

PM_{2.5} Exposure and Cervical Cancer Survival in Liaoning Province, Northeastern China

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Abstract

Particulate matters with a diameter of 2.5 μm or less ($\text{PM}_{2.5}$) were frequently reported to be associated with increased cancer incidences, but few studies have explored the associations between $\text{PM}_{2.5}$ exposure and cancer survival. We retrospectively analyzed the association between $\text{PM}_{2.5}$ exposure and the overall survival (OS) of cervical cancer patients who resided in 14 urban areas of the Liaoning Province, Northeastern China during January 2014-October 2021. Patients from urban areas who finished the recommended treatments with complete follow-up information were included. The $\text{PM}_{2.5}$ monitoring data of each urban area of Liaoning Province was retrieved, and individual exposure to $\text{PM}_{2.5}$ after diagnosis was calculated as the average daily concentration in the residence from the discharged day to death day or the last follow-up day. Log-rank tests and cox-regression were performed to examine the relationships between $\text{PM}_{2.5}$ exposure and cervical cancer survival. A total of 1753 cervical cancer patients were finally included, among whom 804 (45.9%) were from Shenyang City, the capital of Liaoning Province. The median average daily concentration of $\text{PM}_{2.5}$ that the patients were exposed to was 45.0 (interquartile range 38.2-50.0) $\mu\text{g}/\text{m}^3$. Both log-rank tests (grouped by quartiles, $p < 0.001$) and cox-regression (continuous, $\text{HR} = 1.06$, 95%CI 1.04-1.08) indicated that $\text{PM}_{2.5}$ was significantly associated with shorter OS. Sensitivity analysis also confirmed the robustness of our findings. For the subgroup analysis, only the OS of stage II and stage III patients were associated with PM exposure. Our findings gave an insight that $\text{PM}_{2.5}$ exposure was associated with shorter OS of cervical cancer patients.

Introduction

Exposure to ambient particulate matter with a diameter of 2.5 μm or less ($\text{PM}_{2.5}$) has been always been considered a global public health issue. Since 1990, numerous epidemiological studies have been performed to investigate the effects of PMs exposure on population mortality, among which long-term and short-term effects were both frequently investigated (Beelen et al. 2014, Di et al. 2017, Liang et al. 2020, Miller et al. 2007, Raaschou-Nielsen et al. 2013). For the short-term effects, the current studies mainly focused on adverse effects on circulatory and respiratory system-related hospital visits or mortality (Di et al. 2017, Liu et al. 2019, Liu et al. 2021, Rajagopalan et al. 2018).

For the long-term effects, in addition to all-caused or respiratory mortality (Beelen et al. 2014, Liang et al. 2020, Miller et al. 2007), cancer incidences and mortalities with large cohorts have demonstrated that higher PMs were associated with higher cancer incidences and mortality (Andersen et al. 2018, Chen et al. 2021, Cohen et al. 2017, Li et al. 2020, Raaschou-Nielsen et al. 2013, Tseng et al. 2019). Recently, some new evidence suggested that PMs might aggravate the prognosis of cancer patients. Xu et al. and Eckel et al. reported a significant association between higher $\text{PM}_{2.5}$ exposure and poorer overall survival (OS) of lung cancer patients (Eckel et al. 2016, Xu et al. 2013). Interestingly, the associations were also reported to be significant on breast, liver, and ovarian cancer survival (Hu. et al. 2013, Lurmann et al. 2017, Vieira et al. 2017, Villanueva et al. 2021). So far, the mechanisms of the findings above had not been clarified. It is almost confirmed that exposure to PMs would induce higher oxidative stress levels, DNA damage, and

chronic systemic inflammation (Gilbert 2013, Newby et al. 2015, Risom et al. 2005), and all these effects contributed to the development of cancer. Theoretically, these mechanisms also worked in cancer survivors which might induce new carcinosis or recurrences.

