CEBP **FOCUS: Geospatial Approaches to Cancer Control and Population Sciences**

Spatial Analysis of Regional Factors and Lung Cancer Mortality in China, 1973–2013

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Abstract

Background: China's lung cancer crude death rate has increased 6.9-fold from 1973 to 2014. During this time, the country experienced extremely rapid economic growth and social change. It is important to understand the effects of risk factors on lung cancer mortality (LCM) for better allocation of limited resources of cancer prevention and control in China.

Methods: Using three nationwide mortality surveys from 1973 to 2005, Global Health Data Exchange data in 2013, three nationwide smoking surveys from 1984 to 2013, four population censuses from 1964 to 2000, and other datasets, we have compiled datasets and developed spatial random effect models to assess the association of various area-level–contributing factors on LCM. Spatial scan statistics are used to detect high-risk clusters of LCM.

Results: LCM is higher in urban and more industrialized areas (RR = 1.17) compared with those in rural areas. The level of industrial development's effect is higher for men, which accounts for about 70% of all LCM. Smoking is positively associated with regional variation of LCM rates, and the effect is higher for women than for men.

Conclusions: The geographic pattern of high LCM in China is different from that of Western countries. LCM is positively associated with higher socioeconomic status, with more urbanized areas at a higher level of industrial development.

Impact: There is a need to further explore additional risk in the high-risk clusters. The study is about China, but this situation may happen in other countries experiencing rapid industrialization and other developing countries. *Cancer Epidemiol Biomarkers Prev; 26(4); 569–77. ©2017 AACR.*

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Introduction

Lung cancer is the leading cause of cancer-related death in China and has had the fastest increase in death rate among all cancers in the past 40 years. The crude death rate has increased 6.9-fold from 5.46 (1973–1975) to 43.03 per 100,000 and led to approximately 588,500 deaths in 2014 (1–3). Lung cancer accounted for a higher percentage of cancer-related deaths in China (26.8%) when compared with the world average (20%) in 2013 (4, 5). It was reported that the sharp increase of lung cancer mortality (LCM) for both men and women is clearly out of proportion to the population increase and is the least affected by demographic factors among all cancers in China (6, 7).

The regional disparity of LCM across China is very significant and ranges widely, from the highest rate of 66.3 in Liaoning to the lowest rate of 2.9 per 100,000 in Tibet in 2013 (8). Many factors, including cigarette smoking, exposure to carcinogens, environmental pollution, and socioeconomic factors, may directly or indirectly affect LCM, as well as the spatial variation of the rates. In this study, we aim to elucidate the most significant factors that affect the geographical variation of LCM rates in China.

Studies have shown that smoking is the main cause of LCM responsible for approximately 90% of all LCM. (4, 9–12) Researchers have also reported significant and increasing attributable risk of LCM associated with smoking in China (6, 12–16). Although 51.1% to 62.8% of Chinese men and 2.4% to 7% of women were smokers in 1984 to 2013 (13, 14), data show that smoking rate has been 3% to 15.2% lower in urban areas (13, 15, 16), but the LCM rate has been consistently 4.2 to 15.3 per 100,000 higher (17). Hence, in addition to smoking, this project aims to find other regional factors that may have significant contributions to the regional variation of LCM. Exposure to carcinogens has been recognized as one of the causes of lung cancer (9, 18, 19), such as metal mining and asbestos fibers (20–24), as well as household air pollution (2, 25–27). However, the effects are specific to a group of people in specific locations. Air pollution can cause lung cancer (28–32). The International Agency for Research on Cancer (Lyon, France) states that exposures to outdoor air pollution are linked to increased cancer risk in humans (33) and that the top three causes of air pollution are transportation, stationary power generation, and industrial emission (34). In contrast with postindustrial Western countries, China has experienced rapid industrialization since the 1950s. The sharp increase of energy consumption, transportation, and construction has resulted in serious air pollution and frequent smog problems in major cities (35, 36).

Regional socioeconomic status (SES) and its relationship to cancer is a relatively new field (37). Singh and colleagues (38) found that the relationship of SES and lung cancer reversed for

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men, higher male LCM in higher SES areas in the 1950s and lower LCM among the higher SES areas in 1998. Gomez and colleagues (37) reviewed 34 articles that studied the impact of neighborhood SES factors on cancer. They found that numerous associations of varying directions and magnitudes have been reported. European studies have demonstrated similar results in recent years although Vanthomme and colleagues reported that LCM was previously higher in high SES groups (39–41). Although SES may not be a direct determinant of LCM, evidence shows that it can be "highly correlated with differences in outcome and related to unknown environmental influences that cause cancer" (41, 42).

