Trends and risk factors of lung cancer in China

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Abstract

China is faced with heavy burdens caused by lung cancer, which has climbed to the top of both cancer incidence and mortality spectrums. The age-standardized rates of incidence and mortality have shown a trend of gradual up-trends in the last decades, while the crude rates rise much quickly due to the aging of population. Although the improvement in health care has contributed to better survival of lung cancer, its prognosis is still challenging. Apart from the common risk factors such as tobacco use, air pollution, and occupational hazards, some specific factors like Chinese-style cooking also have posed great threats to human health. In light of such national conditions, specific interventions should be conducted to curb the burden of lung cancer including smoking cessation, improvement of air quality, early detection and effective treatment of lung cancer.

Keywords: Burden of disease; China; lung cancer; risk factors; trend

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Introduction

Lung cancer has posed a heavy burden of disease to global health. According to the GLOBOCAN 2018 estimates (1), lung cancer is the primary cause of new cancer cases (2,093,876) and deaths (1,761,007) worldwide, with an incidence rate of 27.4/100,000 (the age-standardized incidence rate by world standard population, ASIRW: 22.5/100,000) and mortality rate of 23.1/100,000 (the age-standardized mortality rate by world standard population, ASMRW: 18.6/100,000). China has the heaviest lung cancer burden, representing 36.98% of cases and 39.21% of deaths globally (2). Given the grim situation of lung cancer burden, the government has promulgated and promoted a series of policies and activities such as environmental improvement, emission limitation, smoking prohibition, and tobacco control. Thus, the purpose of this study is to describe the current burden of lung cancer and its temporary trend in China, report the distributions of major risk factors, and put forward several preventive suggestions.

Burden and its trends of lung cancer in China

Incidence of lung cancer

National Cancer Center of People’s Republic of China is in charge of the data collection, analysis, and publishing of national cancer statistics (3). Based on the reported data from 368 qualified cancer registries in China (4), lung cancer ranked the first in male cancer incidence spectrum (24.17%) and the second in females (15.02%), as breast cancer was the most common cancer (17.10%). As is shown in Table 1, there were 787,000 new cases of lung cancer in China in 2015, accounting for 20.03% of all cancer cases. The crude incidence of lung cancer and the age-
standardized incidence rates by Chinese standard population (ASIRC) were 57.26/100,000 and 35.96/100,000, respectively.

Lung cancer incidence presented significant differences in genders and regional distributions. Lung cancer incidence in males (73.9/100,000) was about twice that of females (39.78/100,000). For both genders, the age-specific incidence remained at a low level before the age of 40 years and started to rise rapidly after that. The incidence spectrum of malignant tumors in urban and rural areas also varied in China. The ASIRC of urban (59.68/100,000) and rural areas (54.16/100,000) were similar, but the former was slightly higher.

According to the cancer registry annual report (5) compiled by National Cancer Center, the rates in the central and eastern regions were higher than those in the western region. Specifically, the highest lung cancer incidence was observed in northeast China and the lowest in northwest China. In all cases of lung cancer, 49.28% had an exact pathological classification. Adenoscarcinoma accounted for over half of lung cancer (53.40%), followed by squamous cell carcinoma (30.24%) and small cell carcinoma (11.72%) (5). Moreover, only 25.59% of the cases reported specific subsites. Among that, nearly half were distributed in the upper lobe (48.01%), followed by the lower lobe (30.74%) and the middle lobe (11.90%).

Mortality of lung cancer

Lung cancer ranked the first in the cancer death spectrum of China for both genders (male: 29.26%, female: 22.96%) and combined. In 2015, 631,000 new lung cancer deaths were reported in China, accounting for 26.99% of all cancer deaths (4). As is shown in Table 2, the crude mortality from lung cancer was 45.87/100,000, whereas the mortality showed obvious decrease after adjusted by age, and the age-standardized mortality rate by Chinese standard population (ASMRC) was 28.16/100,000. Consistent with the incidence, lung cancer mortality in Chinese males (61.52/100,000) was significantly higher than that in females (29.43/100,000), and the gap enlarged in the age group over 40 years old. The age-standardized mortality in rural areas was a little higher than that in urban areas (28.44/100,000 and 27.93/100,000, respectively). Similarly, the lung cancer mortality in the eastern and central regions was close and higher than that in the western region. Moreover, the highest lung cancer mortality was observed in northeast China and the lowest in northwest China (5).

