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A global analysis of the current and future lung cancer mortality in the wake of the changing smoking epidemic. A descriptive case report study.

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Abstract

Objectives

Lung is a highly frequent localization of neoplasms and it ranks as leading cause of cancer death. The purpose of this paper is to present a global overview of the descriptive epidemiology of lung cancer, based on the GLOBOCAN estimates for the year 2020 from the International Agency for Research on Cancer and relate this to current tobacco control policies.

Methods

Age-standardized mortality rates per 100,000 person-years of lung cancer for 185 countries were obtained from GLOBOCAN 2020 database and analysed by sex and levels of HDI. Lung cancer deaths were projected to 2040 based on demographic changes alongside scenarios of increasing, stable or decreasing rates, annually from the baseline year of 2020.

Results

Lung cancer rates exhibited marked variations by geography and sex. Low HDI countries, many of them within sub-Saharan Africa, tend to have low levels of mortality and only an upward trend in the number of lung cancer deaths is predicted for both sexes until 2040 according to all demographic projections. Different picture is true for the very high HDI countries, such as the majority of Europe, entire Northern America and Australia: a clearly improving trends for men and deteriorating for women.

Conclusion

The current and future burden of lung cancer in a country or region largely depends on where its population is placed on the trajectory of the global smoking epidemic. The distinct gender characteristics in smoking are very important, both in transitioning and developed countries. The diminishing sex differences in the smoking related mortality highlight and project the likelihood of increasing inequities in health among women. Further elevations in lung cancer mortality are expected worldwide, raising important social and political questions, especially in low- and middle-income countries.

Keywords: lung cancer, mortality, projection

Word count: 2,766

Strengths and limitations of this study

Strengths

This study:

- presents a detailed picture and figures of current LC burden worldwide by sex and HDI.

- applies a simple and straightforward projection model for the near future along the dimensions above.

- considers broadly the essential literature on the risk factors for lung cancer especially on the smoking epidemic, in order to provide a comprehensive understanding of the phenomenon discussed.

Limitations

This study:

- struggles with large variability in the availability and quality of cancer causes of death data. E.g. in countries where mortality series were not available from national vital registration sources systematic estimates were necessary to calculate.

Introduction

Lung cancer (LC) ranks as the most frequent form of cancer death and premature cancer death (ages 30-69) with still uniformly low 5-year survival even in high-income countries[1]. With one-fifth of the cancer mortality worldwide in 2020 due to LC – an estimated 1.8 million deaths[2] – the single most determining risk factor remains to be tobacco consumption. Up to 9 out of 10 LC cases are caused by smoking in high-income settings, while mortality increases with number of cigarettes smoked and smoking duration[3]. Lopez at al. drew attention to the phases of the global smoking epidemic and the subsequent impact of smoking on LC occurrence by sex[4]; men and women remain in very different phases of the smoking epidemic, as reflected in disease rates by birth cohort. Recent reports have generally described marked variations in rates between sexes, with stable or decreasing rates found predominantly among male while increasing rates among female populations[5,6]. An emerging pattern is a higher rate among young females than males across geographic areas and income levels, that is not fully explained by sex-specific differences in smoking prevalence[7]. Such temporal patterns forewarn of a higher LC burden in women than men at older ages in the decades to follow, especially in higher-income settings. However, low- and middle-income countries exhibit contrasting image: numerically most women are exposed to smoking in developing countries and social constrains that previously prevented them from tobacco consumption are weakening[8], but they not necessarily taking up the habit like men e.g. in China.[9]

The purpose of this paper is to present a global overview on the descriptive epidemiology of LC in the context of tobacco control, based on the recent GLOBOCAN mortality estimates for the year 2020 from the International Agency for Research on Cancer (IARC). In addition, we provide projections of the future mortality burden according to different temporal scenarios to the year 2040, estimating the expected future LC deaths according to levels of Human Development Index (HDI).

Data Sources and Methods

The number of deaths from, cancers of the lung (ICD-10 C33-34, including trachea and bronchus) were extracted from IARC's GLOBOCAN 2020 database for 185 countries or territories, by sex and 18 age groups (0-4, 5-9, ..., 80-84, 85 and over)[2,10,11]. Corresponding population data for 2020 were extracted from the United Nations (UN) website[12]. The data sources and hierarchy of methods used in compiling the cancer estimates have been described in detail elsewhere[10]. In brief, the GLOBOCAN estimates are assembled at the national level using the best available sources of cancer incidence and mortality data within a given country. The methods used to derive the 2020 estimates corresponding to those used to derived for previous years[13–15] where applicable, priority is given to short-term predictions and modelled mortality to incidence (M:I) ratios, while validity is dependent on the degree of representativeness and quality of the source information[10].

We present figures based on the estimated deaths in 2020, as well as two summary measures using direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years based on the 1966 Segi-Doll World standard population[16,17] and the cumulative risk of dying from cancer before the age of 75 expressed as a percentage, assuming the absence of competing causes of death[18]. These measures allow comparisons between populations adjusted for differences in age structures. We also provide a prediction of the future number of LC deaths worldwide for the year 2040, based on demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%) or decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of COVID-19 pandemic was not taken into consideration during the calculations.

The results are presented by country, and aggregated, across 20 UN-defined world regions[12], and according to the UN's four-tier HDI in 2020[19] as a means to assess the cancer burden across four levels of development (low, medium, high and very high HDI). Throughout we use the terms transitioning, emerging and lower HDI countries/economies as synonyms for nations classified as low or medium HDI, and transitioning or higher HDI countries/economies for those classified as high or very high HDI.

The Global Cancer Observatory (GCO, https://gco.iarc.fr) includes facilities for the tabulation and graphical visualization of the GLOBOCAN database, including explorations of the current[2] and future[20] burden for 36 cancer types.

Patient and Public Involvement: Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

Results

Lung cancer mortality – national rankings 2020

Figure 1 presents global maps that indicate LC's position in terms of deaths relative to other common tumors at the national level by sex for the year 2020. In men, LC ranks first in half of the countries included in the GLOBOCAN estimates (93 of 185 countries) and it ranks 2nd or 3rd in 37 countries. LC is a major contributor to cancer mortality around the world, including America, Greater-Europe, Northern Africa, and across the Asia-Pacific region. Only the regions of Central America and Sub-Saharan Africa (but not South Africa) indicating a somewhat less dominant role of the disease, at present. In women, the impact is lesser but still very much in evidence; the disease ranks as the leading form of cancer death in 25 countries including those within North America, Northern, Western and Southern-Central Europe, Eastern Asia and Australia/New Zealand. It ranks as the 2nd or 3rd leading from of cancer mortality in 54 countries worldwide.

According to Figure 2 there is at least a 20-fold variation between the rates in both sexes, with rates uniformly higher among men. Male mortality is higher in Eastern and Southern Europe (especially in Hungary and Serbia with nearly 60 deaths per 100,000), Eastern Asia (particularly in the Democratic

People's Republic of Korea) and Polynesia and Micronesia, while it is lower in Central America, South-Central Asia and most parts of sub-Saharan Africa. The highest female rates are seen in Northern America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia and across the African continent, except for Southern Africa.

Lung cancer mortality burden by 2040

Figure 3 demonstrates that if the trends do not change in the next two decades, LC will claim around 2 million male deaths in 2040, compared to 1.2 million in 2020. For women, the corresponding predicted and registered numbers are approximately half: 1 million and 600 000 deaths, respectively. The projection also shows the different scenarios considering the changing rates per year between -3% and +3%. Keeping in mind the axioms of the theory of global smoking epidemic[4], global declines in the number of LC among males but increases for female are more realistic scenarios in the future, with exceptions. Taking this into account, by 2040, the predicted number of deaths due to LC for men will likely range between 1.1 and 1.6 million and for women between 1.2 and 1.8 million. Appendix Figure 1a-d also reports the projections by HDI levels, which show, that in the lowest category of HDI countries, deaths will markedly increase for both sexes even in the best-case LC mortality scenario.

Discussion

This research highlights the inverse status of low and high HDI countries, in case of the current geographic variability of LC burden and the very different scenarios of changing mortality trends also by sex. Countries with low HDI, can be characterized with low levels of mortality, in mostly sub-Saharan African states and these will probably suffer a higher burden of LC for both sexes until 2040. For higher HDI countries, the burden of the disease is higher for men, but future trends appear be more favourable than for females, where increasing LC mortality is more likely till 2040.

The past smoking histories of nations are a key determinant of the current magnitude of LC in many populations worldwide, as described by the classical model of the global smoking epidemic, first introduced by Lopez et al[4]. In the model, the effect of different smoking patterns was captured by four stages in the population, by an earlier adoption of the habit in men compared with women, and by the progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying cause of the marked inequalities seen in different educational groups[21]. Lopez et al. initially applied their theory on only just a few developed countries[22], but later was tested on greater geographic scales[23,24]. Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline among men in many populations over the last decades, a key focus has been the deteriorating public health situation affecting women, where in many settings, rates of LC mortality continue to rise. This raises several relevant biological, epidemiological and sociological concerns[25], including: the change on the main histological types of LC over time[26], the extent to which females adopted the habit of smoking and their vulnerability to the tobacco industry[27,28], the impact of such a transition in diminishing gender differences in disease burden worldwide[29] and the effects of different political ruling systems on the health awareness of individuals[30,31], which are well reflected e.g. in the current Eastern European vs. Northern European male lung cancer mortality figures. However, this paper clearly proves that for most of the low HDI countries this comprehensive macro theory is not applicable, whereas LC deaths from a relatively low level are expected to simultaneously rise for both sexes.

Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with other factors, e.g., air pollution, climate change[32] and other occupational risk factors such as asbestosis and indoor exposure to cooking fumes etc[33]. The highest exposure to ambient air pollution is the characteristic of mainly Low and Low Middle-Income Countries (LMICs), where only modest reductions in burden will occur in the most polluted countries unless fine particulate matter (PM 2.5) values are decreased substantially[34].

There are several limitations to this study e.g., the large variability in the availability and quality of cancer mortality data. Many African and some Asian countries suffer from weak mortality statistics systems. In GLOBOCAN, in countries where mortality series were not available from national vital registration sources, the predominant means of the estimation of rates were from corresponding national incidence estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in neighbouring countries.

With over 3 million deaths predicted by 2040 in the absence of additional interventions according to the finding of this study, it is imperative to emphasize primary prevention as the most cost-effective strategy of tobacco control. It has been shown that raising the price of cigarettes through increased excise taxes can bring marked reductions in cigarette consumption[35]. Besides this, developing adaptive tobacco control strategies that target different subgroups is imperative; anti-tobacco strategies urgently should, target women living in the EU, in order to halt their rapidly increasing risk of LC, and prevent unnecessary, premature deaths among future generations of women[36]. Amos and Haglund (2000) emphasize that building support for female-centered tobacco control programs through partnerships will be vital to achieve success[28]. Furthermore, Amos (1996) and Mackay and Amos (2003) draw the attention to the problematic situation of women in developing countries, even in which have low levels of female cigarette smoking[27]. In these, smoking among girls is already on the rise, women's spending power is increasing, cigarettes are becoming affordable, they are more exposed to the marketing strategies of the tobacco companies, cultural constraints are weakening and female-specific quitting programs are rare[8]. Additionally, a package of measures to suppress tobacco consumption in a given population, has been recommended through continued efforts to increase the proportion of ex-smokers, as well as a concentrated focus on younger generations[37]. This could perhaps be achieved by implementing coordinated smoking prevention and control strategies from an early age, in the form of educational programs in schools. Other measures that could be introduced include community intervention programs, mass media campaigns and further legislation to ban smoking in public places. One of the main problems is that young people react very differently to anti-smoking messages than do adult long-term smokers[37].

In a trial involving high-risk persons, LC mortality was significantly lower among those who underwent volume computed tomography (CT) screening than among those who underwent no screening[38]. Another clear advantage was the substantial shift to lower-stage cancers at the time of diagnosis as well as to more frequent eligibility for curative treatment (mainly surgical)[39], however concerns have been raised about the potential for overdiagnosis in lung-cancer screening.

In summary, this paper has identified marked geographic variability in the current LC burden across the world and provided potential scenarios in the changing number of deaths due to this disease until 2040. There is much we can do to halt the rising LC deaths. Gredner et al., provided, for example an assessment of future tobacco policy impact based on the relation of current implementation and tobacco smoking prevalence in countries to illustrate the great potential of comprehensive implementation of tobacco control policies in Greater-Europe. According to their estimations 1.65 million LC cases could be prevented over a 20-year period with the highest-level implementation of tobacco control policies[40].

Role of the founding source

This work was supported by the National Laboratories Excellence program (under the National Tumorbiology Laboratory project (NLP-17)) and the Hungarian Thematic Excellence Programme (TKP2021-EGA-44).

Authors' contribution

AW: literature search, data analysis, writing – original draft; JV: methodology, data collection, figures, visualisation; ML: visualisation; EM: writing – review & editing; MP: writing – review & editing; HR: writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology, conceptualisation, data analysis, writing – original draft

Declaration of interests

All authors declare that they have no conflicts of interest.

Data sharing

The data that support the findings of this study are openly available in the Global Cancer Observatory (GLOBOCAN) at https://gco.iarc.fr/

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics Approval Statement

This study does not involve human participants and animal subjects.

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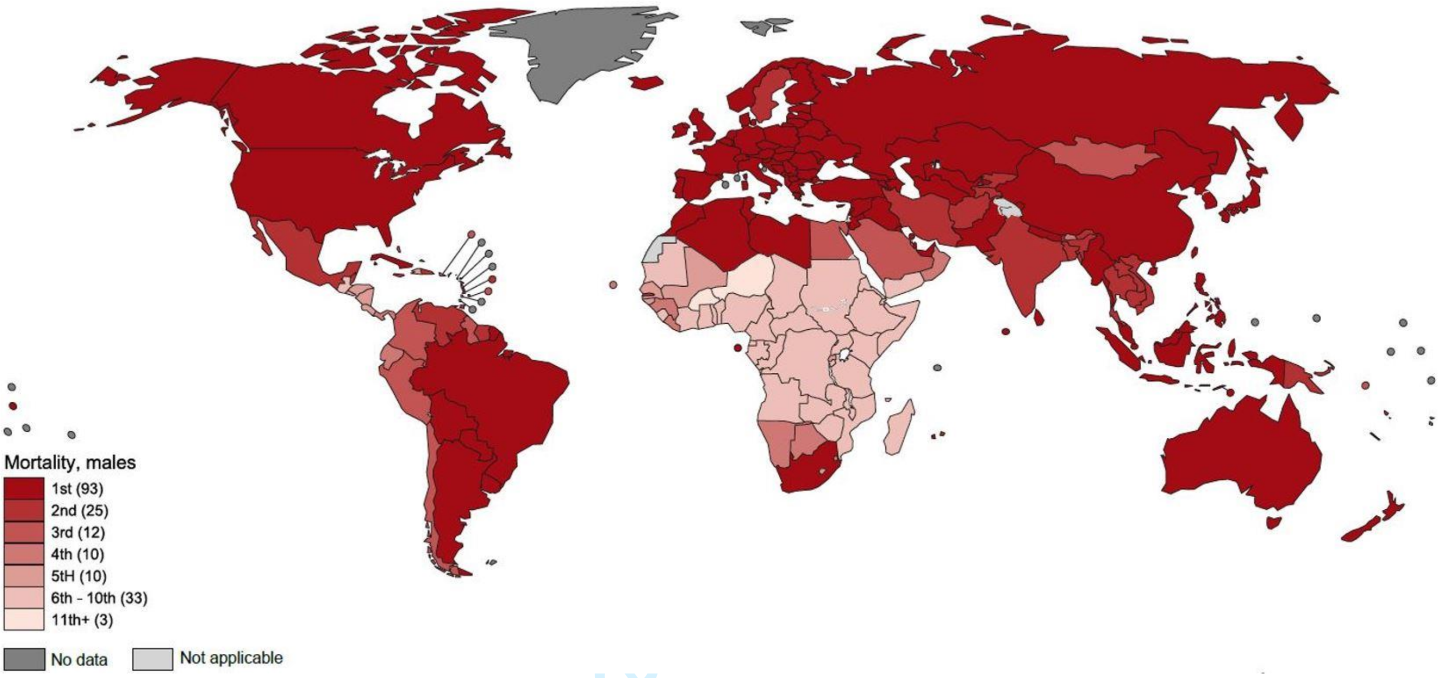
Figure 1: Lung cancer mortality country rankings worldwide in 2020

