

ORIGINAL ARTICLE

Small cell lung cancer (SCLC) incidence and trends vary by gender, geography, age, and subcategory based on population and hospital cancer registries in Hebei, China (2008–2017)

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Keywords

Cancer registry; hospital-based; incidence; population-based; small cell lung cancer (SCLC).

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Abstract

Background: Lung cancer is the leading cause of morbidity and mortality worldwide. Small cell lung cancer (SCLC) has been determined to be the most lethal lung malignancy. Few studies have previously analyzed the epidemiological characteristics of SCLC in China. This study analyzed the epidemiological characteristics of SCLC aiming to provide a reference for the prevention of SCLC in Hebei Province.

Methods: The epidemiological characteristics of SCLC using lung cancer data based on population and hospital cancer registries in Hebei Province between 2008 and 2017 were analyzed.

Results: The proportion of both population- and hospital-based SCLC cases displayed a significant increasing trend. Moreover, the proportion of males was higher than that for female based on population- and hospital-based cases. The proportion of hospital-based SCLC cases in counties was higher than that in cities, whereas there were no significant regional differences between cities and counties based on population. The proportion of both population- and hospital-based SCLC cases decreased consistently with increasing age. There was a difference between population- and hospital-based distribution of subcategories of SCLC.

Conclusions: Significant increases in the proportion of both population- and hospital-based SCLC cases over recent years, particularly in males and in patients aged over 55 years, were observed. Research on the pathogenesis of SCLC in these patients and prevention is urgently required.

Introduction

As predicted by Globocan in 2018, lung cancer is the most common cancer and the leading cause of mortality, with 2.1 million new lung cancer cases and 1.8 million deaths worldwide. Lung cancer has been reported to be the second leading cancer in 37 countries and leading cause of cancer death among men in 93 countries, including China.¹ Lung cancer is also the leading cause of morbidity and mortality in China and Hebei province.² The most common histological types of lung cancer are adenocarcinoma, squamous cell carcinoma, adenosquamous, large cell carcinoma and small cell carcinoma (SCLC).

SCLC remains one of the most lethal lung malignancies. There are currently few therapeutic options for patients with SCLC. Moreover, the five-year survival rate has been reported to be less than 7%.³ Many studies have reported characteristics of the histological types of lung cancer, but few have analyzed the epidemiology of SCLC in China. Hence, in our study we analyzed the epidemiological characteristics of SCLC using lung cancer data based on population and hospital cancer registries in Hebei Province between 2008 and 2017. The aim of the study is to provide a reference for the prevention and control of SCLC in Hebei Province.

Table 1 Distribution of sex of population- and hospital-based SCLC cases, 2008–2017

Gender	Population-based (2010–2015)			Hospital-based (2008–2017)		
	No. of lung cancer	No. of SCLC	Proportion	No. of lung cancer	No. of SCLC	Proportion
Male	16 394	1335	8.1%	17 041	2444	14.3%
Female	8500	586	6.9%	8412	1020	12.1%
Both sexes	24 894	1921	7.7%	25 453	3464	13.6%

Table 2 Lung cancer incidence in Hebei Province, 2008–2017

	Population-based cancer registry					Hospital-based cancer registry				
	Lung cancer cases	SCLC cases	%	MV%	DCO%	Lung cancer cases	SCLC cases	%	MV%	
2008	—	—	—	—	—	2037	235	11.5	64.7	
2009	—	—	—	—	—	1707	202	11.8	68.8	
2010	1522	110	7.2	70.8	6.6	1885	207	11.0	71.5	
2011	2077	132	6.4	70.7	7.3	2126	300	14.1	99.9	
2012	2368	163	6.9	75.2	6.1	2334	288	12.3	100.0	
2013	4938	322	6.5	73.0	4.2	2828	379	13.4	100.0	
2014	7039	513	7.3	72.3	3.8	3019	405	13.4	100.0	
2015	6950	681	9.8	70.9	2.5	3043	466	15.3	100.0	
2016	—	—	—	—	—	3206	489	15.3	100.0	
2017	—	—	—	—	—	3268	493	15.1	100.0	
All	24 894	1921	7.7	72.1	4.2	25 453	3464	13.6	91.0	

