CHEST

Distribution, Risk Factors, and Temporal Trends for Lung Cancer Incidence and Mortality

A Global Analysis

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BACKGROUND: Lung cancer ranks second for cancer incidence and first for cancer mortality. Investigation into its risk factors and epidemiologic trends could help describe geographical distribution and identify high-risk population groups.

RESEARCH QUESTION: What is the global incidence, mortality, associated risk factors, and temporal trends of lung cancer by sex, age, and country?

STUDY DESIGN AND METHODS: Data on incidence and mortality were retrieved from the Global Cancer Observatory (GLOBOCAN), *Cancer Incidence in Five Continents* series I-X, World Health Organization (WHO) mortality database, the Nordic Cancer Registries (NORDCAN), and the Surveillance, Epidemiology, and End Results Program (SEER). We searched the WHO Global Health Observatory data repository for age-adjusted prevalence of current smoking. The Average Annual Percentage Change (AAPC) of the trends were obtained by Joinpoint Regression.

RESULTS: The age-standardized rate of incidence and mortality were 22.4 and 18.0 per 100,000 globally. The lung cancer incidence and mortality were associated with Human Development Index (HDI), Gross Domestic Products (GDP), and prevalence of smoking. For incidence, more countries had increasing trends in females but decreasing trends in males (AAPC, 1.06 to 6.43 for female; −3.53 to −0.64 for male). A similar pattern was found in those 50 years or older, whereas those aged younger than 50 years had declining incidence trends in both sexes in most countries. For mortality, similar to incidence, 17 of 48 countries showed decreasing trends in males and increasing trends in females (AAPC, −3.28 to −1.32 for male, 0.63 to 3.96 for female).

INTERPRETATION: Most countries had increasing trends in females but decreasing trends in males and in lung cancer incidence and mortality. Tobacco related measures and early cancer detection should be implemented to control the increasing trends of lung cancer in females, and in regions identified as having these trends. Future studies may explore the reasons behind these epidemiological transitions. CHEST 2022; 161(4):1101-1111

KEY WORDS: incidence; lung cancer; mortality; temporal trend

ABBREVIATIONS: AAPC = average annual percentage change; ASR = age-standardized rate; GDP = Gross Domestic Products; GLOBOCAN = Global Cancer Observatory; HDI = Human Development Index; NORDCAN = Nordic Cancer Registries; SEER = Surveillance, Epidemiology, and End Results Program; WHO = World Health Organization

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Take-home Points

Study Question: What are the global incidence, mortality, associated risk factors, and temporal trends of lung cancer by sex, age, and country?

Results: There was a wide variation in the disease burden of lung cancer in 2020, with the highest incidence and mortality in Asia and the lowest in Western Africa. Lung cancer incidence and mortality were associated with HDI, GDP, and prevalence of smoking. As for trends of incidence and mortality, more countries presented an increasing trend in females, but the trend was decreasing in males.

Implication: There was an overall increasing trend in females but decreasing trend in males in lung cancer incidence and mortality over the past decade. Tobacco-related measures and early cancer detection should be implemented to control the increasing trends of lung cancer among the high-risk populations. Future studies may further explore the reasons behind these epidemiological transitions.

Globally, lung cancer is the second most common cancer and the most common cause of cancer death.[1] In 2020, a total of 1.8 million new death cases were attributable to lung cancer, accounting for 18% of all cancer mortality.[1] The 5-year survival rate (7%-25%) of lung cancer was much lower than that of other major cancers.[2] Because of its high mortality rate, the distribution of mortality for lung cancer was very similar to that of its incidence, which induced a substantial global burden of disease.[3] Recent improvements in lung cancer mortality are in part caused by treatment advances in some high-income countries, including the United States,[4] the United Kingdom,[5] and Australia.[6]

Smoking is the leading risk factor for lung cancer, with 80% of lung cancer mortality estimated to be attributable to tobacco consumption.[7] Second-hand smoking is also an important contributory factor for lung cancer.[8] Other risk factors include exposure to radon, asbestos, and some cancer-causing agents such as chromium, cadmium, arsenic, radioactivity, and coal products.[7] Because these risk factors are highly reversable by smoking cessation, occupational protection, and clean air initiatives, evidence-based preventive measures could be implemented to reduce its disease burden. Therefore, evaluating its updated distribution, especially for the temporal trends by age, sex, and region, is important.

