



Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors

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Summary

Introduction With respect to reducing mortality, advances in cancer treatment have not been as effective as those for other chronic diseases; effective screening methods are available for only a few cancers. Primary prevention through lifestyle and environmental interventions remains the main way to reduce the burden of cancers. In this report, we estimate mortality from 12 types of cancer attributable to nine risk factors in seven World Bank regions for 2001.

Methods We analysed data from the Comparative Risk Assessment project and from new sources to assess exposure to risk factors and relative risk by age, sex, and region. We applied population attributable fractions for individual and multiple risk factors to site-specific cancer mortality from WHO.

Findings Of the 7 million deaths from cancer worldwide in 2001, an estimated 2·43 million (35%) were attributable to nine potentially modifiable risk factors. Of these, 0·76 million deaths were in high-income countries and 1·67 million in low-and-middle-income nations. Among low-and-middle-income regions, Europe and Central Asia had the highest proportion (39%) of deaths from cancer attributable to the risk factors studied. 1·6 million of the deaths attributable to these risk factors were in men and 0·83 million in women. Smoking, alcohol use, and low fruit and vegetable intake were the leading risk factors for death from cancer worldwide and in low-and-middle-income countries. In high-income countries, smoking, alcohol use, and overweight and obesity were the most important causes of cancer. Sexual transmission of human papilloma virus is a leading risk factor for cervical cancer in women in low-and-middle-income countries.

Interpretation Reduction of exposure to key behavioural and environmental risk factors would prevent a substantial proportion of deaths from cancer.

Introduction

Worldwide, between 1990 and 2001, mortality rates from all cancers fell by 17% in those aged 30–69 years and rose by 0·4% in those aged older than 70 years.^{1,2} This decline was lower than the fall in mortality rates from cardiovascular diseases, which declined by 9% and 14% in men aged 30–69 years and 70 years or older, respectively, and of 15% and 11% for women in the same age groups.^{1,2}

Age-specific mortality rates for chronic diseases are driven by changes in exposure to risk factors, and by availability of screening systems and treatment. Advances in primary and secondary prevention and in treatment have been effective in reducing mortality from cardiovascular diseases over the past few decades, at least in developed countries.³ Therapeutic interventions have had less success in reducing deaths from most cancers. For example, in the USA, age-adjusted death rates for all cancers combined fell slightly in the 1990s (on average 1·5% per year in men and 0·6% per year in women between 1992 and 1999).⁴ The fall in overall cancer mortality in men was mainly a result of reductions in mortality from lung, prostate, and colorectal cancers.⁴ In women, mortality due to lung cancer increased in the 1990s, but there was a decrease in death rates from breast and colorectal cancers.⁴ The fall in lung-cancer mortality in men was mostly due to lower incidence,⁴ itself a result

of a reduction in smoking. The causes of decreased mortality from prostate cancer remain uncertain, since incidence figures over time might not be comparable because of changes in diagnostic techniques and death certification.⁵ Rates of death from colorectal cancer might have fallen because of early detection and removal of precancerous polyps, early detection of tumours, and improved treatment.⁶ For breast cancer in women, increased coverage of mammography screening⁷ and successful treatment with multi-agent chemotherapy and tamoxifen have been effective in reducing mortality.⁸ Treatment has also been effective for some cancers in children and young adults—eg, leukaemia and testicular cancer.^{9,10} 5-year survival rates remain relatively low, however, for lung, oesophageal, liver, stomach, and pancreatic cancers (all <25%).⁹

Although a combination of screening and treatment is increasingly effective in reducing mortality from some cancers, limitations in availability of clinical interventions for other cancers, and in access to and use of existing technologies, clearly constrain the effects of treatment on population trends in cancer mortality, even in developed countries. As such, primary prevention through lifestyle and environmental interventions might offer the best option for reducing the large and increasing burden of cancers worldwide. Policies and programmes to implement such interventions depend

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	Exposure variable	Theoretical-minimum-risk exposure distribution	Cancer sites affected (age groups assessed)†
Diet and physical inactivity			
Overweight and obesity (high BMI) ²³	BMI (kg/m ²)	21 SD 1 kg/m ²	Corpus uteri cancer, colorectal cancers (≥30 years), postmenopausal breast cancer (≥45 years), <i>gallbladder cancer, kidney cancer</i>
Low fruit and vegetable intake ²⁴	Fruit and vegetable intake per day	600 SD 50 g intake per day for adults	Colorectal cancer, stomach cancer, lung cancer, oesophageal cancer (≥15 years)
Physical inactivity ²⁵	Three categories: inactive, insufficiently active (<2.5 h per week of moderate-intensity activity, or <4000 KJ per week), and sufficiently active. Activity in spare time, work, and transport considered	≥2.5 h per week of moderate-intensity activity or equivalent (400 KJ per week)	Breast cancer, colorectal cancer (≥15 years), <i>prostate cancer</i>
Addictive substances			
Smoking ²⁶	Current levels of smoking impact ratio (indirect indicator of accumulated smoking risk based on excess lung-cancer mortality)	No smoking	Lung cancer, mouth and oropharynx cancer, oesophageal cancer, stomach cancer, liver cancer, pancreatic cancer, cervix uteri cancer, bladder cancer, leukaemia (≥30 years)
Alcohol use ²⁷	Current alcohol consumption volumes and patterns	No alcohol use‡	Liver cancer, mouth and oropharynx cancer, breast cancer, oesophageal cancer, selected other cancers (≥15 years)
Sexual and reproductive health			
Unsafe sex ²⁸	Sex with an infected partner without any measures to prevent infection	No unsafe sex	Cervix uteri cancer (all ages)§
Environmental risks			
Urban air pollution ²⁹	Estimated yearly average particulate matter concentration for particles with aerodynamic diameters <2.5 microns or 10 microns (PM _{2.5} or PM ₁₀)	7.5 µg/m ³ for PM _{2.5} 15 µg/m ³ for PM ₁₀	Lung cancer (≥30 years)
Indoor smoke from household use of solid fuels ³⁰	Household use of solid fuels	No household solid fuel use with limited ventilation	Lung cancer (coal) (≥30 years)
Other selected risks			
Contaminated injections in health-care settings ³¹	Exposure to ≥1 contaminated injection (contamination refers to potential transmission of hepatitis B virus and hepatitis C virus)	No contaminated injections	Liver cancer (all ages)

