

Role of smoking in global and regional cancer epidemiology: current patterns and data needs

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Although smoking is widely recognized as a major cause of cancer, there is little information on how it contributes to the global and regional burden of cancers in combination with other risk factors that affect background cancer mortality patterns. We used data from the American Cancer Society's Cancer Prevention Study II (CPS-II) and the WHO and IARC cancer mortality databases to estimate deaths from 8 clusters of site-specific cancers caused by smoking, for 14 epidemiologic 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 1.42 (95% CI 1.27–1.57) million cancer deaths in the world, 21% of total global cancer deaths, were caused by smoking. Of these, 1.18 million deaths were among men and 0.24 million among women; 625,000 (95% CI 485,000–749,000) smoking-caused cancer deaths occurred in the developing world and 794,000 (95% CI 749,000–840,000) in industrialized regions. Lung cancer accounted for 60% of smoking-attributable cancer mortality, followed by cancers of the upper aerodigestive tract (20%). Based on available data, more than one in every 5 cancer deaths in the world in the year 2000 were caused by smoking, making it possibly the single largest preventable cause of cancer mortality. There was significant variability across regions in the role of smoking as a cause of the different site-specific cancers. This variability illustrates the importance of coupling research and surveillance of smoking with that for other risk factors for more effective cancer prevention.

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Key words: smoking; cancer mortality; cause of death; risk assessment; lung cancer

Global cancer mortality rose from 6 million in 1990¹ to 7 million in 2000.² Aging of the world's population is a major factor contributing to the increase in cancer mortality because the incidence of most cancers increases with age. This demographic change is coupled with an epidemiologic shift, in which age-specific mortality has increased for some cancers (*e.g.*, lung and breast) and decreased for others (*e.g.*, stomach and cervix in many industrialized countries). This epidemiologic shift is in turn driven by changes in risk factors for cancers of different sites, including diet and the environment, infectious agents (*e.g.*, for cervix uteri, liver and stomach cancers), behavioral risks such as alcohol and tobacco use and reproductive risks and behaviors. Tobacco smoking is currently the most widespread source of exposure to known carcinogens in the world and is causally associated with at least 15 types of cancer, as summarized in a review by the IARC and the 2004 report of the U.S. surgeon general.^{3–6}

Recent estimates of global cancer mortality attributable to smoking were based on cancers of multiple sites combined.⁷ These estimates are important for motivating global tobacco-control efforts such as the FCTC. Combined estimates do not, however, address regional differences in the background risks of specific cancer sites. This limitation arises because smoking affects cancer incidence and mortality in combination with other behavioral and environmental factors, all with important population-specific dynamics and potentially different biologic mechanisms. For example, coal is used for household heating and/or cooking in many regions of China^{8,9} and has given rise to high background mortality from lung cancer, which is magnified by smoking.¹⁰ Fuel use patterns in China are, however, changing, with wealthier

coastal communities shifting from coal to cleaner fuels (*e.g.*, natural gas) and rural inland communities switching from wood to coal to avoid deforestation.⁹ Chewing betel-quinid with tobacco, common in many parts of southern Asia, is a risk factor for oral cancer in combination with smoking and has been affected by changing social norms.^{11–14} Alcohol consumption, an important risk factor for oral, esophageal and liver cancers, is currently increasing in some developing countries.¹⁵ Cancers with infectious risk factors also exhibit population-specific dynamics, ranging from a consistent decline in stomach cancer in many countries during much of the 20th century to an increase in cervix uteri cancer in some developing regions (*e.g.*, sub-Saharan Africa).

Addressing the large and increasing GBD from cancers therefore requires an understanding of the role of smoking in combination with other risk factors. Data for multirisk factor models are extremely rare, especially in developing countries. In this report, we use 2 unique data sources, the American Cancer Society CPS-II as well as the WHO and the IARC cancer mortality databases, to estimate site-specific cancer mortality caused by smoking in the year 2000 for 8 clusters of site-specific cancers and 14 epidemiologic subregions. Estimates include cervix uteri, liver and stomach cancers, which have been identified as causally related to smoking in the recent IARC review and the 2004 report of the U.S. surgeon general.^{3–5} This report also provides estimates of site-specific cancer mortality for other cancers caused by smoking in different world regions, thus updating a similar attempt made in 1985 based on cancer incidence.¹⁶ New estimates are important because smoking increased in most developing countries over the last quarter of the 20th century, with an estimated 930 million of the world's 1.1 billion smokers currently living in the developing world.^{17,18}

A second contribution of this report is the use of RRs that are systematically and consistently adjusted for potential confounding covariates such as alcohol, diet and occupational exposures. Previous estimates of smoking-caused cancer mortality, whether in aggregate or site-specific estimates from 1985,^{7,16,19} used hazard estimates with no or partial adjustments for major covariates. The

Abbreviations: AFR, African region; AMR, region of the Americas; CI, confidence interval; C_{LC}, age- and sex-specific lung cancer mortality rate in the study population; CPS-II, Cancer Prevention Study phase II; EMR, eastern Mediterranean region; EUR, European region; FCTC, Framework Convention on Tobacco Control; GBD, global burden of disease; HBV/HCV, hepatitis B/C virus; HPV, human papillomavirus; N_{LC}, age- and sex-specific lung cancer mortality rate for never-smokers in the study population; N*_{LC}, age- and sex-specific lung cancer mortality rate for never-smokers in the reference population; P, prevalence; PAF, population-attributable fraction; RR, relative risk; SEAR, Southeast Asia region; SIR, smoking impact ratio; S*_{LC}, age- and sex-specific lung cancer mortality rate for current smokers in the reference population; WPR, Western Pacific region.

