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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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| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-065303 |
| Article Type: | Original research |
| Date Submitted by the Author: | 07-Jun-2022 |
| Complete List of Authors: | Weber, Andras; International Agency for Research on Cancer, Cancer Surveillance Branch; National Institute of Oncology, Hungarian National Cancer Registry Vignat, Jerome; International Agency for Research on Cancer Laversanne, Mathieu; International Agency for Research on Cancer, Cancer Surveillance Branch Morgan, Eileen; International Agency for Research on Cancer Pizzato, Margherita; International Agency for Research on Cancer; University of Milan, Department of Clinical Sciences and Community Health Rumgay, Harriet; International Agency for Research on Cancer Singh, Deependra; International Agency for Research on Cancer Nagy, Péter; National Institute of Oncology, Department of Molecular Immunology and Toxicology; University of Veterinary Medicine, Department of Anatomy and Histology Kenessey, István; National Institute of Oncology; Semmelweis University, Department of Pathology, Forensic and Insurance Medicine Soerjomataram, Isabelle; WHO Bray, Freddie; Int Agcy Res Canc, Cancer Surveillance Branch |
| Keywords: | Epidemiology < TROPICAL MEDICINE, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH |
| | |

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3 **A global analysis of the current and future lung cancer mortality in the wake of the changing**
4 **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 countries¹. With one-fifth of the cancer mortality worldwide in 2020 due to LC – an estimated 1.8 million deaths² – 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 duration³. Lopez et al. drew attention to the phases of the global smoking epidemic and the subsequent impact of smoking on LC occurrence by sex⁴; 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 prevalence⁷. 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 constraints that previously prevented them from tobacco consumption are weakening⁸, 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) website¹². The data sources and hierarchy of methods used in compiling the cancer estimates have been described in detail elsewhere¹⁰. 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 years¹³⁻¹⁵ 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 information¹⁰.

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3 We present figures based on the estimated deaths in 2020, as well as two summary measures using
4 direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years
5 based on the 1966 Segi-Doll World standard population^{16,17} and the cumulative risk of dying from cancer
6 before the age of 75 expressed as a percentage, assuming the absence of competing causes of death¹⁸.
7 These measures allow comparisons between populations adjusted for differences in age structures. We
8 also provide a prediction of the future number of LC deaths worldwide for the year 2040, based on
9 demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%) or
10 decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of
11 COVID-19 pandemic was not taken into consideration during the calculations.

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17 The results are presented by country, and aggregated, across 20 UN-defined world regions¹², and
18 according to the UN's four-tier HDI in 2020¹⁹ as a means to assess the cancer burden across four levels
19 of development (low, medium, high and very high HDI). Throughout we use the terms transitioning,
20 emerging and lower HDI countries/economies as synonyms for nations classified as low or medium
21 HDI, and transitioning or higher HDI countries/economies for those classified as high or very high HDI.

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25 The Global Cancer Observatory (GCO, <https://gco.iarc.fr>) includes facilities for the tabulation
26 and graphical visualization of the GLOBOCAN database, including explorations of the current² and
27 future²⁰ burden for 36 cancer types.

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

38 *Lung cancer mortality – national rankings 2020*

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

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57 According to Figure 2 there is at least a 20-fold variation between the rates in both sexes, with rates
58 uniformly higher among men. Male mortality is higher in Eastern and Southern Europe (especially in
59 Hungary and Serbia with nearly 60 deaths per 100,000), Eastern Asia (particularly in the Democratic
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3 People's Republic of Korea) and Polynesia and Micronesia, while it is lower in Central America, South-
4 Central Asia and most parts of sub-Saharan Africa. The highest female rates are seen in Northern
5 America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark
6 and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia
7 and across the African continent, except for Southern Africa.
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10 11 *Lung cancer mortality burden by 2040*

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13 Figure 3 demonstrates that if the trends do not change in the next two decades, LC will claim
14 around 2 million male deaths in 2040, compared to 1.2 million in 2020. For women, the corresponding
15 predicted and registered numbers are approximately half: 1 million and 600 000 deaths, respectively.
16 The projection also shows the different scenarios considering the changing rates per year between -3%
17 and +3%. Keeping in mind the axioms of the theory of global smoking epidemic⁴, global declines in the
18 number of LC among males but increases for female are more realistic scenarios in the future, with
19 exceptions. Taking this into account, by 2040, the predicted number of deaths due to LC for men will
20 likely range between 1.1 and 1.6 million and for women between 1.2 and 1.8 million. Appendix Figure
21 1a-d also reports the projections by HDI levels, which show, that in the lowest category of HDI
22 countries, deaths will markedly increase for both sexes even in the best-case LC mortality scenario.
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31 **Discussion**

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33 This research highlights the inverse status of low and high HDI countries, in case of the current
34 geographic variability of LC burden and the very different scenarios of changing mortality trends also
35 by sex. Countries with low HDI, can be characterized with low levels of mortality, in mostly sub-
36 Saharan African states and these will probably suffer a higher burden of LC for both sexes until 2040.
37 For higher HDI countries, the burden of the disease is higher for men, but future trends appear be more
38 favourable than for females, where increasing LC mortality is more likely till 2040.
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44 The past smoking histories of nations are a key determinant of the current magnitude of LC in
45 many populations worldwide, as described by the classical model of the global smoking epidemic, first
46 introduced by Lopez et al⁴. In the model, the effect of different smoking patterns was captured by four
47 stages in the population, by an earlier adoption of the habit in men compared with women, and by the
48 progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying
49 cause of the marked inequalities seen in different educational groups²¹. Lopez et al. initially applied their
50 theory on only just a few developed countries²², but later was tested on greater geographic scales^{23,24}.
51 Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline among men in
52 many populations over the last decades, a key focus has been the deteriorating public health situation
53 affecting women, where in many settings, rates of LC mortality continue to rise. This raises several
54 relevant biological, epidemiological and sociological concerns²⁵, including: the change on the main
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3 histological types of LC over time²⁶, the extent to which females adopted the habit of smoking and their
4 vulnerability to the tobacco industry^{27,28}, the impact of such a transition in diminishing gender
5 differences in disease burden worldwide²⁹ and the effects of different political ruling systems on the
6 health awareness of individuals^{30,31}, which are well reflected e.g. in the current Eastern European vs.
7 Northern European male lung cancer mortality figures. However, this paper clearly proves that for most
8 of the low HDI countries this comprehensive macro theory is not applicable, whereas LC deaths from a
9 relatively low level are expected to simultaneously rise for both sexes.
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15 Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with
16 other factors, e.g., air pollution, climate change³² and other occupational risk factors such as asbestosis
17 and indoor exposure to cooking fumes etc³³. The highest exposure to ambient air pollution is the
18 characteristic of mainly Low and Low Middle-Income Countries (LMICs), where only modest
19 reductions in burden will occur in the most polluted countries unless fine particulate matter (PM 2.5)
20 values are decreased substantially³⁴.
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25 There are several limitations to this study e.g., the large variability in the availability and quality
26 of cancer mortality data. Many African and some Asian countries suffer from weak mortality statistics
27 systems. In GLOBOCAN, in countries where mortality series were not available from national vital
28 registration sources, the predominant means of the estimation of rates were from corresponding national
29 incidence estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in
30 neighbouring countries.
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35 With over 3 million deaths predicted by 2040 in the absence of additional interventions according
36 to the finding of this study, it is imperative to emphasize primary prevention as the most cost-effective
37 strategy of tobacco control. It has been shown that raising the price of cigarettes through increased excise
38 taxes can bring marked reductions in cigarette consumption³⁵. Besides this, developing adaptive tobacco
39 control strategies that target different subgroups is imperative; anti-tobacco strategies urgently should,
40 target women living in the EU, in order to halt their rapidly increasing risk of LC, and prevent
41 unnecessary, premature deaths among future generations of women³⁶. Amos and Haglund (2000)
42 emphasize that building support for female-centered tobacco control programs through partnerships will
43 be vital to achieve success²⁸. Furthermore, Amos (1996) and Mackay and Amos (2003) draw the
44 attention to the problematic situation of women in developing countries, even in which have low levels
45 of female cigarette smoking²⁷. In these, smoking among girls is already on the rise, women's spending
46 power is increasing, cigarettes are becoming affordable, they are more exposed to the marketing
47 strategies of the tobacco companies, cultural constraints are weakening and female-specific quitting
48 programs are rare⁸. Additionally, a package of measures to suppress tobacco consumption in a given
49 population, has been recommended through continued efforts to increase the proportion of ex-smokers,
50 as well as a concentrated focus on younger generations³⁷. This could perhaps be achieved by
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3 implementing coordinated smoking prevention and control strategies from an early age, in the form of
4 educational programs in schools. Other measures that could be introduced include community
5 intervention programs, mass media campaigns and further legislation to ban smoking in public places.
6 One of the main problems is that young people react very differently to anti-smoking messages than do
7 adult long-term smokers³⁷.
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11 In a trial involving high-risk persons, LC mortality was significantly lower among those who
12 underwent volume computed tomography (CT) screening than among those who underwent no
13 screening³⁸. Another clear advantage was the substantial shift to lower-stage cancers at the time of
14 diagnosis as well as to more frequent eligibility for curative treatment (mainly surgical)³⁹, however
15 concerns have been raised about the potential for overdiagnosis in lung-cancer screening.
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20 In summary, this paper has identified marked geographic variability in the current LC burden
21 across the world and provided potential scenarios in the changing number of deaths due to this disease
22 until 2040. There is much we can do to halt the rising LC deaths. Gredner et al., provided, for example
23 an assessment of future tobacco policy impact based on the relation of current implementation and
24 tobacco smoking prevalence in countries to illustrate the great potential of comprehensive
25 implementation of tobacco control policies in Greater-Europe. According to their estimations 1.65
26 million LC cases could be prevented over a 20-year period with the highest-level implementation of
27 tobacco control policies⁴⁰.
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35 **Role of the founding source**

36 This work was supported by the National Laboratories Excellence program (under the National
37 Tumorbiology Laboratory project (NLP-17)) and the Hungarian Thematic Excellence Programme
38 (TKP2021-EGA-44).
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43 **Authors' contribution**

44 AW: literature search, data analysis, writing – original draft; JV: methodology, data collection, figures,
45 visualisation; ML: visualisation; EM: writing – review & editing; MP: writing – review & editing; HR:
46 writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding
47 acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology,
48 conceptualisation, data analysis, writing – original draft
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54 **Declaration of interests**

55 All authors declare that they have no conflicts of interest.
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59 **Data sharing**

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3 The data that support the findings of this study are openly available in the Global Cancer Observatory
4 (GLOBOCAN) at <https://gco.iarc.fr/>
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8 **Patient and Public Involvement**

9 Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination
10 plans of our research.
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13 **Ethics Approval Statement**

14 This study does not involve human participants and animal subjects.
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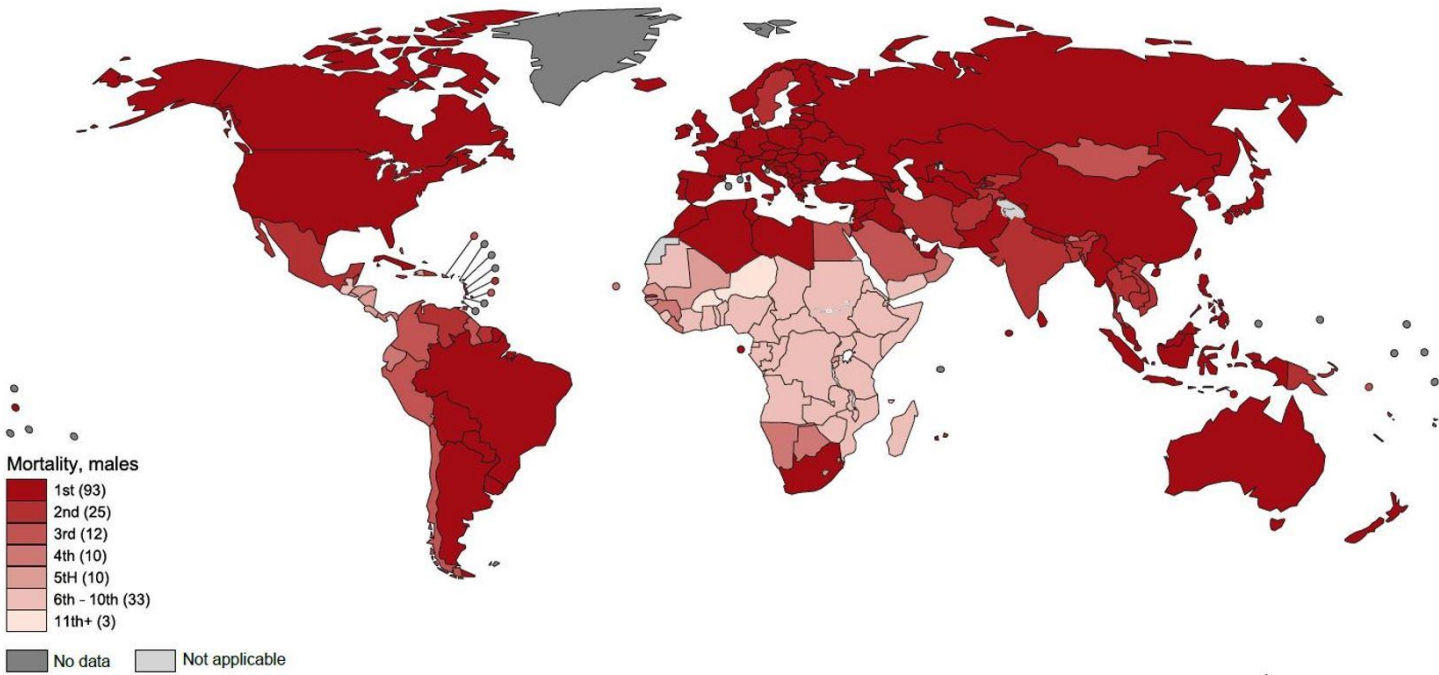
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27 NELSON lung cancer screening trial: implications for clinicians. *Rotterdam, the Netherlands:*
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32 based modeling study. *The Lancet Regional Health - Europe* 2021; 4: 100074.
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Figure 1: Lung cancer mortality country rankings worldwide in 2020
Male



Female

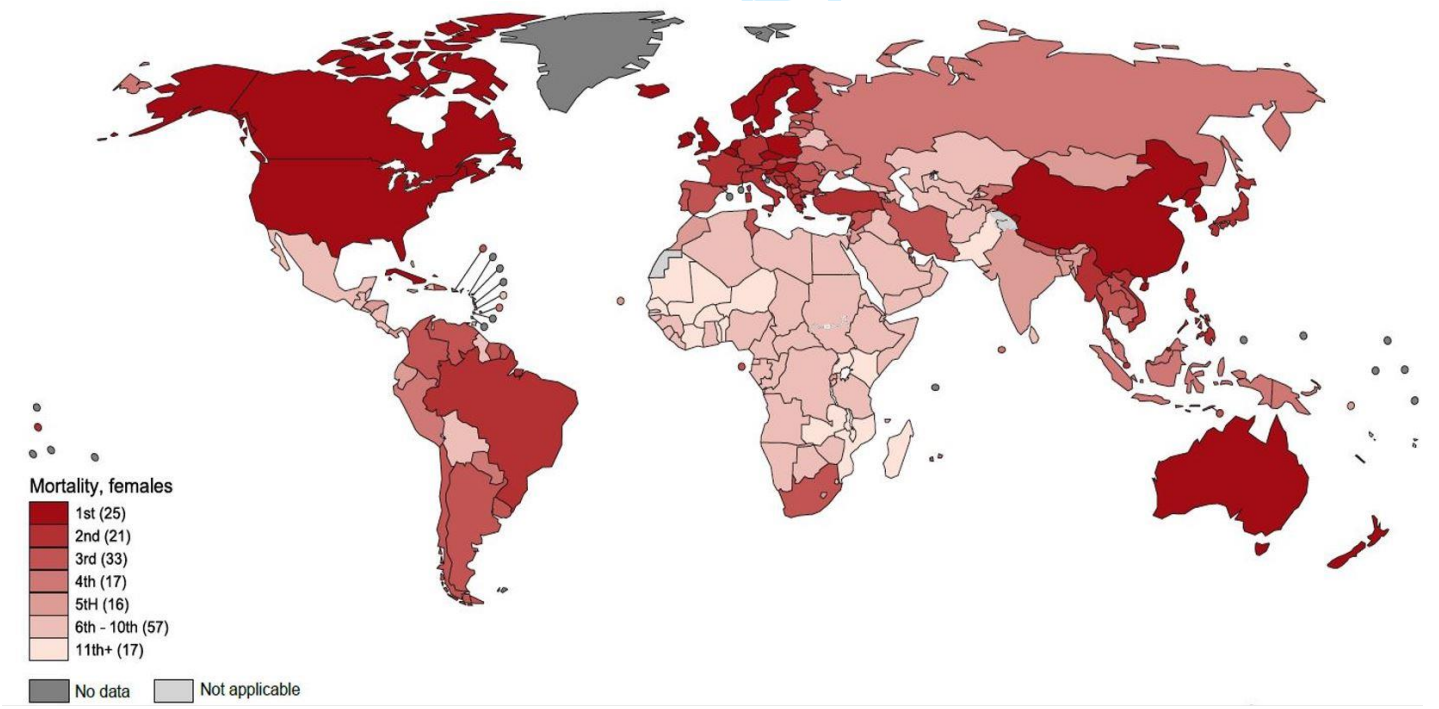
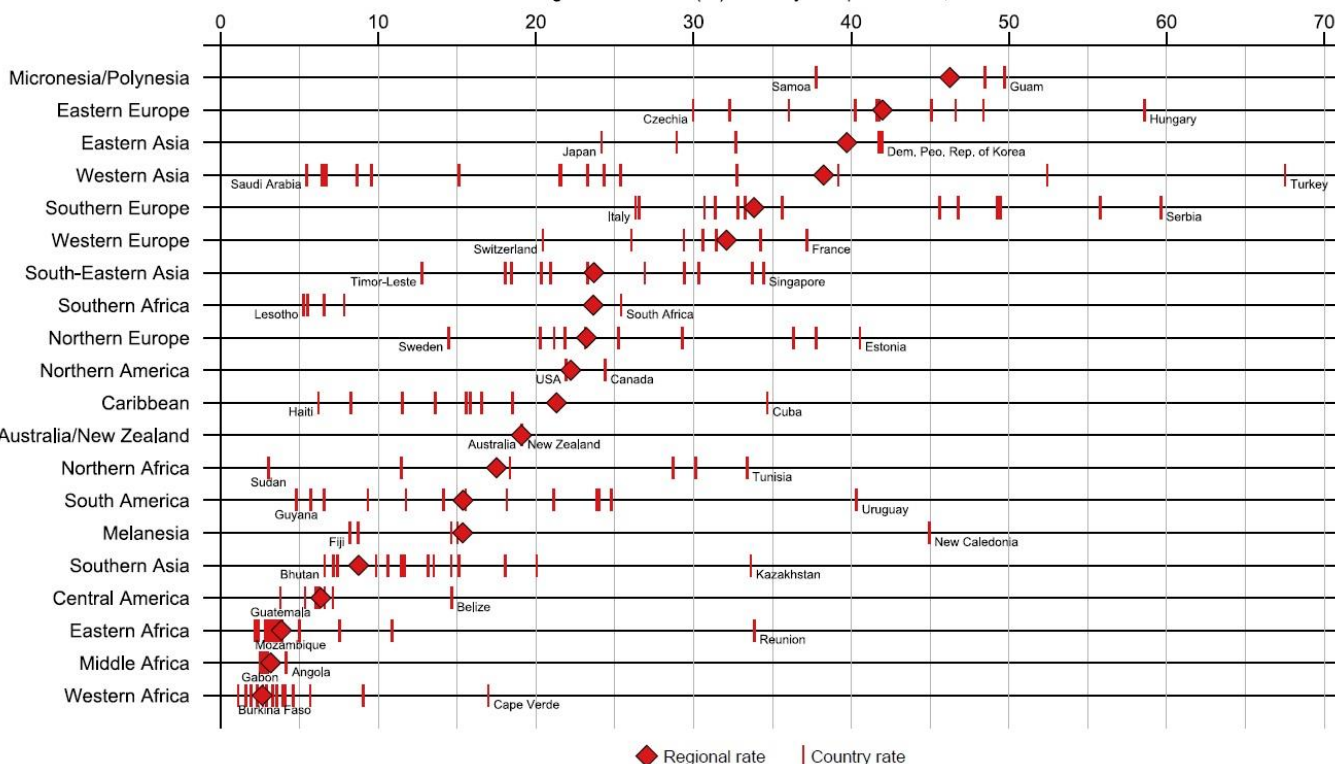


