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Association between air pollution and recurrence of lung cancer after surgery in female never-smokers

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Abstract

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Background: Lung cancer is a common cancer all over the world, and it is the third most common cancer in Korea. While groundbreaking anticancer drugs and radiotherapy have been developed, surgery is still known as the most appropriate treatment in early-stage lung cancer. However, recurrence after surgery is the most common event of treatment failures among lung cancer patients, thereby shortening the survival period. Although stage at diagnosis and vascular lymphatic metastases have been estimated to be risk factors for recurrence, causes for recurrence are still unclear. Smoking is the highest risk factor for lung cancer, but never-smokers account for more than half among female lung cancer patients. Many studies have investigated air pollution as one of the risk factors in lung cancer incidence, but there is little research on the association between air pollution and lung cancer recurrence.

Objectives: Under the hypothesis that air pollution will have an effect on the recurrence of lung cancer after surgery with a similar mechanism to the effect on lung cancer incidence, this study aims to

investigate the association between air pollution and lung cancer recurrence after surgery in female never-smokers.

Methods: This study selected 132 female never-smoker lung cancer patients who had surgery from February 2013 and January 2017 at Seoul National University Hospital and collected clinical information, including stage at diagnosis, primary tumor size, lymph node invasion, *EGFR* (Epidermal growth factor receptor) mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoking. The air pollution data were extracted according to each subject's residence and were merged after calculating the average concentrations at each time-interval (3, 6, 12, 24 and 36 months intervals from surgery until recurrence). Statistical analysis was performed using multiple logistic regression models after adjusting for the aforementioned clinical variables.

Results: Estimated odds ratios for the recurrence of lung cancer with increase of 1 ppb in SO_2 was identified as 1.73 (95% CI: 1.07-2.80) and 2.14 (95% CI: 1.31-3.49) during 24 and 36 months from surgery until recurrence in fully adjusted models. Estimated odds ratios for the recurrence of lung cancer with increase of 10 ppb in NO_2 and 10 $\mu g/m^3$ in $PM_{2.5}$ were respectively 2.02 (95% CI: 1.01-4.04) and 3.35 (1.02-10.99) during 36 months from surgery until recurrence. In the case of increase of 10 ppb in O_3, adjusted odds ratios for the recurrence were 0.32 (0.11-0.94) and 0.34 (0.12-0.98) during 12

and 36 months from surgery until recurrence. These results were identically indicated in two-pollutant models. In subgroup analyses, only O_3 and PM_{10} had interactions with *EGFR* mutation but the patterns of associations between each air pollutant and recurrence of lung cancer differed by the presence of *EGFR* mutation.

Conclusion: This study identified that air pollution can be an associated risk factor for the recurrence of lung cancer in female never-smokers and the association was found to be more relevant with longer exposure periods. However, this study showed that O_3 was negatively associated with the recurrence of lung cancer. It was also shown that the association between air pollution and the recurrence of lung cancer was different according to the presence or absence of *EGFR* mutation. Subsequent studies should further investigate uncertain effect of ozone on lung cancer recurrence. The results of this study will serve as the base for further studies concerning risk factors of lung cancer recurrence in female never-smokers in the interest of public health.

Keywords: Lung cancer, Neoplasm recurrence, Air pollutants, Never-smoker, Female

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Chapter 1. Introduction

1.1 Study background

Lung cancer has been the most common cancer in the world for several decades, with an estimated 2.1 million new cases in 2018 (11.6% of all new cancers) and was also the most common cause of death in 2018, with 1.8 million cases (18.4% of all cancer deaths) (Bray et al., 2018). In South Korea, lung cancer is the third most frequent malignant neoplasm following gastric cancer and colorectal cancer in 2017 and in the case of lung cancer incidence in South Korean women, 8,328 was diagnosed with lung cancer in 2017 (Hong et al., 2020).

Despite the development of chemotherapy and radiotherapy, surgery is regarded as the most proper treatment choice for early-stage non-small-cell lung cancer (NSCLC) (Lang-Lazdunski, 2013). However, postoperative recurrence is the most common cause of treatment failure among lung cancer patients, thereby making it a major hurdle to long-term survival (Cruz, Afonso, Oliveiros, & Pego, 2017). 79.5% of lung cancer patients suffer distant recurrence after surgery (Dziedzic, Rudzinski, Langfort, Orlowski, & Group, 2016).

Smoking is the highest risk factor for the development of lung cancer. It has been estimated that around 85% of male lung cancer patients and 47% of female lung cancer patients are smokers

(Youlden, Cramb, & Baade, 2008). While smoking is one of the major causes of lung cancer, it also occurs in non-smokers, 15% of male lung cancer patients and 53% of female lung cancer patients respectively. Especially, lung cancer occurring in never-smokers was estimated to have increased among Korean women (Park & Jang, 2016). Risk factors for lung cancer among non-smokers are various, including exposure to secondhand tobacco smoke, occupational lung carcinogens, radiation, and indoor and outdoor air pollution (Alberg, Brock, Ford, Samet, & Spivack, 2013), but they have not been clearly clarified (Samet et al., 2009).

Among these environmental risk factors, epidemiological studies have been conducted on the association between long-term exposure to air pollution and lung cancer (Beelen et al., 2014; Hoek et al., 2013; Turner et al., 2011), considering the severe deterioration of air quality due to the release of a variety of air pollutants, which have an adverse effect on humans (Brauer et al., 2012; Kampa & Castanas, 2008). Nitrogen dioxide (NO_2) has been related to increasing the risk of lung cancer (Bakand, Hayes, & Winder, 2007; Nyberg et al., 2000). Also, NO_2 and particulate matter less than 10㎛ (PM_{10}) have shown stronger association with lung cancer among never-smokers (Lamichhane et al., 2017). Lung cancer incidence has been associated with high exposure to sulfur

dioxide (SO_2) in females and this association is much greater for squamous cell carcinoma rather than for adenocarcinoma (Tseng et al., 2012). Ozone (O_3) has influenced in a variety of oxidative stress mechanisms involved in the production of mediators of pulmonary inflammation and mechanisms of carcinogenesis (Valavanidis, Vlachogianni, Fiotakis, & Loridas, 2013) and the risk of lung cancer incidence has been associated with ozone. (Guo et al., 2016). Particulate matter 2.5 ($PM_{2.5}$), a type of air pollutant with a diameter of $\leq$ 2.5㎛, has been identified to have marked association with lung cancer, cardiopulmonary diseases and chronic airway inflammatory diseases (Jerrett et al., 2005; Katanoda et al., 2011).

Although evidence has been accumulated regarding relation between air pollution and lung cancer, relevant information on the association between air pollution exposure and the recurrence of lung cancer in particular is rare. A recent study reported that reduced survival period was associated with higher NO_2, PM_{10}, and $PM_{2.5}$ exposure over the follow-up period after diagnosis, with the largest hazard ratio in early stage non-small cell lung cancer, especially adenocarcinoma (Eckel et al., 2016).

This study presumes if air pollution is a carcinogen affecting lung cancer incidence and survival, then under similar mechanism, air pollutants may also induce tumor recurrence.

1.2 Purpose of research

The aim of this study is to investigate the association between air pollution and lung cancer recurrence after surgery in female never-smokers in Korea.

Chapter 2. Materials and Methods

2.1 Data

2.1.1 Study design and participants

This study is a retrospective study based on a prospective hospital-based cohort for never-smoker lung cancer patients from February 2013 at Seoul National University Hospital (Seoul, South Korea). This cohort is aimed to establish clinical features and genetic characteristics of never-smoker lung cancer patients and to follow up their clinical progress. In this study, patients who had exposure to less than 100 cigarettes in their whole life, were defined as never-smokers.

Only female never-smoker patients who had surgery from February 2013 and January 2017 were selected (n=170). Excluding 28 patients lost to follow-up, only patients residing in air quality monitored regions were chosen (n=136). Patients who were diagnosed with pathologic stage Ⅳ lung cancer after surgery - based on the seventh edition of the American Joint of Cancer Committee (AJCC) on Cancer Staging Manual - were excluded (n=132). This study was approved by the institutional review board of the Seoul National University (IRB No. E2009/003-007). The requirement for informed consent was waived.

