Role of Smoking in Global and Regional Cardiovascular Mortality

Majid Ezzati, PhD; S. Jane Henley, MSPH; Michael J. Thun, MD; Alan D. Lopez, PhD

**Background**—Smoking is a major cause of cardiovascular disease mortality. There is little information on how it contributes to global and regional cause-specific mortality from cardiovascular diseases for which background risk varies because of other risks.

**Method and Results**—We used data from the American Cancer Society’s Cancer Prevention Study II (CPS II) and the World Health Organization Global Burden of Disease mortality database to estimate smoking-attributable deaths from ischemic heart disease, cerebrovascular disease, and a cluster of other cardiovascular diseases for 14 epidemiological subregions of the world by age and sex. We used lung cancer mortality as an indirect marker for accumulated smoking hazard. CPS-II hazards were adjusted for important covariates. In the year 2000, an estimated 1.62 (95% CI, 1.27 to 2.04) million cardiovascular deaths in the world, 11% of total global cardiovascular deaths, were due to smoking. Of these, 1.17 million deaths were among men and 450 000 among women. There were 670 000 (95% CI, 440 000 to 920 000) smoking-attributable cardiovascular deaths in the developing world and 960 000 (95% CI, 770 000 to 1 200 000) in industrialized regions. Ischemic heart disease accounted for 54% of smoking-attributable cardiovascular mortality, followed by cerebrovascular disease (25%). There was variability across regions in the role of smoking as a cause of various cardiovascular diseases.

**Conclusions**—More than 1 in every 10 cardiovascular deaths in the world in the year 2000 were attributable to smoking, demonstrating that it is an important preventable cause of cardiovascular mortality. (Circulation. 2005;112:489-497.)

**Key Words:** cardiovascular diseases ■ health ■ mortality ■ risk factors ■ smoking

Worldwide, the number of deaths from cardiovascular diseases increased from 14 million in 1990 to >16 million in 2000.2 Aging of the world’s population is a major factor contributing to this increase because cardiovascular mortality rates tend to increase with age. Although age-specific mortality rates for all cardiovascular diseases combined have declined in both developing and developed countries,3,4 the rates for specific causes (eg, ischemic heart disease [IHD]) have increased in some populations.5 The basis for this epidemiological change is a population-wide rise in some cardiovascular disease risk factors,6 including decreasing physical activity, changes in diet, tobacco smoking, air pollution,7 and possibly fetal and childhood exposures that may increase the risk of cardiovascular diseases in adulthood.8 Smoking and obesity are 2 cardiovascular risk factors with unequivocal global increase over recent decades. Tobacco use is currently widespread in most populations in industrialized and developing countries and has been causally associated with mortality from multiple cardiovascular diseases.9–12

**See p 456**

Recent estimates of cardiovascular mortality attributable to smoking were based on all cardiovascular diseases combined.13 Such estimates are important for motivating global tobacco control efforts such as the Framework Convention on Tobacco Control. Combined estimates, however, do not address regional differences in the background risks of specific cardiovascular diseases (eg, IHD versus stroke). Background risks vary because of regional differences in nutritional, behavioral, and environmental factors and medical care, all with important population-specific dynamics. For example, background mortality from cardiovascular diseases is substantially lower in China than in India or Eastern Europe.2 As a result, cardiovascular diseases make up a smaller fraction of total smoking-attributable deaths in China compared with India and Eastern Europe; in contrast, chronic obstructive pulmonary disease and lung cancer make up a much larger proportion of total smoking-attributable deaths in China.14,15 Economic development and urbanization, however, are changing diet and exercise in China, with implications for obesity and other cardiovascular risk factors.16

Changes in cardiovascular risks and access to pharmacological interventions are also occurring in other developing and developed countries.6–17 Parallel to changes in these risk factors, smoking increased substantially in most developing countries over the last quarter of the twentieth century, with
Table 1. Relative Risk of Mortality From Different Cardiovascular Diseases for CPS-II Current Smokers Relative to Nonsmokers From Reanalysis of CPS-II Data

