METHODS

Subjects

The setting of this study was the Ichikawa Emergency Clinic in Ichikawa, Japan. The clinic offers emergency care between 7 PM and 12 AM (midnight) on weekdays and Saturdays, and between 10 AM and 12 AM on Sundays and national holidays. Ichikawa City borders Tokyo Bay and is located in the Tokyo metropolitan area, approximately 20 km from central Tokyo. The area of the city is 56 km^2, and its population is 470 000. The subjects were patients aged 0 to 64 years who presented with an asthma attack, lived in Ichikawa City, and visited the municipal emergency primary care clinic between 7 PM and 12 AM from September 1, 2002 through August 31, 2003. We limited the study time to between 7 PM and 12 AM in order to examine the association between daytime exposure and adverse health effects occurring at night. We excluded patients who visited the clinic on national holidays, for reasons discussed in the section on statistical analysis. The medical records of all patients were reviewed retrospectively, and subject age, sex, diagnosis, treatment, medication, and date and time of visits were recorded. Eligible subjects were patients that had paroxysmal dyspnea and were diagnosed with asthma by their primary care physician, and for whom any type of bronchodilator was prescribed. We obtained approval from the Ichikawa local government to use personal identifiable information from the municipal clinic.

Air pollutants

Data on hourly concentrations of NO_2 and O_3 from September 2002 through August 2003 were obtained from the Ichikawa local government. The monitoring station where these air pollutants were measured was located on a residential street in the city. In addition, we measured hourly concentrations of particulate matter with a 50% cut-off aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) using the R&P TEOM-1400 (Rupprecht & Patashnick Co, Inc, Albany, NY) at a location near the monitoring station, from September 2002 through August 2003.

Statistical analysis

We used time-stratified case–crossover analysis, a technique for assessing brief changes in risk associated with transient exposures.[11,12] Case–crossover analyses require exposure data for cases only, and are regarded as a special type of case–control study in which each case serves as his or her own control. This design has the advantage of controlling for potential confounding caused by fixed individual characteristics, such as sex, race, diet, and age. "Time-stratified" indicates the method by which the control periods were chosen. Specifically, we stratified time into months to select days for control periods that fell on the same day of the week within the same month as the date of the primary care visit (day of the index period). For example, if a nighttime primary care visit due to asthma attack were to occur on September 18, the 3 control days would be September 4, 11, and 25. The control periods were also matched by time of index periods. Therefore, this approach also controls for long-term trends, seasonality, day of the week, and circadian rhythms. The merits of case–crossover designs in studies of the health effects of air pollution have been discussed in detail by Schwartz.[13]

We excluded patients who visited the clinic on national holidays because of bias in control selection. That is, if patients whose visits occurred on holidays were included as subjects, the estimated relative risks would be lower than expected because the concentrations of air pollutants on holidays (days for the index periods) were usually, and systematically, lower than on non-holidays (days for control periods).

In our analysis we first converted the hourly air pollution data into 6-hour mean concentrations, and we examined the associations between the 6-hour mean concentrations of each air pollutant and the risk of nighttime primary care visits due to asthma attack. These concentrations were subject-specific values averaged over the 6 hours before the index time. Exposure to air pollutants during the period from 6 hours before a nighttime primary care visit due to asthma attack to the hour of the visit was defined as exposure with a time lag of 0 to 6 hours (lag 0–6), exposure during the period 12 hours before to 6 hours before was defined as exposure with a lag of 6 to 12 hours (lag 6–12), etc. Lagged-hour exposures up to lag 18–24 were examined. We estimated odds ratios (ORs) of nighttime primary care visits due to asthma attack per 10 μg/m^3 difference in $PM_{2.5}$ in a single-pollutant model adjusted for 6-hour mean temperature. In like manner, we also estimated ORs of primary care visits per 10 ppb difference in NO_2, and per 10 ppb difference in O_3. We also estimated ORs of nighttime primary care visits due to asthma attack per 10 μg/m^3 difference in $PM_{2.5}$, per 10 ppb difference in NO_2, and per 10 ppb difference in O_3 in a multipollutant model adjusted for 6-hour mean temperature.

Second, we converted the hourly air pollution data into 24-hour mean concentrations and examined the effect of the 24-hour mean concentration of air pollutants (lag 0–24) on nighttime primary care visits due to asthma attack. We estimated ORs of nighttime primary care visits due to asthma attack per 10 μg/m^3 difference in 24-hour mean $PM_{2.5}$, per 10 ppb difference in NO_2, and per 10 ppb difference in 24-hour mean O_3 in both a single-pollutant model and a multipollutant model adjusted for 24-hour mean temperature.

Third, we examined the effect of the daytime 8-hour mean concentrations of air pollutants in the period from 8 AM through 4 PM on nighttime primary care visits due to asthma attack. We estimated ORs of nighttime primary care visits due to asthma attack per 10 μg/m^3 difference in 8-hour mean $PM_{2.5}$, per 10 ppb difference in 8-hour mean NO_2, and per 10 ppb difference in 8-hour mean O_3 in both a single-pollutant

model and a multipollutant model adjusted for 8-hour mean temperature.

To examine the modifying effects of age on the association between air pollutants and nighttime primary care visits due to asthma attack, the data were grouped into these patient age groups: 0 to 1 year, 2 to 5 years, 6 to 14 years, 0 to 14 years and 15 to 64 years. The aforementioned analyses were performed independently for each of these groups. Moreover, all models took into consideration the effects of seasonality and those due to unusually high and low temperatures: modified effects were examined by using a 2-level indicator variable for the warmer months (April through September) and the colder months (October through March).

The PHREG procedures of SAS release 8.2, SAS Institute, Inc, Cary, NC, USA were used to perform the conditional logistic regression. All tests were 2-tailed, and alpha was set at 0.05. We computed ORs and their 95% confidence intervals (CIs). In this study we used several test procedures; therefore, multiple testing issues arose. However, we elected not to devise a countermeasure to these multiple testing issues because we felt that it was more important to identify all possible elevated risks due to air pollutants.

RESULTS

The characteristics of the subjects are shown in Table 1. Among the 403 subjects, 308 were children aged 0 to 14 years and 95 were adolescents/adults aged 15 to 64 years. Among the 308 children, 47 were younger than 2 years, 176 were preschool children aged 2 to 5 years, and 85 were school children aged 6 to 14 years. Figure 1 shows the number of cases in each month of the study period.

Table 1. Age and sex of subjects

Age group (years)	Sex		Total
	Male	Female	
0–1	26	20	47
2–5	110	66	176
6–14	66	18	85
15–64	55	40	95
Total	257	144	403*

*Data on sex for 2 subjects were missing.

The hourly mean concentrations of air pollutants are shown in Table 2. The mean concentration of O_3 in warmer months was higher than in colder months. However, the mean concentration of NO_2 in warmer months was lower than in colder months. Table 3 shows the correlation coefficients of hourly measured concentrations for the warmer months and colder months from September 2002 through August 2003.

The effect of O_3 on primary care visits due to asthma attack among children and adolescents/adults

Figure 2 shows the association between nighttime primary care visits due to asthma attack among subgroups of children aged 0 to 14 years and adolescents/adults aged 15 to 64 years, stratified by warmer months and colder months. Among children, the ORs of nighttime primary care visits due to asthma attack per 10 ppb increment of O_3 at time lag 6–12, lag 12–18, and lag 18–24 in the single-pollutant model were 1.07 (95% confidential interval [CI], 0.99–1.15), 1.13 (95% CI, 0.99–1.29), and 1.12 (95% CI, 1.01–1.24), respectively. When using the multipollutant model, the ORs were 1.19 (95% CI, 1.06–1.34), 1.32 (95% CI, 1.08–1.60), and 1.22 (95% CI,

