Association between air pollutants and cancer incidence rates in Japan: An ecological study

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Abstract: We investigated the associations between the incidence rates of five typical cancer types and five air pollutants in 317 Japanese municipalities in 2017. We obtained the concentrations of the five air pollutants, i.e., sulfur dioxide (SO_2), nitric oxide (NO), nitric dioxide (NO_2), photochemical oxidants (O_x), and fine particulate matter ($PM_{2.5}$) from Japan's National Institute for Environmental Studies and calculated the yearly mean of each. We identified patients of both sexes with the five most common cancers in Japan's National Cancer Registry, which covers all of the cancer patients in the country. For the males, we included prostate, stomach, colorectal, lung, and liver cancers. For the females, we included breast, colorectal, lung, stomach, and uterine cancers. We calculated the Spearman's correlation coefficients between 25 pairs of air-pollutant concentrations and the age-standardized incidence rate of the cancer types for each sex. We used Poisson regression models to examine the dose-response relationships. We identified 11 significantly positive correlation coefficients at the Bonferroni-corrected alpha level for the five pollutants for the five cancers in both sexes. We observed significantly positive dose-response relationships between NO_2 and colorectal cancer and $PM_{2.5}$ and lung cancer for both sexes. We also observed significant dose-response relationships between SO_2 and $PM_{2.5}$ and liver cancer for the males, and between NO and lung cancer and NO_2 and breast cancer for the females. We did not observe significant associations with prostate, stomach, or uterine cancer. Our findings support the concept that exposure to air pollutants increases cancer incidence rates.

Keywords: air pollution, environmental pollution, cancer, environmental epidemiology

1. Introduction

Air pollution is a primary public health issue worldwide [1]. Many studies have observed an association between long-term exposure to air pollution and the incidence of lung cancer [2]. In response, the International Agency for Research on Cancer (IARC) classified outdoor air pollution as a Group 1 carcinogen (carcinogenic to humans) in 2013 [3].

The relationships between air pollution and cancers other than lung cancer are less clear [2,4]. For example, colorectal cancer is one of the most prevalent cancers globally [5], but studies on the association between this cancer and air pollution are few in number and have obtained inconsistent results [4,6,7]. Laboratory studies have demonstrated a plausible association between air pollution and liver cancer [8], but there have been few epidemiological studies on this topic [9–11] or on cancers other than lung cancer in Japan.

Among the many air pollutants, the adverse effects of exposure to nitric oxide (NO) were rarely examined compared to those of sulfur dioxide (SO_2), nitric oxide (NO_x), nitric dioxide (NO_2), ozone (O_3), and particular matter (PM) [2,12]. Nevertheless, laboratory studies implied that NO might play an essential role in cancer biology [13,14].

In Japan, the nationwide population-based cancer registry, i.e., the National Cancer Registry (NCR) was established in 2016 under the Cancer Registry Promotion Act of 2013 [15]. This law obligated all of Japan's hospitals and some clinics to report all of the cancer patients encountered therein. The NCR thus enabled the accurate capture of the nationwide cancer incidence for the first time in Japan.

By leveraging data from the NCR, we investigated the association between air pollutants and the incidence rates of five typical cancers.

2. Methods

2.1. Study period and area

This study was a cross-sectional, ecological investigation. The study period was from January 1 to December 31, 2017. We included 424 municipalities with more than one monitoring station that measured all included air pollutants. We excluded 105 municipalities where all or part of the air pollutant data was missing. To reduce the risk of exposure misclassification, we also excluded two municipalities that were in the designated evacuation area after the Fukushima Daiichi Nuclear Power Plant accident in 2011 [16]. A final total of 317 municipalities were included in this study; they are located throughout the length of Japan.

2.2. Cancer incidence rates

We obtained anonymized NCR data from the National Cancer Center Japan (NCCJ). The data included the patients' five-year age group, sex, residence at the time of diagnosis, and the diagnosis coded in the International Classification of Diseases (ICD).