Small regional or case–control analyses have been performed for the attributable risk factors of lung cancer (43, 44); few in-depth studies have been conducted on the relationship between comprehensive regional factors and spatial disparity of LCM in a developing country. Study over an extended time period is rather scarce in a developing country, likely due to limited data availability.

Using the largest datasets from three nationwide retrospective mortality surveys from 1973 to 2005, three nationwide smoking surveys from 1984 to 2013, the Global Health Data Exchange in 2013, censuses from 1964 to 2000, and SES data, this research investigates the relationship between area factors and the spatial variation of LCM in men and women at both provincial and county levels over the past 40 years in China. The results offer policy implications on lung cancer control, prevention, and intervention not only in China but also in other developing countries.

Materials and Methods

Data

Outcome measure. This research uses China's two nationwide retrospective cancer mortality surveys (1973–1975 and 1990–1992), the causes of death survey (2004–2005), and the 2013 mortality data (8). Table 1 lists the details of the first three surveys. In addition to the 1973–1975 survey that covered 96.7% of 2,473 counties in China (45), the 1990–1992 and 2004–2005 surveys selected 263 and 158 counties, respectively, using a multistage stratified cluster random sampling method (17, 46, 47). Permanent residents of the selected counties, 848.7 million in 1973–1975, 111.7 million in 1990–1992, and 71.4 million in 2004–2005, were surveyed. To ensure accuracy and completeness, each of the surveys used several uniform questionnaires and organized advisory and quality control groups at the county, provincial, and national levels (17, 46, 48). All 241,650 lung cancer deaths were recorded according to the International Classification of Diseases (ICD) codes and verified by trained survey personnel or medical specialists in the advisory and quality control groups. The LCM data used in this research have the underlying cause of death as "Trachea, bronchus, lung cancers" of the ICD-10 C33-C34 for 2004 to 2005 and ICD-9 162 in the two previous surveys (17, 46, 48).

Covariates. To assess the impact of smoking on LCM, smoking prevalence rates were extracted from two nationwide smoking surveys in 1984 and 1996. The 1984 survey included 519,600 people ages 15 and older (random sample of 5/10,000) in 29 provinces in China (15). The 1996 survey (16) sampled the population in 145 sites of the Disease Surveillance Points System in 30 provinces. More than 1,000 households per surveillance site at the county level were surveyed by a randomized 3-stage sampling of households.

The province-level socioeconomic data are obtained from the 1986 and 1997 China Statistical Yearbook to match the years of the smoking surveys in 1984 and 1996 (49, 50). County-level socioeconomic measures come from the census data, which provide the most accurate county-level data in China. Details on the socioeconomic data are presented in the Supplementary Material and Supplementary Table S1.

Multiple linear regression analysis at the provincial level

The provincial-level analysis includes 14 variables in the following categories: income, employment, education, medical resources, smoking prevalence, and pollution (Supplementary Table S1). An initial correlation analysis (Supplementary Table S2) is performed to screen for variables that may have strong correlation with LCM rates. Area factors highly related to LCM with low collinearity are selected and included in the next step of

Table 1. Summary of China's three retrospective mortality surveys, 1973–2005

Survey	1973–1975	1990–1992	2004–2005
Years covered	3	3	2
Percentage of population surveyed	96.7%	10%	6%
Average annual population surveyed	849 million	112 million	71.4 million
Number of sampling sites (county or city)[a]	2,392	263	158
Total number of lung cancer deaths among surveyed population	139,011	58,646	43,993
Cancer death diagnosed at or above town/township level hospital	92.54%	97.4%	98.54%
Cancer death diagnosed at or above county level hospital	79.15%	91%	93.85%
Antemortem diagnosis was made by method Level I or Level II[b]	70.5%	89.6%	85.16%
Result of spot rechecks on mistakes in diagnosis and missing cases	About 5%	<5%	<5%
Total lung cancer crude death rate (per 100,000 person-year)	5.46	17.54	30.83
County-level lung cancer crude death rate (per 100,000 person-year)			
Minimum: male/female	0/0	2.15/0	0/0
Median: male/female	4.67/2.28	19.15/8.25	35.45/15.14
Mean: male/female	6.06/3.02	22.76/10.25	39.40/18.30
Maximum: male/female	73.21/23.32	93.95/41.80	98.24/83.46

NOTE: Data source: refs. 45–48.

