PM$_{2.5}$ exposure and cervical cancer survival in Liaoning Province, northeastern China

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Abstract
Particulate matter with a diameter of 2.5 μm or less (PM$_{2.5}$) has frequently been reported to be associated with an increased incidence of cancer, but few studies have explored the association between PM$_{2.5}$ exposure and cancer survival. We retrospectively analyzed the association between PM$_{2.5}$ exposure and the overall survival (OS) of cervical cancer patients residing in 14 urban areas of Liaoning Province, northeastern China, during January 2014–October 2021. Patients from urban areas who completed the recommended treatments with complete follow-up information were included. The PM$_{2.5}$ monitoring data of each urban area of Liaoning Province were retrieved, and individual exposure to PM$_{2.5}$ after diagnosis was calculated as the average daily concentration in the city of residence from the date of discharge to the date of death or the last follow-up. Log-rank tests and Cox regression were performed to examine the relationship between 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 PM$_{2.5}$ to which the patients were exposed was 45.0 (interquartile range 38.2–50.0) μg/m$^3$. Both log-rank tests (grouped by quartiles, $p<0.001$) and Cox regression (continuous, HR = 1.06, 95% CI 1.04–1.08) indicated that PM$_{2.5}$ was significantly associated with shorter OS. Sensitivity analysis also confirmed the robustness of our findings. From the subgroup analysis, only the OS of stage II and stage III patients was associated with PM exposure. Our findings provide the insight that PM$_{2.5}$ exposure might be associated with shorter OS of cervical cancer patients.

Keywords Air pollution · PM$_{2.5}$ · Cervical cancer · Overall survival · Cox regression

Introduction
Exposure to ambient particulate matter with a diameter of 2.5 μm or less (PM$_{2.5}$) has long been identified as a global public health issue. Since 1990, numerous epidemiological studies have been performed to investigate the effects of PM exposure on population mortality, in which both long-term and short-term effects were frequently investigated (Beelen et al. 2014; Di et al. 2017; Liang et al. 2020; Miller et al. 2007; Raaschou-Nielsen et al. 2013). Regarding the short-term effects, recent studies have 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).

Regarding the long-term effects, in addition to all-cause or respiratory mortality (Beelen et al. 2014; Liang et al. 2020; Miller et al. 2007), data on cancer incidences and mortalities from large cohorts have demonstrated that higher PM levels were associated with higher cancer incidence 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 has suggested that PM might aggravate the prognosis of cancer patients. Xu et al. and Eckel et al. reported a significant association between higher 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 for breast, liver, and ovarian cancer survival (Hu et al. 2013; Deng et al. 2017; Vietra et al. 2017; Villanueva et al. 2021). However, to date, the mechanisms behind the above findings have not been clarified. Strong evidence has been presented that exposure to PM would induce higher levels of oxidative stress, DNA damage, and chronic systemic inflammation (Loomis 2013; Newby et al. 2015; Risom et al. 2005), and that all of these effects contribute to the development of cancer. Theoretically, these mechanisms also occur in cancer survivors, which might induce new carcinogenesis or recurrence.

It has been reported that PM$_{2.5}$ exposure is associated with the mortality of many types of cancer (Ethan et al. 2020; Yeh et al. 2017; Nabizadeh et al. 2019; Turner et al. 2017; Wang et al. 2019a, 2018), including stomach, liver, pancreatic, breast, and ovarian. Several studies have also linked poorer survival to higher PM$_{2.5}$ exposure in patients with some of these cancer types. However, despite cervical cancer being one of the most common malignant tumors in females worldwide (WHO 2020), to the best of our knowledge no studies on its association with PM$_{2.5}$ have been performed.

In this study, we thus explored the association between PM$_{2.5}$ and the overall survival (OS) of cervical cancer patients. The findings of this study might provide insights into the link between air quality and the prognosis of cervical cancer patients, which is significant in the fields of public health and environmental protection.