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020

Lung cancer

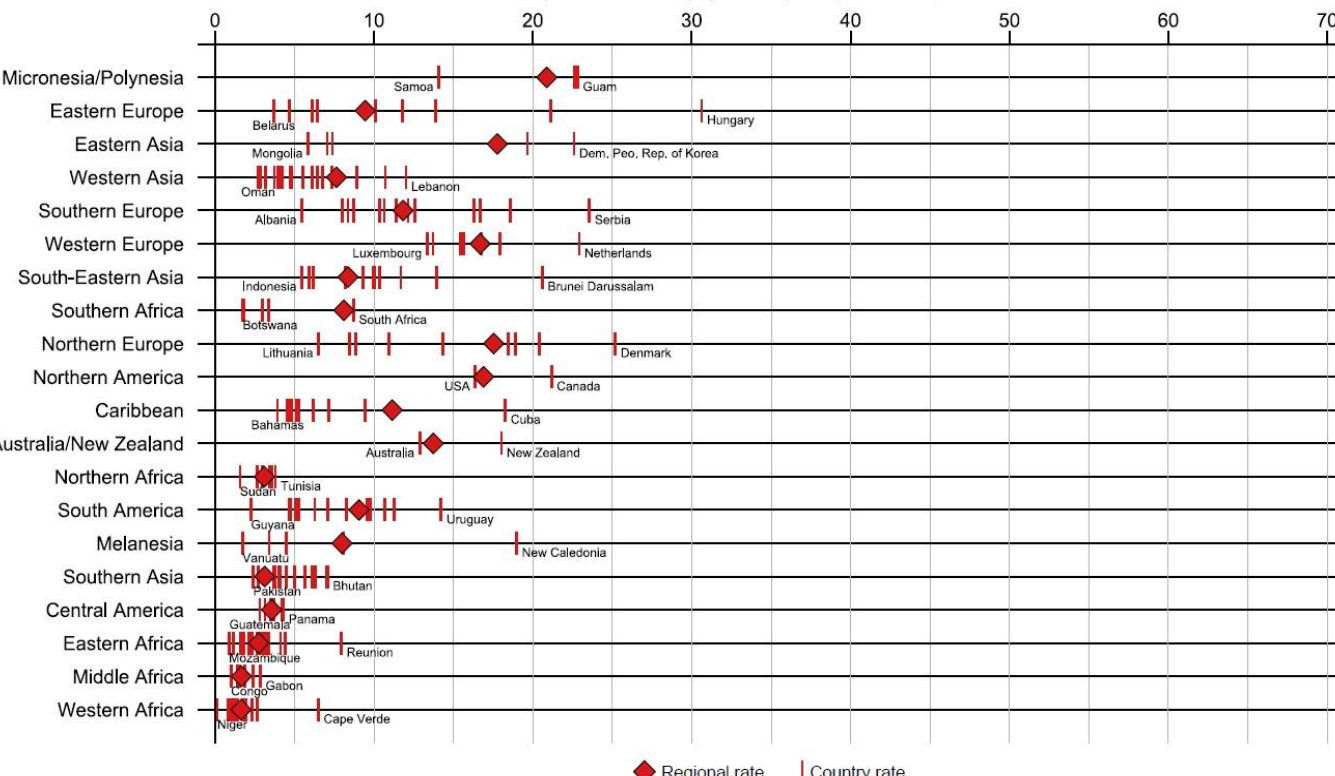
Age-standardized (W) mortality rate per 100000, males



◆ Regional rate | Country rate

Lung cancer

Age-standardized (W) mortality rate per 100000, females

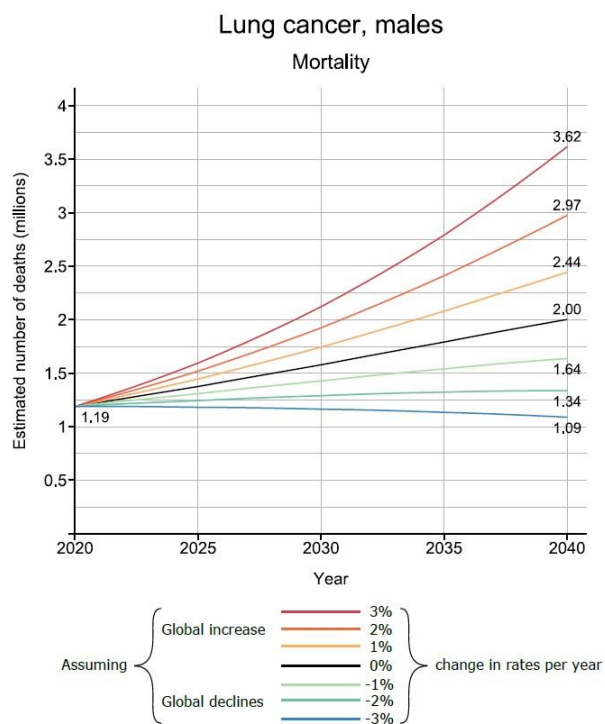


◆ Regional rate | Country rate

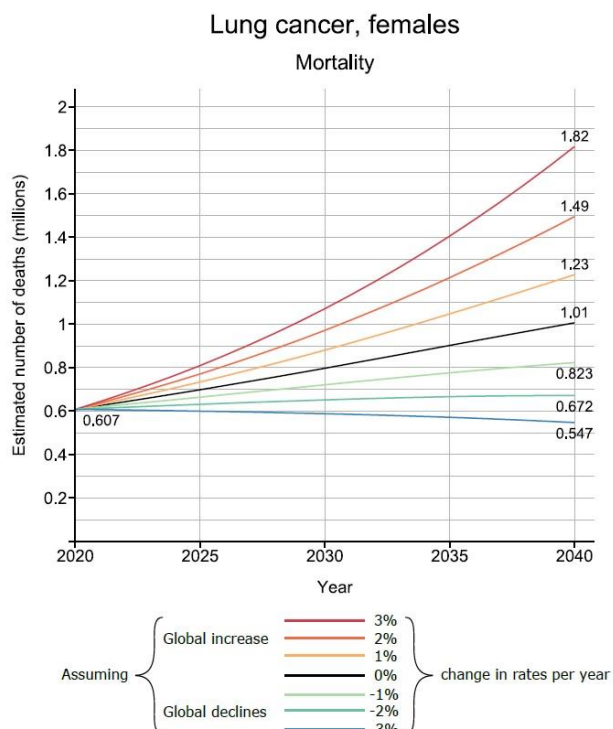
Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A



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view only

Supplemental material - Appendix

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

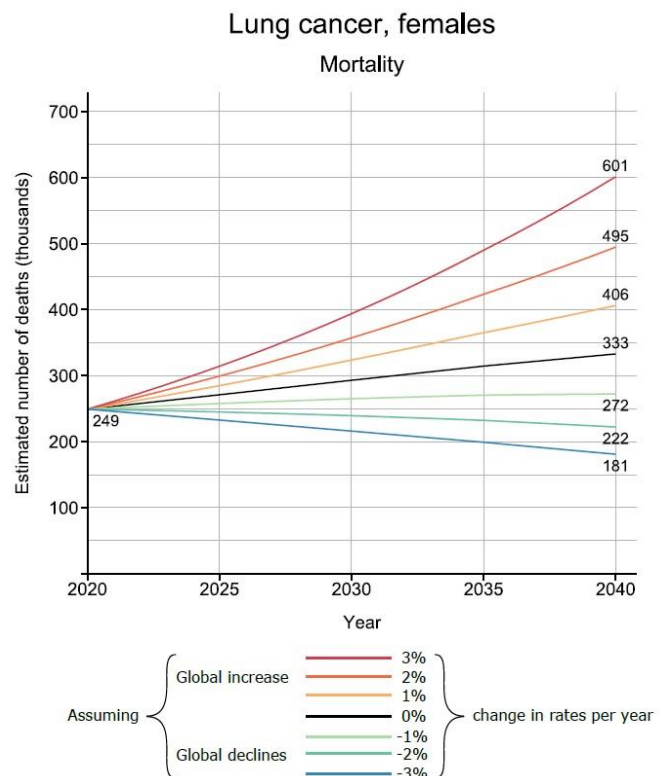
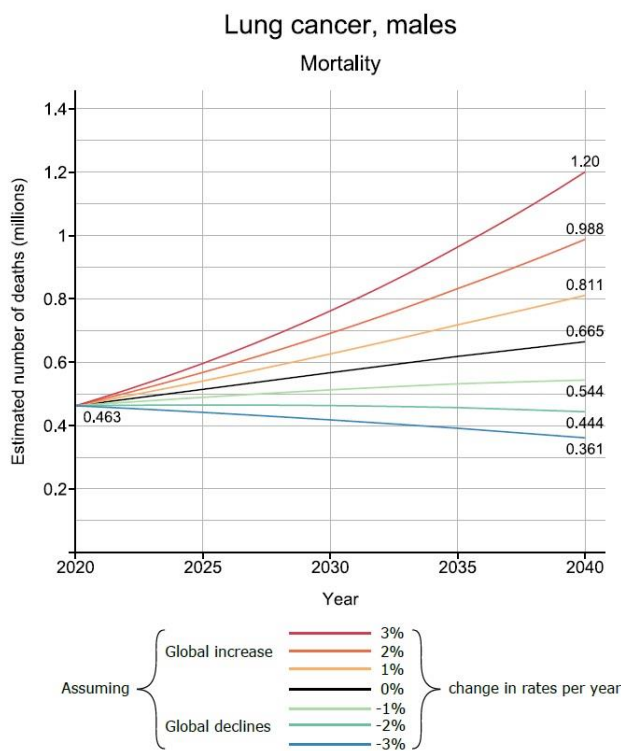
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers 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

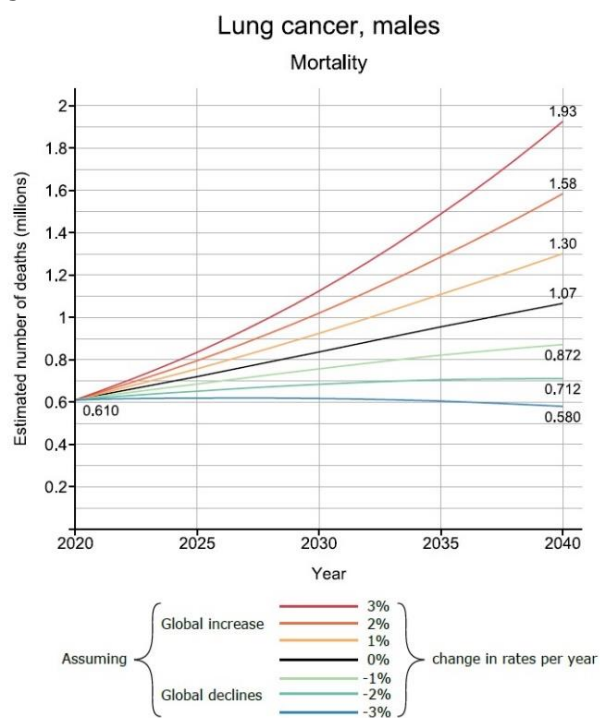
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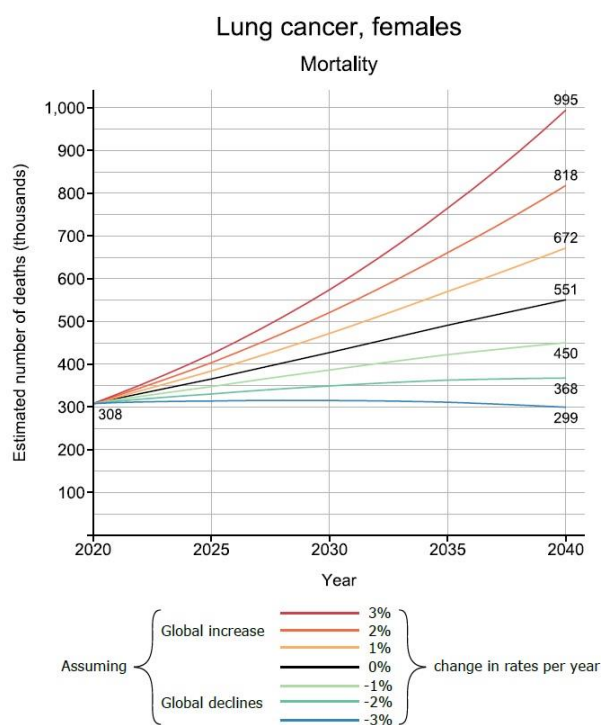


Lung cancer mortality by sex - high HDI countries

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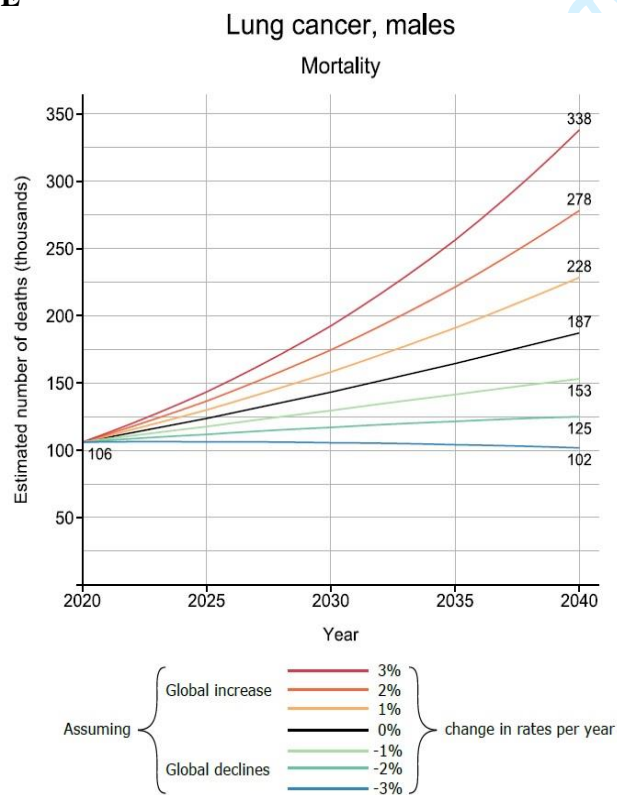


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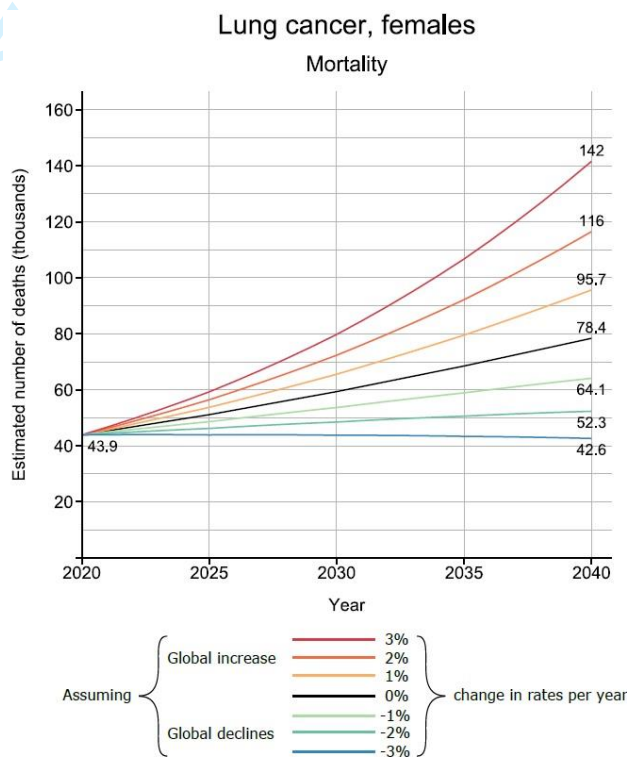


Lung cancer mortality by sex - medium HDI countries

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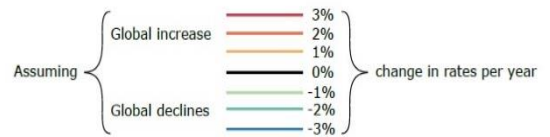
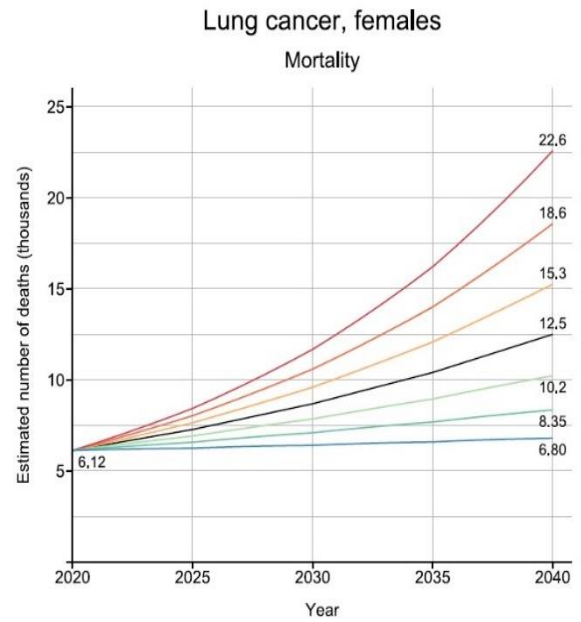
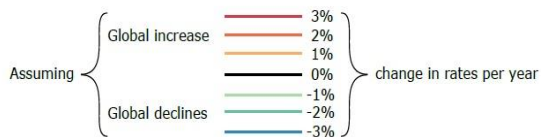
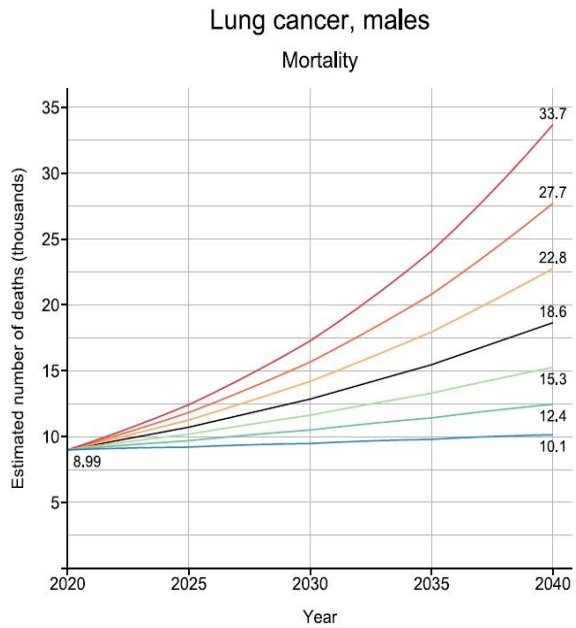
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Lung cancer mortality by sex - low HDI countries

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Review only

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| | | (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) | - |
| Outcome data | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time | - |
| | | <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure | - |
| | | <i>Cross-sectional study</i> —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.

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-065303.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 27-Sep-2022 |
| Complete List of Authors: | Weber, Andras; International Agency for Research on Cancer, Cancer Surveillance Branch; National Institute of Oncology, Hungarian National Cancer Registry Morgan, Eileen; International Agency for Research on Cancer Vignat, Jerome; International Agency for Research on Cancer Laversanne, Mathieu; International Agency for Research on Cancer, Cancer Surveillance Branch Pizzato, Margherita; International Agency for Research on Cancer; University of Milan, Department of Clinical Sciences and Community Health Rumgay, Harriet; International Agency for Research on Cancer Singh, Deependra; International Agency for Research on Cancer Nagy, Péter; National Institute of Oncology, Department of Molecular Immunology and Toxicology; University of Veterinary Medicine, Department of Anatomy and Histology Kenessey, István; National Institute of Oncology; Semmelweis University, Department of Pathology, Forensic and Insurance Medicine Soerjomataram, Isabelle; WHO Bray, Freddie; Int Agcy Res Canc, Cancer Surveillance Branch |
| 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 |
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3 **1 Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the**
4 **2 global burden in 2020 and 2040.**

6
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58 29 National Institute of Oncology
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2
3 31 **Abstract**

4 32
5 33 *Objectives*

6 34
7 35 Lung cancer is the leading cause of cancer death in 2020, responsible for almost one in five
8
9 36 (18.0%) deaths. This paper provides an overview of the descriptive epidemiology of lung cancer on the
10
11 37 basis of national mortality estimates for 2020 from the International Agency for Research on Cancer
12
13 38 (IARC), and in the context of recent tobacco control policies.

14 39
15 40 *Methods*

16 41
17 42 Age-standardized mortality rates per 100,000 person-years of lung cancer for 185 countries by
18
19 43 sex were obtained from the GLOBOCAN 2020 database and stratified by Human Development Index
20
21 44 (HDI). Lung cancer deaths were projected to 2040 based on demographic changes alongside scenarios
22
23 45 of annually increasing, stable or decreasing rates from the baseline year of 2020.

24 46
25 47 *Results*

26 48
27 49 Lung cancer mortality rates exhibited marked variations by geography and sex. Low HDI
28
29 50 countries, many of them within sub-Saharan Africa, tend to have low levels of mortality and an upward
30
31 51 trend in lung cancer deaths is predicted for both sexes until 2040 according to demographic projections,
32
33 52 irrespective of trends in rates. In very high HDI countries, including Europe, Northern America and
34
35 53 Australia/New Zealand, there are broadly decreasing trends in men whereas in women, rates are still
36
37 54 increasing or reaching a plateau.

38 55
39 56 *Conclusion*

40 57
41 58 The current and future burden of lung cancer in a country or region largely depends on the
42
43 59 present trajectory of the smoking epidemic in its constituent populations, with distinct gender differences
44
45 60 in smoking patterns, both in transitioning and transitioned countries. Further elevations in lung cancer
46
47 61 mortality are expected worldwide, raising important social and political questions, especially in low-
48
49 62 and middle-income countries.

50 63
51 64
52 65 **Keywords:** lung cancer, mortality, projection

53 66
54 67 **Word count:** 2510
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3 68 **Strengths and limitations of this study**

4 69

5 70 *Strengths*

6 71

7 72 This study:

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10 74 • presents a detailed profile of the present LC burden in men and women worldwide according to
11 75 national levels of human development.

13 76

15 77 • applies a simple projection to estimate the future lung cancer mortality burden in 2040.

17 78

19 79 • discusses the results in the context of key risk factors for lung cancer, particularly the continually
20 80 evolving smoking epidemic.

22 81

23 82 *Limitations*

24 83

26 84 This study:

27 85

28 86 • is hampered by the limited availability of local cause of death information from national vital
30 87 registration sources, particularly in transitioning countries.

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93 **Introduction**

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

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

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

117

118 **Data Sources and Methods**

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

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2
3 127 to short-term predictions and modelled mortality to incidence (M:I) ratios, while validity is dependent
4 128 on the degree of representativeness and quality of the source information [10].

