Geographical and sexual disparities of lung cancer mortality trends in China: A population-based study

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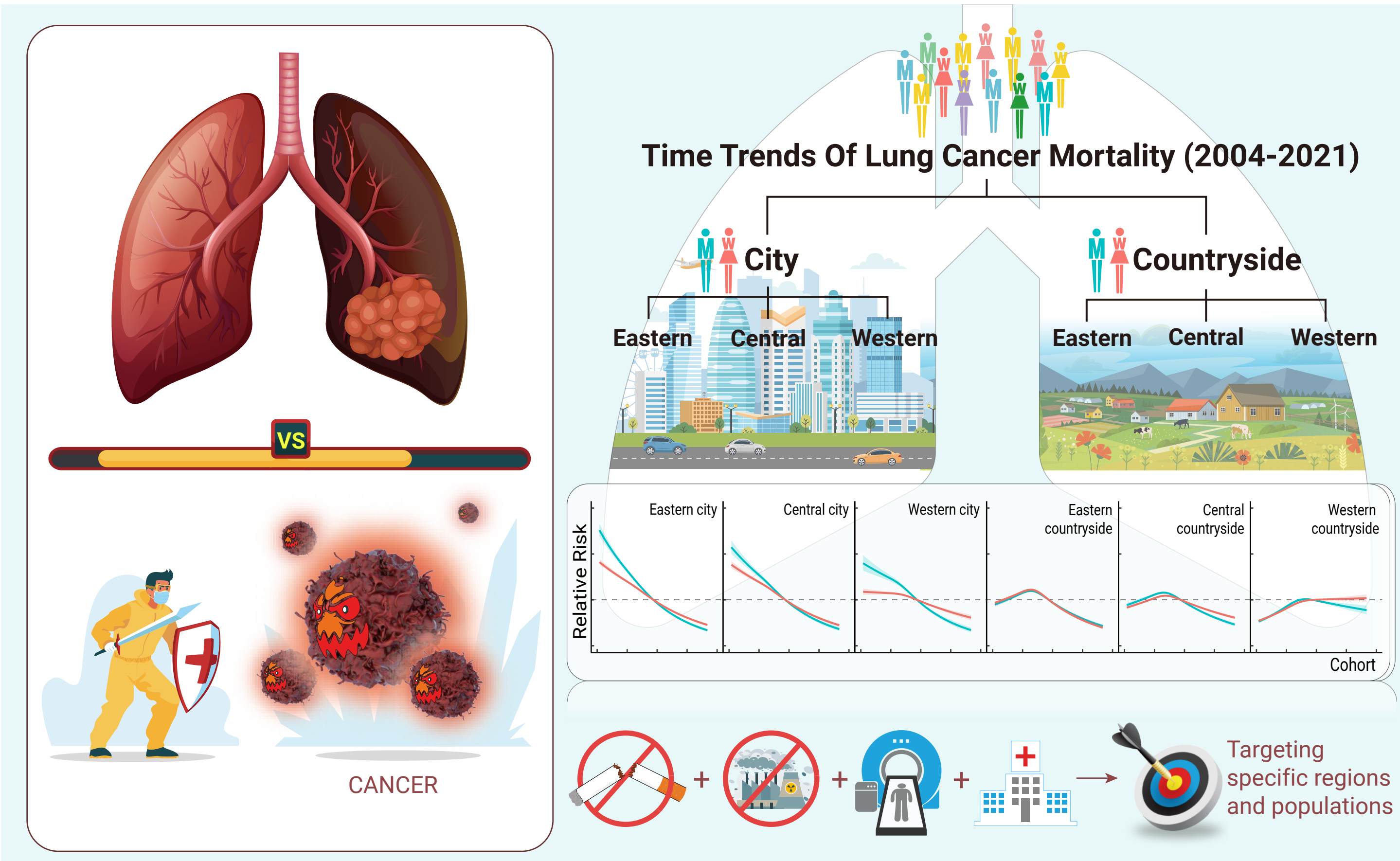
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- This is the most comprehensive and up-to-date analysis of lung cancer mortality trends in China.
- We found contrasting patterns in lung cancer mortality trends between cities and countryside in China.
- Cohort effects illustrated a downward trend in cities, but with an inverted U-shape curve in rural areas.
- It is important to take region- and population-specific primary prevention strategies to reduce the burden of lung cancer.

