Global cancer incidence and mortality caused by behavior and infection

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ABSTRACT

Objective The objective is to systematically estimate the current cancer incidence and mortality from the six leading cancer types globally and by sub-regions resulting from exposure to known risk factors such as tobacco use, elevated body weight, alcohol consumption, inadequate physical activity, unhealthy diet and infections.

Methods Cancer incidence, mortality and burden of disease caused by the main cancer risk factors were calculated using comparative risk assessment methods and updated data on mortality and risks.

Results Lung cancer was the most common cancer in men and breast cancer the most common cancer in women, both in terms of incidence and mortality. The five leading behavioral and dietary risks—high body mass index, low fruit and vegetable intake, physical inactivity, tobacco use and alcohol use—were responsible for 24% of new cancer cases and 30% of cancer deaths. Cancers with the largest proportions attributable to preventable risk factors were cervical cancer (100%) and lung cancer (71%). Seventy percent of liver cancers and 60% of stomach cancers were due to infectious agents. A higher proportion of cancer deaths was attributed to infections in low- and middle-income than in high-income countries.

Conclusions The cancer burden is driven by changes in exposure to influential risk factors and can be influenced by preventive interventions aimed at reducing these exposures.

Keywords cancer, public health, risk assessment

Introduction

Cancer is an important cause of death, responsible for 11.8% of female deaths and 13.4% of male deaths in 2004.[1] Estimates of the global cancer burden indicate that cancer is increasingly prevalent in low- and middle-income countries. This is a result of aging populations which are, in turn, a result of declining fertility and success in combating infectious diseases in children. Total cancer deaths are projected to increase from 7.1 million in 2002 to 11.5 million in 2030.[2] As the major causes of child mortality—nutritional deficiencies and acute infections—continue to decline, cancers and other chronic diseases that primarily affect older adults will cause a larger share of the global burden of disease.[2]

Changes in cancer mortality rates are driven by changes in exposure to risk factors, and efforts in early detection, screening and treatment. A high proportion of deaths from the most common cancer types is attributable to one or more of the top risk factors for the worldwide burden of disease.[3,4] Among them are tobacco use, elevated body weight, alcohol consumption, inadequate physical activity, unhealthy diet characterized by low intake of fruits and vegetables and unsafe sex, which increases the transmission of infectious cancer risks such as human papillomaviruses (HPV), hepatitis b (HBV) and hepatitis c viruses (HCV).

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Planning of preventive health policies and programs that aim to reduce exposure to modifiable risk factors needs to be evidence based, incorporating all available research on the effects of major risks to population health. Previous studies have quantified the effects of risk factors, either by categorical attribution of death or disease to a single risk factor or by counterfactual analysis taking into account joint effects of multiple risk factors.[5] Some studies have analyzed the effects of risks on cancers, but are restricted to particular cancer risk factors,[6] particular cancers[7,8] or one population.[9] In 2005, Danaei et al.[4] estimated the contribution of several risk factors to various cancer types, but did not consider infectious causes of cancer.

Our objective is to systematically estimate the current global and regional cancer incidence and mortality, by cancer site, resulting from exposure to known risk factors. The risk factors were selected based on evidence for causality. Risk factors were included if they were categorized as group one carcinogens to humans, as evaluated in the IARC Monographs, Volumes 1–100A and on the availability of reasonably complete exposure data. The risk of low fruit and vegetable intake, which has been linked to colon cancer and stomach cancer,[10] has been included in addition to current IARC evidence.

This analysis uses updated data on mortality, burden of disease and risks, including infectious cancer risks, all of which have not been considered thus far in assessing the attributable burden by cancer type. Because cancer etiology, prevention and treatment vary considerably by cancer site, we analyzed the effects of each risk factor on six leading cancer types (lung, stomach, breast, colorectal, liver and cervical cancer), and also on all cancers types together.