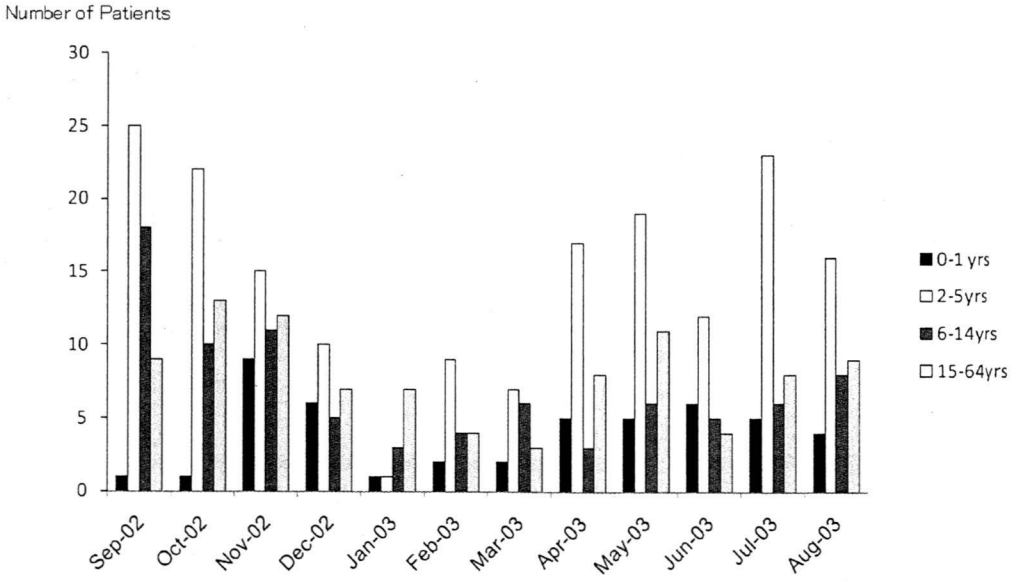


Figure 1. Number of patients who visited the Ichikawa Emergency Clinic due to asthma attack between 7 PM and 12 AM, by month, from September 1, 2002 to August 31, 2003

Table 2. Summary of hourly concentrations of air pollutants

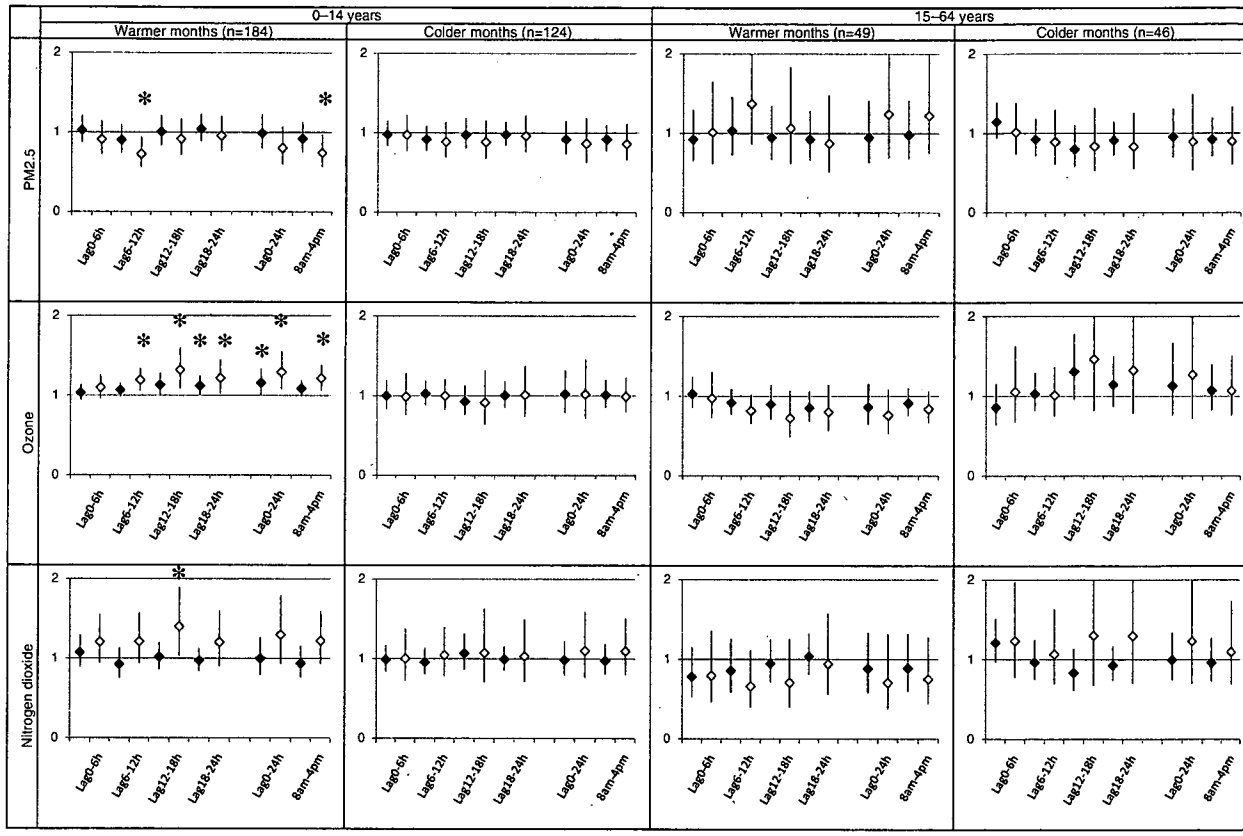
		Total hours measured	Mean	Standard deviation	Maximum
Warmer months (April through September)					
$PM_{2.5}$	$\mu g/m^3$	4159	18.6	(11.4)	221.4
NO_2	ppb	4366	16.9	(11.8)	77.0
O_3	ppb	4359	33.7	(22.9)	224.0
Colder months (October through March)					
$PM_{2.5}$	$\mu g/m^3$	4360	19.6	(15.2)	112.4
NO_2	ppb	4276	27.2	(16.4)	107.0
O_3	ppb	4257	22.5	(18.5)	113.0

$PM_{2.5}$: particulate matter with a 50% cut-off aerodynamic diameter ≤2.5 μm; NO_2: nitrogen dioxide; O_3: ozone.

Table 3. Correlation coefficients between hourly measured concentration of $PM_{2.5}$, ozone (O_3), nitrogen dioxide (NO_2), and temperature

	NO_2	O_3	Temperature
Warmer months (April through September)			
$PM_{2.5}$	0.40	0.18	0.09
NO_2		−0.44	0.03
O_3			0.08
Colder months (October through March)			
$PM_{2.5}$	0.65	−0.41	0.11
NO_2		−0.72	−0.17
O_3			0.30

$PM_{2.5}$: particulate matter with a 50% cut-off aerodynamic diameter ≤2.5 μm; NO_2: nitrogen dioxide; O_3: ozone.

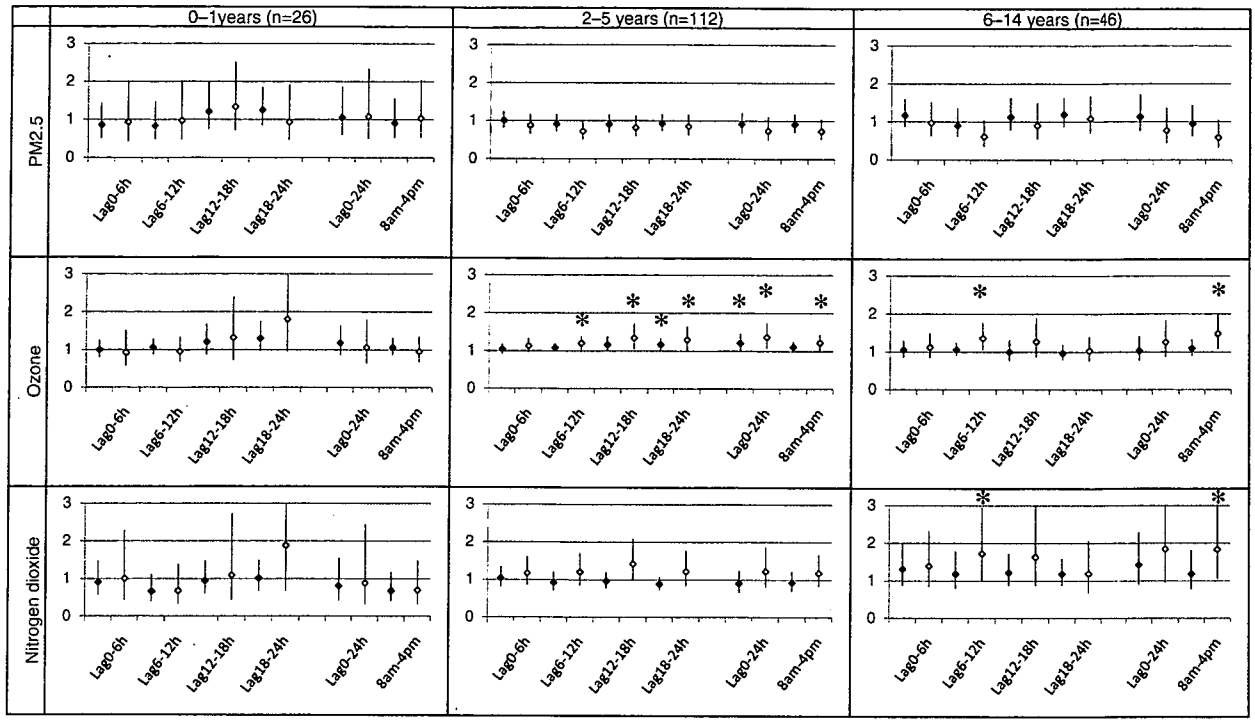


◆ Single-pollutant model ◊ Multipollutant model * $P<0.05$

Warmer months: April through September; Colder months: October through March

Figure 2. Associations between air pollutants and nighttime primary care visits due to asthma attack, by season and age. The associations are shown as odds ratios and their 95% confidence intervals per unit increment of each pollutant. The unit increments were 10 $\mu g/m^3$ for $PM_{2.5}$, 10 ppb for ozone, and 10 ppb for nitrogen dioxide

1.02–1.45), respectively. The 24-hour mean concentration of O_3 was also associated with nighttime primary care visits due to asthma attack in both the single-pollutant model (OR = 1.16; 95% CI, 1.00–1.33) and multipollutant model (OR = 1.29; 95% CI, 1.08–1.55). In addition, the daytime 8-hour mean concentration of O_3 was also associated with nighttime primary care visits due to asthma attack. The ORs in the single-pollutant model and multipollutant model were 1.09 (95% CI, 0.99–1.19) and 1.21 (95% CI, 1.07–1.38), respectively. We found no association between O_3 and nighttime primary care visits due to asthma attack in colder months.