REPORT

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Lung cancer (LC) is one of the major causes of cancer deaths in China. Death burden and mortality of LC vary according to sexes and regions. We aimed to comprehensively evaluate the geographical and sexual disparities in LC mortality trends in China, and a further age-period-cohort analysis to explore underlying factors. LC mortality data during 2004-2021 were extracted from the Disease Surveillance Points system. Annual age-standardized mortality rates (ASMR) were calculated for 36 sub-populations by sex, urban-rural status and geographical regions. The age-period-cohort model was applied to investigate age, period and cohort effects on mortality trends. Time trends of ASMR for LC overall did not show statistical significance during 2004-2021, but contrasting patterns were observed between cities and countryside, with annual average percent changes of -1.58% (95%CI, -2.11%- -1.05%) and 0.57% (95%CI, 0.07%- 1.07%), respectively. ASMR of LC decreased in eastern and central regions and increased markedly in western region. Cohort effects illustrated a downward trend in cities, but an inverted U-shape curve peaking around the 1950s appeared in the countryside, and the decreasing trends were slower in the western region. There are substantial geographical and sexual disparities in LC mortality trends in China, notably with unfavorable trends in the western countryside. The variation in cohort effects on the mortality trends implies the importance of taking region- and population-specific primary prevention strategies to reduce the disease burden of LC in China.

INTRODUCTION

Lung cancer (LC) is the most common cancer in China. According to the GLOBOCAN estimates, there were 816,000 new cases and 715,000 deaths of LC in China, 2020.[1] LC ranks first in the cancer death spectrum of China for both sexes, accounting for over 29% and 22% of all cancer-related deaths in men and women, respectively.[2,3] According to a study based on the national registration data, the number of deaths increased by 123.6% during 2000-2016,[4] while the age-standardized mortality rates (ASMR) of LC have shown a slight downward trend over the country.[2]

Death burden and mortality trends of LC vary according to different sexes and regions in China.[5] Crude mortality rates (CMR) of LC are generally higher in urban areas or eastern regions, and higher in men than women.[3] As for the heterogeneity of time trends, the ASMR of LC in urban areas declined from 1990 to 2017 with an AAPC of −0.4%, whereas the LC mortality in the countryside during the same period increased,[6] and this diverging pattern still exists based on more recent observations.[7] Decreasing trends were observed for both sexes, with a slightly faster decline among women in the recent years especially.[2,7]

The comparisons between different regions and sexes in the mortality trends of LC are crucial in understanding the underlying factors and in making targeted cancer prevention or control strategies. However, current evidence is limited to a more detailed exploration by combining the urban-rural, eastern-central-western, and male-female strata. In this study, we aimed to conduct a comprehensive analysis of the geographical and sexual disparities in the LC mortality trends in China, based on the most recent data from the Disease Surveillance Points (DSP) system. We further performed age-period-cohort analyses to explore potential hypotheses on the underlying factors contributing to the variations in time trends.

MATERIALS AND METHODS

Data sources

LC deaths and populations by 5-year age groups, sex, urban-rural status, and regions, were extracted from the series of annual reports of the Disease Surveillance Points (DSP) system between 2004 and 2021.[8] LC was defined by the International Classification of Diseases, 10th Revision (ICD-10) as C33-C34. DSPs, which was designed primarily to collect data on births, causes of death and the incidence of infectious diseases, was established in 1990 and covered a nationally representative 10 million population from 145 locations through multistage stratified cluster sampling.[9] In 2004, the system was expanded to 161 sites to cover over 70 million population to adapt to social stratification and demographic structure changes.[9] In 2013, the system combined the Ministry of Health vital registration system, covering 24.3% population in the country.[10]

Statistical analysis

The annual crude mortality rates (CMR) of LC were calculated for eastern city, central city, western city, eastern countryside, central countryside and western countryside, by sex and 5-year age group. The eastern region includes Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong and Hainan; the central region includes Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei and Hunan; and the western region includes Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shanxi, Gansu, Qinghai, Ningxia and Xinjiang. Counties (including county-level cities) in the country are defined as rural area and districts in the cities are defined as urban area. Age-standardized mortality rates (ASMR) were calculated by using the national population in 2010 as a reference.[11] The standardized rate ratios (SSR) between men and women were also calculated. We restricted all analyses to individuals aged 25-84 years old due to the few records of LC deaths in DSPs under 25 or over 85 years.

We estimated the average annual percent changes (AAPC) of ASMRs between 2004 and 2021 as $AAPC = 100 \times (e^{\beta} - 1)$, where β is the regression coefficient in the logarithmic linear models between ASMRs and years. We visually detected age, period, and cohort effects using a graphical method.[12] Ages were divided into twelve 5-year groups (25-29, 30-34, ..., 80-84 years). Birth cohorts were obtained by subtracting the midpoint of the 5-year age group from the study year. The age-specific mortality rates were plotted against birth cohorts. We also grouped the study years into four periods (2004-2006, 2007-2011, 2012-2016, 2017-2021) and plotted the age curves over different periods. These analyses were conducted for 36 categories (12 each for men, women and both sexes combined): overall, by eastern-central-western regions, by urban-rural areas, and by more granular categories (eastern city, central city, and western city, eastern countryside, central countryside and western countryside).