*New exposure data and epidemiological evidence on disease outcomes and relative risks used when new epidemiological analyses allowed improvements compared with original analyses of Comparative Risk Assessment project—eg, relative risks for site-specific cancers as a result of smoking with better adjustment for potential confounders and new exposure data sources for overweight and obesity. †Italics—outcomes likely to be causal but not quantified because of insufficient evidence on prevalence or hazard size. Corresponding ICD 9 3-digit codes: bladder cancer 188; breast cancer 174; cervix uteri cancer 180; colorectal cancers 153–154; corpus uteri cancer 179, 182; leukaemia 204–208; liver cancer 155; mouth and oropharynx cancer 140–149; oesophageal cancer 150; pancreatic cancer 157; stomach cancer 151; trachea, bronchus, and lung cancers 162; selected other cancers 210–239. Total deaths from cancer are from WHO. Methods used by WHO^{23,33} are based on a combination of vital statistics for countries with complete vital registration and medical certification of deaths, and on a combination of demographic techniques and information from cancer registries for countries with incomplete vital statistics, with sample registration or surveillance systems, or without vital registration. ‡Alcohol has benefits as well as harms for different diseases, also depending on patterns of alcohol consumption. A theoretical minimum of zero was chosen for alcohol use because, despite benefits for specific diseases (cardiovascular) in some populations global and regional burden of disease due to alcohol use was dominated by its effects on neuropsychological diseases and injuries, which are considerably larger than benefits to vascular diseases. Furthermore, no benefits for neoplastic disease have been noted from alcohol. §A proportion of HPV infections that lead to cervix uteri cancer are transmitted through routes other than sexual contact. PAF for unsafe sex, as defined in the comparative risk assessment project,²⁸ measures current population-level cervix cancer mortality that would be reduced, had there never been any sexual transmission of infection—ie, the consequences of past and current exposure, as we do for accumulated hazards of smoking. By considering health consequences of past and current exposure, nearly all of sexually transmitted diseases are attributable to unsafe sex because, in the absence of sexual transmission in the past, current infections transmitted through other forms of contact would not occur if infected hosts acquired their infection sexually (and so on in the sequence of past infected hosts).

Table 1: Cancer risk factors, exposure variables, theoretical-minimum-risk exposure distributions, disease outcomes*

on reliable and comparable analyses of the effect of risk factors for cancer at the population level.

Several reports have quantified the effects of risk factors on cancer incidence and mortality, as summarised in the World Cancer Report.¹¹ Most of these studies, however, are restricted to one risk factor, one site of cancer, or one population.^{12–18} Pisani and colleagues¹⁹ estimated the worldwide proportion of cancer incidence attributable to selected infectious agents to be about 16%. Parkin and colleagues²⁰ presented attributable fractions for several risk factor-cancer site combinations based on a review of published studies. Our aim was to estimate the worldwide and regional mortality from site-specific cancers attributable to specific risk factors, individually and jointly.

Methods

Risk factors assessed

We used systematic reviews and meta-analyses of the evidence on risk factor exposure and relative risk from

the Comparative Risk Assessment project^{21,22} and data from new sources to quantify the effect of a group of risk factors on cancer mortality (table 1).^{23–31} We selected the risk factors on the basis of the following criteria: likely to be a leading cause of worldwide or regional disease burden; not too specific (eg, specific types of fruits and vegetables) or too broad (eg, diet as a whole) for comparable definition and quantification of exposure in different populations; high likelihood of causality; reasonably complete data on population exposure and risk levels, or appropriate methods for extrapolation when necessary; and potentially modifiable.

Procedures

For every risk factor, an expert working group undertook comprehensive and systematic reviews of published studies and other sources (eg, government reports, international databases) to obtain data on the risk-factor exposure and relative risk (RR). The groups also obtained primary data, and undertook reanalyses of original data

For details of data sources and analyses for each risk factor, see <http://www.who.int/publications/cra/en/index.html>

See [Lancet Online](#) for webtables 1 and 2

sources and meta-analyses of epidemiological studies. The details of data sources and analyses for each risk factor are provided in references cited in table 1. All sources cited in table 1 have been peer-reviewed by external reviewers. The expert working groups presented exposure and RRs separately for men and women, for eight age groups (0–4, 5–14, 15–29, 30–44, 45–59, 60–69, 70–79, and >80 years), and for the 14 epidemiological subregions used in the Global Burden of Disease study;²² converted to World Bank regions here because they correspond better to geographically well known regions of the world (webtables 1 and 2).

