	Cancer site (ICD code)	Number of cases and control choice	Covariate adjustment	Effect size
Bombay (Rao et al. 1994)	Oral (excluding 141.0 and 145.3)	713 male cases; 635 male hospital-based controls without cancer; benign tumour and infectious disease	Age and area of residence	Non-drinkers: $RR_{\text{chewing}} = 3.64$; $RR_{\text{smoking}} = 1.69$; $RR_{\text{chewing+smoking}} = 2.93$ Drinkers: $RR_{\text{chewing}} = 4.32$; $RR_{\text{smoking}} = 2.44$; $RR_{\text{chewing+smoking}} = 8.88$
Bhopal (Dikshit and Kanhere 2000)	Oral cavity (140.0–144.9, 145.0–145.2, 145.5–145.9)	148 male cases; 260 controls randomly selected from a survey of tobacco habits	Age	$OR_{\text{chewing}} = 10.6$; $OR_{\text{smoking}} (<10 \text{ cig/day}) = 1.0$; $OR_{\text{smoking}} (\geq 20 \text{ cig/day}) = 4.9$; $OR_{\text{chewing+smoking}} (<20 \text{ cig/day}) = 8.4$; $OR_{\text{chewing+smoking}} (\geq 20 \text{ cig/day}) = 16.3$
Southern India (Balaram et al. 2002)	Oral	591 cases; hospital-based controls matched by medical centre, age and sex	Age, sex, medical centre, education and alcohol	$OR_{\text{chewing}} = 9.19$; $OR_{\text{smoking}} (<20 \text{ cig/day}) = 1.78$; $OR_{\text{smoking}} (\geq 20 \text{ cig/day}) = 3.69$; $OR_{\text{chewing+smoking}} (<20 \text{ cig/day}) = 8.86$; $OR_{\text{chewing+smoking}} (\geq 20 \text{ cig/day}) = 6.69^b$

^a All studies were case-control and took place in India.

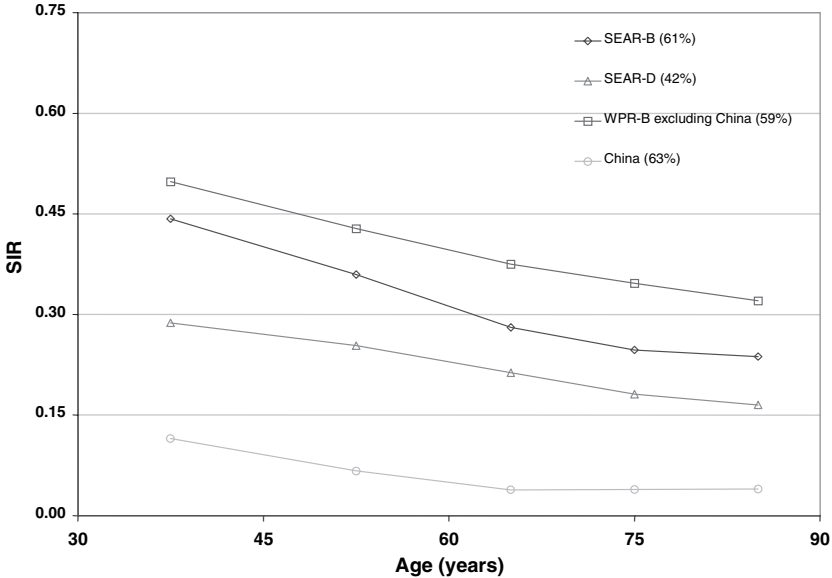
^b The effect estimates are for males only since none or few of the female cases smoked.

Figure 11.4 Estimates of smoking impact ratio (SIR) by age, sex and subregion

(a) Developing countries (male) I



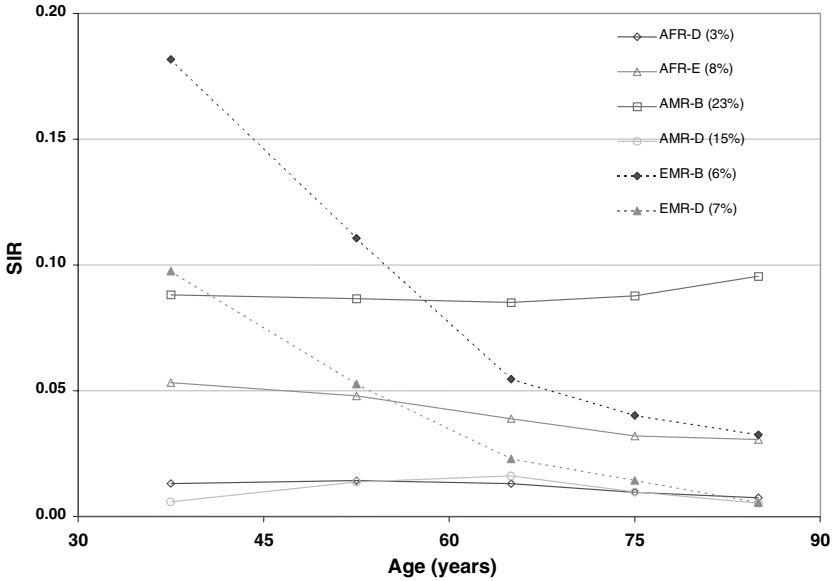
(b) Developing countries (male) II



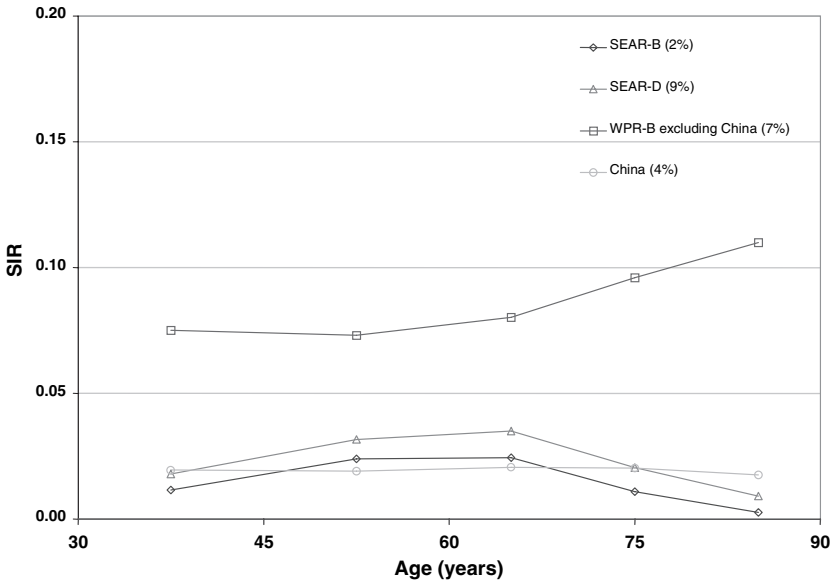
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Figure 11.4 Estimates of smoking impact ratio (SIR) by age, sex and subregion (continued)

(c) Developing countries (female) I



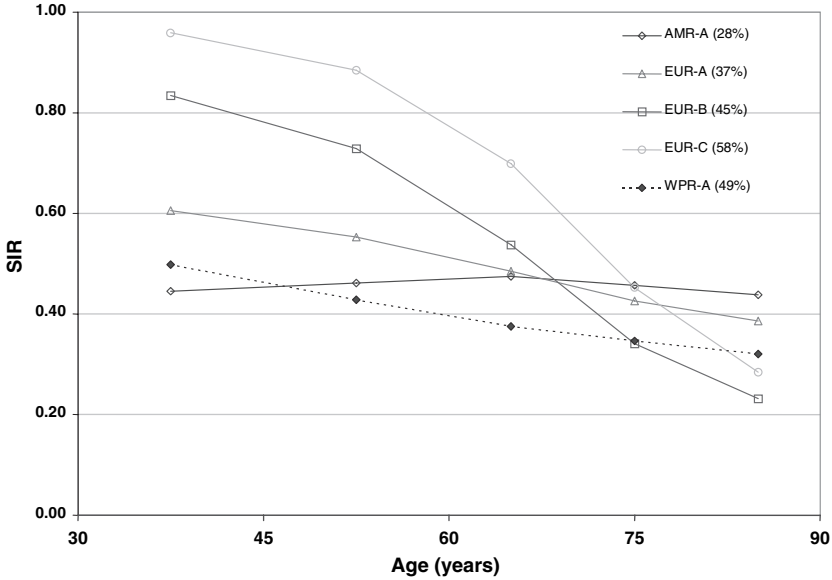
(d) Developing countries (female) II



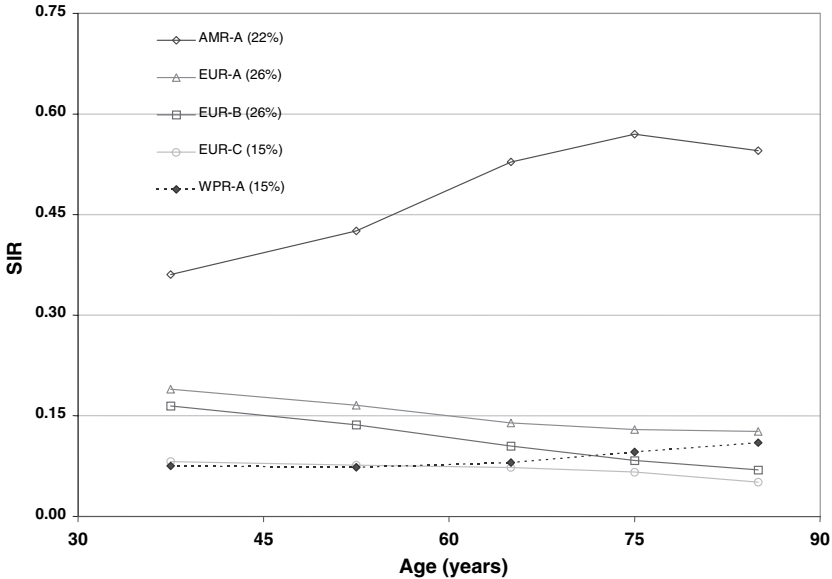
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Figure 11.4 Estimates of smoking impact ratio (SIR) by age, sex and subregion (continued)

(e) Industrialized countries (male)



(f) Industrialized countries (female)



Note: The vertical axis scales are different in the different panels of the figure to increase resolution. The figures in parentheses next to the legend indicate estimates of the subregional prevalence.

Source: Ezzati and Lopez (2003).

Hence the aggregate estimates for this subregion are dominated by the Chinese data. This division allows the characteristics of the other countries in the subregion to also be considered, in particular given the role of higher background lung cancer mortality in China. Table 11.9 provides the *SIR* distribution, divided as defined earlier.

A number of important features of the global smoking epidemic can be seen in the different panels of Figure 11.4:

1. The largest accumulated risk of smoking for males aged <70 years in the countries of eastern Europe and the former Soviet Union (EUR-B and EUR-C). For older males (aged ≥ 70 years), North America and western European countries have the largest accumulated risk. These two results are consistent with the very high current and recent prevalence of smoking among eastern European men which has been sustained for several decades, and the longer history of smoking among North American and western European men.

The accumulated hazards of smoking among men were lowest in AMR-D, AFR-D and AFR-E. In these subregions, the rise in smoking has been a recent phenomenon. The results for China (WPR-B) are particularly important and instructive. The background-adjusted *SIR* values for China were still fairly low, despite high lung cancer mortality in this country. At the time of the Liu et al. (1998) study (in 1990) the relative risk of lung cancer for a Chinese smoker was less than 3.0 because of the more recent start of the epidemic in this country. Over the next few decades, increasing accumulated exposure to smoking may well result in rising lung cancer mortality in China to levels comparable to populations with life-long smokers (such as those in North America and western Europe where the relative risks for lung cancer are approximately 20). Together with the finding of Liu et al. (1998) that smoking acts to “amplify” the high background rates of lung cancer, this increase in accumulated hazard will result in enormous lung cancer (and other) mortality in China.