An Age-Period-Cohort (APC) analysis was used to investigate the effects of the three variables.[13] The general form of the APC model is as follows:

$$log[\lambda(a,p)] = f(a) + g(p) + h(c)$$

where $\lambda(a, p)$ is the mortality rate at age a in period p and cohort c; $f(a)$, $g(p)$ and $h(c)$ represent the functions for the midpoints of age, period, and birth cohort. The APC model suffers from the problem of non-identifiability because of the linear interdependency between age, period, and cohort, and it is therefore impossible to determine the independent effects of the three APC variables. To address this problem, we decomposed the mortality into overall linear (drift). The drift reflects the sum of the linear period and cohort effect.[12] Deviations from linearity, which were not dependent on any model constraint, were then estimated as period and cohort effects, with 1957 and 2012 as the cohort and period reference groups respectively. Age effects were represented as the age-specific rates in the reference cohort after controlling for period and cohort effects, with the period function constrained to be 0 on average with 0 slope.[14] Each term of the three functions was parameterized by natural splines with three, four, five, six and seven knots separately to test the robustness of the model, and we put the results parameterized by natural splines with three knots, the other four results were put in supplementary materials.

All analyses were performed by R software (version 4.1.2). The *apc.fit* function in the "Epi" package was used to fit the age-period-cohort model.

RESULTS

Trends of LC mortality

CMR of LC in China has shown an upward trend, with AAPCs of 2.11% (95%CI, 1.73%- 2.50%). The patterns were similar for both sexes, with AAPCs of 2.35% (95%CI, 1.99%- 2.71%) and 1.71% (95%CI, 1.26%- 2.15%). Similar upward trends were shown in the eastern, central and western region. More specifically, the increase of CMR is obvious in the countryside and western cities for both sexes, with AAPCs shown in Supplement Figure S1 and Table 1. The time trends of ASMR of overall LC mortality were not statistically significant during 2004-2021, with the corresponding AAPCs of -0.33% (95%CI, -0.73%- 0.06%). ASMR in urban areas experienced an obvious downward trend, while the opposite trend was observed in rural areas, with the corresponding AAPCs of -1.58% (95%CI, -2.11%- -1.05%) and 0.57% (95%CI, 0.07%- 1.07%), respectively. The time trends of ASMR prominently decreased in eastern and central regions, and increased markedly in the western region, with the corresponding AAPCs: -0.80% (95%CI, -1.24%- -0.37%); -0.57% (95%CI, -1.06%- -0.07%); 1.05% (95%CI, 0.34%- 1.77%). More specifically, the western countryside experienced the largest increase in the ASMR of LC mortality (AAPC: 1.86% [95%CI, 0.93%- 2.81%]). In the eastern countryside, central countryside and western city, the mortality rates did not change significantly. For the remaining areas, ASMR had been generally decreasing, at a speed ranging from -1.84% in the eastern city to -1.69% in the central city

Table 1. The annual average percent changes (AAPC, 95% confidence interval) of lung cancer mortality rates in different locations during 2004-2021, overall and by sex

