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Updated disease distributions, risk factors, and trends of laryngeal cancer: a global analysis of cancer registries

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Background: Though the laryngeal cancer only has 1% of the total cancer cases and related deaths, it is a type of head and neck cancers with the highest prevalence. This study aims to investigate the epidemiological trend of laryngeal cancer with updated data on the global distribution of the disease burden.

Materials and methods: The incidence and mortality rate of laryngeal cancer was extracted from *GLOBOCAN* (2020), *Cancer Incidence in Five Continents* series I-X, *WHO mortality database*, the *Nordic Cancer Registries*, and the *Surveillance, Epidemiology, and End Results Program.* The *Global Health data exchanges* for the prevalence of its associated risk factors. A Joinpoint regression analysis was used to calculate Average Annual Percentage Change (AAPC).

Results: The age-standardised rate (ASR) of laryngeal cancer incidence and mortality were 2.0 and 1.0 per 100 000 worldwide. The Caribbean (ASR = 4.0) and Central and Eastern Europe (ASR = 3.6) had the highest incidence and mortality rate. Incidence and risk factors associated with laryngeal cancer included tobacco usage, alcohol consumption, poor diet, obesity, diabetes, hypertension, and lipid disorders. There was an overall decreasing trend in incidence, especially for males, but an increasing incidence was observed in female populations and younger subjects.

Conclusions: As overall global trends of laryngeal cancer have been decreasing, especially for the male population, this could possibly be attributed to reduced tobacco use and alcohol consumption. Decrease in mortality may be due to improved diagnostic methods and accessibility to treatment, yet disparity in trend remains potentially because of differences in the level of access to surgical care. Disparities in temporal trends across countries may require further research and exploration to determine other underlying factors influencing this.

Keywords: laryngeal cancer, incidence, mortality, risk factors, temporal trend

Introduction

Laryngeal cancer is one of the most prevalent types of head and neck cancers although it only accounts for around 1% of total cancer cases and related deaths[1]. Laryngeal cancer can be subdivided into subglottic, glottic, and supraglottic cancer, while its most common histological type is squamous cell carcinoma, beginning on the mucosal surface of the larynx[2]. The prognosis of laryngeal cancer is largely dependent on the timing of detection: for cases diagnosed and treated before the cancer has spread outside the larynx, the 5-year survival rate is ~80%[3].

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There have been several well-established risk factors of laryngeal cancer. Cigarette smoking and alcohol consumption was found to have the strongest relation with laryngeal cancer, and an interaction effect between tobacco and alcohol consumptions on the cancer has been identified in previous studies[4–7]. Other potential risk factors include age (≥ 65), sex (male), family history of cancer, chemical workplace exposure, gastro-esophageal reflux, and exposure to human papillomavirus[2,8–10]. It is imperative to examine the associations between preventable risk factors and laryngeal cancer risk to develop its preventive strategies.

Although some prior studies have made assessment on the epidemiological trends of laryngeal cancer, the data they used were relatively old[2,11] or limited to only certain regions or countries[12,13]. The implementation of preventive strategies and early diagnosis for laryngeal rely heavily on updated and accurate epidemiologic data. This study aims to fill the study gap by investigating the epidemiological trend of laryngeal cancer with updated data on the global distribution of the disease burden and to identify sub-groups of populations by evaluating its lifestyle and metabolic risk factors for the consideration of resource allocation in terms of surgery and disease prevention, especially following the interventions and policies on reducing smoking and alcohol consumptions carried out in various countries in the past few decades[14–16].

HIGHLIGHTS

- Highest incidence and mortality of laryngeal cancer were observed in Caribbean, Central and Eastern Europe, Male and higher HDI countries.
- Laryngeal cancer incidence and mortality were associated smoking, alcohol habit, unhealthy diet, physical inactivity, obesity, hypertension, diabetes, and lipid disorders.
- Decreasing trend of laryngeal cancer in overall. However, less evident amongst the female population and younger subjects.

Material and methods

Data collection

The global incidence and mortality rates of laryngeal cancer in 2020 was extracted from the *Global Cancer Observatory (GLOBOCAN)* database, developed by the International Agency for Research on Cancer, WHO (IARC)[17,18]. The Gross Domestics Products (GDP) and Human Development Index (HDI) for each country were retrieved from World Bank and United Nations. For the categorization of HDI rates, <0.550, 0.550–0.699, 0.700–0.700, and ≥ 0.800 are considered low, medium, high, and very high. The *Global Health Data Exchange* (*GHDx*) database was employed to retrieve the data of prevalence of smoking, alcohol drinking, unhealthy dietary, physical inactivity, hypertension, diabetes, and lipid disorders. For trend analysis on laryngeal cancer incidence and mortality, data was accessed from the *Cancer Incidence in Five Continents (CI5)* volumes I-XI and *WHO mortality database*, respectively[19,20]. The *CI5* database contains cancer incidence-related data by age, primary tumor year, and region drawn from a large portion of the global population, and parameters including proportion of cases registered and the rate of cases microscopically recorded, and cancer incidence were used as the inclusion criteria to evaluate the quality of information. Data from 1980 to 2020 were obtained, and the data of the most recent 10 years were used for trend analysis. The WHO mortality database was used for cancer-related death data for each country and region. Cancer mortality data was collected from national civil cancer registries on a local and national level with the registering system logging verified cancer deaths and their causes, which is then reported to WHO annually. To ensure the quality of data, only figures with medium quality or above were published by the WHO mortality database based on the timeliness, completeness and coverage of registration and the proportion of deaths assigned to ill-defined causes. More details on the quality classification of mortality data for different countries can be found in the previous report[21]. The *Nordic Cancer Registries (NORDCAN)*[22,23], and the *Surveillance, Epidemiology, and End Results (SEER) Program*[24] were also searched for more updated incidence and mortality data for the Nordic region and the United States, respectively. All incidence and mortality figures of laryngeal cancer were transformed—using the Segi-Doll world reference population for various nations—into an age-standardised rate (ASR) per 100 000 individuals[25]. Weighting was allocated in accordance with proportions of people in the standard population's corresponding age groups. This enabled the current study to compare incidence and mortality rates across different countries over time.