Trends of lung cancer incidence

The Global Burden of Disease (GBD) study is the most comprehensive worldwide observational epidemiological study to date, led by the Institute for Health Metrics and Evaluation (IHME). Based on estimates by GBD study (6), the crude incidence of lung cancer in China was increasing significantly from 1990 to 2019, regardless of gender. However, the ASIRW has levelled off in recent years (Figure 1). Zhang et al. (7) also found that lung cancer incidence in China increased dramatically for both genders based on data from 22 cancer registries in China from 2000.
to 2014, but the extent of rising decreased after age standardization.

The change trends of lung cancer incidence varied by sex. It is reported that both crude incidence and ASIRC in females were on the rise with different degrees, with an average annual percent change (AAPC) of 4.5% [95% confidence interval (95% CI): 4.1%–5.0%] and 1.4% (95% CI: 1.0%–1.9%), respectively, whereas ASIRC among males decreased from 48.43/100,000 in 2000 to 46.85/100,000 in 2014 (7). Furthermore, AAPC of lung cancer incidence of rural areas in China was 1.76 times that of urban areas, which were 5.8% and 3.3%, respectively. Conversely, there was no significant change in age-standardized incidence in urban areas, and the overall incidence in male declined (7). Liu et al. reported similar trends by analysis of lung cancer incidence between 2008 and 2012 (8).

As for histological subtypes, in general, the proportion of adenocarcinoma increased significantly and has become the primary subtype, while the proportion of squamous cell carcinoma dropped gradually (9-12). However, no consistent changes were observed in surveys conducted in other areas (13,14).

The decrease on lung cancer incidence among males suggests that previous interventions to control male-related risk factors may be proved effective in some way, such as changes in smoking rate and cigarette types. And more attention should be paid to risk factors among females, mainly exposure to secondhand smoke and indoor combustion products. However, although the lung cancer incidence of both genders increased with age in all age groups, there was no noticeable change in each age group from 2000 to 2014 (7), suggesting that population aging is likely to contribute to the lung cancer burden. The regional differences may be associated with stronger controls and higher levels of policy enforcement in urban areas. Considering that the main histological subtype distinguished from gender, the inconsistency of the existing studies is likely due to the regional differences in gender composition or smoking rates, as well as the variation between their sample sizes and reporting years.

### Table 2 Mortality of lung cancer in China by gender and area*

| Areas        | Death (×10^4) | Proportion (%) | Rank | Crude incidence (1/10^5) | ASMRC (1/10^5) |
|--------------|--------------|----------------|------|--------------------------|----------------|
| Nation wide  |              |                |      |                          |                |
| Total        | 63.1         | 26.99          | 1    | 45.87                    | 28.16          |
| Male         | 43.3         | 29.26          | 1    | 61.52                    | 40.15          |
| Female       | 19.7         | 22.96          | 1    | 29.43                    | 16.77          |
| Urban areas  |              |                |      |                          |                |
| Total        | 36.6         | 27.50          | 1    | 47.45                    | 27.93          |
| Male         | 25.1         | 30.06          | 1    | 63.68                    | 39.81          |
| Female       | 11.5         | 23.19          | 1    | 30.53                    | 16.66          |
| Rural areas  |              |                |      |                          |                |
| Total        | 26.5         | 26.34          | 1    | 43.58                    | 28.44          |
| Male         | 18.3         | 28.42          | 1    | 58.79                    | 40.56          |
| Female       | 8.2          | 22.65          | 1    | 28.00                    | 16.91          |

*, Source: Report by National Cancer Center of People’s Republic of China (4); ASMRC, the age-standardized mortality rates by Chinese standard population (China National Population Census, 2000).