<table>
<thead>
<tr>
<th>Disease or Disease Cluster (ICD-9 code)</th>
<th>Age, y</th>
<th>Men (95% CI)</th>
<th></th>
<th></th>
<th>Women (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>IHD (410–414)</td>
<td>30–44</td>
<td>5.49 (2.46–12.25)</td>
<td>5.51 (2.47–12.25)</td>
<td>2.28 (0.83–6.23)</td>
<td>2.26 (0.83–6.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45–59</td>
<td>3.05 (2.67–3.49)</td>
<td>3.04 (2.66–3.48)</td>
<td>3.77 (3.09–4.60)</td>
<td>3.78 (3.10–4.62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>1.87 (1.69–2.08)</td>
<td>1.88 (1.70–2.08)</td>
<td>2.47 (2.17–2.81)</td>
<td>2.53 (2.22–2.87)</td>
<td></td>
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<tr>
<td></td>
<td>70–79</td>
<td>1.40 (1.24–1.58)</td>
<td>1.44 (1.27–1.63)</td>
<td>1.57 (1.37–1.81)</td>
<td>1.68 (1.46–1.93)</td>
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</tr>
<tr>
<td></td>
<td>≥80</td>
<td>1.01 (0.75–1.37)</td>
<td>1.05 (0.78–1.43)</td>
<td>1.34 (1.04–1.72)</td>
<td>1.38 (1.08–1.77)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease (430–438)</td>
<td>30–44</td>
<td>No estimates (insufficient events)</td>
<td>No estimates (insufficient events)</td>
<td>No estimates (insufficient events)</td>
<td>No estimates (insufficient events)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45–59</td>
<td>3.11 (2.09–4.62)</td>
<td>3.12 (2.10–4.64)</td>
<td>4.54 (3.30–6.28)</td>
<td>4.61 (3.34–6.37)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>1.85 (1.42–2.43)</td>
<td>1.87 (1.43–2.44)</td>
<td>2.74 (2.15–3.49)</td>
<td>2.81 (2.21–3.58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>1.35 (1.06–1.72)</td>
<td>1.39 (1.09–1.77)</td>
<td>1.85 (1.48–2.32)</td>
<td>1.95 (1.56–2.45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥80</td>
<td>1.01 (0.60–1.70)</td>
<td>1.05 (0.63–1.77)</td>
<td>0.90 (0.57–1.42)</td>
<td>0.94 (0.60–1.47)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive disease* (401–405)</td>
<td>≥30</td>
<td>1.96 (1.45–2.66)</td>
<td></td>
<td></td>
<td>2.12 (1.59–2.84)</td>
<td></td>
</tr>
<tr>
<td>Other cardiovascular diseases (390–398, 415–429, 440–459)</td>
<td>≥30</td>
<td>2.11 (1.91–2.33)</td>
<td>2.15 (1.94–2.38)</td>
<td>1.95 (1.75–2.16)</td>
<td>2.00 (1.80–2.22)</td>
<td></td>
</tr>
</tbody>
</table>

ICD-9 indicates International Classification of Disease, ninth revision. Relative risks (RRs) were estimated from Cox proportional-hazard models, with nonsmokers as the reference group (RR = 1.0 for nonsmokers). In A, all risks were adjusted for age, race, education, marital status, “blue collar” employment in most recent or current job, weekly consumption of vegetables and citrus fruit, vitamin A, C, and E use, alcohol use, aspirin use, body mass index, exercise, and dietary fat consumption. In B, risks were adjusted for covariates in A and for hypertension and diabetes at baseline. At baseline, the prevalence of hypertension among never smokers, current smokers, and former smokers was 28%, 26%, and 33% for men and 32%, 24%, and 27% for women; the prevalence of diabetes mellitus among never smokers, current smokers, and former smokers was 5%, 5%, and 6% for men and 5%, 4%, and 4% for women.