Statistical analysis

To estimate the population attributable fractions (PAF) for individual risk factors, we used the equation shown in the panel, or its discrete version for risk factors with categorical exposure data. For every risk factor and cancer site, we used PAF to estimate the proportional reduction in site-specific cancer death that would arise if exposure to the risk factor were reduced to the counterfactual distribution. The alternative (counterfactual) scenario used in this study is defined as the exposure distribution that would result in the lowest population risk, referred to as the theoretical-minimum-risk exposure distribution (table 1). This method provides a quantitative assessment of the potential reduction in cancer burden in a consistent and comparable way across risk factors. The theoretical-minimum-risk exposure distribution is zero for risk factors for which zero exposure could be defined, and would indicate minimum risk (eg, the whole population being lifelong non-smokers). For some risk factors, zero exposure is an inappropriate choice, either because it is physiologically impossible (eg, body-mass index [BMI]) or because there are physical lower limits to exposure reduction (eg, concentration of ambient particulate matter). For these risk factors, we used the lowest levels noted in specific populations from epidemiological studies. For risk factors with protective effects (ie, fruit and vegetable intake, physical activity) we chose a counterfactual exposure distribution based on a combination of levels observed in high-intake populations and the level up to which health benefits might accrue.

Panel: Continuous PAF formula

$$PAF = \frac{\int_{\chi=0}^m RR(\chi)P(\chi)d\chi - \int_{\chi=0}^m RR(\chi)P'(\chi)d\chi}{\int_{\chi=0}^m RR(\chi)P(\chi)d\chi}$$

χ =risk factor exposure level
 $P(\chi)$ =population distribution of exposure
 $P'(\chi)$ =counterfactual distribution of exposure
 $RR(\chi)$ =relative risk of mortality from site-specific cancer at exposure level χ
 m =maximum exposure level

Because most cancers are caused by multiple risk factors, PAFs for individual risk factors for the same cancer site overlap and can add to more than 100%. For example, more than 70% of Chinese households rely on solid fuels (coal and biomass) for cooking and heating,³⁰ and more than 60% of Chinese men smoke. Since smoking and coal smoke magnify one another's hazards for lung cancer,¹³ some deaths from lung cancer can be prevented by removal of smoking or of exposure to indoor smoke from coal. Such cases would be attributed to both risk factors. Multicausality also means that a range of interventions can be used for disease prevention, with the specific mix being affected by factors such as cost, technology availability, infrastructure, and preferences. We therefore also estimated the PAFs for multiple risk factors, as described in detail elsewhere.³⁴

We calculated all individual and joint PAFs by sex and by eight age groups. For every World Bank region, age, sex, and cancer site, we multiplied the PAF by total regional site-specific cancer mortality for the year 2001 (from WHO databases) to calculate deaths from site-specific cancer attributable to the risk factor or group of risk factors. Attributable deaths were aggregated into three age groups for presentation (age-specific results available from the corresponding author).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 2 shows the estimated individual and joint contributions of the selected risk factors to mortality for each cancer site, for the world, and separately for low-and-middle-income, and high-income countries. The joint effects are further divided by region for low-and-middle-income countries in figure 1, by sex and by income in figure 2, and by age in table 3. Of the 7 million global deaths from cancer in 2001, an estimated 2.43 million (35%) were attributable to the joint effect of the nine risk factors listed in table 1.

Cancers with the largest proportions (>60%) attributable to these risks were cervix uteri cancer, lung cancer, and oesophagus cancer. The main risk factors for these cancers included sexual transmission of HPV leading to persistent infection with oncogenic viruses, smoking, alcohol use, and low fruit and vegetable intake. Cancers with the smallest joint PAFs (colorectal cancers [13%] and leukaemia [9%]) were those with a large number of risks with heterogeneous and unmeasured exposure patterns across populations, possibly including major genetic susceptibilities.

More than a third (37%) of all risk-factor attributable deaths (908 000 deaths) were from lung cancer,