Male



Female

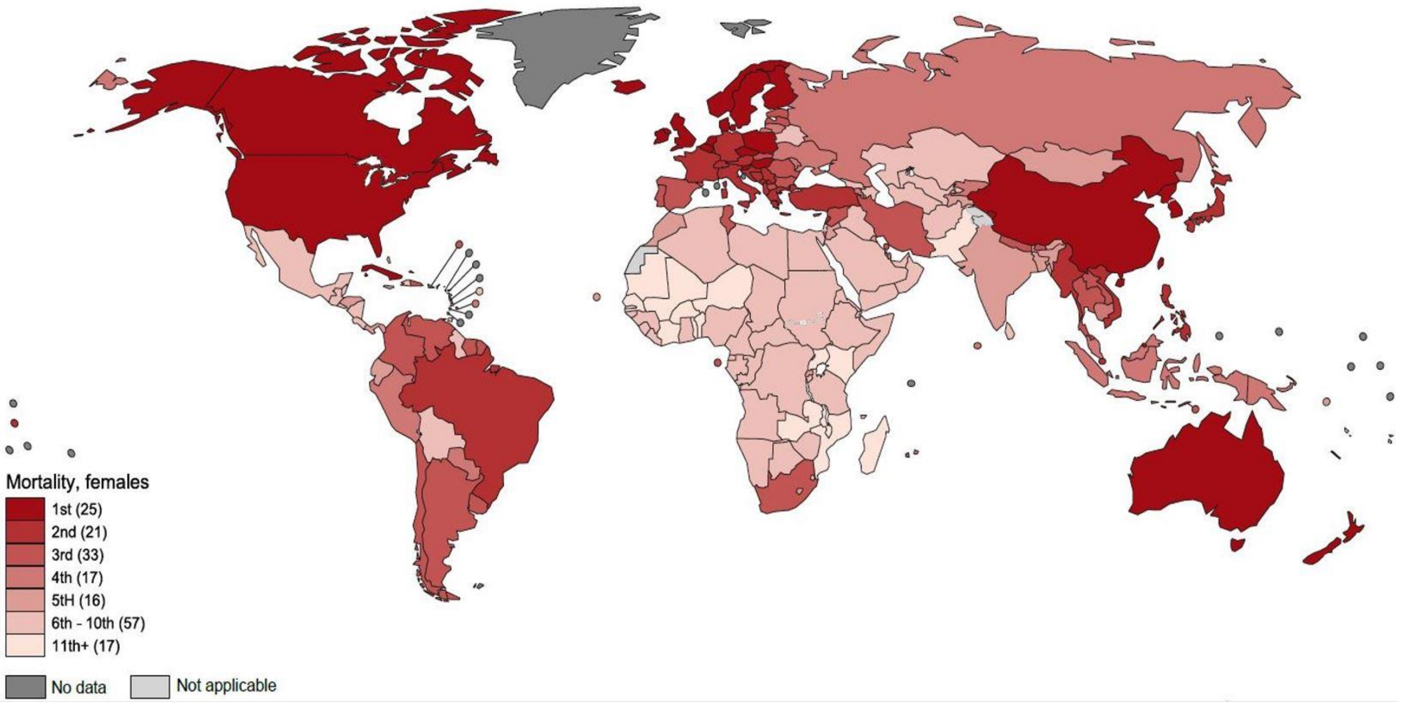


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020

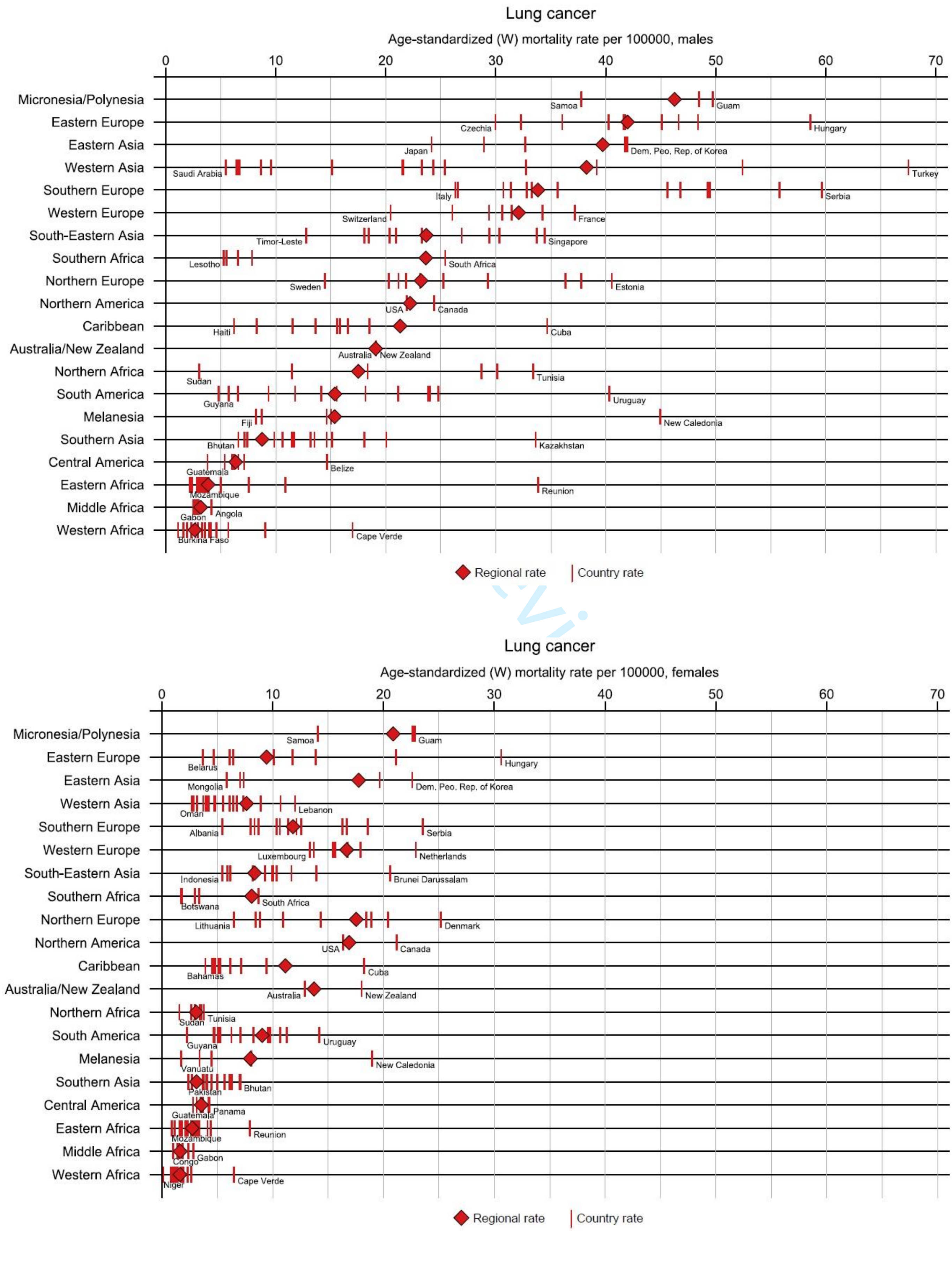
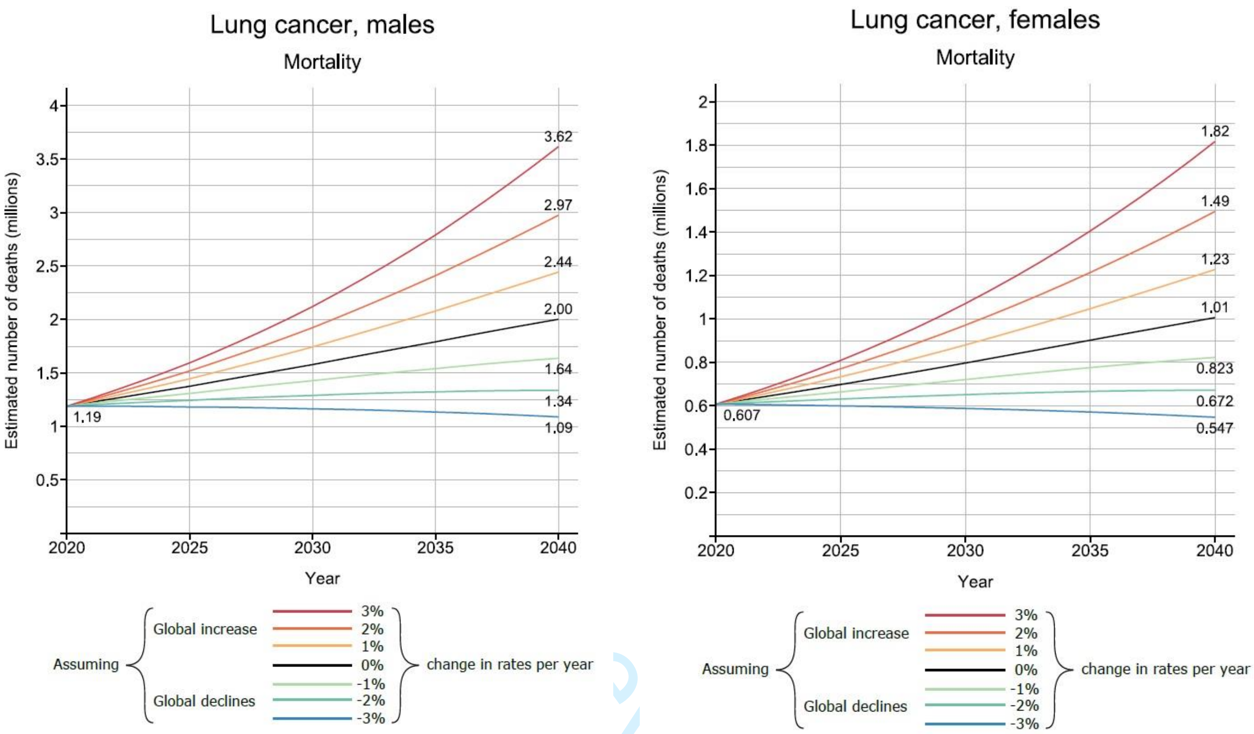


Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A **B**



Supplemental material - Appendix

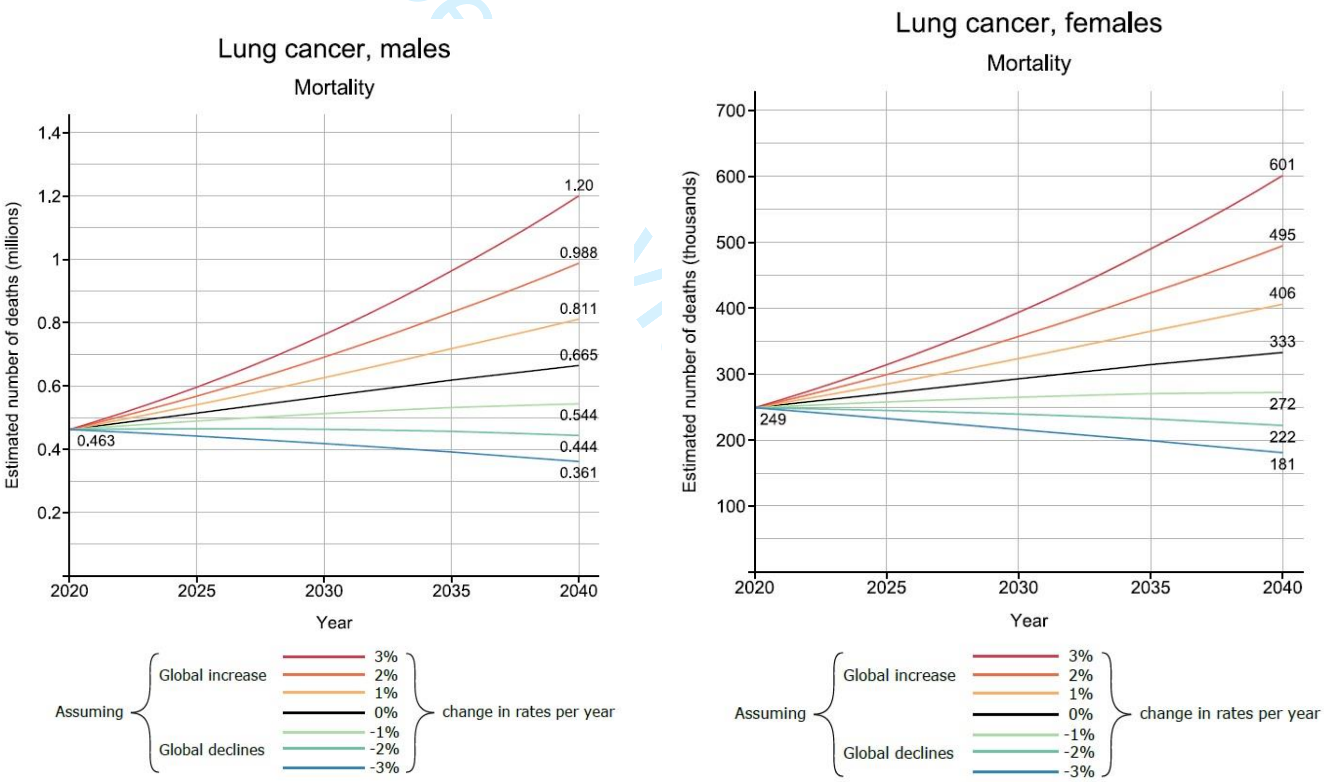
Figure 1: Lung cancer mortality country rankings worldwide in 2020, Male - Female

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. Data source: Globocan 2020, Map production: CSU, World Health Organization

Appendices

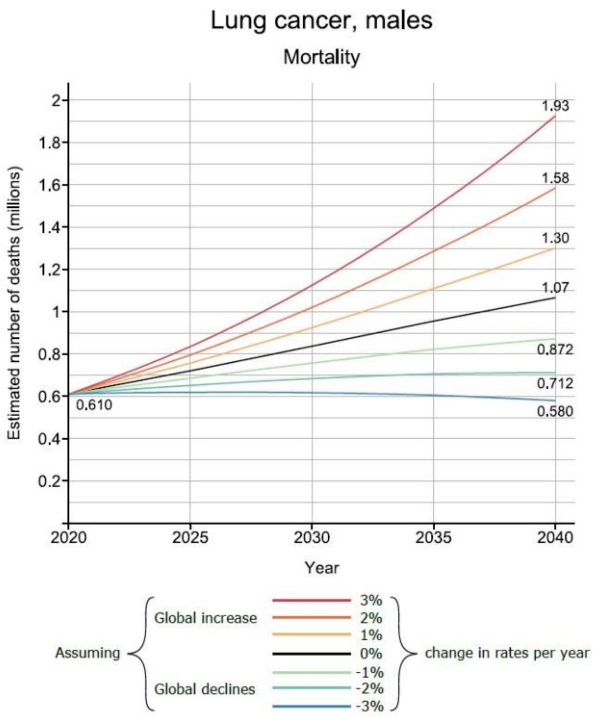
Lung cancer mortality by sex - very high HDI countries

A **B**



Lung cancer mortality by sex - high HDI countries

C



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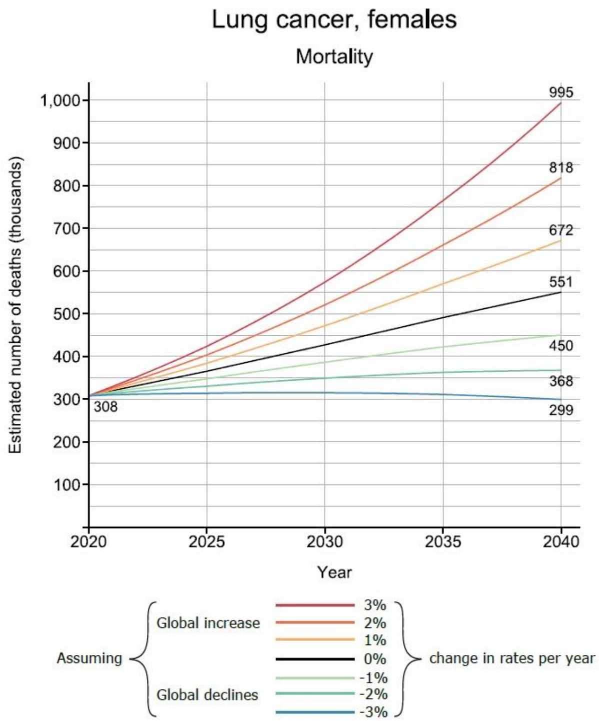
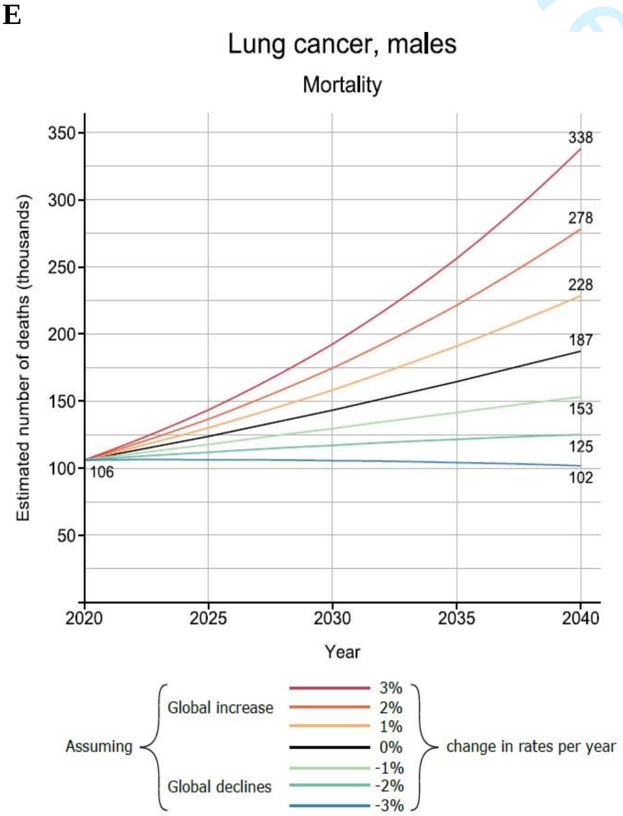
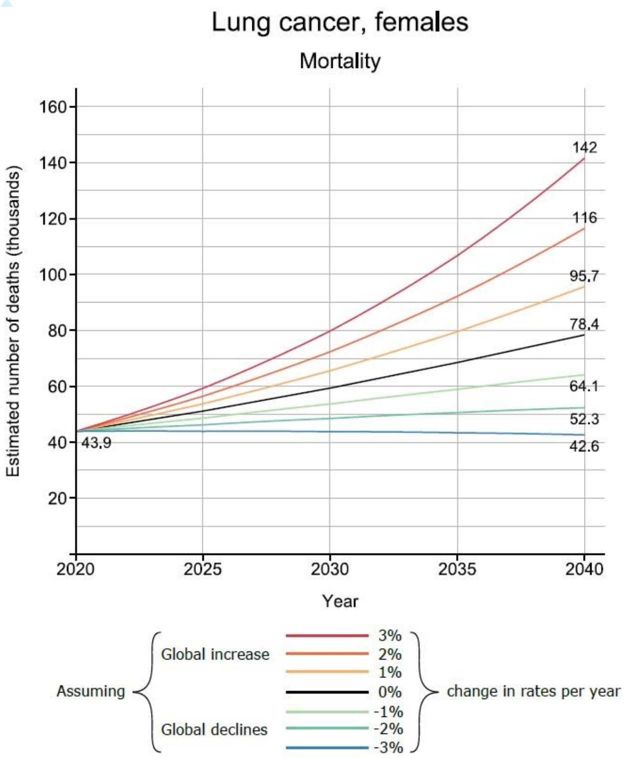


Lung cancer mortality by sex - medium HDI countries

E

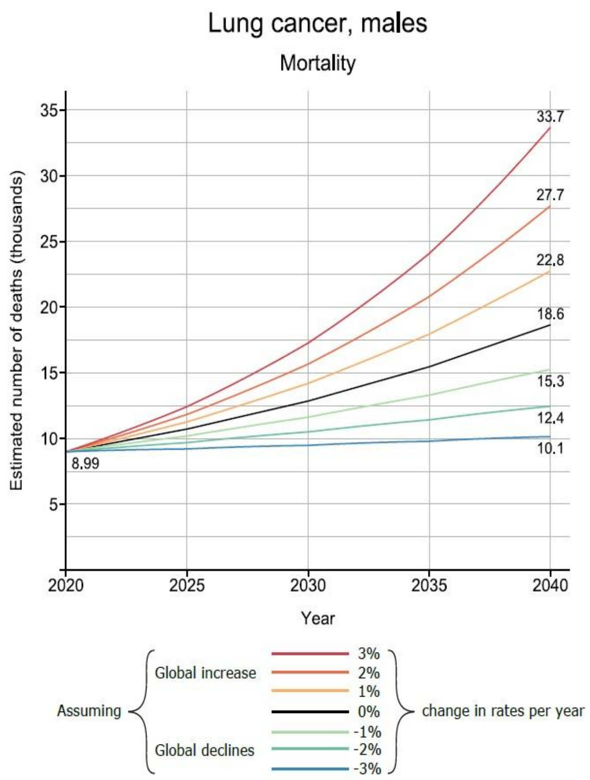


F



Lung cancer mortality by sex - low HDI countries

G



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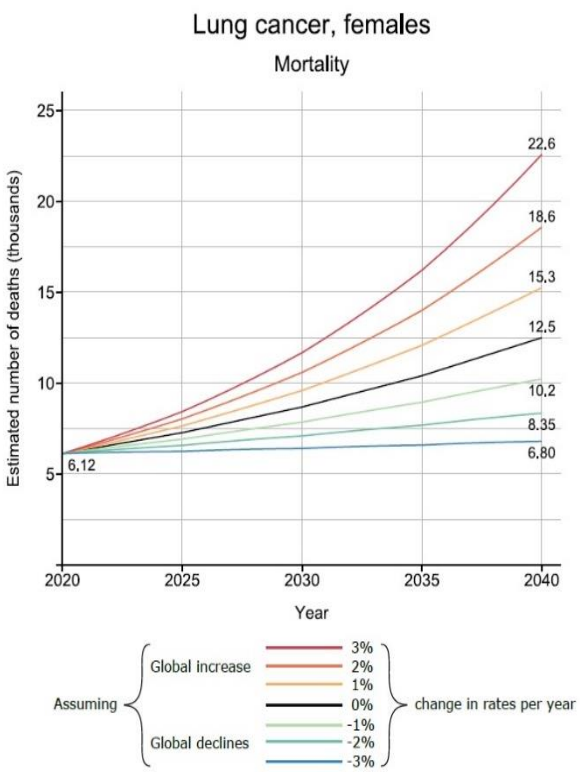

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	-

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040.

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Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040.

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Abstract

Objectives

Lung cancer is the leading cause of cancer death in 2020, responsible for almost one in five (18.0%) deaths. This paper provides an overview of the descriptive epidemiology of lung cancer on the basis of national mortality estimates for 2020 from the International Agency for Research on Cancer (IARC), and in the context of recent tobacco control policies.

Methods

Age-standardized mortality rates per 100,000 person-years of lung cancer for 185 countries by sex were obtained from the GLOBOCAN 2020 database and stratified by Human Development Index (HDI). Lung cancer deaths were projected to 2040 based on demographic changes alongside scenarios of annually increasing, stable or decreasing rates from the baseline year of 2020.

Results

Lung cancer mortality rates exhibited marked variations by geography and sex. Low HDI countries, many of them within sub-Saharan Africa, tend to have low levels of mortality and an upward trend in lung cancer deaths is predicted for both sexes until 2040 according to demographic projections, irrespective of trends in rates. In very high HDI countries, including Europe, Northern America and Australia/New Zealand, there are broadly decreasing trends in men whereas in women, rates are still increasing or reaching a plateau.

Conclusion

The current and future burden of lung cancer in a country or region largely depends on the present trajectory of the smoking epidemic in its constituent populations, with distinct gender differences in smoking patterns, both in transitioning and transitioned countries. Further elevations in lung cancer mortality are expected worldwide, raising important social and political questions, especially in low- and middle-income countries.

Keywords: lung cancer, mortality, projection

Word count: 2510

Strengths and limitations of this study

Strengths

This study:

- presents a detailed profile of the present LC burden in men and women worldwide according to national levels of human development.

- applies a simple projection to estimate the future lung cancer mortality burden in 2040.

