Lung Cancer 128 (2019) 91–100

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Clinical characteristics and medical service utilization of lung cancer in China, 2005–2014: Overall design and results from a multicenter retrospective epidemiologic survey

Ju-Fang Shi[a,1,*], Le Wang[a,1], Ning Wu[b], Jun-Ling Li[c], Zhou-Guang Hui[d], Shang-Mei Liu[e], Bo-Yan Yang[f], Shu-Geng Gao[g], Jian-Song Ren[a], Hui-Yao Huang[a], Juan Zhu[a], Cheng-Cheng Liu[a], Jin-Hu Fan[h], Shi-Jun Zhao[b], Pu-Yuan Xing[c], Ye Zhang[d], Ning Li[f], Wen-Dong Lei[g], De-Bin Wang[i], Yun-Chao Huang[j], Xian-Zhen Liao[k], Xiao-Jing Xing[l], Ling-Bin Du[m], Li Yang[n], Yu-Qin Liu[o], Yong-Zhen Zhang[p], Kai Zhang[q], You-Lin Qiao[h], Jie He[g], Min Dai[a,*], on behalf of the LuCCRES Group

[a] *Office of Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[b] *Department of Diagnostic Radiology (and PET-CT Center), National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[c] *Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[d] *Department of Radiation Oncology (and Department of VIP Medical Services), National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[e] *Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[f] *Department of General Medicine, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[g] *Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[h] *Department of Cancer Epidemiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[i] *School of Health Services Management, Anhui Medical University, Hefei, China*
[j] *Yunnan Cancer Hospital, Kunming, China*
[k] *Hunan Office for Cancer Control and Research, Hunan Cancer Hospital, Changsha, China*
[l] *Liaoning Office for Cancer Control and Research, Liaoning Cancer Hospital & Institute, Shenyang, China*
[m] *Zhejiang Office for Cancer Control and Research, Zhejiang Cancer Hospital, Hangzhou, China*
[n] *School of Public Health, Guangxi Medical University, Nanning, China*
[o] *Cancer Epidemiology Research Center, Gansu Provincial Cancer Hospital, Lanzhou, China*
[p] *Department of Epidemiology, Shanxi Provincial Cancer Hospital, Taiyuan, China*
[q] *Department of Medical Examination for Cancer Prevention, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

ARTICLE INFO

Keywords:
Lung cancer
Clinical epidemiology
Medical service utilization
Medical expenditure
China

ABSTRACT

Objectives: This study aimed to explore the clinical profile and its trajectory of lung cancer on clinicopathological characteristics and medical service utilization in China.
Methods: Patients diagnosed with primary lung cancer in tertiary hospitals during 2005–14 were selected from seven geographic regions of China. Data on clinical characteristics and medical service utilization was extracted

Abbreviations: SES, socio-economic status; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging; CNY, Chinese Yuan; 95% CI, 95% confidential interval; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; NRCMS, new rural cooperative medical system; SD, standard deviation

* Corresponding authors at: 17 Panjiayuan Nanli, Chaoyang District, Beijing, 100021, China.
E-mail addresses: daimin2002@hotmail.com (M. Dai), shijf@cicams.ac.cn (J.-F. Shi).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.lungcan.2018.11.031
Received 2 July 2018; Received in revised form 14 November 2018; Accepted 23 November 2018

from medical record, and the ten-year trends were explored.
Results: A total of 7184 patients were included, the mean age was 58.3 years and the male-to-female-ratio was 2.7. From 2005 to 2014, the proportion of ≥60 year-old patients increased from 41.2% to 56.2% ($p < 0.001$). The smoking rate decreased from 62.9% to 51.1% ($p < 0.001$) and the proportion of females increased from 23.5% to 31.9% ($p < 0.001$). The proportion of advanced stage increased from 41.9% to 47.4% ($p < 0.001$). Adenocarcinoma's proportion increased from 36.4% to 53.5% ($p < 0.001$) while that of squamous carcinoma decreased from 45.4% to 34.4% ($p < 0.001$). The application of chest X-ray dropped from 50.2% to 31.0% ($p < 0.001$) but that of chest CT increased from 65.8% to 81.4% ($p < 0.001$). As two main treatment options, chemotherapy ($p = 0.290$) and surgery ($p = 0.497$) remained stable. The medical expenditure per patient increased from 40,508 to 66,020 Chinese Yuan ($p < 0.001$).
Conclusions: The sustaining high smoking exposure, increasing proportion of female patients, advancing clinical stage, shifting of predominant pathology and increasing medical expenditure demonstrate potential challenges and directions on lung cancer prevention and control in China. Despite substantial changes of clinical characteristics, main treatment options remained unchanged, which needs further investigation.

1. Introduction

Lung cancer is the leading cause of cancer incidence and mortality throughout the world, with the estimate of 2.1 million new cases and 1.8 million death cases, of which China contributed 37.0% new cases and 39.2% death cases [1]. According to the population-based cancer registry data, lung cancer is the most common cancer in China, and the incidence in females kept increasing in the past decade [2]. Moreover, lung cancer brought 13.1 million disability-adjusted-life-years to China in 2016, and it has taken the first place among all neoplasms since 2005 [3]. China faces up with severe predicament of lung cancer burden.

Lung cancer is known as a cancer with poor prognosis, and the 5-year survival rate in Chinese population is only 19.7%, similar to the data from the United States (US), Australia, and Europe countries [4–6]. The survival rate can vary conspicuously among different demographic and clinical characteristics [4,7]. For instance, the 5-year relative survival rate of localized lung cancer was 50.7% in Americans while the rate of distant stage was only 4.3% [4]. Hence, to grip the population-level lung cancer profile in terms of the distribution of socio-demographic characteristics and clinicopathologic features is fundamental for both the decision of medical intervention and the prediction of patients' prognosis. However, nationwide evidence on detailed lung cancer clinical profile in China was still scarce. In addition, more precise imaging techniques and curative treatment options for lung cancer patients has been continuously developed and applied in clinical practice in western countries [8,9]. The adherence of clinical practice to released guidelines was reported by very limited publications from single hospital in China [10–12]. It's worthy to illustrate the adherence from a larger scale population in the longer term.

Meanwhile, with substantially abundant number of newly diagnosed patients, the economic burden caused by lung cancer is another key issue that both the government and the individual families care about [13]. The United States has established a well-designed platform for the analysis and projection of population-level cost of cancer, which provides valuable evidence for policy-making and resource allocation [14]. However in China, only sporadic studies reported short-term medical expenditure of lung cancer patients diagnosed at local medical centers, and the inconsistency in the data source and analytic method [15] made it difficult to estimate the nationwide burden.

Hence, this multicenter retrospective epidemiological study aimed to investigate the current status and the time shift of lung cancer clinical profile in China, including the sociodemographic and clinicopathologic characteristics, the use of diagnostic techniques and treatment regimes, and the medical expenditure.

2. Material and methods

2.1. Study design and sites

Partially base on the platform of the Cancer Screening Program in Urban China (CanSPUC) [16], this hospital-based multi-center lung cancer retrospective clinical epidemiological survey (LuCCRES) was conducted from March 2015 to August 2016. According to the definition of traditional administrative districts taking the urbanization and economic development level into consideration by the National Bureau of Statistics, seven geographic regions were stratified (North, Northeast, Central, South, East, Northwest, and Southwest) in China. Among the total of 16 provinces covered by the CanSPUC program, a convenience sampling was used to select one or two tertiary hospital from each geographic region, mainly considering the capability of comprehensive treatment for lung cancer and the completeness of medical record system in local hospitals. Finally, eight tertiary provincial cancer hospitals were included in this study (shown in Supplemental Fig A1), the corresponding hospitals were Shanxi Cancer Hospital (North), Liaoning Cancer Hospital (Northeast), Anhui Cancer Hospital and Zhejiang Cancer Hospital (East, the only region with two sites), Hunan Cancer Hospital (Central), Guangxi Cancer Hospital (South), Yunnan Cancer Hospital (Southwest), and Gansu Cancer Hospital (Northwest). The study protocol was approved by the Institutional Review Board of the Cancer Hospital of Chinese Academy of Medical Sciences (Approval No. 15-071/998).