5
6 129 We present figures based on the estimated deaths in 2020, as well as two summary measures using
7
8 130 direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years
9
10 131 based on the 1966 Segi-Doll World standard population [16,17] and the cumulative risk of dying from
11 132 cancer before the age of 75 expressed as a percentage, assuming the absence of competing causes of
12
13 133 death [18]. These measures allow comparisons between populations adjusted for differences in age
14 134 structures. We also provide a prediction of the future number of LC deaths worldwide for the year 2040,
15
16 135 based on demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%)
17 136 or decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of
18
19 137 COVID-19 pandemic was not taken into consideration during the calculations.

20
21 138 The results are presented by country, and aggregated across 20 UN-defined world regions [12]
22 139 and according to the UN's four-tier HDI in 2020 [19], as a means to assess the cancer burden across four
23
24 140 levels of development (low, medium, high and very high HDI). Throughout, we use the terms
25 141 *transitioning*, *emerging* and *lower HDI* countries/economies as synonyms for nations classified as low
26
27 142 or medium HDI, and *transitioned* or *higher HDI* countries/economies for those classified as high or very
28
29 143 high HDI.

30 144 The Global Cancer Observatory (GCO, <https://gco.iarc.fr>) includes facilities for the tabulation
31 145 and graphical visualization of the GLOBOCAN database, including explorations of the current [2] and
32
33 146 future [20] burden for 36 cancer types.

34
35 147 Patient and Public Involvement: Patients or the public were not involved in the design, or
36 148 conduct, or reporting, or dissemination plans of our research.

37
38 149

39 150 **Results**

40 151 *Lung cancer mortality – national rankings 2020*

41
42 152 Figure 1 presents global maps that indicate LC's position in terms of deaths relative to other
43
44 153 common tumours at the national level by sex for the year 2020. In 2020, LC ranks first in terms of cancer
45
46 154 death in half, or 93 of the 185 countries included in GLOBOCAN, and either 2nd or 3rd in 37 countries
47
48 155 in men. LC is a major contributor to cancer mortality around the world, including America, greater-
49
50 156 Europe, Northern Africa, and across the Asian-Pacific region. There is a somewhat less dominant role
51
52 157 at present in South America and Sub-Saharan Africa (but not South Africa). In women, the impact is
53
54 158 lesser but still very much in evidence; the disease ranks as the leading form of cancer death in 25
55
56 159 countries including those within North America, Northern, Western and Southern-Central Europe,
57
58 160 Eastern Asia and Australia/New Zealand. LC mortality ranks as the 2nd or 3rd leading form of cancer
59
60 161 mortality in 54 countries worldwide in women.

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2
3 162 There is at least a 20-fold variation in mortality between the sexes, with rates uniformly higher
4 163 among men (Figure 2). Male mortality rates are higher in Eastern and Southern Europe (especially in
5 164 Hungary and Serbia with rates of 60 per 100,000), Eastern Asia (particularly the Democratic People's
6 165 Republic of Korea) and Polynesia and Micronesia, while rates are lower in Central America, South-
7 166 Central Asia and most parts of sub-Saharan Africa. The highest female rates are observed in Northern
8 167 America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark
9 168 and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia
10 169 and across the African continent, other than for South Africa.

16 170 *Lung cancer mortality burden by 2040*

17 171 If the current rates were to remain constant over the next two decades, LC will claim around 2
18 172 million male deaths in 2040, compared to 1.2 million in 2020 (Figure 3). For women, the corresponding
19 173 deaths are approximately half of their male counterparts: a predicted increase to 1 million in 2040 from
20 174 600 000 deaths in 2020. The projection also shows the different scenarios considering the changing rates
21 175 per year between -3% and +3% based on plausible scenarios of the smoking epidemic in the short-term
22 176 future; global declines in the number of LC among males but increases for female are perhaps the more
23 177 realistic scenarios, with national or regional exceptions. Taking this trends-based prediction into
24 178 account, the predicted number of deaths due to LC for men will likely range between 1.1 and 1.6 million
25 179 and for women between 1.2 and 1.8 million by 2040. Deaths will markedly increase for both sexes in
26 180 countries with the lowest HDI, even in the best-case trend scenario (Appendix Figure 1a-h).

34 181

36 182 **Discussion**

38 183 This study highlights the present geographic diversity in LC mortality worldwide, by sex and by
39 184 level of human development. Countries with low HDI tend to have low LC mortality rates but may
40 185 anticipate a higher mortality burden by 2040. For higher HDI countries, the burden of the disease is
41 186 higher among men, but future trends suggest an increasingly greater proportion of the cancer burden
42 187 will be seen among for females. These different scenarios are due to the impact of historic smoking
43 188 trends and the increasingly widespread application of tobacco control measures in the last decades [21].
44 189 While there is an expectation that LC mortality will increase in transitioning countries given there is less
45 190 implementation of effective tobacco control, there is a positivity in the findings of the Global Tobacco
46 191 Control Report: the number of people now living in countries with at least two anti-tobacco policies in
47 192 place rose from 3.5 billion in 2018 to 4.4 billion in 2020 – up from 45% of the world's population to
48 193 56% in two years [22].

56 194 Past smoking histories of nations are a key determinant of the current magnitude of LC in many
57 195 populations worldwide, as described by the classical model of the global smoking epidemic, first
58 196 introduced by Lopez et al [4]. In the model, the effect of different smoking patterns was captured by four

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2
3 197 stages in the population, by an earlier adoption of the habit in men compared with women, and by the
4
5 198 progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying
6
7 199 cause of the marked inequalities seen in different educational groups [23]. Lopez et al. initially applied
8
9 200 the hypothesis on just a few developed countries [24], but later was tested on greater geographic scales
10
11 201 [25,26]. Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline among
12
13 202 men in many populations over the last decades, a key focus has been the deteriorating public health
14
15 203 situation affecting women, where in many settings, rates of LC mortality have continued to rise. This
16
17 204 raises several relevant biological, epidemiological and sociological concerns [27], including: the
18
19 205 changing distribution of the main histological subtypes of LC over time [28], the extent to which females
20
21 206 adopted the habit of smoking and their vulnerability to the tobacco industry [29,30], the impact of such
22
23 207 a transition in diminishing gender differences in disease burden worldwide [31] and the effects of
24
25 208 different political systems on the health awareness of individuals [32,33]. The impact of these factors is
26
27 209 reflected in comparisons of between-country LC mortality rates; for example, the current rate differences
28
29 210 in Eastern vs. Northern European countries.

26 211 Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with
27
28 212 other factors, including air pollution, climate change [34] and other occupational risk factors such as
29
30 213 asbestosis and indoor exposure to cooking fumes etc [35]. The highest exposure to ambient air pollution
31
32 214 is the characteristic of mainly countries in transition, where only modest reductions in burden will occur
33
34 215 in the most polluted countries unless fine particulate matter (PM 2.5) values are decreased substantially
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36 216 [36].

36 217 Several other studies have aimed to forecast the future lung cancer burden in very high HDI
37
38 218 countries e.g., the US [37] and the UK [38] with contradictory findings. While the steeply declining
39
40 219 mortality in the US for both sexes until 2040 fits within the framework of the global smoking epidemic,
41
42 220 the rising deaths reported in the UK for men and women until 2035 somewhat contradict previous
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44 221 findings. One explanation could be the rapidly ageing population age structure, which can increase the
45
46 222 number of these non-standardized figures. Alternatively, these projections do not take into account the
47
48 223 changing smoking prevalence in the past as a key determinant of present and future lung cancers. Our
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50 224 GLOBOCAN 2020 forecasts do not consider these either, however, provide possible scenarios on the
51
52 225 basis of uniform increases or decreases in rates may help provide a realistic overview of the changing
53
54 226 future burden of LC.

52 227 Another limitation of this study is the large variability in the availability and quality of cancer
53
54 228 mortality data. Most African and some Asian countries suffer from weak mortality statistics systems. In
55
56 229 GLOBOCAN, in countries where mortality series were not available from national vital registration
57
58 230 sources, the predominant means of the estimation of rates were from corresponding national incidence
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3 231 estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in
4 232 neighbouring countries.

6
7 233 With over three million deaths predicted by 2040 in the absence of additional interventions
8 234 according to the finding of this study, it is imperative to emphasize primary prevention as the most cost-
9 235 effective strategy of tobacco control. It has been shown that raising the price of cigarettes through
10 236 increased excise taxes can bring marked reductions in cigarette consumption [39]. Besides this,
11 237 developing adaptive tobacco control strategies that target different subgroups is imperative; anti-tobacco
12 238 strategies should urgently target women in settings such as the EU, in order to halt their rapidly
13 239 increasing risk of LC, and prevent unnecessary, premature deaths among future generations of women
14 240 [40]. In Sweden, as an example, policies such as those directed at health promotion have been
15 241 implemented in a gender-specific way with a focus on young and pregnant women. Scotland also has
16 242 gender-specific programs, such as the Women, Low Income, and Smoking Project [41]. Amos and
17 243 Haglund (2000) have emphasized that building support for female-centered tobacco control programs
18 244 through partnerships will be vital to achieve success [30]. Furthermore, Amos (1996) and Mackay and
19 245 Amos (2003) draw attention to the situation of women in transitioning countries with presently low
20 246 levels of cigarette smoking among women [29]. In these countries, smoking among girls is already on
21 247 the rise, women's spending power is increasing, cigarettes are becoming affordable, and women are
22 248 more exposed to the marketing strategies of tobacco companies, in an environment where cultural
23 249 constraints are weakening and female-specific quitting programs are rare [8].

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34 250 A package of measures to suppress tobacco consumption in a given population has been
35 251 recommended through continued efforts to increase the proportion of ex-smokers, with a focus on
36 252 younger generations [42]. This could perhaps be achieved by implementing coordinated smoking
37 253 prevention and control strategies from an early age, in the form of educational programs in schools.
38 254 Other measures that could be introduced include community intervention programs, mass media
39 255 campaigns and further legislation to ban smoking in public places. One of the main problems is that
40 256 young people react very differently to anti-smoking messages compared to adult long-term smokers
41 257 [42]. The harm-reducing role of e-cigarettes and aid to smoking cessation has been proposed [43],
42 258 however their impact on future LC mortality is not yet known [44]. Successful programs have also been
43 259 implemented in rapidly emerging economies such as Brazil, where a reduction in smoking prevalence
44 260 were observed after the ratification of the WHO Framework Convention on Tobacco Control (FCTC)
45 261 in 2005, and the adoption of a national ban on tobacco advertising, a national comprehensive smoke-
46 262 free policy, large pictorial health warnings on cigarette packages, and continuous increases in taxes and
47 263 prices of tobacco products [45]. Other factors may influence the future burden of LC such as the potential
48 264 introduction of screening in high-risk populations. In a recent trial, LC mortality was significantly lower
49 265 among those who underwent volume computed tomography (CT) screening than those who did not
50 266 participate [46]. Screened patients benefitted from a substantial shift to lower-stage cancers at the time

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3 267 of diagnosis as well as more frequent eligibility for curative treatment (mainly surgery) [47]. However,
4
5 268 concerns have been raised about the potential for overdiagnosis in lung-cancer screening.
6

7 269 In summary, this paper has identified marked geographic variations in the current LC burden
8
9 270 worldwide and provided potential scenarios regarding the short-term future LC deaths up until 2040.
10
11 271 Gredner et al., have illustrated the great potential of comprehensive implementation of tobacco control
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13 272 policies in Greater-Europe, with over 1.6 million LC cases preventable over a 20-year period through
14
15 273 the highest-level implementation of tobacco control policies [48]. There is therefore much we can do to
16
17 274 halt the rising deaths from LC – as well as many other forms of cancer and non-communicable diseases
18
19 275 –through the successful implementation of tobacco control policies.
20

21 276

22 277 **Disclosure**

23 278 Where authors are identified as personnel of the International Agency for Research on Cancer/World
24
25 279 Health Organization, the authors alone are responsible for the views expressed in this article, and they
26
27 280 do not necessarily represent the decisions, policy, or views of the International Agency for Research on
28
29 281 Cancer/World Health Organization.
30

31 282

32 283 **Role of the funding source**

33 284 PN: This study was supported by the Topic Excellence Program (TKP2020-NKA-26, TKP2021-EGA-
34
35 285 44), the National Laboratories Program (National Tumor Biology Laboratory-2022-2.1.1-NL-2022-
36
37 286 00010), and Tasks Related to the National Public Health Strategy (IV/4925/2021/ EKF).
38

39 287

40 288 **Authors' contribution**

41 289 AW: literature search, data analysis, writing – original draft; EM: writing – review & editing; JV:
42
43 290 methodology, data collection, figures, visualisation; ML: visualisation; MP: writing – review & editing;
44
45 291 HR: writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding
46
47 292 acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology,
48
49 293 conceptualisation, data analysis, writing – original draft
50

51 294

52 295 **Declaration of interests**

53 296 All authors declare that they have no conflicts of interest.
54

55 297

56 298 **Data sharing**

57 299 The data that support the findings of this study are available at the Global Cancer Observatory
58
59 300 (GLOBOCAN) at <https://gco.iarc.fr/>

60 301 Data are available in a public, open access repository.

302 Ethics Approval Statement

303 This study does not involve human participants and animal subjects.

304

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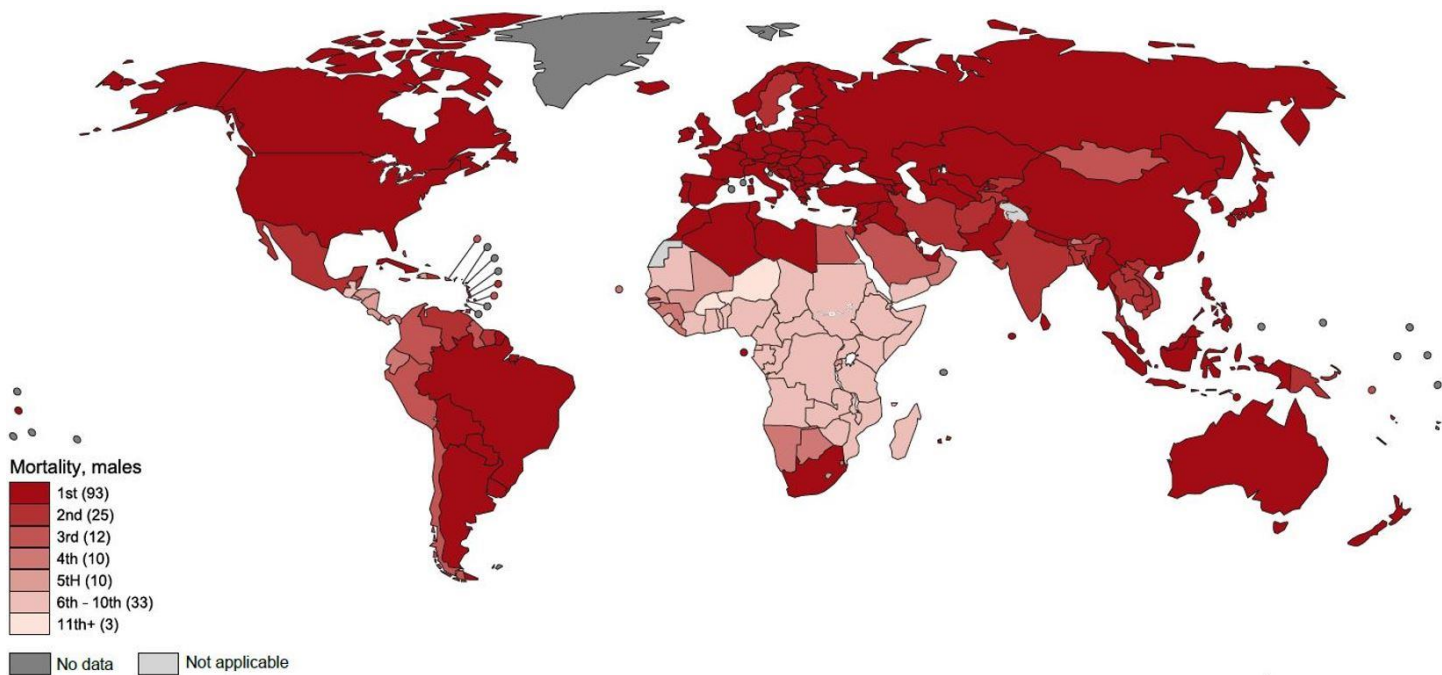
1
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3 417 Figures
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5 418 Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms,
6 419 2020, Male-Female
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8 420 Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020,
9 421 Male-Female
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11 422 Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human
12 423 Development Index (HDI)
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Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020
Male



Female

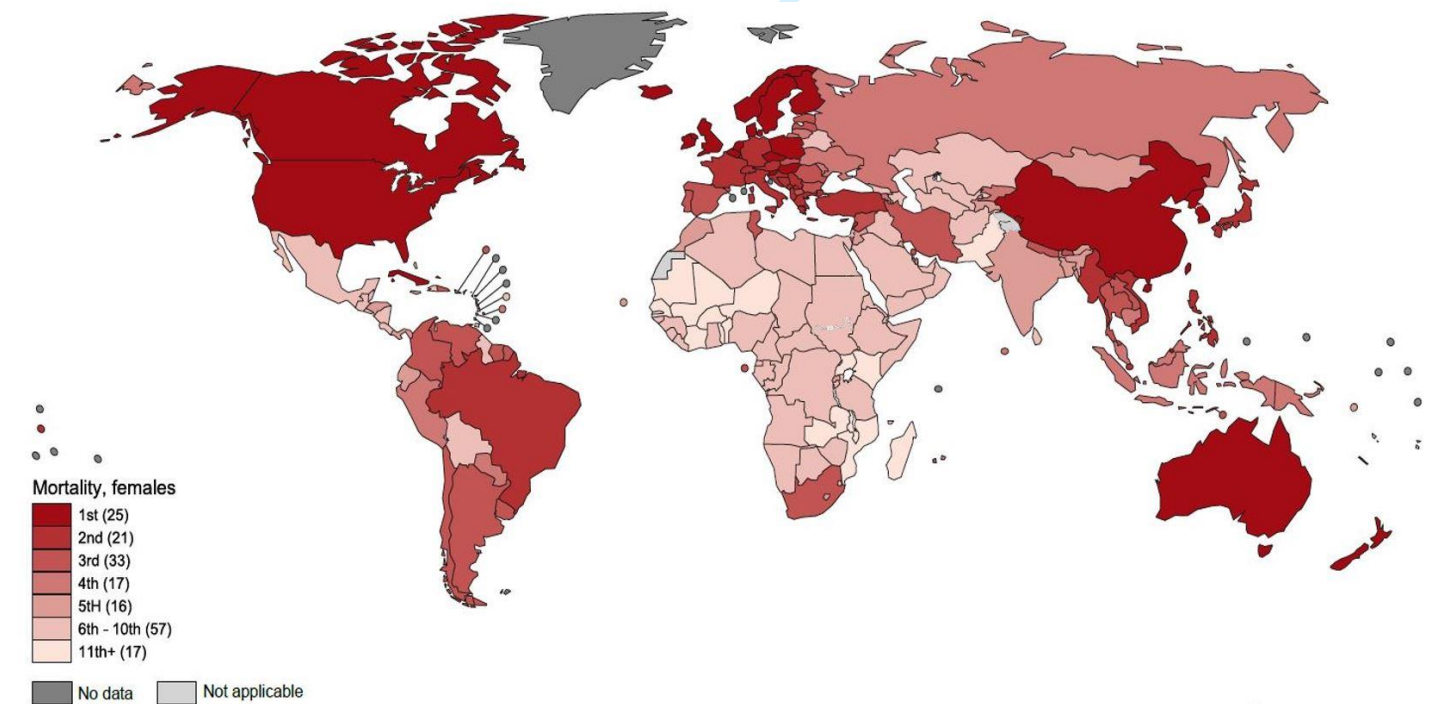
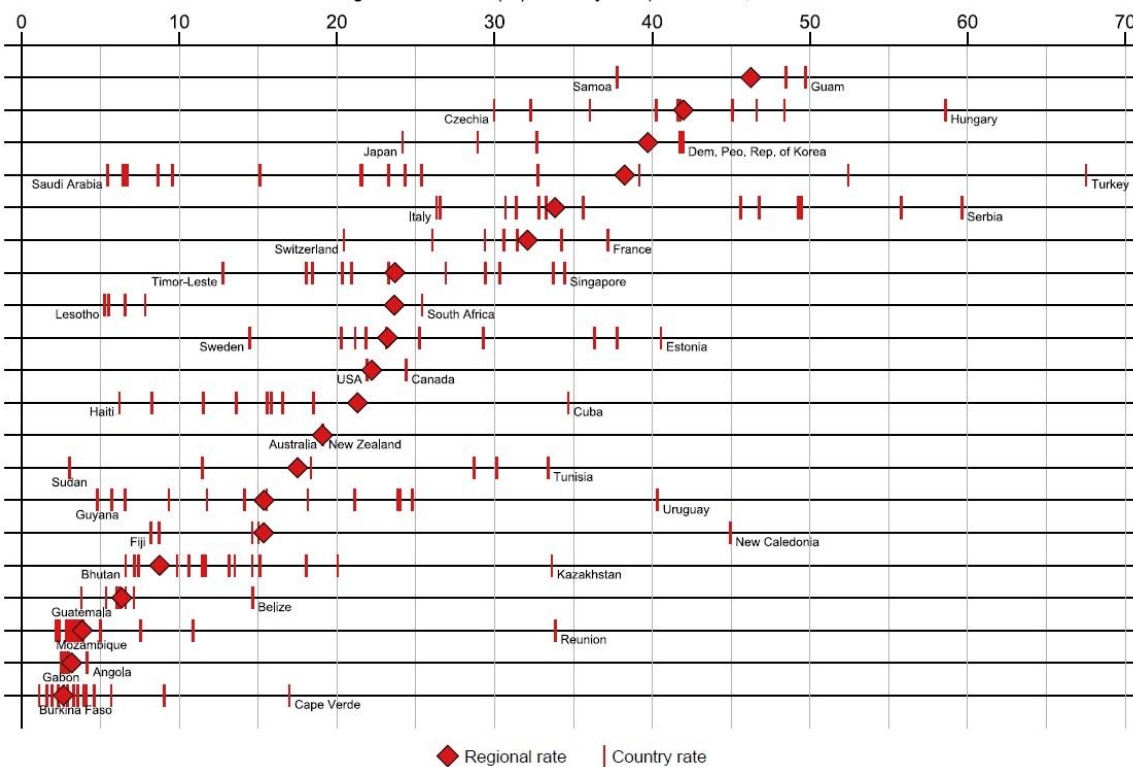