It has been reported that PM_{2.5} exposure is associated with the mortality of many types of cancer (Ethan et al. 2020, Hsin-Ling et al. 2017, Nabizadeh et al. 2019, Turner et al. 2017, Wang et al. 2019a, Wang et al. 2018) including stomach, liver, pancreatic, breast and ovarian. Several studies have linked poorer survival with higher PM_{2.5} exposure in patients with some of these types of cancer. But as one of the most common malignant tumors in females worldwide (WHO 2020), no cervical cancer-related studies have been performed, to our best knowledge.

In this study, we aimed to explore the association between PM_{2.5} and the overall survival of cervical cancer patients. The findings of this study might provide insights into air quality and cervical cancer patients' prognosis, which is of significance in public health and environmental protection decision-making.

Materials & Methods

Study population

A single-center retrospective study was performed in Liaoning Province. Liaoning is located in Northeastern China, with 2 large and 12 small cities and a total population of over 42 million. It had a cool climate with the annual mean daily temperatures ranging from 7 to 11 °C. Liaoning was heavily polluted by PMs because of its heavy industries; besides, in cold seasons the heating by coal-burning made the air quality worse. For example, in Shenyang, the capital of Liaoning, the annual mean PM_{2.5} concentration was 75 µg/m³ in 2014, while the average concentration in November and December was about 110 µg/m³ in the same year.

Cervical cancer patients were enrolled in the Cancer Hospital of Liaoning Province, which is the largest cancer hospital in the Province. The average number of inpatients in the hospital exceeded 120,000 per year. Nearly 50% of the patients were from Shenyang, and over 40% of patients were from other cities of Liaoning. Information of the patients, such as the age of diagnosis, Figo stage, histological types, etc. were retrieved from the electronic medical record system. Considering the air quality monitoring system by the Ministry of Ecology and Environment (MEE) of China were only constructed in the urban areas of each city until the year 2014, we made the inclusion and exclusion criteria were as below:

Inclusion criteria: a. Cervical cancer patients who were initially diagnosed in Cancer Hospital of Liaoning Province after January 1st, 2014; b. Patients who resided in urban areas of Liaoning Province; c. Patients who received and completed the recommended treatments. d. Patients who were not lost at the time of the last follow-up interview. Exclusion criteria: a. Patients who were diagnosed elsewhere, or received treatments previously; b. Patients with incomplete information (including domestic and treatment-related

information); c. Patients who were discharged from the hospital without the recommendation of the doctors. d. the loss of follow-up patients, or patients who died from other diseases than cancer.

PM exposure estimation

Daily average concentrations of PM_{2.5} of the urban areas of Liaoning's 14 cities were obtained from the website <https://aqicn.org/>, whose data were derived from the official environmental monitoring stations. The download PM_{2.5} monitoring data was shown in the air quality index (AQI) of the US, so we transferred them back into concentration in $\mu\text{g}/\text{m}^3$ (reference table shown in table S1 in supplementary files). The PM_{2.5} exposure of each patient was defined as the mean of daily average concentration at the residential city from the date of discharge to the date of the last effective follow-up or the date of death.

Statistical Methods

Kaplan Meier (K-M) curves and log-rank test were performed to identify PM_{2.5} exposure as well as the influencing factors of OS of cervical cancer patients. And cox-regressions were performed to estimate the adjusted Hazard Ratios (HRs) of PM_{2.5} exposure. Subgroup analysis by Figo stages, histological types, and age were performed to check the robustness of our results. For the same purpose, sensitivity analyses were performed, during which we exclude the patients who resided in one city every time, and then analyzed with the remaining patients to compare it with the original results. All tests were two-sided, and a *p*-value less than 0.05 was considered statistically significant. All statistical analyses were done using R version 4.11 from the Comprehensive R Archive Network (<http://cran.r-project.org/>).

Results

Patients

3140 initially diagnosed cervical cancer patients from 2014 to 2021, who resided in the urban areas of Liaoning Province, were identified. 427 patients were excluded, including 26 patients who did not finish the treatments and were discharged without the recommendation of the doctors, and 175 patients who were lost in the follow-up process; 218 patients whose last follow-up time was not available, and 6 patients who died from the diseases other than cancer. In addition, 960 patients were excluded for incomplete clinical stages. Finally, a total of 1753 cervical patients were included.