Methods

Worldwide cancer incidence, mortality and burden of disease caused by selected risk factors and infections in 2004 were calculated, globally and by country. Comparative risk assessment methods, summarized below, were used.[3] For the analysis, countries were grouped according to the six World Health Organization regions, and also according to gross national income per capita in 2004.[11]

Data sources

Risk assessment requires four inputs: (1) data on deaths and disease burden, by cause; (2) data on exposure to risk factors; (3) quantitative information on the hazardous effect of each risk factor on each disease or relative risks, for each causally related disease-risk pair; and (4) a counterfactual exposure level to which actual exposure is compared.

Cancer incidence, burden and mortality

Cancer incidence and mortality were obtained from the WHO's most recent Global Burden of Disease study, which estimates causes of death for 2004 based on data from national civil registration systems and sample registrations systems, cancer registries and epidemiological analyses.[1] Detailed tables are available on the WHO web site (http://www.who.int/evidence/bod). 2004 estimates of cancer incidence and mortality were obtained as follows.

In countries with high-quality death registration, mortality data from death records were adjusted for the proportion of deaths coded as malignant neoplasm of unspecified site (ICD-10: C76–C80) and for the proportion of deaths coded to unknown causes (ICD-10: R00-R99). Malignant neoplasms of unspecified sites were redistributed pro-rata across all other cancer sites, except mouth and pharynx, liver, breast and cervix uteri cancer, which can be diagnosed clinically without further diagnostic tests.[12] Cancer incidence was then calculated using a survival model developed for a previous Global Burden of Disease analysis.[12] In other countries, an epidemiological model was used to estimate the proportion of deaths caused by malignant neoplasms;[1,13] the proportion caused by cancers of different sites was calculated using incidence data from cancer registries that cover entire national populations, or samples of such populations from selected regions[14] and from an analysis of cancer survival using previously described methods.[12]

Exposure to behavioral and dietary risks and infections and their effects

Prevalence of risk factor exposures and relative risk of exposure from a recent WHO report were used (Table 1).[15] WHO estimates were applied for exposure to the behavioral and dietary risk factors, and recent relative risks from large epidemiological studies or meta-analyses were used to estimate the hazards of exposure to the risk factors. Data on exposures to and hazards of infection were from Perz et al.[16] for hepatitis infections (HBV and HCV) and from Parkin[17] for Helicobacter pylori (H. pylori) and HPV infection.

Counterfactual exposure levels

In the comparative risk assessment approach, the health effects of each risk is calculated by comparing the current level of exposure to each risk to a counterfactual level, which is selected in a consistent way for all risks.[18] This ensures that the calculated health effects of different risks are comparable. The counterfactual exposure level is the one that results in the lowest health burden, referred to as the theoretical-minimum-risk exposure. For example, for body-mass index (BMI), zero

Table 1 Major cancer types and causally related risk factors

Risk factor	Exposure variable	Theoretical minimum	Major cancer types causally affected	Exposure estimates	Effect size estimates
Overweight and obesity	Body-mass index (height divided by weight squared)	Mean of 21 kg/m^{2} and standard deviation of 1 kg/m^{2}	Breast cancer (postmenopausal[33]), colorectal cancer[33]	WHO estimates by country[34]	Meta-analysis of 221 data sets[35]
Low fruit and vegetable intake	Fruit and vegetable intake per day	600 g (SD 50 g) intake per day for adults	Colorectal cancer, stomach cancer, lung cancer[10]	Systematic review of food consumption surveys and country food availability data[10]	Systematic review and meta-analyses of published cohort studies[10,36]
Physical inactivity	Four categories of inactive, low, medium and high activity levels.[37] Activity in discretionary-time, work and transport considered	High activity level: minimum 3 days per week of vigorous intensity activity (minimum 1500 MET-min/week), or 7 days per week of any intensity activity (minimum 3000 MET-min/week)	Breast cancer,[33] colorectal cancer.[33]	Prevalence for 14 world regions for three categories of physical inactivity from Bull et al.[38] Sufficiently active category split into moderate and highly active using data for 28 countries[39,40]	Systematic review of published cohort studies[38,40]
Tobacco use	Current levels of smoking impact ratio (indirect indicator of accumulated smoking risk based on excess lung cancer mortality); oral tobacco use prevalence	No tobacco use	Lung cancer,[41,42] stomach cancer,[42,43] liver cancer,[42,44–46] cancer of uterine cervix[42]	Updated smoking impact ratios calculated from GBD 2004 lung cancer mortality estimates;[1] oral tobacco prevalence for South Asia from the World Health Survey, India[47]	American Cancer Society cohort[48]
Alcohol use[a]	Current alcohol consumption volumes	No alcohol use	Breast cancer,[49,50] colorectal cancer,[50] liver cancer[50,51]	Estimates of alcohol consumption by country[52,53]	Systematic reviews of cohort studies for colorectal cancer,[54] breast cancer and liver cancer[55]
HPV	Past or current infection with HPV	No infection	Cervical cancer[56]	PAF = 1, virtually all cervical cancer contain oncogenic HPV DNA[17,57]	
Chronic HBV and HCV infection	Past or current infection with HBV and/or HCV	No infection	Liver cancer[58]	Seroprevalence of HBV or HCV surface antigen[16]	Systematic review of published cohort studies[17]
H. pylori	Past or current infection with H. pylori	No infection	Stomach cancer[59,60]	Seroprevalence of H. pylori antibody[17]	Systematic review of published cohort studies[17]