	Total deaths	PAF (%) and number of attributable cancer deaths (thousands) for individual risk factors	PAF due to joint hazards of risk factors
Worldwide			
Mouth and oropharynx cancers	311 633	Alcohol use (16%, 51), smoking (42%, 131)	52%
Oesophageal cancer	437 511	Alcohol use (26%, 116), smoking (42%, 184), low fruit and vegetable intake (18%, 80)	62%
Stomach cancer	841 693	Smoking (13%, 111), low fruit and vegetable intake (18%, 147)	28%
Colon and rectum cancers	613 740	Overweight and obesity (11%, 69), physical inactivity (15%, 90), low fruit and vegetable intake (2%, 12)	13%
Liver cancer	606 441	Smoking (14%, 85), alcohol use (25%, 150), contaminated injections in health-care settings (18%, 111)	47%
Pancreatic cancer	226 981	Smoking (22%, 50)	22%
Trachea, bronchus, and lung cancers	1 226 574	Smoking (70%, 856), low fruit and vegetable intake (11%, 135), indoor smoke from household use of solid fuels (1%, 16), urban air pollution (5%, 64)	74%
Breast cancer	472 424	Alcohol use (5%, 26), overweight and obesity (9%, 43), physical inactivity (10%, 45)	21%
Cervix uteri cancer	234 728	Smoking (2%, 6), unsafe sex (100%, 235)	100%
Corpus uteri cancer	70 881	Overweight and obesity (40%, 28)	40%
Bladder cancer	175 318	Smoking (28%, 48)	28%
Leukaemia	263 169	Smoking (9%, 23)	9%
Selected other cancers	145 802	Alcohol use (6%, 8)	6%
All other cancers	1 391 507	None of selected risk factors	0%
All cancers	7 018 402	Alcohol use (5%, 351), smoking (21%, 1493), low fruit and vegetable intake (5%, 374), indoor smoke from household use of solid fuels (<0.5%, 16), urban air pollution (1%, 64), overweight and obesity (2%, 139), physical inactivity (2%, 135), contaminated injections in health-care settings (2%, 111), unsafe sex (3%, 235)	35%
Low-and-middle-income countries			
Mouth and oropharynx cancers	271 074	Alcohol use (14%, 38), smoking (37%, 100)	48%
Oesophageal cancer	379 760	Alcohol use (24%, 92) smoking (37%, 141), low fruit and vegetable intake (19%, 73)	58%
Stomach cancer	695 426	Smoking (11%, 74), low fruit and vegetable intake (19%, 130)	27%
Colon and rectum cancers	356 949	Overweight and obesity (9%, 32), physical inactivity (15%, 54), low fruit and vegetable intake (2%, 9)	11%
Liver cancer	504 407	Smoking (11%, 56), alcohol use (23%, 117), contaminated injections in health-care settings (21%, 108)	45%
Pancreatic cancer	116 827	Smoking (15%, 18)	15%
Trachea, bronchus, and lung cancers	770 938	Smoking (60%, 466), low fruit and vegetable intake (13%, 98), indoor smoke from household use of solid fuels (2%, 16), urban air pollution (7%, 52)	66%
Breast cancer	317 195	Alcohol use (4%, 12), overweight and obesity (7%, 23), physical inactivity (10%, 30)	18%
Cervix uteri cancer	218 064	Smoking (2%, 4), unsafe sex (100%, 218)	100%
Corpus uteri cancer	43 926	Overweight and obesity (37%, 16)	37%
Bladder cancer	116 682	Smoking (21%, 24)	21%
Leukaemia	190 059	Smoking (6%, 11)	6%
Selected other cancers	88 706	Alcohol use (4%, 3)	4%
All other cancers	882 001	None of selected risk factors	0%
All cancers	4 952 014	Alcohol use (5%, 262), smoking (18%, 896), low fruit and vegetable intake (6%, 311), indoor smoke from household use of solid fuels (<0.5%, 16), urban air pollution (1%, 52), overweight and obesity (1%, 71), physical inactivity (2%, 84), contaminated injections in health-care settings (2%, 108), unsafe sex (4%, 218)	34%
High-income countries			
Mouth and oropharynx cancers	40 559	Alcohol use (33%, 14), smoking (71%, 29)	80%
Oesophageal cancer	57 752	Alcohol use (41%, 24), smoking (71%, 41), low fruit and vegetable intake (12%, 7)	85%
Stomach cancer	146 267	Smoking (25%, 36), low fruit and vegetable intake (12%, 17)	34%
Colon and rectum cancers	256 791	Overweight and obesity (14%, 37), physical inactivity (14%, 36), low fruit and vegetable intake (1%, 3)	15%
Liver cancer	102 033	Smoking (29%, 29), alcohol use (32%, 33), contaminated injections in health-care settings (3%, 3)	52%
Pancreatic cancer	110 154	Smoking (30%, 33)	30%
Trachea, bronchus, and lung cancers	455 636	Smoking (86%, 391), low fruit and vegetable intake (8%, 36), indoor smoke from household use of solid fuels (0%), urban air pollution (3%, 12)	87%
Breast cancer	155 230	Alcohol use (9%, 14), overweight and obesity (13%, 20), physical inactivity (9%, 15)	27%
Cervix uteri cancer	16 663	Smoking (11%, 2), unsafe sex (100%, 17)	100%
Corpus uteri cancer	26 955	Overweight and obesity (43%, 12)	43%
Bladder cancer	58 636	Smoking (41%, 24)	41%
Leukaemia	73 110	Smoking (17%, 12)	17%
Selected other cancers	57 095	Alcohol use (8%, 5)	8%
All other cancers	509 507	None of selected risk factors	0%
All cancers	2 066 388	Alcohol use (4%, 88), smoking (29%, 596), low fruit and vegetable intake (3%, 64), indoor smoke from household use of solid fuels (0%, 0), urban air pollution (1%, 12), overweight and obesity (3%, 69), physical inactivity (2%, 51), contaminated injections in health-care settings (<0.5%, 3), unsafe sex (1%, 17)	37%

Results for individual regions available from corresponding author.

Table 2: Individual and joint contributions of risk factors in table 1 to mortality from site-specific cancers

