

The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global Burden of Disease Study 2019

Article

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The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global Burden of Disease Study 2019

GBD 2019 Cancer Risk Factors Collaborators*



Summary

Background Understanding the magnitude of cancer burden attributable to potentially modifiable risk factors is crucial for development of effective prevention and mitigation strategies. We analysed results from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 to inform cancer control planning efforts globally.

Methods The GBD 2019 comparative risk assessment framework was used to estimate cancer burden attributable to behavioural, environmental and occupational, and metabolic risk factors. A total of 82 risk–outcome pairs were included on the basis of the World Cancer Research Fund criteria. Estimated cancer deaths and disability-adjusted life-years (DALYs) in 2019 and change in these measures between 2010 and 2019 are presented.

Findings Globally, in 2019, the risk factors included in this analysis accounted for 4·45 million (95% uncertainty interval 4·01–4·94) deaths and 105 million (95·0–116) DALYs for both sexes combined, representing 44·4% (41·3–48·4) of all cancer deaths and 42·0% (39·1–45·6) of all DALYs. There were 2·88 million (2·60–3·18) risk-attributable cancer deaths in males (50·6% [47·8–54·1] of all male cancer deaths) and 1·58 million (1·36–1·84) risk-attributable cancer deaths in females (36·3% [32·5–41·3] of all female cancer deaths). The leading risk factors at the most detailed level globally for risk-attributable cancer deaths and DALYs in 2019 for both sexes combined were smoking, followed by alcohol use and high BMI. Risk-attributable cancer burden varied by world region and Socio-demographic Index (SDI), with smoking, unsafe sex, and alcohol use being the three leading risk factors for risk-attributable cancer DALYs in low SDI locations in 2019, whereas DALYs in high SDI locations mirrored the top three global risk factor rankings. From 2010 to 2019, global risk-attributable cancer deaths increased by 20·4% (12·6–28·4) and DALYs by 16·8% (8·8–25·0), with the greatest percentage increase in metabolic risks (34·7% [27·9–42·8] and 33·3% [25·8–42·0]).

Interpretation The leading risk factors contributing to global cancer burden in 2019 were behavioural, whereas metabolic risk factors saw the largest increases between 2010 and 2019. Reducing exposure to these modifiable risk factors would decrease cancer mortality and DALY rates worldwide, and policies should be tailored appropriately to local cancer risk factor burden.

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Introduction

Cancer is the second leading cause of death worldwide, and exposure to risk factors plays an important role in the biology and burden of many cancer types.^{1–4} Understanding the relative contribution of modifiable risk factors to cancer burden and their trends over time is crucial to informing cancer control efforts both locally and globally. In 2015, the UN released the Sustainable Development Goals (SDGs), with SDG target 3·4 focusing on reducing global premature mortality by a third for non-communicable diseases, including cancer, by 2030. Effectively addressing the growing burden of cancer globally will require comprehensive measures that incorporate both curative and preventive interventions, particularly in light of the anticipated challenges that the COVID-19 pandemic will bring in progress towards SDG target 3·4.^{5–7}

Although some cancer cases are not preventable, governments can work on a population level to support an environment that minimises exposure to known cancer risk factors. Primary prevention, or the prevention of a cancer developing, is a particularly cost-effective strategy,⁸ although it must be paired with more comprehensive efforts to address cancer burden, including secondary prevention initiatives, such as screening programmes, and ensuring effective capacity to diagnose and treat those with cancer. As part of cancer control strategies, prevention requires identification of causal risk factors, determination of contribution to local cancer burden, and development of effective strategies for their mitigation. Previous studies have quantified the burden of cancer attributable to individual risk factors globally or for several risk factors in select countries and regions,^{9–20} providing crucial location and

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For more on SDG target 3·4 see
<https://unstats.un.org/sdgs/metadata/>

Research in context

Evidence before this study

We identified previous work that primarily estimated the attributable cancer burden for single risk factors globally or multiple risk factors for single countries. The Global Cancer Observatory also provides estimates of cancer-attributable burden for select risk factor categories separately. One previous comparative risk assessment project estimated risk-attributable cancer mortality for nine risk factors. We searched titles and abstracts in PubMed for English-language research papers that were published between Jan 1, 2010, and June 1, 2021, using the search terms “cancer or neoplasm or tumor or malignancy” and “risk factor or attributable risk or population attributable fraction” and “global or international or worldwide or world” and “burden or metrics or incidence or mortality”, but did not identify additional informative studies. There is a gap in the literature on global estimates of risk-attributable cancer burden for a comprehensive list of risk factors that incorporate both cancer-related mortality and disability.

Added value of this study

We report, for the first time, the global cancer burden attributable to a comprehensive list of behavioural, metabolic, and environmental and occupational risk factors using Global

Burden of Diseases, Injuries, and Risk Factors 2019 results.

By estimating risk-attributable cancer burden nationally and globally using both mortality and disability-adjusted life-years (DALYs), this study provides a new perspective on attributable cancer burden. Globally, a large portion of cancer deaths and DALYs were attributable to the modifiable risk factors included, with behavioural risks representing the largest attributable burden. We identified substantial differences in attributable cancer death and DALY burden across Socio-demographic Index quintiles and between sexes. Risk-attributable cancer death and DALY burden increased globally from 2010 to 2019, with metabolic risk factors contributing to the largest percentage increases, most notably in low and low-middle Socio-demographic Index countries.

Implications of all the available evidence

The burden of cancer remains an important public health challenge that is growing in magnitude globally. Modifiable risk factors are important contributors to cancer mortality and DALYs globally, with contribution varying by setting. The results from this study highlight the need for context-specific policies aimed at reducing exposure to risk factors as part of comprehensive cancer control efforts.

risk-factor-specific information. However, comprehensive cancer risk factor estimates do not exist for many countries, leaving an important void as countries develop and update their cancer control plans. The Global Cancer Observatory from the International Agency for Research on Cancer provides estimates of global, regional, and national risk-attributable cancer burden for a subset of potentially modifiable risk factors (eg, obesity, alcohol consumption, infections, and ultraviolet radiation), but these estimates are not provided together in a comprehensive fashion across time, and some potentially modifiable risk factors are not estimated as part of this effort.^{21–24}

To our knowledge, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) is the only study to date that quantifies cancer burden attributable to a broad set of modifiable risk factors for each GBD round, for all countries around the world, across age groups, for both sexes, and over time. GBD 2019, the most recent iteration of the GBD study, provides an opportunity to evaluate the global burden of cancer attributable to risk factors. A previous study used a similar comparative risk framework to estimate mortality from 12 cancer types and nine behavioural and environmental risk factors based on WHO cancer mortality data, but this analysis was limited to 2001 and has not been updated in a formal GBD analysis since.²⁵ Herein, we present estimates of 82 risk–outcome pairs, including cancer deaths and disability-adjusted life-years (DALYs) attributable to risk factors at global, regional, and national levels in 2019, and assess

the temporal trends from 2010 to 2019 of cancer burden attributable to environmental and occupational, behavioural, and metabolic risk factors to inform efforts to reduce exposure to cancer risk factors (appendix pp 157–60).²⁶ This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.