Examining prevalence and *SIR* patterns simultaneously also emphasizes the importance of considering accumulated risks. For example, the current prevalence of smoking among adult men in AMR-A was equal to AFR-D and lower than all other subregions in the developing world. At the same time, the *SIR* values for AMR-A males were larger than those of most developing subregions because of the histories of smoking. In AMR-A, smoking has been declining and current prevalence would underestimate the current impacts of smoking. In developing countries, on the other hand, smoking has been rising in recent decades with current prevalence being comparable to AMR-A, but the accumulated hazards were still lower.

2. For women, AMR-A had the single highest accumulated risk from smoking. Although women in many countries in western Europe

Table 11.9 Prevalence of exposure by subregion, age and sex

Subregion	Exposure variable ^a	Prevalence of exposure (%)																	
		0-4 years ^b		5-14 years ^b		15-29 years ^b		30-44 years		45-59 years		60-69 years		70-79 years		≥80 years			
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female		
AFR-D	1	NA	NA	NA	NA	NA	96	96	75	96	75	96	75	96	75	96	75	96	
	2	NA	NA	NA	NA	NA	4	23	4	23	4	23	4	25	4	25	4	4	
	3	NA	NA	NA	NA	NA	0	2	1	2	1	2	1	0	0	0	0	0	
AFR-E	1	NA	NA	NA	NA	NA	88	88	55	88	55	88	55	88	55	88	55	88	
	2	NA	NA	NA	NA	NA	7	43	8	43	8	45	10	45	12	45	11	11	
	3	NA	NA	NA	NA	NA	5	2	4	2	4	0	2	0	0	0	0	0	
AMR-A	1	NA	NA	NA	NA	NA	66	55	55	59	50	45	55	39	72	78	78	78	
	2	NA	NA	NA	NA	NA	0	0	0	0	0	0	0	0	0	0	0	0	
	3	NA	NA	NA	NA	NA	44	34	45	41	50	55	45	61	28	22	22	22	
AMR-B	1	NA	NA	NA	NA	NA	75	60	75	60	75	60	75	60	75	60	75	60	
	2	NA	NA	NA	NA	NA	4	20	15	21	18	20	24	22	25	17	17	17	
	3	NA	NA	NA	NA	NA	35	5	25	4	22	5	16	3	15	8	8		
AMR-D	1	NA	NA	NA	NA	NA	84	61	84	61	84	61	84	61	84	61	84	61	
	2	NA	NA	NA	NA	NA	16	39	16	39	16	39	16	39	16	39	16	16	
	3	NA	NA	NA	NA	NA	0	0	0	0	0	0	0	0	0	0	0	0	
EMR-B	1	NA	NA	NA	NA	NA	66	77	66	94	66	94	66	94	66	94	66	94	
	2	NA	NA	NA	NA	NA	8	0	13	0	8	0	12	0	11	3	3	3	
	3	NA	NA	NA	NA	NA	27	23	22	6	26	6	23	6	24	3	3	3	
EMR-D	1	NA	NA	NA	NA	NA	92	63	92	63	92	63	92	63	92	63	100	100	
	2	NA	NA	NA	NA	NA	0	25	7	29	7	33	8	33	0	0	0	0	
	3	NA	NA	NA	NA	NA	37	8	13	1	8	1	4	0	5	0	0	0	
EUR-A	1	NA	NA	NA	NA	NA	37	74	45	74	52	74	63	74	63	74	63	74	
	2	NA	NA	NA	NA	NA	0	0	0	5	0	13	0	12	0	14	0	14	
	3	NA	NA	NA	NA	NA	63	26	55	20	48	13	37	14	37	12	12	12	

continued

Table 11.9 Prevalence of exposure by subregion, age and sex (continued)

Subregion	Exposure variable ^a	Prevalence of exposure (%)																	
		0–4 years ^b		5–14 years ^b		15–29 years ^b		30–44 years		45–59 years		60–69 years		70–79 years		≥80 years			
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female		
EUR-B	1	NA	NA	NA	NA	74	74	25	74	55	74	55	74	55	74	55	74		
	2	NA	NA	NA	NA	0	2	0	12	0	18	5	21	30	2	30	2		
	3	NA	NA	NA	NA	88	23	75	14	45	8	40	4	15	0	15	0		
EUR-C	1	NA	NA	NA	NA	2	85	7	85	42	85	42	85	42	85	42	85		
	2	NA	NA	NA	NA	0	6	0	7	0	10	0	7	46	15	46	15		
	3	NA	NA	NA	NA	98	9	93	8	58	5	58	9	12	0	12	0		
SEAR-B	1	NA	NA	NA	NA	40	97	40	97	40	97	40	97	40	97	40	100		
	2	NA	NA	NA	NA	0	3	24	0	35	0	43	2	43	0	43	0		
	3	NA	NA	NA	NA	60	0	36	3	25	3	17	0	17	0	17	0		
SEAR-D	1	NA	NA	NA	NA	55	91	55	91	55	91	55	91	55	91	55	91		
	2	NA	NA	NA	NA	6	9	19	6	24	6	33	9	35	9	35	9		
	3	NA	NA	NA	NA	39	0	26	3	21	4	12	0	10	0	10	0		
WPR-A	1	NA	NA	NA	NA	51	85	51	85	51	85	51	84	51	84	51	85		
	2	NA	NA	NA	NA	28	8	37	6	25	4	4	0	0	0	0	0		
	3	NA	NA	NA	NA	20	7	12	9	23	9	45	16	49	15	49	15		
WPR-B (excluding China)	1	NA	NA	NA	NA	31	90	31	90	31	90	31	90	31	90	31	90		
	2	NA	NA	NA	NA	0	0	26	2	27	0	34	0	42	0	42	0		
	3	NA	NA	NA	NA	69	10	43	8	42	10	35	9	27	10	27	10		
China	1	NA	NA	NA	NA	37	96	37	96	37	96	37	96	37	96	37	96		
	2	NA	NA	NA	NA	63	1	63	2	63	1	63	1	63	3	63	3		
	3	NA	NA	NA	NA	0	2	0	1	0	3	0	2	0	0	0	1		

NA Not applicable.

^a The exposure variable is smoking impact ratio (SIR), divided into three categories: 1) $SIR = 0$; 2) $0 < SIR \leq 0.5$; 3) $0.5 < SIR \leq 1.0$ as described earlier.^b No risk is estimated for those aged <30 years.

(EUR-A) have smoked for a long time (in particular in the United Kingdom), smoking is a more recent phenomenon in the southern parts of the continent, and therefore the overall *SIR* is still lower than in AMR-A. *SIR* values for women were consistently low in developing countries except for younger and middle-aged women in AMR-B (Latin America and the Caribbean) and young adult women in EMR-B. Once again, comparing *SIR* values for females in AMR-A, whose current prevalence of smoking is 22% (reflecting recent declines in female smoking in North America), with those for males in many subregions of the developing world, who have higher current prevalence but lower *SIR*, illustrates the inadequacy of current prevalence as a marker for smoking risk.⁸

3. Age patterns of *SIR* estimates for the different subregions also provide information about the state of the smoking epidemic. For each age–sex group, *SIR* is excess lung cancer, relative to the same age–sex group of American smokers in the 1980s. Among men in industrialized countries, the *SIR* values were relatively constant across ages in AMR-A, but decline with age in other industrialized regions, with EUR-A being closest to the constant pattern. These inter-subregional and intra-subregional age patterns imply that, when compared to the same age group of American smokers in the 1980s, age patterns of smoking have been relatively constant in North America whereas smoking has been more concentrated among younger and middle-age men in Europe and the Western Pacific, especially in the former Soviet Union (EUR-C). In the developing countries of Latin America and the Caribbean, the Eastern Mediterranean, and sub-Saharan Africa, smoking also seems to have had fairly constant effects across ages, when each is compared to the same age group of American smokers in the 1980s. In Asia, on the other hand, smoking had a greater impact on younger and middle-aged male cohorts than at older ages when compared to the same age group of American smokers in the 1980s.

Overall, the age patterns of *SIR* were less variant among women in both developing and industrialized countries compared to men. In AMR-B, EMR-B, EMR-D, and the EUR subregions there is more smoking among younger and middle-age women than at older ages, when each is compared to the same age group of female American smokers in the 1980s. In Asia, female smoking seems to peak among the middle-aged cohorts, which may reflect social factors that would prevent smoking among many young women. In North America, the distribution was more towards older age groups when compared to the same age group of female American smokers in the 1980s.

3.2 MORTALITY AND DISEASE BURDEN DUE TO SMOKING

Tables 11.10 and 11.11 provide the estimated number of smoking-attributable deaths and DALYs for males and females in developing and industrialized countries. Table 11.12 divides the estimates of global mortality

due to smoking into broad causes and age groups. Although the results were estimated for the eight age groups described in Table 11.9 (assumed to be zero for the first three age groups <30 years), they are reported in two age groups (30–69 and ≥70 years) to be comparable with previous estimates of mortality due to smoking, such as those in Peto et al. (1992). The distribution of mortality and DALYs by broad disease groups is given in Figures 11.5 and 11.6.

The 4.83 (95% CI 3.94–5.93) million deaths due to smoking accounted for 12% of total global adult (aged ≥30 years) mortality.⁹ The shares of adult male and female total mortality due to smoking were 18% and 5%, respectively. Of these deaths, 2.69 million were among those aged 30–69 years, resulting in a larger number of life years lost to premature mortality, and 2.14 million among those aged >69 years. As seen in a comparison of Tables 11.10 and 11.11, although developing and industrialized countries accounted for virtually equal numbers of global mortality, the burden of disease associated with this risk factor

Table 11.10 Mortality (in millions) due to smoking in developing and industrialized countries, 2000

	Male	Female	Total
Developing ^a	2.02 (1.56–2.50) ^c	0.38 (0.25–0.65) ^c	2.41 (1.80–3.15) ^c
Industrialized ^b	1.81 (1.62–2.02) ^c	0.61 (0.52–0.75) ^c	2.43 (2.13–2.78) ^c
Total	3.84 (3.17–4.53) ^c	1.00 (0.76–1.40) ^c	4.83 (3.94–5.93) ^c

^a Developing countries include those in AFR, AMR-B, AMR-D, EMR, SEAR and WPR-B subregions.

^b Industrialized countries include those in AMR-A, EUR and WPR-A.

^c Numbers in parentheses are 95% confidence intervals.

Table 11.11 Loss of healthy life years (in thousands of DALYs) due to tobacco-caused mortality and morbidity in developing and industrialized countries, 2000

	Male	Female	Total
Developing ^a	28 015 (4.4%) ^c	4 962 (0.8%) ^c	32 977 (2.7%) ^c
Industrialized ^b	20 162 (17%) ^c	5 942 (6.2%) ^c	26 104 (12%) ^c
Total	48 177 (6.3%) ^c	10 904 (1.6%) ^c	59 081 (4.1%) ^c

^a Developing countries include those in AFR, AMR-B, AMR-D, EMR, SEAR and WPR-B subregions.

^b Industrialized countries include those in AMR-A, EUR and WPR-A.

^c Figures in parentheses indicate the proportion of overall disease burden in each category attributable to smoking.

