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Burden of cancer attributable to air pollution in Japan in 2015

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Abstract: $PM_{2.5}$ is a major environmental health problem and a risk factor for lung cancer. Exposure to $PM_{2.5}$ has attracted growing public concern nationwide. Here, we aimed to estimate the cancer in 2015 attributable to $PM_{2.5}$ in Japan. Ambient air pollution level due to excess concentration of $PM_{2.5}$ was estimated using geophysically based satellite-derived $PM_{2.5}$ concentrations in 2005, with a spatial resolution of 0.5° × 0.5° longitude-latitude, and population data presented in a 1 km by 1 km grid. We used the WHO guideline value for $PM_{2.5}$ exposure (≤ 10 μg/m^3) as the optimal level of $PM_{2.5}$ exposure. By using relative risk from a large-scale cohort study in Japan, we estimated the population attributable fraction (PAF) for lung cancer, which is positively associated with $PM_{2.5}$, and aggregated the results to obtain the PAF among total cancer incidence and mortality. Population-weighted mean $PM_{2.5}$ level in 2005 was 14.9 μg/m^3. Approximately 95.7% of the population was exposed to levels above the WHO guideline value. Lung cancer attributable to $PM_{2.5}$ exposure corresponded to 11,922 cases and 7,264 deaths, which accounted for 9.7% and 9.8% of total lung cancer incidence and mortality, respectively, and 1.2% and 2.0% of total cancer incidence and mortality, respectively. Substantial geographic variation in $PM_{2.5}$-attributable incidence and mortality fractions was found, with cities in western Japan and metropolitan areas having a higher PAF than other municipalities. This study provides useful information to aid policy-makers and public health agencies in the efficient establishment of environmental cancer prevention policies.

***Keywords*:** cancer, air pollution, population attributable fraction, Japan

Introduction

Outdoor air pollution, often referred as ambient air pollution, is a major environmental health problem which affects people across all socioeconomic strata in low-, middle, and high-income countries. Types of ambient air pollution include gases (*e.g.*, carbon monoxide, sulfur dioxide, nitrogen oxides, ozone) and fine particulate matter (PM), notably $PM_{2.5}$ - particles less than 2.5 micrometers in diameter - and PM_{10}. In 2013, the International Agency for Research on Cancer (IARC) confirmed that outdoor air pollution, including $PM_{2.5}$, is carcinogenetic to humans (*1*), and the recent Global Burden of Disease (GBD) study (GBD 2017) found that $PM_{2.5}$ accounted for 5.3% of lung cancer mortality worldwide, and 5.5% in Japan (*2*).

Several countries and regions have reported mortality burdens attributable to $PM_{2.5}$ at a subnational level (*3*-*5*). In Taiwan, population attributable fractions (PAFs) for lung cancer were estimated to range from 4.7% to 17.4% in different counties (*6*). An earlier report from the US also revealed starkly localized geographic variation in this mortality burden (*7*). In addition to evaluation of the impact of $PM_{2.5}$ at the national level, a better understanding of geographic patterns in PAF at the subnational level will help policy-makers and public health agencies to improve the quality of public health practice. Nevertheless, few studies have focused on the PAF of cancer due to $PM_{2.5}$ at either the national or subnational level in Japan.

Here, we aimed to estimate cancer incidence and mortality attributable to ambient air pollution, with a special focus on $PM_{2.5}$ concentration, at the national and sub-national level (city level) in Japan.

Materials and Methods

Cancers associated with air pollution

IARC has classified particulate matter, a major component of outdoor air pollution, as carcinogenic to humans (Group 1), finding a consistent association of outdoor air pollution with lung cancer (*1*). Accordingly, we included lung cancer as the target cancer in the present estimate.

Theoretical minimum risk exposure level

For this study, we used the WHO guideline value for $PM_{2.5}$ exposure (10 μg/m^3) as reference (*8*). The latent period - the interval period between "exposure" to $PM_{2.5}$ above the reference and the increase in risk of cancer of the lung - is unknown. Based on previous epidemiological studies of exposure, we assumed a latent period of 10 years, and accordingly calculated the number of avoidable cancers in 2015 using the estimated $PM_{2.5}$ exposure in 2005.

Distribution of $PM_{2.5}$ exposure and population-weighted $PM_{2.5}$ exposure estimates

Because nationwide observation data of $PM_{2.5}$ were not available before 2009, when environmental quality standards for $PM_{2.5}$ were established in Japan, the distribution of $PM_{2.5}$ exposure and population-weighted $PM_{2.5}$ exposure was estimated using population and $PM_{2.5}$ concentrations data.

We obtained the population data from Japanese Census data in 2005 and 2000 (*9,10*). We used the population data in 2005 for the main analysis and that in 2000 for sensitivity analysis. The spatial distribution of population in 2005 is illustrated in Figure 1. The population data are presented in grids of 45 seconds longitude by 30 seconds latitude, which is also known as the Basic Grid Square (*11*). Each grid-square was given a unique ID computed on the basis of geographical position (latitude and longitude). The gridded data covered an area between 122°-154° east longitude and 20°- 46° north latitude.

To assign exposure to $PM_{2.5}$, we used surface $PM_{2.5}$ concentrations estimated by the Atmospheric Composition Analysis Group (*12*). The provided data were estimates of annual mean exposure to $PM_{2.5}$ in 2005 and 2000, with a spatial resolution of 0.01° × 0.01° longitude-latitude. The group estimated $PM_{2.5}$ concentrations using information from satellite-, simulation- and monitor-based sources (*13*). A geographically weighted regression (GWR) model was used to correct discrepancies between the satellite-based estimated $PM_{2.5}$ and monitor-based $PM_{2.5}$ levels.