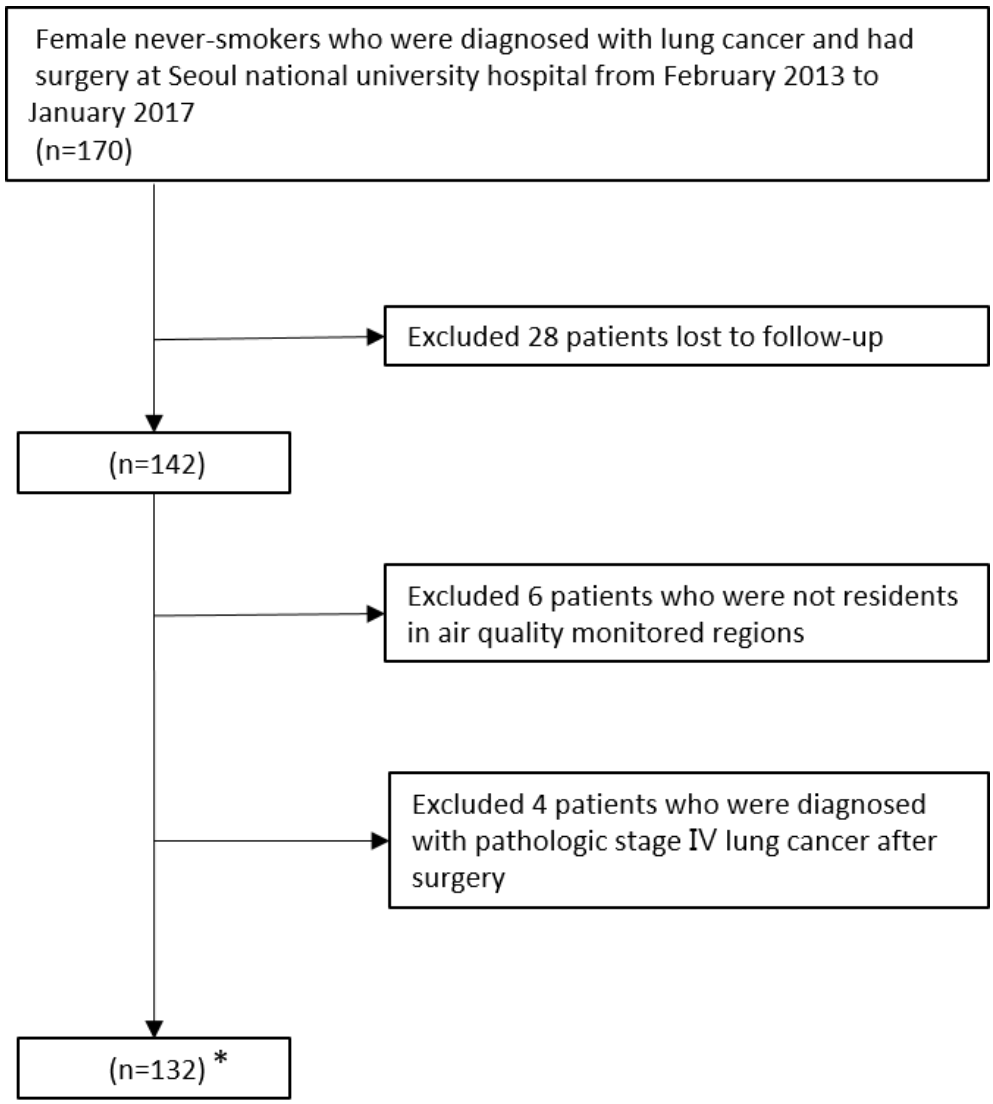


Figure 1. Flow chart of recruitment of study participants.
(*) Air pollution data of the cities where each individual resides was merged.

2.1.2 Assessment of outcome

Per this study, lung cancer recurrence is defined as the first radiologic diagnosis of metastases or cancer recurrence after surgery during the period of follow-up. CT scans were taken according to planned schedules. These schedules were determined by clinicians, but scans were usually taken four times in the first year after surgery, and two times in the second year after surgery, then thereafter every year.

2.1.3 Assessment of air pollution

This study obtained hourly concentrations of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), carbon dioxide (CO), particulate matter less than 10 $\mu g/m^3$ (PM_{10}) and particulate matter less than 2.5 $\mu g/m^3$ ($PM_{2.5}$) from the website on which regional air pollution data are annually posted by The Korean National Institute of Environmental Research (http://www.airkorea.or.kr/). This study included 198 monitoring sites situated in 79 cities (where study participants reside) between January 2013 and February 2020. Daily city-specific concentrations of SO_2, NO_2, CO, O_3, PM_{10} and $PM_{2.5}$ were calculated as below.

First, mean concentrations per hour were obtained by

calculating average of site-specific concentrations in the same city. Second, city-specific mean concentrations per day of SO_2, NO_2, CO, PM_{10} and $PM_{2.5}$ were calculated by averaging those hourly concentrations. In the case of O_3, the maximum 8-hour mean concentration was averaged. Third, the average of each exposure at each time-interval (3, 6, 12, 24 and 36 month intervals from operation date until lung cancer recurrence) was constructed.

2.1.4 Clinical covariates

All demographic and clinical data were ascertained from medical records. The demographic and clinical data included age at diagnosis, residence, family history of lung cancer, symptoms related to lung cancer at diagnosis, exposure to secondhand smoke, history of hypertension, history of Type Ⅱ diabetes mellitus, the stage of cancer and *EGFR* (Epidermal Growth Factor Receptor) gene mutation. Exposure to secondhand smoke was defined as the exposure of at least 2 years in any place including at home and workplace. The stage of cancer was finally classified as pathologic tumor, node and metastasis (TNM) stage-based on the seventh edition of the American Joint Committee on Cancer Staging Manual -after surgery.

2.2 Statistical analysis

Lung cancer recurrence group and non-recurrence group were compared by two-sided independent two sample T-test for continuous variables, chi-square (χ^2) and fisher's exact test for categorical variables where appropriate. Multiple logistic regression models were used to estimate the odds ratio (ORs) and 95% confidence intervals (CIs) to evaluate the association between air pollution and lung cancer recurrence after surgery. The model was adjusted for covariates such as age at diagnosis (0-64 vs. ≥65), clinical stage at diagnosis (stage Ⅰ vs. ≥stage Ⅱ), tumor size (T1 vs. ≥T2), lymph node invasion (no vs. yes), *EGFR* gene mutation (no vs. yes), family history of lung cancer (no vs. yes), symptoms related to lung cancer at diagnosis (no vs. yes), history of hypertension (no vs. yes), history of type 2 diabetes mellitus (no vs. yes), and secondhand smoke (no vs. yes).

To evaluate the air pollution impact on lung cancer recurrence, this study calculated the average concentrations of each air pollutant at certain time-intervals which are after 3, 6, 12, 24 and 36 months from diagnosis date until lung cancer recurrence date. The average concentration of one single pollutant with different time-interval was involved in the model respectively.

Sensitivity analysis was conducted to evaluate the robustness

of the results. Two-pollutant model was used to investigate potential confounding by other air pollutants (e.g., SO_2, NO_2, O_3, CO or PM_{10} were adjusted respectively to estimate the effect of $PM_{2.5}$). Also, subgroup analyses for age and *EGFR* mutation were performed for each time-interval by including interaction term between each air pollutant and subgroup in the full-adjusted model. Odds ratio for each subgroup was calculated based on the interaction-included model.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 3.6.3 (R foundation for Statistical Computing, Vienna, Austria).

Chapter 3. Results

3.1 General characteristics

A total of 132 female never-smokers who were diagnosed with lung cancer and had tumor removal formed the basis of this study. General characteristics of study participants are shown in Table 1. 49 patients (37.12%) had an experience of lung cancer recurrence and 83 (62.88%) did not have a relapse. The mean age at diagnosis in recurrence group was 65.53 and 63.63 in non-recurrence group. More than half of the patients (59.18%) in recurrence group were diagnosed with lung cancer at stage Ⅱ or higher but less than one-fifth (18.07%) were diagnosed at stage Ⅱ or over (p <.0001). Primary tumor size in recurrence group among 71.43 % of patients was confirmed as T2 or over while 51.81% in non-recurrence group was shown to be T2 or over (p=0.029). Higher proportion of lymph node invasion was observed in recurrence group than in non-recurrence group (p <.0001). Among patients in recurrence group, 48.98% were detected to have *EGFR* gene mutations, and among those in non-recurrence group 51.81 % were detected to have the same gene alteration. No significant difference was observed regarding family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension,

history of type 2 diabetes mellitus and secondhand smoking between recurrence group and non-recurrence group.