Table 11.12 Global mortality due to smoking by cause, sex and age, 2000

Cause ^a	Male				Female			
	30–69 years		≥70 years		30–69 years		≥70 years	
	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)
Lung cancer	398	77	294	82	77	44	79	54
Upper aerodigestive cancer ^b	152	46	66	42	17	12	15	13
Other cancer ^b	195	15	135	13	17	1	24	2
COPD ^c	269	54	433	52	86	24	178	19
Other respiratory diseases	274	22	93	11	34	5	32	4
Cardiovascular diseases	848	24	476	12	143	6	223	4
Other attributable medical causes	0	0	0	0.0	0	0	0	0
Other medical causes	145	17	57	8	36	5	35	4
Total medical	2 280	22	1 556	18	410	6	587	5
Non-medical (accidents and injuries)	0	0	0	0.0	0	0	0	0
Total mortality	2 280	19	1 556	18	410	5	587	5

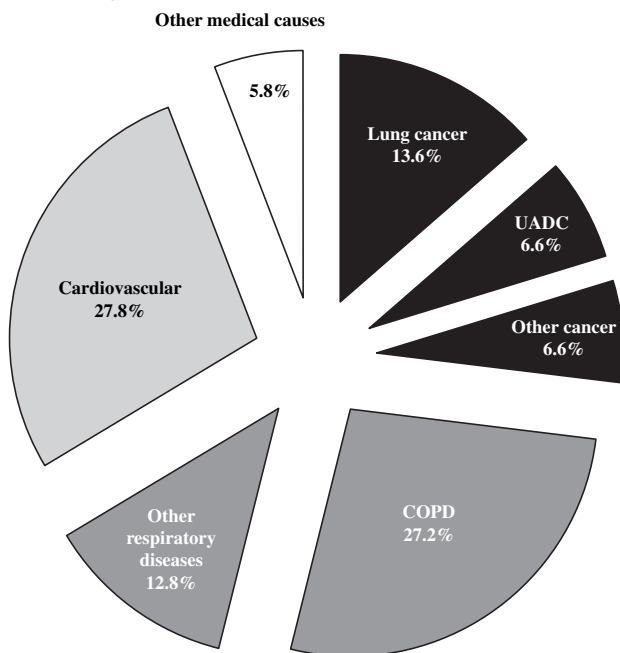
^a See Table 11.1 for details on causes of death.

^b The estimates of mortality for upper aerodigestive cancer include only ICD codes 140–150. ICD code 161 is included with other cancers.

^c The estimates also include ICD 495, which was not included in the CPS-II relative risk estimates, due to GBD grouping; normally this cause would have been included with other medical causes.

Figure 11.5 Distribution of mortality due to smoking by cause and development group, 2000

(a) Developing countries



(b) Industrialized countries

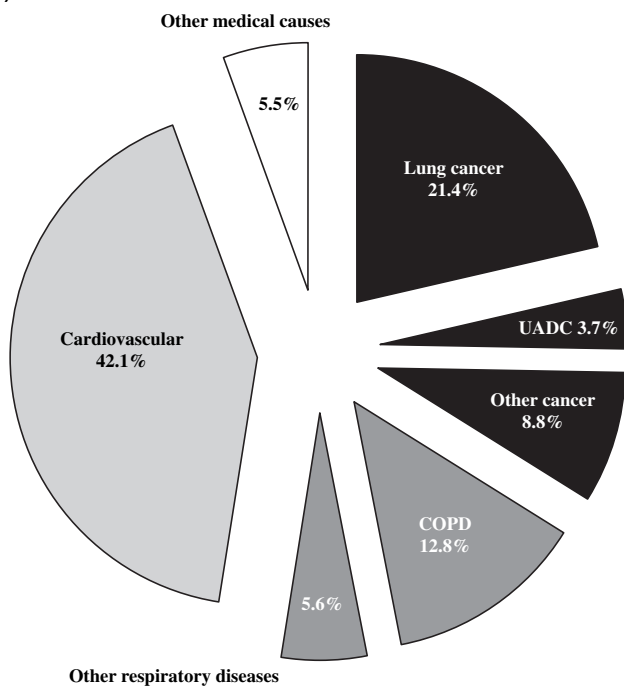
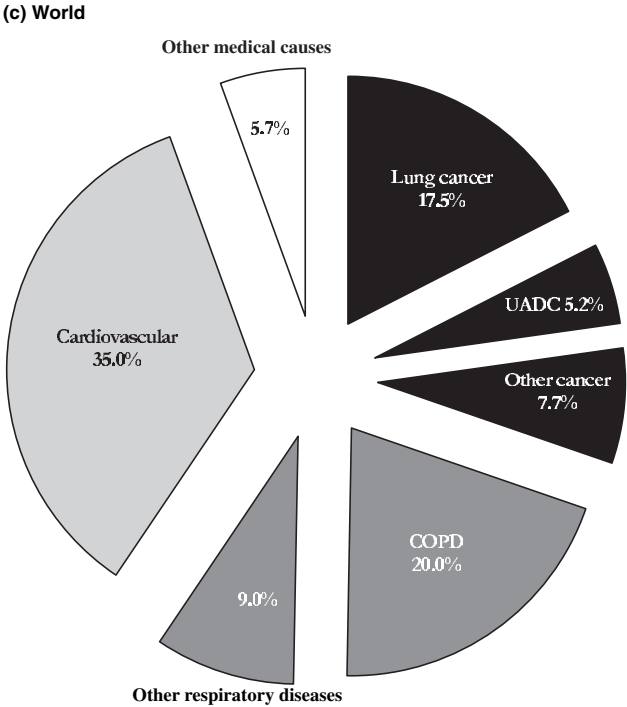


Figure 11.5 Distribution of mortality due to smoking by cause and development group, 2000 (continued)



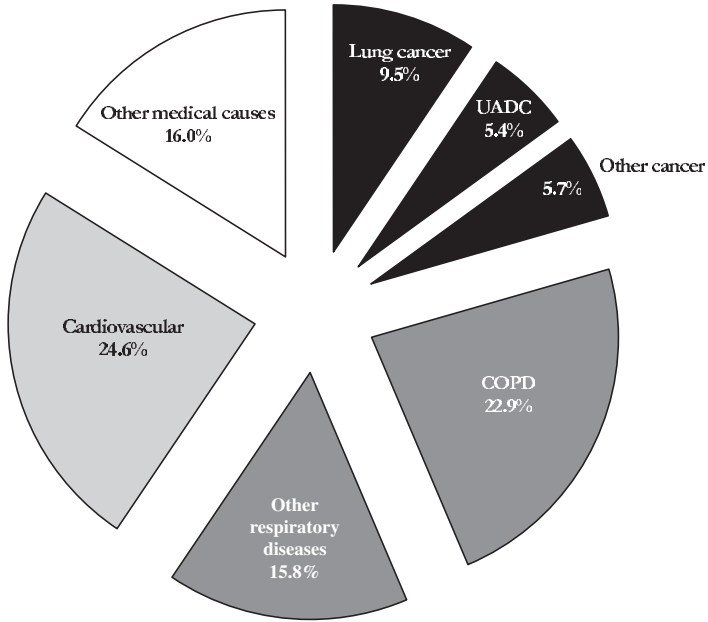
UADC Upper aerodigestive cancer.
Note: See Table 11.1 for details on causes of death.

was much higher in the former. As discussed below, this is because in general smoking-caused mortality in developing countries occurs at earlier ages than in industrialized nations accounting for a larger loss of life from premature mortality. Further, a comparison of Figures 11.5 and 11.6 indicates that the relative share of cancers in terms of the total burden of disease is lower than their comparative role in mortality because of the shorter morbidity associated with cancers compared to the other categories.

Lung cancer was the disease with the highest fraction attributable to smoking. Seventy-one per cent of all lung cancers or 0.85 million deaths (79% or 0.69 million deaths among men and 48% or 0.16 million deaths among women) were attributable to smoking. However, cardiovascular diseases were the largest cause of death due to smoking in terms of number of deaths. One million six hundred and ninety thousand cardiovascular disease deaths (1.37 million among men and 0.32 million

Figure 11.6 Distribution of DALYs due to smoking by cause and development group, 2000

(a) Developing countries



(b) Industrialized countries

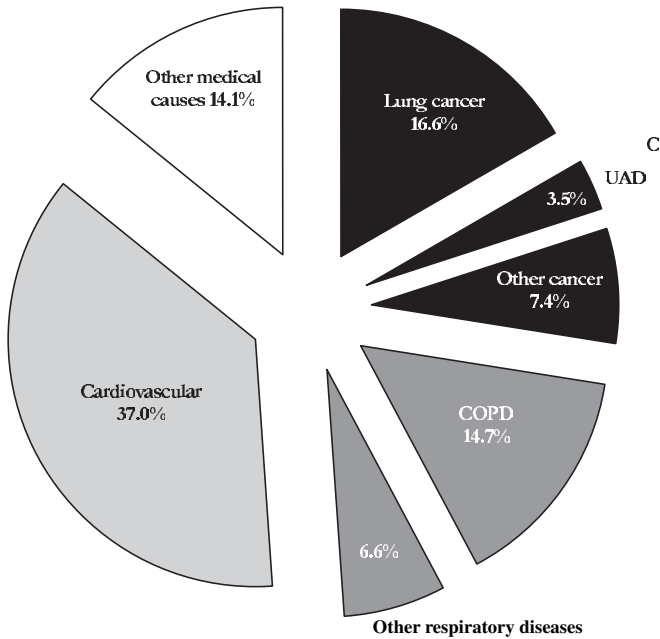
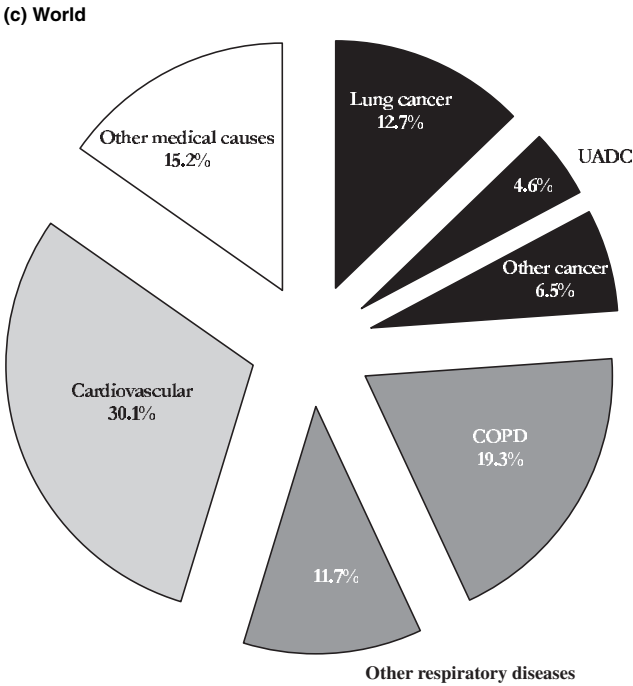


Figure 11.6 Distribution of DALYs due to smoking by cause and development group, 2000 (continued)



UADC Upper aerodigestive cancer.
Note: See Table 11.1 for details on causes of death.

among women) were due to smoking, accounting for 35% of all smoking-attributable deaths (35% among men and 37% among women). Overall, 11% of all cardiovascular deaths in the world were attributable to smoking (17% among men and 4% among women). Only when all cancers are considered together did they approach cardiovascular diseases as the largest cause of death due to smoking. One million four hundred and seventy thousand neoplasm deaths (22% of all cancer deaths; 1.24 million or 33% of all adult male cancer deaths and 0.23 million or 8% of all adult female cancer deaths) were due to smoking, accounting for 30% of all smoking-attributable deaths (32% among men and 23% among women).