Methods

Cancer registry data source

The hospital-based cancer registry collects and stores information on cancer cases treated by local medical institutions to understand and evaluate the diagnosis and treatment of cancer patients. Population-based cancer registries collect data on each individual cancer case in the population in an area to describe the incidence of cancer in the population as a whole. The Hebei Provincial Cancer Registry Center was established in 2009 and mainly responsible for data collection from 2010. The latest data collected were from 2015. A total of 33 population-based cancer registries in Hebei Province submitted the registration data from 2010 to 2015 and the data of 21 population-based cancer registries were qualified as pooled data for final analysis. These cancer registries covered a population of 50 282 025 person-years (25 536 807 males and 24 746 218 females), accounting for 11.46% of the Hebei provincial population. The 21 population-based cancer registries comprised four cities (Baoding, Qinhuangdao, Cangzhou and Shijiazhuang), and 17 counties (Cixian, Shexian, Qianxi, Wuan, Zhanhuang, Fengning, Xinji, Xingtai county, Zhangbei, Shijiazhuang suburb county, Neiqiu, Anguo, Xuanhua, Haixing, Wangdu, Qianan and Lincheng).

The Fourth Hospital of Hebei Medical University, also known as the Tumor Hospital of Hebei, is a large and comprehensive hospital. We collected the hospital-based data of all lung cancer patients diagnosed at the Fourth Hospital of Hebei Medical University between 1 January 2008 and 31 December 2017.

All cancer cases were classified according to the International Classification of Diseases for Oncology, third edition (ICD-O-3), and the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10). Invasive cases of lung cancer (ICD10: C33-C34) were extracted and analyzed from the overall cancer database. SCLC was defined by using International Classification of Diseases for Oncology, Version 3, code as follows: SCLC (8041 and 8043-8045).