[a]The surveys were carried out in all 29 provinces, autonomous regions, and municipalities of mainland China in 1973–1975, 27 provincial-level regions (including the addition of Hainan province) excluding Tibet Autonomous Region, Xinjiang Uygur Autonomous Region, and Qinghai province in 1990–1992, and all 31 provincial-level regions (including the addition of Chongqing municipality) in 2004–2005.

[b]Level I, diagnosis was made by pathologic or cytologic examination of tissue specimens, including bone marrow; Level II, diagnosis was made by X-ray, ultrasound, isotope, scans, endoscopy, exploratory laparotomy (without biopsy), immunologic markers, or chemical laboratory tests.

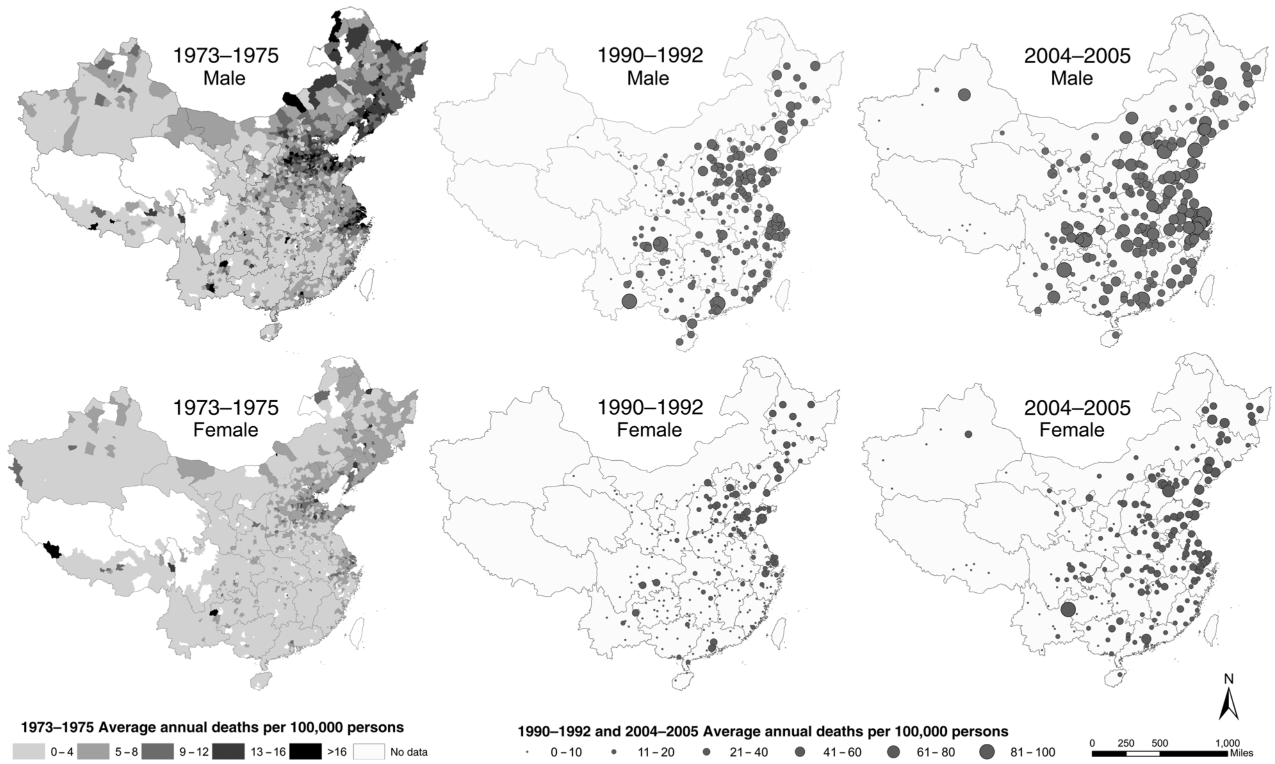

Figure 1.
LCM crude rate by county, sex, and survey year.

analysis. A multiple linear regression is performed to estimate the effects of the area factors on LCM rates. To allow for long lag period between exposure to LCM, the 1990–1992 LCM rates are regressed on the 1984–1985 area factors, and rates for 2004–2005 and 2013 are regressed on the 1984–1985 and 1996 area factors. Among the factors of interest, those identified as highly correlated to LCM are included in the multiple linear regression.

