in vivo *38*: 928-934 (2024)
doi:10.21873/invivo.13521

The Impact of $PM_{2.5}$ on Radiation-induced Pneumonitis in Patients With Breast Cancer

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Abstract. *Background/Aim: Exposure to particulate matter (PM) air pollution is known to adversely affect respiratory disease, but no study has examined its effect on radiation-induced pneumonitis (RIP) in patients with breast cancer. Patients and Methods: We conducted a retrospective review of 2,736 patients with breast cancer who received postoperative radiation therapy (RT) between 2017 and 2020 in a single institution. The distance between the PM measurement station and our institution was only 3.43 km. PM data, including $PM_{2.5}$ and PM_{10}, were retrieved from the open dataset in the official government database. Results: Overall incidence rate of RIP was 1.74%. After adjusting for age, RT technique, regional irradiation, fractionation and boost, the average value of $PM_{2.5}$ was significantly associated with a higher risk of RIP (p=0.047) when patients received ≥20 fractions of RT. Specifically, $PM_{2.5}$ ≥35 (μg/m^3) showed a significantly higher risk of RIP (p=0.019) in patients with ≥20 fractions of RT. Conclusion: This is the first study to reveal the association between $PM_{2.5}$ and RIP in patients with breast cancer who received 20 fractions or more of postoperative RT. We demonstrated that high $PM_{2.5}$ levels around the RT institution were associated with RIP, suggesting that reducing PM air pollution may be a modifiable risk factor.*

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Key Words: Particulate matter, radiation-induced pneumonitis, breast cancer, radiotherapy.

Particulate matter (PM) is a type of air pollutant that can be inhaled as dust and deposited in the lungs, particularly the alveoli (1). PM is divided into PM_{10} with a diameter of less than 10 μm and $PM_{2.5}$ with a diameter of less than 2.5 μm (2). PM is recognized not only as an environmental problem but also as a social problem that can harm public health. The Global Burden of Disease Study 2019 ranked $PM_{2.5}$ as the seventh leading risk factor for death in all ages, particularly fifth rank for 50-74 years old (3). In addition, the International Agency for Research on Cancer under the World Health Organization classified PM as a group 1 carcinogen among air pollutants (4). According to the previous studies, exposure to PM could be harmful to the respiratory system and be associated with increased mortality as well as hospital admissions in patients with underlying respiratory diseases, such as asthma or chronic obstructive pulmonary disease (5-8). Furthermore, PM is known to induce oxidative stress and cause a local inflammatory reaction in direct contact with human respiratory mucosa. PM exposure primarily affects airway macrophages and airway epithelial cells, and secondarily induces a systemic inflammatory response by increasing c-reactive protein or several inflammatory cytokines in the blood (9, 10).

On the other hand, patients with breast cancer who undergo breast-conserving surgery and adjuvant radiation therapy (RT) may develop symptomatic radiation-induced pneumonitis (RIP) (11), which has potentially severe toxicity that can lead to radiation-induced lung fibrosis (12). The mechanism of RIP is known to start from inflammation caused by direct DNA damage and generation of reactive oxygen species (13). Considering the pro-inflammatory reaction of PM, it can be expected that PM can influence the occurrence of RIP by inducing local and systemic inflammatory reactions in the respiratory system. However, to the best of our knowledge, there is no related literature on the relationships between PM and RIP in patients with breast cancer who received adjuvant RT.

Given the growing global concern in the effects of PM on health, we aimed to investigate the impact of PM on RIP in patients with breast cancer with considerations of detailed information of RT parameters, such as total number of fractions, fractionation dose, RT technique, or the receipt of regional nodal irradiation.

Patients and Methods

Collection of patients and particulate matter data. This study was approved by the institutional review board of institution of the Seoul National University Bundang Hospital (SNUBH IRB No. B-2106-692-107). We retrospectively reviewed medical records of 2,762 patients between 2017 and 2020 in a single institution. All the patients were diagnosed with breast cancer and underwent breast cancer surgery followed by adjuvant RT. For breast cancer surgery, we included both breast conserving surgery (N=2,212) and mastectomy (N=550). All patients analyzed in the current study were female and over 18 years of age. We excluded patients with a history of chest RT for other primary cancers, such as lung cancer or esophageal cancer.