![Figure 1 Trends of lung cancer incidence in China between 1990 and 2019 for male, female and combined. Data were extracted from the GBD study (Available online: http://ghdx.healthdata.org/gbdresults-tool). The age-standardized rates were calculated by using the GBD world population age standard. GBD, Global Burden of Disease.](image-url)
**Trends of lung cancer mortality**

Lung cancer is one of the malignancies with the fastest increase in mortality in the last decades, and has become the leading cancer-related deaths. Figure 2 shows the trends of lung cancer mortality in China from 1990 to 2019, based on estimates by GBD study (6). To sum up, the crude mortality stayed relatively constant in the last century and showed an obvious increased trend in the latest two decades. The age-standardized mortality was also generally on an upward trend during 1990–2019, but has shown a decline trend since 2005. In fact, lung cancer has risen to the top of the death spectrum of malignant tumors in many regions of China (15,16). However, analysis based on cancer registry data pointed out there was no apparent upward trend or a significant change in lung cancer mortality (8,17).

To be specific, lung cancer mortality showed an increasing trend in males and females, and the annual percent change (APC) of female mortality was higher, which led to a decrease in the mortality ratio between genders (17). As for age-specific mortality, a downward trend has been observed among those under the age of 35 years, while lung cancer mortality of those at the age of 65 years and over has shown an upward trend (18). The reported trends in mortality of age group of 35–65 years were not consistent (19,20). From the perspective of regional distribution, Cen et al. (21) found that the age-standardized lung cancer mortality in urban areas declined from 1990 to 2017 with AAPC of −0.36%, whereas the lung cancer mortality in rural regions during the same period increased significantly. Similar findings based on cancer registry data were also given by Xin et al. (17), showing that the gap narrowed due to different trends, although the lung cancer mortality stayed substantially higher in urban areas than in rural areas. Nevertheless, Zhang et al. (18) reported an opposite trend.

As for the inconsistent trends reported by studies, one possible reason is that lung cancer mortality in China has fluctuated up and down in different degrees over several decades with the changes of risk and prevention factors, so various results were observed in different periods. Differences in the regions covered by the survey can also partly explain the inconsistency. Besides, the gap between the crude and adjusted rate was also in favor of the possible influence of population aging on the burden of lung cancer. Given distinctions among changes of each age group, decline in young people is probably a benefit of both improving medical technology and adopting of a three-early strategy (early detection, early diagnosis, and early treatment). Moreover, since older patients are more likely to be diagnosed with advanced cancer, the circumstances remain serious. A research (15) pointed out that the increase in lung cancer deaths was mainly caused by non-population factors, accounting for 70.00% of the total increase. Thus, the fact that lung cancer mortality has no distinct decline among middle-aged Chinese males can mainly ascribe to the steadily high smoking rates.

**Survival and its trends of lung cancer in China**

The overall 5-year survival rate of cancer patients in China was about 40.5%, significantly higher than that of lung cancer (19.7%), showing a comparatively poor prognosis among all cancers (22). Median survival time was generally less than 2 years (23-26). The 5-year survival rate of patients with lung cancer decreased with age at diagnosis. In addition, survival in females (25.1%) was better than males (16.8%) (22), which is likely to be related to their physiological characteristics (e.g., hormone levels), healthier lifestyles and less exposure to occupational hazards (26-28). However, some studies have conflicting opinions (29,30), pointing out that the exact effect of gender and age on lung cancer survival is still controversial. It is also found that the survival rate of urban residents was higher than those in rural areas because the former tended to have higher health awareness and better access to health services (31).
The survival may differ between each histological subtype. The prognosis of squamous carcinoma is the best, followed by adenocarcinoma with a high recurrence rate and prone to distant metastasis, and small cell carcinoma has the worst prognosis (24,26,32,33). However, other studies (34) did not find significant differences in survival among the above histological subtypes. Treatment is also an important factor for lung cancer survival. The survival rate of patients with low differentiation degree of lung cancer (stage I) was higher than those with other stage transitions (24,26,35). Furthermore, the survival of patients undergoing surgery was significantly improved (35), which may also be associated with the generally low stage.