Previous studies reported trends of lung cancer in a country or region[9,10] or presented the global trends from data in old cancer registries.[11-13] A global investigation on distribution of, associated risk factors for, and the most recent temporal patterns in lung cancer incidence and mortality could help describe geographical distribution, identify high-risk population groups, and inform the development of its preventive interventions. The findings could also be related to the prospects of prevention and early cancer detection strategies for lung cancer. The objectives of this study are to evaluate the global incidence, mortality, associated risk factors, and temporal trend of lung cancer by age, sex, and region, using data from global and national cancer registries.

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Study Design and Methods

Source of Data

All the lung cancer incidence and mortality data included in this study follow the definition "Malignant neoplasm of bronchus or lung" from the *International Classification of Disease and Related Health Problems,* 10th Revision, codes (C34) to locate suitable data.[14] The data used in this study were drawn from the Global Cancer Observatory (GLOBOCAN), which consists of data from 185 countries around the globe.[15,16] We extracted data on gross domestic products (GDP) per capita from the World Bank. We used the human development index (HDI) for each country from the United Nations. We searched the World Health Organization (WHO) Global Health Observatory data repository for age-adjusted and sex-specific prevalence of current smoking for each country. For its incidence rate, data were retrieved from the following databases: *Cancer Incidence in Five Continents* series I-X,[17] the Nordic Cancer Registries (NORDCAN),[18] and the Surveillance, Epidemiology, and End Results Program (SEER).[19] The *Cancer Incidence in Five Continents* series I-X database collected cancer incidence data on a global scale that included basic demographic data linked to different cancer sites, which allows comparison of cancer incidence rates across regions.[17] The NORDCAN database recorded cancer incidence and mortality rates for countries in northern Europe and the Scandinavian region.[18] The SEER database was developed by the National Institutes of Health, National Cancer Institute in the United States, which provide credible and accurate cancer statistics in the United States.[19] For the mortality rates, the WHO mortality database, NORDCAN, and SEER were accessed to extract data for each country. The WHO mortality database is a global database that focuses on cancer mortality cases.[20] The NORDCAN and SEER database were used to obtain lung cancer mortality in the United States and countries in the Nordic region, and the rest are found in the WHO mortality database. The data of each country were matched with the HDI for grouping and comparison purposes.[21] All data and figures were presented as age-standardized rate (ASRs) per 100,000, with adjustment for the Segi-Doll world standard population to account for differences in each age group, allowing direct and meaningful comparison across countries and regions.[22] The details of the data extraction including description, data sources, and time frame for each country included in this study are presented in e-Table 1. Mortality data for recent years were not available for China, India, and Uganda, and incidence data were not available for Belgium, Latvia, Portugal, Russia, and Singapore in the selected WHO databases.

Statistical Analysis

The sex-specific correlations between the HDI, GDP, smoking, and lung cancer incidence and mortality were examined using univariable linear regression adjusted for age. To calculate the Average Annual Percentage Change (AAPC), ASRs were collected for the most recent 10 years from various databases. Joinpoint regression analysis was selected as the main analysis method in the current study, which aligned with the common approach in other studies of cancer epidemiologic analysis.[23] The AAPC and its 95% CI of each country were computed through the Joint Trend Analysis software.[24] Because the AAPC represents the estimated epidemiological trend of lung cancer in the past decade, the positivity of AAPC represents whether the trend is increasing or declining, and the corresponding 95% CI represents the trend stability (ie, if the 95% CI included 0, the trend should be considered as stable). The analysis and estimation of the epidemiological trend included the incidence and mortality rate of individuals with male- and female-specific AAPCs. A subsequent analysis was conducted by dividing the population into two age groups with a cutoff of 50 years old (< 50 years old and ≥ 50 years old).

Results

Lung Cancer Incidence and Mortality in 2020

There were 2,206,771 new cases of lung cancer and 1,796,144 reported cases of death worldwide in 2020 (Fig 1).[25] The ASR incidence in the world was 22.4 per 100,000, accompanied by the ASR mortality of 18 per 100,000. From its geographical distribution, regions with the highest ASR of incidence included Polynesia (37.3), Micronesia (36.4), and Eastern Asia (34.4). For mortality rates, Micronesia had the highest ASR mortality at 34.9, followed by Polynesia (31.8) and Eastern Asia (28.1).

Associations With HDI, GDP, and Smoking

Higher ASR of lung cancer incidence was associated with a higher HDI (male: $\beta = 6.42$; CI, 4.96-7.87; female: $\beta = 3.18$; CI, 2.51-3.85), GDP (male: $\beta = 2.87$; CI, 1.60-4.14; female: $\beta = 2.52$; CI, 2.01-3.02), and prevalence of smoking (male: $\beta = 0.63$; CI, 0.39-0.87; female: $\beta = 0.43$, CI, 0.30-0.57; Fig 2). Higher ASR of lung cancer mortality was associated with a higher HDI (male: $\beta =$ 4.90; CI, 3.66-6.14; female: $\beta = 2.11$; CI, 1.63-2.60), GDP (male: $\beta = 1.92$; CI, 0.84-2.99; female: $\beta = 1.55$; CI, 1.17-1.94), and prevalence of smoking (male: $\beta = 0.57$; CI, 0.38-0.77; female: $\beta = 0.31$; CI, 0.22-0.40).