The total survival rate of the included patients was 90.35%, of which 169 patients died and 1584 were alive. Most of them had medical insurance ($n=1414$, 80.66%). Patients with squamous cell carcinoma took a proportion of 77.18% of all patients. Stage I patients were the most ($n=580$, 33.09%), and stage IV patients were only 87 cases (4.96). 41.8% ($n=728$) of patients resided in Shenyang City, capital of Liaoning, and only 26 patients were from Dalian City, the other large city of Liaoning. 999 cervical cancer patients resided in the other 12 small cities. Details were shown in Table 1.

Table 1
Descriptives of the domestic information of the study population

Variables	Groups	Counts	Proportions	Survivals		P
				Alive	Deaths	
All	—	1753	—	1584	169	—
Insurance	Not insured	194	11.07%	171	23	0.2
	Normal insurance	1414	80.66%	1284	130	
	Other types	145	8.27%	129	16	
Age	<65-year-old	1490	85.00%	1359	131	<0.001*
	>=65-year-old	263	15.00%	225	38	
Marital status	Married	1101	62.81%	1044	57	0.003*
	SDW	93	5.31%	81	12	
	Others	559	31.89%	459	100	
Histological types	Squamous cell carcinoma	1353	77.18%	1225	128	0.2
	Adenocarcinoma	125	7.13%	113	12	
	Others	54	3.08%	45	9	
	Unknown	221	12.61%	201	20	
Figo stages	I	580	33.09%	558	22	<0.001*
	II	513	29.26%	469	44	
	III	573	32.69%	497	76	
	IV	87	4.96%	60	27	
Residences	Small cities	999	56.99%	898	101	0.4
	Large cities	754	43.01%	686	68	

PM_{2.5} exposure assessments

Figure 1 shows the mean daily PM_{2.5} concentrations in each city of Liaoning. The daily mean concentrations of PM_{2.5} ranged from 30 to 60 µg/m³, and the concentrations of Anshan (C), Fushun (D), Jinzhou (G), and Huludao city (N) were higher than in other cities. In contrast, the ambient air of Dalian (B) and Dandong (F) cities was relatively less polluted. The median average daily concentration of PM_{2.5} that the patients were exposed to was 45.0 (interquartile range 38.2-50.0) µg/m³.

Association between PM_{2.5} exposure and overall survival

The results of log-rank tests were shown in Table 1 and Figure 2. Age, marital status, and Figo status were significantly associated with the OS of cervical cancer patients. In addition, to draw the K-M curve of PM_{2.5}, we transferred them into categorical variables with 3 groups (0~25%, 25%~75%, 75%~100%). And the curves of Q₁ and Q₄ were devious (p<0.001).

The results of cox-regression were shown in Table 2, in which PM_{2.5} exposure was included as a continuous variable. None of the medical insurance status, regional temperature, city scales, or the year at diagnosis was related to the OS. But similar to most of the previous studies, we found elder ages (HR=2.18, 95%CI 1.49-3.40), Adenocarcinoma (HR=2.11, 95%CI 1.15-3.89), and other histological types (HR=3.23, 95%CI 1.61-6.45), and Figo stages were significantly associated with OS. Higher PM_{2.5} (HR=1.060, 95%CI 1.038-1.081) exposure was significantly associated with poorer OS. Subgroup analysis (shown in Table 3) indicated that the OS of patients with squamous cell cancers or adenocarcinoma, aged below or above 65-year-old were both associated with PM_{2.5}. Similar results were found in Figo stage II and stage III patients. However, no associations between the OS of stage I or stage IV patients were found.