Grant sponsors: National Institute on Aging. Grant number: PO1-AG17625; CPS-II is funded by the American Cancer Society.

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Received 25 November 2004; Accepted after revision 26 January 2005

DOI 10.1002/ijc.21100

Published online 4 May 2005 in Wiley InterScience (www.interscience.wiley.com).

TABLE I – RR OF MORTALITY FROM DIFFERENT CANCERS FOR CPS-II CURRENT SMOKERS RELATIVE TO NEVER-SMOKERS¹

Cancer site (ICD-9 code)	Additional covariates adjusted for	Male	Female
Trachea, bronchus and lung cancer (162)	Occupational exposure to asbestos	21.3 (17.7–25.6)	12.5 (10.9–14.3)
Upper aerodigestive tract cancer (140–150)	Alcohol consumption	8.1 (5.7–11.7)	6.0 (4.3–8.5)
Stomach cancer (151)	Family history of stomach cancer, intake of high-fiber grain foods and aspirin use frequency and duration	2.2 (1.8–2.7)	1.5 (1.2–1.9)
Liver cancer (155)	Alcohol consumption	2.3 (1.5–3.8)	1.5 (0.8–2.7)
Pancreatic cancer (157)	Alcohol consumption and aspirin use	2.2 (1.7–2.8)	2.2 (1.8–2.8)
Cervix uteri cancer (180)	Alcohol consumption, aspirin use, age at menarche, number of live births, oral contraceptive use and menopausal status	N/A	1.50 (0.9–2.6)
Bladder cancer (188)	Alcohol consumption, aspirin use and history of kidney stones	3.0 (2.1–4.3)	2.4 (1.5–4.1)
Myeloid leukemia (205) ²	—	1.89 (1.3–2.9)	1.30 (0.8–1.8)
Kidney and other urinary cancers (223) ³	Alcohol consumption and aspirin use	2.5 (1.8–3.6)	1.5 (1.0–2.1)
Colorectal cancer (153–154) ⁴	Family history of colorectal cancer, intake of high-fiber grain foods, alcohol consumption, aspirin use frequency and duration, body mass index and exercise	1.3 (1.2–1.5)	1.4 (1.3–1.6)

¹Data from Thun *et al.*,^{22–24} and reanalysis of CPS-II data. RRs were estimated from Cox proportional hazard models, with never-smokers as the reference group (RR = 1.0 for never-smokers). Numbers in parentheses are 95% CIs. 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 and vitamin (A, C and E) use.^{22–24} Additional covariates adjusted for are given in column 2.²The RR for myeloid leukemia was applied to all leukemias (ICD-9 204–208) because the WHO GBD database provides estimates of mortality for all leukemias. In regions where detailed cause of death data exist (established market economies), myeloid leukemia was 40–55% of all leukemias.³In the WHO GBD database, kidney and other urinary cancers are a part of the residual category “other cancers”, which also includes cancers of multiple other sites. For this reason, no estimates were made for these cancers using the WHO cancer mortality database; estimates were made using the IARC cancer mortality database.⁴Evidence of a causal association between smoking and colorectal cancer was classified as suggestive in the 2004 report of the U.S. surgeon general.⁵ Therefore, colorectal cancer was not included in the main estimates.

use of unadjusted, multicancer hazards necessitated the use of arbitrary hazard correction factors to ensure that the risks of tobacco were not overestimated.^{7,19} This increased uncertainty in the estimates of cancer mortality caused by smoking. By using a comparable measure of exposure and systematically adjusted hazards, the estimates presented here provide a consistent basis for assessing the consequences of smoking in different regions of the world for global cancer epidemiology, and for assessing how global and regional tobacco-control efforts, such as those initiated under the FCTC, may contribute to reducing smoking-caused cancer mortality.

Material and methods

RRs for site-specific cancer mortality

We used data from the American Cancer Society CPS-II to estimate the hazards (RRs) for mortality from multiple site-specific cancers caused by smoking, including adjustment for important covariates (Table I). CPS-II is a prospective study of mortality in 1.2 million Americans aged 30 and older who completed a questionnaire on tobacco and alcohol use, diet and multiple other risk factors in 1982, with the latest published follow-up in 1998. A complete description of the CPS-II study design is provided elsewhere.^{20–22} In 1992, when the first 6-year (1982–1988) results were obtained, mortality follow-up was virtually complete for the first 2 years and about 98–99% complete for the next 4. Analyses of smoking hazards in CPS-II were based on the first 6 years of follow-up (1982–1988) to maximize the number of deaths available for analysis, especially in never-smokers, while minimizing misclassification of exposure due to cessation of smoking during follow-up.^{21,22} Analyses for stomach and colorectal cancers were based on the 1996 follow-up, to increase the number of deaths.^{23,24} This may result in underestimation of the hazard if some baseline current smokers quit smoking during follow-up. RRs for mortality from different cancers among CPS-II current smokers, relative to never-smokers, are provided in Table I.

Measuring exposure to accumulated smoking hazards

The accumulated hazards of smoking for cancers—which have relatively long latency—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.²⁵ Many of these factors vary over time because of changes in the socioeconomic determinants of smoking, including income, tobacco-control efforts such as taxation and advertising laws and cultural norms. Therefore, current smoking prevalence or tobacco consumption alone would be an insufficient indicator 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 over the past few decades.^{17,18}

To capture the accumulated hazard of smoking, we used the SIR method of Peto *et al.*,¹⁹ adapted to the specific conditions of developing countries.²⁶ The method uses lung cancer mortality data, which are available or can be estimated using various methods, as an indirect indicator of the accumulated hazards of tobacco smoking. Background-adjusted 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, adjusted to account for differences in never-smoker lung cancer mortality rates across populations (equation 1).²⁶ SIR is calculated by age and sex. Age groups were 30–44, 45–59, 60–69, 70–79 and 80+. No deaths before the age of 30 were attributed to smoking because there are few cancer deaths before 30 and RRs are unstable.