Table 1. General characteristics of lung cancer recurrence group and non-recurrence group.

Characteristics	Recurrence group n (%)	Non-recurrence group n (%)	p-value*
Total	49 (37.12)	83 (62.88)	
Age at Diagnosis (yrs)			
≥65	22 (44.90)	35 (42.17)	
0-64	27 (55.10)	48 (57.83)	0.760
Mean (SD)	65.53 ± 9.52	63.63 ± 8.69	0.243
Stage at Diagnosis			
Stage Ⅰ	20 (40.82)	68 (81.93)	
≥Stage Ⅱ	29 (59.18)	15 (18.07)	<.0001
Primary Tumor Size			
T1	14 (28.57)	40 (48.19)	
≥T2	35 (71.43)	43 (51.81)	0.029
Lymph Node Invasion			
No	24 (48.98)	71 (85.54)	
Yes	25 (51.02)	12 (14.46)	<.0001

EGFR Gene Mutation			
No	25 (51.02)	40 (48.19)	
Yes	24 (48.98)	43 (51.81)	0.857
Family History of Lung Cancer			
No	43 (87.76)	73 (87.95)	
Yes	6 (12.24)	10 (12.05)	1.000
Symptoms Related to Lung Cancer at Diagnosis			
No	28 (57.14)	41 (49.40)	
Yes	21 (42.86)	42 (50.60)	0.471
History of Hypertension			
No	30 (61.22)	58 (69.88)	
Yes	19 (38.78)	25 (30.12)	0.343
History of Type 2 Diabetes Mellitus			
No	38 (77.55)	74 (89.16)	
Yes	11 (22.45)	9 (10.84)	0.083
Secondhand Smoke			
No	12 (24.49)	26 (31.33)	
Yes	37 (75.51)	57 (68.67)	0.433

SD, standard deviation; EGFR, Epidermal Growth Factor Receptor.

*T-test, Two-sided χ^2 test and fisher's exact test where appropriate.

3.2 Distribution of air pollution

Distribution of air pollution is described in Table 2. Average concentrations of air pollutants from January 2013 to February 2020 were 4.48 ppb for SO_2, 23.85 ppb for NO_2, 0.51 ppm for CO, 26.62 ppb for O_3, 45.52 $\mu g/m^3$ for PM_{10}, and 24.63 $\mu g/m^3$ for $PM_{2.5}$ respectively.

Table 2. Distribution of air pollutants (from January 2013 to February 2020)

	Mean ± SD	Median	IQR	Range
SO_2 (ppb)	4.48 ± 2.04	4.13	2.40	0.00–38.6
NO_2 (ppb)	23.85 ± 13.01	21.17	17.13	1.00–108.69
CO (ppm)	0.51 ± 0.21	0.45	0.24	0.02–2.75
O_3 (ppb)	26.62 ± 13.43	25.40	18.69	0.38–124.87
PM_{10} ($\mu g/m^3$)	45.52 ± 26.11	40.52	28.17	0.00–708.75
$PM_{2.5}$ ($\mu g/m^3$)	24.63 ± 15.30	21.50	17.27	0.00–162.29

SD, standard deviation; IQR, interquartile range; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone; CO, carbon dioxide; PM_{10}, Particulate matter less than 10 $\mu g/m^3$; $PM_{2.5}$, particulate matter less than 2.5 $\mu g/m^3$.

3.3 Association between air pollution and recurrence of lung cancer after surgery

Table 3 shows the association between SO_2 concentration and lung cancer recurrence after surgery. Adjusted for following variables such as age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke, SO_2 concentration during 24 and 36 months from surgery until recurrence were revealed to be significantly associated with lung cancer recurrence. Odds ratio (OR)s for a 1 ppb increase in SO_2 exposure during 24 and 36 months from surgery until recurrence were 1.73 (95% confidence interval (CI): 1.07−2.80) and 2.14 (95% CI: 1.31−3.49).

Table 4 presents the association of NO_2 with lung cancer recurrence. Increase of 10 ppb in NO_2 was significantly associated with lung cancer recurrence during 36 months from surgery until recurrence (adjusted OR [95% CI]: 2.02 [1.01−4.04]). However, in the fully adjusted model, ORs for lung cancer recurrence with exposure to CO did not show significant association (Table 5).

In the case of estimated effects of O_3, the results showed

significant negative association during 12 and 36 months from surgery until recurrence (adjusted OR per each 10 ppb increase [95% CI]: 0.32 [0.11−0.94] and 0.34 [0.12−0.98]) (Table 6). However, in the case of summer ozone − which was calculated as the average concentration of ozone between June and September from surgery until recurrence of lung cancer −, there was no significant association between ozone and the recurrence of lung cancer after surgery (Table S1).

Table 7 shows that there was no significant association between PM_{10} and lung cancer recurrence. In contrast, in the fully adjusted model, the association between $PM_{2.5}$ concentrations and lung cancer recurrence was significant during 36 months from surgery until recurrence (OR per each $\mathbf{10}\ \mu\mathbf{g}/m^3$ increase [95% CI]: 3.35 [1.02−10.99]) (Table 8).

Table 3. ORs (95% CIs) for the association between SO_2 concentrations and recurrence of lung cancer at each time-interval from surgery until recurrence

Time-interval	OR (95% CI)			
	Crude OR (95% CI)	*p*-value	Adjusted model OR (95% CI)	*p*-value
During 3 months	1.13 (0.88-1.45)		0.98 (0.27-1.34)	
During 6 months	1.09 (0.81-1.47)		0.93 (0.64-1.35)	
During 12 months	1.56 (1.08-2.25)	*	1.49 (0.96-2.31)	
During 24 months	1.83 (1.23-2.72)	**	1.73 (1.07-2.80)	**
During 36 months	2.12 (1.40-3.21)	***	2.14 (1.31-3.49)	**

OR, odds ratio; CI, confidence interval; SO_2, sulfur dioxide (per 1 ppb increase).

[*] Adjusted for age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* (Epidermal Growth Factor Receptor) gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke.

* p <0.05 ** p <0.01 *** p <0.001

Table 4. ORs (95% CIs) for the association between NO_2 concentrations and recurrence of lung cancer at each time-interval from surgery until recurrence

Time-interval	OR (95% CI)			
	Crude OR (95% CI)	*p*-value	Adjusted model OR (95% CI)	*p*-value
During 3 months	1.28 (0.89-1.84)		0.95 (0.56-1.60)	
During 6 months	0.99 (0.61-1.63)		0.92 (0.51-1.67)	
During 12 months	1.47 (0.84-2.55)		1.44 (0.73-2.82)	
During 24 months	1.63 (0.91-2.92)		1.58 (0.78-3.18)	
During 36 months	1.97 (1.10-3.53)	*	2.02 (1.01-4.04)	*

OR, odds ratio; CI, confidence interval; NO_2, nitrogen dioxide (per 10 ppb increase).

* Adjusted for age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* (Epidermal Growth Factor Receptor) gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke.

* p <0.05 ** p <0.01 *** p <0.001

Table 5. ORs (95% CIs) for the association between CO concentrations and recurrence of lung cancer at each time-interval from surgery until recurrence

Time-interval	OR (95% CI)			
	Crude OR (95% CI)	*p*-value	Adjusted model OR (95% CI)	*p*-value
During 3 months	0.72 (0.54-0.95)	*	0.72 (0.52-1.00)	
During 6 months	0.70 (0.50-0.97)	*	0.72 (0.48-1.07)	
During 12 months	0.81 (0.52-1.28)		1.02 (0.57-1.80)	
During 24 months	0.89 (0.54-1.48)		1.05 (0.56-1.98)	
During 36 months	1.30 (0.66-2.59)		1.72 (0.74-3.96)	

OR, odds ratio; CI, confidence interval; CO, carbon dioxide (per 0.1 ppm increase).