◆ Single-pollutant model
◊ Multipollutant model
* $P<0.05$

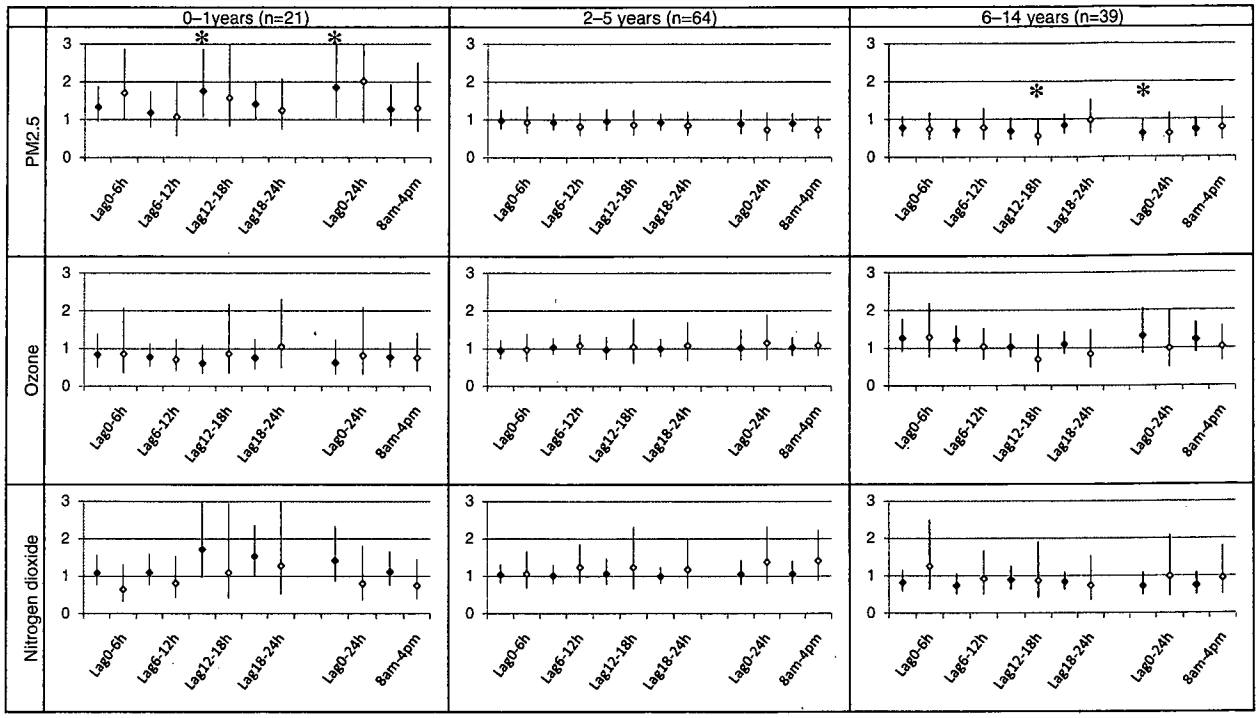
Figure 3. Associations between air pollutants and nighttime primary care visits due to asthma attack in warmer months (April through September), by age. The associations are shown as odds ratios and their 95% confidence intervals per unit increment of each pollutant. The unit increments were 10 μg/m^3 for $PM_{2.5}$, 10 ppb for ozone, and 10 ppb for nitrogen dioxide

The effect of $PM_{2.5}$/NO_2 on primary care visits due to asthma attack among children and adolescents/adults

With respect to $PM_{2.5}$, we observed an association between nighttime primary care visits due to asthma attack and $PM_{2.5}$ among children in warmer months at lag 6–12, and in daytime 8-hour mean concentration among children, but not adults. With respect to NO_2, we found an association between nighttime primary care visits due to asthma attack and NO_2 in warmer months at lag 12–18 among children, but not adults.

Association between O_3 and primary care visits due to asthma attack among children in warmer months, by age subgroup

Figure 3 shows the results of an age-stratified subgroup analysis among children in warmer months. With respect to the association between O_3 and nighttime primary care visits due to asthma attack in the 2- to 5-year-old subgroup, the ORs of nighttime primary care visits due to asthma attack at time lag 6–12, lag 12–18, and lag 18–24 in the single-pollutant model were 1.08 (95% CI, 0.97–1.20), 1.16 (95% CI, 0.98–1.37), and 1.16 (95% CI, 1.01–1.34), respectively. When using the multipollutant model, the ORs were 1.20 (95% CI, 1.03–1.39), 1.34 (95% CI, 1.05–1.71), and 1.30 (95% CI, 1.02–1.64), respectively. The 24-hour mean concentration of O_3 was also associated with nighttime primary care visits due to asthma attack. ORs were 1.20 (95% CI, 1.00–1.45) in the single-pollutant model and 1.37 (95% CI, 1.08–1.73) in the multipollutant model. In addition, daytime 8-hour mean concentration of O_3 was also associated with nighttime primary care visits due to asthma attack. The ORs in the single-pollutant model and in the multipollutant model were 1.10 (95% CI, 0.98–1.24) and 1.22 (95% CI, 1.04–1.44), respectively. Among children aged 6 to 14 years, we noted elevated ORs for nighttime primary care visits due to asthma attack at lag 6–12 and in 24-hour mean concentration of O_3, using a multipollutant model; the ORs were 1.36 (95% CI, 1.05–1.77) and 1.47 (95% CI, 1.08–2.01), respectively. No other associations were observed. For example, the ORs of nighttime primary care visits due to asthma attack for 24-hour mean concentration of O_3 using a multipollutant model among children 0 to 4 years and 6 to 14 years were 1.06 (95% CI, 0.63–1.78) and 1.27 (95% CI, 0.88–1.84), respectively.



◆ Single-pollutant model
◊ Multipollutant model
* $P<0.05$

Figure 4. Associations between air pollutants and nighttime primary care visits due to asthma attack in colder months (October through March), by age. The associations are shown as odds ratios and their 95% confidence intervals per unit increment of each pollutant. The unit increments were 10 μg/m^3 for $PM_{2.5}$, 10 ppb for ozone, and 10 ppb for nitrogen dioxide

Association between $PM_{2.5}$/NO_2 and primary care visits due to asthma attack among children in warmer months, by age subgroup

With respect to NO_2, we observed an association among children aged 6 to 14. The ORs of nighttime primary care visits due to asthma attack at time lag 6–12, and the daytime 8-hour mean concentration of NO_2 in a single-pollutant model, were 1.73 (95% CI, 1.02–2.93) and 1.83 (95% CI, 1.05–3.20), respectively. With respect to $PM_{2.5}$, we found no associations among the various age groups with decreased ORs.

Association between air pollutants and primary care visits due to asthma attack among children in colder months, by age subgroup

Figure 4 shows the results of an age-stratified subgroup analysis of children in colder months. With respect to the association between $PM_{2.5}$ and nighttime primary care visits due to asthma attack in colder months among children aged 0 to 1 years, we observed slightly higher ORs at various time lags within 1 day. For example, the ORs of nighttime primary care visits due to asthma attack for 24-hour mean concentration of $PM_{2.5}$ in single-pollutant and multipollutant models were 1.86 (95% CI, 1.06–3.27) and 2.02 (0.92–4.41), respectively. However, among children aged 6 to 14 years, we found a significant inverse association between $PM_{2.5}$ and nighttime primary care visits due to asthma attack in colder months: the ORs of nighttime primary care visits due to asthma attack at lag 12–18 using a multipollutant model, and for 24-hour mean concentration of $PM_{2.5}$ using a single-pollutant model, were 0.56 (95% CI, 0.31–1.00) and 0.62 (95% CI, 0.40–0.98), respectively.