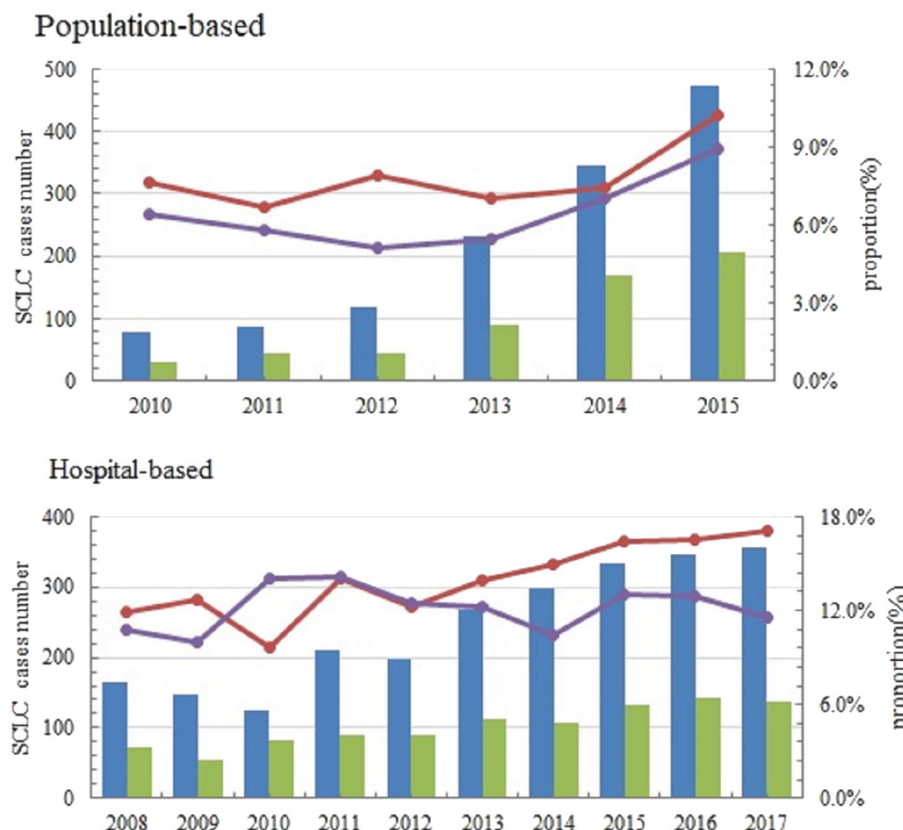
Quality control

Lung cancer data underwent quality control based on the criteria of “Guideline for Chinese Cancer Registration” and “Cancer Incidence in Five Continents Volume XI”⁴ by the International Agency for Research on Cancer/International Association of Cancer Registries (IARC/IACR). The percentage of cases morphologically verified (MV% 66%–85%), the percentage of cases identified with death certification only (DCO% <10%), as well as mortality to incidence rate ratio (M/I 0.6–0.8) were used to evaluate the completeness, validity and comparability of data quality.

Statistical analysis

The IARCrg Tools software issued by IARC and IACR was used for population-based and hospital-based data checking and evaluation. SAS software (version 9.3) was used to review the primeval data and evaluated the validity, reliability, completeness and comparability of the data

Figure 1 Distribution of sex of SCLC based on population (—) Male cases, (—) Female cases, (—) Male proportion, and (—) Female proportion and hospital (—) Male cases, (—) Female cases, (—) Male proportion, and (—) Female proportion, 2008–2017.



quality. Analyzing the SCLC data complied with cancer registration quality control standards. The pooled SCLC data were stratified by calendar year, gender (male/female), area (city/county), age groups (<45, 45–54, 55–64, 65–74 and 75+ years), and subcategories (C33, C34.0–C34.3, C34.8 and C34.9). The data were analyzed using SPSS version 22.0 (IBM, Armonk, NY, USA), including a descriptive analysis of characteristics for 2008 to 2017.

Results

SCLC incidence based on population and hospital

There were 24 894 new lung cancer cases based on the population in Hebei Province from 2010 to 2015. The SCLC cases were 1921, which accounted for 7.7% of all lung cancer cases, and there were 25 453 new lung cancer cases diagnosed in the Fourth Hospital of Hebei Medical University from 2008 to 2017. Among these, SCLC cases were 3464, which accounted for 13.6% of all lung cancer cases. The proportion of hospital-based new SCLC cases in 2008–2017 was higher than that of population-based cases in 2010–2015 for both sexes (Table 1 and 2).

SCLC incidence by gender

The proportion of population-based new SCLC cases displayed a significant increasing trend for both sexes from 2010 to 2015. In 2010, the proportion of SCLC was 7.6% in males, and increased to 10.2% in 2015, while the proportion of SCLC in females increased from 6.4% to 8.9% during 2010–2015. The proportion in males was higher than that for females during the whole period. The proportion of hospital-based new SCLC cases also simultaneously increased for both sexes from 2008 to 2017. In 2008, the proportion of SCLC was 11.9% in males, and increased to 17.1% in 2017. For females, the proportion of SCLC increased from 10.8% to 11.6% during 2010–2015. The overall proportion for males was higher than that for females overall, apart from when it was equal in 2011 and 2012 (Fig 1).

Geographical SCLC incidence

Despite the proportion of population-based SCLC cases revealing a trend of increase in cities and counties, there were no significant regional differences between cities and counties. In cities, the proportion of population-based SCLC cases was 9.2% in 2010, and increased to 15.6% in

