Lung Cancer 132 (2019) 114–118

Contents lists available at ScienceDirect

Lung Cancer

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

Lung cancer incidence in female rises significantly in urban sprawl of Shanghai after introduction of LDCT screening

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ARTICLE INFO

Keywords:
Lung cancer incidence
LDCT screening
China

ABSTRACT

Objectives: LDCT screening for lung cancer has been widely used in China since the release of the NLST trial data in 2011, but little is known about its impact on the incidence and mortality rates of lung cancer in China.
Methods: Official cancer registry data of lung cancer incidence and mortality were collected by Shanghai Municipal Center for Disease Control and Prevention from 2005 to 2014. Two districts (Xuhui and Songjiang Districts) were selected to represent populations with different levels of accessibility to LDCT. Incidence and mortality age-standardized rates (ASRs) were calculated using the Segi/Doll 1960 world standard population. Trends in lung cancer incidence and mortality rate over time, the average annual percent change (APC) and the corresponding 95% confidence interval (CI) were calculated using Joinpoint.
Results: In Shanghai, lung cancer incidence rate in men did not change significantly between 2005 and 2014 (APC = 0.76%; 95% CI: -0.27%, 1.80%; P = 0.127); while lung cancer incidence in women increased significantly (APC: 5.50%; 95% CI: 2.94%, 8.13%; P = 0.001). In Xuhui district, where eight tertiary hospitals was located, including Shanghai Cancer Center and Shanghai Chest Hospital, both of which provided LDCT lung cancer screening for eligible patients, the incidence rate of lung cancer increased significantly in women only since 2011(APC: 19.84%, P < 0.001). Overall mortality rate of lung cancer showed a significantly decreasing trend from 2005 to 2014 in men (APC = -2.68%, P = 0.009) but not in women (APC = -0.91%, P = 0.305). In Songjiang district, where limited access to LDCT was provided, lung cancer incidence in women increased significantly between 2005 and 2014 (APC: 5.42%, P = 0.001). Lung cancer incidence rates did not change significantly in men in either district from 2005 to 2014. Mortality rate of lung cancer did not change significantly from 2005 to 2014 in both men (APC = -0.51%, P = 0.259) and women (APC = -1.46%, P = 0.186).
Conclusion: There is a steady increase in the incidence of lung cancer in women, especially after the wide use of LDCT screening, but without a clear mortality reduction.

1. Introduction

Lung cancer, causing about 600,000 of deaths each year, is a leading cause of cancer-related mortality in both men and women, in China [1]. The morbidity and mortality rates of lung cancer in both urban and rural Chinese populations are higher than the worldwide average, presenting a major public health issue and imposing an enormous burden on patients, health-care professionals and society in China [2]. The average 5-year survival rate of lung cancer in China is 15%, and is more often diagnosed at advanced clinical stages where treatment is typically non-curative [3]. Although there has been progress in the therapy of lung cancer in the last decade, the overall prognosis across all stages has not been substantially improved, and is largely stage-associated. Physicians and their patients have long sought screening methods to detect lung cancer at localized stages, when it can be surgically removed and possibly cured.

In 2011, the National Lung Screening Trial, a randomized US study of 53,454 people ages 55–74 who were at high risk of lung cancer, reported that the use of three annual screens with low-dose spiral CT (LDCT) was associated with a 20% reduction in cancer-related

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https://doi.org/10.1016/j.lungcan.2019.04.020
Received 30 November 2018; Received in revised form 28 February 2019; Accepted 12 April 2019

Table 1
Incidence and mortality rate of lung cancer among male and female in Shanghai from 2005 to 2014. APC, annual percent change.

