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Sex differences in cancer incidence, mortality, and survival: Methodological perspectives

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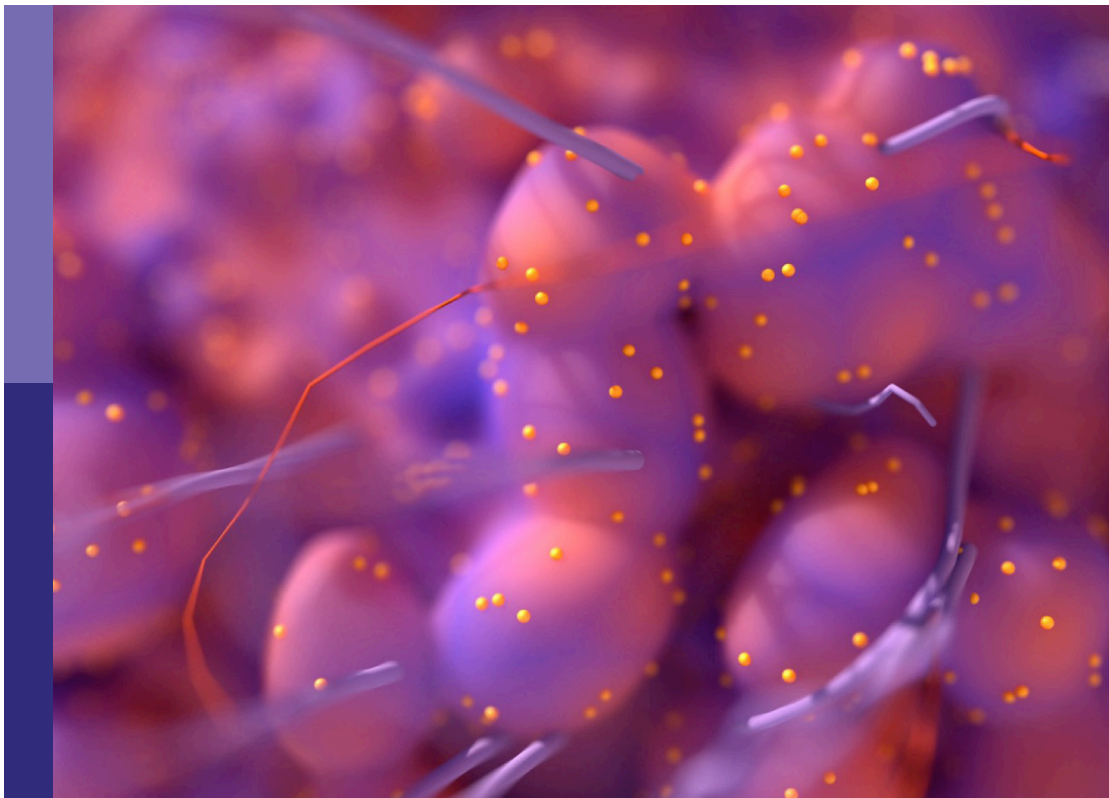

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Sex differences in cancer incidence, mortality, and survival: Methodological perspectives

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Editorial: Sex differences in cancer incidence, mortality, and survival: methodological perspectives

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Editorial on the Research Topic

Sex differences in cancer incidence, mortality, and survival: methodological perspectives

Cancer is a leading cause of death in many developed countries and is the major cause of not only mortality but also morbidity in every region of world regardless of the country's healthcare resources. Based on the principle of epidemiological transition related to aging, changing lifestyles and economic factors, there will be a dramatic world-wide increase in the number of cancers in the next few decades. It has been predicted that the number of incident cases worldwide will be 20.3 million cancer cases by 2030 (Raza et al.).

Sex differences, or the sex ratio (i.e., the male-to-female cancer incidence rate), is a valuable measure for addressing issues of artifacts and imperfect cancer case ascertainment in various cancer registries worldwide. The "Sex-Ratio Methodology" introduced new perspectives in disease epidemiology, especially in cases where the etiology remains unknown or where new hypotheses are needed, while also confirming existing ones. The magnitude of sex ratio is a robust epidemiological marker, and its variability can be used to compare data from different countries and regions across multiple cancer type (Figure 1 provides an example of methodology on magnitude of sex ratio and it's variation in specific time period using publicly available dataset from Cancer Incidence in Five Continents). Recently, the sex ratio has been utilized in cancer epidemiology using country-specific or global cancer registries to explore potential causes of cancers across different time periods (Raza et al).

For this theme on sex differences in cancer burden, cancer researchers were invited to contribute their findings on sex differences in various cancer types across different global regions. Contributions included studies on oropharyngeal cancer (Guo et al); lung cancer (Wang et al., Park et al); brain cancer (Moss et al); and non-small cell lung cancer (Rodriguiz-Lara et al).

The study by Guo et al. highlights the significant impact of HPV vaccination on reducing Oropharyngeal Squamous Cell Carcinoma (OPSCC) incidence in the U.S. Using SEER program, the research shows a decline in HPV-related OPSCC among young adults, in both males and females, during the vaccination era. However, an increase in incidence

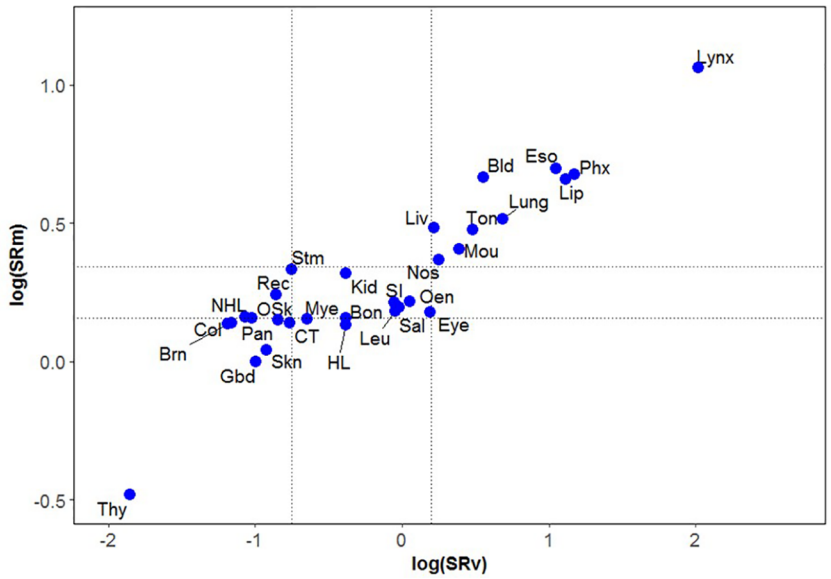

FIGURE 1
Magnitude of the sex ratios (SRm) of 30 cancer types* plotted against their variances (SRv) on log scale for period 2003-07. Footnote (Figure 1). *Bladder (Bld); Bone (Bon); Brain (Brn); Colon (Col); Connective Tissue (CT); Eye (Eye); Gallbladder (Gbd); Hodgkin Lymphoma (HL); Kidney (Kid); Larynx (Lynx); Leukemia (Leu); Lip (Lip); Liver (Liv); Lung (Lung); Melanoma of Skin (Skn); Mouth (Mou); Multiple Myeloma (Mye); Non Hodgkin Lymphoma (NHL); Nose and Sinuses (Nos); Oesophagus (Eso); Other endocrine cancers (Oen); Other Skin cancers (OSk); Pancreas (Pan); Pharynx (Phx); Rectum and Anus (Rec); Salivary glands (Sal); Small Intestine (SI); Stomach (Stm); Thyroid (Thy); Tongue (Ton).

among middle-aged and elderly vaccine-ineligible groups was observed in both males and females. Notably, cancer-specific 5-year survival improved in young males but not females, underscoring the need for further investigation. To strengthen public health messaging, the investigators conclude that efforts must be intensified to improve HPV vaccination coverage among all young females and males.

Air pollution has long been suspected to contribute to the burden of lung cancer, and recent research confirms this association (Wang et al). A study focusing on seven eastern metropolises in China sought to examine the risks and mortality associated with air pollutants such as particulate matter (PM10), nitrogen dioxide (NO2), and sulfur dioxide (SO2). From 2006-2014, decreases in PM10, NO2, and SO2 correlated with lower lung cancer rates. NO2 had the strongest association with increased lung cancer risk and mortality, highlighting the need for stricter air quality regulations. Males compared to females are thought to have a higher risk of lung cancer following exposure to ambient air pollution. The study serves as a clarion call for policymakers to intensify air quality regulations and promote cleaner environments to combat the deadly impact of air pollution on lung cancer. Another study on lung cancer from Korea found that obstructive sleep apnea (OSA) slightly reduced lung cancer risk in males but not in females (Park et al). This first-of-its-kind research analyzed a large 12-year national cohort, highlighting significant gender differences in the impact of OSA on lung cancer development.

In their sex-stratified analysis of methylation differences within medulloblastoma subgroups, Moss et al. identified sex-DMPs (Differentially methylated positions) that varied significantly, with SHH (Sonic Hedgehog) having the highest number. Notably, only SHH medulloblastoma showed sex differences in survival, with females faring worse long-term than males. They found 10 genes with conserved DMPs across subgroups, indicating a shared genetic background that may explain some of the observed sexual dimorphism. Key pathways, including TGF-β, neurotrophic receptors, and NOTCH, were implicated and may vary by sex. Importantly, four genes with sex-DMPs have available chemotherapies, suggesting potential for sex-specific treatments to improve medulloblastoma outcomes.

Rodriguez-Lara et al. presented a mini review on Non-Small Cell Lung Cancer (NSCLC) that exhibited significant differences between males and females, influenced by sex hormones. The roles of estrogen and androgen in NSCLC's immune response remain partially understood, with contradictory data on sex-related responses to PD-L1-based immunotherapy. They point out that sex might predict NSCLC immunotherapy responses, but differences must be validated across diverse populations, considering factors like histological subtypes, mutational profiles, and smoking status. They added that females should be stratified by hormonal status, and serum hormone levels measured to clarify impacts on Programed Cell Death Ligand (PD-L1) control and immunotherapy responses. Emerging data suggest estrogen upregulates PD-L1, indicating Selective Estrogen Receptor Degraders (SERDs) could enhance immunotherapy response. Further research is crucial to understand sex-related differences, identify biomarkers, and improve therapeutic guidelines based on sex and hormonal status.

Additionally, we introduce research on methodological perspectives on measures of cancer burden using diverse datasets such as the Mortality Register System at Wuhan Center for Disease Control (Yan et al.); the Surveillance, Epidemiology, and End Results (SEER) Program (Liu et al.); the Hospital Tumor Registry

at Nantong, China (Chen et al.); the U.S. National Health and Nutrition Examination Surveys (Yang et al.); Global Burden of Disease data (Zhu et al.); the National Cancer Database (Sharan et al.); and the Urban Lung Cancer Early Detection and Treatment Program in Nanchang, China (Zeng et al.).

Yan et al. showed that lung cancer deaths in Wuhan have gradually declined but aging and population growth still impact mortality rates. They concluded that reducing lung cancer mortality in Wuhan requires addressing disparities between central and surrounding urban areas. Another study included in this theme by Liu et al. using SEER Program analyzed Gastrointestinal Neuroendocrine tumors (GI-NT) cases examining incidence, survival, and risk factors. Age, stage, and pathological grade were key risk factors, with men, the elderly, and small intestine, rectum, and GI patients most affected. Race and socioeconomic status also influenced early diagnosis and treatment decisions. Chen et al. highlighted the impact of left truncation on cancer survival estimates. They point out that while hospital-based registries (HBR) evaluate prognosis, left truncation can lead to underestimation. Population-based registries (PBR) reflect overall survival but can suffer from delayed reporting, reducing survival estimates. They conclude that accurate and timely cancer registration is crucial for reliable survival data. Yang et al. presented prospective cohort study using NHANES data and found that being underweight or extremely obese increases mortality risk, primarily from cancer and cardiovascular diseases (CVD). Conversely, overweight or mildly obese conditions were linked to reduced all-cause and non-cancer, non-CVD mortality. These findings highlight the need for tailored survivorship care based on BMI. Zhu et al. highlighted the substantial lung cancer burden in Belt and Road (B&R) countries, notably China, and in South Asia, North Africa, and the Middle East. They highlight that significant gender and age differences exist, particularly in women and those over 75 years. Enhanced multi-country cooperation and policy improvements are crucial under the B&R health Initiative. Using NCDB data in the U.S., Sharan et al. identified significant disparities in treatment timelines for gastric cancer patients, influenced by age, sex, race, insurance, income, facility type, and geography. Understanding these factors is crucial for improving timely care and outcomes. They concluded that future research with updated, prospective designs will enhance strategies to address these disparities.

A screening study in Jiangxi Province, China, from 2018 to 2020, investigated low-dose computed tomography (LDCT) screening compliance among high-risk lung cancer populations (Zeng et al.). The study involved 26,588 participants, identifying 34.4% as high-risk. Screening detected suspected pulmonary tumors or lung nodules in 10.3% of patients. Better compliance was observed in males, ex-smokers, those with chronic respiratory diseases or a family history of cancer, and those with primary education. Poor compliance was linked to a history of harmful occupational exposure. These findings highlight the need to improve screening compliance by addressing these influencing factors. Li et al. in their age-period-cohort analysis showed that esophageal cancer incidence and mortality in China increased and then decreased from 1990 to 2019. They concluded that effective measures are needed to protect the elderly, who are at particularly high risk.

In conclusion, the studies presented in this editorial underscore the critical importance of addressing sex differences in cancer incidence, mortality, and survival. These sex differences offers valuable insights into cancer epidemiology, highlighting the need for robust and comparative data across regions. Research contributions reveal significant findings, such as the impact of HPV vaccination on oropharyngeal cancer, the association between air pollution and lung cancer, and the sex-specific responses to various cancer treatments. These findings emphasize the necessity for tailored public health strategies, including intensified HPV vaccination efforts, stricter air quality regulations, and sex-specific treatment approaches. Additionally, the importance of accurate and timely cancer registration, the impact of socioeconomic factors on cancer treatment, and the need for improved screening compliance are highlighted. Collectively, these studies call for comprehensive and nuanced public health policies to effectively combat the global cancer burden and improve outcomes for diverse populations.

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SR: Conceptualization, Writing – original draft, Writing – review & editing. WC: Writing – review & editing. AT: Writing – review & editing.

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OPINION
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Completeness of Cancer Case Ascertainment in International Cancer Registries: Exploring the Issue of Gender Disparities

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INTRODUCTION

Cancer case ascertainment is commonly called *case-finding* and is the process of identifying patients with malignant cancer who meet the inclusion criteria for a cancer registry. International cancer registries vary according to population size, funding, and trained personnel available for functioning. Most of these registries have strategic and logistical autonomy and follow their own standard registration procedures. The usefulness of population-based cancer registries across different geographic regions depends heavily on quality indices of registration and in particular, on *completeness* (1–6). Completeness is among the most important quality indicators of any cancer registry. It is defined as the *extent, degree or proportion of all incident cancer cases in a defined population that is included in the cancer registry database*. In theory, all cases of cancers in a defined population should be recorded in a population-based cancer registry or should be as close to 100% as possible (7, 8). In this opinion piece, we debate the issue of gender disparities along with rural-urban differences in the cancer registration process. Disparate methods of cancer case ascertainment in the registration process in men and women and their comparisions are also briefly discussed. We also suggest how the issue of gender disparities can be addressed through sex-ratio analysis of smoking associated cancer types by incorporating United Nations' Gender Inequality Index (GII). Because of subtle (and sometimes more elaborate) nuances, we have deliberately kept the terminology of "gender" and "sex" separate in our discussion such as *gender* disparity and *sex* ratios. The purpose of this discussion is to explore the issue of gender disparity in cancer registration and how this kind of potential bias can be recognized.

Differences in Completeness of Ascertainment by Gender

Global collation of data on new cases of cancers through cancer registries provides an opportunity to explore gender differences in cancer incidence across diverse geographical regions (9). These differences are quite often interpreted in light of genetic and environmental causes of cancers across geographical regions (10, 11). Much has been written on gender disparities in specific types of cancer in both developed and resource-constrained parts of the world (12–18), yet there is a paucity of literature on differences in completeness of ascertainment (e.g., under-ascertainment) in cancer registries according to gender. Since the 1990s, there had been an increasing call to systematically quantify the completeness of cancer registries in the region(s) in which they operate (19–21). That call was heeded in the following decade, when studies on completeness of registration started appearing in literature from Africa and Eastern Europe (5, 22) and from developed parts of the world (23, 24). There are few studies that discussed or attempted to quantify the degree of under-reporting among women in a cancer registry (9, 25). Barlow et al. found overall under-reporting

of 3.7% in a well-established Swedish Cancer Registry for the year of 1998 (25). In their study, there seemed to be a pattern of under-reporting that was worse in elderly women. Pearce et al. (9) concluded that the underlying socio-economic patterns of the community is important when interpreting incidence rates, especially among children from low-resource registries, where girls are more likely to be under-diagnosed.

Considering studies mentioned above, it is reasonable to suspect that in some resource-poor countries and conservative societies, due to socio-cultural dynamics, a female cancer patient may be more likely to be omitted from a cancer register. This can have important implications in the reporting and interpretation of incidence statistics and prevention strategies developed based on these data (11). It may be that women who are missed by registries are somewhat different from those who are identified, in terms of diagnostic or prognostic outcomes. It should also be noted that while this underestimation would still be present even if the women missed by registries are not different, there are also other artifacts to be considered that could affect the interpretation of incidence trends. These artifacts in interpreting incidence trends over time from cancer registries have been addressed by Saxem (26), Esteve (27), Muir (28), Swerdlow (29), and relatively recently by Bray (30). The required conditions that ensure truly valid comparisons of cancer incidence, as described by Muir et al. (28) [and quoted by Bray (30)], are worth repeating here unedited: (1) the definition and content of the cancer site being studied have not changed; (2) The criteria of malignancy have not changed; (3) the *likelihood* that a cancer will be diagnosed has not changed; (4) the progress of cancer from inception to diagnosis is not modified by early detection or screening programmes; (5) ascertainment of incident cases and deaths has been equally efficient throughout the period of study; (6) indexing in the International Classification of Diseases (ICD) has not changed; (7) accuracy and specificity of coding is consistent over time; (8) statistics are available at the level of detail required. These authors note, few, if any, databases would meet all of the above criteria. Comparisons of incidence rates of different cancer types between cancer registries under these kinds of a scenarios can therefore be biased, especially if there is also evidence of differences in the degree of under-ascertainment by gender.

Gender Biases and Urban-Rural Gradient

Quantitative assessment of gender bias in registration was inferred using data from the Kampala Cancer Registry in Uganda by Templeton and Bianchi (31). Their publication in 1972 reported registration of women to be half as complete as those of men. However, they also reported that this bias in registration diminished as social patterns of literacy and health awareness evolved and when hospitals became more accessible (31, 32). Even if universal healthcare becomes a possibility in some low-resource countries and with improvements in overall cancer registration, coverage is not likely to be equal in both men and women (33). In addition to problems of health-care accessibility (more so reported in female patients), a cancer diagnosed in a hospital can also be influenced by age, tribal and ethnic affiliations, education, and social status in some countries (34).

Independent studies on cancer case-ascertainment from Bulgaria, Canada, Spain, Italy, India and Gambia have reported *level of completeness* by comparing commonly used indices of completeness (MV%: percent morphologically verified; DCO%: percent death certificate only; M:I Mortality-to-incidence ratio) in men and women (**Table 1**) (35–40). From among these studies, the Canadian registry (36) has shown better completeness indices relative to others in both genders. With the exception of the Gambian registry (40), these population-based registries are included in Cancer Incidence in Five Continents (CI-5) database of International Agency of Research on Cancer (IARC) (41). The Gambian study revealed heterogeneity in quality indicators, in particular, completeness, that suggested ascertainment issues in both genders. The study also reported lower incidence rates for several cancer types in both men and women in comparison with other West African cancer registries such as in Mali, Guinea, Cote d'Ivoire, Niger, and Nigeria (40, 42). According to the authors, the differences in cancer incidence rates between Gambians and other Africans may either represent true geographic variation in risk or there might be other factors at play. One factor was the registry's predominant coverage of the rural population of Gambia, and the related fact that other comparable registries in Africa were not rural. Just like gender disparities, this rural-urban contrast highlights several possible issues such as under-utilization of medical facilities in rural areas, under-diagnoses of cancer in low-resource rural health care settings, and under-reporting of cancer cases from rural populations by registry staff. Conversely, it is possible that it represents a true difference in the risk of cancer between rural and urban regions (in this case, a truly lower incidence in rural Gambia). A similar urban–rural difference in cancer incidence in both genders has been observed elsewhere (43, 44), and much of the difference was attributed to socio-economic deprivation.

Completeness of cancer case-ascertainment can therefore be confounded by gender effects in terms of access to cancer care

TABLE 1 | Completeness of cancer case-ascertainment for all ages in males and females using standard methods of ascertainment.

PBCR	Authors, reference (year)	Male			Female		
		MV (%)	DCO (%)	M:I (%)	MV (%)	DCO (%)	M:I (%)
Bulgaria	Dimitrova, (35) 2015	73.3	9.8	65.9	82.8	6.9	50.5
Canada	Zakaria, (36) 2013	90.0	0.9	48.8	90.0	1.2	48.5
Spain	Navarro, (37) 2010	88.7	2.6	52.3	87.8	3.8	48.0
Italy	Tumino, (38) 2004	83.0	2.0	54.0	85.0	3.0	48.0
India	Mathew, (39) 2011	83.2	1.4	12.6	81.5	1.1	9.3
Gambia	Shimakawa, (40) 2013	18.1	6.6	NR	33.1	3.6	NR

MV%, percent morphologically verified; DCO%, percent death certificate only; M:I, Mortality-to-incidence ratio; NR, not reported. PBCR, Population Based Cancer Registries.

services in urban-rural dynamics. Access to health care services are basic human rights and these rights are not always distributed equitably among men and women in many parts of the world (45, 46). Some of the studies are small-scale (47, 48), but they provide important insights into the experiences of women as they navigate the healthcare system. While the study of cancer care access by Sakellariou and Rotarou (46) focused on comparison among disabled and non-disabled women, their conclusion can be equally applied on the male-female differences in the access to health services (e.g., poor socioeconomic conditions of women and their lack of utilization of cancer care services). Gender effects studies (49, 50) have suggested that men receive more cancer detection tests than women in the same medical practices. Lack of access to health care services in some parts of the world give indication that there is indeed a possibility of a gender gap in cancer registration, but few studies exists that have actually embarked on exploring this issue in the field of cancer surveillance, with emphasis on the registration process itself (9, 51). Parker pointed out an exceptionally high cancer registration ratio (boys relative to girls) for childhood cancers in Afghanistan, Bangladesh, Morocco, Pakistan, and Papua New Guinea. He concluded that the striking gender-bias gives more information on socio-economic dynamics at play than on the etiology of the cancer (51).

METHODS OF CASE ASCERTAINMENT

In the past, several methods were used to assess completeness of case ascertainment in cancer registration (1, 2, 19, 49–54). Parkin and Bray have separated these methods into two broad categories (55): *Qualitative methods* give an indication of the degree of completeness relative to other registries, over time. Examples include historic data methods, percent of morphologically-verified cases (MV %), and mortality-to-incidence (M:I) ratios. *Quantitative methods* include "death certificate methods" and more sophisticated methods such as "capture-recapture" and the "Bullard-Flow" that provide a numerical evaluation of the extent to which all eligible cases are registered. Brief overview of these methods in terms of their uses and shortcomings are as follows:

Morphological Verification (MV) of Diagnosis

Histological verification of cancer or *"Percent of cases morphologically verified (MV %),"* is a measure of the validity of the information and completeness in a registry (41). A very high proportion of cases diagnosed microscopically by histology or cytology/hematology (higher than reasonably expected) suggests over-reliance on the pathological laboratories as a source of information, and failure to find cancer cases diagnosed by other means. The percentage of cancer cases likely to be histologically verified for a given cancer type is dependent upon local regional circumstances where the registries are situated (52). It might be low if the means for taking biopsies, or examining the tissue, are lacking or inadequate such as in low resource countries (e.g., Gambia in **Table 1**).

Mortality:Incidence (M:I) Ratios

The M:I ratio is a key indicator of completeness and involves comparison of the number of deaths (obtained from a source independent of the registry, e.g., the vital statistics system) and the number of incident cancer cases, registered in the same period (41). The M:I ratio may also reflect local conditions because survival and the quality of mortality statistics are at many levels related to the socioeconomic development of the region. Values of M:I over time that are greater than expected signals under-registration (i.e., incident cancers missed by the registry), and becomes more noticeable if this under-registration involves more than one type of cancer in a registry. However, under- or over-reporting of tumors on death certificates distorts this ratio, as will a lack of constancy in incidence and case fatality (the rate of death amongst incident cases) over time. Application of this indicator of ascertainment does require, however, mortality data of good quality (53), something not always possible in low-resource registries.

Death Certificate Methods (DC Methods)

Death certificates are one of the main sources of information in a cancer registry in developed countries (54), and have three main uses in cancer registration: (1) as a complementary source of information on new cancer cases, (2) as a quality control assessment of both completeness and validity, and (3) for studies on survival of registered patients. DC methods cannot be readily applied to cancer registries from low- and medium-income countries (55). Methods used by Ajiki (56) [and quoted by Parkin (57) and Kamo (58)] explains death certificates as a means of capturing information on cases that were not registered during life. Although the DC method is not an ideal indicator of completeness of registration, an elevated proportion of cases diagnosed through this method does suggest some level of incompleteness.

Comparison of Ascertainment Methods

Commonly used indices (e.g., MV, DC, and M:I) as well as complex sophisticated methods [e.g., Bullard's Flow and capture-recapture method (1, 59)] are used in estimating the degree of completeness of ascertainment. This means that with the availability of various methods, the degree of completeness in cancer registries will vary with whatever methods are used. Schmidtmann and Blettner carried out the first survey of its kind to compare different methods that European cancer registries use to assess completeness of ascertainment (**Figure 1A**) (60). The study revealed that 86% of the 56 cancer registries that returned the survey questionnaire (of total of 195 registries that were contacted) had evaluated completeness of case ascertainment. The methods used most frequently were comparing current with historical incidence (73%) and comparisons with a presumably complete reference registry (65%). The M:I ratio was used in 58% of registries. More complex procedures, such as the capture-recapture method (25%) and Bullard's flow method (21%), were employed less often. The use of more than one method was also somewhat infrequent (29%). Zanetti et al. repeated the survey in 2015, with an improved response rate of 65% from cancer registries in Europe (**Figure 1B**) (61). The methods used were

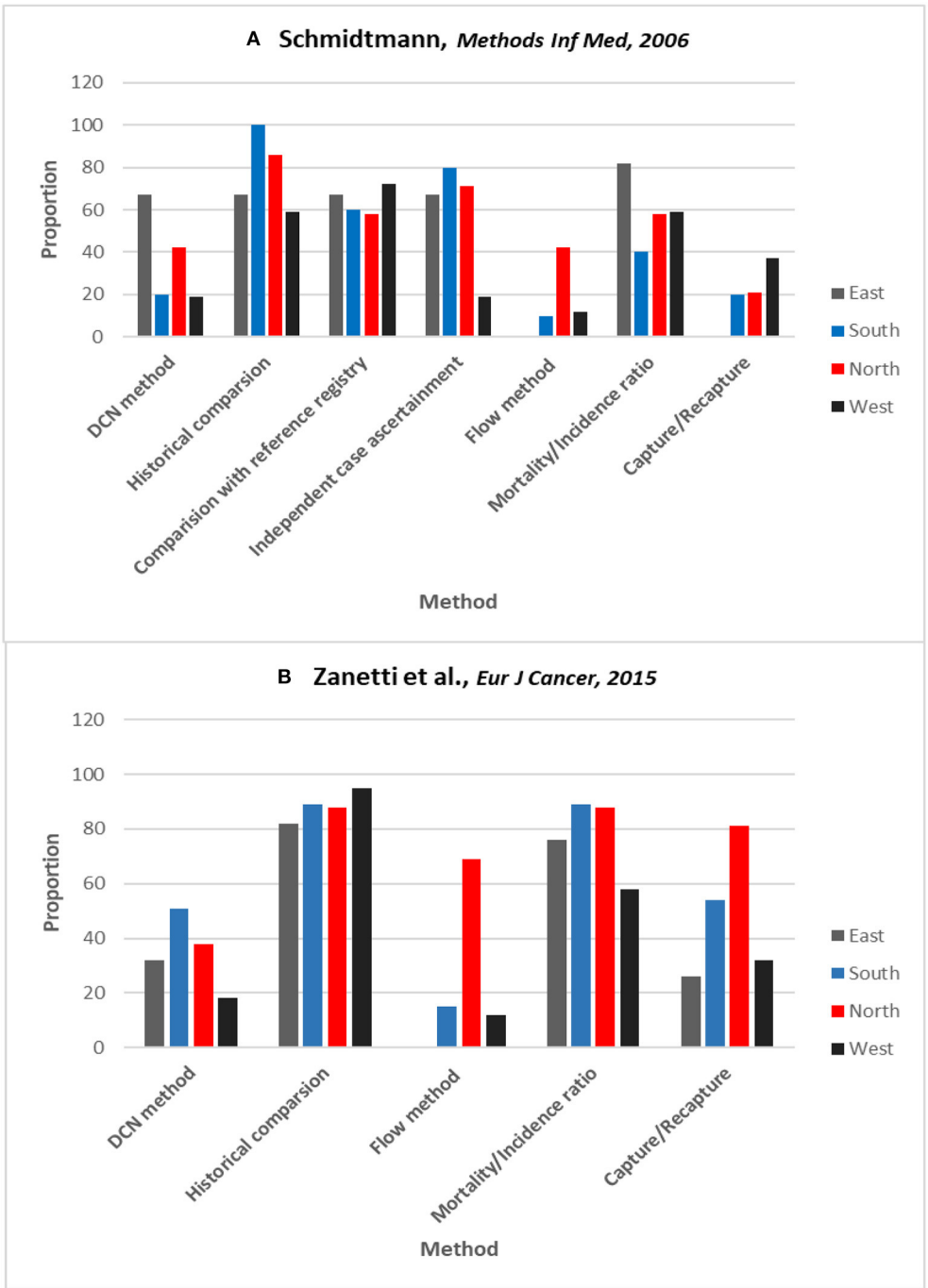

FIGURE 1 | Surveys results on proportion of cancer registries within each region of Europe using different methods of estimating completeness. **(A)** Schmidtmann and Blettner. (60) **(B)** Zanetti et al. (61) in 2015. Countries grouped according to the definition of the UN Population Division (East, South, North, & West). DCN method is from where the no. of cases come from death certificates only (another term for DCO%). Reprinted with permission from authors and publishers (60, 61).

still largely based on simple indices with only slight improvement in the use of quantitative methods. The impression gained from these surveys is that there are different methods in use by individual cancer registries, and there are few comparative studies on their performance in relation to ascertainment in males and females. The authors of these studies suggest that in order to make valid comparisons across regions, modern registries should work more on standardizing methods of assessing completeness (60–62). These studies have underscored the importance of unifying methods for estimating completeness

that could improve validity of incidence comparisons between cancer registries in both males and females.

IDENTIFICATION OF GENDER BIAS IN CANCER REGISTRATION

In order to identify cancer registries with possible gender bias, we suggest a solution i.e., Sex Ratio analysis of cancer incidence that can circumvent some of the problems that exist in interpretations of incidence trends and their comparisons across different geographic areas. As a first step, one can compute sex ratios of different/particular types cancer incidence that can be carried out by identifying those cancer types from international cancer registries where the sex ratio has remained relatively stable (e.g., over time and geography). Secondly, this cancer specific sex ratio can be tallied to United Nations Gender Inequality Index (GII) to rank cancer registries according to their respective countries with low, moderate, and high gender inequalities over time. These categories of index, will help envisage how the stability of sex ratio compares with a geography where the registry is located e.g., a country with a uniquely high sex ratio of a cancer that has remained stably low over time in other regions can indicate bias in registration.

Sex Ratio Analysis of Cancer Incidence

The proposed "Sex-Ratio Methodology" has opened new perspectives in disease epidemiology, specifically where the etiology remains undetermined or where new hypotheses are warranted, and old hypotheses can be confirmed (63–65). In fact, sex ratio is a robust epidemiological marker and its variability can be used for comparing data collected from different countries and regions, and where confounding effects exerted by different factors can be supposedly minimized (64, 66, 67). The sex ratio has also been recently used in cancer epidemiology using country-specific or worldwide cancer registries to speculate on causes of cancers (10, 68, 69).

Using Gender Inequality Index

A well-recognized multidimensional indicator such as GII can be used in the context of exploring gender-bias in cancer registries (70). Completeness of cancer case ascertainment whether it is similar in males and females in international cancer registries can be explored through GII on selected cancer types that have remained stable over time. The measurement of gender inequality has received increasing attention over the past few years (71, 72) and has been explored in epidemiological studies (73, 74). The GII has been designed to capture gender inequality through relatively new functional form to summarize multidimensional information into a real number that can be used to compare countries' performance in this domain over time. The GII reflects gender-based disadvantage in three dimensions namely: reproductive health, empowerment and the labor market, for 160 countries. It shows the loss in potential human development due to inequality between male and female achievements in these three dimensions. It ranges from 0, where women and men fare equally, to 1, where one gender fares as poorly as possible in all measured dimensions (70). As of 2015 data, the lowest gender inequality country is Switzerland (GII: 0.04) and the highest gender inequality of 0.77 is found in Yemen (70). This type of analysis in conjunction with sex ratio of cancer incidence can also provide clues on quality of cancer registries and can inform the public health debate surrounding the contextual problem of gender-bias in cancer registration.

Stable (and Variable) Sex Ratios of Cancer Incidence

To explore the issue of potential gender bias due to the possibility of differential disparities created by health seeking behaviors such as access to health care facilities and therapeutic treatment of cancers, we can select cancers that are somewhat known to be stable across time and geography e.g., kidney, leukemia, multiple myeloma, brain and possibly thyroid that varies to some extent (75–77). Hypothetical mock table (**Table 2**) presents cancer registries in countries that can be listed according to low and high gender inequality index with cancer types where the sex ratios of cancer incidence has been posited as relatively stable in the literature.

Table 2 also shows hypothetical world rankings of countries where the gender inequality is lowest (i.e., where females are likely to have equal access to health care services) e.g., registries 1–8 as well as where gender inequality is highest (registries 11 to 14). In reality, there are 160 countries of world with available GII values over time and rankings (70). Based on the index of gender inequality, it can also be assumed that gender bias can either be less or more of an issue in these cancer registries. For example,

TABLE 2 | Mock table for sex ratios of kidney, leukemia, multiple myeloma, brain, and thyroid cancers with gender inequality index (GII) values over time and their ranking.

Registry (country)	GII values (World Rank)	Sex Ratios				
		Kidney	Leukemia	Multiple myeloma	Brain	Thyroid
1	0.023 (1)	2.2	1.5	1.5	1.3	0.4
2	0.026 (3)	2.3	1.2	1.6	1.7	0.3
3	0.035 (5)	2.1	1.4	1.7	1.5	0.4
4	0.078 (6)	2.4	1.8	1.2	1.6	0.2
5	0.105 (7)	2.3	1.1	1.8	1.7	0.5
6	0.118 (10)	4.5	1.4	1.3	1.6	0.3
7	0.118 (11)	2.1	1.6	1.4	1.5	0.4
8	0.126 (12)	2.6	1.1	1.3	1.5	0.4
9	0.143 (18)	2.2	1.5	1.6	1.8	0.5
10	0.178 (29)	2.5	1.3	1.7	1.8	0.3
11	0.619 (119)	2.3	1.5	1.5	1.6	0.5
12	0.672 (135)	2.2	1.3	1.2	1.5	1.5
13	0.151 (145)	8.1	7.6	6.5	3.5	2.0
14	0.579 (154)	4.7	4.0	4.6	1.7	1.1

Cancer registries in countries with lowest and highest gender inequality index (GII).

relatively similar values of sex ratios for five selected cancer types in Registry 1, 2, and 3 indicate that gender bias might be less of an issue in these registries because of stable sex ratios. One notable observation is Registry 6 where GII shows that it is a fairly gender balanced country in terms of perceived economic advantages and is ranked tenth. However, an extremely high sex ratios of 4.5 in Registry 6 (for kidney cancer) is indicative that the male and female completeness of ascertainment (and other artifacts) might not be similar (i.e., more males are registered than females). Registry 6 is also showing that it is specific for cancer of kidney whereas sex ratios of other cancer types are stable compared to other registries. High GII countries with Registries 13 and 14 also provide evidence of major quality issues in registration process. Hence gender bias can be indicated if we find these kinds of discrepancies in registries located in countries with either low, moderate or high GII.

CONCLUSIONS

In summary, this opinion piece highlights contextual problems that underlie disparities in completeness of ascertainment by gender in cancer registries around the world. Implementing protocols for assessing the completeness of ascertainment by person, place, and time is invaluable in providing clues to the relative quality of cancer registries. Cancer cases can only be recorded once they have been diagnosed, after a patient has sought medical attention. It is possible that in rural areas of developing countries, people can die with their cancer before ever having been seen by a medical doctor. This is less likely to be common in the more urban populations of the twenty-first century (58). In some countries, cancer registration has a legal basis and is funded by governments, but some registries, particularly in developing countries, have operated on a voluntary basis, relying on good will and the tradition of sharing of medical information among different medical specialties (59). Notwithstanding the existence of contextual obstacles in cancer registration, population-based cancer registries do provide a good source of information to study the causes of cancers (37, 60, 61). When we can begin to quantify potential biases in ascertainment across population subgroups (e.g., by gender), we can improve the utility of these data.

AUTHOR CONTRIBUTIONS

SR carried out the literature review and wrote the first draft of the manuscript. IJ, RZ, and JS provided critical revisions of the manuscript and ensured accurate interpretation of the evidence. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Trends in Oropharyngeal Cancer Incidence Among Adult Men and Women in the United States From 2001 to 2018

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Background: The human papillomavirus (HPV) vaccine was approved in 2006 and has been shown to decrease vaccine-related HPV types in the oropharynx. Its impact on the incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) has not been examined. We investigated the impact of HPV vaccination on the incidence of HPV-related OPSCC in the US among male and female adults from different age groups.

Methods: The US Cancer Statistics 2001–2018 database and the National Cancer Institute (NCI)'s Surveillance Epidemiology and End Results (SEER) program were used in this study. OPSCC incidence was age-adjusted to the US standard population in 2000. Cause-specific 5-year survival probability was calculated using 60 monthly intervals in SEER*Stat software.

Results: Incidence of HPV-related OPSCC was much higher in males than in females. Age-adjusted annual incidence of OPSCC was significantly lower in 2014-2018 than in 2002-2006 among males 20-44 years old (11.4 vs 12.8 per 1,000,000, rate ratio 0.89, 95% confidence interval 0.84-0.93) and among females 20-44 years old (3.0 vs 3.6 per 1,000,000, rate ratio 0.86, 95% confidence interval 0.78-0.95), but increased in both 45-64 year old and 65+ year old males and females. Joinpoint regression revealed a significant joint in the HPV-OPSCC incidence trend for 20-44-year-old males in 2008 at which time the incidence began to decrease. Except for 20-44 year old females (74.8% in 2002-2006 vs. 75.7% in 2009-2013, p=0.84), cancer-specific 5-year survivals significantly improved for males and females of all age groups.

Conclusions: HPV-related OPSCC was much more common in males. Incidence of HPV-related OPSCC declined among young adults during the vaccination era compared with pre-vaccination era. Cancer-specific 5-year survival was significantly improved in young males but not in young females.

Keywords: oral squamous cell carcinoma, oral cancer, epidemiology, epidemiology and prevention, human papillomavirus

INTRODUCTION

A persistent oral human papillomavirus (HPV) infection places a person at risk of developing oropharyngeal squamous cell carcinoma (OPSCC) (1–3). OPSCC patients whose cancer tests positive for HPV fare better than those whose cancer tests negative for the virus (3–6). Previous reports revealed increasing incidence of HPV-related OPSCC in both middle-aged and elderly adult populations in the United States (US) (7, 8). The incidence of HPV-related oral squamous cell carcinoma was reported to steadily increase from 1973 to 2004, whereas HPV-unrelated oral squamous cell carcinomas did not increase during this time (7). In elderly patients ≥65 years of age, the incidence of OPSCC was also reported to increase from 2000 to 2012, mainly due to the increasing incidence of HPV-related OPSCC (8).

Prior estimates of OPSCC incidence in the US were largely based on the National Cancer Institute (NCI)'s Surveillance Epidemiology and End Results (SEER) program, which maintains a nationally representative sample of cancer patients (7–12). HPV-related OPSCC are typically estimated based on anatomic sites, of which about 30% are not actually HPV-related (7, 13). Mahal et al. estimated the incidence and demographics of HPV-associated OPSCC patients using SEER data with HPV status information, although almost half of these patients lacked information on HPV status (13). The SEER data only cover about one-fourth of the US population. In contrast, United States Cancer Statistics (USCS) gathers information on cancer cases and patient demographics for essentially the entire US population, which provides an opportunity to accurately estimate cancer incidence trends in the entire US population. Furthermore, close examination of the trends in incidence of HPV-related OPSCC across age groups, race/ethnic groups, and regions of residence among both male and female adults in the US is lacking. The HPV vaccine was approved in 2006 for females and in 2009 for males, and was shown to decrease vaccine-related HPV types in the oropharynx (14). Currently, the Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) recommends a two-dose HPV immunization schedule for persons who initiate the vaccine series at ages 9 through 14 years, while a three-dose schedule is recommended for those 15-26 years of age (15). For adults 27-45 years of age, the ACIP recommends them to get medical counseling about their risk for new HPV infections and potential benefits of vaccination (16). In the US, almost all eligible persons have coverage for HPV vaccine from multiple sources of private and public financing. The impact of HPV vaccine on the incidence of oropharyngeal cancers has not been examined. We investigated the impact of HPV vaccination on the incidence of HPV-related OPSCC in the US among male and female adults from different age groups.

METHODS

We used the USCS database 2001–2018, which combines data from the Centers for Disease Control and Prevention (CDC)'s National Program for Cancer Registries (NPCR) and the SEER program (17). Both contain data on patient demographics and tumor characteristics from hospitals, physicians, and laboratories across the nation. The USCS database 2001–2018 represents the entire US population (excluding Puerto Rico) between 2001 and 2018. The Institutional Review Board at The University of Texas Medical Branch did not consider this study human subjects research; therefore, it did not require approval.

We classified OPSCC cases potentially due to HPV based on anatomic sites identified by ICD-0-3 as follows: base of tongue (C01.9), lingual tonsil (C02.4), overlapping lesion of tongue (C02.8), soft palate (C05.1), uvula (C05.2), tonsil (C09.0-C09.1, C09.8-C09.9), vallecula (C10.0), anterior surface of epiglottis (C10.1), oropharyngeal wall (C10.2-10.3), branchial cleft (C10.4), pharynx (C14.0), Waldeyer ring (C14.2), or other oropharynx site (C10.8-C10.9, C14.8). Invasive squamous cell cases were defined using ICD-O-3 histology codes 8050-8086 and 8120-8131 and only microscopically confirmed cases were included (8). Each case had patient demographics and the cancer diagnosis date. We stratified the data by age and region of residence - Northeast, Midwest, South, and West. Analyses included information about race and ethnicity. Race was grouped into Non-Hispanic White, Non-Hispanic Black, Asian/Pacific Islander, and Other categories, and ethnicity was classified as either Hispanic or non-Hispanic. The North American Association of Central Cancer Registries (NAACCR) Hispanic/Latino Identification Algorithm (NHIA) was used to identify Hispanic ethnicity for all cancer cases (18).

Statistical Analysis

The SEER*Stat statistical software package (version 8.3.8) and SAS for Windows version 9.4 (SAS Institute) were used to conduct the analyses. Differences with two-tailed P values < 0.05 were considered statistically significant. OPSCC incidence rates were calculated as the number of cases per 100,000 persons and were age-adjusted to the 2000 US standard population. The Tiwari method was used to determine the confidence intervals (CI) (19). Annual percentage changes (APCs) in incidence were calculated using the equation, $(\exp[\beta]-1)*100$. A least-squares regression line was fitted to the natural logarithm of the rates, using the calendar year as a regressor variable, to estimate the regression coefficient (β). The statistical significance of APCs and differences between APCs were determined using tests based on previously proposed methods (20). Joinpoint regression uses least squares regression to fit line segments to the natural log of the age-standardized incidence rates, joined at discrete points that represent statistically significant changes in the direction of the trend. Joinpoint regression was performed using the Joinpoint Regression Program from National Cancer Institute. The 5–year average annual incidence rates were calculated for 5 years before the introduction of HPV vaccination (2002–2006) and the latest 5 years in the vaccine era (2014–2018). Differences in age–adjusted rates were evaluated using rate ratios (RRs) and the corresponding 95% confidence intervals (CIs).

Cancer-specific five-year survival probability was calculated using 60 monthly intervals in SEER*Stat software. Data used

were from SEER's 18 registry areas. SEER*Stat software used expected life tables instead of a cohort of cancer-free individuals, assuming that the cancer deaths were a negligible proportion of all deaths. Individuals who died of causes other than OPSCC were considered censored when we estimated cancer-specific survival. Cox proportional hazard models were fitted to compare differences in 5-year survival probability across time by stage at diagnosis, controlling for age at diagnosis and race/ethnicity. Hazard ratios (HRs) and 95% CIs were estimated from the Cox model. Kaplan-Meier curves were plotted to show differences in cumulative probability of death across time. We had successfully used the same software package and similar methods to examine incidence of cervical cancer and breast cancer, and cancer-specific survival (21–23).

RESULTS

There were 229,264 adult males and 55,108 adult females diagnosed with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) from 2001 to 2018. Among these male patients, 4.6% were 20-44 years old, 61.7% were 45-64 years old, and 33.7% were 65+ years old, while among these female patients 5.4% were 20-44 years old, 50.8% were 45-64 years old, and 43.8% were 65+ years old (**Supplemental Table 1**).

Age-adjusted annual incidence of OPSCC was significantly lower in 2014-2018 than in 2002-2006 among males 20-44 years old (11.4 vs 12.8 per 1,000,000, rate ratio 0.89, 95% confidence interval 0.84-0.93, **Table 1**) and among females (3.0 vs 3.6 per 1,000,000, rate ratio 0.86, 95% confidence interval 0.78-0.95), but increased among those 45-64 years old (220.3 vs 170.8 per 100,000 in males, rate ratio 1.29, 95% confidence interval 1.27-1.31; 39.1 vs 33.9 per 100,000 in females, rate ratio 1.15, 95% confidence interval 1.12-1.19) and those 65+ years old (284.4 vs 174.6 per 100,000 in males, rate ratio 1.63, 95% confidence interval 1.60-1.66; 59.0 vs 55.1 per 100,000 in females, rate ratio 1.07, 95% confidence interval 1.04-1.11). Overall negative trends of OPSCC incidence were observed for adults 20-44 years old of both sexes and joinpoint regression revealed a significant joint in the HPV-OPSCC incidence trend for 20-44-year-old males in 2008, after which incidence began to decrease (**Figure 1**). No joints were observed among females of the same age group. Trends in HPV-related OPSCC incidence among males and females 45-64 years old and 65+ years old generally increased over time (**Supplemental Figures 1, 2**). Independent of age group, OPSCC incidence was consistently and significantly greater among male patients.

TABLE 1 | Age-adjusted incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) among US adults by age group and sex during 2002-2006 and 2014-2018.

	Incidence (per 1,000,000 person-years)		Rate ratio 2014-2018/2002-2006
	2002-2006	2014-2018	RR (95% CI)
Male			
20-44 years old			
All	12.8 (12.4-13.3)	11.4 (10.9-11.8)	0.86 (0.78-0.95)
Race/Ethnicity			
Hispanic	5.4 (4.7-6.2)	5.0 (4.4-5.7)	0.93 (0.77-1.14)
Non-Hispanic White	14.8 (14.3-15.4)	14.6 (13.9-15.3)	0.98 (0.93-1.04)
Non-Hispanic Black	12.8 (11.5-14.1)	10.1 (9.0-11.3)	0.79 (0.67-0.92)
Asian/Pacific Islander	4.2 (3.1-5.5)	3.5 (2.7-4.6)	0.85 (0.57-1.26)
Region			
Northeast	11.2 (10.2-12.2)	3.4 (2.9-3.9)	0.95 (0.83-1.08)
Midwest	13.4 (12.5-14.4)	3.5 (3.0-4.0)	1.02 (0.92-1.14)
South	15.5 (14.7-16.3)	4.3 (3.9-4.8)	0.81 (0.74-0.87)
West	9.5 (8.7-10.3)	2.6 (2.2-3.0)	0.87 (0.76-0.98)
45-64 years old			
All	170.8 (168.8-172.7)	220.3 (218.3-222.3)	1.15 (1.12-1.19)
Race/Ethnicity			
Hispanic	92.6 (87.7-97.7)	92.8 (89.2-96.5)	1.00 (0.94-1.07)
Non-Hispanic White	182.7 (180.4-185.0)	266.6 (263.9-269.2)	1.46 (1.44-1.48)
Non-Hispanic Black	198.8 (192.2-205.6)	152.7 (147.8-157.6)	0.77 (0.73-0.80)
Asian/Pacific Islander	39.0 (34.4-43.9)	47.8 (43.8-52.1)	1.23 (1.06-1.43)
Region			
Northeast	161.6 (157.3-166.0)	33.0 (31.2-35.0)	1.29 (1.25-1.34)
Midwest	164.6 (160.6-168.6)	34.6 (32.8-36.4)	1.43 (1.38-1.47)
South	193.1 (189.7-196.6)	37.7 (36.3-39.2)	1.27 (1.24-1.29)
West	149.2 (145.3-153.1)	27.7 (26.1-29.4)	1.19 (1.15-1.23)
65+ years old			
All	174.6 (171.7-177.6)	284.4 (281.2-287.6)	1.07 (1.04-1.11)
Race/Ethnicity			
Hispanic	149.4 (138.1-161.4)	187.4 (178.2-197.1)	1.25 (1.14-1.38)
Non-Hispanic White	175.7 (172.5-179.0)	310.7 (307.0-314.4)	1.77 (1.73-1.81)

(Continued)

TABLE 1 | Continued

	Incidence (per 1,000,000 person-years)		Rate ratio 2014-2018/2002-2006
Non-Hispanic Black	223.1 (211.2-235.5)	227.2 (217.3-237.5)	1.02 (0.95-1.09)
Asian/Pacific Islander	72.7 (61.9-84.8)	83.0 (75.0-91.7)	1.14 (0.95-1.38)
Region			
Northeast	170.8 (164.3-177.5)	53.5 (50.4-56.7)	1.56 (1.49-1.64)
Midwest	159.6 (153.8-165.6)	53.9 (51.0-57.0)	1.69 (1.62-1.77)
South	192.7 (187.6-197.9)	56.3 (53.9-58.7)	1.60 (1.55-1.65)
West	163.5 (157.4-169.9)	56.0 (52.8-59.3)	1.66 (1.58-1.73)
Female			
20-44 years old			
All	3.6 (3.3-3.8)	3.0 (2.8-3.3)	0.89 (0.84-0.93)
Race/Ethnicity			
Hispanic	1.7 (1.3-2.2)	1.9 (1.5-2.3)	1.14 (0.81-1.61)
Non-Hispanic White	4.0 (3.7-4.3)	3.8 (3.4-4.1)	0.95 (0.85-1.07)
Non-Hispanic Black	4.0 (3.3-4.7)	2.4 (1.9-3.0)	0.60 (0.45-0.80)
Asian/Pacific Islander	2.2 (1.5-3.2)	1.5 (1.0-2.1)	0.66 (0.38-1.14)
Region			
Northeast	10.6 (9.6-11.7)	3.3 (2.7-3.9)	0.96 (0.76-1.22)
Midwest	13.7 (12.6-14.8)	3.5 (3.0-4.0)	1.00 (0.81-1.23)
South	12.5 (11.8-13.3)	3.4 (3.0-3.8)	0.79 (0.68-0.92)
West	8.2 (7.5-9.0)	2.0 (1.6-2.4)	0.77 (0.60-0.99)
45-64 years old			
All	33.9 (33.1-34.7)	39.1 (38.3-39.9)	1.29 (1.27-1.31)
Race/Ethnicity			
Hispanic	14.7 (12.8-16.7)	18.0 (16.5-19.7)	1.23 (1.05-1.44)
Non-Hispanic White	36.4 (35.4-37.4)	46.2 (45.1-47.3)	1.27 (1.23-1.32)
Non-Hispanic Black	41.0 (38.3-43.8)	33.9 (31.8-36.1)	0.83 (0.75-0.91)
Asian/Pacific Islander	9.1 (7.1-11.5)	10.1 (8.4-11.9)	1.11 (0.82-1.50)
Region			
Northeast	208.5 (204.0-213.1)	37.9 (36.0-39.8)	1.15 (1.06-1.24)
Midwest	234.7 (230.3-239.1)	41.2 (39.4-43.1)	1.19 (1.11-1.28)
South	244.4 (241.0-247.8)	43.8 (42.4-45.2)	1.16 (1.10-1.22)
West	177.2 (173.5-180.9)	30.2 (28.7-31.8)	1.09 (1.01-1.18)
65+ years old			
All	55.1 (53.6-56.5)	59.0 (57.7-60.4)	1.63 (1.60-1.66)
Race/Ethnicity			
Hispanic	31.5 (27.2-36.3)	33.5 (30.2-37.1)	1.06 (0.89-1.27)
Non-Hispanic White	58.7 (57.1-60.4)	66.3 (64.7-67.9)	1.13 (1.09-1.17)
Non-Hispanic Black	50.1 (45.6-54.8)	39.7 (36.4-43.3)	0.79 (0.70-0.90)
Asian/Pacific Islander	20.4 (15.7-26.2)	23.0 (19.3-27.2)	1.13 (0.83-1.55)
Region			
Northeast	267.0 (259.9-274.4)	61.5 (58.5-64.7)	1.15 (1.06-1.24)
Midwest	270.1 (263.5-276.8)	59.9 (57.1-62.8)	1.11 (1.03-1.20)
South	308.7 (303.4-314.1)	61.4 (59.3-63.6)	1.09 (1.03-1.15)
West	271.0 (264.5-277.6)	52.0 (49.4-54.7)	0.93 (0.86-1.00)

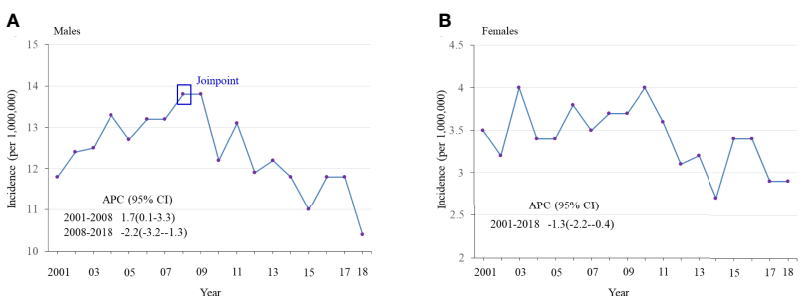

FIGURE 1 | Age-adjusted incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) from 2001 to 2018 among adults 20-44 years old, stratified by sex. **(A)** Males **(B)** Females.

Cancer-specific 5-year survival was significantly improved across age groups among both males and females (**Table 2**), except for 20-44-year-old females (74.8% in 2002-2006 vs. 75.7% in 2009-2013, hazard ratio 0.96, 95% CI 0.64-1.44, p=0.84, **Figure 2**). Hazard ratios obtained from Kaplan-Meier curves of the cumulative probability of death from OPSCC across time among male or female patients 45-64 years old and 65+ years old were lower among men for both age groups relative to women (**Supplemental Figures 3, 4**).

TABLE 2 | Cancer-specific five-year survival among adult males and females with HPV-related oropharyngeal squamous cell carcinoma (OPSCC), SEER 2002-2006 and 2009-2013 (N=29304).

	5-year survival % (95% CI)	
	2002-2006	**2014-2018**
Male		
20-44 years old		
All	73.8 (70.5-76.9)	79.6 (76.3-82.4)
Race/Ethnicity		
Hispanic	71.3 (57.9-81.1)	86.6 (76.4-92.5)
Non-Hispanic White	78.1 (74.4-81.3)	81.6 (77.9-84.8)
Non-Hispanic Black	47.3 (35.9-57.9)	56.7 (44.4-67.3)
Asian/Pacific Islander	73.7 (47.9-88.1)	76.8 (57.3-88.2)
45-64 years old		
All	69.2 (68-70.3)	75.7 (74.8-76.6)
Race/Ethnicity		
Hispanic	67.3 (62.5-71.7)	69.8 (65.9-73.3)
Non-Hispanic White	73.4 (72.1-74.5)	78.4 (77.4-79.3)
Non-Hispanic Black	40.7 (37.1-44.2)	55.7 (52.2-59.0)
Asian/Pacific Islander	68.9 (60.3-76.0)	75.9 (68.9-81.5)
65+ years old		
All	51.3 (49.2-53.3)	62.9 (61.3-64.5)
Race/Ethnicity		
Hispanic	39.9 (31.7-48.0)	53.7 (47.2-59.7)
Non-Hispanic White	54.7 (52.4-57.0)	65.2 (63.4-66.9)
Non-Hispanic Black	30.9 (25.0-37.0)	44.4 (38.3-50.3)
Asian/Pacific Islander	52.4 (41.1-62.6)	64.5 (54.9-72.6)
Female		
20-44 years old		
All	74.8 (68.1-80.3)	75.7 (68.8-81.3)
Race/Ethnicity		
Hispanic	80.0 (50.0-93.1)	67.6 (38.3-85.2)
Non-Hispanic White	77.0 (68.7-83.3)	80.3 (72.4-86.1)
Non-Hispanic Black	50.4 (32.3-66.0)	40.6 (19.5-60.9)
Asian/Pacific Islander	100	92.3 (56.6-98.9)
45-64 years old		
All	67 (64.3-69.6)	71.8 (69.5-73.9)
Race/Ethnicity		
Hispanic	66.6 (53.7-76.6)	73.6 (64.7-80.5)
Non-Hispanic White	70.1 (67.1-73.0)	75.6 (73.1-78.0)
Non-Hispanic Black	47.9 (40.3-55.1)	47.3 (40.3-54.0)
Asian/Pacific Islander	88.5 (68.4-96.1)	80.4 (65.6-89.3)
65+ years old		
All	50.7 (47.4-53.9)	57.6 (54.5-60.6)
Race/Ethnicity		
Hispanic	53.1 (38.1-66.0)	63.5 (49.9-74.3)
Non-Hispanic White	51.4 (47.7-54.9)	58.9 (55.4-62.2)
Non-Hispanic Black	45.3 (33.4-56.4)	49.1 (38.9-58.5)
Asian/Pacific Islander	33.4 (15.9-52.0)	45.0 (30.8-58.2)

DISCUSSION

This study demonstrated a decline in the incidence of HPV-related OPSCC among young males and females during the vaccination era (2014–2018) compared with the pre-vaccination era (2002–2006). Previous research established that changes in HPV prevalence are the primary driver behind increased OPSCC incidence (7, 9, 10). It is likely that HPV vaccination of young girls and boys and the resulting decreased oral HPV infection rates, as well as emerging herd immunity (starting after the 2006 approval of the HPV vaccine in the US), may be partially responsible for this observed decrease in OPSCC incidence among young adults (14, 24). Additionally, smoking rates have been declining since the 1980s, especially among young adults. This decline may also contribute to the decreased incidence in this age group as tobacco use increases susceptibility to oral HPV infection (25, 26). Although HPV vaccine uptake rates steadily increased from 2008 to 2016 (53.6% vs. 65.1%), the Healthy People 2020 goal of vaccinating 80% of all teenagers 13-15 years old has not been met (27). Additional efforts are needed to improve HPV vaccination coverage among young girls and boys to reduce the future burden of HPV-related OPSCC.

Previous literature showed increasing trends in the incidence of HPV-related OPSCC among middle-aged and elder adults in the US (7–12). We also observed an increased incidence of HPV-related OPSCC in middle-aged and elder males and females, which is consistent with those findings (7–12). Data from SEER indicate that increasing trends in HPV-related OPSCC were primarily observed in middle-aged individuals and elders, particularly within recent years (7–9). In contrast, an international study by Chaturvedi et al. that examined the incidence of OPSCC using data from the Cancer Incidence in Five Continents database found increasing incidence in 7 out of 9 counties examined between the years of 1983 to 2002, with significantly stronger increases among patients <60 years old compared to patients ≥ 60 years old (10). Previous research has widely established that changes in HPV prevalence are the primary driver behind increased OPSCC incidence (3, 7–10, 28). High oral HPV infection rates, especially among males, for these age groups can partially explain the observed increase (29, 30). Trends in smoking may also be partially responsible for changes in HPV-related OPSCC incidence (25, 31).

Overall, our data show that HPV-related OPSCC was much more common in males. This likely reflects the higher oral HPV infection rates observed among men (29, 30). Among younger males, a significant inflection point in the trends of OSPCC incidence occurred in 2008, after which the incidence of OPSCC began to decrease. This did not occur among female adults. Among young females, the incidence of OPSCC decreased slightly but gradually during 2001-2018, which may be partly due to HPV vaccination, low prevalence of oral HPV infection (29, 30), and rising use of tobacco. Five-year survival rates also significantly improved among younger males, but not younger females, which may be due to hesitance to administer aggressive multimodality therapy and differences in utilization of definitive treatments. This may also explain why hazard ratios were

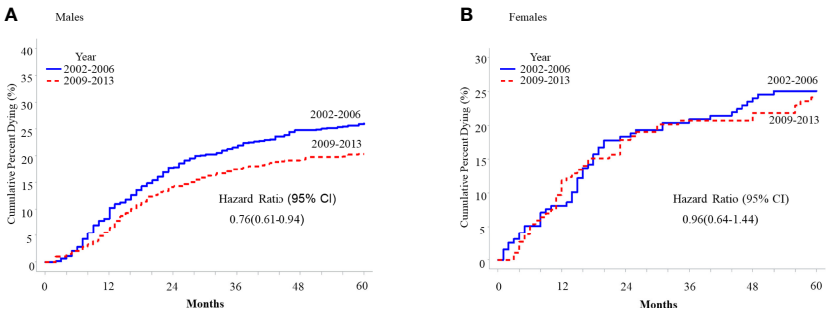

FIGURE 2 | Five-year cumulative probability of death from HPV-related oropharyngeal squamous cell carcinoma (OPSCC) among cancer patients 20-44 years old with HPV-related OPSCC, SEER 2001-2018, stratified by sex. **(A)** Males **(B)** Females.

significantly lower and survival was significantly improved among men in older age groups as well.