DISCUSSION

We found an association between O_3 and nighttime primary care visits due to asthma attack among children aged 0 to 14 years—especially those aged 2 to 5 years—in warmer months. We also found an association between $PM_{2.5}$ and primary care visits among children 0 to 14 years in warmer months (resulting in decreased ORs), among children 0 to 1 years in colder months (resulting in increased ORs), and among children 6 to 14 years in colder months (resulting in decreased ORs). Moreover, we found an association between NO_2 and

primary care visits in warmer months among children 0 to 14 years (resulting in increased ORs).

O_3 and primary care visits due to asthma attack

The association we observed between O_3 and visits due to asthma attack was consistent with previous studies. A recent US Environmental Protection Agency analysis of ambient O_3 health effects concluded that children with asthma suffer acute adverse health consequences at current ambient levels of O_3.[3] Studies of these adverse outcomes have examined asthma-related hospital discharges, but have yielded some of the least consistent data. Babin et al[10] and Moore et al[14] observed an association between pediatric emergency room visits for asthma exacerbations and outdoor O_3.

In the present study, the association among preschool children aged 2 to 5 years was stronger than that among school children aged 6 to 14 years. One reason for this finding may be that the upper and lower airways of preschool children are at an early stage of development, and are thus shorter than in school children. In addition, Babin et al[10] speculated that younger children have higher alveolar ventilation relative to their body mass, as well as a higher peripheral airway resistance, which results in younger children having a greater risk of adverse ventilator effects. However, it is important to note that the association between O_3 and nighttime primary care visits due to asthma attack in infants aged 0 to 1 years could be affected by misestimation of levels of exposure to O_3. Infants might spend more time in their homes, so calculations of exposure levels based on concentrations of outdoor air pollutants would be less accurate than those for preschool children/students, who spend a larger amount of time outside. Moreover, respiratory diseases other than asthma might be misclassified in infants because of the difficulty in diagnosing the respiratory symptoms of asthma in this age group. Therefore, an association between O_3 and nighttime primary care visits due to asthma attack might be more likely to be observed among preschool children aged 2 to 5 years in warmer months.

Why was the strong association between O_3 and primary care visits found only during the warmer months? First, as mentioned above, in colder months, misestimation of exposures to air pollutants might be larger because we were unable to measure the effects of indoor space heaters on the concentrations of air pollutants. Second, people spend more time outdoors and windows are left open longer during warmer months, so indoor concentrations are closer to those found outdoors. Third, the mean concentration of O_3 in warmer months was 1.5 times higher than that in colder months.

Some associations that were found in the multipollutant model were not observed in the single-pollutant model. For example, the increased ORs for higher O_3 were found at lag 6–12 among subjects aged 6 to 14 years in warmer months. Higher ORs for increased NO_2 were also found at lag 6–12 among subjects aged 6 to 14 years in warmer months. However, the reasons for these findings remain unclear. O_3 is formed by the action of short wavelength solar radiation on NO_2. We observed an inverse relation between O_3 and NO_2: the correlation coefficient was −0.44 in warmer months (Table 3).

$PM_{2.5}$ and primary care visits due to asthma attack

The associations between air pollutants other than $PM_{2.5}$ and primary care visits were not consistent. That is, the ORs among infants aged 0 to 1 years were increased, but the ORs among preschool children aged 2 to 5 years and school children aged 6 to 14 years were decreased. We believe that the association between $PM_{2.5}$ and nighttime primary care visits due to asthma attack in subjects aged 0 to 1 years may be a chance result for 3 reasons. First, the sample size of this group was small ($n = 21$). Second, subjects with respiratory diseases other than asthma might have been included in this age group, because it is difficult to diagnose the respiratory symptoms of asthma in infants. Third, in colder months, misestimation of exposure to $PM_{2.5}$ might be larger because we were unable to measure the effect of indoor space heaters on the concentrations of air pollutants. As mentioned above, infants would spend more time in their homes than preschool children or older students. However we cannot explain why the ORs among preschool children and school children were decreased.

Although other studies have shown significant associations between particulates and visits due to asthma-related symptoms,[15–17] Fusco et al[18] and Babin et al[10] found no significant association between pediatric emergency room visits due to asthma-related symptoms and particulates. These contradictory results may be due to different particulate size distributions and concentrations at different locations, different types of pollution sources at those locations, and different periods of investigation. Several epidemiologic studies have shown that the oxidant properties of ambient air contribute to adverse health outcomes. Romieu et al[19] studied the effects of sulfur dioxide, PM_{10}, NO_2, and O_3 on asthmatics in Mexico City and noted that O_3 was most closely associated with decrements in lung function in children.

Time lag

In this study, we assessed nighttime primary care visits due to asthma attack with respect to elevated 6-hour mean concentration of air pollution at various lag times. O_3 is a powerful oxidant, and it reacts with a wide range of cellular components and biological materials. Both experimental and epidemiologic studies have shown short-term reversible deficits in lung function resulting from O_3. These deficits persist for a period ranging from hours to days. However, there would be various time lags between elevated concentrations of air pollutants and asthma exacerbations, and there would also be various time lags between asthma

exacerbations and the time of nighttime primary care visits due to asthma attack. We found no association between nighttime primary care visits due to asthma attack and air pollution at lag 0–6. Therefore, we speculate that although the adverse health effects of O_3 might appear immediately, presentation for medical evaluation might occur somewhat later.

Limitations

The results of this study should be evaluated with caution for 4 reasons. First, the significance of the association between air pollution and nighttime primary care visits due to asthma attack is diminished because primary care visits due to asthma attack are only a surrogate measurement for asthma exacerbations. There would be various time lags between elevated concentrations of an air pollutant and asthma exacerbations, and there would also be various time lags between asthma exacerbations and the time of a primary care visit. These variations in time lags would affect statistical associations between air pollutants and nighttime primary care visits due to asthma attack. Second, we were unable to measure the effect of indoor space heaters on the concentrations of air pollutants. In Japan, indoor space heaters are commonly used in winter, especially in the period from December through February. Therefore, we believe that the effect of indoor space heaters on the association between the concentration of O_3 and nighttime primary care visits due to asthma attack in warmer months was small. Third, ambient concentrations of air pollutants might act as surrogate measures of exposure to other agents or to specific pollution sources that are in fact responsible for the observed association between O_3 and nighttime primary care visits due to asthma attack. Moreover, although we describe our results as O_3-related effects, O_3 is likely to be the best representative of the pollutants available for analysis of the gaseous oxidant species produced by complex photochemistry. Fourth, selection of subjects for this study may have been subject to problems of external validity because we restricted the subjects to nighttime patients.

Conclusion

We found an association between O_3 and nighttime primary care visits due to asthma attack among pediatric patients—especially among preschool children aged 2 to 5 years—in warmer months. This study provides additional support for the present regulatory position, which maintains that regional air quality needs to be modified in consideration of the high sensitivity of children to air pollution.

ACKNOWLEDGEMENT

This study was funded by the Japanese Ministry of the Environment. The authors declare that they have no competing financial interest.

REFERENCES

1. U.S. EPA. Air Quality Criteria for Particulate Matter. U.S. Environmental Protection Agency, Research Triangle Park, NC. 2004. Available from http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=87903 [accessed 5 February 2009].
2. WHO. Air quality guidelines, Global update 2005, Particulate matter, ozone, nitrogen dioxide and sulfur dioxide. WHO Press, Geneva, Switzerland. 2005. Available from http://www.euro.who.int/Document/E90038.pdf [accessed 5 February 2009].
3. U.S. EPA. Air Quality Criteria for Ozone and Related Photochemical Oxidant. US Environmental Protection Agency, Research Triangle Park, NC. 2006. Available from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923 [accessed 5 February 2009].
4. Pope CA 3rd, Dockery DW. Acute health effects of PM10 pollution on symptomatic and asymptomatic children. Am Rev Respir Dis. 1992;145:1123–8.
5. Romieu I, Meneses F, Ruiz S, Sienra JJ, Huerta J, White MC, et al. Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am J Respir Crit Care Med. 1996;154:300–7.
6. Peters A, Dockery DW, Heinrich J, Wichmann HE. Medication use modifies the health effects of particulate sulfate air pollution in children with asthma. Environ Health Perspect. 1997;105:430–5.
7. Gielen MH, van der Zee SC, van Wijnen JH, van Steen CJ, Brunekreef B. Acute effects of summer air pollution on respiratory health of asthmatic children. Am J Respir Crit Care Med. 1997;155:2105–8.
8. Delfino RJ, Zeiger RS, Seltzer JM, Street DH. Symptoms in pediatric asthmatics and air pollution: differences in effects by symptom severity, anti-inflammatory medication use and particulate averaging time. Environ Health Perspect. 1998;106:751–61.
9. Mortimer KM, Tager IB, Dockery DW, Neas LM, Redline S. The effect of ozone on inner-city children with asthma: identification of susceptible subgroups. Am J Respir Crit Care Med. 2000;162:1838–45.
10. Babin SM, Burkom HS, Holtry RS, Tabernero NR, Stokes LD, Davies-Cole JO, et al. Pediatric patient asthma-related emergency department visits and admissions in Washington, DC, from 2001–2004, and associations with air quality, socio-economic status and age group. Environ Health. 2007;6:9.
11. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol. 1991;133:144–53.
12. Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology. 2001;12:186–92.
13. Schwartz J. The effects of particulate air pollution on daily deaths: a multi-city case crossover analysis. Occup Environ Med. 2004;61:956–61.
14. Moore K, Neugebauer R, Lurmann F, Hall J, Brajer V, Alcorn S, et al. Ambient ozone concentrations cause increased hospitalizations for asthma in children: an 18-year study in Southern California. Environ Health Perspect. 2008;116:1063–70.
15. Norris G. YoungPong SN, Koenig JQ, Larson TV, Sheppard L,