3.3 MORTALITY IN INDUSTRIALIZED COUNTRIES

Table 11.13 provides the details of mortality due to smoking in industrialized countries by age, sex and causes of death. In the year 2000,

smoking caused an estimated 2.43 (95% CI 2.13–2.78) million deaths in industrialized countries for people aged >30 years, accounting for 19% of adult mortality. One million eight hundred and ten thousand (95% CI 1.62–2.02) deaths were among men (28% of total mortality of adult males) and 0.61 (95% CI 0.52–0.75) million among women (10% of total mortality of adult females). The magnitude of the years of life lost due to premature mortality becomes more obvious when we note that 1.19 million, or approximately one half, of these deaths were among those aged 30–69 years.

In industrialized countries, smoking-caused deaths accounted for 33% of total mortality among males between the ages of 30 and 69 years (1.00 million deaths), 24% of total mortality among males aged >70 years (0.81 million deaths), 12% of total mortality among females between the ages of 30 and 69 years (0.19 million deaths), and 9% of total mortality among females aged >70 years (0.42 million deaths).

The fraction of smoking-attributable mortality among men was highest in the EUR-C and AMR-A subregions, causing 0.55 million and 0.35 million smoking-attributable male deaths, respectively. These were 32% and 28% of all adult male deaths (36% and 24% of all deaths for 30–69 and ≥ 70 age groups in EUR-C; 31% and 26% of all deaths for 30–69 and ≥ 70 age groups in AMR-A reflecting the fact that the two subregions are at different stages of the tobacco epidemic). Among women the highest fraction of smoking-attributable mortality was in AMR-A where 0.29 million deaths (22% of all mortality) (27% and 20% of all deaths for the 30–69- and ≥ 70 -year age groups, respectively), were caused by smoking. The lowest fraction of smoking-attributable mortality among men in the industrialized world was in WPR-A (22% of all deaths; 18% and 24% of all deaths for 30–69- and ≥ 70 -year age groups, respectively) and among women in EUR-C (4% of all deaths; 6% and 4% of all deaths for 30–69- and ≥ 70 -year age groups, respectively) and EUR-B (6% of all deaths; 10% and 5% of all deaths for the 30–69- and ≥ 70 -age groups, respectively).

For both males and females in all subregions and age groups, lung cancer was the cause of death with the largest fraction attributable to smoking, ranging from a low of 45% among females aged ≥ 30 years in EUR-C to a high of 91–94% among males aged ≥ 30 years in AMR-A, EUR-A, EUR-B and EUR-C. Overall 92% of all lung cancer deaths among adult (≥ 30 years) males (0.40 million lung cancer deaths) and 71% of all lung cancer deaths among adult (≥ 30 years) females (0.12 million lung cancer deaths) in industrialized countries were caused by smoking.

Despite the predominance of smoking as a cause, lung cancer accounted for only 22% (0.40 million) of smoking-attributable deaths among men and 19% (0.12 million) among women in industrialized countries. In fact, in terms of the fraction of all causes of death due

Table 11.13 Mortality due to smoking in industrialized countries by cause, sex and age, 2000

Cause ^a	Male				Female			
	30–69 years		≥70 years		30–69 years		≥70 years	
	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)
Lung cancer	216	91	187	92	50	70	67	72
Upper aerodigestive cancer ^b	52	72	24	66	5	39	9	41
Other cancer ^b	97	21	88	16	11	2	18	3
COPD ^c	63	84	142	77	20	62	86	61
Other respiratory diseases	67	44	38	16	9	15	23	8
Cardiovascular diseases	455	40	298	17	77	13	192	7
Other attributable medical causes	55	32	33	13	17	14	28	7
Other medical causes	0	0	0	0	0	0	0	0
Total medical	1 005	39	810	24	189	13	423	9
Non-medical (accidents and injuries)	0	0	0	0	0	0	0	10
Total mortality	1 005	33	810	24	189	12	423	9

^a See Table 11.1 for details on causes of death.

^b The estimates of mortality for upper aerodigestive cancer include only ICD codes 140–150. ICD code 161 is included with other cancers.

^c The estimates also include ICD 495, which was not included in the CPS-II relative risk estimates, due to GBD grouping; normally this cause would have been included with other medical causes.

to smoking, cardiovascular diseases led the grouping used in Table 11.1 and accounted for 42% and 44% of deaths caused by smoking among men and women, respectively (0.75 million male deaths and 0.27 million female deaths from cardiovascular diseases due to smoking). When all cancers are considered together, however, the numbers approached cardiovascular diseases for men. Neoplasm deaths accounted for 37% and 26% of all smoking caused deaths among men and women, respectively, in industrialized countries (0.66 million male deaths and 0.16 million female deaths from all cancers due to smoking accounting for 43% and 13% of all cancers among men and women, respectively).

3.4 MORTALITY IN DEVELOPING COUNTRIES

Table 11.14 provides the details of mortality due to smoking in developing countries by age, sex and cause of death in 2000. The number of deaths attributable to smoking among people aged >29 years in developing countries in 2000 was 2.41 (95% CI 1.80–3.15) million accounting for 9% of total adult mortality in these countries. Of the smoking-attributable deaths, 2.02 (95% CI 1.56–2.50) million were among men (14% of total adult male mortality) and 0.38 (95% CI 0.25–0.65) million among women (3% of total adult female mortality). About twice as many—1.5 million deaths—deaths were among those between 30 and 69 years compared with 0.91 million among those aged >69 years.

In developing countries also, lung cancer was the disease with the highest fraction due to smoking. Fifty-five per cent of all lung cancers or 0.33 million deaths (67% or 0.29 million deaths among men and 25% or 39 000 deaths among women) were attributable to smoking. But lung cancer accounted for only 14% of all smoking-attributable mortality (14% among men and 10% among women) vs 21% in industrialized countries. As in the industrialized countries, cardiovascular diseases were the largest cause of death due to smoking, followed very closely by COPD. Six hundred and seventy thousand cardiovascular deaths (0.57 million among men and 97 000 among women) were due to smoking, accounting for 28% of all smoking-attributable deaths (28% among men and 25% among women). Six hundred and fifty thousand COPD deaths (0.50 million among men and 0.16 million among women) were due to smoking accounting for 27% of all smoking-attributable deaths (25% among men and 41% among women). This high contribution from COPD is consistent with direct observations of Liu et al. (1998) in China, where the high background (non-smoker) rates of COPD mortality due to other risk factors result in an even larger mortality due to smoking from this cause. Further, the lower contribution of cardiovascular diseases to smoking-caused mortality compared to the 42% in industrialized countries is likely to be due to lower overall cardiovascular disease mortality in these populations. Future changes in dietary risk factors and

Table 11.14 Mortality due to smoking in developing countries by cause, sex and age, 2000

Cause ^a	Male			Female		
	30–69 years		≥70 years	30–69 years		≥70 years
	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)	No. of deaths (000s)	Fraction of total mortality (%)
Lung cancer	181	65	108	69	27	26
Upper aerodigestive cancer ^b	100	38	42	35	12	10
Other cancer ^b	98	11	48	9	7	1
COPD ^c	206	49	290	45	65	20
Other respiratory diseases	207	18	55	9	26	4
Cardiovascular diseases	393	17	178	8	66	4
Other attributable medical causes	90	14	25	5	19	3
Other medical causes	0	0	0	0	0	0
Total medical	1 275	16	746	14	221	4
Non-medical (accidents and injuries)	0	0	0	0	0	0
Total mortality	1 275	14	746	14	221	3

^a See Table 11.1 for details on causes of death.

^b The estimates of mortality for upper aerodigestive cancer include only ICD codes 140–150. ICD code 161 is included with other cancers.

^c The estimates also include ICD 495, which was not included in the CPS-II relative risk estimates, due to GBD grouping; normally this cause would have been included with other medical causes.

increased exposure to other cardiovascular disease risks in developing countries, even with similar attributable fractions, would result in a rise in tobacco-caused mortality in these subregions. As for the global total and in industrialized countries, when all cancers are considered together, they approach cardiovascular diseases and COPD as the largest cause of death due to smoking. Six hundred and fifty thousand neoplasm deaths (16% of all cancer deaths; 0.58 million or 26% of all adult male cancer deaths and 69 000 or 4% of all adult female cancer deaths) were due to smoking, accounting for 27% of all smoking-attributable deaths (29% among men and 18% among women).

In general, there was larger variation in mortality due to smoking among different subregions of developing countries than industrialized countries, because of the variability in the stages of the smoking epidemic. In the sections below, we discuss the estimates for different areas of developing countries, including comparisons with direct estimates where available.

CHINA

Liu et al. (1998) estimated that smoking caused 0.6 million deaths in China in 1990 and expected this number to rise to 0.8 million in 2000 if the fraction of mortality due to smoking remained unchanged. Since smoking had been rising rapidly in China since the 1970s, the fraction of deaths due to smoking was expected to rise, resulting in more deaths than the 0.8 million estimate. The 2000 estimates were based on a projected total adult (≥ 35 years) mortality of 9 million in China in 2000.¹⁰

In fact, total adult mortality in China in 2000 from the GBD mortality database was 7.5 million deaths, reflecting recent health gains in China. Applying the 1990 cause-specific mortality and total mortality attributable fractions from Liu et al. (1998) to the 2000 mortality estimates in China would result in approximately 0.6 million smoking-attributable deaths, with 0.51 million male deaths and 0.09 million female deaths. Actual mortality is expected to be higher, in particular among men, because of the rising trend of smoking (Corrao et al. 2000; WHO 1997). Further, since the proportional mortality analysis of Liu et al. (1998) cannot estimate mortality from those causes in the reference group, smoking-attributable mortality is underestimated (to zero) for these causes, to the extent that smoking caused some deaths from these diseases.

As described above in the section on methods, in estimating smoking-attributable mortality in China, we converted the 1990 relative risks for smoking estimated in Liu et al. (1998) to relative risks per unit of *SIR*. We then estimated the *SIR* for in China in 2000 to capture the impacts of the more recent increase in smoking. Mortality was then estimated by applying the relative risk estimates from 1990 (with some correction for potential confounding) to 2000 *SIR* estimates. The

exception is for diseases in the category “other medical causes” in Table 11.1, for which proportional mortality analysis does not estimate relative risks. For these causes, we used the relative risks of CPS-II from Table 11.1.

Using this method for China we estimated that smoking caused 0.59 million deaths, 0.49 million of which are among men (13% of total adult male mortality) and the remaining 0.10 million among women (3% of total adult female mortality). In China, deaths caused by smoking accounted for 11% of total mortality among males between the ages of 30 and 69 years (0.22 million deaths), 15% of total mortality among males aged >69 years (0.27 million deaths), 2% of total mortality among females between the ages of 35 and 69 years (32 000 deaths), and 3% of total mortality among females aged >69 years (66 000 deaths).

The relatively small fraction of mortality among women due to smoking remained constant between 1990 and 2000, reflecting the stable, low prevalence of smoking among Chinese women. The fraction of mortality among men dropped for the 35–69-year age group from 13% to 11%, and increased from 12% to 15% for the ≥70-year age group. The increase among the older men is due to demographic shifts in smoking patterns. Tobacco consumption in China increased between 1970 and 1990 and then stabilized (Corrao et al. 2000; WHO 1997). Therefore, while many of the younger smokers in 1990 and in 2000 had started smoking around the same age, those in older age groups in 2000 are likely to have smoked for a longer time than those of similar age in 1990. This slight increase in the fraction of mortality attributable to smoking among the older age cohorts with the maturity of the smoking epidemic is consistent with historical trends in age-specific attributable fractions in Canada, the United Kingdom and the United States. The decline among the younger age groups was partially due to the 5% correction factor applied to the hazards for this country.