- discusses the results in the context of key risk factors for lung cancer, particularly the continually evolving smoking epidemic.

Limitations

This study:

- is hampered by the limited availability of local cause of death information from national vital registration sources, particularly in transitioning countries.

Introduction

Lung cancer (LC) ranks as the most frequent form of cancer death and premature cancer death (ages 30-69) with a uniformly low 5-year survival, even in high-income countries [1]. With one-fifth of the present cancer mortality worldwide due to LC – an estimated 1.8 million deaths in 2020 [2] – the key determinant remains tobacco consumption. Up to 9 in 10 LC cases are caused by smoking in high-income settings, while mortality increases with number of cigarettes smoked and smoking duration [3]. Lopez at al. drew attention to the phases of the global smoking epidemic and the subsequent impact of smoking on LC occurrence by sex [4]; men and women remain in very different phases of the smoking epidemic, as reflected in disease rates by birth cohort. Recent reports have generally described marked variations in rates between sexes, with stable or decreasing rates found predominantly among male while increasing rates among female populations [5,6].

An emerging pattern is a higher rate of LC incidence among young females than males across geographic areas and income levels, that is not fully explained by sex-specific differences in smoking prevalence [7]. Such temporal patterns forewarn of a higher LC burden in women than men at older ages in the decades to follow, especially in higher-income settings. Women have been increasingly targeted in marketing campaigns, particularly in transitioning countries, while social constraints that precluded women taking up the habit are weakening [8]; still, smoking prevalence among women varies markedly, with, for example, a small proportion of women in China current smokers, in absolute terms and relative to men [9].

This paper presents a global overview of the descriptive epidemiology of LC in relation to recent tobacco control policies, using the GLOBOCAN mortality estimates for the year 2020 provided by the International Agency for Research on Cancer (IARC) [10]. In addition, we provide projections of the future mortality burden according to different temporal scenarios to the year 2040, estimating the expected future LC deaths according to levels of Human Development Index (HDI).

Data Sources and Methods

The number of deaths from, cancers of the lung (ICD-10 C33-34, including trachea and bronchus) were extracted from IARC's GLOBOCAN 2020 database for 185 countries or territories, by sex and 18 age groups (0-4, 5-9, ..., 80-84, 85 and over) [2,10,11]. Corresponding population data for 2020 were extracted from the United Nations (UN) website [12]. The data sources and hierarchy of methods used in compiling the cancer estimates have been described in detail elsewhere [10]. In brief, the GLOBOCAN estimates are assembled at the national level using the best available sources of cancer incidence and mortality data within a given country. The methods used to derive the 2020 estimates corresponding to those used to derived for previous years [13,14,15] where applicable, priority is given

to short-term predictions and modelled mortality to incidence (M:I) ratios, while validity is dependent on the degree of representativeness and quality of the source information [10].

We present figures based on the estimated deaths in 2020, as well as two summary measures using direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years based on the 1966 Segi-Doll World standard population [16,17] and the cumulative risk of dying from cancer before the age of 75 expressed as a percentage, assuming the absence of competing causes of death [18]. These measures allow comparisons between populations adjusted for differences in age structures. We also provide a prediction of the future number of LC deaths worldwide for the year 2040, based on demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%) or decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of COVID-19 pandemic was not taken into consideration during the calculations.

The results are presented by country, and aggregated across 20 UN-defined world regions [12] and according to the UN's four-tier HDI in 2020 [19], as a means to assess the cancer burden across four levels of development (low, medium, high and very high HDI). Throughout, we use the terms *transitioning*, *emerging* and *lower HDI* countries/economies as synonyms for nations classified as low or medium HDI, and *transitioned* or *higher HDI* countries/economies for those classified as high or very high HDI.

The Global Cancer Observatory (GCO, https://gco.iarc.fr) includes facilities for the tabulation and graphical visualization of the GLOBOCAN database, including explorations of the current [2] and future [20] burden for 36 cancer types.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Lung cancer mortality – national rankings 2020

Figure 1 presents global maps that indicate LC's position in terms of deaths relative to other common tumours at the national level by sex for the year 2020. In 2020, LC ranks first in terms of cancer death in half, or 93 of the 185 countries included in GLOBOCAN, and either 2nd or 3rd in 37 countries in men. LC is a major contributor to cancer mortality around the world, including America, greater-Europe, Northern Africa, and across the Asian-Pacific region. There is a somewhat less dominant role at present in South America and Sub-Saharan Africa (but not South Africa). In women, the impact is lesser but still very much in evidence; the disease ranks as the leading form of cancer death in 25 countries including those within North America, Northern, Western and Southern-Central Europe, Eastern Asia and Australia/New Zealand. LC mortality ranks as the 2nd or 3rd leading form of cancer mortality in 54 countries worldwide in women.

There is at least a 20-fold variation in mortality between the sexes, with rates uniformly higher among men (Figure 2). Male mortality rates are higher in Eastern and Southern Europe (especially in Hungary and Serbia with rates of 60 per 100,000), Eastern Asia (particularly the Democratic People's Republic of Korea) and Polynesia and Micronesia, while rates are lower in Central America, South-Central Asia and most parts of sub-Saharan Africa. The highest female rates are observed in Northern America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia and across the African continent, other than for South Africa.

Lung cancer mortality burden by 2040

If the current rates were to remain constant over the next two decades, LC will claim around 2 million male deaths in 2040, compared to 1.2 million in 2020 (Figure 3). For women, the corresponding deaths are approximately half of their male counterparts: a predicted increase to 1 million in 2040 from 600 000 deaths in 2020. The projection also shows the different scenarios considering the changing rates per year between -3% and +3% based on plausible scenarios of the smoking epidemic in the short-term future; global declines in the number of LC among males but increases for female are perhaps the more realistic scenarios, with national or regional exceptions. Taking this trends-based prediction into account, the predicted number of deaths due to LC for men will likely range between 1.1 and 1.6 million and for women between 1.2 and 1.8 million by 2040. Deaths will markedly increase for both sexes in countries with the lowest HDI, even in the best-case trend scenario (Appendix Figure 1a-h).

Discussion

This study highlights the present geographic diversity in LC mortality worldwide, by sex and by level of human development. Countries with low HDI tend to have low LC mortality rates but may anticipate a higher mortality burden by 2040. For higher HDI countries, the burden of the disease is higher among men, but future trends suggest an increasingly greater proportion of the cancer burden will be seen among for females. These different scenarios are due to the impact of historic smoking trends and the increasingly widespread application of tobacco control measures in the last decades [21]. While there is an expectation that LC mortality will increase in transitioning countries given there is less implementation of effective tobacco control, there is a positivity in the findings of the Global Tobacco Control Report: the number of people now living in countries with at least two anti-tobacco policies in place rose from 3.5 billion in 2018 to 4.4 billion in 2020 – up from 45% of the world's population to 56% in two years [22].

Past smoking histories of nations are a key determinant of the current magnitude of LC in many populations worldwide, as described by the classical model of the global smoking epidemic, first introduced by Lopez et al [4]. In the model, the effect of different smoking patterns was captured by four

stages in the population, by an earlier adoption of the habit in men compared with women, and by the progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying cause of the marked inequalities seen in different educational groups [23]. Lopez et al. initially applied the hypothesis on just a few developed countries [24], but later was tested on greater geographic scales [25,26]. Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline among men in many populations over the last decades, a key focus has been the deteriorating public health situation affecting women, where in many settings, rates of LC mortality have continued to rise. This raises several relevant biological, epidemiological and sociological concerns [27], including: the changing distribution of the main histological subtypes of LC over time [28], the extent to which females adopted the habit of smoking and their vulnerability to the tobacco industry [29,30], the impact of such a transition in diminishing gender differences in disease burden worldwide [31] and the effects of different political systems on the health awareness of individuals [32,33]. The impact of these factors is reflected in comparisons of between-country LC mortality rates; for example, the current rate differences in Eastern vs. Northern European countries.

Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with other factors, including air pollution, climate change [34] and other occupational risk factors such as asbestosis and indoor exposure to cooking fumes etc [35]. The highest exposure to ambient air pollution is the characteristic of mainly countries in transition, where only modest reductions in burden will occur in the most polluted countries unless fine particulate matter (PM 2.5) values are decreased substantially [36].

Several other studies have aimed to forecast the future lung cancer burden in very high HDI countries e.g., the US [37] and the UK [38] with contradictory findings. While the steeply declining mortality in the US for both sexes until 2040 fits within the framework of the global smoking epidemic, the rising deaths reported in the UK for men and women until 2035 somewhat contradict previous findings. One explanation could be the rapidly ageing population age structure, which can increase the number of these non-standardized figures. Alternatively, these projections do not take into account the changing smoking prevalence in the past as a key determinant of present and future lung cancers. Our GLOBOCAN 2020 forecasts do not consider these either, however, provide possible scenarios on the basis of uniform increases or decreases in rates may help provide a realistic overview of the changing future burden of LC.

Another limitation of this study is the large variability in the availability and quality of cancer mortality data. Most African and some Asian countries suffer from weak mortality statistics systems. In GLOBOCAN, in countries where mortality series were not available from national vital registration sources, the predominant means of the estimation of rates were from corresponding national incidence

estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in neighbouring countries.

With over three million deaths predicted by 2040 in the absence of additional interventions according to the finding of this study, it is imperative to emphasize primary prevention as the most cost-effective strategy of tobacco control. It has been shown that raising the price of cigarettes through increased excise taxes can bring marked reductions in cigarette consumption [39]. Besides this, developing adaptive tobacco control strategies that target different subgroups is imperative; anti-tobacco strategies should urgently target women in settings such as the EU, in order to halt their rapidly increasing risk of LC, and prevent unnecessary, premature deaths among future generations of women [40]. In Sweden, as an example, policies such as those directed at health promotion have been implemented in a gender-specific way with a focus on young and pregnant women. Scotland also has gender-specific programs, such as the Women, Low Income, and Smoking Project [41]. Amos and Haglund (2000) have emphasized that building support for female-centered tobacco control programs through partnerships will be vital to achieve success [30]. Furthermore, Amos (1996) and Mackay and Amos (2003) draw attention to the situation of women in transitioning countries with presently low levels of cigarette smoking among women [29]. In these countries, smoking among girls is already on the rise, women's spending power is increasing, cigarettes are becoming affordable, and women are more exposed to the marketing strategies of tobacco companies, in an environment where cultural constraints are weakening and female-specific quitting programs are rare [8].

A package of measures to suppress tobacco consumption in a given population has been recommended through continued efforts to increase the proportion of ex-smokers, with a focus on younger generations [42]. This could perhaps be achieved by implementing coordinated smoking prevention and control strategies from an early age, in the form of educational programs in schools. Other measures that could be introduced include community intervention programs, mass media campaigns and further legislation to ban smoking in public places. One of the main problems is that young people react very differently to anti-smoking messages compared to adult long-term smokers [42]. The harm-reducing role of e-cigarettes and aid to smoking cessation has been proposed [43], however their impact on future LC mortality is not yet known [44]. Successful programs have also been implemented in rapidly emerging economies such as Brazil, where a reduction in smoking prevalence were observed after the ratification of the WHO Framework Convention on Tobacco Control (FCTC) in 2005, and the adoption of a national ban on tobacco advertising, a national comprehensive smoke-free policy, large pictorial health warnings on cigarette packages, and continuous increases in taxes and prices of tobacco products [45]. Other factors may influence the future burden of LC such as the potential introduction of screening in high-risk populations. In a recent trial, LC mortality was significantly lower among those who underwent volume computed tomography (CT) screening than those who did not participate [46]. Screened patients benefitted from a substantial shift to lower-stage cancers at the time of diagnosis as well as more frequent eligibility for curative treatment (mainly surgery) [47]. However, concerns have been raised about the potential for overdiagnosis in lung-cancer screening.

In summary, this paper has identified marked geographic variations in the current LC burden worldwide and provided potential scenarios regarding the short-term future LC deaths up until 2040. Gredner et al., have illustrated the great potential of comprehensive implementation of tobacco control policies in Greater-Europe, with over 1.6 million LC cases preventable over a 20-year period through the highest-level implementation of tobacco control policies [48]. There is therefore much we can do to halt the rising deaths from LC – as well as many other forms of cancer and non-communicable diseases –through the successful implementation of tobacco control policies.

Disclosure

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Role of the founding source

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Authors' contribution

AW: literature search, data analysis, writing – original draft; EM: writing – review & editing; JV: methodology, data collection, figures, visualisation; ML: visualisation; MP: writing – review & editing; HR: writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology, conceptualisation, data analysis, writing – original draft

Declaration of interests

All authors declare that they have no conflicts of interest.

Data sharing

The data that support the findings of this study are available at the Global Cancer Observatory (GLOBOCAN) at https://gco.iarc.fr/

Data are available in a public, open access repository.

Ethics Approval Statement

This study does not involve human participants and animal subjects.

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417 Figures

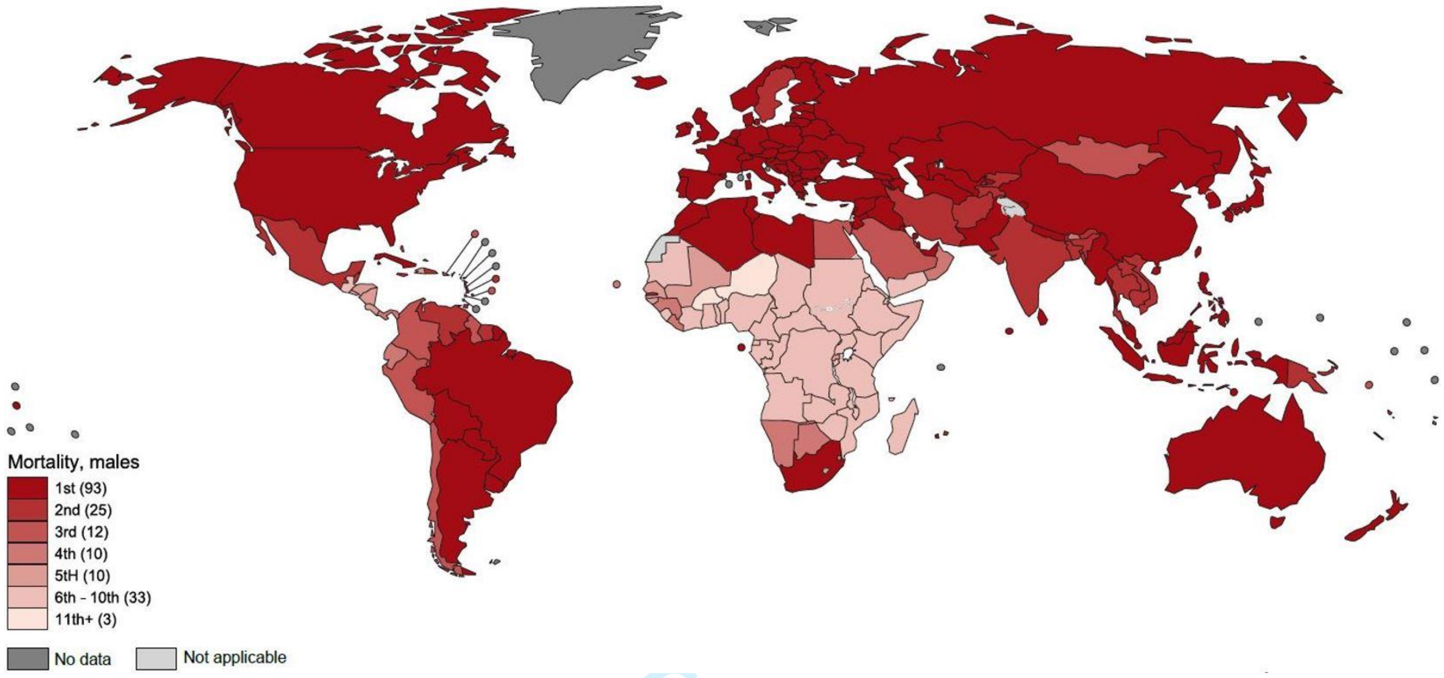
418 Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020, Male-Female

420 Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020, Male-Female

422 Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020

Male



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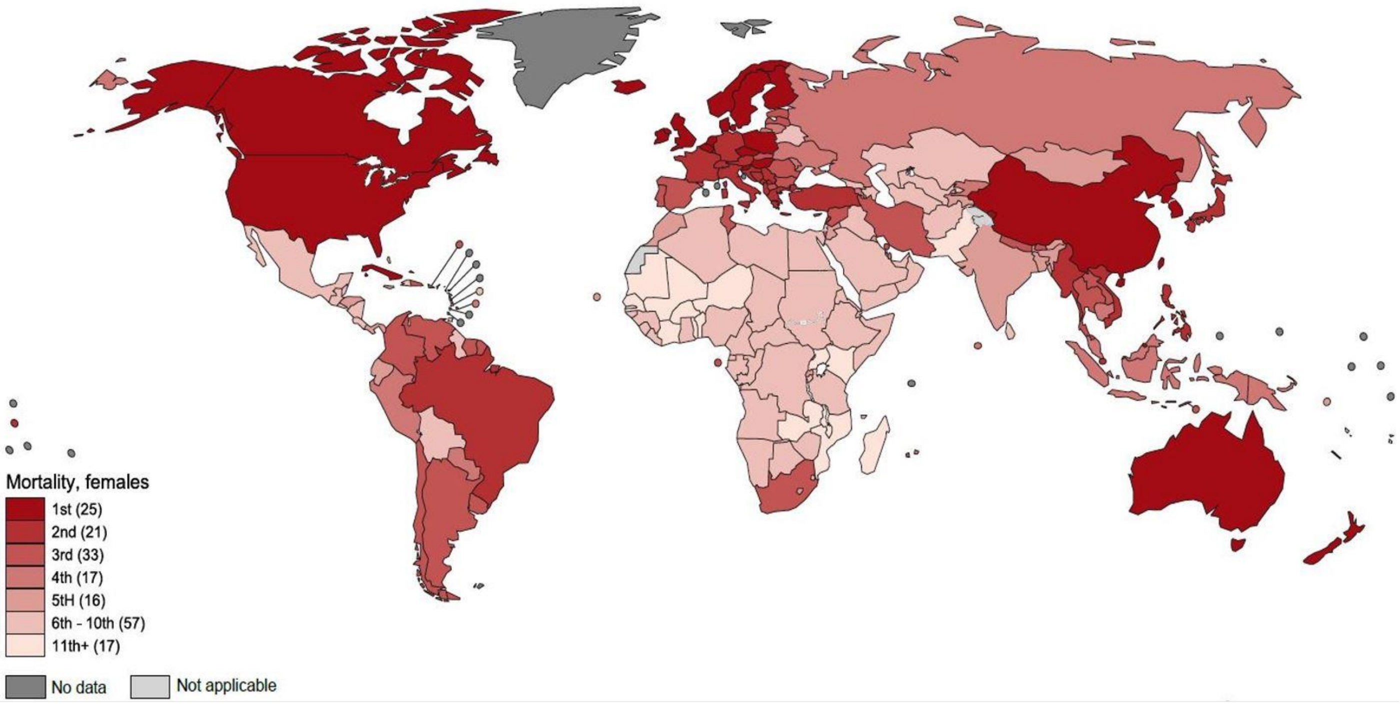