Table 2
The association between PM_{2.5} and the OS of cervical cancer pations

Variables	Factors	References	HR	LL	UL	Sig
Age	>=65-year-old	<65-year-old	2.18	1.49	3.20	*
Insurance	Other	Not insured	1.24	0.64	2.43	
	Normal		0.73	0.46	1.17	
Histological types	Andenocarcinoma	Squamous	2.11	1.15	3.89	*
	Other types	cell	3.23	1.61	6.45	*
	Unknown	carcinoma	1.34	0.82	2.18	
Marrital status	Others	Married	1.53	1.05	2.24	*
	SDW		2.10	1.11	3.98	*
Figo stage	Stage II	Stage I	2.55	1.51	4.32	*
	Stage III		6.78	4.13	11.15	*
	Stage IV		23.96	13.13	43.74	*
PM _{2.5}	PM _{2.5}	—	1.06	1.04	1.08	*
Residence Temperature	Residence Temperature	—	0.88	0.75	1.05	
City scales	Big cities	small cities	1.10	0.78	1.55	
Year of Diagnosis	Year of Diagnosis	—	0.98	0.86	1.12	

Table 3
Subgroup analysis of the association between PM_{2.5} exposure and cervical cancer overall survival

Groups	Subgroups	PM _{2.5}			
		HR	LL	UL	Sig
Histological types	SCC	1.065	1.04	1.09	*
	AC	1.086	1.015	1.161	*
	Other types	0.912	0.684	1.216	
Stages(Figo)	Stagel	1.063	0.986	1.146	
	Stagell	1.071	1.020	1.124	*
	Stage III	1.059	1.029	1.091	*
	StagelV	1.052	0.998	1.109	
Age	<65-year-old	1.06	1.035	1.086	*
	>=65-year-old	1.062	1.018	1.109	*

The results of Sensitivity analysis were shown in Table S2, of which the HRs were extracted from the results of 14 cox-regression. It showed that after eliminating the patients from one city, the HRs of PM_{2.5} kept significant, indicating the robustness of our results

Discussion

To our best knowledge, this is the first study exploring the association between PM_{2.5} exposure and the OS of cervical cancer patients, especially in a relatively heavily polluted region. We found a stable relationship between higher PM_{2.5} exposure and poorer OS among cervical cancer patients. Even after being grouped by age and stages, the results still kept stable, although no significant associations were found in Figo I and Figo IV patients. Sensitivity analysis also excluded the probability that the results were dominated by the patients from some specific cities. Most results in this study accorded with the previous findings. Besides the elder age at diagnosis and higher clinical stages, we also found adenocarcinoma is a risk for OS of cervical cancer compared to squamous cell cancers, and single status was also identified as a risk, which is similar to the currently accepted results(Cohen et al. 2019).

So far, there has been some evidence about ambient air pollution exposure and cancer survival or survival-related symptoms, which includes the association between PM_{2.5} and the OS of lung, breast, liver, and ovarian cancer patients (Eckel et al. 2016, Hu. et al. 2013, Lurmann et al. 2017, Villanueva et al. 2021, Xu et al. 2013). But all these studies were based on Surveillance Epidemiology and End Results (SEER) cohorts or California population. And Eckel et al(Eckel et al. 2016) also found the effects of PM_{2.5} were larger in Asians, which reminds us of more attention on them. Therefore, our study provided

important evidence in both Asian and developing countries' cancer patients, as well as in patients who resided in relatively heavily polluted areas. Further studies are still needed to explore the associations between PM_{2.5} and OS of other types of cancer patients, and also to confirm the current findings.

In addition to the association between the OS of cervical cancer patients and PM_{2.5} exposure, we also obtained some interesting findings from the subgroup analysis. First, both SCC and AC patients' OS was associated with PM_{2.5}, but the HR of SCC is relatively larger. Although we did not find the explanation from the current literature, this finding is similar to Eckel et al. which found that in OS of lung cancer patients (Eckel et al. 2016). Second, the associations in stage I and stage IV patients were negative, but this might be reasonable. Villanueva et al. found the associations between PM_{2.5} and ovarian cancer survival were greater in patients with early stages (Villanueva et al. 2021), and the explanation by more cumulative PM_{2.5} exposure in these patients. But for cervical cancer patients, the survival rate of stage I patients during our study period was 96.2%, which may suggest not long enough periods to examine the associations on this population. As for stage IV patients, the most likely reason for negative results was the small sample size (n=87).