Lung cancer accounted for 20% and 18% of smoking-attributable mortality among men and women, respectively, in China, resulting in 98 000 male deaths and 17 000 female deaths. The fractions of smoking-attributable mortality from all cancers were 44% (215 000 deaths) for males and 29% (28 000 deaths) for females. This suggests that the contribution of smoking to mortality from cancers other than lung cancer is larger in China than in industrialized countries (Lopez 1998). In China, COPD also accounted for a large fraction of smoking-attributable mortality with 33% (163 000 deaths) and 61% (60 000 deaths) of smoking-caused mortality among men and women respectively.

INDIA AND SEAR-D¹¹

Seven hundred and fifty thousand deaths among adult men and 110 000 among adult women were attributable to smoking in SEAR-D accounting for 18% and 3% of total mortality, respectively. Six hundred and thirty thousand of these deaths occurred before the age of 70 (13%

of total mortality) and the remaining 230 000 among those aged ≥ 70 years (8% of total mortality).

Adult male lung cancer mortality, 82% of which (84 000 deaths) in this subregion is caused by smoking, accounted for 11% of smoking-attributable male mortality, the lowest fraction among males in any subregion. The 6000 lung cancer deaths among females attributed to smoking (26% of all female lung cancer deaths) was likewise the smallest fraction (6%) of smoking-attributable deaths compared with other subregions. When all cancers are considered together, smoking caused 0.18 million neoplasm deaths in SEAR-D in 2000 (160 000 among men and 14 000 among women). Cardiovascular diseases, with 0.28 million deaths (240 000 or 16% of all cardiovascular deaths among men and 34 000 or 2% of all cardiovascular deaths among women), were the cause of death with the highest number due to smoking and accounted for 33% of all smoking-attributable deaths (33% among men and 31% among women), reflecting the large contribution of this cause to adult male mortality in this subregion.

No *direct* nationally representative study of mortality due to smoking was available from India or other countries in SEAR-D at the time of writing. Estimates from specific regions within India as well as indirect national estimates, however, are available and can be used for comparison with our results. Gupta and Mehta (2000) estimated that the relative risk for mortality from all causes in a mixed cohort of male smokers and non-smokers aged >34 years in India relative to non-users of tobacco is approximately 1.63. Assuming, as in the case of CPS-II relative risks, that 30% of the excess risk is due to confounding (because of covariates such as chewing tobacco, diet, etc.) this relative risk and a smoking prevalence of 40–50% imply that 15–18% of all male mortality is due to smoking, a result consistent with our estimate of 18% of male mortality attributable to tobacco. Applying the relative risk of 2.1 obtained by Gajalakshmi et al. (2003) with the same correction factor will result in an even higher attributable fraction (23–28%) than ours. The estimates of total mortality in this chapter are lower than those by Gupta (1989) who attributes at least 19% of adult male mortality and 4% of adult female mortality to tobacco use, as well as those in a recent case-control study that finds an unadjusted attributable fraction of approximately 20% for all adult deaths among Indian men (Gajalakshmi et al. 2003).

ADDITIONAL ORAL CANCER MORTALITY DUE TO ORAL TOBACCO USE

Using the methods described above, we estimated that there were 60 000 additional cases of oral cancer due to oral tobacco use (tobacco chewing) in SEAR-D, accounting for an additional 50% of oral cancers in the subregion. Of these, 39 000 were among men (48% of male oral cancer deaths) and 22 000 among women (54% of female oral cancer

deaths). We emphasize that these estimates are those cases of oral cancer that are caused by tobacco chewing *in addition* to smoking. Since many cases of oral cancer are likely to be affected by both habits, the overall effects of tobacco chewing are larger. Important sources of uncertainty in the estimates are the prevalence of oral tobacco use and relative risk estimates as well as the extent of overlap between tobacco smoking and chewing, especially for men.

OTHER DEVELOPING COUNTRIES

The fraction of total adult mortality due to smoking ranged from a low of 2–4% in AFR-D, AMR-D and AFR-E to a high of 11% in SEAR-B and 18% in WPR-B (excluding China). For males the lowest fraction of total mortality due to smoking was in AMR-D (3%), AFR-D (5%) and AFR-E (6%), reflecting the more recent smoking epidemic in these subregions. Given that the current prevalence of smoking among adult men is approximately 25–30% in AFR-D and 35–45% in AFR-E, this finding emphasizes the fact that current prevalence is a poor marker of accumulated smoking risks (see also Figure 11.4).

The highest fractions of adult male mortality due to smoking were in WPR-B (excluding china) (26%), SEAR-B (19%), EMR-B (15%) and AMR-B (15%). For females, the fraction of total mortality due to smoking in 2000 was equal to or below 2% in AFR-D, AFR-E, AMR-D, EMR-D and SEAR-B. The highest fractions of female mortality were in AMR-B (6%) and WPR-B (excluding China) (8%), reflecting more recent increases in female smoking in these subregions, especially with increasing urbanization and economic development.

4. DISCUSSION

We applied the indirect method of Peto et al. (1992), which uses absolute lung cancer mortality in a population as a marker for accumulated hazards of smoking, to estimate the mortality and disease burden due to smoking in different subregions of the world. We chose the parameters of the model, such as relative risks and non-smoker lung cancer mortality, based on direct estimates or by extrapolation from other subregions based on best available evidence, explicitly stating the assumptions and reasons for each choice.

Using this method, we estimated that in 2000, approximately 4.83 (95% CI 3.94–5.93) million deaths worldwide were due to smoking, accounting for 12% of global adult mortality. Of these deaths, 2.41 (95% CI 1.80–3.15) million were in developing countries, marking a transition to an era in which smoking killed as many people in developing countries as in industrialized nations. In fact, even in the earlier stages of the tobacco epidemic, more men died from smoking in developing countries than in the industrialized nations (2.02 million vs 1.81

million). In addition to those cases shared with smokers, there were an estimated 60 000 deaths from oral tobacco use in SEAR-D. Premature mortality and morbidity caused by smoking accounted for an estimated 4.1% of the global burden of disease.

As we discussed under sources of uncertainty, using lung cancer—which has a longer lag than cardiovascular diseases—as the marker for accumulated smoking hazard, would result in an overestimation of hazard where there has been sharp drops in smoking and underestimation of hazard where there has been large increases in smoking. The former is most likely to apply to North America and among males in some countries in western Europe where smoking has declined (partially or fully offset by a continued choice of conservative relative risk estimates). On the other hand, the underestimation scenario would be applicable to most developing countries where smoking has been on the rise in the past few decades.

Total male mortality in terms of numbers of deaths was considerably higher than female mortality—3.0 fold in industrialized nations and 5.3 fold in developing countries. The decline of the male-to-female mortality ratio from 3.6 to 3.0 in industrialized countries between 1990 and 2000, however, reflects the recent relative increases in female smoking in these countries. 2.69 million deaths, more than one-half of the all global deaths due to smoking, were in the 30–69-year age group.

Due to differences in methodology and presentation, the estimates reported here are not fully comparable with those for previous years. The existing estimates of consumption, prevalence and mortality, however, generally indicate that mortality due to smoking (in terms of the fraction of cause-specific or all-cause mortality) has been relatively stable in industrialized countries over the past ten years. Some countries in the established market economies category have seen a small decline in male mortality while in most of these countries female mortality has increased, reflecting differential time trends in male and female smoking. Industrialized countries also have seen a small decline in the fraction of mortality in the 30–69-year age group and an increase in the ≥ 70 -year group, confirming that in these countries as a whole, the smoking epidemic may be shifting with the effects increasingly being felt among the older age groups. There were, nonetheless, subregional differences, and the share of mortality at ages 30–69-years is in fact rising among females in some subregions including AMR-A and EUR-A.

Mortality and disease burden attributable to smoking, including its share of total mortality and sex or age patterns, varied importantly among different geographical regions of developing countries. This inter-regional variation, which is larger than that observed in industrialized countries, occurs because the nature and maturity of the smoking epidemic is highly affected by the varying economic and cultural determinants of smoking in these populations. A few general statements can nonetheless be made about the health effects of smoking in developing

countries. First, current hazards of smoking in these populations are highly concentrated among men. Given that the prevalence of smoking among women is still low in developing countries (with the exception of Latin America and the Caribbean and some countries in Asia), the current level of male mortality should provide an indicator of the large health losses that may well occur if female smoking increases over the next few decades. Second, relative to industrialized countries, developing countries have a higher proportion of smoking-attributable mortality in the 30–69 age group than in the ≥ 70 group (62% in developing countries vs 49% in industrialized countries). Coupled with the 1990–2000 trends in mortality for the two age groups in China, this suggests that as people (mostly men) who began smoking over the past three decades in developing countries become older, mortality due to smoking will continue to rise as a share of cause-specific mortality; and almost inevitably as a share of total mortality.

Smoking prevalence in some developing countries appears to have stabilized, albeit at very high levels. In others, it is still rising. Given the gradually shifting disease patterns and because most of the growth in global population is expected to take place in the developing world, the health effects of smoking, already one of the most important global health hazards, will continue to rise unless effective interventions and policies that curb and reduce smoking among males and prevent increases among females in these countries are implemented.

5. PROJECTED FUTURE EXPOSURE

Many diseases caused by smoking, in particular various malignant neoplasms and COPD, occur after long delays. This motivated using *SIR* as the exposure variable for estimating the accumulated hazards of smoking. Disease burden due to smoking in the next few decades will depend on both past and future smoking patterns. There is therefore a need to link estimates of accumulated current exposure, which are in the form of *SIR* estimates, with future exposure, which is often in the form of projections of prevalence of smoking or tobacco consumption (whether under the business-as-usual scenario or some counterfactual). Further, the combination of past and projected future exposure must be presented in the form of a single exposure variable which accounts for hazard accumulation. We used the following steps to estimate future smoking prevalence and tobacco consumption and convert these to estimates of lung cancer mortality and *SIR*.

1. We estimated past and current age–sex-specific smoking prevalence under the business-as-usual scenario based on a descriptive model of the smoking epidemic (Lopez et al. 1994), calibrated to regional characteristics of the epidemic for different subregions. The tobacco epidemic was divided into five stages (early, rising, peak or maturity, declining and late)

as well as five transitional stages as seen in Figure 11.7. Historical evidence from multiple industrialized countries consistently shows that the youngest and oldest age groups at any stage of the epidemic have lower smoking prevalence (Gajalakshmi et al. 2000; Nicolaides-Bouman et al. 1993), the former probably because of economic and social constraints and the latter because of a higher mortality rate among smokers. The prevalence distribution is also based on the observation that in the rising stages of the epidemic, younger adults begin to smoke more than the older adults but as the epidemic matures the age-pattern becomes more stable (Gajalakshmi et al. 2000). Finally, as observed in historical data we assumed that the prevalence of female smoking is lower than that of males at every stage of the epidemic.