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020

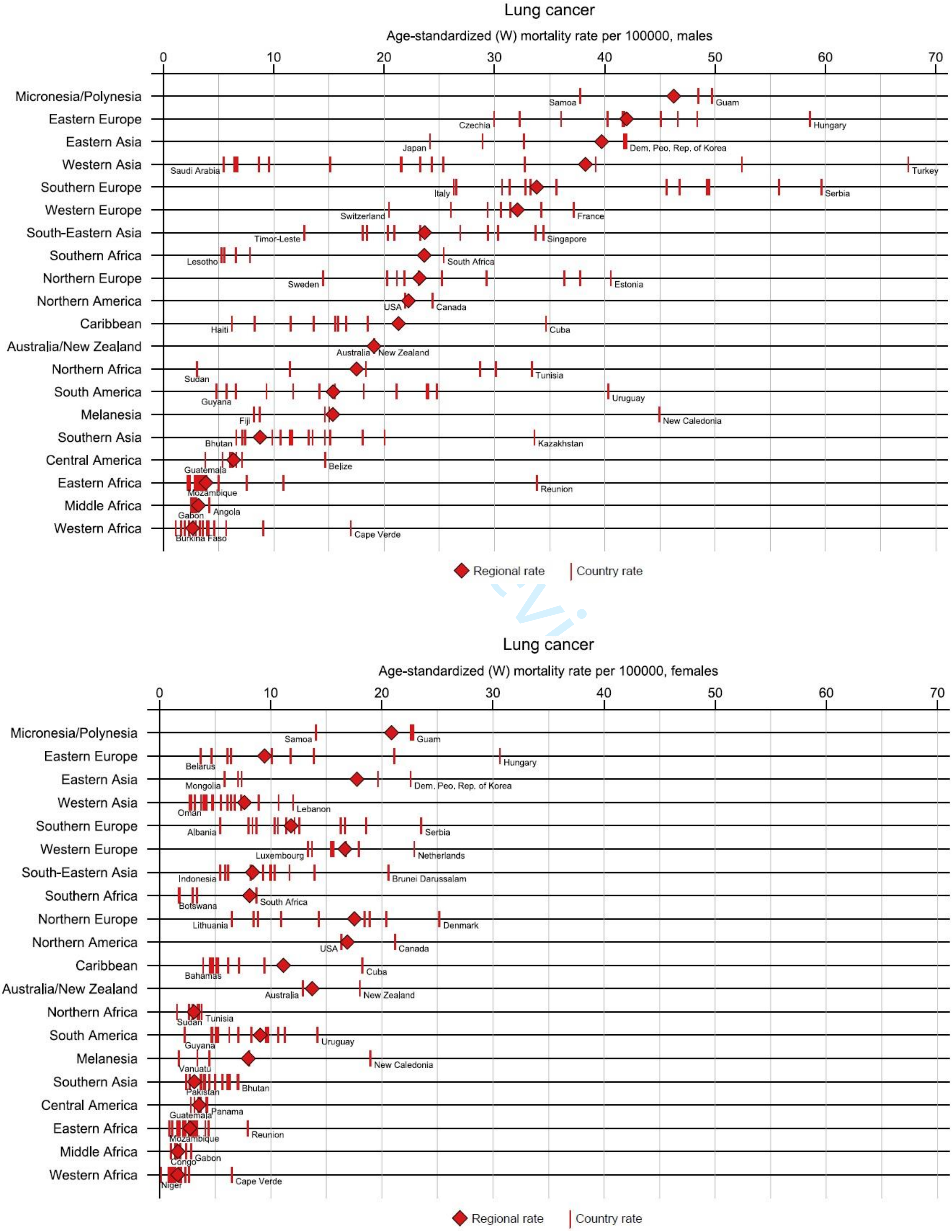
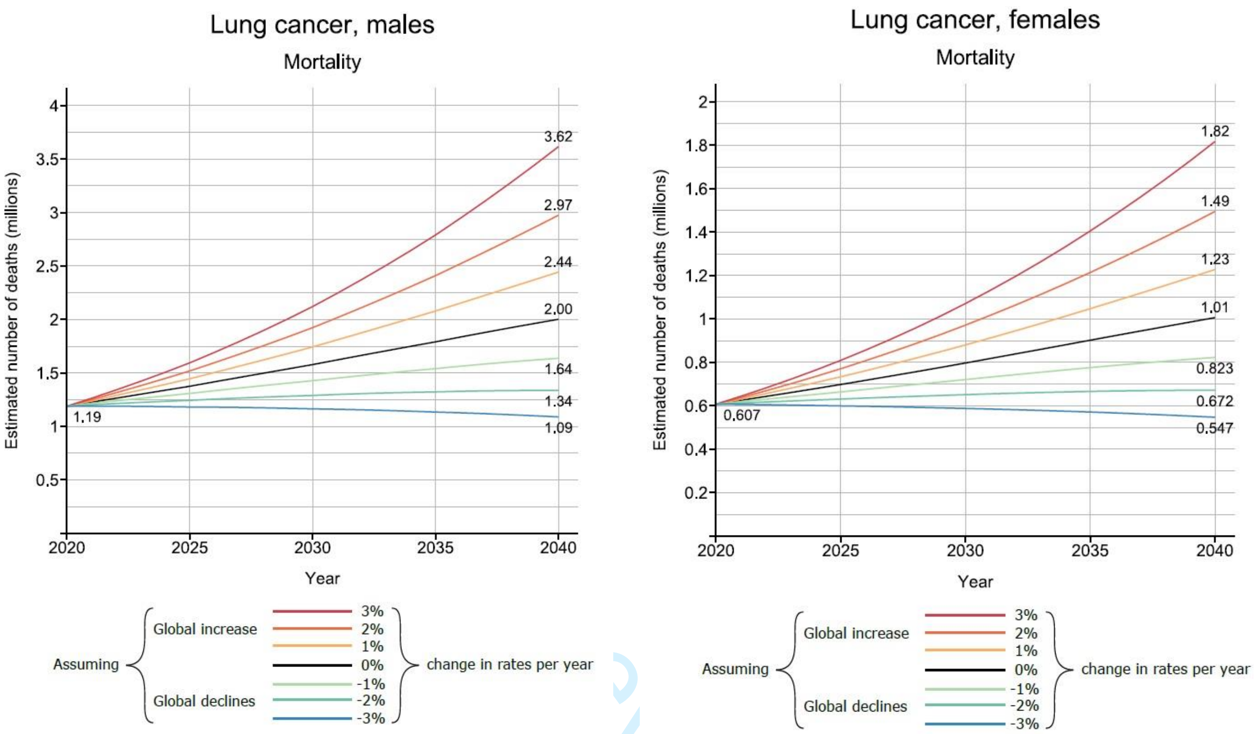


Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A **B**



Supplemental material - Appendix

Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020, Male - Female

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

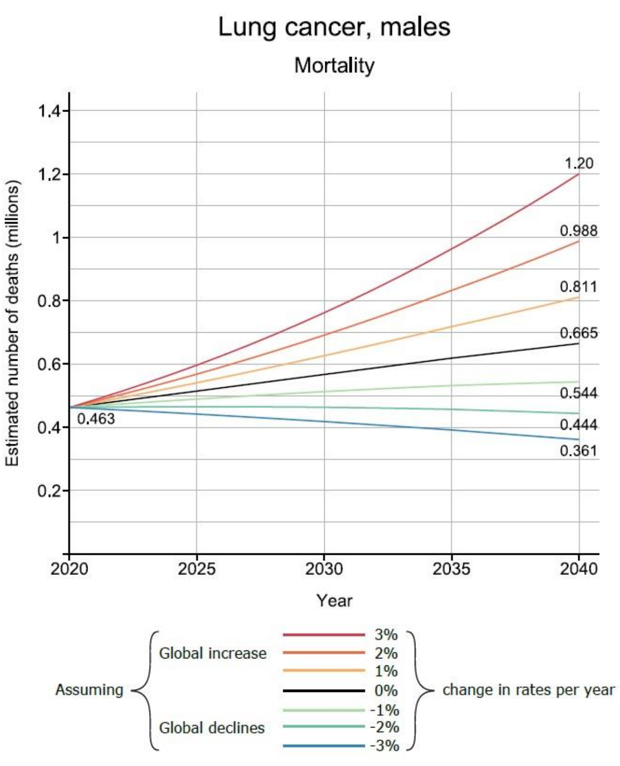
Data source: Globocan 2020, Map production: CSU, World Health Organization

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [13 April 2022].

Appendices

Lung cancer mortality by sex - very high HDI countries

A



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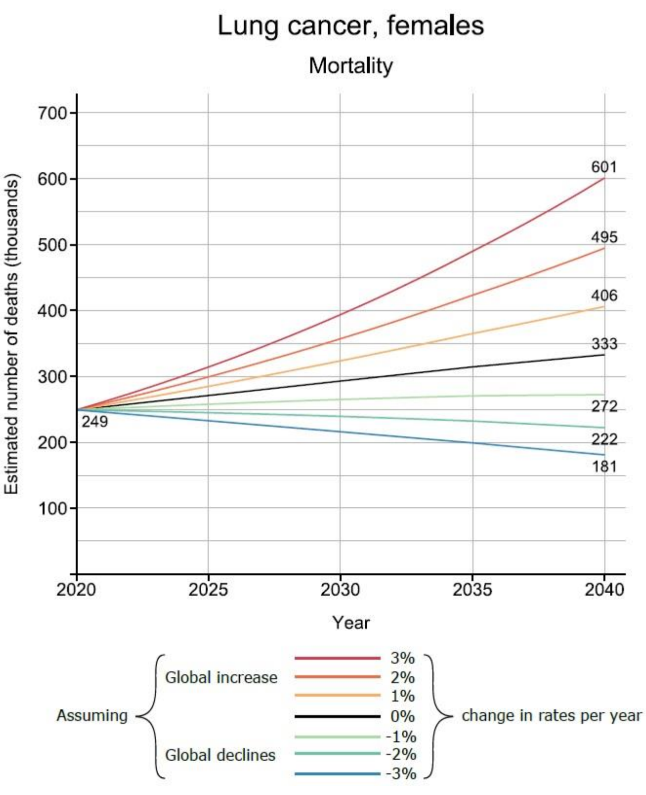
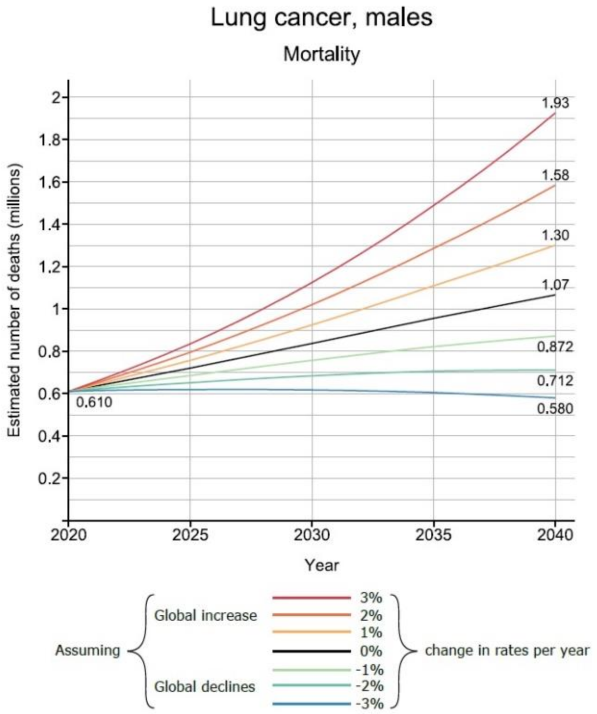


Lung cancer mortality by sex - high HDI countries

C



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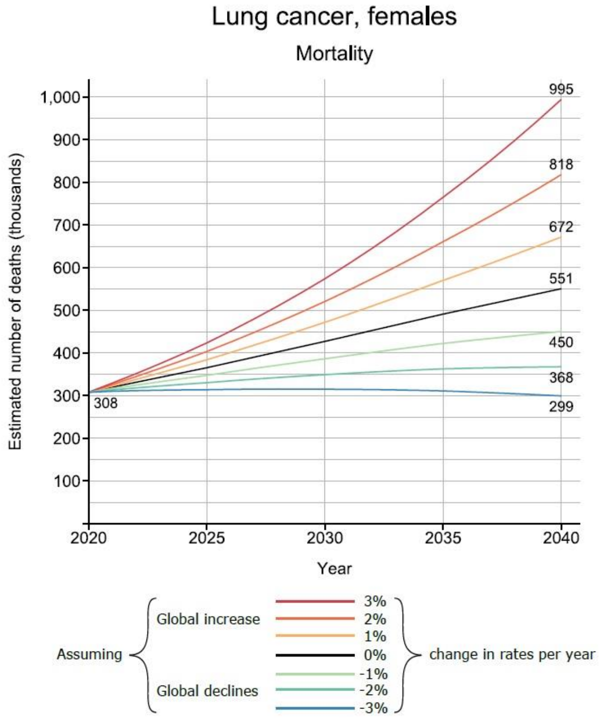
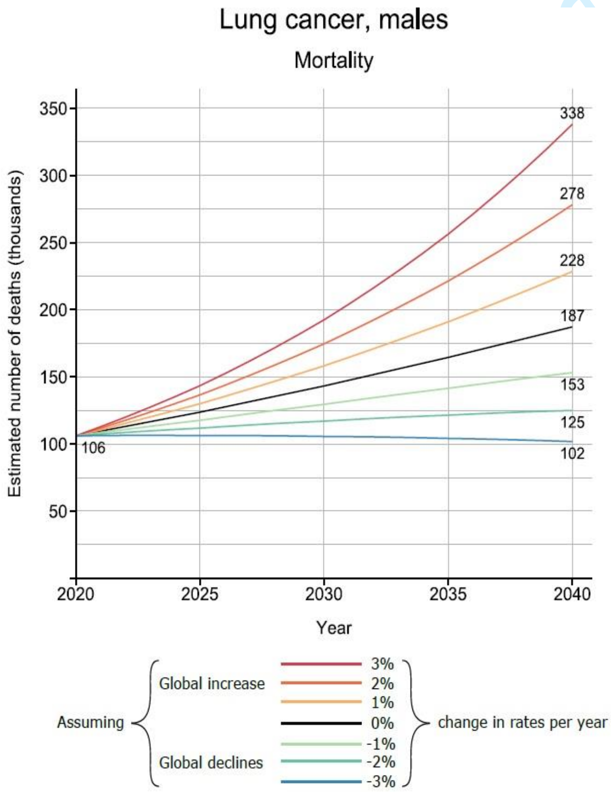


Lung cancer mortality by sex - medium HDI countries

E



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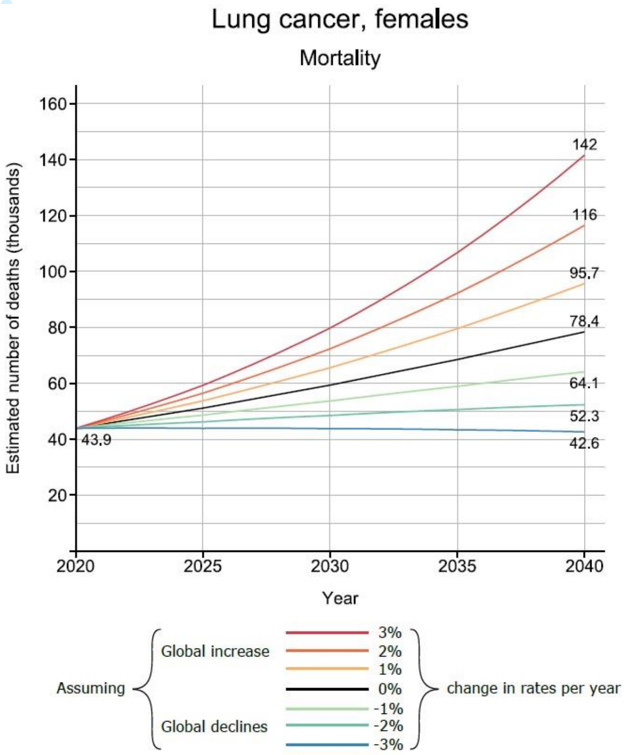
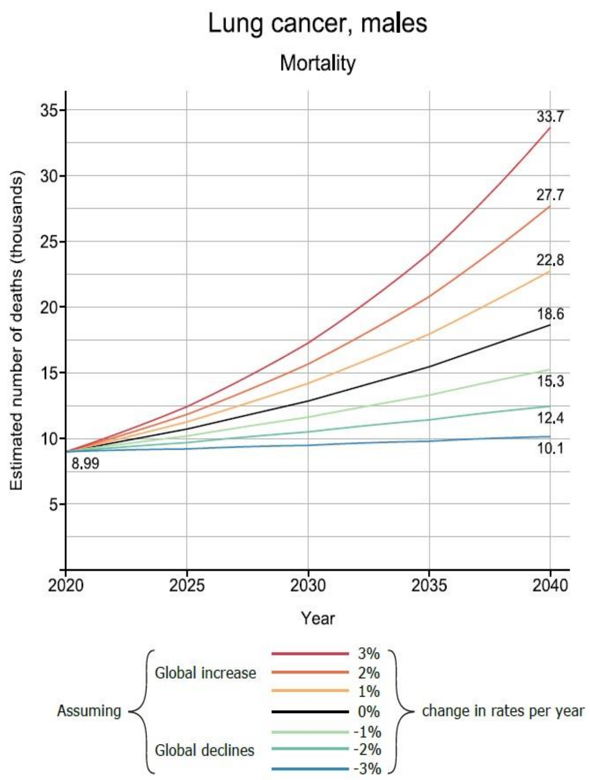


Lung cancer mortality by sex - low HDI countries

G



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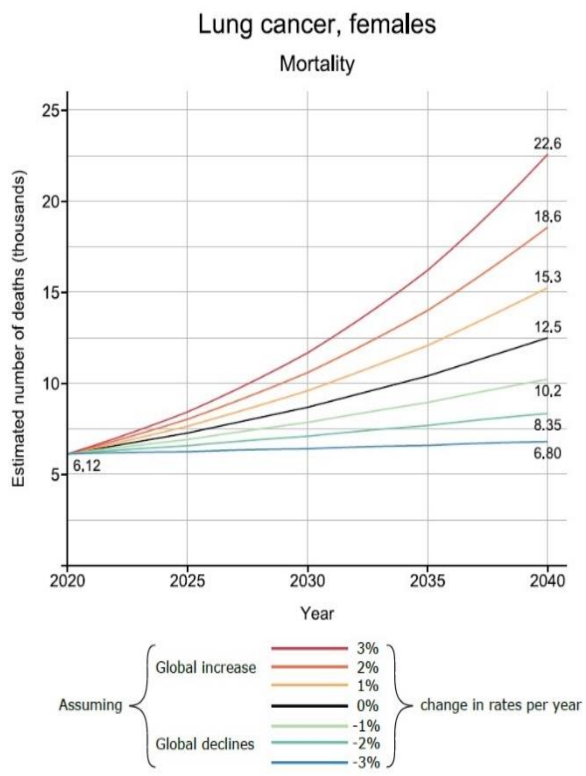

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	-

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Global health, Health policy, Oncology, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH, EPIDEMIOLOGY, Epidemiology < INFECTIOUS DISEASES

Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040

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Abstract

Objectives

Lung cancer is the leading cause of cancer death in 2020, responsible for almost one in five (18.0%) deaths. This paper provides an overview of the descriptive epidemiology of lung cancer based on national mortality estimates for 2020 from the International Agency for Research on Cancer (IARC), and in the context of recent tobacco control policies.

Methods

Age-standardized mortality rates per 100,000 person-years of lung cancer for 185 countries by sex were obtained from the GLOBOCAN 2020 database and stratified by Human Development Index (HDI). Lung cancer deaths were projected to 2040 based on demographic changes alongside scenarios of annually increasing, stable or decreasing rates from the baseline year of 2020.

Results

Lung cancer mortality rates exhibited marked variations by geography and sex. Low HDI countries, many of them within sub-Saharan Africa, tend to have low levels of mortality and an upward trend in lung cancer deaths is predicted for both sexes until 2040 according to demographic projections, irrespective of trends in rates. In very high HDI countries, including Europe, Northern America and Australia/New Zealand, there are broadly decreasing trends in men whereas in women, rates are still increasing or reaching a plateau.

Conclusion

The current and future burden of lung cancer in a country or region largely depends on the present trajectory of the smoking epidemic in its constituent populations, with distinct gender differences in smoking patterns, both in transitioning and transitioned countries. Further elevations in lung cancer mortality are expected worldwide, raising important social and political questions, especially in low- and middle-income countries.

Keywords: lung cancer, mortality, projection

Word count of abstract: 257

Word count of article: 2623

Strengths and limitations of this study

Strengths

This study:

- presents a detailed profile of the present LC burden in men and women worldwide according to national levels of human development.

- applies a simple projection to estimate the future lung cancer mortality burden in 2040.

- discusses the results in the context of key risk factors for lung cancer, particularly the continually evolving smoking epidemic.

Limitations

This study:

- is hampered by the limited availability of local cause of death information from national vital registration sources, particularly in transitioning countries.

Introduction

Lung cancer (LC) ranks as the most frequent form of cancer death and premature cancer mortality (ages 30-69) with uniformly low 5-year survival, even in high-income countries [1]. With one-fifth of the present cancer mortality worldwide due to LC – an estimated 1.8 million deaths in 2020 [2] – the key determinant remains tobacco consumption. Up to 9 in 10 LC cases are caused by smoking in high-income settings, while mortality increases with number of cigarettes smoked and smoking duration [3]. Lopez at al. drew attention to the phases of the global smoking epidemic and the subsequent impact of smoking on LC occurrence by sex [4]; men and women remain in very different phases of the smoking epidemic, as reflected in disease rates by birth cohort. Recent reports have generally described marked variations in rates between sexes, with stable or decreasing rates found predominantly among male while increasing rates among female populations [5,6].