2.2. Study participants

The patients were primarily diagnosed by pathology as lung cancer between January 2005 and December 2014. Patients were included if they underwent main treatments in survey hospital (patients only undertook diagnosis or follow-up clinics without treatment were excluded) with complete medical record data including key personal information, diagnostic information (pathologic TNM stage or clinical TNM stage), treatment regimens, and pathologic characteristics for lung cancer.

2.3. Sampling method

One month was randomly chosen to represent one year for each hospital by allocating a random number, and 100 cases for each month were requested according to previous experiences [17,18]. A set of random numbers were generated for eight provinces by using the UNIFORM (n) function in the SAS software, and the rank of random number was allocated as the initial month in 2005 for each hospital. If the number of eligible cases in selected month was less than 100, we extended to review cases of the next month for supplement. Allowing for the situation of Spring Festival in China, patients were much fewer in January and February than other months and potential bias might exist, patients visiting at January and February were excluded. Detailed sampling results were shown in Table 1.

Table 1
Distributions of included 7184 lung cancer cases by geographic region and calendar year.

Calendar year	Inclusion rate[a]	Total		Northeast (Liaoning)		North (Shanxi)		East (Zhejiang)		East (Anhui)		Northwest (Gansu)		Central (Hunan)		South (Guangxi)		Southwest (Yunnan)	
		n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]	n	%[b]
Overall	50.3%	7184	100.0	997	13.9	488	6.8	985	13.7	999	13.9	743	10.3	999	13.9	963	13.4	1010	14.1
2005	63.0%	684	100.0	96	14.0	23	3.4	97	14.2	100	14.6	67	9.8	100	14.6	98	14.3	103	15.1
2006	47.6%	657	100.0	99	15.1	11	1.7	97	14.8	88	13.4	66	10.0	99	15.1	99	15.1	98	14.9
2007	55.5%	646	100.0	99	15.3	20	3.1	90	13.9	96	14.9	39	6.0	100	15.5	99	15.3	103	15.9
2008	52.1%	683	100.0	101	14.8	31	4.5	104	15.2	100	14.6	56	8.2	100	14.6	92	13.5	99	14.5
2009	59.8%	687	100.0	100	14.6	37	5.4	100	14.6	100	14.6	59	8.6	100	14.6	91	13.2	100	14.6
2010	51.4%	696	100.0	100	14.4	56	8.0	100	14.4	86	12.4	57	8.2	100	14.4	98	14.1	99	14.2
2011	50.6%	749	100.0	102	13.6	59	7.9	100	13.4	126	16.8	55	7.3	101	13.5	98	13.1	108	14.4
2012	54.8%	793	100.0	100	12.6	84	10.6	98	12.4	104	13.1	112	14.1	99	12.5	96	12.1	100	12.6
2013	45.9%	771	100.0	99	12.8	61	7.9	99	12.8	100	13.0	117	15.2	100	13.0	94	12.2	101	13.1
2014	36.7%	818	100.0	101	12.3	106	13.0	100	12.2	99	12.1	115	14.1	100	12.2	98	12.0	99	12.1

[a] Inclusion rate was calculated by dividing the included cases by total screened cases.
[b] The denominators were total number of cases of each row.

2.4. Questionnaire

An 11-page clinical case report was designed by a multidisciplinary expert panel at the National Cancer Center of China, including cancer epidemiology, pathology, diagnostic radiology, thoracic surgery, medical oncology, radiation oncology and general medicine. The case report form was finalized after several rounds of discussion and emendation after a pilot survey. The 11-page questionnaire includes: (1) socio-demography and risk factors, (2) clinical characteristics regarding clinical symptoms and signs, complications and comorbidities, clinical stage and pathology type, (3) medical service utilization on diagnostic imaging techniques, laboratory testing, different treatment options and medical expenditure, and (4) postscript of self-reported data quality.

Besides, a protocol with detailed statement of inclusion criteria and key variables was also designed by the expert panel to emphasis important issues and to explain the definition of vague variables. For example, the "current smoker" was defined as smoking cigarettes or other smoked tobacco products at least once per day for more than 6 months, and the "former smoker" was defined as smoking cigarettes or other smoked tobacco products for more than 6 months but quitting at the time of survey. The "alcohol consumption" was defined as drinking at least once per week for more than 6 months.

2.5. Data collection and quality control

All data were abstracted manually or exported by batch from the medical record system. To improve the data quality, three levels of organized protocol trainings at the national, provincial and hospital-level were conducted for local interviewers, who were clinical doctors or postgraduates with more than two-year clinical experience in lung cancer, or staffs from department of medical record or cancer prevention with requirements of an educational background of clinical medicine or public health. In the process of data collection, the interviewers firstly screened the medical record in local hospitals and recorded whether to include one case according to the above inclusion criteria into a designed form (including birth date, gender, date at diagnosis, clinical stage and other essential information). Reasons for excluded cases were indicated and an identity number was assigned for each eligible case, then complete information was extracted. All the data were double-entered into computer-based database (EpiData 3.1) for consistency, and then sent to National Program Office for the missing value confirmation and logic check using coded programs in the SAS software. After several rounds of the above procedure, confirmed data were included for analysis.

2.6. Data processing

We divided eight provinces into two levels of socioeconomic status (SES) taking consideration of seven dimensions over the 10 years e.g. gross domestic product per capita, percentage of illiteracy, and life expectancy, which was reported before [19]. High SES area included Zhejiang, Liaoning, Shanxi and Hunan province, and low SES area included Guangxi, Anhui, Gansu and Yunnan province. To better present the status, we divided the ten-year period into the recent 3-year (2012–2014) and the past 7-year (2005–2011). Pathology type was integrated in the priority order of postoperative, intraoperative and preoperative pathology. Because two different versions of cancer staging manuals were used by included eight hospitals, we converted the extracted data of detailed T, N, M stage reported by different hospitals into uniform clinical stages (IA, IB, IIA, IIB, IIIA, IIIB and IV) according to lung cancer part of the 7th edition of American Joint Committee on Cancer staging manual [20], except for 171 patients with small cell lung cancer using limited and extensive staging.

2.7. Statistical analysis

To make the medical expenditure data for better comparison, we used the total medical expenditure per patient as the main indicator supplemented with medical expenditure per clinical visit per patient and daily average expenditure per patient. Followings were the corresponding formulas: Medical expenditure per clinical visit per patient = Total medical expenditure/ Number of clinical visits; Daily average expenditure per patient = Total medical expenditure/ Number of inpatient days. Allowing for the dissonance of follow-up period of patients diagnosed at different years, we further calculated the medical expenditure occurred within one year after diagnosis.

Descriptive analysis were conducted to present the overall status from 2005–2014. For continuous variables including medical expenditure, clinical visits and inpatient days, data are presented as mean ± 95% confidential interval (95% CI) except for age at diagnosis with mean (standard deviation, SD). Comparisons of continuous variables between two period groups were analyzed using *t*-test after logarithmic transformation because of the skewness, except for the number of clinical visits per patient using Wilcoxon rank sum test. Categorical variables are presented as frequency and analyzed using Chi-square test or Fisher's Exact Test, including SES level, gender, marriage, occupation, education level, health insurance status, health insurance location, body mass index, smoking status, alcohol consumption, history of chronic respiratory disease, ECOG score, complications, comorbidities, clinical stage, pathological subtype, diagnostic technique utilization and treatment regimens. The simple linear regression was used to test the time trend of number of clinical visits, number of inpatient days and medical expenditure. The time trend of each categorical variable that was divided into two categories was analyzed using the Cochran-Armitage Trend Test.