**Materials and methods**

**Study population**

This work involved a single-center retrospective study performed in Liaoning Province. Liaoning is located in northeastern China, which contains 2 large (cities with populations greater than 5 million) and 12 small cities and has a total population of over 42 million. It has a cool climate with annual mean daily temperature ranging from 7 to 11 °C. Liaoning is heavily polluted by PM because of its heavy industry; besides, at cold times of the year, its air quality is deteriorated further by coal-burning for heating. For example, in Shenyang, the capital of Liaoning, the annual mean PM$_{2.5}$ concentration was reported to be 75 μg/m$^3$ in 2014, while the average concentration in November and December was about 110 μg/m$^3$ in the same year.

Cervical cancer patients enrolled in this study were from the Cancer Hospital of Liaoning Province, which is the largest cancer hospital in the province. The average number of inpatients in the hospital exceeds 120,000. Nearly 50% of the hospital’s patients are from Shenyang, while over 40% are from other cities in Liaoning. Information on the patients included in this study, such as the age at diagnosis, FIGO stage, and histological type, was retrieved from the electronic medical record system. In this study, we set inclusion and exclusion criteria in consideration of the fact that an air quality monitoring system of the Ministry of Ecology and Environment (MEE) of China had only been established in the urban areas in each city in the year 2014.

The inclusion criteria were as follows: a. cervical cancer patients who were initially diagnosed at the 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; and d. patients who were not lost to follow-up. Meanwhile, the exclusion criteria were as follows: a. patients who had been diagnosed elsewhere or received cancer-related treatments previously; b. patients for whom incomplete information (including demographic and treatment-related information) was available; c. patients who were discharged from the hospital against doctors’ advice; and d. patients lost to follow-up or patients who died from diseases other than cancer.

**PM exposure estimation**

The daily average concentrations of PM$_{2.5}$ in the urban areas of Liaoning’s 14 cities were obtained from the website https://aqicn.org/, whose data were derived from environmental monitoring stations of the MEE, China. The downloaded PM$_{2.5}$ monitoring data were in units of the US air quality index (AQI), so we converted them into concentrations in μg/m$^3$ (for reference table, see Table S1). The PM$_{2.5}$ exposure of each patient was defined as the mean daily average concentration at the city of residence 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) curve analysis and log-rank test were performed to identify the effects of PM$_{2.5}$ exposure as well as other influential factors on the OS of cervical cancer patients. Cox regression was also performed to estimate the adjusted hazard ratios (HRs) of PM$_{2.5}$ exposure. Subgroup analyses by FIGO stage, histological type, and age were also performed to determine the robustness of our results. For the same purpose, sensitivity analyses were performed, during which we performed repeated analyses upon excluding the patients residing in each of the cities at a time and then analyzed the remaining patients to compare the findings 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 performed using R version 4.11 from the Comprehensive R Archive Network (http://cran.r-project.org/).
Results

Patients

A total of 3140 cervical cancer patients initially diagnosed from 2014 to 2021, who resided in urban areas of Liaoning Province, were identified in this study. Overall, 427 patients were excluded, including 26 who did not complete the treatments and were discharged against doctors’ advice, 175 who were lost to follow-up, 220 whose last follow-up time was not available, and 6 who died from diseases other than cancer. In addition, 960 patients were excluded due to incomplete information on their clinical stage. Finally, a total of 1753 cervical patients were included. The flowchart of patient selection is shown in Fig. 1.

The total survival rate of the included patients was 90.35%, with 169 patients dying and 1584 surviving. Most of the patients had medical insurance (n = 1414, 80.66%). Patients with squamous cell carcinoma were the largest group, constituting a total of 77.18% of all patients. Stage I patients were also the most common (n = 580, 33.09%), while stage IV patients numbered only 87 (4.96%). In addition, 41.8% (n = 728) of patients resided in Shenyang City, capital of Liaoning, while only 26 patients were from Dalian City, the other large city in Liaoning. Meanwhile, 999 cervical cancer patients resided in the other 12 small cities. The details of included population are shown in Table 1. A comparison between the original and final included cases is shown in Table 2.

PM$_{2.5}$ exposure assessments

Figure 2 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/m$^3$, and the concentrations in Anshan (C), Fushun (D), Jizhong (G), and Huludao cities (N) were higher than those in the other cities. In contrast, the ambient air of Dalian (B) and Dandong cities (F) was less polluted. The median average daily concentration of PM$_{2.5}$ to which the patients were exposed was 45.0 (interquartile range 38.2–50.0) μg/m$^3$.

