Ambient air pollution and lung cancer in China: need for large-scale cohort studies

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Abstract: The lung cancer burden in China is substantial, with more than 0.79 million newly diagnosed cases and about 0.631 million deaths occurring in 2015. The incidence and mortality for lung cancer are relatively stable, however, the number of cancer deaths substantially increased because of the aging and growth of the population. Chinese government has implemented a series of mitigation actions to improving the air environment and protecting human health since 2012, however, the aforementioned facts highlight the importance and challenge of continued efforts. More importantly, in light of the limited cohorts for air pollutants' health effect, large-scale cohort studies with high quality are urgently needed to generate local evidence for developing countries with higher ambient exposures. In addition, an overwhelming need also exists to prioritize and integrate primary prevention and early detection measures into existing healthcare plans to reduce the occurrence of cancer.

Keywords: Lung cancer; ambient air pollution; epidemiology research

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Introduction

Lung cancer is the most commonly diagnosed malignancy and the first leading cause of cancer death in China, accounting for almost 0.787 million new cases and about 0.631 million deaths in 2015 (1). Air pollution, especially ambient air pollution, with the most serious levels in the world, has become one of the biggest threat to the health of the Chinese people (2). Therefore, it is imperative to understand the current patterns of lung cancer, ambient air pollution and researches considering its long-term effect on lung cancer in China from an international perspective, so as to direct future prospects of reducing the burden through targeted cancer prevention and cancer care.

In this review article, we first present an overview of the current lung cancer burden in China with measures of incidence, mortality, and the latest progress in ambient air pollution control. A systematic review was also performed to summarize the current status of related epidemiology studies, especially strengths and shortfalls, in order to supervise future researches and government investment in China as well as other countries facing similar challenge.

Lung cancer in China

Data sources

Cancer incidence and mortality data were sourced from the National Central Cancer Registry of China (NCCR), which collates cancer registry data from 368 local population

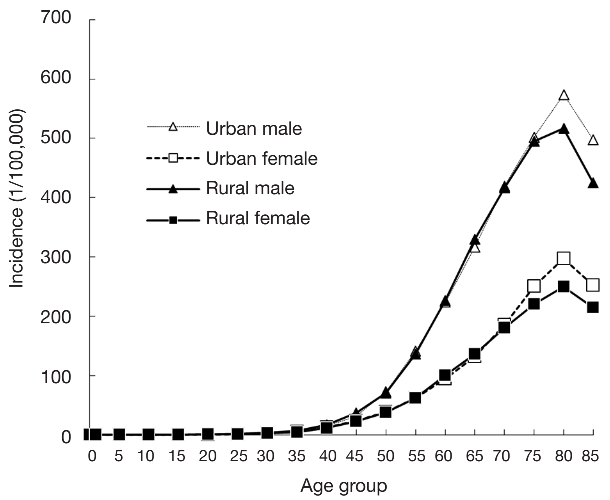

Figure 1 Age-specific incidence rates per 100,000 population, 2014.

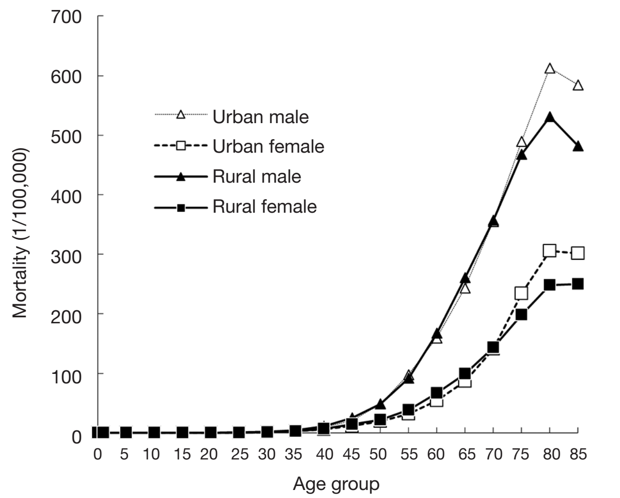

Figure 2 Age-specific mortality rates per 100,000 population, 2014.

based registries in China with a population coverage of 309.55 million in 2015. Detailed introduction of cancer registration in China has been described previously (3). Statistics presented in this review have been extracted mostly from the Chinese cancer registry annual report, in particular from the most recent version. The rest of the data were extracted from various published articles (1,4,5). Rates were age-standardized to the world standard population or Chinese census population, 2000, and reported the former as WASR for short.