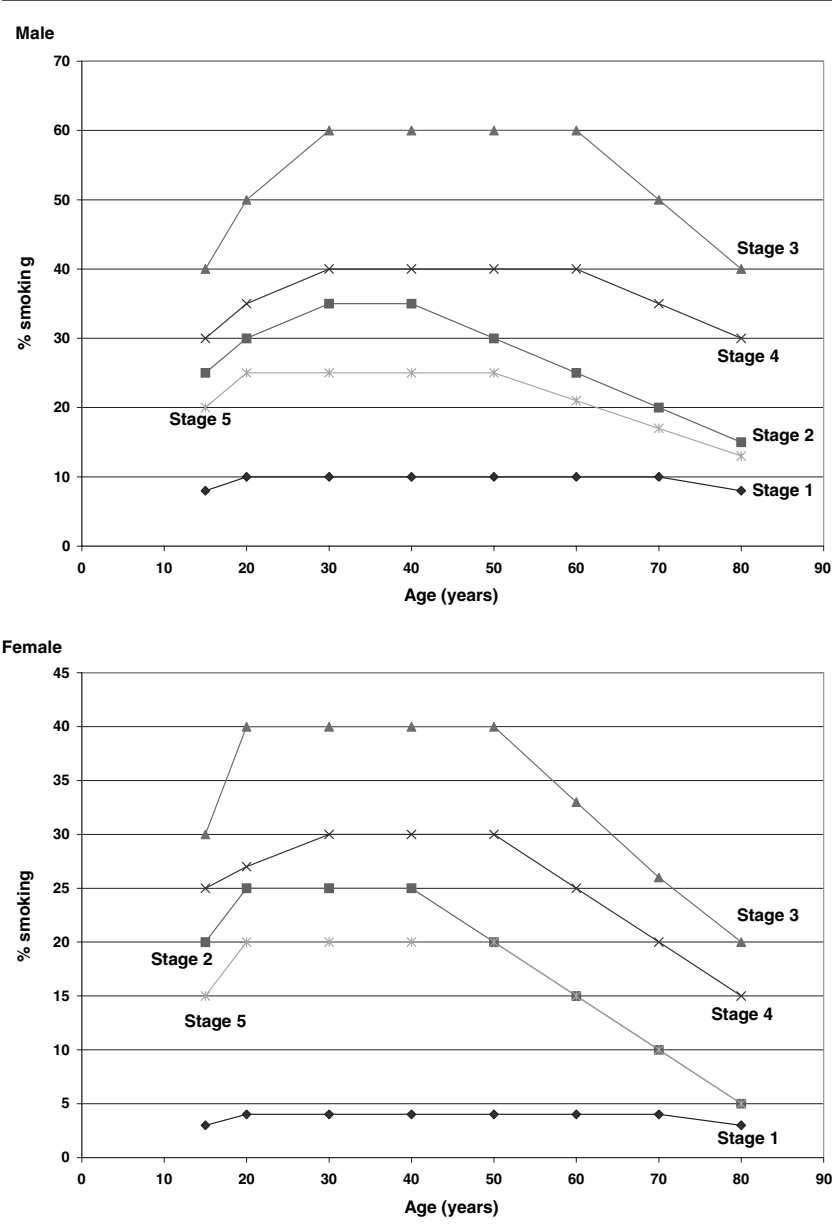
In calibrating the level of the prevalence curves for different regions, we used the available comparative data on current and historical smoking prevalence (Corrao et al. 2000; Gajalakshmi et al. 2000; WHO 1997). Recent data on smoking prevalence show that the male epidemic has peaked at lower levels in Latin America and the Caribbean as well as in sub-Saharan Africa compared to North America, Europe and Asia, possibly because of the economic crises in these regions in the last two decades of the 20th century. Although for most regions female smoking is still in the early stages of the epidemic, we assumed that the peak of the epidemic would be lower in developing countries than what was observed in industrialized countries in the past. This assumption was because in those developing countries where female smoking has been on the rise, prevalence is lower than levels previously observed at similar stages in industrialized countries.

In each country, males and females were assigned to one stage of the epidemic in 2000 (Table 11.15) based on the best available data on smoking patterns in recent years (Corrao et al. 2000; WHO 1997).

2. We divided country-level per capita consumption data into age-sex-specific per capita consumption of smoking based on the above estimates of prevalence. The Tobacco Free Initiative (TFI) of WHO provides time-series estimates of tobacco consumption based on production, export, and import data from the Food and Agriculture Organization of the United Nations (FAO). The consumption numbers are reported as equivalent cigarettes per adult (aged ≥ 15 years) for each country. We used the above estimates of prevalence to divide the past and current country-level per capita consumption numbers (corrected for smuggling and other sources of error whenever possible) into age-sex-specific per capita consumption.

In addition to differences in prevalence, male smokers smoke more cigarettes per day than female smokers (Gajalakshmi et al. 2000; Nicolaides-Bouman et al. 1993). Differences between age groups also exist (Gajalakshmi et al. 2000; Nicolaides-Bouman et al. 1993). The

Figure 11.7 Descriptive model for the main stages of the tobacco epidemic based on the parameter values in industrialized countries



Note: For some developing regions, lower peak values were chosen based on observed prevalence data. The vertical axis scales are different for males and females to increase resolution. The number next to each curve indicates the epidemic stage. An additional transitional stage is also assumed between each pair. With appropriate policies, one can assume declining prevalence even beyond stage 5. We assumed that the business-as-usual scenario would not include this achievement, which is considered as a part of our counterfactuals.

Table 11.15 Status of the tobacco epidemic in 2000 among (a) males and (b) females

(a)	
<i>Epidemic stage^a</i>	<i>Country^b</i>
0.5–1	NA
1.5–2	AFR-D – all except Algeria, Mauritius, Seychelles; AFR-E – all except South Africa; EMR-B – Iran (Islamic Republic of); EMR-D – Afghanistan, Djibouti, Somalia, Sudan; EUR-B – Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan
2.5–3	AFR-D – Algeria, Mauritius, Seychelles; AFR-E – South Africa; AMR-A – Cuba; AMR-B – all except Argentina, Brazil, Chile; AMR-D – all; EMR-B – all except Iran (Islamic Republic of); EMR-D – Egypt, Iraq, Morocco, Pakistan, Yemen; EUR-A – Croatia, Czech Republic, Greece, Portugal, Slovenia; EUR-B – all except Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan; EUR-C – all; SEAR-B – all; SEAR-D – all; WPR-A – Brunei Darussalam, Japan; WPR-B – all
3.5–4	AMR-B – Argentina, Brazil, Chile; EUR-A – Andorra, Austria, Denmark, France, Germany, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, San Marino, Spain, Switzerland
4.5–5	AMR-A – Canada, USA; EUR-A – Belgium, Finland, Iceland, Netherlands, Norway, Sweden, United Kingdom; WPR-A – Australia, New Zealand, Singapore
(b)	
<i>Epidemic stage^a</i>	<i>Country^b</i>
0.5–1	AFR-D – all except Seychelles; AFR-E – all except South Africa; AMR-B – Antigua and Barbuda, Bahamas, Barbados, Belize, Dominica, Grenada, Guyana, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and Grenadines, Suriname; EMR-B – all except Cyprus, Jordan, Lebanon, Syrian Arab Republic; EMR-D – all except Morocco; Albania, Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan; SEAR-B – Indonesia, Sri Lanka; SEAR-D – all except Myanmar, Nepal; WPR-A – Singapore; WPR-B – Cambodia, China, Malaysia, Mongolia, Republic of Korea, Viet Nam
1.5–2	AFR-D – Seychelles; AFR-E – South Africa; AMR-B – Colombia, Costa Rica, Dominican Republic, El Salvador, Honduras, Jamaica, Mexico, Panama, Trinidad and Tobago, Uruguay, Venezuela; AMR-D – all; EMR-B – Cyprus, Jordan, Lebanon, Syrian Arab Republic; Morocco; EUR-A – Croatia, Czech Republic, Greece, Israel, Malta, Portugal, San Marina, Slovenia; EUR-B – all except Albania, Azerbaijan, Tajikistan, Turkmenistan, Uzbekistan; EUR-C – all; SEAR-B – Thailand; SEAR-D – Myanmar, Nepal; WPR-A – Brunei Darussalam, Japan; WPR-B – Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Marshall Islands, Micronesia (Federated States of), Nauru, Niue, Palau, Philippines, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu
2.5–3	AMR-A – Cuba; AMR-B – Argentina, Brazil, Chile; EUR-A – Andorra, Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Monaco, Spain, Switzerland; WPR-B – Papua New Guinea
3.5–4	AMR-A – Canada, USA; EUR-A – Belgium, Iceland, Netherlands, Norway, United Kingdom; WPR-A – Australia, New Zealand
4.5–5	EUR-A – Sweden
NA	Not applicable.

^a The stages of the epidemic refer to those in Figure 11.7.

^b By subregion.

Table 11.16 Ratios of number of cigarettes smoked per day for various demographic groups from historical data in industrialized countries

Age group (years)	Ratios of number of cigarettes smoked	
	Male	Female
15–19	1.00	1.00
20–29	1.22	1.15
30–39	1.42	1.24
40–49	1.37	1.34
50–59	1.26	1.21
60–69	1.15	1.04
70–79	1.15	1.04
≥80	1.15	1.04
Male	1.0	
Female	1/1.25 (stages 4 and 5); ^a	1/1.5 (stage 3);
	1/1.75 (stages 1 and 2)	

^a The stages of the epidemic refer to those in Figure 11.7.

ratios for the number of cigarettes smoked per day between different age groups and men and women have been estimated for industrialized countries (Gajalakshmi et al. 2000) and are presented in Table 11.16. We assumed a lower female-to-male ratio in the earlier stages of the female epidemic.

We emphasize that because the prevalence estimates from the descriptive model are used to *divide* existing total per capita consumption into age–sex-specific estimates, it is only the various male-female and age *ratios* that affect the estimates, rather than the absolute values. Therefore, the age–sex-specific consumption estimates are not sensitive to the level of the prevalence curve or assumptions about the stage of the epidemic, provided that male-to-female and age ratios are close to actual values (i.e. under- or over-estimating male and female prevalence by the same factor would not affect the consumption estimates).

3. We projected age–sex-specific lung cancer mortality based on consumption projections and a statistical model of the relationship between lung cancer mortality and lagged consumption (Giroso and King 2002). Finally, the projections of lung cancer mortality were converted to the projections of *SIR* using the definition of *SIR* above.

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NOTES

- 1 See preface for an explanation of this term.
- 2 If the fraction of smokers in the mixture is x , then the lung cancer mortality for the mixture is $xS_{LC}^* + (1 - x)N_{LC}^*$. Since the *SIR* of the mixture has to equal that of the population, excess lung cancer mortality in the mixture has to be equal to that of the study population. Therefore $xS_{LC}^* + (1 - x)N_{LC}^* - N_{LC}^* = C_{LC} - N_{LC}$. Solving this equation gives $x = \frac{C_{LC} - N_{LC}}{S_{LC}^* - N_{LC}^*}$ which is equal to *SIR* when the study and reference populations have the same non-smoker lung cancer rates. When non-smoker lung cancer rates are not the same in the study and reference populations, the same result can be obtained with algebraic manipulation of Equation 2, accounting for differences in never-smoker rates.
- 3 The discussion in this section is based on age-specific risk estimates. In other words, a decline in risk as a result of cessation does not necessarily imply that risk stops rising in absolute terms. Rather, it implies that at all ages after cessation, relative risk is less than it would be if smoking continued.
- 4 These estimates also assume no new smokers in the cohort.
- 5 No disease with this latter characteristic is known.
- 6 Note that this applies only to current exposure and not to future exposure (avoidable risk) since the difference in decline time is accounted for in estimating risk reversibility, as described earlier.
- 7 Note that the estimates of oral cancer for smokers are based on *SIR* as the exposure variable to capture the accumulated hazards of smoking and not on prevalence. Therefore the fraction of smokers who also chew ($p_{sc} = 1 - p_s$) was applied to *SIR* estimates rather than direct prevalence. Estimating chewing-caused oral cancer by increasing the relative risk for this condition in the *SIR* framework implicitly assumes that the accumulated hazards of the two habits are similar. If oral tobacco use has a longer history in the region, this would result in an underestimation of accumulated hazards.
- 8 Given that *SIR* values are estimated relative to reference populations of the same sex and age, female and male estimates are not directly comparable. At the same time, the large differences are illustrative of the relative magnitudes.