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020

Lung cancer

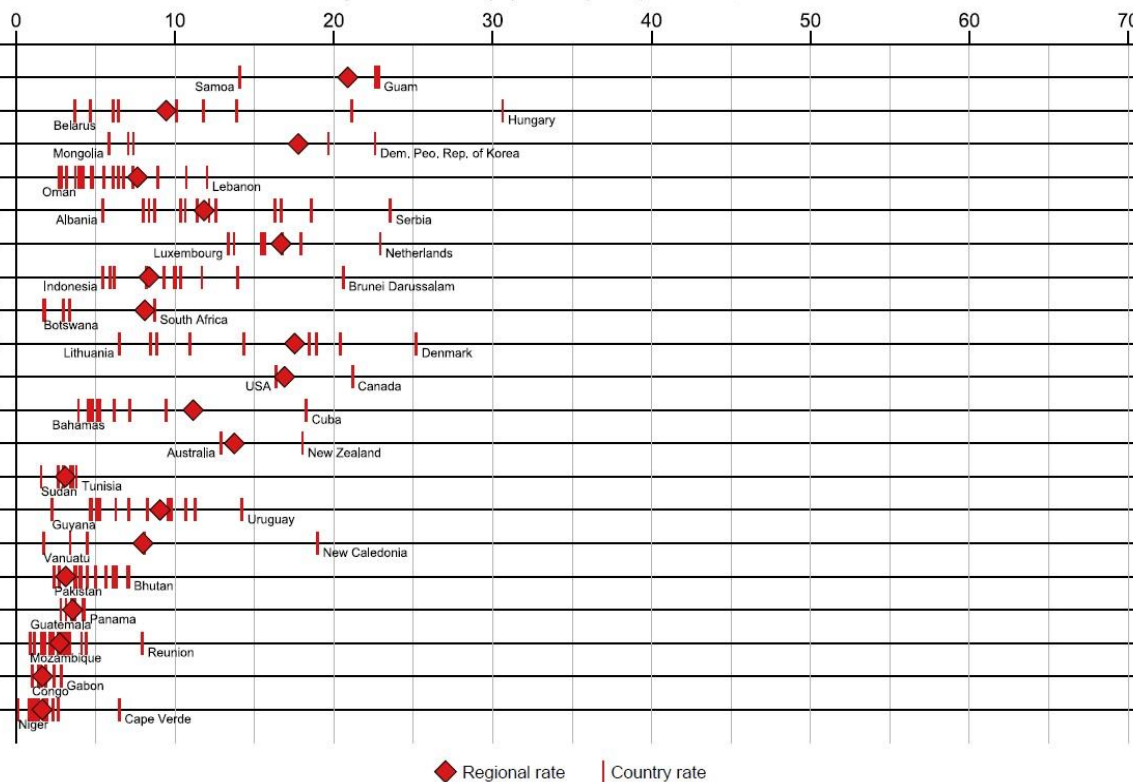
Age-standardized (W) mortality rate per 100000, males



◆ Regional rate | Country rate

Lung cancer

Age-standardized (W) mortality rate per 100000, females

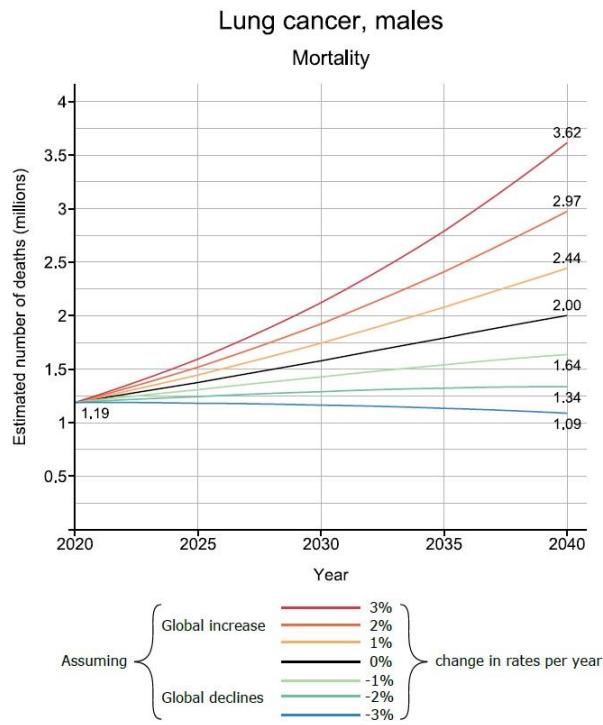


◆ Regional rate | Country rate

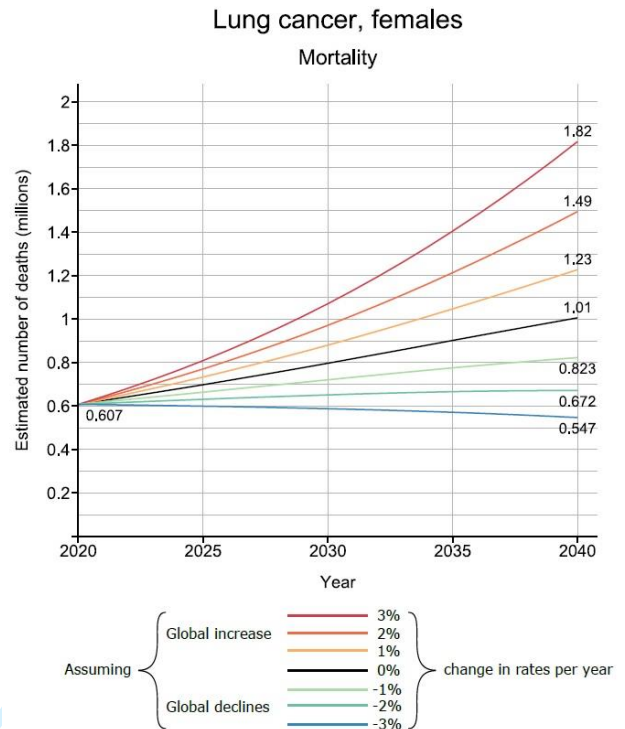
Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A



B



view only

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

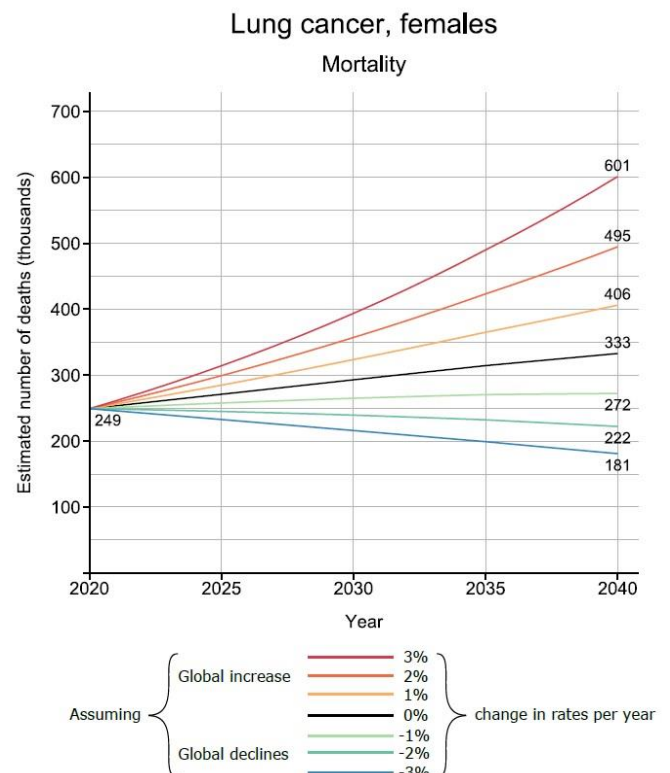
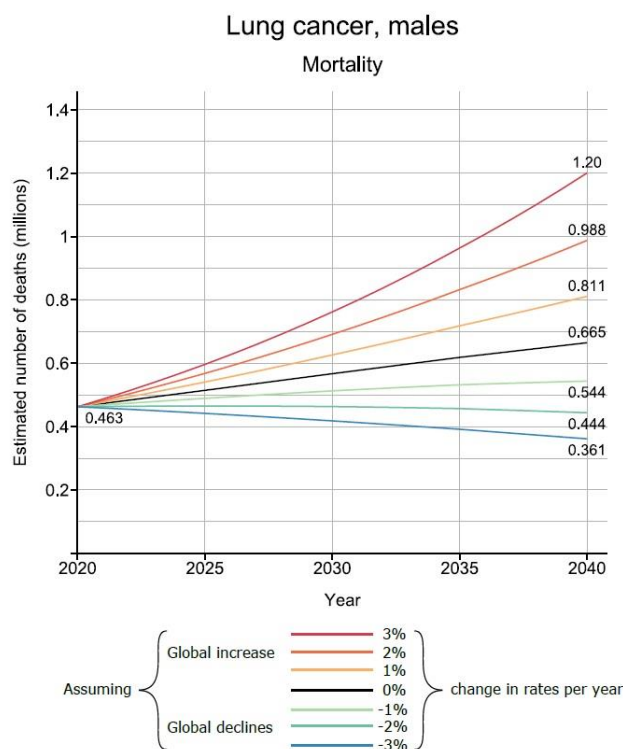
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Appendices

Lung cancer mortality by sex - very high HDI countries

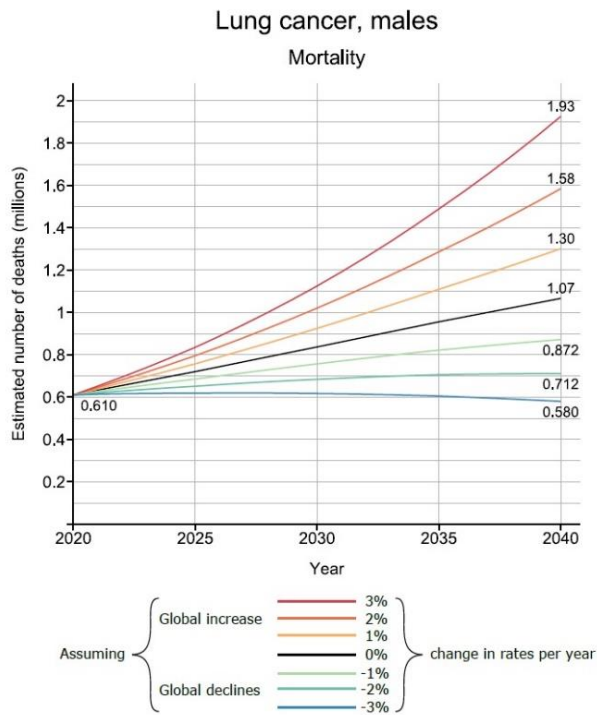
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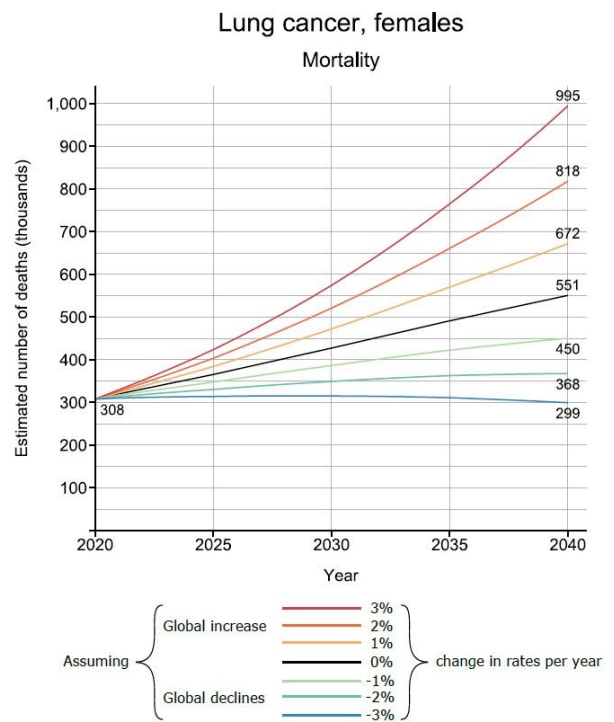


Lung cancer mortality by sex - high HDI countries

C

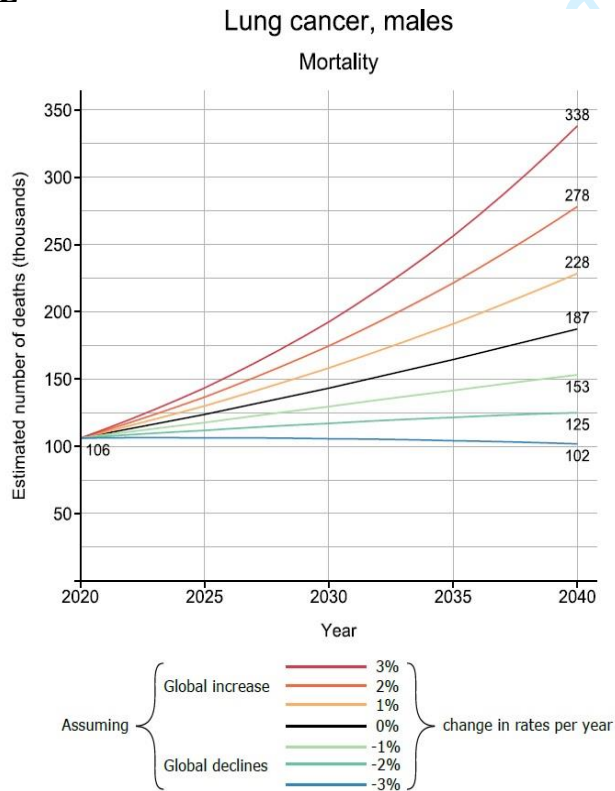


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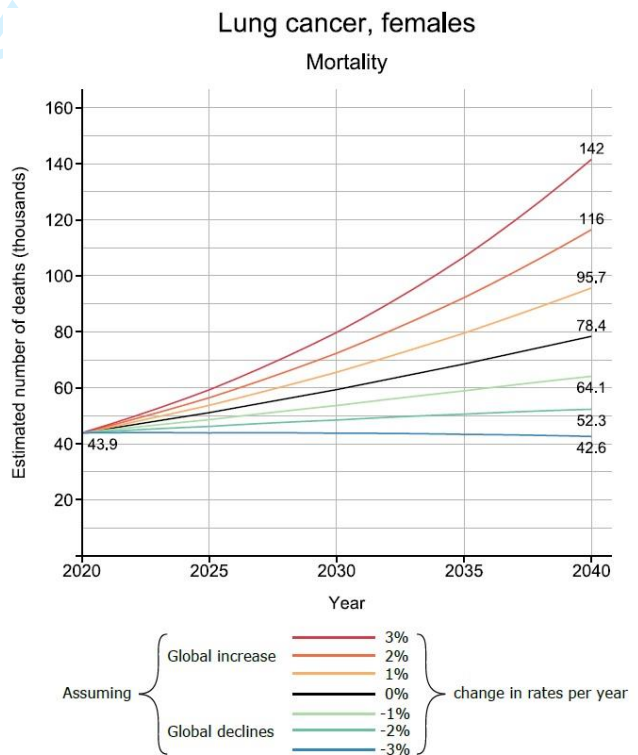


Lung cancer mortality by sex - medium HDI countries

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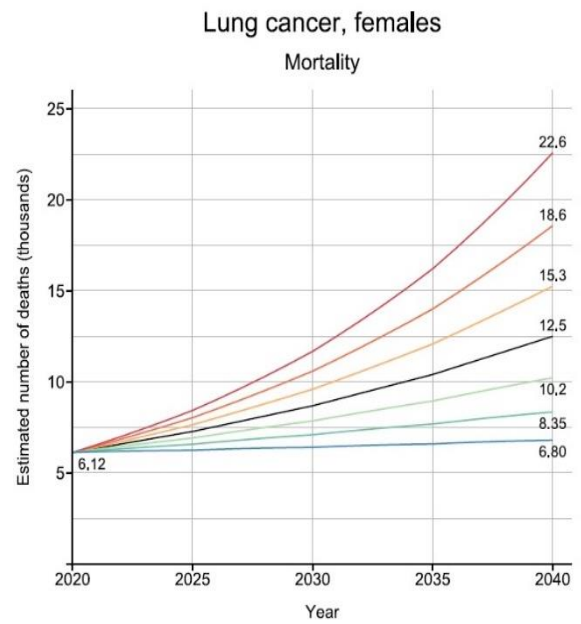
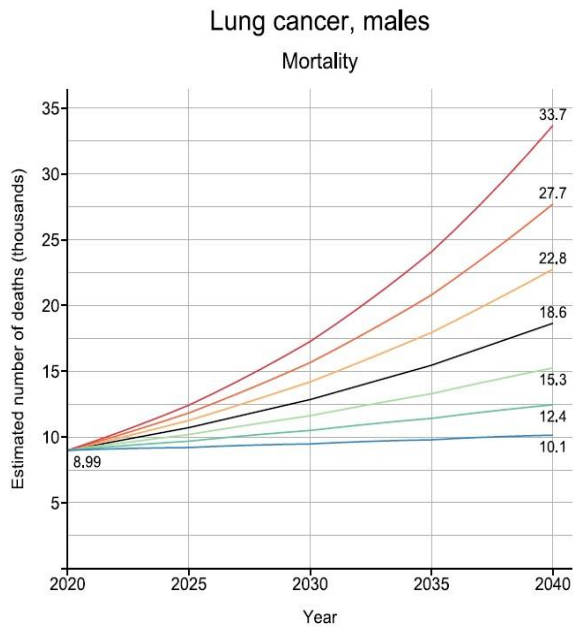
F



Lung cancer mortality by sex - low HDI countries

G

H



Review only

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| | | (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) | - |
| Outcome data | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time | - |
| | | <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure | - |
| | | <i>Cross-sectional study</i> —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.

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-065303.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 01-Mar-2023 |
| Complete List of Authors: | Weber, Andras; International Agency for Research on Cancer, Cancer Surveillance Branch; National Institute of Oncology, Hungarian National Cancer Registry Morgan, Eileen; International Agency for Research on Cancer Vignat, Jerome; International Agency for Research on Cancer Laversanne, Mathieu; International Agency for Research on Cancer, Cancer Surveillance Branch Pizzato, Margherita; International Agency for Research on Cancer; University of Milan, Department of Clinical Sciences and Community Health Rumgay, Harriet; International Agency for Research on Cancer Singh, Deependra; International Agency for Research on Cancer Nagy, Péter; National Institute of Oncology, Department of Molecular Immunology and Toxicology; University of Veterinary Medicine, Department of Anatomy and Histology Kenessey, István; National Institute of Oncology; Semmelweis University, Department of Pathology, Forensic and Insurance Medicine Soerjomataram, Isabelle; WHO Bray, Freddie; Int Agcy Res Canc, Cancer Surveillance Branch |
| 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 |
| | |

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3 **1 Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the**
4 **2 global burden in 2020 and 2040**

6
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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

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3 70 **Strengths and limitations of this study**

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5 72 *Strengths*

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7 74 This study:

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10 76 • presents a detailed profile of the present LC burden in men and women worldwide according to
11 77 national levels of human development.

13 78

15 79 • applies a simple projection to estimate the future lung cancer mortality burden in 2040.

17 80

19 81 • discusses the results in the context of key risk factors for lung cancer, particularly the continually
20 82 evolving smoking epidemic.

22 83

23 84 *Limitations*

24 85

26 86 This study:

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28 88 • is hampered by the limited availability of local cause of death information from national vital
30 89 registration sources, particularly in transitioning countries.

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95 **Introduction**

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

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

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

119

120 **Data Sources and Methods**

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

1
2
3 129 to short-term predictions and modelled mortality to incidence (M:I) ratios, while validity is dependent
4
5 130 on the degree of representativeness and quality of the source information [10].

6 131 We present figures based on the estimated deaths in 2020, as well as two summary measures using
7
8 132 direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years
9
10 133 based on the 1966 Segi-Doll World standard population [16,17] and the cumulative risk of dying from
11
12 134 cancer before the age of 75 expressed as a percentage, assuming the absence of competing causes of
13
14 135 death [18]. These measures allow comparisons between populations adjusted for differences in age
15
16 136 structures. We also provide a prediction of the future number of LC deaths worldwide for the year 2040,
17
18 137 based on demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%)
19
20 138 or decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of
21
22 139 COVID-19 pandemic was not taken into consideration during the calculations.

23
24 140 The results are presented by country and aggregated across 20 UN-defined world regions [12] and
25
26 141 according to the UN's four-tier HDI in 2020 [19], as a means to assess the cancer burden across four
27
28 142 levels of development (low, medium, high and very high HDI). Throughout, we use the terms
29
30 143 *transitioning*, *emerging* and *lower HDI* countries/economies as synonyms for nations classified as low
31
32 144 or medium HDI, and *transitioned* or *higher HDI* countries/economies for those classified as high or very
33
34 145 high HDI.

35 146 The Global Cancer Observatory (GCO, <https://gco.iarc.fr>) includes facilities for the tabulation
36
37 147 and graphical visualization of the GLOBOCAN database, including explorations of the current [2] and
38
39 148 future [20] burden for 36 cancer types.

40 149 Patient and Public Involvement: Patients or the public were not involved in the design, or
41
42 150 conduct, or reporting, or dissemination plans of our research.