A two-tailed test of significance was used, and the significant level was set at α = 0.05. All statistical analyses were performed using SAS version 9.4 software.

3. Results

A total of 14,277 lung cancer patients were initially enrolled for inclusion and exclusion, and 7514 cases were included in the database; After data cleaning and duplicate check, 330 patients whose essential information was not trackable were excluded, thus a total of 7184 primary lung cancer patients were included for this final analysis, with an inclusion rate of 50.3%. Supplemental Table A1 shows the comparisons between included and excluded cases.

3.1. Overall sociodemographic and clinicopathologic characteristics

Among 7184 included lung cancer patients, 4802 cases were diagnosed from 2005 to 2011 and 2382 cases were diagnosed from 2012 to 2014. Table 1 presents the case distribution by province and year. The mean ± SD age at diagnosis of all included patients was 58.3 ± 10.3 years, the male-to-female ratio was 2.7/1.0 (5262/1922), 3099 (43.1%) patients were current smokers and 992 (13.8%) were former smokers. For clinical stage, patients with stage I, stage II-IIIA and IIIB-IV were 1331 (19%), 2626 (37.4%) and 3056 (43.6%), respectively. Adenocarcinoma was the main pathological type, accounting for 40.9%, followed by squamous cell carcinoma (39.1%), others (10.3%) and small cell carcinoma (9.7%). Except for SES level, body mass index and comorbidities, there were significant differences of all sociodemographic and clinicopathologic characteristics between patients in the recent 3 years from 2012 to 2014 and patients in the past 7 years from 2005 to 2011. Table 2 illustrated the detailed results.

Table 2
Sociodemographic and clinicopathological characteristics of 7184 lung cancer patients.

Characteristic	Total (*N* = 7184)	2005-2011 (*N* = 4802)	2012-2014 (*N* = 2382)	p-value[a]
Socioeconomic status, *N* (%)				0.872
High	3469 (48.3)	2322 (48.4)	1147 (48.2)	
Low	3715 (51.7)	2480 (51.6)	1235 (51.8)	
Gender, *N* (%)				< 0.001
Male	5262 (73.2)	3590 (74.8)	1672 (70.2)	
Female	1922 (26.8)	1212 (25.2)	710 (29.8)	
Age at diagnosis, mean (SD)	58.3 (10.3)	58.1 (10.2)	58.8 (10.2)	0.003
Age at diagnosis, *N* (%)				< 0.001
< 45 years	698 (9.7)	491 (10.2)	207 (8.7)	
45-59 years	3116 (43.4)	2139 (44.5)	977 (41.0)	
≥60 years	3370 (46.9)	2172 (45.2)	1198 (50.3)	
Marriage status, *N* (%)				< 0.001
Married	7048 (98.1)	4720 (98.3)	2328 (97.7)	
Unmarried	101 (1.4)	71 (1.5)	30 (1.3)	
Unknown	35 (0.5)	11 (0.2)	24 (1.0)	
Occupation, *N* (%)				< 0.001
Farmer	2974 (41.4)	1802 (37.5)	1172 (49.2)	
Enterprise employee	1339 (18.6)	999 (20.8)	340 (14.3)	
Self-employed	154 (2.1)	89 (1.9)	65 (2.7)	
Retiree	424 (5.9)	274 (5.7)	150 (6.3)	
Unemployed	718 (10.0)	516 (10.7)	202 (8.5)	
Public sector employee	902 (12.6)	732 (15.2)	170 (7.1)	
Other	26 (0.4)	20 (0.4)	6 (0.3)	
Unknown	647 (9.0)	370 (7.7)	277 (11.6)	
Education level, *N* (%)				< 0.001
Primary school or below	1956 (27.2)	1334 (27.8)	622 (26.1)	
High school or above	2449 (34.1)	1896 (39.5)	553 (23.2)	
Unknown	2779 (38.7)	1572 (32.7)	1207 (50.7)	
Health insurance status, *N* (%)				< 0.001
UEBMI	1271 (17.7)	871 (18.1)	400 (16.8)	
URBMI	296 (4.1)	157 (3.3)	139 (5.8)	
NRCMS	1874 (26.1)	984 (20.5)	890 (37.4)	
Self pay	1722 (24.0)	1453 (30.3)	269 (11.3)	
Other	818 (11.4)	684 (14.2)	134 (5.6)	
Unknown	1203 (16.7)	653 (13.6)	550 (23.1)	
Health insurance location, *N* (%)				< 0.001
Local	1830 (25.5)	1285 (26.8)	545 (22.9)	
Non-local	4636 (64.5)	2930 (61.0)	1706 (71.6)	
Unknown	718 (10.0)	587 (12.2)	131 (5.5)	
Body mass index, *N* (%)				0.061
< 18.5 kg/m^2	597 (8.3)	400 (8.3)	197 (8.3)	
18.5-23.9 kg/m^2	3969 (55.2)	2633 (54.8)	1336 (56.1)	
24.0-27.9 kg/m^2	1533 (21.3)	1038 (21.6)	495 (20.8)	
≥28.0 kg/m^2	276 (3.8)	167 (3.5)	109 (4.6)	
Unknown	809 (11.3)	564 (11.7)	245 (10.3)	
Smoking status, *N* (%)				< 0.001
Current smoker	3099 (43.1)	2175 (45.3)	924 (38.8)	
Former smoker	992 (13.8)	695 (14.5)	297 (12.5)	
Never smoker	3009 (41.9)	1878 (39.1)	1131 (47.5)	
Unknown	84 (1.2)	54 (1.1)	30 (1.3)	
Alcohol consumption status, *N* (%)				< 0.001
Yes	2042 (28.4)	1419 (29.6)	623 (26.2)	
No	4798 (66.8)	3117 (64.9)	1681 (70.6)	
Unknown	344 (4.8)	266 (5.5)	78 (3.3)	
History of chronic respiratory disease, *N* (%)				0.013
Yes	466 (6.5)	336 (7.0)	130 (5.5)	
No	6718 (93.5)	4466 (93.0)	2252 (94.5)	
ECOG score, *N* (%)				< 0.001
0-2	2911 (40.5)	1770 (36.9)	1141 (47.9)	
3-5	62 (0.9)	33 (0.7)	29 (1.2)	
Unknown	4211 (58.6)	2999 (62.5)	1212 (50.9)	
Complications, *N* (%)				< 0.001
Yes	1773 (24.7)	1069 (22.3)	704 (29.6)	
No	5389 (75.0)	3717 (77.4)	1672 (70.2)	
Unknown	22 (0.3)	16 (0.3)	6 (0.3)	

(*continued on next page*)

Table 2 (*continued*)

Characteristic	Total (*N* = 7184)	2005-2011 (*N* = 4802)	2012-2014 (*N* = 2382)	p-value[a]
Comorbidities, *N* (%)				0.218
Yes	407 (5.7)	259 (5.4)	148 (6.2)	
No	6755 (94.0)	4526 (94.3)	2229 (93.6)	
Unknown	22 (0.3)	17 (0.4)	5 (0.2)	
Clinical stage[b] *N* (%)				< 0.001
I	1331 (19.0)	884 (18.8)	447 (19.3)	
IIA	563 (8.0)	347 (7.4)	216 (9.3)	
IIB	598 (8.5)	438 (9.3)	160 (6.9)	
IIIA	1465 (20.9)	1048 (22.3)	417 (18.0)	
IIIB	967 (13.8)	683 (14.6)	284 (12.2)	
IV	2089 (29.9)	1291 (27.5)	798 (34.4)	
Pathological subtype, *N* (%)				< 0.001
Adenocarcinoma	2941 (40.9)	1831 (38.1)	1110 (46.6)	
Squamous cell carcinoma	2810 (39.1)	2006 (41.8)	804 (33.8)	
Small cell carcinoma	694 (9.7)	448 (9.3)	246 (10.3)	
Other	739 (10.3)	517 (10.8)	222 (9.3)	

UEBMI; urban employee basic medical insurance; URBMI: urban resident basic medical insurance; NRCMS: new rural cooperative medical system.