- 9 All fractions are based on mortality in the respective age groups 30–69, ≥ 70 , and ≥ 30 years.
- 10 Mortality estimates for China were combined with the remaining countries in WPR-B to obtain subregional estimates.
- 11 Eighty-three per cent of the population of SEAR-D lives in India. Therefore the estimates for the subregion are dominated by, and comparable in terms of fractions with, those from India.

REFERENCES

- Alderson MR, Lee PN, Wang R (1985) Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarettes smoked. *Journal of Epidemiology and Community Health*, **39**:286–293.
- Australia National Health and Medical Research Council (1997) *The health effects of passive smoking*. Commonwealth Department of Health and Family Services, Canberra.
- Balaram P, Sridhar H, Rajkumar T et al. (2002) Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *International Journal of Cancer*, **98**:440–445.
- Bennett NG, Horiuchi S (1984) Mortality estimation from registered deaths in less developed countries. *Demography*, **21**:217–234.
- Best EWR, Josie GH, Walker CB (1961) A Canadian study of mortality in relation to smoking habits: a preliminary report. *Canadian Journal of Public Health*, **52**:99–106.
- Bhonsle RB, Murti PR, Gupta PC (1992) Tobacco habits in India. In: *Control of tobacco related cancers and other diseases*. Gupta PC, Hamner JE, Murti PR, eds. Oxford University Press, Bombay.
- Britton A, McKee M (2000) The relationship between alcohol and cardiovascular disease in eastern Europe: explaining the paradox. *Journal of Epidemiology and Community Health*, **54**:328–332.
- Bronnum-Hansen H, Juel K (2000) Estimating mortality due to cigarette smoking: two methods, same result. *Epidemiology*, **11**:422–426.
- Bruce N, Perez-Padilla R, Albalak R (2000) Indoor air pollution in developing countries: a major environmental and public health challenge. *Bulletin of the World Health Organization*, **78**:1078–1092.
- Cederlof R, Friberg L, Hrubec Z, Lorich U (1975) *The relationship of smoking and some social covariables to mortality and cancer morbidity*. Department of Environmental Hygiene, Karolinska Institute, Stockholm.
- Cook DG, Pocock SJ, Shaper AG, Kussick SJ (1986) Giving up smoking and the risk of heart attacks: a report from the British Regional Heart Study. *The Lancet*, **ii**(8520):1376–1380.
- Corrao MA, Guindon GE, Sharma N, Shokoohi DF, eds. (2000) *Tobacco control: country profiles*. American Cancer Society, Atlanta, GA.
- Dhillon I, Gupta PC, Asma S (2000) *Evidence for a causal link between smoking and tuberculosis: summary of the proceedings of the international scientific*

- expert meeting on the possible causality between smoking and tuberculosis.* TATA Institute of Fundamental Research (with World Health Organization and Centers for Disease Control and Prevention). Thiruvananthapuram, Kerala.
- Dikshit RP, Kanhere S (2000) Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. *International Journal of Epidemiology*, 29:609–614.
- Dobson AJ, Alexander HM, Heller RF, Lloyd DM (1991) How soon after quitting smoking does risk of heart disease decline? *Journal of Clinical Epidemiology*, 44:1247–1253.
- Doll R (1978) Atmospheric pollution and lung cancer. *Environmental Health Perspectives*, 22:23–31.
- Doll R (1986) Tobacco: an overview of health effects. In: *Tobacco: a major international health hazard.* (IARC Scientific Publication No. 74.) Zaridze DG, Peto R, eds. International Agency for Research on Cancer, Lyon.
- Doll R (1998a) Diseases with lower risks in smokers. In: *Report of the Scientific Committee on Tobacco and Health.* UK Department of Health. HMSO, London.
- Doll R (1998b) Uncovering the effects of smoking: historical perspective. *Statistical Methods in Medical Research*, 7:87–117.
- Doll R, Hill AB (1950) Smoking and carcinoma of the lung. *British Medical Journal*, ii:739.
- Doll R, Hill AB (1956) Lung cancer and other causes of death in relation to smoking. *British Medical Journal*, ii:1071–1081.
- Doll R, Peto R (1976) Mortality in relation to smoking: 20 years' observation on male British doctors. *British Medical Journal*, ii:1525–1536.
- Doll R, Peto R, Wheatly K, Gray R, Sutherland I (1994) Mortality in relations to smoking: 40 years' observation on male British doctors. *British Medical Journal*, 309:901–911.
- Du YX, Cha Q, Chen XW et al. (1996) An epidemiological study of risk factors for lung cancer in Guangzhou, China. *Lung Cancer*, 14:S9–S37.
- Dunn JE, Linden G, Brelow L (1960) Lung cancer mortality experience of men of certain occupations in California. *American Journal of Public Health*, 50:1475–1487.
- English DR, Holman CDJ, Milne E et al. (1995) *The quantification of drug caused morbidity and mortality in Australia, Part 2.* Commonwealth Department of Human Services and Health, Canberra.
- Environmental Protection Agency (1992) *Respiratory health effects of passive smoking: lung cancer and other disorders.* (EPA/600/6-90/006F.) U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC.
- Ezzati M, Lopez AD (2003) Measuring the accumulated hazards of smoking: global and regional estimates for 2000. *Tobacco Control*, 12:79–85.

- Finkel A (1990) *Confronting uncertainty in risk management: a guide for decision makers*. Resources for the Future, Washington, DC.
- Flanders WD, Rothman KJ (1982) Interaction of alcohol and tobacco in laryngeal cancer. *American Journal of Epidemiology*, **115**:371–379.
- Fletcher CM, Peto R (1977) The natural history of chronic airflow obstruction. *British Medical Journal*, **i**:1645–1648.
- Gajalakshmi CK, Jha P, Ranson K, Nguyen SN (2000) Global patterns of smoking and smoking-attributable mortality patterns. In: *Tobacco control in developing countries*. Jha P, Chaloupka FJ, eds. Oxford University Press, Oxford.
- Gajalakshmi V, Peto R, Kanaka TS, Jha P (2003) Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43 000 adult deaths and 35 000 controls. *Lancet*, **363**:507–515.
- Garfinkel L (1985) Selection, follow-up, and analysis in the American Cancer Society prospective studies. In *Selection, follow-up, and analysis in prospective studies: a workshop*. (NCI Monograph 67.) Garfinkel L, Ochs O, Mushinski M, eds. National Cancer Institute, Bethesda, MD.
- Giroi F, King G (2002) *Time series cross-sectional analysis with different explanatory variables in each cross-section*. Center for Basic Research in the Social Sciences, Harvard University, Cambridge, MA.
- Gupta PC (1989) An assessment of excess mortality caused by tobacco usage in India. (Proceedings of the UICC workshop “Tobacco or health”.) In: *Tobacco and health: the Indian scene*. Sanghavi LD, Notani P, eds. Tata Memorial Centre, Bombay.
- Gupta PC (1996) Survey of sociodemographic characteristics of tobacco use among 99 598 individuals in Bombay, India using handheld computers. *Tobacco Control*, **5**:114–120.
- Gupta PC, Mehta HC (2000) Cohort study of all-cause mortality among tobacco users in Mumbai, India. *Bulletin of the World Health Organization*, **78**:877–883.
- Gupta PC, Pindborg JJ, Mehta FS (1982) Comparison of carcinogenicity of betel quid with and without tobacco: an epidemiological review. *Ecology of Disease*, **1**:213–219.
- Hackshaw AK, Law MR, Wald NJ (1997) The accumulated evidence on lung cancer and environmental tobacco smoke. *British Medical Journal*, **315**:980–988.
- Hammond EC (1966) Smoking in relation to the death rates of one million men and women. In: *Epidemiological approaches to the study of cancer and other chronic disease*. (National Cancer Institute Monograph No. 19.) Haenszel W, ed. National Cancer Institute, Bethesda, MD.
- Hammond EC, Horn D (1958) Smoking and death rates: report of forty-four months of follow-up of 187 783 men. *Journal of American Medical Association*, **166**:1159–1172 and 1294–1308.

- He XZ, Chen W, Liu ZY, Chapman RS (1991) An epidemiological study of lung cancer in Xuan Wei county, China: current progress. Case-control study on lung cancer and cooking fuel. *Environmental Health Perspectives*, 94:9–13.
- Hecht SS (2003) Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nature Reviews Cancer*, 3:733–744.
- Higgins ITT, Mahan CM, Wynder EL (1988) Lung cancer among cigar and pipe smokers. *Preventive Medicine*, 17:116–128.
- Hill K (1981) Estimating census and death registration completeness. *Asian and Pacific Population Forum*, 1:8–13.
- Hirayama T (1977) *Smoking and cancer: a prospective study on cancer epidemiology based on census population in Japan*. Health Consequences, Education, Cessation Activities, and Governmental Action. Smoking and Health II. (Proceedings of the Third World Conference on Smoking and Health.) DHEW Publication No. [NIH] 77-1413. U.S. Government Printing Office, Washington, DC.
- Hirayama T (1990) *Life-style and mortality: a large-scale census-based cohort study in Japan*, Karger, Tokyo.
- International Agency for Research on Cancer (1984) *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines*. International Agency for Research on Cancer, Lyon, France.
- Jedrychowski W, Becher H, Wahrendorf J, Basa-Cierpialek Z (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. *Journal of Epidemiology and Community Health*, 44:114–120.
- Jee SH, Suh I, Kim IS, Appel LJ (1999) Smoking and atherosclerotic cardiovascular disease in men with low levels of serum cholesterol: the Korea Medical Insurance Corporation study. *Journal of the American Medical Association*, 282:2149–2155.
- Jha P, Ranson MK, Nguyen SN, Yach D (2002) Estimates of global and regional smoking prevalence in 1995 by age and gender. *American Journal of Public Health*, 92:1002–1006.
- Kahn HA (1966) The Dorn study of smoking and mortality among U.S. veterans: report on eight and one half years of observation. In: *Epidemiological approaches to the study of cancer and other chronic disease*. (National Cancer Institute Monograph No. 19.) Haenszel W, ed. National Cancer Institute, Bethesda, MD.
- Kawachi I, Colditz GA, Stampfer MJ et al. (1997) Smoking cessation and decreased risks of total mortality, stroke, and coronary heart disease incidence among women: a prospective cohort study. In: *Changes in cigarette-related disease risks and their implications for prevention and control*. (Smoking and Tobacco Control Monograph No. 8.) National Cancer Institute, ed. National Cancer Institute, Bethesda, MD.
- Kinjo Y, Cui Y, Akiba S et al. (1998) Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *Journal of Epidemiology*, 8:235–243.