Statistical analysis

Choropleth maps were generated on the global incidence and mortality of laryngeal cancer in 2020. For the analysis on risk factors associations, Beta coefficients (β) and the corresponding 95% CI were estimated by the generalized linear regression analysis with negative binomial distribution, with β estimates referring to the degree of change in incidence or mortality of laryngeal cancer. This method was selected as the outcome was event rate and its variance was significantly greater than the mean. To assess the temporal trend of laryngeal cancer incidence and mortality rates across ages (<50 years and ≥ 50 years), sexes (male and female) and geographical regions (Asia, Oceania, Northern America, Southern America, Northern Europe, Western Europe, Southern Europe, Eastern Europe, and Africa). The cut-off was chosen was it was often used as a definition of early-onset cancers, including head and neck cancers[26]. This has allowed us to compare the trends of laryngeal cancer between younger and older populations. A logarithm transformation was performed on the incidence and mortality rates prior to carrying out the Joinpoint regression analysis. The Average Annual Percentage Change over any fixed interval is calculated using a weighted average of the slope coefficients of the underlying joinpoint regression line with the weights equal to the length of each segment over the interval. The final step of the calculation transforms the weighted average of slope coefficients to an annual percent change[27]. To comply with the analysis guideline, a maximum of one joinpoint was recommended for 7–11 data points and therefore used throughout the study[28]. The AAPC and its 95% CI was calculated using Joinpoint regression analysis software (Version 4.8.0.1 - April 2020; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute)[27]. This method has been used in previous studies to determine the epidemiological trend of other forms of cancer, with positive and negative AAPC indicating an increasing or decreasing trend in cancer incidence or mortality

respectively. All *P*-values less than 0.05 were considered statistically significant. This work has been reported in line with the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery (STROCSS) criteria (Supplemental Digital Content 1, http://links.lww.com/JS9/B348)[29].

Results

Global incidence of laryngeal cancer in 2020

There were 184 615 newly reported cases of laryngeal cancer in 2020, with an ASR incidence of 2.0 per 100 000 persons (Fig. 1). Incidence varied geographically, region with the highest incidence was Caribbean (ASR = 4.0) followed by Central and Eastern Europe (ASR = 3.6) and Southern Europe (ASR = 2.9). Regions with the lowest incidence include Middle Africa (ASR = 0.76), Western Africa (ASR = 0.79), and Central America (ASR = 0.86). There was a remarkable disparity among the two sexes in terms of incidence, as the global ASR of males (ASR = 3.6) was more than seven times higher than that of females (ASR = 0.49). The highest incidence was in countries with medium HDI (ASR = 2.5), followed by very high HDI (ASR = 2.3), high HDI (ASR = 1.6), and low HDI (ASR = 0.94).

Global mortality of laryngeal cancer in 2020

In 2020, 99 840 laryngeal cancer-related deaths were reported, which was slightly more than 1% of the total cancer-related deaths. Globally, laryngeal cancer has an ASR of 1.0 per 100 000 persons in mortality. In terms of the geographical distribution, the Caribbean region (ASR = 2.1) had the highest mortality rate, doubling the global average, followed by Central and Eastern Europe (ASR = 1.9), and South-Central Asia (ASR = 1.7). Regions with the lowest mortality were Australia and New Zealand (ASR = 0.34), Micronesia (ASR = 0.45), and Middle Africa (ASR = 0.54). Similar to incidence, the highest mortality was in countries with medium HDI (ASR = 1.6), followed by high HDI (ASR = 0.92), very high HDI (ASR = 0.86), and low HDI (ASR = 0.71).

Associations between risk factors and laryngeal cancer incidence

Among males (Fig. 2, Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/B349), laryngeal cancer incidence was associated with a higher HDI ($\beta = 0.175$, 95% CI: 0.111–0.239, $P < 0.001$), prevalence of smoking ($\beta = 0.051$, 95% CI: 0.041–0.061, $P < 0.001$), alcohol drinking ($\beta = 0.040$, 95% CI: 0.028–0.052, $P < 0.001$), unhealthy dietary ($\beta = 0.012$, 95% CI: 0.006–0.018, $P < 0.001$), obesity ($\beta = 0.022$, 95% CI: 0.012–0.031, $P < 0.001$), hypertension ($\beta = 0.031$, 95% CI: 0.022–0.041, $P < 0.001$), diabetes ($\beta = 0.032$, 95% CI: 0.014–0.051, $P = 0.001$), and lipid disorders ($\beta = 0.021$, 95% CI: 0.013–0.029, $P < 0.001$). Among females, incidence was associated with a higher HDI ($\beta = 0.114$, 95% CI: 0.050–0.178, $P < 0.001$), prevalence of smoking ($\beta = 0.049$, 95% CI: 0.033–0.065, $P < 0.001$), inactivity ($\beta = 0.040$, 95% CI: 0.009–0.072, $P = 0.011$), obesity ($\beta = 0.013$, 95% CI: 0.004–0.022, $P = 0.004$), hypertension ($\beta = 0.012$, 95% CI: 0.002–0.023, $P = 0.024$), diabetes ($\beta = 0.051$, 95% CI: 0.031–0.071, $P < 0.001$), and lipid disorders ($\beta = 0.015$, 95% CI: 0.007–0.023, $P < 0.001$).