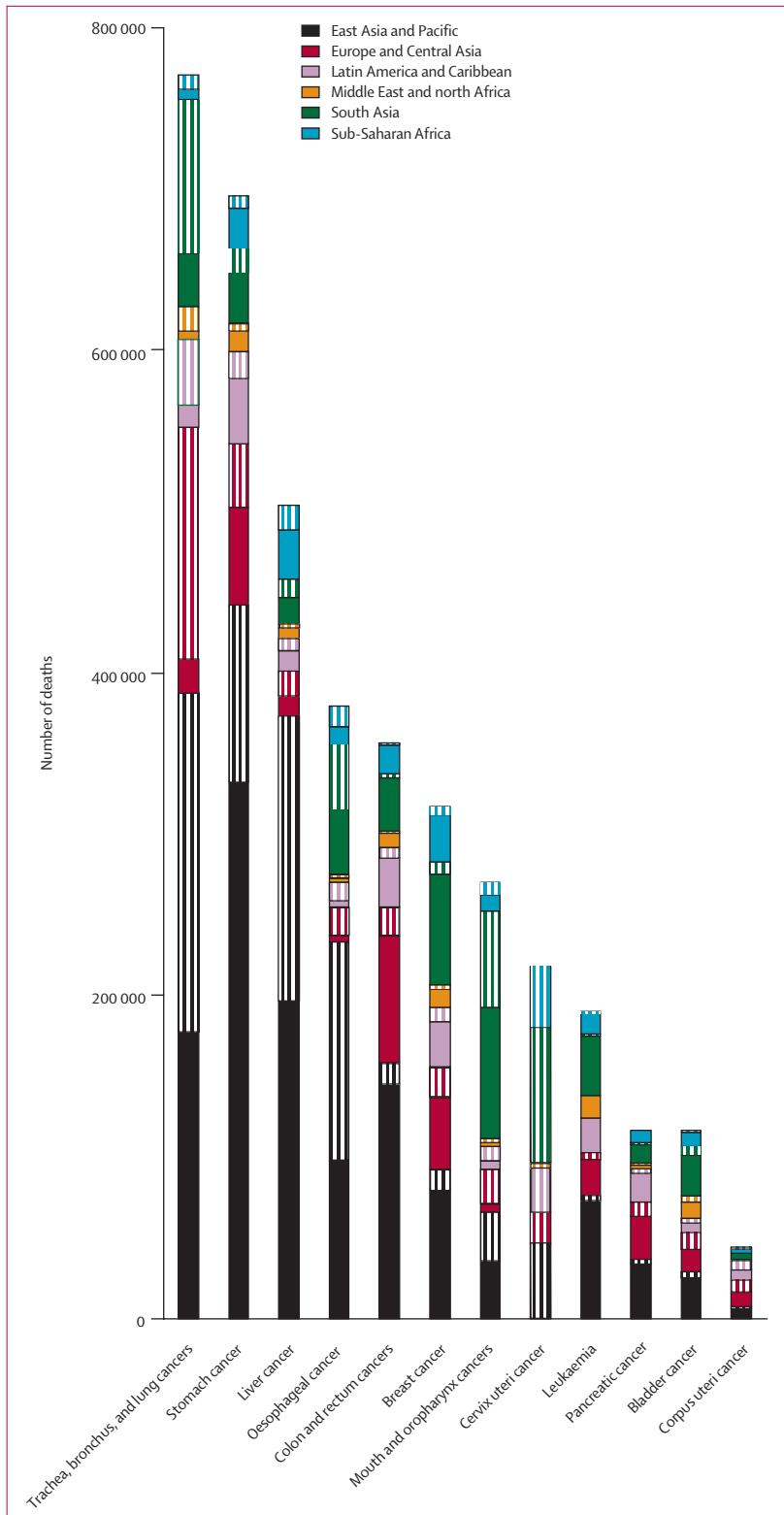


Figure 1: Deaths from site-specific cancers attributable to selected risk factors in low-and-middle-income countries, by region
 For every cancer site, solid blocks of colour represent deaths not attributable to risks assessed and broken blocks of colour represent deaths attributable to selected risk factors in table 1.

12% from liver cancer (283 000 deaths), and 11% from oesophageal cancer (271 000 deaths), reflecting the combinations of relatively large joint PAFs applied to large numbers of deaths from these cancers (table 2). All three cancers have 5-year survival rates of less than 25%. Leukaemia (23 000) and corpus uteri cancer (28 000) had the smallest number of attributable deaths (3% of deaths from leukaemia were attributed to occupational exposures,³⁵ not re-analysed here because of difficulties in converting exposure to new regions).

Despite having only 15% of the world's population (21% of the population aged ≥ 30 years), high-income countries accounted for 29% of the 7 million deaths from cancer worldwide and 31% of the 2.43 million that were attributable to the selected risks in table 1; the remaining 1.67 million attributable deaths occurred in low-and-middle-income countries. Except for cervix uteri cancer, joint PAFs were greater in high-income countries than in low-and-middle-income countries for all cancer sites. This finding is mostly a result of higher and longer population exposure to smoking and alcohol use, and is particularly evident for lung, mouth and oropharynx, and oesophageal cancers, especially in men. The joint PAFs for all cancers combined, however, were similar for both groups of countries (37% in high-income and 34% in low-and-middle-income regions). The smaller difference in all-site PAF than in PAFs for site-specific cancers arises because the contribution of site-specific cancers to total cancer mortality varies (eg, stomach and liver cancers caused 695 000 [14% of all deaths from cancer] and 504 000 [10% of all deaths from cancer] deaths, respectively, in low-and-middle-income countries, and 146 000 [7% of all deaths from cancer] and 102 000 [5% of all deaths from cancer] deaths in high-income countries). Furthermore, those cancer sites that were not affected by risk factors in table 1 accounted for 18% of all deaths from cancer in low-and-middle-income countries, but 25% in high-income nations.

Lung, liver, and oesophageal cancers had the largest number of attributable deaths in low-and-middle-income countries (512 000, 229 000, and 222 000, respectively). In high-income countries, lung cancer alone constituted 52% of all risk-factor attributable deaths from cancer (396 000 deaths); other cancers accounted for 7% or less, indicating the fairly successful preventive interventions for some of these cancers (eg, reduction in liver cancer as a result of reduced exposure to infectious agents) and the disproportionate rise in lung cancer mortality in many high-income countries where smoking prevalence remains high.

In low-and-middle-income countries, the joint PAF for all cancer sites combined was largest in Europe and Central Asia (ECA; 39%) and smallest in the Sub-Saharan Africa (SSA; 24%) and Middle East and North Africa (MENA; 24%) regions. For men, ECA had the largest joint PAF (50%) and SSA the smallest (19%), being strongly affected by the role of smoking, alcohol

use, and overweight and obesity; for women, SSA had the highest PAF (29%) and MENA the smallest (19%). The main driver of the high PAF for women in SSA was the large number of deaths from cervix uteri cancer, which is in turn affected by limited access to cervical screening above and beyond sexual transmission of HPV.