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

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 current smokers in the

TABLE II – GBD 2000 EPIDEMIOLOGIC SUBREGIONS¹

WHO region	Mortality stratum ²	Countries	Population (thousands)
African Region (AFR)	D	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	294,078
	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	345,515
Region of the Americas (AMR)	A	Canada, Cuba, United States of America	325,183
	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	430,932
Eastern Mediterranean Region (EMR)	D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru	71,230
	B	Bahrain, Cyprus, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates	139,059
European Region (EUR)	D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen	342,576
	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	411,889
	B	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, the former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Yugoslavia	218,458
	C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine	243,184
Southeast Asia Region (SEAR)	B	Indonesia, Sri Lanka, Thailand	293,819
	D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal	1,241,806
Western Pacific Region (WPR)	A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore	154,354
	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, Viet Nam	1,532,933

¹Data from WHO.²—A, very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; E, high child mortality and very high adult mortality.

study population, who may have different smoking histories, into equivalent current smokers in the reference population, where hazards for other diseases (*e.g.*, different cancers) have been measured.¹⁹ We used CPS-II as the reference population (S^*_{LC} and N^*_{LC}) because CPS-II data allowed separate hazard estimates for cancers of various sites and systematic adjustment for multiple covariates. SIR was calculated for each age group and sex and for individual countries, then averaged (population-weighted) in each of 14 epidemiologic subregions of the world (Table II). Most of the CPS-II current smokers were lifelong cigarette smokers, with a mean consumption of about 20 cigarettes/day.¹⁹

In applying the method to developing countries, we accounted for the role of coal, a common fuel in parts of the developing world, as an important determinant of lung cancer patterns among never-smokers. In populations that use coal in poorly vented stoves (*e.g.*, China and parts of Southeast Asia), never-smoker lung cancer mortality rates (N_{LC} in equation 1) were estimated based on data on lung cancer mortality among Chinese non-smokers.^{10,26} For China, the observed rates in the retrospective mortality study of Liu *et al.*¹⁰ were used; for all other countries, a weighted average of CPS-II never-smoker and Chinese nonsmoker rates was used, with weights for Chinese rates equal to the prevalence of coal use in poorly vented stoves.⁸ The remaining risk factors for lung cancer mortality (*e.g.*, ambient air pollution, occupational hazards, indoor air pollution from radon or biomass smoke) in various combinations affect a subset of the population of each country. It is unclear what the net impacts of these risks on the relative levels of lung cancer among never-smokers in different

countries may be. Therefore, the impacts of other risk factors were considered as sources of uncertainty in never-smoker lung cancer mortality (Table III).

Estimating tobacco-attributable mortality

For each age, sex and cancer site, the fraction of deaths attributable to smoking was estimated using the standard PAF relationship (equation 2), with prevalence, P , set to the SIR for each age/sex group and RR from Table I. For each cancer site, PAFs were multiplied by regional cancer mortality (from WHO or IARC database) to estimate site-specific cancer deaths caused by smoking in 14 epidemiologic subregions of the world (Table II).

$$PAF = \frac{P(RR - 1)}{P(RR - 1) + 1} \quad (2)$$

Analysis of uncertainty

Despite the recent improvements in the data sources required for global estimates of smoking-caused mortality (*e.g.*, mortality registration and adjusted hazards), there remains substantial uncertainty about levels of smoking-attributable cancer mortality, especially in developing countries where data are more sparse. Some sources of uncertainty were addressed in a quantitative analysis:

- (i) uncertainty in the parameters used in calculating SIR, including

TABLE III – ESTIMATED CANCER MORTALITY AMONG PEOPLE 30 YEARS OF AGE AND OLDER ATTRIBUTABLE TO SMOKING IN DEVELOPING (30+ POPULATION 1,874 MILLION) AND INDUSTRIALIZED (30+ POPULATION 795 MILLION) REGIONS IN THE YEAR 2000¹

	Male	Female	Total
Developing ²	WHO: 549,000 (435,000–637,000) IARC: 464,000	WHO: 75,000 (50,000–112,000) IARC: 64,000	WHO: 625,000 (485,000–749,000) IARC: 528,000
Industrialized ²	WHO: 630,000 (597,000–658,000) IARC: 664,000	WHO: 165,000 (151,000–182,000) IARC: 161,000	WHO: 794,000 (749,000–840,000) IARC: 824,000
World	WHO: 1,179,000 (1,058,000–1,278,000) IARC: 1,127,000	WHO: 240,000 (213,000–286,000) IARC: 225,000	WHO: 1,419,000 (1,272,000–1,565,000) IARC: 1,352,000

¹In each cell, the first number shows estimates using the WHO cancer mortality database, numbers in parentheses show 95% CIs for these estimates and number after parentheses shows the estimate using the IARC cancer mortality database. All estimates exclude colorectal cancer.

²Industrialized regions include AMR-A, EUR-A, EUR-B, EUR-C and WPR-A; developing regions include all other regions. This classification is based on WHO.² See Table II for descriptions of regions.