The $PM_{2.5}$ data used in this study covered an area between 122°-154° east longitude and 20°- 46° north latitude. As with the population data, the $PM_{2.5}$ data in 2005 were used for the main analysis and the $PM_{2.5}$ data in 2000 were used for sensitivity analysis.

To estimate annual average $PM_{2.5}$ concentrations at the national and city levels, we added the longitude-latitude coordinate code computed from the grid-ID to the population data, then linked the population and $PM_{2.5}$ concentration data using the longitude-latitude coordinate code as the matching key with the nearest neighbor matching method.

Next, city codes were assigned to each grid using the intersect tool (ArcToolbox/Analysis tools/Overlay) of the ArcGIS (ArcGIS Pro, version 2.5.2; ESRI Inc, Redlands, CA, USA) geographic information system. This tool can create geometric intersections of any number of feature layers. In this study, we created an intersection between the city layer and gridded data layer; where a grid intersected two or more cities, the grid contained the codes of all intersected cities. Finally, we calculated population-weighted $PM_{2.5}$ concentrations at the city level using following formula (*14*):

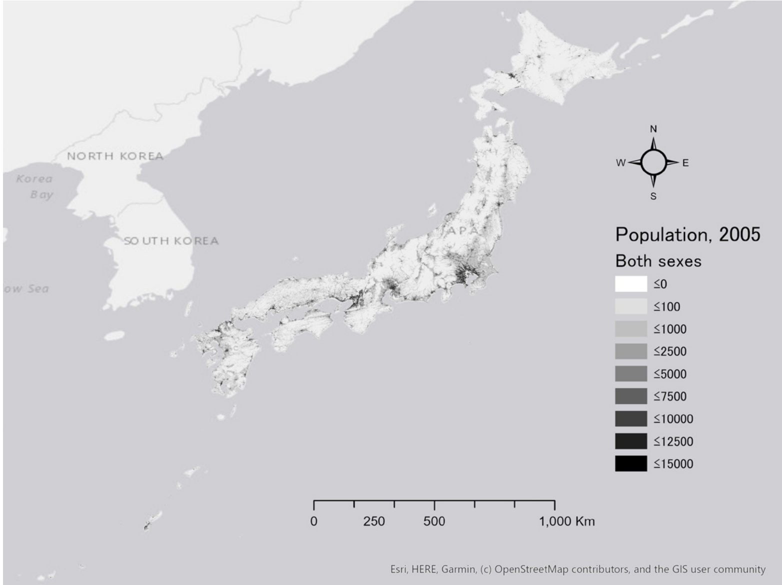

Figure 1. The spatial distribution of population in Japan in 2005, with a spatial resolution of 1km × 1km grid.

$$WPM_k = \sum_{i}^{N_k} PM_{ik} Pop_{ik} \;/\; Pop_k$$

$$Pop_k = \sum_{i}^{N_k} Pop_{ik}$$

where WPM_k is the population-weighted $PM_{2.5}$ concentration estimate in city k, N_k is the number of grid in city k, PM_{ik} is the $PM_{2.5}$ concentration in grid i in city k, Pop_k is the population in city k, and Pop_{ik} is the population in grid i in city k.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan project (*15*). We used an age and period spline model. This type of model is often used for short-term projection of cancer incidence in Japan (*16*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were based on the vital statistics of Japan. We obtained sex- and age-specific mortality data at both the national (*17*) and city level (*18*) by cause of death from available data sources from the Health, Labour, and Welfare Statistics Association, with cause of death classified using 4-digit ICD-10 codes.

Estimation of relative risk

The relative risk (RR) of air pollution exposure on lung cancer was taken from a prospective population-based observational study (*19*), the Three-Prefecture Cohort study, which was conducted from 1983 to 2000 in three prefectures (Miyagi, Aichi, and Osaka) (*20*). The Three-Prefecture Cohort study had a long follow-up period and covered both high and low $PM_{2.5}$ concentration areas. Because RR in the study was reported in 10-unit increases in the average concentration of air pollutants (μg/m^3), we assumed a log-linear association to convert the RR per 10-unit increase using the following formula:

$$\beta = \ln(RR_{10unit})/10$$

$$RR_{x-x_0} = \exp(\beta(x - x_0))$$

where β is the parameter estimate for the association between lung cancer and the exposure of $PM_{2.5}$, RR_{10unit} is the RR per 10-unit increase in the average concentration of $PM_{2.5}$, and $RR_{x\text{-}x0}$ is the RR at exposure x compared to that with the reference exposure x_0. In our study, RRs of $PM_{2.5}$ on lung cancer incidence and mortality were assumed to be equal. Consequently, RR_{10unit} (95% confidence interval) of lung cancer, 1.26 (1.14-1.36) for men and 1.17 (0.98-1.39) for women, was used for estimation of PAF of cancer due to air pollution.

Estimation of population attributable fractions (PAFs)

For lung cancer, PAF at the national level was calculated by sex as:

$$PAF = \frac{\sum(p_x ERR_x)}{1 + \sum(p_x ERR_x)}$$

where p_x is the proportion of the population and ERR_x is the excess relative risk at $PM_{2.5}$ exposure level x.

The excess relative risk for each x level of $PM_{2.5}$ exposure was calculated using the following formula:

$$ERR_x = RR_{x-x_0} - 1 = \exp\big(\beta(x - x_0)\big) - 1$$

We used the WHO guideline value for $PM_{2.5}$ exposure (10 μg/m^3) as reference (*8*).

The number of lung cancer cases/deaths attributable to $PM_{2.5}$ was calculated by sex as:

$$ELC = LC \times PAF$$

where ELC is excess incidence/mortality of lung cancer and LC is lung cancer incidence/mortality.