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	APC(95% CI)	P value
Incidence($1/10^5$)												
Male	44.46	40.08	45.12	43.49	44.05	42.93	42.51	45.73	46.84	45.38	0.76%(−0.27% to 1.80%)	0.127
Female	17.6	13.68	17.3	17.16	17.8	17.83	18.69	21.7	24.22	25.82	5.50%(2.94%–8.13%)	0.001
Mortality($1/10^5$)												
Male	38.19	44.48	39.5	36.46	38.2	35.88	36.07	36.31	36.14	34.64	−1.71%(−2.98% to −0.04%)	0.015
Female	13.61	16.76	13.84	12.77	13.73	12.55	12.69	13.8	12.65	11.95	−1.96%(−3.84% to −0.04%)	0.046

mortality, compared with three annual chest x-ray screens [4]. LDCT screening for lung cancer has thus been widely used in China after the release of the NLST trial data [5]. But no population-based study has assessed the impact of LDCT screening on the incidence of lung cancer in China. Using official cancer registry data of lung cancer incidence and mortality in Shanghai municipality and its two districts with different level of accessibility of LDCT, we try to explore the potential effect of LDCT on the incidence and mortality of lung cancers.

2. Methods

2.1. Data

Official cancer registry data of lung cancer incidence and mortality rates were collected from Shanghai Municipal Center for Disease Control and Prevention (Xuhui District and Songjiang District) between 2005 and 2014. Data on lung cancer incidence and mortality were available from the Shanghai Cancer Registry (SCR), and were previously described [6]. Briefly, the SCR was established in 1963, and is the oldest population-based cancer registry in China and one of the largest cancer registries in the world. Complete incidence and mortality data have been collected in urban areas since 1973 and in suburban areas since 2002. Data from the population in the urban areas, covering 289.4 km^2 and an average of 7 million residents, have consistently reached the standards set by the International Agency for Research on Cancer (IARC), and have been published in its quinquennial publications. Incidences of lung cancer were reported by all the 190 hospitals that capable of diagnosis of malignant tumors. Each case of incidence was reported using standardized malignant tumor case report card. In 2014, 72.33% of lung cancer incidence were pathologically proven, 13.12% were radiological diagnosis, 4.51% through biochemical immunity and nearly 10% were diagnosed through clinical diagnosis. Overall rate of missing data is very low, which ranged from 1.5% to 0.5% between 2005 and 2015.

Xuhui and Songjiang Districts were selected to represent populations in urban and suburban areas in Shanghai, respectively. Xuhui District is located in the southwest of downtown Shanghai, with an area of 54.8 km^2 and a population of 1,089,100 residents at the end of 2015. Eight tertiary hospitals was located in Xuhui District, including Shanghai Cancer Center and Shanghai Chest Hospital, both of which provided LDCT lung cancer screening for eligible patients. Songjiang District is located in the Northwest suburban area of Shanghai, with an area of 464.2 km^2, with a population of 1,568,000 residents at the end of 2015. Only one tertiary hospital was located in Songjiang District.

2.2. Statistical analysis

Incidence and mortality age-standardized rates (ASRs) were calculated using the Segi/Doll 1960 world standard population [7]. Effects of age on incidence and mortality were evaluated using age–period–cohort models [8]. Patients were categorized into 5-year age groups (35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥ 85) based on their age of diagnosis. To characterize trends in lung cancer incidence and mortality rate over time, the average annual percent changes (APC) and the corresponding 95% confidence intervals (CI) were calculated using Joinpoint (version 4.1.1.3) by the National Cancer Institute.

3. Results

3.1. Lung cancer incidence and mortality rate in Shanghai

In Shanghai (including Xuhui and Songjiang Districts), lung cancer incidence in men did not change significantly from 2005 to 2014 (APC = 0.76%; 95% CI: -0.27%, 1.80%; P = 0.127); while lung cancer incidence in women increased significantly during the same time period (APC: 5.50%; 95% CI: 2.94%, 8.13%; P = 0.001) (Table 1). Patients were further stratified into categories according to age at diagnosis (Table 2). In men, lung cancer incidence increased significantly only in two age groups (50–54 and 55–59); while in women, lung cancer incidence increased significantly in all the age subgroups between 35 and 64 years old and 70–74.

Mortality rate of lung cancer showed a significantly decreasing trend in both men (APC = -1.71%, 95% CI: -2.98%–0.04%, P = 0.015) and women (APC = -1.96%, 95% CI: -3.84%–0.04%, P = 0.046) from 2005 to 2014 (Table 1). Age-specific mortality rates in Table 2

3.2. Lung cancer incidence and mortality rate among populations in urban area

In Xuhui district, lung cancer incidence rate in men did not change significantly from 2005 to 2014 (APC = -0.01%, P = 0.427; Table 3, Fig. 1). In women, the incidence rate of lung cancer in women increased significantly since 2011(APC: 19.84%, P < 0.001), but not between

Table 2
Average annual percent change (APC) of incidence and mortality rate of lung cancer in Shanghai among men and women stratified by age at diagnosis from 2005 to 2014.