An emerging pattern is a higher rate of LC incidence among young females than males across geographic areas and income levels, that is not fully explained by sex-specific differences in smoking prevalence [7]. Such temporal patterns forewarn of a higher LC burden in women than men at older ages in decades to follow, especially in higher-income settings. Women have been increasingly targeted in marketing campaigns, particularly in transitioning countries, while social constraints that precluded women taking up the habit are weakening [8]; still, smoking prevalence among women varies markedly, for example, a small proportion of women in China are current smokers, in absolute terms and relative to men [9].

This paper presents a global overview of the descriptive epidemiology of LC in relation to recent tobacco control policies, using the GLOBOCAN mortality estimates for the year 2020 provided by the International Agency for Research on Cancer (IARC) [10]. In addition, we provide projections of the future mortality burden according to different temporal scenarios to the year 2040, estimating the expected future LC deaths according to levels of Human Development Index (HDI).

Data Sources and Methods

The number of deaths from, cancers of the lung (ICD-10 C33-34, including trachea and bronchus) were extracted from IARC's GLOBOCAN 2020 database for 185 countries or territories, by sex and 18 age groups (0-4, 5-9, ..., 80-84, 85 and over) [2,10,11]. Corresponding population data for 2020 were extracted from the United Nations (UN) website [12]. The data sources and hierarchy of methods used in compiling the cancer estimates have been described in detail elsewhere [10]. In brief, the GLOBOCAN estimates are assembled at the national level using the best available sources of cancer incidence and mortality data within a given country. The methods used to derive the 2020 estimates corresponding to those used to derived for previous years [13,14,15] where applicable, priority is given

to short-term predictions and modelled mortality to incidence (M:I) ratios, while validity is dependent on the degree of representativeness and quality of the source information [10].

We present figures based on the estimated deaths in 2020, as well as two summary measures using direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years based on the 1966 Segi-Doll World standard population [16,17] and the cumulative risk of dying from cancer before the age of 75 expressed as a percentage, assuming the absence of competing causes of death [18]. These measures allow comparisons between populations adjusted for differences in age structures. We also provide a prediction of the future number of LC deaths worldwide for the year 2040, based on demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%) or decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of COVID-19 pandemic was not taken into consideration during the calculations.

The results are presented by country and aggregated across 20 UN-defined world regions [12] and according to the UN's four-tier HDI in 2020 [19], as a means to assess the cancer burden across four levels of development (low, medium, high and very high HDI). Throughout, we use the terms *transitioning*, *emerging* and *lower HDI* countries/economies as synonyms for nations classified as low or medium HDI, and *transitioned* or *higher HDI* countries/economies for those classified as high or very high HDI.

The Global Cancer Observatory (GCO, https://gco.iarc.fr) includes facilities for the tabulation and graphical visualization of the GLOBOCAN database, including explorations of the current [2] and future [20] burden for 36 cancer types.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Lung cancer mortality – national rankings 2020

Figure 1 presents global maps that indicate LC's position in terms of deaths relative to other common tumours at the national level, by sex for the year 2020. In 2020, LC ranks first in terms of cancer death in half (93 out of 185) of the countries included in GLOBOCAN, and either 2nd or 3rd in 37 countries, in men. LC is a major contributor to cancer mortality around the world, including America, greater-Europe, Northern Africa, and across the Asian-Pacific region. There is a less dominant role at present in South America and Sub-Saharan Africa (but not South Africa). In women, the impact is lesser but still very much in evidence; the disease ranks as the leading form of cancer death in 25 countries including those within North America, Northern, Western and Southern-Central Europe, Eastern Asia and Australia/New Zealand. LC mortality ranks as the 2nd or 3rd leading form of cancer mortality in 54 countries worldwide in women.

There is at least a 20-fold variation in mortality between the sexes, with rates uniformly higher among men (Figure 2). Male mortality rates are higher in Eastern and Southern Europe (especially in Hungary and Serbia with rates of 60 per 100,000), Eastern Asia (particularly the Democratic People's Republic of Korea) and Polynesia and Micronesia, while rates are lower in Central America, South-Central Asia and most parts of sub-Saharan Africa. The highest female rates are observed in Northern America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia and across the African continent, excluding South Africa.

Lung cancer mortality burden by 2040

If the current rates were to remain constant over the next two decades, LC will claim around 2 million male deaths in 2040, compared to 1.2 million in 2020 (Figure 3). For women, the corresponding deaths are approximately half of their male counterparts: a predicted increase to 1 million in 2040 from 600 000 deaths in 2020. The projection also shows the different scenarios considering the changing rates per year between -3% and +3% based on plausible scenarios of the smoking epidemic in the short-term future; global declines in the number of LC among males but increases for female are perhaps the more realistic scenarios, with national or regional exceptions. Taking this trends-based prediction into account, the predicted number of deaths due to LC for men will likely range between 1.1 and 1.6 million and for women between 1.2 and 1.8 million by 2040. Deaths will markedly increase for both sexes in countries with the lowest HDI, even in the best-case trend scenario (Appendix Figure 1a-h).

Discussion

This study highlights the present geographic diversity in LC mortality worldwide, by sex and by level of human development. Countries with low HDI tend to have low LC mortality rates but may anticipate a higher mortality burden by 2040. For higher HDI countries, the burden of the disease is higher among men, but future trends suggest an increasingly greater proportion of the cancer burden will be seen among females. These different scenarios are due to the impact of historic smoking trends and the increasingly widespread application of tobacco control measures in the last decades [21]. While there is an expectation that LC mortality will increase in transitioning countries given there is less implementation of effective tobacco control, there is a positivity in the findings from the Global Tobacco Control Report: the number of people now living in countries with at least two anti-tobacco policies in place rose from 3.5 billion in 2018 to 4.4 billion in 2020 – up from 45% of the world's population to 56% in two years [22].

Past smoking histories of nations are a key determinant of the current magnitude of LC in many populations worldwide, as described by the classical model of the global smoking epidemic, first introduced by Lopez et al [4]. In the model, the effect of different smoking patterns was captured by four

stages in the population, by an earlier adoption of the habit in men compared with women, and by the progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying cause of the marked inequalities seen in different educational groups [23]. Lopez et al. initially applied the hypothesis on just a few developed countries [24], which was later tested on greater geographic scales [25,26]. Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline among men in many populations over the last decades, a key focus has been the deteriorating public health situation affecting women, where in many settings, rates of LC mortality have continued to rise. This raises several relevant biological, epidemiological and sociological concerns [27], including: the changing distribution of the main histological subtypes of LC over time [28], the extent to which females adopted the habit of smoking and their vulnerability to the tobacco industry [29,30], the impact of such a transition in diminishing gender differences in disease burden worldwide [31] and the effects of different political systems on the health awareness of individuals [32,33]. The impact of these factors is reflected in comparisons of between-country LC mortality rates; for example, the current rate differences in Eastern vs. Northern European countries.

Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with other factors, including air pollution, climate change [34] and other occupational risk factors such as asbestosis and indoor exposure to cooking fumes etc [35]. The highest exposure to ambient air pollution is the characteristic of mainly countries in transition, where only modest reductions in burden will occur in the most polluted countries unless fine particulate matter (PM 2.5) values are decreased substantially [36].

Several other studies have aimed to forecast the future lung cancer burden in very high HDI countries e.g., the US [37] and the UK [38] with contradictory findings. While the steeply declining mortality in the US for both sexes until 2040 fits within the framework of the global smoking epidemic, the rising deaths reported in the UK for men and women until 2035 somewhat contradict previous findings. One explanation could be the rapidly ageing population, which can increase the number of these non-standardized figures. Alternatively, these projections do not take into account the changing smoking prevalence in the past as a key determinant of present and future lung cancers. Our GLOBOCAN 2020 forecasts do not consider these either, however, we provide possible scenarios on the basis of uniform increases or decreases in rates that may help provide a realistic overview of the changing future burden of LC.

Another limitation of this study is the large variability in the availability and quality of cancer mortality data. Most African and some Asian countries suffer from weak mortality statistics systems. In GLOBOCAN, in countries where mortality series were not available from national vital registration sources, the predominant means of the estimation of rates were from corresponding national incidence

estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in neighbouring countries.

With over three million deaths predicted by 2040 in the absence of additional interventions according to the finding of this study, it is imperative to emphasize primary prevention as the most cost-effective strategy of tobacco control. It has been shown that raising the price of cigarettes through increased excise taxes can bring marked reductions in cigarette consumption [39]. Besides this, developing adaptive tobacco control strategies that target different subgroups is imperative.

One key concern is the limited financial and trained resources in middle- and lower-income countries, that can hinder health promotion and cancer prevention strategies in these countries. Based on our findings, decreases in lung cancer rates are not likely in these countries until 2040 and presumably tobacco companies are expected to shift and escalate promotional campaigns to preserve business interests and profits where resistance efforts are the weakest [30].

Additionally, anti-tobacco strategies should urgently target women in also higher-income settings such as the EU, in order to halt their rapidly increasing risk of LC, and prevent unnecessary, premature deaths among future generations of women [40]. In Sweden, as an example, gender-specific policies such as those directed at health promotion have been implemented with a focus on young and pregnant women. Scotland also has gender-specific programs, such as the Women, Low Income, and Smoking Project [41]. Amos and Haglund (2000) have emphasized that building support for female-centered tobacco control programs through partnerships will be vital to achieve success [30]. Furthermore, Amos (1996) and Mackay and Amos (2003) draw attention to the situation of women in transitioning countries with presently low levels of cigarette smoking among women [29]. In these countries, smoking among girls is already on the rise, women's spending power is increasing, cigarettes are becoming affordable, and women are more exposed to the marketing strategies of tobacco companies, in an environment where cultural constraints are weakening and female-specific quitting programs are rare [8].

A package of measures to suppress tobacco consumption in a given population has been recommended through continued efforts to increase the proportion of ex-smokers, with a focus on younger generations [42]. This could perhaps be achieved by implementing coordinated smoking prevention and control strategies from an early age, in the form of educational programs in schools. Other measures that could be introduced include community intervention programs, mass media campaigns and further legislation to ban smoking in public places. One of the main problems is that young people react very differently to anti-smoking messages compared to adult long-term smokers [42]. The harm-reducing role of e-cigarettes and aid to smoking cessation has been proposed [43], however their impact on future LC mortality is not yet known [44]. Successful programs have also been implemented in rapidly emerging economies such as Brazil, where a reduction in smoking prevalence were observed after the ratification of the WHO Framework Convention on Tobacco Control (FCTC) in 2005, and the adoption of a national ban on tobacco advertising, a national comprehensive smoke-free policy, large pictorial health warnings on cigarette packages, and continuous increases in taxes and prices of tobacco products [45]. Other factors may influence the future burden of LC such as the potential introduction of screening in high-risk populations. In a recent trial, LC mortality was significantly lower among those who underwent volume computed tomography (CT) screening than those who did not participate [46]. Screened patients benefitted from a substantial shift to lower-stage cancers at the time of diagnosis as well as more frequent eligibility for curative treatment (mainly surgery) [47]. However, concerns have been raised about the potential for overdiagnosis in lung-cancer screening.

In summary, this paper has identified marked geographic variations in the current LC burden worldwide and provided potential scenarios regarding the short-term future LC deaths up until 2040. Gredner et al., have illustrated the great potential of comprehensive implementation of tobacco control policies in Greater-Europe, with over 1.6 million LC cases preventable over a 20-year period through the highest-level implementation of tobacco control policies [48]. There is therefore much we can do to halt the rising deaths from LC – as well as many other forms of cancer and non-communicable diseases – through the successful implementation of tobacco control policies.

Disclosure

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Role of the funding source

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Authors' contribution

AW: literature search, data analysis, writing – original draft; EM: writing – review & editing; JV: figures, visualisation; ML: methodology, figures, visualisation; MP: writing – review & editing; HR: writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology, conceptualisation, data analysis, writing – original draft

Declaration of interests

All authors declare that they have no conflicts of interest.

Data sharing

Data are available in a public, open access repository.

Ethics Approval Statement

This study does not involve human participants and animal subjects.

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Figures

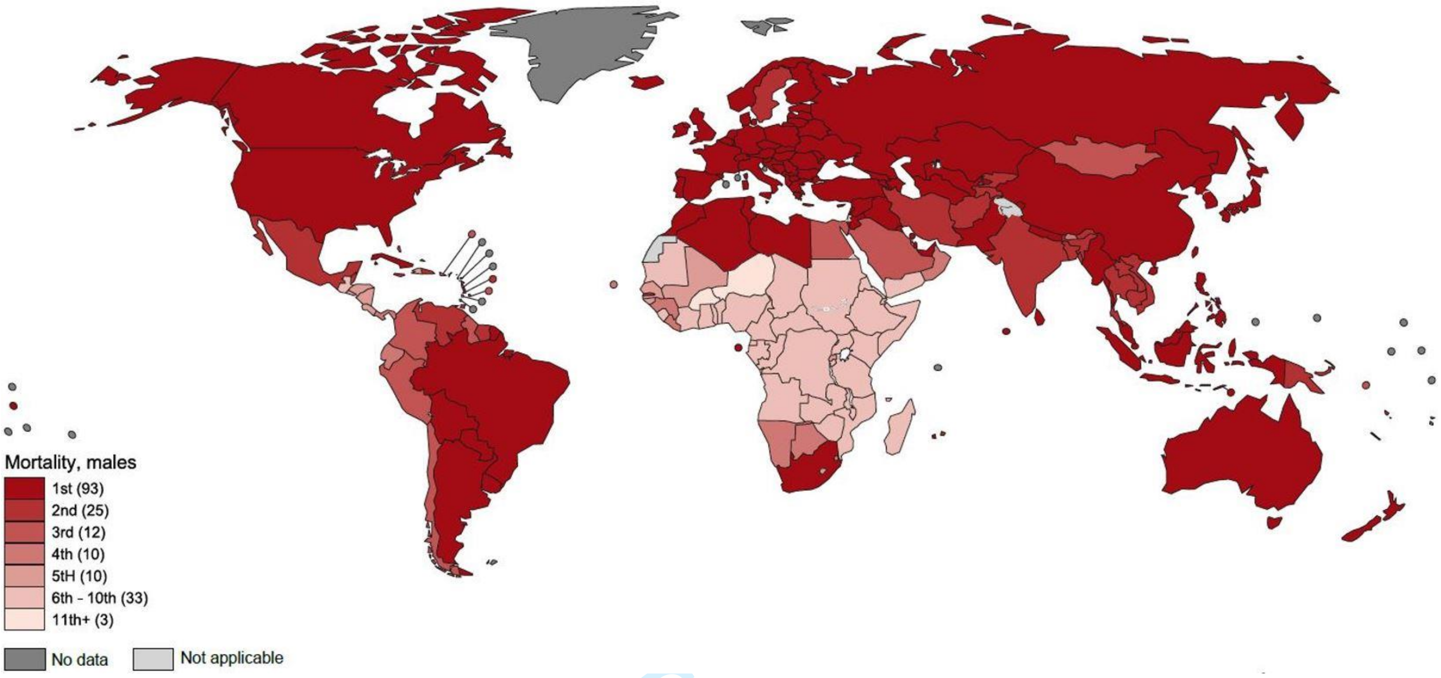
Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020, Male-Female

Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020, Male-Female

Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Figure 1: **Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020**

Male



Female

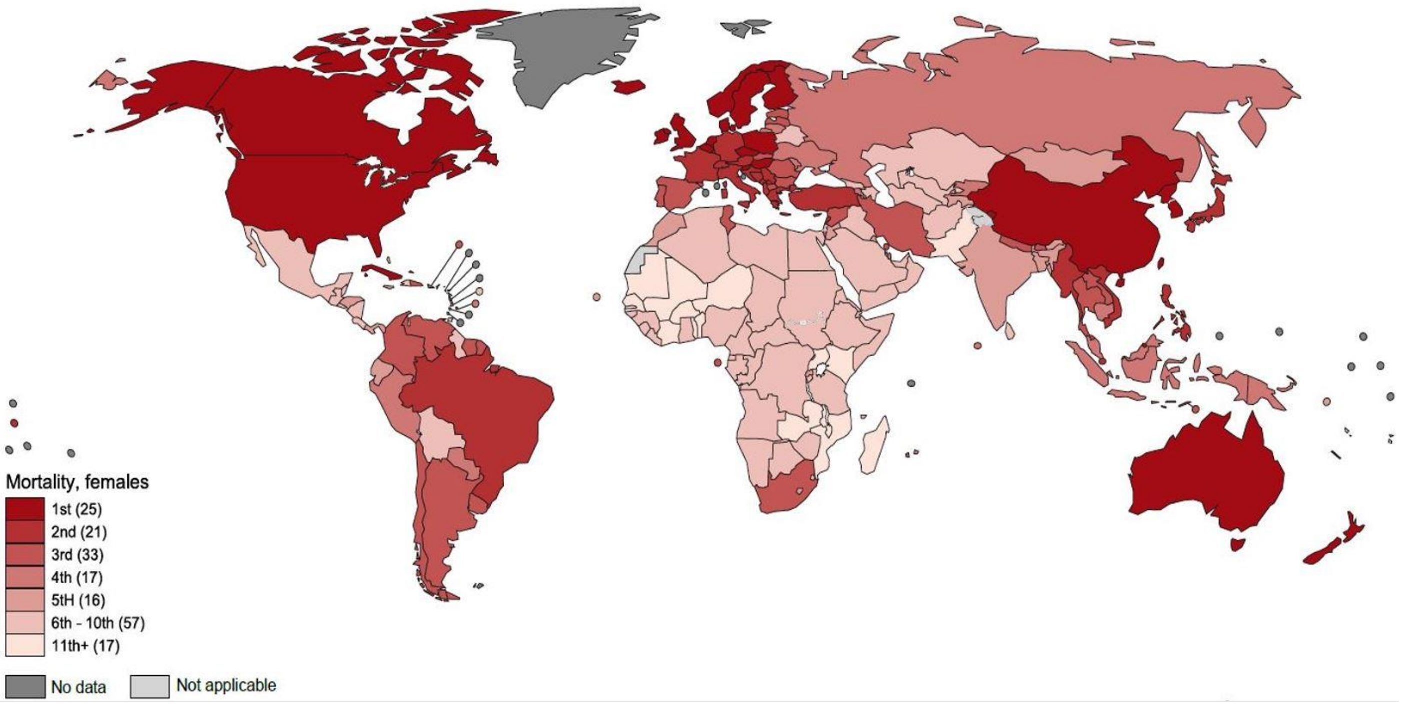
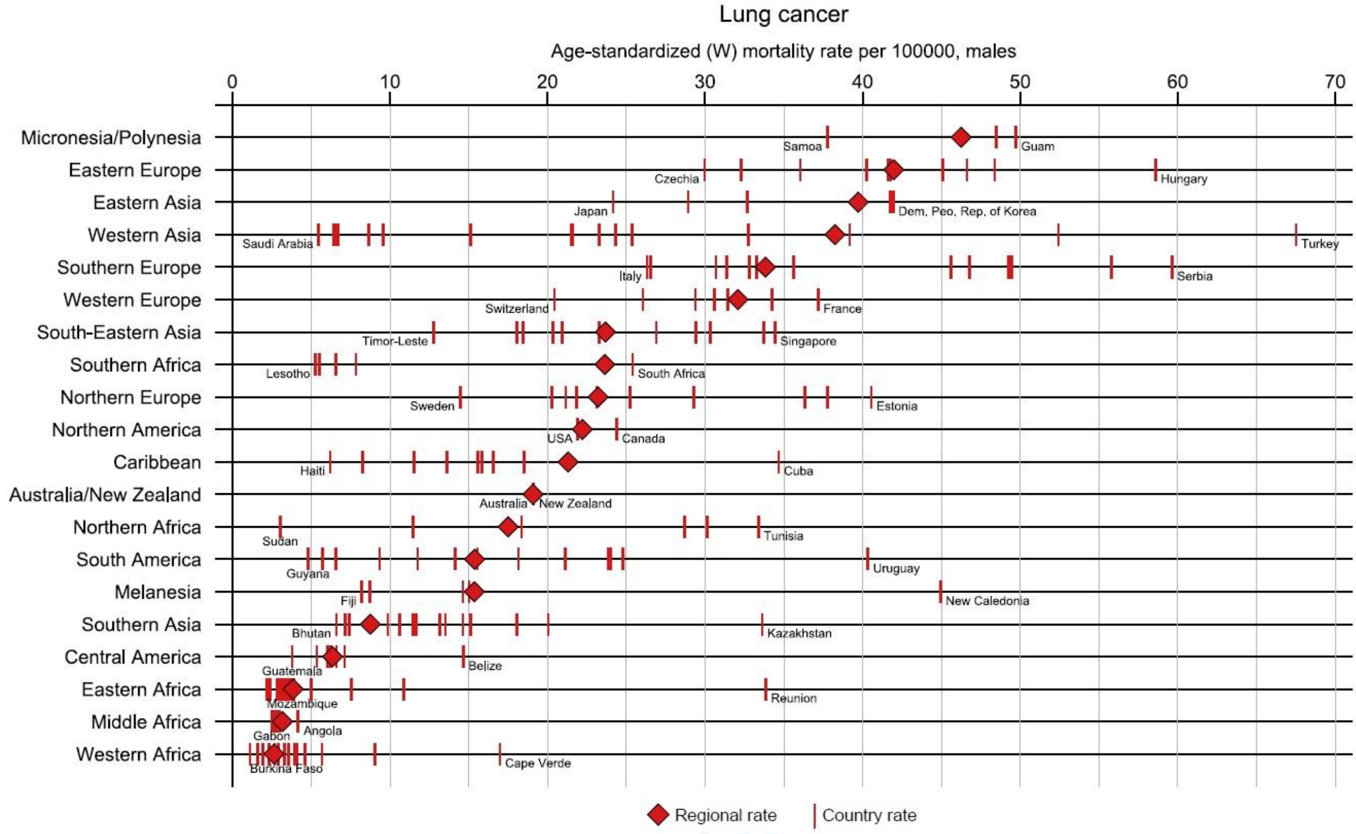