We set the outcome as the incidence of five typical cancer types in Japan [17]. For the males, we included prostate (ICD10: C61, D075), stomach (C16, D002), colorectal (C18–C20, D010–D012), lung (C33–C34 or D021–D022), and liver cancers (C22–C24, D015). For the females, we included breast (C50, D050–D059), colorectal, lung, stomach, and uterine cancer (C53–C55, D60–D73). Notably, unlike the previous report [17], we included in situ neoplasms (D00–D09) to increase the sensitivity of the analysis. We excluded patients whose age (n=8) or sex (n=9) data were missing.

We used the age-adjusted cancer incidence rates per million population as the target variables to adjust for the age structure differences between municipalities. We obtained the data of each municipality's population as of January 1, 2017, from the Basic Resident Registry. As the standard reference population, we used the 2000 World Standard Population values [18].

2.4. Concentrations of air pollutants

We obtained the monthly data of the concentrations of SO_2, NO, NO_2, photochemical oxidants (O_x), and fine particulate matter ($PM_{2.5}$) in 2017 from Japan's National Institute for Environmental Studies and calculated the yearly mean. As few monitoring stations in Japan measured O_3, we used O_x instead. We considered the data 'missing' when measurements were not available for >20% of days in a particular month. We calculated the geometric mean if data from more than one monitoring station were available in a single municipality.

2.5. Ethical considerations

The Committee for Medical Ethics of Shinshu University School of Medicine approved the study protocol (approval code: 4700). We performed all of the analyses by using anonymized data, and no participants were contacted.

2.6. Statical analysis

To explore the associations between air pollutants and cancer, we calculated Spearman's correlation coefficients between the age-adjusted incidence rates and air pollutants concentrations for each sex. We tested a total of 50 hypotheses and used Bonferroni correction for the multiple testing problems.

For the pairs of pollutant and cancer types that indicated a positive correlation at the Bonferroni-corrected alpha level, we used Poisson regression models to examine the dose-response [12,19]. We categorized the air pollutant concentrations into four quartiles. We included four other air pollutants as confounders. We considered p-values <0.05 significant. We performed all of the statistical analyses in R (ver. 4.0.3) [20].

3. Results and Discussion

We analyzed the cases of a total of 288,405 individuals diagnosed with cancer in Japan. Table 1 provides the numbers of cases and the age-adjusted incidence rates of each cancer type.

Table 1. The total number of cases and age-adjusted incidence rates per million population of each cancer type in the 317 Japanese municipalities in 2017.

Male			Female		
Cancer type	No. of cases	Age-adjusted Incidence rate[1]	Cancer type	No. of cases	Age-adjusted Incidence rate[1]
Prostate	35,247	55.71	Breast	42,823	99.32
Stomach	33,733	55.88	Colorectal	31,996	48.41
Colorectal	45,832	84.80	Lung	16,276	22.52
Lung	32,129	52.60	Stomach	15,250	20.40
Liver	14,614	24.04	Uterine	20,505	67.36

[1]Adjusted for the 2000 World Standard Population proportion.

Table 2 shows the air pollution levels by mean and quartiles and Spearman's correlation coefficients between air pollutants in the 317 Japanese municipalities in 2017. The mean concentrations of the air pollutants were as follows: SO_2, 1.52 ppb; NO, 2.31 ppb; NO_2, 9.34 ppb; O_x, 35.16 ppb; and $PM_{2.5}$ 11.56 $\mu g/m^3$. SO_2, NO, NO_2, and $PM_{2.5}$ were positively correlated, but O_x showed negative correlations with the other pollutants.

Table 2. Air pollution levels and Spearman's correlation coefficients between air pollutants in 317 Japanese municipalities in 2017.

Air pollutant, unit	Mean (SD)	Quartile				Spearman's correlation coefficient				
		Q1	Q2	Q3		SO_2	NO	NO_2	O_x	$PM_{2.5}$
SO_2, ppb	1.52 (1.03)	0.92	1.25	2.00	SO_2	-	0.26*	0.32*	-0.11*	0.25*
NO, ppb	2.31 (1.59)	1.08	2.00	3.17	NO		-	0.82*	-0.61*	0.22*
NO_2, ppb	9.34 (4.30)	5.96	8.67	12.50	NO_2			-	-0.57*	0.22*
O_x, ppb	35.16 (3.20)	33.21	34.92	36.92	O_x				-	-0.01
$PM_{2.5}$, $\mu g/m^3$	11.56 (2.29)	10.11	11.62	13.06	$PM_{2.5}$					-

*Significant at the alpha level of 0.05.