Results

Lung cancer incidence in 2015

The total number of newly diagnosed lung cancer cases was 0.787 million (C33–C34) in 2015 in China, corresponding to almost 2,156 new lung cancer diagnoses on average each day. Lung cancer accounted for 20.0% of all sites combined (1), and its WASR incidence was estimated to be 35.92/100,000 in China in 2015 (4). The WASR lung cancer incidence for males and females were 48.87 and 23.52/100,000, respectively, which represented 0.520 million males and 0.267 million females affected. The urban area (48.25/100,000) owned a lower age-standardized incidence rate (by Chinese census population, 2000) for lung cancer incidence in male than that in rural area (49.24/100,000), whereas the rate for female was just the opposite (24.44/100,000 for rural, 22.82/100,000 for urban) (1). The age-specific lung cancer incidence rate was relatively low before 40 years old, and increased dramatically since then, reaching peak at the age group of 80–84 years both in male and female. Since then, incidence rates were significantly lower in females than males (*Figure 1*) (5).

Lung cancer mortality in 2015

The registered number of lung cancer deaths in China is 0.631 million for 2015, which is equivalent to an average of 1,729 deaths each day. Lung cancer accounted for 26.99% of all sites combined (1), and its WASR mortality was estimated to be 28.02/100,000 in China in 2015. The total lung cancer patients include 0.433 million males and 0.197 million females, corresponding to the WASR lung cancer mortality of 40.11 and 16.54/100,000 for males and females, respectively. The rural area showed a higher WASR lung cancer mortality (40.56/100,000) for male than that in rural area (39.81/100,000), and so did the rates for female (16.91/100,000 for rural, 16.66/100,000 for urban) (1). Age-Specific lung cancer mortality rates revealed a similar pattern as aforementioned incidence (*Figure 2*) (5).

Trends in incidence and mortality

Lung cancer was continue to be the leading cause of cancer mortality in China. For lung cancers, the WASR incidence rates were stable over the study period [2000–2013] for males, while slightly upward trends were observed for females (*Figure 3*). Similar to lung cancer incidence for male, the WASR mortality rates showed a stable trend for males, but a declining trend was observed for females (*Figure 3*) (6,7). Despite this favorable trend, however, the number of cancer deaths substantially increased during the

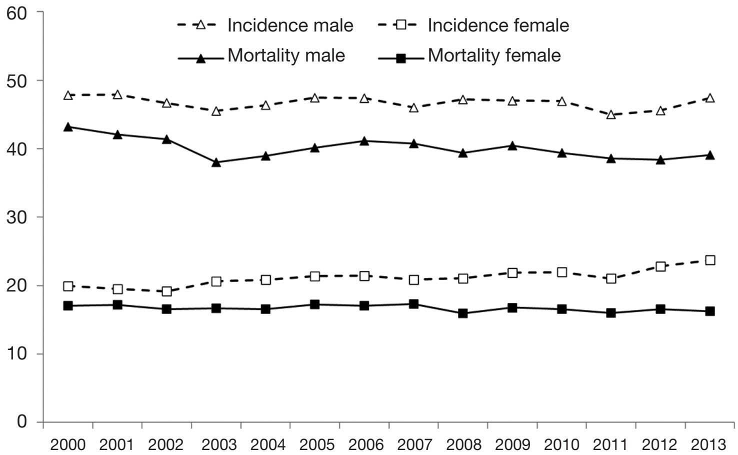

Figure 3 Trends in incidence and mortality rates (age-standardized to the world standard population) for lung cancer in China, grouped by gender.