Age (years)	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+	Overall
Incidence												
Male	1.59	−0.35	1.51	**4.26***	**6.58***	2.04	−0.35	−0.67	**−1.75***	**−1.77***	0.24	0.76
Female	**17.21***	**10.21***	**11.84***	**10.10***	**9.91***	**6.52***	3.27	**2.36***	1.06	0.22	1.08	**5.50***
Mortality												
Male	**−10.57***	**−8.73***	**−4.98***	−0.37	1.52	−1.79	**−3.26***	**−2.08***	**−2.12***	−0.73	2.83	**−1.71***
Female	**−6.51***	−4.73	**−4.09***	−2.95	−2.53	−1.73	**−4.47***	**−2.30***	−0.08	0.61	**2.34***	**−1.96***

* Statistical significance.

Table 3
Incidence and mortality rate of lung cancer in Huxui District and Songjiang District among men and women from 2005 to 2014.

Year			2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Incidence($1/10^5$)	Huxui District	Male	33.31	37.01	36.9	36.7	33.33	35.57	31.39	37.94	37.73	33.71
		Female	19.19	15.94	16.98	18.23	18.57	18.06	17.71	23.11	30.34	28.92
	Songjiang District	Male	53.53	48.27	54.12	52.84	51.2	51.08	58.73	56.19	60.42	49.87
		Female	18.21	14.73	17.03	18.99	13.31	16.15	20.32	22.8	24.79	26.02
Mortality($1/10^5$)	Huxui District	Male	31.31	35.58	28.07	30.84	29.62	31.08	27.52	26.36	28.67	24.06
		Female	12.23	10.75	12.08	12.25	12.58	12.92	11.96	12.06	14.29	11.65
	Songjiang District	Male	44.30	45.00	43.91	44.37	43.38	39.74	45.46	42.89	40.99	44.01
		Female	14.01	14.19	13.15	12.11	13.88	9.45	11.13	13.83	12.21	12.56

2005 and 2011(APC = 1.10%, P = 0.328, Table 3, Fig. 1).After stratified by age groups, lung cancer incidenceincreased significantly among men aged between 55–59 (APC:9.46%), and decreased significantly among men at age 70–74 (APC:-3.24%) and 80–84 (APC:-4.22%). In comparison, lung cancer incidence increased significantly among women in four age subgroups (< 50, 60–64, 65–69, 70–74), with APC of 18.42%, 6.65%, 6.63% and 4.56%, respectively. Among women in the age group of 50–54, the lung cancer incidence did not change significantly between 2005 and 2011(APC = 2.51%, P = 0.218), but increased significantly since 2011(APC: 56.58%, P < 0.001). Overall mortality rate of lung cancer showed a significantly decreasing trend from 2005 to 2014 in men (APC = -2.68%, P = 0.009) but not in women (APC = -0.91%, P = 0.305). In men, lung cancer mortality decreased significantly in two age groups (55–59) with APC of 5.44% and 4.30%, respectively. In women, the mortality did not decrease in any age subgroup (Table 4).