The findings of our study have important health implications. Our observed increasing trends in HPV-related OPSCC among middle-aged and elder males and females call for interventions to reduce risk factors for this type of cancer. Notable actionable risk factors include oral HPV infection (29, 30) and smoking (25, 26, 31). Therefore, avoiding high-risk sex behaviors and tobacco control remain the primary prevention methods to alleviate the burden of HPV-related OPSCC among the US adult population. Our observed sex-based disparities in OPSCC incidence and 5-year cancer survival rates also necessitate future mitigative actions. Such disparities could be reduced by taking measures to mitigate the rising tobacco use among women. Most encouragingly, the potential linkage between decreasing trends in the incidence of HPV-related OPSCC among young adults especially after the introduction of HPV vaccination in 2006 and the high HPV vaccination uptake among young girls and boys in the US indicates the effectiveness of the HPV vaccine.

One strength of our study is the quality of the data from the USCS database, itself comprised from both NPCR and SEER data. In addition to the NPCR/SEER data that cover a diverse cross-section of the entire US population, the USCS includes patient sociodemographics, cancer diagnosis date, and age. Nevertheless, our study has a few limitations. Since HPV infection status is not available for participants in USCS, we classified potentially HPV-related OPSCC based on anatomic site, rather than through direct assessment of HPV DNA-positivity (e.g., *via* p16 immunohistochemistry). Modern estimates of HPV DNA-positive tumor sites classified as HPV-related based on anatomic site are merely 70%; therefore, these anatomic site-based classifications may have led to the occasional misclassification (7). Based on 2003-2004 SEER data from 3917 OPSCC patients with known HPV status, 2903 (74.1%) were HPV positive (13). The data used in this study also lacked information on other risk factors for HPV-related OPSCC. Certain subgroup analyses, such as for sex, racial, and age groups, could not be conducted due to an insufficient number of cases of OPSCC in females. Our study also has the following limitations: potential misclassification bias, residual confounders, potential period effect, and birth cohort effect of the US population.

CONCLUSION

HPV-related OPSCC was much more common in males and is likely attributable to the higher oral HPV infection rates previously observed among men (29, 30). HPV-related OPSCC incidence declined among young adult (20–44) males and females during the vaccination era compared to the pre-vaccination era, suggesting that HPV vaccinations are beginning to reduce OPSCC burden. In contrast, the incidence of HPV-related OPSCC increased among vaccine-ineligible middle-aged (45–64) and elder (65+) males and females. Cancer-specific 5-year survival was significantly improved in young males but not in young females. Additional efforts are needed to improve HPV vaccination coverage in young girls and boys to further reduce the burden of HPV-related OPSCC in the US.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: the National Program for Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) databases (2001-2018).

ETHICS STATEMENT

This study did not involve human subjects and did not require approval by the Institutional Review Board of The University of Texas Medical Branch.

AUTHOR CONTRIBUTIONS

Study concept, methodology, data analyses, manuscript preparation, and funding (FG). Data analyses and manuscript preparation (MC). Manuscript preparation (MS). Study concept and manuscript preparation (BK). Study concept, methodology, data analysis, manuscript preparation, and funding (AB). All

authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.926555/full#supplementary-material

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Trends in incidence and mortality of esophageal cancer in China 1990–2019: A joinpoint and age-period-cohort analysis

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Background: The incidence and mortality trends of esophageal cancer (EC) remain unknown in China. This study aimed to describe the trend in incidence and mortality of EC in China.

Methods: We extracted age-standardized rates and numbers of EC in China for 1990–2019 from the Global Burden of Disease study 2019. The age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) were calculated to describe the trends, while the annual percentage of change and the average annual percent change (AAPC) were analyzed by the joinpoint regression analysis. The incidence and mortality data were analyzed *via* age-period-cohort model analysis.

Results: The ASIR and ASMR decreased slightly before 1999, then increased from 1999 to 2004, and decreased again thereafter, with overall AAPC values of –2.5 (–2.8, –2.1) for females and -0.9 (–1.1, –0.8) for males regarding incidence, with overall AAPC values of –3.1 (–3.3, –2.9) for females and –1.2 (–1.3, –1.1) for males regarding mortality. As a whole, the relative risk (RR) of EC increased with age in both females and males regarding incidence and mortality, except for the 80–84-year-old age group in females and the 85–89-year-old age group in males regarding incidence, where they began to decrease. The RR of EC increased with age in females and males regarding mortality, except for the 85–89-year-old age group in males. The time period showed a trend of first rising and then decreasing, and the RR of time period effect was lower in 2015 than that in 1990 in females regarding both incidence and mortality, whereas males showed a significant upward trend in both incidence and mortality. The birth cohort effect showed an overall downward trend.

Conclusions: The overall incidence and mortality of EC in China shows an increased and then decreased trend from 1990 to 2019. The AAPC decreased in incidence and mortality from 1990 to 2019. The RR of incidence and

mortality of EC in China is greatly affected by age in both sexes, by time period in male, we should be paid more attention to.

KEYWORDS

esophageal cancer, age-period-cohort model, joinpoint analysis, incidence trend, mortality trend

Introduction

The burden of cancer incidence and mortality is rapidly growing worldwide (1). Esophageal cancer is one of the leading causes of cancer death in the world (2, 3). As a whole, esophageal cancer (EC) ranked seventh in incidence (604,000 new cases) and sixth in mortality (544,000 deaths) in 2020 (3). China still has a heavy cancer burden as the largest developing country in the world (4). Although it may be due to economic growth and improved diets, the incidence of EC in China is in decline (3); however, overall trends may mask differences or veil underlying causes. In order to identify the causes of annual trends in incidence and mortality, it is necessary to examine the annual percent change.

An age-period-cohort model (APCM) is a popular analytical method in both sociological and epidemiological research (5, 6), which can enhance our understanding of incidence and mortality trends by disentangling age, time period, and birth-cohort effects (7), and has been used to analyze the quality and character of cancer prevalence trends. Li et al. used APCM analysis to observe time trends of esophageal and gastric cancer mortality in China from 1991 to 2009 (8). Li et al. explored the trends and risk factors of incidence and mortality in China during 2005-2015 (9).

In this study, we present results from the Global Burden of Disease (GBD) 2019 and provide an assessment of current trends in incidence and mortality of EC in China from 1990 to 2019 by using a joinpoint and age-period-cohort analysis. We hope that our findings can provide a reference for policy planning and contribute to improving cancer control measures in China.

Methods

Data sources

The esophageal cancer death number, incidence rate, mortality rate, and national population were obtained from the GBD 2019 study. The GBD study offers a comparative assessment of health loss caused by 328 diseases in 195 countries within 21 regions. Data on the EC were obtained from the Global Health Data Exchange, including individuals aged 20 to 94 years old, from 1990 to 2019, in China (http://ghdx.healthdata.org/gbd-results-tool). When the data were collected, double check was used. The 10th version International Classification of Diseases

codes C15-C15.9, Z85.01 were mapped to EC cancer from GBD 2019 study. Because the data of EC patients under the age of 20 years old was zero, we excluded this part of the data. The APCM analysis requires five-year intervals for each age group (10), and we excluded groups 95 years old and older.

Descriptive study

The age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) were adopted to evaluate the trends in China between 1990 and 2019. They were calculated according to a direct method based on the GBD 2019 China age-standardized population.

Trends analysis

Joinpoint regression was used to analyze trends in the age-standardized EC burden. The joinpoint regression program describes trends by connecting several different line segments at 'joinpoints' and identifying points where the linear slope of a trend changes in a statistically significant way over time (11). The slope of each line segment was expressed as annual percent change (APC) and average annual percent change (AAPC) with a best-fitting model (12). The APC represents the incidence and mortality rate of the change per year at different times, and the AAPC was a weighted average of the APCs, with the weights equal to the length of the joinpoint segment (11, 13). In this study, we used the APC and AAPC to describe the annual change in EC incidence and mortality rates from 1990 to 2019.

Joinpoint regression software developed by the National Cancer Institute (version 4.1.0) was used.

Age-period-cohort model analysis

The APCM is developed to reflect cancer incidence and mortality relative risks by estimating the age, time period, and birth cohort effects (14). Because of the period = age + cohort relationship, in this study, the rates of EC incidence and mortality were recoded into successive age groups (20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94), consecutive 5-year periods (1990, 1995, 2000, 2005, 2010, and 2015) and 20 birth cohorts (1900-1904, 1905-1909, 1910-1914, 1915-1919, 1920-1924, 1925-1929, 1930-1934, 1935-1939, 1940-1944, 1945-1949, 1950-1954, 1955-1959, 1960-1964, 1965-1969, 1970-1974, 1975-1979, 1980-1984, 1985-1989, 1990-1994, and 1995-1999). The APCM intrinsic estimator method presents estimated coefficients for the age, time period, and birth cohort effects, and these coefficients were used to calculate the RR (relative risk (RR) = exp (coef.)) (5). A value of $p < 0.05$ was considered statistically significant.

For data processing, Stata version 17.0 (StataCorp, College Station, TX, USA) was used. Bayesian information criterion, Akaike information criterion, and deviance were used to estimate the degree of model fit. R software was used for drawing (version 4.1.2).

Results

Descriptive analysis of incidence and mortality trends

Figure 1 shows trends of the ASIR for EC from 1990 to 2019 in China. As a whole, ASIR decreased slightly before 1999, then it gradually rose, peaking in 2004. Obviously, the increase was more pronounced in males, and then decreased markedly. The ASIR decreased from 20.97 in 1990 to 13.90 in 2019 in both sexes, from 13.94 in 1990 to 6.83 in 2019 in females, and from 28.70 in 1990 to 21.94 in 2019 in males per 100,000 persons. In Figure 2, the ASMR shows the same curve as in Figure 1; the ASMR decreased from 22.08 in 1990 to 13.15 in 2019 in both sexes, from 14.69 in 1990 to 5.92 in 2019 in females, and from 30.53 in 1990 to 21.69 in 2019 in males per 100,000 persons.

Figure 3 and Table 1 present the jointpoint analysis of trends in the ASIR of EC in China from 1990 to 2019. The joinpoint regression results show that the ASIR decreased from 1990 to 1998, rose from 1998 to 2004, and decreased again from 2004 to 2019 in both sexes, with overall AAPC values of −1.5 (−1.6, −1.3). In females, the ASIR decreased from 1990 to 1998, rose from 1998 to 2004, decreased from 2004 to 2016, and then rose again from 2016 to 2019. There were six trends in all, with overall AAPC values of −2.5 (−2.8, −2.1). In males, the ASIR had a similar trend as in females over time, but there were four trends in all, with overall AAPC values of −0.9 (−1.1, −0.8).

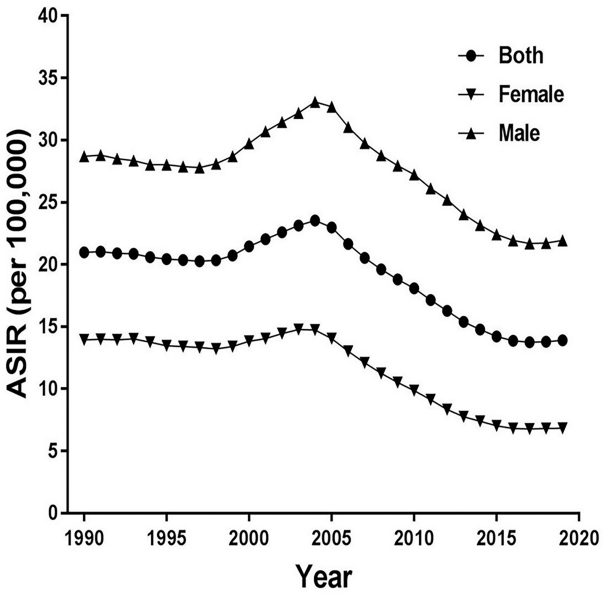

FIGURE 1
Trends of the age-standardized incidence rates (ASIR) for esophageal cancer from 1990 to 2019 in China.

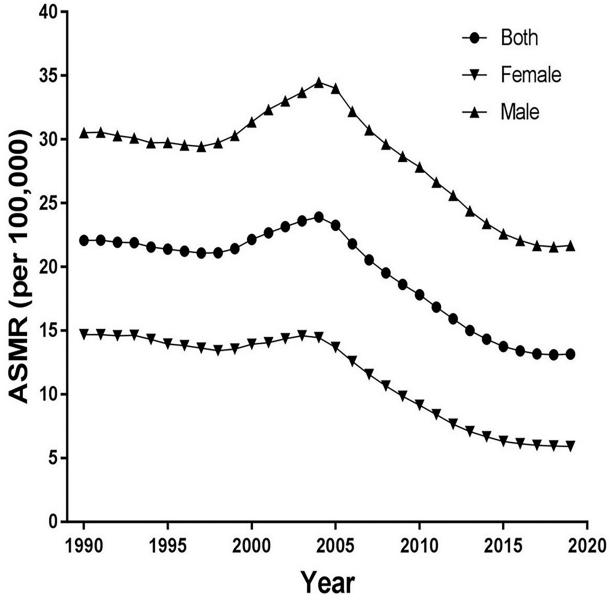

FIGURE 2
Trends of the age-standardized mortality rates (ASMR) for esophageal cancer from 1990 to 2019 in China.

Figure 4 and Table 2 present the joinpoint analysis of trends in the ASMR of EC in China from 1990 to 2019. The ASMR decreased from 1990 to 1998, rose from 1998 to 2004, and then decreased again from 2004 to 2019 in both sexes, with overall AAPC values of −1.8 (−1.9, −1.7). In females, the ASMR decreased from 1990 to 1998, rose from 1998 to 2004, and decreased again from 2004 to 2019. There were six trends in all, with overall AAPC values of −3.1 (−3.3, −2.9). In males, the ASMR decreased from 1990 to 1997, rose from 1997 to 2004, and then decreased again from 2004 to 2019, with overall AAPC values of -−1.2 (−1.3, −1.1).

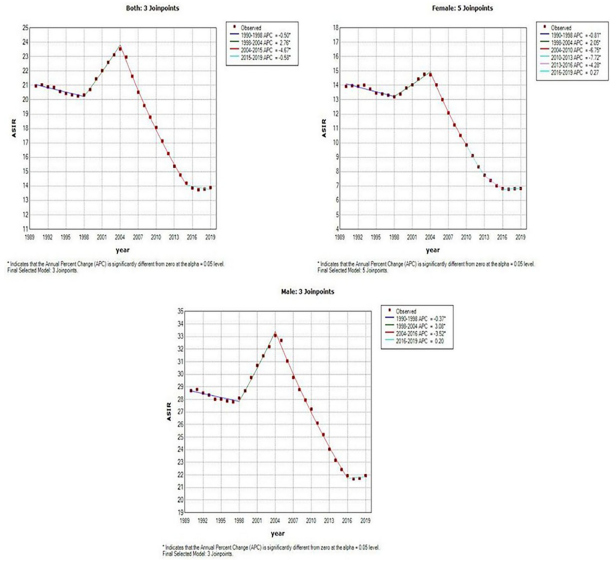

FIGURE 3
Joinpoint analysis of trends in the age-standardized incidence rates (ASIR) of Esophageal cancer.

TABLE 1 Joinpoint analysis of trends in age-standardized incidence rates (ASIR) of esophageal cancer in China, 1990–2019.

Segments	Both			Female			Male		
	Year	APC (95% CI)	AAPC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)
Trend 1	1990 - 1998	-0.5* (-0.7,-0.3)	–	1990 - 1998	-0.8* (-1,-0.6)	–	1990 - 1998	-0.4** (-0.6,-0.2)	–
Trend 2	1998 - 2004	2.8* (2.4,3.1)	–	1998 - 2004	2.1* (1.6,2.5)	–	1998 - 2004	3.1* (2.7,3.5)	–
Trend 3	2004 - 2015	-4.7* (-4.8,-4.6)	–	2004 - 2010	-6.7* (-7.2,-6.3)	–	2004 - 2016	-3.5* (-3.6,-3.4)	–
Trend 4	2015 - 2019	-0.6** (-1.1,-0.1)	–	2010 - 2013	-7.7* (-9.7,-5.7)	–	2016 - 2019	0.2 (-0.7,1.1)	–
Trend 5	–	–	–	2013 - 2016	-4.3** (-6.3,-2.2)	–	–	–	–
Trend 6	–	–	–	2016 - 2019	0.3 (-0.8,1.4)	–	–	–	–
AAPC	1990 - 2019	–	-1.5* (-1.6,-1.3)	1990 - 2019	–	-2.5* (-2.8,-2.1)	1990 - 2019	–	-0.9* (-1.1,-0.8)

APC, the annual percentage of change; AAPC, the average annual percent change; CI, confidence interval; *p<0.001, **p<0.05.

Age–period–cohort analysis

Age effect

Figure 5A shows the EC RR of incidence by gender. The RR of EC increased with age in both females and males, except for the 80-84-year-old age group in females and the 85–89-year-old age group in males, which began to show a reduction. Females aged 50–94 and males aged 45–94 are two risk groups with an RR > 1 in incidence (Table 3). Figure 6A shows the EC RR of mortality by gender. The risk of EC increased with age in females and males, except for the 85–89-year-old male age group. Females aged 50–94 and males aged 45–94 are two risk groups with an RR > 1 in mortality (Table 4).

Period effect

Figure 5B presents the RR of incidence, which rose in time period groups 1990 and 2000, decreased in time period groups 2000, 2005, 2010 and 2015, and group 2015 was lower than group 1990 in females. There is a continuing trend of growth in males, except for groups 2010 and 2015, which were higher than group 1990 (Figure 5B). Period groups 2000 and 2005 are two risk groups with an RR > 1 in females in incidence, but there are four time period groups (2000, 2005, 2010, and 2015) for males (Table 3). The time period effect pattern of RR was similar between incidence and mortality (Figure 6A). Period groups 1990, 1995, 2000, and 2005 are four risk groups with an RR > 1 in females regarding mortality, but 2000, 2005, 2010, and 2015 are another four groups with an RR > 1 in males (Table 4).

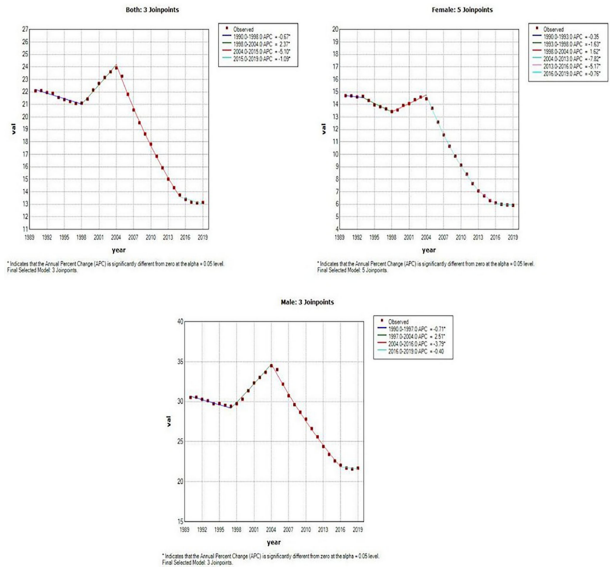

FIGURE 4
Joinpoint analysis of trends in the age-standardized mortality rates (ASMR) of Esophageal cancer.

TABLE 2 Joinpoint analysis of trends in age-standardized mortality rates (ASMR) of esophageal cancer in China, 1990–2019.

Segments	Both			Female			Male		
	Year	APC (95% CI)	AAPC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)
Trend 1	1990 - 1998	-0.7* (-0.8,-0.5)	–	1990 - 1993	-0.4 (-1.1,0.4)	–	1990 - 1997	-0.7* (-0.9,-0.5)	–
Trend 2	1998 - 2004	2.4* (2,2.7)	–	1993 - 1998	-1.6* (-2.1,-1.2)	–	1997 - 2004	2.5* (2.2,2.8)	–
Trend 3	2004 - 2015	-5.1* (-5.2,-5)	–	1998 - 2004	1.6* (1.3,1.9)	–	2004 - 2016	-3.8* (-3.9,-3.7)	–
Trend 4	2015 - 2019	-1.1* (-1.6,-0.6)	–	2004 - 2013	-7.8* (-8,-7.7)	–	2016 - 2019	-0.4 (-1.3,0.5)	–
Trend 5	–	–	–	2013 - 2016	-5.2* (-6.5,-3.8)	–	–	–	–
Trend 6	–	–	–	2016 - 2019	-0.8** (-1.5,-0.1)	–	–	–	–
AAPC	1990 - 2019	–	-1.8* (-1.9,-1.7)	1990 - 2019	–	-3.1* (-3.3,-2.9)	1990 - 2019	–	-1.2* (-1.3,-1.1)

APC, the annual percentage of change; AAPC, the average annual percent change; CI, confidence interval; *p<0.001, **p<0.05.

Cohort Effect

Figures 5C and 6C show the birth cohort RR of incidence and mortality in both sexes, respectively. Overall, both curves show a downward trend in incidence and mortality. In males, the 1900–1959 birth cohort showed a faster decline in incidence (Figure 5C) and the 1900–1964 birth cohort in mortality (Figure 6C), and then it tends to be stable. The 1900–1954 birth cohort is a risk group with an RR > 1 in incidence and mortality in both sexes (Tables 3 and 4).

Discussion

The global ASIR and ASMR of esophageal cancer have decreased over the past three decades, and the numbers of new EC cases and deaths and disability-adjusted life years have increased as a result of population growth and aging (2). Approximately 70% of cases occur in men, and there is a two-to-three-fold difference in incidence and mortality rates between the sexes (3). Since at least the early 1970s, vast areas of Asia

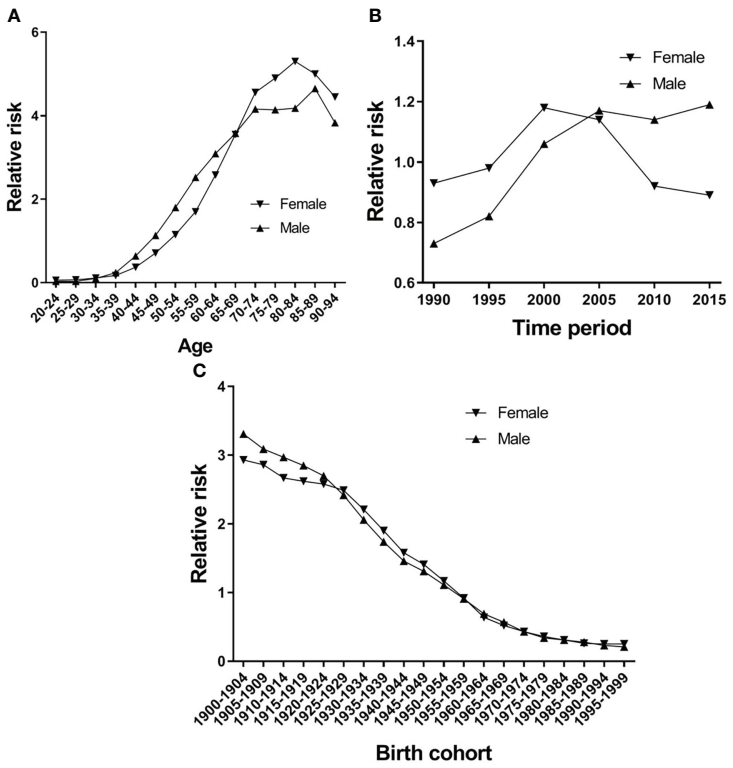

FIGURE 5
Esophageal cancer incidence relative risk due to **(A)** age; **(B)** period; and **(C)** cohort by using age-period-cohort model analysis with the intrinsic estimator period.

TABLE 3 Age–period–cohort (APC) model analysis results of esophageal cancer incidence in China.

Variables Case	Female Coef,95%CI	RR	Male Coef,95%CI	RR
Age				
20-24	-2.82* (-2.86,-2.79)	0.06	-3.62* (-3.66,-3.59)	0.03
25-29	-2.63* (-2.65,-2.6)	0.07	-3.39* (-3.42,-3.37)	0.03
30-34	-2.2* (-2.22,-2.17)	0.11	-2.32* (-2.33,-2.3)	0.1
35-39	-1.78* (-1.8,-1.76)	0.17	-1.41* (-1.42,-1.4)	0.24
40-44	-0.99* (-1.01,-0.98)	0.37	-0.45* (-0.46,-0.44)	0.64
45-49	-0.34* (-0.36,-0.33)	0.71	0.12* (0.11,0.13)	1.13
50-54	0.14* (0.13,0.15)	1.15	0.59* (0.58,0.59)	1.8
55-59	0.53* (0.52,0.54)	1.7	0.92* (0.92,0.93)	2.52
60-64	0.95* (0.94,0.95)	2.58	1.13* (1.12,1.13)	3.09
65-69	1.27* (1.26,1.27)	3.55	1.28* (1.27,1.28)	3.58
70-74	1.52* (1.51,1.52)	4.56	1.43* (1.42,1.43)	4.16
75-79	1.59* (1.58,1.59)	4.9	1.42* (1.42,1.43)	4.14
80-84	1.67* (1.66,1.68)	5.3	1.43* (1.42,1.44)	4.18
85-89	1.61* (1.6,1.62)	5	1.54* (1.53,1.54)	4.65
90-94	1.49* (1.48,1.51)	4.45	1.34* (1.33,1.36)	3.83
Period				
1990	-0.07* (-0.08,-0.07)	0.93	-0.32* (-0.32,-0.31)	0.73
1995	-0.02* (-0.02,-0.02)	0.98	-0.2* (-0.21,-0.2)	0.82
2000	0.17* (0.17,0.17)	1.18	0.06* (0.06,0.06)	1.06
2005	0.13* (0.13,0.13)	1.14	0.16* (0.16,0.16)	1.17
2010	-0.08* (-0.09,-0.08)	0.92	0.13* (0.13,0.13)	1.14
2015	-0.12* (-0.13,-0.12)	0.89	0.17* (0.17,0.18)	1.19
Cohort				
1900-1904	1.07* (1.03,1.11)	2.93	1.2* (1.14,1.26)	3.31
1905-1909	1.05* (1.03,1.07)	2.86	1.13* (1.11,1.15)	3.09
1910-1914	0.98* (0.97,1)	2.67	1.09* (1.07,1.1)	2.97
1915-1919	0.96* (0.95,0.98)	2.62	1.05* (1.04,1.06)	2.85
1920-1924	0.95* (0.94,0.96)	2.58	0.99* (0.98,1)	2.7
1925-1929	0.91* (0.9,0.92)	2.49	0.88* (0.88,0.89)	2.42
1930-1934	0.79* (0.78,0.8)	2.21	0.72* (0.71,0.73)	2.06
1935-1939	0.64* (0.63,0.65)	1.9	0.56* (0.55,0.56)	1.74
1940-1944	0.46* (0.45,0.47)	1.58	0.38* (0.37,0.39)	1.46
1945-1949	0.34* (0.33,0.35)	1.41	0.27* (0.26,0.28)	1.31
1950-1954	0.16* (0.15,0.17)	1.17	0.11* (0.1,0.12)	1.11
1955-1959	-0.08* (-0.1,-0.07)	0.92	-0.09* (-0.1,-0.08)	0.91
1960-1964	-0.44* (-0.45,-0.42)	0.64	-0.37* (-0.38,-0.35)	0.69
1965-1969	-0.66* (-0.67,-0.64)	0.52	-0.57* (-0.58,-0.56)	0.57
1970-1974	-0.85* (-0.86,-0.83)	0.43	-0.84* (-0.86,-0.83)	0.43
1975-1979	-1.01* (-1.04,-0.99)	0.36	-1.09* (-1.11,-1.07)	0.34
1980-1984	-1.16* (-1.2,-1.13)	0.31	-1.16* (-1.18,-1.13)	0.31
1985-1989	-1.34* (-1.39,-1.3)	0.26	-1.26* (-1.29,-1.23)	0.28
1990-1994	-1.38* (-1.44,-1.32)	0.25	-1.46* (-1.51,-1.41)	0.23
1995-1999	-1.4* (-1.52,-1.28)	0.25	-1.54* (-1.64,-1.44)	0.21
AIC	91.7		69.52	
BIC	6952.55		4889.83	
Deviance	7186.54		5123.82	

*p<0.05. BIC, Bayesian information criterion; AIC, Akaike's information criterion.

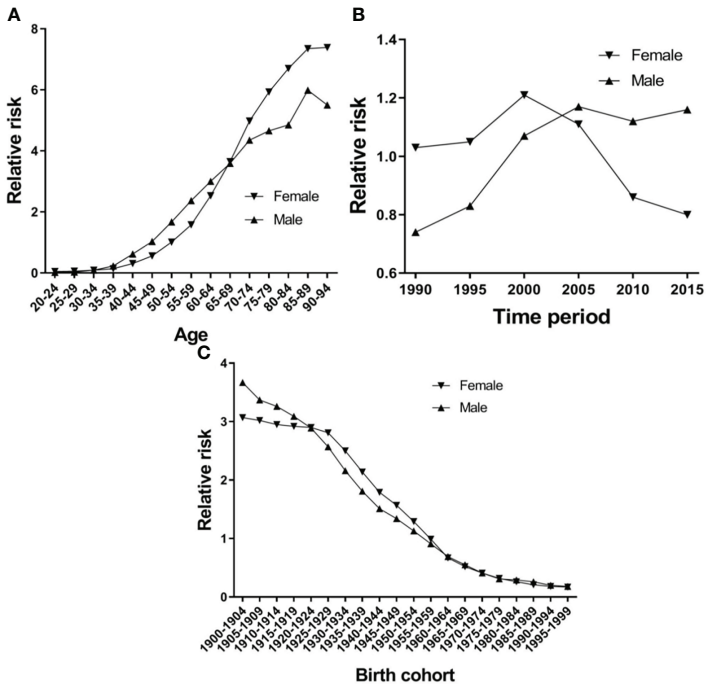

FIGURE 6
Esophageal cancer mortality relative risk due to **(A)** age; **(B)** period; and **(C)** birth by using age-period-birth model analysis with the intrinsic estimator period.

have been known to have high rates of esophageal cancer extending from China and Mongolia to the Caspian Sea (2, 15). More than 90% of EC cases in this part of the world are of the esophageal squamous cell carcinoma type (16, 17). Case-cohort and control studies have found that consumption of hot tea, opium use, low intake of fresh fruits and vegetables, exposure to polycyclic aromatic hydrocarbons, indoor air pollution, low socio-economic status, and lack of access to piped water are also associated with a higher risk of esophageal squamous cell carcinoma (18–20). Age, gender, and area were independent risk factors for EC incidence (5). However, few studies have examined the trends in age-period-cohort incidence and mortality rates of EC.

This study presented the trends in incidence and mortality of EC in China. The trends of the ASIR and ASMR of EC showed a slight decrease from 1990 to 1997. However, this trend reversed in 1998 and peaked in 2004, which may have been driven by rapid economic transitions, urbanization, and political reform. Based on previous studies, we can say that China's urbanization process has been developing faster than its economic growth since 2004 (19, 21). Besides, since 2000, a national screening programme has become available at 17 sites in Hebei Province (22). The "Four Frees and One Care" policy was announced by the Chinese government in 2003 (23). Slight increases were observed in EC ASMR from 1999 to 2004, which might be mainly associated with the early diagnosis and early treatment of esophageal cancer in rural areas. After that, both ASIR and ASMR decreased, which may be attributed to improved medical care. The joinpoint regression analysis showed that there are similar trends in the ASIR and ASMR in both sexes (six trends in females, four trends in males; Tables 1 and 2), although overall AAPC values < 0 for both genders, what we need to pay attention to is the APC > 0 from 2016 to 2019 and its indication of an upward trend. This situation requires effective measures to reduce the increasing incidence and mortality rate of EC in China.

Age, period, and cohort effects affect the risks of disease incidence and mortality in specific ways, and this analysis can provide information about the underlying causes of cancer incidence and death (14). There have been several studies using APCM to analyze the incidence or mortality of GBD diseases (5–8, 10, 14). Our study found that the RR remarkably increased with advancing age; specifically, the RR began to increase in the 35–39 age group, continued to rise until age 80–84 in females and 85–89 in males, when it began to decline. The cancer burden among adults 85 years and older is relatively unknown (24). In our opinion, 85 and older have not received sufficient attention. In the treatment of older patients, there are numerous comorbidities, functional declines, cognitive impairment, and undertreatment. Besides, we did not include

TABLE 4 Age–period–cohort (APC) model analysis results of esophageal cancer mortality in China.

Variables Case	Female Coef,95%CI	RR	Male Coef,95%CI	RR
Age				
20-24	-3.07* (-3.12,-3.02)	0.05	-3.88* (-3.92,-3.84)	0.02
25-29	-2.84* (-2.88,-2.8)	0.06	-3.59* (-3.62,-3.56)	0.03
30-34	-2.36* (-2.39,-2.33)	0.09	-2.43* (-2.45,-2.41)	0.09
35-39	-1.96* (-1.99,-1.94)	0.14	-1.49* (-1.5,-1.48)	0.23
40-44	-1.16* (-1.18,-1.14)	0.31	-0.48* (-0.49,-0.47)	0.62
45-49	-0.57* (-0.59,-0.56)	0.56	0.03* (0.02,0.04)	1.03
50-54	0.01 (0,0.02)	1.01	0.51* (0.51,0.52)	1.67
55-59	0.46* (0.45,0.46)	1.58	0.86* (0.86,0.87)	2.37
60-64	0.93* (0.92,0.93)	2.53	1.1* (1.09,1.1)	3
65-69	1.29* (1.29,1.3)	3.65	1.28* (1.27,1.28)	3.59
70-74	1.6* (1.6,1.61)	4.98	1.47* (1.47,1.48)	4.35
75-79	1.78* (1.77,1.79)	5.93	1.54* (1.53,1.54)	4.66
80-84	1.9* (1.89,1.91)	6.7	1.58* (1.57,1.59)	4.85
85-89	2* (1.98,2.01)	7.35	1.79* (1.78,1.8)	5.99
90-94	2* (1.98,2.01)	7.39	1.71* (1.69,1.72)	5.5
Period				
1990	0.03* (0.02,0.04)	1.03	-0.3* (-0.31,-0.3)	0.74
1995	0.05* (0.04,0.05)	1.05	-0.19* (-0.19,-0.19)	0.83
2000	0.19* (0.19,0.2)	1.21	0.07* (0.07,0.07)	1.07
2005	0.11* (0.1,0.11)	1.11	0.16* (0.15,0.16)	1.17
2010	-0.15* (-0.16,-0.15)	0.86	0.12* (0.11,0.12)	1.12
2015	-0.23* (-0.23,-0.22)	0.8	0.15* (0.15,0.15)	1.16
Cohort				
1900-1904	1.12* (1.09,1.16)	3.07	1.3* (1.25,1.35)	3.67
1905-1909	1.11* (1.09,1.13)	3.02	1.22* (1.2,1.23)	3.37
1910-1914	1.08* (1.07,1.1)	2.95	1.18* (1.17,1.2)	3.26
1915-1919	1.07* (1.06,1.08)	2.92	1.13* (1.12,1.14)	3.09
1920-1924	1.07* (1.05,1.08)	2.9	1.06* (1.05,1.07)	2.89
1925-1929	1.03* (1.02,1.05)	2.81	0.94* (0.94,0.95)	2.57
1930-1934	0.92* (0.91,0.93)	2.5	0.77* (0.76,0.78)	2.16
1935-1939	0.76* (0.75,0.77)	2.14	0.59* (0.58,0.6)	1.81
1940-1944	0.58* (0.57,0.59)	1.79	0.41* (0.4,0.42)	1.51
1945-1949	0.45* (0.44,0.47)	1.57	0.29* (0.28,0.3)	1.34
1950-1954	0.26* (0.24,0.27)	1.29	0.12* (0.11,0.13)	1.13
1955-1959	-0.01 (-0.03,0.01)	0.99	-0.09* (-0.1,-0.08)	0.91
1960-1964	-0.39* (-0.42,-0.37)	0.67	-0.38* (-0.39,-0.36)	0.69
1965-1969	-0.66* (-0.68,-0.63)	0.52	-0.6* (-0.61,-0.58)	0.55
1970-1974	-0.9* (-0.92,-0.87)	0.41	-0.9* (-0.91,-0.88)	0.41
1975-1979	-1.13* (-1.16,-1.09)	0.32	-1.16* (-1.18,-1.14)	0.31
1980-1984	-1.33* (-1.38,-1.28)	0.26	-1.24* (-1.27,-1.22)	0.29
1985-1989	-1.58* (-1.65,-1.52)	0.21	-1.37* (-1.4,-1.33)	0.26
1990-1994	-1.69* (-1.78,-1.6)	0.18	-1.59* (-1.66,-1.53)	0.2
1995-1999	-1.77* (-1.96,-1.58)	0.17	-1.7* (-1.83,-1.57)	0.18
AIC	69.8		67.37	
BIC	5000.48		4700.62	
Deviance	5234.47		4934.61	

*p<0.05. BIC, Bayesian information criterion; AIC, Akaike's information criterion.

the 95 + age group, so we cannot predict how the curve continues. All of these factors may be related to China's aging transition and contribute to the increasing age effect in EC incidence and mortality in older people in China. Period effects are often influenced by a complicated set of environmental factors and historical events, such as epidemics of infectious diseases and socio-economic development (25). Drinking alcohol and smoking tobacco are considered to be important risk factors for EC (26). The RR trend of time period between males and females is different in China, smoking tobacco and alcohol drinking might be associated with the inconsistent results. In this study, females did not seem to be affected by period effects, and the RR continued to rise in incidence and mortality in males by period. Cohort effects in EC incidence and mortality showed continuously decreasing trends. The birth cohort showed a faster decline in incidence and mortality in males, after which it tends to be stable in both sexes. One reason for this was that more of the later cohorts had an improved awareness of health and disease prevention and had received a good education compared to the earlier cohorts (27).

There are some limitations to this study. First, the APCM is a descriptive analysis that use a community as a unit of observation and analysis, which could lead to ecological fallacies, the results are not necessarily valid for individuals. Second, the APCM of estimated parameters can only provide evidence for etiology studies. Third, the study could not estimate trends for the incidence and mortality rate in both rural and urban China, owing to insufficient data. The epidemiology of EC in rural and urban areas needs to be analyzed in the future.

Conclusion

The overall incidence and mortality of esophageal cancer in China shows an increased and then decreased trend from 1990 to 2019, and the AAPC was decreased in incidence and mortality from 1990 to 2019. The RR of incidence and mortality of esophageal cancer increased with age and time period and decreased with birth cohort. Therefore, more effective measures need to be taken to enhance the protection of the elderly, who are at particularly high risk.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: http://ghdx.healthdata.org/gbd-results-tool.

Author contributions

FL wrote the manuscript. ZW and JZ conceived the study and provided guidance. HSL and XS collected and analyzed data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.887011/full#supplementary-material

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The association between outdoor air pollution and lung cancer risk in seven eastern metropolises of China: Trends in 2006-2014 and sex differences

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There is a positive association between air pollution and lung cancer burden. This study aims to identify and examine lung cancer risks and mortality burdens associated with air pollutants, including PM_{10}, NO_2 and SO_2, in seven eastern metropolises of China. The study population comprised a population from seven eastern metropolises of China. The yearly average values (YAV, $\mu g/m^3$) of the PM_{10}, NO_2 and SO_2 levels were extracted from China Statistical Yearbook (CSYB) for each selected city from 2006 to 2014. Data collected in the China Cancer Registry Annual Report (CCRAR) provide lung cancer incidence and mortality information. A two-level normal random intercept regression model was adopted to analyze the association between the lung cancer rates and individual air pollutant concentration within a five-year moving window of past exposure. The yearly average values of PM10, SO2 and NO2 significantly decreased from 2006 to 2014. Consistently, the male age-adjusted incidence rate (MAIR) and male age-adjusted mortality rate (MAMR) decreased significantly from 2006 to 2014.Air pollutants have a lag effect on lung cancer incidence and mortality for 2-3 years. NO2 has the significant association with MAIR (RR=1.57, 95% CI: 1.19-2.05, p=0.002), MAMR (RR=1.70, 95% CI: 1.32-2.18, p=0.0002) and female age-adjusted mortality rate (FAMR) (RR=1.27, 95% CI: 1.08-1.49, p=0.003). Our findings suggested that air pollutants may be related to the occurrence and mortality of lung cancer. NO2 was significantly associated with the risk of lung cancer, followed by SO2. Air pollutants have the strongest lag effect on the incidence and mortality of lung cancer within 2-3 years.

KEYWORDS

outdoor air pollution, lung cancer, PM10, SO2 (sulphur dioxide), NO2

Background

Lung cancer is one of the most common cancers, causing nearly one in five cancer deaths and approximately 1.59 million deaths annually worldwide (1, 2) and China bears the heaviest burden of disease associated with lung cancer (3). China has the largest number of tracheal, bronchus, and lung (TBL) cancer deaths with 757,171 (887,752 – 638,741), accounting for 50% of the global TBL cancer deaths (3). Lung cancer is the result of a constellation of potential risk factors, including tobacco use, environmental factors and genetic predisposition (4, 5). Among these, smoking has been firmly established as the leading cause (2, 5). Accordingly, along with early-stage diagnosis and improved treatment, interventions have partly focused on the reduction of tobacco use, which has made great sense for preventing lung cancer (6). Additionally, promising approaches are identifying other modifiable determinants of lung cancer risks and a modifiable determinant of emerging interest is ambient air pollution (1), which was classified a group I carcinogen to humans by the International Agency for Research on Cancer (IARC) (7).

The high prevalence of air pollutants might be responsible for the increased incidence of lung cancer in the last decades (8). Urbanization and industrialization in China come at the cost of environmental pollution and air pollution is the major environmental hazard in urban areas. The distribution area of haze in China has reached 130000 square kilometers (9). Ambient air pollution represents a complex mixture of a broad range of carcinogenic and mutagenic substances (10). Pollution mix varies considerably from place to place, and people are exposed to different cocktails of pollutants across different cities (11). Among all air pollutants, the most commonly monitored are particulate matter (PM), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) (12).

A growing body of evidence indicates that ambient air pollutants pose a range of adverse effects on the mortality and morbidity of lung cancer (13–16). Several mechanisms have been suggested to explain the effect of air pollutants on cancer risk, such as chronic systemic inflammation, oxidative stress and DNA damage in tissues (10, 17–20). Results of several epidemiological studies have shown higher risks for lung cancer in association with various measures of air pollution (8, 21–23).

In a survey commissioned by Cancer Research, 35% of adults chose cancer as their most feared health problem, leading all other problems by a considerable margin (24). Thus, cancer as one of the major health conditions worsened by pollution exposure may hold particular sway with the public. Given the ubiquity of air pollution exposure and the enormous public health burden of lung cancer, we conducted a population-based retrospective study in seven cities in China, which differ in terms of pollutant concentrations, to assess whether air pollution exposure is associated with incident lung cancer and lung cancer-related mortality. The study aims to identify and examine lung cancer risks and mortality burdens associated with air pollutants including PM_{10}, NO_2 and SO_2, in China. The association between lung cancer burden and air pollution may shift public perceptions and ultimately help to promote policy development on air quality.

Methods

Air pollution data sources

We conducted the analysis using the database from China Statistical Yearbook (CSYB, National Bureau of Statistics) and the National Department of Environment (NDE). The annual concentrations of PM_{10}, NO_2 and SO_2 were reported at the regulatory air pollution monitoring sites. In this study, annual air pollutants data from seven cities were retrospectively collected for consecutive nine years from 2006 to 2014. According to the relevant regulations of the Chinese government, the locations of the air pollutant monitoring stations were far away from traffic and industrial pollution sources. Therefore, their records were not affected by the local pollution sources, buildings, large-scale emissions such as coal, boilers or incineration plants. The monitoring data of these stations reflected the average level of the urban air pollution in China. There was no missing data for the selected seven cities from 2006 to 2014.

Study population

The study population comprised urban residents in seven cities, respectively located in the Beijing-Tianjing-Hebei region (Beijing), the Yangtze River Delta region (Shanghai and Hangzhou), the Pearl River Delta region (Guangzhou), the Northeast region (Shenyang and Harbin) and the Central eastern region (Wuhan). These cities were chosen because they represented the Northeast Plain, the North Plain, the middle and lower reaches of the Yangtze River Plain, and the Pearl River delta plain. Most of them are located in the coastal areas of China, with the same or similar longitudes. They are all located in the plain areas with similar altitudes, representing different

Abbreviations: PM, particulate matter; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CSYB, China Statistical Yearbook; NDE, National Department of Environment; YAV, yearly average values; CCRAR, Chinese Cancer Registration Annual Report; CIR, crude incidence rate; CMR, crude mortality rate; MAIR, male age-adjusted incidence rate; FAIR, female age-adjusted incidence rate; MAMR; male age-adjusted mortality rate; FAMR, female age-adjusted mortality rate.

haze areas in the north and south of China. More importantly, there are approximately 100 million people living and working in these seven cities, which are highly representative of Chinese metropolises' population.

Air pollutant variables

The yearly average values (YAV, $\mu g/m^3$) of PM_{10}, NO_2 and SO_2 levels from 2006 to 2014 were extracted from CSYB. Since the tumorigenesis process always takes several years, in this study a five-year moving window of past exposure was taken into consideration for each pollutant. The YAVs of PM_{10}, NO_2 and SO_2 in the 5 years preceding the outcome assessment were candidate variables for evaluating the effect of air pollutants on the lung cancer incidence and lung cancer-related mortality.

Outcome measurements

Incidence (mortality) just measures new cases (deaths) of a disease that develop over a period of time without considering the denominator population. Incidence (mortality) rate is a measure of how quickly cases (deaths) of a disease of interest occurs, which reflects the speed of transition from disease-free (alive) to affected state (dead). We obtained the information of annual lung cancer incidence rate and mortality rate in selected cities from China Cancer Registry Annual Report (CCRAR) published by the National Cancer Registry Center (25–33). The annual lung cancer-related statistics included the crude incidence rate (CIR), crude mortality rate (CMR), male age-adjusted incidence rate (MAIR), female age-adjusted incidence rate (FAIR), male age-adjusted mortality rate (MAMR) and female age-adjusted mortality rate (FAMR). The detailed data collection and quality evaluation methods were referenced in the annual reports. There is no missing data for the selected cities from 2006 to 2014.

Statistical analysis

All the selected cities except the northeastern region are at the top of China of economic development and have developed their economies mainly through trade, service or technology rather than industry. Besides, people who live in industrialized cities and cosmopolitan cities like Shanghai receive different air pollution levels, types and compositions, so the differences must be considered. In this study, a two-level random intercept regression model was developed to figure out the overall trend, the difference between cities, and explain the variability in the air pollution trend among cities.

A two-level normal random intercept regression model was adopted to analyze the association between pollutant concentrations within the 5 years preceding the outcome assessment and annual lung cancer-related statistics, including CIR, CMR, MAIR, MAMR, FAIR and FAMR. A random intercept model is also known as a two-level variance component model: $y_{ij}=\mu+\theta_i+\beta x_{ij}+\epsilon_{ij}, \theta_i \sim N(0,\tau^2)$, $\epsilon_{ij} \sim N(0,\sigma^2)$, where μ represents the overall intercept (grand mean), θ_i indicates the difference between the mean of city i and the grand mean, β is the vector of coefficients that do not vary between groups, x_{ij} indicates the fixed variables (e.g, 5-year prior NO_2). Here, the estimate of β represents the effect of air pollutions (x_{ij}), which is calculated by the random intercept model (different cities are supposed to have different intercept with a mean of μ and a variance of θ_i. ϵ_{ij} represents the residual error, τ^2 is the heterogeneity variance that represented the between-city variability in the intercept, and σ^2 is the residual variance that represented the within-city variability in the residuals. The intraclass correlation $\rho = {\tau^2}/{(\tau^2+\sigma^2)}$ measured the degree of similarity among same-city observations compared to the residual error σ^2. The heterogeneity τ^2 controlled the amount of shrinkage and how much information to borrow across cities. If the between-city variance τ^2 was not considered, the standard error would be inflated and the p-value became too large. Therefore, compared to fixed estimates, the random effects estimators were more precise and minimize the total mean-square error (MSE). Statistical analyses were conducted by using R3.3.2 software. All tests of hypotheses were two-tailed and conducted at a significance level of 0.05.

Results

According to CCRAR, the trend of the crude lung cancer incidence rate (CIR) and crude mortality rate (CMR) increased significantly from 2006 to 2014 (CIR: RR = 7.46, 95% CI: 3.82-14.59, p<0.0001; CMR: RR = 4.31, 95% CI: 2.59-7.10, p<0.0001; Table 1). However, when stratified by gender and adjusted for age, the female age-adjusted mortality rate (FAMR) and female age-adjusted incidence rate (FAIR) had no significant trend from 2006 to 2014, while the male age-adjusted incidence rate (MAIR) and male age-adjusted mortality rate (MAMR) decreased significantly from 2006 to 2014 (MAIR: RR = 0.50, 95% CI: 0.30-0.84, p=0.01; MAMR: RR =0.51, 95% CI: 0.32-0.81, p=0.006, respectively, Table 1).

Figure 1 shows the illustrative yearly curves for the city specific-CIRs, CMRs, MAIRs, MAMRs, FAIRs and FAMRs from 2006 to 2014. As for the overall trends of the seven cities (red solid line), the CIR and CMR had an increased trend, while the MAIR and MAMR had a decreased trend. From 2006 to 2014, industrial cities such as Shenyang (red dash) and Harbin (green dash) had higher values for the CIR, CMR, MAIR, MAMR, FAIR and FAMR. In particular, Shenyang had the highest risks of lung cancer. Beijing and Shanghai had the lowest MAIR and MAMR. Wuhan had the lowest FAIR, and Shanghai had the lowest

TABLE 1 The integrated year trend of lung cancer risks in seven Chinese cities.

Measurements	Year trend (2006-2014)	
	RR (95% CI)	P value
CIR	7.46 (3.82, 14.59)	<0.0001
CMR	4.31 (2.59, 7.10)	<0.0001
MAIR	0.50 (0.30, 0.84)	0.01
MAMR	0.51 (0.32, 0.81)	0.006
FAIR	0.91 (0.68, 1.23)	0.55
FAMR	0.77 (0.59, 1.01)	0.06

RR represents rate ratio: the ratio of the incidence and mortality rate at one-unit increase of numeric variable versus the incidence and mortality rate at baseline. P value was calculated by using the two-level random intercept regression analysis. CIR, crude incidence rate; CMR, crude mortality rate; MAIR, male age-adjusted incidence rate; FAIR, female age-adjusted incidence rate; MAMR, male age-adjusted mortality rate; FAMR, female age-adjusted mortality rate.

TABLE 2 The integrated year trend of PM_{10}, SO_2 and NO_2 in seven Chinese cities.

Measurements	Year trend (2006-2014)	
	β coefficients (95% CI)	P value
PM_{10}	-1.47 (-0.53, -2.40)	0.003
SO_2	-2.56 (-3.51, -1.61)	<0.0001
NO_2	-0.59 (-1.04, -0.13)	0.015

β coefficients of the random intercept model [$y_{ij}=\mu+\theta_i+\beta x_{ij}+\epsilon_{ij}, \theta_i \sim N(0,\tau^2)$, $\epsilon_{ij} \sim N(0,\sigma^2)$] represented the yearly trend (x_{ij}) of pollutants (y_{ij}). Negative β coefficient suggested a decreasing year trend.

FAMR. In 2014, both the CIR and CMR in Beijing, Hangzhou and Guangzhou were lower than those in Shenyang. These findings suggested that the urban dwellers in Shenyang might have a higher risk of lung cancer than those in other large nonindustrial cities.

The yearly trends in all these air pollutants significantly decreased from 2006 to 2014 (PM_{10}: estimated coefficient = -1.47, 95% CI: -0.53,-2.40, p=0.003; SO_2: estimated coefficient = -2.56, 95%CI: -3.51, -1.61, p<0.0001; NO_2: estimated coefficient = -0.59, 95% CI: -1.04, -0.13, p=0.015; Table 2). As shown in Figure 2, the air pollutants PM_{10}, SO_2 and NO_2 had a decreasing trend from 2006 to 2014, while there was a peak in 2013, especially for SO_2 and NO_2 in Shenyang. The annual trends of the air pollutants were consistent with the annual trend of MAIR, MAMR and FAMR, but not for CIR and CMR, suggesting a potential correlation of the air pollutants with lung cancer-related MAIR, MAMR and FAMR.

We further investigated the potential effects of the air pollutants within a 5-year moving window of past exposure on lung cancer. The forest plot of the association between the concentrations of PM_{10}, SO_2, NO_2 0-5 year (s) before and CIR, CMR of lung cancer was shown in Figure 3. As shown in Supplementary Table 1, SO_2 exposure 4 years before, 2 years before and 1 year before and during the present year, PM_{10} exposure 3 years before and 2 years before, and NO_2 exposure 1 year before seemed to be protective factors for the lung cancer CIR. PM_{10} exposure 2 years before, NO_2 exposure 1 year and 2 years before, SO_2 exposure 1 year before and during the present

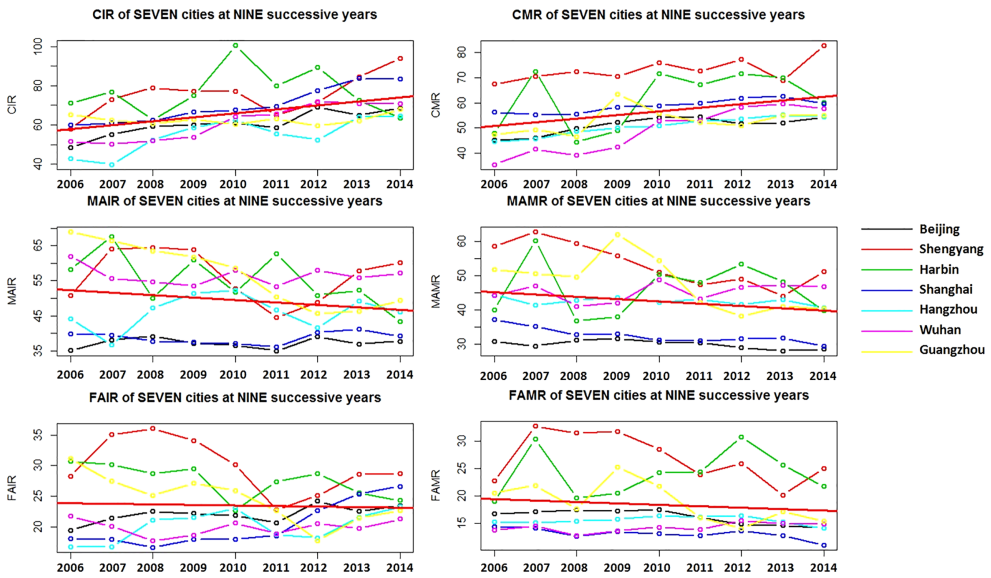


FIGURE 1
Year trends of lung cancer incidence and mortality in the seven selected cities. The Y-axis (%) was fitted with data range. The red bold line represented the estimated year trend based on integrated regression of seven cities.

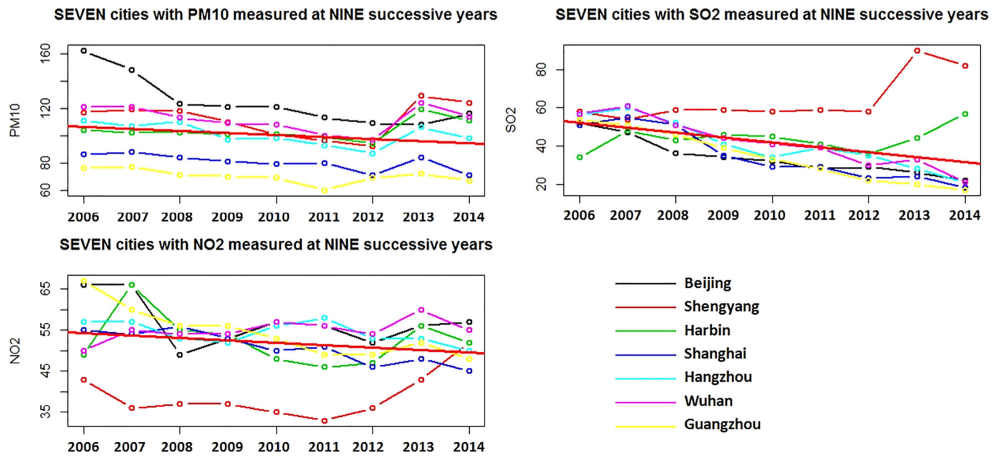


FIGURE 2
Year trends of air pollutants PM_{10}, SO_2 and NO_2 in seven selected cities. The Y-axis (%) was fitted with data range. The red bold line represented the estimated year trend based on integrated regression of seven cities.

year seemed to be protective factors for the lung cancer CMR. However, from common sense, air pollutants should be harmful to health. Because the lung cancer burden was heavy among the aging population, thus it would be not practicable to delineate the relationship between air pollution and lung cancer incidence and mortality without age-adjustment. Moreover, the time-trends of air pollutants and the age-adjusted statistics for MAIR, MAMR, FAIR and FAMR consistently decreased from 2006 to 2014, suggesting a positive correlation between air pollution and cancer burden.

The forest plot of the association between the concentrations of PM_{10}, SO_2, NO_2 0-5 year (s) before and FAIR, FAMR of lung cancer was shown in Figure 4. Supplementary Table 2 demonstrated the significant risky air pollution for FAMR. The

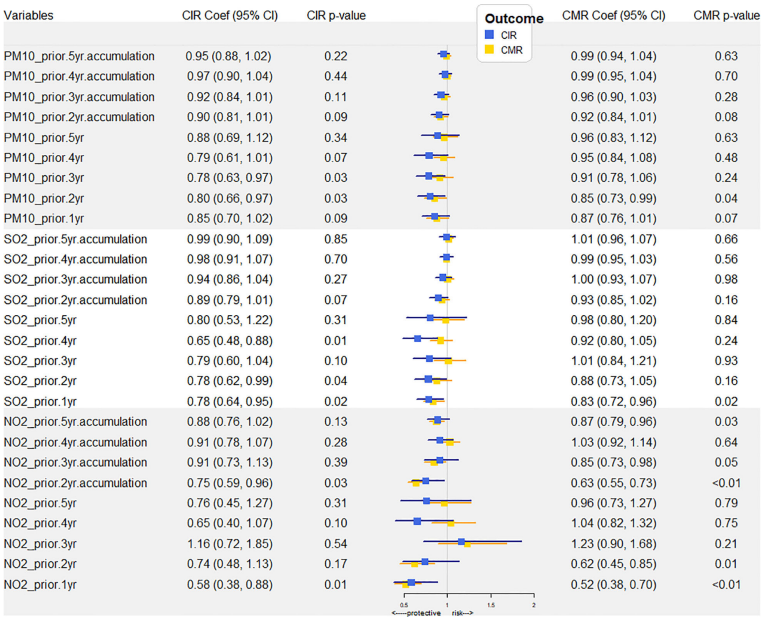
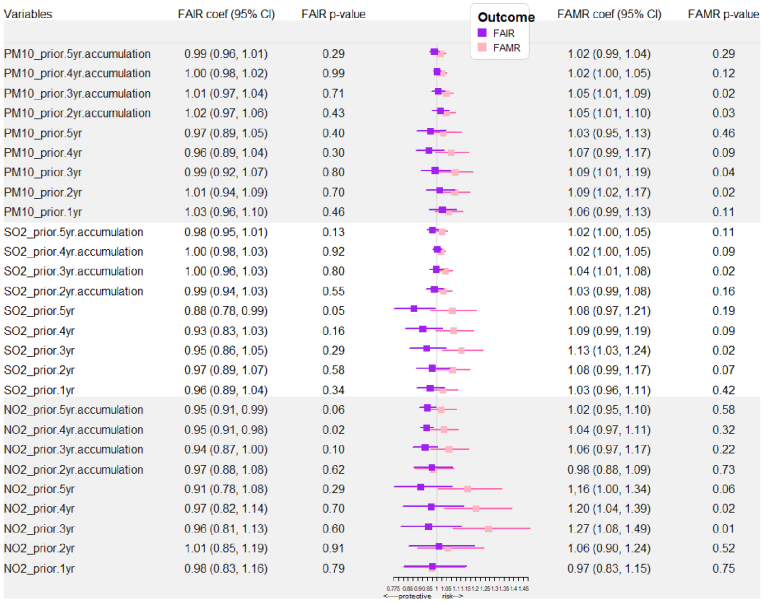


FIGURE 3
Air pollutant exposure-related RRs of CIR and CMR with a 5-year moving window. YAV, yearly average values (μg/m^3); RR, risk ratio (with 95% CI). CIR, crude incidence rate; CMR, crude mortality rate.



Variables	FAIR coef (95% CI)	FAIR p-value	FAMR coef (95% CI)	FAMR p-value
PM10_prior.5yr.accumulation	0.99 (0.96, 1.01)	0.29	1.02 (0.99, 1.04)	0.29
PM10_prior.4yr.accumulation	1.00 (0.98, 1.02)	0.99	1.02 (1.00, 1.05)	0.12
PM10_prior.3yr.accumulation	1.01 (0.97, 1.04)	0.71	1.05 (1.01, 1.09)	0.02
PM10_prior.2yr.accumulation	1.02 (0.97, 1.06)	0.43	1.05 (1.01, 1.10)	0.03
PM10_prior.5yr	0.97 (0.89, 1.05)	0.40	1.03 (0.95, 1.13)	0.46
PM10_prior.4yr	0.96 (0.89, 1.04)	0.30	1.07 (0.99, 1.17)	0.09
PM10_prior.3yr	0.99 (0.92, 1.07)	0.80	1.09 (1.01, 1.19)	0.04
PM10_prior.2yr	1.01 (0.94, 1.09)	0.70	1.09 (1.02, 1.17)	0.02
PM10_prior.1yr	1.03 (0.96, 1.10)	0.46	1.06 (0.99, 1.13)	0.11
SO2_prior.5yr.accumulation	0.98 (0.95, 1.01)	0.13	1.02 (1.00, 1.05)	0.11
SO2_prior.4yr.accumulation	1.00 (0.98, 1.03)	0.92	1.02 (1.00, 1.05)	0.09
SO2_prior.3yr.accumulation	1.00 (0.96, 1.03)	0.80	1.04 (1.01, 1.08)	0.02
SO2_prior.2yr.accumulation	0.99 (0.94, 1.03)	0.55	1.03 (0.99, 1.08)	0.16
SO2_prior.5yr	0.88 (0.78, 0.99)	0.05	1.08 (0.97, 1.21)	0.19
SO2_prior.4yr	0.93 (0.83, 1.03)	0.16	1.09 (0.99, 1.19)	0.09
SO2_prior.3yr	0.95 (0.86, 1.05)	0.29	1.13 (1.03, 1.24)	0.02
SO2_prior.2yr	0.97 (0.89, 1.07)	0.58	1.08 (0.99, 1.17)	0.07
SO2_prior.1yr	0.96 (0.89, 1.04)	0.34	1.03 (0.96, 1.11)	0.42
NO2_prior.5yr.accumulation	0.95 (0.91, 0.99)	0.06	1.02 (0.95, 1.10)	0.58
NO2_prior.4yr.accumulation	0.95 (0.91, 0.98)	0.02	1.04 (0.97, 1.11)	0.32
NO2_prior.3yr.accumulation	0.94 (0.87, 1.00)	0.10	1.06 (0.97, 1.17)	0.22
NO2_prior.2yr.accumulation	0.97 (0.88, 1.08)	0.62	0.98 (0.88, 1.09)	0.73
NO2_prior.5yr	0.91 (0.78, 1.08)	0.29	1.16 (1.00, 1.34)	0.06
NO2_prior.4yr	0.97 (0.82, 1.14)	0.70	1.20 (1.04, 1.39)	0.02
NO2_prior.3yr	0.96 (0.81, 1.13)	0.60	1.27 (1.08, 1.49)	0.01
NO2_prior.2yr	1.01 (0.85, 1.19)	0.91	1.06 (0.90, 1.24)	0.52
NO2_prior.1yr	0.98 (0.83, 1.16)	0.79	0.97 (0.83, 1.15)	0.75

FIGURE 4
Air pollutant exposure-related RRs of FAIR and FAMR with a 5-year moving window. YAV, yearly average values (μg/m^3). RR, risk ratio (with 95% CI); FAIR, female age-adjusted incidence rate; FAMR, female age-adjusted mortality rate.

significant risky air pollution included: NO_2 5 years before (RR = 1.16, 95% CI: 1.00-1.34, p=0.05), NO_2 4 years before (RR = 1.20, 95% CI: 1.04-1.39, p=0.02), NO_2 3 years before (RR = 1.27, 95% CI: 1.08-1.49, p=0.01), PM_{10} 3 years before (RR = 1.09, 95% CI: 1.01-1.19, p=0.04), PM_{10} 2 years before (RR = 1.09, 95% CI: 1.02-1.17, p=0.02), and SO_2 3 years before (RR = 1.13, 95% CI: 1.03-1.24, p=0.02). Based on these analyses, we found that the YAV of air pollutants several years before the outcome assessment might be a significant risk factor for male and female age-adjusted lung cancer-related mortality.