Temporal Trends of Lung Cancer

The incidence and mortality trends of each country and the corresponding results in joinpoint regression can be found in e-Table 2.

Incidence Trend in Individuals Aged 0-85 + Years: We found a consistent pattern of trends in 13 countries: males had a decreasing incidence trend, and females had an increasing incidence trend (Fig 3). Among these countries, the ones with significant AAPC were: Italy (male AAPC = −3.53; 95% CI, −4.53 to −2.52), Slovenia (male AAPC = −3.35; 95% CI, −4.16 to −2.54), and Czech Republic (male AAPC = −2.79; 95% CI, −3.27 to −2.30), where the highest decline in incidence for males was reported. Norway (female AAPC = 1.06; 95% CI, 0.17-1.95), Italy (female AAPC = 1.70; 95% CI, 0.57-2.85), and Australia (female AAPC = 1.73; 95% CI, 0.87-2.59) had the highest increase in incidence for females.

Incidence Trend in Individuals Aged Younger Than 50 Years: Eight countries demonstrated the same pattern that there was a significant decreasing trend of incidence AAPC for both sexes (Fig 4). Among these countries, Czech Republic (male AAPC = −8.73; 95% CI, −10.35 to −7.09), Philippines (male AAPC = −7.65; 95% CI, −10.99 to −4.18), and Poland (male AAPC = −7.39; 95% CI, −12.21 to −2.30) were countries with the highest decreasing trend among males. For females, Poland (female AAPC = −9.32; 95% CI, −14.71 to −3.58), United States (female AAPC = −5.45; 95% CI, −6.94 to −3.93), and Philippines (female AAPC = −5.41; 95% CI, −10.49 to −0.05) had the strongest decreasing trends of lung cancer incidence rates among the younger population.