Group	Overall		Men		Women	
CMR		*P* value		*P* value		*P* value
Overall	2.11(1.73, 2.50)	<0.001	2.35(1.99, 2.71)	<0.001	1.71(1.26, 2.15)	<0.001
Urban	0.31(-0.20, 0.82)	0.256	0.63(0.10, 1.15)	0.032	-0.37(-0.87, 0.13)	0.170
Rural	3.34(2.80,3.88)	<0.001	3.50(2.95, 4.05)	<0.001	3.16(2.58, 3.74)	<0.001
Eastern region	1.51(1.07, 1.95)	<0.001	1.73(1.33, 2.13)	<0.001	1.08(0.54, 1.62)	0.001
Central region	2.05(1.56, 2.53)	<0.001	2.29(1.80, 2.78)	<0.001	1.72(1.19, 2.25)	<0.001
Western region	3.45(2.71, 4.20)	<0.001	3.66(2.91, 4.41)	<0.001	3.06(2.31, 3.81)	<0.001
Eastern city	-0.18(-0.82, 0.46)	0.582	0.10(-0.54, 0.74)	0.765	-0.80(-1.46, -0.14)	0.031
Central city	0.23(-0.34, 0.79)	0.444	0.40(-0.17, 0.97)	0.184	-0.03(-0.65, 0.60)	0.934
Western city	1.90(1.21, 2.59)	<0.001	2.27(1.56, 2.98)	<0.001	1.04(0.33, 1.76)	0.011
Eastern countryside	2.85(2.41, 3.30)	<0.001	2.97(2.53, 3.40)	<0.001	2.72(2.11, 3.34)	<0.001
Central countryside	3.04(2.42, 3.66)	<0.001	3.29(2.66, 3.93)	<0.001	2.73(2.08, 3.38)	<0.001
Western countryside	4.26(3.31, 5.22)	<0.001	4.34(3.33, 5.36)	<0.001	4.18(3.37, 5.00)	<0.001
ASMR						
Overall	-0.33(-0.73, 0.06)	0.118	-0.22(-0.58, 0.15)	0.258	-0.64(-1.11, -0.17)	0.017
Urban	-1.58(-2.11, -1.05)	<0.001	-1.32(-1.81, -0.83)	<0.001	-2.23(-2.79, -1.67)	<0.001
Rural	0.57(0.07, 1.07)	0.040	0.61(0.08, 1.14)	0.038	0.50(-0.05, 1.05)	0.095
Eastern region	-0.80(-1.24, -0.37)	0.002	-0.70(-1.05, -0.34)	0.001	-1.10(-1.68, -0.53)	0.002
Central region	-0.57(-1.06, -0.07)	0.039	-0.51(-1.01, 0.00)	0.069	-0.74(-1.30, -0.19)	0.018
Western region	1.05(0.34, 1.77)	0.011	1.21(0.51, 1.92)	0.004	0.67(-0.05, 1.39)	0.088
Eastern city	-1.84(-2.37, -1.30)	<0.001	-1.60(-2.09, -1.11)	<0.001	-2.44(-3.04, -1.84)	<0.001
Central city	-1.69(-2.34, -1.03)	<0.001	-1.58(-2.21, -0.95)	<0.001	-1.90(-2.65, -1.14)	<0.001
Western city	-0.56(-1.31, 0.20)	0.170	-0.24(-0.96, 0.49)	0.528	-1.39(-2.18, -0.60)	0.003
Eastern countryside	0.05(-0.41, 0.51)	0.839	0.04(-0.37, 0.45)	0.851	0.06(-0.61, 0.74)	0.852
Central countryside	0.11(-0.47, 0.70)	0.712	0.16(-0.47, 0.79)	0.625	-0.02(-0.63, 0.59)	0.948
Western countryside	1.86(0.93, 2.81)	0.001	1.92(0.90, 2.95)	0.002	1.77(0.98, 2.58)	<0.001

Abbreviations: CMR: crude mortality rates; ASMR: age-standardized mortality rates