43 151

44 152 **Results**

45 153 *Lung cancer mortality – national rankings 2020*

46 154 Figure 1 presents global maps that indicate LC's position in terms of deaths relative to other
47
48 155 common tumours at the national level, by sex for the year 2020. In 2020, LC ranks first in terms of
49
50 156 cancer death in half (93 out of 185) of the countries included in GLOBOCAN, and either 2nd or 3rd in 37
51
52 157 countries, in men. LC is a major contributor to cancer mortality around the world, including America,
53
54 158 greater-Europe, Northern Africa, and across the Asian-Pacific region. There is a less dominant role at
55
56 159 present in South America and Sub-Saharan Africa (but not South Africa). In women, the impact is lesser
57
58 160 but still very much in evidence; the disease ranks as the leading form of cancer death in 25 countries
59
60 161 including those within North America, Northern, Western and Southern-Central Europe, Eastern Asia
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163 162 and Australia/New Zealand. LC mortality ranks as the 2nd or 3rd leading form of cancer mortality in 54
164
165 163 countries worldwide in women.

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3 164 There is at least a 20-fold variation in mortality between the sexes, with rates uniformly higher
4
5 165 among men (Figure 2). Male mortality rates are higher in Eastern and Southern Europe (especially in
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7 166 Hungary and Serbia with rates of 60 per 100,000), Eastern Asia (particularly the Democratic People's
8
9 167 Republic of Korea) and Polynesia and Micronesia, while rates are lower in Central America, South-
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11 168 Central Asia and most parts of sub-Saharan Africa. The highest female rates are observed in Northern
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13 169 America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark
14
15 170 and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia
16
17 171 and across the African continent, excluding South Africa.

172 *Lung cancer mortality burden by 2040*

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174 If the current rates were to remain constant over the next two decades, LC will claim around 2
175 million male deaths in 2040, compared to 1.2 million in 2020 (Figure 3). For women, the corresponding
176 deaths are approximately half of their male counterparts: a predicted increase to 1 million in 2040 from
177 600 000 deaths in 2020. The projection also shows the different scenarios considering the changing rates
178 per year between -3% and +3% based on plausible scenarios of the smoking epidemic in the short-term
179 future; global declines in the number of LC among males but increases for female are perhaps the more
180 realistic scenarios, with national or regional exceptions. Taking this trends-based prediction into
181 account, the predicted number of deaths due to LC for men will likely range between 1.1 and 1.6 million
182 and for women between 1.2 and 1.8 million by 2040. Deaths will markedly increase for both sexes in
183 countries with the lowest HDI, even in the best-case trend scenario (Appendix Figure 1a-h).

184 **Discussion**

185
186 This study highlights the present geographic diversity in LC mortality worldwide, by sex and by
187 level of human development. Countries with low HDI tend to have low LC mortality rates but may
188 anticipate a higher mortality burden by 2040. For higher HDI countries, the burden of the disease is
189 higher among men, but future trends suggest an increasingly greater proportion of the cancer burden
190 will be seen among females. These different scenarios are due to the impact of historic smoking trends
191 and the increasingly widespread application of tobacco control measures in the last decades [21]. While
192 there is an expectation that LC mortality will increase in transitioning countries given there is less
193 implementation of effective tobacco control, there is a positivity in the findings from the Global Tobacco
194 Control Report: the number of people now living in countries with at least two anti-tobacco policies in
195 place rose from 3.5 billion in 2018 to 4.4 billion in 2020 – up from 45% of the world's population to
196 56% in two years [22].

197
198 Past smoking histories of nations are a key determinant of the current magnitude of LC in many
199 populations worldwide, as described by the classical model of the global smoking epidemic, first
200 introduced by Lopez et al [4]. In the model, the effect of different smoking patterns was captured by four

1
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3 199 stages in the population, by an earlier adoption of the habit in men compared with women, and by the
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5 200 progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying
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7 201 cause of the marked inequalities seen in different educational groups [23]. Lopez et al. initially applied
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9 202 the hypothesis on just a few developed countries [24], which was later tested on greater geographic
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11 203 scales [25,26]. Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline
12
13 204 among men in many populations over the last decades, a key focus has been the deteriorating public
14
15 205 health situation affecting women, where in many settings, rates of LC mortality have continued to rise.
16
17 206 This raises several relevant biological, epidemiological and sociological concerns [27], including: the
18
19 207 changing distribution of the main histological subtypes of LC over time [28], the extent to which females
20
21 208 adopted the habit of smoking and their vulnerability to the tobacco industry [29,30], the impact of such
22
23 209 a transition in diminishing gender differences in disease burden worldwide [31] and the effects of
24
25 210 different political systems on the health awareness of individuals [32,33]. The impact of these factors is
26
27 211 reflected in comparisons of between-country LC mortality rates; for example, the current rate differences
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29 212 in Eastern vs. Northern European countries.

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31 213 Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with
32
33 214 other factors, including air pollution, climate change [34] and other occupational risk factors such as
34
35 215 asbestosis and indoor exposure to cooking fumes etc [35]. The highest exposure to ambient air pollution
36
37 216 is the characteristic of mainly countries in transition, where only modest reductions in burden will occur
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39 217 in the most polluted countries unless fine particulate matter (PM 2.5) values are decreased substantially
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41 218 [36].

42
43 219 Several other studies have aimed to forecast the future lung cancer burden in very high HDI
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45 220 countries e.g., the US [37] and the UK [38] with contradictory findings. While the steeply declining
46
47 221 mortality in the US for both sexes until 2040 fits within the framework of the global smoking epidemic,
48
49 222 the rising deaths reported in the UK for men and women until 2035 somewhat contradict previous
50
51 223 findings. One explanation could be the rapidly ageing population, which can increase the number of
52
53 224 these non-standardized figures. Alternatively, these projections do not take into account the changing
54
55 225 smoking prevalence in the past as a key determinant of present and future lung cancers. Our
56
57 226 GLOBOCAN 2020 forecasts do not consider these either, however, we provide possible scenarios on
58
59 227 the basis of uniform increases or decreases in rates that may help provide a realistic overview of the
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228 changing future burden of LC.

229
230 229 Another limitation of this study is the large variability in the availability and quality of cancer
231
232 230 mortality data. Most African and some Asian countries suffer from weak mortality statistics systems. In
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234 231 GLOBOCAN, in countries where mortality series were not available from national vital registration
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236 232 sources, the predominant means of the estimation of rates were from corresponding national incidence

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3 233 estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in
4 234 neighbouring countries.

6
7 235 With over three million deaths predicted by 2040 in the absence of additional interventions
8 236 according to the finding of this study, it is imperative to emphasize primary prevention as the most cost-
9 237 effective strategy of tobacco control. It has been shown that raising the price of cigarettes through
11 238 increased excise taxes can bring marked reductions in cigarette consumption [39]. Besides this,
13 239 developing adaptive tobacco control strategies that target different subgroups is imperative.

15 240 One key concern is the limited financial and trained resources in middle- and lower-income
16 241 countries, that can hinder health promotion and cancer prevention strategies in these countries. Based
17 242 on our findings, decreases in lung cancer rates are not likely in these countries until 2040 and presumably
19 243 tobacco companies are expected to shift and escalate promotional campaigns to preserve business
21 244 interests and profits where resistance efforts are the weakest [30].

23
24 245 Additionally, anti-tobacco strategies should urgently target women in also higher-income settings
25 246 such as the EU, in order to halt their rapidly increasing risk of LC, and prevent unnecessary, premature
26 247 deaths among future generations of women [40]. In Sweden, as an example, gender-specific policies
27 248 such as those directed at health promotion have been implemented with a focus on young and pregnant
29 249 women. Scotland also has gender-specific programs, such as the Women, Low Income, and Smoking
31 250 Project [41]. Amos and Haglund (2000) have emphasized that building support for female-centered
32 251 tobacco control programs through partnerships will be vital to achieve success [30]. Furthermore, Amos
33 252 (1996) and Mackay and Amos (2003) draw attention to the situation of women in transitioning countries
34 253 with presently low levels of cigarette smoking among women [29]. In these countries, smoking among
35 254 girls is already on the rise, women's spending power is increasing, cigarettes are becoming affordable,
36 255 and women are more exposed to the marketing strategies of tobacco companies, in an environment
37 256 where cultural constraints are weakening and female-specific quitting programs are rare [8].

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43 257 A package of measures to suppress tobacco consumption in a given population has been
44 258 recommended through continued efforts to increase the proportion of ex-smokers, with a focus on
45 259 younger generations [42]. This could perhaps be achieved by implementing coordinated smoking
46 260 prevention and control strategies from an early age, in the form of educational programs in schools.
47 261 Other measures that could be introduced include community intervention programs, mass media
48 262 campaigns and further legislation to ban smoking in public places. One of the main problems is that
49 263 young people react very differently to anti-smoking messages compared to adult long-term smokers
50 264 [42]. The harm-reducing role of e-cigarettes and aid to smoking cessation has been proposed [43],
51 265 however their impact on future LC mortality is not yet known [44]. Successful programs have also been
52 266 implemented in rapidly emerging economies such as Brazil, where a reduction in smoking prevalence
53 267 were observed after the ratification of the WHO Framework Convention on Tobacco Control (FCTC)

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3 268 in 2005, and the adoption of a national ban on tobacco advertising, a national comprehensive smoke-
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5 269 free policy, large pictorial health warnings on cigarette packages, and continuous increases in taxes and
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7 270 prices of tobacco products [45]. Other factors may influence the future burden of LC such as the potential
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9 271 introduction of screening in high-risk populations. In a recent trial, LC mortality was significantly lower
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11 272 among those who underwent volume computed tomography (CT) screening than those who did not
12
13 273 participate [46]. Screened patients benefitted from a substantial shift to lower-stage cancers at the time
14
15 274 of diagnosis as well as more frequent eligibility for curative treatment (mainly surgery) [47]. However,
16
17 275 concerns have been raised about the potential for overdiagnosis in lung-cancer screening.

16 276 In summary, this paper has identified marked geographic variations in the current LC burden
17
18 277 worldwide and provided potential scenarios regarding the short-term future LC deaths up until 2040.
19
20 278 Gredner et al., have illustrated the great potential of comprehensive implementation of tobacco control
21
22 279 policies in Greater-Europe, with over 1.6 million LC cases preventable over a 20-year period through
23
24 280 the highest-level implementation of tobacco control policies [48]. There is therefore much we can do to
25
26 281 halt the rising deaths from LC – as well as many other forms of cancer and non-communicable diseases
27
28 282 – through the successful implementation of tobacco control policies.

28 283

30 284 **Disclosure**

31 285 Where authors are identified as personnel of the International Agency for Research on Cancer/World
32
33 286 Health Organization, the authors alone are responsible for the views expressed in this article, and they
34
35 287 do not necessarily represent the decisions, policy, or views of the International Agency for Research on
36
37 288 Cancer/World Health Organization.

38 289

39 290 **Role of the funding source**

41 291 PN: This study was supported by the Topic Excellence Program (TKP2020-NKA-26, TKP2021-EGA-
42
43 292 44), the National Laboratories Program (National Tumor Biology Laboratory-2022-2.1.1-NL-2022-
44
45 293 00010), and Tasks Related to the National Public Health Strategy (IV/4925/2021/ EKF).

46 294

47 295 **Authors' contribution**

49 296 AW: literature search, data analysis, writing – original draft; EM: writing – review & editing; JV:
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51 297 figures, visualisation; ML: methodology, figures, visualisation; MP: writing – review & editing; HR:
52
53 298 writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding
54
55 299 acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology,
56
57 300 conceptualisation, data analysis, writing – original draft

57 301

58 302 **Declaration of interests**

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3 303 All authors declare that they have no conflicts of interest.
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6 7 305 **Data sharing**

8 306 Data are available in a public, open access repository.
9
10 307

11 308 **Ethics Approval Statement**

12 309 This study does not involve human participants and animal subjects.
13
14 310

15 311 **References**

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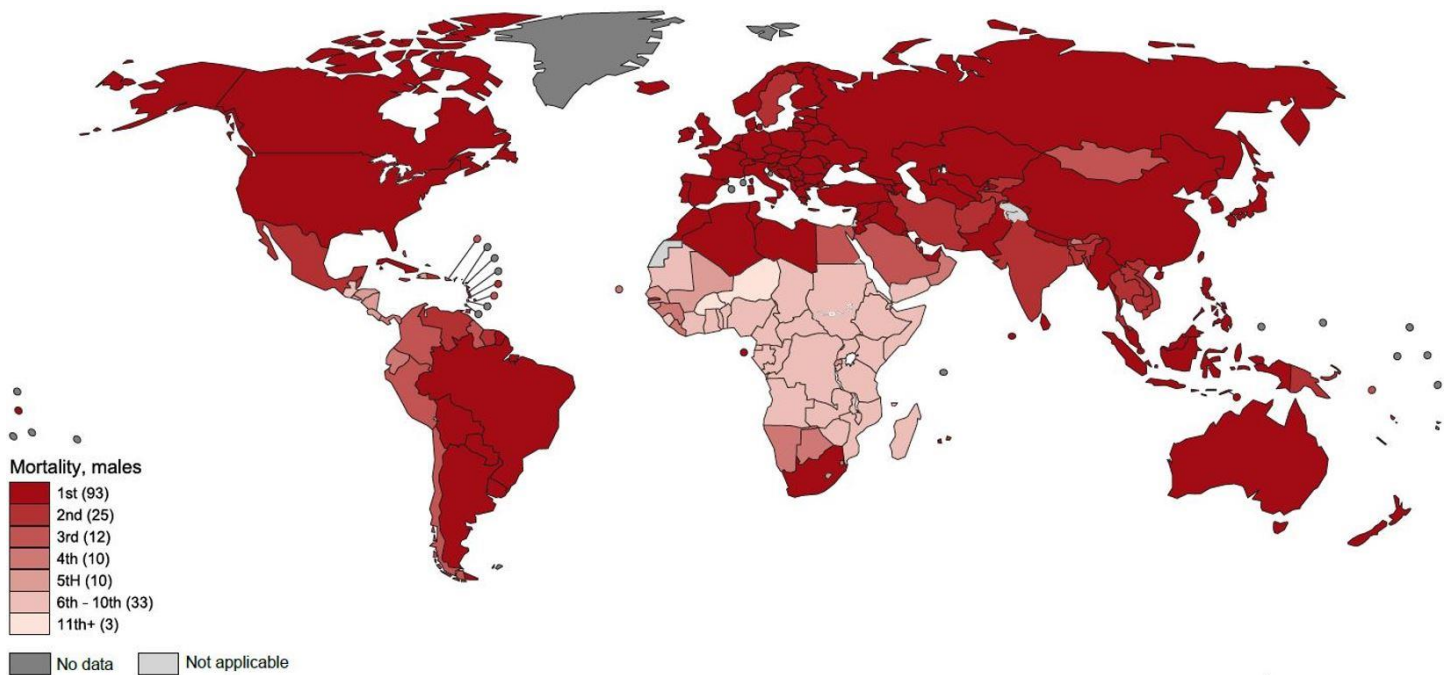
9 423 Figures

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11 424 Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms,
12 425 2020, Male-Female

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14 426 Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020,
15 427 Male-Female

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17 428 Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human
18 429 Development Index (HDI)
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Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms, 2020
Male



Female

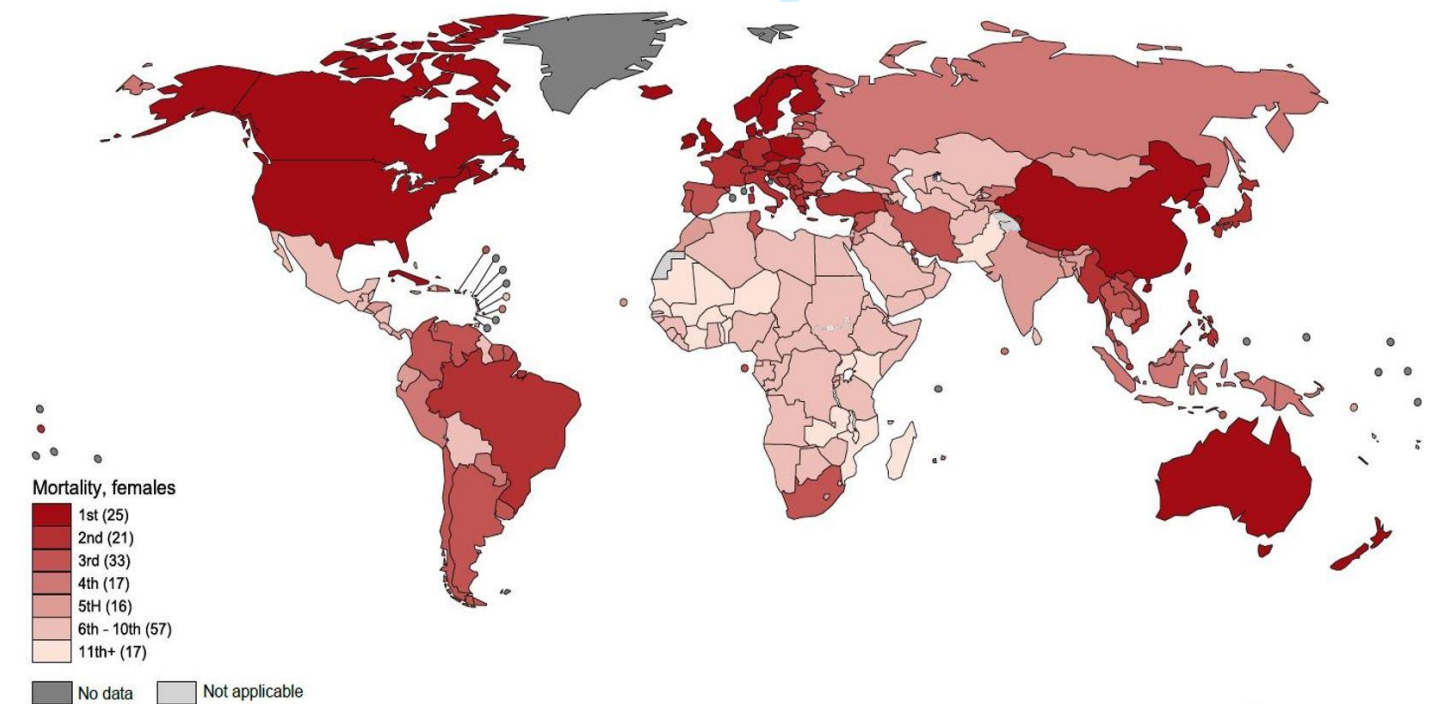
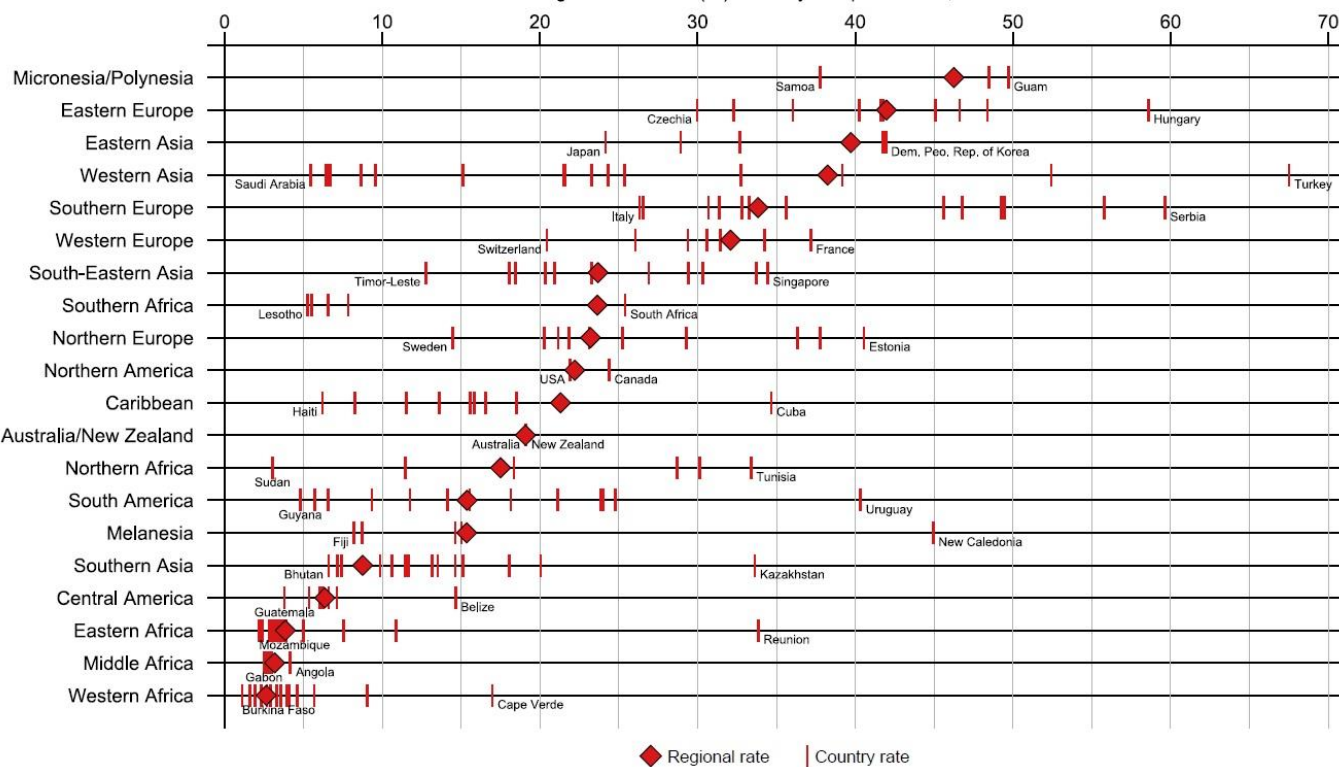