Stout JW. An association between fine particles and asthma emergency department visits for children in Seattle. Environ Health Perspect. 1999;107:489–93.
16. Atkinson RW, Anderson HR, Strachan DP, Bland JM, Bremner SA, Ponce de Leon A. Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur Respir J. 1999;13:257–65.
17. Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, et al. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. Am J Respir Crit Care Med. 2001;164:1860–6.
18. Fusco D, Forastiere F, Michelozzi P, Spadea T, Ostro B, Arcà M, et al. Air pollution and hospital admissions for respiratory conditions in Rome, Italy. Eur Respir J. 2001;17:1143–50.
19. Romieu I, Sienra-Monge JJ, Ramírez-Aguilar M, Téllez-Rojo MM, Moreno-Macías H, Reyes-Ruiz NI, et al. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. Am J Respir Crit Care Med. 2002;166:703–9.

Asian Journal of Atmospheric Environment
Vol. 3-1, pp.9-18, June 2009

An Ecological Study of Lung Cancer Mortality and Severe Air Pollution in the 1960s in an Industrial City in Japan

Masayuki Shima* and Yoshiko Yoda

Department of Public Health, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan

*Corresponding author. Tel: +81-798-45-6565, E-mail: shima-m@hyo-med.ac.jp

ABSTRACT

This study aimed at assessing the association between exposure to severe air pollution in the past and the subsequent transition in lung cancer mortality among persons who lived in an industrial city. Vital statistics from 1983 to 2006 and the data on air pollution measurements from 1960 to 1990 in Amagasaki City, Japan, were used. Pearson correlation coefficients were calculated between the standardized mortality ratios (SMRs) for lung cancer and the air pollution levels in 6 wards of Amagasaki City. The associations between changes in air pollution levels and the annual SMRs were also evaluated in the light of a potential latency period. The levels of air pollution were extremely high in the 1960s, and they decreased since 1970. The SMRs for lung cancer in 1989-1993 among females for 6 wards were significantly associated with the amounts of both sulfur oxides and dust fall in the past for each ward. The positive associations were observed between the annual SMRs among females and the amounts of both pollutants when the lag time of 20-30 years was taken into account. These results suggest that severe air pollution in the 1960s in an industrial city affected the subsequent increase in lung cancer mortality.

Key words: Air pollution, Sulfur oxides, Dust fall, Lung cancer, Standardized mortality ratio

1. INTRODUCTION

In Japan, lung cancer mortality has been consistently increasing since the 1950s (Marugame and Sobue, 2004). Numerous epidemiological studies have consistently reported smoking as a major risk factor for lung cancer (Marugame *et al.*, 2005; Doll *et al.*, 1994; Stevens and Moolgavkar, 1984). On the other hand, varius ecological studies reported that lung cancer mortality was higher in urban districts than in rural districts (Nawrot *et al.*, 2007; Iwai *et al.*, 2005; Archer, 1990; Buffler *et al.*, 1988; Shimizu *et al.*, 1979; Henderson *et al.*, 1975), and adverse effects of air pollution on lung cancer have been suggested (Cohen and Pope, 1995).

Recently, a prospective cohort study by the American Cancer Society (Pope *et al.*, 2002) reported that high concentrations of air pollutants were significantly associated with the increase in lung cancer mortality. However, European epidemiological studies have not shown a clear association between air pollution and lung cancer (Vineis *et al.*, 2006; Filleul *et al.*, 2005; Hoek *et al.*, 2002; Barbone *et al.*, 1995). Thus, the available epidemiologic evidence is discordant, and the effect of air pollution on lung cancer is not conclusive (Gallus *et al.*, 2008).

It is generally agreed that the latency period from exposure to smoking to occurrence of lung cancer is about 20-30 years (Thun *et al.*, 1997; Doll *et al.*, 1994). In many industrial cities in Japan and in Western countries, the levels of air pollutants were considerably higher in the past several decades (Committee on Japan's Experience in the Battle against Air Pollution; Chairman: Sawa, 1997). If the period from exposure to air pollution to occurrence of lung cancer is similar to the period for smoking, we should consider the possibility that the incidence of lung cancer may increase even if the levels of air pollution have decreased. However, most of the previous epidemiological studies have only compared lung cancer mortality in relation to different levels of air pollution (Gallus *et al.*, 2008; Cohen and Pope, 1995). Few studies have evaluated the long-term transition in lung cancer mortalities in relation to the change in air pollution levels (Filleul *et al.*, 2005; Stevens and Moolgavkar, 1984).

Amagasaki is an industrial city located in Western Japan. The levels of air pollutants, such as sulfur oxides and dust fall, in the city were extremely high from the later 1950s to the 1960s. Thereafter, various pollution control measures were taken in the 1970s, and the levels of both pollutants decreased considerably (Committee on Japan's Experience in the Battle against Air Pollution; Chairman: Sawa, 1997). In the present study,

the data on air pollution measurements and vital statistics of Amagasaki City were used to evaluate the associations between changes in air pollution levels for several decades and the subsequent transition in lung cancer mortality.

2. METHODS

Amagasaki City was chosen to evaluate the effects of air pollution in the past on the transition in lung cancer mortality, because the levels of air pollution have changed dramatically during the past several decades. The city is located in the center of Hanshin industrial zone in Western Japan and faces Osaka Bay. Its population is about 460,000 (2008), and its area is about 49.8 square kilometers. The city is divided municipally into 6 wards (Fig. 1). In the southern coastal district (A, B, and C Wards), many factories, such as steel mills, power plants, and oil refinery plants, were located, and the levels of air pollutants exhausted from the factories used to be extremely high. On the other hand, the northern district (D, E, and F Wards) was a residential zone, although there were a few small-scale factories.

The amounts of sulfur oxides were monitored using the lead dioxide (PbO_2) method at various stations in the city from 1960 through 1992 (Department of Environment, 1961-1993). The average amounts of sulfur oxides measured at 3-9 stations for each ward were calculated by year. In addition, the concentrations of sulfur dioxide have been continuously monitored using the electrical conductivity method at ambient air monitoring stations in 4 wards since 1969. The average amounts of sulfur oxides (1960-1969) by the PbO_2 method in 4 wards strongly correlated with the concentrations of sulfur dioxides by the electrical conductivity method (1969-1973) in the corresponding wards (R^2=0.989). The amounts of dust fall have been measured using the deposit gauge method at 1-5 stations in each ward since 1959 (Department of Environment, 1961-1993). The annual average amounts of dust fall for each ward were calculated in the same manner as for sulfur oxides. However, the amounts of dust fall for every ward were measured only until 1962.