According to the analysis conducted by Zeng et al. (22), the age-standardized 5-year relative survival of lung cancer increased from 16.1% (95% CI, 15.6–16.6) in 2003–2005 to 19.7% (95% CI, 19.3–20.1) in 2012–2015, with an APC of 1.3% (95% CI, −0.8–3.5). In both urban and rural areas of China, upward trends of lung cancer survival were observed, from 19.5% to 23.8% in urban areas and from 11.2% to 15.4% in rural areas, respectively. Similar trends were also observed in both genders, and the increase significantly accelerated after the 1990s (23,26). Such favorable results may be contributed by the continuous improvement of medical technology and adopting strategies for early detection and cancer treatment. For example, Asian populations have been found to have a higher proportion of epidermal growth factor receptor mutations and are more likely to benefit from the targeted drug, such as Gefitinib and Erlotinib (36). Therefore, research and development of targeted therapies may have made great contributions to higher survival.

**Main risk factors of lung cancer and distributions in China**

**Tobacco use**

Tobacco use is one of the major threats to public health, especially in China (37). It is estimated that 366,980 deaths (26.4%) in males and 32,510 deaths (4.0%) in females are attributable to smoking, and ever-smoking contributed to approximately 42.7% of lung cancer deaths (38). China is the largest producer and consumer of tobacco, as well as the most severe victim (39,40). Thus, Chinese government has made efforts to curb tobacco epidemic, including signing of World Health Organization (WHO) Framework Convention on Tobacco Control, developing a range of anti-smoking policies, and carrying out tobacco control activities. However, the situation of tobacco control in China is still not optimistic, particular in northern and northeastern China (41).

Since the last century, there have been several National Tobacco Epidemic Surveys (39,42-45), reporting that the current smokers were over 300 million in 2002, and still increased. Although the overall smoking rate shows a downward trend from 1996 to 2018, the current rate remains high in China, which falls short of the target rate in Health China 2030 and other plans. Furthermore, WHO reported that the western Pacific region (where China is located) was expected to experience the slowest decline between 2010 and 2025 and would soon replace South-East Asia as the region with the highest average smoking rate (46).

Moreover, teenagers are an important reserve for smokers. The smoking rate of Chinese youth aged 15−24 years has increased significantly in recent years, with more than half of young daily smokers (20–34 years old) turning to heavy smokers before the age of 20 years, so it is particularly important to monitor tobacco use among the teenagers (44). The latest nationwide surveys (47,48) found that both the proportion of junior high school students trying cigarette smoking and the current smoking rate have declined in the past five years, while more students have heard about or even tried electronic cigarette, probably owing to the curiosity about new things. Besides, lower prices and greater access to tobacco advertising pose new challenges to teen smoking control.

Exposure to secondhand (passive) smoke is also a matter of concern. Almost 70% of Chinese adults were exposed to secondhand smoke (39,42-45) and nearly 60,000 lung cancer deaths (8%) in China each year were linked to secondhand smoking (6). Higher passive smoking rates are reported even in places where smoking is explicitly prohibited, such as public transport and indoor public places. Regardless of improvements in household secondhand smoke exposure, education should be strengthened to protect the health of nonsmokers in policy-free settings.

**Indoor air pollution**

Environmental exposure to radon is the leading cause of lung cancer among nonsmokers, and the second strongest cause for people who smoke (49), which is responsible for 3.78% of lung cancer deaths in China (6). It is a colorless
and odorless radioactive gas and is ubiquitous because it is naturally occurring and can be released in rock, soil, and water. The concentration of radon is diluted to a very low level in the outdoor air and is not a serious concern (50). However, more and more gangue, steel slag, and other industrial waste being used in construction and decoration materials, resulted in a rapid increasing risk of exposure to radon for indoor workers. There are few nationwide indoor radon pollutants investigation in China. The survey (51) conducted in 26 cities of China during May 2002 and November 2004 reported that the radon level in residence in part of China was 43.8±37.7 (range: 6.6–596) Bq m\(^{-3}\), with 6.4% of the monitoring rooms higher than 100 Bq m\(^{-3}\). Another survey (52) conducted from 2006 to 2010, covering 12% of the whole Chinese population, reported that the weighted mean level by population was 30.7±4.3 (range: 5.3–183.0) Bq m\(^{-3}\), with 1.8% of the monitoring rooms higher than 100 Bq m\(^{-3}\). The ratio between results of this survey and measurements in the 1980s and 1990s was 1.80 (52), suggesting an overall increasing trend of the indoor radon level. It also found that the high radon region in China was scattered. Specifically, the content of uranium (radium) in rock soil contributed to the high level in southern regions, while in the north, it depended on the type of building, ventilation, and decoration materials (51).