Associations between risk factors and laryngeal cancer mortality

Among males (Fig. 3, Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/B349), laryngeal cancer mortality was associated with a higher HDI ($\beta = 0.094$, 95% CI: 0.025–0.163, $P < 0.001$), prevalence of smoking ($\beta = 0.044$, 95% CI: 0.033–0.054, $P < 0.001$), alcohol drinking ($\beta = 0.025$, 95% CI: 0.013–0.038, $P < 0.001$), unhealthy dietary ($\beta = 0.009$, 95% CI: 0.003–0.015, $P = 0.002$), obesity ($\beta = 0.016$, 95% CI: 0.006–0.025, $P = 0.001$), hypertension ($\beta = 0.025$, 95% CI: 0.015–0.034, $P < 0.001$), and lipid disorders ($\beta = 0.013$, 95% CI: 0.004–0.021, $P = 0.003$). Among females, mortality was associated with a lower GDP per capita ($\beta = -0.076$, 95% CI: −0.126–0.027, $P = 0.003$), and prevalence of alcohol drinking ($\beta = -0.060$, 95% CI: −0.085–0.035, $P < 0.001$).

Temporal trends of laryngeal cancer

The incidence and mortality trends of laryngeal cancer for each country between 1980 and 2017 are shown in alphabetical order according to their continents in Supplementary Figure 1 (Supplemental Digital Content 3, http://links.lww.com/JS9/B350), and the trend regression is presented in Supplementary Figure 2 (Supplemental Digital Content 3, http://links.lww.com/JS9/B350). Overall, more countries were showing decreasing trends than increasing trends in laryngeal cancer while such trends were less evidence among female population, younger subjects, and countries from Europe.

Incidence trends of all individuals aged 0–85 +

The overall incidence for males was decreasing while females reported mixed trends (Fig. 4). For males, significant increases were found only in Cyprus (AAPC = 5.88; 95% CI: 0.52–11.52; $P = 0.035$), whilst decreasing trends were reported in 24 countries evenly distributed in different continents, Chile (AAPC = −11.5; 95% CI: −20.99–0.88; $P = 0.038$) reported the largest decrease, followed by the Philippines (AAPC = −7.71; 95% CI: −12.15–3.05; $P = 0.006$), and Norway (AAPC = −5; 95% CI: −8.71–1.14; $P = 0.018$). For females, three countries showed significant increasing trends: Japan (AAPC = 6.01; 95% CI: = 1.51, 10.71; $P = 0.015$), Switzerland (AAPC = 5.61; 95% CI: 0.05–11.49; $P = 0.048$), and Czech Republic (AAPC = 3.31; 95% CI: 1.28–5.39; $P = 0.005$). Evident decreases were found in six countries, with India (AAPC = −8.35; 95% CI: −13.62–2.75; $P = 0.009$), Korea (AAPC = −8.28; 95% CI: −11.68–4.74; $P = 0.001$), and Turkey (AAPC = −6.05; 95% CI: −10.21–1.69; $P = 0.013$) reporting the largest decreases.

Mortality trends of all individuals aged 0–85 +

Similar to the incidence trends, there was a remarkable difference between the mortality trends of males and females (Fig. 5). For males, only Thailand (AAPC = 5.41; 95% CI: 3.56–7.30; $P < 0.001$) reported significant increases. On the contrary, significant decreases were observed in 30 countries. The largest decreases were found in Korea (AAPC = −7.17; 95% CI: −8.65–5.66; $P < 0.001$), Singapore (AAPC = −7.10; 95% CI: −13.59–0.11; $P = 0.047$), and France (AAPC = −5.96; 95% CI: −6.76–5.15; $P < 0.001$). For females, significant increasing trends were found in Israel