Association between PM$_{2.5}$ exposure and overall survival

The results of log-rank tests are shown in Table 1 and Fig. 3. Age, marital status, and FIGO status were significantly associated with the OS of cervical cancer patients. In addition, to create a K-M curve of PM$_{2.5}$, we converted the PM$_{2.5}$ values into a categorical variable with three groups as follows: 0–25% (Q1), 25–75% (Q2–Q3), and 75–100% (Q4). There was a significant difference in the curves of Q1 and Q4 (p < 0.001).
The results of Cox regression are shown in Table 3, in which PM$_{2.5}$ exposure was included as a continuous variable. No relationship with the OS was found for medical insurance status, regional temperature, size of city, or year at diagnosis. However, similar to the findings in most previous studies, we found that older age (HR = 2.18, 95% CI 1.49–3.40), adenocarcinoma (HR = 2.11, 95% CI 1.15–3.89), other histological types (HR = 3.23, 95% CI 1.61–6.45), and FIGO stage were significantly associated with OS. Higher PM$_{2.5}$ (HR = 1.06, 95% CI 1.04–1.08) exposure was significantly associated with poorer OS. Subgroup analysis (as shown in Table 4) indicated that the OS of patients with squamous cell cancer or adenocarcinoma, aged below or above 65 years old, was associated with PM$_{2.5}$ exposure. Similar results were found in FIGO stage II and stage III patients. However, no associations between PM$_{2.5}$ and the OS of stage I or stage IV patients were found.

The results of sensitivity analysis are shown in Table S2, in which the HRs of PM$_{2.5}$ were extracted from the results of 14 Cox regressions. It showed that after eliminating the patients from each city one at a time, the HRs of PM$_{2.5}$ remained significant, indicating the robustness of our results.

### Discussion

To the best of our 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. Although adjustment was not performed for some confounding factors, we found a stable relationship between higher PM$_{2.5}$ exposure and poorer OS among cervical cancer patients. Even upon grouping the patients by age and clinical stage, the significant association remained stable, but no significant associations were found in FIGO I and FIGO IV patients. Sensitivity analysis also ruled out the probability that the significant findings were simply due to the patients from some specific cities. Most of the findings obtained in this study matched those from previous work. Besides older age at diagnosis and higher clinical stage, we also found that adenocarcinoma and being single were potential risk factors for the OS of cervical cancer, which is similar to previously reported results (Cohen et al. 2019).

To date, some evidence has been reported about the link between exposure to ambient air pollution 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; Deng et al. 2017; Villanueva et al. 2021; Xu et al. 2013). However, all of these studies were based on Surveillance Epidemiology and End Results (SEER) cohorts or the Californian population. Eckel et al. (2016) also found that the effects of PM$_{2.5}$ on the survival of cancer patients were more pronounced in Asians, which reminds us of more attention on Asian patients. Therefore, our study provides important evidence for cancer patients in both Asian and developing countries, as well as for patients residing in heavily polluted areas. Further studies are still needed to explore the associations between PM$_{2.5}$ and the OS of other types of cancer, 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, we

![Figure 2](image1.png)

**Fig. 2** Locations as well as the average daily PM$_{2.5}$ concentrations from 2014 to 2021 in each city in Liaoning Province. Note that the average concentration is only for urban areas of each city, which is not displayed in this figure. In this figure, A: Shenyang; B: Dalian; C: Anshan; D: Fushun; E: Benxi; F: Dandong; G: Jinhua; H: Yingkou; I: Fuxin; J: Liaoyang; K: Panjin; L: Tieling; M: Chaoyang; N: Huludao

![Figure 3](image2.png)