*N*Evidence of a causal association between smoking and hypertensive disease has consistently been observed in epidemiological studies.*11,15* These findings are also supported by physiological evidence (eg. on increased blood pressure as a result of smoking48), also summarized in the 2001 Report of the Surgeon General.49* The 2004 Report of the Surgeon General excluded hypertensive disease among the end points considered for smoking-attributable mortality.9* To be consistent with the 2004 Report of the Surgeon General, we have excluded this outcome in the main estimates.

Measuring Exposure to Accumulated Smoking Hazards

The accumulated hazards of smoking depend on factors such as the age at which smoking began or stopped, duration of smoking, number of cigarettes smoked per day, whether the smoked tobacco product was in the form of cigarettes or in other forms such as bidis or cigars, cigarette characteristics, and smoking behavior such as degree of inhalation.23 Many of these factors vary over time because of changes in the socioeconomic determinants of smoking, including income, marketing by the tobacco industry, the effects of tobacco control programs, prices, taxes, and sociocultural norms. Therefore, current smoking prevalence or tobacco consumption alone would be insufficient indicators of the accumulated hazards of smoking, even if detailed data were available in all countries. This is particularly
important in low- and middle-income countries, where smoking has increased substantially over the past few decades.\textsuperscript{18,19}

To capture the accumulated hazard of smoking, we used the smoking impact ratio (SIR) method of Peto et al\textsuperscript{12} adapted to the specific conditions of developing countries.\textsuperscript{23} The method uses lung cancer mortality, data on which are available or can be estimated from validated methods in most populations, as an indirect indicator of the accumulated hazards of smoking. A background-adjusted SIR is defined as population lung cancer mortality in excess of that for never smokers relative to excess lung cancer mortality for a known reference group of smokers, adjusted to account for differences in never-smoker lung cancer mortality rates across populations: $SIR = (C_{LC} - N_{LC})/S^*_{LC} - N^*_{LC}) \times (N^*_{LC}/N_{LC})$, where $C_{LC}$ is age- and sex-specific lung cancer mortality rate for 2000 in the study population (eg, country of analysis) from the WHO GBD database, $N_{LC}$ is age- and sex-specific lung cancer mortality rate for 2000 in the reference population in which hazards for other causes are controlled, $S^*_{LC}$ and $N^*_{LC}$ are age- and sex-specific lung cancer mortality rates for smokers and never smokers in a reference population, SIR was calculated for each age group, each sex, individual countries and then averaged (population weighted) in each of 14 epidemiological subregions of the world (Table 2). The age groups used in the analysis were 30 to 44, 45 to 59, 60 to 69, 70 to 79, and $\geq 80$ years. No deaths before 30 years of age were attributed to smoking because there are few cardiovascular deaths in individuals $<30$ years of age and relative risks are unstable.

Conceptually, by using excess lung cancer mortality as the indicator of the accumulated hazards of smoking in both study and reference populations, SIR converts the smokers in the study population, who may have different smoking histories, into equivalent smokers in the reference population in which hazards for other diseases (eg, different cardiovascular diseases) have been measured.\textsuperscript{12} We used CPS-II as the reference population ($S^*_{LC}$ and $N^*_{LC}$). CPS-II is 1 of the few studies of smoking and cause-specific mortality that capture the full effects of the smoking epidemic because most of the CPS-II current smokers were lifelong cigarette smokers (with a mean consumption of $\approx 20$ cigarettes per day).\textsuperscript{12}

In applying the method to developing countries, we accounted for the important contribution of coal, a common fuel used in parts of the developing world, as a determinant of lung cancer among never smokers. For those populations that use coal in poorly vented stoves (eg, China and parts of Southeast Asia), never-smoker lung cancer mortality rates ($N_{LC}$) were estimated from data on lung cancer mortality among Chinese nonsmokers and prevalence of coal use in poorly vented stoves.\textsuperscript{15,23,24} The remaining risk factors for lung cancer mortality (ambient air pollution, occupational hazards, indoor air pollution from radon or biomass smoke, etc) in various combinations affect a subset of the population of each country. It is unclear what the net impact of these risks on lung cancer rates among never smokers in specific countries may be. Therefore, the impacts of risk factors other than coal were considered as sources of uncertainty for never-smoker lung cancer mortality (Table 3).