[a] Comparison between 2005–2011 and 2012–2014. *t*-test after logarithmic transformation for continuous variable and Chi-square test or Fisher's Exact Test for category variables.

[b] 171 cases of small cell carcinoma using limited and extensive stage were not reported.

3.2. Ten-year trends in sociodemographic and clinicopathologic characteristics

Over the decade from 2005 to 2014, the proportion of male lung cancer patients decreased from 76.5% in 2005 to 68.1% in 2014 ($p < 0.001$) while the proportion of female patients increased from 23.5% in 2005 to 31.9% ($p < 0.001$). The proportion of patients aged ≥60 years increased from 41.2% in 2005 to 56.2% in 2014 ($p < 0.001$), along with the decreasing trend for the proportion of patients younger than 60 years. Similar trends of the proportions of gender and age at diagnosis were found in all screened 14,277 lung cancer patients (Supplemental Fig A2). The proportion of low education level patients (primary school or below) increased from 31.7% to 53.6% ($p < 0.001$). Notably, the rate of smokers in lung cancer patients showed a decrease, from 45.7% to 38.2% ($p < 0.001$) for current smokers and from 17.1% to 15.2% ($p = 0.002$) for former smokers. Similar trends were found in male lung cancer patients, whereas the smoking prevalence in females remained at a low level (Supplemental Fig A3). The proportion of advanced stage cancer (IIIB-IV) increased from 41.9% to 47.4% ($p = 0.002$), while the proportion of stage II-IIIA decreased from 41.9% to 31.5% ($p < 0.001$). As for the pathology type, squamous carcinoma was the leading type in 2005 (48.4%) but decreased to 33.4% in 2014 ($p < 0.001$), whereas adenocarcinoma took the leading place since 2010 with the proportion increasing from 34.5% in 2005 to 50.1% in 2014 ($p < 0.001$). Fig. 1 illustrated the details.

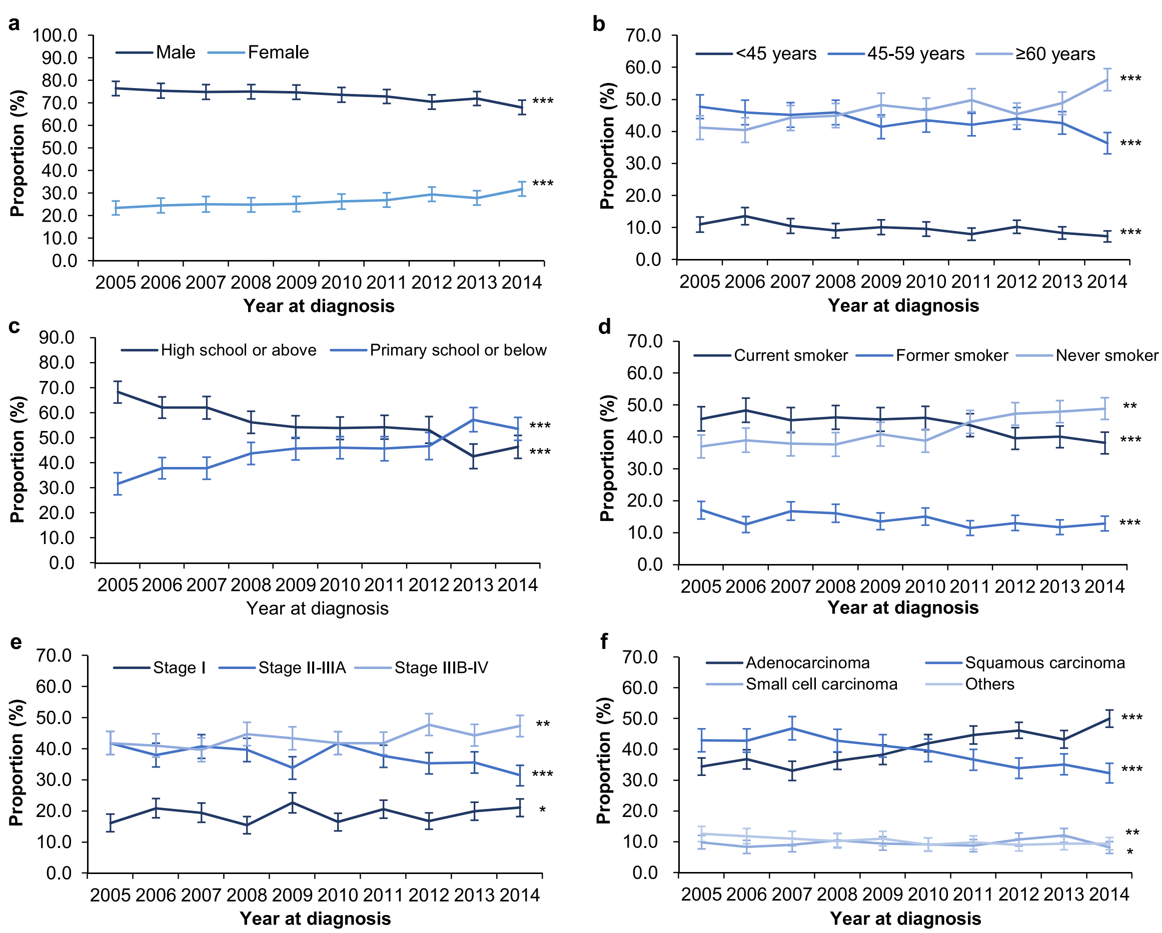


Fig. 1. Trends in the sociodemographic and clinicopathologic characteristics of Chinese lung cancer patients, 2005–2014. (a) Gender. (b) Age at diagnosis. (c) Educational level. (d) Smoking status. (e) Clinical stage. (f) Pathological type. Proportions and 95% confidential intervals were estimated. Cochran-Armitage Trend Test was used to test the trend. *p > 0.05, **p < 0.05, ***p < 0.001.

3.3. Overall status of medical service utilization

As for the diagnostic imaging techniques, chest computed tomography (CT) scan was the mostly used (5552, 77.3%) while only 2691 (37.5%) cases used the Chest X-ray. 2509 (34.9%) patients used head CT and 2211 (30.8%) patients used head magnetic resonance imaging (MRI). Only 448 (6.2%) patients used positron emission tomography-computed tomography (PET-CT). Bronchoscopy, as one diagnostic technique, was used by 4517 (63.6%) patients. Compared with patients in 2005–2011, patients in 2012–2014 used more Chest CT ($p < 0.001$), bronchoscopy ($p < 0.001$), head MRI ($p < 0.001$), and PET-CT ($p < 0.001$) while they used less chest X-ray ($p = 0.017$) and head CT ($p = 0.007$). Among all treatment regimens, chemotherapy only was mostly used by 2611 (36.3%) patients, followed by surgery only (2,178, 30.3%), surgery and chemotherapy (927, 12.9%), and the combination of chemotherapy and radiotherapy (482, 6.7%). There was significant difference in the composition of treatment regimens between the year 2005–2011 and the year 2012–2014 ($p = 0.032$). See in Table 3.