Another important cause of indoor air pollution is solid fuels (mainly coal and unprocessed biomass fuel) for cooking, heating, or lighting. When incompletely combusted, they may produce carbon monoxide, particulate matter (PM), and other toxic organic compounds (including polycyclic aromatic hydrocarbons, and heterocyclic aromatic compounds), which have been reported to be associated with lung toxicity and cancer risk (53,54). According to WHO (55), about 45% of the population in China still used solid fuels in 2013, with an even higher proportion in rural areas (79%). However, there are less than 5% of population using solid fuels in most developed countries. In 2010, emissions from burning coal were classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer (IARC) (56). Considering that females usually play a leading role in domestic cooking, the high lung cancer incidence among Chinese females with a low prevalence of smoking may be explained by relatively high exposure to solid fuel smoke.

Moreover, economically underdeveloped areas tend to face problems of both low utilization of non-clean energy and poor or absent ventilation (54), increasing the local disease burden of lung cancer. Improving ventilation is also proven to be effective in the houses using clean energy since indoor air pollution is unavoidable (57,58). Also, Chinese-style cooking is a noteworthy risk factor for lung cancer because it often involves more volatilization of heated non-refined oil and exposure to more fumes (53,59).

**Outdoor air pollution**

Outdoor air pollution is also the focus of environmental issues catching global attention and has been classified as carcinogen to humans (IARC Group 1) (60). It has been reported that both long-term (61,62) and short-term (63-66) exposure to air pollutants have posed a great threat to human health, especially the cardiopulmonary system, which involved several mechanisms including genetic changes, stimulation of inflammatory, immune, and oxidative stress response, and epigenetic effects (67).

Air quality in China is among the worst in the world (63,68). In recent years, the government has adopted such strategies as bulk coal control, emission reduction, vehicle flow limitation, and other comprehensive methods to improve air quality. The ambient monitoring data collected from 388 cities across the country show that the compliance rate of annual air quality in China has doubled in the past five years, with a nearly 28% dropping in the average concentration of PM (Table 3) (69). In addition, the proportion of days when the concentration of each pollutant exceeded the standard has decreased significantly, and several pollutants (SO\(_2\), NO\(_2\), and CO) were even less than 0.1%. Such trends affirm the effectiveness of national governance. However, health damage can be observed even at a low level of exposure to outdoor pollutants. Besides, due to the co-existence of factors such as the development of coal-fired industries and the rise of automobile utilization rate, a more complex mix of air contaminants were discharged (70), which also poses new challenges to the governance.

**Occupational hazard**

The respiratory tract is a primary pathway that carcinogen enters the human body and the organ of direct action. Correspondingly, lung cancer is one of the most common types of occupational cancer. In China, there are six risk factors included in the current occupational disease catalogue, covering asbestos (all forms), bis (chloromethyl) ether and chloromethyl methyl ether, arsenic and inorganic arsenic compounds, chromium (VI) compounds, erionite, and coke oven emission, which have been basically
identified as a class I carcinogen by IARC (71). Those working in light industries, chemical industries, and coke oven workers tend to face higher exposure to such occupational hazards, given the wide range of sources including raw materials, end products, and unexpected by-products.

As reported in the China Statistical Yearbook 2019 (72), more than 120 million people were employed in mining, manufacturing, construction, and energy supply industries, which suggests that there are still quite numbers of people facing the risk of developing occupational lung cancer. According to the annual occupational disease report issued by the Chinese Center for Disease Control and Prevention (73), taking no account of unidentified cases, there were dozens of occupational lung cancer cases every year, accounting for about half of all diagnosed occupational tumors. In addition, other occupations have not yet been included but are also at high risk of lung cancer, for instance, traffic police, welding workers, painters, and workers in metal smelting industry and rubber factory.