[a]In the view of inconsistent results on the relation of alcohol drinking and stomach cancer, no causal role for alcohol drinking in stomach cancer was established.[50,51]

exposure is an inappropriate choice. The level that resulted in the lowest health risk, as observed in epidemiological studies, was used as the counterfactual exposure level. For the protective factors of fruit and vegetable intake and physical activity, a counterfactual exposure distribution was chosen based on high-intake populations that would have the lowest levels of disease burden. The theoretical-minimum-risk exposures are listed in Table 1.

Statistical analysis

The population attributable fraction (PAF) was calculated for each of the selected cancer sites affected by their respective risk factors. The PAF is defined as the proportional reduction in death or disease incidence that would occur if exposure to a risk factor was reduced to a counterfactual distribution with all other factors remaining the same.[19,20] The PAF is calculated using equation 1:

$$\text{PAF} = \frac{\int_{x=0}^{m} \text{RR}(x)P(x)\,dx - \int_{x=0}^{m} \text{RR}(x)P'(x)\,dx}{\int_{x=0}^{m} \text{RR}(x)P(x)\,dx}, \quad (1)$$

where $\text{RR}(x)$ is the relative risk at each exposure level x, $P(x)$, the proportion of population at each exposure level, $P'(x)$, the counterfactual proportion of population at each exposure level, x, the exposure level and m, the maximum exposure level.

We also calculated the fraction of mortality attributed to the combined effects of these risk factors. Among those people exposed to multiple risk factors, disease-specific deaths may be caused by the simultaneous effects of multiple exposures, and hence can be prevented by reducing exposure to any of the risks. The joint effects of risks to health were combined under three specific assumptions about the correlation of the exposures to multiple risks and the interactions of their causal effects.[5,21] First, we assumed that the exposure to the risks are uncorrelated within a given country. Second, we assumed that the level of exposure to one risk factor does not affect the proportional increase in risk caused by another (i.e., no effect modification). Third, we assumed that the effect of one risk factor does not act through another (i.e. no mediated effects). We use equation 2 to calculate the combined effects of risk factors:

$$\text{PAF} = 1 - \prod_{i=1}^{n}(1 - \text{PAF}_i), \quad (2)$$

where PAF_i is the PAF for individual risk factor i, and n, the total number of risk factors that affect the same disease outcome.

