The Lag Effect of Long-Term Exposure to PM2.5 on Esophageal Cancer in Urban-Rural Areas Across China

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Long-term exposure to PM_{2.5} pollution is a significant health concern and increases risks for cancers in China. However, the studies regarding the effect of PM_{2.5} and esophageal cancer incidence (ECI) among urban-rural areas are limited. In this study, we examined the sex- and area-specific association between long-term exposure to PM_{2.5} and ECI, as well as explored the corresponding lag effects on ECI using a geographical weighted Poisson regression. We found that each 10 ug/m³ PM_{2.5} caused ECI risk increases of 1.22% (95% CI: 1.09%, 1.36%) and 1.90% (95% CI: 1.66%, 2.14%) for males and females after covariates controlled, respectively, during the study period. Moreover, the higher 0.17% and 0.64% incidence risks for males and females in rural areas than urban areas, as well as a larger lag period in rural areas, respectively. In addition, higher risks for both sexes appeared in north, northwestern, and east China. The findings indicated that long-term exposure to PM_{2.5} was significantly associated with increased risks for ECI, which reinforce a comprehensive understanding for ECI related to PM_{2.5}.

Key words: PM_{2.5}, Esophageal cancer incidence (ECI), lag effect, risk, China

Introduction

Esophageal cancer (EC) is one of common and leading cause of cancer in China and worldwide. In 2017, there were new 473,000 cases of EC in world, 49.68% of which occurred in China (Kamangar et al., 2020). Therefore, China has the most cases and heaviest burden. According to a report from National Cancer Center of China, esophageal cancer incidence (ECI) ranks the sixth leading cause and consists of 6.69% of all cancer cases. In 2015, there were 44,067 and 17,667 cases, accounting for 8.64% and 4.28% for males and females of all cancer cases, respectively (Chen et al., 2016).

Several studies have showed that considerable proportion of EC were attributable to smoking and alcohol (Ishiguro et al., 2009; Steevens et al., 2010). However, some multi-site cohort studies from China and Iran proved these risks factors contributed little to EC in high-risk areas as they were rarely occurred (Gholipour et al., 2016; Wen et al., 2017). Moreover, the prevalence of smoking and alcohol drinking significantly differed among men and women in high-risk areas, but the ECI was similar (Abedi-Ardekani et al., 2010). These implied that other risk factors play important roles in ECI. Particulate Matter (PM_{2.5}) has been identified as Group I carcinogen by the International Agency for Research on Cancer (IARC), contributing to 4.2 million premature deaths worldwide (Cohen et al., 2017). Furthermore, it has elevated to the fourth leading risk factor of deaths and led to more than 1.1 million deaths in China (Zhou et al., 2019). Therefore, PM_{2.5} has become a growing concern whose impacts on health need to be explored.

Most studies related to the PM_{2.5} risks in developed countries revealed that the adverse effects of PM_{2.5} on health was a severe threat to cancers, including EC. For example, a meta-analysis included 5 case-control and 15 prospective cohort studies proved that a significant association between PM_{2.5} and non-lung cancers (Kim et al., 2020). The studies from European cohorts also found that PM_{2.5} pollution was associated with lung, breast, stomach and upper aerodigestive tract cancers (Raaschou-Nielsen et al., 2013; Weinmayr et al., 2018). In addition, some studies also reported EC risks related PM_{2.5} or air pollution. An ecological study from China found a significant association between PM_{2.5} and EC (Wang et al., 2019). Similar study suggested that some air pollutants were a contributor on EC after controlling other confounders (Huang et al., 2017). A case-control study from Europe showed a significant exposure-response relationship of indoor air pollution and EC, and reported an elevated 2.71-fold risk for EC (Sapkota et al., 2013). Moreover, other studies further reinforced the evidence of significant effects of PM_{2.5} pollution caused by biomass fuel on EC (Okello et al., 2019; Sheikh et al., 2019; Sheikh et al., 2020). However, such studies were still lacked as they were either from developed countries or limited in a small area.