Methods

Overview of the GBD study

The GBD study was developed to provide global health estimates that are comprehensive and comparable for causes of death, disability, and their associated risk factors. GBD 2019 estimates mortality, incidence, prevalence, years of life lost (YLLs), years of life lived with disability (YLDs), and DALYs for 369 causes of death and disability and 87 risk factors, and groups of risk factors at the global level, regionally, and for 204 countries and territories. The 2019 iteration of the GBD is the most up to date and supersedes all previous iterations. This Article reports estimates from 2010 to 2019, but extended years of estimates (1990–2019) are available online via the GBD Compare Tool and GBD Results Tool. Rates are reported per 100 000 person-years, and age-standardised rates were calculated with the GBD world population standard.²⁷ Select results in this Article are presented by Socio-demographic Index (SDI) to describe differences in cancer burden attributable to risk factors across the spectrum of sociodemographic development.²⁸ SDI is a summary index calculated from the total fertility rate in

For the Global Cancer
Observatory see
<https://gco.iarc.fr/>

For the GBD Compare Tool see
<https://vizhub.healthdata.org/gbd-compare/>

For the GBD Results Tool see
<http://ghdx.healthdata.org/gbd-results-tool>

women younger than 25 years, lag-distributed income per capita, and mean education for individuals aged 15 years and older (appendix p 55). The index ranges from 0 (low SDI) to 100 (high SDI), with quintiles used to describe low, low-middle, middle, high-middle, and high SDI countries in 2019. Although both cancer deaths and DALYs attributable to risk factors are presented here, the majority of cancer DALYs globally are due to YLLs, reflective of cancer deaths with weighting for the age at death.¹ Thus, we do not present here estimates of risk-attributable YLLs and YLDs, but they are available in the online tools.

The GBD study is compliant with the Guidelines for Accurate and Transparent Health Estimates Reporting, and additional details from this Article and the appendix are available in the GBD 2019 summary papers.^{1,26–29}

Data sources for cancer burden estimates

Cancers included in the GBD study were those defined in chapter 2 (neoplasms) in the tenth revision of the International Classification of Diseases, with the exception of Kaposi sarcoma, for which most deaths are attributed to HIV/AIDS (appendix p 29).³⁰ Data sources used to inform the cancer estimates were obtained from vital registration systems, sample vital registration systems, verbal autopsy reports, and national and subnational population-based cancer registries. All data sources are provided with a unique identifier and compiled in the Global Health Data Exchange, which is publicly accessible.

Cancer burden estimation

Cancer registry, vital registration systems, and verbal autopsy data are used to inform cancer mortality modelling in the GBD study, as one of these data sources might exist in a location where others do not. In some locations, cancer mortality data are sparse, but cancer incidence is reported by national or subnational population-based cancer registries. To maximise data informing mortality models, cancer incidence data were transformed into cancer mortality estimates with modelled mortality-to-incidence ratios (MIRs). MIRs specific to cancer causes (cancer types) were modelled with a spatiotemporal Gaussian process regression (appendix pp 30–31).^{1,26} Mortality estimates from MIR-transformed incidence data were then pooled with mortality data from vital registration systems and verbal autopsies and used as inputs in cancer-specific Cause of Death Ensemble models.³¹ These models use all available data and location-level covariates to test individual and ensemble models, and produce estimates of death for every cause, sex, age group, location, and year estimated within GBD 2019, selecting models on the basis of out-of-sample predictive validity. Finally, the predicted mortality estimates were adjusted to align with independently modelled all-cause mortality estimates for each age, group, sex, location, and year.²⁸

Non-fatal cancer-specific computations began by generating incidence estimates from the modelled

cancer mortality estimates using the MIRs corresponding to each cancer cause, age group, sex, location, and year. Cancer 10-year prevalence was modelled with incidence, background mortality, and estimated relative survival curves and their correlation with modelled MIRs (appendix pp 49–53). Cancer-specific prevalence for each sequela, age, group, sex, location, and year combination is made up by four sequelae phases: (1) diagnosis and treatment, (2) remission, (3) metastatic and disseminated, and (4) terminal. To generate YLDs, each sequela prevalence was multiplied by its corresponding sequela-specific disability weight (appendix pp 53–54). Disability weights describe the severity of health loss associated with a sequela-specific condition and range from 0 (equivalent to full health) to 1 (equivalent to death).²⁸ YLLs were computed by multiplying the number of deaths in a specific age group for each cancer cause by the remaining standard life expectancy at the age of death.²⁷ Finally, DALYs were calculated as the sum of YLDs and YLLs.

Risk-factor-attributable cancer burden estimation

GBD 2019 includes risk factors that are broadly categorised into three groups: (1) environmental and occupational, (2) behavioural, and (3) metabolic. This study includes 82 cancer risk–outcome pairs (23 cancer types and 34 risk factors), with risk factors identified with the World Cancer Research Fund criteria³² (appendix pp 154–56). Risk–outcome pairs are organised into four mutually exclusive levels with increasing risk factor resolution (appendix pp 152–53). The general approach to risk factor estimation in the GBD study is described in this paper, and details on the modelling approach for each risk factor are available in the GBD 2019 risk factors summary paper²⁶ and the appendix (pp 72–145). For percentages of risk-attributable cancer deaths or DALYs reported, the total cancer burden (risk and non-risk cancer burden) included non-melanoma skin cancers.

The GBD comparative risk assessment framework was used to compute the fraction of cancer-specific burden attributable to each risk factor. The framework is divided into six main steps that are followed for each risk–outcome pair. First, the World Cancer Research Fund criteria were used to identify risk factors with convincing or probable evidence for a causal association.³² For GBD 2019, systematic reviews were updated to ensure appropriate inclusion of risk–outcome pairs.²⁶ Second, to estimate relative risks for each risk–outcome pair as a function of exposure, existing systematic reviews were updated and meta-analyses of relative risks were done. In GBD 2019, the meta-analytic approach was updated for a selected set of continuous risk factors with GBD's meta-regression-Bayesian, regularised, trimmed tool (appendix pp 58–59). Third, risk factor exposure levels and distributions were modelled for each age, sex, location, and year combination with data available from

See Online for appendix

For the Global Health Data Exchange see <http://ghdx.healthdata.org/gbd-2019>

published studies, household surveys, censuses, administrative data, ground monitor data, or remote sensing data. To model risk factor exposure level, the GBD uses either Bayesian meta-regression modelling (DisMod-MR 2.1), a flexible approach that can incorporate sex-specific and age-specific data, or spatiotemporal Gaussian process regression, the preferred approach when exposure is stable across age groups (appendix p 62). Fourth, for each risk factor, the theoretical minimum risk exposure level was identified, a counterfactual scenario in which a given population receives the optimal level of risk exposure (ie, no exposure for monotonically increasing risk functions such as smoking, the lowest point of the risk function of exposure for J-shaped or U-shaped risks such as high BMI, and the 85th percentile of exposure in cohorts and trials for protective risks such as fruit intake, weighted by the relative global magnitude of each outcome). Fifth, the population attributable fraction for each risk–outcome pair was calculated across age, sex, location, and year, taking into account the risk function (ie, relative risk), exposure level, and the theoretical minimum risk exposure level (appendix pp 62–64). Sixth, for some risk factors it was necessary to estimate the population attributable fraction in combination with other risk factors by considering mediation. For instance, calculating the population attributable fraction for fruit intake should account for the potential mediating effect of fibre intake. Thus, a mediation matrix was used to correct for population attributable fraction overestimation that would occur if independence of specific risk factors was assumed.²⁶ Last, to estimate the cancer burden attributable to each estimated risk factor, the YLLs, YLDs, and deaths for a given cancer type were multiplied by the corresponding risk factor population attributable fraction. The sum of YLLs and YLDs was used to estimate the cancer DALYs attributable to risk factors.

Estimating uncertainty

To account for uncertainty in the attributable burden estimates, a total of 1000 draws were estimated, from which the lower and upper bounds of the 95% uncertainty interval (UI) were obtained from the 25th and 975th ranked values. Error was propagated through each estimation step, including the estimation of cancer deaths and DALYs, exposure, relative risk functions, and for relevant risk factors the theoretical minimum risk exposure level.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In 2019, the total number of cancer deaths globally attributable to all estimated risk factors was 4.45 million

(95% UI 4.01–4.94) for both sexes combined, accounting for 44.4% (41.3–48.4) of all cancer deaths. There were 2.88 million (2.60–3.18) risk-attributable cancer deaths in males and 1.58 million (1.36–1.84) in females, representing 50.6% (47.8–54.1) of all cancer deaths in males and 36.3% (32.5–41.3) in females (appendix pp 191–99). The total number of cancer DALYs globally attributable to all estimated risk factors in 2019 was 105 million (95.0–116) for both sexes combined, which accounted for 42.0% (39.1–45.6) of all cancer DALYs. Males were estimated to have 67.5 million (60.8–75.1) cancer DALYs attributable to risk factors, or 48.0% (45.3–51.5) of all cancer DALYs in males, whereas females were estimated to have 37.6 million (32.8–43.1) cancer DALYs attributable to risk factors, or 34.3% (30.9–38.7) of all cancer DALYs in females.