We considered potential interactions among the risks that would affect the calculation of the joint effect of the risks by violating one of the three assumptions listed above. For liver cancer, there is evidence that infection with hepatitis A virus, HBV and alcohol each reduce the relative risk of exposure to the others.[22] This means that using equation 2 to calculate the joint effect of the three risk factors would overestimate total PAF. However, there is also evidence that tobacco and alcohol together have a super-multiplicative effect on liver cancer incidence,[23] which would have the opposite effect of underestimating the joint PAF calculated using equation 2. In addition, a synergism between HBV and HCV infections indicates that the risk for co-infection is greater than the sum but lower than the product of those for each infection.[24] However, because of the nature of joint PAF calculations, any bias would be small compared with other sources of uncertainty. In addition, the evidence for these interactions is sparse, thus it is unclear whether they should be accounted for. Therefore, we assume the effects of all risk factors are independent.

All PAFs were calculated by sex, by eight age groups and by country. In order to derive cancer cases and deaths from site-specific cancer attributable to the risk factor or group of risk factors, PAFs were multiplied by national site-specific cancer incidence and mortality for the year 2004. Table 1 shows the established risk factors in their relation to the major cancer types. These cancers are: trachea, bronchus and lung cancers (ICD-10 C33-C34), stomach cancer (ICD-10 C16), liver cancer (ICD-10 C22), colorectal cancer (ICD-10 C18-C21), breast cancer (ICD-10 C50) and, fifth leading among females, cancer of the cervix uteri (ICD-10 C-53). In addition, we include estimates of the effects of these risk factors on other cancer sites[15] to calculate their effect on all cancers.

Results

Global cancer incidence and mortality

Figure 1 shows the estimated age-standardized incidence and mortality rates in 2004 by sex and income for the major cancer types. In high-income countries, where 15% of the global population lives, 35% of 11.4 million estimated incident cancers and 29% of 7.5 million cancer deaths occurred. Globally, 5.3 million cancer deaths occurred in low-income regions compared with 2.2 million deaths in high-income countries (Supplementary data, Table S1A). Cancer incidence rates were higher in men than women. However, because older women outnumber older men, there were more cancers overall in women than in men.

Globally, lung cancer was the most common cancer in men, both in terms of incidence and mortality. There were more lung cancers in men than any other type (39 per 100 000) and lung cancer was also the leading cause of male cancer deaths in all subregions, except for Africa. For both sexes combined, the age-standardized lung cancer death rate on a global level was 23.4 per 100 000—the highest among all single cancer sites. Lung cancer mortality rates were over
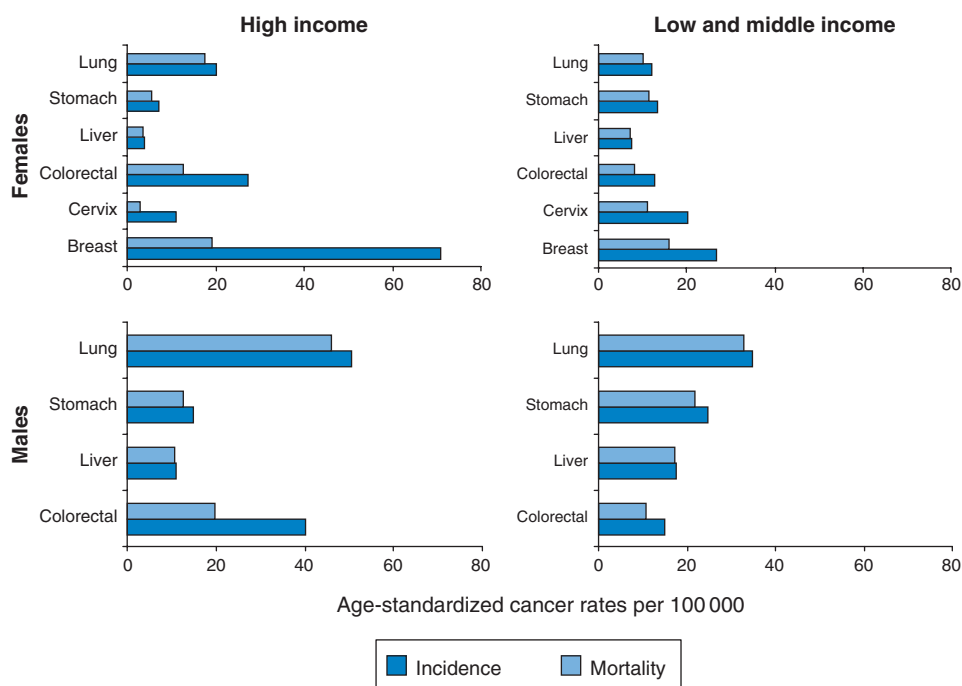
Fig. 1 Incidence and mortality rates (age standardized, per 100 000), by cancer site, males and females, high-income countries and low- and middle-income countries. Low-income countries had a gross national income per capita less than US $825 in 2004, whereas for high-income countries it was greater than US $10 066.[11]