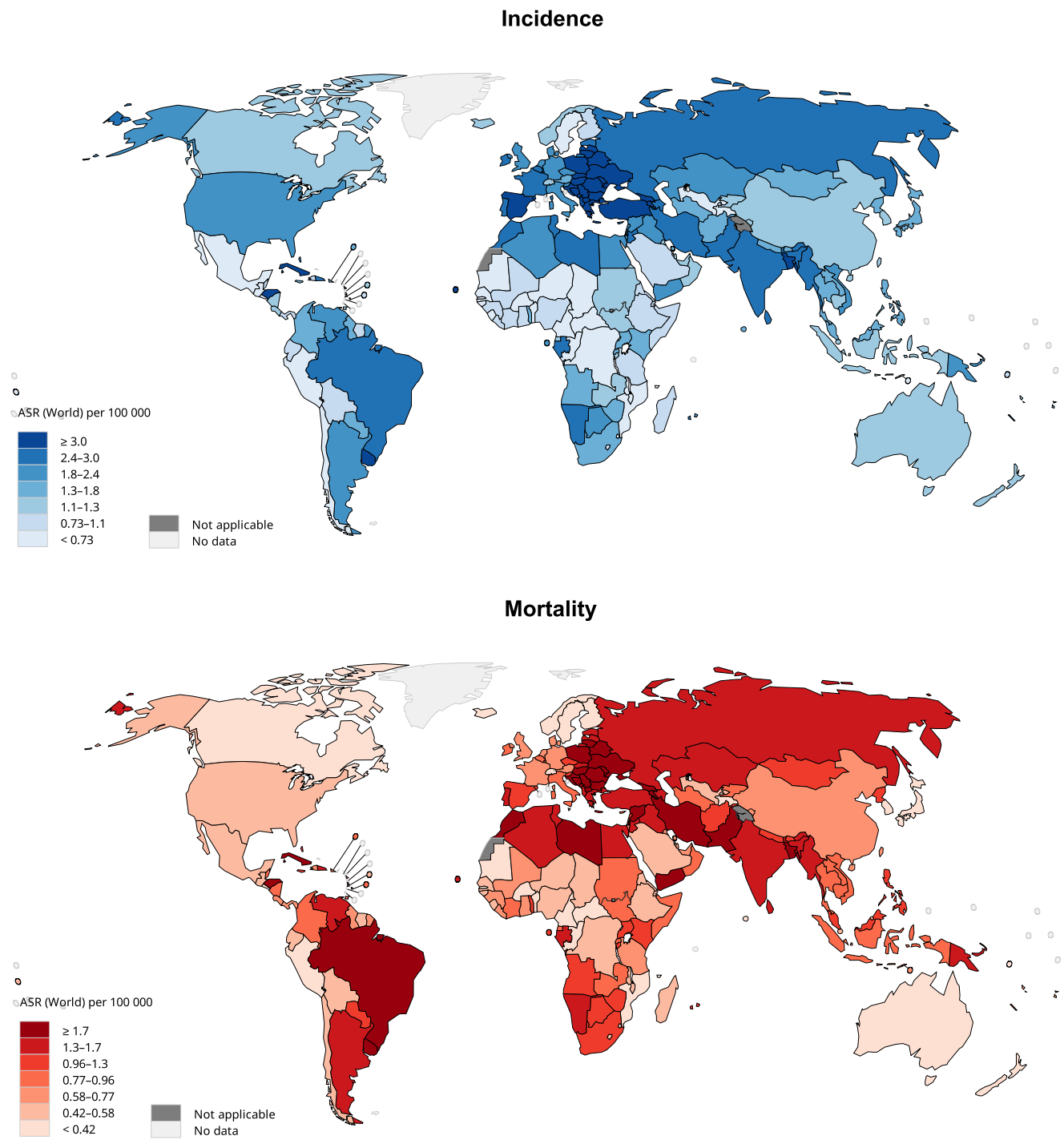

Figure 1. Global incidence and mortality of laryngeal cancer, both sexes, all ages, in 2020.

(AAPC = 12.49; 95% CI: 0.81–25.51; $P = 0.038$); while significant decreases were reported in eight countries, with Korea (AAPC = −10.58; 95% CI: −15.61–5.24; $P = 0.002$), Belarus (AAPC = −7.93; 95% CI: −13.55–1.95; $P = 0.010$), and Colombia (AAPC = −5.68; 95% CI: −8.04–3.27; $P = 0.001$) reported the most evident decreases.

Incidence trends of individuals in specific age groups

For the older males aged 50 or above (Supplementary Figure 3, Supplemental Digital Content 3, http://links.lww.com/JS9/B350), two countries reported significant increases: Cyprus (AAPC = 6.87; 95% CI: 1.16–12.91; $P = 0.024$), and Belarus (AAPC = 1.41; 95% CI: 0.28–2.55; $P = 0.021$). In contrast,