The leading Level 2 risk factor (appendix pp 152–53) in males in terms of attributable cancer DALYs was tobacco (figure 1), which accounted for 33.9% (32.3–35.4) of all cancer DALYs in males in 2019 (appendix pp 191–93). Alcohol use, dietary risks, and air pollution were the next greatest risk factors, accounting for 7.4% (6.7–8.2), 5.9% (4.4–8.3), and 4.4% (3.4–5.5), respectively, of all male cancer DALYs in 2019. Tobacco was also the leading Level 2 risk factor for females globally in terms of attributable cancer DALYs (figure 1) and accounted for 10.7% (9.9–11.5) of all female cancer DALYs in 2019 (appendix pp 191–93). Unsafe sex was the second leading risk factor for females, accounting for 8.2% (7.0–8.8) of all female cancer DALYs in 2019, followed by dietary risks (5.1% [4.0–6.7]), high BMI (4.7% [2.8–7.0]), and high fasting plasma glucose (3.6% [1.0–7.5]). Ranking of Level 2 risk factors by attributable cancer deaths globally in 2019 showed similar ranking as by attributable cancer DALYs (appendix pp 181–87).

The leading cancer in terms of risk-attributable deaths globally in 2019 for both males and females was tracheal, bronchus, and lung cancer (36.9% [34.2–39.3] of all attributable cancer deaths), followed by colon and rectum cancer, oesophageal cancer, and stomach cancer in males, and cervical cancer, colon and rectum cancer, and breast cancer in females (figure 2, appendix p 210). Deaths caused by cancer and risk-attributable deaths caused by cancer tended to be greater in males than females for leading causes of cancer death globally, with the exception of cancer types that occur predominantly in women (eg, breast) or are exclusively estimated in women in the GBD study (eg, cervical, ovarian, and uterine cancers; figure 2; for male-to-female ratios for risk-attributable cancer deaths see appendix pp 206–07). When excluding the sex-specific cancers with risk-attributable burden (cervical, ovarian, uterine, and prostate cancers) the male-to-female ratios for risk-attributable cancer deaths tended to be smaller in high SDI countries than in non-high SDI countries (low, low-middle, middle, and high-middle SDI countries; appendix pp 213–14, 217–18). Cancer deaths and

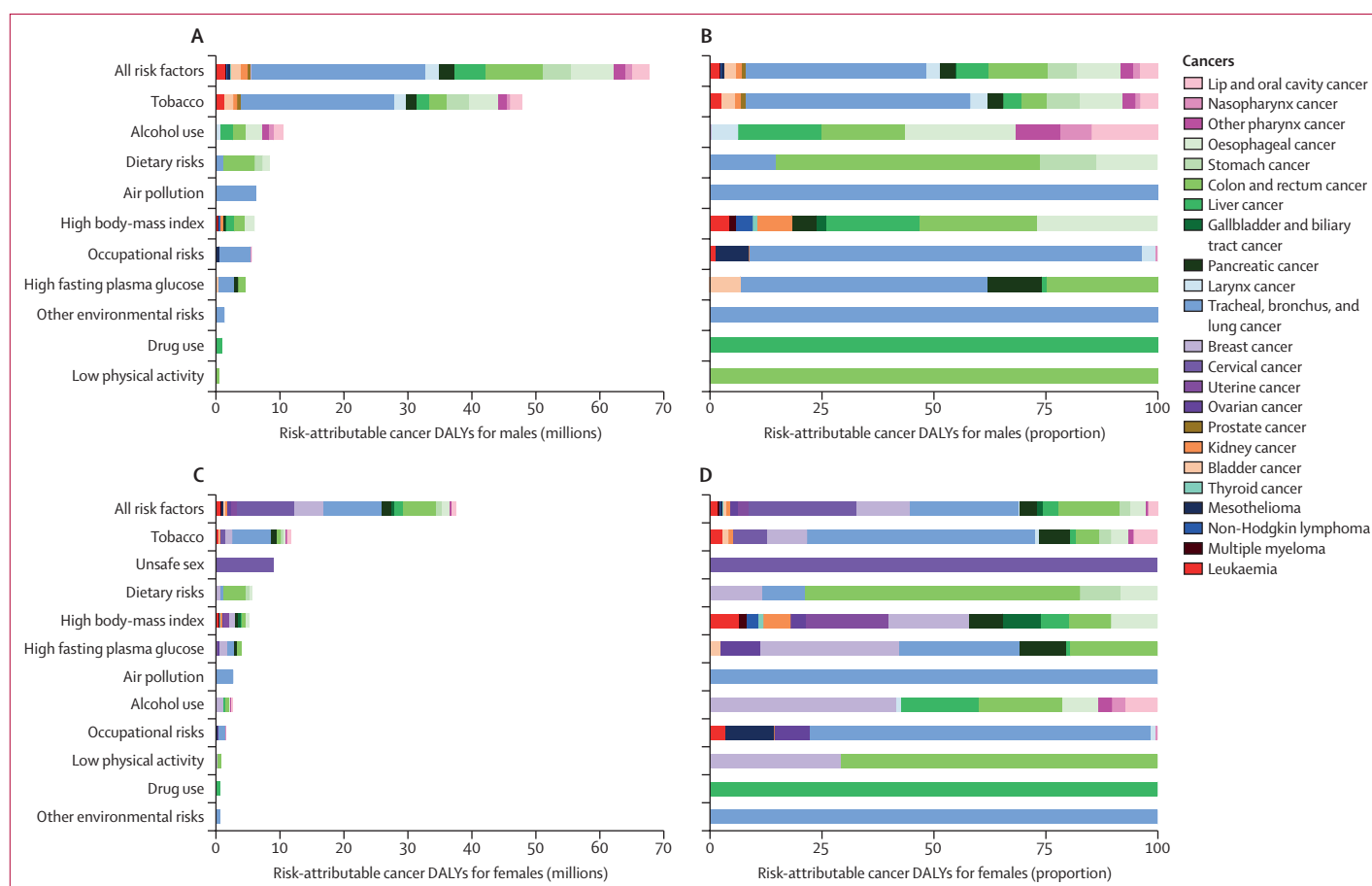


Figure 1: Cancer DALYs attributable to 11 Level 2 risk factors globally in 2019

(A) Absolute cancer DALYs for males. (B) Proportional cancer DALYs for males. (C) Absolute cancer DALYs for females. (D) Proportional cancer DALYs for females. Air pollution includes ambient particulate matter pollution and household air pollution from solid fuels. Other environmental risks include residential radon. Occupational risks include exposure to 13 specific carcinogens. Dietary risks include nine specific risk factors relevant to cancer. Tobacco includes smoking, chewing tobacco, and second-hand smoke. See appendix (pp 157–60) for details and definitions of each Level 2 risk factor on the y-axis. See appendix (p 161) for further details about global absolute and proportional cancer deaths attributable to Level 2 risk factors. DALYs=disability-adjusted life-years.

risk-attributable cancer deaths globally for both sexes combined in 2019 occurred over-proportionally frequently in high SDI countries, with 25·4% (24·0–26·7) of cancer deaths and 26·5% (24·9–28·1) of risk-attributable cancer deaths occurring in high SDI countries, even though these countries had only 13·1% (12·5–13·8) of the global population (appendix p 221). The leading cancers, sex analysis, and results by SDI remained largely the same when the cancers were ranked by risk-attributable DALYs instead of deaths (appendix p 162).