The forest plot of the association between the concentrations of PM_{10}, SO_2, NO_2 0-5 year (s) before and MAIR, MAMR of lung cancer was shown in Figure 5. As shown in Supplementary Table 3, the risky air pollutions were listed. The significant air pollution risk factors for MAIR included SO_2 2 years before (RR = 1.20, 95% CI: 1.03-1.39, p=0.02), NO_2 2 years before (RR = 1.57, 95% CI: 1.32-2.05, p=0.002), and NO_2 during the present year (RR=1.38, 95% CI: 1.04-1.83, p=0.03). The significant air pollution risk factors for MAMR included NO_2 4 years before (RR = 1.30, 95% CI: 1.03-1.64, p=0.04), NO_2 3 years before (RR = 1.70, 95% CI: 1.32-2.18, p=0.0002), SO_2 3 years before (RR = 1.27, 95% CI: 1.09-1.49, p=0.004), and SO_2 2 years before (RR = 1.20, 95% CI: 1.04-1.38, p=0.02). In terms of the age-adjusted lung cancer incidence rate, the NO_2 and SO_2 within the 2-year exposure window were significant risk factor for males not females. These findings suggested that high NO_2 and SO_2 exposure within 2 years is related to lung cancer occurrence, and high NO_2 and SO_2 exposure within three years also increased lung cancer-related mortality; however, PM_{10} was not significant.

To further discriminate the impact of individual air pollutant on the sex- and age-adjusted lung cancer incidence and mortality, the RRs of MAIR, MAMR, FAIR and FAMR were individually presented in curves within a 5-year moving window of past exposure. As shown in Figure 6A, MAIR had higher RRs in the 5-year moving window, indicating stronger effects of air pollutants on MAIR than on FAIR. As shown in Figures 6B, C, the highest RR for both MAIR and FAIR came at the yearly concentration of air pollutant two years before, indicating the most significant lag effect for two years on lung cancer incidence. As shown in Figure 6C, NO_2 exposure had the highest RR value for both MAIR.

As shown in Figure 7A, MAMR had higher RRs in the 5-year moving window, indicating stronger effects of air pollutants on MAMR than on FAMR. As shown in Figures 7B, C, NO_2 exposure had the highest RR value for both MAMR and FAMR, indicating that the NO_2 level was the most important air pollutants affecting lung cancer-related mortality. In Figures 7B, C, the time effect of environmental pollutants on lung cancer mortality rate presents an inverted "U" structure. The highest RR for both MAMR and FAMR came at the yearly concentration of air pollutant 3 years before, indicating that the effects of air pollutants on MAMR and FAMR presented time lag distribution with the most significant lag effect for three years.

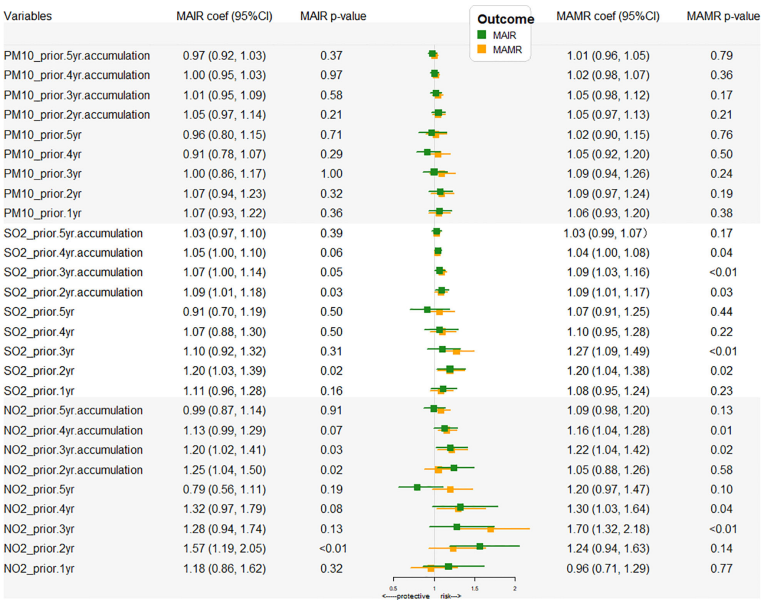


FIGURE 5
Air pollutant exposure-related RRs of MAIR and MAMR with a 5-year moving window. YAV, yearly average values (μg/m^3). RR, risk ratio (with 95% CI); MAIR, male age-adjusted incidence rate; MAMR, male age-adjusted mortality rate.

Discussion

According to the annual report data from the China Statistical Yearbook, the official Chinese government air quality testing stations obligatorily report, the air pollutants PM_{10}, SO_2 and NO_2 had overall decreasing trends year by year in seven major cities in China from 2006 to 2014. These trends were closely related to the great efforts made by the state and the general public in regard to environmental sanitation in recent years.

Air pollutants have been identified as group I carcinogens for lung cancer by International Agency for Research on Cancer (IARC) (24). According to the annual report of China Cancer Registry (CCRAR), we are surprised to find that crude lung cancer incidence and mortality rate are increasing year by year in these seven cities and are not in line with the concentrations of PM_{10}, SO_2 and NO_2.

This is probably attributable to the aging population structure. Aging is a firmly established risk factor for cancers, and aging population have higher absolute incidence rates of cancer (34). The population age structure is introduced as an important control variable for cancer risks. China has been in the ranks of aging society and has a large aging population, even at an increasing speed of aging (35). Thus, it is advisable to adopt age-adjusted cancer incidence and mortality rates to evaluate the effects of cancer risk factors, as suggested in previous studies (36, 37). Therefore, the incidence and mortality rates of lung cancer were modified by age according to a standard world population structure.

The age-adjusted incidence rate and mortality rate of male lung cancer decreased year by year in the past ten years, consistent with the trend of air pollution concentration, suggesting that air pollutants may be related to the occurrence and mortality of male lung cancer. Although air pollutants had an overall decreasing trend in the seven major cities, the air pollution indicators of several industrial cities had peak levels from 2013 to 2014, especially in the northern industrial city such as Shenyang. From 2013 to 2014, the concentrations of SO_2 and NO_2 in Shenyang were significantly increased. The annual lung cancer incidence rate and mortality rate rose consistently during this period. The age standardized incidence rate and survival rate are common international measures for studying malignant tumors (38). In fact, they are more practicable in the correlation analysis between air pollutants and lung cancer.

Gender is another important control variable for cancer risk. The time-trends of air pollutants and the age-adjusted statistics MAIR/MAMR consistently decreased from 2006 to 2014. The female age-adjusted mortality rate (FAMR) and female age-adjusted incidence rate (FAIR) had no significant trend from 2006 to 2014. Additionally, we found that YAV of SO_2 and NO_2 at 2-years before the outcome were most associated with lung cancer incidence in males without significant effects on lung cancer incidence in females. The findings of our study suggested that compared to women, men may have a higher risk of lung cancer following exposure to ambient air pollution. YAV of SO_2 and NO_2 at 3-years before the outcome had the most significant effects on lung cancer-related mortality in males and females, but

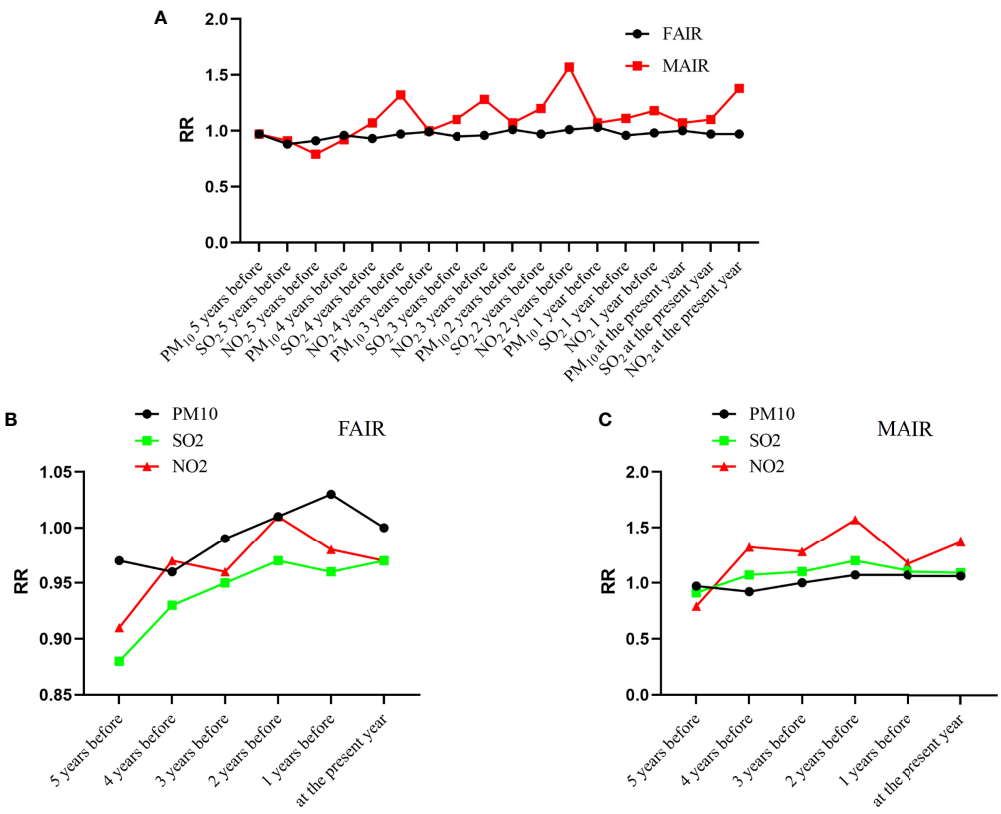


FIGURE 6
Air pollutant-related lung cancer incidence within a 5-year moving exposure window. **(A)** RR values of FAIR and MAIR related to the air pollutants; **(B)** RR values of FAIR related to individual air pollutants PM_{10}, SO_2 and NO_2; **(C)** RR values of MAIR related to individual air pollutants PM_{10}, SO_2 and NO_2. RR, risk ratio; FAIR, female age-adjusted incidence rate; MAIR, male age-adjusted incidence rate.

air pollutants presented stronger effects on males than females. Our results showed males may be more sensitive to air pollutants than females.

There are gender differences in the pathogenesis of smoking-related lung cancer. Female smokers suffer a higher risk of lung cancer than male smokers. There is insufficient evidence of gender differences in air pollutant-related lung cancer risks. Until now, sex-specific observations were not consistent among study locations and health outcomes. Some studies reported a larger mortality effect in males because of higher exposure associated with more outdoor activities, but some other studies also observed a stronger effect among females (39, 40). Our finding is consistent with most previous studies that reported slightly stronger health effects of air pollution for males compared to females (41). However, inconsistent results were observed in single-city studies in Shanghai, Guangzhou and Beijing in China (42–44).

The gender differences might be due to biological (e.g., physiopathological responses), demographic and behavioral differences (e.g., type of occupations, smoking, and lifestyle) between males and females (42, 45). Gender differences may be partly attributed to physiological differences (46). For instance, estrogens protect against the development of lung cancer (47). On the other hand, all major known risk factors, including smoking and occupational exposures, are more prevalent in males. The underlying reasons are still unclear and need to be further investigated.

The effects of single air pollutants are difficult to disentangle in an epidemiological study because pollutants are part of complex mixtures. The pollution mix varies considerably from place to place-from Shenyang to Beijing to Shanghai to Hangzhou to Wuhan, people are exposed to different cocktails of pollutants across different cities. PM_{10}, NO_2 and SO_2 represent different characteristics of the air pollution mixture, which may be related to the source of the pollution variability. In our study, it seems likely that NO_2 is the most important component for lung cancer risk and is more consistently associated with mortality than PM_{10} and SO_2. In the correlation analysis between air pollutants and the lung cancer incidence and mortality rates, SO_2 and NO_2 were associated with MAIR, MAMR and FAMR. For PM_{10}, there was no significant correlation with the male lung cancer incidence and mortality rates. NO_2 presented higher RRs than SO_2 for MAIR,

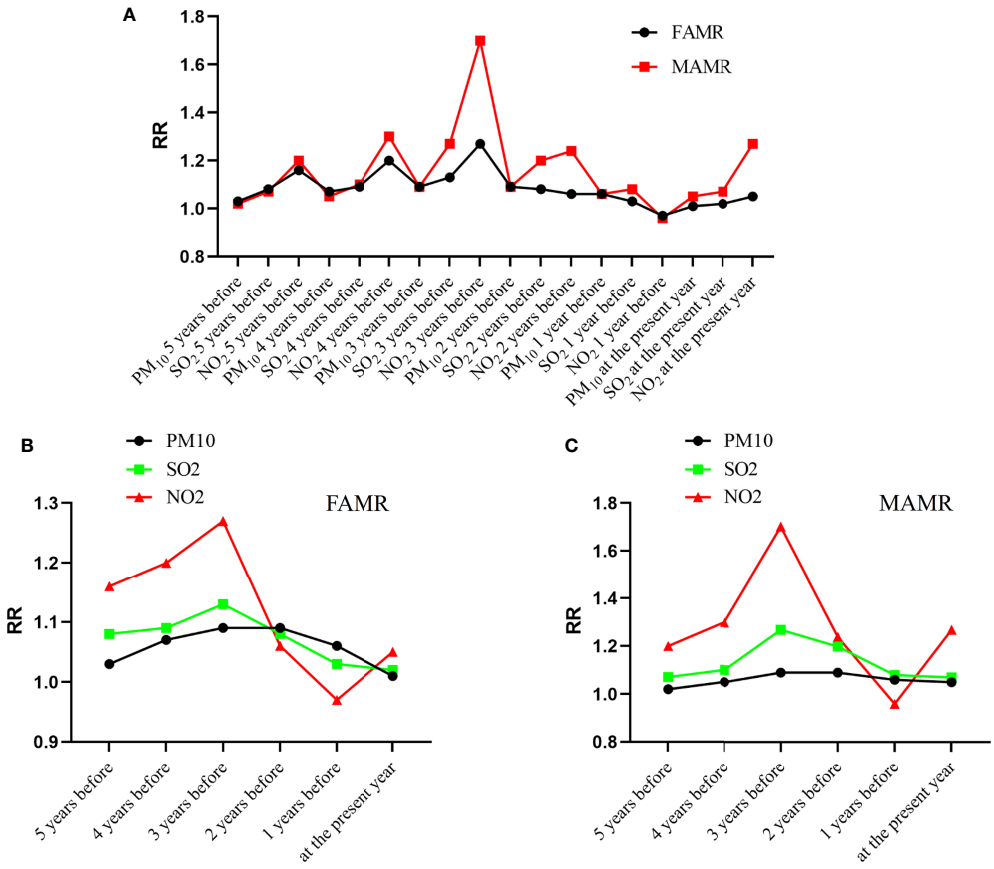


FIGURE 7
Air pollutant-related lung cancer mortality within a 5-year moving exposure window. **(A)** RR values of FAMR and MAMR related to the air pollutants; **(B)** RR values of FAMR related to individual air pollutants PM_{10}, SO_2 and NO_2; **(C)** RR values of MAMR related to individual air pollutants PM_{10}, SO_2 and NO_2. RR, risk ratio; FAMR, female age-adjusted mortality rate; MAMR, male age-adjusted mortality rate.

MAMR and FAMR, suggesting stronger impact of NO_2 on the burden of lung cancer.

There were reports of the correlation between NO_2 exposure and cancer incidence rates in Europe and America (48, 49). NO_2 has a significant positive correlation with cancer incidence rates, especially lung cancer, prostate cancer and breast cancer (49, 50). In a Danish study, it was demonstrated that NO_2 concentration was more associated with lung squamous cell carcinoma and small cell carcinoma than lung adenocarcinoma (51). A population-based case-control study including 908 lung cancer patients and 908 controls provided positive evidence for the association between exposure to ambient air pollution and lung cancer incidence in Koreans. The increase in the lung cancer incidence (OR) was 1.10 (95% CI: 1.00-1.22) for every 10 $\mu g/m^3$ increase in NO_2. Stronger associations between air pollution and lung cancer incidence were noted among never smokers and those with low fruit consumption (50).

Compared with that in developed countries in Europe and the United States, the air pollution in China is undoubtedly high. This study covers a wide range of regions and population in China, providing important information that NO_2 is closely related to the incidence and mortality of lung cancer. It is warranted that more attention be paid to promote national policies and raise public awareness of pollutant control, especially of NO_2.

There are only a few studies on the correlation between SO_2 and the tumor incidence rate and results of most studies were negative (52). Our study found that SO_2 is closely related to MAIR, MAMR and FAMR of lung cancer. This outcome suggests that China should pay attention to the control of SO_2 and to other air pollutants, and thus indirectly control the incidence rate and mortality of lung cancer.

Our study found that there was no strong evidence associating PM_{10} with the incidence rate and mortality of lung cancer. Some studies from low-pollution areas in Europe and America have investigated the relationship between PM_{10} and cancer incidence rate, most of which focused on lung cancer (49, 53, 54). A few studies evaluated the effects of PM_{10} on nonlung cancer mortality, including breast cancer (55), nasopharyngeal

carcinoma (56), liver cancer, colorectal cancer, bladder cancer, and kidney cancer mortality (57). Hamra et al. provided meta-analysis of increased lung cancer risk associated with exposure to PM in outdoor air from 17 cohort studies (14). An increase of 7 $\mu g/m^3$ in PM_{10} was associated with an increased HR of 1.84 for lung cancer mortality (95% CI: 1.23-2.74) (49). However, not all studies are consistent. In their case-control studies of Europeans, Vineis et al. found a nonsignificant correlation between PM_{10} and lung cancer incidence rate (52).

Because of the imperfection of air pollution detection systems in China, the detection of $PM_{2.5}$ started late. It was not available to obtain the relatively complete data of $PM_{2.5}$ in our study. Whether $PM_{2.5}$ is closely related to the incidence and mortality of lung cancer remains to be further studied. Our study showed that the chemical components of air pollutants, such as NO_2 and SO_2, seem to contribute more to the burden of lung cancer than PM_{10}. Therefore, the control of exhaust emissions is of parallel importance with the prevention of haze particles.

Our results showed that PM_{10} had no significant correlation with the lung cancer MAIR and FAIR, while the YAV of SO_2 and NO_2 2 years before the outcome and the YAV of NO_2 during the present year were significant risk factors for the lung cancer MAIR, especially the YAV of SO_2 and NO_2 2 years before the outcome, suggesting that NO_2 and SO_2 may have a 2-year lag in their effects on male lung cancer. The cumulative time effect of environmental pollutants on tumor incidence rate presents an inverted U structure. With the exposure period getting longer, the impact of environmental pollutants on the tumor incidence rate increased in the first period and reached the highest level. After the peak, it decreased gradually. The strongest effect points of PM_{10}, SO_2 or NO_2 on lung cancer MAIR are at the time of 2 years before the cancer occurrence. The most important factor affecting the incidence rate of MAIR is industrial NO_2.

In addition to cancer incidence, lung cancer mortality is another end point in the study. There is insufficient evidence of whether ambient air pollution may be related to cancer progression or survival. One recent study in California enrolled >350,000 lung cancer patients and reported that higher residential ambient air pollution concentrations (NO_2, $PM_{2.5}$, PM_{10}) were associated with poorer survival, particularly among patients diagnosed in earlier disease states (i.e., with localized disease) (2).

Lung cancer is rapidly fatal with 5-year survival rates of 18%, thus, the use of mortality data reasonably approximates disease incidence. Actually, survival is of greater significance for lung cancer, which reflects both disease incidence and survival following diagnosis. Our results suggest that NO_2 and SO_2 levels three years before cancer occurrence are most closely related to the lung cancer MAMR and FAMR. PM_{10} had no significant effect on the mortality of lung cancer in males, but had a certain correlation with the mortality of females. The cumulative time effect of environmental pollutants on the lung cancer mortality rate also presents an inverted-U structure. With exposure period getting longer, the impact of environmental pollutants on tumor incidence rate increased in the first period and reached the highest level. After the peak, it decreased gradually. The strongest effect points of SO_2 and NO_2 on lung cancer MAMR and FAMR are 3 years before the cancer occurrence. The data in Figure 3 show that the most important factor affecting the incidence rate of MAMR and FAMR is industrial NO_2.

The study has the following limitations: (1) China enforces a household register system and the annual data of China cancer registration are collected from permanent resident population in each city, lacking data from the transient population in the city. These seven cities are important representative cities in China with large transient populations and the transient population was more likely to participate in outdoor activities. Thus, a part of the population of each city was not included in the analysis, discounting the accuracy of the results. (2) The mechanism of lung cancer is not fully understood. The risk factors are diverse and complex and there are inherent differences in population susceptibility. The mortality of lung cancer is also affected by many aspects including timely diagnosis and active treatment. Although air pollutants have adverse effects on public health, the analysis of their correlation with lung cancer may be interfered by biological (e.g., physiopathological responses), demographic and behavioral differences (e.g., type of occupation, smoking, and lifestyle) (5). Although some of the confounding factors can be eliminated by horizontal comparison in multiple cities, this study was not be stratified by other potential confounding factors (such as smoking, lifestyle, obesity and socioeconomic status) other than age and gender. Therefore, to some degree the conclusions obtained are one-sided. (3) Although the incidence of lung cancer in rural areas is lower than that in urban areas, the former is on the rise. The main components of air pollution in rural areas may be different from those in cities. As China has a vast territory with a large population, at present, air pollution detection points have been only established in cities and suburbs and do not cover rural areas. Thus, this study did not involve data from rural areas and the relationship between air pollutants and lung cancer occurrence and mortality in rural areas needs further study.

With the rapid development of China's economy, air pollution has become a threatening public health problem (19). Many experiments and epidemiological studies have shown that air pollution has health hazards, such as carcinogenesis, cardiovascular and respiratory harms. It is an urgent and important task to evaluate the correlation between air pollution and disease-specific incidence and mortality rates in China. Our research demonstrated that the lung cancer incidence and mortality rates were consistent with the degree of air pollution, based on air pollutant data and lung cancer registration data from seven cities in China. PM_{10}, SO_2 and NO_2 were selected as air pollution monitoring indicators. Among them, NO_2 was the most closely related to lung cancer, followed by SO_2, and PM_{10} exhibited the weakest effects. Air pollutants have the strongest cumulative effect on the incidence and mortality of lung cancer at

2-3 years of exposure. There are gender differences in air pollution-associated lung cancer risks. The air pollutant presented stronger effects on males than females and males may be more sensitive to air pollutants than females.

Air pollutants have very complex physical and chemical properties and have strong temporal and spatial heterogeneity. There are far more components of air pollution than PM_{10}, SO_2 and NO_2. To formulate corresponding environmental protection measures, it is necessary to identify the components of air pollution and to explore the major sources of air pollution emission. Further research needs to be conducted to evaluate the health hazards of individual components, aiming at providing guidance for environmental pollution control and public health protection. The association between lung cancer burden and air pollution may shift public perceptions and ultimately help to promote policy development on air quality.

Besides air pollution, there is a lot of risk factor for lung cancer, such as smoking (58), family history of lung cancer, and so on, which were the confounders. More than 50% of men smoke in China, and there are more than 300 million smokers in China (59). Smoking and air pollution combined to account for the elevated rates of lung cancer mortality in Shenyang of China (60). Family history of lung cancer, history of tuberculosis are also the independent risk factors for lung cancer (61). These risk factors are confounders, but in this study, we focused on the air pollutants and performed univariate analysis without considering other factors. Because the air pollutants are too complex to perform multivariate analysis.

Conclusions

Our research demonstrated that the lung cancer incidence and mortality rates were consistent with the degree of air pollution, based on air pollutant data and lung cancer registration data from seven cities in China. NO_2 was the most closely related to lung cancer, followed by SO_2 and then PM_{10}. Air pollutants have the strongest cumulative effect on the incidence and mortality of lung cancer at 2-3 years of exposure.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Ethics Committee of Hunan Cancer Hospital. The lung cancer incidence and mortality data were extracted from the "China Cancer Registry Annual Report, 2009~2017" published by the National Cancer Registry Center, research and academic use permitted.

Author contributions

WW provided the idea and designed the article. LM and ZH collected the data. WW, LM, ZH, XY, WZ, KL, HL and MT analyzed the data. XZ, XT, CL, YH and SY edited the figures. WW, LM and XY wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Temporal trends in lung cancer mortality and years of life lost in Wuhan, China, 2010-2019

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Objective: Lung cancer is responsible for millions of deaths yearly, and its burden is severe worldwide. This study aimed to investigate the burden of lung cancer in the population of Wuhan based on the surveillance data from 2010 to 2019.

Methods: Data of this study was obtained from the Mortality Register System established by the Wuhan Center for Disease Control and Prevention. The study systematically analyzed the burden of lung cancer deaths in the population of Wuhan and its 13 administrative regions from 2010 to 2019 *via* the Joinpoint regression models, Age-Period-Cohort (APC) models, and decomposition analysis.

Results: This study found the upward and downward trends in the age-standardized mortality rates (ASMRs) and age-standardized years of life lost rates (ASYLLRs) of lung cancer from 2010 to 2019. In Joinpoint regression models, the corresponding estimated annual percentage change (EAPC) were 1.00% and -1.90%, 0.60%, and -3.00%, respectively. In APC models, lung cancer mortality tended to increase with age for both sexes in Wuhan, peaking at the 85-89 age group; The period effects for different populations have started to gradually decline in recent years. In addition, the cohort effects indicated that the risk of lung cancer death was highest among those born in the 1950s-1955s, at 1.08 (males) and 1.01 (females). Among all administrative districts in Wuhan, the ASMR of lung cancer in the Xinzhou District has remained the highest over the study period. In decomposition analysis, both population aging (P<0.01) and population growth (P<0.01) aggravated (Z>0) lung cancer deaths in the Wuhan population.

Conclusions: The burden of lung cancer death in the Wuhan population has shown a gradual decline in recent years, but the impact of aging and population growth on lung cancer mortality should not be ignored. Therefore, lung cancer surveillance must be strengthened to reduce the burden of lung cancer in Wuhan.

KEYWORDS

lung cancer, mortality, years of life lost, temporal trends, burden of disease

Introduction

As a multi-stage and multi-factor cancer, lung cancer is the leading cause of cancer-related death in China, especially for males (1). Due to the poor prognosis and high patient mortality rate, lung cancer also proves to be the leading cause of cancer-related death globally (2). In China, the mortality rate of lung cancer has increased about four times over the past decades, and deaths caused by lung cancer account for 27.3% of all cancer-related deaths in 2020 (3, 4). In recent years, lung cancer has replaced stomach cancer as the leading cause of cancer death. China is the most populous country in the world, and the disease burden of lung cancer varies among populations living in different regions of China because of the vast geographical area (5). According to the global limitation of disease study 2019, the age-standardized mortality rates (ASMRs) rose from 31.18/100,000 in 1990 to 38.70/100,000 in 2019, much higher than the global average level (6). Therefore, the lung cancer epidemic poses a severe health burden to the Chinese population.

Wuhan, located in Hubei province, is the largest city in central China. As a highly developed metropolis in China, Wuhan has a large population and a prosperous economy. Being the first leading cause of death in Wuhan, lung cancer represents a significant challenge to public health in Wuhan (7). Lung cancer is related to diverse factors, such as tobacco exposure, indoor and outdoor air pollution, poor dietary habits, occupational exposure, previous chronic lung infections (tuberculosis or bronchial infections), etc. (8, 9). Most of the current studies were conducted at the national level, but few of them focused on the lung cancer burden at the provincial or municipal level. The temporal trend of lung cancer deaths in Wuhan could reflect the movement and variations in the population of Hubei province and other cities in Central China.

This study aimed to explore the temporal trends of lung cancer mortality by sex and administrative regions over the last decade in Wuhan, with an emphasis on decomposing the contributions of demographic factors and investigating the detached effects of age, period, and cohort. Furthermore, this study could also shed light on priorities that deserve policymakers' attention for targeted interventions by comparing discrepancies in lung cancer burden between the central and surrounding urban areas.

Abbreviations: CDC, Disease Control and Prevention; ICD-10, International Statistical Classification of Diseases 10th Revision; ASMRs, age-standardized mortality rates; YLLs, years of life lost;YLLRs, years of life lost rates; ASYLLRs, age-standardized years of life lost rates; ASRs, age-standardized rates; EAPCs, annual percent changes; AAPCs, the average annual percent changes; CIs, confidence intervals; APC, age-period-cohort model; Ad, age-drift model; AP, age-period model; AC, age-cohort model; LDCT, low-dose computed tomography.

Method

Data sources

Data for this study was derived from the Mortality Register System established by the Wuhan Center for Disease Control and Prevention (CDC). We included all death cases of lung cancer in Wuhan recorded between Jan 1, 2010, and Dec 31, 2019. The death cases were classified according to the International Statistical Classification of Diseases 10th Revision (ICD-10: C33, C34-C34.92, D02.1-D02.3, D14.2-D14.3, D38.1, Z12.2, Z80.1-Z80.2, and Z85.1-Z85.20). Demographic data consisted of information on age, sex, date of death, and cause of death were also included in our analysis. Annual population data for the whole study period were obtained from the Wuhan Public Security Bureau. The reason for data in this study was surveillance data. The informed consent was unnecessary. In addition, this study was approved by the Ethical Committee of the Wuhan CDC and was conducted in compliance with the tenets of the Declaration of Helsinki. The results were reported under the STORBE statement.

There are 13 administrative districts in Wuhan, of which Jiang'an District, Jianghan District, Qiaokou District, Hanyang District, Wuchang District, Qingshan District, and Hongshan District are the central urban areas, and Dongxihu District, Hannan District, Caidian District, Jiangxia District,

Huangpi District, and Xinzhou District are the surrounding metropolitan areas.

Statistical analysis

Death cases were directly counted according to the origin data. The years of life lost (YLLs) was an index representing premature death in the population. It was estimated by summing up the remaining life expectancy for people dying in each age group (10). The reference life expectancy was 86.6 years, derived from the first age group (0-4 age group) in the standardized life expectancy table in the global burden of disease study 2016 (11). Meanwhile, we use the data obtained from the sixth Chinese census (http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm) as the standard population. This study then calculated the mortality rate, ASMRs, years of life lost rates (YLLRs), and age-standardized years of life lost rates (ASYLLRs) by age groups, sex, and administrative regions.

In the Joinpoint model, the estimated annual percent changes (EAPCs) and the average annual percent changes (AAPCs) were calculated to depict the temporal trends of the age-standardized rates (ASRs) (12). If the lower boundary of the EAPCs' 95% confidence intervals (CIs) were higher than 0, the ASRs were deemed to keep increasing during the study period. While the higher boundary of the EAPCs' 95% CIs was lower than 0, the ASRs were considered to decline (13).

A latest developed decomposition method was performed to explore the attributable demographic factors (population growth, population aging, and changes in age-specific mortality in lung cancer), which drove the changes in lung cancer deaths in Wuhan from 2010 to 2019 (14). This method has considered the two-way and three-way interactions between the mentioned demographic factors. The influence of these factors on the changes in lung cancer deaths in Wuhan was presented by the absolute and relative contributions. The real contribution was the total of lung cancer deaths attributed to each mentioned demographic factor. At the same time, the relative contribution was the absolute contribution divided by the total lung cancer deaths. Furthermore, we detected the monotonic trends of the absolute or relative contributions during 2010-2019 in Wuhan *via* the Mann-Kendall monotonic trend test (14). A positive Z value indicates a monotonic increasing trend in the whole or relative contributions. In contrast, a negative Z value means a monotonic decreasing trend in the absolute or relative contributions.

The age-period-cohort (APC) model could decompose the risks of death that are experienced by individuals in the current year and the accumulation of health risks since birth (15). To fit the APC model, death cases of lung cancer between 20-89 years old were divided into 12 consecutive 5- year age groups (death cases below 20 years old were excluded due to few people dying younger than 20). The study period was arranged into two consecutive 5- years period groups and 15 successive 5- years cohort groups. For dealing with the "non-identifiable problem" in the APC model, this study fitted a sequence of models, such as the one-factor age model, the two-factor age-drift (Ad), age-period (AP) and age-cohort (AC) models, and the full three-factor APC model (16). The statistical significances of different terms added models were tested. We selected the best-fitting model by comparing the differences in model deviances and with the degree of freedom *via* the Chi-square test (17).

The detailed information about the models used in analyses in Supplementary Material. All analyses in this study proceeded in R software (version 4.0.1, package: epitools (0.5-10.1), Epi (2.44)) and the Joinpoint regression program (version 4.8.0.1). Two-tailed tests were performed to determine all *P* values, and *P* less than 0.05 is considered statistically significant.

Results

The temporal trends of lung cancer deaths in Wuhan

Descriptive data with essential characteristics for lung cancer in Wuhan were summarized in Table 1. In both males and females, the mortality rate and YLLRs of lung cancer kept increasing during 2010-2019. But after standardization, the ASMRs of lung cancer in the whole population of Wuhan first rose from 48.89/100,000 in 2010 to 52.61/100,000 in 2017, then declined to 50.48/100,000 in 2019. The trend of ASYLLRs corresponds with the trend of ASMRs in the same period. Moreover, there was a significant difference between men and women in ASR of lung cancer ($P<0.05$). Males have experienced a more severe burden of lung cancer death than females in Wuhan over the study period.

The Joinpoint regression analysis

By fitting the Joinpoint regression model, a turnaround in the trend of ASMRs or ASYLLRs for lung cancer in the population of Wuhan was observed from 1990 to 2019 (Table 2). The EAPCs of ASMRs were 1.00% (0.40%, 1.70%) and -1.90% (-6.40%, 2.80%) in 2010-2017 and 2017-2019, respectively. Yet, only the upward trend between 2010-2017 was statistically significant ($P<0.05$). The upward and downward trends in both males (1.90% in 2010-2015, -1.70% in 2015-2019) and females (1.40% in 2010-2016, -2.30% in 2016-2019) were statistically significant ($P<0.05$). In terms of ASYLLRs of lung cancer in Wuhan, the EAPCs were 0.60% (-0.50%, 1.80%) and -3.30% (-6.30%, -0.10%) in 2010-2016 and 2016-2019. Among different sex groups, only the downward trend in males (-3.00% in 2016-2019) was statistically significant ($P<0.05$).

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TABLE 1 Trends in the burden of lung cancer death in Wuhan, 2010-2019.

Year	Deaths	Mortality (1/100,000)	ASMRs (1/100,000)	YLLs	YLLRs (1/100,000)	ASYLLRs (1/100,000)
Both						
2010	3363	68.86	48.89	83238	1277.14	1199.47
2011	3485	51.60	48.48	84821	1320.41	1225.57
2012	3779	54.24	49.43	89196	1344.70	1222.42
2013	3885	56.96	50.84	90840	1327.59	1185.70
2014	4263	56.78	49.92	100235	1489.50	1258.00
2015	4393	63.35	51.87	102488	1504.20	1237.62
2016	4702	64.48	51.05	107340	1564.94	1255.66
2017	4632	68.54	52.61	104601	1520.26	1194.25
2018	4878	67.32	50.57	107953	1542.96	1172.54
2019	4948	69.73	50.48	109016	1516.92	1130.66
Male						
2010	2488	75.53	72.94	62692	1903.15	1834.15
2011	2591	79.82	76.51	63049	1942.17	1854.98
2012	2767	82.62	77.98	65917	1968.13	1845.66
2013	2889	83.67	78.79	68034	1970.78	1813.81
2014	3180	93.54	80.71	75040	2207.43	1915.86
2015	3235	94.12	80.34	76139	2214.98	1869.14
2016	3478	100.50	81.20	80233	2318.38	1907.91
2017	3423	98.71	78.45	78293	2257.57	1830.15
2018	3610	102.48	78.53	81105	2302.49	1802.22
2019	3649	101.01	75.74	81254	2249.35	1723.33
Female						
2010	875	27.15	23.43	20546	637.41	578.96
2011	893	28.11	24.43	21772	685.20	622.62
2012	1011	30.80	24.91	23279	708.88	627.13
2013	996	29.39	24.46	22806	672.68	587.16
2014	1083	32.52	25.24	25194	756.59	628.58
2015	1158	34.30	25.68	26349	780.48	631.29
2016	1223	36.00	26.09	27107	797.65	632.80
2017	1209	35.42	24.73	26309	770.95	587.57
2018	1269	36.52	24.69	26848	772.83	576.75
2019	1300	36.36	24.30	27762	776.70	572.29

Decomposition analysis

Decomposition analysis showed that both the population aging and the population growth drove the number of lung cancer deaths in Wuhan. The population aging played the dominant role (Z = 3.94), followed by the population growth (Z = 3.58), but the lung cancer deaths due to the changes in the age-specific mortality rate were insignificant (P = 0.11) after the Mann-Kendall monotonic trend test (Table 3).

There was an increase of 147.13% (additional 1585 deaths) in lung cancer deaths in Wuhan in 2019 from 2010. According to Figure 1, this increase was primarily driven by the population aging (28.69% increase from 2010) and the population growth (15.36% increase from 2010).

We also conducted the decomposition analysis to study the lung cancer deaths influenced by demographic factors in both central and surrounding urban areas of Wuhan (Table S1). For lung cancer deaths in the population of central urban areas in Wuhan, the absolute and relative contributions from the population aging (616.07 deaths and 29.19% increase in 2019 compared to 2010) and the population growth (362.83 deaths and 17.19% increase in 2019 compared to 2010) still dominantly affected the increasement of lung cancer deaths. But the relative contribution for the changes in age-specific mortality rate was in

TABLE 2 The Joinpoint regression models for ASMRs and YLLRs of cancer in Wuhan, 2010-2019.

	Trend	Year	EAPCs (%, 95% CIs)	*P* value
ASMRs				
Both	Trend 1	2010-2017	1.00 (0.40, 1.70) *	**<0.01***
Both	Trend 2	2017-2019	-1.90 (-6.40, 2.80)	0.30
Male	Trend 1	2010-2015	1.90 (1.00, 2.90) *	**<0.01***
Male	Trend 2	2015-2019	-1.70 (-2.90, -0.50) *	**<0.01***
Female	Trend 1	2010-2016	1.40 (0.60, 2.20) *	**<0.01***
Female	Trend 2	2016-2019	-2.30 (-4.50, -0.10) *	**<0.01***
YLLRs				
Both	Trend 1	2010-2016	0.60 (-0.50, 1.80)	0.18
Both	Trend 2	2016-2019	-3.30 (-6.30, -0.10) *	**<0.01***
Male	Trend 1	2010-2016	0.60 (-0.50, 1.70)	0.21
Male	Trend 2	2016-2019	-3.00 (-5.9, -0.10) *	**<0.01***
Female	Trend 1	2010-2015	1.30 (-1.70, 4.20)	0.32
Both	Trend 2	2015-2019	-2.70 (-6.40, 1.10)	0.11

P in bold represent statistically significance at $P < 0.05$ (*).
CIs denote confidence intervals.

decline, with 5.84% reductions in 2019 compared to 2010. For lung cancer deaths in the population of surrounding urban areas in Wuhan, though the contributions from the population aging (360.08 deaths and 28.76% increase in 2019 compared to 2010) and the population growth (153.89 deaths and 12.28% increase in 2019 compared to 2010) kept increase, the changes of age-specific mortality rate became the main demographic factor (789.71 deaths and 25.65% increase in 2019 compared to 2010) driving the increase of lung cancer deaths during the study period. All the monotonic increasing trends of lung cancer deaths due to demographic factors in both central and surrounding urban areas of Wuhan were statistically significant ($P < 0.05$) (Figure S1).

Age-period-cohort model

The goodness of fit for the APC models of lung cancer mortality in Wuhan was summarized in Table S2. We selected the best model based on the deviance and *P* value of fitted models (17). Since there is the "non-identifiable problem" in the APC model, we usually fit the AP or AC model first and then fit the remaining cohort or period effects to the residuals. According to Table S2, we found that among all the models, the AC-P model may be the most suitable for our data. Therefore, we choose the AC-P model as our final model for analysis.

Figures 2, 3 illustrated the estimates of age, period, and cohort effects for lung cancer mortality by sex. The age effects escalated

TABLE 3 Contribution of changes in population aging, population growth, and age-specific mortality rate of lung cancer to variations of lung cancer deaths in Wuhan, 2010-2019.

Year	Due to population aging	Due to population growth	Due to age-specific mortality rate	Net change
2010 (reference)	–	–	–	–
2011	29.68	-52.1	141.48	121.53
2012	82.31	68.98	270.45	415.54
2013	131.85	192.98	213.9	521.9
2014	411.1	146.4	367.38	899.98
2015	543.68	209.44	315.5	1030.5
2016	682.75	262.16	451.5	1338.53
2017	750.99	272.1	303.02	1269.04
2018	875.2	375.74	351.33	1515.44
2019	964.82	516.48	219.59	1585.42
Z values	3.94	3.58	1.61	3.76
P values	**<0.01***	**<0.01***	0.11	**<0.01***

P in bold represent statistically significance at $P < 0.05$ (*).

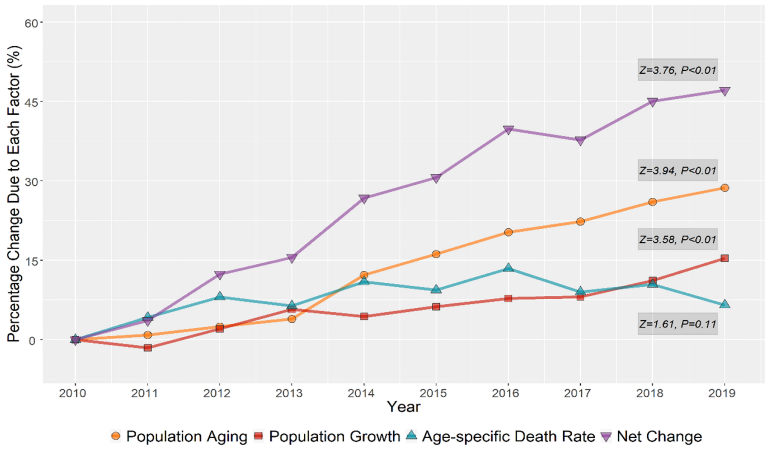

FIGURE 1
Relative contributions of changes in population aging, population growth, and age-specific lung cancer mortality rate to variations of lung cancer deaths in the population of Wuhan, 2010-2019.

exponentially with age and peaked in the 85-89 age group, with males higher than females in the same age group. Throughout the study period, the period effects of lung cancer mortality for different populations in Wuhan showed a trend of increasing and then decreasing, with the period effects for males and females decreasing from 1.02 in 2014 to 0.98 in 2019. For the cohort effects of lung cancer mortality, upward trends were revealed by the model in generations born earlier than 1950s-1955s. While there were reductions in death risk in the cohorts born after 1950s-1955s for both sexes in Wuhan. Compared to those born in the 1950s-1955s, the risk of lung cancer death decreased by 80.42% and 63.40% for males and females born after 1995s, respectively.

The temporal trends of lung cancer deaths in 13 administrative regions of Wuhan

Figure 4 demonstrated changes in the ASMRs and ASYLLRs of lung cancer and the corresponding ranks of the ASRs in the population of 13 administrative regions in Wuhan. The ASMRs of lung cancer in the population of Xinzhou District were the highest among all administrative regions over the whole study period, followed by Jiangxia District. Residents in Wuchang District and Hannan District suffered severe death from lung cancer during 2011-2013 or 2016-2017, but the situations been

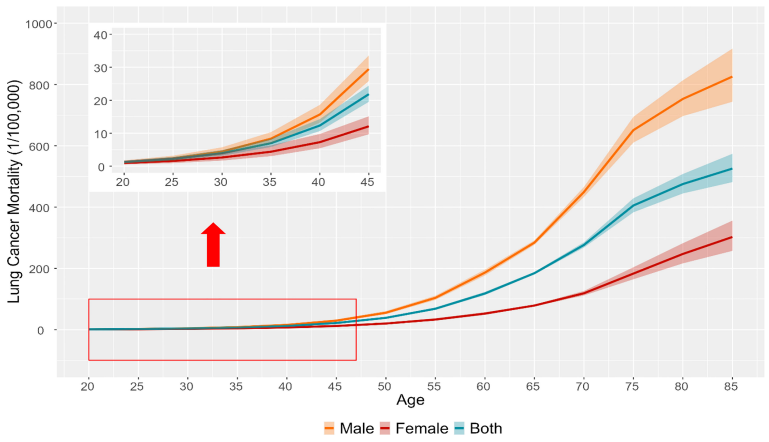

FIGURE 2
The longitudinal age curves of lung cancer mortality rate and the corresponding 95% CIs for different groups of population in Wuhan (the y-axis for the inside graph was lung cancer mortality, and the x-axis for the inside graph was age).

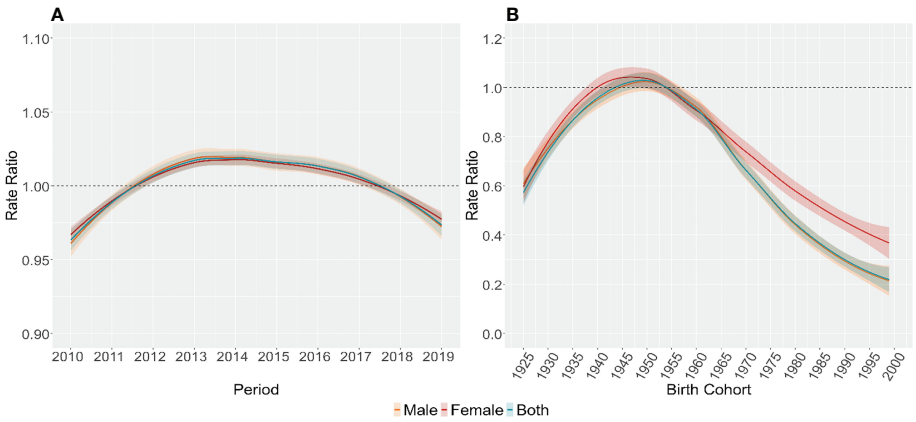

FIGURE 3
Parameter estimates of period **(A)** and cohort effects **(B)** on lung cancer mortality rate for different groups of population in Wuhan, 2010-2019.

better in recent years. The situations of the ASYLLRs in 13 administrative regions of Wuhan were much like that of the ASMRs.

Discussion

Our study provided an in-depth insight into temporal trends of lung cancer mortality in Wuhan. There were upward and then downward trends in both ASMRs and ASYLLRs of lung cancer from 2010 to 2019. Among all sociodemographic factors, both the population aging and the population growth could aggravate lung cancer deaths. In the whole Wuhan population, aging was proved to be the most severe influence factor on lung cancer deaths, and the relative contribution increased from 0.88% in 2011 to 28.69% in 2019. Although the changes in age-specific mortality rate have no significant effect on lung cancer deaths in the whole population of Wuhan, its influences on lung cancer deaths in the people of the central urban and surrounding areas presented opposite situations. The results of the APC model showed that after adjusting for the period and cohort effects, lung cancer mortality tended to increase with age for both sexes in Wuhan, peaking at the 85-89 age group. The period effects for different populations have started to gradually decline in recent years. In addition, the cohort effects indicated that the risk of lung cancer death was highest among those born in the 1950s-1955s, at 1.08 (males) and 1.01 (females). The risk of lung cancer death began to decline in subsequent birth cohorts, reaching the lowest level in those born after 1995s. For all administrative districts in Wuhan, the ASMRs and ASYLLR of lung cancer in the Xinzhou District remained the highest over the study period.

The mortality rate of lung cancer has increased in the population of Wuhan from 2010 to 2019. Meanwhile, the mortality was more severe in Wuhan than at the national level

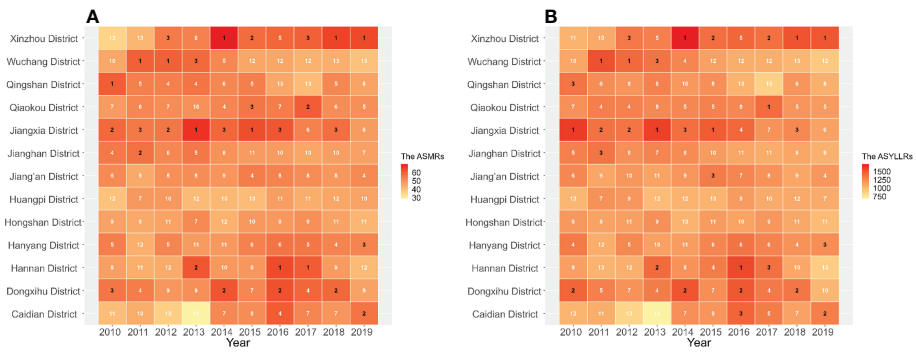

FIGURE 4
Changes of the ASMRs **(A)** and ASYLLRs **(B)** for lung cancer and the corresponding ranks of the ASRs in the population of 13 administrative regions in Wuhan, 2010-2019.

in the same period (18). The ASMRs of lung cancer for males in Wuhan were higher than the ASMRs in the Chinese male population, whereas a similar level of lung cancer ASMRs was found in females of Wuhan and China. By the decomposition method, this study discovered that the population aging and the population growth were two main factors contributing to the severe burden of lung cancer deaths in Wuhan. According to previous studies, the average annual growth rate of people aged over 60 years old in Wuhan was 3.00% since Wuhan was listed as a city with an aging population in 1993 (19). By the end of 2017, the number of older adults over 60 in Wuhan had accounted for 20.95% of the total population, which was much higher than the international standard of 10% (20). The large proportion of older adults in the population may lead to a series of problems, such as reduced immunity to disease, lower metabolic levels, or poor nutrition. It is no doubt that the risk of lung cancer death will increase once the elderly population becomes more vulnerable to lung cancer risk factors (air pollution or tobacco exposure, etc.) (21).

Moreover, the age effects that the risk of lung cancer death in the population increases with age in the APC model strengthened findings from the former research, which also confirmed the impact of the population aging on the burden of lung cancer deaths in Wuhan (22–24). The population growth in Wuhan, in addition to driving the population aging, also poses a challenge to the medical system or environmental protection in the city (25). That potential threat might also aggravate the burden of lung cancer deaths in Wuhan.

In the early 2000s, some lung cancer screening studies using low-dose computed tomography (LDCT) were initiated only in some economically developed urban areas or in high-risk rural areas of China (26). The population-based lung cancer screening program using LDCT has been available in the Chinese National Lung Cancer Screening cohort since 2013, which covers major cities and rural areas and facilitates the early detection and treatment of potential lung cancer patients (27). At the same time, medical insurance coverage for cancer treatment has been gradually expanded in Wuhan due to the serious threat of cancer to the health of residents (28). Furthermore, with the adoption of health-related policies such as tobacco control and emission reduction in Wuhan, the rising trend of lung cancer mortality burden has been curbed and started to decline gradually in recent years (29). The cohort effects of lung cancer mortality in the Wuhan population were found to have a turning point around the period when the People's Republic of China was founded, reflecting that those born in a stable social context could access better medical care or educational resources and have more opportunity to avoid exposure to risk factors related to lung cancer deaths (e.g., smoking, occupational exposure, and poor lifestyles etc.) (30). Also, patients with lung cancer in the same period could be in touch with better treatment after diagnosis and therefore face a lower risk of lung cancer death. Sex was another critical factor affecting lung cancer deaths besides the above factors. The results of this work demonstrated a higher risk of lung cancer deaths in males than in females, which is consistent with previous studies (31, 32). The discrepancy might be attributed to the differences in physiological susceptibilities and behavioral preferences in populations with different sex (33).

Another key finding of our study was that the population's burden of lung cancer deaths presented a more complex situation in the surrounding urban areas than in the central urban areas in Wuhan. The surrounding urban regions mainly consist of rural areas and large, heavy industrial areas, while the main urban areas include commercial and residential areas. This status might ascribe to the following reasons: First, the medical resources were unevenly distributed in the administrative regions of Wuhan. Because the resources are mainly distributed in the central urban areas, the medical resources allocated in the surrounding urban areas were inferior. They were once even lower than the national average (34). Second, many studies have identified that tobacco exposure was more severe in surrounding urban areas. The epidemic of smoking among adults, tobacco intake among smokers, and secondhand smoke exposure among non-smokers in surrounding urban areas were significantly higher than in central urban areas (35–37).

Furthermore, the heavy industrial areas with more severe air pollution were generally located in surrounding urban areas. Manly considerable cohort research has provided evidence about the relationships between air pollution and lung cancer death, especially in particulate matters (38, 39). A 10 mg/m3 increment in the particulate matter was associated with a 6.2% (PM2.5) and 4.3% (PM10) increase in overall lung cancer mortality, especially among the susceptible population (40). Finally, the gaps in lung cancer mortality between the central and surrounding urban areas of Wuhan might also relate to residents' education levels, family income, or medical preferences (41). In the city's future development, the only way to bring the mortality rate of lung cancer under control in the population of Wuhan can only be achieved by addressing the abovementioned issues.

There were some limitations in this study. On the one hand, due to short of the related information about the subtypes of lung cancer subtypes and risk factors of lung cancer in the original data, the analysis of the lung cancer mortality by subtypes and the calculation of risk factors attributable to lung cancer mortality have not been conducted in our study. On the other hand, an ecological fallacy might occur as a type of research based on the population level since this study has paid more attention to the population level rather than the individual level. Thus, subsequent studies should consider the above limitations and make them more complete.

Conclusion

The burden of lung cancer death in the Wuhan population has shown a gradual decline in recent years, but the impact of aging and population growth on lung cancer mortality should not be ignored. The burden of lung cancer deaths presented a more complex situation in the population of the surrounding urban areas than in the central urban areas in Wuhan. Therefore, the burden of lung cancer deaths in Wuhan might reduce only when the gaps in lung cancer mortality between the central and surrounding urban areas have dwindled.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

Conceptualization: CY, YY and NY; methodology: YY and YM; software: YM and YL; validation: YM and YY; formal analysis: YM; resources: CY, YY, XZ, YZ, and NY; data correction: CY, YY, XZ, YZ, and NY; writing-original draft preparation: YM; writing-review and editing: YM and YL; visualization: YM; supervision: CY; project administration: CY, YY. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1030684/full#supplementary-material

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Trends in incidence and survival in patients with gastrointestinal neuroendocrine tumors: A SEER database analysis, 1977-2016

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Objectives: We aimed to determine trends in incidence and survival in patients with gastrointestinal neuroendocrine tumors (GI-NETs) from 1977 to 2016, and then analyze the potential risk factors including sex, age, race, grade, Socioeconomic status (SES), site, and stage.

Methods: Data were obtained from Surveillance, Epidemiology, and End Results Program (SEER) database. Kaplan-Meier survival analysis, relative survival rates (RSRs), and Cox proportional risk regression model were used to evaluate the relationship between these factors and prognosis.

Results: Compared with other sites, the small intestine and rectum have the highest incidence, and the appendix and rectum had the highest survival rate. The incidence was higher in males than in females, and the survival rate in males was close to females. Blacks had a higher incidence rate than whites, but similar survival rates. Incidence and survival rates were lower for G3&4 than for G1 and G2. Age, stage, and grade are risk factors.

Conclusions: This study described changes in the incidence and survival rates of GI-NETs from 1977 to 2016 and performed risk factor analyses related to GI-NETs.

KEYWORDS

gastrointestinal neuroendocrine tumors, incidence, survival, relative, risk factors

1 Introduction

Neuroendocrine tumors (NETs) are heterogeneous malignancies arising from the diffuse neuroendocrine system. NETs frequently originate in the gastroenteropancreatic (GEP) tract and the bronchopulmonary tree, and the incidence has steadily increased in the last 3 decades (1). Gastroenteropancreatic NETs (GEP-NETs) include gastrointestinal NETs (GI-NETs) and pancreatic NETs (pNETs). GI-NETs currently account for 80% of all primary NETs.

Notably, the GI-NETs incidence and prevalence have been increasing in the United States. Recent studies indicated the highest incidence of GI-NETs to be 3.56 per 100,000 population (2).

GI-NETs can occur in the stomach, colon, rectum, appendix, and small intestine. Recent studies have shown that the overall incidence and prognosis of patients with GI-NETs are related to the location and stage of the tumor (3). However, there is seldom a comprehensive analysis of GI-NETs in a large population, so more epidemiological studies are needed to analyze and evaluate the clinical characteristics of GI-NETs, providing important information for rapid diagnosis, accurate treatment, and effective prognosis assessment.

The epidemiological statistical analysis variables for most diseases include age, sex, and race. In addition, pathology grade and Socioeconomic status (SES) are also important. Pathological grade analysis of tumors may be helpful for treatment selection and prognosis assessment. It has been reported that SES is related to timely and effective access to medical resources by patients with malignant tumors. People with high SES can afford more testing and treatment costs. Therefore, to describe overall morbidity and survival trends and to assess factors associated with the survival and prognosis of GI-NETs, we analyzed 7 variables, including age, sex, race, SES, pathological grade, site, and stage, in a large population in the United States.

2 Material and methods

2.1 Data selection

All data on GI-NETs patients from 9 original Surveillance, Epidemiology, and End Results Program (SEER) over 4 decades (1977–2016) were collected from the SEER∗ Stat software program (version 8.4.0). The original 9 SEER sites include the states of San Francisco-Oakland (SF-O) Standard Metropolitan Statistical Area (SMSA), Connecticut, Hawaii, Iowa, New Mexico, Utah, Atlanta (metropolitan), Detroit (metropolitan), and Seattle (Puget Sound). The database, which registers about 400,000 cancer cases and stores cancer data for one-third of the U.S. population, is a great aid to medical researchers in the statistical analysis of diseases. Oncology and histologic codes of GI-NETs were determined by the International Classification of Diseases for Oncology (3rd editions) (ICD-O-3) codes. Primary locations of tumors of the gastrointestinal tract: C16.0-C20.9. Therefore, GI-NETs mainly include the following diseases: gastrinoma, malignant (8153/3); somatostatinoma, malignant (8156/3); carcinoid tumor, NOS (8240/3); enterochromaffin cell carcinoid (8241/3); enterochromaffin-like cell tumor, malignant (8242/3); goblet cell carcinoid (8243/3); mixed adenoneuroendocrine carcinoma (8244/3); adenocarcinoma tumor (8245/3); neuroendocrine carcinoma, NOS (8246/3); and atypical carcinoid tumor (8249/3). Data analyzed in this study included the incidence and relative survival rates (RSRs) of GI-NETs. Patients diagnosed with GI-NETs between 1977 and 2016 were enrolled and continued active follow-up was maintained. And excluded the patients diagnosed by autopsy or as stated on a death certificate. The time of follow-up for all analyses was from the date of diagnosis until death, the date of the last contact, or the end of the study period.

2.2 Variable definition

Sex, age, race, grade, SES, site, and stage were the patient variables examined in this study. The socioeconomic status (SES) of the area was determined using the county poverty rate (4, 5), which is the percentage of persons in the county living below the national poverty threshold in the Census 2000 (The 0-9.99%, 10%-19.9%, and 20%-56.92% of persons whose incomes are below the poverty 2000 level are defined as low-poverty, medium-poverty, and high-poverty, these can be selected in the SEER*Stat software) (6). The patients in the current study were classified by socioeconomic status (SES) (low-poverty, medium-poverty, high-poverty), sex, race (White, Black, and others), and age at diagnosis (0-44, 45-59, 60-74, and 75^{+}y). We used SEER histologic grade information to classify cases as grade (G) 1, well-differentiated; G2, moderately differentiated; G3, poorly differentiated; and G4, undifferentiated or anaplastic (7). Because of the small number of patients with low differentiation, we combined G3 and G4 into 1 category for all analyses. The stage of the tumor uses the "Combined Summary Stage (2004+) new" based on SEER, including localized, regional, and distant. Localized disease is defined as NETs that have not spread outside the wall of the primary organ, regional metastasis includes NETs that have spread beyond the wall into surrounding tissue or lymph nodes, and distant metastasis includes NETs that have spread to tissue or organs away from the primary organ (3).

2.3 Statistical analysis

We categorized all data of incidences and relative survival rates (RSRs) on GI-NETs patients by period: 1977–1986, 1987–1996, 1997–2006, and 2007-2016. The 12-month, 60-month, and 120-month RSRs were demonstrated by survival rate curves. The two-tailed log-rank test was used to access the difference in survival, using the Kaplan–Meier curves generated by GraphPad Prism 5.0. A two-tailed p-value < 0.05 was considered statistically significant. The Cox proportional hazard univariate and multivariate models were used to identify survival risk factors, including sex, age, race, grade, SES, site, and stage for the entire cohort.

3 Results

3.1 Trends in GI-NETs incidence at the nine original SEER sites over four decades from 1977-2016

A total of 21,983 patients diagnosed with GI-NETs between 1977 and 2016 in the SEER program of the National Cancer Institute at the nine original registry sites were collected. As indicated in Figure 1 and Supplementary Table 1, the GI-NETs incidence in the four decades continually increased (0.5 per 100,000 from 1977 to 1986, 1.2 per 100,000 from 1987 to 1996, 2.1 per 100,000 from 1997 to 2006, and 4.0 per 100,000 from 2007 to 2016). Similar trends were observed across all age groups in the study over the past 40 years, with the highest incidence in the 75+ age group in the first two decades and the highest incidence in the 60-74 age group in the last two decades.