The vital statistics of Amagasaki City for the 24-year period from 1983 to 2006 (Health and Welfare Bureau, 1985-2008), which were officially published by the municipal office, were used to observe lung cancer mortality [the International Classification of Diseases, ninth revision (ICD-9): 162 in 1983-1994; ICD-10: C33-C34 in 1995-2006]. The population and the number of deaths from lung cancer by ward and year were calculated using the officially published

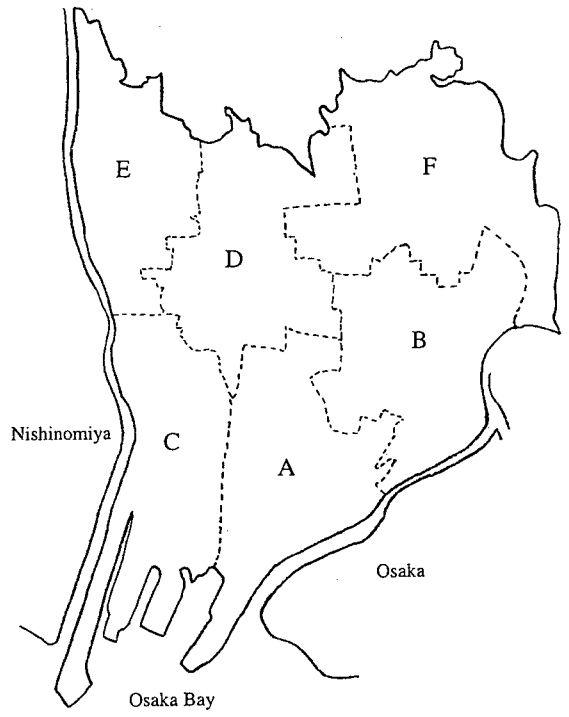


Fig. 1. Locations of the six wards in Amagasaki City, Japan.

data, except for 1999, when the number of deaths by ward was not published. The standardized mortality ratio (SMR) was used to estimate lung cancer mortality by ward and year. Expected deaths in each year and ward were calculated using a sex- and 5-year age-specific population and the corresponding national mortality for lung cancer in each year. The SMRs for each ward were calculated for four periods (1983-1988, 1989-1993, 1994-1998, and 2000-2006), because the number of annual deaths for lung cancer is small (average: 24.6 in males, 9.3 in females). Pearson correlation coefficients were obtained to evaluate the association between the SMRs for lung cancer in each period and the amounts of sulfur oxides and dust fall in the 1960s, when the levels of air pollution were extremely high.

In addition, to evaluate the transition in lung cancer mortality for several decades, the annual SMRs were calculated from 3-year moving averages of observed and expected deaths for the whole city, the northern district, and the southern district. To assess the potential of a latency period from the time of exposure to air pollution to the occurrence of lung cancer, a lag time of 15-30 years was considered, and Pearson correlation coefficients between the annual SMRs and the annual average amounts of sulfur oxides and dust fall in the past were calculated.

All statistical analyses were performed using SPSS

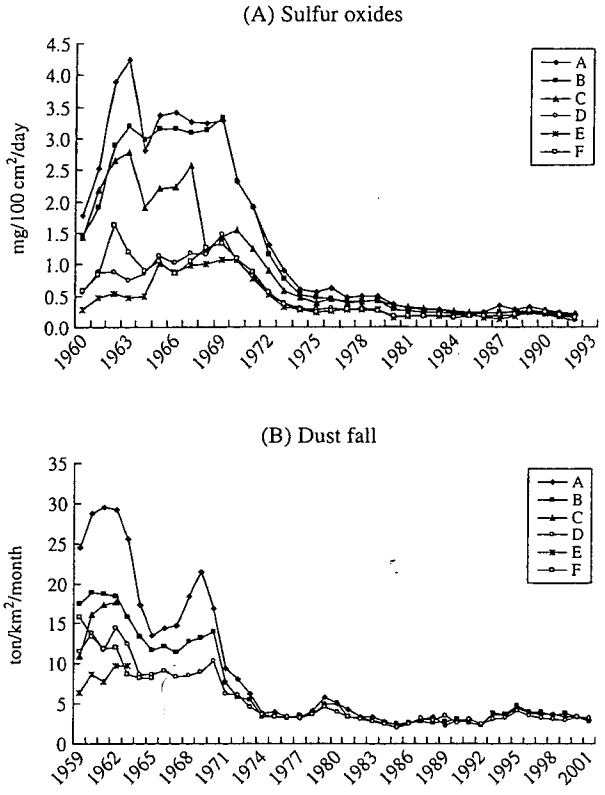


Fig. 2. Annual averages of the amounts of sulfur oxides (A) and dust fall (B) in the six wards in Amagasaki City.

15.0 software (SPSS Inc., Chicago, IL, USA).

3. RESULTS

The annual average amounts of sulfur oxides and dust fall in Amagasaki City are shown in Fig. 2. The amounts of sulfur oxides were high in the 1960s in all wards, particularly in A, B, and C Wards. The amounts began to decrease in all wards in about 1970, and no difference among the wards has been observed since 1980. The amounts of dust fall were also high in the 1960s, but they decreased markedly since 1970. Although the amounts of dust fall were highest in A Ward through the 1960s, the difference among the wards was smaller than that for the sulfur oxides.

The crude mortality rates for lung cancer in Amagasaki City are shown in Fig. 3 with nationwide data. The 3-year moving averages of the crude mortality rates are shown for Amagasaki City. The mortality rates for lung cancer in Japan have consistently increased among both males and females. The rates in Amagasaki City are similar to those in Japan, and they are higher among both males and females than those in

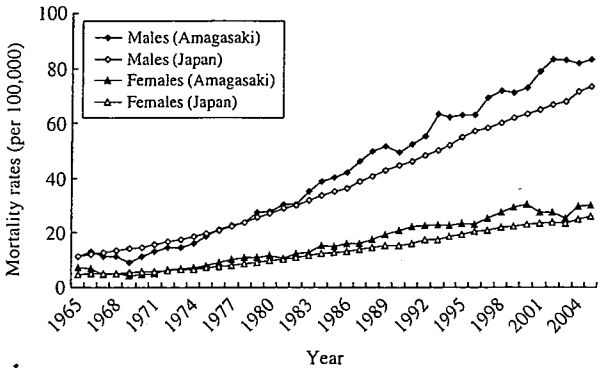


Fig. 3. Time trend of crude mortality rates due to lung cancer in Amagasaki City and Japan. The 3-year moving averages of crude mortality rates are shown for Amagasaki City.

Japan since 1980.

Table 1 shows the observed numbers of deaths, SMRs, and their 95% confidence intervals (CIs) for lung cancer in Amagasaki City, by sex, ward, and period. The SMRs for the whole city were significantly higher among both males and females for all periods. For each ward, the SMRs were higher than 1, except for those among females in E Ward in 2000-2006, and most of them were significant among males. The SMRs among females in 1989-1993 were considerably higher for A and B Wards (1.69 [95%CI: 1.23-2.15] and 1.76 [95%CI: 1.32-2.19] respectively).

Fig. 4 shows the correlations between the SMRs for lung cancer and the amounts of sulfur oxides and dust fall for each ward in the 1960s, when the levels of air pollution were extremely high. The amounts of dust fall were used for 1959-1962, because the amounts for every ward were obtained only during those years. Among females in 1989-1993, the correlation coefficients of the SMRs with the amounts of sulfur oxides (0.929) and dust fall (0.850) were statistically significant (Table 2). However, the SMRs in the other periods were not correlated with the amounts of either sulfur oxides or dust fall. Among males, no correlations were observed between the SMRs and the amounts of air pollutants in any periods.

The transitions in the annual SMRs for lung cancer, which were calculated from 3-year moving averages of observed and expected deaths, are shown in Fig. 5. Among males, the SMRs ranged from 1.19 to 1.52, and from 1.14 to 1.52 for the southern and northern districts, respectively. The SMRs varied in cycles of several years in both districts. Among females, they ranged from 1.18 to 1.82, and from 1.04 to 1.37 for the southern and northern districts, respectively. For most of the years, the SMRs were higher in the southern district than in the northern district. In parti-

Table 1. Observed numbers of deaths and standardized mortality ratios (SMRs) for lung cancer in Amagasaki City.

District	1983-1988		1989-1993		1994-1998		2000-2006	
	Observed deaths	SMR (95%CI)	Observed deaths	SMR (95%CI)	Observed deaths	SMR (95%CI)	Observed deaths	SMR (95%CI)
Males								
A	108	1.33 (1.08-1.58)	104	1.29 (1.04-1.54)	124	1.38 (1.14-1.62)	186	1.34 (1.14-1.53)
B	137	1.45 (1.20-1.69)	118	1.22 (1.00-1.44)	154	1.35 (1.14-1.57)	237	1.29 (1.13-1.46)
C	109	1.40 (1.14-1.67)	100	1.22 (0.98-1.46)	111	1.16 (0.94-1.37)	213	1.42 (1.23-1.61)
D	111	1.02 (0.83-1.21)	147	1.27 (1.07-1.48)	171	1.23 (1.04-1.41)	278	1.20 (1.06-1.34)
E	67	1.30 (0.99-1.62)	83	1.39 (1.09-1.69)	109	1.44 (1.17-1.71)	175	1.28 (1.09-1.47)
F	106	1.48 (1.20-1.76)	104	1.32 (1.07-1.58)	131	1.34 (1.11-1.57)	203	1.20 (1.04-1.37)
Northern district	284	1.23 (1.08-1.37)	334	1.32 (1.18-1.46)	411	1.31 (1.19-1.44)	656	1.22 (1.13-1.32)
Southern district	354	1.40 (1.25-1.54)	322	1.24 (1.11-1.38)	389	1.30 (1.17-1.43)	636	1.35 (1.24-1.45)
Total	638	1.31 (1.21-1.42)	656	1.28 (1.18-1.38)	800	1.31 (1.21-1.40)	1292	1.28 (1.21-1.35)
Females								
A	39	1.27 (0.87-1.67)	51	1.69 (1.23-2.15)	42	1.24 (0.86-1.61)	60	1.15 (0.86-1.44)
B	48	1.36 (0.97-1.74)	63	1.76 (1.32-2.19)	56	1.31 (0.96-1.65)	103	1.46 (1.18-1.75)
C	44	1.59 (1.12-2.06)	39	1.37 (0.94-1.80)	49	1.46 (1.05-1.86)	82	1.51 (1.18-1.84)
D	49	1.27 (0.91-1.62)	51	1.24 (0.90-1.58)	53	1.06 (0.77-1.34)	102	1.19 (0.96-1.42)
E	25	1.31 (0.80-1.82)	22	1.01 (0.59-1.43)	37	1.30 (0.88-1.72)	45	0.88 (0.63-1.14)
F	36	1.37 (0.92-1.81)	39	1.34 (0.92-1.76)	55	1.52 (1.12-1.92)	82	1.33 (1.04-1.62)
Northern district	110	1.31 (1.06-1.55)	112	1.22 (0.99-1.44)	145	1.26 (1.06-1.47)	229	1.16 (1.01-1.30)
Southern district	131	1.40 (1.16-1.64)	153	1.62 (1.36-1.87)	147	1.33 (1.12-1.55)	245	1.38 (1.21-1.56)
Total	241	1.36 (1.18-1.53)	265	1.42 (1.25-1.59)	292	1.30 (1.15-1.44)	474	1.26 (1.15-1.38)