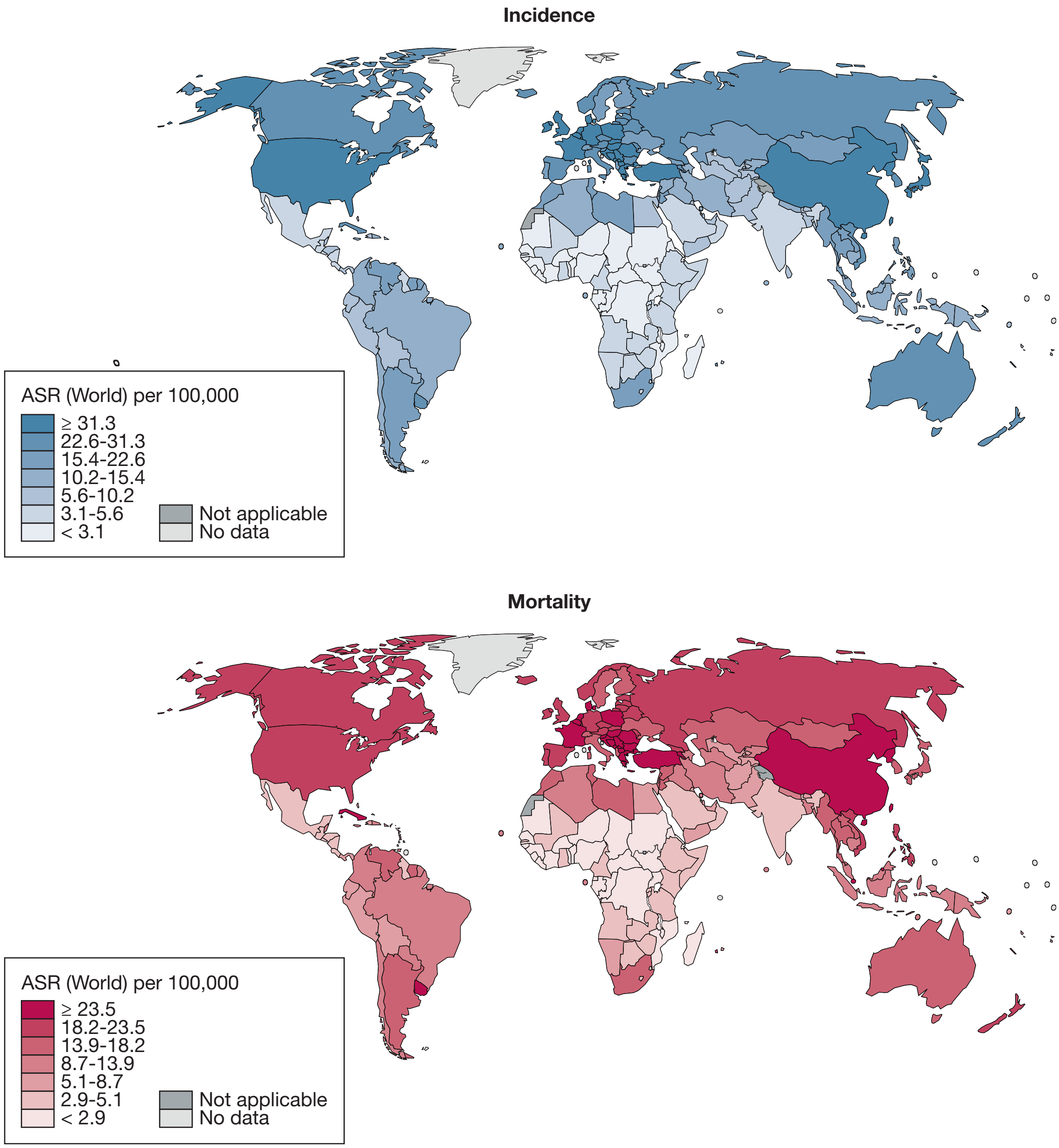

Figure 1 – *Global burden of lung cancer in 2020, both sexes, all ages. ASR = age-standardized rate.*

Incidence Trend in Individuals Aged 50 Years and Older: A consistent pattern of trends was seen in 14 countries: males had a significant decreasing trend, and females had a significant increasing trend (Fig 5). Among these countries, Greenland (male AAPC = −7.63; 95% CI, −13.16 to −1.75), Italy (male AAPC = −3.37; 95% CI, −4.37 to −2.36), and Slovenia (male AAPC = −2.92; 95% CI, −3.74 to −2.09) had the most decline in male incidence trends. Slovakia (female AAPC = 6.13; 95% CI, 4.64-7.65), Poland (female AAPC = 4.27; 95% CI, 1.44-7.19), and the Netherlands (female AAPC = 4.27; 95% CI, 3.49-5.05) showed the greatest increases in lung cancer incidence rates among older female populations.

Mortality Trend in Individuals Aged 0-85 + Years: Seventeen countries demonstrated a similar pattern that aligned with the previous figures: males had a decreasing trend and females had an increasing trend of lung cancer mortality rates (Fig 6). Within these countries, the Netherlands (male AAPC = −3.28; 95% CI, −3.74 to −2.81) and Belgium (male AAPC = −3.21; 95% CI, −4.17 to −2.25) had the largest decrease in mortality rates. Among females, Spain (female AAPC =