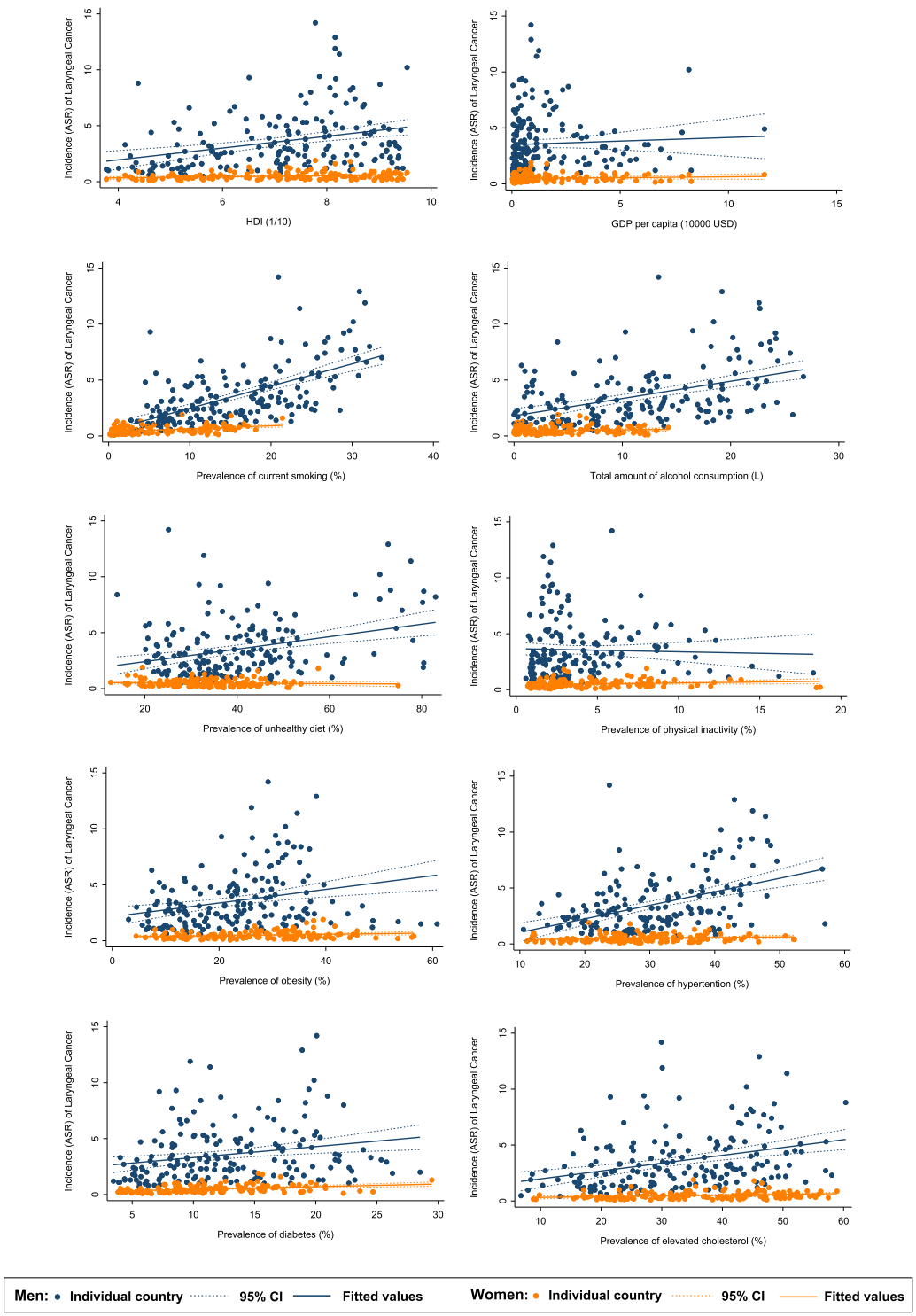

Figure 2. Associations between risk factors and laryngeal cancer incidence.

significant decreases were observed in 21 countries sporadically distributed worldwide. The largest decreases were found in Chile (AAPC = – 10.31; 95% CI: – 19.44– 0.14; $P = 0.048$), Philippines (AAPC = – 7.57; 95%; CI: – 11.86– 3.08; $P = 0.005$), and Norway (AAPC = – 5.69; 95% CI: – 8.87– 2.41; $P = 0.004$). For females aged 50 or above, three countries, all European countries, reported significant increases: Spain (AAPC = 6.76; 95% CI: 2.03–11.72; $P = 0.01$), Switzerland (AAPC = 5.38; 95% CI: 0.25–10.78; $P = 0.042$), and Czech Republic (AAPC = 4.00; 95% CI: 1.73–6.32; $P = 0.003$) reported the largest increases. On the other hand, four populations showed significant decreasing

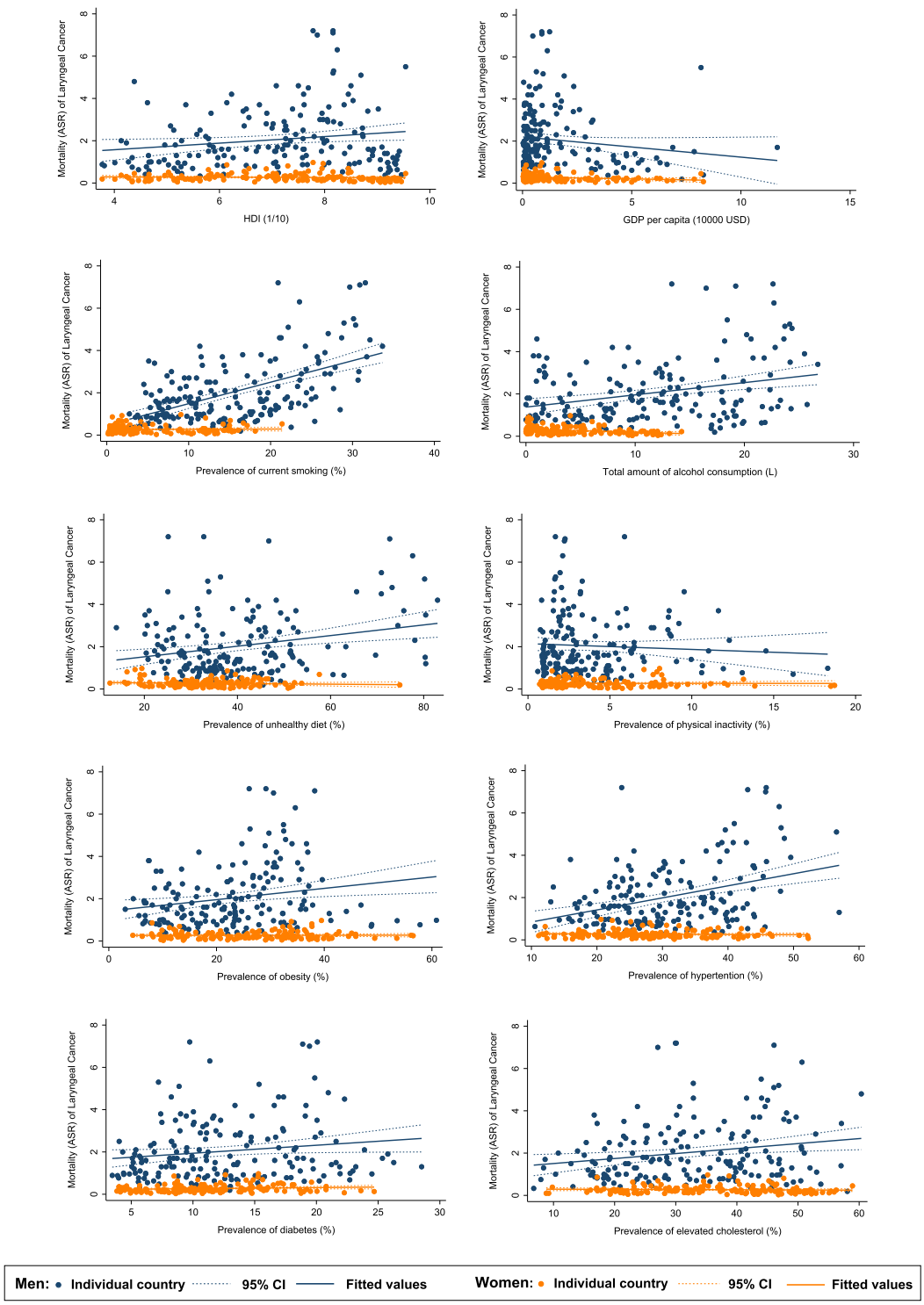

Figure 3. Associations between risk factors and laryngeal cancer mortality.