Particulate matter data were retrieved from the open dataset named the 'Gyeonggi Data Dream', sourced from the official government database. 'Gyeonggi Data Dream' serves to actively open public data to the private sector, creating public value by discovering public data held by affiliated public institutions and making them accessible through an integrated portal. Anyone can access this dataset through the website (https://data.gg.go.kr/) without charge. The dataset provided measurement values of $PM_{2.5}$ and PM_{10} by time zone for 24 hours at each station in Gyeonggi-do. The distance between the PM measurement station and our institution was only 3.43 km in a straight line (Figure 1). We used the average, median and maximum values of the $PM_{2.5}$ and PM_{10}, which have been measured during daytime when a patient visited to the hospital for RT. The PM metrics used in the analyses were measured during all days of RT. We processed the measured PM open dataset and extracted values for each patient for each day of RT. Most of the PM measurement values were provided, but missing values were recorded when measurement errors were detected. Patients were excluded if missing PM data exceeded 50% of the total treatment period (N=26). Thus, a total of 2,736 patients were analyzed in the current study. Patients who underwent both breast conserving surgery (N=2,190) and mastectomy (N=546) were included.

On the other hand, the concentration of $PM_{2.5}$ was classified based on 35 μg/m^3, because current regulation of $PM_{2.5}$ as a daily standard is below 35 by the Korean Ministry of Environment. The criteria for daily $PM_{2.5}$ alerts are set as 'good' for 0~15 μg/m^3, 'fair' for 16~35 μg/m^3, and 'bad' for more than 35 μg/m^3. In addition, the U.S. Environmental Protection Agency has implemented the nation's air quality standards for $PM_{2.5}$ to improve public health protection by retaining the 24-hour fine particle standard of 35 μg/m^3.

Definitions of radiation-induced pneumonitis. RT can cause adjacent lung tissue damage ranging from asymptomatic radiological changes to severe respiratory failure in patients with breast cancer (14). Radiographic changes, such as consolidation, ground-glass opacity, linear or dense opacity, and lung volume loss on chest radiographs may suggest RIP. Typical clinical manifestations of RIP include cough, dyspnea, and fever, but many cases are asymptomatic even

Figure 1. *A map representation of the distance between particulate matter measurement stations and our institution (Only 3.43 km in a straight line).*

if radiographic changes are detected in medical images (15). RIP was confirmed when the patient was diagnosed with the International Classification of Diseases 10th Revision (ICD-10) code J700 (Acute pulmonary manifestations due to radiation) or J.700.001 (Radiation pneumonitis) after RT. Because the diagnosis of RIP could be ambiguous only by reviewing clinical symptoms or changes on chest images, RIP was defined as having occurred only when the aforementioned ICD code for RIP was present in the patient's medical record.

Statistical analysis. All patients were classified according to the presence or absence of RIP, and the difference in radiation treatment [RT fractionation (conventional RT *vs*. hypofractionated RT), boost, RT technique (3-dimentional conformal RT *vs*. intensity-modulated RT), and regional nodal irradiation] between the two groups was analyzed. Especially, we tried to reveal the relationship between PM concentrations and RIP occurrence according to the number of RT fractions. Since the number of radiation treatments is directly related to fractionation, the effect of hypofractionation and conventional fractionation on the occurrence of RIP was also investigated. The stepwise logistic regression model was used for univariate and multivariate analyses to analyze prognostic factors for incidence of RIP. In the multivariate logistic model, a stepwise procedure was applied to include only factors with a univariate significance level of $p<0.1$. All statistical analyses were 2-sided and performed with STATA/MP, version 15.0 (StataCorp, College Station, TX, USA), with a significance of $p<0.05$.

Table I. *Baseline characteristics according to the radiation-induced pneumonitis (RIP) in breast cancer patients undergoing postoperative radiation therapy (RT).*