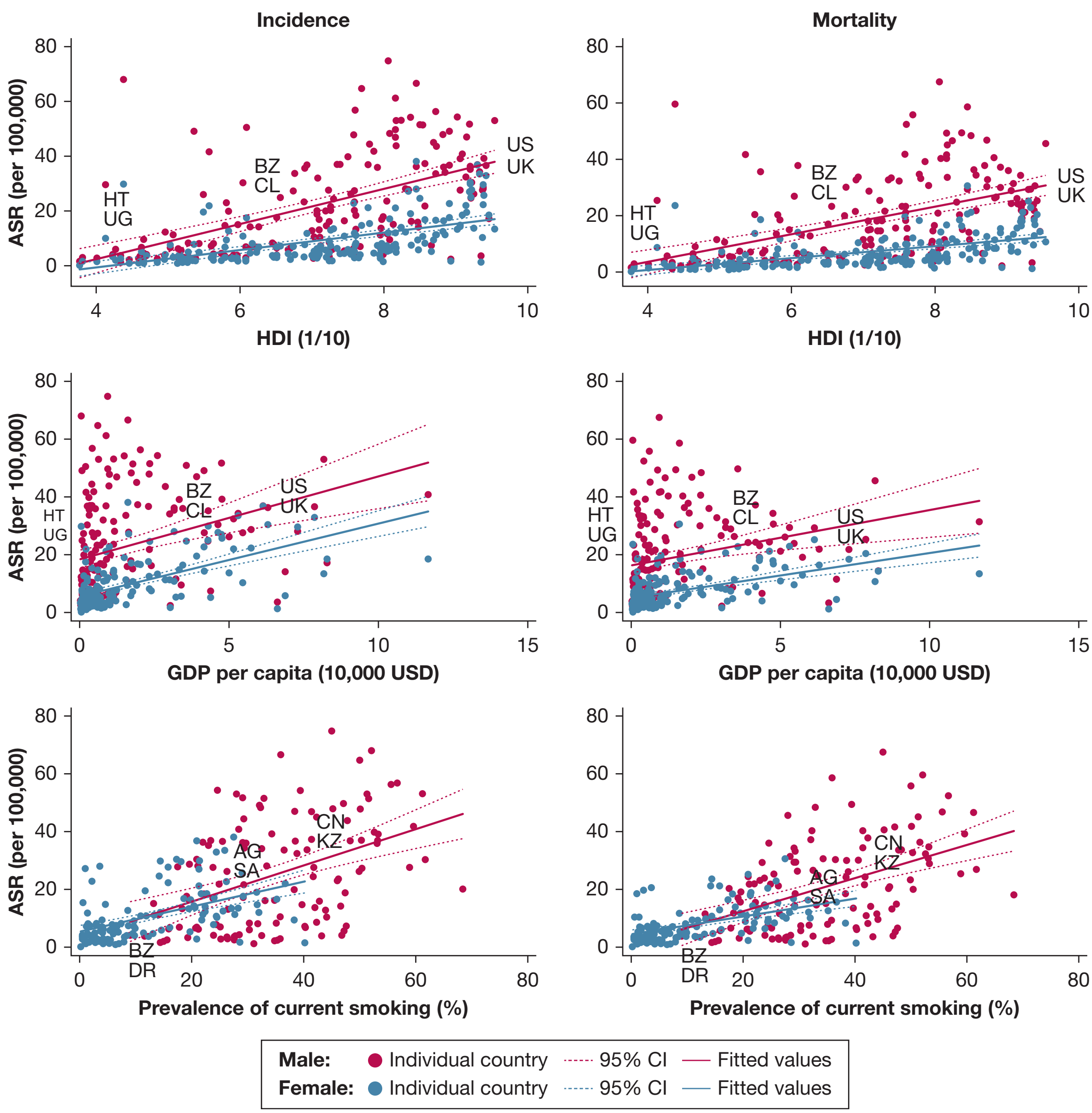

Figure 2 – *Associations with HDI, GDP, and smoking. AG = Argentina; ASR = age-standardized rate; BZ = Brazil; CL = Colombia; CN = China; DR = Dominican Republic; GDP = Gross Domestic Product; HDI = Human Development Index; HT = Haiti; KZ = Kazakhstan; SA = South Africa; UG = Uganda; UK = United Kingdom; US = United States; USD = United States dollar.*

3.96; 95% CI, 3.27-4.66), Slovakia (female AAPC = 3.26; 95% CI, 1.37-5.19), and France (female AAPC = 2.66; 95% CI, 2.09-3.23) had the highest increases in mortality trends.

Discussion

Summary of the Current Study Findings

We reported the most updated data on global lung cancer incidence and mortality, its associated risk factors, and the temporal trends by age, sex, and countries based on high-quality data. The results showed the highest lung cancer incidence and mortality was observed in Asia and associated with HDI, GDP, and prevalence of smoking. As for the trend of incidence, more countries presented an increasing trend in females but the trend was decreasing in males, especially in those 50 years of age or older. However, population aged less than 50 years had declining incidence trends in both sexes in more countries. In terms of mortality, more countries showed a decreasing trend in males but increasing mortality trends in females.