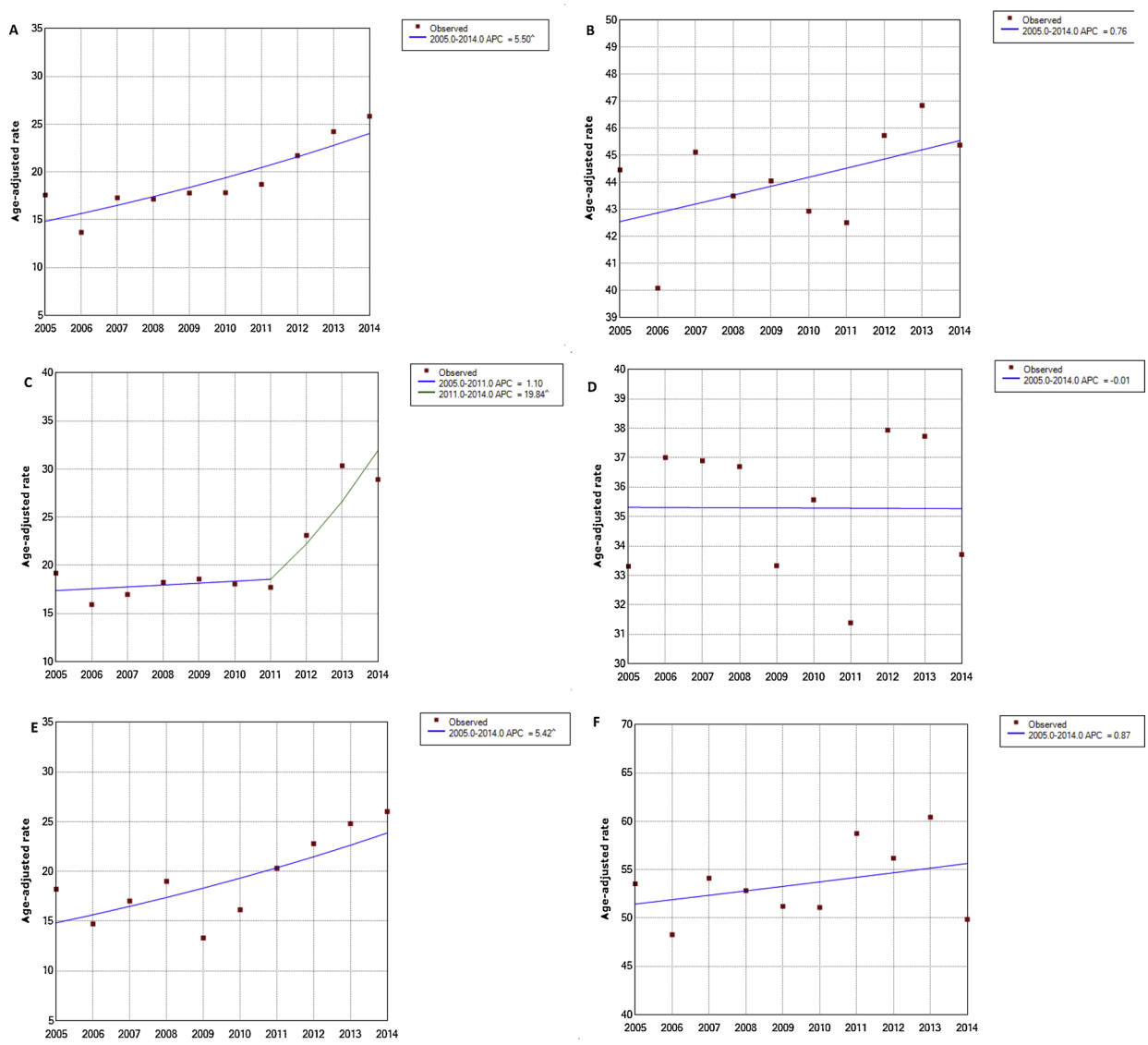

Fig. 1. Lung cancer incidence in women and men in Shanghai (A and B), Xuxhui District (C and D) and Songjiang District (E and F) between 2005 and 2014.

Table 4
Average annual percent change (APC) of incidence and mortality rate of lung cancer in Huxui District among men and women stratified by age at diagnosis from 2005 to 2014.

Age (years)	< 50	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85 +	Overall
Incidence										
Male	4.65	5.36	**9.46***	1.04	−1.46	−3.24*	−3.70	−4.22*	−3.89	−0.01
Female	**18.42***	2.51(2005–2011) **56.58* (2011–2014)**	5.94	**6.65***	**6.63***	**4.56***	0.34	−0.40	−2.35	1.10(2005–2011) **19.84* (2011–2014)**
Mortality										
Male	0.45	1.89	3.92	−1.51	−1.53	−3.44	**−5.44***	**−4.30***	−1.68	**−2.68***
Female	0.86	−3.66	−2.29	4.84	−0.79	3.33	−0.01	1.53	−1.03	0.91

* Statistical significance.