- lung cancer mortality in each country based on its mortality reporting system (C_{LC} in equation 1)
 - levels of background lung cancer mortality among never-smokers as a result of exposure to other risk factors, such as occupational exposures and indoor air pollution from sources other than coal (N_{LC} in equation 1)
 - lung cancer mortality in CPS-II smokers and never-smokers (S^*_{LC} and N^*_{LC} in equation 1)
- (ii) statistical uncertainty (as a result of random error) in the estimated CPS-II RRs for site-specific cancer mortality among smokers (Table I)

Uncertainty for each of the parameters was estimated separately, as described elsewhere.⁷ Uncertainties for individual parameters were combined in a stratified sampling simulation²⁷ to obtain the uncertainty distribution for the fraction of cause-specific mortality attributable to smoking. Uncertainty in lung cancer mortality (C_{LC}) was assumed to be correlated across age/sex groups (*i.e.*, underestimation of lung cancer in one age/sex group implies underestimation in other age/sex groups). Uncertainties of different parameters were assumed to be independent. 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, using lung cancer as the marker for accumulated smoking hazard for other cancers can introduce additional uncertainty because the role of factors such as lag in disease causation can vary across diseases and across cigarette types or other tobacco products (*e.g.*, bidis or cigars). This source of uncertainty is likely to be smaller for cancers than for cardiovascular or respiratory diseases, where the mechanisms and time dimension of hazards may be fundamentally different.

Second, there is uncertainty in WHO cancer mortality estimates to which the estimated PAFs are applied. This is discussed in detail elsewhere.^{28,29} Currently, 75 countries have reasonably complete vital registration and medical certification of deaths.^{28,29} Another 51 countries have incomplete vital statistics or use sample registration and/or surveillance systems. The remaining 65 countries, mostly in sub-Saharan Africa, have no reliable data on adult mortality. WHO, through its GBD project, uses standard demographic techniques^{30–32} to estimate all-cause death rates by age for these populations. Cause-of-death models are then used to estimate the total number of cancer deaths for countries with poor data. The distribution of cancer deaths by site is based on regional incidence or mortality patterns from cancer registries reporting to the IARC³³ or on cancer survival models when such data are unavailable.

The IARC also provides estimates of cancer mortality by site for most WHO member states. The differences between the 2 reflects the direct use of reported cancer incidence or mortality from registries by the IARC and model-based corrections for underreporting by the WHO. The impact of these different

approaches is discussed in detail elsewhere, including an assessment of consistency and validity of WHO and IARC estimates.^{28,29} The net effect is that the WHO estimates of global cancer mortality are 11% higher than those of the IARC, with larger differences in the AFR, EMR and SEAR regions. Regional and cause-specific cancer mortality rates attributable to smoking in this report are presented using both databases (Tables III–V), both of which are subject to uncertainty.

A third source of uncertainty involves the extrapolation of hazards from CPS-II to other populations that have different exposure distributions for other cancer risk factors and background disease patterns. The nature of this source of uncertainty and its implications for research and surveillance are described in detail below (see Discussion).

Results

The estimated number of cancer deaths caused by smoking is summarized in Table III and presented by region and sex in Table IV. Deaths by region and cancer site are shown in Figure 1. Globally, an estimated 1.42 (95% CI 1.27–1.57) million cancer deaths were caused by smoking in the year 2000, 21% of total global adult (age 30+) cancer mortality. The proportions of adult cancer mortality caused by smoking were 32% for males and 8% for females and 16% and 29% for developing and industrialized countries, respectively. The total number of smoking-caused cancer deaths using the IARC database was an estimated 1.35 million, or about 95% of the global total estimated using the WHO figures.

Regional patterns

The regions with the largest number of cancer deaths caused by smoking were the industrialized regions of western Europe (EUR-A; 272,000 deaths, 27% of all cancer deaths) and North America (AMR-A; 211,000 deaths, 34% of all cancer deaths) and the developing regions of the Western Pacific (WPR-B, dominated by China in terms of population; 244,000 deaths, 14% of all cancer deaths) and Southeast Asia (SEAR-D, dominated by India in terms of population; 190,000 deaths, 24% of all cancer deaths), followed by the remaining industrialized regions. The large number of cancer deaths attributable to smoking in WPR-B and SEAR-D is due to a combination of 2 factors: (i) the large number of total cancer deaths, due to both population size and other cancer risk factors, and (ii) accumulated hazards of smoking. For example, while the fraction of total cancer mortality was lower in WPR-B (14%) than SEAR-D (24%), the absolute number of smoking-caused cancer deaths was higher in the former (244,000 vs. 190,000), due to higher background cancer deaths. Higher background cancer deaths in turn were due to the larger population in WPR-B and other risk factors that affect background cancer levels (*e.g.*, indoor coal smoke).