- Ko YC, Lee CH, Chen MJ et al. (1997) Risk factors for primary lung cancer among non-smoking women in Taiwan. *International Journal of Epidemiology*, 26:24–31.
- LaCroix AZ, Lang J, Scherr P et al. (1991) Smoking and mortality among older men and women in three communities. *New England Journal of Medicine*, 324:1619–1625.
- Lam TH, Ho SY, Hedley AJ, Mak KH, Peto R (2001) Mortality and smoking in Hong Kong: Case-control study of all adult deaths in 1998. *British Medical Journal*, 323:361–363.
- Law MR, Morris JK, Wald NJ (1997) Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *British Medical Journal*, 315:973–980.
- Lee PN (1996) Mortality from tobacco in developed countries: are indirect estimates reliable? *Regulatory Toxicology and Pharmacology*, 24:60–68.
- Levin ML, Goldstein H, Gerhardt PR (1950) Cancer and tobacco smoking. *Journal of American Medical Association*, 143:336–338.
- Liu BQ, Peto R, Chen ZM et al. (1998) Emerging tobacco hazards in China: 1. Retrospective proportional mortality study of one million deaths. *British Medical Journal*, 317:1411–1422.
- Lopez AD (1998) Counting the dead in China. *British Medical Journal*, 317:1399.
- Lopez AD (1999) Alcohol and smoking as risk factors. In: *Health and mortality: issues of global concern*. (Proceedings of the United Nations Symposium on Health and Mortality, Brussels, 19–22 November, 1997.) Chamie J, Cliquet RL, eds. United Nations Population Division, New York.
- Lopez AD, Ahmad OB, Guillot M et al. (2002) *World mortality in 2002: life tables for 191 countries*. World Health Organization, Geneva.
- Lopez AD, Collishaw NE, Piha T (1994) A descriptive model of the cigarette epidemic in developed countries. *Tobacco Control*, 3:242–247.
- Lubin JH, Blot WJ, Berrino F et al. (1984) Modifying risk of developing lung cancer by changing habits of cigarette smoking. *British Medical Journal*, 288:1953–1956.
- Malarcher AM, Schuman J, Epstein LA et al. (2000) Methodological issues in estimating smoking-attributable mortality in the United States. *American Journal of Epidemiology*, 152:573–584.
- Mathers CD, Stein C, Ma Fat D et al. (2002) The global burden of disease 2000: version 2, methods and results. (GPE Discussion Paper No. 50.) World Health Organization, Global Programme on Evidence for Health Policy, Geneva. (Available at <http://www.who.int/evidence>).
- Mills CA, Porter MM (1950) Tobacco smoking habits and cancer of the mouth and respiratory system. *Cancer Research*, 10:539–542.
- Moolgavkar SH, Venzon DJ (1987) General relative risk regression models for epidemiologic studies. *American Journal of Epidemiology*, 126:949–961.
- Muller FH (1939) Tobacco abuse and carcinoma of the lung. *Zeitschrift fur Krebsforschung*, 49:57–85.

- Nandakumar A, Thimmasetty KT, Sreeramareddy NM et al. (1990) A population-based case-control investigation on cancers of the oral cavity in Bangalore, India. *British Journal of Cancer*, **62**:847–851.
- National Research Council (1994) *Science and judgment in risk assessment*, National Academy Press, Washington, DC.
- Nicolaides-Bouman A, Wald N, Forey B, Lee P, eds. (1993) *International smoking statistics: a collection of historical data from 22 economically developed countries*. The Wolfson Institute of Preventive Medicine and Oxford University Press, London and Oxford.
- Niu SR, Yang GH, Chen ZM et al. (1998) Emerging tobacco hazards in China: 2. Early mortality results from a prospective study. *British Medical Journal*, **317**:1423–1424.
- Nyberg F, Gustavsson P, Jarup L et al. (2000) Urban air pollution and lung cancer in Stockholm. *Epidemiology*, **11**:487–495.
- Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J, eds. (1992) *Cancer incidence in five continents: Volume VI*. (IARC Scientific Publications No. 120.) International Agency for Research on Cancer (IARC), Lyon.
- Parkin DM, Whelan SL, Ferlay J, Black RJ, eds. (1997) *Cancer incidence in five continents: Volume VII*. (IARC Scientific Publications No. 143.) International Agency for Research on Cancer, Lyon.
- Pathak DR, Samet JM, Humble CG, Skipper BJ (1986) Determinants of lung cancer risk in cigarette smokers in New Mexico. *Journal of the National Cancer Institute*, **76**:597–604.
- Percy C, Miller BA, Gloeckler Reis LA (1990) Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. *Annals of New York Academy of Sciences*, **609**:87–97.
- Percy C, Muir C (1989) The international comparability of cancer mortality data: results of an international death certificate study. *American Journal of Epidemiology*, **129**:934–946.
- Peto R (1978) Carcinogenic effects of chronic exposure to very low levels of toxic substances. *Environmental Health Perspectives*, **22**:155–159.
- Peto R (1986) Influence of dose and duration of smoking on lung cancer rates. In: *Tobacco: a major international health hazard*. Zaridze D, Peto R, eds. (IARC Scientific Publication No. 7) International Agency for Research on Cancer, Lyon.
- Peto R, Darby S, Silcocks P, Whitley E, Doll R (2000) Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *British Medical Journal*, **321**:323–329.
- Peto R, Doll R (1984) Keynote address: the control of lung cancer. In: *Lung cancer: causes and prevention*. Mizell M, Correa P, eds. Verlag Chemie International, Deerfield Beach, FL.
- Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr (1992) Mortality from tobacco in developed countries. *The Lancet*, **339**:1268–1278.

- Pope CA, III, Burnett RT, Thun MJ et al. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *Journal of American Medical Association*, **287**:1132–1141.
- Preston SH, Heuveline P, Guillot M (2000) *Demography: measuring and modelling population processes*. Blackwell, Oxford.
- Puddey IB, Rakic V, Dimmitt SB, Beilin LJ (1999) Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors: a review. *Addiction*, **94**:649–663.
- Rao DN, Ganesh B, Rao RS, Desa PB (1994) Risk assessment of tobacco, alcohol, and diet in oral cancer: a case-control study. *International Journal of Cancer*, **58**:469–473.
- Rogot E, Murray JL (1980) Smoking and causes of death among U.S. Veterans: 16 years of observation. *Public Health Reports*, **95**:213–222.
- Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S (1985) The risk of myocardial infarction after quitting smoking in men under 55 years of age. *New England Journal of Medicine*, **313**:1511–1514.
- Rosenberg L, Palmer JR, Shapiro S (1990) The risk of myocardial infarction among women who stop smoking. *New England Journal of Medicine*, **322**:213–217.
- Sankaranarayanan R, Duffy SW, Day NE, Nair MK, Padmakumary G (1989a) A case-control investigation of cancer of the oral tongue and the floor of the mouth in southern India. *International Journal of Cancer*, **44**:617–621.
- Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Nair MK (1990) Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. *Journal of Epidemiology and Community Health*, **44**:286–292.
- Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Padmanabhan TK (1989b) Tobacco chewing, alcohol, and nasal snuff in cancer of the gingiva in Kerala, India. *British Journal of Cancer*, **60**:638–643.
- Schairer E, Schoniger E (1943) Lung cancer and tobacco use. *Zeitschrift fur Krebsforschung*, **54**:261–269.
- Schrek R, Baker LA, Ballard GP, Dolgoff S (1950) Tobacco smoking as an etiologic factor in disease. *Cancer Research*, **10**:49–58.
- Smith KR, Liu Y (1993) Indoor air pollution in developing countries. In: *Epidemiology of lung cancer: lung biology in health and disease*. Samet J, ed. Marcel Dekker, New York.
- Smith KR, Shuhua G, Kun H, Daxiong Q (1993) One hundred million improved cookstoves in China: How was it done? *World Development*, **21**:941–961.
- Sobue T (1990) Association of indoor air pollution and lifestyle with lung cancer in Osaka, Japan. *International Journal of Epidemiology*, **19**:S62–66.
- Sobue T, Suzuki T, Fujimoto I et al. (1991) Lung cancer risk among ex-smokers. *Japanese Journal of Cancer Research*, **82**:273–279.
- Sterling TD, Rosenbaum WL, Weinkam JJ (1993) Risk attribution and tobacco-related deaths. *American Journal of Epidemiology*, **138**:128–139.

- Thomas P, Zelikoff J (1999) Air pollutants: moderators of pulmonary host resistance against infection. In: *Air pollution and health*. Holgate ST, Samet JM, Maynard RL, Koren HS, eds. Academic Press, San Diego, CA.
- Thun MJ, Apicella LF, Henley SJ (2000) Smoking vs other risk factors as the cause of smoking-attributable mortality. *Journal of American Medical Association*, 284:706–712.
- Thun MJ, Day-Lally CA, Calle EE, Flanders WD, Heath CW Jr (1995) Excess mortality among cigarette smokers: changes in a 20-year interval. *American Journal of Public Health*, 85:1223–1230.
- Thun MJ, Day-Lally CA, Myers DG et al. (1997a) Trends in tobacco smoking and mortality from cigarette use in cancer prevention studies I (1959 through 1965) and II (1982 through 1988). In: *Changes in cigarette-related disease risks and their implications for prevention and control*. (Smoking and Tobacco Control Monograph No. 8.) National Cancer Institute, ed. National Cancer Institute, Bethesda, MD.
- Thun MJ, Myers DG, Day-Lally C et al. (1997b) Age and exposure-response relationships between cigarette smoking and premature death in cancer prevention study II. In: *Age and exposure-response relationships between cigarette smoking and premature death in cancer prevention study II*. National Cancer Institute, Bethesda.
- Thun MJ, Peto R, Lopez AD et al. (1997c) Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *New England Journal of Medicine*, 337:1705–1714.
- U.S. Department of Health and Human Services (1986) *The health consequences of using smokeless tobacco. A report of the advisory committee to the Surgeon General*. (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.
- U.S. Department of Health and Human Services (1989) *Reducing the consequences of smoking: 25 years of progress. A report of the Surgeon General, 1989*. (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.
- U.S. Department of Health and Human Services (1990a) Chapter 4: smoking cessation and respiratory cancers. In: *The health benefits of smoking cessation. A report of the Surgeon General, 1990*. U.S. Department of Health and Human Services, ed. USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.
- U.S. Department of Health and Human Services (1990b) Chapter 6: Smoking cessation and cardiovascular disease. In: *The health benefits of smoking cessation. A report of the Surgeon General, 1990*. U.S. Department of Health and Human Services, ed. USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.

- U.S. Department of Health and Human Services (1990c) *The health benefits of smoking cessation. A report of the Surgeon General, 1990.* (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Bethesda, MD.
- U.S. Department of Health and Human Services (2001) *Women and smoking. A report of the Surgeon General.* (DHHS Publication No. [CDC] 89-8411.) USDHHS, Public Health Service, Centers for Disease Control and Prevention. Office on Smoking and Health, Bethesda, MD.
- UK Department of Health, Scientific Committee on Tobacco and Health (1998) *Report of the scientific committee on tobacco and health.* UK Department of Health, London.
- Valkonen T, van Poppel F (1997) Smoking. The contribution of smoking to sex differences in life expectancy. *European Journal of Public Health, 7*:302–310.
- Vena JE (1982) Air pollution as a risk factor in lung cancer. *American Journal of Epidemiology, 116*:42–56.
- Wang TJ, Zhou BS, Shi JP (1996) Lung cancer in nonsmoking Chinese women: a case control study. *Lung Cancer, 14*:S93–98.
- Wassink WF (1948) Onstaansvoorwarden voor Longkanker [Etiology of lung cancer]. *Tijdschrift voor Geneeskunde, 92*:3732–3747.
- WHO (1997) *Tobacco or health: a global status report.* World Health Organization, Geneva.
- Wynder EL, Graham EA (1950) Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *Journal of American Medical Association, 143*:329–336.
- Yamaguchi N, Mochizuki-Kobayashi Y, Utsunomiya O (2000) Quantitative relationship between cumulative cigarette smoking and lung cancer mortality in Japan. *International Journal of Epidemiology, 29*:963–968.
- Zaridze D, Peto R, eds. (1986) *Tobacco: a major international health hazard.* (IARC Scientific Publication No. 7.) International Agency for Research on Cancer, Lyon.