3.3. Lung cancer incidence and mortality rate among population in suburban area

In Songjiang district, lung cancer incidence rates in men did not change significantly from 2005 to 2014 (APC = 0.87%, P = 0.405) (Table 3, Fig. 1); while lung cancer incidence in women increased significantly during the same time period (APC: 5.42%, P = 0.001) (Table 3, Fig. 1). In men, lung cancer incidence did not change significantly in any age group; while in women, lung cancer incidence increased significantly in two age subgroups (60–64 and 80–84) with APC of 14.34% and 5.24%, respectively. Mortality rate of lung cancer did not change significantly from 2005 to 2014 in both men (APC = -0.51%, P = 0.259) and women (APC = -1.46%, P = 0.186). Lung cancer mortality did not change significantly in any age group for both men and women (Table 5). The absolute number of lung cancer incidence and mortality in Xuhui District and Songjiang District were provided in Supplementary Table 1.

4. Discussion

Using population-based incidence of lung cancer, we found that lung cancer incidence did not change significantly in men from 2005 to 2014 (APC = 0.76%, 95% CI: -0.27%-1.80%, P = 0.127); while lung cancer incidence increased significantly in women (APC: 5.50%, 95% CI: 2.94%–8.13%, P = 0.001) in Shanghai. The increase of lung cancer incidence among women was identified in both urban and suburban areas, but the patterns of change were different. In Xuhui District, lung cancer incidence in women did not change significantly between 2005 and 2011(APC = 1.10%, P = 0.328), but increased significantly since 2011(APC: 19.84%, P < 0.001), while in Songjiang district, lung cancer incidence in women increased significantly from 2005 to 2014(APC: 5.42%, P = 0.001).

The rapid increase in the incidence of lung cancers among women may be attributed to the introduction of LDCT screening. The incidence of lung cancer among women in Xuhui District rises sharply since 2011, when the results of NLST released. Xuhui district located in the center of Shanghai, while Songjiang district in the suburban of the city. There are several tertiary hospitals in Xuhui District, including Shanghai Cancer Center and Shanghai Chest Hospital, both of which provided LDCT lung cancer screening for eligible patients. While in the Songjiang district, health resources including LDCT are limited. The different accessibility of LDCT may contribute to the different patterns of lung cancer incidence of the two districts.

One alternative explanation for the different pattern of lung cancer incidence between male and female is that more indolent lung tumors were detected through LDCT in female than male. A study of baseline computed tomographic (CT) screening for lung cancer in North America showed that the prevalence of lung cancer among women was nearly twice as high as that among men of similar age and with similar smoking history, which suggested that lung cancer may progress faster in women [9]. LDCT screening for lung cancer is becoming increasingly popular in China over the last decade. Several community-based LDCT screening program is ongoing in Shanghai [5,10]. In a community-based LDCT screening program conducted in mainly in Xuhui District from 2013 to 2014, a high detection rate was found among females and non-smokers [5].

Our study has some limitations. First, we cannot determine which patients were diagnosed through LDCT screening, or how many people were screened in the different regions. There were no large scale of organized LDCT screening program in Shanghai, since LDCT screening were not offered by the government as a public health service item. However, due to the better accessibility of LDCT screening for patients in Xuhui District compared to Songjiang District, the different pattern of lung cancer incidence of male after 2011 may be attribute to introduction of LDCT screening. Second, those who died in one year could have been diagnosed in previous years, which may limit the evaluation effect of LDCT on the mortality rate of lung cancer. Third, the stages of lung were not available, thus the incidence and mortality rates could not be further stratified by lung cancer stages. Secondly, individual-level information on smoking behavior and other known risk factors for lung cancer except age are not routinely captured in medical records or in cancer registries, so we were not able to directly measure the contribution of these factors to the emerging higher risk among younger women. But the prevalence of smoking among women did not increased substantially. The use of tobacco products other than cigarettes, such as cigars and smokeless tobacco (e.g., chewing tobacco), has been much lower among women than among men [11]. The increase of lung cancer incidence is especially remarkable among relatively younger women, in which smoking prevalence is substantially lower. Futhermore, specific information about the LDCT screening received by each person is not known, and thus precluded the quantitative analysis of LDCT screening and incidence of lung cancer. Last, the interaction test showed the

Table 5
Average annual percent change (APC) of incidence and mortality rate of lung cancer in Songjiang District among men and women stratified by age at diagnosis.