3.4. Ten-year trends in the medical service utilization

From 2005 to 2014, the application of chest X-ray dropped from 50.2% to 31.0% ($p < 0.001$) but that of chest CT increased from 65.8% to 81.4% ($p < 0.001$). The use rate of head MRI continuously increased from 8.8% in 2005 to 40.7% in 2014 ($p < 0.001$), accompanied by the decrease of head CT use ($p = 0.015$). The use of bronchofiberscopy showed an increase from 55.3% in 2005 to 68.8% in 2014 ($p < 0.001$). The use of PET-CT, a combined imaging technique with high accuracy and cost, remarkably increased from 0.7% in 2005 to 9.3% in 2014 ($p < 0.001$). Among all treatment regimens, chemotherapy and surgery, the two most commonly used options, remained stable over the period, from 36.0% to 36.4% ($p = 0.497$) and from 28.8% to 32.0% ($p = 0.290$). Fig. 2 presented the results.

3.5. Overall status of medical expenditure

The mean total medical expenditure was 54,376 (95% CI: 53,137–55,614) CNY per patient and the mean medical expenditure within one year after diagnosis was slightly lower (49,689, 95% CI: 48,736–50,642 CNY). The mean number of clinical visits was 2.9 (95% CI: 2.8–2.9) times per patient and the mean number of inpatient days was 43.8 (95% CI: 42.7–44.8) per patient. The corresponding mean expenditure per clinical visit and daily average expenditure per patient was 24,838 (95% CI: 24,398–25,279) CNY and 1505 (95% CI: 1,458–1,552) CNY. Significant differences were found in the medical expenditure between the recent 3-year group and the past 7-year group ($p < 0.001$). Table 3 presented the detail.

3.6. Ten-year trends in the medical expenditure

Over the ten years, the mean medical expenditure per patient increased from 40,508 (95% CI: 36,172–44,843) CNY in 2005 to 66,020 (95% CI: 62,664–69,376) CNY in 2014 ($p < 0.001$; Fig. 3a.). Similar trend of the mean 1-year medical expenditure per patient was also found ($p < 0.001$; Fig. 3b.). The mean number of clinical visit per patient showed a slight increase from 2.3 times in 2005 to 2.6 times in 2014 ($p < 0.001$; Fig. 3e.), while the number of inpatient days significantly decreased from 50.8 days in 2005 to 36.0 days in 2014 ($p < 0.001$; Fig. 3f.). Correspondingly, the mean expenditure per clinical visit per patient increased from 21,513 (95% CI: 20,341–22,685) CNY in 2005 to 32,926 (95% CI: 31,237–34,615) CNY in 2014 ($p < 0.001$; Fig. 3c.), and the daily average expenditure per patient increased from 902 (95% CI: 870–933) CNY in 2005 to 2143 (95% CI: 1,938-2,348) CNY in 2014 ($p < 0.001$; Fig. 3d.).

4. Discussion

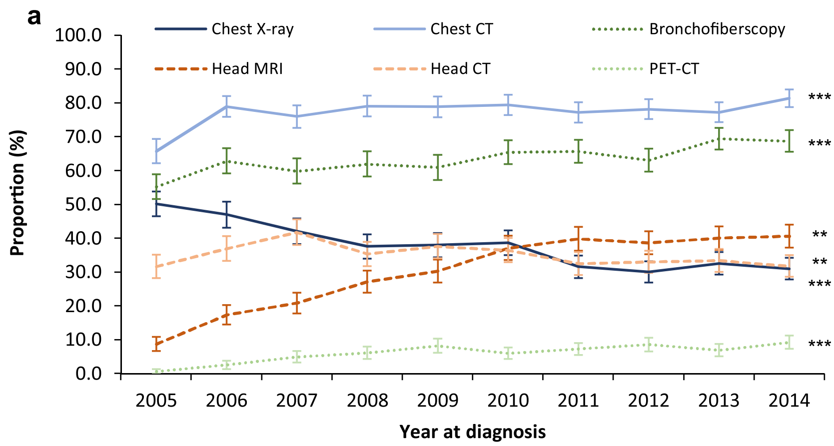
This was the first multicenter long-term retrospective epidemiology survey of lung cancer in China. We found that both socio-demographic and clinical characteristics for lung cancer patients were changing over the decade, such as increasing proportion of female patients, upstaging of clinical stage and changing patterns of pathological types. The use of diagnostic techniques changed a lot while treatment options kept unchanged. Notably, medical expenditure showed sustaining increase

Table 3
Medical services utilization and medical expenditure of 7184 lung cancer patients.

Characteristic	Total (*N* = 7184)	2005–2011 (*N* = 4802)	2012–2014 (*N* = 2382)	p-value[a]
Diagnostic technique utilization, *N* (%)				
Chest X-ray	2691 (37.5)	1948 (40.6)	743 (31.2)	< 0.001
Chest CT	5552 (77.3)	3671 (76.5)	1881 (79.0)	0.017
Bronchoscopy	4517 (63.6)	2946 (61.8)	1571 (67.1)	< 0.001
Head CT	2509 (34.9)	1729 (36.0)	780 (32.8)	0.007
Head MRI	2211 (30.8)	1262 (26.3)	949 (39.8)	< 0.001
PET-CT	448 (6.2)	250 (5.2)	198 (8.3)	< 0.001
Treatment regimens, *N* (%)				
Surgery only	2178 (30.3)	1482 (30.9)	696 (29.2)	0.032
Chemotherapy only	2611 (36.3)	1728 (36.0)	883 (37.1)	
Radiotherapy only	281 (3.9)	201 (4.2)	80 (3.4)	
Targeted therapy	53 (0.7)	27 (0.6)	26 (1.1)	
Surgery and chemotherapy	927 (12.9)	618 (12.9)	309 (13.0)	
Chemotherapy and radiotherapy	482 (6.7)	332 (6.9)	150 (6.3)	
Surgery and chemotherapy and radiotherapy	16 (0.2)	9 (0.2)	7 (0.3)	
Other	636 (8.9)	405 (8.4)	231 (9.7)	
Medical expenditure, Chinese Yuan, mean (95%CI)				
Total expenditure per patient	54,376 (53,137–55,614)	49,482 (47,948–51,016)	64,021(61,976–66,066)	< 0.001
1-year expenditure per patient[b]	49,689 (48,736–50,642)	43,608 (42,560–44,655)	61,667 (59,821–63,512)	< 0.001
Expenditure per clinical visit per patient	24,838 (24,398–25,279)	22,699 (22,229–23,168)	29,055 (28,154–29,957)	< 0.001
Daily average expenditure per patient	1505 (1458–1552)	1300 (1251–1350)	1902 (1805–1998)	< 0.001
Number of clinical visits per patient, mean (95%CI)	2.9 (2.8–2.9)	2.8 (2.7–3.0)	2.9 (2.8–3.0)	< 0.001
Number of clinical visits per patient, median (P5-P95)	1.0 (1.0–9.0)	1.0 (1.0–9.0)	2.0 (1.0–8.0)	< 0.001
Number of inpatient days per patient, mean (95%CI)	43.8 (42.7–44.8)	46.4 (44.8–47.8)	38.6 (37.3–39.9)	< 0.001

[a] Comparison between 2005–2011 and 2012–2014. *t*-test after logarithmic transformation for all continuous variables, except for the number of clinical visits per patient using Wilcoxon rank sum test. Chi-square test or Fisher's Exact Test for categorical variables.

[b] Cumulative medical expenditure occurred within one year after diagnosis.