Table 3 lists the Spearman's correlation coefficients between the age-adjusted cancer incidence rates and the air pollutant concentrations. A total of 18 correlation coefficients were significantly positive at an alpha level of 0.05, and 11 of them remained significant at the level of Bonferroni correlation of 0.001.

Table 3. Spearman's correlation coefficients between the age-adjusted cancer incidence of five typical cancer types and the air pollutants stratified by sex.

| | **Male** | | | | | | **Female** | | | | |
Cancer type	SO_2	NO	NO_2	O_x	$PM_{2.5}$	Cancer type	SO_2	NO	NO_2	O_x	$PM_{2.5}$
Prostate	0.01	0.09	0.15[a]	-0.08	-0.14[a]	Breast	0.19[b]	0.34[b]	0.39[b]	-0.24[b]	0.08
Stomach	-0.03	-0.12[a]	-0.07	0.10	-0.04	Colorectal	0.05	0.25[b]	0.30[b]	-0.23[b]	-0.03
Colorectal	0.02	0.14[a]	0.19[b]	-0.17[a]	-0.03	Lung	0.11[a]	0.20[b]	0.18[a]	-0.07	0.21[b]
Lung	0.05	0.09	0.08	-0.03	0.26[b]	Stomach	0.01	-0.06	-0.04	0.09	-0.12[a]
Liver	0.20[b]	-0.03	-0.11	0.12[a]	0.42[b]	Uterine	0.12[a]	-0.12[a]	-0.15[a]	0.09	0.17[a]

[a]Significant at an alpha level of 0.05. [b]Significant at the Bonferroni-corrected alpha level of 0.001.

Table 4 provides the results of Poisson regression models of 11 pollutant-cancer pairs. We observed positive dose-response relationships between NO_2 and colorectal cancer and between $PM_{2.5}$ and lung cancer for both sexes. For the males, SO_2 and $PM_{2.5}$ also showed positive dose-response relationships with liver cancer. For the females, NO and lung cancer and NO_2 and breast cancer also showed positive dose-response relationships.

Table 4. Poisson regression analysis of selected pairs between air pollutants and cancer types.

| Cancer type (sex) | **Liver (male)** | | **Breast (female)** | | | |
	RR[a] (95% CI)	p	RR[a] (95% CI)	p		
SO_2 conc., ppb						
≤0.92	1.00		1.00			
0.92–1.25	0.99 (0.92 - 1.05)	0.71	1.05 (1.01 - 1.08)	<0.01		
1.25–2.00	1.07 (1.00 - 1.14)	0.04	1.03 (1.00 - 1.07)	0.06		
>2.00	1.08 (1.01 - 1.15)	0.03	1.02 (0.99 - 1.06)	0.17		
p for trend		<0.01		0.25		

| Cancer type (sex) | **Breast (female)** | | **Colorectal (female)** | | **Lung (female)** | |
	RR[a] (95% CI)	p	RR[a] (95% CI)	p	RR[a] (95% CI)	p
NO conc., ppb						
≤1.08	1.00		1.00		1.00	
1.08–2.00	1.05 (1.01 - 1.08)	<0.01	0.97 (0.92 - 1.02)	0.19	1.02 (0.95 - 1.10)	0.56
2.00–3.17	1.03 (1.00 - 1.07)	0.06	1.01 (0.95 - 1.08)	0.67	1.08 (0.99 - 1.18)	0.09
>3.17	1.02 (0.99 - 1.06)	0.17	1.00 (0.92 - 1.08)	0.93	1.13 (1.01 - 1.26)	0.04
p for trend		0.25		0.76		0.03

| Cancer type (sex) | **Colorectal (male)** | | **Breast (female)** | | **Colorectal (female)** | |
	RR[a] (95% CI)	p	RR[a] (95% CI)	p	RR[a] (95% CI)	p
NO_2 conc., ppb						
≤5.96	1.00		1.00		1.00	
5.96–8.67	0.98 (0.94 - 1.02)	0.25	1.01 (0.97 - 1.04)	0.76	1.13 (1.08 - 1.19)	<0.01
8.67–12.50	1.01 (0.97 - 1.05)	0.59	1.09 (1.05 - 1.14)	<0.01	1.12 (1.06 - 1.18)	<0.01
>12.50	1.11 (1.05 - 1.17)	<0.01	1.20 (1.14 - 1.26)	<0.01	1.24 (1.15 - 1.33)	<0.01
p for trend		<0.01		<0.01		<0.01