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020

Lung cancer

Age-standardized (W) mortality rate per 100000, males



Lung cancer

Age-standardized (W) mortality rate per 100000, females

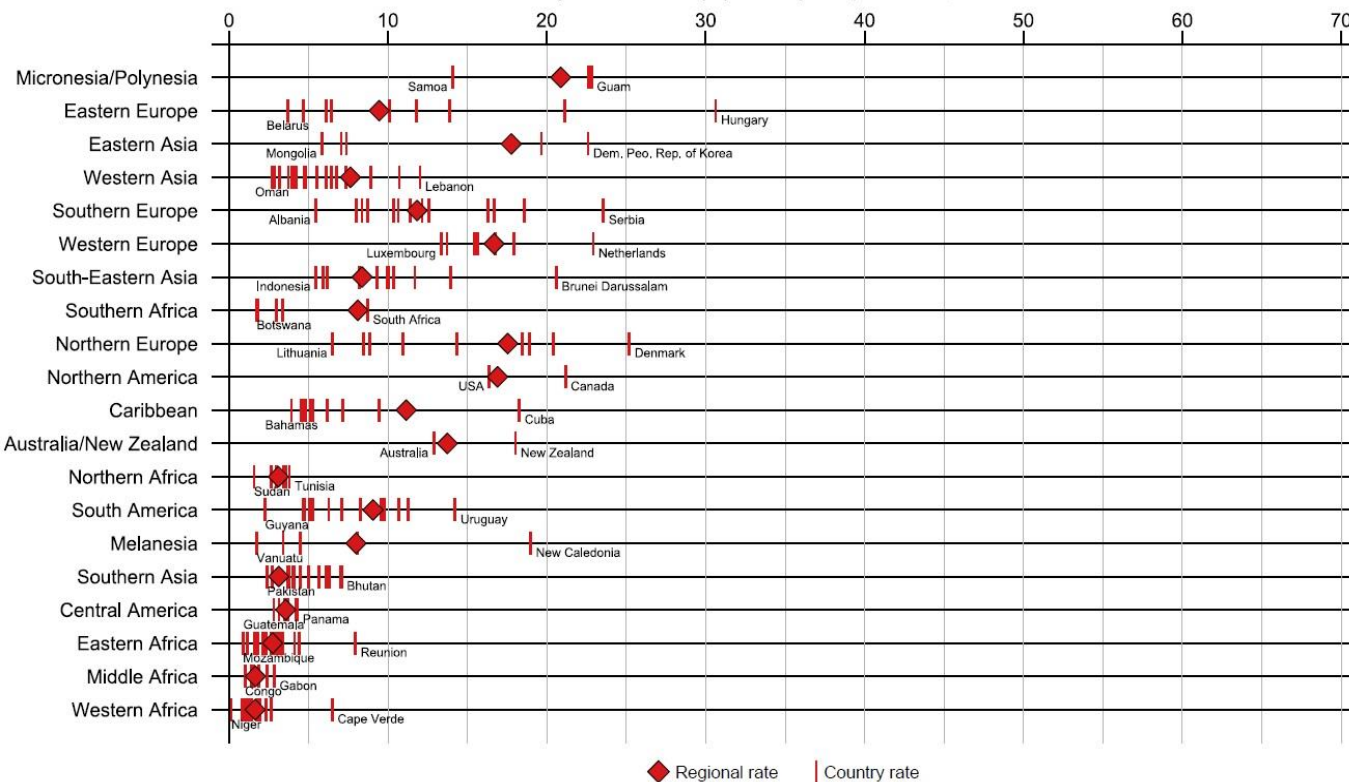
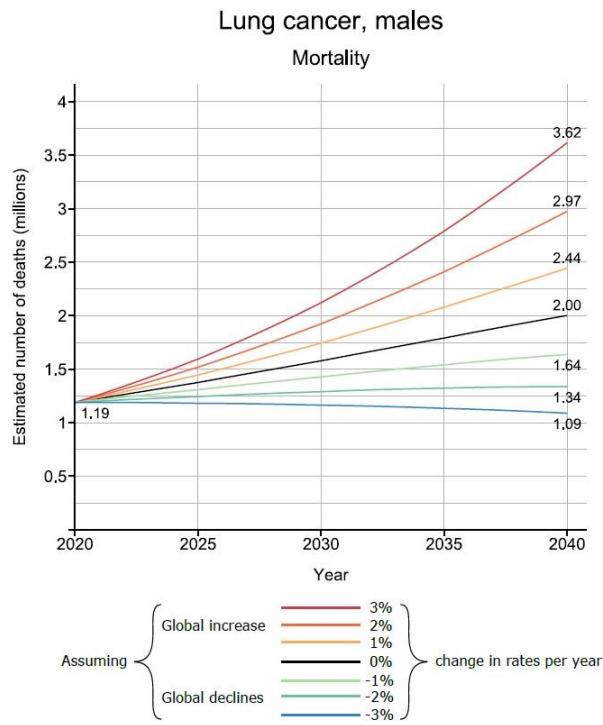


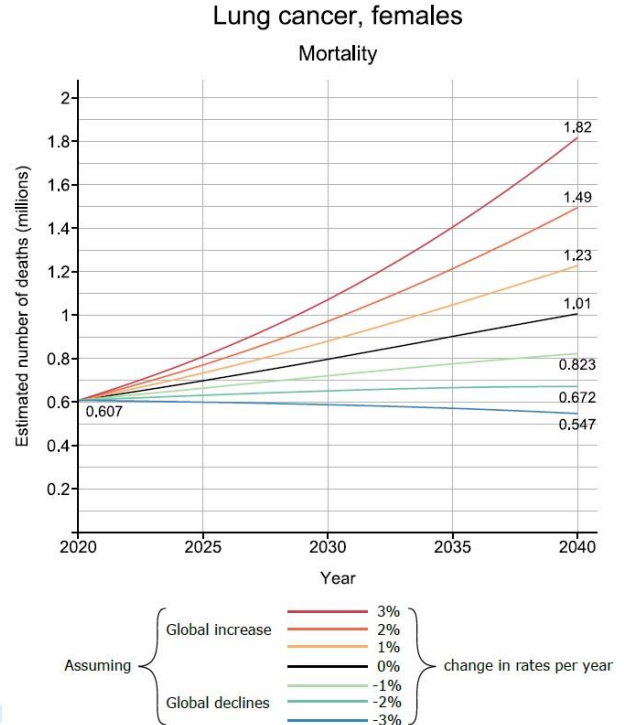
Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A



B



view only

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

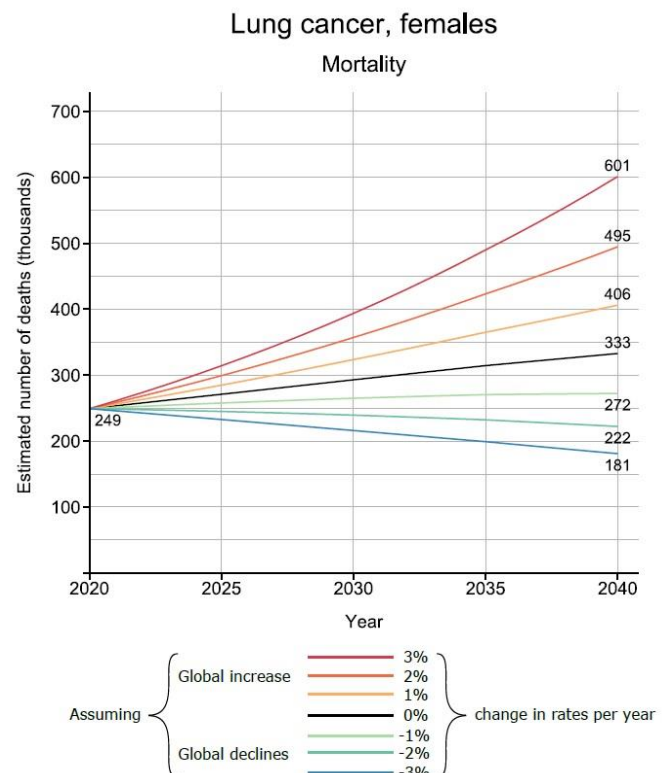
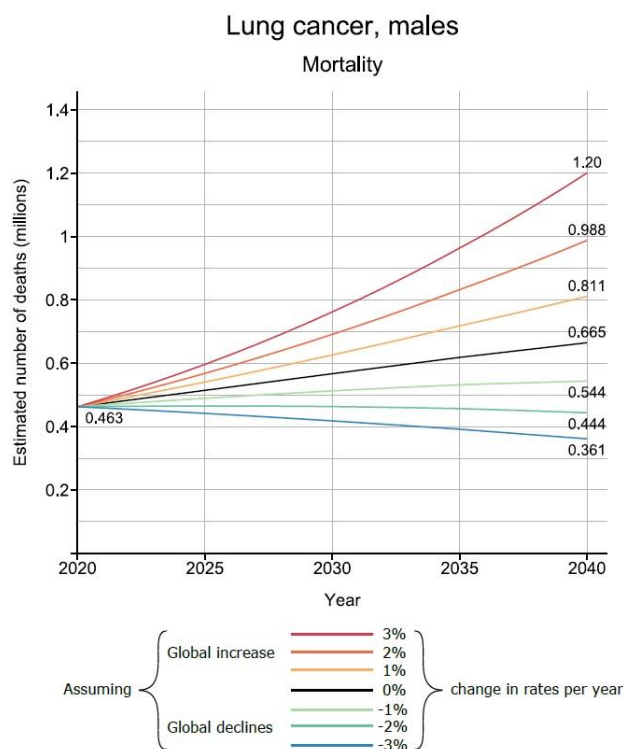
Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.fr/today>, accessed [13 April 2022].

Appendices

Lung cancer mortality by sex - very high HDI countries

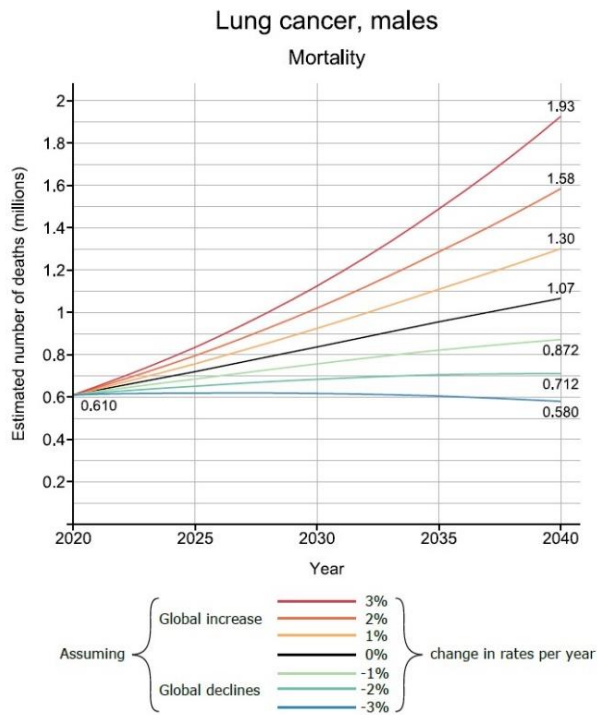
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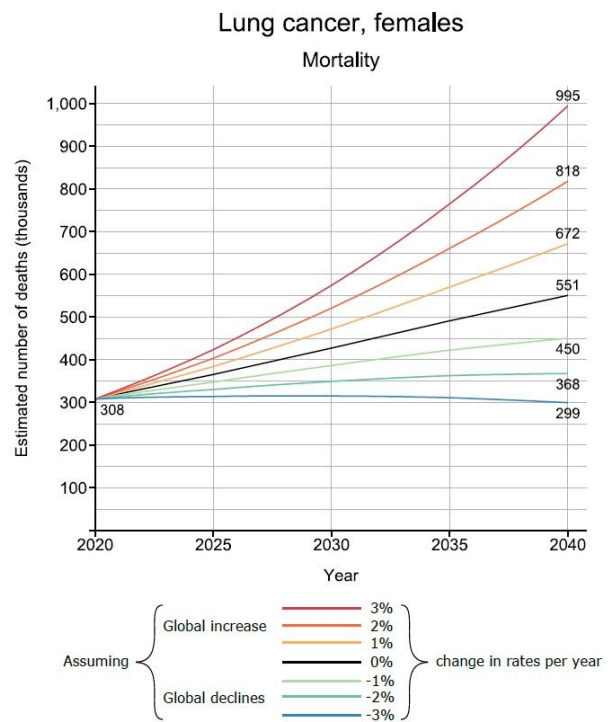


Lung cancer mortality by sex - high HDI countries

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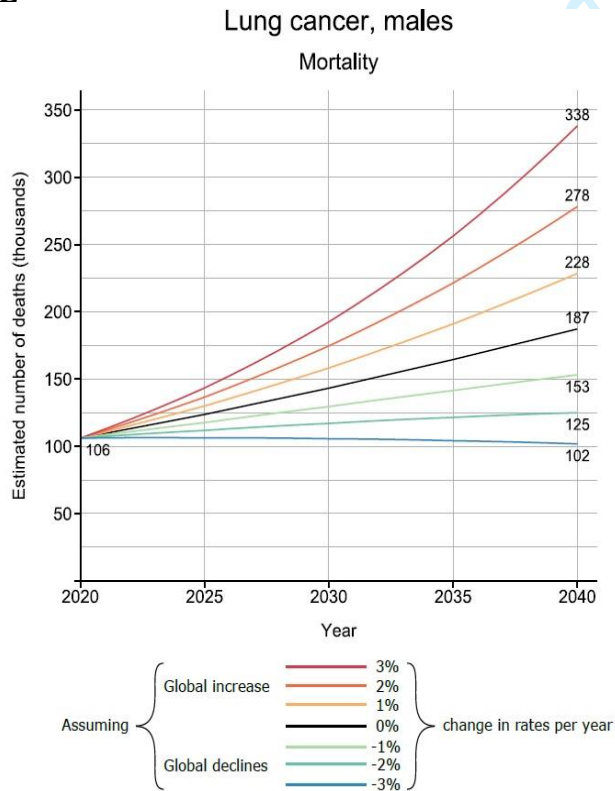


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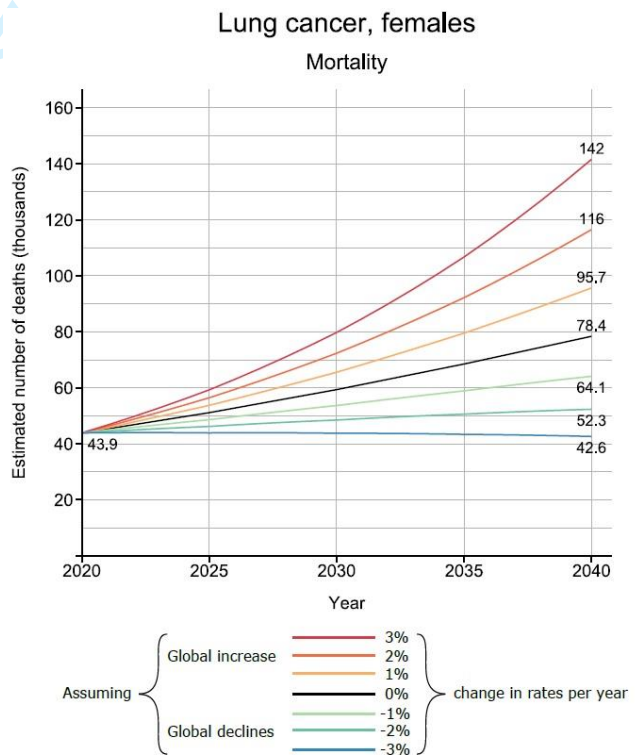


Lung cancer mortality by sex - medium HDI countries

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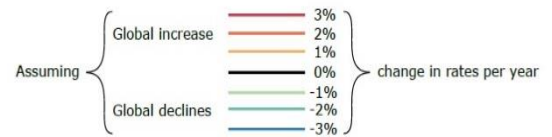
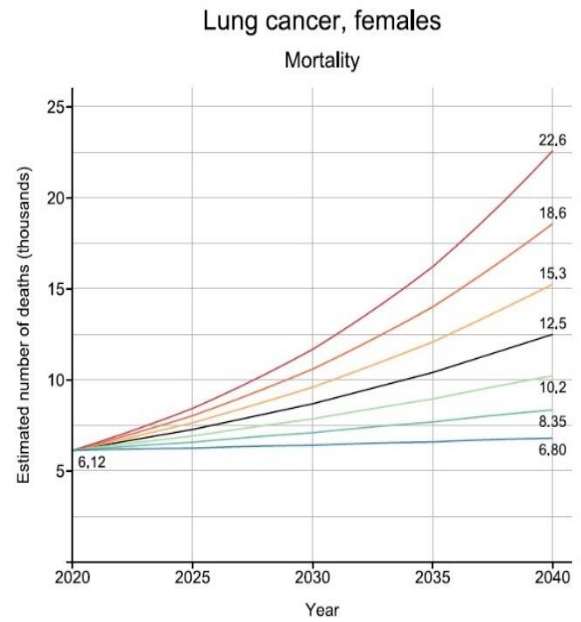
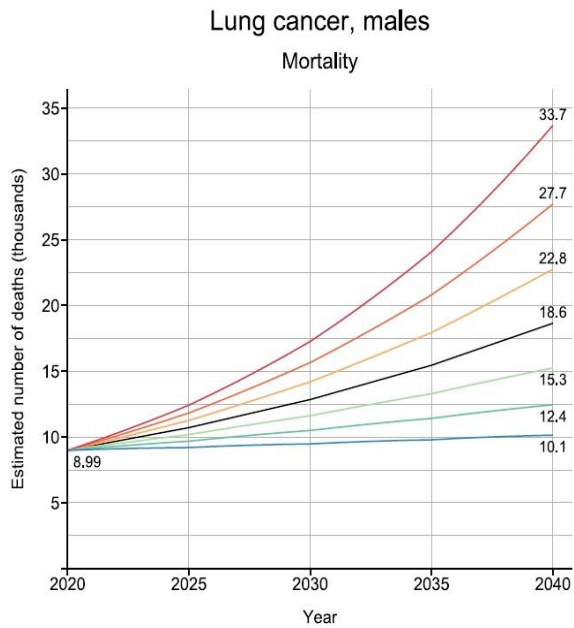
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Lung cancer mortality by sex - low HDI countries

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Review only

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| | | (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) | - |
| Outcome data | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time | - |
| | | <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure | - |
| | | <i>Cross-sectional study</i> —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.

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-065303.R3 |
| Article Type: | Original research |
| Date Submitted by the Author: | 03-Mar-2023 |
| Complete List of Authors: | Weber, Andras; International Agency for Research on Cancer, Cancer Surveillance Branch; National Institute of Oncology, Hungarian National Cancer Registry Morgan, Eileen; International Agency for Research on Cancer Vignat, Jerome; International Agency for Research on Cancer Laversanne, Mathieu; International Agency for Research on Cancer, Cancer Surveillance Branch Pizzato, Margherita; International Agency for Research on Cancer; University of Milan, Department of Clinical Sciences and Community Health Rumgay, Harriet; International Agency for Research on Cancer Singh, Deependra; International Agency for Research on Cancer Nagy, Péter; National Institute of Oncology, Department of Molecular Immunology and Toxicology; University of Veterinary Medicine, Department of Anatomy and Histology Kenessey, István; National Institute of Oncology; Semmelweis University, Department of Pathology, Forensic and Insurance Medicine Soerjomataram, Isabelle; WHO Bray, Freddie; Int Agcy Res Canc, Cancer Surveillance Branch |
| 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 |
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3 **1 Lung cancer mortality in the wake of the changing smoking epidemic: a descriptive study of the**
4 **2 global burden in 2020 and 2040**

6
7 3 András Wéber PhD^{1,2}, Eileen Morgan PhD¹, Jerome Vignat MSc¹, Mathieu Laversanne
8 MSc¹, Margherita Pizzato PhD^{1,3}, Harriet Rungay PhD¹, Deependra Singh PhD¹, Péter Nagy DSc⁴,
9 István Kenessey MD PhD², Isabelle Soerjomataram PhD¹, Freddie Bray PhD¹
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3 31 **Abstract**

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5 33 *Objectives*

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7 35 Lung cancer is the leading cause of cancer death in 2020, responsible for almost one in five
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9 36 (18.0%) deaths. This paper provides an overview of the descriptive epidemiology of lung cancer based
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11 37 on national mortality estimates for 2020 from the International Agency for Research on Cancer (IARC),
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13 38 and in the context of recent tobacco control policies.

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15 40 *Design and setting*

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17 42 For this descriptive study age-standardized mortality rates per 100,000 person-years of lung
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19 43 cancer for 185 countries by sex were obtained from the GLOBOCAN 2020 database and stratified by
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21 44 Human Development Index (HDI). Lung cancer deaths were projected to 2040 based on demographic
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23 45 changes alongside scenarios of annually increasing, stable or decreasing rates from the baseline year of
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25 46 2020.

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27 48 *Results*

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29 50 Lung cancer mortality rates exhibited marked variations by geography and sex. Low HDI
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31 51 countries, many of them within sub-Saharan Africa, tend to have low levels of mortality and an upward
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33 52 trend in lung cancer deaths is predicted for both sexes until 2040 according to demographic projections,
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35 53 irrespective of trends in rates. In very high HDI countries, including Europe, Northern America and
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37 54 Australia/New Zealand, there are broadly decreasing trends in men whereas in women, rates are still
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39 55 increasing or reaching a plateau.

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41 57 *Conclusion*

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43 59 The current and future burden of lung cancer in a country or region largely depends on the
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45 60 present trajectory of the smoking epidemic in its constituent populations, with distinct gender differences
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47 61 in smoking patterns, both in transitioning and transitioned countries. Further elevations in lung cancer
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49 62 mortality are expected worldwide, raising important social and political questions, especially in low-
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51 63 and middle-income countries.