two times higher in men than in women, reflecting the lower past smoking rates in females.

Among females, the most frequent cancer was breast cancer with an age-standardized incidence rate of 37 per 100 000 that encompasses great geographical variation, ranging from 71 in high-income countries to 17 in the low-income regions of the Western Pacific. For breast cancer a smaller difference in mortality between high- and low-income regions was observed than for incidence due to higher case-fatality rates in low-income countries. Another significant difference in female cancer mortality between the regions exists for cervical cancer, a rare cause of cancer deaths in the developed world, but the leading cancer type in Africa and South-East Asia.

Individual contributions of selected risk factors to cancer mortality and incidence

Tables 2 and 3 show the estimated individual and joint contribution of the selected risk factors to cancer mortality by sex (Table 2), separately for high- and low- and middle income countries (Table 3), and by region (Tables S2A, S3A). Cancers with the largest proportions attributable to preventable risk factors were cervical cancer and lung cancer. The main risk factor for cancer of the cervix uteri is infection with oncogenic HPV and for lung cancer it is tobacco smoking.

Addictive substances

Tobacco was the world's leading risk factor for overall cancer mortality and for lung cancer in particular, causing 22% of global cancer deaths and 71% of global lung cancer deaths. A higher lung cancer mortality rate was attributable to tobacco use in high-income countries (25.7 per 100 000; age-standardized rates used throughout) than in low- and middle-income countries (13.0), because of the historically greater tobacco use and the high intensity of tobacco use among current smokers in high-income countries.[15] However, because of the larger overall population in low- and middle-income countries, the absolute number of smoking-attributable lung cancer deaths was higher in these countries (987 000 cancer deaths in low- and middle-income countries vs. 627 000 in high-income countries; Table S3A).

Tobacco was a leading risk factor for both high-income countries and low- and middle-income regions, whereas alcohol contributed more significantly to cancer mortality in low- and middle-income countries (Figure 2). Countries with the highest proportions of cancer deaths attributed to alcohol were the low- and middle-income countries of the Western Pacific region, but alcohol had a relatively low contribution to the burden of cancer in the Eastern Mediterranean subregion (11% of cancer deaths vs. 1%, respectively).

Table 2 Overall and site-specific cancer deaths attributable to each risk factor (%), males and females

Cancer site	All selected risks	Alcohol use	Infection with HBV, HCV, H. pylori, or HPV	Low fruit and vegetable intake	Overweight and obesity	Physical inactivity	Tobacco use
Males (%)							
All sites[a]	49	9	15	7	1	2	31
Colon and rectum	19	5		2	17	19	
Liver	86	37	73				16
Stomach	70		61	17			16
Lung	79			11			78
Females (%)							
All sites[a]	35	3	19	5	3	6	10
Breast	21	7			9	25	
Cervix	100		100				3
Colon and rectum	14	1		2	9	20	
Liver	78	16	72				4
Stomach	70		66	17			4
Lung	56			11			53

[a]When calculating the effect of these risk factors on all cancers, the following additional effects were also considered: the effect of alcohol on mouth, oropharynx and esophageal cancers; the effect of low fruit and vegetable intake on esophageal cancer; the effect of overweight and obesity on uterine cancer; the effect of tobacco smoking on upper aerodigestive, pancreas, bladder and kidney cancers and myeloid leukaemia; and the effect of oral tobacco use on mouth and oropharynx cancers.