The number of attributable cancers was then totaled across all sex and age categories to show the percentage of the total number of all incidence and mortality of cancer in Japan in 2015.

In addition, the PAF of mortality of lung cancer was estimated at the city level, using population-weighted $PM_{2.5}$ concentration by city. As we assumed that $PM_{2.5}$ levels were uniform within each city, that is *WPM*, PAF at city k, which is PAF at the city level, was calculated by sex as:

$$PAF_k = \frac{ERR_{WPM_k}}{1 + ERR_{WPM_k}}$$

Sensitivity analysis

In addition to the main analysis, the impact of $PM_{2.5}$ on cancer incidence and mortality was assessed using three alternative reference levels, namely the national ambient air quality standards in Japan (15.0 µg/m^3) (*21*) and the USA (12.0 µg/m^3) (*22*), and a value which may be close to the background $PM_{2.5}$ concentration in Japan (4.0 µg/m^3), based on a previous estimated background concentration of about 4.4 µg/m^3 in Taiwan and surrounding oceanic regions (*23*). We also investigated the influence of time lag between $PM_{2.5}$ exposure and lung cancer incidence and mortality by using the population and $PM_{2.5}$ concentration data in 2000, which is 15-year time lag analysis.

Results

Fine particular matter exposure

The distribution of the population-weighted exposure to $PM_{2.5}$ in 2005 is shown in Figure 2. The 5th, 50th and 95th percentiles of population-weighted $PM_{2.5}$ levels in that year were 10.2, 15.1, 20.5 µg/m^3, respectively, and the population-weighted annual average exposure was 14.9 µg/m^3. Approximately 95.7% of the study population was exposed above the yearly average WHO guideline value of 10 µg/m^3, while 56.6% was above the Japan standard value of 15.0 µg/m^3.

The spatial distribution of population-weighted $PM_{2.5}$ concentrations at the city level in 2005 in Japan is shown in Figure 3. The Kanto region, including Tokyo and Kanagawa prefectures, and the Kansai region, including Osaka prefecture, had high $PM_{2.5}$ concentrations. Western Japan, including the Kyushu and Chugoku regions, also had higher $PM_{2.5}$ concentrations than other areas. In contrast, $PM_{2.5}$ concentrations were lower in northern Japan, such as the Hokkaido and Tohoku regions.

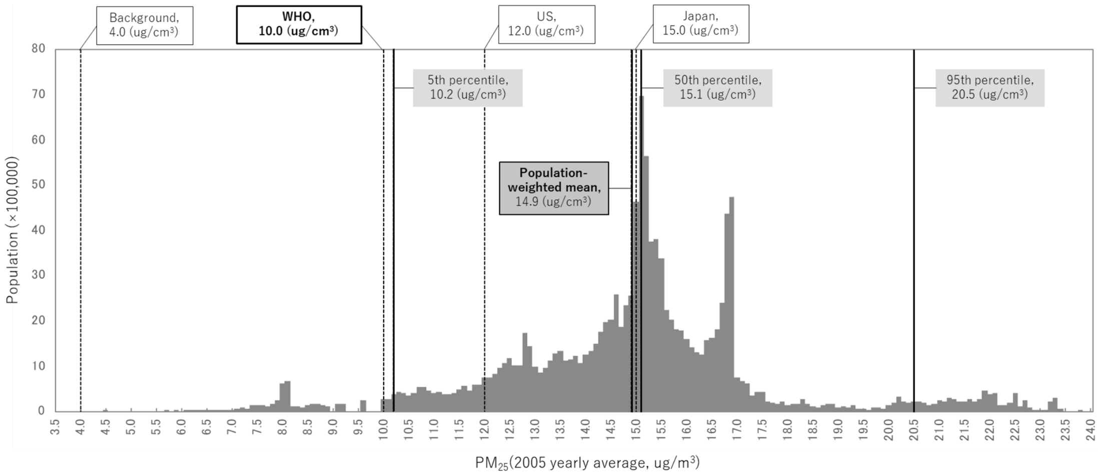

Figure 2. Distribution of exposures to $PM_{2.5}$ in Japan in 2005. Background: Expected value of background $PM_{2.5}$ concentration in Japan; WHO: WHO Air quality guideline values for annual average $PM_{2.5}$ concentrations; US: National Ambient Air Quality Standards for annual average $PM_{2.5}$ concentrations in the US; Japan: Environmental Quality Standards for annual average $PM_{2.5}$ concentrations in Japan.

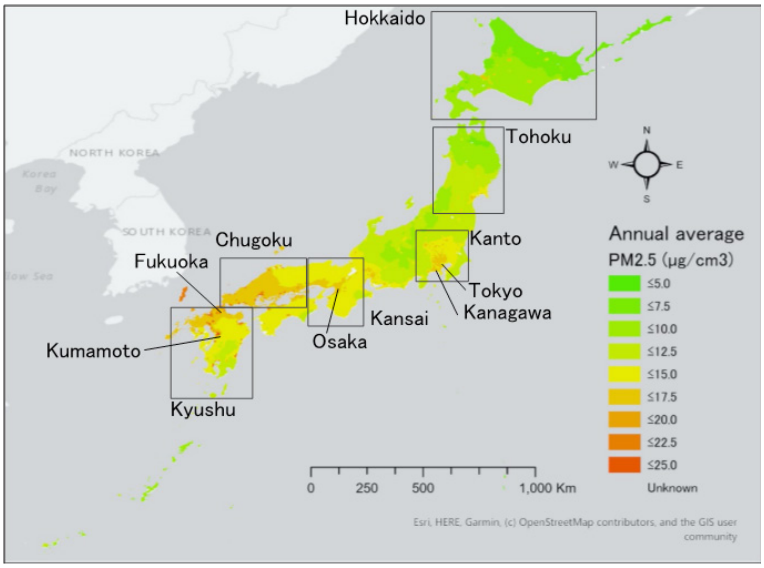

Figure 3. Annual average of population-weighted $PM_{2.5}$ concentrations at the city level in 2005 in Japan.