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3.2 GI-NETs incidence by sex, race, SES, grade, and site

Males had a higher incidence of GI-NETs per 100,000 people than females (Figure 1). In race groups, the incidence of Blacks was higher than Whites and other races, and from 1977 to 2006, the rate of Blacks was approximately 2-fold higher than the average Whites (Supplementary Table 1). But there were significant racial differences, with whites in particular far outnumbering blacks. The medium-poverty group showed a slightly higher GI-NETs incidence than that of the low- and high-poverty groups. GI-NETs incidence per 100,000 in all poverty groups exhibited an increasing trend (from 0.5 to 1.0 to 2.0 to 4.0 in the low-poverty group, from 0.5 to 1.4 to 2.2 to 4.0 in the medium-poverty group and from 0.7 to 1.1 to 2.1 to 3.0 in the high-poverty group). In addition, we also analyzed the distribution characteristics of SES in different ethnic groups. The share of rich and poor by race has remained nearly constant in each decade (Figure 2). The incidence of the G1 group increased significantly in the last decade and the number of patients increased dramatically.

We divided the pathogenic sites of GI-NETs into five parts, including the stomach, small intestine, appendix, colon, and rectum. The incidence of GI-NETs in each site has increased significantly over the past four decades. The small intestine and rectum have the highest incidence in each decade (Figure 3). The incidence was highest in the last decade compared to the previous three (from 0.2 to 0.5 to 0.7 to 1.3 in the small intestine and from 0.1 to 0.4 to 0.7 to 1.3 in the rectum) (Supplementary Table 1).

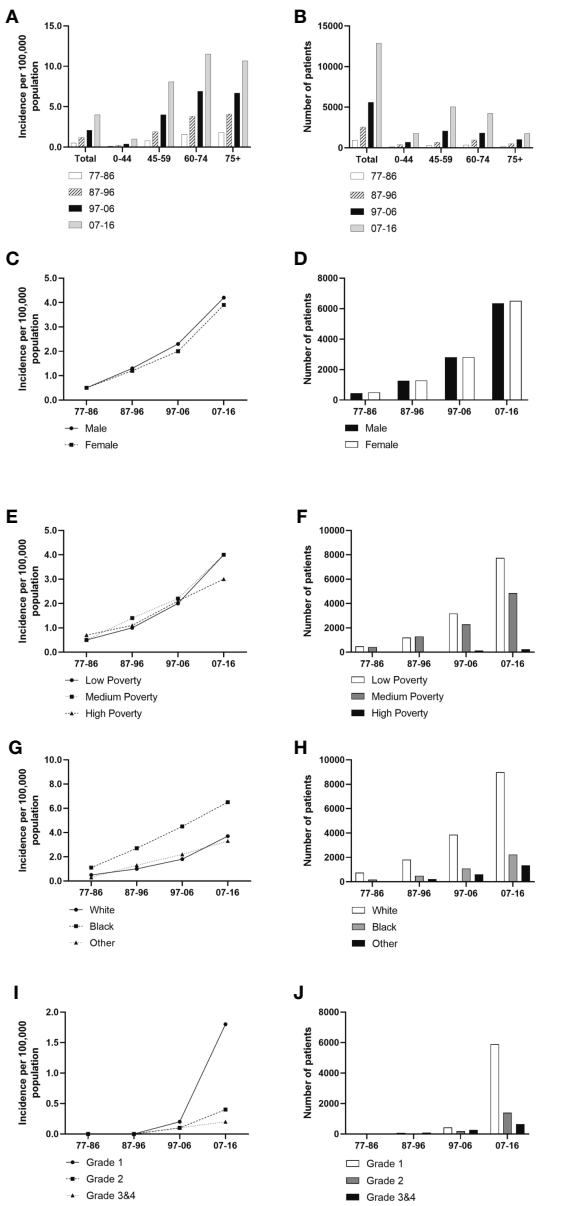

FIGURE 1
Incidence of Patients diagnosed with GI-NETs at the original nine SEER sites between 1977 and 2016. The incidence and number of GI-NETs cases are shown by age group (total and age 0-44 years, 45-59 years, 60-74 years, and over 75 years) and four-time periods. Incidence **(A, C, E, G, I)** and number **(B, D, F, H, J)** of GI-Nets cases were grouped by sex, SES, race, and grade, respectively.

3.3 Relative survival estimates for the 9 SEER sites over four decades in 1977-2016

The RSRs and survival times of patients with GI-NETs across the four decades improved for each age group analyzed (Figure 4). The one-year RSR gradually increased over time (83.9% from 1977 to 1986, 89.5% from 1987 to 1996, 92.4% from 1997 to 2006, and 95.3%

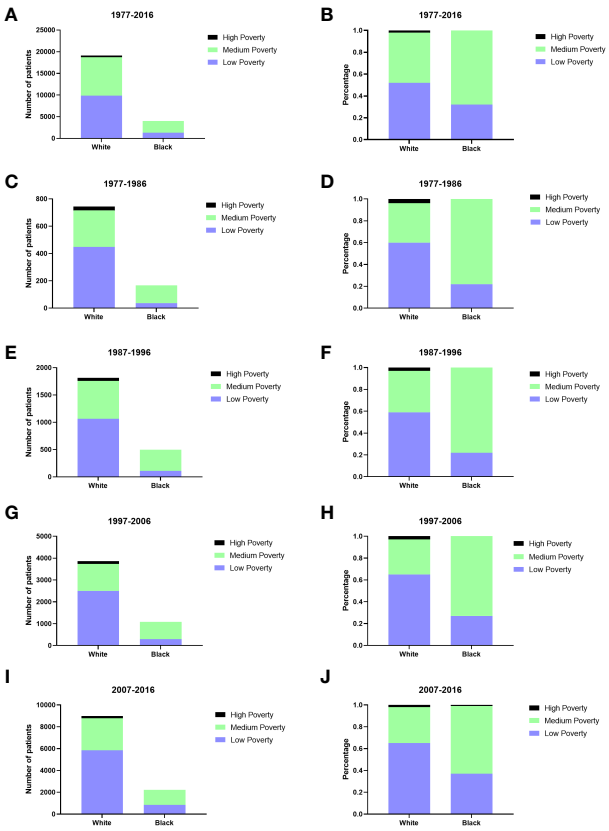

FIGURE 2
The numbers of patients with GI-NETs of SES in different races across four decades **(A, C, E, G, I)**; Changes in the distribution of SES in different races across four decades **(B, D, F, H, J)**.

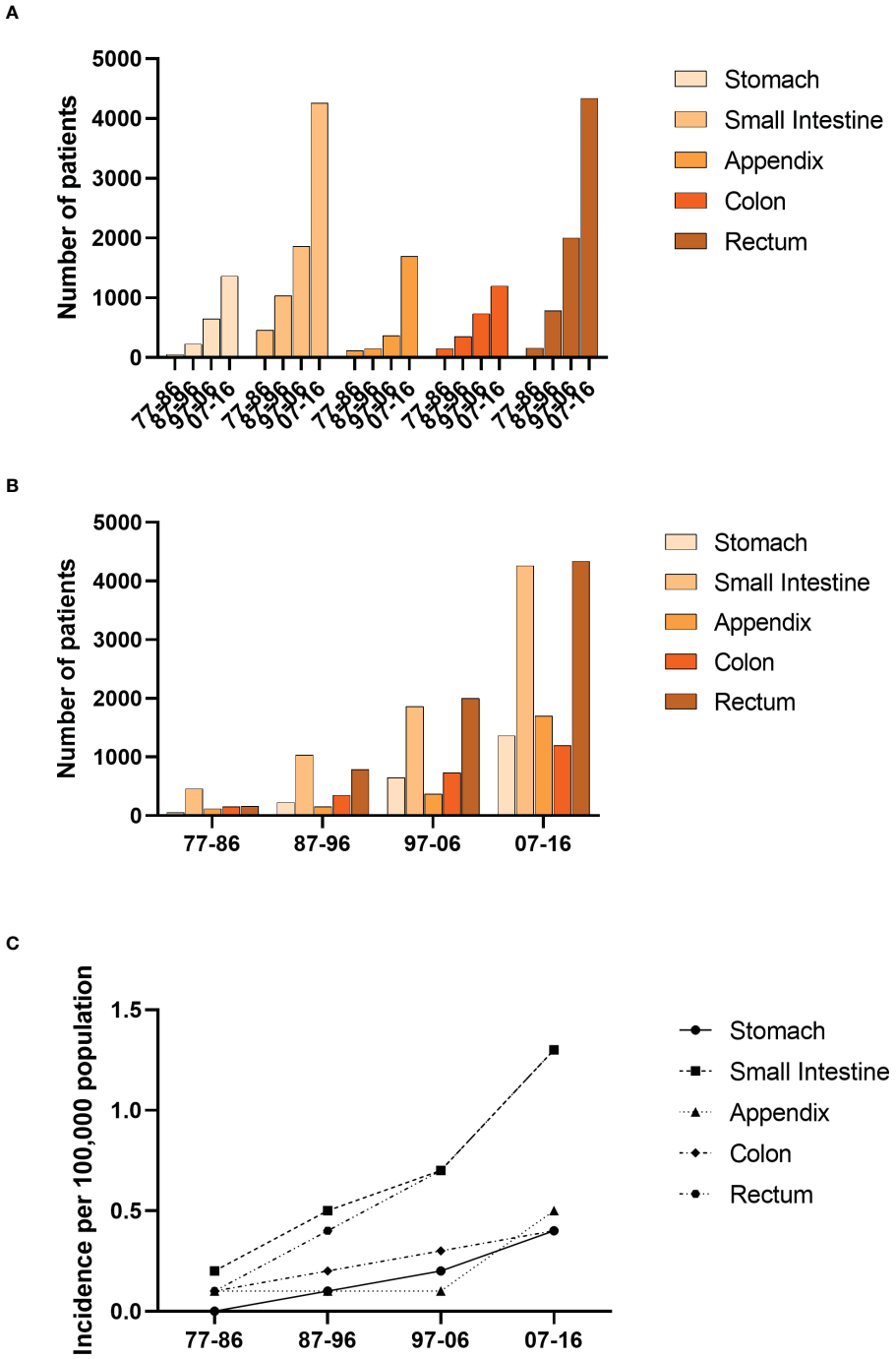

FIGURE 3
Incidence of Patients diagnosed with GI-NETs at the original nine SEER sites between 1977 and 2016. The number **(A, B)** and incidence **(C)** of GI-Nets cases are shown by site group (stomach, small intestine, appendix, colon, rectum) and four-time periods.

from 2007 to 2016; P < 0.0001 for each decade) (Table 1). Kaplan-Meier survival analysis indicated increases in survival time over the four decades for all age groups. The 5-year RSR increased from 69.9% to 80.3% to 85.9% to 90.1% over the four decades. The 10-year RSR increased from 62.4% to 72.1% to 80.7% to 86.3% over the fourth decade. The data indicate that the gap between five-year RSRs and 10-year RSRs has increased over the past four decades in the 45-59 and 60-74 age groups. (Figure 4 and Table 1).

The survival rate in both sexes over the four decades improved (Figure 5). Females showed a slightly higher 12-month RSR than males from 1977 to 2016 (84.5% for females vs. 83.3% for males from 1977 to 1986, 89.5% for females vs. 89.4% for males from 1987 to 1996, 92.9% for females vs. 91.8% for males from 1997 to 2006, 95.7% for females vs. 94.8% for males from 2007 to 2016) (Supplementary Table 2). However, from 1987 to 1996, the 60-month RSR of males was slightly higher than that of females (80.5% vs. 80.0%). The 120-month RSR of males was slightly higher than that of females in the first three decades (61.8% for females vs. 62.6% for males from 1977 to 1986, 70.0% for females vs. 74.2% for males from 1987 to 1996, 80.7% for females vs. 80.8% for males from 1997 to 2006). Only in the fourth

decade females have a higher 120-month RSR than males (86.6% for females vs. 85.9% for males from 2007 to 2016). The results showed that gender was statistically significant in the first decade, the third decade, and the last decade (p = 0.0035 in 1977–1986, p=0.0083 in 1997–2006, p <0.0001 in 2007-2016) (Figure 5). Notably, we found no significant sex disparities in age groups at 12- and 60- months of RSR. Therefore, the improvement in the overall survival rate of patients of different genders may be due to the improvement in social medical conditions and people's concerns.

3.4 Survival of GI-NETs in different race, SES, grade, and site groups

White patients exhibited a slightly higher 12-month RSR than Black patients in the first three decades (84.9% vs. 78.6% from 1977 to 1986, 89.1% vs. 88.6% from 1987 to 1996, 91.9% vs. 91.4% from 1997 to 2006) but the last decade was the opposite (94.7% vs. 96.2% from 2007 to 2016) (Supplementary Table 3). A similar tendency over time was observed in the 60-month survival rates. Overall, whites have slightly higher survival rates than blacks. The 12-, 60-, and 120-month RSR of other race groups was significantly higher than Whites and Blacks over the four decades. This is due to the low number of other ethnic groups (Figure 6 and Supplementary Table 3).

All SES groups showed improvement in survival rate across the four decades (Supplementary Figure 1). The low-poverty group consistently exhibited the highest 12-, 60-, and 120-month RSRs, except the 12-month RSR group in the second decade. In comparison with the low poverty group, the medium poverty groups of the 60-month RSR in the penultimate decade and 120-month RSR in the fourth decade were statistically significant (91.8%vs.83.8%%, p<0.0001;87.6%vs.83.9%, p<0.001) (Supplementary Table 4). Notably, Different SES groups were distributed differently among blacks and whites. There were more whites than blacks in the low poverty group (52% vs.32%), and more blacks than whites in the middle poverty group (68% vs. 46%) (Figure 2). The difference in survival between whites and blacks reflects the difference between the different SES groups, which have a certain connection. A similar trend was indicated in the Kaplan-Meier survival analysis for the three SES groups over the four decades. Lower poverty may be associated with higher survival.

Differences in long-term survival in pathologic grades have increased over the past 40 years (p=0.0005 in 1977–1986, p < 0.0001 in 1987–1996, p < 0.0001 in 1997–20066, and p < 0.0001 in 2007–2016) (Supplementary Figure 2). In grade groups, the G3&4 group consistently exhibited the lowest 12-, 60-, and 120-month RSRs, whereas the G1 group consistently showed the highest survival rates, except for the 12-month RSR group in the first decade. Overall, the RSR gap between G1 and G2 groups gradually narrowed, while the RSR gap between G3&4 groups continued to be significantly lower than that between the G1 and G2 groups. Kaplan Meier survival curve and log-rank test showed that the survival rate of low-grade GI-NETs increased year by year, suggesting that low-grade GI-NETs treatment was satisfactory. Although the incidence of G3&4 was low, there was little improvement in 40-year long-term survival (Supplementary Table 5). We can't ignore poorly differentiated GI-NETs. Therefore, clinical and medical workers need to pay more attention to this disease, to achieve a complete grasp of the disease.

The 12-, 60-, and 120-month RSR of the colon group was significantly lower than the remaining four groups over the four decades (Supplementary Figure 3 and Supplementary Table 6). The same trend was observed in all age groups. And the 12-, 60-, and 120-month RSR of the appendix group during the first decade was the highest. However, during the next three decades, the 12-, 60-, and 120-month RSR in the rectum was highest and remained stable. There was almost no significant difference in RSR between the stomach and the other four sites during the first decade. In the 75+ age group of the second decade, the 12-month RSR of the small intestine and rectum was

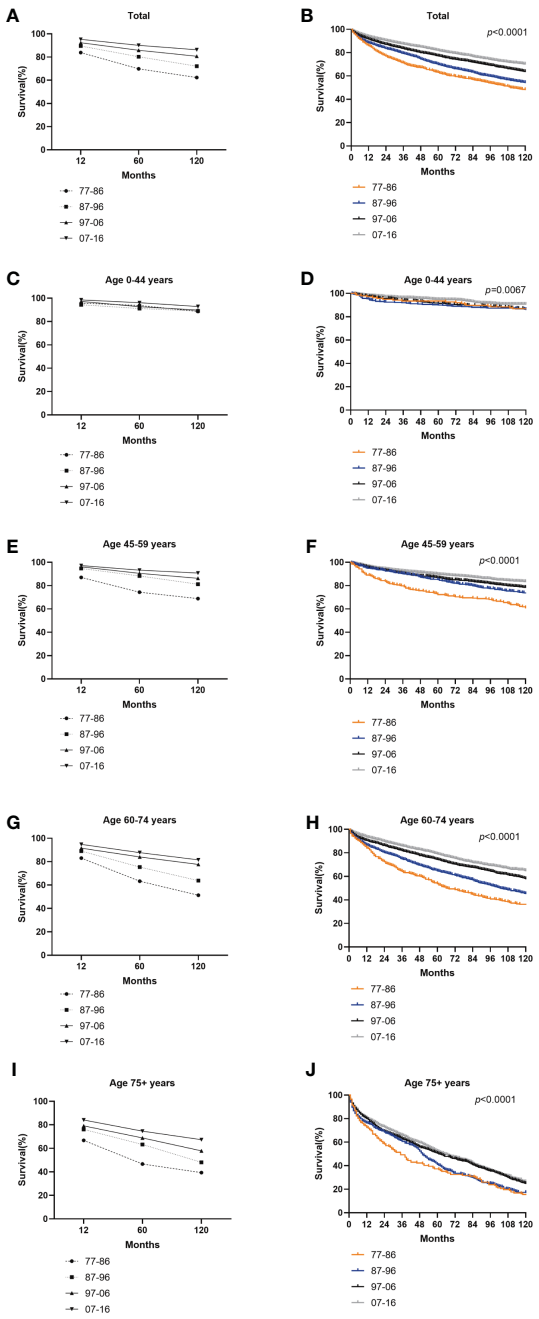

FIGURE 4
Trends in 10-year relative survival **(A, C, E, G, I)** and Kaplan-Meier survival analysis **(B, D, F, H, J)** for PATIENTS with GI-NETs during 1977-1986 (orange), 1987-1996 (blue), 1997-2006 (black), and 2007-2016 (gray), grouped by age (total and age 0-44 years, 45-59 years, 60-74 years and over 75 years).

TABLE 1 Relative survival rates of GI-NETs during the periods of 1977-1986, 1987-1996, 1997-2006, and 2007-2016 at nine SEER sites.

Age group	Decade			
	1977-1986	1987-1996	1997-2006	2007-2016
12-Mo Rs				
All	83.9 ± 1.4 (801)	89.5 ± 0.7 (2105)***	92.4 ± 0.4 (4623)**	95.3 ± 0.2 (10422)***
0-44	95.7 ± 1.8 (133)	94.4 ± 1.2 (363)	97.2 ± 0.7 (675)	98.5 ± 0.3 (1665)
45-59	87.0 ± 2.2 (255)	94.7 ± 1.0 (624)**	96.1 ± 0.5 (1846)	97.2 ± 0.3 (4465)
60-74	83.0 ± 2.4 (288)	89.0 ± 1.3 (752)*	91.5 ± 0.8 (1425)	94.8 ± 0.5 (3156)**
75+	66.8 ± 4.7 (125)	76.1 ± 2.5 (366)*	79.1 ± 1.8 (677)	84.1 ± 1.3 (1136)**
60-Mo Rs				
All	69.9 ± 1.9 (801)	80.3 ± 1.1 (2105)***	85.9 ± 0.7 (4623)***	90.1 ± 0.4 (10422)***
0-44	93.8 ± 2.2 (133)	91.1 ± 1.6 (363)	92.7 ± 1.1 (675)	96.1 ± 0.6 (1665)
45-59	74.4 ± 3.0 (255)	88.3 ± 1.5 (624)**	90.5 ± 0.8 (1846)	93.3 ± 0.5 (4465)
60-74	63.3 ± 3.4 (288)	75.4 ± 2.0 (752)**	84.0 ± 1.3 (1425)**	87.7 ± 0.8 (3156)
75+	46.7 ± 6.4 (125)	63.3 ± 4.0 (366)*	69.8 ± 2.8 (677)	74.6 ± 2.3 (1136)
120-Mo Rs				
All	62.4 ± 1.8 (801)	72.1 ± 1.4 (2105)*	80.7 ± 0.8 (4623)***	86.3 ± 0.7 (10422)***
0-44	88.6 ± 3.1 (133)	89.0 ± 1.9 (363)	89.8 ± 1.3 (675)	92.9 ± 1.1 (1665)
45-59	68.9 ± 3.4 (255)	81.2 ± 1.9 (624)	86.3 ± 1.0 (1846)	90.8 ± 0.8 (4465)
60-74	51.3 ± 4.0 (288)	63.8 ± 2.5 (752)	77.6 ± 1.7 (1425)***	81.5 ± 1.4 (3156)
75+	39.4 ± 8.4 (125)	48.1 ± 5.4 (366)	57.9 ± 3.9 (677)	67.4 ± 3.9 (1136)

Data are represented as mean ± standard error of the mean, with the number of patients in parentheses.
Mo, month; RS, relative survival; SEM, standard error of the mean.
*P < 0.01 for comparisons with the preceding decade.
**P < 0.001 for comparisons with the preceding decade.
***P < 0.0001 for comparisons with the preceding decade.

significantly higher than that of the stomach (52.3% vs. 79.4, p<0.01;52.3% vs. 90.3%, p<0.001). Over the next three decades, rectum relative survival rates at 12-, 60-, and 120- months increased significantly. Differences in long-term survival have gradually diminished over the past four decades (Supplementary Figure 4).

Cox risk-proportional regression model assessed the prognostic value of seven risk factors (sex, age, race, SES, grade, stage, and site) for GI-NETs. Due to the incomplete update of the database, we have analyzed the effect of tumor stage on prognosis only in the last two decades. Analysis showed that stage, age, and pathological grade are risk factors for the prognosis of patients with GI-NETs. Data analysis results showed that the hazard ratio of the stage (p<0.001 and p<0.001), age (p=0.015, p < 0.001, p < 0.001 and p < 0.001 in 1977–2016), and grade (p=0.046, p < 0.001, p < 0.001, and p < 0.001 in 1977–2016) were greater than 1, indicating that the higher the stage, the shorter the survival time. Similarly, the older the age, the shorter the survival time; the less differentiated, the shorter the survival time. Other risk factors, such as race, were a risk factor for GI-NETs over the first, second, and last decades and were no longer a risk factor for GI-NETs in the third decade (p=0.012, HR=3.081, 95% CI 1.280–7.418 in 1977-1986, p=0.008, HR=2.365, 95% CI 1.252–4.470 in 1987-1996, p<0.001, HR=1.349, 95% CI 1.166-1.562 in 2007-2016). In addition, sex was not a risk factor for GI-NETs from 1977 to 1996, but became a risk factor for GI-NETs in the following two

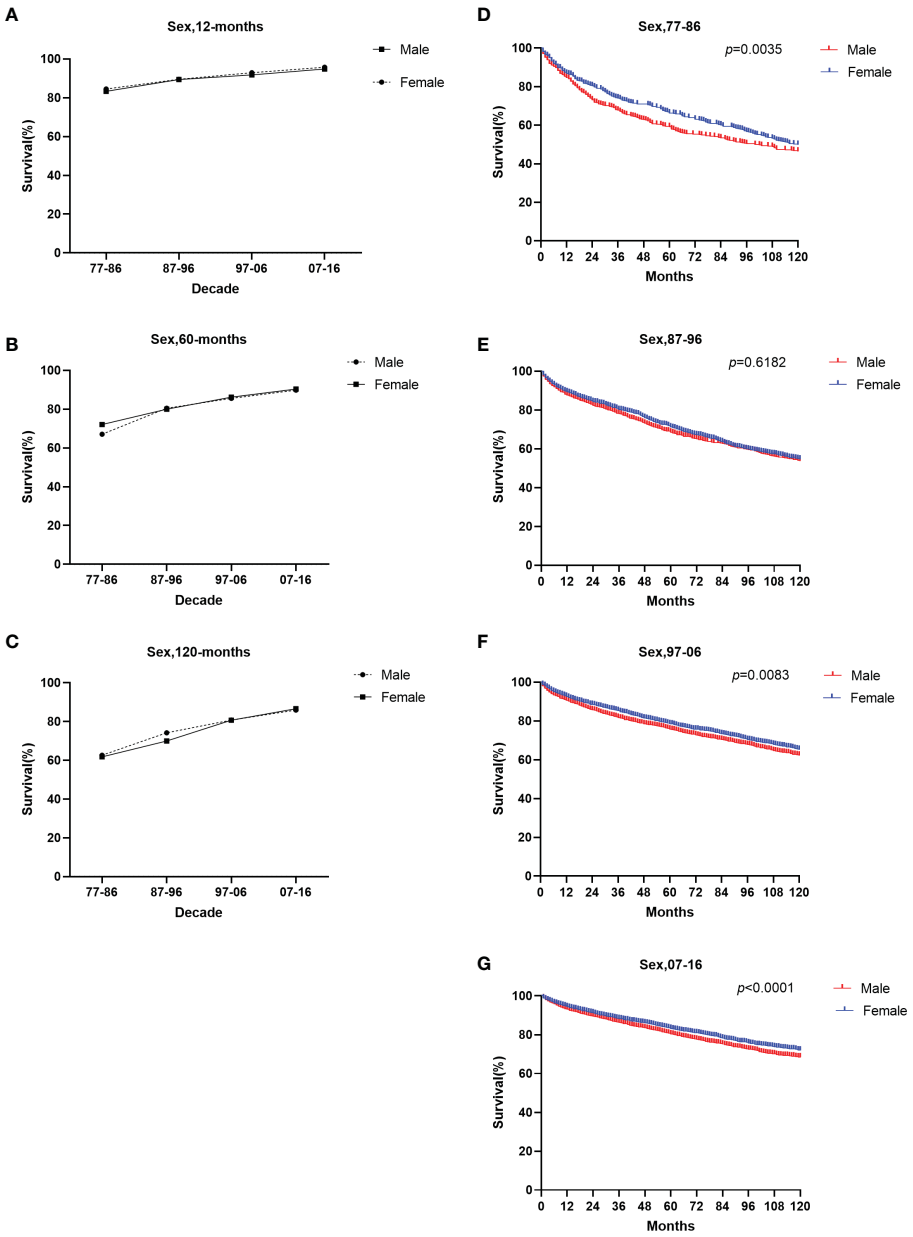

FIGURE 5
Trends in relative survival rate **(A–C)** and Kaplan–Meier survival curves **(D–G)** for patients with GI-NETs at 9 SEER sites according to sex group (male and female) in 1977–1986, 1987–1996, 1997–2006, and 2007-2016.

decades, influencing patient outcomes (p=0.011, HR=1.396, 95% CI 1.081-1.804 in 1997-2006, p<0.001, HR=1.220, 95% CI 1.108-1.344 in 2007-2016). Site of GI-NETs in the last two decades as a risk factor affecting GI-NETs prognosis. (Table 2).

4 Discussion

The GI-NETs incidence and the RSRs (relative survival rates) for GI-NETs both increased in each decade from 1977 to 2016. In particular, the number of GI-NETs had increased significantly over the past decade (Figure 1). Across all the variables we looked at, the gap in long-term survival narrowed. However, ten-year relative survival remained very low for the occurrence of GI-NETs in the colon, poorly differentiated and undifferentiated GI-NETs. Relative survival rates have ranged from 13.7% to 27.1% over the past four decades, indicating an urgent need to develop effective therapies to improve this situation to significantly improve survival in patients with poorly differentiated GI-NETs.

In our population-based study, the incidence of GI-NETs has increased dramatically over the past four decades. From the first decade to the fourth decade, the incidence increased eightfold from 0.5 to 4.0. This may be related to the fact that there was little understanding of GI-NETs in the past, and in 2000 WHO classification published, carcinoid was used separately from neuroendocrine neoplasms and neuroendocrine neoplasms for the first time, which made the classification of endocrine neoplasms clearer (8). The most significant change in 2019 WHO classification

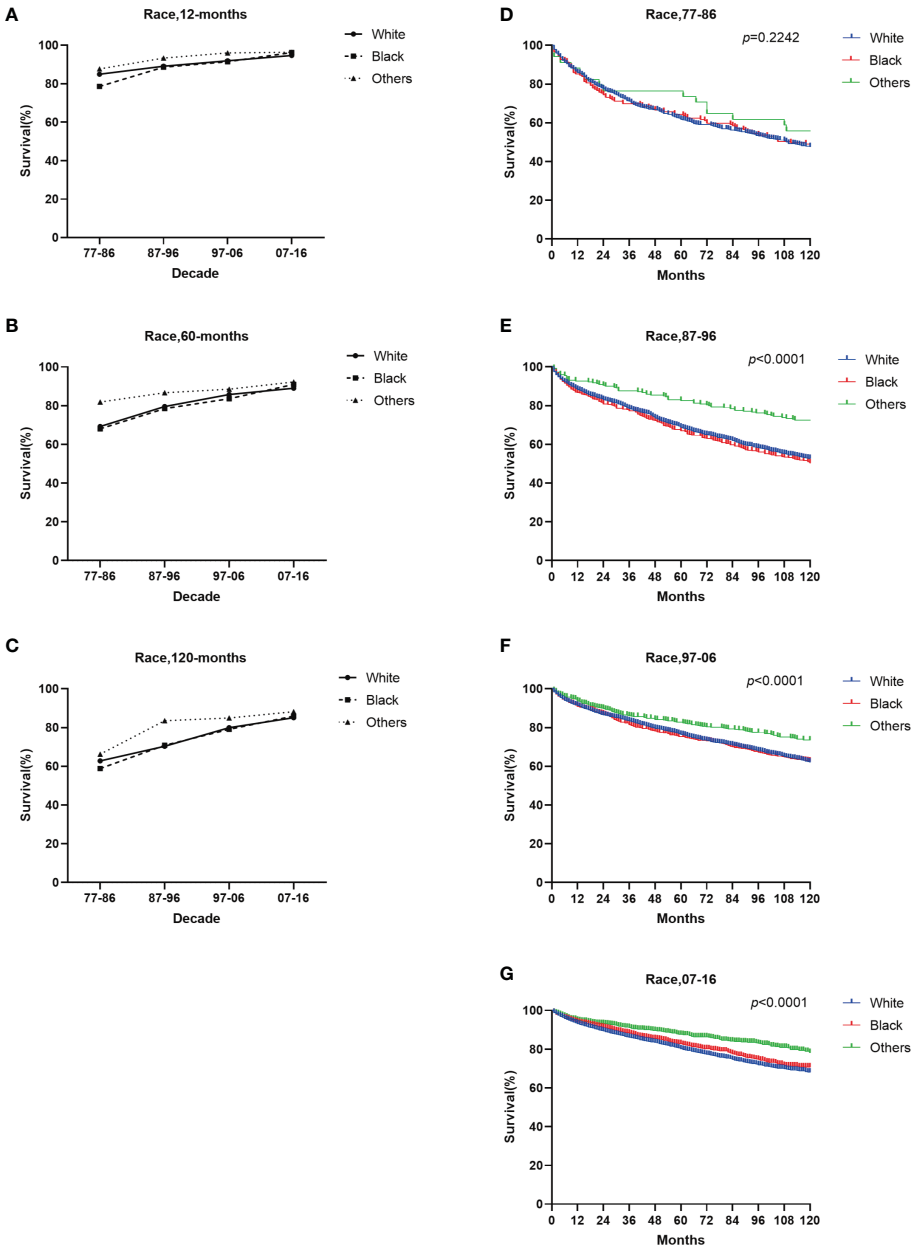

FIGURE 6
Trends in relative survival rate **(A–C)** and Kaplan–Meier survival curves **(D–G)** for patients with GI-NETs at 9 SEER sites according to race group (whites, blacks, and others) in 1977–1986, 1987–1996, 1997–2006, and 2007-2016.

of digestive tumors is the neuroendocrine tumor classification system (9). In addition, the increased incidence may be due to the increased prevalence and use of gastrointestinal endoscopy, resulting in a higher detection rate of GI-NETs (10). With the development of medical technology, in addition to conventional imaging examinations such as CT and MRI, more and more imaging techniques such as SSTR positron emission tomography/computed tomography (PET/CT) using 68Ga-labeled somatostatin analog (11–13) and endoscopic ultrasonography (14, 15), have been used to detect tumors. These tests have greatly increased the detection of GI-NETs. With the improvement in people's living standards, people pay more attention to their health status, which makes them sensitive to the possible early symptoms of GI-NETs. The widespread and vigorous promotion of physical examination has also made it important to detect tumors earlier, especially in the early and asymptomatic stages of the disease.

The overall incidence of GI-NETs per 100,000 people increased significantly from 0.5 to 1.2 to 2.1 to 4.0 per decade. And patients over 60 years old account for the majority of the population. At the same time, the incidence of GI-NETs was higher in men than in women per 100,000 people in the study, which may be because men smoke more than women. Based on one population study, smoking may increase the risk of developing GI-NETs (16). Blacks were more likely to develop GI-NETs than whites and other ethnic groups, and the gap in their incidence widened each year over the 40 years studied. The incidence continued to increase throughout the study period in all SES groups. Compared with the previous three decades, the fourth decade saw the largest increase in all SES groups, especially the low

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TABLE 2 Summary data for Cox regression analysis of survival in patients with GI-NETs from 1977 to 2016 at nine SEER sites.

Variable	Relative risk (95% CI)	*P* value
All 1977-1986		
Univariate		
Sex		
Female	1	
Male	1.223 (0.652-2.295)	0.530
Age	1.043 (1.019-1.068)	<0.001
Race		
White	1	
Black	3.786 (1.650-8.685)	0.002
Other	0.541 (0.129-2.277)	0.402
SES		
Low poverty	1	
Medium poverty	1.071 (0.566-2.027)	0.832
High poverty	2.690 (0.342-21.158)	0.347
Grade		
G1	1	
G2	2.477 (0.863-7.113)	0.092
G3&4	3.071 (1.502-6.277)	0.002
Site		
Stomach	1	
Small intestine	0.562 (0.169-1.872)	0.348
Appendix	0.294 (0.072-1.204)	0.089
Colon	0.703 (0.233-2.120)	0.532
Rectum	0.339 (0.093-1.237)	0.101
Multivariate		
Age	1.033 (1.006-1.060)	0.015
Race		
White	1	
Black	3.081 (1.280-7.418)	0.012
Other	0.926 (0.208-4.117)	0.920
Grade		
G1	1	
G2	2.124 (0.704-6.402)	0.181
G3&4	2.170 (1.015-4.642)	0.046
All 1987-1996		
Univariate		
Sex		
Female	1	
Male	0.912 (0.681-1.221)	0.537

(Continued)

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TABLE 2 Continued

Variable	Relative risk (95% CI)	*P* value
Age	1.051 (1.038-1.065)	<0.001
Race		
White	1	
Black	1.142 (0.761-1.714)	0.521
Other	1.858(1.004-3.439)	0.049
SES		
Low poverty	1	
Medium poverty	1.090 (0.814-1.460)	0.564
High poverty	0.000	0.953
Grade		
G1	1	
G2	1.339 (0.894-2.005)	0.156
G3&4	3.066 (2.167-4.338)	<0.001
Site		
Stomach	1	
Small intestine	0.455 (0.279-0.740)	0.002
Appendix	0.248 (0.101-0.613)	0.003
Colon	0.735 (0.457-1.181)	0.203
Rectum	0.497 (0.285-0.867)	0.014
Multivariate		
Age	1.048 (1.035-1.063)	<0.001
Race		
White	1	
Black	1.285 (0.838-1.969)	0.250
Other	2.365 (1.252-4.470)	0.008
Grade		
G1	1	
G2	1.095 (0.715-1.678)	0.676
G3&4	2.258 (1.555-3.278)	<0.001
Site		
Stomach	1	
Small intestine	0.662 (0.400-1.095)	0.108
Appendix	0.499 (0.198-1.254)	0.139
Colon	0.777 (0.475-1.270)	0.314
Rectum	0.740 (0.421-1.304)	0.298
All 1997-2006		
Univariate		
Sex		
Female	1	

(Continued)

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TABLE 2 Continued

Variable	Relative risk (95% CI)	*P* value
Male	1.261 (1.069-1.486)	0.006
Age	1.051 (1.044-1.059)	<0.001
Race		
White	1	
Black	1.184 (0.941-1.488)	0.149
Other	0.904 0.665-1.228)	0.517
SES		
Low poverty	1	
Medium poverty	1.097 (0.927-1.298)	0.283
High poverty	0.731 (0.428-1.248)	0.251
Grade		
G1	1	
G2	1.922 (1.543-2.394)	<0.001
G3&4	4.750 (3.917-5.760)	<0.001
Site		
Stomach	1	
Small intestine	0.682 (0.539-0.863)	0.001
Appendix	0.613 (0.399-0.941)	0.025
Colon	1.234 (0.971-1.567)	0.085
Rectum	0.369 (0.269-0.506)	<0.001
Stage		
Localized	1	
Regional	1.678 (1.232-2.285)	0.001
Distant	4.508 (3.318-6.125)	<0.001
Multivariate		
Sex		
Female	1	
Male	1.396 (1.081-1.804)	0.011
Age	1.045 (1.034-1.057)	<0.001
Grade		
G1	1	
G2	1.745 (1.241-2.452)	0.001
G3&4	3.278 (2.369-4.536)	<0.001
Site		
Stomach	1	
Small intestine	0.516 (0.345-0.771)	0.001
Appendix	0.458 (0.233-0.902)	0.024
Colon	0.619 (0.413-0.928)	0.020
Rectum	0.541 (0.339-0.861)	0.010

(Continued)

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TABLE 2 Continued

Variable	Relative risk (95% CI)	*P* value
Stage		
Localized	1	
Regional	1.194 (0.842-1.693)	0.320
Distant	4.253 (2.952-6.126)	<0.001
All 2007-2016		
Univariate		
Sex		
Female	1	
Male	1.168 (1.062-1.285)	0.001
Age	1.066 (1.062-1.070)	<0.001
Race		
White	1	
Black	0.820 (0.711-0.946)	0.007
Other	0.719 (0.596-0.866)	0.001
SES		
Low poverty	1	
Medium poverty	1.017 (0.920-1.125)	0.736
High poverty	1.077 (0.749-1.548)	0.689
Grade		
G1	1	
G2	1.547 (1.358-1.762)	<0.001
G3&4	8.468 (7.587-9.450)	<0.001
Site		
Stomach	1	
Small intestine	.826 (0.708-0.964)	0.015
Appendix	0.456 (0.368-0.564)	<0.001
Colon	1.728 (1.460-2.046)	<0.001
Rectum	0.377 (0.312-0.457)	<0.001
Stage		
Localized	1	
Regional	2.040 (1.804-2.306)	<0.001
Distant	6.260 (5.580-7.024)	<0.001
Multivariate		
Sex		
Female	1	
Male	1.220(1.108-1.344)	<0.001
Age	1.058(1.054-1.063)	<0.001
Race		
White	1	

(Continued)

TABLE 2 Continued

Variable	Relative risk (95% CI)	*P* value
Black	1.349 (1.166-1.562)	<0.001
Other	0.958 (0.792-1.159)	0.658
Grade		
G1	1	
G2	1.297 (1.137-1.479)	<0.001
G3&4	4.443 (3.889-5.076)	<0.001
Site		
Stomach	1	
Small intestine	0.636 (0.536-0.754)	<0.001
Appendix	0.654 (0.525-0.814)	<0.001
Colon	0.934 (0.783-1.114)	0.446
Rectum	0.647 (0.532-0.786)	<0.001
Stage		
Localized	1	
Regional	1.402 (1.220-1.611)	<0.001
Distant	4.245 (3.712-4.856)	<0.001

95% CI, 95% confidence interval; SES, socioeconomic status.

and middle poverty groups. This may be because the low and middle poverty groups pay more and more attention to their health over time, and the detection rate of GI-NETs is higher and higher. However, due to the heavy medical economic burden of the high poverty group, compared with the low and middle poverty groups, it showed steady and continuous growth. With the classification of digestive neuroendocrine tumors by WHO, the incidence of G1 increased significantly compared with poorly differentiated GI-NETs. The G1 has seen the biggest growth over the past decade. This may be due to the clear classification of GI-NETs and the deepening understanding of GI-NETs. Our study showed that the incidence was significantly higher in the small intestine and rectum than in other sites. The results of this study are consistent with those of other studies (17, 18).

Long-term survival has shown a similar trend to the incidence of GI-NETs over the past 40 years (Figure 1 and Figure 2). It is worth noting that the RSR of the 120 months 2007-2016 was 1.38 times that of 1977-1986. Similar to the incidence rate, RSR increases gradually with each decade. Among them, the RSR of 12, 60, and 120 months from 1977 to 1986 showed the most significant increase compared with the RSR of 1987 to 1996 (Table 1). This may indicate that since 1987, more attention has been paid to gastrointestinal neuroendocrine tumors, as well as the search for sensitive detection methods and effective treatment. During the last 30 years, the RSR grew steadily each decade. It shows that clinicians are increasingly improving detection rates with more sensitive tests and improving survival rates with more effective treatments. With the continuous improvement of medical treatment, the emergence of new biomarkers and accurate histological assessment and pathological biopsy have greatly improved the survival rate of GI-NETs.

In our study, the prognosis was best in the rectum and appendix. The 60-months survival rates of the rectum and appendix were 97.6% and 90.5%. In addition, the 60-months survival rates of GI-NETs in the other three sites were stomach (83.3%), small intestine (88.6%), and colon (69.9%), respectively. At the same time, our study found that the prognosis of the colon and stomach was worse compared to the rectum and appendix. Long-term survival of the colon and stomach has improved significantly over time but remains low. Moreover, the long-term survival of the rectum and appendix was more stable than that of other sites in our study. With the increased use of colonoscopy and the maturation of treatment modalities, the survival of colonic NET and gastric NET has improved, but it remains in a precarious state. Newer techniques and treatments are needed to further improve survival.

Improvements in long-term survival were observed for both sexes, with females generally having higher survival rates than males (Figure 5). The incidence rate for blacks has been significantly higher than for whites and other races over the past four decades, but the survival rate for blacks has been lower than for whites and other races over the last 30 years. Only in the last decade, slightly higher than whites (Figure 6). Therefore, the etiology and treatment of black disease need further attention and research. We looked at the socioeconomic status of diagnosed GI-NETs patients over the last 40 years, and survival was higher in the low poverty group (Supplementary Figure 1). The higher survival rates of whites compared to blacks may be attributed to the fact that most whites may have sufficient economic conditions to ensure a comfortable living environment and diet, as well as better access to medical services and more accurate diagnosis of diseases than other races. In terms of

grade, the incidence of highly differentiated tumors was higher than that of undifferentiated tumors. Survival rates are on a similar trend (Supplementary Figure 2). The increasing incidence of poorly differentiated and undifferentiated tumors over the past four decades, while survival remains low, suggests that medical researchers need to pay more attention to the treatment of poorly differentiated and undifferentiated tumors.

Age, stage, and pathological grade were the risk factors for GI-NETs by Cox proportional risk regression model (Table 2). Through age grouping comparison, the incidence rate of elderly patients over 60 years old increased significantly, while the survival rate decreased significantly, which may be attributed to the deterioration of physical function, decreased immunity, and poor tolerance to drugs, surgery, and other treatments in elderly patients. At the same time, the elderly suffer from more basic diseases, such as high blood pressure and diabetes, which put a heavy burden on their bodies. Recent studies have shown that more than 80% of GI-NETs patients have metastases by the time they are diagnosed (19). The liver is the most common site of metastasis. For patients with advanced metastasis, there is currently no clinically effective treatment, resulting in a reduced survival rate for these patients (20). Current treatment methods mainly include drug therapy to relieve hormone-related symptoms or syndromes (21, 22) tumor growth control (23, 24) endoscopic therapy (lesions confined to the mucosa and submucosa) (25, 26) gastrointestinal surgery, interventional therapy (mainly for liver metastases) (27, 28) and radionuclide therapy (29, 30). However, these treatments can be too taxing for elderly patients. Although some progress has been made in the treatment of GI-NETs, there is still no relatively safe and effective treatment, especially in elderly patients with metastasis.

Tumor grade was an important prognostic factor by multivariate Cox regression analysis (Table 2). The worse the differentiation, the worse the prognosis and the lower the patient's survival rate. With advances in medical technology, the incidence of G1 GI-NETs has increased steeply in the last decade, probably due to the greater understanding of the nomenclature, classification, and histological and pathological features of GI-NETs (1, 31). In our study, the relative risk of tumor grade was the highest. Patients with highly differentiated GI-NETs can survive for a long time even with metastasis. However, poorly differentiated or undifferentiated GI-NETs are considered to be likely to transition to cancer, leading to a significant reduction in patient survival. Therefore, it is necessary to clarify the tumor grade of patients and carry out close observation and follow-up of patients.

Yao et al. reported an increase in the incidence of neuroendocrine tumors, but there was no significant gender difference (32). However, the overall incidence was higher in men than women in our study. In multivariate Cox regression analysis, gender and site of tumor gradually became an independent risk factors for GI-NETs over time, while race might not be considered as an independent risk factor for GI-NETs. We might argue that gender differences emerge as the number of cases increases, while racial differences decrease in the context of the current global integration. This is good news for us, which can promote our further understanding of GI-NETs and improve the clinical management of patients.

Some studies have analyzed different sites of GI-NETs and reached conclusions (3), but no study has analyzed the overall epidemiological characteristics of GI-NETs at present., but no study has analyzed the overall epidemiological characteristics of GI-NETs at present. Here, our analysis of the epidemiology of GI-NETs from 1977 to 2016 may provide additional information about the disease to emphasize the urgency of early diagnosis and improved treatment of GI-NETs and help guide the development of clinical management programs.

There are some limitations in our study. First of all, the classification and definition of neuroendocrine tumors were not clear in the early stage, and most of them were benign lesions, which may result in the lack of certain information on unregistered GI-NETs in the SEER database. Deviations in data availability will have a certain impact on our results and conclusions. Secondly, some investigations have shown that the incidence of GI-NETs is related to other potential prognostic factors, such as marital status, but we did not include the analysis in this study.

5 Conclusion

Here, we collected eligible cases of GI-NETS from the U.S. Cancer Database from 1977 to 2016 for a new epidemiological analysis of the disease, including its incidence, survival, and risk factor assessment. In recent years, with the improvement of medical technology, the detection and treatment of GI-NETs have greatly helped, so the incidence and survival rate of GI-NETs has increased significantly. Age, stage, and pathological grade are considered independent risk factors for GI-NETs. According to our study, patients in the 60-74 age group, the small intestine group, the rectum group, and G1 patients had the highest incidence. The incidence is higher in men than women. The interaction between race and SES affects early diagnosis and treatment decisions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

PX, ML, and LW contributed to conception and design of the study. ML and MG organized the database. WL and SC performed the statistical analysis. YZ and ML wrote the first draft of the manuscript. ZG, RL, MG, and ML wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1079575/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Trends in relative survival rate **(A–C)** and Kaplan–Meier survival curves **(D–G)** for patients with GI-NETs at 9 SEER sites according to SES group (low poverty, medium poverty, and high poverty) in 1977–1986, 1987–1996, 1997–2006, and 2007-2016.

SUPPLEMENTARY FIGURE 2
Trends in relative survival rate **(A–C)** and Kaplan–Meier survival curves **(D–G)** for patients with GI-NETs at 9 SEER sites according to grade group (G1, G1, and G3&4) in 1977–1986, 1987–1996, 1997–2006, and 2007-2016.

SUPPLEMENTARY FIGURE 3
Trends in relative survival rate **(A–C)** for patients with GI-NETs at 9 SEER sites according to site group (stomach, small intestine, appendix, colon, rectum) in 1977–1986, 1987–1996, 1997–2006, and 2007-2016.

SUPPLEMENTARY FIGURE 4
Kaplan–Meier survival curves **(A–E)** for patients with GI-NETs at 9 SEER sites according to site group (stomach, small intestine, appendix, colon, rectum) in 1977-2016, 1977–1986, 1987–1996, 1997–2006, and 2007-2016.

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Sex differences in methylation profiles are apparent in medulloblastoma, particularly among SHH tumors

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Background: Medulloblastoma, the most common malignant pediatric brain tumor, displays marked sex differences in prevalence of the four main molecular subgroups: SHH, WNT, Group 3 and Group 4. Males are more frequently diagnosed with SHH, Group 3 and 4 tumors, which have worse prognoses than WNT tumors. Little is known about sex differences in methylation profiles within subgroups.

Methods: Using publicly available methylation data (Illumina HumanMethylation450K array), we compared beta values for males versus females. Differentially methylated positions (DMP) by sex within medulloblastoma subgroups were identified on the autosomes. DMPs were mapped to genes and Reactome pathway analysis was run by subgroup. Kaplan-Meier survival curves (Log-Rank p-values) were assessed for each sex within subgroup. *MethylCIBERSORT* was used to investigate the tumor microenvironment using deconvolution to estimate the abundances of immune cell types using DNA methylation data.

Results: There were statistically significant differences in sex by medulloblastoma subgroups (chi-squared p-value=0.00004): Group 3 (n=144; 65% male), Group 4 (n=326; 67% male), SHH (n=223; 57% male) and WNT (n=70; 41% male). Females had worse survival than males for SHH (p-value=0.02). DMPs by sex were identified within subgroups: SHH (n=131), Group 4 (n=29), Group 3 (n=19), and WNT (n=16) and validated in an independent dataset. Unsupervised hierarchical clustering showed that sex-DMPs in SHH did not correlate with other tumor attributes. Ten genes with sex DMPs (*RFTN1*, *C1orf103*, *FKBP1B*,

COL25A1, *NPDC1*, *B3GNT1*, *FOXN3*, *RNASEH2C*, *TLE1*, and *PHF17)* were shared across subgroups. Significant pathways ($p<0.05$) associated with DMPs were identified for SHH (n=22) and Group 4 (n=4) and included signaling pathways for RET proto-oncogene, advanced glycosylation end product receptor, regulation of KIT, neurotrophic receptors, NOTCH, and TGF-β. In SHH, we identified DMPs in four genes (*CDK6*, *COL25A1*, *MMP16*, *PRIM2)* that encode proteins which are the target of therapies in clinical trials for other cancers. There were few sex differences in immune cell composition within tumor subgroups.

Conclusion: There are sexually dimorphic methylation profiles for SHH medulloblastoma where survival differences were observed. Sex-specific therapies in medulloblastoma may impact outcomes.

KEYWORDS

medulloblastoma, sex differences, methylation, survival, pediatric and young adult cancer

1 Introduction

Medulloblastoma is the most common malignant pediatric brain tumor (1) affecting 400 United States (US) children each year (2). Medulloblastoma is comprised of four main molecular subgroups (3) that are prognostic with sonic hedgehog (SHH), Group 3 and Group 4 tumors associated with worse prognoses than wingless (WNT) tumors (4). We have shown there to be a male predominance in medulloblastoma incidence and risk in the US and around the globe in population-based studies (5–7). Unfortunately, with the recent use of these subgroups for prognosis they are almost entirely lacking in population-based and registry studies. As such, we must rely on clinical studies to understand sex differences in outcomes. From clinical studies, there are documented differences in the distribution of medulloblastoma subgroups by sex, with males more frequently diagnosed with the high-risk Groups 3 and 4 subgroups (8). While there are differences in survival between subgroups, little is known about sex differences in survival within subgroups. Further, there is no work examining sex differences in the genomic landscape of medulloblastoma, which may have significant implications for treatment and outcomes.

Sex differences in brain tumor development and progression are multifactorial and depend on the sex chromosome complement (9), immune regulation (10), and intrinsic differences in methylation that begin at conception through the life course (11). Based on the male excess in brain tumor diagnoses at all ages, it is unlikely that sex hormones are a main driving force mechanistically (12). Sex differences in epigenetics as measured by methylation have been documented throughout various organ systems in the body including the brain (13). DNA hypomethylation is often associated with carcinogenesis. Therefore, sex differences in methylation patterns could impact medulloblastoma formation and growth (13). Further, as methylation plays an integral role in brain tumor development and progression, it is important to identify sex differences in methylation profiles, which may help us understand etiology of the disease and identify potential therapeutic targets. Therefore, using publicly available medulloblastoma methylation data (14, 15), we aimed to identify sex differences in methylation profiles within subgroups.

Abbreviations: US, United States; SHH, sonic hedgehog; WNT, wingless; HR, hazard ratios; 95% CI, 95% confidence intervals; SNPs, single nucleotide polymorphisms; DMPs, Differentially methylated positions; IPA, Ingenuity Pathway Analysis.

2 Materials and methods

2.1 Data source

Using publicly available DNA methylation data collected by Cavalli et al. (2017) (14), 763 primary medulloblastoma samples were considered in our main analysis. Briefly, patient samples were collected from a number of treatment institutions including The Hospital for Sick Children, Children's Hospital of Philadelphia, the Mayo Clinic and others (14). Patient samples were only included in the initial study if their medulloblastoma diagnosis required surgical resection. Flash frozen tissues were obtained, DNA from these samples was extracted, and methylation values were determined using Illumina Infinium HumanMethylation450 BeadChips.

2.2 Survival analyses

Chi-squared tests were performed to identify sex differences in the distribution of medulloblastoma subgroups. Fisher's Exact tests ($p<0.05$) were performed to test for subgroup-specific sex differences in the distribution of selected covariates including age at diagnosis (years; 0-<5, 5-<10, 10-<15, 15-<20, ≥20), histology (classic, desmoplastic, large-cell anaplastic, medulloblastoma with

extensive nodularity), metastasis (yes, no), and vital status (dead, alive). Kaplan-Meier survival curves were constructed and Log-Rank p-values were utilized to compare 12.5-year overall survival differences between sexes. Figures were created using *survminor* (R v4.0.2). Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) as the measure of association between sex and death within each subgroup adjusting for covariates listed above (SAS v9.4). No violation of the proportional hazard's assumption was detected as determined by entering a sex and time interaction term in the model.

2.3 Quality control and sex prediction

The R *minfi* package (Bioconductor v.3.12) (16) was used to convert the original methylation array experiment to an RGChannel Set object and perform quality control. The RGChannel Set contains the raw intensities of each probe. To detect and remove probes with unreliable signals, a function producing a detection p-value for each probe in every sample was run. Probes that returned p-values above 0.01 were removed from the analysis (n=44,069). The RGChannel Set was processed before differential methylation analysis by undergoing functional normalization, thus transforming it into a Genomic Ratio Set. Functional normalization was used as it is commonly applied to datasets with different tissues and cell types. Probes containing single nucleotide polymorphisms (SNPs) at either the CpG interrogation and/or at the single nucleotide extension were removed (n=60,291). Similarly, we removed non-specific, cross-reactive probes previously found to hybridize to autosomal and sex chromosomes by Chen et al. (2013) (n=106,931) (17).

Sex of each patient's tissue was predicted by observing the median intensity of the X and Y chromosome probes (getSex() *minfi*). Any samples with discordant sex from the clinical information and predicted sex from the methylation data were dropped from the analysis (n=55). The sex chromosomes were excluded from all differentially methylated position analyses.

2.4 Differential methylation and mapping of differentially methylated positions to genes

After removal of the aforementioned probes, beta values, a standard estimate of the percentage methylation as a ratio of methylation probe fluorescent signal intensity to total probe signal (*Beta = Meth/(Meth + Unmeth + offset)* of the remaining probes were retrieved using the *minfi* function getBeta on the functionally normalized Genomic Ratio Set. The *bumphunter* package was used to run a multivariate model to examine differentially methylated regions, or "bumps", by sex and subgroup, including adjustment for age at diagnosis (years; 0-<5, 5-<10, 10-<15, 15-<20, ≥20). A cut-off value of 0.05 was used in the model and 500 permutations were run. Differentially methylated positions (DMPs) between sex (male-female) were identified using the lmFit function in custom R code, with adjustment for age at diagnosis as in the DMR analysis. Differential methylation analysis by sex was done within each medulloblastoma subgroup (SHH, Group 3, Group 4 and WNT) and subsequently within each SHH subtype (SHH_alpha, SHH_beta, SHH_gamma, SHH_delta) as defined in Cavalli et al. (2017) (14). Significant DMP's (Benjamini Hochberg adjusted p-value <0.05) within each subgroup were mapped to their nearest genes using the gene annotations from the 450k probe annotation information for genome hg19 (Supplemental Tables 1–5). Samples missing age data were excluded from this analysis (n=34). Additional healthy adult cerebellum samples detailed in the CNV analysis below were processed in the same manner to identify sex-DMPs in non-diseased tissues. Heatmaps were created using *ComplexHeatmap* and the Venn diagram of overlapping genes in subgroups was created using Venny (18).

2.5 Reactome pathway analysis

Reactome pathway analysis was used to identify biologic pathways over-represented by genes that had significant DMPs by sex for each medulloblastoma subgroup (p-value <0.05; date accessed: 10/15/2022). Pathways composed of ≥2 genes that had a significant p-value were included herein. IPA BioProfiler was used to identify chemotherapies available in clinical trials for other human cancers for the genes that contained DMPs by sex (date accessed: 2/24/2021).

2.6 Immune cell profiling based on methylation values

The *MethylCIBERSORT* R package (version 0.2.0) (19) and CIBERSORTx (https://cibersortx.stanford.edu/) (20) were used to investigate the tumor microenvironment using deconvolution to estimate the abundances of immune cell types using DNA methylation data. The *Stromal_v2* reference from MethylCIBERSORT was used as the methylation signature matrix file. Input matrices of beta values for the reference probes in the signature matrix were created as percentages and uploaded to CIBERSORTx with the signature matrix. CIBERSORTx was run in absolute mode using 1,000 permutations without quantile normalization.

2.7 Copy number variation analysis

CNV analysis was performed using the *conumee* R package on raw methylation data (IDAT files) from the Illumina 450k methylation arrays to confirm that differentially methylated regions or positions were not copy number driven. [http://bioconductor.org/packages/conumee/] *Conumee* requires control data for analysis. Therefore, we downloaded a publicly available dataset that measured DNA methylation using Illumina's 450K array in non-demented control brain tissue of the cerebellum

(n=179, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE134379). *Conumee* normalizes the combined intensity values of the methylated and unmethylated probes of each CpG site using these controls (representing genomes with no copy number alterations). Surrounding probes are then combined to create bins of a minimum size and probe number (default values and *conumee exclude_regions* data were used) prior to segmentation into clusters of the same state of variation in the number of copies *via* the circular binary segmentation algorithm. Segment tables were created for all samples and segment means for male versus female samples within subgroups at each DMP/gene/chromosome region of interest were calculated using pairwise Wilcoxon Rank Sum test.

2.8 Validation analysis

DMP analysis was validated in an independent cohort using publicly available DNA methylation data collected by Schwalbe et al. (2017) (15). This set consisted of 428 clinically annotated primary medulloblastoma samples. These tumor samples were part of a UK Children's Cancer and Leukaemia Group (CCLG) study with approval from Newcastle North Tyneside Research Ethics committee (heretofore referred to as the Newcastle cohort). The Newcastle patient samples were also tested using Illumina HumanMethylation 450 BeadChips. Quality control and sex prediction were performed as described above. Samples were removed that had lower median intensities and did not cluster using *minfi plotQC* (badSampleCutoff=10.5, n=21). Additionally, 36 samples were removed as they were discordant between reported and predicted sex. As subgroup classification data was not available for the Newcastle cohort, the R package *MethPed* was used to perform classification (R package version 1.24.0.) (21). Ten additional samples were removed based on classification to categories outside of medulloblastoma by this algorithm, leaving a total of 361 samples used in the DMP validation analysis (Table 1A). Survival data, metastasis, and vital status were unavailable for the Newcastle cohort.

3 Results

There were 708 cases included in this analysis: SHH (N=213, 59.6% male), WNT (N= 67, 43.3% male), Group 3 (N= 128, 71.9% male), and Group 4 (N=300, 70.3% male) (Table 1B). We observed significant 12.5-year overall survival differences by sex in the SHH subgroup (Figure 1A) non-significant differences were observed in other subgroups, (Figures 1B–D) such that females had lower survival than males (Log-Rank p=0.016). Using Cox proportional hazards models adjusted for age at diagnosis, histology, and metastasis, SHH females had nearly three times the risk of death compared to males (hazard ratio: 2.89, 95% CI: 1.29-6.24). There were no significant differences in survival between males and females in the other three subgroups.

We used the *bumphunter* package to run a multivariate model to examine sex differences globally by sex and subgroup and found 12 statistically significant DMPs (Supplemental Table 1). After finding this small number of DMPs globally, we then investigated subgroup-specific differentially methylated positions by analysis within each subgroup of tumor as medulloblastoma subgroups are molecularly and prognostically distinct (4). We observed statistically significant sex differences in DNA methylation within each subgroup (Supplemental Tables 2–5). SHH had the highest number of DMPs by sex (n=131), followed by Group 4 (n=29), Group 3 (n=19), and WNT (n=16). Ten genes had statistically significant DMPs by sex in all subgroups: *RFTN1*, *C1orf103*, *FKBP1B*, *COL25A1*, *NPDC1*, *B3GNT1*, *FOXN3*, *RNASEH2C*, *TLE1*, and *PHF17*. We performed unsupervised hierarchical clustering using significant DMPs by sex within each subgroup (Figures 2A–D). Clustering of samples using these DMPs was independent of other clinically relevant characteristics such as histology and vital status. The SHH group showed the strongest clustering by sex-DMPs (Figure 2A).

CNV analysis was performed to confirm that differentially methylated regions or positions were not copy number driven (Supplemental Tables 2–5). Less than ten percent of sex-DMPs in each subgroup were statistically significantly different when we intersected CNV segments with DMP locations and compared mean values for males versus females (SHH=9.9%, Group 4 = 3.5%, Group3 = 0%, WNT=0%). The same approach confirms that in the SHH subgroup samples there is no statistically different level of amplification at *GLI2*, *MYCN*, and *TP53* or 14q and 17p chromosome arm loss between sexes (results not shown).

To validate our sex-DMPs, we performed subgroup analysis on the validation set arising from the Newcastle cases, which resulted in a smaller, but consistent group of statistically significant sex-DMPs in each subgroup. Again, SHH had the highest number of DMPs by sex (n=11), followed by Group 4 (n=5), Group 3 (n=4), and WNT (n=2) (Supplemental Tables 6–9). All but one of these subgroup sex-DMPs, the gene *LTK* in the WNT subgroup, were already found in the corresponding Cavalli subgroup analysis. One gene, *RFTN1*, was a statistically significant DMP by sex in all subgroups. Unsupervised hierarchical clustering of subgroup samples using significant sex-DMPs demonstrates that the clustering is independent of other clinically relevant characteristics, specifically age at diagnosis and histology, and the SHH group shows the strongest clustering by sex (Supplementary Figure 1).

Statistically significant pathways resulting from the Cavalli sex-DMPs for each subgroup are presented in Table 2A. To explore tumor specific pathways, we removed genes associated with sex-DMPs that overlap with those found in the control cerebellum brain samples (Supplementary Table 10) and repeated the pathway analysis (Table 2B). No pathways were identified in WNT or Group 3 in either analysis. The top two pathways in Group 4 (both overall and tumor only sex-DMPs) were activation of *HOX* genes during differentiation and anterior *HOX* genes in hindbrain development during early embryogenesis. Both are also found in the top pathways of SHH using all sex-DMPs. Tumor specific sex-DMP pathways in SHH included G alpha (s) signaling events, diseases associated with N-glycosylation of proteins, telomere C-strand (lagging strand) synthesis, and interleukin-1 signaling. The top

TABLE 1A Cavalli case demographics and clinical characteristics stratified by sex and medulloblastoma subgroup.