PM_{2.5} remains an elevated level and includes hazardous substances such as polycyclic aromatic hydrocarbons (PAHs) in China for a long time. 500 PAHs and their derivatives have been detected in air where more than 90% PAHs with 4-6 rings or high toxicity distributed in PM_{2.5}, since PAHs tend to appear in PM_{2.5} compared to coarse particles as well as coal consumption was a common source of PAHs and PM_{2.5} (Liu et al., 2017; Zhang et al., 2017). Besides, PM_{2.5} is a carrier of toxic compounds that includes various hazardous substances (i.e. chemical elements, heavy metals, PAHs), leading to the damage of chromosomes, DNA, and other genetic materials (Chu et al., 2015; Ghio et al., 2018; Wang et al., 2020). A case-control study in Iran provided the evidence for a causal role for PAHs in EC and suggested a dose-response relationship (Abedi-Ardekani et al., 2010). Similar studies from China, Brazil and South African all proved the roles of PAHs in EC pathogenesis (Abedi-Ardekani et al., 2010; Abnet et al., 2018; Ferndale et al., 2020).

PM_{2.5} pollution still is a severe health concern as PM_{2.5} concentration and carcinogenic constitutes remain a marked urban-rural difference across China. Thus, it is essential to understand the health effects of PM_{2.5} on EC in view of geographical variations and sex differences. In this study, we firstly examined the association between long-term exposure to PM_{2.5} and ECI using yearly incidence and the annual PM_{2.5} concentration of 2007-2015. Then, we explored the sex- and area-specific ECI risks for long-term exposure to PM_{2.5} by applying a geographic weighted Poisson regression. Finally, we quantified the lag effects of PM_{2.5} with successive 9 years before ECI for sexes and urban-rural differences across China. The results of this study provide evidence for targeting priority areas of ECI risks related to PM_{2.5} and valuable information for specific health policies.

2. Materials and Methods

2.1 Data collection

2.1.1 Health outcome

We collected ECI from China Cancer Registry Annual Report, released by National Cancer Center (NCC) in terms of International Classification of Diseases version 10 (ICD-10). According to Guideline of Chinese Cancer Registration and the criteria of cancer registration by International Agency for Research on Cancer (IARC), some indicators, such as metastasis verify (MV, %) death certificate only (DCO, %) and ratio of mortality to incidence (M/I) were used to control quality. The assessment result assured the data comparability, completeness, validity and timeliness.

Specifically, we extracted ECI in 2015 from 2018 China Cancer Annual Report, and collected EC cases, sex-specific incidence and age-specific standardized incidence (standardized by Segi's world population) at 388 cancer registries institutes (CRIs, county-level areas) in the mainland of China. These CRIs covered 31 provinces, autonomous regions and municipalities, including over 320 million population (162 million males vs 152 million females), which accounted for 23.35% national population (48.03% urban population and 51.97% rural population). Because of population density, these CRIs were not evenly distributed in China (Fig. S1).

2.1.2 Variable

PM_{2.5} data (spatial resolution: $0.01^{\circ} \times 0.01^{\circ}$) from 2007 to 2015 were captured from data center of Global Annual PM_{2.5} Grids from MODIS, MISR and Sea WiFS Aerosol Optical Depth (AOD) with China Regional Estimate, released by National Aeronautics and Space Administration, NASA (<https://search.earthdata.nasa.gov/>). In this dataset, the Aerosol Optical Depth (AOD) product was retrieved by multiple satellite instruments of the NASA Moderate Resolution Imaging Spectroradiometer (MODIS), the Multi-Angle Imaging Spectroradiometer (MISR), and the Sea-Viewing Wide Field-of-View Sensor (SeaWiFS) using a GEOS-Chem chemical transport model. Subsequently, regional ground-based observations of both total and compositional mass were calibrated by Geographically Weighted Regression (GWR). Van Donkelaar employed a GWR model to demonstrate the accuracy of satellite data in Mainland of China ($R^2=0.81$) (van Donkelaar et al., 2019). To date, this dataset has been widely used to assess health risks (Guo et al., 2020b; Liu et al., 2020). We calculated and extracted the average concentration of PM_{2.5} by the polygon of each county over the periods of 2007-2015.