Geographical patterns for cancer age-standardised death and DALY rates attributable to environmental and occupational, behavioural, and metabolic risks in 2019 differed around the world (figure 3, appendix pp 165–66), with generally higher age-standardised DALY rates within these Level 1 risk factor categories (appendix pp 152–53) notable in high-income North America, and central, western, and eastern Europe, and variably elevated rates by risk category in east and southeast Asia, southern Latin America, and

southern Africa. Globally in 2019, the leading five regions in terms of risk-attributable cancer age-standardised death rates were central Europe (82·0 [71·0–94·9] per 100 000 person-years), east Asia (69·8 [58·0–83·0]), high-income North America (66·0 [60·5–72·1]), southern Latin America (64·2 [58·2–71·8]), and western Europe (63·8 [58·4–69·7]; appendix pp 174, 234–39). Details of risk-attributable cancer age-standardised death and DALY rates at the country level are available in the appendix (pp 234–239) and in the online GBD Compare and GBD Results Tools.

Figure 4 shows age-specific attributable cancer DALY rates in 2019 by SDI quintiles. For the same age group, cancer DALY rates attributable to behavioural risks were generally greater than those attributable to environmental and occupational risks and metabolic risks, and attributable cancer DALY rates were generally greater with increasing SDI quintile. Attributable cancer DALY rates increased with age for each Level 1 risk category, before peaking at ages 70–74 years or ages 75–79 years,

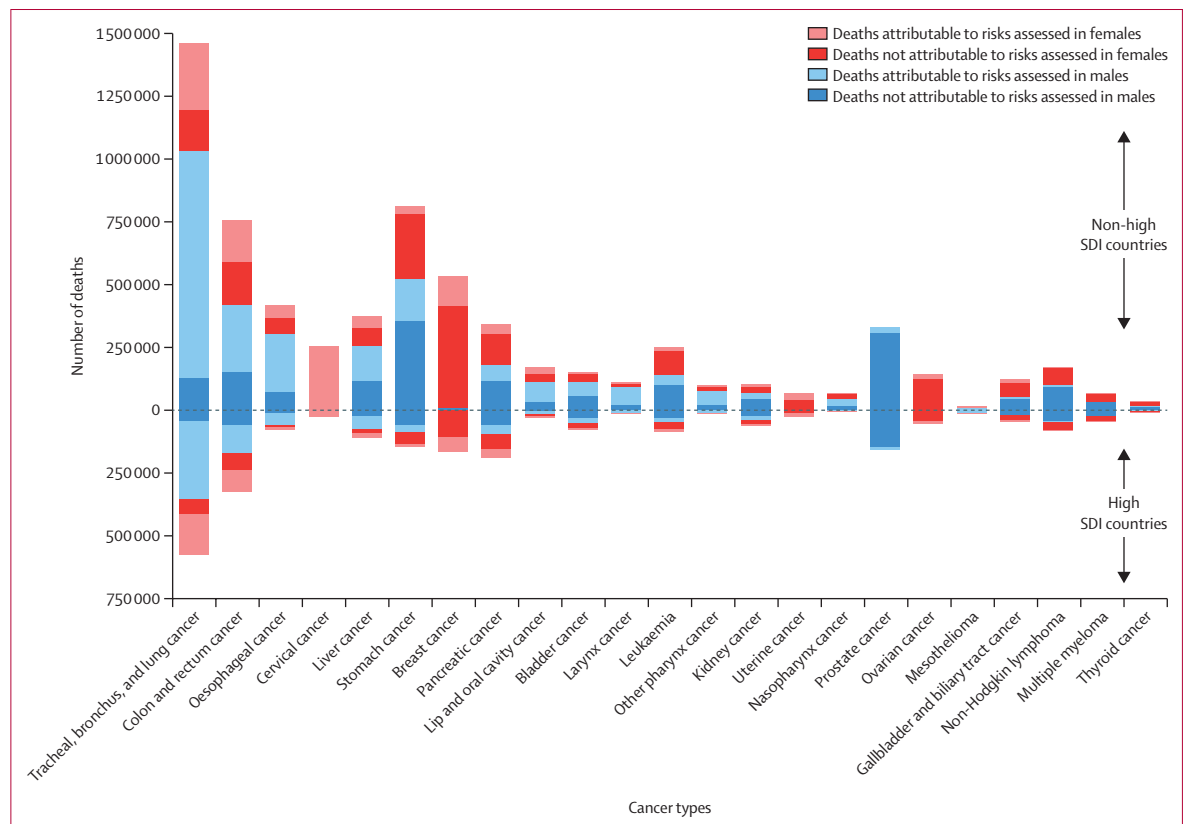


Figure 2: Global deaths from cancers attributable to risk factors in 2019 by sex and SDI

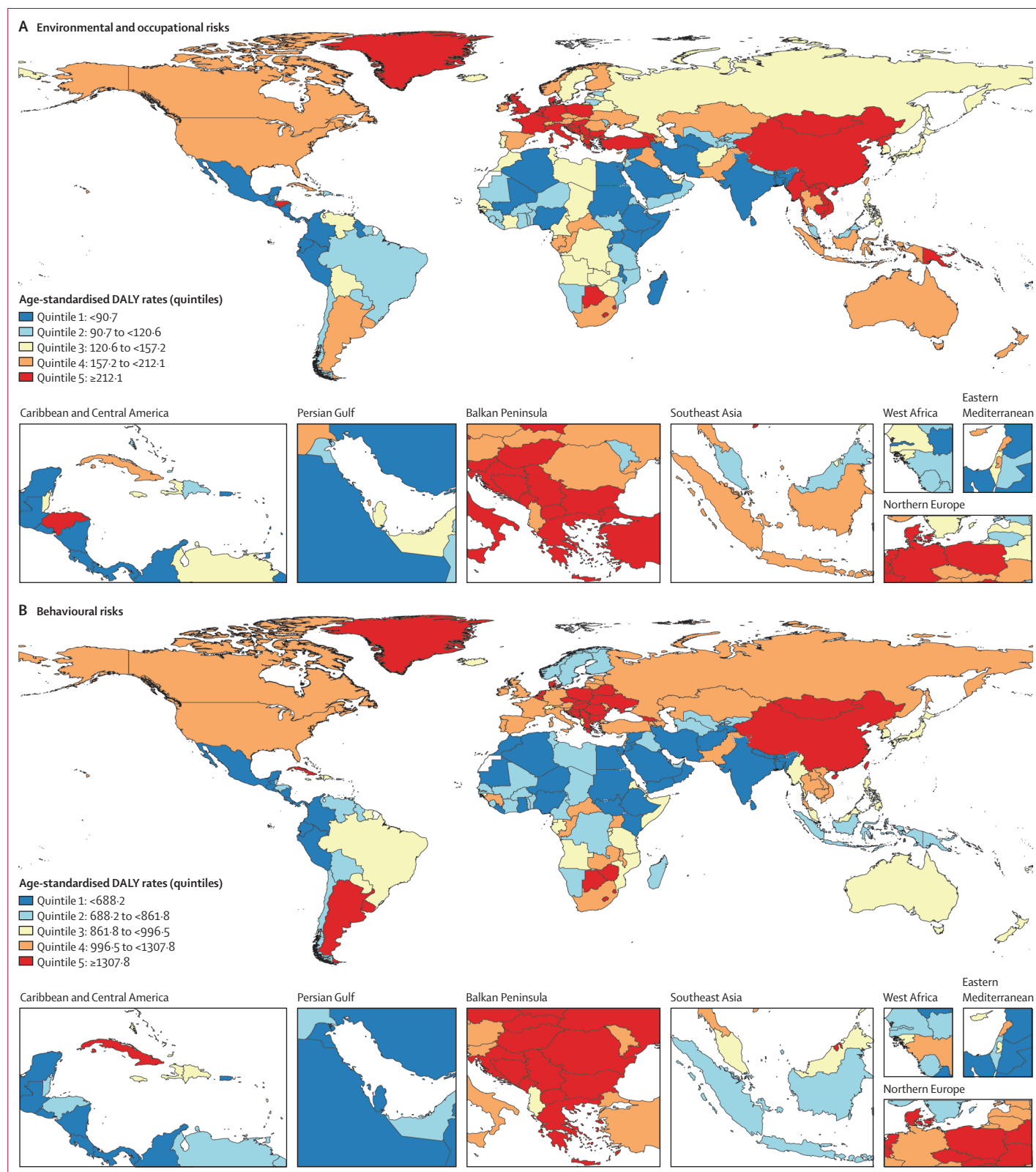
Non-high SDI countries include low, low-middle, middle, and high-middle SDI countries. Cancer types are listed from left to right in order of greatest to least risk-attributable deaths. See appendix (pp 213–14, 217–18) for estimates for risk-attributable cancer deaths in high and non-high SDI locations by sex. See appendix (p 162) for further details about DALYs from cancers attributable to risk factors in 2019 by sex and SDI. For additional versions of this figure showing age-standardised mortality and DALY rates see appendix (pp 163–64). DALYs=disability-adjusted life-years. SDI=Socio-demographic Index.