Table 3 Overall and site-specific cancer death rate (age standardized, per 100 000) attributable to each risk factor, high-income countries and low- and middle-income countries[a]

Cancer site	All risks	Alcohol use	Infection with HBV, HCV, H. pylori, or HPV	Low fruit and vegetable intake	Overweight and obesity	Physical inactivity	Tobacco use
High income							
All sites[b]	56.2	7.4	11.9	4.5	4.5	5.9	39.1
Breast	2.8	1.3			1.2	2.8	
Cervix	1.6		1.6				0.2
Colon and rectum	2.9	0.6		0.2	2.7	3.1	
Liver	6.0	2.6	4.9				1.8
Stomach	6.3		5.3	1.0			2.0
Lung	25.9			2.5			25.7
Low and middle income							
All sites[b]	55.5	8.7	24.8	8.5	1.9	3.9	24.1
Breast	1.6	0.5			0.6	2.1	
Cervix	5.8		5.8				0.1
Colon and rectum	1.5	0.2		0.2	1.0	1.8	
Liver	9.8	3.4	8.7				1.1
Stomach	11.3		10.3	2.9			1.5
Lung	13.4			2.5			13.0

[a]High-income countries had a gross national income per capita greater than US $10 066 in 2004, according to World Bank.[11]
[b]When calculating the effect of these risk factors on all cancers, the following additional effects were also considered: the effect of alcohol on mouth, oropharynx and esophageal cancers; the effect of low fruit and vegetable intake on esophageal cancer; the effect of overweight and obesity on uterine cancer; the effect of tobacco smoking on upper aerodigestive, pancreas, bladder and kidney cancers, and myeloid leukaemia; and the effect of oral tobacco use on mouth and oropharynx cancers.

The cancer type with the largest number of deaths attributable to alcohol was liver cancer. Both alcohol and tobacco showed a strong gender pattern, with 78 and 79% of alcohol- and tobacco-caused cancer deaths occurring among men, respectively.

Dietary-related risks and physical inactivity

Globally, 7% of cancers in men and 5% of cancers in women were attributable to insufficient intake of fruits and vegetables. Low fruit and vegetable intake caused 17% of stomach cancer and 11% of lung cancer mortality globally. The proportion of cancer mortality attributable to this risk factor was higher in low- and middle-income regions (7 vs. 3% in high-income countries), which may be related to availability of fresh fruits and vegetables and cultural nutrition habits.

Both body weight and physical activity have strong effects on metabolic factors related to colorectal cancer, the cancer that is most affected by these two risk factors. Globally, around 20% of colorectal cancers were caused by physical inactivity. Overweight and obesity caused more colorectal cancer in men than women (incidence of 4.0 per 100 000 in men vs. 1.5 per 100 000 in women). Physical inactivity, on the other hand, was a significant risk factor for female breast cancer, causing 26% of breast cancer mortality in high-income countries and 25% of breast cancer mortality in low-income countries.

Infections

Infections with HPV, HBV and HCV and *H. pylori*, are leading causes of cervical, liver and stomach cancers, respectively. Worldwide, 63% of stomach cancer deaths were caused by infection with *H. pylori*, 73% of liver cancer
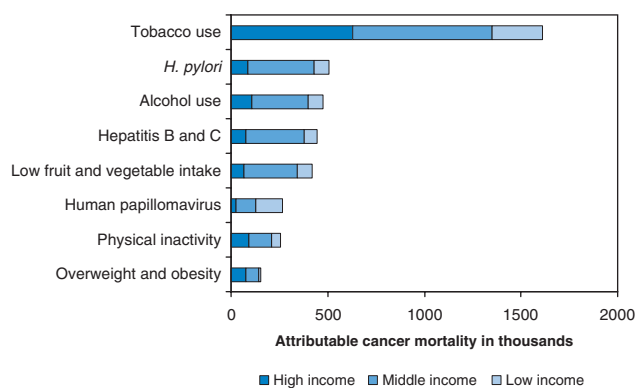
deaths were caused by infection with hepatitis viruses and all cervical cancer deaths were caused by infection with HPV.