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020



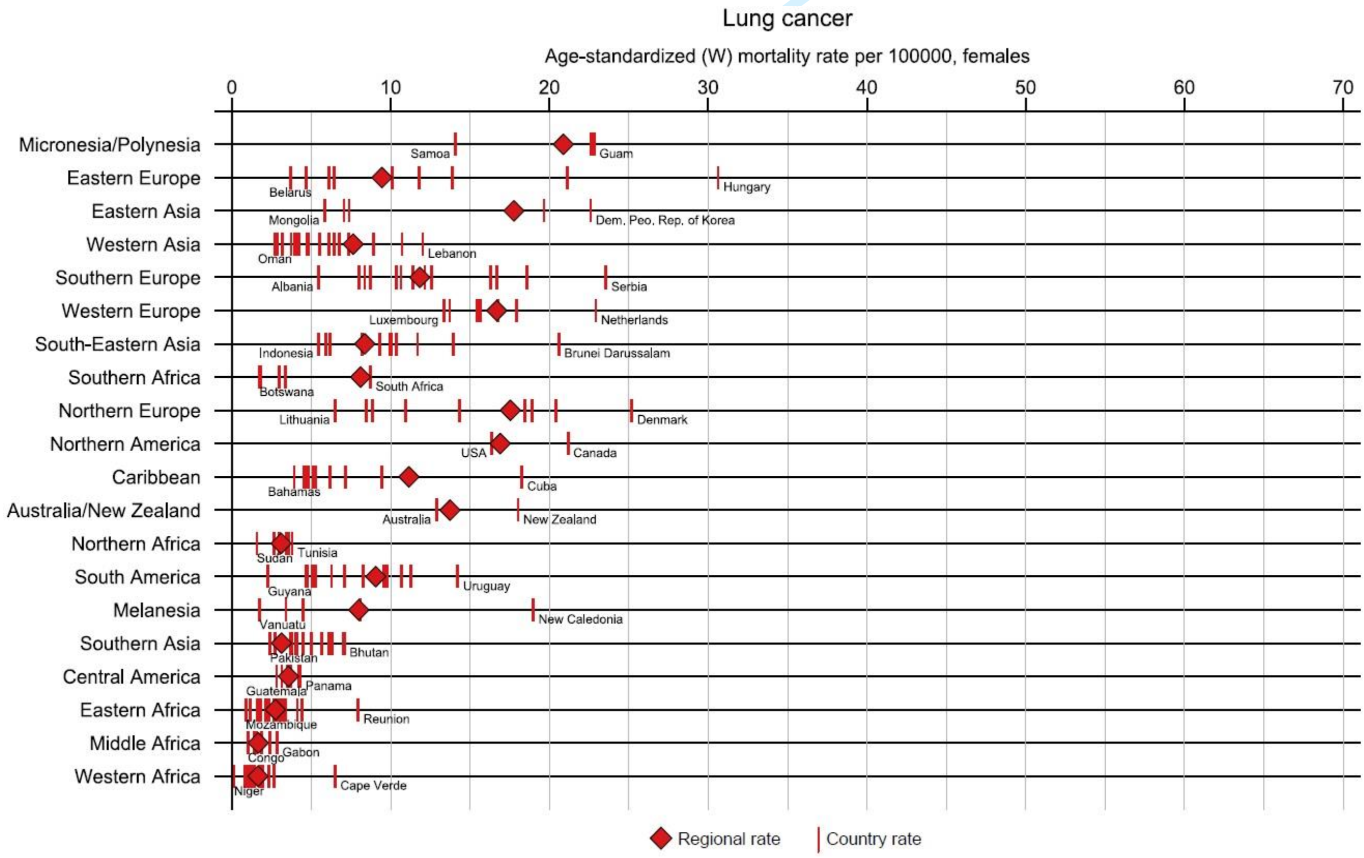
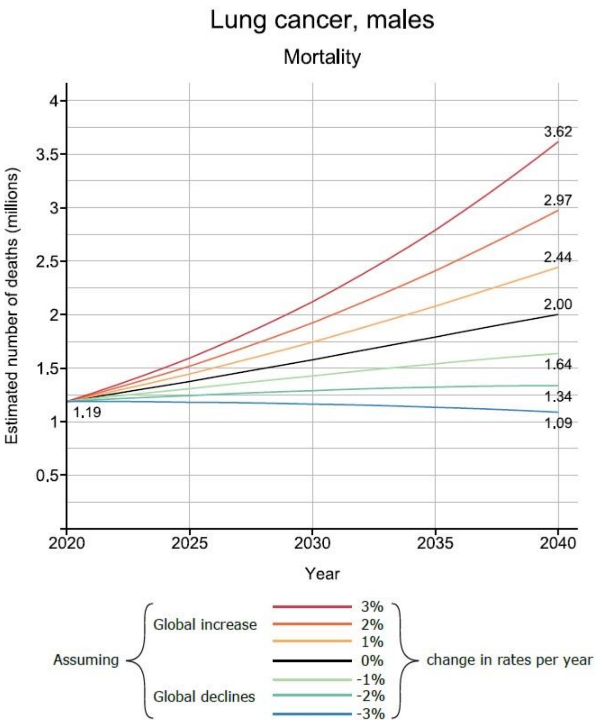


Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A



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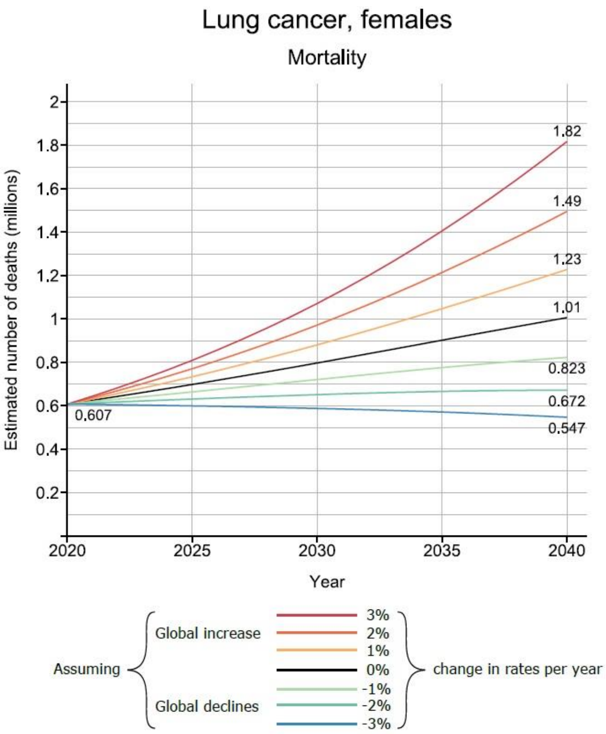


Supplemental material - Appendix

Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020, Male - Female

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

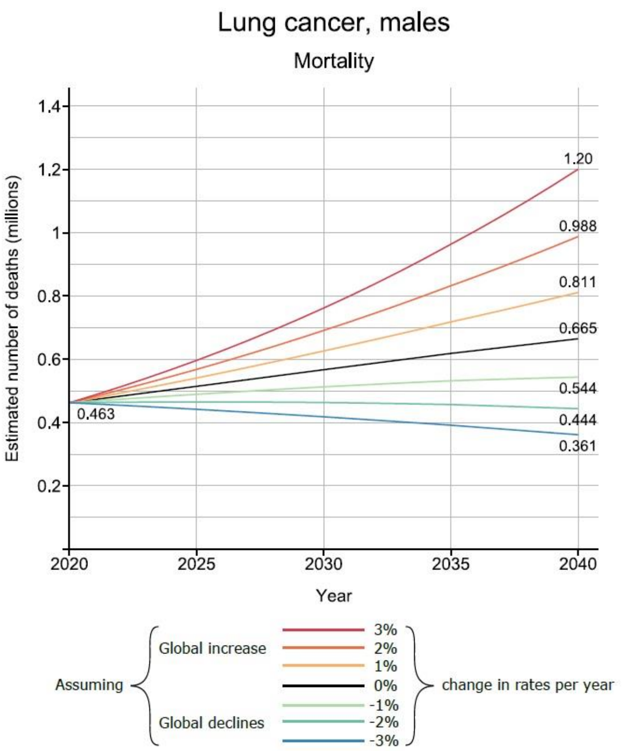
Data source: Globocan 2020, Map production: CSU, World Health Organization

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [13 April 2022].

Appendices

Lung cancer mortality by sex - very high HDI countries

A



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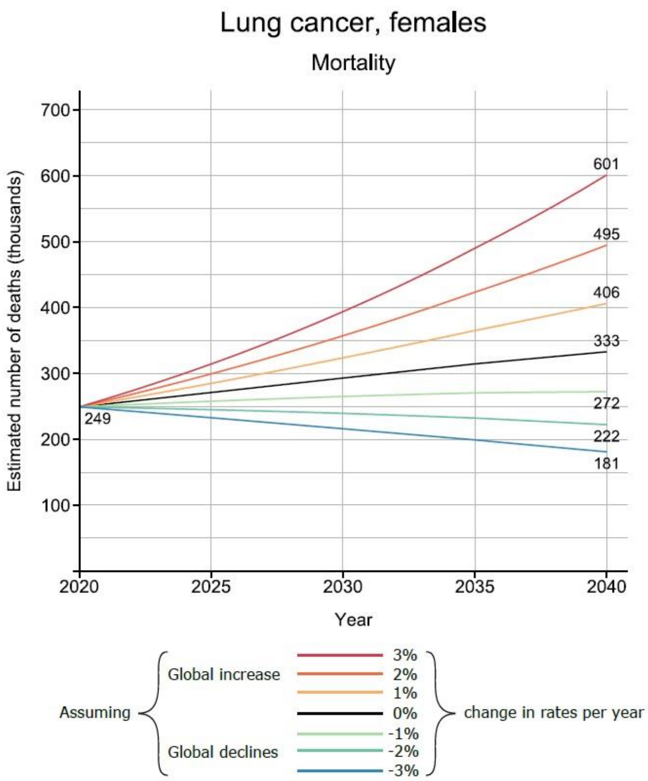
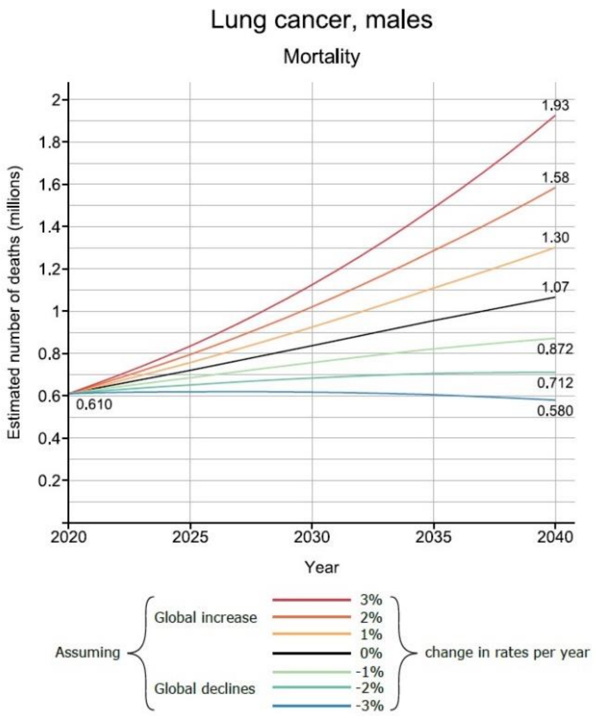


Lung cancer mortality by sex - high HDI countries

C



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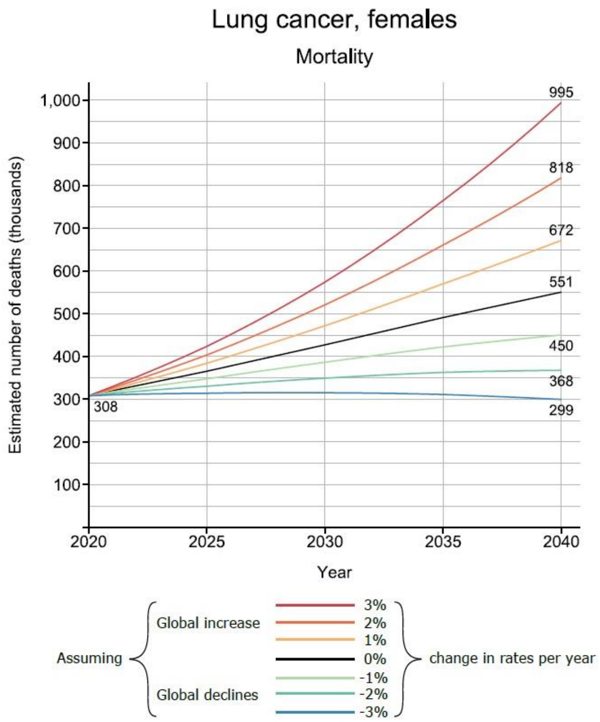

Lung cancer mortality by sex - medium HDI countries

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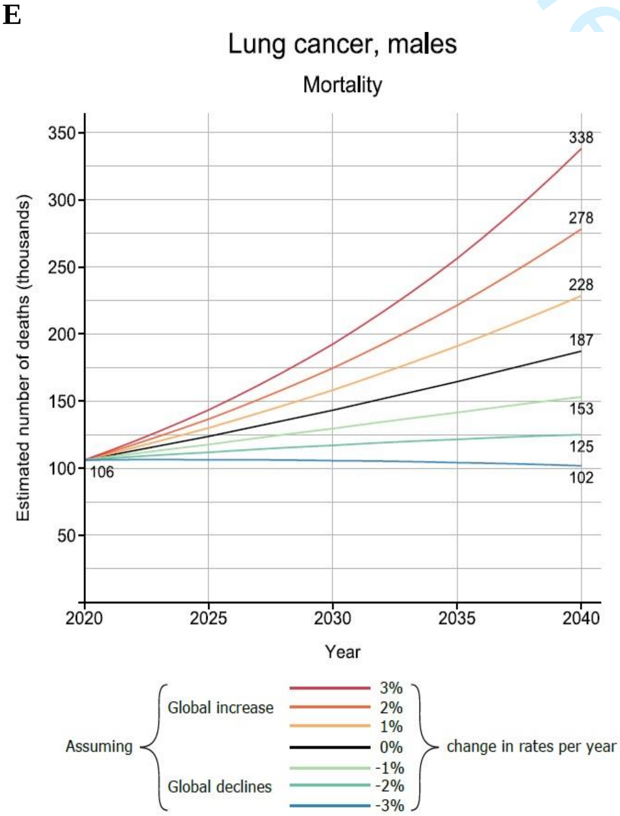

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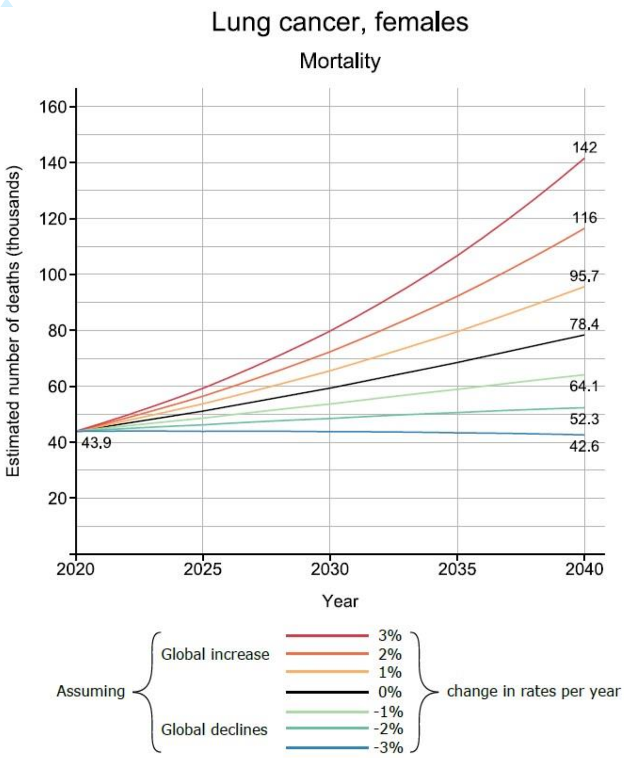
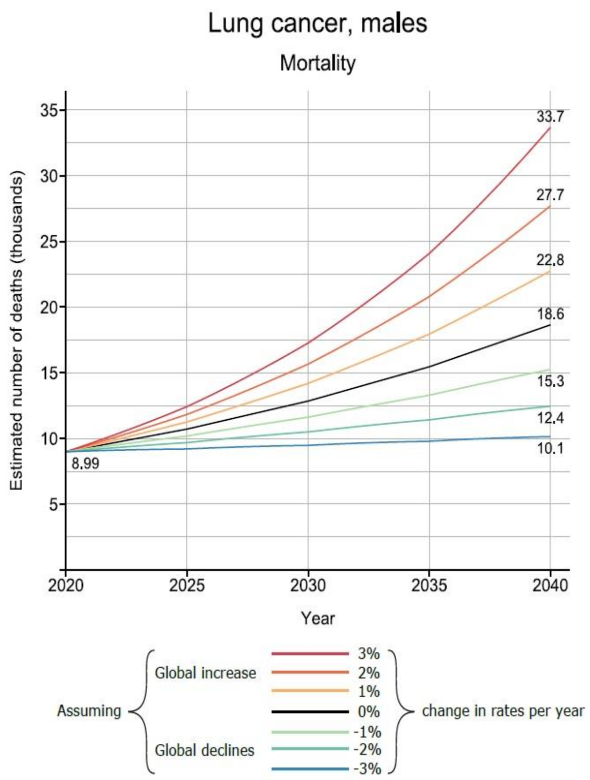


Lung cancer mortality by sex - low HDI countries

G



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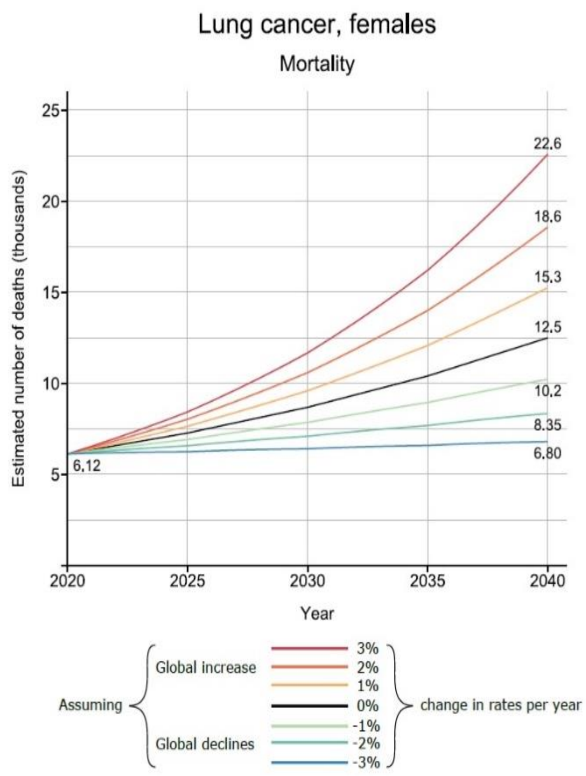

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	-

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Global health, Health policy, Oncology, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH, EPIDEMIOLOGY, Epidemiology < INFECTIOUS DISEASES

Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the global burden in 2020 and 2040

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Abstract

Objectives

Lung cancer is the leading cause of cancer death in 2020, responsible for almost one in five (18.0%) deaths. This paper provides an overview of the descriptive epidemiology of lung cancer based on national mortality estimates for 2020 from the International Agency for Research on Cancer (IARC), and in the context of recent tobacco control policies.