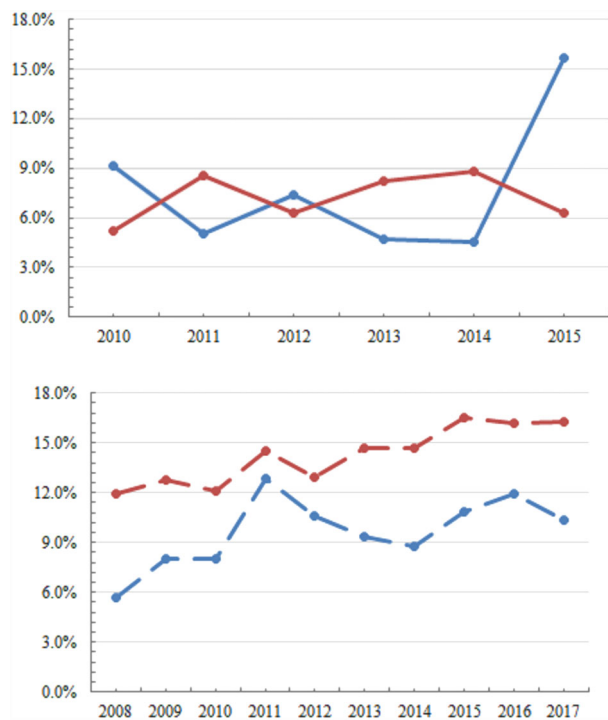


Figure 2 Geographical distribution of SCLC in Hebei Province based on population (—●—) City (population-based), and (—●—) Country (population-based) and hospital (—●—) City (hospital-based), and (—●—) Country (hospital-based), 2008–2017.

2015, while the proportion of population-based SCLC cases in counties increased relatively slowly from 5.2% to 6.3% during 2010–2015. The proportion of hospital-based SCLC cases was notably different from that of population-based SCLC cases. The proportion of hospital-based SCLC cases in counties was higher than that in cities from 2008 to 2017. Moreover, in cities, the proportion of hospital-based SCLC cases was 5.7% in 2008, and increased to 10.4% in 2017, while the proportion of hospital-based SCLC cases in counties also increased relatively slowly, from 12.0% to 16.3% during 2008–2017 (Fig 2).

SCLC incidence by age group

In total, the proportion of both population-based and hospital-based SCLC cases decreased consistently with increasing age. According to this study based on population, the proportion of SCLC age group younger than 45-years-old was the highest (10.9%), followed by age group 45–54 years (9.4%) and 55–64 years (9.5%) during 2010–2015. The proportion of SCLC between 65- and 74-years-old was 7.0%, and the proportion over 75-years-old was the smallest at 4.9%. The proportion of population-based SCLC age group younger than 45-years-old decreased from 14.3% (2010) to 7.0% (2012), then increased to 10.5%

(2015) and it also decreased from 12.9% (2010) to 11.1% (2015) for age group 45–54 years. However, it increased for age group 55–64, 65–74 and over 75 years from 7.8%, 5.6% and 2.1% in 2010 to 11.6%, 9.1% and 8.0% in 2015.

Similar to the population-based SCLC, the highest proportion of hospital-based SCLC cases during 2008–2017 was the age group younger than 45-years-old (18.8%), which was higher than the group aged 45–54 years (16.0%) and 55–64 years (13.8%). The second lowest proportion of SCLC between 65- and 74-years-old was 12.1%, while the lowest age group of over 75 years was 8.1%. The proportion of hospital-based SCLC age group younger than 45-years-old decreased from 28.2% (2010) to 13.5% (2015) and for age group 45–54 years it remained basically stable (15.4% in 2010 vs. 16.0% in 2015). However, it increased in age group 55–64, 65–74 and over 75 years from 10.5%, 7.6% and 2.7% in 2010 to 16.0%, 14.1% and 13.1% in 2015 (Fig 3).

SCLC incidence by subcategories

According to the results, there was a difference between population- and hospital-based distribution of subcategories of SCLC. The same point was that the proportion of SCLC for C34.0 and C33 based on population and hospital was the highest (14.7% & 29.7%) and the lowest (0%), respectively. Other subcategories of SCLC were markedly different. The proportions of population-based SCLC cases for C34.3, C34.1, C34.2, C34.9 and C34.8 were 10.7%, 10.0%, 6.9%, 6.8% and 6.3% in 2010–2015, respectively, while those of hospital-based cases were 9.8%, 6.6%, 8.2%, 17.9% and 15.8%, in 2008–2017, respectively (Fig 4).

Discussion

Lung cancer in males is the leading cause of death in most countries in Eastern Europe, Western Asia, Northern Africa, and specific countries in Eastern Asia (China) and South-Eastern Asia. For females, lung cancer has also been reported to be the leading cause of cancer death in 28 countries.¹ There is a great worldwide lung cancer burden. Hebei Province also suffers a heavy disease burden of lung cancer and a noticeable increasing trend has been observed over the past 40 years.⁵ SCLC is an aggressive neuroendocrine tumor with early dissemination and poor prognosis, accounting for 15%–20% of lung cancer cases and approximately 200 000 deaths each year. Most cases of SCLC are inoperable, resulting in fewer biopsies in order to study the biology of SCLC.⁶ It is particularly important to determine the epidemiological characteristics of SCLC. This study analyzed the epidemiological characteristics of SCLC based on population and hospital cancer registries in Hebei Province during 2008–2017, aiming to offer a scientific basis for prevention and control strategies of SCLC in Hebei Province.