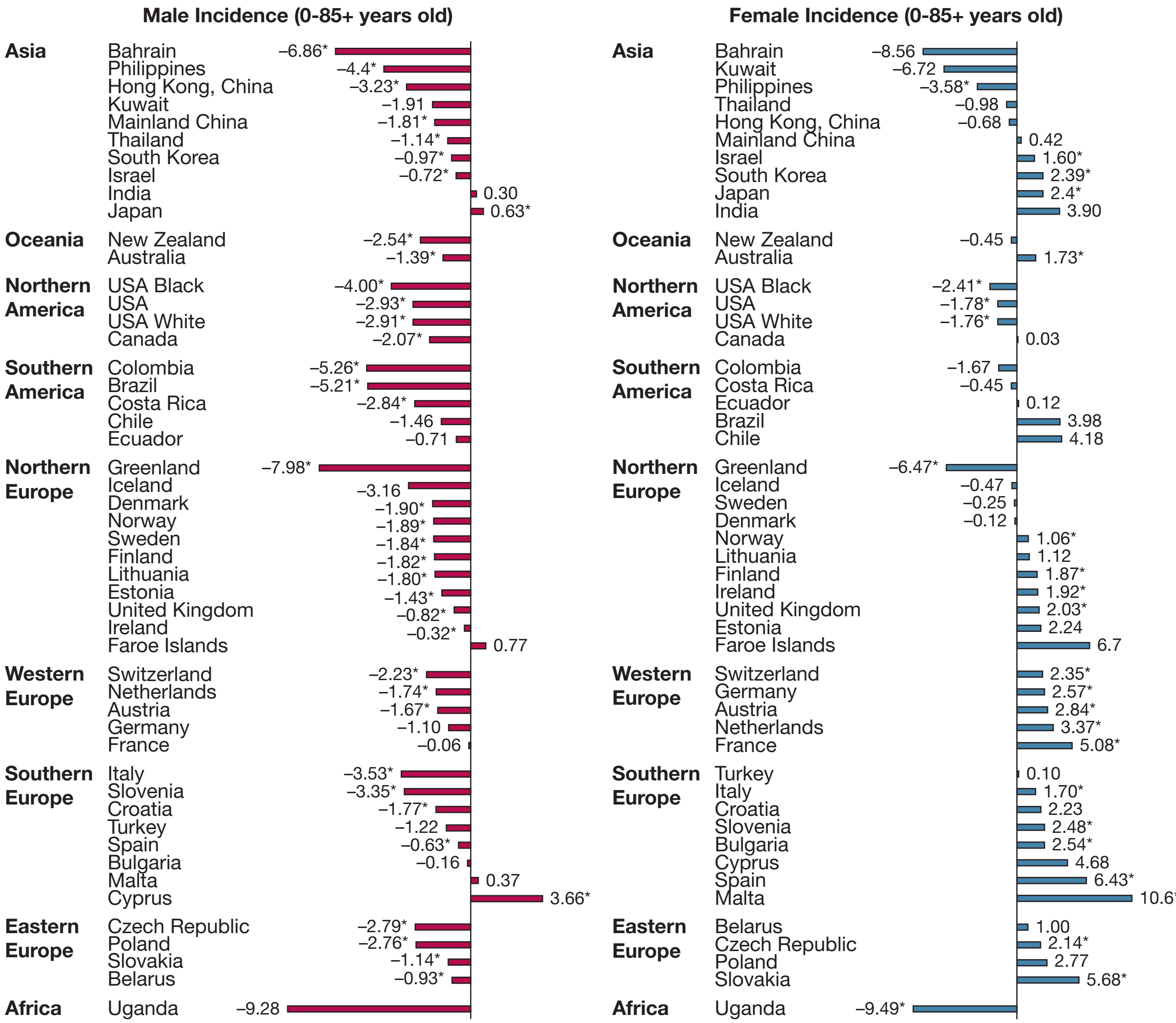

Figure 3 – *AAPC of lung cancer incidence in individuals aged 0-85 + years. AAPC = average annual percentage change.*

Explanation of Findings and Comparison With Existing Literature

According to the association analyses, lung cancer incidence and mortality was associated with HDI, GDP, and prevalence of smoking. This can be explained using some representative countries highlighted in Figure 2. Lung cancer incidence increased from countries with low HDI/GDP (Uganda, 4.3; Haiti, 6.0), medium (Colombia, 12.7; Brazil, 16.4), to high (United Kingdom, 35.5; United States, 40.1), whereas these countries had a similar prevalence of current smoking. Similarly, lung cancer incidence increased from countries with low rates of current smoking (Dominican Republic, 14.6; Brazil, 16.4), medium rates (Argentina, 26.3; South Africa, 28.2), to high rates (Kazakhstan, 43.8; China, 47.8), although these countries shared a similar HDI/GDP. These observations were also found for lung cancer mortality.

We found significant sex differences in lung cancer incidence and mortality in the past decade, in which most countries showed declining trends in males and rising trends in females. For age differences in incidence, people aged 50 years and older showed similar incidence patterns as compared with the general population in most regions (decreasing trends in males and increasing trends in females), and those aged younger than 50 years had declining incidence trends in both sexes in most countries. These results are generally in line with those of previous studies. A study indicated that 57.9% (22 of 38) and 83.3% (30 of 36) of countries showed a decrease in lung cancer incidence and mortality in males, and