trends, Turkey (AAPC = −6.50; 95% CI: −11.64–1.07; $P = 0.025$) reported the largest decline, followed by Canada (AAPC = −4.36; 95% CI: −6.94–1.70; $P = 0.006$), and the white population in the USA (AAPC = −2.98; 95% CI: −5.13–0.78; $P = 0.014$).

Similar distribution but larger increase was found in males aged below 50 (Supplementary Figure 4, Supplemental Digital Content 3, http://links.lww.com/JS9/B350), Norway (AAPC = 18.77; 95% CI: 4.55–34.92; $P = 0.014$) and Thailand (AAPC = 10.24; 95% CI: 0.36–21.09; $P = 0.044$) reported significant increasing trends,

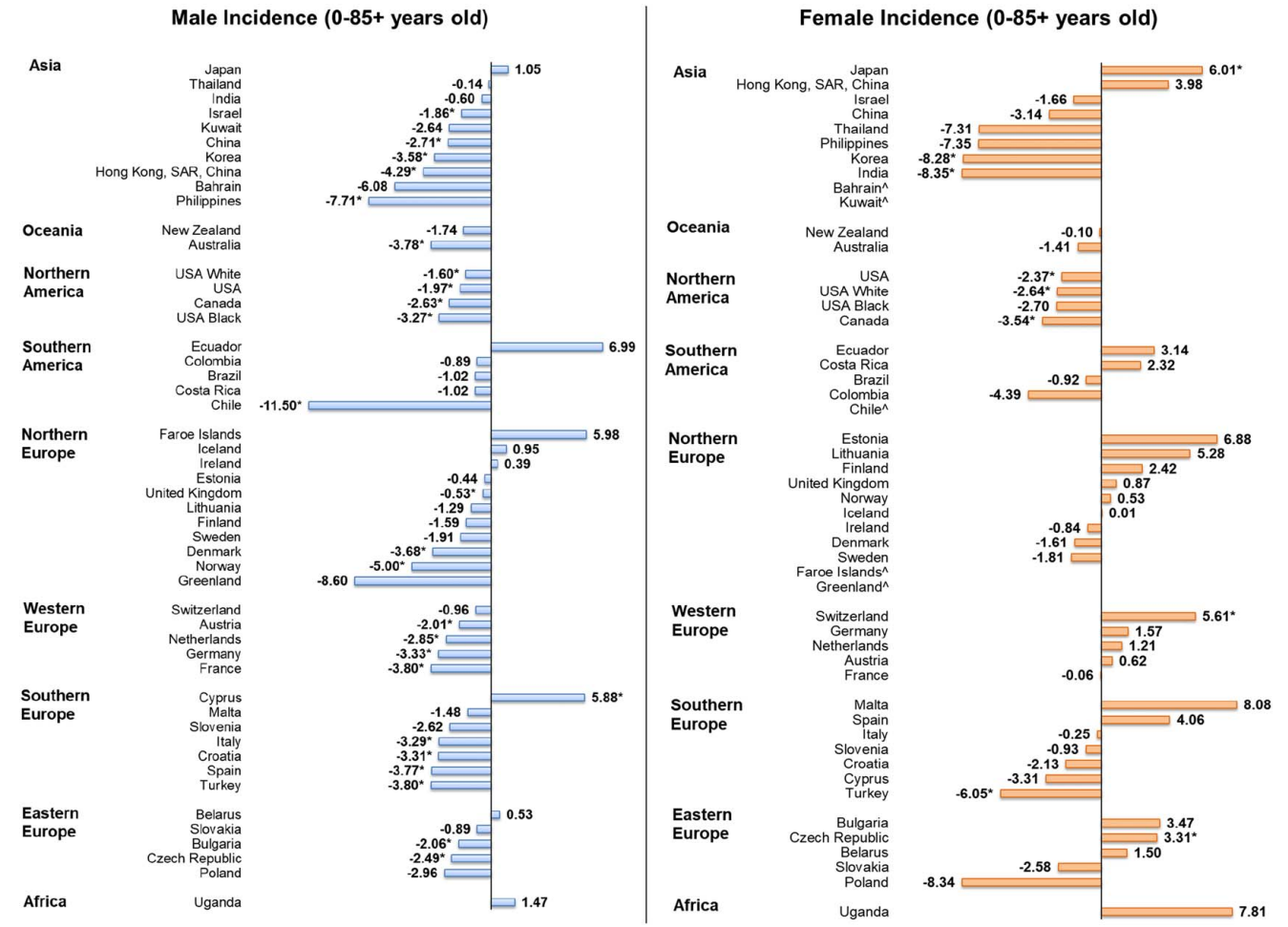

Figure 4. Average Annual Percentage Change of laryngeal cancer incidence in individuals aged 0–85 + years.

whereas evident decreasing trends were observed in 17 countries, predominately Asian and European countries, with Germany (AAPC = – 17.17; 95% CI: – 26.66– 6.44; $P = 0.007$), Denmark (AAPC = – 9.88; 95% CI: – 17.74– 1.26; $P = 0.030$), and France (AAPC = – 9.66; 95% CI: – 14.70– 4.32; $P = 0.004$) showing the greatest decreases. From the raw data, the highly significant increasing trend observed in the younger male population of Norway and Thailand was likely due to the statistical base effect as unusually low ASR was reported in the start of the 10-year interval 2010–2011 (Norway); 2003 (Thailand). For their younger females aged below 50, significant decreases were observed in two countries/regions: Hong Kong, SAR, China (AAPC = – 12.44; 95% CI: – 21.77– 1.99; $P = 0.026$) and Korea (AAPC = – 11.79; 95% CI: – 21.66– 0.67; $P = 0.041$), while no country reported significant increase.