**Fig. 3** Kaplan–Meier curves of age at diagnosis, marital status, histological type, FIGO stage, city size, and PM$_{2.5}$ exposure level (in quartiles) versus the overall survival of cervical cancer patients.
found that the OS of both SCC and AC patients was associated with PM$_{2.5}$, but the HR of SCC was greater. Although we did not find an explanation for this in the literature, this finding is similar to that of Eckel et al., who obtained the same result regarding the OS of lung cancer patients (Eckel et al. 2016). Second, the associations between PM$_{2.5}$ exposure and stage I or stage IV cervical cancer patients were negative, but this might be reasonable. Indeed, Villanueva et al. found that the associations between PM$_{2.5}$ and ovarian cancer survival were greater in patients at early disease stages (Villanueva et al. 2021), which could be explained by these patients having more cumulative PM$_{2.5}$ exposure. However, for cervical cancer patients, the survival rate of stage I patients during our study period was 96.2%, which suggests that the study period was too short to examine the associations in this population. As for stage IV patients, the most likely reason for the negative results between PM$_{2.5}$ exposure and the OS of these patients was the small sample size ($n=87$).

As mentioned above, the mortality of many types of cancer has been reported to be associated with exposure to ambient air pollution. The reasons for this may simply lie in higher incidences of cancer being associated with higher exposure to ambient air pollution. However, this trend may not apply in cervical cancer, which is mainly caused by high-risk HPV infection (Cohen et al. 2019). Therefore, more attention should be paid to the adverse effects of air pollution on cervical cancer patients, rather than those prior to disease development. Unfortunately, owing to the limited number of relevant studies, it is not clear whether there is a causal relationship between PM$_{2.5}$ and cancer survival, or the potential mechanisms involved in any such relationship. However, ambient air pollution, especially PM$_{2.5}$, has been definitively classified as a carcinogen. In other words, the carcinogenic effects of PM$_{2.5}$, including the induction of oxidative stress, DNA damage, cell proliferation, or epigenetic modifications, may still be exerted in cancer survivors (Eckel et al. 2016). Meanwhile, PM$_{2.5}$ can directly harm respiratory function, which is particularly crucial for the recovery from and survival of cancer. Another potential reason for the association between PM$_{2.5}$ and the OS of cancer patients may be the short-term adverse effects of PM$_{2.5}$ exposure. It has frequently been reported that short-term PM$_{2.5}$ exposure is significantly associated with higher mortality of lung cancer (Berger et al. 2018; Chung et al. 2021; Wang et al. 2019b). Therefore, the mortality displacement may also exist in the mortality of cancer patients.

Some limitations of this study should be noted. First, our study was based at Liaoning Cancer Hospital, which

| 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 | Adenocarcinoma | Squamous cell carcinoma | 2.11 | 1.15 | 3.89 | *   |
|           | Other types |         | 3.23 | 1.61 | 6.45 | *   |
|           | Unknown |         | 1.34 | 0.82 | 2.18 |    |
| Marital 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  The association between PM$_{2.5}$ and the OS of cervical cancer patients

Table 4  Subgroup analysis of the association between PM$_{2.5}$ exposure and cervical cancer overall survival

| Groups | Subgroups | PM$_{2.5}$ |
|--------|-----------|------------|
| 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) | Stage I | 1.063 0.986 1.146 |    |
|           | Stage II | 1.071 1.020 1.124 | *   |
|           | Stage III | 1.059 1.029 1.091 | *   |
|           | Stage IV | 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 | *   |

Note: * p <0.05
is the largest oncology hospitals in Liaoning Province, at which patients with low socioeconomic status might be less likely to be treated. Therefore, the fact that this was a single-center study may have led to bias in the enrollment of patients. Second, in the Cox regression analysis, there was no adjustment for confounders such as temperature, humidity, and SES-related factors, which might also impact on the survival period of cancer patients. This might also have led to bias in the results of this study. Third, among all types of cancer, patients with cervical cancer have relatively high survival rates, so cervical cancer-related studies require a long follow-up period. Unfortunately, owing to a lack of provincial PM$_{2.5}$ data from before 2014, we could only enroll patients diagnosed since then. Nevertheless, our findings still provide insight into the association between PM$_{2.5}$ exposure and cervical cancer survival, which is important in the fields of both environmental protection and oncology.

### Conclusion

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

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The authors are grateful to all research staff that contributed to the data collection required for this study.

### 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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### Data availability

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.

### Declarations

#### Ethics approval

This study was approved by the Ethics Committee of Cancer Hospital of China Medical University (number: 2021G0301).

#### Consent for publication

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

#### Competing interests

The authors declare no competing interests.

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