Design and setting

For this descriptive study age-standardized mortality rates per 100,000 person-years of lung cancer for 185 countries by sex were obtained from the GLOBOCAN 2020 database and stratified by Human Development Index (HDI). Lung cancer deaths were projected to 2040 based on demographic changes alongside scenarios of annually increasing, stable or decreasing rates from the baseline year of 2020.

Results

Lung cancer mortality rates exhibited marked variations by geography and sex. Low HDI countries, many of them within sub-Saharan Africa, tend to have low levels of mortality and an upward trend in lung cancer deaths is predicted for both sexes until 2040 according to demographic projections, irrespective of trends in rates. In very high HDI countries, including Europe, Northern America and Australia/New Zealand, there are broadly decreasing trends in men whereas in women, rates are still increasing or reaching a plateau.

Conclusion

The current and future burden of lung cancer in a country or region largely depends on the present trajectory of the smoking epidemic in its constituent populations, with distinct gender differences in smoking patterns, both in transitioning and transitioned countries. Further elevations in lung cancer mortality are expected worldwide, raising important social and political questions, especially in low- and middle-income countries.

Keywords: lung cancer, mortality, projection

Word count of abstract: 257

Word count of article: 2623

Strengths and limitations of this study

- This study presents a detailed profile of the present LC burden in men and women worldwide according to national levels of human development.

- Our research applies a simple projection to estimate the future lung cancer mortality burden in 2040.

- We discuss the results in the context of key risk factors for lung cancer, particularly the continually evolving smoking epidemic.

- This examination is hampered by the limited availability of local cause of death information from national vital registration sources, particularly in transitioning countries.

Introduction

Lung cancer (LC) ranks as the most frequent form of cancer death and premature cancer mortality (ages 30-69) with uniformly low 5-year survival, even in high-income countries [1]. With one-fifth of the present cancer mortality worldwide due to LC – an estimated 1.8 million deaths in 2020 [2] – the key determinant remains tobacco consumption. Up to 9 in 10 LC cases are caused by smoking in high-income settings, while mortality increases with number of cigarettes smoked and smoking duration [3]. Lopez at al. drew attention to the phases of the global smoking epidemic and the subsequent impact of smoking on LC occurrence by sex [4]; men and women remain in very different phases of the smoking epidemic, as reflected in disease rates by birth cohort. Recent reports have generally described marked variations in rates between sexes, with stable or decreasing rates found predominantly among male while increasing rates among female populations [5,6].

An emerging pattern is a higher rate of LC incidence among young females than males across geographic areas and income levels, that is not fully explained by sex-specific differences in smoking prevalence [7]. Such temporal patterns forewarn of a higher LC burden in women than men at older ages in decades to follow, especially in higher-income settings. Women have been increasingly targeted in marketing campaigns, particularly in transitioning countries, while social constraints that precluded women taking up the habit are weakening [8]; still, smoking prevalence among women varies markedly, for example, a small proportion of women in China are current smokers, in absolute terms and relative to men [9].

This paper presents a global overview of the descriptive epidemiology of LC in relation to recent tobacco control policies, using the GLOBOCAN mortality estimates for the year 2020 provided by the International Agency for Research on Cancer (IARC) [10]. In addition, we provide projections of the future mortality burden according to different temporal scenarios to the year 2040, estimating the expected future LC deaths according to levels of Human Development Index (HDI).

Data Sources and Methods

The number of deaths from, cancers of the lung (ICD-10 C33-34, including trachea and bronchus) were extracted from IARC's GLOBOCAN 2020 database for 185 countries or territories, by sex and 18 age groups (0-4, 5-9, ..., 80-84, 85 and over) [2,10,11]. Corresponding population data for 2020 were extracted from the United Nations (UN) website [12]. The data sources and hierarchy of methods used in compiling the cancer estimates have been described in detail elsewhere [10]. In brief, the GLOBOCAN estimates are assembled at the national level using the best available sources of cancer incidence and mortality data within a given country. The methods used to derive the 2020 estimates corresponding to those used to derived for previous years [13,14,15] where applicable, priority is given

to short-term predictions and modelled mortality to incidence (M:I) ratios, while validity is dependent on the degree of representativeness and quality of the source information [10].

We present figures based on the estimated deaths in 2020, as well as two summary measures using direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years based on the 1966 Segi-Doll World standard population [16,17] and the cumulative risk of dying from cancer before the age of 75 expressed as a percentage, assuming the absence of competing causes of death [18]. These measures allow comparisons between populations adjusted for differences in age structures. We also provide a prediction of the future number of LC deaths worldwide for the year 2040, based on demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%) or decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of COVID-19 pandemic was not taken into consideration during the calculations.

The results are presented by country and aggregated across 20 UN-defined world regions [12] and according to the UN's four-tier HDI in 2020 [19], as a means to assess the cancer burden across four levels of development (low, medium, high and very high HDI). Throughout, we use the terms *transitioning*, *emerging* and *lower HDI* countries/economies as synonyms for nations classified as low or medium HDI, and *transitioned* or *higher HDI* countries/economies for those classified as high or very high HDI.

The Global Cancer Observatory (GCO, https://gco.iarc.fr) includes facilities for the tabulation and graphical visualization of the GLOBOCAN database, including explorations of the current [2] and future [20] burden for 36 cancer types.

Patient and Public Involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Lung cancer mortality – national rankings 2020

Figure 1 presents global maps that indicate LC's position in terms of deaths relative to other common tumours at the national level, by sex for the year 2020. In 2020, LC ranks first in terms of cancer death in half (93 out of 185) of the countries included in GLOBOCAN, and either 2nd or 3rd in 37 countries, in men. LC is a major contributor to cancer mortality around the world, including America, greater-Europe, Northern Africa, and across the Asian-Pacific region. There is a less dominant role at present in South America and Sub-Saharan Africa (but not South Africa). In women, the impact is lesser but still very much in evidence; the disease ranks as the leading form of cancer death in 25 countries including those within North America, Northern, Western and Southern-Central Europe, Eastern Asia and Australia/New Zealand. LC mortality ranks as the 2nd or 3rd leading form of cancer mortality in 54 countries worldwide in women.

There is at least a 20-fold variation in mortality between the sexes, with rates uniformly higher among men (Figure 2). Male mortality rates are higher in Eastern and Southern Europe (especially in Hungary and Serbia with rates of 60 per 100,000), Eastern Asia (particularly the Democratic People's Republic of Korea) and Polynesia and Micronesia, while rates are lower in Central America, South-Central Asia and most parts of sub-Saharan Africa. The highest female rates are observed in Northern America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia and across the African continent, excluding South Africa.

Lung cancer mortality burden by 2040

If the current rates were to remain constant over the next two decades, LC will claim around 2 million male deaths in 2040, compared to 1.2 million in 2020 (Figure 3). For women, the corresponding deaths are approximately half of their male counterparts: a predicted increase to 1 million in 2040 from 600 000 deaths in 2020. The projection also shows the different scenarios considering the changing rates per year between -3% and +3% based on plausible scenarios of the smoking epidemic in the short-term future; global declines in the number of LC among males but increases for female are perhaps the more realistic scenarios, with national or regional exceptions. Taking this trends-based prediction into account, the predicted number of deaths due to LC for men will likely range between 1.1 and 1.6 million and for women between 1.2 and 1.8 million by 2040. Deaths will markedly increase for both sexes in countries with the lowest HDI, even in the best-case trend scenario (Appendix Figure 1a-h).

Discussion

This study highlights the present geographic diversity in LC mortality worldwide, by sex and by level of human development. Countries with low HDI tend to have low LC mortality rates but may anticipate a higher mortality burden by 2040. For higher HDI countries, the burden of the disease is higher among men, but future trends suggest an increasingly greater proportion of the cancer burden will be seen among females. These different scenarios are due to the impact of historic smoking trends and the increasingly widespread application of tobacco control measures in the last decades [21]. While there is an expectation that LC mortality will increase in transitioning countries given there is less implementation of effective tobacco control, there is a positivity in the findings from the Global Tobacco Control Report: the number of people now living in countries with at least two anti-tobacco policies in place rose from 3.5 billion in 2018 to 4.4 billion in 2020 – up from 45% of the world's population to 56% in two years [22].

Past smoking histories of nations are a key determinant of the current magnitude of LC in many populations worldwide, as described by the classical model of the global smoking epidemic, first introduced by Lopez et al [4]. In the model, the effect of different smoking patterns was captured by four

stages in the population, by an earlier adoption of the habit in men compared with women, and by the progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying cause of the marked inequalities seen in different educational groups [23]. Lopez et al. initially applied the hypothesis on just a few developed countries [24], which was later tested on greater geographic scales [25,26]. Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline among men in many populations over the last decades, a key focus has been the deteriorating public health situation affecting women, where in many settings, rates of LC mortality have continued to rise. This raises several relevant biological, epidemiological and sociological concerns [27], including: the changing distribution of the main histological subtypes of LC over time [28], the extent to which females adopted the habit of smoking and their vulnerability to the tobacco industry [29,30], the impact of such a transition in diminishing gender differences in disease burden worldwide [31] and the effects of different political systems on the health awareness of individuals [32,33]. The impact of these factors is reflected in comparisons of between-country LC mortality rates; for example, the current rate differences in Eastern vs. Northern European countries.

Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with other factors, including air pollution, climate change [34] and other occupational risk factors such as asbestosis and indoor exposure to cooking fumes etc [35]. The highest exposure to ambient air pollution is the characteristic of mainly countries in transition, where only modest reductions in burden will occur in the most polluted countries unless fine particulate matter (PM 2.5) values are decreased substantially [36].

Several other studies have aimed to forecast the future lung cancer burden in very high HDI countries e.g., the US [37] and the UK [38] with contradictory findings. While the steeply declining mortality in the US for both sexes until 2040 fits within the framework of the global smoking epidemic, the rising deaths reported in the UK for men and women until 2035 somewhat contradict previous findings. One explanation could be the rapidly ageing population, which can increase the number of these non-standardized figures. Alternatively, these projections do not take into account the changing smoking prevalence in the past as a key determinant of present and future lung cancers. Our GLOBOCAN 2020 forecasts do not consider these either, however, we provide possible scenarios on the basis of uniform increases or decreases in rates that may help provide a realistic overview of the changing future burden of LC.

Another limitation of this study is the large variability in the availability and quality of cancer mortality data. Most African and some Asian countries suffer from weak mortality statistics systems. In GLOBOCAN, in countries where mortality series were not available from national vital registration sources, the predominant means of the estimation of rates were from corresponding national incidence

estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in neighbouring countries.

With over three million deaths predicted by 2040 in the absence of additional interventions according to the finding of this study, it is imperative to emphasize primary prevention as the most cost-effective strategy of tobacco control. It has been shown that raising the price of cigarettes through increased excise taxes can bring marked reductions in cigarette consumption [39]. Besides this, developing adaptive tobacco control strategies that target different subgroups is imperative.

One key concern is the limited financial and trained resources in middle- and lower-income countries, that can hinder health promotion and cancer prevention strategies in these countries. Based on our findings, decreases in lung cancer rates are not likely in these countries until 2040 and presumably tobacco companies are expected to shift and escalate promotional campaigns to preserve business interests and profits where resistance efforts are the weakest [30].

Additionally, anti-tobacco strategies should urgently target women in also higher-income settings such as the EU, in order to halt their rapidly increasing risk of LC, and prevent unnecessary, premature deaths among future generations of women [40]. In Sweden, as an example, gender-specific policies such as those directed at health promotion have been implemented with a focus on young and pregnant women. Scotland also has gender-specific programs, such as the Women, Low Income, and Smoking Project [41]. Amos and Haglund (2000) have emphasized that building support for female-centered tobacco control programs through partnerships will be vital to achieve success [30]. Furthermore, Amos (1996) and Mackay and Amos (2003) draw attention to the situation of women in transitioning countries with presently low levels of cigarette smoking among women [29]. In these countries, smoking among girls is already on the rise, women's spending power is increasing, cigarettes are becoming affordable, and women are more exposed to the marketing strategies of tobacco companies, in an environment where cultural constraints are weakening and female-specific quitting programs are rare [8].

A package of measures to suppress tobacco consumption in a given population has been recommended through continued efforts to increase the proportion of ex-smokers, with a focus on younger generations [42]. This could perhaps be achieved by implementing coordinated smoking prevention and control strategies from an early age, in the form of educational programs in schools. Other measures that could be introduced include community intervention programs, mass media campaigns and further legislation to ban smoking in public places. One of the main problems is that young people react very differently to anti-smoking messages compared to adult long-term smokers [42]. The harm-reducing role of e-cigarettes and aid to smoking cessation has been proposed [43], however their impact on future LC mortality is not yet known [44]. Successful programs have also been implemented in rapidly emerging economies such as Brazil, where a reduction in smoking prevalence were observed after the ratification of the WHO Framework Convention on Tobacco Control (FCTC) in 2005, and the adoption of a national ban on tobacco advertising, a national comprehensive smoke-free policy, large pictorial health warnings on cigarette packages, and continuous increases in taxes and prices of tobacco products [45]. Other factors may influence the future burden of LC such as the potential introduction of screening in high-risk populations. In a recent trial, LC mortality was significantly lower among those who underwent volume computed tomography (CT) screening than those who did not participate [46]. Screened patients benefitted from a substantial shift to lower-stage cancers at the time of diagnosis as well as more frequent eligibility for curative treatment (mainly surgery) [47]. However, concerns have been raised about the potential for overdiagnosis in lung-cancer screening.

In summary, this paper has identified marked geographic variations in the current LC burden worldwide and provided potential scenarios regarding the short-term future LC deaths up until 2040. Gredner et al., have illustrated the great potential of comprehensive implementation of tobacco control policies in Greater-Europe, with over 1.6 million LC cases preventable over a 20-year period through the highest-level implementation of tobacco control policies [48]. There is therefore much we can do to halt the rising deaths from LC – as well as many other forms of cancer and non-communicable diseases – through the successful implementation of tobacco control policies.

Disclosure

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Role of the funding source

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Authors' contribution

AW: literature search, data analysis, writing – original draft; EM: writing – review & editing; JV: figures, visualisation; ML: methodology, figures, visualisation; MP: writing – review & editing; HR: writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology, conceptualisation, data analysis, writing – original draft

Declaration of interests

All authors declare that they have no conflicts of interest.

Data sharing

Data are available in a public, open access repository.

Ethics Approval Statement

This study does not involve human participants and animal subjects.

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Figures

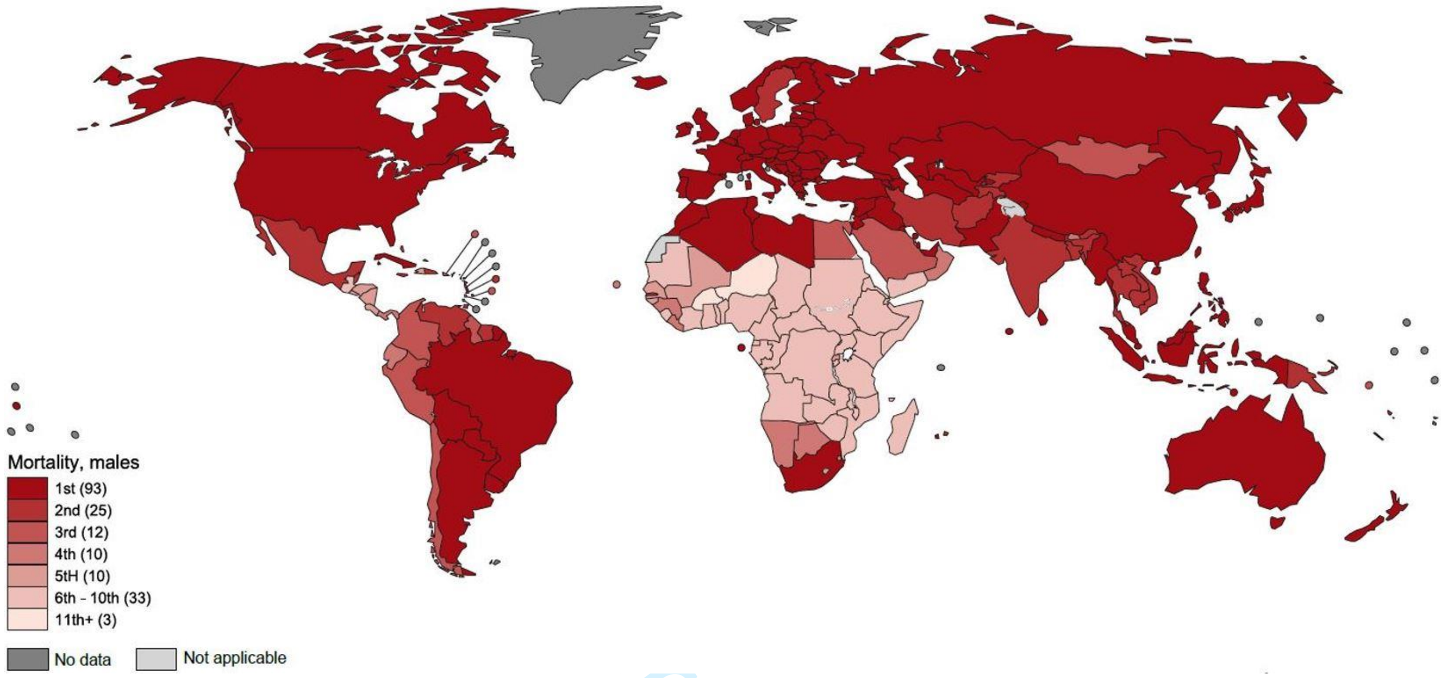
Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020, Male-Female

Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020, Male-Female

Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020

Male



Female

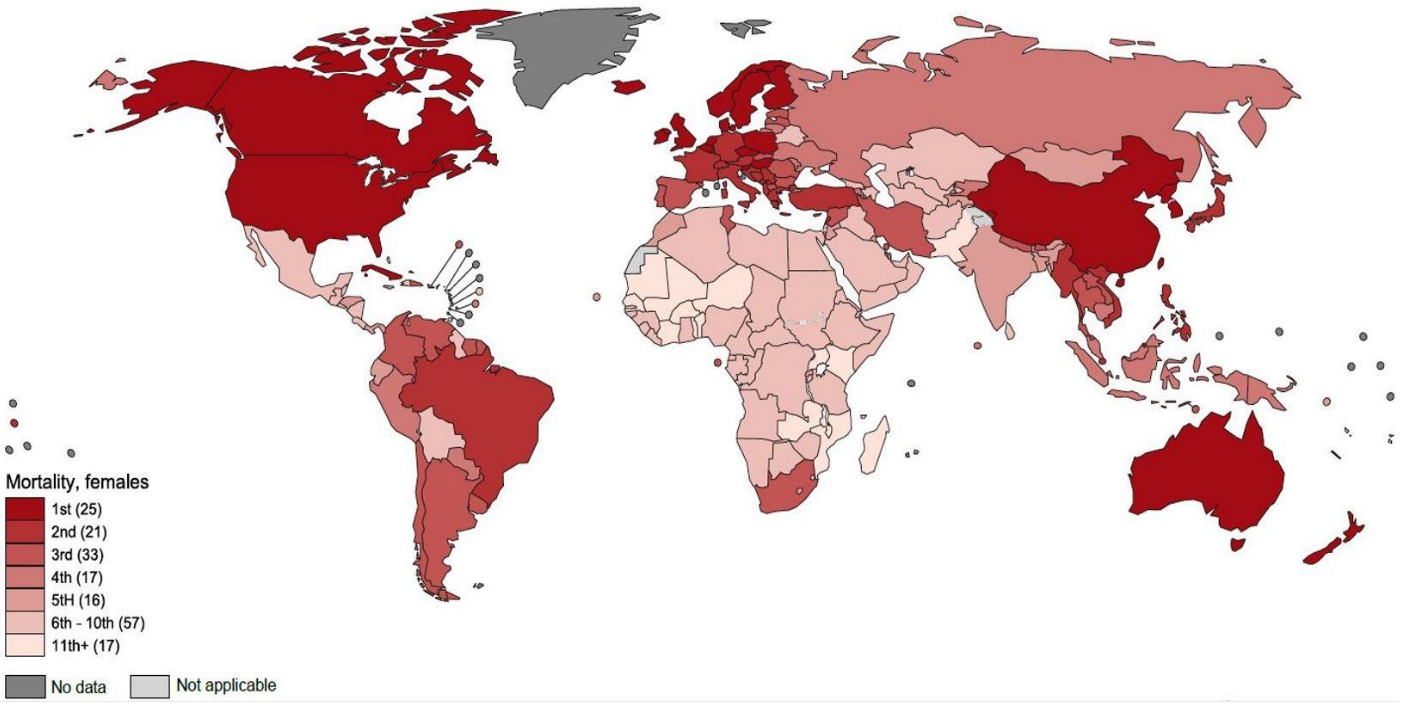


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020

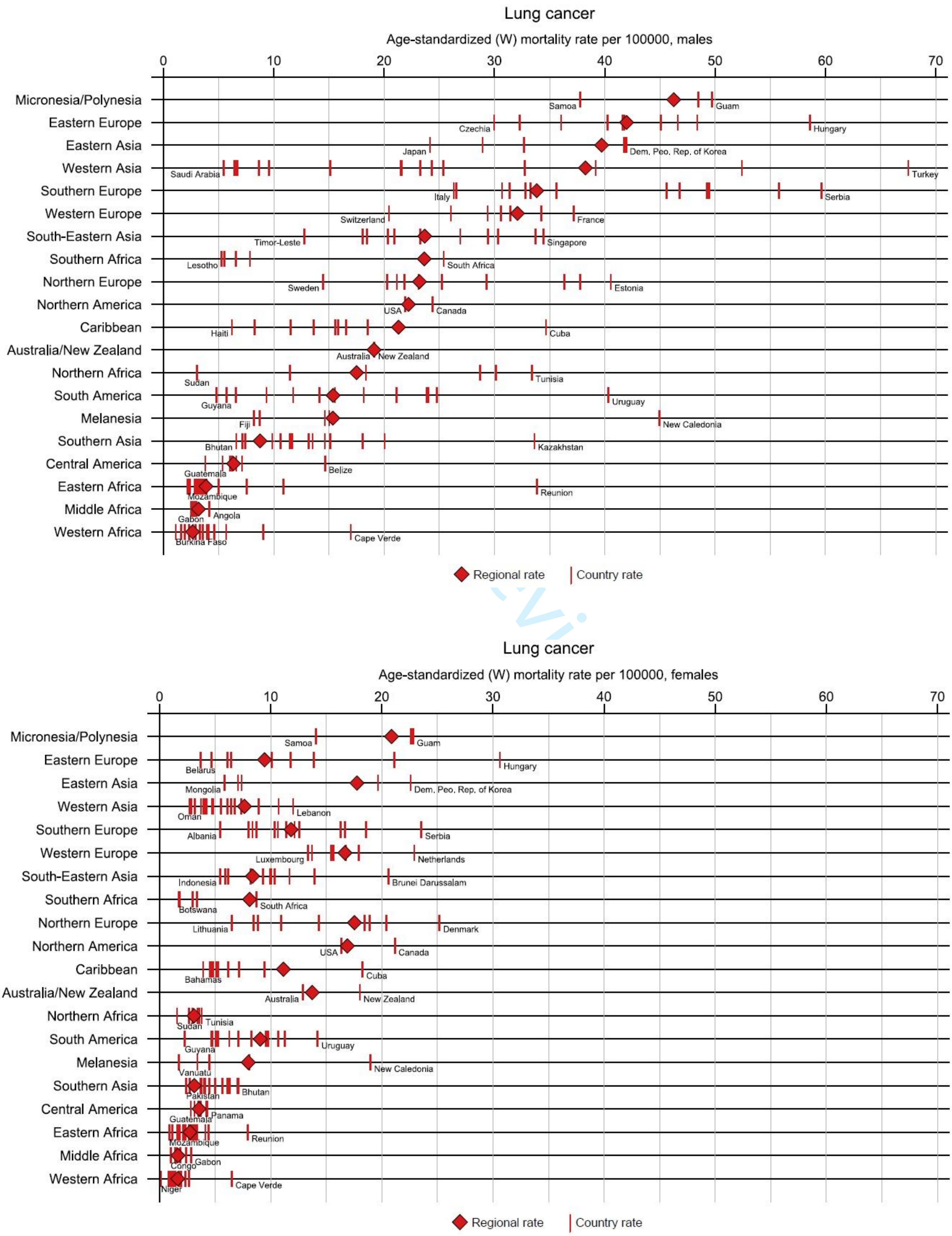
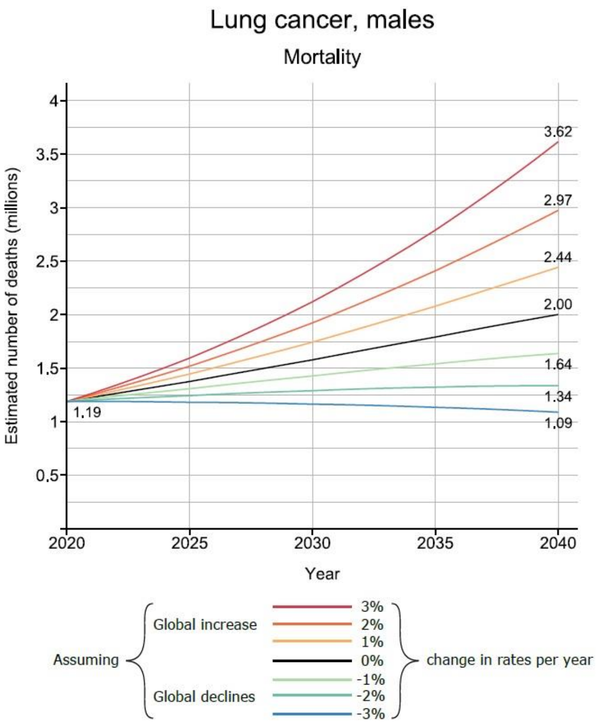


Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A



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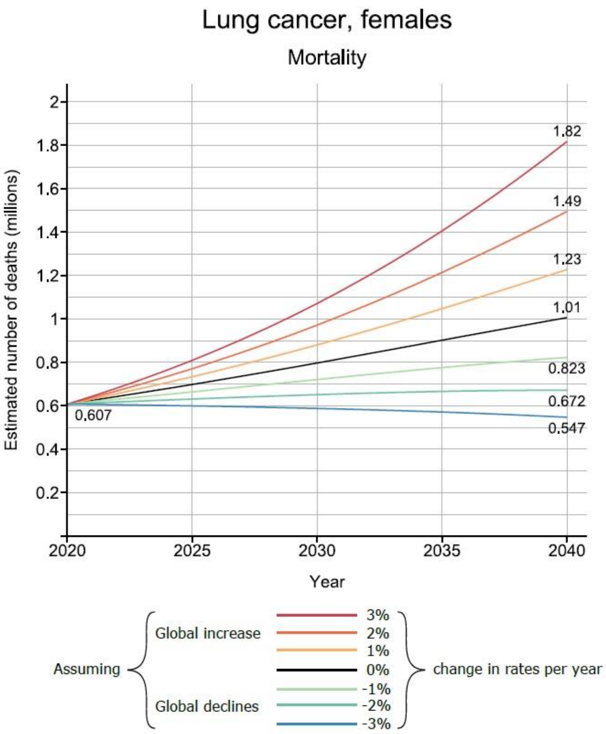


Supplemental material - Appendix

Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020, Male - Female

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

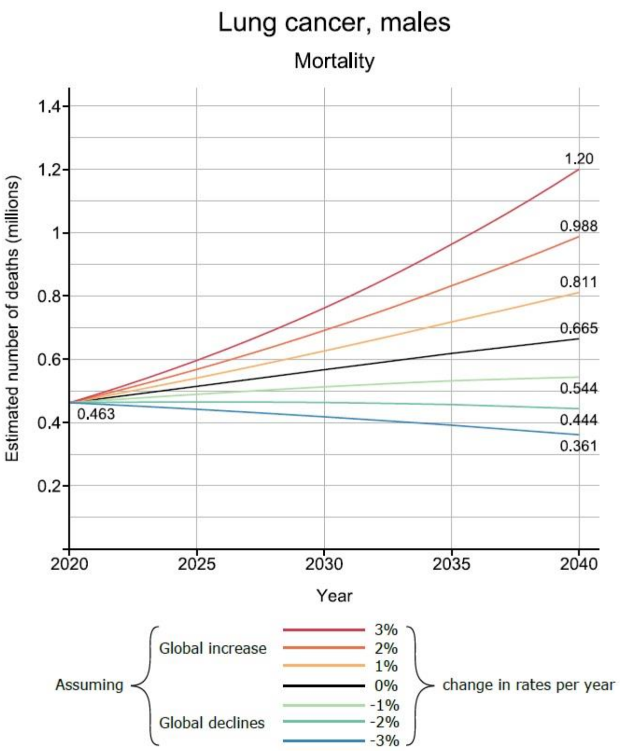
Data source: Globocan 2020, Map production: CSU, World Health Organization

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [13 April 2022].

Appendices

Lung cancer mortality by sex - very high HDI countries

A



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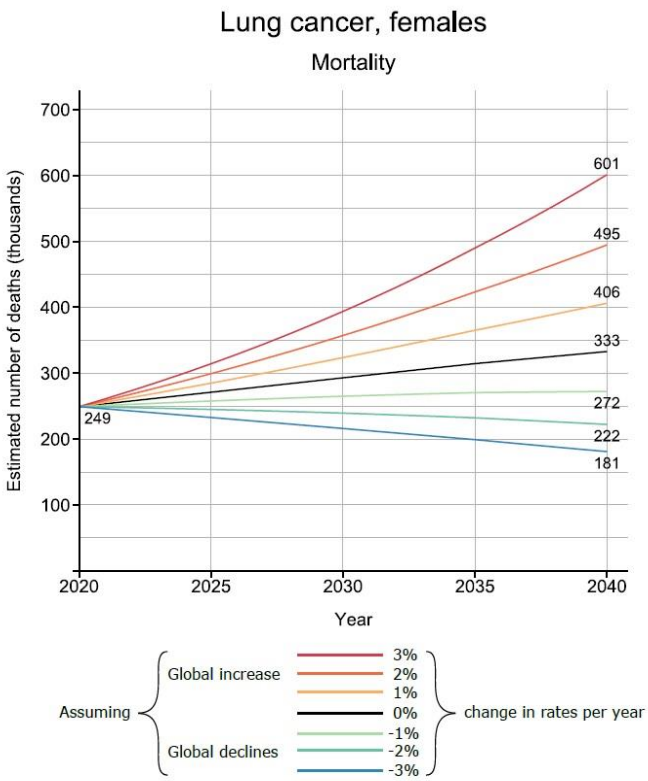
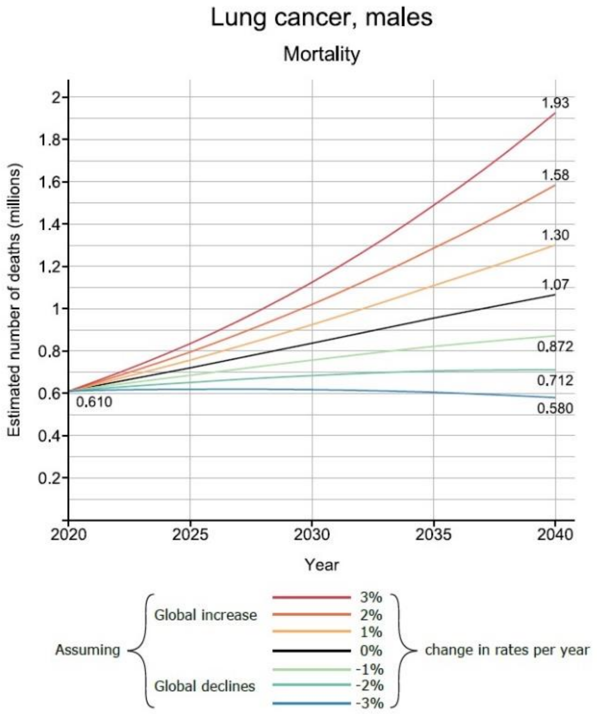


Lung cancer mortality by sex - high HDI countries

C



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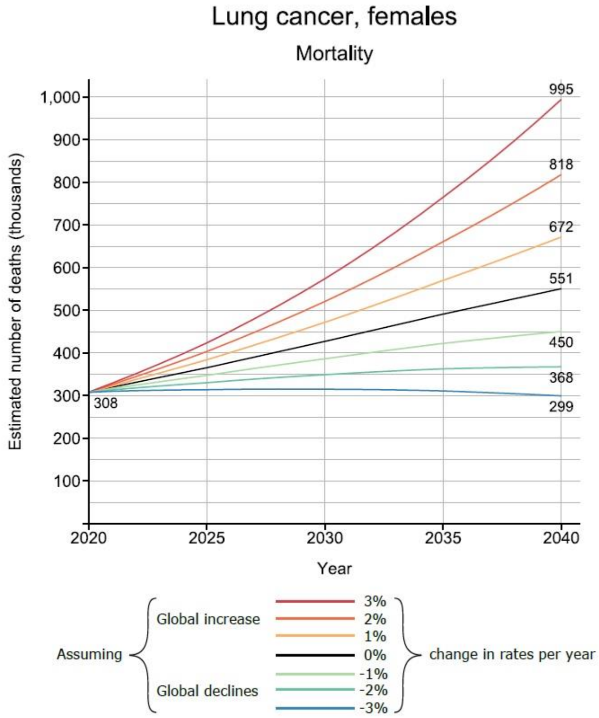
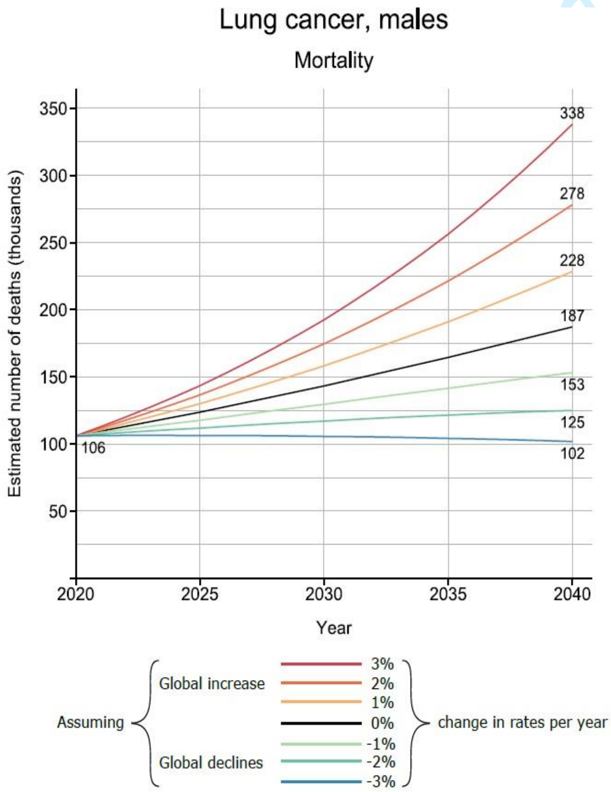


Lung cancer mortality by sex - medium HDI countries

E



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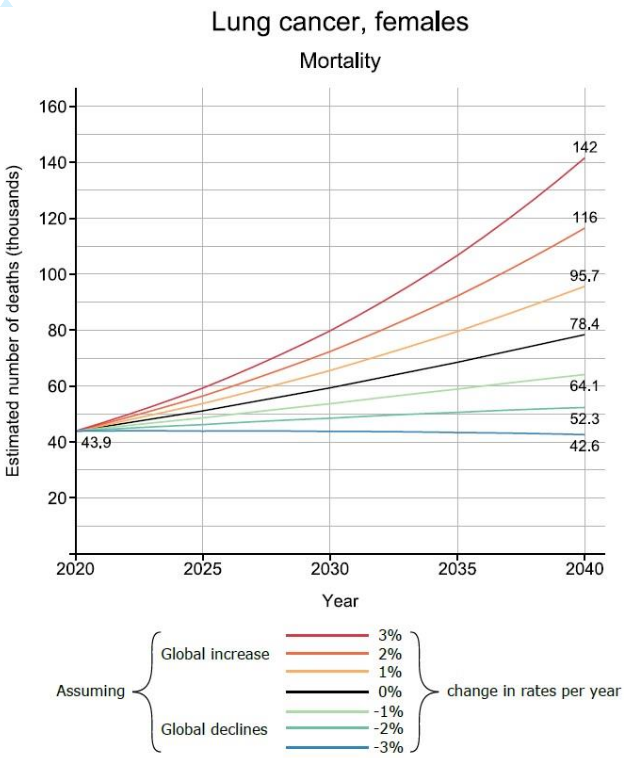
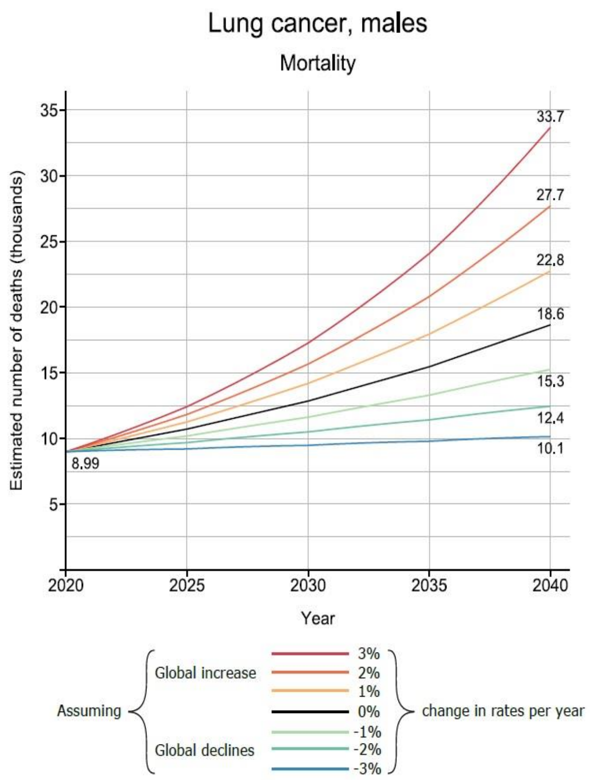
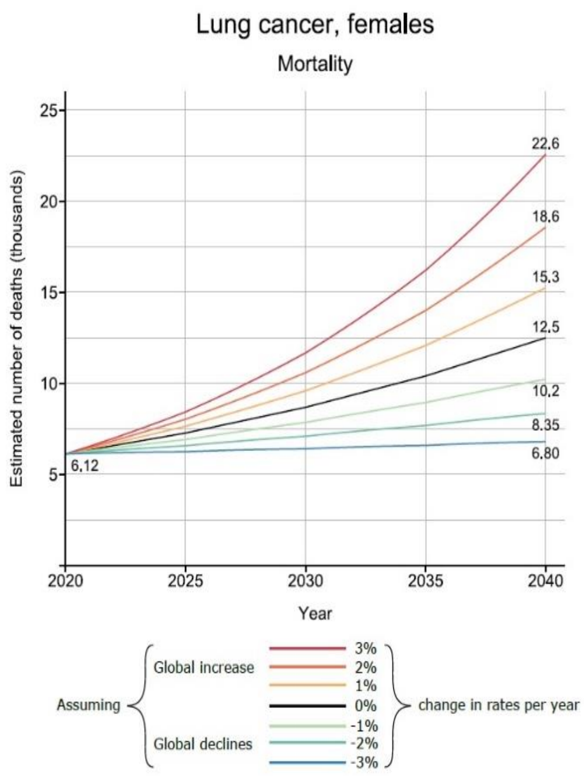


Lung cancer mortality by sex - low HDI countries

G



H



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	-

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6
Generalisability	21	Discuss the generalisability (external validity) of the study results	6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.