* Adjusted for age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* (Epidermal Growth Factor Receptor) gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke.

* p <0.05 ** p <0.01 *** p <0.001

Table 6. ORs (95% CIs) for the association between O_3 concentrations and recurrence of lung cancer at each time-interval from surgery until recurrence

Time-interval	OR (95% CI)			
	Crude OR (95% CI)	*p*-value	Adjusted model OR (95% CI)	*p*-value
During 3 months	1.27 (0.95-1.70)		1.20 (0.85-1.69)	
During 6 months	1.11 (0.74-1.65)		0.97 (0.60-1.59)	
During 12 months	0.50 (0.22-1.13)		0.32 (0.11-0.94)	*
During 24 months	0.57 (0.25-1.32)		0.41 (0.14-1.19)	
During 36 months	0.50 (0.22-1.13)		0.34 (0.12-0.98)	*

OR, odds ratio; CI, confidence interval; O_3, ozone (per 10 ppb increase).

* Adjusted for age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* (Epidermal Growth Factor Receptor) gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke.

* p <0.05 ** p <0.01 *** p <0.001

Table 7. ORs (95% CIs) for the association between PM_{10} concentrations and recurrence of lung cancer at each time-interval from surgery until recurrence

Time-interval	OR (95% CI)			
	Crude OR (95% CI)	*p*-value	Adjusted model OR (95% CI)	*p*-value
During 3 months	0.97 (0.70-1.33)		0.99 (0.67-1.46)	
During 6 months	0.71 (0.48-1.03)		0.70 (0.44-1.10)	
During 12 months	0.97 (0.52-1.79)		1.14 (0.55-2.36)	
During 24 months	1.12 (0.57-2.18)		1.45 (0.65-3.23)	
During 36 months	1.30 (0.66-2.59)		1.72 (0.74-3.96)	

OR, odds ratio; CI, confidence interval; PM_{10}, Particulate matter less than 10 $\mu g/m^3$ (per **10** $\mu g/m^3$ increase).

* Adjusted for age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* (Epidermal Growth Factor Receptor) gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke.

* p <0.05 ** p <0.01 *** p <0.001

Table 8. ORs (95% CIs) for the association between $PM_{2.5}$ concentrations and recurrence of lung cancer at each time-interval from surgery until recurrence

Time-interval	OR (95% CI)			
	Crude OR (95% CI)	p-value	Adjusted model OR (95% CI)	p-value
During 3 months	0.75 (0.31-1.85)		0.90 (0.26-3.16)	
During 6 months	0.58 (0.23-1.50)		0.71 (0.20-2.55)	
During 12 months	0.66 (0.18-2.38)		0.59 (0.10-3.47)	
During 24 months	1.37 (0.47-4.04)		2.62 (0.69-9.92)	
During 36 months	1.60 (0.60-4.29)		3.35 (1.02-10.99)	*

OR, odds ratio; CI, confidence interval; $PM_{2.5}$, particulate matter less than 2.5 $\mu g/m^3$ (per 10 $\mu g/m^3$ increase).

* Adjusted for age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* (Epidermal Growth Factor Receptor) gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke.

* p <0.05 ** p <0.01 *** p <0.001

3.4 Sensitivity analysis

SO_2, NO_2, CO, PM_{10} and $PM_{2.5}$ were positively correlated with each other (Spearman correlation coefficient r=0.39−0.88, p−value <0.001), except for O_3 (Table 9).

In two−pollutant models, estimated ORs of the association of air pollutants with lung cancer recurrence did not show significant association when adjusting for other pollutants, except in the case of CO after controlling for SO_2 and NO_2 during 3 months from surgery until recurrence (Table 10). In addition, when controlling for the effects of other pollutants, the results did not demonstrate significant association during 6 months from surgery until recurrence (Table 11). During 12 months from surgery until recurrence, O_3 was revealed to have significant negative association with lung cancer recurrence when controlling for CO and PM_{10} respectively (Table 12). In the case of summer ozone, however, there was no significant association with the recurrence of lung cancer when adjusting for other pollutants (Table S2).

Estimated ORs of the association between SO_2 and lung cancer recurrence were statistically significant when controlling for other air pollutants except for O_3 during 24 months from surgery until recurrence (Table 13). Significant association of SO_2 with lung

cancer recurrence remained consistent after adjusting for other air pollutants during 36 months from surgery until recurrence. Also, estimated effects of NO_2 turned out to be relevant after adjusting for $PM_{2.5}$. Exposure to $PM_{2.5}$ – while controlling NO_2, CO and O_3 - showed significant association as well during 36 months from surgery until recurrence (Table 14). Overall, in the sensitivity analysis, the estimated effects of air pollutants revealed homogenous trends with the main results.

Table 9. Correlations between air pollutants (from January 2013 to February 2020)

Air pollutant	SO_2	NO_2	CO	O_3	PM_{10}	$PM_{2.5}$
SO_2	1.00	0.49^{***}	0.40^{***}	-0.13^{***}	0.44^{***}	0.39^{***}
NO_2		1.00	0.59^{***}	-0.46^{***}	0.48^{***}	0.51^{***}
CO			1.00	-0.33^{***}	0.53^{***}	0.57^{***}
O_3				1.00	0.02^{***}	-0.03^{***}
PM_{10}					1.00	0.88^{***}
$PM_{2.5}$						1.00

SO_2, sulfur dioxide (per ppb); NO_2, nitrogen dioxide (per 10 ppb); O_3, ozone (per 10 ppb); CO, carbon dioxide(per 0.1 ppm); PM_{10}, Particulate matter less than 10 $\mu g/m^3$ (per 10 $\mu g/m^3$); $PM_{2.5}$, particulate matter less than 2.5 $\mu g/m^3$ (per 10 $\mu g/m^3$).

*** p <0.001

Table 10. ORs (95% CIs) for the association between average concentrations of air pollutants and recurrence of lung cancer during 3 months from surgery until recurrence in two-pollutant models

Air pollutant	SO_2	NO_2	CO	O_3	PM_{10}	$PM_{2.5}$
Adjusted for SO_2	-	0.84 (0.47-1.50)	0.69* (0.48-0.98)	1.28 (0.89-1.84)	0.93 (0.60-1.44)	0.86 (0.33-1.93)
Adjusted for NO_2	1.02 (0.73-1.43)	-	0.63* (0.40-0.97)	1.24 (0.84-1.84)	1.01 (0.66-1.53)	0.78 (0.22-2.86)
Adjusted for CO	1.13 (0.80-1.58)	1.43 (0.69-2.94)	-	0.99 (0.61-1.59)	1.13 (0.72-1.77)	1.65 (0.29-9.53)
Adjusted for O_3	1.04 (0.75-1.44)	1.12 (0.61-2.05)	0.71 (0.46-1.11)	-	1.04 (0.70-1.54)	0.77 (0.20-2.91)
Adjusted for PM_{10}	1.01 (0.71-1.42)	0.94 (0.53-1.66)	0.69 (0.48-1.00)	1.21 (0.85-1.71)	-	0.42 (0.07-2.40)
Adjusted for $PM_{2.5}$	0.80 (0.33-1.93)	1.48 (0.57-3.81)	0.55 (0.23-1.35)	0.77 (0.380-1.56)	1.93 (0.80-4.67)	-

* p <0.05 ** p <0.01 *** p <0.001

Table 11. ORs (95% CIs) for the association between average concentrations of air pollutants and recurrence of lung cancer during 6 months from surgery until recurrence in two-pollutant models