Discussion

Major findings

In this analysis, updated cancer registries were used to evaluate the global burden, risk factors, and age-specific and country-specific epidemiological trends of laryngeal cancer. There are some major findings: (1) both the highest incidence and mortality of laryngeal cancer were observed in the Caribbean, Central, and Eastern Europe, male subjects, and countries with higher HDI; (2) higher laryngeal cancer incidence mortality were associated smoking, alcohol drinking, unhealthy diet, physical inactivity, obesity, hypertension, diabetes, and lipid disorders; (3) there was an evident overall decreasing trend of laryngeal cancer incidence and mortality for the last decade while such trends were less evident amongst the female population and younger subjects.

Explanations and comparisons with previous literature

Laryngeal cancer burden was associated with HDI, GDP, which reinforces findings from previous studies wherein incidence was higher in most developed countries with higher HDI due to an improvement in early-cancer detection and interventions targeting risk factors[30,31]. Incidence and mortality rates were found to be lowest amongst countries of low HDI. This may be attributed to under-diagnosis and under-reporting of cancer cases in regions at a lower socio-economic level due to limited treatment options and a lack of infrastructure[32]. Highest number of laryngeal cancer-related deaths and highest incidence was previously reported in Europe[2,33]. This is further supported by findings of the present study where the Caribbean and Central and Eastern Europe were found to have the highest incidence and mortality

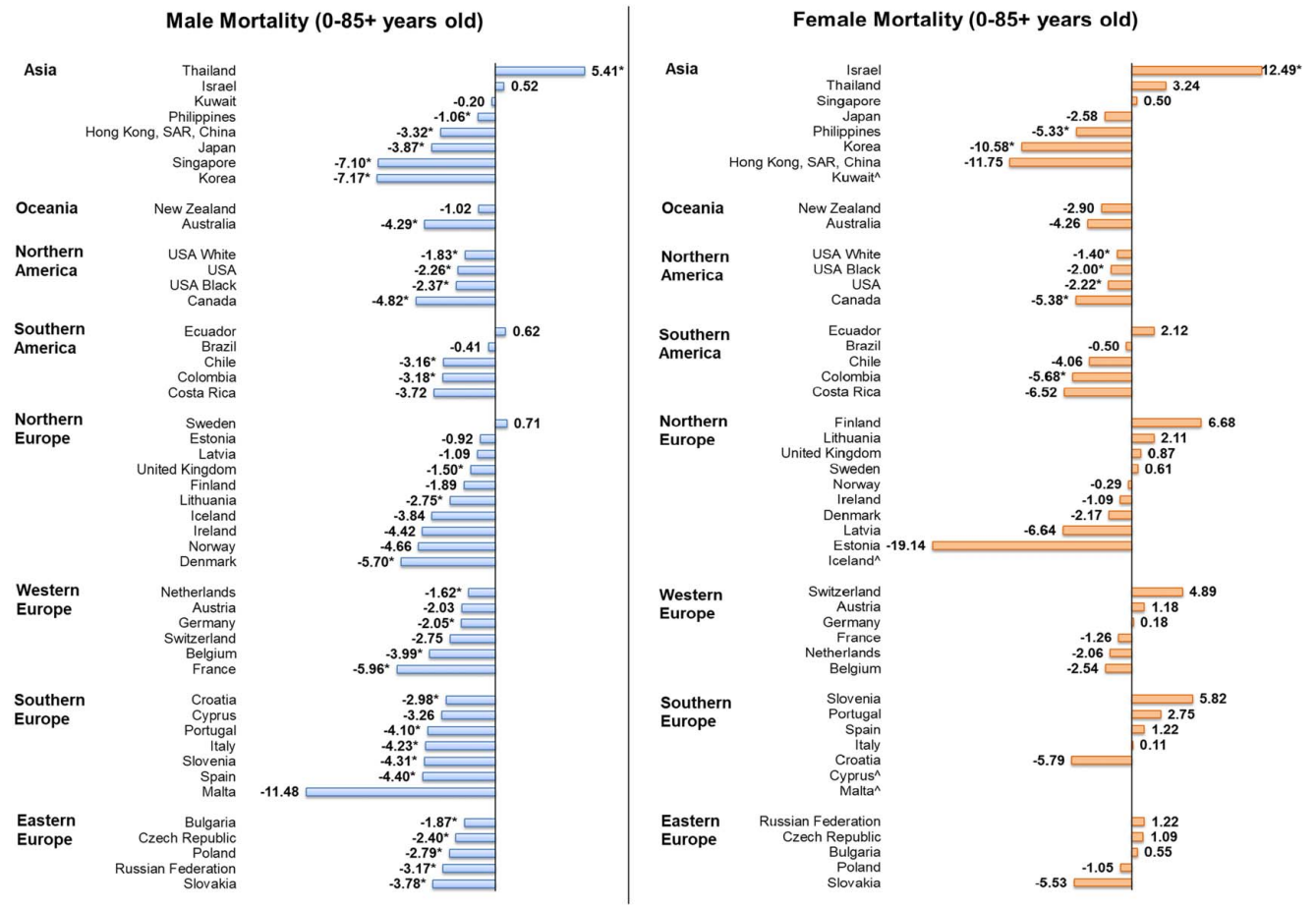

Figure 5. Average Annual Percentage Change of laryngeal cancer mortality in individuals aged 0–85 + years.