As mentioned above, the mortality of many types of cancers was reported to be associated with ambient air pollution exposure. The explanations may lie in higher incidences of cancer with higher exposure to ambient air pollution. However, it may not be suitable for cervical cancer that were mainly caused by high-risk HPV infection (Cohen et al. 2019). Therefore, more attention should be paid to the adverse effects on cervical cancer patients rather than before cancer. Unfortunately, due to the limited relevant studies, it is not clear if there is a causal relationship between PM_{2.5} and cancer survival, as well as the potential mechanism of how PM_{2.5} affects survival. But it is clear that ambient air pollution, especially PM_{2.5}, has been classified as a carcinogen. That is to say, the carcinogenesis of PM_{2.5} including oxidative stress, DNA damage, cell proliferation, or epigenetic modifications may still work in survivors of cancers (Eckel et al. 2016). On the other hand, PM_{2.5} can directly harm respiratory function, which is particularly crucial for the recovery of cancer survival. Another potential reason for the association may be the short-term adverse effects of PM_{2.5} exposure. It has frequently been reported that short-term PM_{2.5} exposure was significantly associated with higher lung cancer daily mortality (Berger et al. 2018, Chung et al. 2021, Wang et al. 2019b), and the mortality displacement may also exist in the mortality of cancer patients.

Limitations of this study should be noted. First, our study was based on Liaoning cancer hospital, which is one of the best hospitals on oncology in Liaoning Province, where patients with low social-economic status might be less likely to come. Therefore as a single-center study, the enrollment of the patients might be biased due to the source of patients. Second, although we have designed the items of income levels and occupations, most patients refused to fill in this information. Therefore we could not control for SES-related confounders except for medical insurance in the cox-regression. Third, among all types of cancers, patients with cervical cancer have higher survival rates. As a result, cervical cancer-related studies also required a longer follow-up period. But due to no available Provincial PM_{2.5} data until 2014, we could only enroll patients diagnosed since then. Nevertheless, our finding still provides insights into

the association between PM_{2.5} exposure and cervical cancer survival, which is of importance in both environmental sciences and oncology.

Conclusion

Higher PM_{2.5} exposure levels are significantly associated with decreased overall survival of cervical cancer patients, but this association among early-staged patients still needs further exploration.

Declarations

Acknowledgments

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Consent to submission and publication

All authors approved of this submission, as well as the further publication on ESPR.

Ethical Approval

This study was approved by the Ethics Committee of Cancer Hospital of China medical university (number: 2021G0301)

Author contribution

All authors contributed to the study's conception and design. This study was designed and supervised by **Danbo Wang**. Data collection was finished by **Guangcong Liu** and **Chenyu Wang**; Data analysis, as well as the first draft, was finished by **Guangcong Liu** and **Zhuo Yang**. All authors read and approved the final manuscript

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and materials

Detailed patients' information was not available because of the privacy-related regulation of the Cancer Hospital of China Medical University. PM_{2.5} monitoring data have been attached in supplementary files.