Age (years)	< 50	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85 +	Overall
Incidence										
Male	3.04	1.82	3.34	0.10	−1.95	0.73	2.85	1.14	7.48	0.87
Female	5.91	4.78	4.43	**14.34***	0.92	4.22	5.06	2.11	**5.24***	**5.42***
Mortality										
Male	2.19	−5.84	0.54	−1.91	−3.54	−1.51	2.58	1.08	9.37	−0.51
Female	1.42	−10.51	−2.58	2.79	−7.69	−1.28	3.22	5.57	7.39	−1.46

different patterns of lung cancer incidence between Xuhui District and Songjiang District is not statistically significant, probably due to the fact only data from 2005 to 2014 were available, and further studies including more data from the years after 2014 are needed. But current data did indicate there is a clear trend toward definitely difference.

This study has several strengths and important implications for public health. This is the first population-based study to assess the impact of LDCT screening on lung cancer incidence and mortality rates in both urban and suburban area in China. Complete data on incidence and mortality rates were collected throughout the study time period in both areas. Results from this study suggested a higher future burden of overall lung cancer among women than among men as younger cohorts age, which further underscores the need to intensify prevention and screening measures to decrease lung cancer incidence among young women. Furthermore, our findings highlighted the importance of continued monitoring of sex-specific risks of lung cancer. Etiologic studies, including studies of sex differences in smoking-related susceptibility to lung cancer, are needed to further investigate the higher rates of lung cancer among young women [12].

In summary, we found that there is a steady increase in the incidence of lung cancer in women, especially after the wide use of LDCT screening, while there is no significant increase for men. Further studies are needed.

Conflict of interest

Fei Liang: None.
Chunxiao Wu: None.
Haiyan Gu: None.
Meiying Zhu: None.
Zeliang Xuan: None.
Yonggen Jiang: None.
Haiquan Chen: None.
Chen Fu: None.
Ying Zheng: None.

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.2019.04.020.

References

[1] W. Chen, R. Zheng, P.D. Baade, et al., Cancer Statistics in China, 2015, CA Cancer J. Clin. 66 (2) (2016) 115–132.
[2] J.B. Wang, Y.G. Fan, Y. Jiang, et al., Attributable causes of lung cancer incidence and mortality in China, Thorac. Cancer 2 (4) (2011) 156–163.
[3] K.M. Deppermann, H. Hoffmann, W.E. Eberhardt, Benefits and risks of lung cancer screening, Oncol. Res. Treat. 37 (Suppl 3) (2014) 58–66.
[4] 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.
[5] W. Yang, F. Qian, J. Teng, et al., Community-based lung cancer screening with low-dose CT in China: results of the baseline screening, Lung Cancer 117 (2018) 20–26.
[6] Z. Huang, W. Wen, Y. Zheng, et al., Breast cancer incidence and mortality: trends over 40 years among women in Shanghai, China, Ann. Oncol. 27 (6) (2016) 1129–1134.
[7] R. Doll, P. Cook, Summarizing indices for comparison of cancer incidence data, Int. J. Cancer 2 (3) (1967) 269–279.
[8] D. Clayton, E. Schifflers, Models for temporal variation in cancer rates. I: age-period and age-cohort models, Stat. Med. 6 (4) (1987) 449–467.
[9] C.I. Henschke, R. Yip, O.S. Miettinen, Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer, JAMA 296 (2) (2006) 180–184.
[10] X. Luo, S. Zheng, Q. Liu, et al., Should nonsmokers be excluded from early lung cancer screening with low-dose spiral computed tomography? Community-based practice in Shanghai, Transl. Oncol. 10 (4) (2017) 485–490.
[11] Prevention SCfDCa, The Shanghai Non-Communicable and Chronic Disease Surveillance Report 2013, Shanghai science popularization press, Shanghai, 2014.
[12] A. Jemal, K.D. Miller, J. Ma, et al., Higher lung cancer incidence in young women than young men in the United States, N. Engl. J. Med. 378 (21) (2018) 1999–2009.