Air pollutant	SO_2	NO_2	CO	O_3	PM_{10}	$PM_{2.5}$
Adjusted for SO_2	-	0.79 (0.40-1.55)	0.72 (0.47-1.08)	0.99 (0.58-1.67)	0.60 (0.35-1.01)	0.70 (0.18-2.73)
Adjusted for NO_2	0.98 (0.66-1.47)	-	0.69 (0.42-1.14)	0.93 (0.54-1.60)	0.69 (0.43-1.11)	0.71 (0.20-2.55)
Adjusted for CO	1.03 (0.70-1.51)	1.10 (0.51-2.39)	-	0.69 (0.36-1.31)	0.68 (0.41-1.15)	0.83 (0.19-3.68)
Adjusted for O_3	0.93 (0.63-1.37)	0.89 (0.46-1.72)	0.60 (0.34-1.00)	-	0.70 (0.44-1.10)	0.78 (0.21-2.87)
Adjusted for PM_{10}	1.09 (0.72-1.61)	1.08 (0.57-2.02)	0.81 (0.53-1.25)	0.94 (0.57-1.53)	-	0.30 (0.03-2.42)
Adjusted for $PM_{2.5}$	1.35 (0.61-3.00)	1.45 (0.57-3.69)	0.80 (0.36-1.75)	0.60 (0.26-1.38)	2.07 (0.58-7.41)	-

* p <0.05 ** p <0.01 *** p <0.001

Table 12. ORs (95% CIs) for the association between average concentrations of air pollutants and recurrence of lung cancer during 12 months from surgery until recurrence in two-pollutant models

Air pollutant	SO_2	NO_2	CO	O_3	PM_{10}	$PM_{2.5}$
Adjusted for SO_2	-	0.99 (0.47-2.09)	0.95 (0.53-1.72)	0.40 (0.13-1.25)	1.02 (0.47-2.22)	0.77 (0.12-4.94)
Adjusted for NO_2	1.49 (0.94-2.38)	-	0.91 (0.47-1.77)	0.31 (0.09-1.10)	1.07 (0.50-2.26)	0.59 (0.10-3.51)
Adjusted for CO	1.49 (0.96-2.32)	1.32 (0.59-2.92)	-	0.27* (0.08-0.94)	1.08 (0.50-2.33)	0.92 (0.13-6.32)
Adjusted for O_3	1.36 (0.86-2.16)	0.95 (0.42-2.12)	0.75 (0.39-1.45)	-	1.23 (0.57-2.70)	0.61 (0.10-3.67)
Adjusted for PM_{10}	1.49 (0.96-2.31)	1.42 (0.72-2.82)	1.01 (0.56-1.80)	0.31* (0.11-0.92)	-	0.59 (0.06-5.90)
Adjusted for $PM_{2.5}$	1.39 (0.71-2.75)	1.16 (0.48-2.81)	0.45 (0.20-1.00)	0.55 (0.12-2.62)	1.00 (0.22-4.50)	-

* p <0.05 ** p <0.01 *** p <0.001

Table 13. ORs (95% CIs) for the association between average concentrations of air pollutants and recurrence of lung cancer during 24 months from surgery until recurrence in two-pollutant models

Air pollutant	SO_2	NO_2	CO	O_3	PM_{10}	$PM_{2.5}$
Adjusted for SO_2	-	0.92 (0.41-2.08)	0.91 (0.46-1.80)	0.59 (0.18-1.92)	1.13 (0.47-2.70)	2.67 (0.62-11.53)
Adjusted for NO_2	1.77* (1.05-2.99)	-	0.89 (0.42-1.88)	0.45 (0.11-1.84)	1.34 (0.59-3.05)	2.78 (0.69-11.23)
Adjusted for CO	1.75* (1.08-2.84)	1.44 (0.63-3.32)	-	0.31 (0.08-1.15)	1.34 (0.58-3.13)	3.19 (0.79-12.81)
Adjusted for O_3	1.61 (0.97-2.67)	1.10 (0.44-2.80)	0.73 (0.34-1.57)	-	1.45 (0.64-3.30)	2.68 (0.69-10.44)
Adjusted for PM_{10}	1.71* (1.05-2.79)	1.52 (0.74-3.10)	1.00 (0.53-1.92)	0.41 (0.14-1.20)	-	3.09 (0.53-17.97)
Adjusted for $PM_{2.5}$	1.93* (1.09-3.41)	1.92 (0.84-4.39)	0.82 (0.40-1.71)	0.38 (0.11-1.36)	0.84 (0.25-2.86)	-

* p <0.05 ** p <0.01 *** p <0.001

Table 14. ORs (95% CIs) for the association between average concentrations of air pollutants and recurrence of lung cancer during 36 months from surgery until recurrence in two-pollutant models

Air pollutant	SO_2	NO_2	CO	O_3	PM_{10}	$PM_{2.5}$
Adjusted for SO_2	-	1.05 (0.46-2.39)	0.88 (0.43-1.78)	0.60 (0.18-2.00)	1.36 (0.54-3.37)	3.33 (0.89-12.41)
Adjusted for NO_2	2.10*** (1.20-3.67)	-	0.77 (0.36-1.62)	0.52 (0.12-2.37)	1.60 (0.67-3.80)	4.65* (1.24-17.45)
Adjusted for CO	2.17*** (1.32-3.55)	2.12 (0.94-4.78)	-	0.23 (0.06-0.87)	1.73 (0.71-4.24)	4.03* (1.17-13.91)
Adjusted for O_3	1.96* (1.16-3.31)	1.48 (0.55-4.00)	0.67 (0.31-1.44)	-	1.68 (0.70-4.00)	3.87* (1.12-13.43)
Adjusted for PM_{10}	2.09*** (1.27-3.43)	1.96 (0.97-3.95)	0.98 (0.52-1.85)	0.35 (0.12-1.01)	-	2.97 (0.48-18.44)
Adjusted for $PM_{2.5}$	2.30*** (1.32-4.01)	2.84* (1.27-6.34)	0.88 (0.45-1.73)	0.26 (0.08-0.86)	1.12 (0.30-4.21)	-

* p <0.05 ** p <0.01 *** p <0.001

3.5 Subgroup analysis in interaction-included model

Subgroup analyses for age and *EGFR* mutation were performed by including interaction terms between each air pollutant and subgroup in the full-adjusted model. Figure 2 presents specific association for the age and for *EGFR* mutation between air pollution and lung cancer recurrence. In the age-specific analysis, the interaction between air pollutants and age was shown to be insignificant. In regard to *EGFR* mutation-specific results, O_3 concentration during 3 months from surgery until recurrence revealed a significantly stronger association in *EGFR* mutation groups (p interaction= 0.0023). However, PM_{10} concentration during 6 months from surgery until recurrence showed significantly stronger association in non-*EGFR* mutation groups (p interaction= 0.0086). In the case of summer ozone, however, there was no significant interaction between ozone and *EGFR* mutation (Figure S1). Additionally, interactions of clinical stage, primary tumor size and lymph node invasion with air pollution were not observed in subgroup analyses for clinical stage, primary tumor size and lymph node invasion (Figure S2).