	No (%) RIP (+) (N=48)	No (%) RIP (–) (N=2,688)	*p*-Value
Age, years [median (range)]	52 (39-79)	51 (22-91)	0.259
Total number of RT fractions [median (range)]	19 (16-30)	19 (16-33)	0.733
Fractionation of RT			
Conventional RT	6 (12.5)	259 (9.6)	0.506
Hypofractionated RT	42 (87.5)	2,429 (90.4)	
Boost			
Yes	36 (75.0)	2,100 (78.1)	0.604
No	12 (25.0)	588 (21.9)	
RT Technique			
3-dimentional conformal RT	20 (41.7)	776 (28.9)	0.053
Intensity-modulated RT	28 (58.3)	1,912 (71.1)	
Regional nodal irradiation			
Yes	9 (18.8)	502 (18.7)	0.990
No	39 (81.3)	2,186 (81.3)	
Regional RT details			
Breast/CW alone	39 (81.2)	2,186 (81.3)	0.116
Breast/CW+SCL	9 (18.8)	339 (12.6)	
Breast/CW+SCL+IMN	0 (0.0)	163 (6.1)	
Average value of $PM_{2.5}$ $^{+*}$	22.3 (10.5-57.5)	22.6 (7.8-64.8)	0.588
Median value of $^{+*}PM_{2.5}$ $^{+*}$	21.3 (6.4-53.0)	19.9 (5.7-55.7)	0.601
Maximum value of $PM_{2.5}$ $^{+*}$	45.7 (16.2-150.1)	45.8 (12.8-150.1)	0.699
Average value of PM_{10} $^{+*}$	41.9 (21.0-81.8)	42.5 (18.2-88.9)	0.566
Median value of PM_{10} $^{+*}$	39.8 (20.2-68.2)	39.4 (13.1-75.1)	0.761
Maximum value of PM_{10} $^{+*}$	85.6 (33.0-205.1)	85.2 (29.9-205.1)	0.826
Average value of $PM_{2.5}$ *			
<35	41 (85.4)	2,494 (92.8)	0.053
≥35	7 (14.6)	194 (7.2)	

RIP: Radiation-induced pneumonitis; SCL: supraclavicular LN; IMN: internal mammary LN; PM: particulate matter; CW: chest wall. *μg/m^3; $^+$continuous value.

Results

We classified patients according to whether they experienced RIP [RIP (+) *vs*. RIP (–)]. Of all 2,736 patients with breast cancer who received adjuvant RT, there were 48 cases who showed RIP after the treatment, indicating that overall incidence rate of RIP was 1.74%. Baseline characteristics are shown in Table I. Median age for both groups was 52 years old, suggesting that age was not a significant factor affecting the incidence of RIP (*p*=0.259). There were no significant differences in RT fractionation (conventional *vs*. hypofractionated RT) (*p*=0.506), and use of boost (*p*=0.604) between RIP (+) and RIP (–) groups. Marginal difference was found in RT techniques (3D-CRT *vs*. IMRT) (*p*=0.053), showing the benefit of IMRT in terms of reduced incidence of RIP. Regional nodal irradiation did not affect the occurrence of RIP (*p*=0.990). Particularly, supraclavicular (SCL) and/or internal mammary (IMN) lymph node involvement to RT field was not associated with the risk of RIP (*p*=0.116). There were no significant differences in average, median, maximum value of $PM_{2.5}$ and PM_{10} during individual RT sessions between the two groups. However, the proportion of $PM_{2.5}$ values ≥35 (μg/m^3) was higher in the RIP (+) group, which showed statistically borderline significance.

When analyzing relationship between PM data and RIP considering the number of RT fractions, we found that 20 or more fractions were related with increasing trend of odds ratio (OR) in terms of the incidence of RIP in the overall population (Figure 2A) and in patients exposed with $PM_{2.5}$ values ≥35 (Figure 2B). For example, when patients received the 20 fractions of RT, an elevated risk of RIP was associated with the higher average value of $PM_{2.5}$ [OR=1.05, 95% confidential incidence (CI)=1.00-1.10, *p*=0.047] and $PM_{2.5}$ values ≥35 (μg/m^3) (OR=4.32, 95%CI=1.34-13.87, *p*=0.014).

The results of the univariate and multivariate analyses of prognostic factors for incidence of RIP in patients receiving ≥20 fractions of RT are shown in Table II. On univariate analyses, boost, average value of $PM_{2.5}$, and $PM_{2.5}$ ≥35