### Table 2. Global Burden of Disease 2000 Reporting Regions\textsuperscript{2,26}

<table>
<thead>
<tr>
<th>Region</th>
<th>Stratum</th>
<th>Countries</th>
<th>Population in Thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR D</td>
<td>Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo</td>
<td>294 078</td>
<td></td>
</tr>
<tr>
<td>E Botswana, Burundi, Central African Republic, Congo, Côte d’Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe</td>
<td>345 515</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMR A Canada, Cuba, United States</td>
<td>325 183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela</td>
<td>430 932</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru</td>
<td>71 230</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR B Bahrain, Cyprus, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates</td>
<td>139 059</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUR A Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom</td>
<td>342 576</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Yugoslavia</td>
<td>218 458</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine</td>
<td>243 184</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEAR B Indonesia, Sri Lanka, Thailand</td>
<td>293 819</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D Bangladesh, Bhutan, Democratic People’s Republic of Korea, India, Maldives, Myanmar, Nepal</td>
<td>1 241 806</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WPR A Australia, Brunei Darussalam, Japan, New Zealand, Singapore</td>
<td>154 354</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People’s Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Vietnam</td>
<td>1 532 933</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A indicates very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; and E, high child mortality and very high adult mortality.
and nonsmokers (S*LC and N*LC), and (2) statistical uncertainty in the complete.26 Second, using SIR, which is based on excess lung cancer developing countries where vital registration is absent or incomplete.13 Uncertainties of individual parameters were estimated CPS-II relative risks for each disease (Table 1).

The above quantitative analysis does not include a number of other sources of uncertainty. First, there is uncertainty in the total number of cardiovascular deaths in this region (2.0 million) is more sparse. Some sources of uncertainty were addressed in a quantitative uncertainty analysis. These include (1) uncertainty in the parameters used to calculate the SIR, including lung cancer mortality in each country based on its mortality reporting system (CLC), air pollution (NLC), and lung cancer mortality in CPS-II smokers and nonsmokers (S* and N*), and (2) statistical uncertainty in the estimated SIR relative risks for each disease (Table 1).

Uncertainty for each of the inputs was estimated separately, as described elsewhere.13 Uncertainties of individual parameters were combined in a stratified sampling simulation25 to estimate an uncertainty distribution for the fraction of cause-specific mortality attributable to smoking. The uncertainty reported here is the 95% range of the combined distribution.

The above quantitative analysis does not include a number of other sources of uncertainty. First, there is uncertainty in the total number of cardiovascular deaths (from the GBD database), especially in developing countries where vital registration is absent or incomplete. Second, using SIR, which is based on excess lung cancer mortality as the marker for accumulated smoking hazard for cardiovascular diseases introduces additional uncertainty. Because lung cancer has a longer lag than cardiovascular diseases, using SIR as the metric of accumulated hazard could result in an overestimation of risk when there has been a sharp decline in smoking (eg, North America and those countries in Western Europe where smoking has declined) and an underestimation of risk when there have been large increases in smoking. On the other hand, the cardiovascular impacts of smoking may be underestimated in developing countries, where smoking has been rising. A third source of uncertainty is the extrapolation of relative risks from CPS-II to other populations, which may have different exposure to other cardiovascular risk factors and background disease levels. The nature of this source of uncertainty and its implications for research and surveillance are described in detail in the Discussion.

Results
The estimated numbers of cardiovascular deaths attributable to smoking are summarized in Table 3, disaggregated by region and sex in Table 4, and displayed by region and disease in the Figure. Globally, an estimated 1.62 (95% CI, 1.27 to 2.04) million cardiovascular deaths were attributable to smoking in 2000, 11% of total global adult (≥30 years of age) cardiovascular deaths. The proportion of adult cardiovascular deaths attributable to smoking was 17% for men and 5% for women and 7% and 16% for developing and industrialized countries, respectively. An additional 90 000 deaths from hypertensive disease were excluded from these estimates, consistent with the analysis of the 2004 Report of the Surgeon General.9