2.1.3 Covariates

Water quality was obtained from National Environmental Monitoring Center that monitors water quality according to Technical Specifications Requirements for Monitoring of Surface Water and Waste Water (HJ/T 91-2002). The public can freely access to the indicators of water quality (<http://www.cnemc.cn>). In this study, we used ammonia nitrogen (NH₃-N) and chemical oxygen demand (COD_{Mn}) to evaluate water quality as they were available and consecutive. The indicators were examined by methods of gas-phase molecular adsorption spectrometry and fast digestion spectrometry, respectively (<http://www.cnemc.cn/jcgf/shj/>). We collected NH₃-N and COD_{Mn} concentrations from all national water quality surveillance points (WQSPs) in 2007-2015. For example, there were 245 WQSPs that distributed over 31 provincial administrative regions in mainland China in 2015. Subsequently, we estimated the NH₃-N and COD_{Mn} concentrations

of missing areas through Kring interpolation and zonal statistics(Belkhiri et al., 2020).

Socioeconomic covariates included nightlight level (NLL) and average education year. NLL is a comprehensive proxy of urbanization, population density, GDP and economic activities, which has been widely applied in related health concerns (Nadybal et al., 2020; Wu et al., 2020). In this study, NLL layers with a spatial resolution of 1 km were downloaded from the Data Center for Resources and Environmental Sciences, Chinese Academy of Sciences (RESDC) (<http://www.resdc.cn>). Its light intensity ranges from 0 to 63, the larger values mean the higher socioeconomic levels. Because the NLL data were available in 2000-2013, we estimated the corresponding data in 2014-2015 by average variation rate. Moreover, average education year was defined as the average year among population aged 6 years or older in each area, derived from China Population Census in 2010.

Past literature showed that PM_{2.5} was influenced by temperature, precipitation, and normalized vegetation index (NDVI)(Wei et al., 2019). We adjusted the corresponding confounders of annual PM_{2.5} in each county. Moreover, spatial location (longitude and latitude) and a dummy variable for also were adjusted. In this study, these indicators were derived from website (<http://www.resdc.cn>). The involved variables and covariates were presented in Fig. S2.

2.2 Statistical analysis

We used geographically weighted Poisson regression function (GWPRF) with temporal and spatial terms to examine the effect of PM_{2.5} on ECI. We examined the effect from global view where the spatial term was smooth the spatial disparities by a natural cubic spline function. However, given the spatial non-stationarity and heterogeneity of health outcome, we calibrated GWPRF through introducing local terms. Moreover, an adaptive bi-square kernel and golden selection search were used to determine spatial weights and bandwidth, respectively. The function framework was presented below, and the other detailed information was elaborated in published literature (Cheng et al., 2011).

$$y_i = \beta_0(u_i, v_i) + \sum_{j=1}^n \beta_k(u_i, v_i)x_{ij} + \varepsilon_i \quad i = 1, 2, \dots, n$$

Where y_i represents the ECI at county i . u_i, v_i marks the geographic coordinate of county i , β_k is the coefficients for variable x_{ij} at different counties. β_0 and ε_i are the intercept and stochastic variables, respectively.

We constructed three models based on GWPRF to estimate the effect. Model 1 only included the annual PM_{2.5} and time, location and urban-rural dummy variables. Model 2 further adjusted for water quality (i.e., NH₃-N and COD_{Mn}). Model 3 further adjusted for socioeconomic factors based on Model 2. Notably, to examine the lag effect of long-term exposure to PM_{2.5} on ECI, we established the models with single-year lags (same year (lag0), 1 year prior (lag1) ... 8 year prior (lag8)). Given that single-year lag structures might underestimate the lag effects, we also evaluated the cumulative ECI risks using moving average-year lags (lag01, lag02 ... lag08) before baseline incidence.