Table 1 Annual concentrations of the six criteria air pollutants in 74 key cities in China in 2017 and their ambient air quality standards in China and WHO 2005 guidelines (unit: μg/m^3)

Air pollutants	2017 level, mean (SD)	GB3095-2012		WHO			
		Class 1	Class 2	IT-1	IT-2	IT-3	AQG
$PM_{2.5}$	47.0 (15.8)	15	35	35	25	15	10
PM_{10}	83.3 (29.8)	40	70	70	50	30	20
Nitrogen dioxide	39.2 (10.1)	40	40	–	–	–	40
Sulphur dioxide	17.0 (9.8)	20	60	125[a]	50[a]	–	20[a]
Carbon monoxide	1.7 (0.8)	4,000a	4,000[a]	–	–	–	–
Ozone	162.9 (24.0)	100[b]	160[b]	160[b]	–	–	100[b]

[a], 24 hours averaging time; [b], daily maximum 8-hour average concentration. SD, standard deviation; IT, interim targets.

corresponding period (up to 610,200 in 2015) because of the aging and growth of the population (*Figure 3*) (3).

Ambient air pollution in China

Air pollution levels remain dangerously high in China as reported by World Health Organization (WHO) in 2018, and of which ambient air pollution issue is much more outstanding (8). Indoor air pollution is beyond the scope of this review, we focused on outdoor air pollution. A more recent paper reported the annual concentrations of the six criteria air pollutants in the 74 key cities in China in 2017 (*Table 1*) (9), of which the concentrations of $PM_{2.5}$ and PM_{10} were very close to the values reported by WHO Global Ambient Air Quality Database (8). Reductions of annual average concentrations for $PM_{2.5}$, PM_{10}, sulphur dioxide, and carbon monoxide were observed from 2013, but the current concentrations for fine particulate were still more than four times higher than WHO recommendations, as well as were far above the Chinese Ambient Air Quality Standards (GB 3095-2012) for residential, commercial, cultural, industrial and rural areas (9-12). In addition, multi-contaminant air pollution was common in Chinese cities, while this phenomenon was less common in cities with a population of more than 10 million than in smaller cities (13).

Although the current situation of ambient air pollution is still not satisfactory, Chinese government has declared "war on air pollution", and implemented a series of mitigation actions to improving the air environment and protecting human health since 2012. China set limits for the first time on $PM_{2.5}$ and tightened up the standard thresholds for other pollutants in GB 3095-2012. Soon afterwards, to mitigate the serious levels of air pollution and the related adverse health impacts in China, the State Council of China issued the Air Pollution Prevention and Control Action Plan (APPCAP) in 2013. This action was considered to be the most stringent air pollution control policy in China to date, which comprises ten specific measures, and specific concentration goals were proposed for achievement by 2017 (14). The effectiveness has been evaluated with a significant decrease in levels of air pollution in the 5-year period (9). This finding brought inspiration for air quality management and public health interventions both in China and in other countries. Recently, China initiated another long-awaited three-year action plan for "winning the war for blue skies" for 2018 to 2020, which is regarded as the second phase of APPCAP but with tightened targets for specific pollutants as well as enlarged application cities (15).

Related epidemiology researches in China

Data sources

The PubMed, Embase, Cochrane library with four Chinese databases including CBMDisc, CNKI, VIP and Wanfang data were systematically searched to identify studies published until 20 November 2018 (date of last search), which examined the association between ambient air pollutants and lung cancer risk in China. The air pollutants of interest included particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), nitrogen oxides (NO_X), sulfur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3), which were measured as concentration.

Results

A total of 27 unique studies reporting about the association between air pollutants and cancer were identified, including six cohort studies, one case-control studies, and 20 ecological studies. Twelve of them were published in Chinese, and were all ecological studies. The research areas mainly covered Beijing-Tianjin-Hebei region (Beijing, Shanxi), The Yangtze River Delta region (Shanghai, Jiangsu, Zhejiang), Pearl River Delta region (Guangdong, Hong Kong), and Taiwan.

Overall, the studies contain 260 pollutants-cancer pairs, and 90.4% were from ecological studies. The outcome index for cohort and case-control study was exclusively morality or death, while only half of the ecological studies focused on incidence (*Table 2*). The top three attentions were focused on $PM_{2.5}$, SO_2 and NO_2. Primary sources of measurement for cancer were vital registry/death certificate and cancer registry, while those for pollutants were air-monitoring stations and environmental protection agency.