Regional Patterns
The largest numbers of cardiovascular deaths attributable to smoking were seen in the industrialized regions (340 000 deaths, 17% of total adult cardiovascular deaths in Eastern Europe and the former Soviet republics [EUR-C]; 220 000 deaths, 22% of total adult cardiovascular deaths in North America [AMR-A]; 200 000 deaths, 13% of total adult cardiovascular deaths in Western Europe [EUR-A]) and the high-mortality developing region of Southeast Asia (SEAR-D; 300 000 deaths, 10% of total adult cardiovascular deaths, dominated by India in terms of population). The large numbers of cardiovascular deaths attributable to smoking in EUR-C and SEAR-D are due to a combination of 2 factors: (1) the large number of cardiovascular deaths resulting from large population size and high background rates of cardiovascular deaths caused by other cardiovascular risk factors such as blood pressure, cholesterol, and body mass index27–29 and (2) a relatively high proportion of cardiovascular deaths caused by smoking. For example, SEAR-D has substantially less adult population than the developing regions of the Western Pacific (WPR-B; dominated by China in terms of population) (480 million versus 740 million) but a similar number of adult cardiovascular deaths (2.9 million versus 3.1 million). Together with a higher smoking-attributable fraction, smoking caused a considerably larger number of cardiovascular deaths in SEAR-D (300 000 deaths; 10%) than in WPR-B (120 000; 4%). This is in contrast to similar estimates for cancers, where WPR-B had a much higher total number of deaths (1.8 million cancer deaths in WPR-B versus 800 000 in SEAR-D) and hence higher smoking-attributable cancer deaths (240 000 in WPR-B versus 190 000 in SEAR-D) even with a lower smoking-attributable fraction (14% in WPR-B versus 24% in SEAR-D). Similarly, the adult population of EUR-C (140 million) is substantially smaller than that of EUR-A (260 million) and AMR-A (190 million), yet the total number of cardiovascular deaths in this region (2.0 million) is

TABLE 3. Estimated Cardiovascular Mortality Among People ≥30 Years of Age Attributable to Smoking in Developing (≥30-Year-Old Population, 1,874 Million) and Industrialized (≥30-Year-Old Population, 795 Million) Regions in the Year 2000

<table>
<thead>
<tr>
<th>Region</th>
<th>Male (95% CI)</th>
<th>Female (95% CI)</th>
<th>Total†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing*</td>
<td>A: 520 000 (340 000–670 000)</td>
<td>A:150 000 (100 000–250 000)</td>
<td>A: 670 000 (440 000–920 000)</td>
</tr>
<tr>
<td></td>
<td>B: 530 000 (380 000–670 000)</td>
<td>B:154 000 (100 000–270 000)</td>
<td>B: 680 000 (480 000–940 000)</td>
</tr>
<tr>
<td>Industrialized*</td>
<td>A: 650 000 (550 000–740 000)</td>
<td>A:300 000 (220 000–420 000)</td>
<td>A: 960 000 (770 000–160 000)</td>
</tr>
<tr>
<td></td>
<td>B: 660 000 (570 000–750 000)</td>
<td>B:320 000 (240 000–440 000)</td>
<td>B: 980 000 (810 000–1 190 000)</td>
</tr>
<tr>
<td>World</td>
<td>A:1 170 000 (930 000–1 400 000)</td>
<td>A:450 000 (340 000–640 000)</td>
<td>A:1 620 000 (1 270 000–2 040 000)</td>
</tr>
<tr>
<td></td>
<td>B:1 190 000 (980 000–1 390 000)</td>
<td>B:480 000 (360 000–690 000)</td>
<td>B:1 670 000 (1 340 000–2 080 000)</td>
</tr>
</tbody>
</table>

The estimates exclude hypertensive disease. A and B correspond to the 2 sets of relative risks in Table 1.

*Industrialized regions include AMR-A, EUR-A, EUR-B, EUR-C, and WPR-A; developing regions include all other regions. This classification is based on the World Health Report 2002.2 See Table 2 for a description of regions.