	SHH		WNT		Group 3		Group 4		Chi-square p-value
	Females	Males	Females	Males	Females	Males	Females	Males	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Sex	86 (40.4)	127 (59.6)	38 (56.7)	29 (43.3)	36 (28.1)	92 (71.9)	89 (29.7)	211 (70.3)	**0.00004**
Age at diagnosis									
0-<5	33 (40.2)	42 (34.1)	2 (5.7)	0 (0)	10 (28.6)	43 (50.6)	15 (17.2)	33 (16.4)	
5-<10	15 (18.3)	23 (18.7)	10 (28.6)	10 (38.5)	19 (54.3)	30 (35.3)	47 (54.0)	86 (42.8)	
10-<15	5 (6.1)	11 (8.9)	13 (37.1)	4 (15.4)	6 (17.1)	7 (8.2)	21 (24.1)	60 (29.9)	
15-<20	8 (9.8)	11 (8.9)	8 (22.9)	4 (15.4)	0 (0.0)	1 (1.2)	2 (2.3)	18 (9.0)	
≥20	21 (25.6)	36 (29.3)	2 (5.7)	8 (30.8)	0 (0.0)	4 (4.7)	2 (2.3)	4 (2.0)	
missing	4	4	3	3	1	7	2	10	
Fisher's p-value		0.88		**0.03**		0.05		0.15	
Histology									
Classic	32 (44.4)	43 (42.2)	24 (88.9)	14 (70.0)	18 (64.3)	42 (67.7)	59 (81.9)	126 (78.3)	
Desmoplastic	27 (37.5)	42 (41.2)	1 (3.7)	4 (20.0)	3 (10.7)	3 (4.8)	8 (11.1)	14 (8.7)	
LCA	7 (9.7)	13 (12.7)	2 (7.4)	2 (10.0)	7 (25.0)	15 (24.2)	5 (6.9)	16 (9.9)	
MBEN	6 (8.3)	4 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	5 (3.1)	
missing	14	25	11	9	8	30	17	50	
Fisher's p-value		0.60		0.19		0.65		0.44	
Metastasis									
No	52 (82.5)	79 (85.9)	24 (92.3)	17 (85.0)	17 (60.7)	43 (60.6)	48 (63.2)	92 (58.2)	
Yes	11 (17.5)	13 (14.1)	2 (7.7)	3 (15.0)	11 (39.3)	28 (39.4)	28 (36.8)	66 (41.8)	
missing	23	23	23	23	23	23	23	23	
Fisher's p-value		0.65		0.64		1.00		0.48	
Vital Status									
Alive	48 (70.6)	87 (84.5)	33 (97.1)	24 (92.3)	19 (67.9)	44 (58.7)	59 (72.8)	121 (70.8)	
Deceased	20 (29.4)	16 (15.5)	1 (2.9)	2 (7.7)	9 (32.1)	31 (41.3)	22 (27.2)	50 (29.2)	
missing	18	24	4	3	8	17	8	40	
Fisher's p-value		**0.036**		0.57		0.50		0.77	

Statistically significant p-values (<0.05) are in bold.

four pathways in this SHH tumor-specific pathway analysis overlaped with the overall sex-DMP pathway analysis. The top pathway in the non-tumor-specific sex-DMPs of SHH is YAP1- and WWTR1 (TAZ)-stimulated gene expression. Other top pathways identified in SHH include signaling and loss of function of TGF-β receptor in cancer, SOS-mediated signaling, signal attenuation, signaling in RET, and advanced glycosylation end product receptor. Using the IPA BioProfiler, we identified four genes that encode proteins that are the target of therapies approved or in clinical trials for other human cancers that contained sex-DMPs including *CDK6*, *COL25A1*, *MMP16*, *PRIM2* in SHH and *COL25A1* in WNT and Group 4.

As the SHH subgroup had significant overall survival differences by sex, we explored sex-DMPs in the four clinically and cytogenetically distinct SHH subtype groups: SHH alpha (N = 59, 61.0% male), SHH beta (N = 32, 46.9% male), SHH gamma (N = 45, 55.6% male), and SHH delta (N = 69, 68.1% male). Although smaller sample sizes in these subtypes limited our ability to find methylation differences due to sex, we observed that SHH delta subtype had the largest number of sex-DMPs within SHH delta subtypes (n=38). SHH delta likely drove many of the differences by sex found in SHH overall (Supplementary Tables 11–14; Supplementary Figure 2).

Due to the complex nature of the tumor microenvironment and role of the immune system in tumor development, medulloblastoma

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TABLE 1B Newcastle case demographics and clinical characteristics stratified by sex and medulloblastoma subgroup.

	SHH		WNT		Group 3		Group 4		Chi-square p-value
	Females	Males	Females	Males	Females	Males	Females	Males	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Sex	35 (39.8)	53 (60.2)	16 (55.2)	13 (44.8)	31 (32.3)	65 (67.7)	47 (31.8)	101 (68.2)	0.075
Age at Diagnosis									
0-<5	23 (65.7)	31 (58.5)	0 (0)	2 (15.4)	18 (58.1)	37 (56.9)	11 (23.4)	16 (15.8)	
5-<10	7 (20.0)	10 (18.9)	11 (68.)	4 (30.8)	10 (32.3)	25 (38.5)	24 (51.1)	61 (60.4)	
10-<15	4 (11.4)	10 (18.9)	5 (31.3)	6 (46.2)	2 (6.5)	2 (3.1)	12 (25.5)	20 (19.8)	
15-<20	1 (2.9)	2 (3.8)	0 (0)	1 (7.7)	1 (3.2)	1 (1.5)	0 (0)	4 (4.0)	
>=20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Fisher's p-value		0.85		0.08		0.69		0.33	
Histology									
Classic	7 (20.0)	17 (32.1)	11 (68.8)	10 (76.9)	22 (71.0)	41 (63.1)	35 (74.5)	81 (80.2)	
Desmoplastic	12 (34.3)	19 (35.8)	0 (0)	1 (7.7)	0 (0)	2 (3.1)	4 (8.5)	5 (5.0)	
LCA	8 (22.9)	8 (15.1)	3 (18.8)	0 (0)	4 (12.9)	18 (27.7)	3 (6.4)	8 (7.9)	
MBEN	6 (17.1)	6 (11.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
NOS	2 (5.)	3 (5.7)	2 (12.5)	2 (15.4)	5 (16.1)	4 (6.2)	5 (10.6)	7 (6.9)	
Fisher's p-value		0.65		0.33		0.16		0.65	

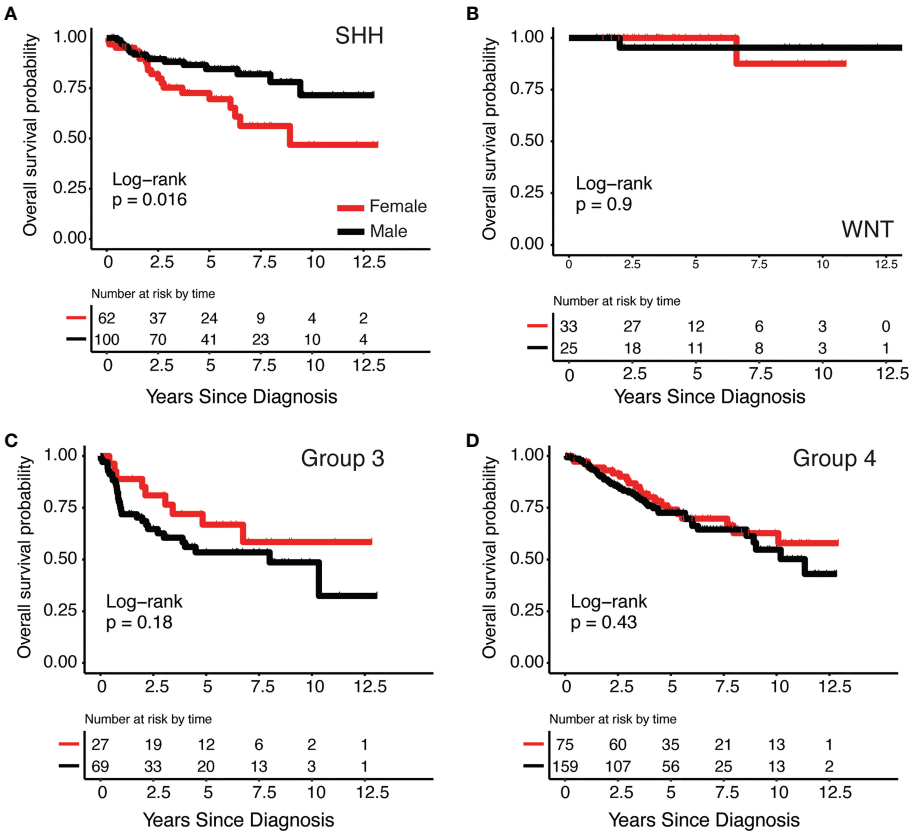

FIGURE 1
Kaplan-Meier survival curves by medulloblastoma subgroup and sex **(A)** SHH, **(B)** WNT, **(C)** Group 3 and **(D)** Group 4.

TABLE 2A Reactome pathway analysis for enriched pathways (p<0.05) comprised of at least two genes with significant differences in methylation by sex for each medulloblastoma subgroup*.

Reactome Pathway Name	pValue	Submitted entities found
SHH		
YAP1- and WWTR1 (TAZ)-stimulated gene expression	0.00005	TEAD4;RUNX2
Loss of Function of TGFBR1 in Cancer	0.00283	SMAD2;FKBP1B
Signaling by TGF-beta Receptor Complex in Cancer	0.00462	SMAD2;FKBP1B
SOS-mediated signalling	0.00566	GRB2;IRS2
Signal attenuation	0.00936	GRB2;IRS2
RET signaling	0.01247	GRB2;IRS2;SHANK3
Advanced glycosylation endproduct receptor signaling	0.01387	PRKCSH;CAPZA1
Regulation of RUNX2 expression and activity	0.01409	RUNX2;RBX1
Regulation of KIT signaling	0.01731	GRB2;SOCS6
Pre-NOTCH Transcription and Translation	0.01772	NOTCH3;H3F3A
Erythropoietin activates RAS	0.01915	GRB2;IRS2
WNT5A-dependent internalization of FZD4	0.02107	ARRB2;AP2B1
Signaling by NTRK1 (TRKA)	0.02211	ADCYAP1;NAB1;GRB2;IRS2;AP2B1
Signaling by NOTCH	0.02602	NOTCH3;TLE1;H3F3A;ARRB2;RBX1
Intrinsic Pathway for Apoptosis	0.03480	YWHAQ;APAF1
Signaling by NTRKs	0.03823	ADCYAP1;NAB1;GRB2;IRS2;AP2B1
Pre-NOTCH Expression and Processing	0.03872	NOTCH3;H3F3A
mTORC1-mediated signalling	0.03900	FKBP1B;EIF4EBP1
RAB geranylgeranylation	0.04045	RAB23;RAB12;RAB33B
Activation of anterior HOX genes in hindbrain development during early embryogenesis	0.04083	H3F3A;HOXC4
Activation of HOX genes during differentiation	0.04083	H3F3A;HOXC4
SARS-CoV-1-host interactions	0.04300	YWHAQ;NAB1;FKBP1B
Group 4		
Activation of HOX genes during differentiation	0.00020	HOXC4;POLR2L
Activation of anterior HOX genes in hindbrain development during early embryogenesis	0.00020	HOXC4;POLR2L
Organelle biogenesis and maintenance	0.00149	ATP5J;CSNK1D;RAB11FIP3;GABPA
Mitochondrial biogenesis	0.00405	ATP5J;GABPA

*No pathways were detected for WNT or Group 3.

subgroup and sex differences in tumor immune cell composition were assessed using MethylCIBERSORT. Comparisons of medulloblastoma subgroups overall for each immune cell type assessed in the MethylCIBERSORT deconvolution pipeline show statistically significant differences in distribution between at least two subgroups in each cell type (all p<0.0001, Figure 3A) though the absolute scores of these cell types were low overall. Within subgroup comparisons of males versus females cell type composition showed statistically significant differences in regulatory T cells in Group 3 (Figure 3B). No other subgroups displayed statistically significant sex differences in immune cell types identified in MethylCIBERSORT (Figure 3B).

4 Discussion

From 708 primary medulloblastoma samples, we identified statistically significant sex differences in survival in the SHH subgroup, with females demonstrating worse long-term survival than males. There were no survival differences between sexes in the Group 3, Group 4, or WNT subgroups. We identified sex differences in methylation within the four subgroups and SHH had the highest number of sex-DMPs (n=131), followed by Group 4 (n=29), Group 3 (n=19), and WNT (n=16). In our validation cohort, sex-DMPs were identified in smaller numbers, but were

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TABLE 2B Reactome pathway analysis for enriched pathways (p<0.05) comprised of at least two genes with significant differences in methylation by sex for each medulloblastoma subgroup (without overlap with non-tumor cerebellum sex-DMPs) *.

Reactome Pathway Name	pValue	Submitted entities found
SHH		
Regulation of RUNX2 expression and activity	0.00223	RUNX2;RBX1
Advanced glycosylation endproduct receptor signaling	0.00503	PRKCSH;CAPZA1
Transcriptional regulation by RUNX2	0.01599	RUNX2;RBX1
Signaling by NOTCH	0.02767	NOTCH3;ARRB2;RBX1
G alpha (s) signalling events	0.03564	ADCYAP1;PDE2A;ARRB2;TAPBP
Diseases associated with N-glycosylation of proteins	0.03669	ALG9;ALG6
Telomere C-strand (Lagging Strand) Synthesis	0.04111	PRIM2;WRN
Interleukin-1 signaling	0.04889	IKBIP;RBX1
Group 4		
Activation of anterior HOX genes in hindbrain development during early embryogenesis	0.00001	HOXC4;POLR2L
Activation of HOX genes during differentiation	0.00001	HOXC4;POLR2L
Mitochondrial biogenesis	0.00031	ATP5J;GABPA
Organelle biogenesis and maintenance	0.00036	ATP5J;RAB11FIP3;GABPA
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	0.01109	ATP5J;COX5B
The citric acid (TCA) cycle and respiratory electron transport	0.02549	ATP5J;COX5B
VxPx cargo-targeting to cilium	0.02602	RAB11FIP3
Developmental Biology	0.04028	HOXC4;POLR2L

*No pathways were detected for WNT or Group 3.

largely the same as those seen in the Cavalli data further strengthening the evidence of sex differences in methylation in medulloblastoma. Unsupervised hierarchical clustering based on sex-DMPs did not appear to be driven by any other clinically-relevant factors. The strongest sex driven clustering was observed in the SHH subgroup, which comprise approximately 30% of medulloblastomas in general (1, 4). These findings suggest there are true sex differences in DMPs within each subgroup that are independent of important clinical factors.

After mapping the sex-DMPs to the nearest gene, there were ten genes shared between all four subgroups. Nine of these ten genes were also found as sex-DMPs in the healthy adult cerebellum tissue analysis, suggesting more global sex differences in brain methylation that may be not disease- or age- specific. The genes identified in all four subgroups were *RFTN1*, *C1orf103*, *FKBP1B*, *COL25A1*, *NPDC1*, *B3GNT1*, *FOXN3*, *RNASEH2C*, *TLE1*, and *PHF17*. Of these, *RFTN1*, *COL25A1*, *TLE1*, and *RNASEH2C* have been found to have sex differences in methylation in leukocytes (22), which are known to impact tumor maintenance (23) and be regulated by sex hormones (24, 25). Remaining genes from this list are involved in various neuron-related processes, such as *FKBP1B* and neuronal aging (26), *NPDC1* and neuronal differentiation (27), and *FOXN3* and neuronal activation (28). Sex differences in brain development have been reported extensively in the psychiatric literature such that males not only have larger brain volumes by approximately 10% (12, 29) they also have a larger volume of gray matter (30). Gray matter is composed of various neuronal cell types (30) and may contribute to the sex differences in brain tumor incidence we see in populations as well as the sex differences we observed herein. We did not find that sex-DMPs corresponded to numerous sex differences in CNVs again suggesting a true role for sex-DMPs in medulloblastoma. Collectively, these findings suggest that sexually dimorphic epigenetic regulation of these genes may underlie medulloblastoma etiology more broadly and may operate through leukocyte-mediated mechanisms and neuronal development.

In our analysis, we also identified biologic pathways from the lists of sex-DMPs that may be sexually dimorphic in medulloblastomas. The top pathway in SHH is YAP1- and WWTR1 (TAZ)-stimulated gene expression. YAP1 and WWTR1 are both transcriptional co-activators regulated *via* HIPPO signaling with transcriptional targets crucial to cell proliferation and apoptosis. HIPPO signaling has previously been associated with pediatric cancers, including a known interaction with Sonic Hedgehog that upregulates the nuclear localization of *YAP* (31). Several top pathways identified using only tumor specific sex-DMPs in SHH were also found in the top SHH pathways using all sex-DMPs, including regulation of *RUNX2* expression and activity. *RUNX2* has been previously implicated in SHH tumorigenesis (32). Additional pathways from the tumor-specific sex-DMPs in SHH include G α (s) signaling events and diseases associated with N-glycosylation of proteins. The G α (s) signaling pathway can suppress SHH tumorigenesis through negative regulation of the

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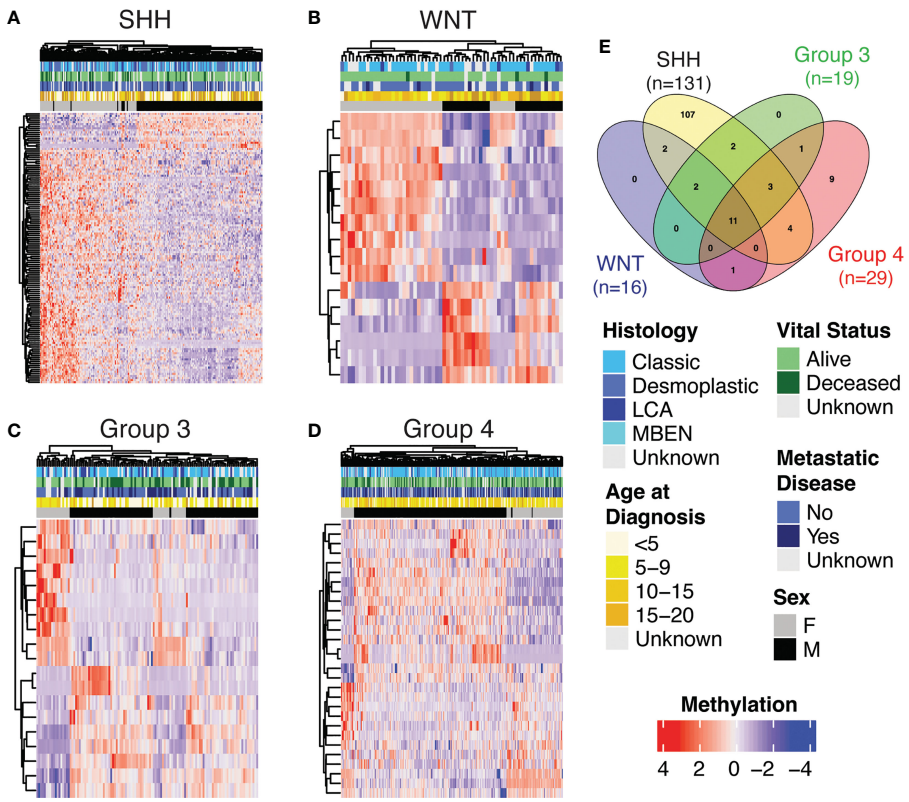

FIGURE 2
Heatmap showing methylation levels (row-scaled β-values) of statistically significantly differentially methylated positions (DMPs) by sex (adjusted p<0.05) from the autosomes in Cavalli cohort within subgroup **(A)** SHH, **(B)** WNT, **(C)** Group 3 and **(D)** Group 4. **(E)** The number of genes that contained a DMP by sex for each subgroup and the overlap of those gene sets.

Hippo pathway. The top two pathways in Group 4 are activation of *HOX* genes during differentiation and anterior *HOX* genes in hindbrain development during early embryogenesis, and both are also found in the top pathways of SHH. *HOX* genes are critical to embryonic development, with their expression accompanied by specific epigenetic states with noted changes to DNA methylation in other brain tumors (33). Other top pathways identified in SHH include signaling and loss of function of TGF-β receptor in cancer, SOS-mediated signaling, signal attenuation, and signaling in RET and advanced glycosylation end product receptor. TGF-β secretion has been documented in medulloblastomas and TGF-β pathway activity is potentially a predictor of survival in SHH-driven medulloblastomas (34). We then went on to identify four genes from our IPA BioProfiler analysis that had current targeted therapies approved for use in other cancers: *CDK6*, *COL25A1*, *MMP16*, *PRIM2*, which highlights the potential sex-specific utility of these genes and their encoded proteins as therapeutic targets for future study.

Population-based studies show incidence rates for medulloblastoma vary by sex both within the United States and around the world, with males more frequently diagnosed and male-to-female incidence rate ratios ranging between 1.4-2.2 (5, 6, 24); however, these studies often lack modern subgroup classifications. Based on findings from clinical-based studies, male-to-female ratios differ between molecular subgroups, with WNT and SHH groups showing approximately equal male and female distributions, but Group 3 and Group 4 medulloblastoma comprised with about twice as many males (11, 35). In our study, we observed an excess of males in SHH medulloblastoma rather than a 1:1 distribution by sex. Characterizing the sex ratio in population-based studies with genomic samples is critical.

Ten-year survival rates by sex in medulloblastoma are similar among all ages in studies, including our previous publication (24, 36), while five-year survival rates in children aged 0-19 indicate a lower risk of death in females than males (HR: 0.79) (37). Group 3 and 4 subgroup tumors are often found to have poorer survival than WNT tumors across the age-spectrum (35) yet we did not observe survival differences by sex in our study within these groups. Conversely, we observed that females in our study had worse survival than males for SHH tumors, which have an approximate 5-year survival of 50-75% depending on *TP53* mutation status (1, 38). Unfortunately, we could not evaluate *TP53* mutation status in our SHH tumors as we were unable to match samples to their mutation status based on the publicly available data (14), but there was no indication of sex differences in *TP53* CNV in our analyses. However, we did observe that SHH females had a 5-year survival of approximately 60% in our study suggesting the association between *TP53* mutation status and sex should be evaluated in future studies. Age-stratified analyses among SHH tumors where *TP53* mutation is thought to occur more commonly in children (8) were non-informative in our analysis likely

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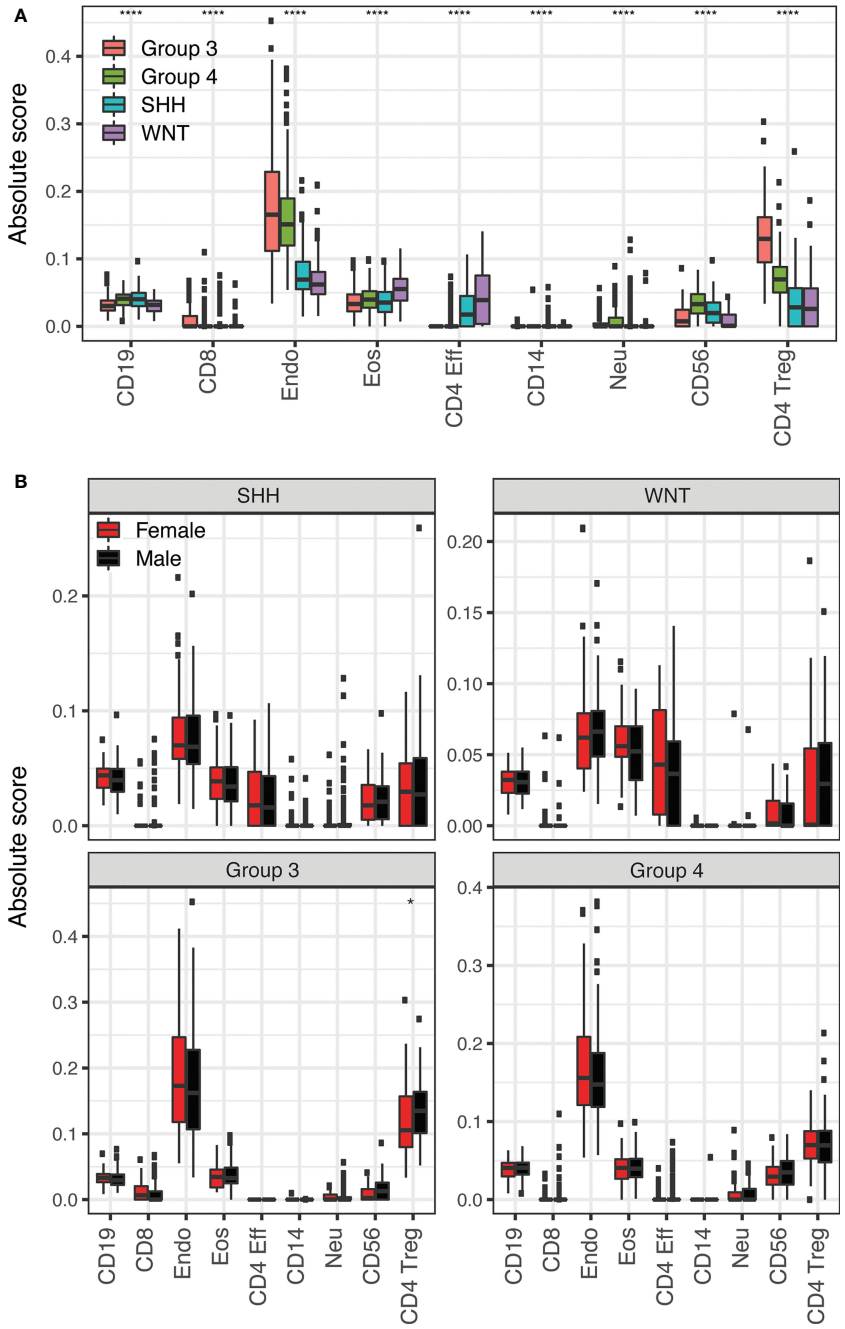

FIGURE 3
(A) Application of the MethylCIBERSORT stromal signature matrix to deconvolution of 708 medulloblastoma 450K methylation arrays using CIBERSORT. Boxplots compare medulloblastoma subgroup means for each cell type. Significance is calculated using pairwise Wilcoxon Rank Sum test with p-values (*p <= 0.05; ****: p <= 0.0001). The symbol is shown for the highest significance between two different subgroups for each cell type. **(B)** Boxplots comparing female (red) and male (black) means for each cell type in each medulloblastoma subgroup as labeled.

due to sample size limitations (results not shown). The male excess in brain tumor incidence is not confined to medulloblastoma. There is a male excess in gliomas (39) and significantly decreased overall survival in males for recurrent gliomas (40). Notably, Johansen et al. (2020) found genome-wide differences in DNA methylation by sex, with distinct patterns in glioma molecular subgroups as we have observed in medulloblastoma (41).

Sex differences in brain tumor genomics and epigenetics have been discussed extensively by Rubin and colleagues (11, 12). Sex can influence tumorigenesis through the sex chromosome complement, direct hormone action, and epigenetic disparities (11). Given that the molecular subgroups of medulloblastoma are suspected to arise from different cells of origin (1), it is reasonable to hypothesize that distinct mechanisms of carcinogenesis and/or progenitor cell types are more susceptible to the impact of sex. In SHH medulloblastoma, the cell of origin is hypothesized to be the cerebellar granule neuron precursor that may be particularly susceptible to *TP53* mutagenesis (1, 42). In our study, we observed the highest number of sex-DMPs

in SHH in which females had worse outcomes than males. Whether these sex differences in epigenetics of SHH are a coincidental product of the cell of origin or themselves drive outcomes remains to be investigated in other studies. During early development, sex hormones enact vast changes in epigenetics that determine sexual phenotypes (11). Using *in vitro* and *in vivo* models of medulloblastoma where sex of the host and tumor is known may help to further uncover sexually dimorphic biologic mechanisms of medulloblastoma development.

Though we have a large sample size and a validation cohort with which we conducted sex-stratified analyses within medulloblastoma subgroups, our study is not without limitations. While medulloblastoma is the most common malignant brain tumor in children less than 19 years of age (1), the parent study was not conducted exclusively in children and limiting it to children would have greatly diminished our sample size. It may be that pediatric and young adult medulloblastomas have different sex-specific methylation profiles and this should be investigated in appropriate studies in the future as there are endogenous changes that occur between childhood and adulthood that may impact tumor etiology. While the parent study had various clinical data, including survival, we are lacking risk factor data such as birth characteristics and other exposures such as radiation (43), which are hypothesized to impact medulloblastoma risk. We cannot rule out the possibility that the lower survival reported here in females versus males in SHH tumors may be due to subsequent cancers or long-term adverse events rather than tumor progression, as this data is also lacking. This study did contain gene expression data from microarrays, but there were few sex differences in gene expression (results not shown) identified in our initial analyses. RNA sequencing data with greater breadth and depth of gene coverage may allow for the identification of gene expression differences that could further help identify biologic mechanisms underlying sex differences in methylation and medulloblastoma tumorigenesis as we have reported previously in osteosarcoma (44). Additionally, single cell RNA sequencing and tumor microdissection might further highlight sex differences in medulloblastoma genomics as has been observed in adult glioblastomas where sex differences were found to be dependent on the sex chromosome composition of the tumor rather than the host (45). Sex differences in treatment received or response to therapy (46) may underlie the observed sex differences, particularly in SHH medulloblastoma, but this information was not available for evaluation herein.

To conclude, in our sex-stratified analysis of methylation differences within medulloblastoma subgroups, we identified sex-DMPs that varied by subgroup with SHH having the highest number of DMPs. Interestingly, in this study we only observed sex differences in survival in SHH medulloblastoma where females had worse long-term survival than males. We found 10 genes with DMPs that were conserved across subgroups suggesting a shared genetic background by subgroup may underlie some of the observed sexual dimorphism in medulloblastoma. Pathways identified within subgroups were largely signaling pathways including TGF-β, neurotrophic receptors, and NOTCH, which are known to impact prognosis in medulloblastoma and according to our findings may vary by sex within subgroups (34, 47, 48). Importantly, we identified four genes that housed sex-DMPs that also have chemotherapies available that could be studied in a sex-specific manner to improve outcomes for males and females with medulloblastoma.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: GEO Series GSE85218 - https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE85218 GEO Series GSE93646 - https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE93646 GEO Series GSE134379 - https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE134379.

Ethics statement

As this is publicly available data the study does not require consent for participation.

Author contributions

NS, RM: Data analysis, results interpretation, manuscript drafting and editing. LM: conceptualization of study, study design, data analysis, manuscript editing. LS, DL, CM, TH: conceptualization of study, manuscript drafting and editing. LW: study oversight, conceptualization of study, study design, data analysis, manuscript drafting and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

DAL is a co-founder and co-owner of NeoClone Biotechnologies, Inc., Discovery Genomics, Inc. recently acquired by Immunsoft, Inc., B-MoGen Biotechnologies, Inc. recently acquired by Bio-Techne corporation, and Luminary Therapeutics, Inc. DAL holds equity in, is a Board of Directors member, and serves as a senior scientific advisor of Recombinetics, a genome-editing company. DAL holds equity in and consults for Styx Biotechnologies Inc. as a member of their scientific advisory board. DAL consults for Genentech, Inc., which is funding some of his research. The business of all these companies is unrelated to the contents of this manuscript.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor SR declared a shared affiliation with the author TH at the time of review.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1113121/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Heatmap showing methylation levels (row-scaled β-values) of statistically significantly differentially methylated positions (DMPs) by sex (adjusted p<0.05) from the autosomes in Newcastle cohort within subgroup **(A)** SHH, **(B)** WNT, **(C)** Group 3 and **(D)** Group 4. **(E)** The number of genes that contained a DMP by sex for each subgroup and the overlap of those gene sets.

SUPPLEMENTARY FIGURE 2
The number of sex-DMPs for each SHH subtype and the overlap of those probes.

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Association of body mass index with survival in U.S. cancer survivors: a cross-sectional study of NHANES 1999–2018

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Background: Understanding the association between relative mortality with body mass index (BMI) may aid clinicians in making suitable clinical decisions. Our study evaluated the impact of BMI on mortality among cancer survivors.

Methods: We used data from the US National Health and Nutrition Examination Surveys (NHANES) spanning from 1999 to 2018. Relevant mortality data were retrieved up until December 31, 2019. Adjusted Cox models were employed to examine the association of BMI with the risks for total and cause-specific mortality.

Results: Among 4135 cancer survivors, 1486 (35.9%) were obese (21.0% class 1 obesity [BMI 30-< 35 kg/m^2], 9.2% class 2 obesity [BMI 35 -< 40 kg/m^2], 5.7% class 3 obesity [BMI ≥ 40 kg/m^2]), 1475(35.7%) were overweight (BMI 25-< 30 kg/m^2). During an average follow-up of 8.9 years (35895 person-years), a total of 1361 deaths were reported (cancer 392; 356 cardiovascular disease [CVD]; 613, non-cancer, non-CVD). In multivariable models, underweight participants (BMI < 18.5 kg/m^2) were associated with significantly higher risks of cancer-specific (HR, 3.31; 95% CI, 1.37-8.03, *P*=0.01) and CVD cause (HR, 3.18; 95% CI, 1.44-7.02, *P* < 0.001) mortality compared to individuals with normal weight. Being overweight was associated with significantly lower risks of non-cancer, non-CVD cause mortality (HR, 0.66; 95% CI, 0.51-0.87, *P* < 0.001). Class 1 obesity was associated with significantly reduced risks of all-cause (HR, 0.78; 95% CI, 0.61-0.99, *P* = 0.04), and non-cancer, non-CVD cause (HR, 0.60; 95% CI, 0.42-0.86, *P* = 0.01) mortality. A higher risk of CVD-related mortality (HR, 2.35; 95% CI, 1.07-5.18, *P* = 0.03) was observed in class 3 obesity cases. Lower risks of all-cause mortality were detected in men (overweight, HR, 0.76; 95% CI, 0.59-0.99, *P*=0.04; class 1 obesity, HR, 0.69; 95% CI, 0.49-0.98, *P* = 0.04) but not in woman, in never-smokers (class 1 obesity, HR, 0.61; 95% CI, 0.41-0.90, *P*=0.01) and former smokers (overweight, HR, 0.77; 95% CI, 0.60-0.98, *P*=0.04) but not in current smokers; in obesity-related cancer (class 2 obesity, HR, 0.49; 95% CI, 0.27-0.89, *P*=0.01) but not in non-obesity-related cancers.

Conclusions: In the United States, cancer survivors with overweight or moderate obesity (class 1 or class 2 obesity) demonstrated a lower risk of all-cause and noncancer, non-CVD cause mortality.

KEYWORDS

body mass index (BMI), all-cause mortality, obesity, cancer survivors, National Health and Nutrition Examination Survey (NHANES)

Introduction

A 33% increase in the global incidence of cancer was reported between 2005 and 2015 (1). In the United States, the population of cancer survivors is approximately 15.5 million, and this number is projected to reach up to 22.1 million by 2030 (2). The growing number of cancer survivors has underscored the urgent need to establish standards for survivorship care to improve their long-term health outcomes. Weight management plays a crucial role in cancer survivors, as several clinical guidelines suggest that a higher body mass index (BMI) is associated with poorer survival among this population. Consequently, they are advised to achieve or maintain a normal body weight (3–5). Increased BMI has been shown to be significantly associated with a heightened risk of morbidity and mortality in conditions such as cardiovascular disease (CVD), specific types of cancer, and metabolic diseases (6–8). However, numerous studies have proposed that elevated BMI may lead to an "obesity paradox," which confers a survival advantage among patients with chronic diseases due to increased BMI (9–11).

A survival benefit has been reported in overweight and moderately obese cancer survivors which supports the obesity paradox associated with cancer (12–15). This phenomenon is less recognized in cancer and presents disputable explanations (16–18). Inconsistent results in previous studies could be attributed to methodological choices (e.g., whether the study accounts for collider bias and confounding due to smoking) and biologically plausible clinical explanations, as well as true causal association. Therefore, this study aimed to exam the association between BMI and survival among cancer survivors in the United States.

Methods

Study design and population

In this study, data were procured from 10 survey cycles of NHANES spanning from 1999 to 2018 (19). The National Center for Health Statistics (NCHS) and Center for Disease Control and Prevention (CDC) have conducted a 2-year cycle survey since 1999 to assess the health and nutritional status of the civilian US population. The NHANES protocols were approved by the NCHS ethics review board, and informed consent was obtained from all study participants. Subject characteristics were collected during the body measurement examinations. BMI was calculated as weight (kg)/(height [(m])^2). According to the standard WHO criteria, BMI was categorized into four groups (underweight BMI < 18.5 kg/m^2, the normal weight 18.5 to < 25 kg/m^2, overweight 25 to <30 kg/m^2, obesity ≥ 30 kg/m^2) (20). Obesity was further classified into three categories: class 1 obesity (BMI 30 to < 35 kg/m^2), class 2 obesity (BMI 35 to < 40 kg/m^2), and class 3 obesity (BMI ≥ 40.0 kg/m^2) (21).

Diagnosis of cancer

Date on self-reported history of cancer were obtained from "medical conditions" section of NHANES which contain information on health conditions. Cancer survivors were identified based on the response to the question: "Have you ever been told by a doctor or other health professional that you had cancer or malignancy of any kind?". The age at the time of the first cancer diagnosis was collected by asking, "How old were you when cancer was first diagnosed?". The years since cancer diagnosis was calculated as the difference between participants' current age and their age at first cancer diagnosis, and they were subsequently categorized into (< 2 years, 2 to < 5 years, 5 to < 10 years, and ≥ 10 years) (22). Cancer types were confirmed by asking, "What kind of cancer was it?" and were classified into obesity-related (cancers of the colon, breast, esophagus, rectum, pancreas, gallbladder, stomach, liver, kidney, blood, uterus, and ovary) and non-obesity-related (lung, prostate, cervix, uterus, melanoma, skin, lymphoma/Hodgkin's disease, and thyroid) cancers (23).

Ascertainment of mortality

Mortality data were collected from National Death Index up to December 31, 2019. The cause of death was recorded following ICD-10 (International Statistical Classification of Diseases, 10th revision) codes. The primary outcomes included cancer mortality (ICD-10 codes C00-C97) and CVD-cause mortality, encompassing heart disease (ICD-10 codes I00-I09, I11, I13, I20-I51) and cerebrovascular diseases (ICD-10 codes I60-I69) The mortality follow-up time was calculated from the date when the body measurements were taken to the date of patient's death or December 31, 2019 (24). To reduce the probability of reverse causality, we excluded the participants who died within the first 24 months of follow-up.

Sociodemographic and health-related covariates

Self-reported sociodemographic characteristics included gender, race/ethnicity (Hispanic, Mexican American, non-Hispanic White, non-Hispanic Black, and others), marital status (married/living with a partner and separated/divorced/widowed/never married), educational level (high school or less, and more than high school), and family poverty income ratio level (< 1.30, 1.3 to < 3.5, ≥ 3.5). we also collected data on alcohol consumption, smoking status, and total Healthy Eating Index-2015 score (HEI-2015, collected through 24-h dietary recall). HEI-2015 is indicative of overall dietary quality, and the value ranges between 0–100 (worst-best). For cigarette smoking status, participants were grouped as current smokers (smoking cigarettes daily or frequently), never smokers (fewer than one hundred cigarettes throughout their entire life), or former smokers (not currently smoking but haves smoked more than 100 cigarettes throughout their entire life). Based on drinking status, participants were classified as never drinkers (had < 12 drinks throughout their life) and current drinkers (currently drinking, daily or frequently). A history of CVDs (coronary heart disease, congestive heart failure, heart attack, angina, and stroke). Diabetes was self-reported by participants who had been previously diagnosed with diabetes or if they were taking prescribed medications for diabetes (24).

Statistical analysis

All statistical analyses were performed in R (v.4.2.2) (25) and were carried out following the analytical guidelines provided by NHANES. Survey analyses were weighted to account for sample weights to guarantee nationally representative estimates. A 2-sided p-value of < 0.05 indicated the statistically significance level.

The sociodemographic and lifestyle factors of participants were overall described by BMI categories. The differences in characteristics by BMI categories were analyzed using linear regression models. The association between BMI and all-cause, cause-specific mortality adjusted for covariates was described by means of restricted cubic spine analysis. Hazard ratios (HRs) and 95% CIs for the associations of BMI categories with all-cause, cancer, CVD and non-cancer, non-CVD mortality, were evaluated using multivariable Cox proportional hazards regression models. Cox models were adjusted for covariates including age, sex, race, family poverty income ratio, marital status, education, alcohol consumption, smoking status, HEI-2015 score, cardiovascular disease, diabetes, years since diagnosis, and cancer types. Additionally, subgroup analyses were conducted by sex, age, smoking status, and cancer type.

Results

Baseline characteristics

A total of 4135 cancer survivors representing 18.4 million noninstitutionalized residents of the United States were recruited in the analyzed cohort. Table 1 includes the participant characteristics by BMI categories. The age of the participants ranged between 20–85 years. A total of 1829 (44.2%) participants reported an age > 70 years. The majority of participants were non-Hispanic White 2893(70.0%), married/living with a partner 2545 (61.5%) and had more than a high school level of education 2232 (54.0%). Among 4135 cancer survivors, 1486 (35.9%) were obese (21.0% class 1 obesity, 9.2% class 2 obesity, and 5.7% class 3 obesity, 1475(35.7%) were overweight, 1106 (26.7%) had normal weight, and 68 (1.6%) were underweight. Although the difference of the prevalence of obesity between female (36.4%) and male (34.7%) participants was not statistically significant, men (41.6%) had a higher prevalence of being overweight than women (29.0%). Cancer survivors aged between 55–70 years (40.6%) had a higher prevalence of obesity than those < 55 years (36.6%) and > 70 years (29.5%). A higher prevalence of obesity was observed in Mexican American (53.4%) participants than that in non-Hispanic Black participants (47.8%), Hispanic (38.1%), and non-Hispanic White participants (34.6%). Obesity was more predominant among cancer survivors with a lower family-income-to-poverty ratio as well as those with CVD and diabetes.

BMI categories and survival

During an average 8.9 years of follow-up (35895 person-years), 1361 deaths occurred; 356 patients died of CVD, 392 of cancer, and 613 of non-cancer, non-CVD causes. Figure 1 presents the association of baseline BMI with mortality from all-cause, cancer, CVD, and non-cancer, non-CVD. The relationship of BMI with mortality was U-shaped for all-cause and non-cancer, non-CVD mortality. While there was no significant correlation between whole obesity group and mortality, class 1 obesity was related to significantly decreased mortality as compared to normal weight from all-cause mortality (HR, 0.78; 95% CI, 0.61-0.99) among cancer survivors after adjusting for covariates (Table 2).

For CVD mortality, both underweight (HR, 3,18;95% CI, 1.44-7.02) and class 3 obesity (HR, 2.35; 95% CI, 1.07-5.18) showed a significant positive association with higher rates of mortality. For cancer mortality, underweight group was associated with an elevated risk of mortality (HR, 3.31; 95% CI, 1.37-8.03). The association between cancer mortality with overweight and obesity did not reach significantly difference. For non-cancer, non-CVD mortality, overweight and class 1 obesity were found to be associated with a significantly lower number of excess deaths, with HRs of 0.66(0.51,0.87) and 0.60 (0.42,0.86), respectively.

Subgroup analyses

The stratified analysis was conducted by age at in-person interview (<55, 55–70, and >70 years), cancer types of survivors (obesity-related and non-obesity-related cancers), and smoking status (former smokers, never-smokers, and current smokers). We observed an association of overweight and class 1 obesity with reduced mortality among male survivors, but the association was not significant in women (Table 3).

TABLE 1 Sample size [a] and characteristics of cancer survivors by BMI in the NHANES 1999 to 2018.

Characteristic	All (n=4135)	Underweight (n=68)	Normal (n=1106)	Overweight (n=1475)	Obesity 1 (n=869)	Obesity 2 (n=382)	Obesity 3 (n=235)	*P*-value[b]
Mean (SD) BMI (kg/m2)	28.7(0.1)	17.3(0.2)	22.5(0.1)	27.4(0.0)	32.2(0.1)	37.0(0.1)	44.9(0.4)	< 0.0001
Age(years), %								< 0.0001
<55	901(21.8)	16(37.3)	271(34.0)	259(26.3)	177(28.7)	104(33.1)	74(37.0)	
55-70	1405(34.0)	19(22.3)	319(32.5)	469(34.6)	326(39.3)	155(41.3)	117(47.3)	
>70	1829(44.2)	33(40.4)	516(33.5)	747(39.1)	366(32.0)	123(25.6)	44(15.8)	
Gender, %								< 0.0001
Female	2216(53.6)	49(85.1)	634(65.6)	666(48.9)	448(53.5)	245(62.4)	174(72.9)	
Male	1919(46.4)	19(14.9)	472(34.4)	809(51.1)	421(46.5)	137(37.6)	61(27.1)	
Race/ethnicity, %								< 0.0001
Hispanic	221(5.3)	3(3.4)	47(2.0)	88(2.5)	47(2.2)	25(3.8)	11(2.0)	
Mexican American	296(7.2)	2(0.6)	46(1.2)	106(2.0)	79(3.2)	40(3.4)	23(3.8)	
Non-Hispanic Black	552(13.3)	11(4.1)	106(3.3)	179(4.9)	133(6.1)	71(7.3)	52(9.2)	
Non-Hispanic White	2893(70.0)	48(89.4)	835(88.8)	1058(87.8)	578(85.3)	234(83.1)	140(81.8)	
Other	173(4.2)	4(2.4)	72(4.7)	44(2.7)	32(3.2)	12(2.3)	9(3.2)	
Marital status, %								0.02
Married or living with partner	2545(62)	35(54.2)	657(64.4)	952(70.9)	540(68.0)	233(67.4)	128(60.4)	
widowed/divorced/separated/never married	1560(38)	32(45.8)	436(35.6)	515(29.1)	323(32.0)	147(32.6)	107(39.6)	
Education, %								0.1
High school or less	1898(46.0)	36(50.8)	448(32.6)	703(38.2)	416(37.7)	181(35.2)	114(39.8)	
More than high school	2232(54.0)	32(49.2)	656(67.4)	770(61.8)	452(62.3)	201(64.8)	121(60.2)	
Mean (SD) HEI score[c]	52.9(0.3)	54.3(2.5)	54.5(0.5)	53.8(0.5)	51.3(0.5)	49.7(0.9)	50.3(1.0)	< 0.0001
Family poverty income ratio, %								< 0.0001
<1.3	899(23.8)	26(40.1)	208(13.4)	290(12.7)	200(17.0)	94(20.1)	81(27.2)	
1.3 to <3.5	1515(40.1)	20(28.5)	397(33.9)	553(37.2)	317(35.4)	141(39.4)	87(36.8)	
≥3.5	1367(36.2)	17(31.4)	405(52.7)	503(50.1)	276(47.6)	112(40.6)	54(36.0)	
Smoking, %								< 0.0001
Never smoker	1844(44.6)	17(27.3)	512(46.3)	651(45.3)	380(43.1)	176(44.7)	108(47.2)	
Former smoker	1646(39.8)	23(28.5)	366(31.7)	621(41.0)	374(41.9)	168(45.0)	94(35.9)	
Current smoker	642(15.5)	28(44.2)	227(22.0)	201(13.7)	115(15.0)	38(10.3)	33(16.9)	
Alcohol								0.002
Never drinker	509(13.4)	6(7.2)	128(9.8)	188(11.9)	105(10.0)	45(10.0)	37(14.1)	
Former drinker	956(25.1)	21(30.5)	224(17.9)	337(19.7)	207(22.9)	94(20.7)	73(31.7)	
Current drinker	2341(61.5)	33(62.3)	670(72.2)	837(68.5)	477(67.1)	216(69.3)	108(54.1)	
Cancer type, %								< 0.001
Obesity-related	1393(33.7)	25(35.1)	355(30.1)	468(27.4)	295(28.5)	141(27.9)	109(39.7)	
Non-obesity-related	2742(66.3)	43(64.9)	751(69.9)	1007(72.6)	574(71.5)	241(72.1)	126(60.3)	
Cardiovascular disease, %								0.01

(Continued)

TABLE 1 Continued

Characteristic	All (n=4135)	Underweight (n=68)	Normal (n=1106)	Overweight (n=1475)	Obesity 1 (n=869)	Obesity 2 (n=382)	Obesity 3 (n=235)	*P*-value[b]
No	3190(77.1)	52(77.0)	906(86.3)	1117(80.3)	635(78.0)	300(80.5)	180(79.7)	
Yes	945(22.9)	16(23.0)	200(13.7)	358(19.7)	234(22.0)	82(19.5)	55(20.3)	
Diabetes, %								< 0.0001
Yes	824(20.1)	4(4.0)	108(6.5)	265(13.9)	234(22.0)	126(30.5)	87(34.9)	
no	3285(79.9)	64(96.0)	993(93.5)	1198(86.1)	632(78.0)	252(69.5)	146(65.1)	
Years since diagnosis, %								0.3
<2	591(14.3)	12(20.1)	164(15.2)	204(13.4)	144(16.3)	41(13.2)	26(9.5)	
2 to <5	768(18.6)	11(12.1)	177(17.2)	282(19.9)	171(16.9)	77(18.9)	50(24.2)	
5 to<10	965(23.3)	9(11.0)	267(22.9)	343(22.8)	209(24.1)	82(21.3)	55(24.7)	
>=10	1811(43.8)	36(56.7)	498(44.7)	646(43.8)	345(42.7)	182(46.6)	104(41.5)	
Cause of death, %								0.003
Cancer	392(9.5)	13(16.6)	102(6.6)	154(8.0)	81(6.8)	32(6.8)	10(3.2)	
Cardiovascular disease	356(8.6)	6(8.0)	97(6.1)	146(7.4)	69(5.7)	21(3.9)	17(7.6)	
Noncancer, non-CVD	613(14.8)	16(20.1)	212(12.8)	212(10.7)	105(9.0)	46(9.2)	22(10.1)	

[a]weighted to be nationally representative.
[b]significance determined by survey-weighted one-way analysis of variance.
[c]Healthy Eating Index-2015 score based on the NHANES dietary data.

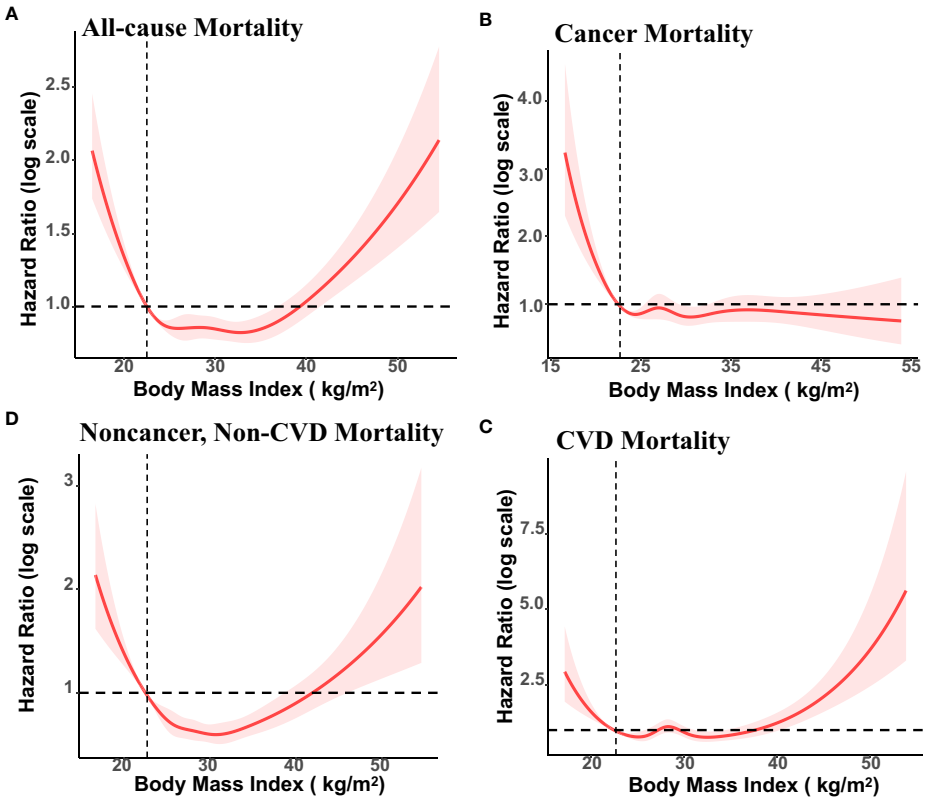

FIGURE 1
Association of Body Mass Index (BMI) with All-cause, Cancer, Cardiovascular Disease (CVD) and Non-cancer, Non-CVD Mortality Among US cancer Survivors, NHANES 1999 to 2018. BMI of 22.5 kg/m2 was the reference value. The vertical axis represents hazard ratio of mortality (log scale). Solid lines represent hazard ratios (HRs) calculated in restricted cubic spline Cox proportional hazards regression adjusted for age, ethnicity, education, family poverty income ratio, marital status, smoking status, alcohol consumption, HEI-2015 score, cardiovascular disease, and diabetes, years since diagnosis and cancer types.

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TABLE 2 Body mass index (BMI) and cause-specific mortality in the multiethnic cohort, NHANES 1999 to 2018.

Mortality outcome	Death, n	Hazard Ratio (95% CI)		
		Model 1[a]	Model 2[a,b]	Model 3[a,b,c]
All-cause				
Underweight	35	**2.19(1.34,3.61)** **	1.43(0.73,2.81)	1.40(0.70,2.80)
Normal	411	1.00(reference)	1.00(reference)	1.00(reference)
Overweight	512	0.88(0.75,1.02)	0.86(0.72,1.02)	0.86(0.72,1.03)
Obese	403	0.97(0.80,1.16)	0.86(0.69,1.07)	0.87(0.70,1.08)
Obese class 1	255	0.86(0.70,1.06)	**0.77(0.61,0.98)** *	**0.78(0.61,0.99)** *
Obese class 2	99	1.05(0.80,1.37)	0.94(0.69,1.29)	0.95(0.69,1.31)
Obese class 3	49	1.42(0.98,2.05)	1.19(0.79,1.80)	1.20(0.80,1.80)
P for trend		0.96	0.41	0.46
Cancer				
Underweight	13	**4.10(1.86,9.05)** **	**3.15(1.35,7.33)** *	**3.31(1.37,8.03)** *
Normal	102	1.00(reference)	1.00(reference)	1.00(reference)
Overweight	154	0.97(0.71,1.31)	0.87(0.61,1.25)	0.88(0.61,1.26)
Obese	123	0.94(0.67,1.32)	0.83(0.55,1.27)	0.83(0.54,1.28)
Obese class 1	81	0.89(0.60,1.33)	0.81(0.50,1.33)	0.82(0.50,1.34)
Obese class 2	32	1.22(0.76,1.96)	1.08(0.64,1.82)	1.06(0.62,1.82)
Obese class 3	10	0.65(0.31,1.37)	0.56(0.25,1.25)	0.55(0.25,1.25)
P for trend		0.48	0.25	0.25
CVD				
Underweight	6	**4.01(1.71,9.39)** **	**3.32(1.50,7.38)** **	**3.18(1.44,7.02)** **
Normal	97	1.00(reference)	1.00(reference)	1.00(reference)
Overweight	146	0.97(0.71,1.32)	0.98(0.69,1.39)	1.00(0.70,1.43)
Obese	107	1.14(0.80,1.62)	0.91(0.60,1.39)	0.95(0.63,1.45)
Obese class 1	69	0.97(0.67,1.40)	0.78(0.51,1.21)	0.81(0.52,1.26)
Obese class 2	21	1.01(0.57,1.77)	0.76(0.40,1.43)	0.80(0.42,1.52)
Obese class 3	17	**2.89(1.41,5.90)** **	**2.21(1.00,4.89)** *	**2.35(1.07,5.18)** *
P for trend		0.26	0.85	0.68
Noncancer, non-CVD disease				
Underweight	16	**1.92(1.12,3.29)** *	1.24(0.58,2.66)	1.21(0.53,2.74)
Normal	212	1.00(reference)	1.00(reference)	1.00(reference)
Overweight	212	**0.70(0.56,0.87)** **	**0.66(0.50,0.86)** **	**0.66(0.51,0.87)** **
Obese	173	0.84(0.65,1.07)	**0.70(0.52,0.94)** *	**0.71(0.52,0.96)** *
Obese class 1	105	**0.72(0.53,0.97)** *	**0.60(0.42,0.85)** **	**0.60(0.42,0.86)** *
Obese class 2	46	0.93(0.65,1.35)	0.80(0.50,1.26)	0.81(0.51,1.29)
Obese class 3	22	1.36(0.82,2.26)	1.02(0.59,1.78)	1.03(0.59,1.77)
P for trend		0.31	0.06	0.08

**P < 0.01; *P < 0.05, Significant results ($P < 0.05$) are indicated in bold.

[a]Adjusted for age, sex and ethnicity.

[b]Multivariable model additionally adjusted for education, family poverty income ratio, marital status, smoking status, alcohol consumption, HEI-2015 score, cardiovascular disease, and diabetes.

[C]Additionally adjusted for years since diagnosis and cancer types.

Compared to the normal weight group, cancer survivors (age older than 70 years) who were overweight and class 1 obese had better overall survival. Cancer survivors with class 2 obesity (age < 55 years) and cancer survivors (at the age of 55-70 years) with class 1 obesity had a reduced risk in all-cause mortality (Table 4). Overweight among former smokers or class 1 obesity among never-smokers had a lower risk of all-cause mortality, while overweight or obese current smokers did not have a significantly reduced risk of mortality. However, being underweight was associated with an elevated risk for all-cause mortality in current smokers (Table 5). Among survivors with diagnoses of obesity-related cancers, individuals with class 2 obesity showed a decreased risk of all-cause mortality (HR, 0.49; 95% CI, 0.27-0.87). For survivors with diagnoses of non-obesity-related cancers, being underweight was correlated with a higher risk of all-cause mortality (Table 6). A further exploration of the association of BMI with the death risk for each specific cancer and mortality was conducted (eTable 1 in the Supplement). For prostate cancer survivor, being overweight was associated with reduced risk in all-cause mortality (HR, 0.57; 95% CI, 0.39-0.82).

Discussion

In this cohort of cancer survivors from the United States, nearly three-quarters of the participants were identified as overweight or obese. This study evaluated the association of BMI categories with survival outcomes among cancer survivors. Over an 8.9-years of follow-up period, underweight status was significantly associated with increased mortality risk in both cancer and CVD cases, but not in all-cause, or non-cancer, non-CVD mortality. Overweight and moderate obesity were linked with a reduced risk of all-cause and non-cancer, non-CVD mortality in cancer survivors after accounting for confounding factors such as smoking, co-morbid conditions, and other covariates. This finding suggests the existence of an "obesity paradox". Comparable associations were observed among the never-smoker and former smoker group, but not in current smokers; in male participants, but not in female participants; in obesity-related cancers, but not in non-obesity-related cancers. Class 3 obesity was associated with elevated risks for CVD mortality.

TABLE 3 Body mass index (BMI) and total mortality in the multiethnic cohort, by sex, NHANES 1999 to 2018[a].

BMI	Male(n=956)		Female(n=698)	
	Death, n	HR (95%CI)	Death, n	HR (95%CI)
Underweight	11	2.36(0.91,6.12)	24	1.32(0.63,2.79)
Normal	220	1.00(reference)	191	1.00(reference)
Overweight	333	**0.76(0.59,0.99)** *	179	0.94(0.75,1.18)
Obese	210	0.81(0.58,1.13)	193	0.91(0.70,1.18)
Obese class 1	149	**0.69(0.49,0.98)** *	106	0.88(0.63,1.24)
Obese class 2	47	1.05(0.66,1.66)	52	0.89(0.62,1.28)
Obese class 3	14	1.75(0.80,3.86)	35	1.04(0.69,1.56)
P for trend		0.565		0.519

HR, hazard ratio; *P < 0.05. Significant results ($P < 0.05$) are indicated in bold.
[a]Multivariable model adjusted for age, ethnicity, education, family poverty income ratio, marital status, smoking status, alcohol consumption, HEI-2015 score, cardiovascular disease, and diabetes, years since diagnosis and cancer types.

TABLE 4 Body mass index (BMI) and total mortality in the multiethnic cohort, by age group, NHANES 1999 to 2018[a].

BMI	<55y(n=66)		55-70y(n=330)		>70y(n=965)	
	Death, n	HR (95%CI)	Death, n	HR (95%CI)	Death, n	HR (95%CI)
Underweight	2	2.96(0.47,18.58)	8	1.81(0.70,4.65)	25	1.30(0.59,2.83)
Normal	21	1.00(reference)	87	1.00(reference)	303	1.00(reference)
Overweight	18	0.66(0.25, 1.76)	104	0.85(0.55,1.31)	390	0.87(0.71,1.05)
Obese	25	1.19(0.53, 2.67)	131	0.76(0.48,1.19)	247	**0.74(0.57,0.95)** *
Obese class 1	**11**	**0.88(0.30, 2.62)**	**69**	**0.61(0.39,0.96)** *	**175**	**0.74(0.55,0.98)** *
Obese class 2	11	**2.70(1.07, 6.83)** *	33	0.89(0.48,1.66)	55	**0.68(0.47,0.98)** *
Obese class 3	3	0.50(0.14, 1.80)	29	1.14(0.59,2.23)	17	0.92(0.53,1.60)
P for trend		0.724		0.650		0.02

HR, hazard ratio, *P < 0.05. Significant results ($P < 0.05$) are indicated in bold.
[a]Multivariable model adjusted for sex, ethnicity, education, family poverty income ratio, marital status, smoking status, alcohol consumption, HEI-2015 score, cardiovascular disease, and diabetes, years since diagnosis and cancer types.

TABLE 5 Body mass index (BMI) and total mortality in the multiethnic cohort, by smoking status, NHANES 1999 to 2018[a].

BMI	Never-Smokers(n=519)		Former-Smokers (n=664)		Current-Smokers (n=178)	
	Death, n	HR (95%CI)	Death, n	HR (95%CI)	Death, n	HR (95%CI)
Underweight	5	1.59(0.85,2.97)	15	1.13(0.41,3.08)	15	**2.84(1.24,6.52)** *
Normal	171	1.00(reference)	172	1.00(reference)	68	1.00(reference)
Overweight	202	0.92(0.72,1.18)	258	**0.77(0.60,0.98)** *	52	0.87(0.51,1.46)
Obese	141	**0.68(0.48,0.97)**	219	0.88(0.66,1.17)	43	1.11(0.63,1.95)
Obese class 1	92	**0.61(0.41,0.90)** *	132	0.79(0.58,1.09)	31	1.00(0.54,1.87)
Obese class 2	31	0.79(0.48,1.30)	61	0.94(0.61,1.46)	7	1.02(0.25,4.23)
Obese class 3	18	0.86(0.44,1.69)	26	1.23(0.75,2.04)	5	1.50(0.43,5.27)
P for trend		0.089		0.659		0.840

HR, hazard ratio; *P < 0.05. Significant results ($P < 0.05$) are indicated in bold.
[a]Multivariable model adjusted for age, sex, ethnicity, education, family poverty income ratio, marital status, alcohol consumption, HEI-2015 score, cardiovascular disease, and diabetes, years since diagnosis and cancer types.