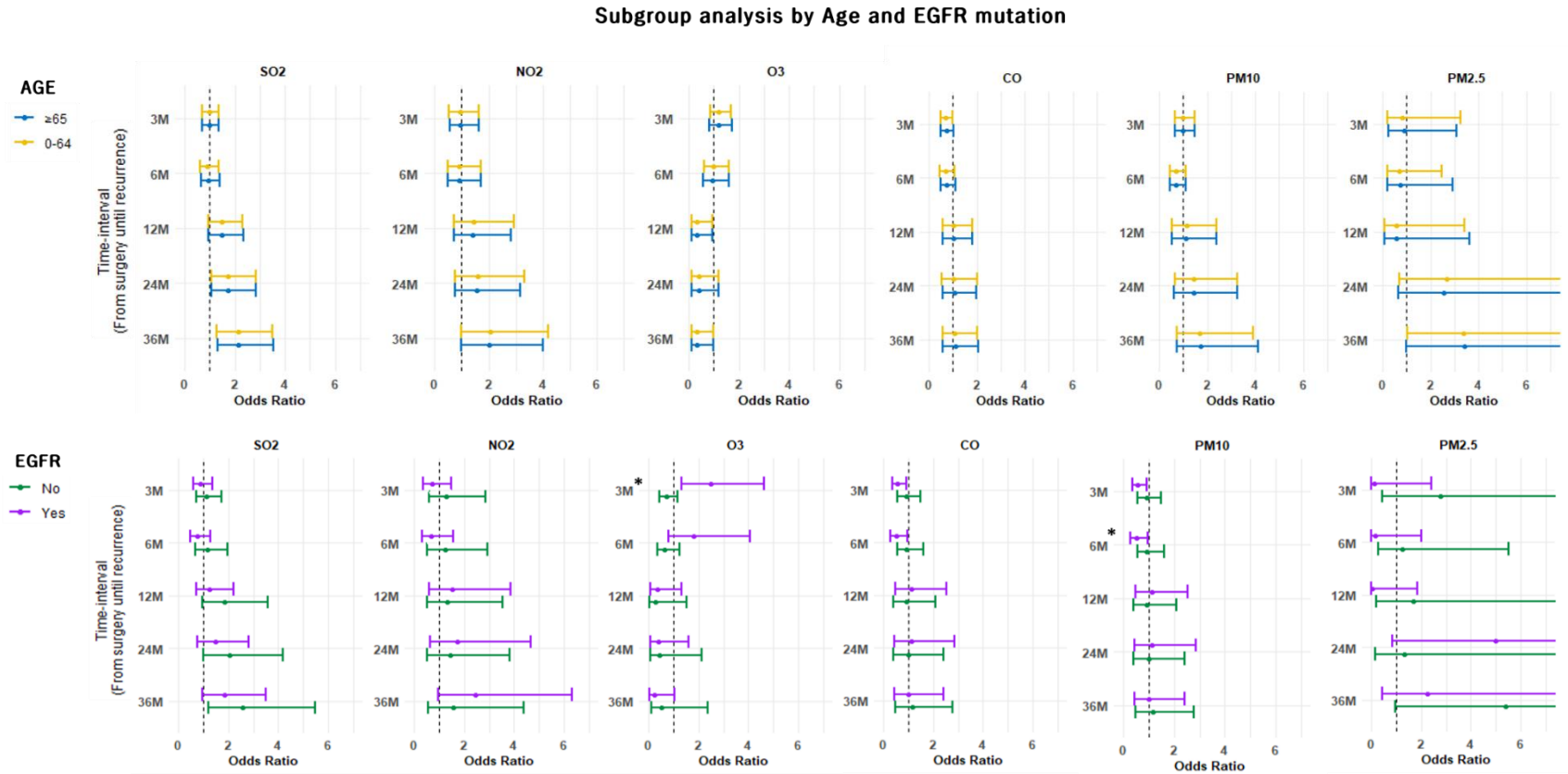


Figure 2 a. EGFR, Epidermal Growth Factor Receptor. **b.** Subgroup analysis was performed for each time-interval by including interaction terms between each air pollutant and subgroup in the full-adjusted model. Odds ratio for each subgroup was calculated in the same model. **c.** star sign (*) indicates statistically significant interaction (p <0.05).

Chapter 4. Discussion

This study revealed that air pollutants such as SO_2, NO_2, and $PM_{2.5}$ are significantly associated with lung cancer recurrence in female never-smokers after adjusting for covariates, including cancer-related variables. These associations were generally found to be more relevant with longer exposure periods. O_3 was also revealed to have significant association with lung cancer recurrence, but unlike other air pollutants, it was found to have negative associations. Furthermore, associations of those air pollutants with lung cancer recurrence remained significant in two-pollutant models. In subgroup analyses for age and *EGFR* mutation, only *EGFR* mutation had significant interaction with air pollutants such as O_3 and PM_{10} but the patterns of associations differed according to *EGFR* mutation. To the best of our knowledge, this is the first study to focus on the relationship between air pollution and lung cancer recurrence in female never-smokers.

The results of this study are consistent with previous toxicological and epidemiological studies. In the case of SO_2, the activation of proto-oncogenes and inactivation of tumor suppressor genes can be induced by SO_2 as a role of pathogenesis of lung cancer (Qin & Meng, 2009). In addition, exposure to traffic-related air

pollution such as NO_2 is related to lung cancer (Chen, Wan, Yang, & Zou, 2015; Hamra et al., 2015). Furthermore, $PM_{2.5}$ affect various oxidative stress mechanisms, which are involved in the production of mediators of pulmonary inflammation and mechanisms of carcinogenesis (Valavanidis et al., 2013) and it may affect lung cancer incidence through EGFR, MAP kinase, nuclear factor (NF)-κB, and IL (Interleukin)-8 induced toxicity signaling (Jeong, Cho, Song, Lee, & Ryu, 2017). In contrast to prior studies which reported that ozone was related to the incidence of lung cancer, in this research, negative association between O_3 and lung cancer recurrence was observed. McDonnell, Abbey, Nishino, and Lebowitz (1999) reported that long-term exposure to O_3 is associated with development of asthma in male non-smokers. Just as the O_3 effect on the development of asthma varies according to sex in non-smokers, the effects of O_3 on lung cancer recurrence might also vary according to sex in non-smokers. In the case of summer ozone in this research, however, no significant association between air pollution and the recurrence of lung cancer was shown. Regarding uncertain effect of ozone on lung cancer recurrence, future studies should investigate the association between O_3 and the recurrence of lung cancer in never-smokers.

The estimated effects of air pollutants on lung cancer

recurrence showed mostly identical trends with main results in two-pollutant models. Among air pollutants, SO_2 was consistently associated after adjusting for other air pollutants. However, the association of NO_2 with lung cancer recurrence was significant after controlling for only $PM_{2.5}$. Furthermore, $PM_{2.5}$ was significantly associated when adjusting for NO_2, CO, and O_3. As with the single-pollutant model results, however, exposure to O_3 had significant negative association with the recurrence of lung cancer when controlling for CO and PM_{10}. And exposure to CO-which did not show significant association with lung cancer recurrence in single-pollutant model-had significant negative association after controlling for SO_2 and NO_2. In the additionally implemented two-pollutant model analysis with summer ozone, same as single-pollutant model, no significant association with the recurrence of lung cancer was observed when adjusting for other pollutants.

SO_2 is an air pollutant that occurs when coal, oil and diesel are used, and has long been caused by diesel vehicles and power plant emissions. NO_2 is usually representative of traffic-related pollutions because of its strong relation to vehicle emissions. Also, $PM_{2.5}$ is directly produced from specific emission sources, such as workplace combustion and car fuel combustion. O_3 is a well-known secondary pollutant and it is a strongly oxidizing substance. CO is known to be

produced when the carbon molecules in the fuel is incompletely burned and is known as a lethal substance in the respiratory tract because of its high affinity with hemoglobin. Unlike what is known to be harmful, O_3 and CO were found to have negative association with lung cancer recurrence in two-pollutant models. The reason for the difference of estimated effects of air pollutants on lung cancer recurrence in two-pollutant models may be due to the effects confounded by other air pollutants.

This study also performed subgroup analyses for age and *EGFR* mutation. Only *EGFR* mutation had significant interaction with air pollutants such as O_3 and PM_{10} but the patterns of associations differed according to the presence of *EGFR* mutation. The association of O_3 with the recurrence of lung cancer was stronger in *EGFR* mutation groups. However, in contrast to O_3, the association of PM_{10} was stronger in groups where *EGFR* mutation were absent. *EGFR* phosphorylation can be caused by O_3 (Feng et al., 2016) and it is also associated with poor prognosis of non-small cell lung cancer (Kanematsu, Yano, Uehara, Bando, & Sone, 2003). These might be a possible reason for strong association between O_3 and the recurrence of lung cancer in *EGFR* mutation groups. In the case of summer ozone, on the other hand, no significant interaction with *EGFR* mutation was observed. Future studies should examine the unrevealed interaction

between each air pollutant and *EGFR* mutation.

There was little research which examined the association between air pollution and lung cancer recurrence. But, Eckel et al. (2016) reported that reduced survival was associated with higher NO_2, PM_{10}, and $PM_{2.5}$ exposure over the follow-up period after diagnosis, with the largest hazard ratio in early stage non-small cell lung cancer. Similarly, the significant role of air pollution in the recurrence of lung cancer – which is a hurdle for survival – was observed in this study. This is in line with the previous study. This research is the first study which investigated the association between air pollution and lung cancer recurrence in female never-smokers using a prospective hospital-based cohort. Reliability of results were enhanced by collecting clinical data, and by adjusting for confounding variables.

This study has several limitations. There is a potential measurement error of exposure. This is because the concentration of daily average may not represent the actual exposure of an individual to air pollution. Heid et al. (2002) reported that odd ratio estimates are attenuated by measurement error towards the null. Therefore, it is thought that the possibility of exaggeration of outcomes may be limited. In addition, misclassification of the recurrence of lung cancer resulting from diagnostic error should be

considered when interpreting the present study. This is because it was difficult to know the exact date of recurrence since there is the possibility that the actual recurrence occurred before CT scans.