A much higher proportion of cancer deaths was attributed to these infections in low- and middle-income countries than in high-income countries, with 9% of all cancer deaths attributed to an infection in high-income countries and 20% in low- and middle-income regions. These differences were also reflected in the incidence of specific cancer types attributed to infection, such as cervical, liver and stomach cancers.

Joint contributions of selected risk factors to cancer mortality

The five behavioral and dietary risks considered in this analysis—overweight and obesity, low fruit and vegetable intake, physical inactivity, tobacco use and alcohol use—were responsible for 24% of new cancer cases (32% for men and 16% for women) and 30% of cancer deaths (39% for men and 19% for women). The difference between males and females was almost entirely caused by the higher tobacco use in men: 1.4 million cancer cases (1.3 million deaths) were caused by tobacco use in men, while only 410 000 cases (340 000 deaths) were caused by tobacco in women. Alcohol and low fruit and vegetable intake caused more cancers in men, while overweight and obesity and lack of physical activity each had a greater effect on women.

A total of 4.1 million cancer cases (35%) and 3.2 million cancer deaths (43%) were due to the modifiable risk factors evaluated in this analysis. These factors cause the largest percentage of total cancers among men in the Western Pacific region (53%) and men in middle-income European countries (46%). This is due to hepatitis virus infection, *H. pylori* infection and tobacco use in the Western Pacific region, and primarily due to tobacco in the middle-income European countries.

Discussion

Main findings of this study

The study provides estimates of the effects of leading modifiable risk factors for major cancer types using comparative risk assessment methods.[3] For some cancers, mainly those with a lower relative survival, greater differences in incidence and mortality in high-income vs. low-income regions were observed. This might be a result of differences in treatment and early detection efforts and, thus a higher cure rate for some cancer types in high-income countries. The leading cancers considered here—lung cancer, liver cancer, breast cancer, cervical cancer, colorectal cancer, stomach cancer—

Fig. 2 Overall cancer deaths in thousands attributable to five behavioral and dietary risk factors and to infections, high-income countries and low-and middle-income countries. Low-income countries had a gross national income per capita less than US $825 in 2004, whereas for high-income countries it was greater than US $10 066.[11]

were substantially a result of exposure to established modifiable risk factors. Overall, 35% of female cancers and nearly half of male cancers could potentially be prevented by reducing exposure to these risk factors. For some cancer types, the specific attributable fractions are higher. The two cancer types most affected by modifiable risk factors were lung cancer and cervical cancer.

Some of the major risk factors, such as overweight and physical inactivity, are associated with high-income countries. However, over half of the global cancer burden caused by each of these risks occurred in low- and middle-income regions, suggesting a transition of health risks related to economic, market and demographic factors. Consumption habits including insufficient fruit and vegetable intake and alcohol consumption are related to cancer. Seventeen percent of stomach cancer, for example, was caused by low intake for fruit and vegetables, whereas liver cancer showed the largest number of deaths attributable to alcohol consumption. Infections caused a large proportion of cancers in low- and middle-income countries (18% of new cancer cases and 20% of cancer deaths). The cancer sites that are to a great extent attributable to infectious cancer risks are stomach, liver and cervical cancer.

What is already known on this topic

Sufficient knowledge on the potentially modifiable causes of some cancers is known from epidemiological studies, which justify the development and implementation of cancer prevention policies. A few studies have analyzed the effects of risks on cancers in a quantitative way, mainly restricted to particular risk factors,[6] particular cancers[7,8] or to one population.[9] Danaei et al.[4] has estimated that out of 7 million deaths from cancer in the world in 2001, 35% were attributable to the combined effects of 9 potentially modifiable risk factors. The impact of behavioral and environmental risks on cancer mortality was assessed but infectious causes of cancer were not included. All estimates provided referred to the attributable cancer mortality only and no information on the attributable cancer incidence has been published.