52 64
53 65
54 66 **Keywords:** lung cancer, mortality, projection

55 67
56 68 **Word count of abstract:** 257

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58 70 **Word count of article:** 2623
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3 71 **Strengths and limitations of this study**
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- 8 75 • This study presents a detailed profile of the present LC burden in men and women worldwide
9 76 according to national levels of human development.
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12 77 • Our research applies a simple projection to estimate the future lung cancer mortality burden in
13 78 2040.
14 78
15 79
16 79
17 80 • We discuss the results in the context of key risk factors for lung cancer, particularly the
18 81 continually evolving smoking epidemic.
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21 82
22 83 • This examination is hampered by the limited availability of local cause of death information
23 84 from national vital registration sources, particularly in transitioning countries.
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90 **Introduction**

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

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

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

114

115 **Data Sources and Methods**

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

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3 124 to short-term predictions and modelled mortality to incidence (M:I) ratios, while validity is dependent
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5 125 on the degree of representativeness and quality of the source information [10].

6 126 We present figures based on the estimated deaths in 2020, as well as two summary measures using
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8 127 direct standardization, namely the age-standardized mortality rate (ASR) per 100,000 person-years
9
10 128 based on the 1966 Segi-Doll World standard population [16,17] and the cumulative risk of dying from
11
12 129 cancer before the age of 75 expressed as a percentage, assuming the absence of competing causes of
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14 130 death [18]. These measures allow comparisons between populations adjusted for differences in age
15
16 131 structures. We also provide a prediction of the future number of LC deaths worldwide for the year 2040,
17
18 132 based on demographic projections and scenarios of uniformly increasing (+3%, +2%, +1%), stable (0%)
19
20 133 or decreasing (-1%, -2%, -3%) rates annually from the baseline year of 2020. The possible impact of
21
22 134 COVID-19 pandemic was not taken into consideration during the calculations.

23
24 135 The results are presented by country and aggregated across 20 UN-defined world regions [12] and
25
26 136 according to the UN's four-tier HDI in 2020 [19], as a means to assess the cancer burden across four
27
28 137 levels of development (low, medium, high and very high HDI). Throughout, we use the terms
29
30 138 *transitioning*, *emerging* and *lower HDI* countries/economies as synonyms for nations classified as low
31
32 139 or medium HDI, and *transitioned* or *higher HDI* countries/economies for those classified as high or very
33
34 140 high HDI.

35
36 141 The Global Cancer Observatory (GCO, <https://gco.iarc.fr>) includes facilities for the tabulation
37
38 142 and graphical visualization of the GLOBOCAN database, including explorations of the current [2] and
39
40 143 future [20] burden for 36 cancer types.

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42 144 Patient and Public Involvement: Patients or the public were not involved in the design, or
43
44 145 conduct, or reporting, or dissemination plans of our research.

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47 48 147 **Results**

49 50 148 *Lung cancer mortality – national rankings 2020*

51
52 149 Figure 1 presents global maps that indicate LC's position in terms of deaths relative to other
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54 150 common tumours at the national level, by sex for the year 2020. In 2020, LC ranks first in terms of
55
56 151 cancer death in half (93 out of 185) of the countries included in GLOBOCAN, and either 2nd or 3rd in 37
57
58 152 countries, in men. LC is a major contributor to cancer mortality around the world, including America,
59
60 153 greater-Europe, Northern Africa, and across the Asian-Pacific region. There is a less dominant role at
154
155 154 present in South America and Sub-Saharan Africa (but not South Africa). In women, the impact is lesser
156
157 155 but still very much in evidence; the disease ranks as the leading form of cancer death in 25 countries
158
159 156 including those within North America, Northern, Western and Southern-Central Europe, Eastern Asia
160
157 and Australia/New Zealand. LC mortality ranks as the 2nd or 3rd leading form of cancer mortality in 54
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159 158 countries worldwide in women.

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3 159 There is at least a 20-fold variation in mortality between the sexes, with rates uniformly higher
4 160 among men (Figure 2). Male mortality rates are higher in Eastern and Southern Europe (especially in
5 161 Hungary and Serbia with rates of 60 per 100,000), Eastern Asia (particularly the Democratic People's
6 162 Republic of Korea) and Polynesia and Micronesia, while rates are lower in Central America, South-
7 163 Central Asia and most parts of sub-Saharan Africa. The highest female rates are observed in Northern
8 164 America, Northern and Western Europe, and Australia/New Zealand specifically in Canada, Denmark
9 165 and the Netherlands, respectively. Relatively low rates are observed in Western-, South-Eastern Asia
10 166 and across the African continent, excluding South Africa.

167 *Lung cancer mortality burden by 2040*

168 If the current rates were to remain constant over the next two decades, LC will claim around 2
169 million male deaths in 2040, compared to 1.2 million in 2020 (Figure 3). For women, the corresponding
170 deaths are approximately half of their male counterparts: a predicted increase to 1 million in 2040 from
171 600 000 deaths in 2020. The projection also shows the different scenarios considering the changing rates
172 per year between -3% and +3% based on plausible scenarios of the smoking epidemic in the short-term
173 future; global declines in the number of LC among males but increases for female are perhaps the more
174 realistic scenarios, with national or regional exceptions. Taking this trends-based prediction into
175 account, the predicted number of deaths due to LC for men will likely range between 1.1 and 1.6 million
176 and for women between 1.2 and 1.8 million by 2040. Deaths will markedly increase for both sexes in
177 countries with the lowest HDI, even in the best-case trend scenario (Appendix Figure 1a-h).

179 **Discussion**

180 This study highlights the present geographic diversity in LC mortality worldwide, by sex and by
181 level of human development. Countries with low HDI tend to have low LC mortality rates but may
182 anticipate a higher mortality burden by 2040. For higher HDI countries, the burden of the disease is
183 higher among men, but future trends suggest an increasingly greater proportion of the cancer burden
184 will be seen among females. These different scenarios are due to the impact of historic smoking trends
185 and the increasingly widespread application of tobacco control measures in the last decades [21]. While
186 there is an expectation that LC mortality will increase in transitioning countries given there is less
187 implementation of effective tobacco control, there is a positivity in the findings from the Global Tobacco
188 Control Report: the number of people now living in countries with at least two anti-tobacco policies in
189 place rose from 3.5 billion in 2018 to 4.4 billion in 2020 – up from 45% of the world's population to
190 56% in two years [22].

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

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3 194 stages in the population, by an earlier adoption of the habit in men compared with women, and by the
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5 195 progressive adoption among lower socioeconomic classes, where the habit continues to be an underlying
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7 196 cause of the marked inequalities seen in different educational groups [23]. Lopez et al. initially applied
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9 197 the hypothesis on just a few developed countries [24], which was later tested on greater geographic
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11 198 scales [25,26]. Nevertheless, as smoking prevalence and subsequent LC rates began to peak and decline
12
13 199 among men in many populations over the last decades, a key focus has been the deteriorating public
14
15 200 health situation affecting women, where in many settings, rates of LC mortality have continued to rise.
16
17 201 This raises several relevant biological, epidemiological and sociological concerns [27], including: the
18
19 202 changing distribution of the main histological subtypes of LC over time [28], the extent to which females
20
21 203 adopted the habit of smoking and their vulnerability to the tobacco industry [29,30], the impact of such
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23 204 a transition in diminishing gender differences in disease burden worldwide [31] and the effects of
24
25 205 different political systems on the health awareness of individuals [32,33]. The impact of these factors is
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27 206 reflected in comparisons of between-country LC mortality rates; for example, the current rate differences
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29 207 in Eastern vs. Northern European countries.

30
31 208 Smoking is of course not the only risk factor for LC. There is strong evidence of a relation with
32
33 209 other factors, including air pollution, climate change [34] and other occupational risk factors such as
34
35 210 asbestosis and indoor exposure to cooking fumes etc [35]. The highest exposure to ambient air pollution
36
37 211 is the characteristic of mainly countries in transition, where only modest reductions in burden will occur
38
39 212 in the most polluted countries unless fine particulate matter (PM 2.5) values are decreased substantially
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41 213 [36].

42
43 214 Several other studies have aimed to forecast the future lung cancer burden in very high HDI
44
45 215 countries e.g., the US [37] and the UK [38] with contradictory findings. While the steeply declining
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47 216 mortality in the US for both sexes until 2040 fits within the framework of the global smoking epidemic,
48
49 217 the rising deaths reported in the UK for men and women until 2035 somewhat contradict previous
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51 218 findings. One explanation could be the rapidly ageing population, which can increase the number of
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53 219 these non-standardized figures. Alternatively, these projections do not take into account the changing
54
55 220 smoking prevalence in the past as a key determinant of present and future lung cancers. Our
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57 221 GLOBOCAN 2020 forecasts do not consider these either, however, we provide possible scenarios on
58
59 222 the basis of uniform increases or decreases in rates that may help provide a realistic overview of the
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223 changing future burden of LC.

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

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3 228 estimates via modelling, using incidence-to-mortality ratios derived from cancer registries in
4 229 neighbouring countries.

6
7 230 With over three million deaths predicted by 2040 in the absence of additional interventions
8 231 according to the finding of this study, it is imperative to emphasize primary prevention as the most cost-
9 232 effective strategy of tobacco control. It has been shown that raising the price of cigarettes through
11 233 increased excise taxes can bring marked reductions in cigarette consumption [39]. Besides this,
13 234 developing adaptive tobacco control strategies that target different subgroups is imperative.

15 235 One key concern is the limited financial and trained resources in middle- and lower-income
16 236 countries, that can hinder health promotion and cancer prevention strategies in these countries. Based
17 237 on our findings, decreases in lung cancer rates are not likely in these countries until 2040 and presumably
19 238 tobacco companies are expected to shift and escalate promotional campaigns to preserve business
21 239 interests and profits where resistance efforts are the weakest [30].

23
24 240 Additionally, anti-tobacco strategies should urgently target women in also higher-income settings
25 241 such as the EU, in order to halt their rapidly increasing risk of LC, and prevent unnecessary, premature
26 242 deaths among future generations of women [40]. In Sweden, as an example, gender-specific policies
27 243 such as those directed at health promotion have been implemented with a focus on young and pregnant
28 244 women. Scotland also has gender-specific programs, such as the Women, Low Income, and Smoking
29 245 Project [41]. Amos and Haglund (2000) have emphasized that building support for female-centered
30 246 tobacco control programs through partnerships will be vital to achieve success [30]. Furthermore, Amos
31 247 (1996) and Mackay and Amos (2003) draw attention to the situation of women in transitioning countries
32 248 with presently low levels of cigarette smoking among women [29]. In these countries, smoking among
33 249 girls is already on the rise, women's spending power is increasing, cigarettes are becoming affordable,
34 250 and women are more exposed to the marketing strategies of tobacco companies, in an environment
35 251 where cultural constraints are weakening and female-specific quitting programs are rare [8].

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43 252 A package of measures to suppress tobacco consumption in a given population has been
44 253 recommended through continued efforts to increase the proportion of ex-smokers, with a focus on
45 254 younger generations [42]. This could perhaps be achieved by implementing coordinated smoking
46 255 prevention and control strategies from an early age, in the form of educational programs in schools.
47 256 Other measures that could be introduced include community intervention programs, mass media
48 257 campaigns and further legislation to ban smoking in public places. One of the main problems is that
49 258 young people react very differently to anti-smoking messages compared to adult long-term smokers
50 259 [42]. The harm-reducing role of e-cigarettes and aid to smoking cessation has been proposed [43],
51 260 however their impact on future LC mortality is not yet known [44]. Successful programs have also been
52 261 implemented in rapidly emerging economies such as Brazil, where a reduction in smoking prevalence
53 262 were observed after the ratification of the WHO Framework Convention on Tobacco Control (FCTC)

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3 263 in 2005, and the adoption of a national ban on tobacco advertising, a national comprehensive smoke-
4 264 free policy, large pictorial health warnings on cigarette packages, and continuous increases in taxes and
5 265 prices of tobacco products [45]. Other factors may influence the future burden of LC such as the potential
6 266 introduction of screening in high-risk populations. In a recent trial, LC mortality was significantly lower
7 267 among those who underwent volume computed tomography (CT) screening than those who did not
8 268 participate [46]. Screened patients benefitted from a substantial shift to lower-stage cancers at the time
9 269 of diagnosis as well as more frequent eligibility for curative treatment (mainly surgery) [47]. However,
10 270 concerns have been raised about the potential for overdiagnosis in lung-cancer screening.

11 271 In summary, this paper has identified marked geographic variations in the current LC burden
12 272 worldwide and provided potential scenarios regarding the short-term future LC deaths up until 2040.
13 273 Gredner et al., have illustrated the great potential of comprehensive implementation of tobacco control
14 274 policies in Greater-Europe, with over 1.6 million LC cases preventable over a 20-year period through
15 275 the highest-level implementation of tobacco control policies [48]. There is therefore much we can do to
16 276 halt the rising deaths from LC – as well as many other forms of cancer and non-communicable diseases
17 277 – through the successful implementation of tobacco control policies.

18 278

19 279 **Disclosure**

20 280 Where authors are identified as personnel of the International Agency for Research on Cancer/World
21 281 Health Organization, the authors alone are responsible for the views expressed in this article, and they
22 282 do not necessarily represent the decisions, policy, or views of the International Agency for Research on
23 283 Cancer/World Health Organization.

24 284

25 285 **Role of the funding source**

26 286 PN: This study was supported by the Topic Excellence Program (TKP2020-NKA-26, TKP2021-EGA-
27 287 44), the National Laboratories Program (National Tumor Biology Laboratory-2022-2.1.1-NL-2022-
28 288 00010), and Tasks Related to the National Public Health Strategy (IV/4925/2021/ EKF).

29 289

30 290 **Authors' contribution**

31 291 AW: literature search, data analysis, writing – original draft; EM: writing – review & editing; JV:
32 292 figures, visualisation; ML: methodology, figures, visualisation; MP: writing – review & editing; HR:
33 293 writing – review & editing; DS: writing – review & editing; PN: writing – review & editing, funding
34 294 acquisition; IK: writing – review & editing; IS: writing – review & editing; FB: methodology,
35 295 conceptualisation, data analysis, writing – original draft

36 296

37 297 **Declaration of interests**

38 60

298 All authors declare that they have no conflicts of interest.

299

300 **Data sharing**

301 Data are available in a public, open access repository.

302

303 **Ethics Approval Statement**

304 This study does not involve human participants and animal subjects.

305

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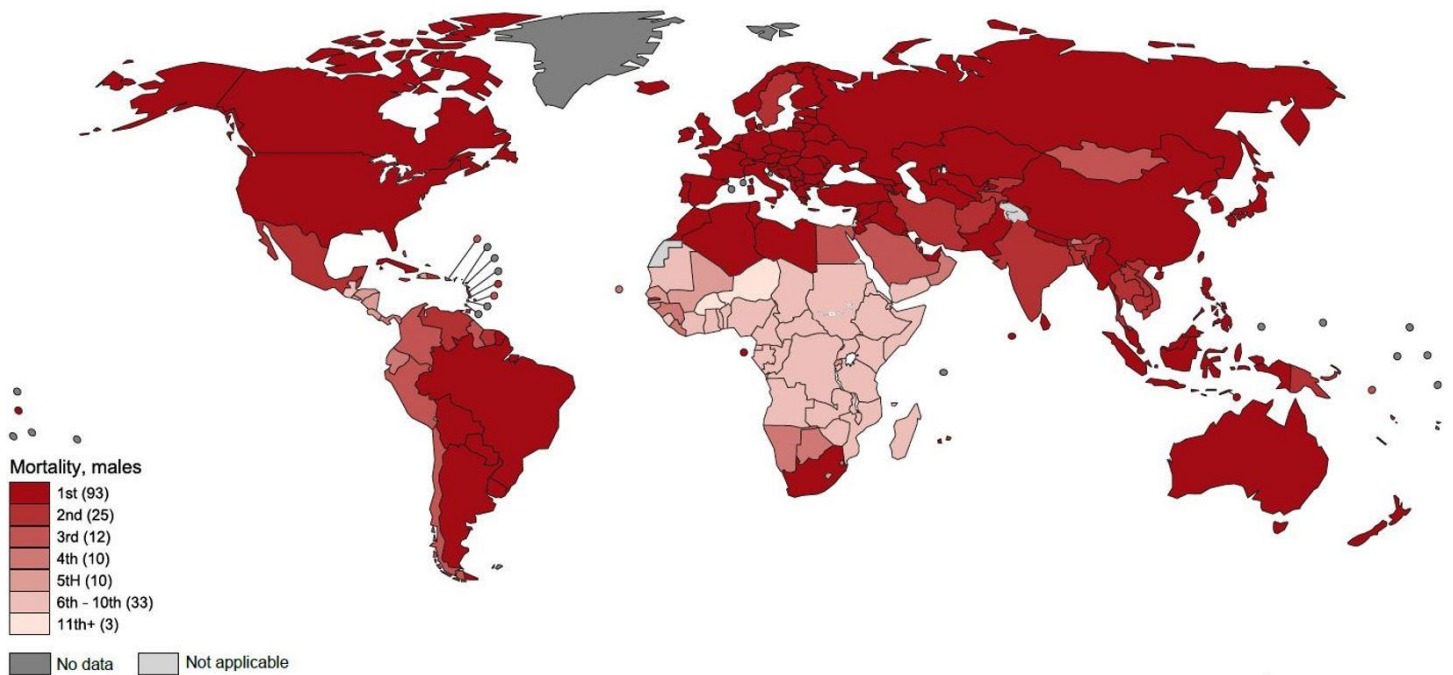
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9 418 Figures

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11 419 Figure 1: Lung cancer mortality compared with mortality from other causes of malignant neoplasms,
12 420 2020, Male-Female

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14 421 Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020,
15 422 Male-Female

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17 423 Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human
18 424 Development Index (HDI)

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



Female

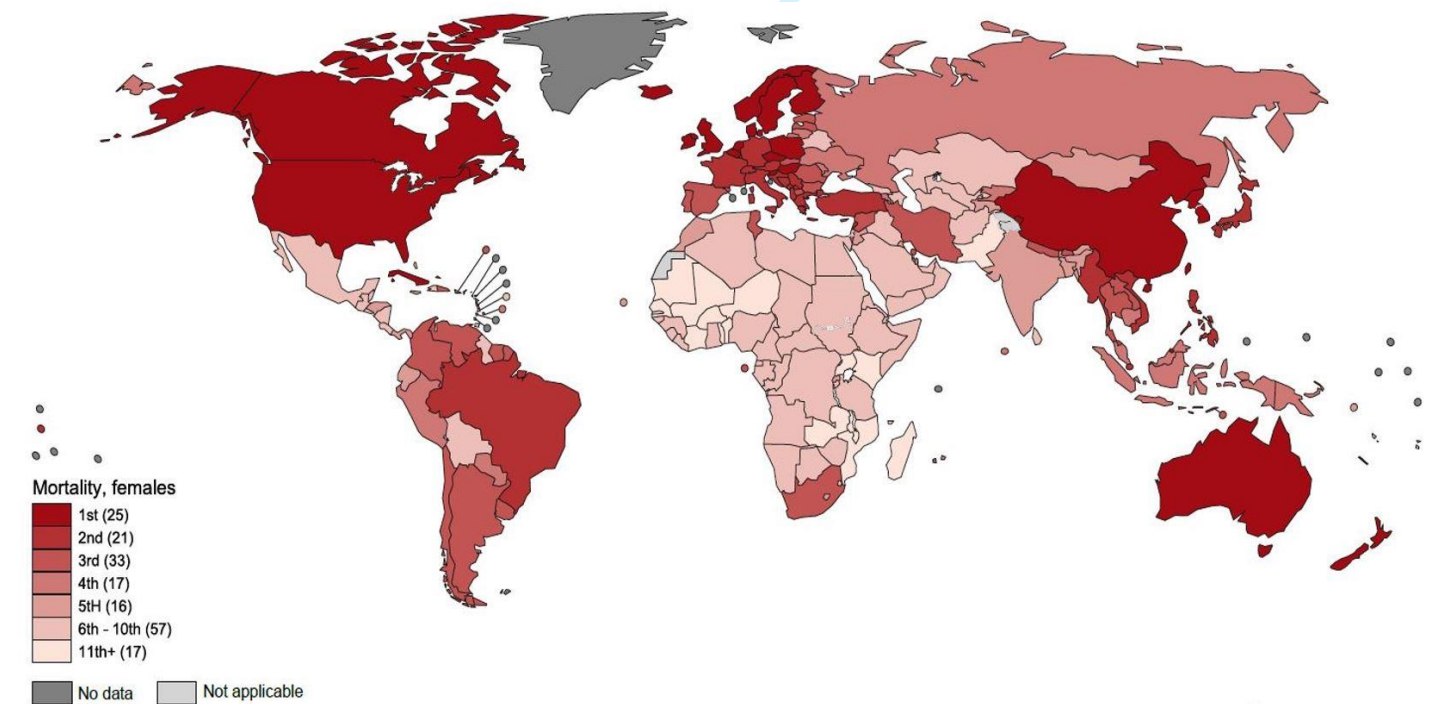


Figure 2: Lung cancer age-standardized mortality rates per 100,000 by world regions and sex in 2020