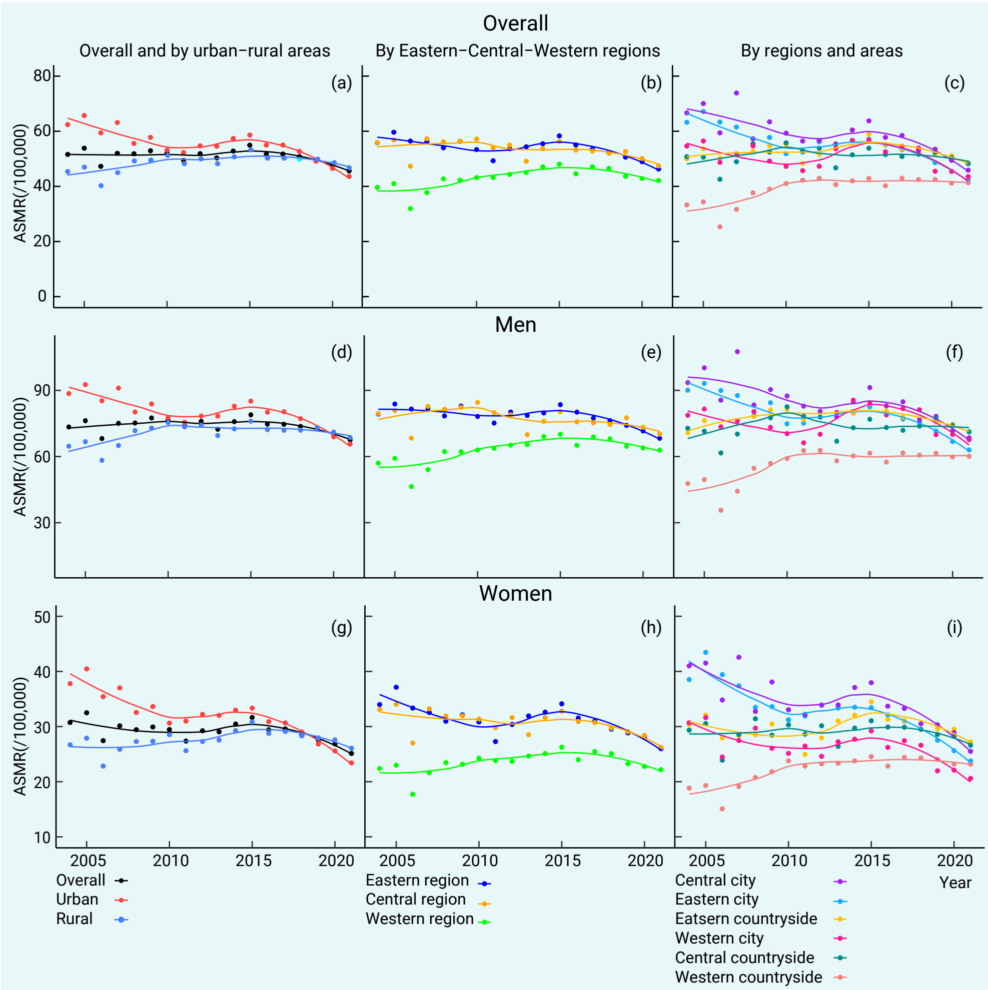

Figure 1. Trends of the age-standardized rates for lung cancer mortality in Chinese population stratified by gender, regions and areas from 2004 to 2021.

(Figure 1 and Table 1).

Statistically significance of declining trends of LC mortality ASMR was not observed in men (AAPCs: -0.22% [95%CI, -0.58%- 0.15%]), but observed in women (-0.64% [95%CI, -1.11%- -0.17%]). The increasing trends of ASMR in the western region were statistically significant in men (AAPCs: 1.21% [95%CI, 0.51%- 1.92%]) and marginally significant in women (AAPCs: 0.67% [95%CI, -0.05%- 1.39%]). ASMR of LC in men was around 2.5 times higher than that in women and the SSR of ASMR between men and women (men/women) manifested a weak upward trend which was more obvious in urban area, especially in western city (Supplement Figure S2). The most noticeable sexual disparities were in western city, where a marked downward trend was observed in women, while no statistically significant trend in men (Figure 1 and Table 1).

Age-specific rates by periods and birth cohorts.

LC mortality rates in urban and rural areas both showed an exponential increase after the age of 45, with a faster speed in urban area. The differences in rates across the 4 periods were mainly found for those aged 70 and older, especially in the eastern city, central city, eastern countryside and western countryside in men (Supplement Figure S3).

Time trends of age-specific rates differed by locations. In urban areas, most of the age groups for both sexes experienced a prominent declining trend, but a striking increasing trend among aged 55-64 for men occurred in western city. In rural areas, there was an obvious upward trend among older people, while the lower age groups showed a declining trend except for some groups with relatively stable trends (Supplement Figure S4).

LC mortality rates decreased over birth cohorts for most age groups in cities, except for those aged 60-69 years. While upward trends were observed in rural people aged 60 years and above. Mortality rates also increased among the middle-aged groups in the western countryside (Figure 3).

Age-period-cohort effects on lung cancer

After controlling the period and cohort effects, similar age patterns were observed between urban and rural areas stratified by regions, with mortality rates increasing exponentially by age. While age effects presented large sexual differences that mortality rates increased sharper in men than in women for all regions. The mortality rates for the older age groups in the reference cohort were lower in eastern and central city than in other regions (Figures 4a-f). Period effects were similar across regions with a peak around 2015, except for men and women in the central countryside, where no significant period effects were found (Figures 4g-l).

Contrasting patterns were observed for the cohort effects between urban and rural areas, with downward trends in cities, while an inverted U-shape curve peaking around the 1950s for the countryside, for both men and women. An exception was found for the increasing trend in the western countryside for men. Even within cities, there were differences in the magnitude of changes in the cohort effects, with a slower decreasing trend in western city. In the countryside, similar disparities appeared between western regions versus eastern or central regions, with a slower downward trend in the western countryside after the 1950s (Figures 4m-r).

DISCUSSION

Our study used data from the DSPs to provide a comprehensive analysis of the geographical and sexual disparities of LC mortality trends in China. The major findings manifested that time trends of ASMR decreased in urban area, eastern and central regions, but increased markedly in rural area and western regions. Western countryside experienced the largest increase in the ASMR of LC. SSR was around 2.5 times and manifested upward trends in cities, especially in the West. LC mortality rates decreased over birth cohorts for most age groups in cities, while an increase was observed for people over 60 years in the countryside. For the western countryside, increases were also observed among the middle-aged groups. Period effects were similar across regions with a peak around 2015, except in the central countryside. Cohort effects illustrated a downward trend in cities, but with an inversed U-shape curve peaking around the 1950s in the countryside. Slower decreasing trends in cohort effects were observed in western cities and the countryside.