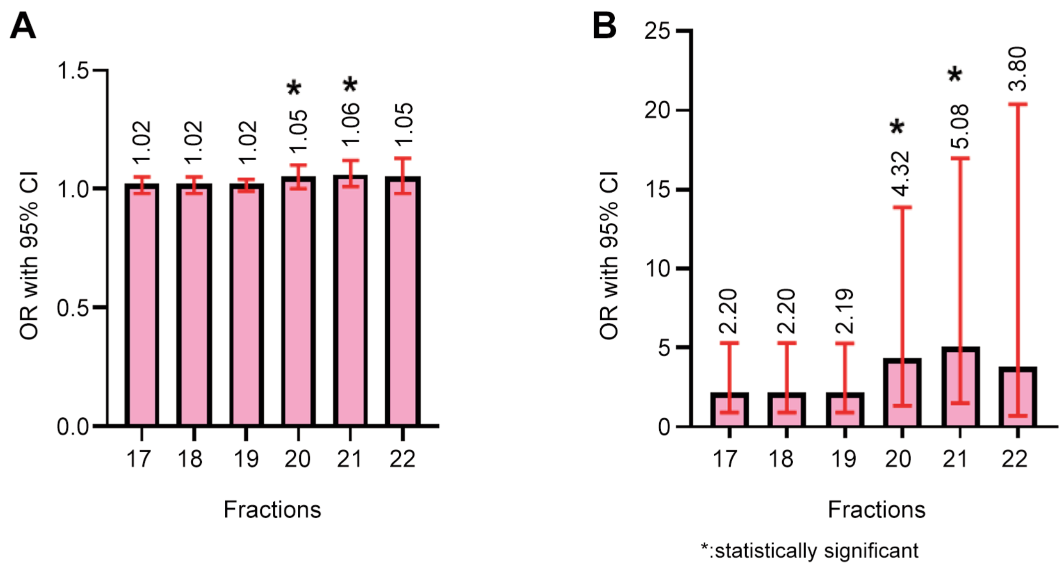

Figure 2. *Analyses of the relationship between particulate matter (PM) data [overall average $PM_{2.5}$ values (A) and $PM_{2.5}$ values ≥35 (B)] and radiation-induced pneumonitis, stratifying the number of radiation therapy (RT) fractions. Significantly increased odds ratio (OR) over 20 fractions of RT for both overall average $PM_{2.5}$ values and $PM_{2.5}$ values ≥35 was found. CI: Confidence interval.*

(μg/m^3) were statistically or marginally significant factors for the occurrence of RIP. After performing a stepwise multivariate regression analysis, $PM_{2.5}$ ≥35 (μg/m^3) showed a significantly higher risk of RIP (OR=4.06, 95%CI=1.25-13.13, *p*=0.019) in patients with ≥20 fractions of RT after adjustment of the aforementioned covariates.

Other PM data (median, maximum value of $PM_{2.5}$ and all PM_{10} values) were not related to the RIP regardless of the number of RT fractions. On the other hand, the results of analyzing the average value of $PM_{2.5}$ as a continuous variable through a logistic model with the category of the tertile of the average value of $PM_{2.5}$ and the median of the fractions as an interaction term are shown in Table III.

Discussion

PM is a factor that threatens public health, and concerns are gradually increasing due to its adverse effects on the respiratory system (16-18). Constant exposure to PM can induce airway inflammation, which increases responsiveness to particle pollution and causes bronchoconstriction (19). This inflammation reaction may damage the integrity of alveolar-capillary barrier and lead to chronic inflammation that impairs the pulmonary immune system (20). Also, previous epidemiological studies have reported that PM adversely affects respiratory diseases. Cheng *et al*. revealed coarse PM was associated with higher risk of hospital admission for respiratory disease in Taiwan (6) and even increased the risk of hospital admissions for pneumonia (21). Moreover, a recent study found that $PM_{2.5}$ may play an important role in emergency visits for pneumonia with septicemia in relatively healthy residents (8). Based on these studies, we initiated this research based on the assumption that RIP might also be affected by PM. Adjuvant RT for patients with breast cancer is generally well tolerated, but the lung is a major dose-constraint organ for RT planning, since more severe RIP might occur after several weeks after RT (22). Known risk factors for the occurrence of RIP in patients with breast cancer are mainly lung dosimetric parameters in RT plans (23-25) or other treatments such as chemotherapy (26). There are no studies revealing that air pollution, such as PM, is a risk factor for RIP in patients with breast cancer who receive post-operative RT.

In the current study, the average value of $PM_{2.5}$ ≥35 (μg/m^3) was significantly associated with a higher risk of RIP in patients receiving ≥20 fractions of RT, after adjusting for age, boost, RT fractionation, RT technique (3D-CRT *vs*. IMRT), regional nodal irradiation, and other PM data. It was noteworthy that the association between PM and RIP in patients receiving RT has not been investigated. Especially, the effect of PM on RIP was found to be significant when the RT fractions were 20 or more, confirming that the relationship with the number of RT treatments would be helpful in actual clinical practice. The number of RT fractions in the treatment plan of breast cancer has undergone significant changes recently. In order to reduce the dose-volume of the ipsilateral lung and heart, IMRT was introduced and has begun to replace the existing 3D-CRT (27-29). IMRT showed a better conformity with better homogeneity index (27). Also, hypofractionated RT, which

Table II. *Prognostic factors for incidence of radiation-induced pneumonitis (RIP) in patients with ≥20 fractions of radiation therapy (RT).*