Among cancer survivors, an increased BMI has been association with survival benefits compared with normal-weight patients. The obesity paradox was observed in various types of cancer, including in patients undergoing surgery for stages I-III colorectal cancer (12), patients undergoing renal mass surgery (14), patients who had liver resection for colorectal cancer metastases (26); elderly patients receiving chemotherapy for acute myeloid leukemia (27); and cancer patients with distant metastases who received radiotherapy (28). In alignment with previous studies, our research demonstrated a reduced risk of all-cause and non-cancer, non-CVD death among cancer survivors with overweight or class 1 obesity. Interestingly, the association seem to vary based on gender; consistent with this study, the reverse association was more prevalent in men than in women (29). Such differences may arise from variations in disease mechanisms at the cellular and molecular level or differing reactions to treatment. The disparity in the muscle-to-fat ratio may help explain the gender differences (30, 31). Further investigation is required to explore these differences. Nevertheless, some researchers have argued that inverse associations may result from methodological limitations including reverse causality, collider bias, or confounding by smoking and comorbidities (16, 32, 33).

Reverse causality might arise when weight loss results from cancer rather than being its cause. To minimize the possibility of reverse causality in this study, patients who died within the initial 24 months of follow-up were excluded. With adequate covariate adjustment, including smoking and comorbidities, the prognosis was found to be most favorable for cancer survivors who were overweight or had class 1 obesity. Moreover, survivors with class 2 obesity and obesity-related cancer exhibited better overall prognosis compared to normal-weight patients, although similar statistically significant associations were not observed among non-obesity-related cancer survivors. A strength of the present study is the comprehensive adjustment for smoking, a potent cancer risk factor that could lead to an inverse association with mortality. When examining the association between BMI and all-cause mortality stratified by smoking status, the obesity paradox persisted among never smokers and former smokers. The associations between

TABLE 6 Body mass index (BMI) and total mortality in the multiethnic cohort, by cancer types, NHANES 1999 to 2018[a].

BMI	Obesity-related cancer(n=469)		Non–obesity-related cancer(n=892)	
	Death, n	HR (95%CI)	Death, n	HR (95%CI)
Underweight	11	0.70(0.33,1.47)	24	**3.39(1.88,6.10)** **
Normal	220	1.00(reference)	191	1.00(reference)
Overweight	333	0.80(0.59,1.10)	179	0.86(0.68,1.08)
Obese	210	0.74(0.53,1.03)	193	0.94(0.73,1.22)
Obese class 1	149	0.75(0.51,1.10)	106	0.79(0.60,1.04)
Obese class 2	47	**0.49(0.27,0.87)** *	52	1.25(0.85,1.86)
Obese class 3	14	1.07(0.64,1.78)	35	1.25(0.69,2.27)
P for trend		0.164		0.917

HR, hazard ratio; **P < 0.01*P < 0.05. Significant results ($P < 0.05$) are indicated in bold.
[a]Multivariable model adjusted for age, sex, ethnicity, education, family poverty income ratio, marital status, smoking status, alcohol consumption, HEI-2015 score, cardiovascular disease, and diabetes, and years since diagnosis.

BMI and the leading causes of death were also investigated. Reduced mortality among overweight and class 1 obese patients was primarily associated with non-cancer, non-CVD causes, rather than cancer or CVD. It appears that confounding by smoking and comorbidities or collider bias may not explain the survival benefits observed among cancer survivors with overweight and moderately obese BMI.

Limited sample sizes and broad weight group categorizations may have led to the absence of associations between obesity and outcomes in previous studies (7, 34). Some studies have redefined BMI categories, such as obese class 1 (BMI 25-29.9kg/m^2), obese class 2 (BMI ≥ 30kg/m^2) (35), while others have used standard WHO criteria (obese BMI > 30.0kg/m^2), which is a broad categorization. In the current study, obesity was divided into three categories. Class 1 obesity, rather than whole obesity or class 2/3 obesity, was significantly associated with reduced mortality risks of all-cause and non-cancer, non-CVD causes, suggesting that existing standard BMI categories are insufficiently refined to accurately assess mortality risk in similar studies.

Several potential explanations for the obesity paradox appear biologically plausible. Within the context of disease, survival benefits of being overweight or obese could be attributed to improved nutritional status (36), reduced thromboxane B2 levels (37), and enhanced mobilization of endothelial progenitor cells (38). Additionally, certain tumor subtypes might be less aggressive in overweight or obese cancer survivors. For instance, clear-cell renal cell carcinoma in obese patients may be more indolent compared to normal-weight patients due to differential expressions of metabolic and fatty acid genes (14). Moreover, overweight and obese cancer survivors may respond differently to treatment and potentially benefiting from the influence on treatment outcomes. Among these cancer survivors, excess adipose tissue serves as nutrient reserves, helping to counteract decreased energy intake and increased demands during cancer progression and treatment (39).

Strengths and limitations

One of the primary strengths of the study is the use of NHANES, which allowed for access to a large and nationally representative sample. Additionally, a wide range of confounding factors, including age, race/ethnicity, sex, education, family poverty income ratio, HEI, marital status, alcohol intake, smoking consumption, diabetes, CVD, and cancer type, were adjusted in the analyses. However, there are certain limitations that must be considered. Covariates were assessed at baseline, and these may have changed significantly during the follow-up period. A one-time BMI measure, not taken before or near the time of cancer diagnosis, does not reflect the cumulative impact of being overweight or obese on cancer survival. Moreover, there was insufficient data on cancer stage, histology type, and treatments. Nevertheless, the obesity paradox was still observed after excluding deaths in the initial 24-month follow-up period.

Conclusions

In this prospective cohort study of cancer survivors in the United States, it was discovered that being underweight or extremely obese was associated with a heightened risk for mortality, primarily in cancer and CVD-related causes. Overweight or mildly obese conditions were associated with significantly reduced mortality from all-cause and non-cancer, non-CVD causes and were not associated with mortality from cancer and CVD. Therefore, this study demonstrates that the associated of BMI with mortality varies substantially depending on the cause of death. To provide comprehensive survivorship care, future efforts are needed to investigate the effect of body weight on different outcomes among cancer survivors.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YY designed the study, analyzed and wrote the manuscript. DC and DZ provided the statistical analyses. YZ provided critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1180442/full#supplementary-material

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Cancer survival: left truncation and comparison of results from hospital-based cancer registry and population-based cancer registry

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Background: Cancer survival is an important indicator for evaluating cancer prognosis and cancer care outcomes. The incidence dates used in calculating survival differ between population-based registries and hospital-based registries. Studies examining the effects of the left truncation of incidence dates and delayed reporting on survival estimates are scarce in real-world applications.

Methods: Cancer cases hospitalized at Nantong Tumor Hospital during the years 2002–2017 were traced with their records registered in the Qidong Cancer Registry. Survival was calculated using the life table method for cancer patients with the first visit dates recorded in the hospital-based cancer registry (HBR) as the diagnosis date (OS_H), those with the registered dates of population-based cancer (PBR) registered as the incidence date (OS_P), and those with corrected dates when the delayed report dates were calibrated (OS_C).

Results: Among 2,636 cases, 1,307 had incidence dates registered in PBR prior to the diagnosis dates of the first hospitalization registered in HBR, while 667 cases with incidence dates registered in PBR were later than the diagnosis dates registered in HBR. The 5-year OS_H, OS_P, and OS_C were 36.1%, 37.4%, and 39.0%, respectively. The "lost" proportion of 5-year survival due to the left truncation for HBR data was estimated to be between 3.5% and 7.4%, and the "delayed-report" proportion of 5-year survival for PBR data was found to be 4.1%.

Conclusion: Left truncation of survival in HBR cases was demonstrated. The pseudo-left truncation in PBR should be reduced by controlling delayed reporting and maximizing completeness. Our study provides practical references and suggestions for evaluating the survival of cancer patients with HBR and PBR.

KEYWORDS

neoplasm, survival, left truncation, delayed report, hospital-based cancer registry, population-based cancer registry

1 Introduction

Cancer survival is a crucial measure of prognosis and a key factor in evaluating the effectiveness of cancer prevention and control. Over the past three decades, an increasing number of cancer survival studies have used data from population-based cancer registries (PBR) to compare cancer survival in populations worldwide, including major projects such as EUROCARE, CONCORD, SURVCAN, and others (1–5). However, most clinical applications and reports of cancer survival come from hospital-based cancer registries (HBR) (6–9). While survival indicators from both sources are useful for assessing the prognosis of cancer patients, the benchmarks used in the prognosis calculation are different, and their application of these concepts in public health decision-making and medical practice is not the same.

Cancer patient survival is typically measured from the incidence date, which is determined differently for PBRs and HBRs. PBRs collect incidence information for all cancer patients in the catchment area and use the "incidence" definition given by the International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR) (10–12), namely: (1) Date of first consultation at, or admission to, a hospital, clinic or institution for the cancer in question; (2) Date of first diagnosis of the cancer made by a recognized medical practitioner; (3) Date of histological confirmation or date of the first pathology report; (4) Date of death when the cancer is first ascertained from the death certificate; and (5) Date of death preceding an autopsy when the cancer was first diagnosed at autopsy. A slightly different definition has been recommended for use by the European Network of Cancer Registries, which prioritizes the date of histological proof of diagnosis as the date of incidence (13).

The starting date for cancer survival calculation in a HBR is the date when the patient first visited the target hospital where the cancer was ascertained (7–10). Figure 1 shows an algorithm of the possible relationships between PBR incidence date and HBR diagnosis date for a cancer patient: the starting (incident) date of his/her registration by a PBR should always be earlier than, or at least not later, than the date of diagnosis from any hospital (HBR) source.

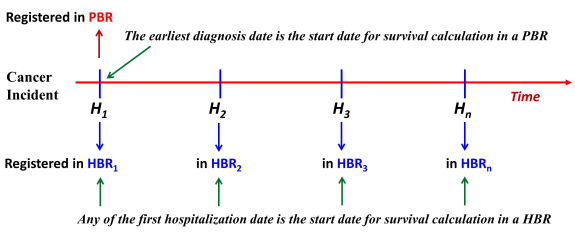

FIGURE 1
The relationship of start dates between patients from the PBR and the HBR. For the PBR, if a case of cancer is not reported first from H_1, but from H_2 or H_n, then this case is called a "delayed report." Under this circumstance, the left truncation occurs (PBR, population-based cancer registry; HBR, hospital-based cancer registry).

Furthermore, the figure shows that if a patient's visit to a HBR is not the patient's first hospital visit (HBR_1), then the patient's date of registration at the *n*th hospital (HBR_n) should not be earlier than the date registered at a PBR (or the HBR_1). Therefore, in the same series of patients, the survival of cases diagnosed/treated in a certain hospital (HBR_n) should always be, theoretically, less than that calculated based on data from a PBR. Thus, the diagnosis date for survival calculation from a hospital series has been "left truncated" (a statistical phenomenon that occurs before the start of an event). Assuming that the incidence date of a cancer patient from PBR is D_P, the date of his/her first registration at any hospital (HBR_n) is D_H, and the length of time between the two registration dates is L, then, obviously, $L = D_H - D_P$ ($L \geq 0$). For example, if the registered date of a patient is 3 January 2022 in PBR data and his/her first diagnosis date registered in HBR is 5 May 2022, then the difference (L) between the two dates is $L = D_H - D_P$ = (5 May 2022) − (3 January 2022) = 122 days. In accordance with IARC/IACR definitions of incident date, this date for a case registered in a PBR should, in theory, never be later than the date registered in any hospital, so the length of L is always ≥ 0. As can be seen, L represents the amount of "left truncation." However, in some cases, delayed reporting can cause the registered D_P in a PBR to be later than the registered D_H in an HBR, resulting in an artificial pseudo-left truncation. Say, D_H was 5 May 2022, while D_P was 8 August 2022, so that $L = D_H - D_P$ = (5 May 2022) − (8 August 2022) = −95 (days). Such cases are due to "delayed reporting" (14, 15), and "left truncation" occurs due to the "lost" days from PBR. Obviously, this artificial pseudo-left truncation affects the estimates of survival, although the effect of left truncation on these estimates of survival has not been quantified in comparative studies (1–3). To understand the impact of left truncation on survival estimates using registry data, as well as the impact of delayed reporting on cancer patient survival from PBR data, we looked at data from the population-based Qidong Cancer Registry (QCR) and the hospital-based Nantong Cancer Registry (NCR), China, for a comparative study of survival.

2 Materials and methods

2.1 Hospital-based registry

The NCR was established in 2012, and all cancer inpatient data from the hospital information system at the Nantong Tumor Hospital (NTH) has been included in the registry database since 2002 (7). Between 2002 and 2017, a total of 74,503 patients had 226,527 visits registered in the NCR database. Among these, there were 7,375 hospitalization records for patient residents in Qidong City, involving 2,920 patients with cancer. After 2014, in addition to routine telephone follow-up, three on-site active follow-ups have been conducted on these Qidong patients to determine vital status for the evaluation of survival.

2.2 Population-based registry

The QCR was established in 1972, and its results have been published in successive volumes of the *Cancer Incidence in Five*

Continents as well as scientific papers (3, 5, 11, 16). During the period of 2002 to 2017, a total of 62,742 cancer cases were registered. The incidence date (the earliest diagnosis date) could be from provincial and municipal tertiary hospitals (3A or 3B hospitals, including Nantong Tumor Hospital), county hospitals (2A or 2B hospitals), and others (including township hospitals). Each year, cancer patient survival outcomes were tracked and audited using both passive and active methods. Every 5 years, all registered cases not known to have died are systematically followed up.

2.3 Definition of survival time

HBR diagnosis date (D_H): A patient may have multiple admissions to the same hospital, and the HBR diagnosis date D_H refers to the date when the earliest (first) admission to the hospital with a cancer diagnosis occurred (between 2002 and 2017).

PBR diagnosis date (D_P): This date is defined using the IARC/IACR rules for date of incidence (10–12), i.e., the earliest date that a patient was first diagnosed with cancer at any hospital. Accordingly, the date of incidence in the PBR should always be earlier than the hospital date ($D_P \leq D_H$), and if the reverse situation ($D_P > D_H$) occurs, the date of incidence (diagnosis) of the PBR is referred to as "delayed."

The survival time of cancer patients clearly depends upon the recorded date of incidence/diagnosis, as shown in Figure 1. For population-based survival, based on PBR data, the survival period (S_P) is the difference between the date of last follow-up (D_F) [or the date of death (D_D)] and the date of incidence (D_P), i.e., $S_P = D_F - D_P$. In the HBR data, the survival period (S_H) is the difference between the diagnosis date (D_H) of a patient and the D_F, i.e., $S_H = D_F - D_H$. There may be a difference $L = (D_H - D_P)$ between S_P and S_H, as indicated before. Thus, the survival period of the PBR patients (S_P) is $S_P = D_F - D_P = (D_F - D_H) + (D_H - D_P)$, where $D_F - D_H$ is S_H, $D_H - D_P$ is L, So, $S_P = S_H + L$, or, $S_H = S_P - L$. The L represents the left truncation, the difference compared to S_P in PBR cases.

2.4 Follow-up and registration status

The closing date, or follow-up deadline (D_F), for this study was 31 December 2020. In the QCR, most of the incidence dates of the patients were earlier than the diagnosis dates in the NCR, i.e., $D_P < D_H$, although for some cases, the source of information for the QCR was the first hospital visit to NTH, so the two dates were the same, i.e., $D_P = D_H$. However, there were also some cases whose PBR registered dates were later than the HBR registered dates, which means that a case was first registered in the NCR but the QCR did not receive the case report. Only when this case was admitted to another hospital in the QCR coverage area was the case registered in the NCR as an incident case, resulting in $D_P > D_H$.

2.5 Processing of data

Survival was calculated using the life table method implemented in SPSS 22 software. In view of the above-mentioned differences in the diagnosis (incidence) dates among patients from HBR and PBR, three sets of survival indicators were used in this paper: 1) the observed survival with the first visit date of HBR as the diagnosis date, OS_H; 2) the observed survival with the registered date of PBR as the incidence date, OS_P; and 3) the corrected observed survival, that is, if $D_P > D_H$ (PBR delayed-report), then let $D_P = D_H$ (calibration to the earlier date) to form the corrected PBR series (cPBR), and then recalculate the observed survival, OS_C. The ages of the patients whose diagnosis/incidence date was changed were adjusted accordingly.

A comparative analysis of the three observed survival indicators (OS_H, OS_P, and OS_C) mentioned earlier is performed. The time of the "left truncation" from hospital survival data is estimated, and the differences between the survival from the HBR cases and the corrected survival from the "correction" PBR series are evaluated. The loss of survival due to the "left truncation" in HBR cases is assessed by the computation $(1 - OS_H/OS_C)$, and the loss of survival due to the "delayed report" in PBR series is delineated by the computation $(1 - OS_P/OS_C)$.

3 Results

3.1 Case data distribution

From 2002 to 2017, a total of 2,920 cancer patients (HBR cases) who were residents of Qidong were registered in the NCR. Of these, 2,636 cases were used to estimate survival, while 284 cases were excluded because they were non-residents or were lost to follow-up (with no records in QCR). The age and sex distribution of NCR cases at the time of their first admission is shown in Table 1.

Upon linkage with the QCR database, it was discovered that 1,307 cases had an incidence date registered in PBR that was prior to the diagnosis date (first hospitalization) registered in HBR ($D_P < D_H$). For 662 cases, the dates in the HBR and PBR were the same ($D_P = D_H$). Meanwhile, for 667 cases, the incidence dates registered in the PBR were later than the diagnosis dates registered in the HBR ($D_P > D_H$), as illustrated in Figure 2, meaning that among 2,636 cancer patients, 1,969 cases (1,307 + 662) were reported and registered "timely" in the PBR, while 667 cases (25.3%) were "delayed-reported." The average delay in the incidence date was 397 days, but the median time was 86 days. The delay exhibited a skewed distribution, ranging from 1 day to 5,585 days. Of the 2,636

TABLE 1 The distribution of 2,636 HBR cases by age group and by sex.

Age group	Male	Female	Total
0–14	3	0	3
15–34	27	45	72
35–59	505	768	1,273
60–79	707	473	1,180
80–99	61	47	108
Total	1,303	1,333	2,636

HBR, hospital-based cancer registry.

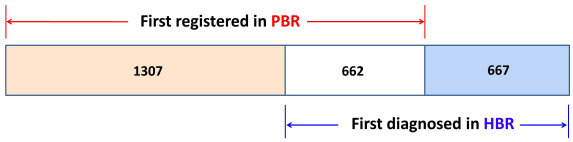

FIGURE 2
The distribution of 2,636 cases in the PBR and in the HBR. $D_P < D_H$: 1,307 cases; $D_P = D_H$: 662 cases; and $D_P > D_H$: 667 cases (PBR, population-based cancer registry; HBR, hospital-based cancer registry).

cancer patients, 1,307 had left truncated dates because their first diagnosis was not registered in the NCR (2002 as the reference truncated date). The average length of truncation was 477 days, with a median of 109 days and a skewed distribution ranging from 1 day to over 33 years (12,253 days).

3.2 HBR observed survival (OS_H)

The date of first admission defined the diagnosis date (D_H) and was the starting point for calculating observed survival in HBR (OS_H). The 1-, 5-, 10-, and 15-year OS_H rates were 64.5%, 36.1%, 28.6%, and 25.1%, respectively. The 5-year OS_H rates of patients aged 15–34, 35–39, 60–79, and 80–99 was 55.5%, 42.9%, 29.0%, and 18.4%, respectively (Figure 3A).

3.3 PBR observed survival (OS_P)

The incidence date (D_P) of a PBR-registered case was used as the starting date for the calculation of PBR survival (OS_P). The 1-, 5-, 10-, and 15-year OS_P were 70.7%, 37.4%, 29.6%, and 25.3%, respectively. The 5-year OS_P of patients aged 15–34, 35–59, 60–79, and 80–99 was 61.1%, 42.9%, 30.3%, and 20.5%, respectively (Figure 3B).

3.4 Corrected PBR observed survival (OS_C)

After adjusting the incidence dates (D_P) of PBR registered cases for those $D_P > D_H$ (PBR delayed report), the updated incidence date in cPBR cases was used for the calculation of the cPBR observed survival (OS_C). The 1-, 5-, 10-, and 15-year OS_C were 76.9%, 39.0%, 29.6%, and 24.7%, respectively. The 5-year OS_C of patients aged 15–34, 35–39, 60–79, and 80–99 was 62.3%, 44.7%, 31.3%, and 23.7%, respectively (Figure 3C).

3.5 Comparison of three sets of observed survival

Since there was clearly a "lost" survival time due to the left truncation in the diagnosis date of the HBR series, the ratio of OS_H/OS_P (36.1/37.4) was 0.97 when compared to the 5-year survival between HBR and PBR, i.e., the "lost" proportion of 5-year OS_H was approximately 3.5% ($1 - OS_H/OS_P$). But when corrected for the incidence dates in "delayed-report" PBR cases, the OS_H/OS_C ratio (36.1/39.0) was 0.93, meaning the "real" loss of 5-year OS_H for HBR cases was up to 7.4% ($1 - OS_H/OS_C$) due to the "true" left truncation. For the comparison between the PBR and cPBR series, the OS_P/OS_C ratio was 0.96, i.e., when adjusted for "delayed-report," the cPBR series mitigated the loss of approximately 4.1% ($1 - OS_P/OS_C$) on 5-year observed survival (Table 2).

A comparison of the survival curves from three "series" shows that survival, essentially, was $OS_C > OS_P > OS_H$, and the differences in survival before 10 years were larger; after 10 years, the differences had narrowed (Figure 4).

4 Discussion

Over the past 30 years, cancer survival, as an effective indicator of the prognosis or outcomes for patients in medical practice, has

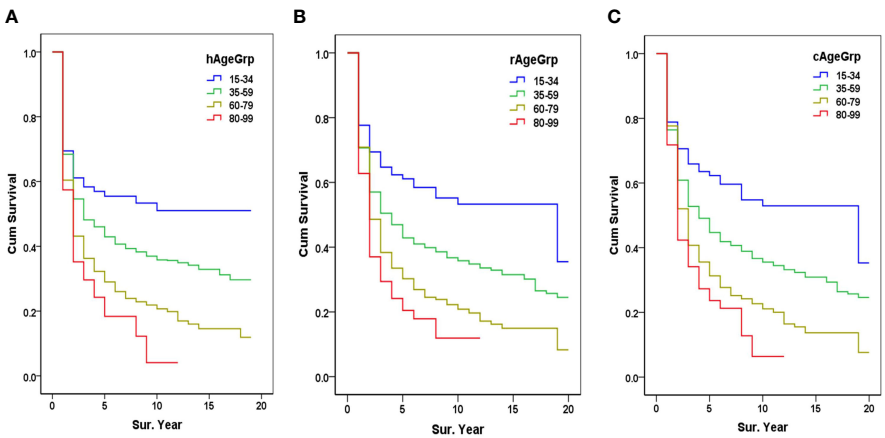

FIGURE 3
Survival from HBR and PBR by age group. **(A)** The HBR survival by age group, hAgeGrp, Age group when diagnosed in HBR; **(B)** The PBR survival by age group, rAgeGrp, Age group when registered in PBR; **(C)** Corrected PBR (cPBR) survival by age group, cAgeGrp, Age group after being corrected in the PBR (PBR, population-based cancer registry; HBR, hospital-based cancer registry).

TABLE 2 Comparison of three sets of observed 5-year survival (%) and their ratios.

Age group	OS_H	OS_P	OS_C	OS_H/OS_P	OS_H/OS_C	OS_P/OS_C
15–34	55.5	61.1	62.3	0.91	0.89	0.98
35–59	42.9	42.9	44.7	1.00	0.96	0.96
60–79	29.0	30.3	31.3	0.96	0.93	0.97
80–99	18.4	20.5	23.7	0.90	0.78	0.86
Total	36.1	37.4	39.0	0.97	0.93	0.96

OS_H, observed survival with the first visit date of HBR as the diagnosis date; OS_P, observed survival with the registered date of PBR as the incidence date; OS_C, corrected observed survival after calibration to the earlier date.

been widely used in the evaluation of global cancer control and health services (1–3). However, this index is easily affected by left truncation because, for the data involving lifetimes, it may be observed within the limits of the time window. The "incompleteness" of the observed "time origin" occurs with the truncation of information in real-world data (17–19). Therefore, a common challenge in survival data is that patients are often included in the data only after a period of risk, i.e., delayed inclusion, such as genetic testing for lung cancer before clinical diagnosis or an asymptomatic stage (which can be detected by screening) before liver cancer hospitalization, etc. (20, 21). That is why cancer registries should follow rigorous definitions for determining incidence dates (10–13); it is the only possibility that survival estimations are comparable between registries and that the survival estimates are not biased.

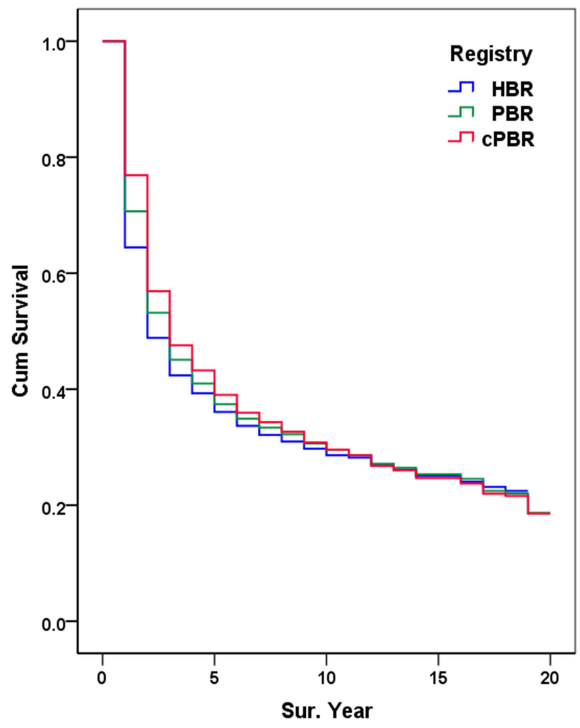

FIGURE 4
Comparison of three observed survival series. The Wilcoxon statistic (*df* = *2*) is 41.24, with a *P*-value of 0.0000.

In the study of survival in clinical practice, more attention is paid to the "incompleteness" of follow-up data at the closing date, which is the well-known phenomenon of "right censoring" (15, 22–24). However, for "left-truncated" data (such as hospitalization case series), although there are some theoretical studies in the literature, mostly involving estimation using parametric, simulation, or modeling methods (18, 19, 25, 26), there are very few practical examples. In one study that evaluated colorectal cancer screening modalities using a multivariate model with left-truncated and right-censored data, 62% of subjects were found to be left-truncated, with an average left-truncated duration of 4.5 years (range: 0.1–9.9 years) (27).

A cancer patient, from onset to death, may visit hospitals many times; moreover, in each of these hospitals, the incidence (diagnosis) date would be the respective date of first admission. Apparently, the survival time of each hospital case will be reduced due to "left truncation" in relation to earlier admissions elsewhere (or indeed earlier outpatient attendances), and the result would be a biased estimation (19); hence, the survival produced by the left-truncated data from hospital patients are under-estimates (27). HBR cases are a special group of cancer cases in the population of the covered area, and the starting date for survival calculation could only be the date of the first visit (treatment) to this hospital (7, 28). This "first" date may be the real first time in his/her "lifetime" as a patient, but it may also be the "first" only at this target hospital after "walking around" several hospitals for diagnosis (as shown in Figure 1). The interval between the diagnosis date at this hospital and the real first diagnosis with cancer could be very short (if it was the first diagnosis in his/her lifetime) or it could be very long (after *n* times visits to other hospitals, then to "this" target hospital), implying that the diagnosis date of HBR case series inevitably has the problem of "left truncation," and this truncation *L* may be a "random" variable.

In this series, the 2,636 Qidong cases registered at the NCR show that a minimum of 49.6% (1,307) of the cases had "left truncation" (cancer had been diagnosed elsewhere before the NCR). The extent of left truncation of survival time in these 1,307 cases registered in HBR had an arithmetic mean of 477 days and a median of 109 days [compared to the survival time based on the incidence date registered in PBR (QCR)]. According to QCR data, the observed longest delay in reporting was up to 33 years, but since HBR was not established until 2002, the longest possible truncated interval would be 15 years (2017–2002).

The observed survival (OS_H) of HBR cases is obviously different from the observed survival (OS_P) in PBR because of "left truncation," where $L = D_H - D_P$ ($L \geq 0$). In our series, the 5-year OS_H of HBR cases was 36.1%, and the 5-year OS_P of PBR cases was 37.4%, a percentage difference of 3.5% ($1 - OS_H/OS_P$). Artificial (false) "left truncation" due to "delayed report" also exists in the PBR case series. Some degree of late reporting in PBR is inevitable (12, 14, 29). If the patient's incidence date registered in PBR is not from the first hospital visited (H_1) but from the second or even later visited hospitals (H_2,…, H_n), then the difference between the dates of PBR and H_1 would be negative ($L < 0$). This is apparently a false "left truncation" caused by the "delayed report" in PBR. In our study, 667 PBR cases were reported late by an average of 397 days (about 13 months) and showed an obvious skewed distribution with a median of 86 days, telling us that 50% of the delayed reports occurred within 3 months. The delayed report could happen before a deadline for survival calculation in registry practice; thus, a PBR should timely check-up the delayed-report cases in the workflow so that the patient's incidence date could be dynamically updated as the "earliest" diagnosis date. A study showed that there were variations in recorded dates of incidence, and as cancer registries have access to different sources of information, for liver cancer and pancreatic cancer in Norway and ovarian cancer in England, larger 1-year survival differences were found to be 2%–3%, although it is considered to have a very limited impact on survival estimation (30).

There are many factors that affect survival from PBR in international comparisons (29, 31) and delayed reporting may be another factor influencing survival calculated from PBR. In our study, when this length of the pseudo-left truncation time is corrected, the 5-year OS_C of PBR cases was 39.0% compared with an uncorrected value of 37.4%, a difference of about 4.1%. Similarly, the 5-year OS_H of HBR cases, compared with the corrected 5-year OS_C in PBR, had a 'true' loss (left truncation) of 7.4%. Another factor that affects survival may be the definition of "incidence date." In North America and in Europe, for example, where the SEER definition and ENCR definition (13) were recommended, the incidence date could be before any hospital admission, which would make the "left truncation" even greater in magnitude.

Our observation has certain limitations. Firstly, this study is based on data from a population-based registry and a hospital-based registry in a region in China, which may not be directly applicable to the comparative evaluation of PBR and HBR in other regions, but the research approach to cancer and the problems and significance revealed by this study have general applicability. Secondly, PBR cases come from numerous HBRs (or hospitals), and each hospital's attraction to the local patients is different, and the length (or distribution) of the "left truncation" will depend on the hospital's service capacity or impact force on cancer patients.

In conclusion, our study demonstrates that left truncation can affect the survival of cancer patients. Although the survival of HBR case series is utilized to evaluate the prognosis (and effectiveness of treatment in the hospital), it is inevitable that a certain degree of underestimation occurs due to "left truncation," even if its magnitude cannot be assessed. The survival of PBR cases is used to assess the survival outcomes of all cancer patients, which primarily reflects medical service capacity—given the nature of the patient population—in the area covered. Delayed reporting to the PBR leads to artificially "false" lost (reduced) survival for the PBR series. This pseudo-left truncation that affects survival from PBR should be industriously controlled by ensuring data completeness and timely reporting in cancer registration practice. The findings underscore the importance of accurate and complete cancer registration data, as it can significantly affect the evaluation of cancer survival outcomes and the efficacy of treatment. Therefore, we recommend that cancer registration authorities establish robust quality control measures to ensure the completeness and accuracy of the data. Additionally, we suggest that future studies investigate the impact of left truncation on other disease types and assess the effectiveness of various methods to control this phenomenon. We believe that our study has provided us with practical references and suggestions for evaluating the survival of cancer patients with HBR and PBR.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

J-GC and X-YS were responsible for the conceptualization and design of the study. J-GC and DP searched literatures and supervised the study. J-GC, H-ZC, JZ, and A-GS collected and analyzed data. J-GC wrote the first draft of the manuscript. J-GC and DP interpreted the results and revised the content critically. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Incidence disparities of obstructive sleep apnea-associated lung cancer by gender; Korean National Health Insurance data analysis

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Introduction: Obstructive sleep apnea (OSA) is known to increase the risk of various cancers. By analyzing the Korea National Health Insurance Service (KNHIS) registry, the impact of OSA on the lung cancer incidence was analyzed in a retrospective cohort group.

Methods: A retrospective cohort of adult patients newly registered with OSA in the KNHIS data from 2007 to 2017 was included and observed until December 2019 (12 years). The main outcome measure was newly diagnosed lung cancer. The control group was set with age and sex that matched those in the OSA group.

Results: The hazard ratio (HR) of OSA for lung cancer incidence showed a significantly reduced HR of 0.87 (95% CI, 0.82–0.93). The observed significance of this finding was limited to male OSA patients [HR, 0.84 (95% CI, 0.78–0.90)], while no significant association was found in female OSA patients [HR, 1.05 (95% CI, 0.91–1.21)], irrespective of their age.

Discussion: OSA patients have a lower risk of developing lung cancer, but this risk reduction is gender-specific, as female OSA patients do not show a reduction in hazard ratio.

KEYWORDS

lung cancer, sleep apnea, obstructive sleep apnea, incidence, national health programs

Introduction

The incidence of obstructive sleep apnea (OSA) is increasing worldwide, affecting approximately 15% of males and 5% of females in the North American population (1). In South Korea, the prevalence of OSA is reportedly 4.5% in males and 3.2% in females (2). Patients with OSA show intermittent hypoxemia (IH) with or without hypercapnia, resulting in functional changes in the autonomous nerve system (3–5), as well as structural or molecular changes in the cardiovascular (6), neurologic (7), immune (8), or endocrine organs (9). Therefore, OSA acts as an independent predisposing factor for developing various cerebrovascular and metabolic disorders (10). One additional aspect of managing OSA lies in its efficacy in reducing the risk of the development of, for example, ischemic heart disease, stroke, and type 2 diabetes mellitus (DM) with decreased morbidity (11, 12).

Interestingly, it has been claimed that OSA may be positively associated with various malignant neoplasms in humans (13). Justeau et al. (14) reported that patients with more severe nocturnal IH who were untreated showed a significant increased risk in all-cancer incidence independently; of all the cancers, lung cancer showed the most statistical significance.

Lung cancer stands as the leading cause of cancer-related deaths in men and second-greatest cause in women; approximately 2.1 million patients were diagnosed, and 1.8 million deaths were recorded worldwide in 2018 (15). In South Korea, the crude incidence of lung cancer reported in 2019 was 58.4 per 100,000, affecting males and females at rates of 79.4% and 37.4%, respectively (16). Although the exact mechanism through which OSA develops into lung cancer is uncertain, the possible carcinogenetic and cancer-progression potential of OSA in lung cancer was reported in the previous study (17).

To date, numerous meta-analysis studies regarding OSA and cancer incidence have been published, suggesting that lung cancer is one of the cancers correlated with OSA (12, 17–20). Nevertheless, a study focusing on the incidence of newly diagnosed lung cancer in patients diagnosed with OSA in a large, nation-wide cohort has not yet been published to the authors' knowledge, particularly in the East Asian population. Additionally, no previous studies have conducted a subgroup analysis on the impact of gender differences regarding OSA and lung cancer development.

The authors sought to determine the incidence and hazard ratio of lung cancer in patients with OSA using a large, nationwide retrospective cohort stretching twelve years, utilizing data from the Korea National Health Insurance Service (KNHIS) database. The study incorporated analyses of subgroups based on gender and age.

Materials and methods

Ethical declaration

This study was approved by the Institutional Review Board (IRB) of Inha University Hospital (IRB no. 2022-11-004). The IRB has reviewed and approved the study design and issued an exemption for the informed consent of the study subjects. The authors adhered precisely to the research standards while being formally monitored by the IRB.

Source of data: the KNHIS database

The current study was conducted with data from the KNHIS. Since 2000, the South Korean government has mandated that all South Korean citizens are registered and covered by the KNHIS in terms of seeking medical care (21). Upon submitting a formal dissertation protocol in addition to ethical approval from the official review committee, the KNHIS offers the usage of the data registered in the KNHIS archive. Each person registered in the KNHIS receives a unique resident registration number, thereby eliminating the possibility of duplication or omission upon data analysis. Both inpatient and outpatient claims are examined by the KNHIS, with data on the patients' demographics, clinical diagnoses, medical expenses, and interventions for diagnostic or therapeutic purposes. The KNHIS reviews all medical claims and classifies and stratifies the received data based on the Korean Standard Classification of Diseases, 6th edition (KCD-6), a modified version of the International Classification of Diseases, 10th Revision (ICD-10).

Acquisition of the data from the KNHIS dataset

The identification of patients diagnosed with OSA was performed with a search of the operational code for OSA (G47.30) in the KNHIS dataset. The patients' demographic data for age, gender, and income level were obtained. The details of the patients' medical history, including diagnoses of hypertension (HTN), diabetes, dyslipidemia, ischemic heart disease, chronic obstructive pulmonary disease, and stroke, were additionally gathered from the claimed insurance data. The operational definition and search requirements regarding each disease are further elaborated in Table 1.

In the KNHIS dataset, each individual's diagnosis is represented by a unique designation (e.g., G4730 for OSA, C33 or C34 for lung cancer, E11 to 14 for diabetes, etc.). Therefore, we could only acquire the presence of specific disease diagnoses and the date of each diagnosis. As stated previously, in order to search for OSA patients during the research period, we searched the KNHIS database for individuals who were claimed with the G4730 diagnosis code during the study period, as well as other diseases.

Primary endpoint and study design

This study included adults (age ≥ 20) who were newly diagnosed with OSA (G47.30) from Jan 2007 to Dec 2017. The primary endpoint of this observational study was the incidence of newly diagnosed lung cancer in these newly diagnosed OSA patients. Patients who were newly diagnosed with OSA in that period were enrolled as a retrospective cohort, and the claimed insurance data of

TABLE 1 The KNHIS database search criteria and processes for patients with each condition.

Name of Each Disease		Search Protocols of Each Disease
Study subjects	OSA	Patients who were registered with G47.3 in the ICD-10 code in the KNHIS dataset, with a minimum of a single claim
Primary endpoint measurements	Lung cancer	Patients registered with C33 or C34 in the ICD-10 code in the National Medical Expenses Support Program, with a minimum of a single registration
Various diseases analyzed for confounding variables	Diabetes	Patients who were prescribed anti-diabetic medication under ICD-10 code E11-14, with a minimum of a single prescription per year, in the KNHIS dataset
	Hypertension	Patients who were prescribed anti-hypertensive medication under ICD-10 code I10, I11, I13, or I15, with a minimum of a single prescription per year in the KNHIS dataset
	Dyslipidemia	Patients who were prescribed anti-hypertensive medication under ICD-10 code E78, with a minimum of a single prescription per year in the KNHIS dataset
	Stroke	Patients who were registered with I63 or I64 in the ICD-10 code in the KNHIS dataset, with a minimum of a single claim
	COPD	Patients who were registered with G47.3 in the ICD-10 code in the KNHIS dataset, with a minimum of a single claim
	IHD	Patients who were registered with G47.3 in the ICD-10 code in the KNHIS dataset, with a minimum of a single claim

KNHIS, Korea National Health Insurance Service; OSA, obstructive sleep apnea; ICD, International Classification of Diseases; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease.

the cohort were retrospectively reviewed up to the end of 2019, creating an observation period of twelve consecutive years.

The presence of newly diagnosed lung cancer (ICD-10 code C 33 or C 34) was re-viewed in this cohort period in a retrospective manner in the National Medical Expenses Support Program registry (Table 1). The patients were excluded according to the timing of lung cancer diagnosis or if they had been withdrawn from the KNHIS upon death. The time interval between the OSA diagnosis and lung cancer diagnosis was calculated; it was defined as a 'person-year at risk' for developing a new onset of lung cancer, which was calculated for all included subjects.

To compare the cumulative risk of lung cancer incidence in OSA patients, a control group was recruited. The controls were chosen using propensity score matching by gender and age and selected from among patients without an OSA diagnosis from Jan 2007 to Dec 2017. The overall number of participants in the control group was set to be five times that of the OSA patients.

Prior to the enrollment, patients with any malignant tumors (determined through a search for all operation codes for malignant neoplasm) were excluded from both the OSA and control groups. A flowchart regarding the details of the retrospective OSA cohort with the selection process of the control groups is further illustrated in Figure 1.

Statistical analysis

Descriptive statistical analysis was conducted for various types of demographic and clinical information. Regarding each type of clinical variable, Student's t-test or a chi-square test was adopted to compare the OSA and control groups. To compare the incidence rate of newly diagnosed lung cancer patients between the OSA group and control group, a log-rank test was conducted, and a cumulative-incidence plot was drawn. The hazard ratio (HR) for lung cancer development was calculated with the adoption of two different Cox proportional hazards models in both the OSA and control groups. In model A, the covariate was not considered for HR calculation. In model B, the HR was adjusted for all cofounding variables: income level, HTN, diabetes, dyslipidemia, stroke, COPD, and ischemic heart disease. Additionally, subgroup analyses were performed to deter-mine the odds ratio (OR) of OSA for developing lung cancer in the various subgroups, i.e., gender (two groups) and age (three groups), using a logistic regression analysis.

Two hypotheses underlie the Cox proportional hazards model. First, stratum survival curves must have proportionate hazard functions over time. Residual plots indicate the linearity of the log hazard-covariate relationship. During the retrospective cohort research, Korean lung cancer incidence increased somewhat, which may have impacted our findings. Logistic regression models analyze the association between a binary result and a collection of covariables. Logarithmic regression analysis might be biased if the sample size is too small. We mitigated this bias by using a large sample size in our analyses. The p value for the interaction was calculated to validate the statistical reliability of the sub-group analyses. A p-value that was less than.05 was considered statistically significant. All statistical analyses were executed in a two-tailed manner, and the results were presented with a 95% confidence interval (CI). SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) or R ver. 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria) was utilized for statistical analyses.

Results

According to the KNHIS records, the total number of registered individuals in 2007 was 49,570,064. Throughout the patient recruitment phase ranging from January 2007 to December 2017, a total of 310,557 patients were registered with newly diagnosed OSA, as depicted in Figure 1. The control group comprised a total of 1,339,245 individuals who were recruited. During the observation period spanning from January 2007 to December 2019, the retrospective cohort's mean follow-up time interval was 5.9 ± 3.1 years, as determined by the calculated mean and standard deviation. A p-value below.05 was deemed statistically significant.

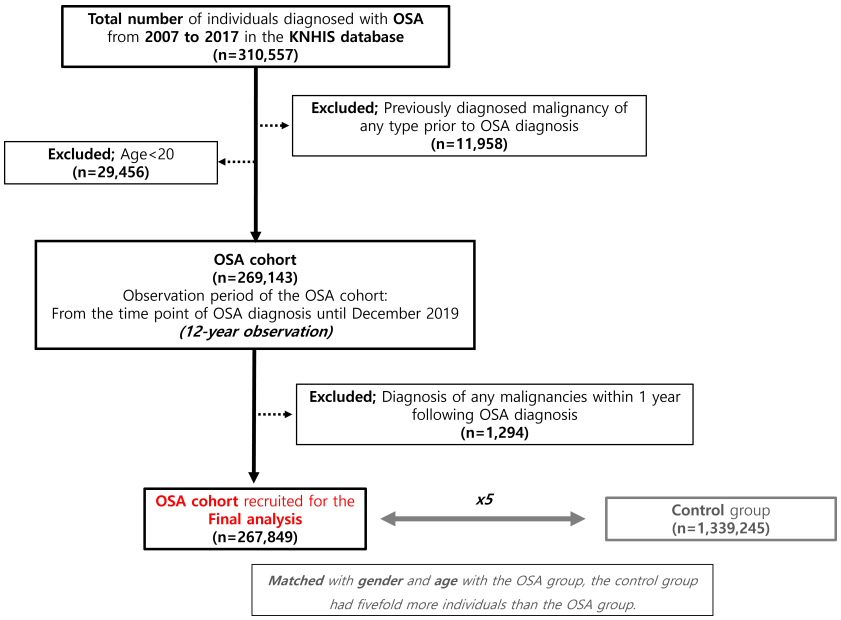

FIGURE 1
Recruitment of patients with obstructive sleep apnea (OSA) and the control group. A flow diagram elaborating the recruitment process of the OSA group and control group from the Korea National Health Insurance Service (KNHIS) database.

Demographic differences between the OSA and control groups

Various demographic data and clinical diagnoses of the OSA group and control group are presented in Table 2. As the OSA patients' gender and age were matched upon the recruitment of the control group, the age and sex between the two groups showed statistical consistency, with a p-value of 1.0. By contrast, other demographical variables showed significantly different distributions between the two groups. The OSA group had a significantly higher rate of underlying comorbidities, including chronic obstructive pulmonary disease (COPD). The OSA group had a significantly lower number of subjects on the lowest incomes (Table 2).

The impact of OSA on lung cancer development

In the 12-year retrospective cohort, the OSA group showed a significantly reduced rate of cumulative lung cancer incidence than the control group. As represented in the cumulative incidence plot for the development of new onset lung cancer, a significant

TABLE 2 Demographics of OSA patients and controls.

	OSA (n = 267,849)	Controls (n = 1,339,245)	p-Value
Age (years)	45.68 ± 13.17	45.68 ± 13.17	1.000
Age ≥ 65 years	22220 (8.3)	111100 (8.3)	1.000
Gender (male)	203026 (75.8)	1015130 (75.8)	1.000
No. of subjects with income in the bottom quintile	35208 (13.14)	238775 (17.83)	<0.001
Diabetes	18622 (6.95)	81748 (6.1)	<0.001
Hypertension	66391 (24.79)	210889 (15.75)	<0.001
Dyslipidemia	47290 (17.66)	131316 (9.81)	<0.001
Stroke	3176 (1.19)	4367 (0.33)	<0.001
COPD	21428 (8)	59753 (4.46)	<0.001
IHD	2564 (0.96)	5815 (0.43)	<0.001
Follow-up duration (years)	5.92 ± 3.14	5.89 ± 3.13	<.0001

Values presented in mean ± standard deviation or number (%).
OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease.

difference in the incidence probability between the OSA and control groups was observed (p=0.003) (Figure 2).

The mean follow-up duration (from the point of OSA diagnosis to the lung cancer diagnosis, censoring, or termination of the cohort) of the OSA patients was 5.92 ± 3.14 years, whereas the follow-up duration of the control group was 5.89 ± 3.13 years (p<0.001; Table 2). The significantly shorter observation time interval observed in the control group than in the OSA group indicates that OSA patients were lesser prone to developing lung cancers than the control group.

The HR calculated from the Cox proportional hazard model to evaluate the impact of OSA on the development of lung cancer showed a statistically significantly reduced risk of developing lung cancer in the non-adjusted model (Model A, HR of 0.91 (95% CI, 0.85–0.97)) and a greater reduction in the adjusted model [Model B, HR of 0.87 (95% CI, 0.82–0.93)] (Table 3).

In both the gender and the three different age subgroups, the male subgroup showed only a significantly reduced adjusted HR of 0.84 (95% CI, 0.78–0.90; Table 4). By contrast, this significantly reduced effect of OSA on lung cancer development did not prevail in the female subgroup, as the adjusted HR was 1.05 (95% CI, 0.91–1.21). By contrast, no significant risk reduction or increase were shown in the young adult (aged between 20 to 40) and middle-aged adult (aged between 40 to 65) (Table 5). On the other hand, the old age sub-group (aged > 65) showed a decreased HR of 0.74 and 0.70 in both models (Table 5). The p values for interactions in all subgroup analyses were less than 0.025, indicating the statis-tical validity of the subgroup analysis.

A further breakdown of the analysis was performed to evaluate the gender-specific effects according to different age groups (Supplementary Table 1). Regardless of male and female sex, there was no significance in the lung cancer risk according to the presence of OSA diagnosis. The demographics of the male OSA and female OSA patients exhibited some distinctive differences regarding the development of lung cancer (Supplementary Table 2). The male OSA lung cancer group showed significantly higher rates of older age, low income, and all comorbid systemic diseases than the male OSA lung cancer-free patients. On the other hand, the female OSA lung cancer patients showed only an increased number of older age, hypertension, and COPD patients than the female OSA lung cancer-free patients.

Discussion

The results of this current study, which were obtained from the nation-wide retrospective cohort from 2007 to 2017 with a 12-year observation period (2007 to 2019), showed that the adult patients diagnosed with OSA had a significantly reduced risk of developing lung cancer. This reduced risk was significantly valid when the cofounding demographic variables were adjusted. However, in the subgroup analysis according to each gender, only the male OSA

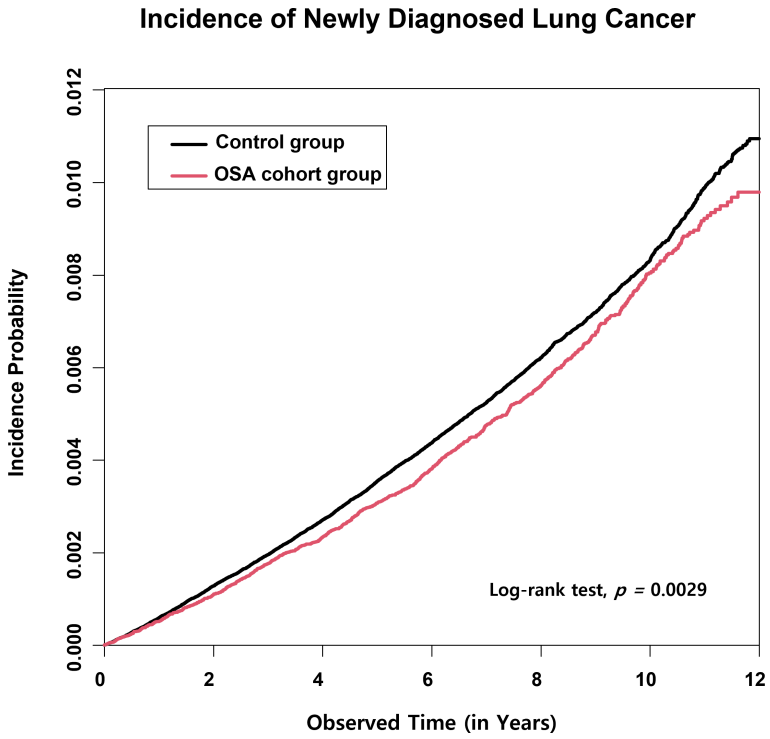

FIGURE 2
Lung cancer cumulative incidence plot in the obstructive sleep apnea (OSA) group and the control group. The cumulative incidence of lung cancer in a twelve-consecutive-year retrospective cohort showed a statistically significantly reduced risk of lung cancer development in the OSA group compared with the control group.

TABLE 3 The HR of OSA for developing lung cancer.

	n	Event (Newly diagnosed lung cancer)	Rate (%) (Event/*n*)*100	HR Calculated in Model A[1]	HR Calculated in Model B[2]
				HR (95% CI)	HR (95% CI)
Control	1339245	6141	0.779	1 (ref)	1 (ref)
OSA	267849	1122	0.708	0.91 (0.85–0.97)	0.87 (0.82–0.93)

HR, hazard ratio; OSA, obstructive sleep apnea; CI, confidence interval.
[1]Model A was derived using Cox proportional hazards analysis with no confounding variables.
[2]Model B was derived using Cox proportional hazards analysis adjusted for sex, age, subjects' income levels, diabetes, hypertension, dyslipidemia, stroke, chronic obstructive pulmonary disease, and ischemic heart disease.

patients showed a significantly reduced adjusted HR of 0.84 (95% CI; 0.78–0.90), whereas the adjusted HR of the females did not show such statis-tical significance. Despite potential limitations such as selection bias and inadequate adjustment for various lung cancer risk factors, our analysis of the KHNIS dataset suggests that male patients with obstructive sleep apnea have a lower risk of developing lung cancer. Gender disparity in the carcinogenesis pathway of lung cancer may exist, as females may not exhibit the same pattern.

The strength of our study lies in its large statistical power, owing to the fact that all South Korean citizens are mandatorily covered by the National Health Insurance Service. In addition, the observation of both the OSA and the control group for twelve consecutive years in a retrospective manner may strongly support the causal association of the carcinogenic potential of OSA with lung cancer in our results when compared with cross-sectional or case-control studies. Moreover, the application of a subgroup analysis of the lung cancer risk of OSA according to the gender and age-group differences in the large retrospective cohort in this study was not reported in previous studies. To the authors' knowledge, this study provides the largest recorded power and causality for revealing the incidence of lung malignancies in OSA patients.

Recently, sleep-related breathing disorders (SBD), including OSA, as independent risk factors for developing various malignant tumors in the human body, have gained interest from many researchers (13, 14, 22). The chronic IH in OSA followed by various responses in the neuroendocrine, cardiovascular, and respiratory organs may facilitate tumor growth and progression in various organs (23). Many studies from various nations have suggested OSA as an independent risk factor for all-cancer incidence. For instance, the relative risk was 1.26 in Sillah et al.'s study (24), and three meta-analyses resulted in all-cancer-risk values of 1.49, 1.53, and 1.52. Additionally, previous results showed dose–response relationships between OSA and cancer incidence. Palamaner Subash Shantha et al. (18) reported that overall cancer incidence and mortality were higher by up to three times in severe OSA than in mild-to-moderate OSA. However, some studies presented results that opposed this finding, suggesting instead that OSA was not a significant risk factor in the development of all types of cancer (25, 26). Some cancers are more likely to be correlated with OSA, while other types of malignant tumors are not (14, 20). In the previous analyses, in terms of cancers of various organs, colorectal (27), breast (28), prostate (9), pancreas (29), and renal-cell carcinomas (29) were shown to be significantly affected by OSA, as OSA served as a significant risk factor for developing these malignancies. Together, the outcomes of previous clinical and epidemiological studies suggest the potential clinical impact of OSA on the incidences of various cancers.

Contradictory results were obtained regarding whether OSA may affect lung cancer incidence and mortality in previous studies. In some cross-sectional studies with relatively large numbers of subjects, the incidence of SBD or OSA reached 49% to 80% in all patients newly diagnosed with lung cancer, and approximately half of the lung cancer patients had moderate-to-severe OSA (30–33).

TABLE 4 The HR of OSA with lung cancer development according to each gender group.

	Individuals who were diagnosed with lung cancer following OSA diagnosis					
		N	Event (Newly diagnosed lung cancer)	Rate (%) (Event/*n*)*100	HR Calculated in Model A[1]	HR Calculated in Model B[2]
					HR (95% CI)	HR (95% CI)
Male	Control	1,015,130	5094	0.849	1 (ref)	1 (ref)
	OSA	203,026	897	0.742	0.87 (0.81–0.94)	0.84 (0.78–0.90)
Female	Control	324,115	1,047	0.555	1 (ref)	1 (ref)
	OSA	64,823	225	0.597	1.08 (0.93–1.24)	1.05 (0.91–1.21)
P for interaction					0.011	0.007

HR, hazard ratio; OSA, obstructive sleep apnea; CI, confidence interval.
[1]The HR in Model A was derived using Cox proportional hazards analysis with no confounding.
[2]The HR in Model B was derived using Cox proportional hazards analysis adjusted for sex, age, subjects' income levels, diabetes, hypertension, dyslipidemia, stroke, chronic obstructive pulmonary disease, and ischemic heart disease.

TABLE 5 The HR of OSA with lung cancer development according to each age group.

	Individuals who were diagnosed with lung cancer following OSA diagnosis					
		N	Event (Newly diagnosed lung cancer)	Rate (%) (Event/*n*)*100	HR Calculated in Model A[1]	HR Calculated in Model B[2]
					HR (95% CI)	HR (95% CI)
Age 20-40 Years	Control	474515	181	0.063	1 (ref)	1 (ref)
	OSA	94903	45	0.078	1.25 (0.90–1.73)	1.23 (0.89–1.71)
Age 40-65 Years	Control	753630	3843	0.863	1 (ref)	1 (ref)
	OSA	150726	756	0.844	0.98 (0.90–1.06)	0.95 (0.88–1.03)
Age > 65 Years	Control	111100	2117	3.828	1 (ref)	1 (ref)
	OSA	22220	321	2.849	0.74 (0.66–0.83)	0.70 (0.63–0.79)
P value for the interaction					< 0.001	< 0.001

HR, hazard ratio; OSA, obstructive sleep apnea; CI, confidence interval.
[1]The HR in Model A was derived using Cox proportional hazards analysis with no confounding.
[2]The HR in Model B was derived using Cox proportional hazards analysis adjusted for sex, age, subjects' income level, diabetes, hypertension, dyslipidemia, stroke, chronic obstructive pulmonary disease, and ischemic heart disease.

Huang et al. (32) reported that stage III and IV advanced-lung cancer patients with an apnea–hypopnea index (AHI) greater than 30 had a three-year mortality rate of 80%, which was reduced to 25% in patients with an AHI less than 15. This study strongly connected the effect of the IH of OSA with carcinogenesis and tumor progression in lung cancer. A large-scale cohort followed for a further 5 years and population-based studies further support OSA as an independent risk factor for higher lung cancer incidence. Huang et al. (32) reported an HR of 1.52 (95% CI, 1.07–2.16), and Jara et al. (34) reported an HR of 1.32 (95% CI, 1.27–1.37), showing a significantly in-creased HR of OSA in lung cancer incidence. Nonetheless, Kendzerska et al. (35) reported an HR of 1.38 (95% CI, 0.94–2.03) showing no statistical significance; insignificance was also reported in Gozal et al.'s study (29). Furthermore, Sillah et al. (24) reported that OSA was associated with a significantly reduced lung cancer incidence, as their HR value was 0.66 (95% CI, 0.54-0.79). The disagreement in the previous studies suggests the need for a well-designed, large, nation-wide cohort study with a relatively long duration of observation. The 12-year retrospective nation-wide cohort in our study design might explain and further support the discordant results on whether OSA might play a role in lung cancer development.

Our results demonstrate that the HR for developing new-onset lung cancer in OSA patients compared with the control group with different ages, sexes, incomes, and various comorbid diseases was 0.91 (95% CI; 0.85–0.97), showing a significantly reduced risk of developing lung cancer. An even greater risk reduction was observed in a model in which cofounding variables were considered, showing a significantly adjusted HR of 0.87 (95% CI; 0.82–0.93). Moreover, the cumulative incidence plot showed a significant difference between the OSA and control groups in the twelve-year retrospective cohort. The results indicate that OSA may not be associated with lung cancer development in the general adult population, regardless of other cofounding clinical variables. Our results provide a remarkable addition to the knowledge on this subject, as previous researchers disagreed over whether OSA increases the risk of lung cancer development.

In our study, there was a significant reduced risk of lung cancer in OSA individuals. Like our results, Sillah et al. s' report where the OSA showed as a significantly protective agent for developing lung cancer (24). In Siallah et al. s' study, all the included subjects were aged over 64 years. Similarly, our study subgroup analysis showed a significantly reduced risk only in the senile age (age>65) group, which carefully suggests a rather protective effect of OSA for lung cancer development in the geriatric population, but not in the young and mid-aged adult population. Moreover, Christensen et al. reported an increased risk of lung cancer in OSA patients in the patients under 50 years old (25), and an animal study on an intermittent hypoxic model revealed rather a protective effect for lung cancer development in the aged group, which the younger group did not (36). The impact of age on the increased susceptibility to OSA in lung cancer development should be more clarified and discovered in the future studies.

Theoretically, the sleep fragmentation (SF) and IH observed in OSA patients are two major features that could explain the increased cancer incidence in the OSA population. Although the exact mechanism of IH in carcinogenesis is not yet understood, the frequent hypoxia followed by normoxia in IH mimics a condition similar to the reperfusion injury in tissues that undergo ischemic stress (37). The production of reactive oxygen species by the endothelial cells of vascular structures exposed to chronic IH may predispose patients to carcinogenesis in normal tissues (38). Moreover, IH may up-regulate various hypoxia-inducible factors (HIFs) in many organs, which may promote carcinogenesis (39, 40). On the other hand, SF has been shown to result in activated sympathetic tone, chronic inflammation, and altered immune cell functions, all of which may promote carcinogenesis in various organs (41, 42). Furthermore, it has been also suggested that nasal obstruction, which is a common accompanying findings in OSA patients might also play a role attributing in chronic

inflammation and oxidative stress, which all together lead to carcinogenesis (43).

Owing to the fact that OSA is caused by a narrowing of the upper airway in most cases, the lower airway tract and the lung are anatomically the principal areas affected by the sustained decrease in oxygen concentration following hypoventilation in OSA patients (44). Thus, the carcinogenic potential of IH in lower airway tract cells in OSA patients is a field of interest for many researchers (45). The chronic inflammation as a result of IH may synergize with various known inhalant carcinogens, such as tobacco smoking, in the lower airway, thus facilitating the formation of a microenvironment suited to lung cancer development (46). Another possible mechanism for lung cancer development and progression in OSA is *via* HIFs, as HIF-2α has shown potential for carcinogenesis, angiogenesis, and metastasis in lung cancer in various studies (38–40, 45, 47). Furthermore, Wnt/β-catenin signaling, which is thought to be enhanced through interaction with up-regulated HIF pathways, has been shown to activate the oncogenic potential in non-small-cell carcinomas of the lung (48).

In addition, managing OSA has been shown to reduce oxidative stress, free radicals, and inflammation, all of which can reduce the risk of carcinogenesis. Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and the ability of antioxidants to neutralize them. Multiple forms of cancer, including laryngeal cancer, have been associated with its presence (49, 50). Due to intermittent hypoxia and reoxygenation during sleep, obstructive sleep apnea syndrome (OSAS) has also been correlated with oxidative stress. OSAS may contribute to the development of laryngeal cancer by fostering chronic inflammation and oxidative stress, which can cause DNA damage and promote tumor growth (49). Moreover, OSAS may impede immune function, making it more difficult for the body to combat cancer cells.

Furthermore, it has been suggested that disruptions in the human circadian rhythm potentially lead to carcinogenesis in various organs (51); this includes lung cancer, which is one of the cancers related to disrupted circadian rhythms (52). As suggested in Koritala et al.'s article, various biomarkers and molecular changes indicating a disrupted circadian rhythm are observed in OSA patients, associated with sleep fragmentation and sleep arousal (53). Melatonin, an endogenous molecule secreted in the pineal gland and regulated by the circadian rhythm (54), is reportedly insufficiently secreted in OSA patients (55–57). Interestingly, many scholars have suggested the defensive role of melatonin in the carcinogenesis pathway (58, 59), and the decreased secretion of melatonin in OSA patients may lead to increased cancer risk (60). Taken together, the results of previous cellular and animal studies offer a molecular basis for further support for the oncogenic potential of OSA, including carcinomas of the lung.