The basic information of included cohort studies and case-control studies were displayed in *Table 3*. Those studies were mainly published in the past ten years, and only one study has a sample sizes above 100,000. The follow-up years for cohort were entirely longer than ten years, however, none of them has set latent period. All cohort studies have adjusted age, sex and smoking status, while the majority (5/6) have also adjusted body mass index in original analysis. However, only one cohort study has adjusted other pollutants in the analysis, whereas few covariates were considered in case-control study. We didn't conduct meta-analysis, because there were no more than two studies focusing on the same pollutants-cancer pairs.

Discussion

We found an embarrassing situation that China faces with the heaviest burden from lung cancer and the most serious threat from ambient air pollution, but conducted disproportionately limited epidemiology studies about its effect on lung cancer, especially the cohort studies with higher level of evidence. Furthermore, a couple of disadvantages still need to be underscored in research scope, study design, as well as data analysis for few existing researches. All of the above lead to a reality that not only the parameters adapted in recent effectiveness evaluation but also the evidence of Chinese Ambient Air Quality Standards (GB 3095-2012) actually referred to data from United States and Europe (9,16). However, ambient exposures are much higher in China and the relative contribution of specific sources of air pollution differs from those in North America and Europe (17). Those inconsistences at least brought one major concern that whether it is applicable for simple extrapolation from other developed counties' data (18).

Three of the most essential cohorts in this field are Harvard Six Cities Study (HSCS) (19), European Study of Cohorts for Air Pollution Effects (ESCAPE) (20), and American Cancer Society Cancer Prevention Study-II (CPS-II) (21). Except for the eldest HSCS, their common features include basing on general population with super large sample size, being followed at least 15 years, collecting both incidence and mortality data, and focusing on various

Table 2 The distribution of included pollutants-cancer pairs according to basic characteristics (n=260)

Characteristics	Cohort study	Case-control study	Ecological study
Research pairs	20	5	235
Outcome index			
Incidence/occurrence	0 (0.0)	0 (0.0)	128 (54.5)
Mortality/death	20 (100.0)	5 (100.0)	101 (43.0)
Case number	–	–	6 (2.5)
Pollutants			
$PM_{2.5}$	8 (40.0)	0 (0.0)	68 (28.9)
PM_{10}	4 (20.0)	1 (20.0)	15 (6.4)
NO_2	3 (15.0)	1 (20.0)	36 (15.3)
NO_X	1 (5.0)	0 (0.0)	24 (10.2)
SO_2	4 (20.0)	1 (20.0)	74 (31.5)
CO	0 (0.0)	1 (20.0)	11 (4.7)
O_3	0 (0.0)	1 (20.0)	7 (3.0)
Outcome measurement			
Cancer registry	0 (0.0)	0 (0.0)	145 (61.7)
Hospital diagnosis	0 (0.0)	0 (0.0)	20 (8.5)
Surveillance	0 (0.0)	0 (0.0)	7 (3.0)
Vital registry/death certificate	20 (100.0)	5 (100.0)	63 (26.8)
Pollutants measurement			
Air-monitoring stations	19 (95.0)	5 (100.0)	20 (8.5)
Satellite/GIS based model	1 (5.0)	0 (0.0)	39 (16.6)
Published paper/data	0 (0.0)	0 (0.0)	52 (22.1)
Environmental protection agency/others	0 (0.0)	0 (0.0)	124 (52.8)

pollutants including $PM_{2.5}$, PM_{10}, NO_2, NO_X, SO_2, CO, and O_3, as well as adjusting critical covariates such as age, sex, smoking and body mass index in the analysis (19-21). Learning from those classical cohorts, a couple of suggestions could be summarized for further cohort studies in China as well as other developing countries.

First, the cohort sample size should be appropriately enlarged to at least hundreds of thousands given that the weak effect estimated for previous studies in developing countries and developed countries (19-23). Second, ozone should be investigated simultaneously with particulate matter and sulfur dioxide, especially in the context that an increase of average annual ozone concentrations were observed from 2013 to 2017 even with the effect of Air Pollution Prevention and Control Action Plan (9). Third, the majority of analyses in China as well as three classic cohorts have focused on individual pollutants, and without adjusting for other pollutants (24-26). The underlying assumption is that each pollutant has an independent impact, however, people in reality, especially in rapidly urbanizing developing countries where mixtures of contaminants are common, are more likely to be exposed to a mixture of pollutants (13). This calls for a shift from a single-pollutant to a multi-pollutant approach to countering the health effects of air pollution.