As most of the provincial-level regions in China are very large in both population and area, the provincial-level analysis may have covered a lot of variations at finer resolution. With the available county-level data from the mortality surveys and censuses, the county-level analyses were conducted in more details.

Poisson regression and cluster analysis at the county level

The number of deaths due to lung cancer is available by sex and county for each of the three mortality surveys. The number of deaths is assumed to follow a Poisson probability distribution, with expected deaths modeled as a function of population, the covariates, and spatial random effects between counties. Detail on the Poisson regression model is presented in Supplementary Material.

Results from the Poisson regression model explain the impact of each contributing area factor to LCM. What cannot be attributed to the contributing factors is revealed via residuals. Further investigation into the residuals points to areas where the contributing factors cannot fully explain the elevated LCM rates. A cluster analysis is performed on the original death counts (without model adjustment), as well as on the model-adjusted counts using the spatial scan statistics in the freely available software SaTScan™ (51). Details are presented in Supplementary Material.

Results

Figure 1 maps the crude LCM rate (deaths per 100,000 people) by county, sex, and survey year. For each of the three surveys, male rate is higher than female rate. Male LCM accounts for about 70% of all LCM in the three surveys. High rates tend to be clustered around major cities like Beijing and Shanghai.

The provincial level stepwise model selection identifies factors that are statistically significant ($P < 0.05$) on LCM (Table 2). Results show that female smoking prevalence is positively associated with female LCM rate in all the analyses; male smoking has no significant effect on male LCM. Industrial development, GDP level, solid and water pollution, and literacy level are all positively linked to LCM. The early measure of density of medical personnel is positively linked to LCM, and the later measure is negatively linked to LCM. The adjusted R^2 ranges between 0.344 and 0.855 in the provincial regression models.

Table 3 summarizes the results from the county level Poisson regression. Death count by county and sex is modeled with regional risk factors prior to the mortality survey year. For the 1973–1975 mortality, percentage of nonagriculture population has an increased risk of LCM for both males and females. On average, there was a 1% increase in LCM RR for every one percentage point increase of nonagriculture population for both sexes. The same factor was also positively correlated with LCM throughout the two later surveys for both sexes. During the 1990–1992 survey, LCM increased for urban areas, with higher high school education attainment level, percentage of industry labors, and smoking prevalence. Male LCM has more significant contributing factors when compared with female LCM. The men in urban

Table 2. Results of multiple linear regression (point estimate and 95% CI) of province-level area factors (1984–1996) on LCM rates (1990–2013)

	1990–1992 lung cancer death rate (26 regions)		2004–2005 lung cancer death rate (29 regions)		2013 lung cancer death rate (29 regions)	
Area level factor[a] and data source	**Male Slope (95% CI)**	**Female Slope (95% CI)**	**Male Slope (95% CI)**	**Female Slope (95% CI)**	**Male Slope (95% CI)**	**Female Slope (95% CI)**
1984–1985 China Statistical Yearbook						
% Female smoker		0.81[b] (0.60–1.02)		1.17[b] (0.78–1.56)		0.68[b] (0.32–1.05)
% Ind. labor	1.39[c] (0.51–2.26)		1.83[b] (1.35–2.31)			
% Serv. labor	−2.76[a] (−4.08 to −1.44)					
Cons. p.c.	0.08[c] (0.03–0.136)					
GDP p.c.		0.007[b] (0.004–0.009)				
Med. persn.			1.05[b] (0.55–1.55)	0.45[c] (0.13–0.76)	1.98[b] (1.31–2.65)	0.66[b] (0.40–0.91)
Waste water p.c.				0.12[c] (0.05–0.19)		
Solid waste p.c.					13.01[c] (3.27–22.75)	6.52[c] (1.98–11.08)
Adj. R^2	0.786	0.855	0.736	0.736	0.649	0.768
1996 China Statistical Yearbook						
% Female smoker				1.08[c] (0.25–1.92)		
% Ind. labor			3.42[b] (2.59–4.26)	1.38[b] (0.91–1.86)		
Med. persn.			−3.34[c] (−5.96 to −0.72)		−3.83[c] (−7.29 to −0.38)	
Literacy					1.23[b] (0.71–1.74)	0.47[b] (0.23–0.71)
Adj. R^2			0.748	0.608	0.430	0.344

[a]% of active female smokers among female population (% female smoker), % of industry labor force in population (% ind. labor), % of service labor force in population (% serv. labor), consumption per capita (cons p.c.), GDP per capita (GDP p.c.), medical personnel per 1,000 persons (med. persn.), % of literate people in population 12 years and over (literacy), and solid waste and waste water per capita (waste water p.c. and solid waste p.c.).
[b]$P < 0.001$.
[c]$0.001 < P < 0.05$.