Moreover, two sensitive analysis were implemented to examine the robustness of the results. Firstly, we applied Model 3 in three economic regions (East, Middle and West China) to examine the results in different economic levels. Secondly, other confounding factors (i.e., temperature,

170 precipitation and NDVI) were further included based on Model 3, as well as exposure windows
171 were also adjusted to check whether the effects of PM_{2.5} on ECI would be modified. All the results
172 were examined at 95% confidence interval (CI). All analysis was processed in GWR 4.0 (GWR4
173 Development Team) and the results were visualized in ArcGIS 10.6 (ESRI, Redlands, CA, USA).
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3. Results

3.1 Descriptive statistics

The mean ECI for males was 19.48±17.73 per 100,000 persons, ranging from 0.48 per 100,000 persons in Xinning to 113.56 per 100,000 persons in Cixian. In parallel, the mean ECI for females was 7.50±11.06 per 100,000 persons, ranging from 0.00 per 100,000 persons in Xiajiang, Furong, Linwu, Wuzhishan, Shimian and Chengjiang to 63.36 per 100,000 persons in Cixian. These suggested a great variation among areas. Moreover, there was a marked distinction of ECI between rural areas and urban areas (Table 1).

During the study period, the mean PM_{2.5} concentration was 50.32 ug/m³ that was greatly higher than the guideline value (10 ug/m³) of WHO. Furthermore, PM_{2.5} showed a marked difference varying from 4.22 ug/m³ to 102 ug/m³. Similarly, the differences for NH₃-N and COD_{Mn} were 13.15-fold and 6.62-fold among areas. The detailed information of other covariates was presented in Table 1 and Figure S2.

Table 1. Descriptive statistics of ECI (age-standardized, per 100,000) and exposure variables

		Mean	SD	Min	P ₂₅	P ₅₀	P ₇₅	Max
Incidence	All							
	Male	19.48	17.73	0.48	7.78	13.27	24.29	113.56
	Female	7.29	10.04	0.00	1.15	3.25	8.71	63.36
	Urban							
	Male	16.26	13.86	1.15	7.61	11.00	20.50	84.44
	Female	5.10	7.40	0.00	0.91	2.11	6.00	40.46
	Rural							
	Male	21.57	19.60	0.48	8.27	14.84	30.77	113.56
	Female	8.71	11.23	0.00	1.46	3.58	12.11	63.36
Exposure	Edu (male)	9.47	1.02	6.90	8.81	9.26	9.84	13.39
	Edu (female)	8.60	1.25	4.80	7.80	8.34	9.20	12.64
	NH ₃ -N	0.98	0.49	0.26	0.70	0.86	1.11	3.42
	COD _{Mn}	4.88	2.00	1.33	3.40	4.56	6.06	13.23
	PM _{2.5}	50.32	19.00	4.22	38.33	50.95	62.75	102.00
	TEM	15.30	4.85	4.93	13.66	16.10	18.22	25.86
	PER	903.60	558.78	3.33	531.00	897.43	1349.51	2485.58
	NDVI	0.70	0.15	0.11	0.65	0.75	0.81	0.90
	NLL	13.17	14.93	0.16	2.73	7.71	16.13	63.00

(P₂₅, P₅₀, P₇₅ denote the 25, 50, and 75 percentiles, respectively, SD: Standard deviation; Min: Minimum; Max: Maximum; Edu: Average education year; TEM: Mean temperature (°C); PER: Mean precipitation (mm); NDVI: Normalized difference vegetation index; NLL: Mean nightlight level.)

3.2 Lag effect of PM_{2.5} on ECI risks

We found a significantly positive association between PM_{2.5} and ECI, as well as a stronger association for females than males. Model 1 showed that the greatest risk for males and females was 1.32% (95% CI: 1.20%, 1.45%) and 2.70% (95% CI: 2.49%, 2.92%) at lag4, respectively. When water quality was included in Model 2, the greatest risk for males was 1.17% (95% CI: 1.03%, 1.31%) occurring at lag7, the corresponding risk for females was 2.09% (95% CI: 1.87%, 2.30%) at lag4. Model 3 was further adjusted for socioeconomic covariates based on Model 2, presenting the maximum magnitude of risks was 1.44% (95% CI: 1.30%, 1.59%) and 2.42% (95% CI: 2.17%, 2.66%) for males and females at lag7 and lag4, respectively (Figure 1).