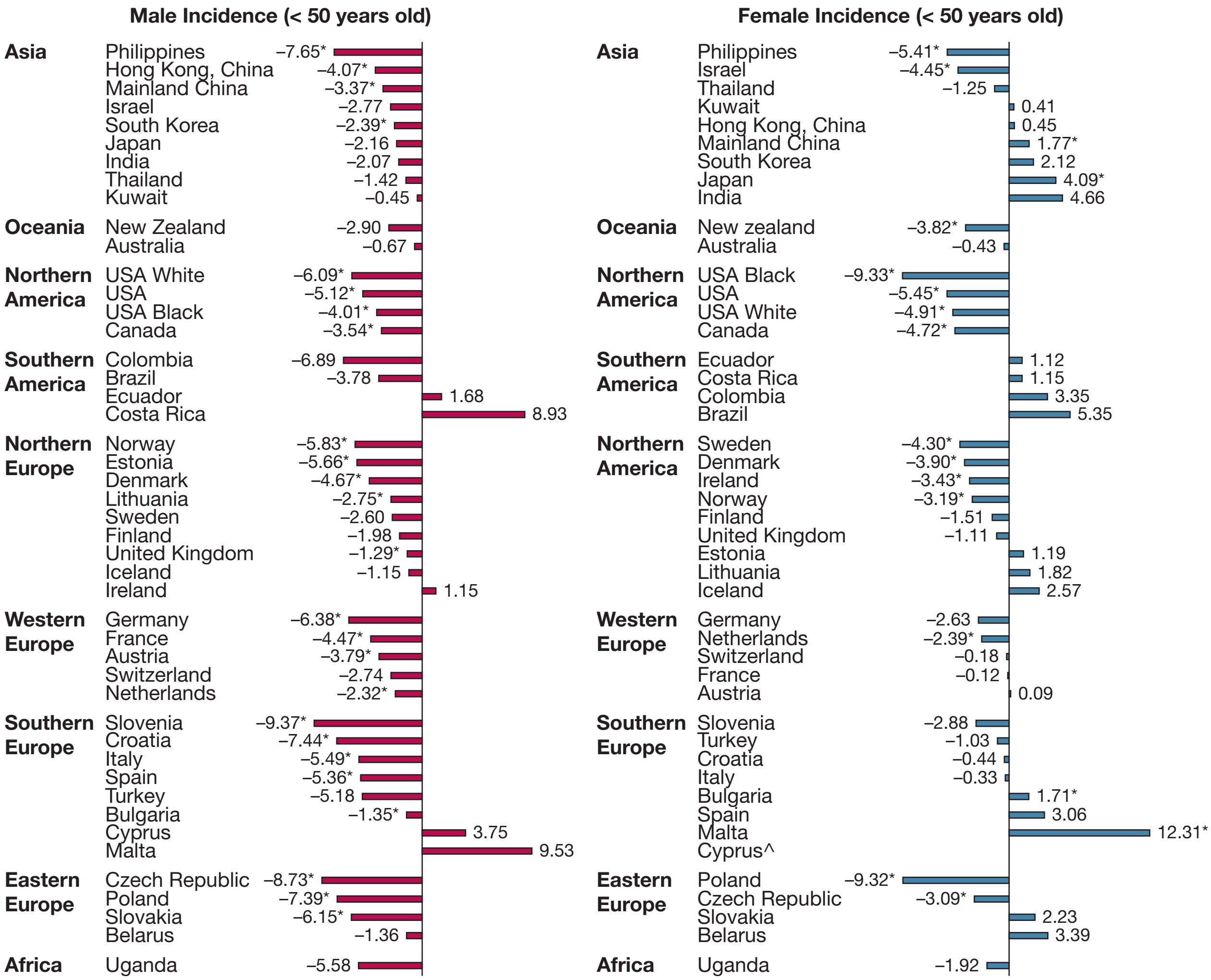

Figure 4 – *AAPC of lung cancer incidence in individuals aged below 50 years. AAPC = average annual percentage change.*

50.0% (19 of 38) and 44.4% (16 of 36) countries had increasing incidence and mortality trends in females.[8] Another study also suggested that the incidence and mortality rates of lung cancer in the United States declined among males and increased among females between 1975 and 2005.[3]

The reasons for the age, sex, and regional differences in temporal trends of lung cancer incidence and mortality may be related to tobacco consumption and other risk factors. Differences in tobacco epidemic and control played significant roles, because smoking accounted for approximately 80% of lung cancer deaths in males and 50% in females globally.[26,27] The prevalence of smoking may vary by sex in some countries (e-Fig 1). For instance, the smoking rate in females was particularly low (2%) in China compared with that among males (48%). The obvious delayed increase in incidence and mortality in females may be associated with the later uptake of cigarette smoking among females. It was reported that most females began smoking during or after World War II, whereas most males started smoking in the early 20th century, and the number of male smokers reached a peak during World War II.[28] In addition, tobacco control programs, such as smoking cessation, also played a role in sex differences. A study using the National Health Interview Surveys showed that smoking cessation rates were significantly higher in older males as compared with older females, although the differences in smoking quitting rates between males and females reduced from 1965 to 1970 (50%) to 1990 to 1994 (15%-19%) in people aged 65 years or older.[29] Second-hand smoke also may have affected this epidemic transition, especially in countries where female smoking prevalence is relatively low compared with that of males. According to a global study of 192 countries,