areas have a LCM risk 17% higher than their counterparts in rural areas, whereas the risk for women is not significantly different between urban and rural areas. Smoking increases LCM rates in a region for both male and female, and the impact on female is higher than that on male. For every 1% point increase in smoking prevalence, male lung cancer RR increases 1% and female lung cancer RR increases 4%. Both the percentage of nonagriculture population in 1964 and the percentage of industry labor in 1990 were positively and significantly correlated with LCM in later years, but the 1982 measure of industry labor is not significant for either male or female data. The impact of percentage industry labor on LCM is slightly higher among males than females, with an estimated RR = 1.028 and the 95% confidence interval (CI), 1.013–1.042 for males, compared with RR = 1.015 and the 95% CI, 1.004–1.026 for females. During the 2004–2005 survey, counties were grouped as in the Eastern, Central, or Western regions in China (see Supplementary Fig. S1). Compared with Western China, Eastern China has higher RR of 1.29 (95% CI, 1.07–1.56) for male LCM and 1.21 (95% CI, 0.97–1.51) for female LCM. Central China did not show a significantly higher risk than Western China. Other factors that contributed to increased LCM risk were economic development level (measured by % of nonagriculture population in the 1964 census or % of industry labor in the later censuses) and higher smoking prevalence. Again, effect of smoking on regional variation of LCM is higher among women than among men (RR = 1.04 for female vs. RR = 1.009 for male). Across the three surveys, the pseudo R^2 ranges between 0.68 and 0.92, indicating a reasonably good model fit for the mixed effect model in the Poisson regression.

Figure 2 maps the clusters of high LCM risk without and with the Poisson regression model for the three sources of survey data. These are all statistically significant clusters with $P < 0.05$. Table 4 summarizes the male and female clusters in the 1973–1975 survey. Without model adjustment, five areas are identified as high-risk clusters for male LCM (Fig. 2, top left). They are listed as Clusters #1 through #5 with descending RR. Shanghai and the surrounding area have the highest RR of 3.59. The other clusters are all in major cities. With model adjustment that considers the percentage of nonagriculture population in the 1964 census, Cluster #1 is split into two, one smaller and more concentrated in the Shanghai area and the other "spilled" over to the neighboring Jiangxi Province (see Supplementary Fig. S1) in the more rural areas. A possible explanation is that although the crude

Table 3. Estimated RR (point and 95% CI) on effect of area-level risk factors on lung cancer deaths by county, sex, and year, China

Area-level factor and data source		1973–1975 ($n = 2,110$) Male Point (95% CI)	1973–1975 ($n = 2,110$) Female Point (95% CI)	1990–1992 ($n = 241$) Male Point (95% CI)	1990–1992 ($n = 241$) Female Point (95% CI)	2004–2005 ($n = 158$) Male Point (95% CI)	2004–2005 ($n = 158$) Female Point (95% CI)
1964 Census	% Nonagr pop	1.013[a] (1.012–1.013)	1.012[a] (1.012–1.013)	1.005[b] (1.001–1.009)	1.007[a] (1.004–1.010)	1.004[c] (1.000–1.007)	1.006[a] (1.003–1.009)
1982 Census	Urban			1.174[c] (0.982–1.402)	NS[d] (NS)	NS (NS)	NS (NS)
	HS edu			1.012[c] (0.999–1.025)	NS (NS)	NS (NS)	NS (NS)
	% Ind. labor			NS (NS)	NS (NS)	1.011[b] (1.001–1.021)	NS (NS)
1984 Smoking Survey	Smoking			1.013[b] (1.002–1.023)	1.042[a] (1.033–1.052)	1.009[c] (0.998–1.021)	1.040[a] (1.023–1.056)
1990 Census	% Ind. labor			1.028[a] (1.013–1.042)	1.015[b] (1.004–1.026)	NS (NS)	NS (NS)
2004 Mortality Survey	East					1.291[a] (1.067–1.563)	1.212[c] (0.972–1.512)
Pseudo R^2		0.728	0.676	0.887	0.924	0.881	0.904

Abbreviations: HS edu, high school population; ind. labor, industrial labor; nonagr pop, nonagriculture population.
[a]$P < 0.001$.
[b]$0.001 < P < 0.05$.
[c]$0.05 < P < 0.1$.
[d]NS, $P > 0.1$.