depending on the SDI quintile, with a later age peak generally on the higher end of the SDI spectrum.

For all risk factors estimated for both sexes combined between 2010 and 2019, global attributable cancer deaths increased by 20.4% (12.6–28.4) and DALYs by 16.8% (8.8–25.0), whereas the global age-standardised rates of attributable cancer deaths decreased by 6.9% (0.9–12.8) and cancer DALYs by 7.8% (1.4–14.0; appendix pp 240–42). The greatest percentage increase in attributable cancer deaths and DALYs among the Level 1 risk factor categories was in metabolic risks, which increased by 34.7% (27.9–42.8) and 33.3% (25.8–42.0), respectively, from 2010 to 2019, whereas behavioural risk-attributable cancer deaths and DALYs increased by 17.9% (10.4–26.0) and 14.4% (6.5–22.5), and environmental and occupational risk-attributable cancer deaths and DALYs increased by 16.7% (7.9–26.2) and 13.1% (3.9–23.1), respectively. Similarly, the greatest percentage increase in global risk-attributable cancer age-standardised death and DALY rates was in metabolic risk factors, which increased by 2.8% (–2.2 to 8.8) and 3.8% (–2.0 to 10.5), respectively, whereas behavioural risk factors decreased

by 8.7% (2.7–14.5) and 9.6% (3.2–15.8), respectively, and environmental and occupational risk factors declined by 10.0% (2.8–16.7) and 11.4% (3.5–18.5), respectively.

Furthermore, the magnitude of change in risk-attributable cancer DALYs and deaths and age-standardised DALY and mortality rates varied greatly among super-regions and SDI quintiles (figure 5, appendix pp 148, 172, 223–25). The greatest increases in age-standardised DALY rates due to metabolic risks were seen in south Asia, north Africa and the Middle East, and sub-Saharan African super-regions, and in the low-middle and low SDI quintiles, whereas the greatest decreases in behavioural and environmental and occupational risks were seen in central Europe, eastern Europe, and central Asia; high-income; Latin American and the Caribbean super-regions; and in the high and high-middle SDI quintiles (appendix p 224). Generally, the super-regions and SDI quintiles with the greatest increase in age-standardised cancer DALY burden attributable to metabolic risks between 2010 and 2019 were those with the least improvement in cancer burden attributable to behavioural risks and environmental and



(Figure 3 continues on next page)

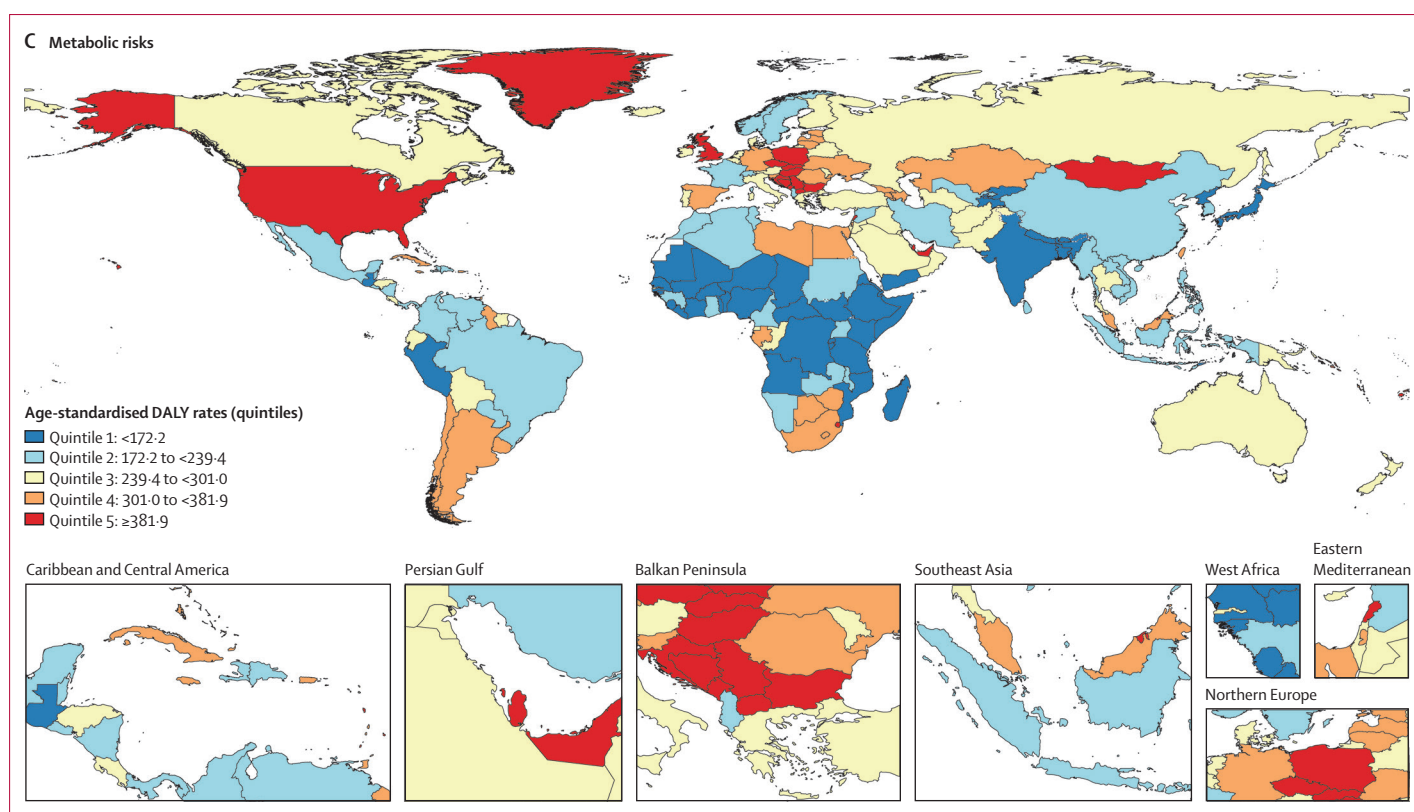


Figure 3: Global map of age-standardised DALY rate quintiles for risk-attributable cancer burden, both sexes combined, 2019

(A) Environmental and occupational risks. (B) Behavioural risks. (C) Metabolic risks. Each map represents estimates at the national level. Quintiles are based on age-standardised DALY rates per 100 000 person-years. See appendix (pp 165–68, 234–39) for further details of risk-attributable cancer deaths and DALYs for each country and territory. DALYs=disability-adjusted life-years.

occupational risks across the same time period (appendix p 224).