The distribution of risk factors and ASMR were generally consistent. Smoking is the leading risk factor for LC,[15,16] and the smoking rates in China were relatively higher in the central and eastern regions compared to the west, higher in cities compared with the countryside, and higher in men than in women.[17] Air pollution is another important risk factor for LC, which in urban area is more serious than in rural area owing to the higher degree of industrialization.[18] Studies showed that from 2000 to 2018, the concentration of $PM_{2.5}$ in urban area was 3.3 μg/m³ higher than that in rural area on average.[19] Besides, most cities in the western region were slightly polluted compared with central and eastern regions.[20]

As for geographical disparities of ASMR mortality trends, changes in smoking rates regardless of regions may partially explain these phenomena. Studies reported that the smoking rates in the eastern region showed a downward trend, but in the western and central regions remained high, and

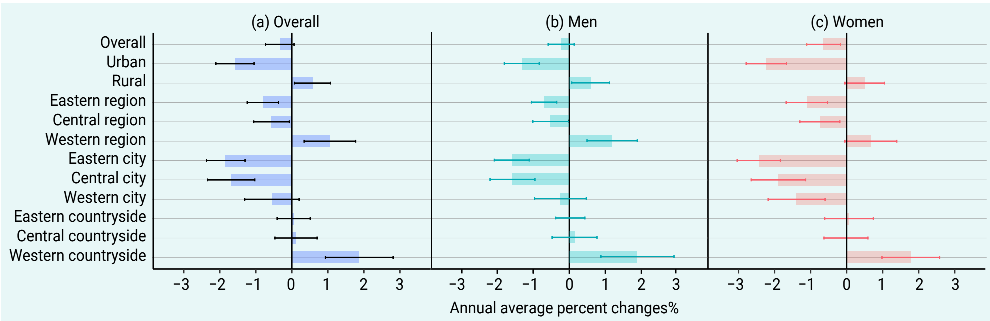

Figure 2. The annual average percent changes of age-standardized lung cancer mortality rates in different locations during 2004-2021, overall and by sex.

Period effects remained relatively stable during our study timeframe, but there was a peak around 2015, which may be due to the changes in the classification of LC. World Health Organization (WHO) published a new classification of lung tumor histology in 2015, which classified LC according to molecular forms to provide more precise and individualized protocols in terms of prognosis and treatment. These molecular subtypes include non-small cell lung cancers with kinase variants such as EGFR, ALK and ROS1, as well as subtypes such as small cell lung cancer and neuroendocrine tumors.[39] This molecular classification approach allows a better prediction of patient prognosis and treatment response and therefore provides more precise treatment options for patients, such as targeted therapy. Early adoption of this targeted therapy has been shown to have a positive impact on patient outcomes.[40] Therefore, the 2015 WHO lung cancer classification has contributed to advances in LC treatment and may help reduce LC mortality. In America, the major changes have affected these improved patient outcomes by providing greater diagnostic accuracy and better therapeutic strategies through more efficient molecular and biomarker testing.[41] Although the DSP system expanded since 2013, studies have proven the consistency and representativeness of DSPs during the study period,[10] so we believe that the effect of the expansion of the DSP system coverage on the trend of age-standardized lung cancer mortality is minimal.

the downward trends of smoking rates in cities were more obvious than that in the countryside. Simultaneously, with the implementation of the plan for preventing and controlling air pollution, $PM_{2.5}$ concentrations in both cities and the countryside decreased rapidly during 2013-2018, with an average annual decline of 3.2 and 2.8 μg/m³, and a faster decrease was shown in cities.[19] Indoor air pollution is an important risk factor for women,[21-25] and solid fuel usage is an important source of indoor air pollution. By 2014, despite a continuing downward trend, many people in rural area still used solid fuels for cooking (48%) and heating (72%), mostly without adequate ventilation (51%), in contrast to urban residents (all <5%).[26] Despite marked progress in fuel modernization in the last 50 years, substantial rural-urban inequalities remain in China, especially for those older or of lower socioeconomic status (usually in rural areas). The uptake of cleaner heating fuel and ventilation has been slow,[26-29] which may explain why SSR increased more obvious in cites than that in the countryside. Socioeconomic factors may also influence the regional difference in LC mortality trends.[30] LC patients among the deprived communities have a worse survival,[31,32] partially because people from lower socio-economic status (SES) may be less likely to undergo screening for LC and more likely to be diagnosed as an emergency,[33,34] studies revealed that more urban patients received cancer treatment than rural patients and patients with high SES received a higher proportion of surgical and chemotherapy treatments compared to patients with low SES.[35,36] Thus, the socio-economic gradient that exists across regions may contribute to the geographical disparities of ASMR mortality trends.