†Discrepancies between components and totals are a result of rounding.
considerably larger than those in EUR-A (1.6 million) and AMR-A (980,000 million) because of the background risk of cardiovascular mortality resulting from other risks such as elevated blood pressure and overweight and obesity.30 Therefore, although the fraction of all cardiovascular deaths attributable to smoking in EUR-C (17%) is lower than in AMR-A (22%) and only slightly higher than in EUR-A (13%), the number of smoking-attributable deaths in this region is the largest of all industrialized regions.

The proportions of total adult cardiovascular deaths attributable to smoking were generally highest in industrialized regions (12% to 22%), where smoking has been entrenched for several generations (Table 4). At the same time, the increase in smoking over the last quarter of the twentieth century in a number of developing regions, including parts of Latin America, the Eastern Mediterranean, and Southeast Asia, has resulted in 10% of all current adult cardiovascular deaths being attributable to smoking; the number is higher among men (Table 4).

The number of cardiovascular deaths attributable to smoking among men was higher than among women (Tables 3 and 4), with men accounting for 68% of all smoking-attributable cardiovascular deaths in industrialized regions and 78% in developing regions. The exception to this pattern was AMR-A, where female deaths accounted for 58% of total smoking-attributable cardiovascular deaths. Even in North America the fraction of smoking-attributable cardiovascular deaths was slightly lower among women (21% for women versus 23% for men). Because total cardiovascular deaths were higher among women, however, population-attributable fractions were applied to larger baselines for women than for men. Eighty-one percent of smoking-attributable cardiovascular deaths in developing regions were in individuals between 30 and 69 years of age compared with 61% in industrialized regions.

### Disease-Specific Patterns

Globally, IHD accounted for the largest number of cardiovascular deaths attributable to smoking (870,000 deaths; 54%
of all smoking-attributable cardiovascular deaths), more than twice as many cerebrovascular disease deaths attributable to smoking (400,000 deaths; 25%) (Table 5). The relative contributions of different diseases to smoking-attributable cardiovascular deaths varied across developing and industrialized regions because of variations in both background death rates and fractions attributable to smoking (the Figure). In developing regions, 360,000 IHD and 200,000 cerebrovascular deaths made up 54% and 30% of all smoking-attributable cardiovascular deaths, respectively. In industrialized regions, cerebrovascular disease had a smaller role relative to developing regions, with 510,000 IHD and 210,000 cerebrovascular deaths making up 54% and 22% of all smoking-attributable cardiovascular deaths (see also the article by Yusuf at al). The relatively smaller role of cerebrovascular disease in industrialized countries was countered by a larger role for the cluster of “other cardiovascular diseases” (25% of all smoking-attributable cardiovascular deaths in industrialized regions versus 16% in developing regions). The contribution of IHD to total smoking-attributable cardiovascular deaths varied from a low of 30% to 40% in the Western Pacific (WPR-A and WPR-B) and parts of sub-Saharan Africa (AFR-E) to a high of 60% to 70% in the Eastern Mediterranean (EMR-B and EMR-D), SEAR-D, and EUR-C.

TABLE 5. Estimated Cardiovascular Mortality Attributable to Smoking by Cause in the Year 2000 and to Other Major Risk Factors