Figure 3 Distribution of age group of SCLC in Hebei Province based on population (■ <45, ■ 45–54, ■ 55–64, ■ 65–74 and hospital (■ <45, ■ 45–54, ■ 55–64, ■ 65–74, and ■ ≥75, 2008–2017.

This study showed that the proportion of both population- and hospital-based SCLC cases displayed a significant increasing trend. Moreover, the proportion of males was higher than females based on population- and hospital-based cases. This illustrated data stability and reliability of population- and hospital-based SCLC cases. The proportion of hospital-based cases was 1.77 times higher than those based on population. One reason for this may be that there were possibly fewer SCLC cases, or that the collection channel of SCLC based on population was diverse. There were four main collection channels: medical institutions, medical insurance, new rural cooperative medical system and cause of death monitoring. Only the identified pathologic types from medical institutions had a higher proportion. Other channels had fewer identified pathologic types. There was a difference in geographical distribution of SCLC based on population and hospital in

Hebei Province. The proportion of hospital-based SCLC cases in counties was higher than that in cities, whereas there were no significant regional differences between cities and counties based on population. The reason for this was that it was likely more areas were covered based on hospital cases. The population-based cancer registry areas were fixed and limited. The population-based cancer registries should have certain conditions, such as covering the entire population, establishing an improved and normative all-cause monitoring system, and having good quality of data. The patients coming to the hospital were from many different areas, and many were not population-based cancer registry areas. Irrespective of age, the proportion of both population-based and hospital-based SCLC cases decreased consistently with increasing age. A downward trend was seen in the proportion of SCLC in the age group younger than 45-years-old. It increased in the patients in the older