TABLE IV – ESTIMATED CANCER MORTALITY ATTRIBUTABLE TO SMOKING BY REGION IN THE YEAR 2000¹

Region	Adult (30+) population (millions)		Smoking-attributable cancer mortality		% Total adult (30+) cancer mortality		
	M	F	M	F	M	F	M+F
African region D	41	43	WHO: 10,000 (6,000–16,000) IARC: 5,000	WHO: 1,000 (200–3,000) IARC: 400	9	1	5
African region E	47	50	WHO: 23,000 (17,000–31,000) IARC: 12,000	WHO: 5,000 (3,000–8,000) IARC: 3,000	17	4	10
Region of the Americas A	91	98	WHO: 131,000 (119,000–143,000) IARC: 141,000	WHO: 80,000 (71,000–89,000) IARC: 80,000	42	26	34
Region of the Americas B	85	92	WHO: 48,000 (38,000–58,000) IARC: 52,000	WHO: 12,000 (7,000–17,000) IARC: 12,000	27	6	17
Region of the Americas D	12	12	WHO: 2,000 (1,000–3,000) IARC: 2,000	WHO: 300 (100–1,000) IARC: 200	6	1	3
Eastern Mediterranean region B	25	22	WHO: 12,000 (8,000–16,000) IARC: 12,000	WHO: 2,000 (400–4,000) IARC: 2,000	30	7	21
Eastern Mediterranean region D	52	52	WHO: 26,000 (16,000–35,000) IARC: 24,000	WHO: 3,000 (1,000–6,000) IARC: 2,000	28	3	16
European region A	125	137	WHO: 225,000 (209,000–241,000) IARC: 234,000	WHO: 47,000 (38,000–55,000) IARC: 43,000	40	10	27
European region B	50	54	WHO: 72,000 (62,000–81,000) IARC: 70,000	WHO: 9,000 (7,000–12,000) IARC: 8,000	44	8	29
European region C	63	80	WHO: 133,000 (122,000–141,000) IARC: 143,000	WHO: 11,000 (8,000–15,000) IARC: 12,000	49	5	29
Southeast Asia region B	61	62	WHO: 45,000 (22,000–63,000) IARC: 32,000	WHO: 2,000 (200–6,000) IARC: 2,000	43	4	24
Southeast Asia region D	244	235	WHO: 174,000 (66,000–249,000) IARC: 124,000	WHO: 16,000 (3,000–47,000) IARC: 11,000	43	4	24
Western Pacific region A	47	51	WHO: 69,000 (61,000–80,000) IARC: 76,000	WHO: 18,000 (14,000–22,000) IARC: 19,000	36	13	27
Western Pacific region B	374	367	WHO: 209,000 (156,000–262,000) IARC: 201,000	WHO: 35,000 (11,000–61,000) IARC: 31,000	20	5	14

¹In each cell, the first number shows estimates using the WHO cancer mortality database, numbers in parentheses show 95% CIs for these estimates and the number after the parentheses shows estimates using the IARC cancer mortality database. All estimates exclude colorectal cancer.

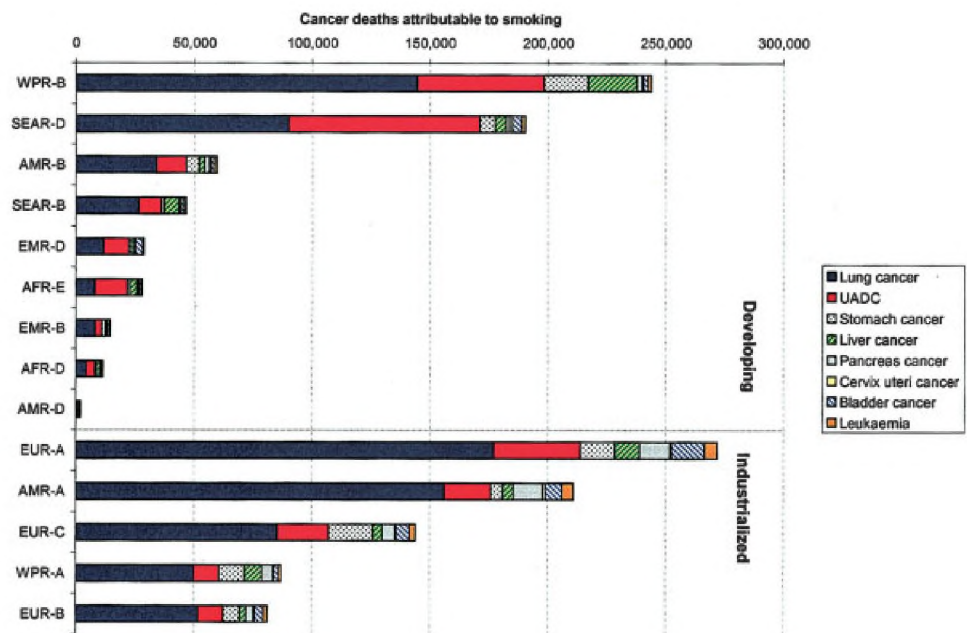


FIGURE 1 – Adult (age 30+) cancer mortality due to smoking in GBD epidemiologic subregions, by cancer site. Estimates are based on the WHO cancer mortality database. See Table II for description of subregions. UADC, upper aerodigestive tract cancer.

The proportions of total adult cancer deaths caused by smoking were generally highest in industrialized regions (27–34%), where smoking has a longer history (Table IV). At the same time, the rise in smoking over the last quarter of the 20th century in a number of developing regions, including parts of Latin America, the eastern Mediterranean and Southeast Asia, has resulted in 15% or more of all current adult cancer deaths being caused by smoking—higher among men (Table IV).

Current cancer mortality due to smoking was larger among men than women (Tables III, IV), with 79% of smoking-attributable cancer deaths in industrialized regions and 88% in developing regions occurring among men. The exception to this pattern was North America (AMR-A), where women have smoked for several decades and female deaths accounted for 38% of total smoking-attributable cancer mortality (note that women in AMR-A had a higher number of cardiovascular deaths attributable to smoking³⁴).