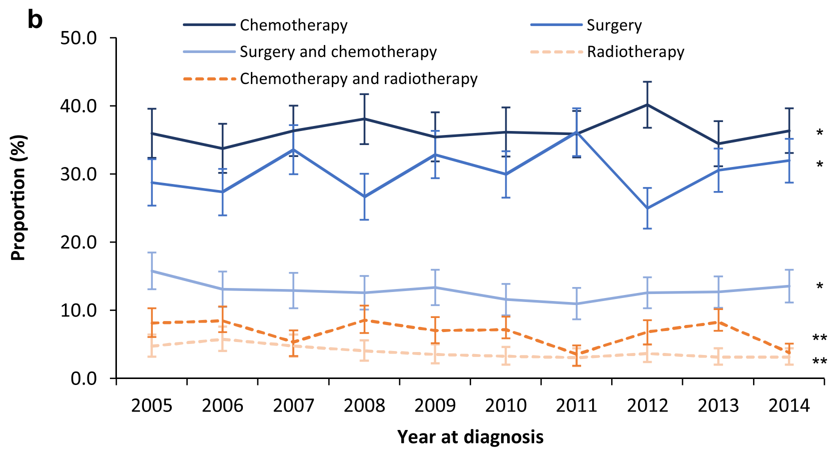


Fig. 2. Trends in the utilization of diagnostic techniques and treatment regimens of Chinese lung cancer patients, 2005–2014. (a) Diagnostic techniques. (b) Treatment regimens. Proportions and 95% confidential intervals were estimated. Cochran-Armitage Trend Test was used to test the trend. *p > 0.05, **p < 0.05, ***p < 0.001.

over the decade. Our findings demonstrate potential challenges and future directions on lung cancer prevention, control and clinical practice in China.

This study found that the mean age at diagnosis during 2012–2014 was slightly higher than that of 2004–2011, which is indicative of the increasing proportion of ageing patients (aged ≥60 years). Data from national cancer registries showed that the lung cancer incidence in ageing population was more than 6 times higher than that in all population in China [21]. Compared with results from developed countries, the mean age at diagnosis in this study was 58.3 years, lower than 71 years reported for Americans [22] and 68 years for Australians [7]. The continuous acceleration of population ageing may further aggravate the lung cancer burden in older population [23].

Contrasting changing trends of gender proportions over time were observed in this study, downward in males and upward in females. On the whole, the gender proportions in lung cancer patients could be determined by the corresponding proportions by gender in general population multiplied by the specific incidence rates of lung cancer. Population data showed that the proportion of females slightly decreased over the period along with increasing trend in males' proportion [23], and data from cancer registries showed that the incidence rate of lung cancer significantly increased in females whereas steadily decreased in males [2,24], which coincided with the findings in our study. The steady decrease of male patients could be mainly attributed to the slightly decreased cigarette smoking rate in lung cancer patients and general population [25,26]. However, the increasing trend of incidence rate in females could not be explained by the unchanged smoking prevalence in females [25,26]. Secondhand smoke exposure might be a major risk factor [27]. The prevalence of secondhand smoke among never smoking Chinese women was as high as 71.6% [28], which was estimated to account for 24% of lung cancer cases [29]. Indoor air pollution from burning biomass fuels, exposed to most traditional Chinese females, accounted for nearly 20% of lung cancer cases [29]. Other factors including the prevalence of other lung diseases like tuberculosis [27], residential radon exposure [30] and outdoor air pollution [31] may also result in the upward trend in females.

This study observed that the proportion of adenocarcinoma increased over time and surpassed the squamous cell carcinoma to be the predominant histological subtype of lung cancer, which is in accordance with previous findings reported from single institute in Beijing [32,33] and Sichuan [11], and other countries like Australia [7], United States [34] and European countries [35]. Some possible reasons may exist as follows. The first key factor is the reduction of cigarette smoking, given that the intensity of cancer risk of smoking varies by histological type, with higher odds ratios for squamous and small cell carcinomas and lower ratios for adenocarcinoma [36]. Cigarette filter ventilation may be the second reason. The replacement of non-filtered cigarettes from filtered cigarettes leads to higher levels of mutagens and carcinogens, compensation with the greater depth of inhalation, and deposition of smoke, and then increases to toxicants' exposure in the peripheral portion of lungs [37]. Advances in diagnostic technology can also help detect more lesions in the peripheral parts than central parts, where adenocarcinoma usually locates [38], and our study found an increase of the use of chest CT and bronchofiberscopy.

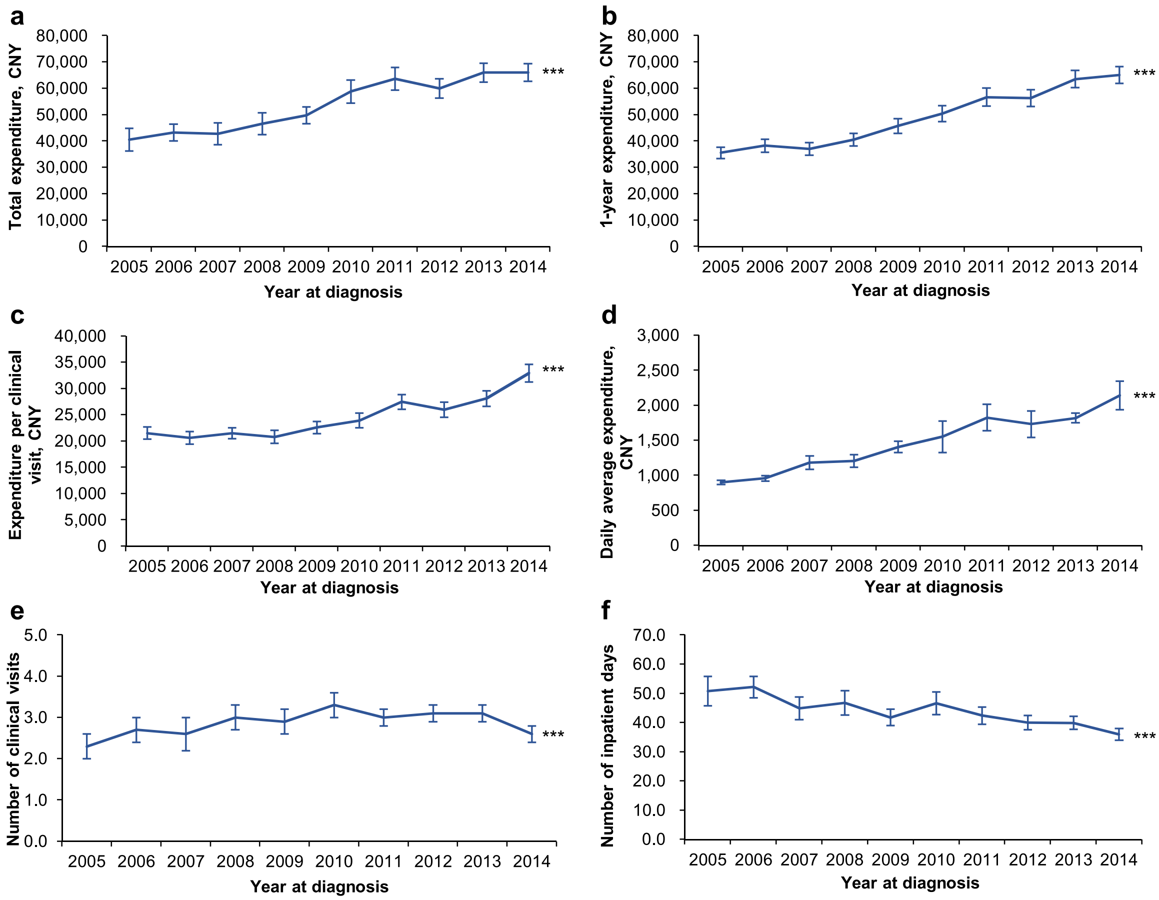


Fig. 3. Trends in the medical expenditure, clinical visits and number of inpatient days of Chinese lung cancer patients, 2005–2014. (a) Medical expenditure. (b) Medical expenditure within the first year after diagnosis. (c) Medical expenditure per clinical visit. (d) Daily average expenditure. (e) Number of clinical visits/admissions. (f) Number of inpatient days. Mean and 95% confidential interval was estimated. Linear regression model was used to test the trend. *p > 0.05, **p < 0.05, ***p < 0.001.