A positive feature of current studies in China is the attention on confounding adjustment, especially adjusting smoking and body mass index, which are well known risk

Table 3 Summary of studies included in the systematic review

Outcome index	Study	Journal	Quality score	Population source	Cohort	Pollutant duration	Outcome duration	Follow-up year	Cancer type	Pollutant type	Age	Sex	Sample size	# of case
Prospective cohort (n=6)														
Mortality	Zhou *et al*. 2014	*Environmental Pollution*	9	General population	China's 145 Disease Surveillance Points (DSPs).	1990–2005	1990–2006	17	Lung cancer	PM_{10}	40+	Male	71,431	817
Mortality	Cao *et al*. 2011	*Journal of Hazardous Materials*	9	General population	China National Hypertension Survey	1991–2000	1991–2000	10	Lung cancer	NO_X, SO_2	15+	Both	70,947	624
Mortality	Wong *et al*. 2016	*Cancer Epidemiol Biomarkers Prev*	9	General population	Elderly Health Centres cohort	1998–2001	1998–2001	10.3	Multiple types	$PM_{2.5}$	65+	Both	66,820	4,531
Mortality	Chen *et al*. 2016	*Sci Total Environ*	9	General population	Four Northern Chinese cities cohort	1998	1998–2009	12	Lung cancer	PM_{10}, NO_2, SO_2	23–89	Both	39,054	140
Mortality	Yin *et al*. 2017	*Environ Health Perspect*	9	General population	China's 145 Disease Surveillance Points (DSPs).	2000–2005	1990–2006	17	Lung cancer	$PM_{2.5}$	40+	Male	189,793	2,523
Mortality	Peng *et al*. 2017	*Sci Total Environ*	8	Patients	Chinese TB patients cohort	2000–2013	2003–2013	11	Respiratory cancer	$PM_{2.5}$	All	Both	4,444	91
Case-control study (n=1)														
Death	Liu *et al*. 2009	*Inhal Toxicol*	7	Hospital based	–	1995–2005	1995–2005	–	Lung cancer	PM_{10}, NO_2, SO_2, CO, O_3	50–69	Female	3,352	1,676

Note: The "sample size" column for case-control study means the number of controls.

factors for lung cancer (27,28). The existing studies, no matter their qualities, initiated the first phase for Chinese air pollution researches, and are exactly the impetus to open a new phase at the present stage. The Chinese government has also been fully conscious of the arduous challenge to tackle its air pollution problem as well as the urgency and importance to collect specific evidence for Chinese population. The Chinese government funding has supported and started a dozen of population cohorts, and established the Premier funding project to overcome key technical issues in air pollution studies. The ongoing projects contain the China Kadoorie Biobank (CKB-Air) (29), 33 community Chinese health study (33CCHS) (30), the WHO Study on Global Ageing and Adult Health (SAGE) (31), the Prospective Urban and Rural Epidemiological study in China (PURE-China) (32), CHARLES-Air, China-Leap, etc. Most of those cohorts include tens of thousands participants, and focus on several types of pollutants including at least $PM_{2.5}$, PM_{10}, Nitrogen dioxide, Sulphur dioxide, Carbon monoxide, and Ozone. The outcome is not just cancer but also cardiovascular diseases, respiratory diseases, as well as plenty of physiological indexes, such as lipids level, blood pressure.

Conclusions

As the largest developing country in the world, China faces with one of the most serious levels of air pollution as well the biggest size of lung cancer patients in the world. Public concern and awareness about ambient air pollution and health including lung cancer have risen to an unprecedented level in China. The aforementioned facts highlight the importance of continued efforts to monitor trends in lung cancer and air quality. But more importantly, in light of the limited cohorts for air pollutants' health effect, large-scale cohort studies with high quality are urgently needed to generate local evidence for developing countries with higher ambient exposures. In addition, an overwhelming need also exists to prioritize and integrate primary prevention and early detection measures into existing healthcare plans to reduce the occurrence of cancer.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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