When stratified by urban-rural dummy variables, the three models all showed the stronger association in rural areas than urban areas, suggesting rural residents were more sensitive to PM_{2.5}. Moreover, a shorter lag period occurred in urban than rural areas due to the higher PM_{2.5} concentrations. Figure 3 (a, b) showed that the geographical variation of the relative risks (RRs) of PM_{2.5} for males and females, respectively. The higher RRs appeared in north, northwest, and east of China; meanwhile, a higher RRs only for females also appeared in south areas of Northeastern China.

Figure 1. The lag effect of PM_{2.5} on ECI (per 100, 000) (Model 1 includes a, b, c; Model 2 includes d, e, f; Model 3 includes g, h, i.)

3.3 Cumulative ECI risks

During the study period, the cumulative risks tended to be generally stable with fluctuation in different exposure windows. We calculated the cumulative ECI risks of exposure to $PM_{2.5}$ in different models, the results of which supported the association of $PM_{2.5}$ and ECI as well. Model 1 showed that each $10\mu g/m^3$ $PM_{2.5}$ caused the maximum elevation of 1.28% (95% CI: 1.16%, 1.41%) and 2.49% (95% CI: 2.29%, 2.70%) for ECI risks among males and females in average 5-year exposure (lag05), respectively (Figure 2a). When all covariates were controlled, the cumulative risks were 1.22% (95% CI: 1.09%, 1.36%) and 1.90% (95% CI: 1.66%, 2.14 %) for males and females, respectively (Figure 2g). In addition, the higher cumulative risks of exposure to $PM_{2.5}$ in rural than urban areas.

Figures 3 (c, d) represents that cumulative risks geographically varied among areas. During the study period, the areas of higher RRs did not change dramatically. Although the more risk areas were in males, the risk magnitude was lower than that of females.

Figure 2 Cumulative $PM_{2.5}$ risks for ECI (per 100,000) (Model 1 includes a, b, c; Model 2 includes d, e, f; Model 3 includes g, h, i.)

Figure 3. Spatial variation of the association between PM_{2.5} and ECI among males and females in 388 areas (a, b denote the single risks for males and females, respectively; c, d denote the cumulative risks for males and females, respectively)

3.4 Sensitive analysis

The results of sensitive analysis were showed in Figure S3, stratified by economic regions, the positive association between PM_{2.5} and ECI was unaffected. When other confounding factors were controlled, the association between PM_{2.5} and ECI still remained significant (Figure S4). These suggested that our analysis was stable and robust.

4. Discussion

This study analyzed the lag effect of long-term exposure on PM_{2.5} and ECI in 388 areas across China. Moreover, we also explored the disparities of ECI risks by urban-rural areas and sexes using GWPRF to construct different models. Our findings provide valuable information for prevention and control strategies in China, and experience for alike countries.

We found that long-term exposure to PM_{2.5} was significantly associated with the increased ECI, which was consistent with our previous findings (Li et al., 2020). Similarly, a cross-sectional study from China observed multiple air pollutants were an contributor for ECI after controlling other confounders (Huang et al., 2017). Moreover, a case-control study from Europe demonstrated a significant exposure-response relationship of indoor air pollution and EC and found an elevated 2.71-fold risk for EC (Sapkota et al., 2013). Although the estimated effects of PM_{2.5} on ECI, PM_{2.5} is a representative component of air pollution in view of its ubiquity and potential carcinogenicity. Biologically, PM_{2.5} includes numerous toxic compounds such as heavy metals (i. e. lead, mercury, cadmium), PAHs (i. e. BaP, PHE, BaA, IcdP) and pathogenic microorganisms (i. e. bacteria, viruses and fungi), causing oxidative stress on epithelial cells to produce reactive oxygen species that can damage DNA, proteins and lipids, and further to invade malignant cells in organs (Wong et al., 2016; Liang et al., 2019; Cheng et al., 2020). Plenty of studies explored that the association of PM_{2.5} with health outcomes, and generally proved the adverse effect of PM_{2.5} on health outcomes and elevated cancer risks (Coleman et al., 2020; Xu et al., 2020; Li et al., 2021). Han et al assessed the cancer risks of PAHs in air pollution and found that exposure to PAHs was estimated to cause 15,198 excess cancer cases in China (Han et al., 2020). PAHs bind to DNA to generate PAH-DNA adducts that could lead to mutations of proto-oncogenes and tumor-suppressor genes (Qin et al., 2020). Moreover, PAH-DNA adducts preferentially occur at mutational hotspots of P53 gene that has higher mutational frequencies in Asian EC (Olivier et al., 2010; McCormack et al., 2017; Hwa Yun et al., 2020). Similar results also have been confirmed in epidemiological studies from China (Guo et al., 2020b), Japan (Ueda et al., 2016), United States (Wei et al., 2020) and Iran (Ali-Taleshi et al., 2020).