This study suggests that the recurrence of lung cancer is associated with air pollution in female never-smokers. Also, this study recommends that subsequent studies should be conducted for the effects of ozone on lung cancer recurrence and interaction between air pollution and *EGFR* mutation. It is expected that this study will serve as a base for future research on risk factors for recurrence in female never-smokers in the interest of public health.

Appendix

Table S1. ORs (95% CIs) for the association between summer O_3 concentrations and recurrence of lung cancer at each time-interval from surgery until recurrence

Time-interval	OR (95% CI)			
	Crude OR (95% CI)	*p*-value	Adjusted model OR (95% CI)	*p*-value
During 3 months	0.85 (0.51-1.42)		0.62 (0.28-1.38)	
During 6 months	0.73 (0.44-1.22)		0.61 (0.31-1.19)	
During 12 months	0.69 (0.35-1.36)		0.48 (0.20-1.17)	
During 24 months	0.65 (0.29-1.47)		0.53 (0.20-1.43)	
During 36 months	0.68 (0.29-1.58)		0.55 (0.20-1.57)	

OR, odds ratio; CI, confidence interval; O_3, ozone (per 10 ppb increase).

[a] Adjusted for age at diagnosis, stage at diagnosis, lymph node invasion, *EGFR* (Epidermal Growth Factor Receptor) gene mutation, family history of lung cancer, symptoms related to lung cancer at diagnosis, history of hypertension, history of type 2 diabetes mellitus and secondhand smoke. [b] The average concentration of summer ozone was calculated from June to September.

* p <0.05 ** p <0.01 *** p <0.001

Table S2. ORs (95% CIs) for the association between average concentrations of summer O_3 and recurrence of lung cancer at each time-interval from surgery until recurrence in two-pollutant models

Time-interval	Adjusted for SO_2	Adjusted for NO_2	Adjusted for CO	Adjusted for PM_{10}	Adjusted for $PM_{2.5}$
During 3 months	0.66 (0.29-1.49)	0.62 (0.28-1.38)	0.64 (0.28-1.46)	0.39 (0.25-1.04)	-[a]
During 6 months	0.59 (0.29-1.22)	0.61 (0.31-1.20)	0.57 (0.28-1.18)	0.61 (0.29-1.27)	0.65 (0.14-2.97)
During 12 months	0.49 (0.19-1.26)	0.49 (0.20-1.21)	0.45 (0.18-1.12)	0.46 (0.18-1.16)	2.17 (0.50-9.38)
During 24 months	0.58 (0.20-1.73)	0.58 (0.21-1.62)	0.47 (0.17-1.32)	0.48 (0.17-1.34)	0.75 (0.25-2.25)
During 36 months	0.70 (0.21-2.30)	0.68 (0.23-2.07)	0.48 (0.16-1.43)	0.45 (0.15-1.35)	0.55 (0.18-1.69)

[a] It was not able to derive stable estimates due to the insufficient data. [b] The average concentration of summer ozone was calculated between June and September.

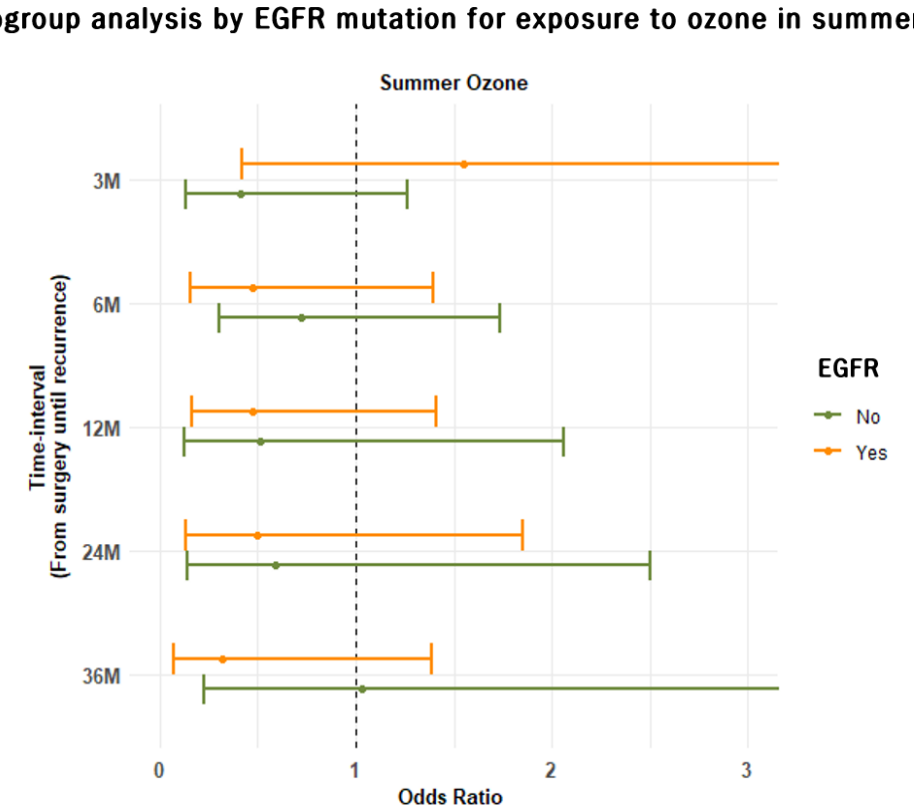
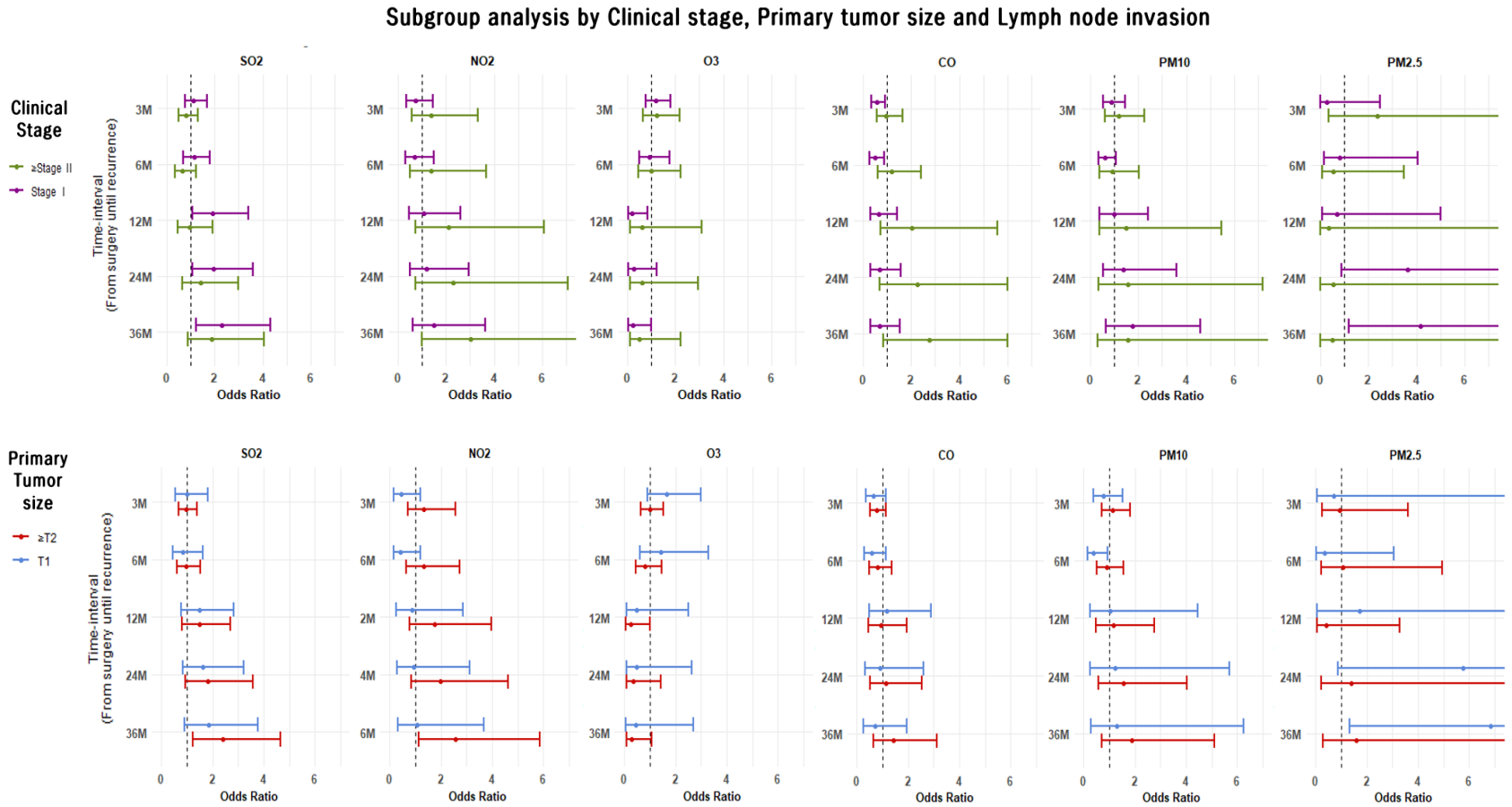