mortality rate is not high in Jiangxi, when considering the percentage of the nonagriculture population, the lung cancer risk in Jiangxi is about 33% higher than the areas not in the clusters. Similarly, "shift" or "spillover" is observed in other clusters except for Cluster #3. The RR in the original Cluster #3 is 1.92. After model adjustment, the cluster is split into two smaller ones, both with smaller RRs. For the female LCM data (Fig. 2, bottom left), 7 clusters are identified without the model adjustment. With model adjustment, one cluster (#5) disappears as it is mainly associated with the percentage of nonagriculture population. Three new clusters (#8–#10) appear as the percentage of nonagriculture population is not high enough to explain the elevated female LCM in those areas. It is also worth noting that the RR gets smaller after model adjustment for most of the clusters, and the remaining RR would be the result of a model for additional risk factors not considered already.

As the 1990–1992 and 2004–2005 surveys sampled noncongruent counties that were determined to be representative of province, the locations of these two datasets appear to be isolated counties in the map. The middle and the right panels in Fig. 2 are clusters for the 1990–1992 and 2004–2005 surveys. Without model adjustment, they all reveal a large cluster that spans from the Northeast to Shanghai. With model adjustment, the cluster shrinks to either mainly Shandong (female) or from Beijing to Shanghai (male). This implies that for the vast area of Northeast China, where there has been rapid industrial

Table 4. High-risk clusters for male and female LCM, 1973–1975, without and with model adjustment (columns are cluster #, major provinces, observed death count, expected death count, and RR)

Without model adjustment: Cluster (# of counties)	Major province	Death	Expect	RR	With model adjustment: Cluster (#of counties)	Major province	Death	Expect	RR
Male									
1 (42)	Shanghai	4,157	1,307	3.59	1-A (16)	Shanghai	2,262	1,052	2.26
					1-B (88)	Zhejiang, Jiangxi	1,106	843	1.33
2 (2)	Guangdong	227	106	2.15	2 (13)	Guangdong	439	328	1.34
3 (85)	Liaoning, Jilin	2,821	1,549	1.92	3-A (10)	Liaoning	470	340	1.39
					3-B (10)	Liaoning, Jilin	225	154	1.47
4 (89)	Beijing, Tianjin, Shandong, Hebei	2,694	1,550	1.82	4 (3)	Shandong	1,891	1,044	1.87
5 (122)	Shanxi, Henan	2,092	1,523	1.41	5-A (78)		1,344	1,023	1.33
					5-B (88)		1,106	843	1.33
Female									
1 (17)	Shanghai	1,293	404	3.45	1 (30)	Shanghai	1,212	704	1.80
2 (58)	Tianjin	1,216	503	2.57	2 (73)	Tianjin, Hebei	765	569	1.37
3 (52)	Liaoning, Shandong	1,105	507	2.29	3 (10)	Liaoning	205	134	1.54
4 (16)	Shandong	353	173	2.07	4 (59)	Shandong	1,006	535	1.96
5 (26)	Jilin	503	254	2.02					
6 (89)	Beijing, Hebei	785	497	1.62	6 (73)	Beijing, Hebei	765	569	1.37
7 (33)	Zhejiang	411	299	1.39	7 (33)	Zhejiang	392	267	1.48
					8 (2)	Chongqing	138	61	2.28
					9 (7)	Guangdong	192	111	1.74
					10 (29)	Shaanxi	168	84	2.01