PM_{2.5} exerted higher effect on ECI in rural areas. The result seems unexpected, but similar results have been proved by previous studies. Wang et al conducted an ecological study to explore the relationship between PM_{2.5} and common cancers in urban and rural areas and the results showed that PM_{2.5} significantly elevated the risks of certain cancers (Wang et al., 2019). Garcia et al developed a Poisson model to estimate risk difference caused by PM_{2.5} in urban and rural California. They also observed that PM_{2.5} was significantly associated with all-cause mortality in rural areas (Garcia et al., 2016). Although air pollution was heavier in urban areas, the incidence risk was higher in rural areas as this might be influenced by outdoor activity patterns, socioeconomic status, anti-pollution behaviors. One explanation lied in disparities of domestic fuel in urban-rural areas. Prior study showed that biomass fuel still dominated in rural residents as they still extensively use traditional stove (Shen et al., 2013). For instance, Zhao et al estimated 7% and 49% biomass fuel used for cooking in urban and rural residents, respectively. Furthermore, they also found that PM_{2.5} reduced by 47% in 2005-2015, 90% of which was attributable to reduced household biomass fuels; Meanwhile, such reduction was estimated to avoid 0.40 (95% CI: 0.25-0.57) million premature deaths (Zhao et al., 2018). Deziel found that household coal burning in Chinese rural areas had an elevated rate of EC, and PAHs from air was an important pathway for EC (Deziel et al., 2013). Similarly, Hassanvand et al found that more than 80% PAHs were connected with PM_{2.5}, and the concentrations of PAHs largely relied on PM_{2.5} (Hassanvand et al., 2015). Moreover, Liang et al estimated 132 cancer cases caused by inhalation PM_{2.5}-bound PAHs in summer, while the number

increased to 686 cases in winter of southwest China (Liang et al., 2020). Meanwhile, DNA damage depended on the concentrations of PM_{2.5}-bound PAHs and relied on their oxidation and bioavailability (Turap et al., 2018). Another explanation considered that social infrastructure and health service were limited, as well as environmental protection sources was not accessible in rural areas. Generally, rural residents conducted more outdoor activities, resulting in higher PM_{2.5} exposure (Han et al., 2021). They less use anti-PM_{2.5} air filters and take special face masks to reduce exposure to PM_{2.5}, which increases the exposure risks in rural areas (Zhao et al., 2021). In addition, our sex-specific model showed women are more sensitive to PM_{2.5}, which attributes to biological, demographical, and behavioral differences. Women generally have higher life expectancy and less-educated attainment than men in China, so sex might modify the effect of PM_{2.5} on incidence (Beelen et al., 2015; Shan et al., 2020). Biologically, women are lack of effective protections against environmental toxicants and reactive oxygen species, because their mtDNA content and expression levels of respiratory electron chain genes are more sensitive to air pollution compared to men (Winckelmans et al., 2017). Furthermore, Women have smaller lung size and airway diameter, which might increase women's airway reactivity and exacerbate particulate deposition (Abed Al Ahad et al., 2020).