In this study, the proportion of patients at stage IIIB-IV increased and that of stage II-IIIA dropped. Similar trends were found among population from the US during 2004–2010 [39], and England during 2008–2012 [40]. Previous studies have demonstrated, though the controversy exists, that patients with lower socio-economic status are likely to be diagnosed at more advanced stage [19,41]. Education level is a common SES indicator. The proportion of patients with high school or above education level continued to decrease over time in our study, which partly explains the increase of advanced stage. Low-dose CT screening has been confirmed by randomized controlled trials as an effective method to reduce the composition of advanced stage cancer and eventually to reduce the lung cancer mortality [42]. Two government-sponsored low-dose CT lung cancer screening programs were initiated in rural China since 2009 [43] and urban China since 2012 [16], however, the magnitude of the stage shift in lung cancer from two screening programs cannot be estimated in the case of unavailable data.

As for the medical service use, diagnostic techniques made substantial improvements while treatment regimens had no obvious change over time. The shift from chest X-ray to chest CT, from head CT to head MRI and increasing adoptions of bronchofiberscopy and PET/CT, though the rates seem lower than the recommendations of clinical guidelines [8,44], have provided valuable assistance in better diagnosis for lung cancer in China. The reason for unchanged composition of treatment regimens needs to be further explored. Kaniski et al reported that surgery among stage I/II patients remained stable decreased whereas receipt of chemotherapy among stage IIIB/IV patients increased significantly from 1996 to 2010 in US population [45]. Yang et al. demonstrated large disparities between the clinical practice and the national treatment guidelines by clinical stage in an institute in Guangdong [12]. Due to the lack of subgroup analysis in the diagnostic techniques and treatment regimens, the overall findings of our study need to be interpreted with caution. Further analysis of the temporal trends of stage-specific and region-specific diagnostic techniques and therapy regimens in our study are supposed to be performed and published.

The medical expenditure due to the diagnosis and treatment of lung cancer results in severe burden to both the patients' families and the society. The expenditure per case was estimated at 64,021 CNY during 2012–2014, slightly higher than the result of a large-scale study [13], whereas both expenditure tremendously surpass the mean GDP per capita (43,687 CNY) in the same period in China [46]. Meanwhile, medical expenditure per patient calculated in this study showed a continuous increase, which is consistent with the trend in a systematic review [15] and the increase of national total payments due to lung cancer [47]. The trend could be jointly attributed to the increase at composition of advanced stage patients, the improvement of diagnostic techniques and more choices of adjuvant drugs. To ease the financial burden of patients with cancer, the Chinese government has initiated several policies like including some targeted drugs in the national medical insurance [48] and exempting tariffs on imported cancer drugs [49].

Our findings should be interpreted with caution because of the limitations. (1) Selection bias may exist, because on the one hand only a few of provincial hospitals were selected in this study while lack of hospitals at municipal or prefecture level, on the other hand only limited information on basic characteristics of excluded cases were collected, making it difficult to explain the representativeness of included cases. (2) Information bias, the nature of retrospective study, could be brought because all the collected data was subject to the integrity and accuracy of the medical record systems in surveyed hospitals. Meanwhile, information that occurred in the hospitals other than the surveyed were missed, which may mislead the conclusions. (3) Current results were reported via basic descriptions, in which potential confounders may exist. Thus, subgroup analysis and multivariate regression are supposed to be performed in further studies. (4) The survival rate of lung cancer, the ultimate outcome of all medical interventions and clinical practices, was not included in this study.

In conclusion, this multicenter retrospective epidemiology survey depicts a full view and the trajectory of the demographic and clinicopathological characteristics, medical service utilizations and medical expenditure among lung cancer patients in China. The sustaining high smoking exposure, diminishing male-to-female ratio, increasing patients with advanced stage and shift of predominant pathological subtype demonstrate potential challenges and future directions on lung cancer prevention and control in China. The most updated clinical guidelines need to be disseminated to doctors at all levels to benefit the patients. Increasing medical expenditure have potential implications for policy makers for prioritizing future resource allocation.