Risk factors for LC have prominent gender differences, smoking rates in men are higher than that in women and indoor air pollution are more important for women, considering that women mostly play a dominant role in domestic cooking.[37] Studies revealed that 24% and 4.8% of LC deaths in Chinese men and women can be attributed to smoking.[38] Researches showed that smoking rates among women younger than 40 years increased from 2003 to 2013 in China, while remaining high among men.[17] Moreover, during 1968-2014, the proportion of self-reported solid fuel using for cooking or heating decreased by two-thirds (from 84% to 27%), whereas those having complete kitchen ventilation tripled (from 19% to 66%),[26] which may elucidate the reason why ASMR declined in women but kept stable in men.

Age-specific rates by cohorts and cohort effects also show huge differences between urban and rural areas, and recent birth cohorts have a lower risk of LC death in cities. This phenomenon suggests a kind of similarity in three stratified regions and different genders. Some long-term contributing factors may lead to the decreasing risk, including better medical level, education and awareness of health in younger generations.[42] In the countryside, cohort-specific mortality rates of LC had a peak in the 1950s birth cohorts, while in the western area, the peak appeared earlier. This phenomenon experienced in the cohort effect of the APC model as an inversed U-shaped curve which was also reported by the previous studies on other cancers in China such as esophageal and gastric cancer.[12,43] Similar birth cohort effects of LC were also detected in 26 countries for men, and the highest risks mainly occurred in the 1950s birth cohorts.[44] Those born in that period experienced the Great Famine in China, which may further lead to fostering unhealthy eating habits including a high salt diet, and these habits may increase susceptibility to LC. [45]

The strength of our study includes using the most updated data of DSPs to conduct a comprehensive analysis of the mortality trends of LC stratified by

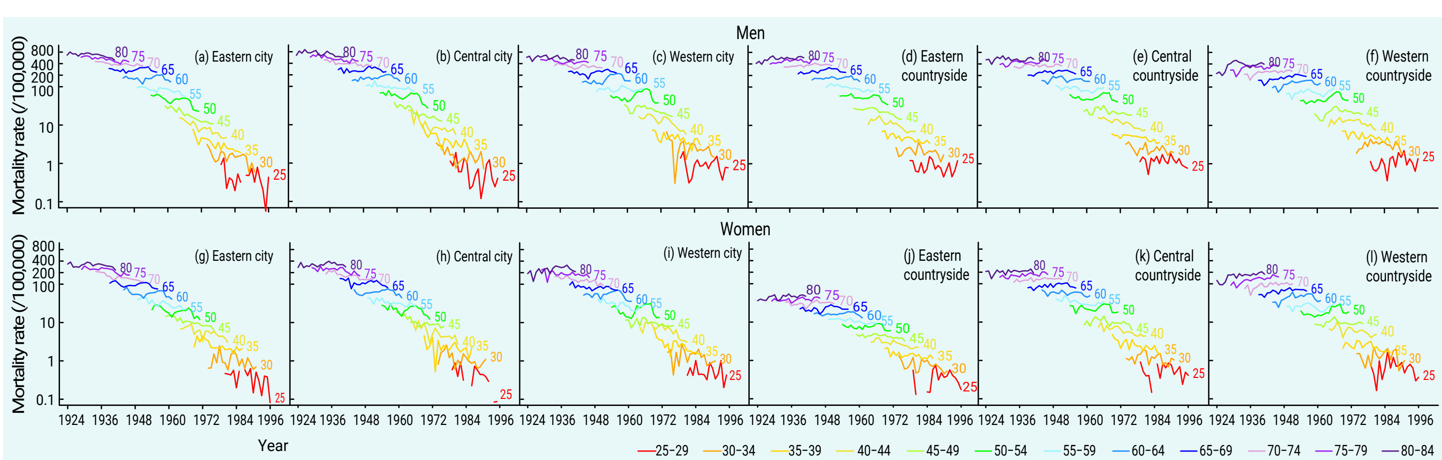

Figure 3. Cohort-specific mortality rates of lung cancer on a semilogarithmic scale in different age groups, stratified by gender, regions and areas.