Finally, different patterns in the leading risk factors for attributable cancer age-standardised DALY rates were observed globally and across the SDI spectrum (figure 6, appendix pp 175–80). The leading nine risk factors at the most detailed level contributing to global cancer burden defined by age-standardised DALY rates did not change between 2010 and 2019, and the top three risk factors (smoking, alcohol use, and high BMI) were the same in the high SDI quintile as globally. Smoking and alcohol use remained the top two leading risk factors in the middle SDI quintile in 2010 and 2019, with unsafe sex decreasing from third to fifth position, high BMI rising from fourth to third position, and ambient particulate matter pollution rising from fifth to fourth position (appendix p 178). In the low SDI quintile, smoking remained the leading risk factor for risk-attributable cancer burden, with unsafe sex ranked second and alcohol use third in both 2010 and 2019. Within the top five leading risk factors in the low SDI quintile, high BMI and high fasting plasma glucose both increased (fifth to fourth, and sixth to fifth, respectively), and household air pollution from solid fuels decreased (fourth to sixth) between 2010 and 2019 (appendix pp 175–80).

Discussion

Our analysis found that 44.4% (95% UI 41.3–48.4) of global cancer deaths and 42.0% (39.1–45.6) of global cancer DALYs were attributable to estimated risk factors in 2019. These findings highlight that a substantial proportion of cancer burden globally has potential for prevention through interventions aimed at reducing exposure to known cancer risk factors but also that a large proportion of cancer burden might not be avoidable through control of the risk factors currently estimated. Thus, cancer risk reduction efforts must be coupled with comprehensive cancer control strategies that include efforts to support early diagnosis and effective treatment. Most attributable cancer DALYs were accounted for by behavioural risk factors, such as tobacco use, alcohol use, unsafe sex, and dietary risks, suggesting a need for concerted efforts to address behavioural risk factors to effectively reduce cancer burden globally. Attributable cancer DALYs from each Level 1 risk factor group generally increased with increasing SDI, and although there were similarities in the leading risk factors across the SDI spectrum for both sexes combined (ie, smoking and alcohol use), there were differences in risk factor patterns following these leading risks, highlighting the need for cancer risk reduction efforts to be context

specific. Between 2010 and 2019, age-standardised cancer DALYs attributable to all risk factors declined by 7·8% (1·4 to 14·0). Despite this decline, a global increase in age-standardised cancer DALYs (3·8% [−2·0 to 10·5]) attributable to metabolic risks was seen, largely driven by substantial increases in low and low-middle SDI countries. Furthermore, total risk-attributable cancer absolute DALY burden globally and in all SDI quintiles grew between 2010 and 2019, underscoring an expanding need for health systems around the world with capacity to comprehensively care for individuals with cancer, while developing and implementing cancer control efforts that consider risk reduction strategies. These estimates might help inform cancer control planning by identifying leading modifiable risk factors for cancer around the world, including for countries that might not have previous local research on cancer burden and cancer risk factor exposures.

To our knowledge, this study represents the largest effort to date to determine the global burden of cancer attributable to risk factors, and it contributes to a growing body of evidence aimed at estimating the risk-attributable burden for specific cancers nationally,^{9,13–20,33,34} internationally,³⁵ and globally.^{21–25} Our study builds on existing evidence by estimating both deaths and DALYs due to risk-attributable cancer burden, across a spectrum of cancer types and risk factors, for all countries, age groups, and sexes, over time. When comparing the results from this study with studies reporting national-level population attributable fraction estimates, GBD 2019 generally reported higher values for all risk factors combined. These comparisons are between cases and deaths for a subset of countries and differences might be due to a greater number of risk factors estimated and greater estimates for select risk factors, such as smoking, potentially due to differences in exposure definitions and risk–outcome pairs estimated.^{13–20} When compared with a previous effort to quantify the fatal burden of cancer attributable to risk factors globally, this study found a greater percentage of cancer deaths attributable to risk factors when estimating more risk factors (44·4% [95% UI 41·6–48·2] in 2001 in GBD 2019 compared with 35% in 2001 in the previous study), although both studies found leading contributions by smoking and alcohol use globally and unsafe sex in lower-income settings.²⁵ Comparisons to comprehensive global risk-attributable cancer burden in the Global Cancer Observatory are not possible, as incidence estimates are provided only for individual risk categories, but for alcohol consumption and elevated BMI, risk factors estimated by both studies, similar estimates of risk-attributable cancer burden were noted (4·1% of new cancer cases in 2020 attributable to alcohol consumption in the Global Cancer Observatory and 4·9% [4·4–5·5] of cancer deaths in 2019 attributable to alcohol use in the GBD study; 3·6% of new cancer cases in 2012 attributable to high BMI in the Global Cancer Observatory and 4·6% [2·7–7·1] of cancer deaths

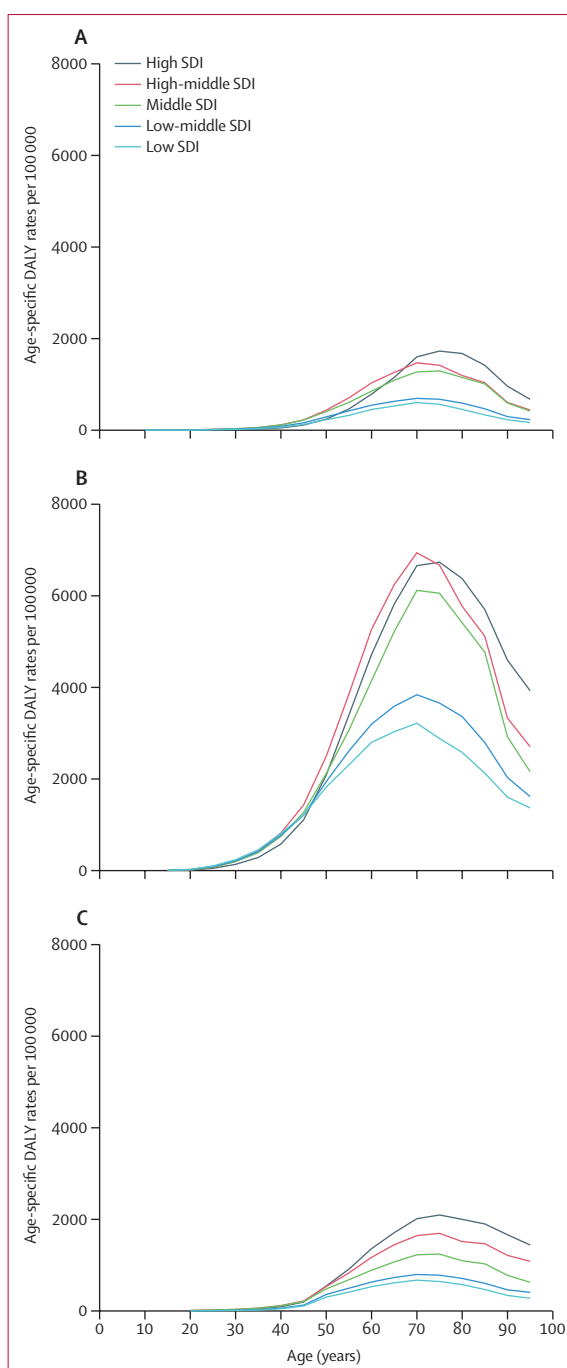


Figure 4: Estimates of age-specific rates of risk-attributable cancer DALYs, SDI quintiles, both sexes combined, 2019

(A) Environmental and occupational risks. (B) Behavioural risks. (C) Metabolic risks. Rates are expressed per 100 000 person-years. See appendix (pp 146–47) for details and definitions of the SDI regions. DALYs=disability-adjusted life-years. SDI=Socio-demographic Index.

in 2019 attributable to high BMI in the GBD study).^{21,22} For cancer risk factors not included in this study, estimates from the Global Cancer Observatory suggest that an additional approximately 8·9% of cancer cases would