Figure 5 – *AAPC of lung cancer mortality in individuals aged 50 years and older. AAPC = average annual percentage change.*

second-hand smoking exposure causes 21,400 deaths of lung cancer in nonsmokers per year.[30] There are clear inequalities in the burden of disease from second-hand smoke by sex. Females have much higher burden of deaths of the total attributable to second-hand smoke.

In terms of age differences in incidence, the differences in smoking cessation rates between younger and middle-aged and old populations may be an important factor. A study revealed that cessation rates increased during 1980 and 2010 among young people (16-40 years) in all studied regions (North, East, South, and West Europe). However, among middle-aged and older populations (> 40 years), the increasing trend was only found in North Europe, whereas stable trends were observed in the other three regions (East, South, and West Europe). The peak in smoking cessation rates was around age 30 years.[31] Another tobacco-related reason for the age incidence difference was the adherence to tobacco control policies. A study showed that higher Tobacco Control Scale in 2007 was associated with a lower prevalence of smokers in 2014 among 27 European Union countries, especially in young adults aged 25 to 34 years ($r = -0.41$, $P = .03$). No such significant inverse association was found in other age groups.[32]

The incidence and mortality variations across countries and regions can also be closely related to regional differences in the tobacco epidemic. In high-income countries, including the United States, the United Kingdom, and Canada, people tended to begin smoking earlier than those in low- and-middle-income countries. Thus, the tobacco epidemic was well established and had peaked in these high-income countries. As a result, lung cancer incidence and mortality rates tend to plateau or decrease.[3,33] In contrast, in low- and-middle-income

Figure 6 – *AAPC of lung cancer mortality in individuals aged 0-85 + years. AAPC = average annual percentage change.*

countries where the number of smokers has just peaked or continues to increase, lung cancer incidence and mortality rates are more likely to increase.[33-35] This may explain the current findings that among the 11 countries where the death rate declined in both sexes; 10 of them were high-income countries. In addition, we observed that the Philippines and Thailand had decreasing incidence but with increasing mortality for the past 10 years. Possible reasons include less early diagnostic and detection capacity for lung cancer or a disparity in the trend of lung cancer by different histological subtypes. Further studies are needed to explore the reasons behind these observations.

In addition to the differences in tobacco-related factors (tobacco epidemic and control), other factors play a role in the sex and regional variations observed.[7] These include radiation, coal products, asbestos, and exposure to some chemicals such as chromium, cadmium, and arsenic. For instance, a Chinese case-control study showed that among nonsmoking females, lung cancer was significantly related to indoor air pollution, including exposure to tobacco smoke at work, high frequency of cooking, and solid fuel usage for cooking and heating.[36]

To control the increasing trends of lung cancer incidence and mortality in females, evidence-based and tailored preventive strategies should be implemented. For example, a program initiated by the WHO named WHO Framework Convention on Tobacco Control has provided several effective actions to control tobacco use, including price and tax measures, smoking cessation assistance, health education, and the regulation of tobacco products, packaging, labeling and advertisement.[37]

Strengths and Limitations

The current study provided the most updated global lung cancer incidence and mortality and its temporal trends by age, sex, and countries based on high-quality cancer registries. However, several limitations should be noted. First, there may be potential bias caused by differences in cancer registration between developed and developing regions. The data of incidence and mortality were likely to be overreported in developed regions and underestimated in developing regions, because the number of high-quality cancer registries and the corresponding number of participants in developed regions were higher than that in developing regions. Besides, detailed data on the stages and subtypes of lung cancer were not included in this study.

Interpretation

The current study found an overall increasing trend in females but decreasing trends in males for lung cancer over the past decade. A similar pattern was found in those 50 years of age or older, whereas those younger than 50 years had declining incidence trends in both sexes in most countries. The sex, age, and regional variations in lung cancer incidence and mortality can be attributable to the differences in tobacco epidemic and related population-based policy. Tobacco related measures and early cancer detection should be implemented to control the increasing trends of lung cancer among high-risk populations. Future studies may further explore the reasons behind these epidemiological transitions.

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Additional information: The e-Figure and e-Tables can be found in the Supplemental Materials section of the online article.

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