Cancer attributable to PM$_{2.5}$

Table 1 summarized the estimated PAF of cancer incidence and mortality in Japan in 2015 attributed to ambient air pollution (PM$_{2.5}$). Detailed results by sex and age group are shown in Tables S1 (incidence) and S2 (mortality) (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=40*). The estimated PAF was 9.7% (10.7% for men, 7.5% for women) of lung cancer incidence, corresponding to 11,922 cases (8,907 in men, 3,014 in women), and 9.8% (10.7% for men, 7.5% for women) of lung cancer mortality, corresponding to 7,264 deaths (5,682 in men, 1,582 in women). Accordingly, 1.2% of cancer incidence (1.6% in men, 0.7% in women) and 2.0% of cancer mortality (2.6% in men, 1.0% in women) in 2015 were due to excessive PM$_{2.5}$ exposure.

Figure 4 shows the geographic variation in PAF of lung cancer mortality associated with PM$_{2.5}$ exposure at the city level across Japan. Cities in western Japan had a higher PAF than other cities, with Kumamoto City in the Kyushu region having the highest PAF (26% for males, 19% for females). Estimated PAFs were also higher in cities in Tokyo, Kanagawa, and Osaka prefectures compared to other cities. On the other hand, PAF was lower in northern Japan, such as in the Hokkaido and Tohoku regions.

Figure 5 shows the number of lung cancer deaths attributable to PM$_{2.5}$ exposure at the city level across

Table 1. Proportion (%) of cancer in 2015 attributable to ambient air pollution (PM$_{2.5}$) in Japan

Factors	Cancer Incidence			Cancer Mortality		
	Men	Women	Both sexes	Men	Women	Both sexes
Lung (C33-34)						
Exceed 10 µg/cm^3 (WHO[a])	10.7	7.5	9.7	10.7	7.5	9.8
Exceed 12 µg/cm^3 (US[b])	6.9	4.8	6.2	6.8	4.8	6.2
Exceed 15 µg/cm^3 (Japan[c])	2.0	1.4	1.8	2.0	1.4	1.8
Exceed 4 µg/cm^3 (background[d])	22.0	15.8	20.0	22.0	15.7	20.2
Total cancer (C00-C96)						
Exceed 10 µg/cm^3 (WHO[a])	1.6	0.7	1.2	2.6	1.0	2.0

[a]WHO Air quality guideline values for annual average PM$_{2.5}$ concentrations; [b]National Ambient Air Quality Standards for annual average PM$_{2.5}$ concentrations in the US; [c]Environmental Quality Standards for annual average PM$_{2.5}$ concentrations in Japan; [d]Expected value of background PM$_{2.5}$ concentration in Japan.

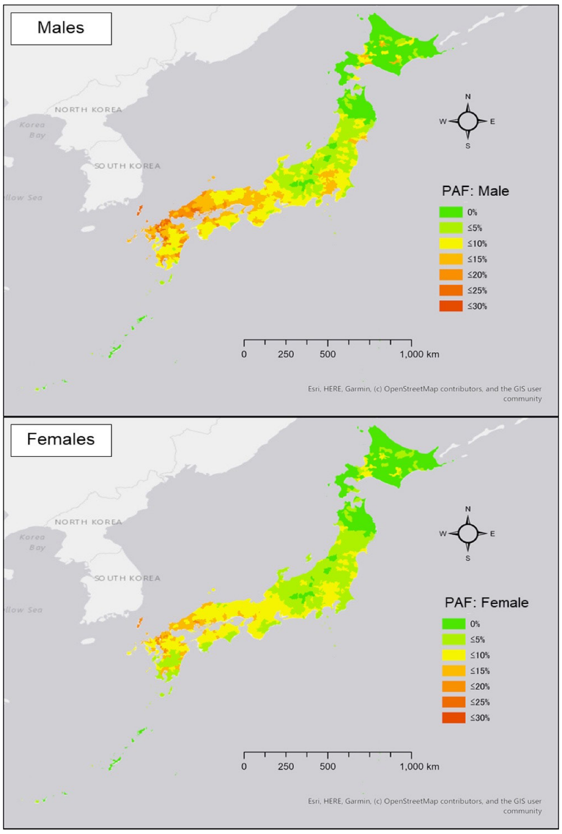

Figure 4. Spatial variations in the PAF (%) of lung cancer due to PM$_{2.5}$ at the city level by sex in Japan in 2015.

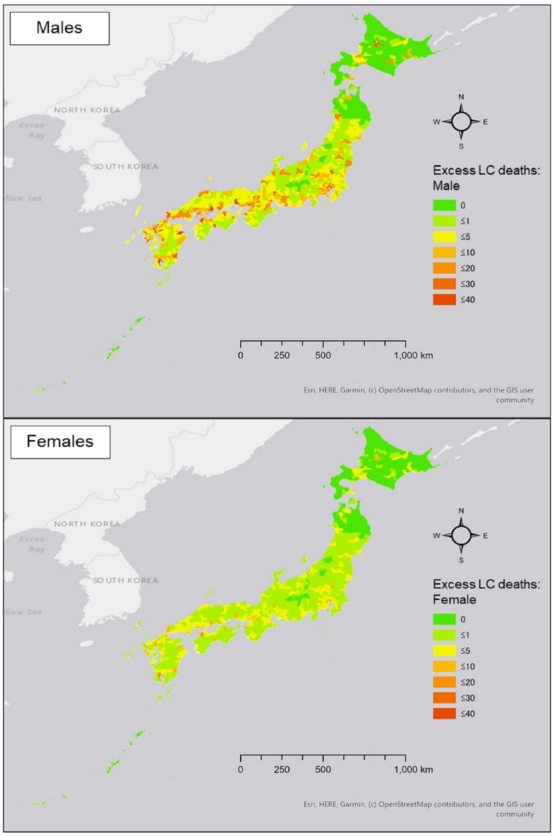

Figure 5. Spatial variations of the number of lung cancer deaths due to PM$_{2.5}$ at the city level by sex in Japan in 2015.