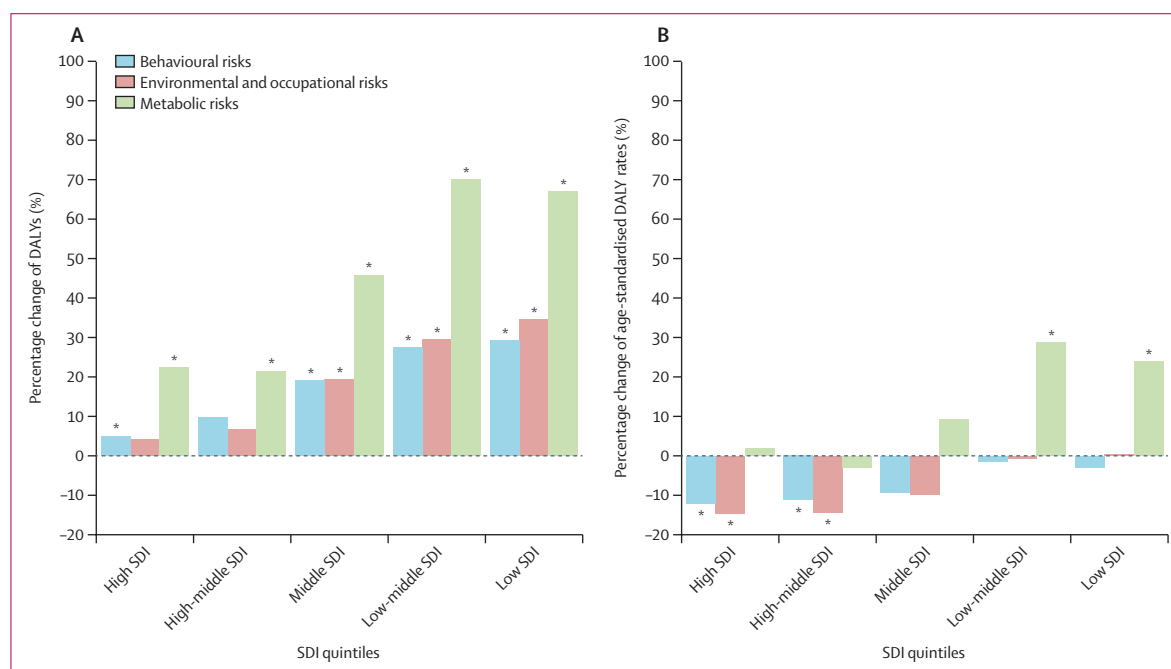


Figure 5: Percentage change of risk-attributable cancer DALY counts and age-standardised DALY rates for Level 1 risk factors by SDI quintile, both sexes combined, 2010–19

(A) Percentage change of risk-attributable cancer DALY counts by SDI quintile. (B) Percentage change of risk-attributable age-standardised cancer DALY rates by SDI quintile. See appendix (pp 146–47) for more information on SDI quintiles. See appendix (p172) for further information about the percentage change of risk-attributable cancer DALYs and age-standardised DALY rates for risk factors by GBD world super-region. See appendix (p 173) for percentage change of risk-attributable cancer deaths and age-standardised mortality rates by SDI quintile and GBD world super-region. DALYs=disability-adjusted life-years. GBD=Global Burden of Disease, Injuries, and Risk Factors Study. SDI=Socio-demographic Index. *95% uncertainty intervals that do not include zero.

be attributable to infections²³ (appendix p 67) and an additional 1.2% of cancer cases would be attributable to ultraviolet radiation.²⁴ These estimates should be interpreted with some caution given the different estimation approaches used, but might provide useful information for crucial remaining risk factors not yet included in the GBD study.

In GBD 2019, large all-age sex differences were seen in the global cancer burden attributable to all risk factors combined (48.0% [95% UI 45.3–51.5] of male cancer DALYs versus 34.3% [30.9–38.7] of female cancer DALYs). These sex differences are well documented, with several studies reporting higher attributable cancer burden in males compared with females.^{13,17–19} In this study, we identified sex differences across two primary risk factor groupings. For instance, there were disparities in cancer DALYs attributable to behavioural risk factors, such as smoking (33.2% [31.7–34.7] for males vs 8.9% [8.3–9.6] for females) and alcohol use (7.4% [6.7–8.2] for males vs 2.3% [2.0–2.6] for females), which might be driven by higher exposure to these behavioural risk factors among males than females. Similarly, for environmental and occupational risks, for example, the cancer DALYs attributable to occupational carcinogens were three times higher among males (3.9% [3.1–4.8]) than females (1.3% [1.0–1.6]), which might reflect that males are more likely than females to

be employed in workplaces with higher risk of exposure to carcinogens. Between 2010 and 2019, the change in global age-standardised risk-attributable cancer DALY rates decreased slightly among females (–4.6% [–11.0 to 2.2]), whereas there was a more notable decline among males (–9.6% [–17.6 to –1.3]). This result might suggest inequities in our approach to cancer prevention by sex and a need for future sex-specific assessments of effective cancer risk factor interventions.

Our results show a gradient across the socio-demographic spectrum in 2019, with the risk-attributable cancer age-standardised DALY rates generally increasing with higher SDI quintiles. However, from 2010 to 2019, age-standardised cancer DALY rates attributable to all risks combined declined in high, high-middle, and middle SDI countries, whereas these values increased in low-middle SDI countries or were approximately stable in low SDI countries. This increase was largely due to metabolic risks, which include risk factors such as high BMI. The growth in metabolic risk-attributable cancer burden might be the result of these countries experiencing an epidemiological transition in which improvements in country-level developmental status are related to increasing obesity levels.^{36,37}

Globally, there has been substantial progress in reducing exposure to tobacco that can be linked to coordinated international and national prevention

Leading risk 2010	Age-standardised rate of DALYs, 2010	Leading risk 2019	Age-standardised rate of DALYs, 2019	Percentage change in age-standardised rate of DALYs, 2010–19
1 Smoking	774.1 (729.9 to 818.1)	1 Smoking	677.3 (616.4 to 740.3)	–12.5 (–19.6 to –4.8)
2 Alcohol use	164.4 (148.3 to 182.3)	2 Alcohol use	155.2 (138.4 to 173.5)	–5.6 (–12.9 to 2.2)
3 High body-mass index	127.9 (71.4 to 200.3)	3 High body-mass index	133.9 (76.2 to 206.8)	4.8 (–1.8 to 12.9)
4 Unsafe sex	112.6 (99.2 to 125.4)	4 Unsafe sex	107.2 (90.5 to 119.4)	–4.8 (–12.7 to 3.7)
5 High fasting plasma glucose	101.3 (27.4 to 207.0)	5 High fasting plasma glucose	104.2 (28.7 to 212.9)	2.9 (–2.8 to 9.5)
6 Ambient particulate matter pollution	86.3 (63.0 to 109.0)	6 Ambient particulate matter pollution	84.2 (62.1 to 108.3)	–2.4 (–12.5 to 10.1)
7 Occupational exposure to asbestos	61.1 (45.0 to 77.6)	7 Occupational exposure to asbestos	50.9 (37.8 to 64.7)	–16.7 (–21.8 to –11.5)
8 Diet low in whole grains	48.1 (18.4 to 63.0)	8 Diet low in whole grains	46.3 (17.8 to 61.1)	–3.6 (–9.1 to 1.9)
9 Diet low in milk	45.3 (29.4 to 61.2)	9 Diet low in milk	46.1 (29.8 to 62.2)	1.7 (–4.8 to 8.9)
10 Diet low in fruits	43.6 (22.1 to 68.7)	10 Second-hand smoke	38.5 (24.8 to 55.5)	–5.2 (–13.7 to 4.0)
11 Second-hand smoke	40.7 (26.6 to 57.9)	12 Diet low in fruits	36.0 (18.5 to 56.2)	–17.5 (–26.5 to –8.1)