Other risk factors of lung cancer

Given that cancer is the result of long-term interaction between internal factors and external environment, there are also other risk factors that may contribute to the burden of lung cancer. For one thing, dietary habits, such as drinking water containing arsenic, taking high-dose beta-carotene supplements for smokers, and consuming red meat, processed meat and alcoholic drinks, have been reported to increase the risk of lung cancer (74). It is reported that about 27% of lung cancer deaths in China can be attributable to low vegetable intake (38). For another, internal factors are also of great importance, including genetics (41) and a history of lung disease (mainly emphysema, chronic bronchitis, tuberculosis or pneumonia) (75), which have been reported as independent causes of lung cancer.

Prevention strategies for lung cancer

Smoking cessation

Primary prevention is also the most fundamental prevention, aiming to reduce exposure to risk factors. The priority is to control smoking rates and secondhand smoke exposure. The incidence of lung cancer in the United States has declined in recent years, which is significantly attributable to the effective control of tobacco use (76). Considering that China has the fastest-growing cigarette ability to pay on a world scale (77), there is still much room for the flowing of tobacco tax, which will exert a constraint effect on people of all ages. Smoking bans in public places and some special places should also be strengthened to create more smoke-free environment. In addition, comprehensive education on dangers of tobacco use,
together with a total ban on tobacco advertising is also urgently needed, particularly for teenagers.

**Improvement in air quality**

First, more publicity should be given to the dangers of radon, because many people have not yet paid attention to this invisible health killer. At the same time, the experience of the United States should be learned (78). In this regard, a special department for examining and improving indoor radon content should be established to monitor radon exposure in all regions of the country and take measures timely. Setting standard should also be strengthened, such as the approval of construction in areas with high background contamination and the level limit of radon level in building materials.

Second, it has been reported that a significant reduction occurred in mortality from cardiopulmonary diseases after withdrawing solid fuels (57). Although the utilization rate of clean energy in China has been increasing from 43% to 64% between 2000 and 2018 (79), there is still a big gap between China and the United States, Europe, and other developed countries (with a proportion over 95%), indicating that promoting the use of clean energy (e.g., electricity and natural gas) can effectively alleviate the burden of lung cancer disease in China, which is of great urgency.

Third, even though the current air quality has been improved to a certain extent, the pollutants may cause damages to health even at low levels of exposure (within the recommended range), so the existing comprehensive treatment plan should be maintained in consideration of the rapid ongoing development of urbanization and modern industry in China. In addition, more importance should be attached to the monitoring and analysis of air pollutants in order to better deal with the degradation of complex compounds and the exploration of their sources.

**Early detection and effective treatment**

Early diagnosis and treatment of lung cancer were also of vital significance. The prognosis of lung cancer was poor because most cases were initially asymptomatic and typically discovered at advanced stages (80). A large prospective randomized screening trial found a 20% decrease in lung cancer mortality in the screening group by low-dose computed tomography, compared with unscreened group (81). This result was also verified by another large-scale randomized trial conducted in Netherland (82).

There are already several ongoing lung cancer screening programs in China, including Early Detection and Early Treatment of Cancer in Urban Areas, and Early Detection and Early Treatment of Cancer in Rural Cancer. It will be of great help for such programs being promoted on a larger scale. Besides, attention should be paid to monitoring the health status of high-risk groups, such as regular medical examinations and job rotation among relevant occupational groups, to reduce morbidity and mortality. For lung cancer patients detected through screening, it is responsible for public health providers to urge them to receive standardized treatment as early as possible, so as to prolong their survival.

**Conclusions**

Lung cancer incidence and mortality presented an increased trend over the past decade, which can partly be attributed to the exposure to those persistent-existing risk factors, including high smoking rate, the use of solid fuel, indoor radon level. Additionally, emerging health threats continue to threaten human health. Therefore, the Chinese government is supposed to synthesize all aspects of measures, such as etiology control, the implementation of lung cancer screening and increasing the investment on researches of treatment and rehabilitation, to change this situation.

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**Footnote**

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