	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age	1.02	0.98-1.07	0.388	–	–	–
Conventional RT (*vs*. Hypofractionated RT)	1.95	0.69-5.53	0.209	–	–	–
Boost (*vs*. No Boost)	0.35	0.12-1.05	0.061	0.38	0.13-1.13	0.082
IMRT (*vs*. 3D-CRT)	0.88	0.30-2.59	0.812	–	–	–
Regional nodal irradiation Yes (*vs*. No)	1.20	0.34-4.31	0.777	–	–	–
Average value of $PM_{2.5}$+*	1.05	1.00-1.10	0.047	–	–	–
Median value of $PM_{2.5}$+*	1.05	0.98-1.14	0.184	–	–	–
Maximum value of $PM_{2.5}$+*	1.01	1.00-1.03	0.177	–	–	–
Average value of PM_{10}+*	1.01	0.97-1.05	0.691	–	–	–
Median value of PM_{10}+*	1.00	0.95-1.05	0.999	–	–	–
Maximum value of PM_{10}+*	1.00	0.99-1.01	0.872	–	–	–
Average value of $PM_{2.5}$* ≥35 (*vs*. <35)	4.32	1.34-13.87	0.014	4.06	1.25-13.13	0.019

PM: Particulate matter. *μg/m³; +continuous value.

Table III. *Analysis of the average value of PM2.5 as a continuous variable through a logistic model with the category of the tertile of the average value of PM2.5 and the median of the fractions.*

RIP	Odds ratio	Standard error	z	*p*>|z|	95% confidence interval
Average value of PM2.5+*	1.053	0.027	2.01	0.044	1.00-1.11
$PM_{2.5}$_avg #3 – fractions#2					
$PM_{2.5}$ Q1 –Fr Q2	0.229	0.174	–1.94	0.052	0.05-1.01
$PM_{2.5}$ Q2 –Fr Q1	0.458	0.215	–1.67	0.096	0.18-1.15
$PM_{2.5}$ Q2 –Fr Q2	0.463	0.249	–1.43	0.152	0.16-1.33
$PM_{2.5}$ Q3 –Fr Q1	0.239	0.165	–2.08	0.038	0.06-0.92
$PM_{2.5}$ Q3 –Fr Q2	0.297	0.213	–1.69	0.091	0.07-1.21

Fr: Fraction. *μg/m³; +continuous value.

implicates less fractionations, has gradually become a standard of care, replacing conventional fractionated RT. This is supported by evidence from studies, such as START A, START B, and a recent large-scale randomized controlled trial from China (30-32). Although the total number of RT fractions has been decreasing compared to the past, owing to results of the aforementioned clinical trial, there is still a wide variety of RT practices depending on radiation oncologists. Based on our results, attention can be given to individual patients according to the total number of RT fractions in some regions or seasons polluted with severe PM. When high PM is expected, a decision could be individualized to modify the total number of RT fractions to less than 20 fractions. Also, while receiving RT for breast cancer, physicians may recommend that patients wear a mask to block PM as possible during outpatient treatment sessions. It can also be helpful to actively check PM monitoring alerts individually and pay attention to outdoor activities on days when PM is above a certain level.

Study limitations. First, the average concentration of PM measured at a fixed measurement station may not completely reflect the patients' actual exposure within a institution. Second, the ambient PM concentrations measured by a fixed station might differ from true concentrations nearby due to differences in distance from the institution. Third, since we included patients who were actually diagnosed with RIP confirmed by ICD-10 codes (J700, J700.001), some cases might have been missed if the diagnosis was not documented in the medical records. However, in the case of the first limitations, the PM data between 8 AM and 6 PM, the daytime when the patient visited the hospital, was used for the analyses. Furthermore, it was inevitable to assume that the PM measurements by the nearby fixed station are commonly used as proxies for estimating individual exposure. Moreover, since our institution was only 3.43 km away from the measurement station, this assumption could be maintained. Furthermore, though inclusion criteria related to ICD codes are likely to result in missing cases of RIP, excluding RIP in cases of ambiguity and including RIP in cases requiring actual medication or intervention contributed to improving the accuracy of the study results.

Conclusion

Taken together, this is the first study that showed a significant relationship between PM and RIP in patients with breast cancer who received adjuvant RT. Our novel findings could help physicians decide how to treat patients with breast cancer with RT in an era when PM is recognized as a serious environmental problem.

Funding

This study was supported by grant no. 04-2023-2220 from the SNUH Research Fund.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

DYK: Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. IAK: Data curation, Resources, Supervision, Validation. BSJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing.

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Received December 4, 2023
Revised January 10, 2024
Accepted January 11, 2024