■ Behavioural risks
■ Environmental and occupational risks
■ Metabolic risks

Figure 6: Leading risk factors at the most detailed level for risk-attributable cancer age-standardised DALY rates globally, both sexes combined, 2010–19

Top ten risk factors for age-standardised rates of cancer DALYs and risk factors moving in or out of the top ten between 2010 and 2019 are displayed for the global level. Dashed lines indicate decrease in rank. Solid lines indicate increase or no change in rank. Data in parentheses are 95% uncertainty intervals. Risk factors at the most detailed level reflect the GBD hierarchy in which these categories of risks fall, ranging from Levels 2 to 4 (see appendix p 152 for more information on risk factor levels in the GBD hierarchy). See appendix (pp 175–80) for an expanded version of this figure, which contains the top ten risk factors for risk-attributable cancer age-standardised DALY rates in males, females, and both sexes combined globally and by SDI quintile. See appendix (pp 181–87) for further details about the top ten risk factors for risk-attributable cancer age-standardised death rates for males, females, and both sexes combined globally and by SDI quintile. DALYs=disability-adjusted life-years. GBD=Global Burden of Disease, Injuries, and Risk Factors Study. SDI=Socio-demographic Index.

efforts.^{38,39} Interventions through taxation and regulatory policies for tobacco smoking, including smoke-free policies, increased tobacco taxes, and advertisement bans guided by the WHO Framework Convention on Tobacco Control, have played a major role in these efforts.^{38,40} Similar efforts, including taxation and advertisement bans, have been recommended to help reduce the harmful use of alcohol.^{41–43} Behavioural risk factors are strongly influenced by the environment in which people live and individuals with cancer should not be blamed for their disease. Future research is needed to investigate the effect of population health approaches to cancer risk factor reduction that go beyond individual-oriented prevention and might be more effective long-term strategies than placing the onus on individuals to modify exposures to prevent cancer.⁴⁴ Many risk factors for cancer have been well established for decades, but greater political commitment to implementing policies addressing cancer prevention is needed. Improving social determinants of health, such as access to education and reduction of poverty, might be a feasible approach to reducing exposure to certain risks across populations.^{45,46} Population-based approaches aimed at improving social determinants of health might provide an equitable cancer control approach to overcome the systemic barriers promoting disproportionate risk-attributable cancer burden growth in some regions, countries, and subpopulations within countries. For these reasons, future research should not overlook the importance of context-specific interventions that are guided or led by those with an understanding of local cultural and behavioural patterns. Finally, cancers remain

fundamentally linked to genetics and ageing, and although addressing contributing risk factors is crucial for cancer prevention, this will never eliminate cancer burden. As a result, countries should continue to invest in comprehensive cancer control strategies beyond risk factor reduction, which include health-care systems capable of early diagnosis, detection through screening for select cancers, and effective treatment options for those diagnosed with cancer.

Although GBD 2019 is the largest effort to date to estimate the global burden of cancer attributable to risk factors, there remain opportunities for improvement. First, some limitations are inherent in the data sources available. For instance, some countries do not have population-based cancer registries, which are an important data source for estimating cancer burden. As is apparent in the relative uncertainty of risk-attributable cancer burden estimated by GBD 2019 (appendix p 171), there is greater uncertainty relative to point estimates in many lower SDI countries as compared with higher SDI countries. GBD study models rely on available data, and estimates should not supplant but rather complement the ongoing crucial work to expand and improve directly observed data around the world. Cancer registry development and support are integral in cancer control efforts and should be considered in broader cancer control planning initiatives. Delays are inherent with the release of cancer registry and vital statistics reports, which result in more recent cancer mortality estimates often relying on historical data. The data used to estimate risk factor exposure is at times sparse and many data sources do not provide sufficient information to assess for potential measurement error or

bias. Where there is information available, the GBD study aims to correct for systematic bias in risk exposure data by establishing a reference definition of each risk exposure and adjusting acceptable alternative exposure measurements on the basis of studies with observed data pairs of the two different definitions. However, after these adjustments, residual measurement bias is likely to persist and might vary around the world, over time, and by risk factor. Formal assessments of exposure model performance would be beneficial in future GBD iterations. Second, the risk factors included in this study are based on current knowledge of risk factors for cancer, but as knowledge expands there might be additional risk factors important to incorporate in future iterations of the GBD study. In addition, there are known risk factors for cancer, such as sunlight exposure (ie, ultraviolet radiation), and infectious agents, such as *Helicobacter pylori*, which are not included in the GBD study.^{47,48} Unsafe sex is estimated as a risk factor, but human papillomavirus, a known risk factor for several cancer types, is not explicitly estimated; and although liver cancer burden due to hepatitis B and C is estimated within the GBD cause hierarchy, these viral infections are not estimated as risk factors, making their inclusion in robust risk-attributable cancer burden estimation challenging. Infection-associated cancers are more notable in lower SDI settings, so addressing these will be important to producing comprehensive global assessments of cancer-attributable risk and disparities. Third, second-order measures of cancer-relevant risk factors, including aspects such as income inequality and racism, would be challenging to comprehensively account for, but could add important context for future health policy work. Finally, GBD 2019 results were estimated before the COVID-19 pandemic. Evaluating the effect of the COVID-19 pandemic on risk-attributable cancer burden is an important area for future research. However, several leading risk factors identified in this study are also linked to an increase in the severity of illness in individuals with COVID-19 and to burden of other non-communicable diseases besides cancer. Thus, reducing exposure to these harmful risk factors might not only have a positive effect on cancer burden reduction efforts, but synergistically improve population health more broadly.

Worldwide, a large percentage of cancer deaths and DALYs were attributable to risk factors in 2019, with most being attributable to behavioural risks. Smoking continues to be the leading cancer risk factor globally, with other substantial contributors to cancer burden varying around the world. Targeting leading location-specific cancer risk factors might help countries make progress towards reducing non-communicable disease premature mortality by a third by 2030, as highlighted in SDG target 3.4. Although progress has been seen in high and high-middle SDI countries for behavioural and environmental and occupational risk-attributable cancer age-standardised DALY rates between 2010 and 2019, in low and low-middle SDI countries, metabolic

risk-attributable cancer burden has grown considerably. Considerable cancer burden is not avoidable through the currently estimated risk factors, and, as such, countries should continue to simultaneously invest in risk reduction strategies while strengthening health systems to support early diagnosis and effective treatment of those with cancer. Given the increasing burden of cancer worldwide, this study can help policy makers and researchers identify important modifiable risk factors that could be targeted in efforts to reduce cancer burden globally, regionally, and nationally.

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See appendix (pp 260–69) for detailed information about individual author contributions to the research, divided into the following categories: managing the overall research enterprise; writing the first draft of the manuscript; primary responsibility for applying analytical methods to produce estimates; primary responsibility for seeking, cataloguing, extracting, or cleaning data; designing or coding figures and tables; providing data or critical feedback on data sources; developing methods or computational machinery; providing critical feedback on methods or results; drafting the manuscript or revising it critically for important intellectual content; and managing the estimation or publications process. Members of the core research team for this topic area had full access to the underlying data used to generate estimates presented in this Article. All other authors had access to and reviewed estimates as part of the research evaluation process, which includes additional stages of formal review. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing

This paper summarises key findings from our analysis of GBD 2019 estimates. Citations for the data used in this study can be accessed from the Global Health Data Exchange data input sources tool (<http://ghdx.healthdata.org/gbd-2019/data-input-sources>). Files containing all GBD 2019 estimates are available on the Global Health Data Exchange website (<http://ghdx.healthdata.org/gbd-2019>) and can also be downloaded from the Global Health Data Exchange results tool (<http://healthdata.org/gbd-results-tool>). Additional results can be explored through online interactive visualisations (<https://vizhub.healthdata.org/gbd-compare/>).

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