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Figures

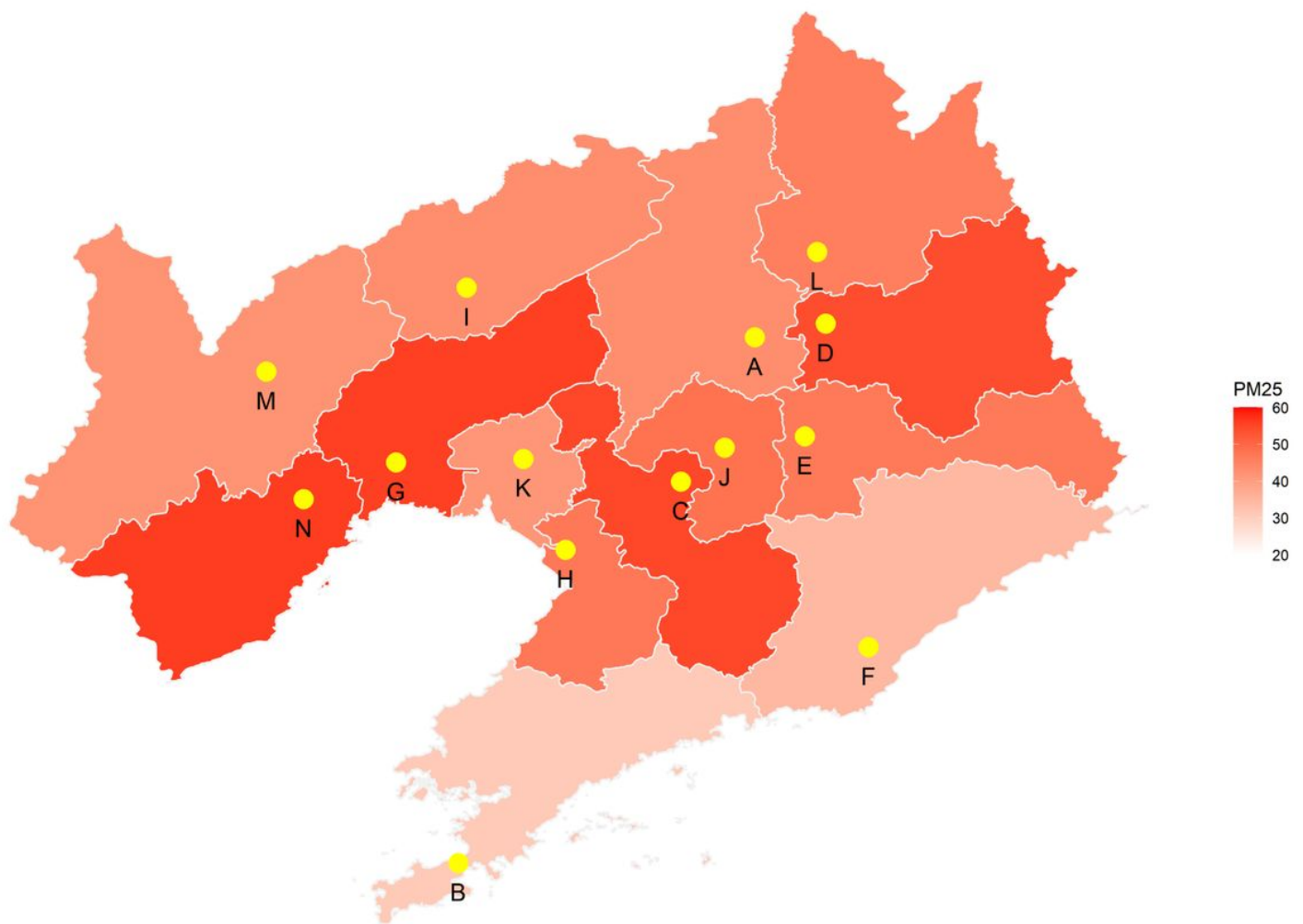


Figure 1

Locations, as well as the average daily PM_{2.5} concentrations from 2014 to 2021 of each city in Liaoning Province. Note that the average concentration was only for urban areas of each city, which was not displayed in this figure.

In this figure, A: Shenyang; B: Dalian; C: Anshan; D: Fushun; E: Benxi; F: Dandong; G: Jinzhou; H: Yingkou; I: Fuxin; J: Liaoyang; K: Panjin; L: Tieling; M: Chaoyang; N: Huludao.

Figure 2

K-M curves of age at diagnosis, marital status, histological types, Figo stages, city categories, and PM_{2.5} exposure level (in quartiles) versus the overall survival of cervical cancer patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytables.pdf](#)