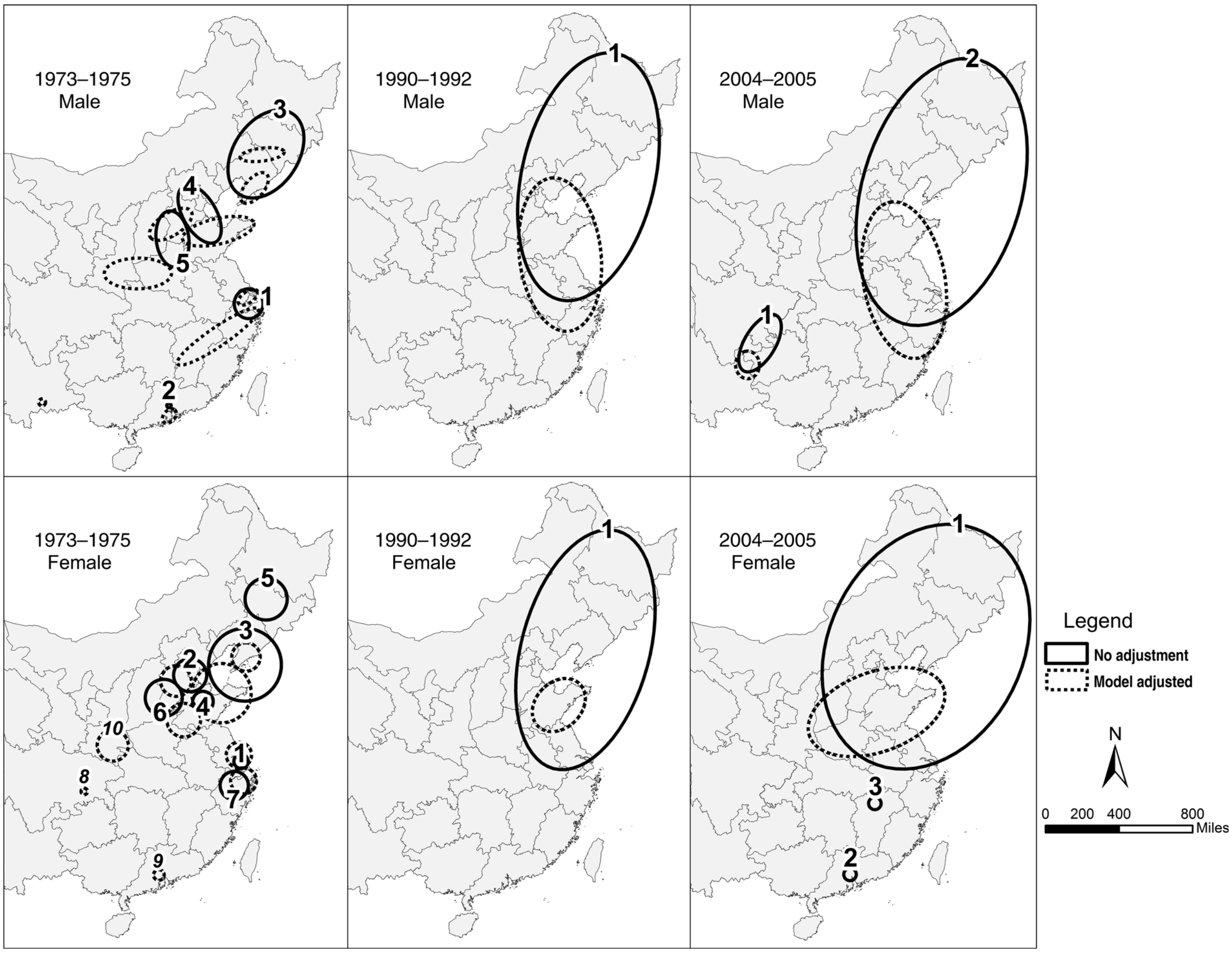

Figure 2.
Sigificant high-risk lung cancer mortality clusters detected without and with model adjustment, by sex and survey year.

development, the high LCM rate is most likely explained by the high industrial development level. In the middle part of East China (from Beijing to Shanghai), the industrial development level is not high enough to fully explain the high LCM rate, and further research is needed to explore more factors not considered in our study.

Discussion

The geographic pattern of high LCM in China is different from the current pattern in Europe and the United States, where higher LCM is associated with lower SES. However, during the economic expansion of post–World War II, LCM in the United States was higher in areas with higher SES. (38) It is possible that the trend of LCM in different level of SES in China is following the trend of the LCM in the United States, with a lag consistent to the lag in economic development. During the initial industrialization in a traditional agricultural society, higher cancer rates existed in more affluent areas where people are exposed to more pollution. Such areas also experience a faster increase of energy consumption and significant lifestyle changes from outdoor physical activities to indoor machine operation. In this period, people in more affluent areas may have more resources to buy and consume tobacco products. The pollution exposure and smoking behavior may interact and result in more complicated LCM patterns. These interactions may be responsible for a portion of LCM and at least partially explain the sharp increase and regional variation of LCM in the past 40 years in China.