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deaths Attributable to Smoking (95% CI)</th>
<th>Proportion Attributable to Smoking, %</th>
<th>Other Major Risk Factors (PAF)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>A: 870,000 (700,000–1,010,000)</td>
<td>13</td>
<td>High blood pressure (42%), high cholesterol (51%), overweight and obesity (17%), low fruit and vegetable consumption (26%), physical inactivity (19%), alcohol use (1%),† urban air pollution (3%),‡ lead exposure (2%)§</td>
</tr>
<tr>
<td></td>
<td>B: 890,000 (750,000–1,050,000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>A: 410,000 (320,000–540,000)</td>
<td>8</td>
<td>High blood pressure (59%), high cholesterol (15%), overweight and obesity (9%), low fruit and vegetable consumption (9%), physical inactivity (6%), alcohol use (2%),† urban air pollution (3%),‡ lead exposure (2%)§</td>
</tr>
<tr>
<td></td>
<td>B: 420,000 (320,000–550,000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive disease</td>
<td></td>
<td>Excluded</td>
<td>NA</td>
</tr>
<tr>
<td>Other cardiovascular diseases</td>
<td>A: 350,000 (320,000–400,000)</td>
<td>13</td>
<td>No estimates available because of heterogeneous mix of diseases and hazards for different risk factors</td>
</tr>
<tr>
<td></td>
<td>B: 360,000 (320,000–420,000)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A and B correspond to the 2 sets of relative risks in Table 1.
*Source: reanalysis of data on 26 major global risk factors. The figure shows the estimated mortality for each risk factor considered individually. These risks act jointly with one another. Consequently, the burden resulting from groups of risk factors will be less than the sum of individual risks.
†Estimates for alcohol are net estimates that include beneficial effects in those populations with moderate drinking patterns and harmful effects in populations with hazardous drinking patterns (eg, binge drinking).
‡Estimates for urban air pollution apply to selected cardiopulmonary diseases together, which include IHD, cerebrovascular disease, and hypertensive disease.
§Estimates for lead exposure are mediated through increased blood pressure.
Evidence of a causal association between smoking and hypertensive disease has been consistently observed in epidemiological studies. These findings are also supported by physiological evidence (eg, increased blood pressure as a result of smoking), also summarized in the 2001 Report of the Surgeon General. The 2004 Report of the Surgeon General did include hypertensive disease among the end points considered for smoking-attributable mortality. To be consistent with the 2004 Report of the Surgeon General, we have not excluded this outcome from the main estimates. Using the relative risks in Table 1 would give an estimated 90,000 (80,000–110,000) deaths from hypertensive disease attributable to smoking.
Discussion

Smoking is currently a very important determinant of cardiovascular mortality among men in all regions of the world and among women in industrialized countries. The proportion of cardiovascular deaths caused by smoking exhibited large variations among different regions of the world (men, from \( \leq 10\% \) of total cardiovascular mortality in sub-Saharan Africa and parts of Latin America and the Western Pacific to \( \geq 23\% \) in industrialized regions of Europe and North America; women, from \( \leq 5\% \) of total cardiovascular mortality in the developing world to \( \geq 20\% \) in North America). The interregional variation was even more apparent for deaths caused by smoking from specific cardiovascular conditions. In particular, the contribution of IHD to smoking-attributable mortality varied by a factor of \( \approx 2 \). Smoking also caused large numbers of deaths from cerebrovascular disease in several developing regions. This interregional variation occurs because the shape and maturity of the smoking epidemic is highly affected by region-specific socioeconomic and cultural determinants of smoking, and because background mortality varies across populations.5

Clinical, experimental, and epidemiological evidence has established the role of environmental tobacco smoke as a risk factor for cardiovascular disease in otherwise healthy non-smokers.31–35 Because environmental tobacco smoke is also a risk factor for lung cancer,36,37 its effects are captured partially by the SIR, as described in detail elsewhere.38 Separate estimates of cardiovascular mortality as a result of exposure to environmental tobacco smoke would have to consider the physical proximity of smokers and nonsmokers and building ventilation. These parameters, in turn, depend on cultural and geographical factors and on regulation of smoking in public areas.

The estimated number of global cardiovascular deaths attributable to smoking in this analysis (1.62 million) was practically identical to the number obtained by applying a constant “correction factor” of 30% to unadjusted hazards for multiple diseases combined (1.69 million).13 The differences in estimates from the 2 methods across regions and sexes ranged from \( >25\% \) underestimation among women in sub-Saharan Africa and parts of Southeast Asia, the Western Pacific to \( >20\% \) overestimation among men in North America, Western Europe, and the Western Pacific when covariate-adjusted site-specific hazards were not used. This variation in underestimation or overestimation arises because all cardiovascular diseases, which in reality have different distributions in different regions and different hazards, were grouped together in previous estimates. Using relative risks with additional adjustment for hypertension and diabetes mellitus resulted in practically identical global estimates (1.62 million versus 1.67 million deaths; difference not statistically significant) and for individual regions and diseases. This robustness to additional adjustment is consistent with the findings of Malarcher and colleagues39 (CPS-II) and Kawachi and colleagues40 (Nurse’s Health Study) who found that relative risks for smoking and cardiovascular diseases were not affected by residual confounding as a result of history of hypertension and diabetes.