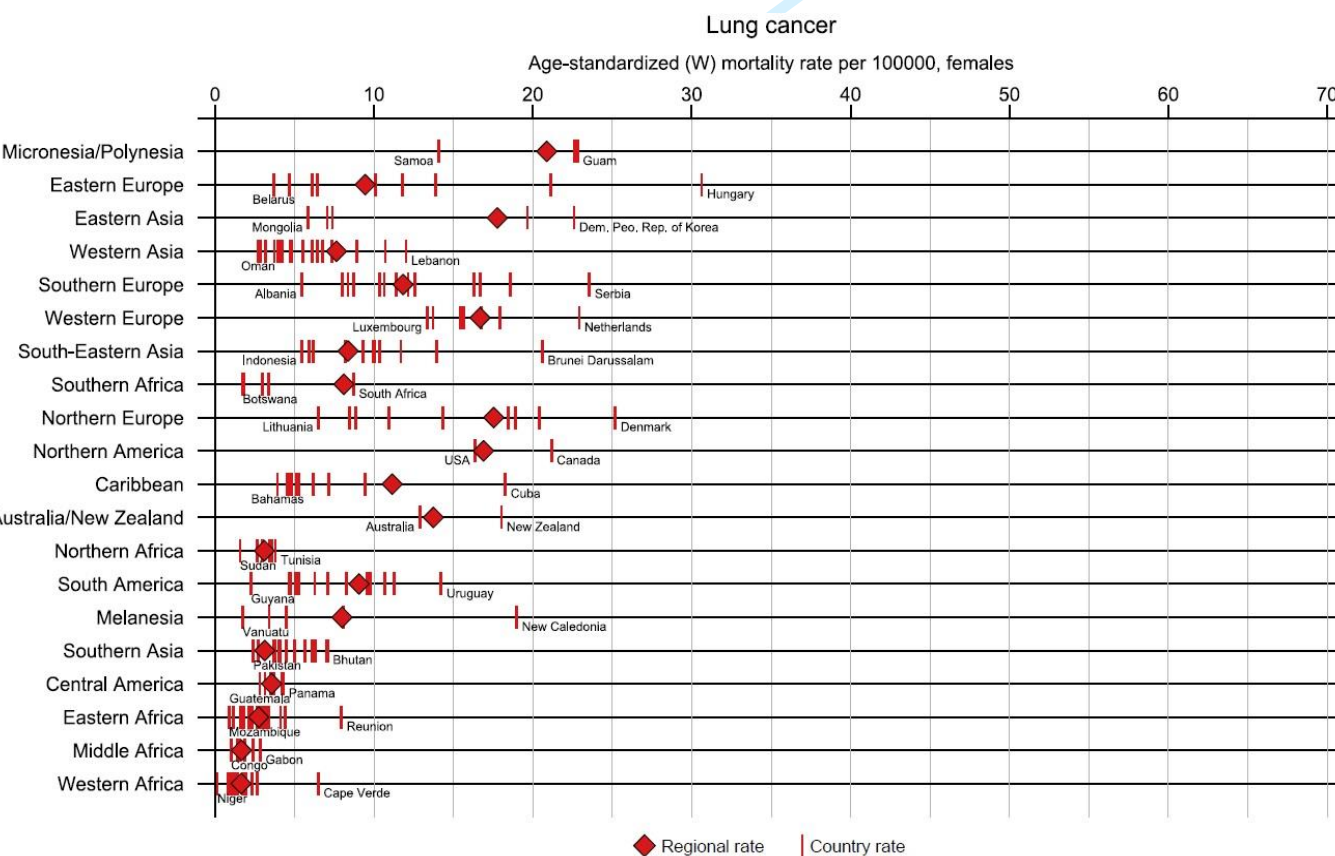
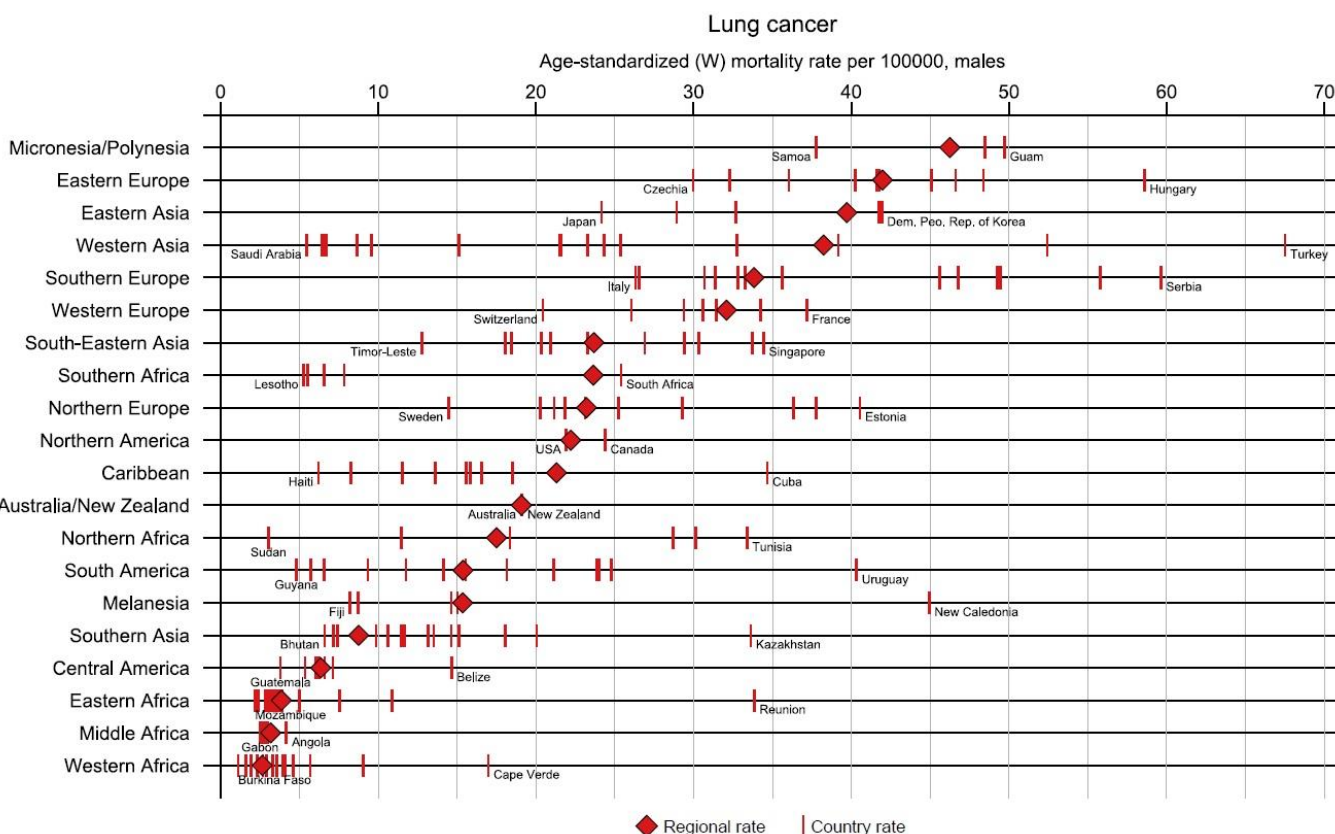
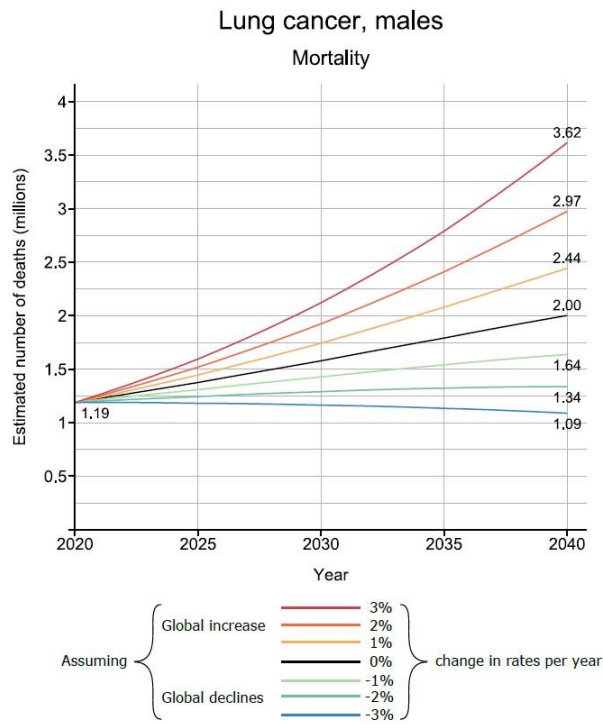


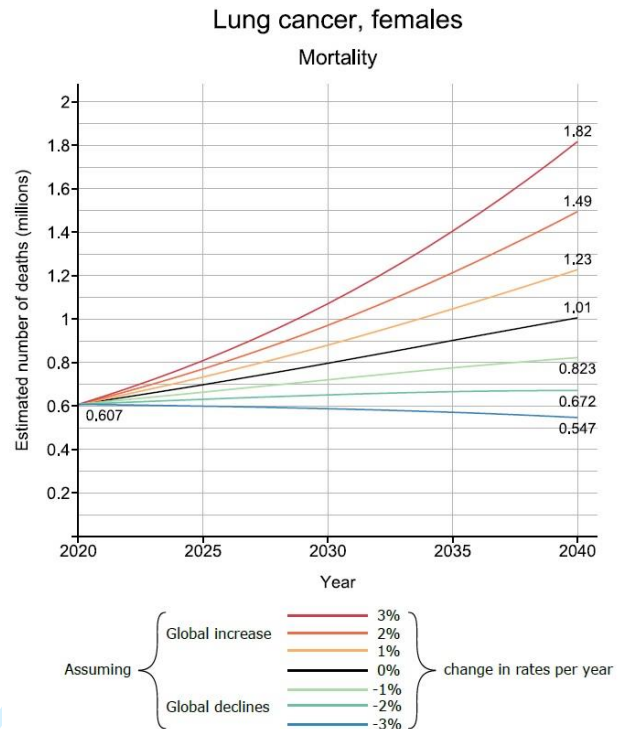
Figure 3: Lung cancer mortality projections worldwide from 2020 to 2040 by sex and the Human Development Index (HDI)

Lung cancer mortality by sex

A



B



view only

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

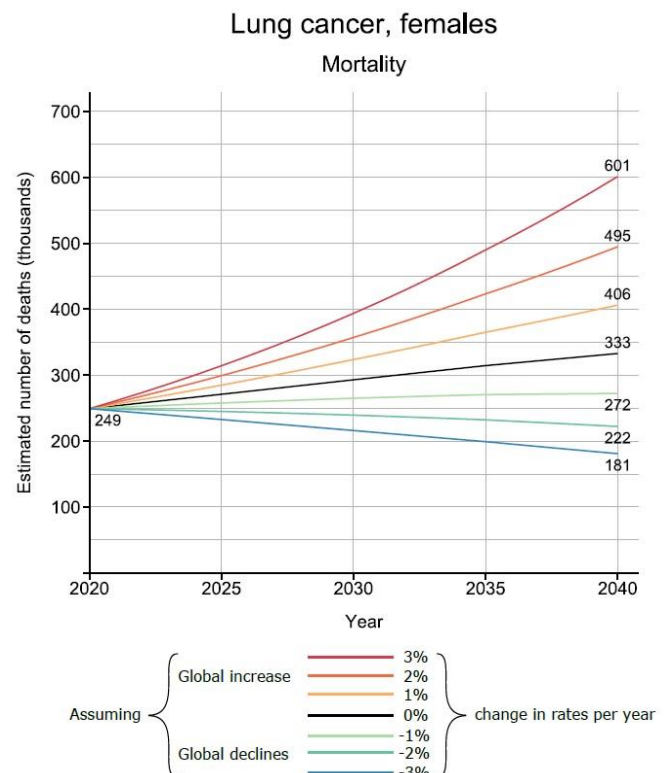
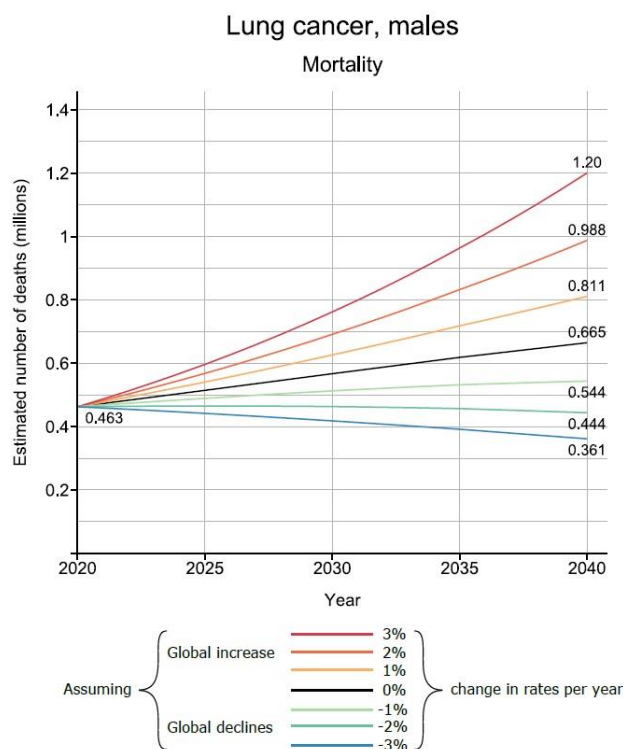
Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.fr/today>, accessed [13 April 2022].

Appendices

Lung cancer mortality by sex - very high HDI countries

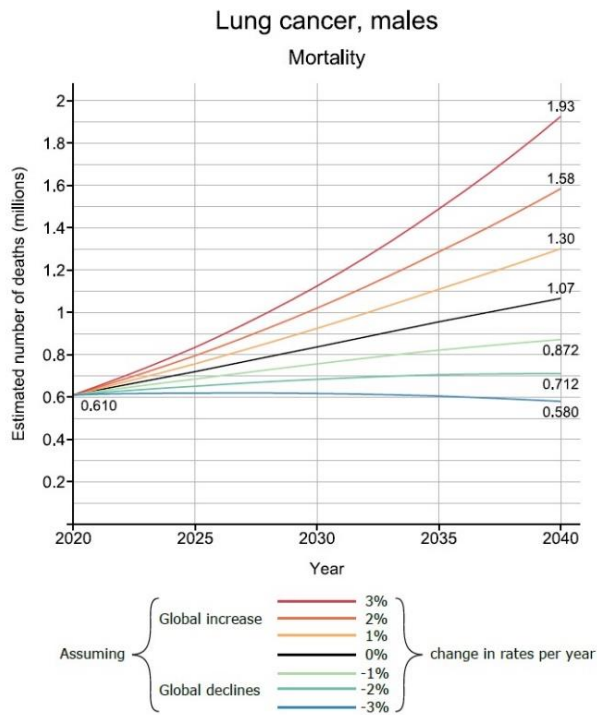
A

B

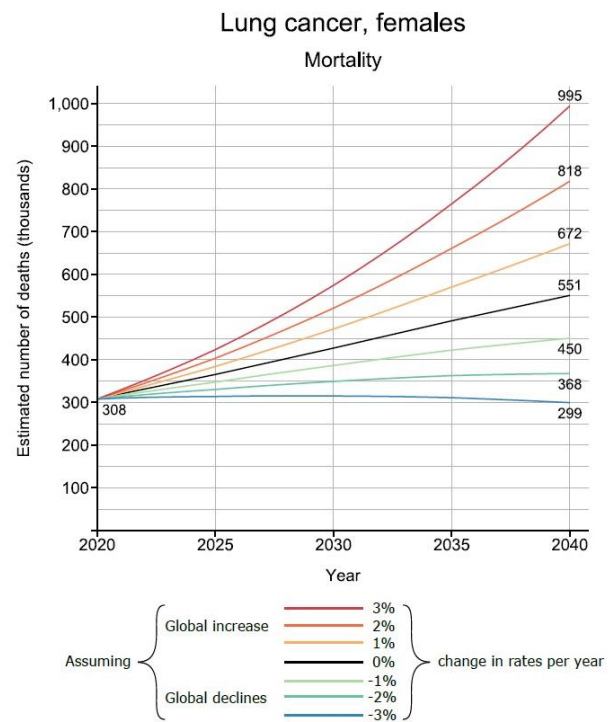


Lung cancer mortality by sex - high HDI countries

C

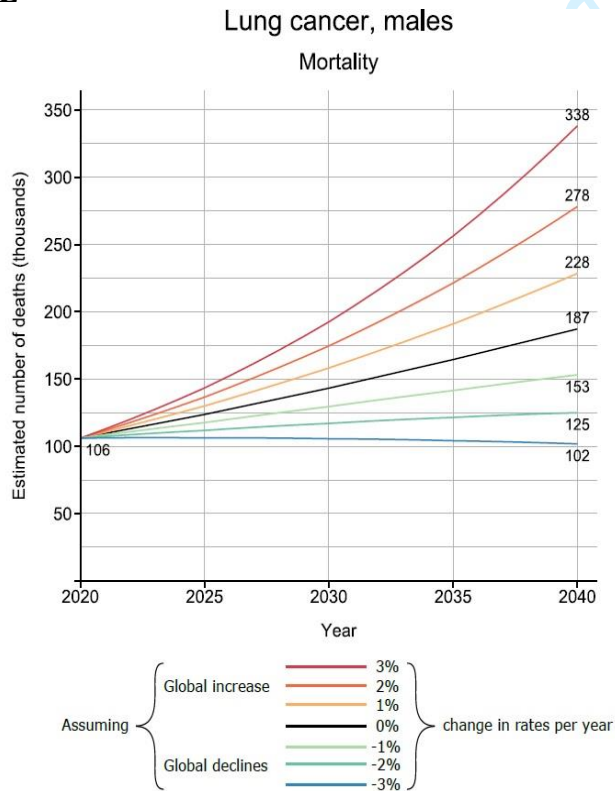


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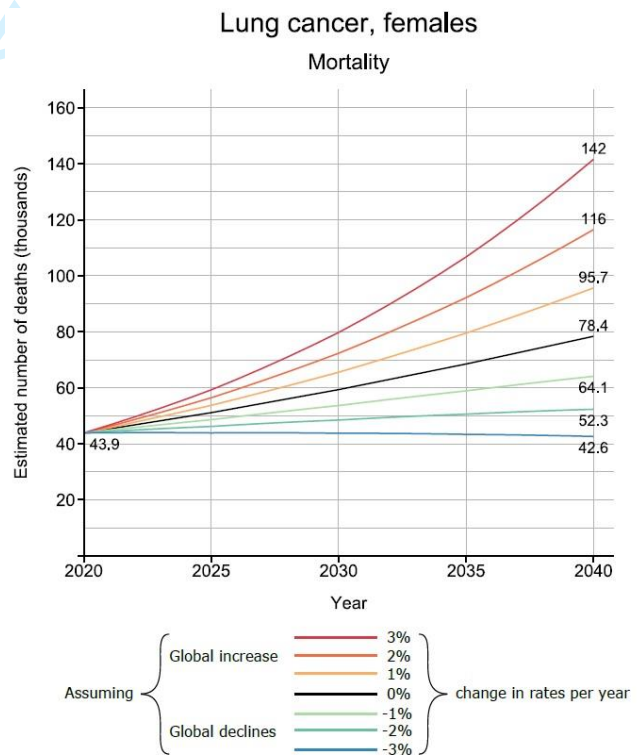


Lung cancer mortality by sex - medium HDI countries

E



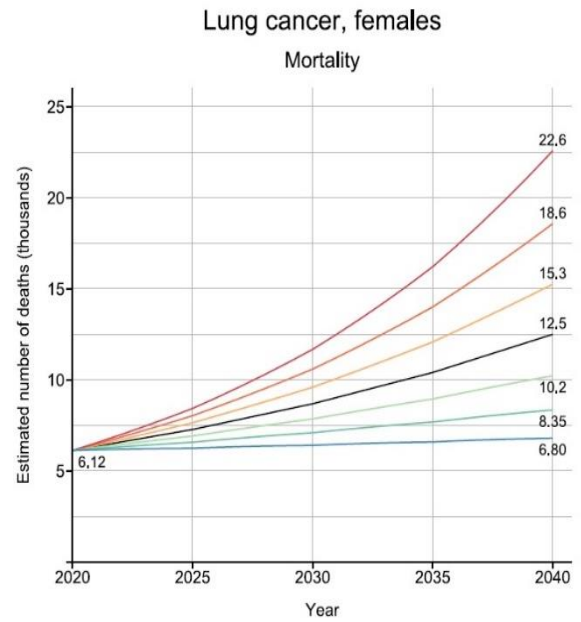
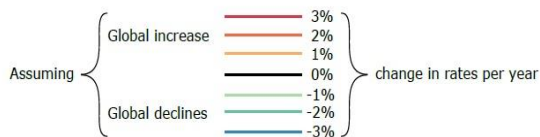
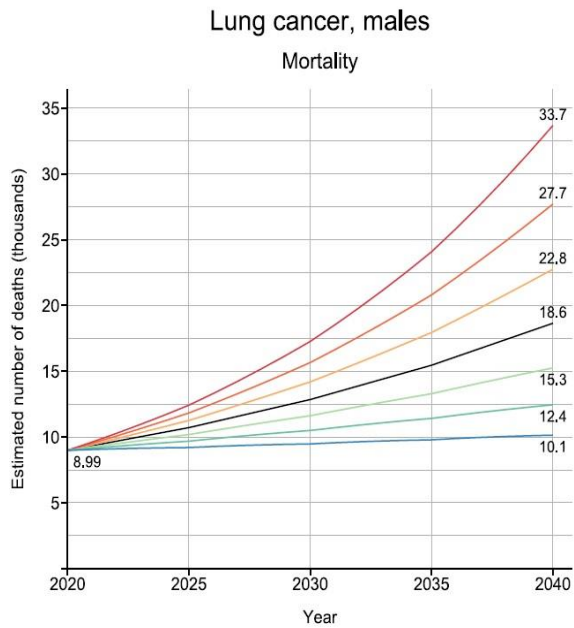
F



Lung cancer mortality by sex - low HDI countries

G

H



Review only

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants | 4 |
| | | (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) | - |
| Outcome data | 15* | <i>Cohort study</i> —Report numbers of outcome events or summary measures over time | - |
| | | <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure | - |
| | | <i>Cross-sectional study</i> —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.