TABLE V – ESTIMATED CANCER MORTALITY ATTRIBUTABLE TO SMOKING BY SITE IN THE YEAR 2000 AND TO OTHER MAJOR RISK FACTORS¹

Cancer type	Deaths caused by smoking	% Caused by smoking	Other major risk factors (PAF) ²
Trachea, bronchus and lung cancer	WHO: 848,000 (781,000–940,000) IARC: 800,000	71	Low fruit and vegetable consumption (12%), urban air pollution (5%), indoor air pollution from household use of solid fuels (coal only) (1%), selected occupational carcinogens (8%)
Upper aerodigestive tract cancer	WHO: 287,000 (245,000–327,000) IARC: 291,000	39	Low fruit and vegetable consumption (12% for esophageal cancer), alcohol use (16% for mouth and oropharyngeal cancers, 27% for esophageal cancer)
Stomach cancer	WHO: 94,000 (82,000–111,000) IARC: 85,000	11	Low fruit and vegetable consumption (18%)
Liver cancer	WHO: 69,000 (51,000–91,000) IARC: 65,000	12	Alcohol use (24%), contaminated injections in health-care settings (as an outcome of HBV and HCV infection) (27%)
Pancreatic cancer	WHO: 47,000 (42,000–54,000) IARC: 44,000	21	None of the other 25 analyzed risk factors
Cervix uteri cancer	WHO: 6,000 (3,000–13,000) IARC: 7,000	3	Unsafe sex (defined as unprotected sex with an infected partner) (100% by definition)
Bladder cancer	WHO: 47,000 (40,000–54,000) IARC: 39,000	27	None of the other 25 analyzed risk factors
Leukemia ³	WHO: 21,000 (14,000–29,000) IARC: 22,000	12	Selected occupational carcinogens (3%)
Kidney and other urinary cancers ⁴			None of the other 25 analyzed risk factors
Colorectal cancer ⁵	No estimates	No estimates	Overweight and obesity (12%), low fruit and vegetable consumption (2%), physical inactivity (15%)
Other cancers ⁶	0	0	

¹In each cell, the first number shows estimates using the WHO cancer mortality database, numbers in parentheses show 95% CIs for these estimates and the number after the parentheses shows estimates using the IARC cancer mortality database.—²Source: Reanalysis of data on 26 major global risk factors.⁴³ The figure shows the estimated cancer mortality for each risk factor considered individually. These risks act jointly with one another. Consequently, the burden due to groups of risk factors will usually be less than the sum of individual risks.^{38–39} The RR for myeloid leukemia (ICD-9 205) was applied to all leukemias (ICD-9 204–208) because the WHO GBD database provides estimates of mortality for all leukemias. In regions where detailed cause of death data exist (established market economies), myeloid leukemia was 40–55% of all leukemias.—⁴In the WHO GBD database, kidney and other urinary cancers are a part of the residual category “other cancers”, which also includes cancers of multiple other sites. For this reason, no estimates were made for these cancers using the WHO cancer mortality database; estimates using the IARC cancer mortality database indicate approximately 20,000 kidney cancer deaths attributable to smoking.—⁵Evidence of a causal association between smoking and colorectal cancer was classified as suggestive in the 2004 report of the U.S. surgeon general.⁵ Therefore, colorectal cancer was not included in the main estimates in Tables III and IV and Figures 1 and 2. If the evidence on causality is confirmed, the RR figures in Table I give an estimated 43,000 colorectal cancer deaths attributable to smoking in 2000.—⁶This group also includes cancers of the nasal cavity and paranasal sinuses (ICD-9 160) and larynx (ICD-9 161), for which there is sufficient evidence of causality.^{3,4}

In developing regions, 67% of smoking-attributable cancer deaths were between the ages of 30 and 69 compared to 52% in industrialized regions. Cancer deaths at younger ages result in a larger loss of potential life years, as described in detail elsewhere.¹

Site-specific patterns

Globally, the leading cancers caused by smoking were lung cancer (848,000 deaths, 60% of all smoking-attributable cancer deaths) and upper aerodigestive tract cancer (287,000, 20% of all smoking-attributable cancer deaths) (Table V). The site distributions of smoking-attributable cancer deaths varied across developing and industrialized regions because of variations in both the site distributions of total cancer deaths and the fractions attributable to smoking (Figs. 1, 2). In developing regions, the 328,000 lung and 188,000 upper aerodigestive tract cancer deaths caused by smoking comprised 53% and 30% of all smoking-attributable cancer deaths, respectively. In industrialized regions, 520,000 lung and 100,000 upper aerodigestive tract cancer deaths were estimated to have been due to smoking, comprising 65% and 12% of all smoking-caused cancer deaths, respectively.

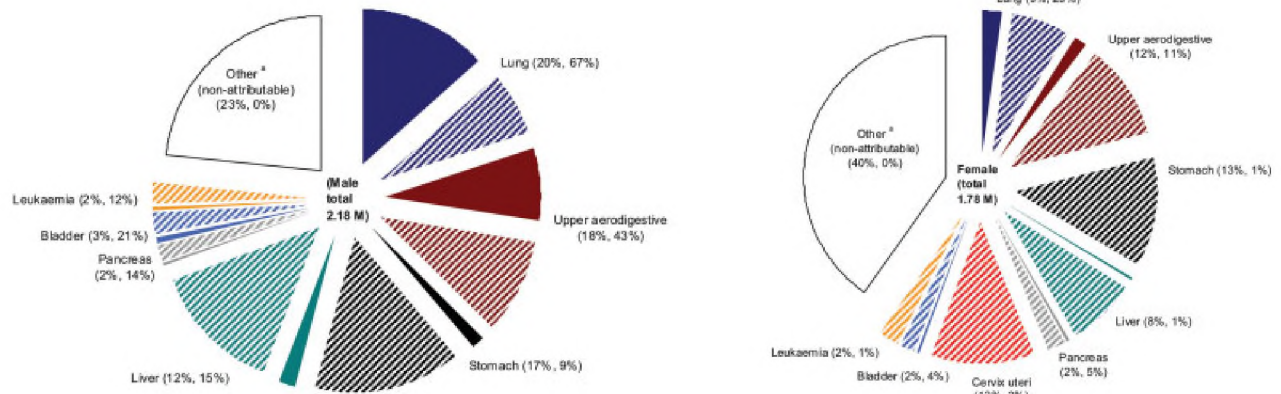
The contribution of lung cancer to total smoking-attributable cancer deaths varied from a low of 30–40% in sub-Saharan Africa and parts of the eastern Mediterranean region to a high of 60–70% in North America and Europe (Fig. 1). Upper aerodigestive tract cancer had a considerably larger proportional contribution to total smoking-caused cancer deaths in some developing regions, especially in SEAR-D, a region dominated by India in terms of population (43% of all smoking-caused cancer deaths). In this region, oral tobacco use and dietary factors result in high background