The spatial distribution of RRs was not consistent with the distribution of ECI, partly attributing to spatial heterogeneities of covariates. Generally, location with higher PM_{2.5} or higher prevalence of covariates (e. g. NH₃-N and COD_{Mn}) tended to be accompanied with higher RRs. For instance, PM_{2.5} was higher in some areas of south and southwestern and east China where RRs was also greater, but the ECI was not higher. This suggested that socioeconomic factors possibly modified the association and PM_{2.5} and ECI. Prior studies from China, Iran, India and America all proved a significantly inverse association between EC and socioeconomic status or urbanization (Dar et al., 2013; Gao et al., 2018; Wong et al., 2018). In this study, we also detected that socioeconomic covariate can reduce ECI risks related to PM_{2.5} (Model 3). Moreover, some areas with higher ECI burdens also had higher PM_{2.5} and RRs than the adjacent areas. These suggested that PM_{2.5} caused risk for ECI, but other covariates can modify their relationship and thus showed spatial heterogeneities of RRs. In addition, the differences of activity patterns and PM_{2.5} components might influence the exposure risks in different areas, further modified the association between them (Chen et al., 2020). More evidence is needed to provide in the future epidemiological studies to verify this assumption.

The effects of PM_{2.5} on ECI increased with the exposure extension of average-year lags, but finally levelled off. The stronger effects occurred in level-off window before incidence, partly because long-term exposure to lower PM_{2.5} concentration elevated the cumulative risks of carcinogens, further lead to a slow and subtle change of reactor for PM_{2.5}. A cohort study from Taiwan of China indicated the long-term exposure to low concentrations of PM_{2.5} was associated with the increased hazard risks of 1.09 (95% CI: 1.03-1.16) and 1.13 (95% CI: 1.02-1.24) for gastrointestinal and liver cancers (Guo et al., 2020a). Similar cohort study included 139,534 individuals from the United States demonstrated that PM_{2.5} was significantly associated with the elevated risk of 1.27 (95% CI: 1.17-1.37) for colorectal cancer at a median of 10.43 years exposure (Chu et al., 2020). Moreover, Kim et al discussed how to conduct time-series studies of air pollution on health using different lag structures and models (Kim and Lee, 2019). In addition, the shorter lag window in urban than rural might result from the higher PM_{2.5} concentrations in urban areas. Long-term exposure higher dose of PM_{2.5} could reduce response time, leading to a prolonged lag window

in rural areas. This finding stressed that the incidence risks were not only related with exposure dose of PM_{2.5} but were influenced by exposure time.

Our findings have several public health implications. Although the level of PM_{2.5} has dramatically decreased in China, the level still exceeded the mortality cut-off value (10 ug/m³, WHO) and the first stage of WHO transition period (35 ug/m³). Long-term exposure to PM_{2.5} over 35 ug/m³ would cause 15% increase in mortality risks (WHO, 2006). Therefore, current control policies of PM_{2.5} still need to be continued. At the same time, preferred to reduce dependence of economic advancement on coal fuels, cut back the number of coal-fired power plants and set a coal consumption cap on pollutants' emission, upgrade energy structure and formulate stricter emission guidelines to improve air quality in China. Furthermore, governments should plan specific strategies concerning air pollutants in residents' health, because components vary from different areas. Secondly, given the vulnerabilities in rural areas, specific public health policies and interventions, such as installing chimneys or using natural gas and electricity, could effectively reduce exposure risks for rural residents. Thirdly, higher economic and educational levels could offset the adverse effects of PM_{2.5} to some extent, especially in rural areas. The increase in economic and educational investments, improvement of infrastructures and health services and formulation of assistance system for serious diseases could reduce risks and prevent residents from vicious circle of poverty. Lastly, we encourage the use of anti-PM_{2.5} instruments and face-mask to reduce exposure risks, especially in heavily polluted days.