cular, the values in the southern district were markedly higher in 1989-1995.

The lag time of 15-30 years was considered as the potential latency period from the time of exposure to air pollution to the occurrence of lung cancer. Pearson correlation coefficients between the annual SMRs and the annual average amounts of sulfur oxides (Table 3) and dust fall (Table 4) were calculated. Among males, the SMRs in the whole city were not associated with the amounts of either sulfur oxides or dust fall after considering the lag time of 15-30 years. Among males in the northern district, the SMRs were positively associated with the amounts of dust fall for 24- to 26-year lags. Among females, the SMRs in the whole city were positively associated with the amounts of sulfur oxides for 21- to 30-year lags and dust fall for 20- to 23-year and 28- to 30-year lags. In both the southern and northern districts, most of the associations between the SMRs and the amounts of air pollutants were positive after considering a lag time of 15-30 years, and some of them were statistically significant.

4. DISCUSSION

The present study showed that lung cancer mortality increased since 1980 in Amagasaki City, in which the air pollution levels were extremely high from the later 1950s to the 1960s. After considering the lag time of 20-30 years from the time of exposure to air pollution to the occurrence of lung cancer, positive associations were observed between the annual SMRs for lung cancer among females and the amounts of both sulfur oxides and dust fall, especially in the southern district of the city where the levels of air pollution were markedly higher.

Some epidemiological studies have suggested an association between lung cancer and air pollution (Nafstad *et al.*, 2003; Nyberg *et al.*, 2000; Jedrychowski *et al.*, 1990; Shimizu *et al.*, 1979). In the ACS study (Pope *et al.*, 2002), long-term exposure to fine particulate air pollution was reported to be a risk factor for lung cancer, after adjustment for confounding factors including smoking. Other cohort studies observed a slightly increased mortality for lung cancer in communities with high levels of air pollution (Naess *et al.*, 2007; Laden *et al.*, 2006; Pope *et al.*, 2002; Dockery *et al.*, 1993), although most of them were not statistically significant. European epidemiological studies have not shown a clear association between lung cancer and air pollution (Vineis *et al.*, 2006; Filleul *et al.*, 2005; Hoek *et al.*, 2002; Barbone *et al.*, 1995), but there have been uncertainties about latency from the time of exposure to occurrence (Gallus *et al.*, 2008).

Smoking has been confirmed to be the greatest risk factor for lung cancer (Marugame *et al.*, 2005; Doll *et al.*, 1994; Stevens and Moolgavkar, 1984). The latency period from exposure to smoking to occurrence of lung

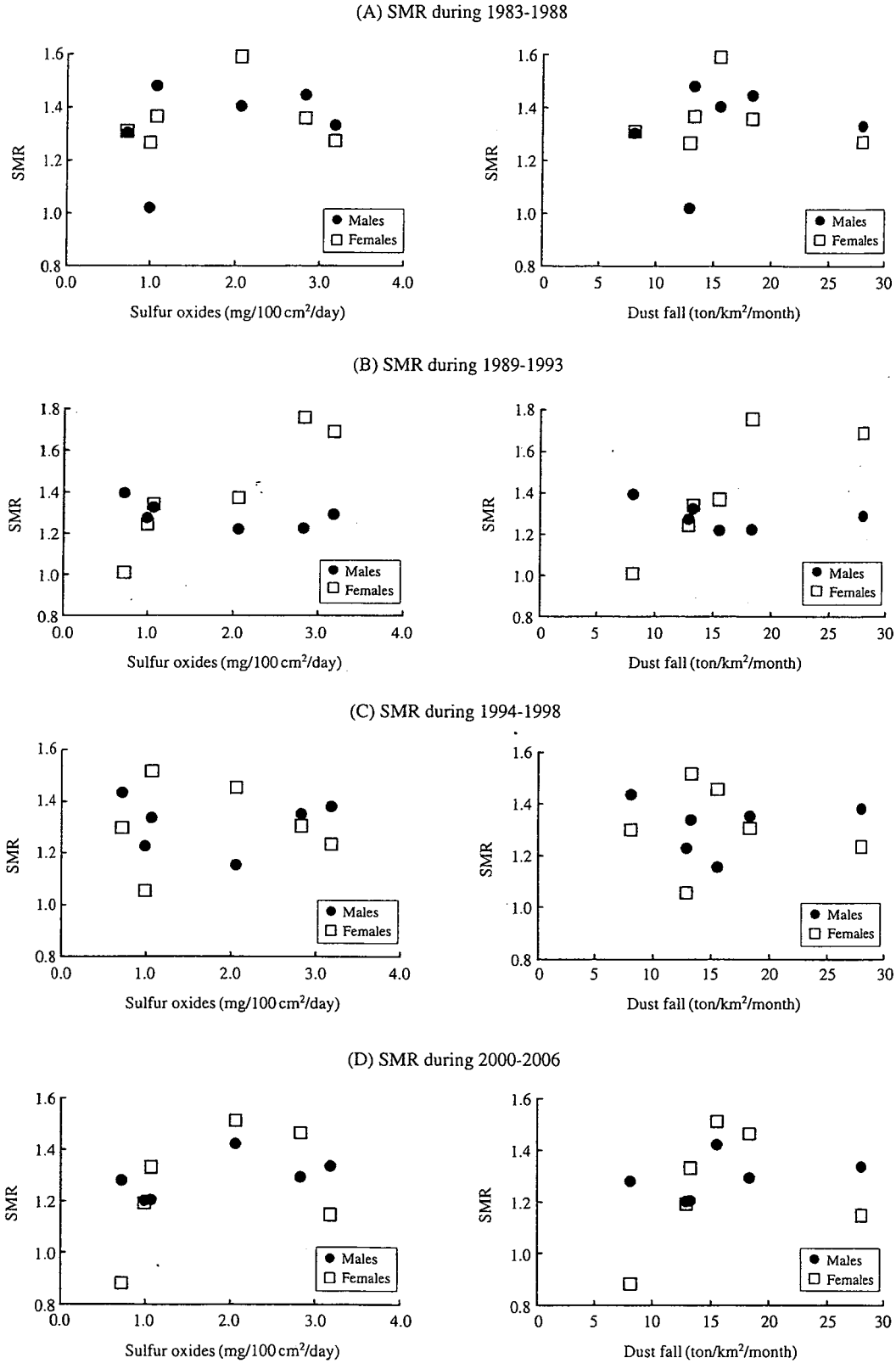


Fig. 4. Correlation between standardized mortality ratios (SMRs) for lung cancer and air pollution. The SMRs for lung cancer and the amounts of sulfur oxides (1960-1969) or dust fall (1959-1962) are shown.

Table 2. Correlation coefficient between standardized mortality ratios (SMRs) for lung cancer and air pollution in the past.

Period	Correlation coefficients with sulfur oxides		Correlation coefficients with dust fall amounts	
	r	p	r	p
Males				
1983-1988	0.364	0.478	0.184	0.727
1989-1993	−0.617	0.192	−0.442	0.381
1994-1998	0.022	0.967	0.062	0.907
2000-2006	0.568	0.239	0.384	0.452
Females				
1983-1988	0.089	0.867	−0.134	0.800
1989-1993	0.929	0.007	0.850	0.032
1994-1998	−0.003	0.995	−0.120	0.821
2000-2006	0.442	0.380	0.255	0.626

Correlation coefficient of the SMRs for lung cancer by sex, ward, and period with the amounts of sulfur oxides (1960-1969) or dust fall (1959-1962) are shown.