levels and/or interact with smoking to result in increased risk for this group of cancers.¹¹ The relatively large estimated PAF for upper aerodigestive tract cancer attributable to smoking in this work is consistent with recent direct estimates of Gajalakshmi *et al.*,³⁵ who estimated that 52% of mouth, laryngeal and pharyngeal cancers in India and 36% of esophageal cancers for men between 25 and 69 years of age were caused by smoking. Because most smokers in SEAR-D are also oral tobacco users, many of these deaths are attributable to both risk factors. Oral tobacco use also results in upper aerodigestive tract cancer deaths above and beyond those which are affected jointly by smoking. Upper aerodigestive tract cancer also had a relatively large smoking-attributable fraction in sub-Saharan Africa (32–49%) because of high background levels.

Cancers of the stomach and liver, 2 sites identified in the recent IARC review and the 2004 report of the U.S. surgeon general as important new targets for studying the hazards of smoking,^{3–5} made relatively large contributions to smoking-attributable cancer deaths in a number of industrialized and developing regions: stomach cancer represented 10% or more of all smoking-caused cancer deaths in parts of Latin America, the Western Pacific and eastern Europe and liver cancer, 9–13% in sub-Saharan Africa, the Western Pacific and parts of Southeast Asia. Other sites with relatively large contributions to smoking-caused cancer mortality include the pancreas in all industrialized regions and parts of Latin America and the bladder in the eastern Mediterranean and parts of Europe.

Cervix uteri cancer, also identified by the IARC and U.S. surgeon general reports as causally related to smoking, made a small contribution to total smoking-caused cancer deaths. This was

A



B

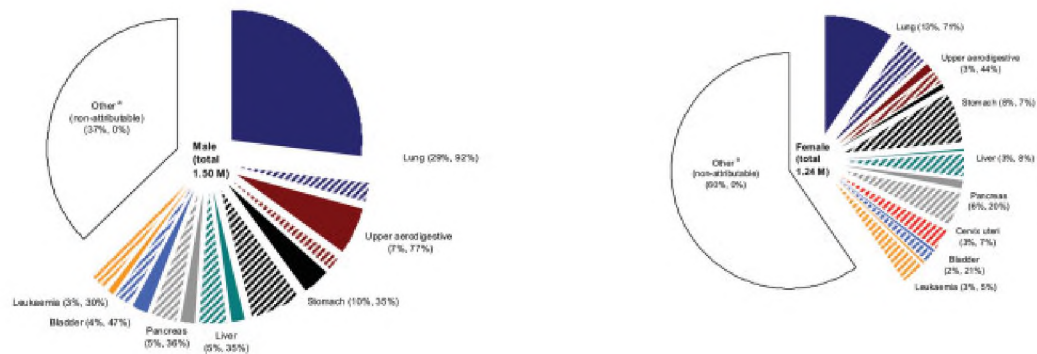


FIGURE 2 – Distribution of total and smoking-caused cancer mortality for males and females by site for (a) developing regions and (b) industrialized regions. Estimates are based on the WHO cancer mortality database. Solid parts are the proportion caused by smoking and hatched parts are the proportion not attributable to smoking. See Table V for contributions of other important risk factors. Colorectal cancer is not included because evidence for causality has been classified as suggestive. For each cancer site or cluster of sites, the first number in the parentheses represents the proportion of all cancer deaths and the second number, the PAF for smoking (e.g., 20% of all cancer deaths among men in developing countries were from lung cancer and 67% of these deaths were attributable to smoking). Where the fraction attributable to smoking is very small, the solid part cannot be seen (e.g., bladder cancer and leukemia among females in developing regions). The size of circles is proportional to the total number of deaths.

because in developing regions (e.g., sub-Saharan Africa), where limited access to cervical screening (including for HPV) and interventions result in a large number of cervix uteri cancer deaths, the prevalence of smoking among females has been low, resulting in small PAFs. If the site distribution of smoking-attributable cancer deaths is considered among females alone, then 12–14% of all smoking-caused cancer deaths are from cervix uteri cancer in the 2 African regions and 5–10% in Latin America and Southeast Asia (vs., e.g., 1% in western Europe and North America).

Discussion

This work estimates the global and regional burdens of site-specific cancer mortality attributable to smoking and includes cancer sites recently identified as important targets for the hazards of smoking,^{3–5} using consistently adjusted hazards. According to these estimates, in the year 2000, 1.42 (95% CI 1.27–1.57) million cancer deaths in the world, 21% of total global cancer deaths, were due to smoking. The results illustrate that smoking is currently a very important determinant of cancer mortality among men in all regions of the world and among women in industrialized countries. This estimate is higher than the 16% of all incident cancer cases estimated by Parkin *et al.*¹⁶ to be caused by smoking in 1985. Because we focused on mortality (vs. incidence), included new cancer types based on more recent evidence and used consistently adjusted haz-

ards, our results are not directly comparable to those of Parkin *et al.*¹⁶ Broad comparison of the 2 estimates together with evidence of an increase in smoking in the developing world nonetheless point to a likely overall increase in smoking-caused cancer burden between 1985 and 2000.