The largest number of deaths attributable to the selected risks in table 1 in the low-and-middle-income countries was in EAP (746 000; 45% of all attributable deaths from cancer in low-and-middle-income countries), ECA (324 000; 19%) and South Asia region (SAR: 322 000; 19%). In all three regions, the total number of deaths from cancer is large, mostly because of the large population size in EAP and SAR. The population of ECA is smaller, but the total number of deaths from cancer is relatively high and larger proportions are attributable to the individual and joint hazards of these risk factors, especially smoking. MENA and SSA had the smallest number of deaths from cancer attributable to the risk factors considered here (40 000 and 97 000, respectively), because of both the smaller total number of deaths from cancer and the lower PAFs attributable to these risks.

Smoking alone is estimated to have caused 21% of deaths from cancer worldwide. Alcohol use and low fruit and vegetable intake caused another 5% each. Smoking was responsible for a higher fraction of deaths from cancer in high-income countries (29%) than in low-and-middle-income regions (18%), because of the shorter history of smoking and lower prevalence among women. However, the number of smoking-attributable deaths from cancer was larger in the low-and-middle-income countries (896 000 vs 596 000) because of the larger total number of deaths from cancer. All-cancer-site PAF for alcohol use was almost equal in the two groups of countries because of large numbers of alcohol-attributable deaths in ECA and EAP. In EAP, liver and oesophagus were the cancer sites with the largest number of deaths attributable to alcohol use. In addition to smoking and alcohol use, some risks with well established interventions also caused considerable excess cancer mortality in low-and-middle-income regions: contaminated injections in health-care settings caused 108 000 deaths in the six regions, 91 000 of them in EAP; the cancer hazards of indoor smoke from solid fuels were restricted to EAP and SAR, where coal is used, causing 16 000 deaths from lung cancer (other regions use biomass fuels for which lung cancer hazards have not yet been established³⁰). The proportion of all-site-cancer deaths attributable to overweight or obesity and physical inactivity was highest in ECA, indicating the relatively high population exposure to these lifestyle related risk factors, which coexist with the risk from smoking and alcohol use.

The risk factors studied caused about twice as many deaths from cancer in men as in women (1.6 vs 0.83 million); the fraction of deaths from cancer

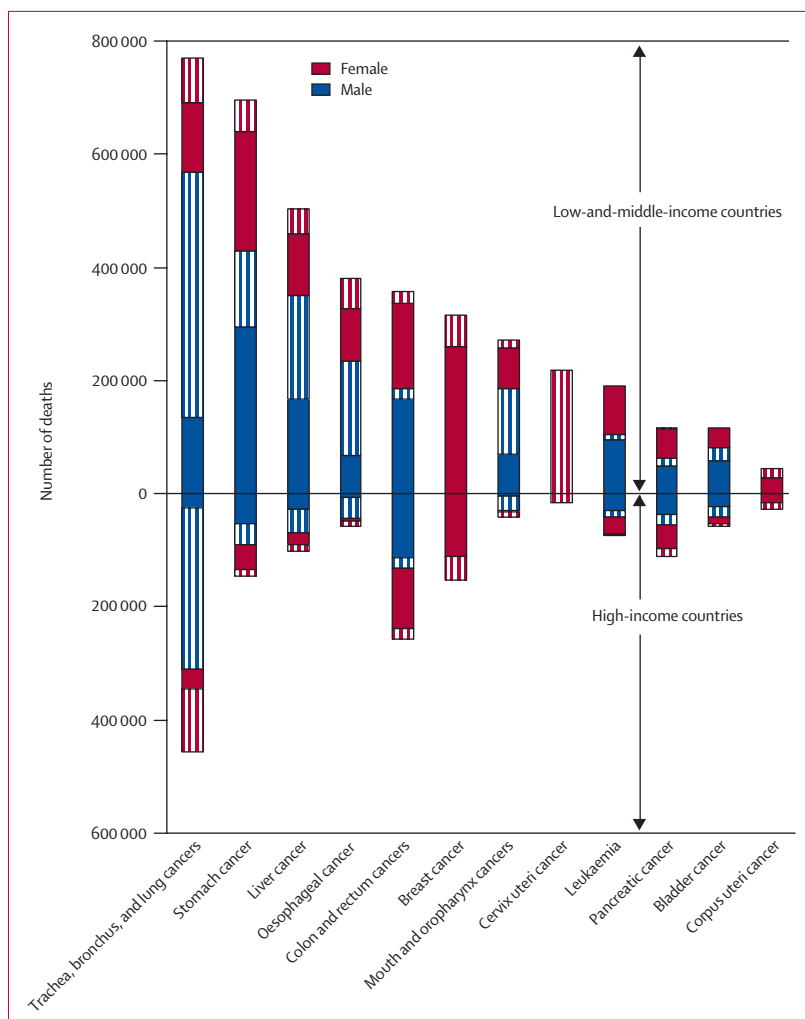


Figure 2: Worldwide deaths from site-specific cancers attributable to selected risk factors by sex

For every cancer site, solid blocks of colour represent deaths not attributable to risks assessed and broken blocks of colour represent deaths attributable to selected risk factors in table 1.

attributable to these risks was 41% for men versus 27% for women. Lung cancer contributed the most to the risk-factor attributable deaths in men (45% of all attributable deaths) and cervix uteri cancer in women (28% of all attributable deaths). Smoking and alcohol use played an important part in male–female differences in PAFs and attributable deaths. Excluding cervix, corpus uteri, and breast cancers, and their specific risk factors, which almost exclusively affect women, the total number of deaths from major cancers (lung, stomach, and liver) as well as the number attributable to the major risks, was higher in men than women (figure 2). This pattern did not follow for colorectal cancer, where smoking and alcohol use have no established role. The largest male–female difference in PAFs was for mouth or oropharynx cancer, which is strongly affected by alcohol use and smoking (66% for men vs 23% for women). Mouth or oropharynx cancer also had the