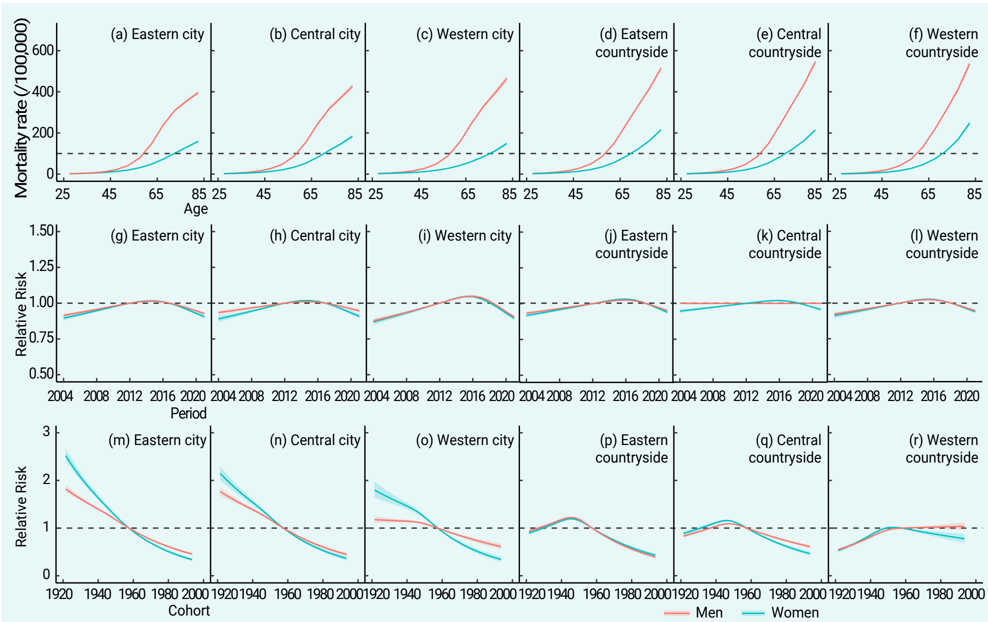

Figure 4. Age, period, and cohort effects on lung cancer mortality, stratified by regions, areas and gender (parameterized by natural splines with three knots) (a-f) The panels in the first row represent age effects; (g-l) In the second row represent period effects; (m-r) In the third row represent cohort effects

regions, areas and gender in China. Compared to previous studies, we combined the urban-rural, eastern-central-western, and male-female strata for the first time to probe the disparities. Our findings enable the health authorities to understand the geographical and sexual disparities of LC in China and to design region- and population-specific primary prevention strategies to reduce the disease burden of LC in China. We also implemented an age-period-cohort model to discern the effects of the three variables, which provided a refined estimation crucial for identifying the priority intervention group and adjusting intervention measures.

Our study has several limitations. First, death data from DSPs in 2004-2005 were based on retrospective surveys, while those in 2006-2021 were based on routine surveillance. In 2013, the system was combined with the Ministry of Health vital registration system, covering a larger population.[10] Therefore, changes in the way of death cases collection may influence the consistency of data included for the time trend analysis. Second, we are not able to perform a sensitivity analysis incorporating only the continuous surveillance points because the more granular data is not available, but we reckon that the difference is likely to be minimal due to reasons aforementioned. Third, underreporting is a common problem in disease surveillance, but we were not able to adjust for it due to the unavailability of the underreporting rates in each year, by sex, urban/rural areas, and by regions. Furthermore, the underreporting rates for lung cancer mortality specifically are not known. Fourth, due to the unavailability of data on specific histological types of LC, we cannot analyze the different effects of age, period and cohort in different histology lung cancers. Finally, the COVID-19 pandemic might have influenced the time trends of LC mortality, as it may increase the death risk of LC patients or produce the effects of competing deaths. However, we did not observe apparent waves of LC deaths during 2020-2021.

In conclusion, substantial geographical and sexual disparities in LC mortality trends still exist in China, notably with unfavorable trends in the western countryside. The variation in cohort effects on the mortality trends implies the importance of taking region- and population-specific primary prevention strategies to reduce the disease burden of LC in China.

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AUTHOR CONTRIBUTIONS

ML and JY conceived and designed the study. WH and GZ collected the data, performed the statistical analyses and drafted the first version of the manuscript under the supervision of ML. HD, GL and JY contributed to the interpretation of data and critically revised the manuscript. All authors have read and approved the final manuscript for publication.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND MATERIALS AVAILABILITY

The data that support the findings of this study are openly available in the series of DSPs annual reports; https://ncncd.chinacdc.cn/xzzq_1/202101/t20210111_223706.htm

SUPPLEMENTAL INFORMATION

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