Funding

This work was supported by the Major Chronic Non-Communicable Diseases Prevention and Control Special Research Program (No. 2017YFC1308705, No. 2017YFC1308700), National Key R&D Program of China (No. 2017YFC0907900, No. 2017YFC0907901), National Natural Science Foundation of China (No. 81773521), and the Cancer Screening Program in Urban China, supported by the National Health and Family Planning Committee (currently National Health Commission) of P. R. China.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors thank all the members of the LuCCRES Group (Clinical Characteristics and Medical Service Utilization of Lung Cancer in China, 2005–2014: a Multicenter Retrospective Epidemiologic Survey) from the National Cancer Center of China and eight field provinces, and all the members of the Health Economic Evaluation Working Group, Cancer Screening Program in Urban China (CanSPUC).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.031.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA-Cancer J. Clin. 68 (6) (2018) 398–424.
[2] W.Q. Chen, R.S. Zheng, P.D. Baade, et al., Cancer statistics in China, 2015, CA Cancer J. Clin. 66 (2) (2016) 115–132.
[3] GBD Compare Data Visualization, IHME, University of Washington, 2016 Accessed 2018-01-08 http://vizhub.healthdata.org/gbd-compare.
[4] Cancer Statistics, SEER* Explorer, (2017) (Accessed 08 January 2018), https://seer.cancer.gov/explorer/.
[5] M.P. Coleman, D. Forman, H. Bryant, et al., Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer benchmarking Partnership): an analysis of population-based cancer registry data, Lancet 377 (9772) (2011) 1149–1150.
[6] H. Zeng, W. Chen, R. Zheng, et al., Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries, Lancet Glob. Health 6 (5) (2018) e555–e567.
[7] E.J. Denton, D. Hart, Z. Wainer, et al., Changing trends in diagnosis, staging, treatment and survival in lung cancer: comparison of three consecutive cohorts in an Australian lung cancer centre, Intern. Med. J. 46 (8) (2016) 946–954.
[8] D.S. Ettinger, D.E. Wood, D.L. Aisner, et al., Non-small cell lung Cancer, version 5.2017, NCCN clinical practice guidelines in oncology, J. Compr. Canc. Netw. 15 (4) (2017) 504–535.
[9] M.G. Kris, L.E. Gaspar, J.E. Chaft, et al., Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American society of clinical oncology/cancer care ontario clinical practice guideline update, J. Clin. Oncol. 35 (25) (2017) 2960–2974.
[10] Y. Chen, S. Han, M.J. Zheng, et al., Clinical characteristics of 274 non-small cell lung Cancer patients in China, Onkologie 36 (5) (2013) 248–254.
[11] X.J. Yao, H.W. Zhnag, Q. Pu, et al., Clinical epidemiology and histological characteristics of patients with lung cancer in West China Hospital of Sichuan University, J. Sichuan Univ. 45 (2) (2014) 309–315.
[12] L.L. Yang, X.C. Zhang, X.N. Yang, et al., Lung cancer treatment disparities in China: a question in need of an answer, Oncologist 19 (10) (2014) 1084–1090.
[13] H.Y. Huang, J.F. Shi, L.W. Guo, et al., Expenditure and financial burden for common cancers in China: a hospital-based multicentre cross-sectional study, Lancet 388 (2016) S10.
[14] L.M. Hess, Z.L. Cui, Y. Wu, et al., Current and projected patient and insurer costs for the care of patients with non-small cell lung cancer in the United States through 2040, J. Med. Econ. 20 (8) (2017) 850–862.
[15] C.L. Shi, P.A. Lou, J.F. Shi, et al., Economic burden of lung cancer in mainland China,1996–2014: a systematic review, Zhongguo Gong Gong Wei Sheng 33 (12) (2017) 1767–1774.
[16] M. Dai, J.F. Shi, N. Li, The design and expectation of the cancer screening program in urban China, Zhonghua Yu Fang Yi Xue Za Zhi 47 (3) (2012) 179–182.
[17] J. Li, B.N. Zhang, J.H. Fan, et al., A nation-wide multicenter 10-year (1999–2008) retrospective clinical epidemiological study of female breast cancer in China, BMC Cancer 11 (2011) 364.
[18] Y.Q. Zhang, J.H. Fan, Y.L. Qiao, A nation-wide multicenter 10-year (2001-2010) retrospective clinical epidemiological study of pancreatic neuroendocrine tumors in China, Pancreatology 16 (1) (2016) S45.
[19] Y. Li, J. Shi, S. Yu, et al., Effect of socioeconomic status on stage at diagnosis of lung cancer in a hospital-based multicenter retrospective clinical epidemiological study in China, 2005-2014, Cancer Med. 6 (10) (2017) 2440–2452.
[20] S.B. Edge, C.C. Compton, The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM, Ann. Surg. Oncol. 17 (6) (2010) 1471–1474.
[21] W.Q. Chen, R.S. Zheng, S.W. Zhang, et al., Analysis of cancer incidence and mortality in elderly population in China, 2013, Zhonghua Zhong Liu Za Zhi 39 (1) (2017) 60.
[22] K.S. Bilello, S. Murin, R.A. Matthay, Epidemiology, etiology, and prevention of lung cancer, Clin. Chest Med. 23 (1) (2002) 1–35.
[23] World Population Prospects, (2017) https://esa.un.org/unpd/wpp/Download/Standard/Population/.
[24] Y. Zhang, J.S. Ren, H.Y. Huang, et al., International trends in lung cancer incidence from 1973 to 2007, Cancer Med. 7 (4) (2018) 1479–1489.
[25] M. Wang, X. Luo, S. Xu, et al., Trends in smoking prevalence and implication for chronic diseases in China: serial national cross-sectional surveys from 2003 to 2013, Lancet Respir. Med. (2018).
[26] Tobacco Viz. https://vizhub.healthdata.org/tobacco/. (Accessed 18 January 2018).
[27] H.Y. Liang, X.L. Li, X.S. Yu, et al., Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review, Int. J. Cancer 125 (12) (2009) 2936–2944.
[28] X. Lin, Y. Yan, L. Qiang, et al., Population-based survey of secondhand smoke exposure in China, Biomed. Environ. Sci. 23 (6) (2010) 430–436.
[29] J. Sisti, P. Boffetta, What proportion of lung cancer in never-smokers can be attributed to known risk factors? Int. J. Cancer 131 (2) (2012) 265–275.
[30] S. Darby, D. Hill, A. Auvinen, et al., Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies, BMJ 330 (7485) (2005) 223–226.
[31] B. Pan, R. Yao, Q.L. Zhu, et al., Clinicopathological characteristics and long-term prognosis of screening detected non-palpable breast cancer by ultrasound in hospital-based Chinese population (2001–2014), Oncotarget 7 (47) (2016) 76840–76851.
[32] X.N. Zou, D. Lin, A. Chao, et al., Histological subtypes of lung cancer in Chinese women from 2000 to 2012, Biomed. Environ. Sci. 5 (5) (2014) 447–454.
[33] X.N. Zou, D.M. Lin, X. Wan, et al., Histological subtypes of lung cancer in Chinese males from 2000 to 2012, Biomed. Environ. Sci. 27 (1) (2014) 3–9.
[34] R. Meza, C. Meernik, J. Jeon, et al., Lung Cancer incidence trends by gender, race and histology in the United States, 1973–2010, PLoS One 10 (3) (2015) e0121323.
[35] J. Lortet-Tieulent, I. Soerjomataram, J. Ferlay, et al., International trends in lung cancer incidence by histological subtype: adenocarcinoma stabilizing in men but still increasing in women, Lung Cancer 84 (1) (2014) 13–22.
[36] B. Pesch, B. Kendzia, P. Gustavsson, et al., Cigarette smoking and lung cancer – relative risk estimates for the major histological types from a pooled analysis of case-control studies, Int. J. Cancer 131 (5) (2012) 1210–1219.
[37] M.A. Song, N.L. Benowitz, M. Berman, et al., Cigarette filter ventilation and its relationship to increasing rates of lung adenocarcinoma, J. Natl. Cancer Inst. 109 (12) (2017).
[38] X. Jiang, G.M. De, S. Liu, et al., Rising incidence of adenocarcinoma of the lung in Canada, Lung Cancer 78 (1) (2012) 16–22.
[39] V.W. Chen, Bernardo A. Ruiz, M.C. Hsieh, et al., Analysis of stage and clinical/

prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system, Cancer 120 (S23) (2014) 3781–3792.
[40] S. Benitez-Majano, H. Fowler, C. Maringe, et al., Deriving stage at diagnosis from multiple population-based sources: colorectal and lung cancer in England, Br. J. Cancer 115 (3) (2016) 391–400.
[41] L.F. Forrest, S. Sowden, G. Rubin, et al., Socio-economic inequalities in stage at diagnosis, and in time intervals on the lung cancer pathway from first symptom to treatment: systematic review and meta-analysis, Thorax 72 (5) (2016).
[42] D.R. Aberle, A.M. Adams, C.D. Berg, et al., Reduced lung-cancer mortality with low-dose computed tomographic screening, N. Engl. J. Med. 365 (5) (2011) 395–409.
[43] Q. Zhou, Y. Fan, W. Ning, et al., Demonstration program of population-based lung cancer screening in China: rationale and study design, Thorac. Cancer 5 (3) (2014) 197–203.
[44] Q. Zhou, Y. Fan, Y. Wang, et al., China national guideline of classification, diagnosis and treatment for lung nodules (2016 version), Zhongguo Fei Ai Za Zhi 19 (12) (2016) 793–798.
[45] F. Kaniski, L. Enewold, A. Thomas, et al., Temporal patterns of care and outcomes of non-small cell lung cancer patients in the United States diagnosed in 1996, 2005, and 2010, Lung Cancer 103 (2017) 66–74.
[46] F. Qiu, X. Shao, X. Wang, et al., Comparison of clinical and pathological characteristics between screen-detected and self-detected breast cancers: a Hong Kong study, BMC Cancer 22 (3) (2016) 202–209.
[47] Y. Cai, M. Xue, W. Chen, et al., Expenditure of hospital care on cancer in China, from 2011 to 2015, Chin. J. Cancer 29 (3) (2017) 253–262.
[48] S. Wu, Y. Zhu, Z. Yang, et al., Low rate of positive margins and re-excision after partial mastectomy in highly selected breast cancer patients: a Chinese single-institution experience, Oncotarget 8 (7) (2017) 12225–12233.
[49] Lancet, Cancer drugs in China: affordability and creativity, Lancet 391 (10133) (2018) 1866.