Gender is an important factor that influences the impact of other regional covariates. In China, most men smoke. The average regional men's smoking rate remained around 60% in this study, with very little variation among regions. In a more recent report of 2010 data (52), men's smoking was still as high as 53%. Results in this study show that the impact of industrial development level on LCM is stronger than it is for women. A possible explanation is that in a work environment dominated by men, workers are exposed to air pollution as well as smoking and secondhand smoking, and the interaction makes the impact stronger. For women, the impact of smoking on the regional variation of LCM is stronger than that for men. Because of traditional views on women's behavior in China, smoking among women is relatively rare, but smoking among women varies widely between regions, largely due to local customs in some regions and rural areas. Regional female smoking rate ranges between 2% and 24% in the 1984 smoking survey. It is possible where female smoking rate is high, other confounders interact with smoking to increase the female LCM. Americans have more than halved smoking rates over the past five decades (53) through relentless pursuit of tobacco control; it is a long way to go on China's public view, policy making, and collective effort to control tobacco use, and it will remain an important task to monitor and report trends of LCM and its regional variations.

The results are particularly significant because China's resident registration system keeps the vast majority of the population in a place for decades. China's industrial development was highly controlled by the government for more than four decades after 1949. Under this central command system, more than 80% of the industrial output was produced by state-owned industries, and industrial laborers were permanent employees working in the same enterprises until retirement. Although rural industrialization and migrant workers gained momentum after the mid-1990s (54), the influence on the regional LCM rates in this research should be minimal because lung cancer's long latency period would require a period of at least 20 years from the date of exposure before assessing the risk of cancer. (55) Given China's 1.3 billion population and relatively stable regional inhabitants during our study period, the spatial variation of LCM explained by regional industrialization should be more reliable and provide a better understanding of the effect of early-stage industrialization on LCM.

Further study is necessary to identify the locations where the LCM may occur in the future so that early action for prevention and treatment measures can be taken. There is also a need to explore other risk factors that are not included in this study, especially in areas that are identified as high clusters with model adjustment. This study is about China, but this situation may happen in other countries experiencing rapid industrialization, such as India and other developing countries.

This study is not without limitations. First, the LCM rate is crude rate instead of age-adjusted rate, making it difficult to compare with other studies. The crude rate is used mainly because it is difficult to choose a standard population. Over the four decades of the study period, China implemented a family planning policy aiming to control population increase. The breadth and strength of implementing the policy, though, varies widely, making the population profiles complicated between regions. Using any standard population, age adjustment unavoidably under- or overestimates the LCM burden in certain areas, making it subjective to evaluate regional LCM burdens. On the basis of this consideration, crude rate is analyzed to evaluate the absolute burden on LCM and help the cancer control and prevention effort in allocating resources where they are mostly needed. Another possible issue is the sparseness of the county units in the two later surveys. As described, the county survey units were selected from the whole spectrum of LCM severity in a province, so that they provide a complete picture of LCM in their respective province. They are actually samples within a province representing the whole province's LCM status. As such, the resulting clusters actually span across provinces instead of counties. Any analysis of a sample needs to consider the sampling errors in the statistical model, which will bring extra computation burden. For simplicity and interpretation of results, this study does not seek approaches that involve survey design or sampling error. With the creation and development of cancer surveillance systems in China, it is with hope that population-based cancer surveillance data will become available in the near future, so that small-area spatial analysis based on county-level data is possible.

Conclusions

A spatial mixed effect model is applied to explain differences in LCM in China by gender, economic development level, and smoking behavior, Factors that significantly impact LCM are identified. Regions with high risk for LCM are identified. Those that remain to be high LCM clusters after model adjustment deserve further exploration in other risk factors.

This study shows that the Eastern China has a higher risk for LCM than the Western China and that the risk is higher in urban areas. At the provincial level, smoking increases the risk of LCM for women, and the association of regional variation of smoking rates to male LCM is not significant. At the county level, smoking increases the risk of LCM for both men and women, and the impact on the female regional variation of LCM rate is about 4 times as high as that of males. Both province and county level analysis show that a higher level of industrial development is associated with elevated LCM rates, with higher impact on males, which account for about 70% of all LCM. Higher education levels are linked to higher LCM rates, more for men than for women. High-risk areas are clustered in major cities and more affluent areas. After adjusting for a model that considers smoking, urban/rural status, region, education level, and industrial development level, high-risk clusters either shrink to smaller areas or shift to nearby areas. Additional factors contributing to high LCM risk is a topic for further epidemiologic study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: X. Shen, L. Wang, L. Zhu
Development of methodology: X. Shen, L. Wang, L. Zhu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X. Shen, L. Wang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): X. Shen, L. Wang, L. Zhu
Writing, review, and/or revision of the manuscript: X. Shen, L. Zhu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X. Shen, L. Wang
Study supervision: X. Shen, L. Wang, L. Zhu

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