The present study has several strengths. In contrast to other studies without stratifications, our study not only estimated the effects of PM_{2.5} by urban-rural areas but examined the corresponding effects by sexes, adding more knowledge and experience for other developing countries regarding health-risk assessment. Secondly, the application of GWPR function allows us to evaluate ECI risks related to PM_{2.5} at national and county scales, which is pivotal for policy maker to target priority intervention areas and allocate health sources, more precisely. Thirdly, we firstly introduced NLL, NH₃-N and COD_{Mn} into ECI risks study related to PM_{2.5}, which not only could effectively avoid multicollinearity caused by multivariable but control the interference of water pollution for results through adjusting for NH₃-N and COD_{Mn}. Lastly, we examined the lag effects of long-term exposure to PM_{2.5} on ECI through various lag structures, which was important to select appropriate exposure window for future studies.

Several limitations should be discussed in our study. Firstly, we did not distinguish the subtypes of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) due to inaccessible data. Nevertheless, ESCC is a dominate subtype that accounts for over 87% of total EC in China. Meanwhile, we not considered exposure risks in different age groups, which might underestimate the adverse effects of PM_{2.5}. Secondly, we did not include other potential confounders such as smoking, alcohol, diet and genetics, etc. These might affect the pattern of ECI and bias our estimation. Thirdly, the 9-year (single and moving-average) lag structures constructed in the study might be still too short to estimate the lag effect of PM_{2.5} on ECI. If all variables and covariates become available, this limitation would be addressed in the future studies. Fourthly, because of population density and economic disparities, the various PM_{2.5} components in China and limited CRIs of Western China might have bias in the association between PM_{2.5} and ECI. However, the existing analysis still contains some risk signal related to PM_{2.5}. Finally, this is an ecological study just explore the related PM_{2.5} risks at county-level but not involved in individual exposure. County-level exposure may cause exposure bias which might misestimate the real associations and even

cause non-significant results, if it existed. However, this study still is useful and provide valuable information for policy maker to acknowledge ECI associated with PM_{2.5} and tailor efficient policies to reduce incidence risks.

Conclusion

Long-term exposure to PM_{2.5} is significantly associated with increased ECI risks for both sexes in China where the estimated adverse effects are higher in rural areas and females. Furthermore, there is a larger exposure window and higher lag effects of PM_{2.5} in rural areas, while socioeconomic covariates can mitigate the risks for population. These findings are critical to prioritize intervention areas and target risk population, as well as carry out stricter guidelines and formulate early warning system of PM_{2.5} to reduce exposure risks. In addition, although the estimated effects of PM_{2.5} on ECI was so small to be clinically negligible, from a public health perspective, a slight change of ECI induced by PM_{2.5} may contribute to a great burden. Furthermore, the control and mitigation of PM_{2.5} pollution not only can reduce the risks for population exposures but also decline the burden of other diseases.

Declarations:

Ethics approval and consent to participate

The study used publicly available data and participate consent is not required. the study has been approved by the institutional Review Board at Xi'an Jiaotong University.

Consent for publication

Not applicable

Availability of supporting data

Esophageal cancer data were collected from 2018 China Cancer Registry Annual Report. PM_{2.5} exposure data were publicly available at <https://search.earthdata.nasa.gov/>. Other covariates data were available from the Data Center for Resources and Environmental Sciences, Chinese Academy of Sciences (RESDC) <http://www.resdc.cn> and National Environmental Monitoring Center <http://www.cnemc.cn>.

Competing interests

The authors declare that we do not have conflict of interest.

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Authors' contributions

PL: Data collection, analysis and manuscript draft. XG and JJ: manuscript and model revision. WH: Methods revision and statistical assistance. XQ: Study guidance and manuscript review & revision. WQW and GZ: Study design and data management. All authors have contributed to study design and approved the final manuscript.

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Figures

Figure 1

The lag effect of PM2.5 on ECI (per 100, 000) (Model 1 includes a, b, c; Model 2 includes d, e, f; Model 3 includes g, h, i.)

Figure 2

Cumulative PM2.5 risks for ECI (per 100,000) (Model 1 includes a, b, c; Model 2 includes d, e, f; Model 3 includes g, h, i.)

Figure 3

Spatial variation of the association between PM2.5 and ECI among males and females in 388 areas (a, b denote the single risks for males and females, respectively; c, d denote the cumulative risks for males and females, respectively) Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

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