| Cancer type (sex) | **Lung (male)** | | **Liver (male)** | | **Lung (female)** | |
	RR[a] (95% CI)	p	RR[a] (95% CI)	p	RR[a] (95% CI)	p
$PM_{2.5}$ conc., µg/m3						
≤ 10.11	1.00		1.00		1.00	
10.11 - 11.62	1.01 (0.97 - 1.06)	0.63	1.05 (0.98 - 1.13)	0.13	0.97 (0.90 - 1.04)	0.37
11.62 - 13.06	1.05 (1.00 - 1.10)	0.05	1.17 (1.09 - 1.25)	<0.01	1.07 (1.00 - 1.15)	0.06
> 13.06	1.12 (1.07 - 1.17)	<0.01	1.38 (1.29 - 1.48)	<0.01	1.10 (1.03 - 1.18)	<0.01
p for trend		<0.01		<0.01		<0.01

[a]Adjusted for age and the other four air pollutants. CI: confidence interval, RR: relative risk.

In this ecological study, we examined the associations between air pollutants and cancer incidence rates in 317 Japanese municipalities, and our analyses revealed significant positive dose-response relationships in some pollutant-cancer pairs.

The association between lung cancer and air pollution is well established [2,21]. In accord with previous reports, we observed positive correlations between lung cancer and all of the included pollutants except O_x. Dose-response relationships between lung cancer and $PM_{2.5}$ were present after adjusting for other air pollutants in both sexes. Our results thus

provide further evidence of the associations between air pollutants — especially $PM_{2.5}$ — and lung cancer.

As noted above, there have been few investigations of the relationship between air pollutants and cancer types other than lung cancer, but those investigations have suggested some associations. An analysis of the Cancer Prevention Study II results examined the associations between $PM_{2.5}$, NO_2, and O_3 and many cancer types; only the relationships between $PM_{2.5}$ and kidney cancer, $PM_{2.5}$ and bladder cancer, and NO_2 and colorectal cancer were significant [4]. A study of $PM_{2.5}$ exposure in Taiwan reported that $PM_{2.5}$ was associated with gastrointestinal, liver, and colorectal cancers but not stomach cancer [22]. Positive correlations between PM and lung, breast, uterine, and ovarian cancers but not other types of cancer were obtained in a study of PM exposure in Japan [23]. A 2018 review demonstrated that breast cancer was associated with NO_2 and less clearly with $PM_{2.5}$ [24]. The present study's results are similar to those of the previous studies in general, and some additional associations were revealed for the first time in the Japanese population.

Among the air pollutants, examinations of NO in epidemiological studies are scarce. We observed a positive dose-response relationship between NO and lung cancer in the female population in this study. An ecological study from Taiwan reported a positive association between NO and lung cancer of a specific cell type [12]. Further investigations are necessary to determine the above-described associations by using individual-level data.

There are several study limitations to address. This was a cross-sectional, ecological study. We observed significant correlations, but this does not establish an individual-level association or causation. We considered confounding by age and sex, but we did not consider other known confounders, such as smoking for lung cancer and human papillomavirus infection for cervical cancer, and unknown confounders. Thus, the observed associations could be the results of factors other than air pollution. In the study's design, we assumed that the patients lived in the municipality for most of their lives, and that the yearly mean air pollutants concentrations in 2017 reasonably reflect the patients' long-term exposure. We observed strong positive correlations between the yearly mean concentration in 2017 and the 5-year mean concentration in 2012-2016 among 71 monitors (SO_2, $r = 0.86$; NO, $r = 0.94$; NO_2, $r = 0.98$; O_x, $r = 0.84$; $PM_{2.5}$, $r = 0.82$). However, this assumption may have caused exposure misclassifications and biased our results.

4. Conclusions

Our findings support the concept that exposure to air pollutants increases cancer incidence rates.

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