Japan. Cities in metropolitan areas, such as Tokyo and Osaka prefectures, tended to have a large number of deaths associated with $PM_{2.5}$. In the northern part of the Kyushu region and southern part of the Chugoku region also, many cities had a large number of deaths due to $PM_{2.5}$ exposure.

Sensitivity analysis

When the $PM_{2.5}$ reference level was replaced by the national ambient air quality standards in the US (12.0 μg/m^3) and in Japan (15.0 μg/m^3), the PAF for both sexes combined decreased to 6.2% and 1.8% for incidence and mortality, respectively. When the reference level for $PM_{2.5}$ was changed to 4.0 μg/m^3, which is regarded as consistent with the background concentration in Japan, PAF was 20% for both incidence and mortality. Results with the 15-year time lag analysis were similar to those with a 10-year time lag analysis.

Discussion

We estimated the cancer incidence and mortality attributed to ambient air pollution ($PM_{2.5}$) exposure in Japan in 2015 by applying GIS spatial analysis data. This is the first nationwide report of the PAF of cancer attributable to ambient air pollution in Japan and PAF of lung cancer mortality due to $PM_{2.5}$ at a sub-national level. We identified a large geographic variation in PAF, namely a higher ratio in the western part in Japan. Further, the large metropolitan areas around Tokyo and Osaka had a large number of excess attributable cases due to $PM_{2.5}$ exposure.

Cigarette smoking is the single biggest risk factor for lung cancer. In Japan, the PAF of lung cancer mortality caused by cigarette smoking in 2015 was about 60.9% for men and 18.3% for women (*24*). Although the PAF of lung cancer due to $PM_{2.5}$ was small compared to that due to cigarette smoking in men, it was about half as large as that due to cigarette smoking for women. Moreover, the PAF due to $PM_{2.5}$ was comparable to that due to secondhand smoking (SHS) for women (8.7%) and larger than that due to SHS for the total population (3.7%). In addition to the inclusion of tobacco control in indoor air policies, environmental approaches to air quality management are also important for cancer prevention, including lung.

The GBD 2015 study reported that lung cancer mortality attributable to $PM_{2.5}$ was about 6,800 deaths (males 4,700, females 2,000), or 8.7% of total lung cancer mortality in Japan (*25*). Our national-level estimates of PAF were higher than the GBD 2015 estimates. One reason is the year of $PM_{2.5}$ exposure data: the GBD study used $PM_{2.5}$ exposure and mortality data from the same year (2015), whereas we used $PM_{2.5}$ exposure data in 2005 and mortality in 2015. In other words, we assumed a 10-year time lag between $PM_{2.5}$ exposure and lung cancer mortality. In fact, several studies have reported that lung cancer has a long latency period (*26-28*). To our knowledge, however, uncertainties are still present in the time lag between $PM_{2.5}$ and lung cancer mortality. We therefore assumed that a time lag of 10 years accounted for longer-term exposure, as has also been done in previous studies (*29*). In Japan, average $PM_{2.5}$ concentrations in rural areas have leveled off, whereas those measured at the roadside have greatly decreased since 2000 (*30*). The GBD approach might therefore have provided lower attributable deaths due to $PM_{2.5}$. Another difference between the GBD and our present study is the choice of $PM_{2.5}$ reference level, which has a major impact on PAF estimation. The GBD study applied a uniform distribution between 2.4 μg/m^3 and 5.9 μg/m^3 as the reference level of $PM_{2.5}$ (*25*), whereas our main analysis was set to 10.0 μg/m^3. The reference level of 4.0 μg/m^3 in our sensitivity analysis is similar to the reference level applied in the GBD. Under this setting, our PAFs were much larger than those of the GBD study. The large differences in PAF were considered due to the differences in $PM_{2.5}$ exposure data.

Unlike the differences in $PM_{2.5}$ exposure data between the GBD and our present study, the differences between $PM_{2.5}$ concentrations in 2000 and 2005 in our study were small. Accordingly, replacement of the $PM_{2.5}$ concentration in 2005 with that in 2000 resulted in almost no change in PAF at the national level.

Our estimates revealed the geographic variation in the PAF of lung cancer due to $PM_{2.5}$ exposure in Japan. We found a high PAF in major metropolitan areas such as Tokyo, Kanagawa and Osaka. In our method, PAFs are thoroughly dependent on the population-weighted concentration of $PM_{2.5}$. Tokyo, Kanagawa and Osaka are among the most densely populated areas in Japan. These areas had higher $PM_{2.5}$ concentrations, mainly as a result of local industrial and traffic pollution (*31*). Accordingly, the PAFs were also relatively high in the major metropolitan areas. Moreover, Japan's 2005 census showed that 30% of the overall population was concentrated in the metropolitan areas (*32*). Therefore, trends in $PM_{2.5}$ in the area would have a substantial impact on the national estimates of PAF.