Interestingly, significant lung cancer risk reduction was seen only in the males, and not in the females, regardless of the patients' age group. The exclusive significance of female susceptibility to lung cancer after OSA highlights the novelty of our study. Wu et al. (20) reported an increased risk of OSA for all-cancer development, especially in the female population. However, in the previous literature, it was not clarified whether OSA increases cancer risk predominantly in females; for instance, Cheong et al. (17) raised this issue as a limitation in their meta-analysis. Previous studies, including some meta-analyses, reported a significantly increased risk of OSA with lung cancer incidence (17, 32, 34), while some studies did not (20, 29), and others even reported a significantly decreased risk (24). These contradictory results are thought to result from differences between the demo-graphic characteristics in each study. Huang et al.'s study (32) was based on a female-only cohort, which showed an HR of 1.52, while Jara et al.'s study (34) was mostly (94%) on male patients, resulting in an HR of 1.32 for lung cancer incidence in OSA patients, showing a significantly increased lung cancer incidence in both genders. However, it must be noted that both studies were derived from predominantly white and relatively homogenous occupational groups, as Huang et al.'s study (32) consisted of nurses and Jara et al.'s study (34) consisted of veterans. Thus, the conclusions derived from their results might be limited for the general population. Furthermore, it should be stated that most of the previous studies were published in Western countries, in which those of East Asian heritage form only a small proportion of the population.

The lung cancer epidemiology in East Asian populations showed a distinctive pat-tern compared with the Caucasian population; in South Korea, 36% were never-smokers, and more than up 70% of the never-smoking lung cancer patients were female and were histologically diagnosed with adenocarcinoma-expressing epidermal growth factor receptor (EGFR) mutations (61). Interestingly, Marhuenda et al. (62) reported different tumor proliferation patterns, expression levels of epithelial cell adhesion molecule, and different amounts of HIF-1α nuclear translocation between squamous cell carcinoma and EGFR mutation-positive and -negative adenocarcinomas derived from human pulmonary cell lines.

The exclusive increase in lung cancer incidence in the female population regardless of age might aid in the addition of new knowledge. Since our results showed the susceptibility of female patients with OSA specifically to developing lung cancer, the question of whether pulmonary tissues from never-smoking females are more vulnerable to IH in developing adenocarcinoma with EGFR mutations would be an interesting investigation topic in the future. An increased HR of 1.52 in Huang et al.s' study which only consists of female (32), shows a higher HR compared with HR in Jara et al.s' study, showing a HR of 1.32, which their study group only included male patients (34). The results of these two cohort studies goes in line with our results, suggesting an increased susceptibility to lung cancer development in the female OSA than the male OSA. Nonetheless, these two studies are separate, two independent studies, and there are no well-designed systemic study investigating on the gender difference in the incidence of lung cancer development in OSA patients. Therefore, we suggest that this gender difference in the incidence of lung cancer in OSA group might be an interesting topic in the future research.

Although our study presented some unprecedented findings with a twelve-year retrospective cohort on a nation-wide scale, we acknowledge some limitations that must be declared. First, we were not able to consider the social history, such as smoking and alcohol abuse, or familial history of lung cancer, which are some of the

known major risk factors for lung cancer (63), in each patient, as these demographics were not included in the KNHIS data. Although we acquired data on the presence of COPD diagnosis, which is known to occur at a high rate in heavy tobacco smokers, we declare that these data might not quite represent the effect of tobacco smoking in our study. Furthermore, the study sub-jects' nutritional status (i.e., body mass index), which is known to be associated with OSA, was not evaluated, as this information is not available in the KNHIS registry. Second, we were not able to provide a subgroup analysis on the subtypes of lung cancer in terms of the histological diagnoses or genetic profiles of lung cancer among the study subjects. Third, the KNHIS data only provided patients diagnosed with OSA, with no details regarding the OSA severity (represented as apnea-hypopnea index, etc.), obesity degree represented as body mass index, or whether the patients underwent treatment for OSA. Therefore, we were not able to analyze the dose-response of OSA severity and confounding impact of obesity in lung cancer development in OSA individuals. Along with the severity of OSA, BMI shall also be considered to elucidate this matter in the future study. Fourth, our research classified adult population as those over 20, whereas others have characterized it as 18 to 19. Consequently, the disparity in adult age criteria may limit the comparability of OSA's effect on lung cancers with other studies. Last, the control group was only set to have 5 times larger number than the study group, and only matched with age and gender. These might possess the possibility of selection bias, thereby limit the results of our study. Furthermore. it should be stated that there is the possibility of an undiagnosed OSA population in the 'control' group in our cohort, as the OSA group in our cohort consisted of patients who received medical care and were confirmed to have OSA by a physician.

Conclusions

Adults with OSA had a slightly lower hazard ratio (0.87) for lung cancer development in the Korean population. The risk reduction was observed only in male OSA patients in the subgroup analysis by gender. Our study is the first study in the literature to raise the gender differences in the OSA impact in lung cancer development, analyzed with the largest number of retrospect cohort of 12 years on a national-wide scale.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Inha University Hospital (IRB no. 2022-11-004). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: MP, JCho, and JChoi. Formal analysis: K-DH, JCho, and JChoi. Investigation: K-DH, JCho, and JChoi. Methodology: K-DH, JCho, and JChoi. Resources: JCho and JChoi. Writing–original draft: MP, JCho, and JChoi. Writing–reviewing and editing: MP, JCho, and JChoi. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1214279/full#supplementary-material

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Role of sex and sex hormones in PD-L1 expression in NSCLC: clinical and therapeutic implications

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Currently, immunotherapy based on PD-1/PD-L1 pathway blockade has improved survival of non-small cell lung cancer (NSCLC) patients. However, differential responses have been observed by sex, where men appear to respond better than women. Additionally, adverse effects of immunotherapy are mainly observed in women. Studies in some types of hormone-dependent cancer have revealed a role of sex hormones in anti-tumor response, tumor microenvironment and immune evasion. Estrogens mainly promote immune tolerance regulating T-cell function and modifying tumor microenvironment, while androgens attenuate anti-tumor immune responses. The precise mechanism by which sex and sex hormones may modulate immune response to tumor, modify PD-L1 expression in cancer cells and promote immune escape in NSCLC is still unclear, but current data show how sexual differences affect immune therapy response and prognosis. This review provides update information regarding anti-PD-1/PD-L immunotherapeutic efficacy in NSCLC by sex, analyzing potential roles for sex hormones on PD-L1 expression, and discussing a plausible of sex and sex hormones as predictive response factors to immunotherapy.

KEYWORDS

NSCLC, PD-1/PD-L1 pathway, immunotherapy, estrogen, androgen

1 Introduction

Lung cancer (LC) holds the highest cancer-related incidence and mortality worldwide and is expected to reach 3.2 million deaths globally in 2050 (1). The LC prognosis after diagnosis remains poor, and the 5-year survival rate is less than 20% (2). LC is classified into small (SCLC, 15%) and non-small types (NSCLC, 85%) (3–5). NSCLC exhibits several differences by sex; since women are frequently non-smoker, diagnosed at younger age, and present adenocarcinoma with EGFR mutations. Women also respond better to chemotherapy and men to immunotherapy, whereas outcomes and survival are significantly better in women (4, 6–8). Furthermore, NSCLC is influenced by sex hormones, mainly estrogens (4, 9).

Targeted and immune therapies have increased LC patients' survival (10). Median overall survival (OS) for chemotherapy is less than a year, while combined with immunotherapy, OS almost doubles (11). PD-1/PD-L1 based immunotherapy improves NSCLC survival, however sex-derived differences have been reported, suggesting sex as a potential predictor for immunotherapy response (12–14). Sex hormones regulate immune response modifying PD-L1 expression, however in LC this relation is still being explored. This article focuses on PD-1/PD-L1 NSCLC immunotherapy, discussing sex differences in response to PD-L1 blockade, as well as sex-related effects and sex hormones impact on the PD-1/PD-L1 pathway and therapeutic responses implications.

2 PD-1/PD-L1 pathway

PD-1 is a transmembrane protein from the CD28/CTLA-4 immunoglobulin family expressed on different immune cells. PD-1 controls immune responses and T-cell activation, proliferation, and effector activity by binding PD-L1/2. Cancer cells inactivate T-cells and accomplish immune evasion through PD-L1 expression (15, 16). Intrinsic PD-L1 regulation includes genetic (transcriptional regulation through KRAS, EGFR, ALK pathways) and epigenetic factors (DNMT1, HDAC, miR-135). Conversely, cytokines (INF-γ), growth factors (EGF, VEGF), hypoxia, post-translational modifications (phosphorylation, glycosylation, palmitoylation, ubiquitination), and even treatments including chemotherapy, radiotherapy, and tyrosine kinase inhibitors, extrinsically modify PD-L1 expression (16, 17).

Among several immune evasion mechanisms, tumor PD-L1 expression alone induces immune escape, inactivating cytotoxic T-cells (18). Therefore, this pathway is an important therapeutic target for multiple cancers including NSCLC, since PD-1/PD-L1 blockade restores immune response increasing patient survival. To date, six PD-1/PD-L1 inhibitors have been approved including nivolumab, pembrolizumab, cemiplimab (anti-PD-1), atezolizumab, durvalumab, and avelumab (anti-PD-L1) (19).

3 LC treatment options and PD-1/PD-L1 blockade immunotherapy

LC diagnosis and treatment has developed substantially over the last decade, improving OS, progression-free survival (PFS), treatment response, and quality of life. NSCLC patients undergo EGFR, KRAS and ALK genes mutation. Unfortunately, not all patients are targeted therapies candidates, and may appear mutations resistance and recurrence. In this context, immune PD-1/PD-L1 inhibitors, have completely changed NSCLC management.

Baseline PD-L1 levels stratifies patients with a potentially better response. A higher PD-L1 tumor proportion score (TPS) correlates with improved outcomes. Among NSCLC patients with PD-L1 ≥ 50% treated with pembrolizumab, those with 90-100% PD-L1 TPS show better response (20).

For patients with elevated PD-L1 (≥50%), treatment includes immunotherapy as monotherapy, chemoimmunotherapy, or dual immunotherapy. Those with PD-L1 ≥ 50% without EGFR/ALK mutations who received pembrolizumab had greater OS compared with chemotherapy (30 *vs* 14.2 months) (21). Pembrolizumab also resulted in longer OS compared to other PD1-/PD-L1 inhibitors (26.3 vs. ≤14 months). Additionally, pembrolizumab improved OS combined with chemotherapy and radiotherapy (22, 23). Dual immunotherapy has exhibited durable benefits in OS and PFS regardless of PD-L1 expression compared to chemotherapy (24, 25). Combined immunotherapy or dual immunotherapy might also increase adverse effects (AE) (26).

Moreover, PD-L1 blockade has improved OS and PFS regardless of PD-L1 levels. Low PD-L1 (1-49%) cases are treated with immunotherapy + chemotherapy or dual immunotherapy (25, 27). More patients reached 12-months OS in pembrolizumab plus chemotherapy compared to the placebo (69.2% *vs*. 49.9%) irrespective of PD-L1 levels (28). Similarly, the IMpower 150 showed atezolizumab + chemotherapy increased OS and PFS independently of PD-L1 levels (29).

Finally, patients with negative (<1%) PD-L1 are still candidates for combined immunotherapy with chemotherapy or targeted therapy and dual immunotherapy (25, 30, 31). PD-L1 blockade has significantly improved clinical outcomes mainly in patients with higher PD-L1 levels. However, PD-L1inhibitors are considered the choice treatment even in those without PD-L1 expression, making these agents the LC new gold standard therapy.

4 Sex-related differences in response to PD-1/PD-L1 blockade in NSCLC

Although PD-1/PD-L1 blockade improved survival compared to chemotherapy and targeted therapy, sex-related differences have been reported (13, 14, 32). A systematic review (11,351 patients; 67% men and 37% women) showed different ICI efficacy by sex in melanoma and NSCLC. The pooled OS hazard ratio (HR) of ICI treatment was higher for women (12). Moreover, 4 NSCLC trials (1,672 patients; 73.2% men and 26.8 women) evaluated pooled OS-HR of PD1/PD-L1 ICI *vs* chemotherapy, resulting higher risk for females (13) Women also experience more immunotherapy AE (33).This data suggests a significant benefit of ICIs in males. Conversely, women with advanced NSCLC responded better to chemotherapy+PD-1/PD-L1-immunotherapy than men who benefited from PD-L1 blockade monotherapy (14).

A systematic review of trials and observational studies reported improved survival for male patients after pembrolizumab/nivolumab as monotherapy. Otherwise, women experienced increased survival rates, in chemoimmunotherapy (34). Additionally, the pooled HRs comparing ICIs *vs* chemotherapy were 0.74 (95% CI0.67-0.81) for men and 0.83 (95% CI 0.73-0.95) for women (35). Better PFS was also observed in advanced NSCLC male patients treated with ICI (5 months *vs* 4). Nivolumab exhibited significantly higher PFS in males *vs.* females also disease control rate was higher in male (55.7 *vs* 45.7%) and their disease progression was lower (44.3 *vs* 54.3%) (36). All above, supports the increased benefit of ICIs monotherapy for males and ICIs+chemotherapy for female patients.

Contradictory results have also emerged, showing no sex differences in response to immunotherapy as monotherapy or combined. A study involving advanced NSCLC patients treated with ICI monotherapy and ICI+chemotherapy observed no differences in PFS by sex, although differences in prognostic factors were noticed (37). Additionally, no sex-related differences were observed in squamous cell NSCLC patients treated with chemotherapy+PD-L1-inhibitors, although different AE were observed by sex (38).

A higher response to chemotherapy has been reported in women than in men (39, 40). Differences in DNA repair capacity between sexes (41) could explain women's higher sensitivity to chemotherapy (42). Additionally, chemotherapy might improve immunotherapy by enhancing anti-tumor immune response, recruiting, and activating cytotoxic T-cells, inducing immunogenic cell death, releasing tumor antigens and damage-associated molecular patterns, activating dendritic cells, and reducing T regulatory cells (Treg). But chemotherapy enhancing effects to immunotherapy are produced when administered locally since systemic chemotherapy produces high non-specific toxicity (43, 44). These facts could explain the higher chemotherapy response plus immunotherapy observed in women. Higher sensitivity to immunotherapy as monotherapy in men could be explained by disparities in PD-L1 expression.

Some confounding variables including previous treatments, tumor mutational burden (TMB), and smoking habit could explain the controversial response to ICI by sex. Since, there is a sex bias in NSCLC features, it is critical to elucidate sex effects on immunotherapy responses to improve future therapies.

5 Sex-driven distinct PD-L1 expression in NSCLC

Sex determines diverse conditions, including lifestyle and toxicant exposure, as well as genetic, and immune features that modify cancer biomarker expression, promoting significant differences in treatment response, including PD-L1 inhibitors. Ye et al., found differences by sex in immune characteristics impacting NSCLC immunotherapy (45).

Several studies show sex differences in PD-L1 levels, which might explain LC immunotherapy response disparities (46–49). A high percentage of PD-L1 positive NSCLC tumors correspond to men, who exhibit higher PD-L1 TPS than females (48–51). Fu et al., reported 18.3% of women with NSCLC *vs* 26% of men with PD-L1 TPS of 1-49%, and only 5.5% of women *vs* 17% of men with PD-L1 TPS ≥ 50% (49). Lin et al., reported 13.6% of men with high PD-L1 TPS (≥50%) *vs.* only 3.8% in females NSCLC patients (52). These findings have been supported by several studies summarized in Table 1 (47–55). Conversely, no association between PD-L1 expression and sex has also been reported (56). Despite the discrepancies, accumulating evidence discloses differences by sex in PD-L1 status in NSCLC (40, 42, 44–49).

Some intrinsic and extrinsic sex factors might drive differences in PD-L1 levels. Smoking status, generally associated with LC male patients, has been related to PD-L1 expression. High PD-L1 TPS was correlated with smoking history and better immunotherapy response. Smoking patients presented higher and prolonged OS and PFS in ICI *vs.* chemotherapy (57–62). KRAS mutation and squamous histology associate with PD-L1 expression, and tobacco smoking could partially explain differences in PD-L1 levels in NSCLC patients by sex (63). Further studies are needed to confirm sex differences in PD-L1 levels and factors affecting its expression. More women must be integrated into studies, being generally underrepresented. Also, TMB, histology, smoking status, and hormonal factors should be considered.

Steroids sex hormones participate in several carcinogenic pathways in LC and could probably play a role in sex PD-L1 disparities (64, 65). Although many LC patients exhibit low sex hormone levels (mainly estrogen) due to age and menopause, lung tumors produce sex hormones locally through aromatase (ARO) overexpression (66–69). ARO and hormone receptors could modify PD-L1 expression regardless of sex and hormonal status.

6 Role of steroid sex hormones in PD-L1 expression

6.1 Estrogens in NSCLC

The estrogen pathway has taken relevance in NSCLC given its role in lung carcinogenesis. Estrogen receptor (ER)-β, the most common LC isoform and ARO expression, correlate with poor prognosis and survival (68). ERβ is overexpressed in 60-80% of male and female NSCLC patients. Estrogen (E2), through its nuclear receptors (ERα/ERβ) and G-protein-coupled estrogen receptor (GPER), promotes LC progression by cell proliferation, apoptosis resistance, angiogenesis, epithelial mesenchymal transition (EMT), cell migration and metastases (4, 9, 70, 71). Moreover, an important role for estrogen related receptor alpha (ERRα) has been reported in NSCLC, which stimulates proliferation and EMT (72, 73).

E2 also modifies tumor microenvironment through pro-inflammatory cytokines and recruiting Tregs promoting immune evasion (74). Additionally, E2 up-regulates chemokine receptor CXCR4, contributing to immune evasion and metastases in NSCLC (75, 76). Currently the role of E2 in immune evasion and PD-L1 control in LC is being explored.

6.1.1 PD-L1 regulation by estrogen pathway in cancer

Estrogens downregulate PD-L1 expression in endometrial and breast cancer (BC) and correlates with ER-negative status in BC (77, 78). In MCF-7 cells, E2 negatively regulated PD-L1 transcription (79). Moreover, antiestrogens increased PD-L1 expression in ER+ BC (80). E2 probably decreases PD-L1 expression through IL-17 signaling (77). Also, E2/GPER pathway downregulated PD-L1 through COP9-signalosome subunit 5 degradation, as reported in melanoma and pancreatic ductal adenocarcinoma (81, 82).

Paradoxically, PD-L1 expression correlated with ER+, PR+, and Ki67+ in BC (83). E2/ERα increased PD-L1 but not PD-L2 expression in endometrial and BC. PD-L1 expression may be controlled through the PI3K/AKT pathway and post-transcriptional PD-L1-mRNA stabilization in BC (84). In metastatic renal cell carcinoma nivolumab increased E2 levels in male patients (85). Decreased PD-L1 levels by nivolumab increase IL-6 in melanoma animal models, consequently, increasing E2 synthesis and promoting immune evasion (85–87).

In melanoma and prostate cancer (PC), estrogen receptor modulators (SERMs) have been suggested to improve immunotherapy (88, 89). Besides, SERMs and degraders (SERDs) significantly improved immunotherapy efficacy in BC, suggesting an E2 role in up-regulated PD-L1 (90).

Estrogen mechanisms modifying PD-L1 seem to be complex and may depend on several factors such as cancer type, histology, TMB, ER isoforms, ARO expression, estrogen levels, and microenvironmental features (Figure 1). This relationship needs to be explored since E2 pathway blocking could improve immunotherapy in some cancers, including NSCLC.

6.1.2 PD-L1 and estrogen pathway in NSCLC

The E2 role in NSCLC immune evasion has been scarcely investigated, and its PD-L1 relationship is emerging. For instance, E2 reduced cytotoxic lymphocyte activity by inducing ERβ1/5. Also, E2 up-regulated PD-L1 by increasing ERβ/SIRT1, Snail transcriptional factor while reducing FOXO3a (91). ERβ could be a critical target to improve immunotherapy given its higher expression in male and female NSCLC patients.

E2/ERα increased PD-L1 transcription was recently reported *in vitro*. Additionally, *in vivo*, letrozole (ARO inhibitor) improved pembrolizumab efficacy, while in NSCLC patients, ERα was a predictive response factor to pembrolizumab, even stronger than sex and PD-L1 levels (92). This could be explained by high ER expression independently of sex in NSCLC (9). Thus, ER could become a biomarker to predict to immunotherapy response in NSCLC.

TABLE 1 Differences in PD-L1 expression by sex in NSCLC patients.

Sex	PD-L1 TPS			Reference
	<1 (%)	1-49 (%)	>50 (%)	
Male	57	26	17	(49)
Female	76.2	18.3	5.5	
Male		26	25	(51)
Female		34	15	
Male	44.5	29.9	25.6	(53)
Female	54.9	30.9	14.2	
Male	59.4	71.4	79.7	(48)
Female	40.5	28.5	20.3	
Male		55.9		(50)
Female		44.1		
Male			13.6	(52)
Female			3.8	
Male	>30		>10	(54)
Female	< 20		< 5	
Male	64.81			(46)
Female	35.19			
Male	36	35	28	(47)
Female	37	31	32	
Male	49.4	16.7	7.73	(55)
Female	17.9	5.5	20.6	

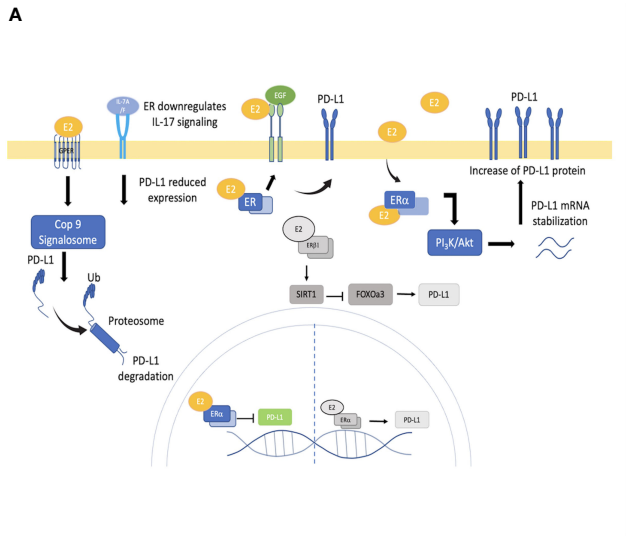

FIGURE 1
Mechanisms involved in PD-L1 control by estrogen and androgen in cancer and NSCLC. **(A)** Estrogen pathway downregulates PD-L1 by repressing its transcription, promoting its proteosomal degradation and IL-17 downregulation. E2/ER also activates the PI3k/Akt pathway promoting RNA stabilization and increasing PD-L1 protein as observed in breast cancer. E2/ER through EGFR/EGF pathway might stimulate PD-L1 increase in lung cancer. Emerging mechanisms by E2 pathway might up-regulates PD-L1 in NSCLC are represented in gray. E2/ERα increases PD-L1 transcription. Moreover, E2/ERβ activates SIRT1 promoting FOXOa3 degradation and consequently PD-L1 increases **(B)** Androgen pathway downregulates PD-L1 transcriptionally, mainly by inhibiting NF-kB translocation and decreasing promoter activation. AR regulates PD-L1 expression post-transcriptionally by modifying circRNAs.

Decreased levels of the receptor for advanced glycation end products (RAGE) associate with lung carcinogenesis and metastasis regulating PI3K/AKT and KRAS-RAF1 signaling. RAGE participates in redox regulation, and its polymorphisms are linked to LC incidence and progression (93). Thus, RAGE is an important axis in LC development. Recently it was reported that HMGB-RAGE promotes PD-L1 expression in BC (94). Also, E2 treatment up-regulated RAGE in human microvascular endothelial cells (94). The association between E2, RAGE and PD-L1 in NSCLC has not been elucidated; however, it could represent a key mechanism underlying carcinogenesis and immune evasion.

Besides, estrogens could modify PD-L1 in NSCLC through the EGFR pathway. EGFR/EGF activation increases E2 through ARO up-regulation (9, 67, 95). Since EGF enhancing PD-L1 in NSCLC (96), E2 could stimulates PD-L1 through the EGF/EGFR pathway; however, this hypothesis needs to be tested.

Differences in serum PD-1 (sPD-1) by sex were reported in NSCLC patients, where females exhibited higher sPD-1 and PD-1 on CD4+ T cells. Increased testosterone levels were also reported (97) suggesting sex hormones could control PD-1.

All these data support E2 contribution to immune evasion up-regulating PD-L1 through diverse mechanisms involving both ERα/ERβ in NSCLC (Figure 1). Antiestrogens could improve immunotherapy even in low PD-L1 conditions due to high ER expression in NSCLC. This is a new approach showing how estrogen pathway promotes lung carcinogenesis and how antiestrogens could improve immunotherapy as well as targeted therapy. However further studies are warranted to explore these mechanisms and their potential therapeutic impact.

6.2 Androgens in NSCLC

LC androgen participation is still poorly explored and contradictory. Androgen receptor (AR) is downregulated in NSCLC tissues and cell lines, without differences by sex and staining. Higher AR levels associate to better survival rates. miR-224-5p is up-regulated in NSCLC promoting proliferation, decreased apoptosis, migration, and metastasis by, downregulating AR (98). Furthermore, AR+ status relate to favorable OS in NSCLC metastatic disease (99), not in early stages (100).

On the other hand, AR was overexpressed mainly in NSCLC male patients (101). AR was detected in 20% of LC patients; higher levels were in advanced LC stages associated with progression and metastasis (102). Moreover, targeting androgen pathway in NSCLC patients resulted in better survival (103), and reduced risk to second primary LC for PC patients (104). Androgen deprivation therapy (ADT) for PC, improved survival in NSCLC after diagnosis, particularly in Caucasians (105). *In vitro*, androgen up-regulated gene expression involved in DNA repair, oxygen transport, apoptosis, and hemoglobin synthesis while downregulated CYP1A1 (106). Also, AR promotes proliferation through cyclin D1 regulation, stimulate migration and invasion and regulates OCT-4 protein supporting stemness (101, 107, 108). Finally, KRAS mutational profiles are linked to AR levels in NSCLC (109). Despite controversial data, androgen pathway apparently plays an important role in lung carcinogenesis highlighting its therapeutic potential.

6.2.1 Androgen pathway and PD-L1 regulation

Although men appear to respond better to immunotherapy in NSCLC, androgen activity on immune response, evasion

mechanisms and PD-L1 expression in LC has not been elucidated. However, AR down-regulates PD-L1 across different malignances.

Inverse correlation between AR and PD-L1 levels has been reported in muscle invasive or metastatic urothelial (110), thyroid (111) and hepatocellular carcinomas (112), suggesting PD-L1 downregulation through the AR pathway. In thyroid cancer, dihydrotestosterone reduced PD-L1 in a time- and dose-dependent manner, while flutamide (AR antagonist) restored PD-L1 expression. AR could decrease PD-L1 expression inhibiting NF-kB nuclear translocation and reducing PD-L1 promoter activation (111). In hepatocellular carcinoma AR downregulates PD-L1 acting as PD-L1 transcriptional repressor (112). In contrast, in bladder cancer targeting AR enhances NK activity decreasing PD-L1 expression; both anti-androgen treatment and knockdown significantly reduced PD-L1 expression and stimulated NK cell-mediated bladder cancer cell death by downregulating circRNA circ_0001005 (113). Also, Tang and coworkers (114) demonstrated how dihydrotestosterone/AR higher dose increased PD-L1 expression and suppressed NK cells immunotherapy efficacy in castration- resistant PC cells (CRPC) (Figure 1). AR-blockade improved sex-bias BRAF/MEK-targeted therapy response in melanoma (115), and enhanced CD8/T-cells activity in CRPC improving PD-1/PD-L1-inhibitors response (116), suggesting that AR promote targeted and immunotherapy resistance, and shows sex impact in treatment.

Although androgen immunosuppressive effects have been documented, and ADT improves PC immunotherapy (117), its relationship with PD-L1 in clinical and experimental conditions remains contradictory. Future studies are necessary to clarify androgen´s impact on PD-L1control in NSCLC, since PD-L1 is a key target in immunotherapy, to which men appear to respond better.

7 Conclusion and perspectives

NSCLC is a significantly different disease between women and men, influenced by sex hormones. The estrogen and androgen roles in NSCLC immune response is not completely understood. Currently, data remain contradictory on differential response to PD-L1-based immunotherapy sex-related. Nevertheless, several studies show higher benefit in male NSCLC patients which could be explained by higher PD-L1 levels. Sex could be a predictive response factor to NSCLC immunotherapy; however, sex-derived differences must be validated as well as consistency across different populations, equilibrated groups by sex, histological subtypes, mutational profiles, and smoking status. Additionally, women should be stratified by hormonal status and serum hormonal levels could be measured to clarify the sex and sex hormones impact on PD-L1 control and immunotherapy responses.

Some factors sex-associated as TMB and tobacco smoking modify PD-L1 which partially explains immunotherapy differential responses. Hormones, mainly estrogen also affect the PD-L1 pathway in NSCLC. Although PD-L1 control by E2 remains controversial in different cancers; in NSCLC emerging data shows E2/ER up-regulates PD-L1 suggesting that SERDs might enhance NSCLC immunotherapy response. Studies on sex and sex hormones effects in immune evasion are critical, since antihormonal therapy might be easily extrapolated to NSCLC treatment, but a wide gap still exists in this field. Androgen effect on immune evasion mechanisms through PD-1/PD-L1 in NSCLC remains to be elucidated.

Finally, all this data shows the sex and sex hormones relevance in LC progression and its impact on PD-L1 based immunotherapy response. However, it is essential to strength research on sex-related differences to understand LC behavior, identify biomarkers, predict immunotherapy response, and establish better therapeutic guidelines according to sex and hormonal status.

Author contributions

VR-L designed, wrote, review, edited the manuscript, made the final version and coordinated teamwork. All authors contributed to the article by writing or final editing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Diversities of disability caused by lung cancer in the 66 Belt and Road initiative countries: a secondary analysis from the Global Burden of Disease Study 2019

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Objectives: Due to the increase in life expectancy and the aging of the global population, the "Belt and Road" ("B&R") countries are faced with varying degrees of lung cancer threat. The purpose of this study is to analyze the differences in the burden and trend of lung cancer disability in the "B&R" countries from 1990 to 2019 so as to provide an analytical strategic basis to build a healthy "B&R".

Methods: Data were derived from the Global Burden of Disease 2019 (GBD 2019). Incidence, mortality, prevalence, the years lived with disability (YLDs), and disability-adjusted life years (DALYs) of lung cancer and those attributable to different risk factors were measured from 1990 to 2019. Trends of disease burden were estimated by using the average annual percent change (AAPC), and the 95% uncertainty interval (UI) was reported.

Results: China, India, and the Russian Federation were the three countries with the highest burden of lung cancer in 2019. From 1990 to 2019, the AAPC of incidence, prevalence, mortality, and DALYs generally showed a downward trend in Central Asia (except Georgia) and Eastern Europe, while in China, South Asia (except Bangladesh), most countries in North Africa, and the Middle East, the trend was mainly upward. The AAPC of age-standardized incidence was 1.33% (1.15%–1.50%); the AAPC of prevalence, mortality, and DALYs from lung cancer in China increased by 24% (2.10%–2.38%), 0.94% (0.74%–1.14%), and 0.42% (0.25%–0.59%), respectively. A downward trend of the AAPC values of age-standardized YLD rate in men was shown in the vast majority of "B&R" countries, but for women, most countries had an upward trend. For adults aged 75 years or older, the age-standardized YLD rate showed an increasing trend in most of the "B&R" countries. Except for the DALY rate of lung cancer attributable to metabolic risks, a downward trend of the DALY rate attributable to all risk

factors, behavioral risks, and environmental/occupational risks was shown in the vast majority of "B&R" countries.

Conclusion: The burden of lung cancer in "B&R" countries varied significantly between regions, genders, and risk factors. Strengthening health cooperation among the "B&R" countries will help to jointly build a community with a shared future for mankind.

KEYWORDS

"B&R" countries, lung cancer, burden of disease, risk factors, average annual percent change, years lived with disability (YLDs), disability-adjusted life years (DALYs)

Introduction

The "Belt and Road" ("B&R") Initiative refers to the "Silk Road Economic Belt" and the "21st Century Maritime Silk Road", which was first proposed by China in 2013. "B&R" countries run through Eurasia, connecting the Asia Pacific Economic Circle in the east and the European Economic Circle in the west (1). "B&R" Initiative can fully rely on the existing bilateral and multilateral mechanisms between China and relevant countries and leverage existing and effective regional cooperation platforms. Health crises are cross-border issues that require collective action to address (2, 3). In 2017, the Chinese government proposed the "Health Silk Road" (HSR) initiative to strengthen global health cooperation. "B&R" health exchange and cooperation helps to share successful experiences in the medical and health field. HSR initiative can promote cooperation in health, build a strong and resilient health system for transnational cooperation, and jointly build a "community of human health" in order to deal with disease epidemics.

Lung cancer is one of the main causes of new cancer cases and cancer-related deaths worldwide (4). In the past two decades, significant improvements have been made in understanding the biology and targeted therapy in lung cancer and the application of immune checkpoint inhibitors (ICIs), which have changed the prognosis of many patients (5). In terms of disability-adjusted life years (DALYs), the disease burden is evolving to be dominated by the years lived with disability (YLDs) (6). YLDs measure the amount of time that people lose to illnesses and injuries that do not cause death but reduce health. These areas are becoming hot topics for measuring and improving health outcomes due to transitions in aging populations and mortality in different countries.

Currently, "B&R" member countries are facing varying degrees of lung cancer threat. It is crucial to have comparable and comprehensive analysis and assessment of lung cancer incidence, mortality, disease burden, and long-term trends in China and its partner countries in order to improve public health and the success of the organizations. However, little is known about the status and extent of lung cancer in the 66 countries under the "B&R" Initiative. Our objective is to estimate the burden and trends of lung cancer from 1990 to 2019 through this study, providing a basis for formulating disease prevention and control policies and building a "community of human health" by strengthening health industry cooperation among the "B&R" countries.

Methods

Data sources

This study was conducted using the Global Burden of Disease 2019 (GBD 2019) study obtained from the Institute for Health Metrics and Evaluation (IHME) website. All data for this study were obtained from the Institute for Health Metrics and Evaluation (IHME) website (https://www.healthdata.org/data-tools-practices/data-sources). Detailed methodology has been published elsewhere (7, 8).

Estimation of lung cancer burden

Incidence, mortality, prevalence, YLDs, and DALYs were used in this study. Age-standardized rates for incidence, mortality, prevalence, YLDs, and DALYs were calculated according to a global age structure from 2019. YLDs were estimated by multiplying lung cancer prevalence with the corresponding disability weight. DALYs assess comprehensively premature death and the disease burden of disability. DALYs are equal to YLDs plus years of life lost (YLLs). YLLs are calculated as the product of counts of deaths caused by lung cancer and a standard remaining life expectancy at the age of death. The age-standardized rates were corrected by the direct method and the world standard population to account for differences in the population age structure. Our study follows the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) to ensure transparency and replicability (Table 1) (9).

TABLE 1 GATHER checklist of information included in reports of global health estimates.

#	Checklist item	Section/ paragraph/ interpretation
Objectives and funding		
1	Define the indicators, populations, and time periods for which estimates were made.	Methods/"Data sources"
2	List the funding sources for the work.	Funding
Data inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	As mentioned in the Methods/"Data sources" section, the details have been published previously.
4	Specify the inclusion and exclusion criteria. Identify all *ad-hoc* exclusions.	As mentioned in the Methods/"Data sources" section, the details have been published previously.
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Available *via* online data source tools (http://ghdx.healthdata.org/gbd-2019/data-input-sources).
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	As mentioned in the Methods, the details have been published previously.
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	Available *via* online data source tools (http://ghdx.healthdata.org/gbd-2019/data-input-sources).
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet as opposed to a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared due to ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Available *via* online data source tools (http://ghdx.healthdata.org/gbd-2019/data-input-sources).
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Flow diagrams of the overall methodological processes were available online (http://ghdx.healthdata.org/gbd-2019/code/nonfatal-12).
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	As mentioned in the Methods/"Statistical analyses" section.
11	Describe how candidate models were evaluated and how the final models were selected.	As mentioned in the Methods/"Statistical analyses" section, the details have been published previously.
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	As mentioned in the Methods/"Statistical analyses" section, the details have been published previously.
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Methods/"Statistical analyses" section.
14	State how analytic or statistical source code used to generate estimates can be accessed.	Methods/"Statistical analyses" section.
Results and discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Results and online data tools (data visualization tools and data query tools, http://ghdx.healthdata.org/gbd-2019).
16	Report a quantitative measure of the uncertainty of the estimates (e.g., uncertainty intervals).	Results and online data tools (data visualization tools and data query tools, http://ghdx.healthdata.org/gbd-2019).
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Discussion, paragraphs 1–7
18	Discuss limitations of the estimates. Include a discussion of any modeling assumptions or data limitations that affect interpretation of the estimates.	Discussion, paragraph 8

GATHER, the Guidelines for Accurate and Transparent Health Estimates Reporting.

"B&R" countries

The 66 members of "B&R" countries are as follows: 1) East Asia: China; 2) Central Asia: Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, and Uzbekistan; 3) South Asia: Bangladesh, Bhutan, India, Nepal, and Pakistan; 4) Southeast Asia: Cambodia, Indonesia, Laos, Malaysia, Maldives, Burma, the Philippines, Sri Lanka, Thailand, and Vietnam; 5) high-income Asia Pacific: Brunei and Singapore; 6) North Africa and the Middle East: Afghanistan, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, the United Arab Emirates, and Yemen; 7) Central Europe: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czechia, Hungary, Montenegro, North Macedonia, Poland, Romania, Serbia, Slovakia, and Slovenia; 8) Eastern Europe: Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russia, and Ukraine; 9) Western Europe: Cyprus, Greece, and Israel. See Figure 1 for more details.

Statistical analyses

We calculated absolute numbers and age-standardized rates of incidence, mortality, YLDs, and DALYs to quantify the burden of lung cancer, grouped by gender and age in the "B&R" countries. Age-standardized estimates allow comparisons across time, countries, and subregions and are adjusted for differences in the age distribution of the population. Age was divided into three groups: 20–54 years, 55–74 years, and ≥75 years. The three risk factors (behavioral risks, environmental/occupational risks, and metabolic risks) were included in the present study. Data were stratified by region [high, high-middle, middle, low-middle, and low socio-demographic index (SDI)]. SDI is a composite indicator of a country's lag-distributed income per capita, educational attainment, and the total fertility rate in women younger than 25 years. Methods of SDI development and computation are detailed elsewhere (10). Trends of disease burden from 1990 to 2019 were evaluated using average annual percent change (AAPC), which was calculated by the Joinpoint Regression Program (Version 4.9.0.0, March 2021) (11). Uncertainty intervals (UIs) of 95% were calculated with the 2.5th and 97.5th percentiles of 1,000 drawn by age, sex, location, and year (12). The map visualization of the "B&R" member states was performed using the "ggmap" package in R software (version 4.3.0, R Core Team). The "ggmap" package is an extension package, which obtains shapefiles from Google Maps. $p < 0.05$ was considered statistically significant.

Patient and public involvement

Being involved in the Global Burden of Disease 2019 and other open databases rather than directly speaking to patients inspired this research. Although no patient was directly involved in this study, members of the public read our manuscript, and all agreed on the specific findings of this study.

Results

The absolute number of incidence, mortality, prevalence, YLDs, and DALYs due to lung cancer in 2019

The absolute number of incidence, mortality, YLDs, and DALYs in 2019 caused by lung cancer in each member country of the "B&R" are shown in Table 2. We noted that there were significant geographic differences in the number of lung cancer incidence,

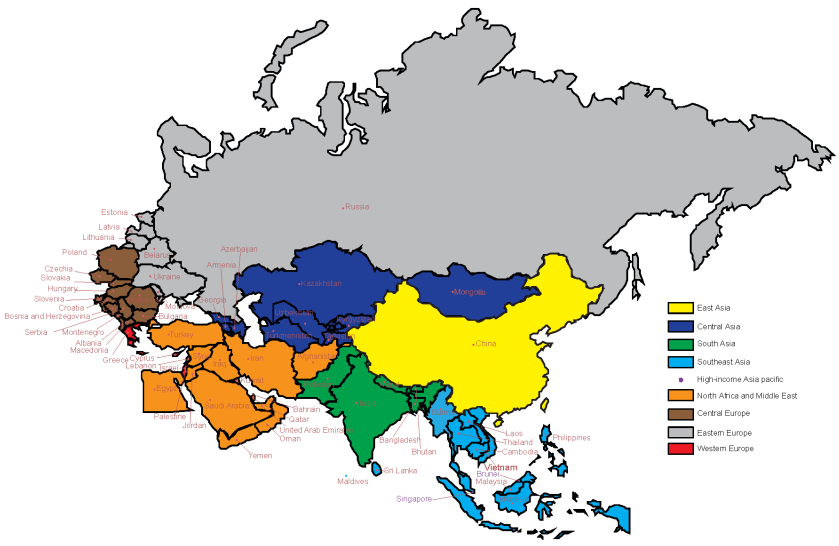

FIGURE 1
GBD regions of 66 B&R countries. GBD, Global Burden of Disease; B&R, Belt and Road.

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TABLE 2 The absolute number of incidence, mortality, prevalence, YLDs, and DALYs due to lung cancer in 2019.

Countries	Incidence		Mortality		Prevalence		YLDs		DALYs	
	Number	95% UI	Number	95% UI	Number	95% UI	Number	95% UI	Number	95% UI
East Asia										
China	832,922.16	700,293.15, 981,631.63	757,171.25	638,741.18, 887,751.81	1,137,880.03	950,548.16, 1,344,733.04	199,351.51	138,983.38, 264,035.88	17,128,584.02	14,340,490.76, 20,231,342.32
Central Asia										
Armenia	1,345.78	1,129.72, 1,595.96	1,333.76	1,121.61, 1,577.50	1,489.61	1,239.77, 1,771.27	306.99	214.18, 415.51	32,529.70	27,097.00, 38,700.25
Azerbaijan	2,375.07	1,746.37, 3,041.88	2,296.14	1,687.24, 2,920.62	2,746.29	2,010.70, 3,521.50	562.84	346.47, 816.76	67,384.39	49,095.71, 86,484.43
Georgia	1,783.98	1,487.37, 2,108.03	1,769.96	1,485.09, 2,079.83	1,948.70	1,613.94, 2,329.43	405.58	275.92, 552.45	45,743.10	37,924.68, 54,187.58
Kazakhstan	3,829.27	3,259.16, 4,405.84	3,716.64	3,184.40, 4,260.53	4,337.40	3,675.62, 5,018.90	886.63	608.48, 1,203.93	99,097.82	84,119.24, 114,546.55
Kyrgyzstan	568.77	492.88, 646.55	560.10	485.65, 635.73	636.25	550.11, 726.34	135.63	92.30, 187.42	15,377.13	13,279.03, 17,539.43
Mongolia	662.38	512.20, 863.46	671.76	522.79, 869.20	691.49	531.75, 911.41	150.83	97.87, 218.46	17,529.17	13,388.76, 23,175.99
Tajikistan	593.28	478.94, 740.28	585.82	476.34, 731.84	665.01	531.77, 838.13	143.33	93.00, 206.53	17,301.77	13,762.61, 21,771.91
Turkmenistan	412.75	326.10, 520.92	399.22	316.22, 503.72	478.24	376.27, 606.32	101.55	65.45, 147.24	11,915.03	9,357.08, 15,098.17
Uzbekistan	2,770.81	2,282.13, 3,324.29	2,656.35	2,188.76, 3,178.98	3,246.61	2,682.20, 3,914.21	672.72	444.33, 942.78	80,569.90	66,295.49, 96,840.99
South Asia										
Bangladesh	9,652.31	6,331.50, 15,119.70	9,970.50	6,568.78, 15,550.09	9,890.12	6,398.48, 15,551.36	2,280.53	1,252.41, 4,049.16	245,789.45	158,425.89, 385,218.27
Bhutan	42.59	30.65, 58.41	44.43	32.07, 60.68	43.39	31.15, 59.94	9.94	6.19, 15.08	1,071.70	764.16, 1,473.98
India	87,339.21	71,865.33, 103,504.12	89,241.82	73,674.82, 105,402.83	90,057.70	73,919.11, 106,986.69	20,367.52	14,189.78, 27,535.34	2,275,225.20	1,871,749.98, 2,691,295.16
Nepal	1,759.15	1,263.39, 2,275.02	1,837.31	1,333.96, 2,370.52	1,763.67	1,266.75, 2,294.01	412.71	253.56, 614.19	45,196.18	32,343.42, 59,231.11
Pakistan	18,401.25	13,969.72, 24,265.21	18,550.27	14,209.46, 23,969.10	19,631.92	14,826.19, 26,083.02	4,258.89	2,794.58, 6,129.06	522,647.78	400,317.47, 680,663.37
Southeast Asia										
Cambodia	2,887.60	2,266.60, 3,576.17	2,985.13	2,340.29, 3,698.58	2,961.87	2,290.27, 3,680.80	649.54	419.97, 907.18	76,026.47	58,766.84, 94,334.05
Indonesia	48,198.90	35,265.54, 59,309.34	49,437.42	36,066.08, 61,104.64	50,233.86	36,772.54, 62,097.63	10,918.72	6,937.99, 15,201.44	1,279,980.70	927,626.41, 1,596,039.79
Lao	973.36	717.55, 1,264.48	999.82	742.13, 1,290.39	1,007.06	730.37, 1,329.52	220.41	135.86, 318.98	26,517.75	19,142.26, 35,091.64
Malaysia	5,164.65	3,997.20, 6,560.78	5,221.07	4,059.90, 6,639.41	5,544.16	4,257.62, 7,066.08	1,176.14	742.18, 1,703.49	125,453.88	95,771.77, 158,721.18
Maldives	26.49	21.86, 31.61	27.05	22.37, 32.28	29.29	24.05, 34.90	6.22	4.23, 8.68	620.39	510.83, 742.20
Burma	10,291.14	7,607.84, 14,071.02	10,613.63	7,896.38, 14,367.52	10,552.35	7,739.66, 14,580.53	2,328.96	1,471.64, 3,601.85	271,545.66	199,769.30, 374,582.84
Philippines	13,827.24	11,026.21, 17,100.02	13,964.25	11,341.93, 17,103.21	14,616.29	11,580.69, 18,202.20	3,186.74	2,119.98, 4,428.65	373,177.18	300,744.74, 458,874.13
Sri Lanka	2,506.52	1,822.45, 3,413.75	2,478.00	1,803.77, 3,369.01	2,833.98	2,039.40, 3,892.40	594.40	357.87, 901.65	61,124.63	44,055.48, 83,501.03
Thailand	22,545.27	17,018.46, 29,559.74	23,108.96	17,522.52, 30,147.58	24,360.83	18,211.19, 32,137.58	5,127.12	3,158.71, 7,512.38	524,356.39	389,890.72, 698,681.26

(Continued)

TABLE 2 Continued

Countries	Incidence		Mortality		Prevalence		YLDs		DALYs	
	Number	95% UI	Number	95% UI	Number	95% UI	Number	95% UI	Number	95% UI
Vietnam	25,549.85	19,741.34, 32,387.02	25,160.99	19,493.53, 31,704.25	28,986.91	22,215.48, 37,389.29	5,927.12	3,923.01, 8,367.67	676,894.23	514,965.51, 873,764.92
High-income Asia Pacific										
Brunei	115.51	101.92, 130.45	103.45	91.60, 116.42	158.56	138.78, 179.78	27.44	19.35, 36.46	2,578.18	2,267.53, 2,923.29
Singapore	2,161.73	1,723.69, 2,713.17	1,565.88	1,413.73, 1,681.72	4,818.05	3,740.53, 6,167.55	609.71	414.16, 849.56	32,007.52	29,533.23, 34,270.58
North Africa and the Middle East										
Afghanistan	1,476.18	871.21, 2,335.11	1,492.27	891.59, 2,356.46	1,575.60	895.10, 2,505.23	345.82	177.19, 583.85	44,553.01	25,083.00, 71,319.35
Bahrain	140.72	106.64, 185.66	141.65	107.06, 186.90	154.53	116.66, 205.12	32.61	21.35, 48.65	3,546.09	2,674.88, 4,751.20
Egypt	6,123.00	4,303.05, 8,313.47	6,070.21	4,274.39, 8,216.10	6,731.47	4,752.21, 9,204.81	1,475.30	859.49, 2,283.70	174,974.92	123,445.87, 239,223.91
Iran	8,704.66	8,039.65, 9,366.32	8,923.24	8,247.20, 9,594.73	9,365.61	8,688.94, 10,053.26	2,023.34	1,445.19, 2,616.98	218,990.46	203,461.41, 234,522.71
Iraq	4,154.17	3,199.79, 5,128.84	4,231.66	3,274.77, 5,189.57	4,484.06	3,427.98, 5,628.77	957.44	629.52, 1,387.75	110,712.08	84,177.90, 139,886.99
Jordan	914.37	748.42, 1,109.93	917.40	749.29, 1,110.25	1,014.69	835.62, 1,232.58	216.36	142.14, 305.80	24,230.86	19,817.36, 29,412.55
Kuwait	225.33	184.58, 271.79	227.62	185.21, 274.59	258.87	215.66, 310.17	53.59	36.47, 74.87	5,540.99	4,539.37, 6,683.20
Lebanon	1,421.22	1,168.08, 1,867.91	1,433.09	1,184.23, 1,897.57	1,576.93	1,266.34, 2,051.06	319.65	213.78, 461.41	32,711.82	26,403.35, 42,585.37
Oman	146.86	116.66, 192.09	144.15	115.03, 187.19	168.86	132.47, 223.90	35.38	22.71, 52.66	3,875.69	3,001.88, 5,245.22
Palestine	523.49	443.92, 612.56	529.72	448.08, 617.82	568.27	481.15, 667.11	119.68	81.65, 162.68	14,203.36	12,042.86, 16,666.89
Qatar	124.76	88.77, 174.19	118.88	84.87, 165.47	152.93	107.22, 212.71	30.46	18.89, 47.90	3,497.10	2,442.30, 4,860.15
Saudi Arabia	1,544.89	1,187.06, 1,899.53	1,491.92	1,146.38, 1,829.70	1,848.16	1,411.21, 2,304.75	382.08	252.06, 553.89	45,487.57	34,469.24, 57,171.88
Syrian Arab Republic	1,372.09	1,006.81, 1,813.76	1,374.32	1,011.39, 1,813.03	1,509.37	1,100.36, 2,011.15	327.33	200.65, 485.27	36,951.19	26,937.04, 49,538.15
Turkey	29,510.56	23,370.09, 36,799.05	29,831.89	23,752.46, 37,028.28	31,739.56	25,030.55, 39,550.04	6,701.50	4,547.53, 9,477.92	743,637.07	585,408.24, 929,198.85
United Arab Emirates	541.68	393.37, 721.35	522.71	379.61, 696.70	627.40	453.55, 834.77	130.88	79.82, 199.43	16,697.74	12,066.29, 22,165.92
Yemen	1,302.23	885.33, 1,929.71	1,335.82	912.37, 1,971.91	1,345.21	909.07, 2,008.32	308.48	181.41, 504.79	36,208.29	24,430.35, 53,798.79
Central Europe										
Albania	1,174.38	861.50, 1,565.46	1,158.09	856.22, 1,531.85	1,330.78	964.24, 1,798.00	269.13	166.28, 405.31	25,926.45	18,893.57, 34,823.40
Bosnia and Herzegovina	2,434.60	1,889.96, 3,062.17	2,389.72	1,862.76, 2,986.22	2,753.69	2,126.68, 3,521.20	548.22	350.37, 785.91	56,744.93	43,565.61, 71,913.73
Bulgaria	4,837.61	3,859.19, 6,016.14	4,608.05	3,700.92, 5,714.36	5,737.34	4,490.47, 7,219.35	1,116.79	742.86, 1,571.90	116,517.16	91,572.63, 146,444.17
Croatia	3,430.52	2,706.26, 4,299.04	2,875.17	2,281.74, 3,607.40	5,337.58	4,123.26, 6,768.04	835.54	552.30, 1,173.56	64,967.90	50,856.24, 82,444.42
Czechia	6,942.77	5,695.06, 8,448.38	6,238.20	5,137.40, 7,580.23	9,367.69	7,573.79, 11,559.44	1,603.63	1,072.79, 2,221.38	133,507.49	108,873.62, 164,136.95

(Continued)

TABLE 2 Continued

Countries	Incidence		Mortality		Prevalence		YLDs		DALYs	
	Number	95% UI	Number	95% UI	Number	95% UI	Number	95% UI	Number	95% UI
Hungary	9,509.80	7,849.06, 11,561.74	8,972.12	7,426.86, 10,848.33	11,679.77	9,517.11, 14,391.77	2,173.52	1,496.36, 2,962.28	212,473.60	173,458.78, 259,387.67
Montenegro	563.10	460.56, 685.03	531.01	437.42, 642.57	692.01	568.35, 840.10	129.94	85.64, 179.75	13,081.40	10,674.96, 15,950.14
Macedonia	1,339.70	1,025.41, 1,703.60	1,280.91	984.80, 1,625.14	1,598.14	1,208.28, 2,059.36	309.54	204.23, 443.17	33,072.32	25,235.20, 42,379.20
Poland	30,018.42	25,154.02, 35,717.87	31,205.87	26,089.58, 36,995.56	30,292.81	25,281.18, 36,146.49	6,569.69	4,446.70, 8,871.31	709,154.38	585,977.92, 846,722.76
Romania	11,544.70	9,482.85, 14,024.50	11,013.61	9,115.52, 13,362.10	13,733.60	11,257.44, 16,702.58	2,669.03	1,820.10, 3,667.51	273,221.57	223,948.07, 333,461.23
Serbia	7,699.56	6,057.60, 9,693.98	7,261.74	5,732.48, 9,070.69	9,489.67	7,405.09, 12,061.00	1,770.51	1,174.47, 2,490.33	176,690.62	137,757.74, 222,904.29
Slovakia	3,129.61	2,429.99, 4,052.56	2,529.50	1,975.84, 3,282.98	5,221.87	3,981.14, 6,781.43	787.63	508.69, 1,132.43	59,373.34	45,646.30, 77,497.77
Slovenia	1,395.08	1,081.70, 1,823.05	1,269.39	983.94, 1,644.08	1,980.98	1,511.20, 2,609.22	332.41	217.43, 468.18	27,659.86	21,218.09, 36,013.86
Eastern Europe										
Belarus	3,801.17	2,924.07, 4,935.88	3,543.49	2,747.82, 4,593.90	4,689.51	3,579.91, 6,124.14	889.54	574.52, 1,271.17	89,491.43	68,311.87, 117,562.44
Estonia	721.23	563.53, 905.64	714.05	560.79, 896.25	805.94	626.22, 1,015.01	163.17	107.96, 233.29	15,109.63	11,745.47, 19,172.87
Latvia	1,017.98	837.52, 1,237.70	950.20	787.73, 1,149.33	1,259.20	1,022.81, 1,549.30	236.21	161.52, 331.71	21,229.54	17,376.43, 25,943.39
Lithuania	1,395.18	1,139.09, 1,690.82	1,312.79	1,072.09, 1,586.10	1,673.09	1,352.39, 2,042.87	320.29	218.53, 443.07	29,561.11	23,885.14, 36,018.11
Moldova	1,067.45	919.87, 1,227.46	1,033.12	891.61, 1,184.85	1,218.09	1,046.71, 1,406.65	249.50	170.32, 348.20	27,405.49	23,509.08, 31,628.84
Russian Federation	58,183.52	49,720.66, 67,801.76	54,139.52	46,120.95, 63,100.09	74,012.48	63,149.49, 86,679.28	13,686.73	9,517.07, 18,088.91	1,345,629.42	1,140,036.53, 1,580,080.63
Ukraine	20,132.69	16,536.45, 24,383.32	17,023.08	14,127.24, 20,205.10	30,169.60	24,474.94, 36,910.48	5,007.00	3,353.86, 6,839.24	451,770.69	371,193.40, 538,851.86
Western Europe										
Cyprus	514.05	444.19, 591.86	461.97	403.78, 525.47	737.54	626.65, 856.86	124.12	88.25, 167.66	9,676.94	8,510.71, 10,948.28
Greece	9,237.89	7,274.26, 11,548.65	8,643.21	8,026.85, 9,193.05	12,189.65	9,411.58, 15,495.83	2,173.21	1,423.32, 3,070.77	172,150.80	161,828.94, 181,875.91
Israel	2,670.18	2,087.83, 3,391.41	2,518.13	2,313.63, 2,684.20	3,480.03	2,683.12, 4,483.52	633.62	413.76, 901.61	52,636.78	49,094.67, 55,907.37

YLDs, years lived with disability; DALYs, disability-adjusted life years; UI, uncertainty interval.

mortality, YLDs, and DALYs across countries, with China, India, and the Russian Federation being the three countries with the highest burden of lung cancer. In 2019, there were 832,922.16 (95% UI 700,293.15 to 981,631.63) lung cancer incidences, 757,171.25 (95% UI 638,741.18 to 887,751.81) deaths, 199,351.51 (95% UI 138,983.38 to 264,035.88) YLDs, and 17,128,584.02 (95% UI 14,340,490.76 to 20,231,342.32) DALYs due to lung cancer in China. The country with the lowest number of lung cancer incidences is the Maldives in Southeast Asia (26.49, 95% UI 21.86 to 31.61).

The incidence, mortality, prevalence, YLDs, and DALYs in 1990 and 2019

Figure 2 shows the age-standardized rates of incidence, mortality, prevalence, YLDs, and DALYs due to lung cancer in 1990 and 2019 in member countries of the "Belt and Road" Initiative. From 1990 to 2019, the incidence, mortality, prevalence, YLDs, and DALYs of lung cancer in South and Southeast Asia were generally low. In 1990, the country with the highest incidence of YLDs and DALYs of lung cancer was Hungary

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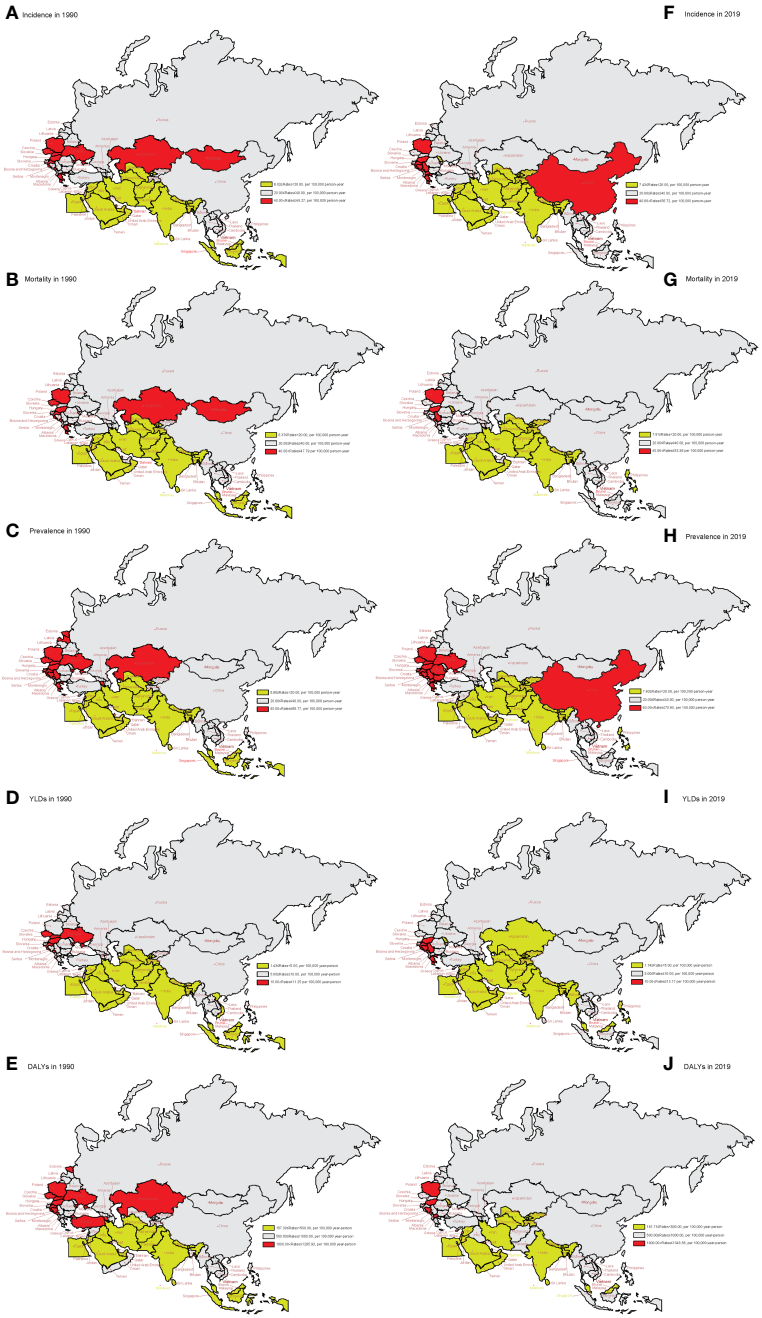

FIGURE 2
The age-standardized rates of incidence, mortality, prevalence, YLDs, and DALYs in 1990 and 2019 in "the Belt & Road" countries. **(A)** Age-standardized incidence rate in 1990. **(B)** Age-standardized mortality rate in 1990. **(C)** Age-standardized prevalence rate in 1990. **(D)** Age-standardized YLD rate in 1990. **(E)** Age-standardized DALY rate in 1990. **(F)** Age-standardized incidence rate in 2019. **(G)** Age-standardized mortality rate in 2019. **(H)** Age-standardized prevalence rate in 2019. **(I)** Age-standardized YLD rate in 2019. **(J)** Age-standardized DALY rate in 2019. YLDs, years lived with disability; DALYs, disability-adjusted life years.

(49.27 per 100,000, 11.25 per 100,000, and 1,295.93 per 100,000). Bhutan had the lowest rates of incidence, mortality, prevalence, YLDs, and DALYs (6.03 per 100,000, 6.37 per 100,000, 5.90 per 100,000, 1.43 per 100,000, and 157.30 per 100,000, respectively). In 2019, Montenegro had the highest incidence, mortality, prevalence, YLDs, and DALYs (56.72 per 100,000, 53.36 per 100,000, 70.60 per 100,000, 13.17 per 100,000, and 1,343.58 per 100,000, respectively). Bangladesh had the lowest rates of incidence, mortality, prevalence, YLDs, and DALYs (7.43 per 100,000, 7.81 per 100,000, 7.40 per 100,000, 1.74 per 100,000, and 181.71 per 100,000, respectively). Prevalence, YLDs, and DALYs due to lung cancer declined most rapidly in Kazakhstan, while incidence, prevalence, and YLDs increased the fastest in China from 1990 to 2019. See Supplementary Table 1 for more details.