	Age			Total attributable deaths
	0–29 years	30–69 years	≥70 years	
World				
Mouth and oropharynx cancers	6 (15%, 1)	204 (58%, 118)	101 (44%, 44)	163
Oesophageal cancer	2 (38%, 0.8)	264 (66%, 175)	172 (55%, 95)	271
Stomach cancer	9 (21%, 2)	455 (32%, 145)	378 (24%, 92)	240
Colon and rectum cancers	6 (3%, 0.2)	282 (14%, 40)	326 (12%, 40)	79
Liver cancer	16 (36%, 6)	394 (49%, 195)	196 (42%, 82)	283
Pancreatic cancer	0.7 (0%, 0)	111 (23%, 25)	115 (22%, 25)	50
Trachea, bronchus, and lung cancers	5 (11%, 0.5)	684 (74%, 503)	537 (75%, 405)	908
Breast cancer	2 (0%, 0)	305 (20%, 61)	165 (22%, 37)	98
Cervix uteri cancer	11 (100%, 11)	156 (100%, 156)	67 (100%, 67)	235
Corpus uteri cancer	0.4 (0%, 0)	35 (43%, 15)	36 (37%, 13)	28
Bladder cancer	1 (0%, 0)	67 (29%, 19)	106 (27%, 29)	48
Leukaemia	75 (0%, 0)	107 (12%, 13)	81 (12%, 10)	23
All cancers	222 (10%, 21)	3783 (39%, 1467)	3013 (31%, 939)	2427
Low-and-middle-income countries				
Mouth and oropharynx cancers	6 (14%, 0.9)	180 (55%, 98)	85 (37%, 32)	131
Oesophageal cancer	2 (38%, 0.8)	235 (64%, 150)	143 (50%, 71)	222
Stomach cancer	8 (21%, 2)	399 (31%, 124)	288 (22%, 64)	191
Colon and rectum cancers	6 (3%, 0.2)	193 (12%, 24)	158 (10%, 16)	40
Liver cancer	16 (36%, 6)	346 (48%, 167)	142 (40%, 56)	229
Pancreatic cancer	0.6 (0%, 0)	68 (18%, 12)	48 (11%, 5)	18
Trachea, bronchus, and lung cancers	4 (11%, 0.5)	482 (68%, 329)	284 (64%, 183)	512
Breast cancer	2 (0%, 0)	227 (18%, 40)	89 (18%, 16)	56
Cervix uteri cancer	11 (100%, 11)	146 (100%, 146)	61 (100%, 61)	218
Corpus uteri cancer	0.4 (0%, 0)	25 (41%, 10)	19 (34%, 6)	16
Bladder cancer	1 (0%, 0)	53 (25%, 13)	62 (18%, 11)	24
Leukaemia	70 (0%, 0)	81 (10%, 8)	39 (7%, 3)	11
All cancers	206 (10%, 20)	2946 (38%, 1123)	1800 (29%, 524)	1668
High-income countries				
Mouth and oropharynx cancers	0.2 (34%, 0)	24 (82%, 20)	16 (78%, 13)	32
Oesophageal cancer	0.1 (55%, 0)	29 (87%, 25)	29 (83%, 24)	49
Stomach cancer	0.5 (19%, 0)	56 (37%, 21)	90 (31%, 28)	49
Colon and rectum cancers	0.5 (2%, 0)	88 (18%, 16)	168 (14%, 24)	40
Liver cancer	0.4 (33%, 0.1)	48 (57%, 28)	54 (48%, 26)	53
Pancreatic cancer	0.1 (0%, 0)	43 (30%, 13)	67 (30%, 20)	33
Trachea, bronchus, and lung cancers	0.3 (11%, 0)	202 (86%, 174)	253 (88%, 222)	396
Breast cancer	0.3 (0%, 0)	79 (27%, 22)	76 (27%, 21)	42
Cervix uteri cancer	0.2 (100%, 0.2)	10 (100%, 10)	6 (100%, 6)	17
Corpus uteri cancer	0 (0%, 0)	10 (48%, 5)	17 (41%, 7)	12
Bladder cancer	0 (0%, 0)	14 (43%, 6)	44 (40%, 18)	24
Leukaemia	4 (0%, 0)	26 (19%, 5)	43 (17%, 7)	12
All cancers	16 (4%, 0.6)	837 (41%, 343)	1212 (34%, 415)	759

Numbers in brackets show PAF (%) and number of attributable deaths (thousands) for the joint effects of risk factors in table 1. Only cancer sites affected by risk factors in table 1 are shown.

Table 3: Total cancer deaths (thousands) by age and cancer site

largest sex difference in low-and-middle-income countries (63% for men vs 17% for women); in high-income countries, liver cancer had the largest sex difference in PAFs (59% for men vs 37% for women).