Higher concentrations of $PM_{2.5}$ and bigger PAF were also found in many parts of rural areas in western Japan. The main reason is $PM_{2.5}$ arising from foreign anthropogenic sources, especially from the Chinese mainland (*31,33-35*). In Japan, the main contributor to $PM_{2.5}$ differ according to region. Contributions from foreign anthropogenic sources were greater than those from domestic pollution in the Kyushu region (*33,35*).

China has a very large PAF compared to Japan, although variations in PAF have been assigned according to the setting of reference levels of $PM_{2.5}$ and the time lag between $PM_{2.5}$ exposure and lung cancer mortality/incidence (*36-40*). One of the Chinese studies estimated that the PAF in China in 2015 was 23.9% overall (*38*). However, the study applied a high reference level of $PM_{2.5}$ (40 μg/m^3). If we use the same reference level as the Chinese study, the number of lung cancer deaths attributed to $PM_{2.5}$ would be zero in Japan because there were no areas which had a $PM_{2.5}$ concentration over 30 μg/m^3. A previous study in the Republic of Korea estimated that the PAF was 26.9% (95% CI: 15.5%-37.0%) by applying a uniform distribution between 2.4 μg/m^3 and 5.9 μg/m^3 as the reference level of $PM_{2.5}$ (*41*). The reference level of 4.0 μg/m^3 in our sensitivity analysis is similar to this level in the Korean study. Under this setting, the PAFs were slightly larger in the Korea than Japan. The larger PAFs in China and Korea were caused by exposure to higher $PM_{2.5}$ concentrations. Average concentrations in China, Republic of Korea and Japan were 66.2 μg/m^3, 30.4 μg/m^3 , and 14.3 μg/m^3 in 2005, respectively (*42*). The south and south-east Asia region had much higher concentrations of $PM_{2.5}$ than other Asian countries (*43*). Japan was considered to have smaller PAFs of $PM_{2.5}$ among Asian countries.

On the other hand, a recent study in Canada, where air pollution levels are much lower than in Japan, estimated that 2-6% of incident lung cancer cases in 2012 might have been attributable to $PM_{2.5}$ exposure by applying different reference levels of $PM_{2.5}$ (7.5 μg/m^3 and 3.18 μg/m^3, respectively) (*44*). In the GBD study, the fraction of lung cancer mortalities attributable to $PM_{2.5}$ was estimated to be 8.6% in Western Europe and 4.6% in the US (*25*). The health impact of $PM_{2.5}$ exposure in Japan is large compared to these European and North American countries.

One strength of the present study was that we used the estimated annual average of $PM_{2.5}$ concentration-based satellite-, simulation- and monitor-based concentrations. Agreement with the estimated data we used and ground-observed $PM_{2.5}$ concentrations were improved by applying the GWR model. Since establishment of the national ambient air quality standards in 2009 (*21*), the number of $PM_{2.5}$ monitoring stations in Japan has been increasing year by year (*45*). Nevertheless, there are still insufficient monitoring stations to monitor spatial distribution at the city level with ground-based monitoring alone (*46*). By using satellite-, simulation- and monitor-based concentration data, not only monitoring data alone, our analysis provided subnational information.

Another strength of the present study was that we used small grid-square level mortality data instead of city-level mortality data. Our analysis therefore provided national and subnational information that was more accurate than the previous estimate.

The RR used for the present study was based on a large-scale prospective cohort study from three prefectures in Japan. An advantage of this RR is that the large number of confounders (age, smoking status, pack-years, smoking status of family members, indoor charcoal or briquette braziers used for heating, and occupation) were directly adjusted using individual data.

On the other hand, the RR used for present study involves several uncertainties regarding the estimation of $PM_{2.5}$ concentration and time lag between $PM_{2.5}$ exposure and lung cancer outcome. However, the RR values from the analysis were generally comparable to those reported in previous studies conducted in the US and European countries (*28,47-49*).

This study has several limitations. First, our analysis did not account for cumulative $PM_{2.5}$ exposure. Adverse health effects are dependent not only on concentration but also on the length of $PM_{2.5}$ exposure. In Japan, more than two million people move across prefectural boundaries every year (*50*). Rates of inter-prefectural migration vary among prefectures. Migration has an effect on both the length of $PM_{2.5}$ exposure and cumulative $PM_{2.5}$ exposure. Adjustment for migration may improve the estimation of PAF and its distribution in Japan.

Second, we could not obtain individual measurements of exposure to ambient $PM_{2.5}$ in this analysis. Individuals also constantly move in time and space. To support health impact assessment, it is essential to develop a better understanding of individual exposure pathways in people's everyday lives by taking account of all environments in which people spend time.

Finally, smoking prevalence varies across prefectures in Japan, ranging in 2019 from 26.5% in Ehime to 35.8% in Saga (Japan total: 28.8%) (*51*). A previous meta-analysis reported the presence of smoking-related confounding bias in the RR of $PM_{2.5}$ on lung cancer, and suggested that never- and former smokers may have an elevated risk of lung cancer associated with $PM_{2.5}$ compared to current smokers (*52,53*). However, because we had no information on smoking prevalence among cities, we used the overall RRs adjusted for multiple covariates, including smoking status, instead of RRs by smoking status.

Conclusion

Our findings indicate that nearly 10% of lung cancer and 1-2% of total cancer were attributable to excess $PM_{2.5}$ exposure in Japan, with regional differences. This study provides useful information for policy-makers and public health agencies to aid the efficient development of their environmental cancer prevention policies.