Trends in age-standardized incidence, prevalence, mortality, and DALYs

From 1990 to 2019, the AAPC of age-standardized incidence, prevalence, mortality, and DALYs generally showed a downward trend in Central Asia (except Georgia) and Eastern Europe, while in China, South Asia (except Bangladesh), and most countries in North Africa and the Middle East, the trend was mainly upward (Figure 3). The AAPC of age-standardized incidence, prevalence, mortality, and DALYs from lung cancer in China increased by 1.33% (95%CI: 1.15% to 1.50%, $p < 0.001$), 2.24% (95%CI: 2.10% to 2.38%, $p < 0.001$), 0.94% (95%CI: 0.74% to 1.14%, $p < 0.001$), and 0.42% (95%CI: 0.25% to 0.59%, $p < 0.001$), respectively. See Supplementary Table 2 for more details.

Trends in age-standardized YLDs

Figure 4 shows the AAPC values of age-standardized YLD rate in member countries. Turkmenistan, Uzbekistan, Lao, the Philippines, Albania, and Ukraine had an upward trend of age-standardized YLDs from 2010 to 2019 and a downward trend from 1990 to 2019. Pakistan, Malaysia, Sri Lanka, Jordan, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Yemen, Bosnia and Herzegovina, Bulgaria, Macedonia, and Serbia showed a downward trend in age-standardized YLDs from 2010 to 2019, while an upward trend was observed from 1990 to 2019 ($p < 0.05$) (Supplementary Table 3). There were also differences in the trend of changes in AAPC between men and women from 1990 to 2019. A downward trend of the AAPC values of age-standardized YLD rate in men was shown in the vast majority of "B&R" countries. For women, the change trend of YLDs was stable in Georgia and Russia, while the upward trend was observed in most other countries (Supplementary Table 4).

Trends in age-standardized YLDs stratified by age groups

Figure 5 shows the long-term trends of age-standardized YLD rate due to lung cancer, stratified by age from 1990 to 2019 for the "B&R" countries. We found that in Maldives, the Philippines, Bahrain, Belarus, and Ukraine, the age-standardized YLDs of all ages showed a downward trend, while in China, Bhutan, India, Pakistan, Indonesia, Malaysia, Sri Lanka, Egypt, Iraq, Jordan, Lebanon, Bulgaria, Montenegro, Macedonia, Serbia, and Cyprus, the age-standardized YLDs of all ages showed an upward trend ($p < 0.05$). For adults aged 75 years or older, the age-standardized YLD rate from 1990 to 2019 showed an increasing trend in the "B&R" countries, except Kazakhstan, Kyrgyzstan, Turkmenistan, Mongolia, Bangladesh, Maldives, Afghanistan, Bahrain, the United Arab Emirates, Belarus, Moldova, Ukraine, Greece, and the Philippines. In China, age-standardized YLDs showed an increasing trend with the increase of age, and the highest AAPC value of age-standardized YLD rate from 1990 to 2019 was in adults aged 75 years or older: 2.87% (95%CI: 2.60%–3.14%, $p < 0.001$). See Supplementary Table 5 for more details.

Trends in age-standardized DALYs stratified by risk factors

Figure 6 shows the long-term trends of the age-standardized DALY rate due to lung cancer, stratified by risk factors from 1990 to

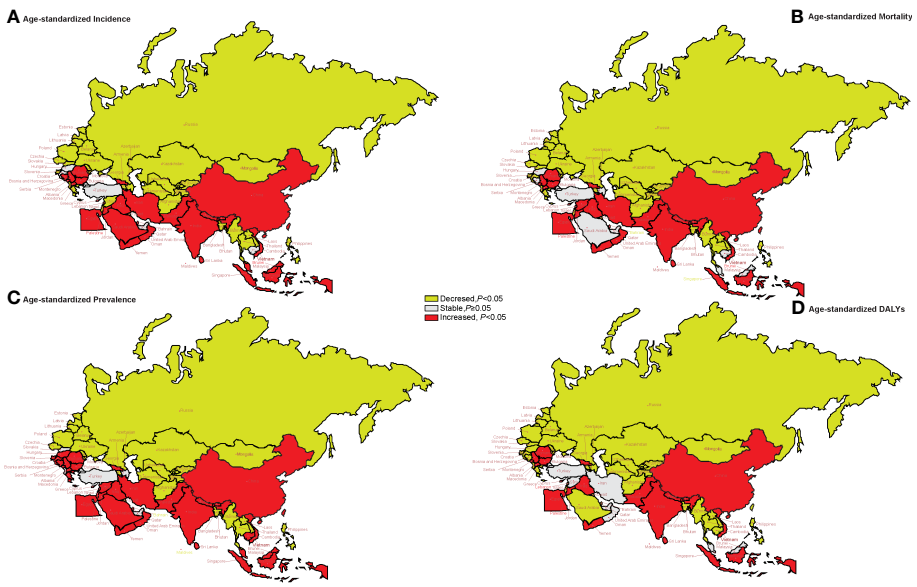

FIGURE 3
The trends of age-standardized rates of incidence, mortality, prevalence, and DALYs in 1990–2019 in "the Belt & Road" countries. **(A)** The AAPC of age-standardized incidence rate. **(B)** The AAPC of age-standardized mortality rate. **(C)** The AAPC of age-standardized prevalence rate. **(D)** The AAPC of age-standardized DALY rate. AAPC, average annual percent change; DALYs, disability-adjusted life years.

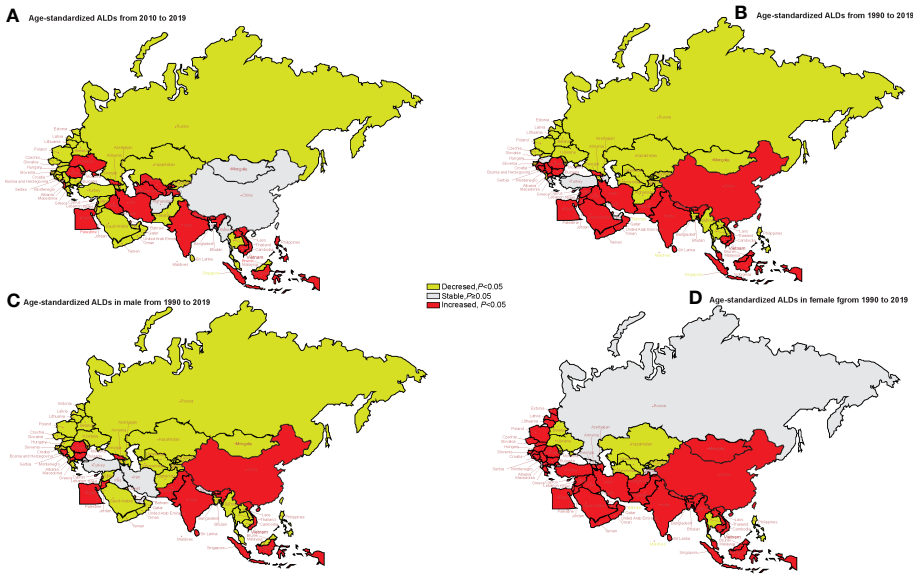

FIGURE 4
The trends of age-standardized rates of YLDs in genders in 2010–2019 and in 1990–2019 in "the Belt & Road" countries. **(A)** The AAPC of age-standardized rates of YLDs in 2010–2019. **(B)** The AAPC of age-standardized rates of YLDs in 1990–2019. **(C)** The AAPC of age-standardized rates of YLDs in men in 1990–2019. **(D)** The AAPC of age-standardized rates of YLDs in women in 1990–2019. AAPC, average annual percent change; YLDs, years lived with disability.

2019 for the "B&R" countries. We found that in middle SDI regions, China, Georgia, Bhutan, Indonesia, Sri Lanka, Vietnam, Egypt, Iraq, Jordan, Lebanon, Palestine, Yemen, Bulgaria, Montenegro, Macedonia, Serbia, and Cyprus, the age-standardized DALYs due to all risk factors showed an upward trend, while globally and in the other "B&R" countries, the age-standardized DALYs of all risk factors showed a downward trend ($p < 0.05$).

For DALYs of lung cancer attributable to behavioral risks, the age-standardized DALY rate of middle SDI regions, China, Georgia, Bhutan, Bhutan, Indonesia, Sri Lanka, Vietnam, Afghanistan, Egypt, Jordan, Lebanon, Palestine, Bulgaria, Montenegro, Macedonia, Serbia, and Cyprus showed an increasing trend in the "B&R" countries from 1990 to 2019 (all $p < 0.05$).

For DALYs of lung cancer due to environmental/occupational risks, the age-standardized DALY rate of Georgia, Bhutan, Pakistan, Sri Lanka, Egypt, Iran, Iraq, Jordan, Lebanon, and Bulgaria showed an increasing trend in the "B&R" countries from 1990 to 2019 (all $p < 0.05$).

For DALYs of lung cancer attributable to metabolic risks, the age-standardized DALY rate of Kazakhstan, Kyrgyzstan, Turkmenistan, Maldives, the Philippines, Thailand, Singapore, Bahrain, Slovakia, Belarus, and Ukraine showed a decreasing trend in the "B&R" countries from 1990 to 2019 (all $p < 0.05$). See Supplementary Table 6 for more details.

Discussion

With an estimated 1.79 million deaths per year, lung cancer is one of the leading causes of cancer-related deaths (5). Smoking, poor diet, lack of exercise, genetic factors, air pollution, and occupational exposure are all risk factors for cancer (13). Smoking is an important risk factor for increasing cancer risk (14). Cigarettes contain polycyclic aromatic hydrocarbons and nitrosamines. Nicotine is an addictive substance, so it leads to frequent use among smokers, and therefore, lung cancer is more

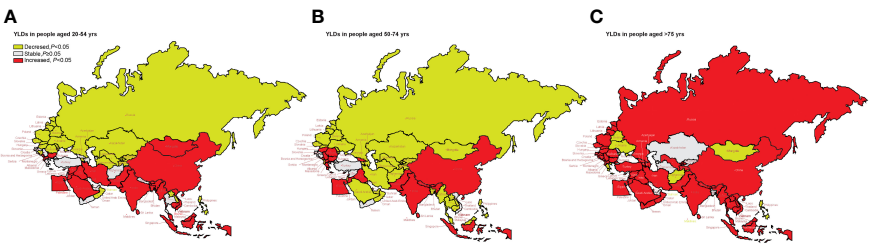

FIGURE 5
Visualization of the trends of age-standardized YLD rate stratified by age from 1990 to 2019 in "the Belt & Road" countries. **(A)** YLD rate in people aged 20–54 years. **(B)** YLD rate in people aged 55–74 years. **(C)** YLD rate in people aged ≥75 years. YLDs, years lived with disability.

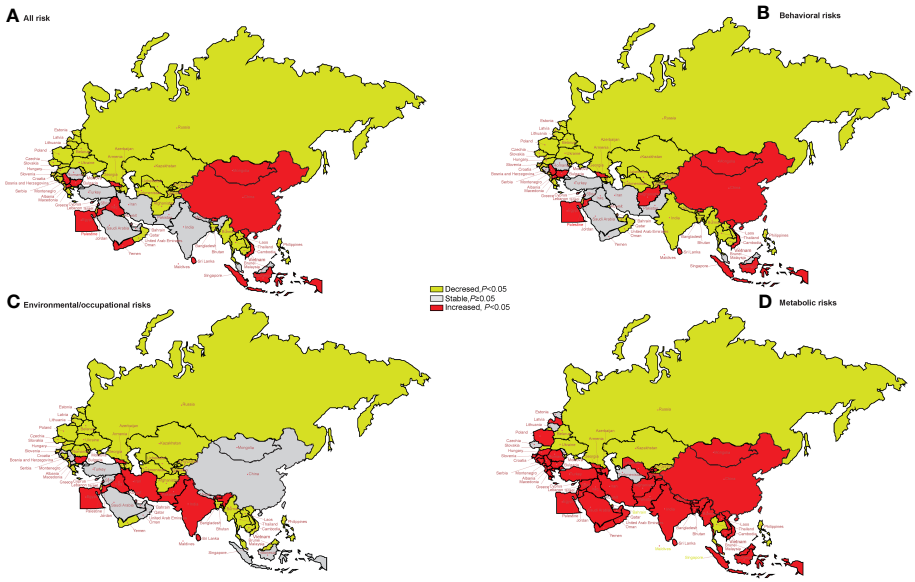

FIGURE 6
The temporal trend in the DALY rate of lung cancer attributed to risk factors for 1990–2019 in the "B&R" countries. **(A)** All risk factors. **(B)** Behavioral risks. **(C)** Environmental/occupational risks. **(D)** Metabolic risks. DALYs, disability-adjusted life years.

common among them (15, 16). In the last decade, the age-standardized incidence rate in high-socio-demographic index countries has been decreasing due to tobacco control (17). We found that the incidence, prevalence, and YLDs increased the fastest in China from 1990 to 2019, and the age-standardized incidence, prevalence, mortality, and DALYs showed an upward trend in China, South Asia, North Africa, and the Middle East, which may be related to a large number of smokers in these countries.

Our study found significant differences in the trend of age-standardized YLDs between genders. A downward trend of the AAPC values of age-standardized YLD rate in men was shown in the "B&R" countries. For women, the upward change trend of YLDs was observed in most countries. The global incidence of lung cancer in men is declining twice as fast as in women (5). The age-standardized incidence rates of lung cancer among women are predicted to increase before 2035 and are expected to peak after the 2020s, while those among men are expected to decrease in almost all countries (18). The mortality of cancers due to smoking has substantially increased among women in most countries of the North Africa and Middle East region (19). These studies all suggest that the "B&R" and even countries around the world need to strengthen the publicity and education of female smoking cessation and attach importance to physical examination and lung screening, which will help control the incidence rate and mortality of female lung cancer.

The increase in life expectancy has led to a greater global burden of diseases. Global population aging is the principal medical and social demographic problem worldwide. In the Non-Organisation for Economic Co-operation and Development countries, the fastest-aging countries are Saudi Arabia, Brazil, and China (20). Since 2000, China has gradually entered an aging society, the aging in China has not been alleviated but has gradually increased recently, and the burden of lung cancer on elderly patients is also increasing (21). In the "B&R" member countries, the age-standardized YLDs in most countries showed an upward trend with the increase of age, and the highest AAPC value of the age-standardized YLDs in 1990–2019 was in adults aged 75 years or older. A satisfactory and appropriate understanding of the health problems of older people caused by aging is a common challenge in the world. The goal vision is to establish a world where everyone has the chance to live a healthy and long life (20). This requires close cooperation between multiple sectors and departments in the "B&R" member countries to promote healthy aging.

In recent decades, countries within the Middle East have faced social, political, and financial instability brought about by war. These conflicts have directly led to a significant decline in the overall level of local medical services and a shortage of professional experts, seriously affecting the provision of cancer diagnosis services. The cancer patients in these areas cannot be diagnosed early and cannot receive effective healthcare (22, 23). In addition, the use of depleted uranium and white phosphorus bombs in wars may cause environmental pollution and even cancer (24). Therefore, many cancer patients must bear the cost of traveling to neighboring countries in order to receive medical services. Our study also found that from 1990 to 2019, the AAPC of age-standardized incidence rate, morbidity, mortality, and DALYs showed an upward trend in most countries in the Middle East. It is important to alleviate the shortage of medical services for these countries through the "B&R" Initiative.

With a deeper understanding of the biology of lung cancer, many advances have been made in the treatment of lung cancer, such as minimally invasive techniques, stereotactic ablative radiotherapy, targeted therapies, and ICIs (25). New therapies have benefited patients and reduced the burden of disease.

However, due to various reasons such as economic development and healthcare systems, countries have varying opportunities to access drugs and healthcare (5). In low-income countries, new lung cancer cases and mortality continue to increase, which may be related to limited access to healthcare and outdated treatment methods in these countries (5). By implementing large-scale infrastructure construction and trade facilitation, poor and low-income countries can return to the mainstream of global development from a state of global marginalization, thereby providing bright prospects for comprehensive and long-term economic growth in the "B&R" member countries. In addition, the medical field should also be highly valued. The exchange of medical knowledge and experience among medical institutions in the "B&R" countries should be continuously promoted so that medical technology and health services will be extended from higher-level countries to lower-level ones, thus improving the medical level of each country and benefiting low-income people.

YLDs can reflect the amount of time lived in states of less than good health due to a specific disease or injury and are calculated as the prevalence of a sequela of any given cause multiplied by the average duration until death or remission and by the disability weight for that sequela. The YLDs are the sum of each of the sequelae associated with the disease or injury (26, 27). YLL refers to the loss of life caused by early death. Although YLDs and YLLs can reflect the burden on society, YLDs are more likely to be affected by diseases and injuries in their lives. Reducing the burden of disease involves not only prolonging the survival period of patients but also improving the quality of life of patients. The interventions required to reduce the causes of death may differ from those needed to reduce risk factors and disability rates for disease burden. This is why we chose to calculate YLDs in this study.

Globally, from 2010 to 2019, the number of lung cancer increased by 23.3%, and the age-standardized incidence rates decreased by 7.4% in men and increased by 0.9% in women (4). Compared to the USA and UK, China had lower incidence but higher cancer mortality and DALYs (28). All the age-standardized incidences had a decreasing trend in men and an increasing trend in women from 1990 to 2019 in the North Africa and Middle East region. Over 80% of DALYs could be decreased by controlling tobacco use (23). The number of new cases is predicted to increase by 50.19% from 2010 to 2035. When stratified by geographic region, the most rapid increases were predicted in Eastern Asia (79.00% for men and 140.05% for women) (18). We found that in the "B&R" countries, especially in middle SDI regions, DALYs due to all risk factors showed an upward trend, while globally, DALYs had a downward trend.

Unlike previous lung cancer burden studies based on GBD data, this study focuses on the "B&R" countries proposed by China, the world's second-largest economy, under the global community of shared future strategy. It not only describes the changes in disease burden in a specific region or globally but also provides targeted data support for how countries with significant differences in social demographic indices but strong political and economic connections can formulate policies to reduce the burden of lung cancer. Preventive measures such as smoking control interventions and air quality management should be prioritized in low and middle SDI regions. Our research also suggested that we should pay more attention to female lung cancer patients. For women, the upward trend of YLDs was observed in the "B&R" countries, and it may continue to rise in the future (18). By studying the continuous transformation of epidemiology in the "B&R" countries, the necessity of resource redistribution and improvement of lung cancer control measures is highlighted.

This study also has several limitations. First, GBD 2019 has inherent limitations that are applicable to this study. Second, the GBD database lacks lung cancer's pathological staging and classification. In the future, the "B&R" countries can use economic development as a link to drive the construction of information-based disease monitoring systems, providing sufficient support for the estimation of disease burden and policy adjustments.

Conclusion

In summary, the overall burden of lung cancer in the "B&R" countries is still huge, especially in China, South Asia, North Africa, and the Middle East. There are significant differences between genders and ages. The lung cancer prevention and treatment policies in women and adults aged 75 years or older need to be improved. With the background of the health "B&R" Initiative, multi-country cooperation and experience sharing will play an important role in jointly facing the challenges caused by lung cancer and promoting the positive development of healthcare in all member countries.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

XL conceived and designed the study. ZZhu, WY, LZ, WJ, BC, QW, XC, SY, and ZZhang analyzed the data. ZZhu, XL, and YD provided significant advice and consultation. WY and XL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1247006/full#supplementary-material

SUPPLEMENTARY TABLE 1
The age-standardized rates of incidence, mortality, prevanlence, YLDs and DALYs in member countries of the "Belt and Road" initiative from 1990 to 2019. (YLDs, years lived with disability; DALYs, disability-adjusted life-years; UI, uncertainty interval).

SUPPLEMENTARY TABLE 2
The average annual percentage change (AAPC) of age-standardized incidence, mortality, prevanlence and DALYs from 1990 to 2019 in the "Belt & Road" countries. (AAPC, average annual percent change; DALYs, disability-adjusted life-years).

SUPPLEMENTARY TABLE 3
The average annual percentage change (AAPC) of age-standardized YLDs in 2010-2019 and 1990-2019 in the "Belt & Road" countries. (AAPC, average annual percent change; YLDs, years lived with disability).

SUPPLEMENTARY TABLE 4
The average annual percentage change (AAPC) of age-standardized rates for YLDs in male and female from 1990 to 2019 in the "Belt & Road" countries. (AAPC,average annual percent change; YLDs, years lived with disability).

SUPPLEMENTARY TABLE 5
The average annual percentage change (AAPC) of age-standardized rates for YLDs stratified by age from 1990 to 2019 in the "Belt & Road" countries. (AAPC,average annual percent change; YLDs, years lived with disability).

SUPPLEMENTARY TABLE 6
The average annual percentage change (AAPC) of age-standardized rates for DALYs stratified by risk factors from 1990 to 2019 in the "Belt & Road" countries. (AAPC, average annual percent change; DALYs, disability-adjusted life-years).

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Time to treatment disparities in gastric cancer patients in the United States of America: a comprehensive retrospective analysis

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Introduction: Gastric cancer ranks as the 5th most prevalent cancer and the 4th leading cause of cancer-related deaths worldwide. Various treatment modalities, including surgical resection, chemotherapy, and radiotherapy, are available for gastric cancer patients. However, disparities related to age, sex, race, socioeconomic factors, insurance status, and demographic factors often lead to delayed time to treatment.

Methods: In this retrospective study, conducted between 2004 and 2019, we utilized data from the National Cancer Database (NCDB) to investigate the factors contributing to disparities in the time to first treatment, surgery, chemotherapy, and radiotherapy among gastric cancer patients. Our analysis incorporated several variables, and statistical analysis was conducted to provide valuable insights into these disparities.

Results: We observed notable disparities in the timing of treatment for various demographic groups, including age, sex, race, insurance status, geographic location, and facility type. These disparities include longer time to treatment in males (32.67 vs 30.75), Native Americans (35.10 vs 31.09 in Asians), low-income patients (32 vs 31.15), patients getting treatment in an academic setting (36.11 vs 29.61 in community setting), significantly longer time to chemotherapy in 70+ age group (51.13 vs 40.38 in <40 y age group), black race (55.81 vs 47.05 in whites), low income people (49.64 vs 46.74), significantly longer time to radiotherapy in females (101.61 vs 79.75), blacks and Asians (109.68 and 113.96 respectively vs 92.68 in Native Americans) etc. There are various other disparities in time to surgery, chemotherapy, and radiotherapy.

Conclusions: Understanding these disparities is crucial in developing targeted strategies to improve timely access to appropriate treatments and enhance outcomes for gastric cancer patients. Future research with updated data and prospective study designs can provide a more comprehensive understanding of the factors influencing patient outcomes in gastric cancer.

KEYWORDS

time to treatment, gastric cancer, disparities, disparities in treatment, cancer, sociodemographic factors

1 Introduction

In the year 2020, gastric cancer ranked as the 5th most prevalent cancer and the 4th leading cause of cancer-related deaths worldwide (1). Year 2020 reported over 1 million newly diagnosed cases of gastric cancer, with Eastern Asia and Eastern Europe reporting the highest incidences (2). In the United States, it is estimated that approximately 26,500 individuals will be diagnosed with gastric cancer in 2023, with the highest incidence observed in Japanese and Korean populations (2, 3). Despite a declining trend in incidence rates over the past few decades, the global burden of gastric cancer is projected to increase by 62% by 2040 (4). In the United States, black males and Hispanic females exhibit the highest incidence and mortality rates (5).

The primary causative agent of gastric cancer is Helicobacter pylori, responsible for nearly 90% of cases, while other risk factors include cigarette smoking, high salt diet, and processed meat consumption (2, 4). Various treatment modalities are available for gastric cancer, including surgical resection, chemotherapy, and radiotherapy. However, disparities related to age, sex, race, socioeconomic factors, insurance status, and demographic factors often lead to delayed time to treatment for patients with gastric cancer. While there are studies showing poor survival rates with a longer time to treatment in certain cancers (6), there is very little data demonstrating a correlation between time to treatment and overall survival in gastric cancer (5). For individuals who chose to undergo surgery as the initial treatment, there was a bimodal relationship concerning the time to treatment. Specifically, when the time to treatment was 8 weeks or less, a lengthier time to treatment correlated with an extended median overall survival. On the other hand, when the time to treatment ranged from 14 to 20 weeks, a prolonged time to treatment was linked to a diminished median overall survival (7).

This study aimed to investigate the different disparities affecting the time to treatment for individuals diagnosed with gastric cancer in the United States of America from 2004 to 2019. There have been studies done on disparities in gastric cancer treatment by Lemini et al. (8) and Rana et al. (9) but our paper focuses on more wider spectrum of sociodemographic groups including income, geographic location etc. as showed in below tables. By gaining a comprehensive understanding of these disparities, we may identify targeted strategies and interventions to improve timely access to appropriate treatments and enhance outcomes for all gastric cancer patients.

2 Methods

We performed a retrospective analysis utilizing data from the National Cancer Database (NCDB) covering the period from 2004 to 2019. The National Cancer Data Base (NCDB) is a comprehensive oncology outcomes database, capturing 70% of annual new invasive cancer diagnoses in the U.S. It serves as a crucial clinical surveillance and quality improvement tool for cancer programs under the American College of Surgeons Commission on Cancer approvals program. The information is employed to examine trends in cancer care, set benchmarks at regional and national levels, and facilitate quality improvement initiatives (9, 10). To access this data, the request was submitted through the American College of Surgeons to obtain the NCDB Participant User File (PUF), which is accessible to individuals affiliated with hospitals participating in the Commission on Cancer. Our study did not require Institutional Review Board approval. The study focused on patients who had been diagnosed with gastric cancer and adhered to the guidelines outlined by the American Joint Committee on Cancer (AJCC) 6th and 7th editions (11). The analysis encompassed a wide range of variables, including race, age, sex, income, insurance status, geographic location (rural/urban), treatment facility type, cancer stage, cancer grade, and Charlson-Deyo Comorbidity (CDC) score. Staging, grading and CDC scoring of gastric cancer is done similar to earlier studies (8, 11).

To evaluate the timing of treatment, specifically surgery, chemotherapy, and/or radiation, we computed and summarized the respective durations. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Our research findings were presented through summaries of clinical and demographic characteristics, disease outcome

measures, and treatment variables. For continuous variables, such as mean, median, standard deviation, and ranges, the Kruskal-Wallis test was utilized for analysis. Categorical variables were presented as frequencies and relative frequencies, and chi-square tests were employed for analysis.

By employing a robust methodology and rigorous statistical analysis, we aimed to provide valuable insights into the disparities related to the timing of treatment among gastric cancer patients and contribute to the advancement of knowledge in this field.

3 Results

3.1 Time to treatment

It is a crucial metric in cancer management, yet there is limited data comparing its impact on overall survival in patients with gastric cancer (5). Study by Ramanathan et al. indicates longer time to treatment has no correlation with overall survival (12) whereas according to Fisher et al. patients who had urgent surgery had worse outcomes as compared to elective surgery patients (13). Some studies indicate a bimodal relationship between overall survival and time to surgical treatment, with decreased survival rates observed in patients with treatment initiated either <4 weeks or >14 weeks after diagnosis (7). So, more studies are needed to know about the exact effect of time to treatment on overall survival. Notably, as shown in Table 1, longer time to treatment is associated with specific factors, including male sex, Native American race, Government Insurance, income less than 63000, and treatment received at academic settings.

3.2 Time to surgery

Surgery plays a pivotal role in the treatment of gastric cancer, with surgical intervention serving as the mainstay approach. For patients diagnosed with early-stage gastric cancer, total, subtotal, or distal gastrectomy with D2 lymphadenectomy offers a curative treatment option (14). In recent times, laparoscopic gastrectomy, performed by skilled surgeons, has gained prominence due to its associated benefits, such as reduced blood loss, fewer post-operative complications, and quicker recovery (15). A recent systematic review and meta-analysis of 16 studies comparing robotic gastrectomy (RG) and laparoscopic gastrectomy (LG) for gastric cancer indicated that RG is associated with a decreased risk of postoperative complications, shorter hospital stays, and lower rates of conversion to open surgery. Nevertheless, there were no significant differences observed in terms of overall survival, disease-free survival, or the number of harvested lymph nodes between the two procedures (16). However, disparities in time to surgery have been observed in certain patient groups as shown in Table 2. Males, Native Americans, individuals residing in urban areas, those with insurance coverage, and patients receiving treatment in academic settings experience longer time intervals before undergoing surgery.

3.3 Time to chemotherapy

It plays a vital role in the management of advanced gastric cancers, serving as a mainstay approach to improve patient outcomes. Studies have demonstrated that chemotherapy can extend survival by approximately 7 months compared to best supportive treatment (17). Additionally, neoadjuvant chemotherapy has been shown to reduce mortality in patients with advanced gastric cancer without increasing complications or post-operative mortality rates (18). However, certain patient groups experience longer time intervals before initiating chemotherapy as shown in Table 3. The 70+ age group, females, individuals of Asian or black race, those with low income, government insurance, and patients receiving treatment at academic settings tend to encounter delays in receiving chemotherapy.

3.4 Time to radiotherapy

It is a critical aspect in the management of locally advanced gastric cancer, particularly for alleviating local symptoms such as bleeding, pain, and obstruction. Palliative radiotherapy has shown promising response rates for these symptoms, with studies, like Tey et al. reporting rates as high as 74% for bleeding, 67% for pain, and 68% for obstruction (19). Low-dose radiotherapy is often preferred to minimize adverse effects, as it yields similar response rates with fewer side effects (19). However, certain patient groups experience delays in receiving radiotherapy as shown in Table 4. Females, individuals of black and Asian ethnicity, uninsured patients, and those residing in metropolitan cities tend to encounter longer intervals before commencing radiotherapy.

4 Discussion

In our study, we have investigated the factors contributing to disparities in the time to first treatment, surgery, chemotherapy, and radiotherapy among gastric cancer patients. Age, sex, race, insurance, income, facility type, and geographic setting emerged as influential factors influencing these treatment timelines.

Intriguingly, our data reveals that the time to surgery is notably shorter for individuals aged <40 years and >70 years compared to other age groups. The primary reason for this disparity likely lies in the early-stage diagnosis and lower prevalence of comorbidities among individuals under 40 years, making them highly suitable candidates for early surgical intervention (20). Conversely, patients over 70 years of age are typically diagnosed at an advanced stage of the disease, necessitating immediate surgical action due to the severity of their condition. This finding aligns with the observations made by Brenkman et al., who demonstrated that individuals with advanced tumor stages undergo surgery more promptly than those with early-stage tumors (21).

In our study, a notable disparity was observed between females and males regarding the time to first treatment and surgery, as well as the time to chemotherapy and radiotherapy. The findings suggest

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TABLE 1 Time to first treatment.

		n	Mean (SD)	P-value
Age Categories	<40	6045	25.77 (33.85)	<.001
	40-50	14194	28.81 (33.76)	
	50-60	32153	31.47 (38.13)	
	60-70	45582	33.05 (37.60)	
	70+	68755	32.68 (37.07)	
Sex	Male	105474	**32.67** (36.09)	<.001
	Female	61255	30.75 (38.70)	
Race	White	126905	31.92 (35.66)	0.014
	Black	24877	32.30 (43.16)	
	Native American	643	**35.10** (39.06)	
	Asian	9052	31.09 (34.38)	
	Other	3572	32.44 (42.76)	
Rural/Urban	Metro	138964	31.87 (37.22)	0.47
	Urban	19753	32.21 (35.44)	
	Rural	2546	31.79 (39.21)	
Insurance Status	Not Insured	6007	28.88 (38.02)	<.001
	Private	59189	30.16 (34.87)	
	Government	97596	33.09 (38.16)	
	Unknown	3937	**35.96** (39.28)	
Income	<63,000	100688	**32.00** (37.51)	<.001
	>63,000	54199	31.15 (35.63)	
Grade	Well	14185	32.50 (46.45)	<.001
	Moderately	37154	34.14 (35.04)	
	Poorly	77374	31.64 (31.91)	
	Undifferentiated	3226	26.96 (33.26)	
Stage	0	2110	34.94 (46.26)	<.001
	I	28159	38.72 (44.33)	
	II	20181	38.72 (33.60)	
	III	19570	34.84 (28.41)	
	IV	40865	29.06 (31.35)	
Facility Type	Community	13081	29.61 (33.85)	<.001
	Comprehensive	57737	28.83 (35.06)	
	Academic	68410	**36.11** (39.55)	
	Other	21456	30.39 (35.65)	

Bold values indicate longest time to treatment in the respective sociodemographic group.

that females tended to receive earlier treatment, particularly surgical intervention, potentially hindering the progression to advanced stages of gastric cancer. In contrast, males experienced delays in surgical treatment compared to females, leading to a higher incidence of advanced-stage disease and subsequent initiation of chemotherapy and radiotherapy at an earlier stage.

The underlying reasons for this sex-based variation may stem from inherent sex-related characteristics. Males, in general, have

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TABLE 2 Time to surgery.

		n	Mean (SD)	P-value
Age Categories	<40	3415	55.75 (72.90)	<.001
	40-50	8784	60.61 (69.90)	
	50-60	20219	65.90 (73.30)	
	60-70	29750	65.54 (73.19)	
	70+	44497	47.67 (59.87)	
Sex	Male	64561	**63.05** (69.25)	<.001
	Female	42104	48.82 (65.66)	
Race	White	79438	59.84 (67.35)	<.001
	Black	16651	49.39 (72.65)	
	Native American	393	**61.35** (77.63)	
	Asian	6718	47.88 (60.29)	
	Other	2327	59.73 (75.50)	
Rural/Urban	Metro	89020	56.59 (68.08)	<.001
	Urban	12387	**61.72** (67.95)	
	Rural	1635	57.81 (68.14)	
Insurance Status	Not Insured	3148	51.76 (71.26)	<.001
	Private	38797	**63.37** (70.15)	
	Government	62699	54.20 (66.50)	
	Unknown	2021	52.78 (70.27)	
Income	<63,000	63671	55.67 (67.43)	<.001
	>63,000	34509	**57.78** (67.24)	
Grade	Well	12772	43.96 (63.09)	<.001
	Moderately	25356	62.04 (65.69)	
	Poorly	46747	60.87 (64.47)	
	Undifferentiated	2390	43.04 (59.10)	
Stage	0	2003	43.05 (62.93)	<.001
	I	24550	53.51 (61.74)	
	II	14997	93.61 (72.69)	
	III	12470	100.00 (73.08)	
	IV	5006	60.72 (91.28)	
Facility Type	Community	7511	42.49 (58.75)	<.001
	Comprehensive	35806	48.18 (61.48)	
	Academic	46025	**68.34** (73.53)	
	Other	13908	53.67 (64.37)	

Bold values indicate longest time to treatment in the respective sociodemographic group.

been reported to display reluctance in utilizing healthcare services, whereas females tend to be more frequent users of such services (22). This discrepancy in healthcare-seeking behavior may contribute to the observed differences in treatment timelines. Furthermore, existing literature on other cancer types, such as lung cancer, has shown that women are more likely than men to opt for surgical treatments. This factor may account for the prevention of advanced disease progression in females, leaving males with limited options and necessitating earlier reliance on chemotherapy and radiotherapy (22).

TABLE 3 Time to chemotherapy.

		n	Mean (SD)	P-value
Age Categories	<40	4305	40.38 (38.36)	<.001
	40-50	9958	46.35 (44.54)	
	50-60	22055	47.71 (50.90)	
	60-70	29216	49.19 (50.85)	
	70+	32987	51.13 (45.07)	
Sex	Male	66950	47.76 (48.90)	<.001
	Female	31571	51.12 (45.72)	
Race	White	75848	47.05 (45.94)	<.001
	Black	14283	55.81 (57.17)	
	Native American	398	49.65 (38.74)	
	Asian	4876	55.77 (48.32)	
	Other	2216	49.33 (42.87)	
Rural/Urban	Metro	81592	48.95 (47.57)	0.22
	Urban	12148	48.14 (47.82)	
	Rural	1540	48.68 (41.50)	
Insurance Status	Not Insured	4304	48.58 (44.70)	<.001
	Private	39009	46.14 (48.40)	
	Government	52650	50.85 (47.67)	
	Unknown	2558	48.92 (49.41)	
Income	<63,000	59435	49.64 (48.54)	<.001
	>63,000	32126	46.74 (47.65)	
Grade	Well	3056	57.11 (79.18)	<.001
	Moderately	21260	50.51 (42.76)	
	Poorly	53054	49.20 (45.24)	
	Undifferentiated	1953	52.54 (43.84)	
Stage	0	197	71.63 (50.62)	<.001
	I	8753	64.42 (50.12)	
	II	15094	51.24 (38.88)	
	III	16451	45.61 (34.12)	
	IV	34471	36.00 (34.64)	
Facility Type	Community	7764	49.76 (45.49)	<.001
	Comprehensive	33873	47.01 (48.90)	
	Academic	40078	51.09 (46.58)	
	Other	12501	48.89 (53.21)	

In the studied population, we observed significant differences in the time to first treatment and time to surgery between the Asian and Native American groups. Asian individuals exhibited notably shorter intervals to treatment initiation and surgical intervention, while Native Americans experienced prolonged time to treatment and surgery, yet shorter time to chemotherapy and radiotherapy. This disparity can be attributed to higher awareness levels among Asian individuals regarding gastric cancer, likely influenced by the higher incidence of gastric cancer in this population. Consequently, this heightened awareness leads to earlier diagnosis, rendering Asian individuals better candidates for prompt surgical treatment (5, 8, 23, 24).

TABLE 4 Time to radiotherapy.

		n	Mean (SD)	P-value
Age Categories	<40	946	97.62 (73.49)	<.001
	40-50	2836	92.11 (99.44)	
	50-60	6800	84.97 (65.95)	
	60-70	9132	81.67 (63.51)	
	70+	7938	87.42 (60.02)	
Sex	Male	20059	79.75 (62.04)	<.001
	Female	7593	**101.61** (80.11)	
Race	White	21798	79.41 (67.40)	<.001
	Black	3433	109.68 (66.14)	
	Native American	91	92.68 (71.39)	
	Asian	1514	**113.96** (61.00)	
	Other	591	105.89 (72.93)	
Rural/Urban	Metro	22576	**87.95** (69.66)	<.001
	Urban	3682	75.58 (61.17)	
	Rural	471	75.08 (53.56)	
Insurance Status	Not Insured	968	**99.00** (71.56)	<.001
	Private	12311	82.30 (63.56)	
	Government	13919	87.55 (63.80)	
	Unknown	454	96.04 (192.69)	
Income	<63,000	16476	86.48 (70.88)	0.08
	>63,000	8964	84.90 (63.50)	
Grade	Well	897	79.44 (66.21)	<.001
	Moderately	7396	76.66 (59.11)	
	Poorly	16363	92.04 (65.24)	
	Undifferentiated	547	94.48 (62.23)	
Stage	0	90	107.26 (64.00)	<.001
	I	3166	99.92 (67.08)	
	II	6173	77.72 (65.53)	
	III	6973	65.57 (56.55)	
	IV	1303	79.14 (82.18)	
Facility Type	Community	2028	88.88 (61.90)	0.052
	Comprehensive	9447	85.55 (74.07)	
	Academic	11305	85.02 (65.52)	
	Other	3926	83.85 (62.16)	

Bold values indicate longest time to treatment in the respective sociodemographic group.

It is a known fact that gastric cancer patients without insurance have higher mortality rates compared to those with insurance (9, 25). Surprisingly, patients without insurance demonstrated significantly shorter time to treatment and time to surgery when compared to their insured counterparts. This observation may seem counterintuitive at first, but the most plausible explanation for this difference lies in the worse presentation of the disease at the time of diagnosis among patients without insurance, which necessitates more urgent surgical intervention.

Patients without insurance often face barriers to accessing healthcare services, resulting in delayed diagnosis and limited access

to regular medical care. Consequently, gastric cancer may be detected at more advanced stages, leading to a more critical condition that requires immediate surgical intervention. On the other hand, patients with insurance, who likely have better access to healthcare services and early diagnosis, may have the luxury of time for a more comprehensive evaluation and preparatory measures before surgery.

Our study unveiled a concerning trend among gastric cancer patients, indicating that individuals with lower income experience significantly longer intervals to treatment, chemotherapy, and radiotherapy. Notably, this disparity may be compounded by lower education levels, which further diminish the likelihood of receiving timely medical intervention, possibly due to limited health literacy and a lack of awareness regarding the potential consequences of forgoing treatment (23, 26, 27). Tragically, this phenomenon contributes to higher mortality rates among gastric cancer patients from lower-income backgrounds and with lower educational attainment (28).

In our study, we observed notable differences in the time to treatment, surgery, and chemotherapy between patients receiving care in academic settings and those in other healthcare settings. This observation is consistent with findings from previous research for gastric cancer patients and patients with other malignancies (6, 29). The longer treatment duration at academic centers could be attributed to several factors, including a higher patient load, reduced scheduling flexibility, and a substantial number of referral cases that necessitate thorough reanalysis before offering treatment. Academic medical centers often serve as referral centers, receiving complex cases from various regions. Consequently, the need for comprehensive evaluations and consultations can lead to longer timeframes before treatment initiation.

Similarly, time to surgery and radiotherapy was more prolonged in patients living in urban and metropolitan cities respectively than in rural areas. Clinics in rural areas often experience a lower patient load than their urban and metropolitan counterparts. This lower patient volume can be advantageous in offering early appointments and enabling timely treatment for patients in rural communities.

It is essential to acknowledge that while the study identified statistically significant disparities in various factors, these differences may not have significant clinical implications. The large number of patients included in the database enabled the attainment of statistical significance, but the actual differences in the time to treatment among various treatment variables might not result in substantial variations in patient outcomes. While our study extensively covers various aspects in time to treatment disparities of gastric cancer, the analysis of survival rates is beyond the scope of our study. Future research could explore survival rates in the context of gastric cancer.

Although utilizing a large database enhances the generalizability of the study, it is crucial to recognize it as a noteworthy limitation. The sheer volume of patient information may lead to missing data and inaccurately documented information, potentially affecting the study's reliability. Additionally, the study's retrospective nature poses limitations, as the data might not fully represent current practices and disparities in the field. Changes in healthcare practices and advancements in treatments over time could influence the relevance of the study's findings to current medical practices. Moreover, the inherent variability in hospital charges for cancer treatment poses a limiting factor. Different hospitals, particularly private institutions versus safety net hospitals, may employ distinct cost structures for healthcare services which could result in different time to treatment for patients. NCDB, which serves as the primary data source for our study does not provide any information on this. Nonetheless, our study appears to be the first that analyses disparities among gastric cancer patients across all stages and socioeconomic factors.

5 Conclusions

In conclusion, our retrospective study identified significant disparities in the time to treatment, surgery, chemotherapy, and radiotherapy among gastric cancer patients. Age, sex, race, insurance, income, facility type, and geographic setting were key factors influencing treatment timelines. Understanding these disparities is crucial for targeted interventions to improve timely access to care and enhance patient outcomes. However, it is important to interpret the findings cautiously due to the potential limitations of the study. Future research with updated data and prospective designs will further enhance our understanding of these disparities and help develop effective strategies to address them.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

SS: Writing – original draft, Writing – review & editing. SB: Writing – original draft, Writing – review & editing. EG: Supervision, Writing – review & editing. HM: Writing – review & editing. PJ: Writing – review & editing. SR: Writing – review & editing. SA: Writing – review & editing. RP: Writing – review & editing. KP: Writing – review & editing. KS: Writing – review & editing. GK: Writing – review & editing. FM: Writing – review & editing.

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Analysis of screening outcomes and factors influencing compliance among community-based lung cancer high-risk population in Nanchang, China, 2018-2020

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Objective: To investigate the screening results and compliance of low-dose computed tomography (LDCT) screening among the high-risk lung cancer populations in Jiangxi Province from 2018 to 2020, and to explore the related influencing factors of compliance.

Methods: From November 2018 to October 2020, permanent residents in Nanchang City were selected and their demographic data and lung cancer risk factor data were collected to screen high-risk groups, and LDCT screening was performed on high-risk groups with diagnostic reports by 2 chief physicians. Descriptive analysis method was used to analyze the basic information of screening, screening results and screening compliance. $\chi 2$ and logistic regression test were used to conduct single and multi-factor analysis of screening compliance.

Results: A total of 26,588 people participated in this screening, of which 34.4% (n=9,139) were at high risk of lung cancer, 3,773 participants were completed LDCT screening, and the screening compliance rate was 41.3%. Screening results showed that 389 participants were positive for suspected pulmonary tumor or lung nodules, the screening positive rate of 10.3%. The logistic multivariable results of screening compliance showed that the compliance was better in males, those who quit smoking, those with chronic respiratory diseases and family history of cancer, and those who have primary education, those with a history of occupational harmful exposure had a poor compliance.

Conclusion: Compliance with lung cancer screening in Jiangxi Province, China still needs to be improved, and gender, education level, harmful occupational exposure, smoking, chronic respiratory diseases, and family history of tumors cancer play an important role on screening compliance.

KEYWORDS

lung cancer, high-risk population screening, low dose spiral CT, compliance, Jiangxi Province

1 Introduction

Lung cancer is the second most common diagnosed cancer and the leading cause of cancer death in 2020, accounting for 20% of cancer-related death (1). The National Cancer Center's latest statistics indicated that there were approximately 2,413,500 cancer-related deaths in China in 2016. Lung cancer was the most common cause of cancer deaths in both sexes, accounting for 22.92% (202,300) of the total number of cancer deaths in females and 29.71% (454,700) in males (2). Lung cancer has long latency without explicit symptoms which lead to approximately 70% of patients are diagnosed at advanced stage with a poor prognosis (3, 4). The advances in cancer diagnosis and treatment improve patients' outcomes, while the patients who are diagnosed at advanced stage have a low 5-year survival rate (5). The most effective preventive strategy for lung cancer is to diagnose lung cancer patients at early stage which allows for timely intervention to improve the life quality of patients and extend their survival rate (6). Therefore, as the biggest developing country, it is imperative to implement lung cancer screening program to enrolls the communities that are potentially exposed at risk environment. LDCT screening provides an effective method for the early detection of lung cancer. Increasing studies have shown that LDCT can reduce the overall mortality of lung cancer by 20% compared with chest X-ray (7). The effectiveness of screening work largely depends on the compliance of the population on the screening, and a lower compliance could hinder the implementation of screening program to move forward (8). Therefore, it is of great significance to identify the factors affecting screening compliance which contributes to improve the early diagnosis and treatment of lung cancer, and to prolong the survival. This study intends to analyze the potential factors affecting screening compliance to participate in LDCT screening in the Urban Cancer Screening and Early Detection and Treatment Program, providing data support for further optimization of lung cancer screening and improvement of screening compliance.

2 Materials and methods

2.1 Participants

The study subjects were from the Urban Lung Cancer Early Detection and Treatment Program, and residents who met the inclusion criteria were recruited by community service center based on the principle of voluntariness for survey and assessment. Inclusion criteria: 1. household residents of Nanchang City who have lived in the city for more than 3 years; 2. aged 40-74 years old; 3. signed written informed consent; 4. have full behavioral ability. Exclusion criteria: 1. previous history of tumor; 2. suffering from serious heart, brain, lung disease or renal dysfunction.

2.2 Investigation contents and high-risk assessment methods

The survey used a cancer risk assessment questionnaire, which included information on socio-demographic data, lifestyle behavioral habits, past history of disease, and family history of tumors. Survey respondents were surveyed by uniformly trained surveyors using a face-to-face survey format. The questionnaire information was then entered into the National Cancer Prevention and Control Platform's Early Diagnosis and Early Treatment Risk Assessment Database by a specially designed database to assess the lung cancer risk group. The database is based on the Harvard Cancer Risk Index, which is a comprehensive evaluation system of individual cancer risk that is suitable for Chinese population and has been discussed and approved by a multidisciplinary panel of experts (9). For those who are confirmed to be high-risk groups, we recommend them to go to Jiangxi Cancer Hospital for free LDCT screening, and the results of the screening will be assessed by at least two chief physicians for diagnosis.

2.3 Result judgment and definition

Positive nodules: non-solid nodules ≥8 mm; solid nodules or partially solid nodules ≥5 mm.2. Suspected lung cancer: determined by a senior physician based on imaging data and clinicopathologic diagnosis.3. The index for evaluating screening adherence was the screening participation rate, which was defined as screening participation rate = number of people who participated in LDCT screening/number of people who were at high risk of lung cancer screening*100% (8). 4. Smokers were defined as smoking more than one cigarette per day for more than 6 months. 5. People who drink at least once pre week for one year were defined as drinkers. 6. Physical exercise was defined as an average of more than 3 times per week for more than 30 minutes. 7. Harmful occupational exposure was defined as cumulative exposure to hazardous substances for more than 1 year.

2.4 Statistical analysis

SPSS25.0 software was used for data processing and analysis. Descriptive analysis method was used to analyze the basic information of screening, screening results and screening compliance. $\chi 2$ test and logistic regression test were used to conduct single and multi-factor analysis of screening compliance. Two-sided P-values < 0.05 was considered as statistically significant.

3 Result

3.1 Screening basic information

A total of 26,588 participants were enrolled in this study as shown in Table 1, of which 34.4% (9,139) were identified as high-risk for lung cancer and 65.6% (17,449) were excluded as non-high-risk for lung cancer. The average age of high-risk participants was 63.670 ± 6.597 years, and that of non-high-risk enrollment was 61.510 ± 8.692 years. Among these high-risk participants, there were 3,603 males, accounting for 39.4% and women (5,536) account for 60.6%. There were 3,541 smokers fall in the high-risk group while 9.6% (1,673) smokers were out of high-risk group.

3.2 Screening results

Among 3,773 people were screened by LDCT, 355 cases showed positive lung nodules, accounting for 9.4%; 34 cases of suspected lung cancer, accounting for 0.9%; 1,343 cases exhibited inflammation in the lungs or other diseases of the lungs, accounting for 35.6%. A total of 2,041 cases showed no abnormality measured using CT screening. accounting for 54.1%. The positive rate of suspected lung cancer or positive lung nodules was 10.3%, of which 10.9% (197/1808) were male and 9.8% (192/1965) were female; of which 9.8% (120/1224) were in the 50-59 years, 10.0% (177/1773) in the 60-69 years, and the positive rate of participants with greater than 70 years was 11.3% (92/816).

3.3 One-way analysis of compliance

People who completed LDCT screening in high-risk lung cancer groups were included in compliance analysis, and those who did not complete LDCT screening were included in non-compliance group. As displayed in Table 2, 3,773 who completed LDCT screening have a screening compliance rate of 41.3%. The gender, age, education level, marital status, occupational exposure to harmful substances, smoking, drinking, regular physical exercise, chronic respiratory diseases and family history of cancer ($P \leq 0.05$) showed statistically difference in screening compliance vs non-compliance groups.

3.4 Logistic multi-factor analysis

A logistic multivariable analysis was conducted with the screening adherence subgroups of lung cancer high-risk groups as the dependent variable, and gender, age, education level, marital status, occupational exposure to harmful substances, smoking, drinking, regular participation in physical exercise, chronic respiratory disease and family history of cancer as independent variables (Table 3). We found that screening compliance was worse in women (OR=0.623,95%CI: 0.532-0.728) as compared with men. The compliance of people aged 60 to 70 years was better than that of people aged over 70 years (OR=1.137,95%CI: 1.016 to 1.273). Compared with the population with education level in primary school or below, the population with education level in junior high school (OR=1.412,95%CI: 1.206~1.653), senior high school (OR=1.393,95%CI: 1.186~1.635)/middle college/technical college (OR=1.587,95%CI: 1.335~1.886) had better compliance; The compliance of the population with harmful occupational exposure was lower than that of the population without harmful occupational exposure (OR=0.842,95%CI: 0.761-0.932). The compliance of quitter was better than that of non-smokers and smokers (OR=0.603,95%CI: 0.422~0.863), (OR=0.660,95%CI: 0.472~0.924). People with chronic respiratory disease had better screening compliance than those without chronic respiratory disease (OR=1.280,95%CI: 1.161~1.410). People with a family history of cancer had better compliance (OR=1.457,95%CI: 1.326~1.601).

TABLE 1 Basic information on high-risk and non-risk groups for lung cancer.

basic characteristic	high-risk group (n=9139)	non-high-risk group (n=17449)	*P* value
Age (years, $\bar{x} \pm s$)	63.670 ± 6.597	61.510 ± 8.692	<0.01
BMI (kg/m^2, $\bar{x} \pm s$)	23.942 ± 4.910	23.749 ± 5.991	0.733
Gender			<0.01
Male	3603 (39.4)	6166 (35.3)	
Female	5536 (60.6)	11283 (64.7)	
Educational level			<0.01
Primary and under	1071 (11.7)	1930 (11.1)	
Junior High School	3030 (33.2)	5825 (33.4)	
High School/Middle College/ Technical College	2765 (30.3)	5284 (30.3)	
Specialty	1697 (18.6)	3087 (17.7)	
Undergraduate	376 (4.1)	898 (5.1)	
Postgraduate or above	200 (2.2)	425 (2.4)	
Marital status			<0.01
Unmarried	41 (0.4)	94 (0.5)	
Married	8728 (95.5)	16561 (94.9)	
Remarried	63 (0.7)	181 (1.0)	
Divorced	45 (0.5)	133 (0.8)	
Widowed	261 (2.9)	478 (2.7)	
Harmful occupational exposure [a]			<0.01
No	6396 (70.0)	16836 (96.5)	
Yes	2743 (30.0)	613 (3.5)	
Smoking			<0.01
Non-smoking	5301 (58.0)	15396 (88.2)	
Smoking	3541 (38.7)	1673 (9.6)	
Quit	297 (3.2)	380 (2.2)	
Drinking			<0.01
No	6383 (69.8)	15678 (89.9)	
Yes	2756 (30.2)	1771 (10.1)	
Physical exercise			<0.01
No	5459 (59.7)	7763 (44.5)	
Yes	3680 (40.3)	9686 (55.5)	
Chronic respiratory diseases [b]			<0.01
No	5134 (56.2)	16072 (92.1)	
Yes	4005 (43.8)	1377 (7.9)	

(Continued)

TABLE 1 Continued

basic characteristic	high-risk group (n=9139)	non-high-risk group (n=17449)	*P* value
Family history of tumors			<0.01
No	4658 (51.0)	14124 (80.9)	
Yes	4481 (49.0)	3325 (19.1)	

[a] Hazardous occupational exposure includes exposure to asbestos, radon, beryllium, uranium, benzene and coal tar, etc., which have been clearly identified as carcinogenic; [b] Chronic respiratory diseases include tuberculosis, chronic bronchitis, emphysema, asthma, bronchiectasis, silicosis or pneumoconiosis.

4 Discussions

Lung cancer is the most common and deadly tumor in the world, and the largest public health challenge posed by pulmonary tumor is the poor prognosis in the advanced stage. Studies have found that the prognosis of patients with lung cancer is closely related to disease stage. The five-year survival rate of patients with early stage lung cancer is 60%, and that of patients with middle and advanced stage lung cancer strikely decrease to 5%-40% (10). Therefore, the implementation of lung cancer screening to detect patients with early stage lung cancer is one of the main steps needed to reduce lung cancer-related deaths and improve survival. The

TABLE 2 Results of one-way analysis of factors influencing lung cancer screening compliance.

Factor	Number of non-adherent groups (n=5366)	Number of adherent groups (n=3773)	Compliance rate (%)	χ^2	*P* value
Gender				194.177	<0.01
Male	1795	1808	50.2		
Female	3571	1965	35.5		
Age groups (years)				8.193	0.017
50~	1772	1224	40.9		
60~	2320	1733	42.8		
≥70	1274	816	39.0		
BMI groups				0.471	0.925
≤18.5	138	103	42.7		
18.5~	2814	1969	41.2		
24~	1939	1356	41.2		
≥28	475	345	42.1		
Educational level				105.036	<0.01
Primary and under	770	301	28.1		
Junior High School	1774	1256	41.5		
High School/Middle College/ Technical College	1581	1184	42.8		
Specialty	900	797	47.0		
Undergraduate	213	163	43.4		
Postgraduate or above	128	72	36.0		
Marital status				27.754	<0.01
Unmarried	21	20	48.8		
Married	5108	3620	41.5		
Remarried	29	34	54.0		
Divorced	20	25	55.6		
Widowed	188	74	28.2		
Harmful occupational exposure				4.659	0.031

(Continued)

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TABLE 2 Continued

Factor	Number of non-adherent groups (n=5366)	Number of adherent groups (n=3773)	Compliance rate (%)	χ^2	*P* value
No	3802	2594	40.6		
Yes	1564	1179	43.0		
Smoking				182.603	<0.01
Non-smoking	3509	1940	35.6		
Smoking	1792	1749	49.4		
Quit	65	84	56.4		
Drinking				52.959	<0.01
No	3905	2478	38.8		
Yes	1461	1295	47.0		
Physical exercise				11.794	<0.01
No	3126	2333	42.7		
Yes	2240	1440	39.1		
Chronic respiratory diseases				94.942	<0.01
No	3242	1892	36.9		
Yes	2124	1881	47.0		
Family history of tumors				115.652	<0.01
No	2988	1670	35.9		
Yes	2378	2103	46.9		

study analyzed the screening data from the urban cancer early detection and early treatment project of Jiangxi Province from 2018 to 2020. The screening involved 26,588 participants in 8 administrative regions of Nanchang City. The results showed that there were 9,139 high-risk groups of lung cancer, among which 3,773 completed LDCT screening, and the screening compliance rate was 41.3%, which is higher than the overall participation rate of 34.8% (8) in Zhejiang, Anhui and Liaoning provinces, 37.5% (11) in Henan Province and 37.10% (12) in Beijing. Among 3,773 participants in LDCT screening, 355 were positive for nodules, 34 were suspected of lung cancer, and the positive rate of suspected lung cancer or lung nodules was 10.3%.

This study also further analyzed the influencing factors of screening compliance among high-risk groups of lung cancer, and found that gender, educational level, harmful occupational exposure, smoking, chronic respiratory diseases and family history of cancer had important effects on screening compliance. The results show that the compliance of men is better than that of women, which may be related to smoking. The majority of men had smoking history, which has been demonstrated to be the risk factor of a variety of lung diseases (13). These smokers are willing to take care of their lungs condition, and LDCT can provide a preliminary detection of the lungs, so the compliance of those men may be better than that of women. Among different age groups, the compliance of

TABLE 3 Results of logistic multivariable analysis of factors influencing compliance with lung cancer screening.

Factor	*P* value	*OR*	*OR95% CI*
Gender			
Male		1.000	
Female	<0.01	0.623	(0.532~0.728)
Age groups (years)			
50~	0.227	1.078	(0.954~1.217)
60~	0.025	1.137	(1.016~1.273)
≥70		1.000	
Educational level			
Primary and under		1.000	
Junior High School	<0.01	1.412	(1.206~1.653)
High School/Middle College/ Technical College	<0.01	1.393	(1.186~1.635)
Specialty	<0.01	1.587	(1.335~1.886)
Undergraduate	0.074	1.261	(0.978~1.626)
Postgraduate or above	0.283	0.835	(0.600~1.161)

(Continued)

TABLE 3 Continued

Factor	*P* value	*OR*	*OR95% CI*
Harmful occupational exposure			
No		1.000	
Yes	<0.01	0.842	(0.761~0.932)
Smoking			
Non-smoking	<0.01	0.603	(0.422~0.863)
Smoking	0.016	0.660	(0.472~0.924)
Quit		1.000	
Chronic respiratory diseases			
No		1.000	
Yes	<0.01	1.280	(1.161~1.410)
Family history of tumors			
No		1.000	
Yes	<0.01	1.457	(1.326~1.601)

people aged 60-70 is better than that of people aged over 70, which is consistent with the results of other studies (8, 14). Participants with greater than 70 years might have basic diseases such as hypertension and diabetes, which made them in poor physical condition and inconvenient to participate, weaken their enthusiasm to be involved. Some elders have unfavorable life condition or live far from the screening center which decrease their willingness. The low compliance of people with primary school education may be due to their low health awareness and poor knowledge of lung cancer, and failing to recognize the importance of screening for early detection and diagnosis, which is consistent with the results of studies in Guangzhou (15) and Hebei (16). The compliance of people exposed to occupational harmful factors is lower than that of people not exposed to occupational harmful factors, which may be due to the fact that people exposed to occupational harmful factors will arrange a regular time for physical screening, and they are relatively aware of their own conditions, so they fail to participate in screening.

Studies have shown that smoking, chronic respiratory diseases and family history of cancer are risk factors for lung cancer (17, 18). The results of the screening showed that the compliance with screening was better in quitters than in non-smokers and smokers, probably because they believed that due to not smoking, their lung condition is better, so there is no need to check their lungs; the quitters were more likely to undergo LDCT screening compared with the smokers, probably because they were gradually learning about the relationship between smoking and lung cancer, and they knew that smokers had a higher relative risk of lung cancer (19) and that they had smoked before. In addition, it is consistent with previous studies (8, 15) that people with chronic respiratory diseases and family history of tumors have better screening compliance, which may be due to the fact that people with chronic respiratory diseases are relatively more familiar with lung diseases, and it is also recommended by doctors to check their lung conditions regularly. For people with a family history of cancer, the illness of relatives makes them have more understanding of cancer, and they have a higher sense of identity for early detection of cancer by screening, so this may be the reason for the relatively good compliance of these two groups of people.

In conclusion, the compliance in this area still needs to be improved, and our relevant staff should strengthen the publicity and education work on early detection and early diagnosis and early treatment of cancer in ordinary times. Screening staff should pay attention to the factors that have an important influence on screening compliance and try to avoid them during the implementation of screening work in the future, so as to further improve screening compliance, increase the cancer detection rate, and enable patients with early stage of lung cancer to receive treatment in time, so as to improve their quality of life and prolong their survival time. Based on the results of the survey, we suggest that we focus on strengthening publicity and education for people over 70 years of age and those with elementary school education because the incidence of lung cancer in people over 70 years of age is the highest compared with the other two age groups (14, 20), but their compliance is still poor, therefore, maybe we could screen them when they regularly get prescriptions or screen the inconvenient elders at their home, and the compliance of those with elementary school education is also lower than that of those with other levels of education, therefore, it is very necessary to let them know the health hazards of lung cancer to the population, and to recognize the importance of screening for early detection, diagnosis, and treatment, so as to encourage them to actively participate in the screening, and to increase the screening compliance. However, this study still has potential limitations. Since the screening was completed in the form of investigation, the recall bias generated during the investigation was unavoidable; As the analysis is based on a local population, the generalizability of this study is limited; We only analyzed the screening compliance of high-risk group, and did not evaluate in non-high-risk group. Further improvement of the research content is warranted by including comprehensive factors, which helps to produce meaningful findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the medical ethical review committee of Jiangxi Provincial Cancer Hospital.

Author contributions

FZ: Methodology, Validation, Writing – original draft, Data curation, Software. XBW: Data curation, Investigation, Writing – original draft. CW: Data curation, Writing – original draft. YZ: Software, Writing – original draft. DF: Writing – review & editing, Formal Analysis. XW: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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