rates of laryngeal cancer. The higher proportion of population without access to surgery may also have led to the higher mortality rate, as Caribbean (88.2%, 95% CI: 80.7–93.5%), Eastern Europe (79.2%, 95% CI: 64.9–89.4%), and Central Europe (56.2%, 95% CI: 46.6–64.6%) have some remarkably higher proportions than regions with higher income such as Western Europe (5.9%, 95% CI: 2.7–10.4%) and North America (0.2%, 95% CI: 0.0–1.5%)[34].

Risk factors such as tobacco usage and alcohol consumption are reoccurring variables commonly associated with laryngeal cancer incidence and mortality[35]. Previous studies have indicated that derivatives of burning cigarette, in particular nitrosamines and polycyclic aromatic hydrocarbons act as carcinogens in the laryngeal epithelium, causing mutations in the DNA and triggering the mechanism of carcinogenesis[36]. Smoking cessation interventions to help reduce laryngeal cancer rates has resulted in marked decrease amongst males in the past decade, but the steady increase in smoking prevalence amongst young women and adolescents may be a cause for concern[37–39]. Maintaining a healthy diet may help reduce likelihood of developing cancer. Increased laryngeal cancer risk has been found to be associated with diets rich in animal-products and fats with an inverse relationship found with vegetables and fruits[40–42]. The findings of the current study reflect the risk of cancer indigence and mortality linked to unhealthy diets. Consequently, poor dietary habits leading to the consumption of nutrition-dense foods and excessive energy intake correlates with a greater prevalence of obesity and related health conditions such as hypertension, diabetes, and lipid disorders—all of which have been shown to be positively associated with a greater risk of developing laryngeal cancer[43,44]. In fact, diabetes was found to increase mucin secretion, altering the protective oral mucin layer and thence allowing risk factors to promote cancer growth[45]. In recent years, digital interventions have been found to improve glycaemic control among diabetes patients[46,47], potentially lowering the chance of developing laryngeal cancer.

The mixed trends of incidence and mortality in different regions may be related to the changing prevalence of associated risk factors caused by the disparity in lifestyle conditions, environmental exposures, and individual health decisions. As an overall decreasing trend was observed in the older population, particularly in males, the incidence increase in the younger population may be related to the improved availability of healthcare resources enabled by socio-economic development. Laryngeal cancer mortality rates are declining for both sexes but has been observed to decrease more substantially in males[48]. Drop in laryngeal cancer mortality rates were predominately found in higher income countries in Asia and Europe, possibly ascribed to better access to surgical care[34]. Early detection and treatment of laryngeal cancer at younger ages may contribute towards reduced mortality rates

across all age groups within the population. The recent development of PD-L1 immunohistochemical scoring also allowed laryngeal cancer patients to receive properly targeted therapies, potentially improving patient outcome[49,50]. There was less evidence for a decrease in females and younger subjects. This may be driven by prevalence of potential risk factors since smoking and diabetes have previously been shown to be more significant factors for females, whilst the younger population are more at risk of excessive weight gain and obesity[51–53].

Limitations

The current study has a few limitations in that there is a possibility of the under-reporting of incidence and mortality of laryngeal cancer in developing countries due to the absence of well-established infrastructure and mechanisms for cancer reporting. Conversely, there is a potential for the over-estimation of incidence and mortality rates for some countries where figures were obtained from cancer registries of major cities and capitals. Additionally, difficulties may be encountered when drawing direct comparison of incidence and mortality trends due to the inconsistencies of periods selected for some countries. However, it had limited impact on the comparisons within the same country. Lastly, an analysis of the different stages and subtypes of laryngeal cancer was not conducted due to limited availability of data; beneficial information that would provide further insight into the epidemiology of laryngeal cancer.

Conclusions

The reported incidence for laryngeal cancer has been decreasing remarkably for the past decades, especially for the male population, potentially due to the reduced consumptions of cigarettes and alcohol. Its mortality has also been decreasing, possibly attributable to broader availability and applications of treatments. However, regional disparity in mortality remains due to difference in level of access to surgical care. On the contrary, it is alarming that some evident increases were observed in the female populations and younger subjects from some countries. If no mitigation interventions are implemented, such trends may continue. It is also recommended that governments should continue the implementation of smoking and alcohol reduction campaigns, to minimize further burden on healthcare system. Since significant disparities in the temporal trends among countries were observed, further research should be done to explore the reasons behind the trends to provide insights into the prognosis of laryngeal cancer.

Ethical approval

This study was approved by the Survey and Behavioral Research Ethics Committee, The Chinese University of Hong Kong (No. SBRE-20-332).

Consent

Not applicable.

Sources of funding

None.

Author contribution

M.C.S.W.: conceptualized and supervised the study; S.C.C.: was responsible for data curation and formal analysis; J.H., S.C.C., and S.K.: drafted the manuscript; V.L., L.Z., X.L., D.E.L., W.X., Z.J.Z., E.E., and M.W.: reviewed and revised the manuscript.

Conflicts of interest disclosure

The authors declare that they have no financial conflicts of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Junjie Huang and Martin CS Wong.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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