Figure S1. a. *EGFR*, Epidermal Growth Factor Receptor. **b.** Subgroup analysis was performed for each time-interval by including interaction terms between each air pollutant and subgroup in the full-adjusted model. Odds ratio for each subgroup was calculated in the same model. **c.** The average concentration of ozone in summer was calculated between June and September.


Subgroup analysis by Clinical stage, Primary tumor size and Lymph node invasion
Clinical Stage
≥Stage II
Stage I
Primary Tumor size
≥T2
T1
SO2
NO2
O3
CO
PM10
PM2.5
Time-interval (From surgery until recurrence)
3M
6M
12M
24M
36M
Odds Ratio
0
2
4
6

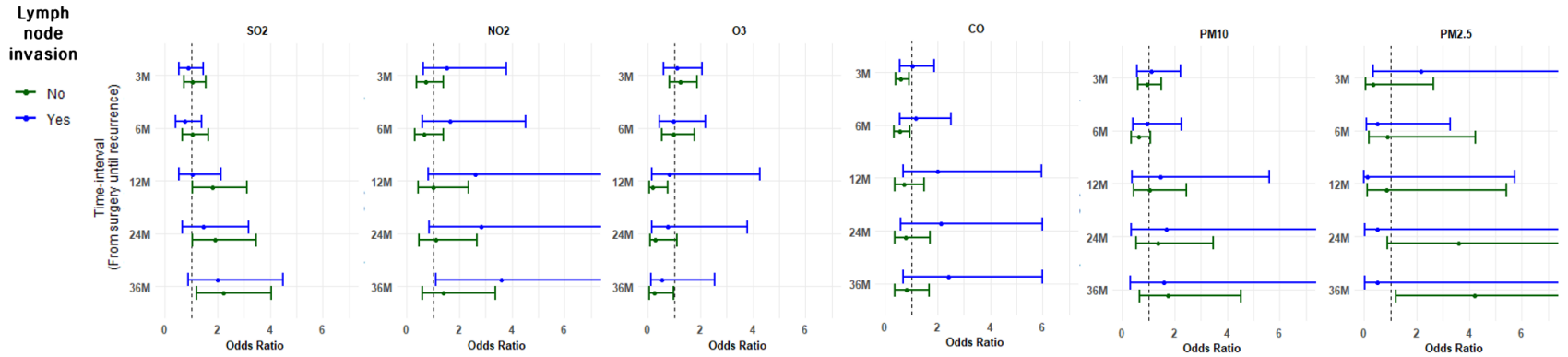


Figure S2. a. Subgroup analysis was performed for each time-interval by including interaction term of each air pollutant and subgroup in the full-adjusted model and odds ratio for each subgroup was calculated in the same model.

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국 문 초 록

비흡연 여성 폐암 환자의 수술 후 재발과 대기오염 간의 연관성 연구

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연구배경: 폐암은 전 세계적으로 흔한 암으로, 우리나라에서는 세 번째로 흔한 암이다. 획기적인 항암제와 방사선 치료법이 개발되어왔으나, 여전히 초기 폐암에서는 수술적 치료가 가장 적절한 치료로 알려져 있다. 그러나 수술 후 재발은 많은 폐암 환자들이 경험하는 치료 실패이자 생존기간을 단축시키는 원인으로, 진단 당시 암 병기, 혈관림프절 전이 여부가 재발 위험요인으로 추정되지만 그 원인은 아직까지 명확하게 밝혀진 바가 없다. 폐암의 가장 큰 위험요인으로 흡연이 꼽히지만, 여성 폐암에서 비흡연인 경우는 절반 이상을 차지한다. 대기오염은 폐암의 위험요인으로 많은 연구가 진행되어 왔으나 수술 후 재발과의 연관성에 대한 연구는 거의 전무하다.

연구목적: 본 연구는 대기오염이 폐암 유발에 미치는 영향과 유사한 메커니즘으로 수술 후 재발에도 영향이 있을 것이라는 가설 아래, 한국에서 대기오염과 비흡연 여성 폐암 환자의 수술 후 재발 간의 연관성에 대해 확인하고자 한다.

연구방법: 본 연구는 2013년 2월부터 2017년 1월까지 서울대학교병원에서 폐암 진단 후 수술을 받은 비흡연 여성 폐암환자 132명을 대상으로, 진단 당시 암 병기, 암 크기, 림프절 전이 여부, *EGFR* 변이 여부, 폐암 가족력, 진단 당시 암 관련 증상 여부, 고혈압 및 당뇨 병력, 간접

흡연 노출 여부 등 임상 관련 특성에 관한 정보를 수집하였다. 대기오염 자료는 대상자 거주지 별 대기오염 자료를 추출하여, 수술 후 재발까지 3, 6, 12, 24, 36개월 간격의 각 평균 농도를 산출하여 병합하였다. 통계 분석은 다중 로지스틱 회귀분석을 이용하여, 임상관련 특성을 보정한 후 폐암 재발과의 연관성을 확인하였다.

연구결과: SO_2 평균 농도의 1 ppb 단위 증가에 따른 폐암 재발 오즈비는 수술 후 재발까지 24개월 및 36개월 동안 1.73 (95% CI: 1.07−2.80)와 2.14 (95% CI: 1.31−3.49)로 나타났다. NO_2의 10 ppb 단위 증가에 따른 폐암 재발 오즈비와 $PM_{2.5}$의 $10\,\mu g/m^3$ 단위 증가에 따른 폐암 재발 오즈비는 수술 후 재발까지 36개월 동안 각각 2.02 (95% CI: 1.01−4.04) 및 3.35 (1.02−10.99)로 관찰되었다. O_3의 경우, 수술 후 재발까지 12개월 및 36개월 동안 10 ppb 증가 당 폐암 재발 오즈비는 0.32 (0.11−0.94), 0.34 (0.12−0.98)로 나타났다. 이러한 결과는 두 오염물질 모형 (two−pollutant model)에서도 동일하게 나타났다. 하위그룹 분석에서 유일하게 O_3와 PM_{10}이 *EGFR* 변이 간에 교호작용이 있는 것으로 관찰되었으나, 그 연관성이 상반된 것으로 나타났다.

결　론: 본 연구를 통해 비흡연 여성 폐암의 재발에 대기오염이 영향을 미치며, 대기오염에 대한 장기 노출이 보다 더 관련이 있는 것을 확인하였다. 본 연구에서는 오존과 수술 후 재발 간 음의 연관성으로 확인되었다. 또한 *EGFR* 변이 여부에 따른 대기오염과 폐암 재발 간의 연관성이 서로 다른 것으로 나타났다. 수술 후 폐암 재발에 대한 오존의 불확실한 영향에 대하여서는 후속 연구에서 추가로 시행되어야 할 것이다. 본 연구 결과는 보건학적 관심이 필요한 비흡연 여성 폐암 환자의 재발 위험요인에 대한 연구의 기반이 될 것이다.

주 요 어: 폐암, 신생물 재발, 대기오염, 비흡연, 여성

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