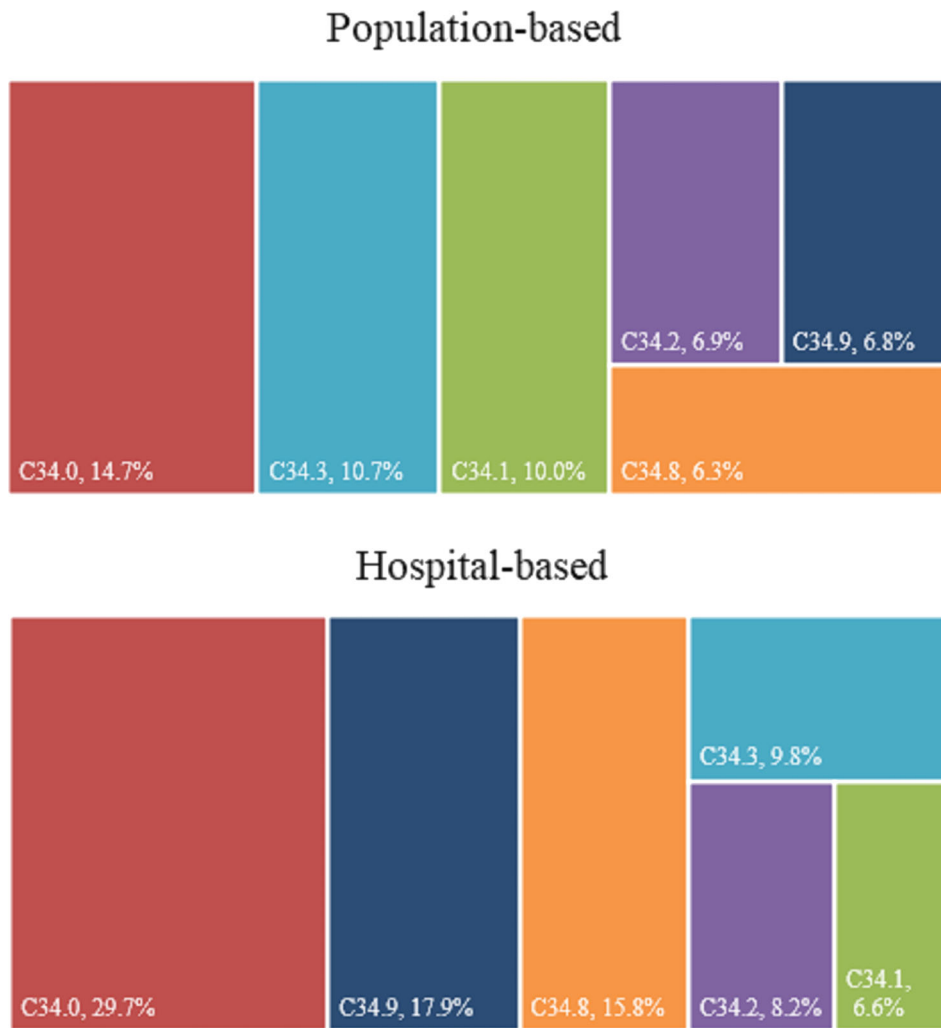


Figure 4 Distribution of subcategories of SCLC in Hebei Province based on population (■ C33, ■ C34.0, ■ C34.1, ■ C34.2, ■ C34.3, ■ C34.8, and ■ C34.9 and hospital (■ C33, ■ C34.0, ■ C34.1, ■ C34.2, ■ C34.3, ■ C34.8, and ■ C34.9, 2008–2017.

age group. This result is the same as the results of analysis reported in Sichuan Province and a SEER database analysis of elderly SCLC patients in the United States.^{7,8} The same point was that the proportion of SCLC C34.0 and C33 based on population and hospital was the highest (14.7% & 29.7%) and the lowest (0%), respectively, and indicates that the anatomical site of SCLC is usually located in the main bronchus of the lung. This provides a reference for the accurate diagnosis and treatment of SCLC.

It is well known that lung cancer is the leading cause of cancer mortality in men and women worldwide. About 90% of lung cancer cases are caused by smoking and the use of tobacco products.^{9,10} Smoking is also the main risk factor that is responsible for the high mutation burden of SCLC.^{11,12} The decrease in cigarette smoking in Western societies has reduced the incidence of SCLC over the last 20 years.¹³ The results of this study showed that the increase in the incidence of SCLC was closely related to the increased percentage of smokers and the change in cigarette composition. Cigarette smoking is a very strong risk factor for the development of

SCLC. One study showed that more than 90% of patients with SCLC were current or former smokers and the risk was associated with the duration and intensity of smoking.¹³ Another study reported an increased odds ratio (OR) for the development of SCLC based on the number of cigarettes consumed daily and the age individuals starting smoking. The OR has been reported to decrease from 14.5 in current smokers to 10.9 in patients who quit smoking for fewer than four years to 2.2 in patients with more than 25 years of abstinence.¹³ An earlier meta-analysis assessed the influences of smoking on different histologic types of lung cancer. The results showed that, compared with large cell lung cancer and adenocarcinoma, SCLC is more strongly associated with current and former smokers. The current smokers with SCLC had the highest OR (72.5). The OR value of current female smokers (79.9) was higher than that of male smokers (20.3). Therefore, the decrease in the proportion of smokers may be the reason for the proportionally higher decrease of SCLC. Moreover, the histological type of SCLC and smoking were closely correlated.¹³ According to the latest Chinese

Adult Tobacco Survey in 2018 released by the Chinese Center for Disease Control and Prevention, the smoking rate of people over the age of 15 in China fell further to 26.6% in 2018, with the male smoking rate falling to 50.5% and the female smoking rate falling to 2.1%.¹⁴ However, the smoking rate among men was still at a high level, and the smoking rate in rural areas was significantly higher than that in urban areas. China, India, and Indonesia, the three leading countries in total number of male smokers, accounted for 51.4% of the world's male smokers in 2015.¹⁵ The latest data showed that in Hebei Province, the overall smoking rate among adult residents was 29.1%, and 61.4% for males and 6.4% for females, respectively. City residents had a smoking rate of 27.6%, which was similar to those living in rural areas (29.7%). The adult smoking rate in Hebei Province was relatively high. Many challenges and difficulties exist in tobacco control.¹⁶ There has been an increase in the awareness of the public of the dangers of smoking, but the willingness to quit smoking is not strong, and the rate of smoking cessation has not changed significantly. However, the proportion of public support for smoke-free environmental policies has further increased. It is worth noting that the situation of tobacco control among young people is still severe, and that controlling tobacco smoking is a key factor in the prevention of SCLC.