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References

1. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group IARC. The carcinogenicity of outdoor air pollution. Lancet Oncol. 2013; 14:1262-1263.
2. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392:1923-1994.
3. Moore JX, Moore JX, Akinyemiju T, Wang HE. Pollution and regional variations of lung cancer mortality in the United States. Cancer Epidemiol. 2017; 49:118-127.
4. Pinichka C, Makka N, Sukkumnoed D, Chariyalertsak S, Inchai P, Bundhamcharoen K. Burden of disease attributed to ambient air pollution in Thailand: A GIS-based approach. PLoS One. 2017; 12:e0189909.
5. Zhou M, Wang H, Zeng X, *et al.* Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2019; 394:1145-1158.
6. Lo WC, Shie RH, Chan CC, Lin HH. Burden of disease attributable to ambient fine particulate matter exposure in Taiwan. J Formos Med Assoc. 2017; 116:32-40.
7. Fann N, Lamson AD, Anenberg SC, Wesson K, Risley D, Hubbell BJ. Estimating the national public health burden associated with exposure to ambient PM$_{2.5}$ and ozone. Risk Anal. 2012; 32:81-95.
8. World Health Organization. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide.*http://apps.who.int/iris/bitstream/10665/69477/1/WHO_SDE_PHE_OEH_06.02_eng.pdf* (accessed November 10, 2021).
9. Statistics Bureau of Japan. Grid Square Statistics of 2005 Population Census. *https://www.e-stat.go.jp/gis/statmap-search?page=1&type=1&toukeiCode=00200521* (accessed November 10, 2021). (in Japanese)
10. Statistics Bureau of Japan. Grid Square Statistics of 2000 Population Census. *https://www.e-stat.go.jp/gis/statmap-search?page=1&type=1&toukeiCode=00200521* (accessed November 10, 2021) (in Japanese)
11. Statistics Bureau of Japan. Standard Grid Square and Grid Square Code Used for the Statistics. *https://www.stat.go.jp/english/data/mesh/02.html* (accessed November 10, 2021).
12. Atmospheric Composition Analysis Group. Surface PM$_{2.5}$. *https://sites.wustl.edu/acag/datasets/surface-pm2-5/* (accessed November 10, 2021).
13. van Donkelaar A, Martin RV, Brauer M, Hsu NC, Kahn RA, Levy RC, Lyapustin A, Sayer AM, Winker DM. Global estimates of fine particulate matter using a combined geophysical-statistical method with information from satellites, models, and monitors. Environ Sci Technol. 2016; 50:3762-3772.
14. Korhonen A, Lehtomäki H, Rumrich I, Karvosenoja N, Paunu V-V, Kupiainen K, Sofiev M, Palamarchuk Y, Kukkonen J, Kangas L, Karppinen A, Hänninen O. Influence of spatial resolution on population PM$_{2.5}$ exposure and health impacts. Air Qual Atmos Health. 2019; 12:705-718.
15. Cancer Statistics. Cancer Information Service, National Cancer Center, Japan (Monitoring of cancer incidence in Japan (MCIJ)) *https://ganjoho.jp/reg_stat/statistics/data/dl/en.html* (accessed November 1, 2021).
16. Katanoda K, Kamo K, Saika K, Matsuda T, Shibata A, Matsuda A, Nishino Y, Hattori M, Soda M, Ioka A, Sobue T, Nishimoto H. Short-term projection of cancer incidence in Japan using an age-period interaction model with spline smoothing. Jpn J Clin Oncol. 2014; 44:36-41.
17. Ministry of Health Labour and Welfare. Sex and age specific mortality statistics in Japan (2015) by ICD-10, by 4-digit. Health, Labour and Welfare Statistics Association. *http://www.hws-kyokai.or.jp/information/mortality.html* (accessed November 1, 2021). (in Japanese)
18. Ministry of Health Labour and Welfare. Specified report of vital statistics 2013-2017. *https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450013&tstat=000001143831&cycle=7&stat_infid=000031976397&result_page=1&tclass1val=0* (accessed November 10, 2021). (in Japanese)
19. Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, Takezaki T, Nakayama T, Nitta H, Tanabe K, Tominaga S. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J Epidemiol. 2011; 21:132-143.
20. Sado J, Kitamura T, Kitamura Y, Zha L, Liu R, Sobue T, Nishino Y, Tanaka H, Nakayama T, Tsuji I, Ito H, Suzuki T, Katanoda K, Tominaga S; Three-prefecture cohort study group. Rationale, design, and profile of the three-prefecture cohort in Japan: a 15-year follow-up. J Epidemiol. 2017; 27:193-199.
21. Ministry of the Environment, Government of Japan. Environmental Quality Standards in Japan for the PM$_{2.5}$. *https://www.env.go.jp/en/air/aq/aq.html* (accessed November 10, 2021).
22. Federal Register. National Ambient Air Quality Standards for Particulate Matter. *https://www.federalregister.gov/documents/2013/01/15/2012-30946/national-ambient-air-quality-standards-for-particulate-matter* (accessed November 10, 2021).
23. Wang SH, Hung RY, Lin NH, Gómez-Losada Á, Pires JCM, Shimada K, Hatakeyama S, Takami A. Estimation of background PM$_{2.5}$ concentrations for an air-polluted environment. Atmos Res. 2020; 231:104636.
24. Katanoda K, Hirabayashi M, Saito E, Hori M, Abe SK, Matsuda T, Inoue M, the Cancer PAF Japan Collaborators. Burden of cancer attributable to tobacco smoke in Japan in 2015. GHM Open. 2021; 1:43-50
25. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet. 2016; 388:1659-1724.
26. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst. 1981; 66:1191-1308.
27. Elliott P, Shaddick G, Wakefield JC, de Hoogh C, Briggs DJ. Long-term associations of outdoor air pollution with mortality in Great Britain. Thorax. 2007; 62:1088-1094.
28. Pope CA, 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 2002; 287:1132-1141.