Cancer mortality attributable to smoking varied substantially across different regions of the world (men, from $\leq 10\%$ of total cancer deaths in parts of Latin America and parts of sub-Saharan Africa to $\geq 40\%$ in parts of Southeast Asia and most industrialized regions; women, from $\leq 5\%$ of total cancer deaths in much of the developing world and $\leq 10\%$ in the industrialized regions of eastern Europe to $> 25\%$ in North America). The interregional variation was even more apparent for site-specific cancer deaths. Lung cancer was the leading cause of smoking-caused cancer mortality in nearly all regions, but its contribution varied from a low of 30–40% in sub-Saharan Africa and parts of the eastern Mediterranean region to a high of 60–70% in North America and Europe. In addition to lung cancer, upper aerodigestive tract, stomach, liver and pancreatic cancers were important sites for smoking-attributable cancer mortality in different developing and industrialized regions. This interregional variation arises because the shape and maturity of the smoking epidemic is highly affected by the socioeconomic and cultural determinants of smoking and because the prevalence and distribution of other risk factors for cancers, whose hazards are magnified by smoking, vary across populations.

The estimated number of global cancer deaths attributable to smoking in this analysis (1.42 million, excluding colorectal cancer) was practically identical to the number obtained by applying a constant correction factor of 30% to unadjusted hazards for multiple cancers combined (1.47 million).⁷ The differences in estimates from the 2 methods across regions and sexes ranged from a 15–20% underestimation among females in parts of sub-Saharan Africa, Latin America and the Western Pacific to about a 10–20% overestimation among males in North America and other parts of the Western Pacific, when covariate-adjusted site-specific hazards were not used. Using the IARC database of global cancer mortality instead of that of the WHO reduced the total number of global cancer deaths attributable to smoking by approximately 5%. This global decrease corresponds to a 16% decrease in developing countries and a 4% increase in industrialized countries because the difference between the WHO and IARC estimates of total cancer deaths is larger for the developing world. In the vast majority of subanalyses (*e.g.*, by region or by cancer site), the IARC-based estimates were within the 95% CIs of the WHO-based estimates, suggesting that the implications of the differences in global and regional descriptive epidemiology for assessing the contribution of smoking are minor.

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.³⁶ Uncertainty nonetheless remains, especially in developing countries where complete mortality records and detailed studies of cancer risk factors are less common. Some sources of uncertainty were described earlier. Two additional and important sources of uncertainty in the current estimates with implications for future research are (i) the correlation between smoking and other risks for any cancer within populations and (ii) biologic interactions between smoking and other risks, which would result in uncertainty when extrapolating CPS-II RRs to other populations. For many diseases, multiple risk factors magnify one another's total risks, as represented in standard proportional hazard models. If multiple risks for the same cancer are concentrated (positively correlated) among specific population subgroups, total (absolute) hazards would be larger than those estimated here, even if RRs remain unchanged (and smaller with negative correlation).^{37,38} Higher consumption of alcohol among smokers is one example of such positive correlation among exposures; lower smoking rates among females in rural areas of developing countries, who also have more limited access to HPV screening and interventions and hence higher risk of cervical cancer, is an example of negative correlation. In addition to correlation of risk factor exposures, multiple risks for the same cancer may modify one another's RR. Examples include tobacco and alcohol as risk factors for oral cancer.³⁹ Both issues may be particularly relevant for cancers whose risk factors include infectious and noninfectious agents, particularly cervical (HPV), liver (alcohol, HBV and HCV infections, aflatoxin exposure) and stomach (alcohol, diet and *Helicobacter pylori* infection) cancers.^{40,41} The 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 illustrated that background mortality rates, which varied by up to a factor of 10 for some cancers, did not change the RR of mortality as a result of smoking (Figs. 4 and 5 in Liu *et al.*¹⁰). Similarly, the differences in RRs for stomach cancer among smokers in various geographic regions of the world were not statistically significant.⁴² Despite these assurances, extrapolation of CPS-II RRs is a source of additional uncertainty but necessary in the absence of local epidemiologic studies in developing countries (at any point in time, only recent epidemiologic studies can be used for direct estimates because of changes in smoking patterns over time).

The above data gaps and uncertainties also emphasize 2 important research and surveillance needs in order to better understand how tobacco affects global and regional cancer epidemiology together with other risks. First, there is a need for epidemiologic and toxicologic research on how smoking interacts with other factors to affect hazards for any cancer. This includes identifying whether a proportional hazard model is appropriate, as observed for exposure to coal and tobacco smoke in China,¹⁰ or whether smoking and other infectious and toxic cofactors potentiate each others' hazards, hence resulting in modified population-specific RRs. For example infectious agents may result in subtypes of stomach cancer that are affected differently by smoking compared to stomach cancer in CPS-II subjects, which may be caused more by noninfectious risk factors (carcinoma of the corpus *vs.* carcinoma of the cardia). Parallel to this individual-level analysis, there is a need in population-level risk factor surveillance for data on correlation of cancer risks in specific population subgroups based on factors such as income, education, race/ethnicity or place of residence. Data on multiple risk factor interaction and correlation would allow better estimation of total health effects of cancer risk factors. Equally, data on correlated multiple-risk exposure would be essential for targeting preventive interventions or treatment toward subgroups at highest risk.

Currently, cancer mortality attributable to smoking is higher in industrialized regions than in the developing world (Table III). The data on smoking trends, however, suggest that smoking has increased in much of the developing world over the past few decades,¹⁷ with the likely implication that the attributable cancer burden has also. Accumulated hazards in developing countries coupled with the shifting demographic and epidemiologic patterns suggest that cancer mortality as a consequence of smoking will continue to rise in the near future in the developing world. Effective interventions and policies (*e.g.*, through enforcing the FCTC) that reduce smoking among males and prevent increases among females in the developing world can curb and eventually reverse this increase, as has been seen in a number of industrialized nations. Our estimates of the current level and patterns of smoking-attributable cancer mortality provide an important baseline for evaluating how FCTC and related national tobacco-control efforts may contribute to reducing the global and regional burden of cancers.

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