What this study adds

Using updated data on mortality, burden of disease and risks, this study assesses the attributable burden for six leading cancer types (lung, stomach, breast, colorectal, liver and cervical cancer) and includes an assessment of the effects of infectious causes of cancer, which were not considered in conjunction with other cancer risk factors in previous analyses. In addition to the attributable cancer deaths, the cancer incidence attributable to particular risk factors was calculated.

The differentiation by cancer type and the risk-specific attribution is crucial since the etiology, natural history, epidemiology and biology differs widely among the various cancer types and preventive interventions, early diagnosis and treatments are specific for each cancer type.[25] There is also a geographical pattern associated with the cancer type-specific distribution and accordingly with risk factor exposure. The high cancer burden from infections, poor diet and addictive substances in low- and middle-income countries found in this study together with the potentially rising cancer burden from high body weight and physical inactivity present challenges for health systems in these countries. Preventive interventions aiming at reducing these potentially modifiable risk factors are of particular relevance for the main cancers such as of lung, breast, cervix, stomach, colorectum and liver and can play an important role in mitigating the current and expected increases in cancer incidence and mortality.

Although a larger proportion of cancers can be attributed to behavioral and dietary risks in high-income countries than in low- and middle-income countries, this could be because most epidemiologic studies focus on these countries and less consistent information is available on behavioral and environmental factors that may affect cancer incidence in other regions. Research on cancer risks specific to low- and middle-income countries is needed to identify additional preventive measures that could reduce cancer incidence in these countries.

Limitations of this study

Quantitative risk assessment is generally subject to uncertainty at several steps of the process. Quantitative estimates of exposures and risks are affected by statistical uncertainty. Depending on the country and the availability of demographic surveillance systems, data on risk factor prevalence worldwide or on a regional level are often missing, and prevalences were modeled for the missing populations, further increasing uncertainty. While adjusted relative risks from large, well-designed studies or meta-analyses were used, these could be affected by confounding from unmeasured factors such as efforts of early diagnosis, access to health care and quality of treatment.

We also assume that relative risks are transferable between countries. Although it has been shown that relative risks are consistent across populations for many risk factors and diseases,[26] there might be interactions between risk factors and indicators such as poverty and malnutrition, which may have introduced bias. Finally, if risks and diseases are concentrated in specific subgroups, the accuracy of our calculations would be affected.[5,27]

Some of the risk factors considered, particularly dietary risks, have been associated with cancer based on other causality assessments. We base our assessment of causality on IARC evidence and on an analysis of fruits and vegetables.[10] For the six leading cancer types, our analysis is also consistent with the 'probable' and 'convincing' associations found in the WCRF 2007 report on diet and physical activity.[28] The exception is the effect of fruits and vegetables on colorectal cancer, which WCRF found 'limited-suggestive' but is included in this analysis. Nevertheless, excluding this association would not change the conclusions of our analysis (Tables 1 and 2).

We have also excluded some risk factors and interactions between risk factors due to the limitations in deriving reliable stratified exposure estimates. For example, the group of naturally occurring aflatoxins are carcionogenic to humans and a risk factor for liver cancer.[29] However, it is difficult to estimate the percentage of liver cancer attributable to aflatoxin exposure since the number of people exposed to high levels of aflatoxin is unknown.[30] Exposure data are also difficult to obtain for many environmental and occupational risks such as radon and arsenic, which have been established as risk factors for lung cancer.[31,32] Interactions between hepatitis infections and other factors were suggested, however none of these other factors is established as a causal risk factor for liver cancer by itself.[22]

Conclusions

Understanding the preventable fraction of the current cancer burden has major implications for national cancer control programs and health policy decision-making. It indicates the path for preventing a substantial percentage of global cancer incidence and mortality, which is particularly needed in the light of aging populations and an associated rise in cancer deaths in the next decades.[2]

With an analyses like the present one we demonstrate the utility of data on cancer incidence, mortality and population exposure to risks. In order to appropriately set research and intervention priorities in cancer prevention, reliable estimates of cancer risk factor exposure and of cancer mortality and incidence are essential. Therefore, vital registration, cancer registries and availability of data on risk factors need to be particularly strengthened in the poorer regions of the world.

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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