29. Kulhánová I, Morelli X, Le Tertre A, Loomis D, Charbotel B, Medina S, Ormsby JN, Lepeule J, Slama R, Soerjomataram I. The fraction of lung cancer incidence attributable to fine particulate air pollution in France: Impact of spatial resolution of air pollution models. Environ Int. 2018; 121:1079-1086.
30. Ministry of the Environment, Government of Japan. Central Environment Council Report on Environmental Quality Standards for Fine Particulate matter. 2009. *http://www.env.go.jp/council/former2013/07air/yoshi07.html* (accessed November 10, 2021). (in Japanese)
31. Ikeda K, Yamaji K, Kanaya Y, Taketani F, Pan X, Komazaki Y, Kurokawa J, Ohara T. Sensitivity analysis of source regions to $PM_{2.5}$ concentration at fukue island, Japan. J Air Waste Manag Assoc. 2014; 64:445-452.
32. Statistics Bureau of Japan. Population of Japan 2005. *https://www.stat.go.jp/english/data/kokusei/2005/poj/mokuji.html* (accessed November 1, 2021).
33. Ikeda K, Yamaji K, Kanaya Y, Taketani F, Pan X, Komazaki Y, Kurokawa J-i, Ohara T. Source region attribution of $PM_{2.5}$ mass concentrations over Japan. Geochem Jour. 2015; 49:185-194.
34. Chatani S, Morikawa T, Nakatsuka S, Matsunaga S. Sensitivity analyses of domestic emission sources and transboundary transport on $PM_{2.5}$ concentrations in three major Japanese urban areas for the year 2005 with the three-dimensional air quality simulation. J. Japan Soc Atmos Environ. 2011; 46:101-110. (in Japanese)
35. Itahashi S, Hayami H. Source apportionments of $PM_{2.5}$ in Japan on 2010 fiscal year evaluated by the tracer method on regional air quality model. J Jpn Soc Atmos Environ. 2016; 51:197-217. (in Japanese)
36. Song C, He J, Wu L, Jin T, Chen X, Li R, Ren P, Zhang L, Mao H. Health burden attributable to ambient $PM_{2.5}$ in China. Environ Pollut. 2017; 223:575-586.
37. Guo Y, Zeng H, Zheng R, Li S, Pereira G, Liu Q, Chen W, Huxley R. The burden of lung cancer mortality attributable to fine particles in China. Sci Total Environ. 2017; 579:1460-1466.
38. Yang L, Xue T, Wang N, Yuan Y, Liu S, Li H, Zhang X, Ren A, Ji J. Burden of lung cancer attributable to ambient fine particles and potential benefits from air quality improvements in Beijing, China: A population-based study. Sci Total Environ. 2020; 738:140313.
39. He Y, Gao Z, Guo T, Qu F, Liang D, Li D, Shi J, Shan B. Fine particulate matter associated mortality burden of lung cancer in Hebei Province, China. Thorac Cancer. 2018; 9:820-826.
40. Liao Y, Xu L, Lin X, Hao YT. Temporal trend in lung cancer burden attributed to ambient fine particulate matter in Guangzhou, China. Biomed Environ Sci. 2017; 30:708-717.
41. Kim JH, Oh IH, Park JH, Cheong HK. Premature deaths attributable to long-term exposure to ambient fine particulate matter in the Republic of Korea. J Korean Med Sci. 2018; 33:e251.
42. The Word Bank. $PM_{2.5}$ air pollution, mean annual exposure (micrograms per cubic meter) *https://data.worldbank.org/indicator/EN.ATM.PM25.MC.M3?name_desc=false&view=map* (accessed January 19, 2021).
43. Cohen AJ, Brauer M, Burnett R, *et al.* Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the global burden of diseases study 2015. Lancet. 2017; 389:1907-1918.
44. Poirier AE, Grundy A, Khandwala F, Friedenreich CM, Brenner DR. Cancer incidence attributable to air pollution in Alberta in 2012. CMAJ Open. 2017; 5:E524-E528.
45. Ministry of the Environment, Government of Japan. Annual Report of Air Pollution for FY 2017. *http://www.env.go.jp/air/osen/report/h29report/index.html* (accessed November 10, 2021). (in Japanese)
46. Asia Center for Air Pollution Research. Monitoring of $PM_{2.5}$ - Experience in Japan. *https://www.acap.asia/wp-content/uploads/Monitoring-of-*PM2.5*-Experience-in-Japan.pdf* (accessed November 10, 2021).
47. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Jerrett M, Hughes E, Armstrong B, Brunekreef B. Long-term effects of traffic-related air pollution on mortality in a dutch cohort (NLCS-AIR study). Environ Health Perspect. 2008; 116:196-202.
48. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the harvard six cities study. Am J Respir Crit Care Med. 2006; 173:667-672.
49. Naess Ø, Nafstad P, Aamodt G, Claussen B, Rosland P. Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. Am J Epidemiol. 2007; 165:435-443.
50. Statistics Bureau of Japan. Report on Internal Migration in Japan. *https://www.stat.go.jp/english/data/idou/3.html* (accessed November 10, 2021).
51. Foundation for Promotion of Cancer Research. Cancer. Cancer Statistics in Japan. *https://ganjoho.jp/public/qa_links/report/statistics/en.html* (accessed November 10, 2021).
52. Kawaguchi T, Takada M, Kubo A, Matsumura A, Fukai S, Tamura A, Saito R, Maruyama Y, Kawahara M, Ignatius Ou SH. Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC. J Thorac Oncol. 2010; 5:620-630.
53. Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, Vineis P, Forastiere F, Saldiva P, Yorifuji T, Loomis D. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect. 2014; 122:906-911.

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