In conclusion, this study describes the epidemiological characteristics of SCLC using lung cancer data based on population and hospital cancer registries in Hebei Province between 2008 and 2017. The proportion of SCLC cases displayed a significantly increasing trend with the proportion of males being higher than females. The proportion of SCLC cases decreased consistently with increasing age. There was a downward trend in the proportion of SCLC in the age group younger than 45-years-old, but this increased in patients in the older age group. The proportion of hospital-based SCLC cases in counties was higher than those recorded in cities. On the basis of these conclusions, the aim should be to focus on primary and secondary prevention of the predominant population developing SCLC. Studies for the prevention and control of SCLC, especially for smoking prevalence and lung cancer screening, should be urgently addressed in the future.

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Disclosure

The authors declare that there are no competing interests.

References

- 1 Bray F, Ferlay J, Soerjomataram I *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68** (6): 394–424.
- 2 He Y, Liang D, Li D *et al.* Cancer incidence and mortality in Hebei province, 2013. *Medicine (Baltimore)* 2017; **96** (26): e7293.
- 3 Tsoukalas N, Aravantinou-Fatorou E, Baxevanos P *et al.* Advanced small cell lung cancer (SCLC): New challenges and new expectations. *Ann Transl Med* 2018; **6** (8): 145.
- 4 Bray F, Colombet M, Mery L *et al.* *Cancer Incidence in Five Continents*, Vol. **XI**. IARC Scientific Publications, Lyon 2017; 166.
- 5 He Y, Li D, Song G *et al.* Lung cancer burden has increased during the last 40 years in Hebei Province. *China Thorac Cancer* 2016; **7** (3): 323–32.
- 6 Hodgkinson CL, Morrow CJ, Li Y *et al.* Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer. *Nat Med* 2014; **20** (8): 897–903.
- 7 Zhang X, Wu L, Xu Y *et al.* Trends in the incidence rate of lung cancer by histological type and gender in Sichuan, China, 1995–2015: A single-center retrospective study. *Thorac Cancer* 2018; **9** (5): 532–41.
- 8 Abdel-Rahman O. Changing epidemiology of elderly small cell lung cancer patients over the last 40 years; a SEER database analysis. *Clin Respir J* 2018; **12** (3): 1093–9.
- 9 Lemjabbar-Alaoui H, Hassan OU, Yang YW *et al.* Lung cancer: Biology and treatment options. *Biochim Biophys Acta* 2015; **1856** (2): 189–210.
- 10 O'Keefe LM, Taylor G, Huxley RR *et al.* Smoking as a risk factor for lung cancer in women and men: A systematic review and meta-analysis. *BMJ Open* 2018; **8** (10): e021611.
- 11 Pleasance ED, Stephens PJ, O'Meara S *et al.* A small-cell lung cancer genome with complex signatures of tobacco exposure. *Nature* 2010; **463**: 184–90.
- 12 Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: What we know, what we need to know and the path forward. *Nat Rev Cancer* 2017; **17** (12): 725–37.
- 13 Govindan R, Page N, Morgensztern D *et al.* Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006; **24**: 4539–44.
- 14 Chinese Center for Disease Control and Prevention. Chinese Adult Tobacco Survey in 2018. 2019. Available from URL: http://www.chinacdc.cn/yw_9324/201905/t20190530_202932.html (in Chinese.)
- 15 GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: A systematic analysis from the global burden of disease study 2015. *Lancet* 2017; **389** (10082): 1885–906.
- 16 Wang L, Zhou L, Zhang J *et al.* Status survey on smoking behavior among adult residents in Hebei Province. *Chin J Health Educ* 2008; **10**: 739–41 (in Chinese.).