The validity of smoking-attributable mortality estimates using the indirect SIR method has been confirmed against alternative methods that account for accumulated hazards of smoking.41 Uncertainty nonetheless remains, especially in developing countries where both complete mortality records and detailed studies of cardiovascular risk factors are less common. Some sources of uncertainty were described earlier. Two important additional sources of uncertainty in the current estimates with implications for future research are (1) the correlation between smoking and other cardiovascular disease risks within populations and (2) biological interactions between smoking and other risks that would result in uncertainty above and beyond that quantified in statistical hazard models when CPS-II relative risks are extrapolated to other populations. For many diseases, multiple risk factors “magnify” each other’s total risks as determined from standard proportional-hazard models. If multiple risks for the same disease are more common (positively correlated) in specific population subgroups, total (absolute) hazards would be larger than those estimated here, even if relative risks remain unchanged (smaller with negative correlation).42,43 Unhealthy diet among smokers is an example of positive correlation. In addition to correlation of risk factor exposures, multiple risks for the same disease may modify one another’s relative risk (eg, the relative risk of smoking may depend on diet or other factors that affect background cardiovascular mortality). The existing evidence indicates that extrapolation of hazards from CPS-II to other populations is a valid option. For example, the Chinese retrospective study of smoking and mortality demonstrated that background mortality rates, which varied by up to a factor of 4 for cardiovascular diseases, did not change the relative risk of mortality as a result of smoking (Figure 5 in Liu et al15). The robustness of relative risks for smoking to changes in other risk factors has also been confirmed in studies that stratified on serum cholesterol.44 More recently, a study in >50 countries illustrated that, when comparable methods were used, hazards of smoking for myocardial infarction did not vary significantly across regions of the world (Western Europe, Central and Eastern Europe, North America, South America and Mexico, Australia and New Zealand, the Middle East, Africa, South Asia, China and Hong Kong, Southeast Asia, and Japan).45,46 Despite these assurances, extrapolation of CPS-II relative risks is a source of additional uncertainty but necessary in the absence of recent local epidemiological studies in developing countries. (At any point in time, only recent epidemiological studies can be used for direct estimates because of changes in smoking patterns over time.)

The uncertainties in our analysis also identify 2 important research and surveillance needs to better understand how tobacco affects the global and regional cardiovascular epidemiology in combination with other risks. First, there is a need for epidemiological research on how smoking may interact with other risk factors. Parallel to this individual-level analysis, there is a need to improve population-level risk factor surveillance to collect data on correlation of multiple cardio-
vascular risks in population subgroups, differentiated according to factors such as income or education, race or ethnicity, or place of residence. Data on multiple risk factor interaction and correlation would allow better estimation of the total health effects of individual cardiovascular risk factors such as smoking. More important, data on correlated multiple risk exposure would be invaluable for targeting preventive interventions or treatment toward those subgroups at highest risk of cardiovascular disease.

Such research and surveillance needs are particularly important in developing countries. Currently, the number of cardiovascular deaths attributable to smoking is larger in industrialized regions than in the developing world (Table 3). However, available data on smoking trends suggest that smoking has increased in much of the developing world over the past few decades,18 as has population exposure to other cardiovascular risks such as overweight and obesity.3 Because the effects of smoking on cardiovascular disease emerge sooner than other diseases affected by smoking (eg, cancers and chronic obstructive pulmonary disease), this implies an expected increase in cardiovascular mortality in the developing world. At the same time, because the health benefits of smoking cessation occur faster for cardiovascular than other diseases,47 policies that prevent and reduce smoking will have immediate and large benefits for reducing cardiovascular mortality.48–52

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