Except for lung cancer in high-income countries, joint PAFs were largest for those aged 30–69 years. This finding is in part the result of the cohort effects of exposure to smoking and alcohol use. More than half of all deaths from cancer were between ages 30 years and 69 years (table 3). The largest number of attributable deaths for all cancer sites, except bladder, was also noted in this age group, pointing to the potential large gains in life expectancy that could be achieved by reducing exposure to these risk factors. Leukaemia claimed the largest total number of deaths from cancer in the youngest age group

(<30 years). None of the leukaemia deaths in these ages were attributed to the risk factors we assessed because most epidemiological studies only estimate hazards after the age of 30 years. Although the total number of deaths from cancer in those younger than age 30 years was generally low, the low-and-middle-income countries had noticeably larger numbers of deaths and higher PAFs in this age group (largely due to the large number of deaths from liver cancer attributable to contaminated injections), indicating the success of the cancer control programmes for young people in high-income nations.

Discussion

More than one in every three of the 7 million deaths from cancer worldwide is caused by nine potentially

modifiable risk factors, with smoking and alcohol use having particularly important roles in both high-income and low-and-middle-income countries. Sexual transmission of HPV, leading to persistent infection with oncogenic types of virus, as a risk factor for cervix uteri cancer is a major risk factor for women, especially in the poorest regions (SSA and SAR) where access to screening for cervical cancer is limited. Other potentially modifiable risk factors, which have not been assessed here, might increase this proportion substantially for some cancer sites. Our estimate of the proportion of deaths attributable worldwide to the nine risk factors we studied is about half of what Doll and Peto estimated¹⁸ by comparing age-standardised incidence rates from the USA from 1978 with the lowest reliably observed incidence rates in other populations. Because Doll and Peto¹⁸ used comparison of incidence rates, their estimates include differences in exposure to all known and unknown risk factors. Furthermore, their estimates applied to the USA only. Therefore the estimates of Doll and Peto are not directly comparable to ours.

Some important cancers (eg, prostate, kidney, melanoma, and lymphomas) were not attributable to any of the risks we assessed. These cancers are those with multiple confirmed or suspected environmental and behavioural risks, with heterogeneous exposure patterns that make exposure and hazard quantification difficult. Furthermore, we did not assess some fairly well known risk factors, such as occupational exposures, which are responsible for 102 000 deaths from cancer worldwide;³⁵ *Helicobacter pylori* exposure in food; and exposure to ultraviolet light and environmental tobacco smoke. We excluded these factors for the main part because of the limitations of deriving detailed exposure estimates from existing data (eg, extent of exposure to environmental tobacco smoke depends on public smoking regulation, exposure to ultraviolet light depends on the time spent outdoors and use of protection, and exposure to *H pylori* depends on methods of food preservation).

There are several sources of uncertainty for exposure and relative risks in our estimates, especially those that involve extrapolation of exposure and hazard from one population to another. These are described in more detail in the descriptions of the data sources for each risk factor.^{21, 23–31} The sources of uncertainty in methods and assumptions for estimating joint PAFs, and the sensitivity of results to these assumptions, have also been described elsewhere.³⁴ In addition to uncertainty in individual and joint PAFs, there is uncertainty in total site-specific cancer mortality to which the PAFs are applied.^{32,33} 75 countries have reasonably complete vital registration and medical certification of deaths.^{32,33} Another 51 countries have incomplete vital statistics, or use sample registration or surveillance systems. The remaining 65 countries, mostly in sub-Saharan Africa, have no reliable data on adult mortality. WHO uses standard demographic techniques³⁶ to estimate all-cause

death rates by age for these populations. Cause-of-death models are then used to estimate the total number of deaths from cancer for countries with poor data. The distribution of deaths from cancer by site is based on regional incidence or mortality patterns from cancer registries, which report to the International Agency for Research on Cancer (IARC),³⁷ or on cancer survival models when such data are unavailable. IARC also provides estimates of cancer mortality by site for most WHO member states. The implications of these different approaches have been discussed previously, including an assessment of their comparability.^{32,33} The net result is that the WHO estimates of global cancer mortality are 11% higher than those of IARC, with larger differences for SSA, SAR, and MENA.

Decades of biomedical research in developed nations have resulted in many effective interventions that affect cancer incidence and mortality. Examples include hepatitis B vaccine for liver cancer, screening methods for cervical cancer,^{38,39} faecal occult blood test for colorectal cancer,^{40–42} mammography for breast cancer,^{43,44} and surgical prevention for those at high risk of colorectal cancers.⁴⁵ Undoubtedly, increased coverage of the above technologies, especially those that involve early detection, would help reduce further the burden of cancers. There has, however, been less success with respect to other cancers: sputum cytology and chest radiographs for lung cancer have not been promising, and multiple chest radiographs might even be harmful,⁴⁶ and vaccines for *H pylori* and HPV are still under investigation.^{47,48} The efficacy of chemotherapy and radiotherapy varies from cancer to cancer and depends on multiple technical and biological factors, such as stage of cancer.

Summarising the changes made in cancer therapy over the past three decades, Sporn⁴⁹ states that the obsession with curing advanced disease has prevented progress in the war on cancer. Furthermore, preventive, screening, and treatment interventions will only affect population statistics if they are accessible and used, factors that are highly dependent on cost and health-system characteristics. These factors limit large-scale application of these interventions in resource-poor settings. These limitations further reinforce the importance of our results for policies and programmes that modify behavioural and environmental factors to reduce the burden of cancers.

Contributors

M Ezzati, S Vander Hoorn, A D Lopez, and C J L Murray designed the study. M Ezzati and S Vander Hoorn developed a framework and methods for joint-effect analyses. S Vander Hoorn and G Danaei did the statistical analysis. G Danaei, M Ezzati, and A D Lopez wrote the report. The Comparative Risk Assessment collaborating group reviewed scientific evidence and data sources for every risk factor and selected and summarised data on exposure, outcomes, and hazard. M Ezzati oversaw the research and the writing of this report.

Conflict of interest statement

We declare that we have no conflict of interest.

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