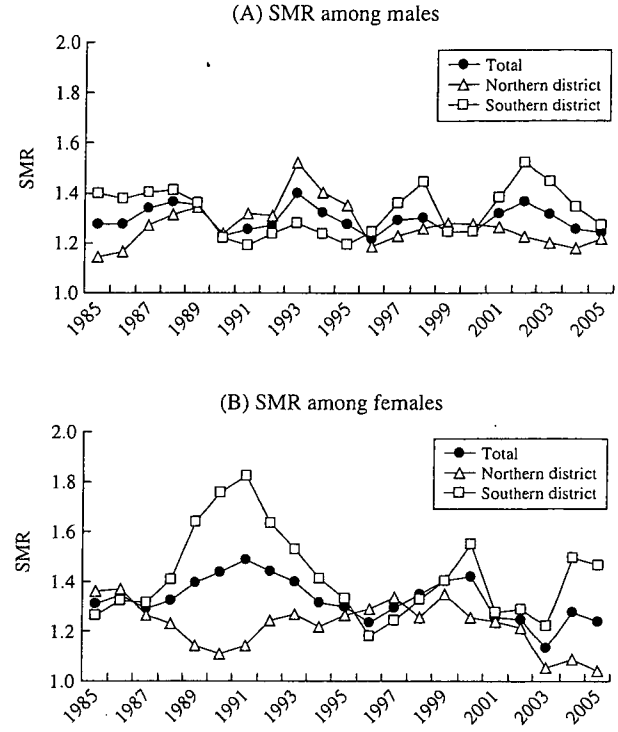


Fig. 5. Time trend of standardized mortality ratios (SMRs) (3-year moving averages) for lung cancer.

cancer is considered to be several decades (Doll *et al.*, 1994; Stevens and Moolgavkar, 1984). Therefore, we should consider a similar latency period to estimate the association between air pollution and lung cancer. However, most previous epidemiological studies have compared lung cancer mortality among areas with different levels of air pollution. Only a few studies have reported the transition in lung cancer mortality in a certain area in relation to the change in air pollution levels (Parodi *et al.*, 2005; Archer, 1990; Stevens and Moolgavkar, 1984). Archer (1990) reported that lung cancer mortality increased within about 15 years after an increase in air pollution by a steel mill, and the increase in lung cancer mortality has persisted. In another study, Stevens and Moolgavkar (1984) found that lung cancer incidence among nonsmoking males in England and Wales was coincident with substantial declines in levels of sulfur dioxide and particulate matter.

In the present study, the data on past air pollution measurements and vital statistics in a Japanese industrial city were used to estimate the transition in lung cancer mortality in relation to changes in air pollution levels. The concentrations of air pollutants in the city were very high in the 1960s, especially in the southern district of the city, and the concentrations decreased markedly since 1970. The SMRs among females were higher in the southern district than in the northern district, and the peak was observed in 1989-1995. The SMRs were significantly associated with the amounts of sulfur oxides and dust fall for 20- to 30-year lags. In addition, the SMRs in 1989-1993 among females for 6 wards were positively correlated with the amounts of sulfur oxides and dust fall in the past. These findings suggest the possibility that air pollution in the past affects the subsequent increase of lung cancer mortality among females. However, this study includes some major limitations that should be considered.

First, this study was an ecological study that was not conducted as a cohort study (Cohen and Pope, 1995; Greenland and Robins, 1994). We could not identify the population in the past when the level of air pollution was high, and there should have been considerable migration. However, the SMR of mesothelioma has been reported to be still high in the district where an asbestos cement factory had been located in the same city several decades ago (Kurumatani and Kumagai, 2008). Therefore, many of the current population are considered to have lived in the city for a long period.

Second, accurate information on the smoking habits of the subjects was not available (Katsouyanni *et al.*, 1991; Jedrychowski *et al.*, 1990; Vena, 1982). In the survey conducted by the municipal office in 2002 (Health and Welfare Bureau, 2003), the prevalence of current smokers was 43.2% for males and 10.5% for females, almost equal to the results of the national survey in 2002 (Ministry of Health, 2004) (43.4% and 10.2%, respectively). In the survey that had been conducted in this area in 1965-1966 (Hitosugi, 1968), the prevalence of smokers was reported to be 86.8% for

Table 3. Correlation coefficients between standardized mortality ratios (SMRs) for lung cancer and the amounts of sulfur oxides.

Lag years	Total			Northern district			Southern district		
	r	p	N	r	p	N	r	p	N
Males									
15	0.037	0.869	22	−0.305	0.168	22	0.254	0.254	22
16	0.004	0.987	22	−0.342	0.120	22	0.285	0.198	22
17	0.061	0.789	22	−0.273	0.218	22	0.313	0.156	22
18	0.193	0.389	22	−0.199	0.375	22	0.343	0.118	22
19	0.257	0.248	22	−0.090	0.690	22	0.294	0.184	22
20	0.159	0.481	22	−0.072	0.749	22	0.127	0.573	22
21	0.087	0.701	22	0.029	0.898	22	0.000	0.999	22
22	0.073	0.746	22	0.003	0.990	22	−0.032	0.888	22
23	0.184	0.413	22	0.124	0.583	22	−0.021	0.927	22
24	0.224	0.317	22	0.085	0.707	22	−0.050	0.824	22
25	0.259	0.257	21	0.200	0.384	21	−0.130	0.573	21
26	0.187	0.429	20	0.259	0.271	20	−0.229	0.331	20
27	0.146	0.550	19	0.412	0.080	19	−0.277	0.250	19
28	0.020	0.936	18	0.410	0.091	18	−0.309	0.212	18
29	−0.078	0.766	17	0.464	0.061	17	−0.425	0.089	17
30	−0.083	0.759	16	0.470	0.066	16	−0.543	0.030	16
Females									
15	0.212	0.343	22	0.490	0.021	22	−0.142	0.530	22
16	0.163	0.469	22	0.508	0.016	22	−0.190	0.396	22
17	0.174	0.439	22	0.474	0.026	22	−0.179	0.426	22
18	0.192	0.393	22	0.364	0.096	22	−0.061	0.788	22
19	0.283	0.202	22	0.253	0.257	22	0.127	0.574	22
20	0.375	0.086	22	0.131	0.561	22	0.371	0.089	22
21	0.513	0.015	22	0.088	0.698	22	0.511	0.015	22
22	0.551	0.008	22	0.096	0.672	22	0.474	0.026	22
23	0.537	0.010	22	0.147	0.514	22	0.358	0.102	22
24	0.491	0.020	22	0.123	0.586	22	0.235	0.292	22
25	0.459	0.036	21	0.137	0.554	21	0.147	0.525	21
26	0.474	0.035	20	0.220	0.352	20	0.147	0.537	20
27	0.516	0.024	19	0.409	0.082	19	0.233	0.336	19
28	0.583	0.011	18	0.589	0.010	18	0.372	0.129	18
29	0.573	0.016	17	0.747	0.001	17	0.490	0.046	17
30	0.509	0.044	16	0.922	0.000	16	0.520	0.039	16

The SMRs for lung cancer and the amounts of sulfur oxides are shown by lag years.

males and 19.5% for females. The prevalence was also similar to the contemporary national survey. In addition, we could obtain information on neither exposure to environmental tobacco smoke (Hirayama, 1981) nor occupational exposure to pollutants (Jedrychowski *et al.*, 1990; Vena, 1982). Since there had been many factories in the city, many persons might have been exposed to various pollutants, such as dust or asbestos, which are risk factors for lung cancer (Committee on Japan's Experience in the Battle against Air Pollution; Chairman: Sawa, 1997; Hitosugi, 1968). In the present study, the association between air pollution and lung cancer was significant only among females. The prevalence of smokers and occupational exposure to dust should be higher among males than among females, and lung cancer mortality among males is more than twice that among females. Therefore, we might not be able to detect any effects of air pollution on lung cancer mortality among males. This finding is consistent with the result of a previous study showing that the association between the level of air pollution and lung cancer mortality was larger among females than among males (Naess *et al.*, 2007; Shimizu *et al.*, 1979). In the previous studies, females were reported to have a greater risk associated with air pollution compared to males (Annesi-Maesano *et al.*, 2003).

Third, the levels of air pollution in the past were evaluated using the amounts of sulfur oxides and dust fall. Although these amounts had been measured intermittently at various points in the city, they were strongly correlated with the concentrations of pollutants that were monitored continuously later. In recent years, the effects of fine particles, including diesel exhaust particles, on the incidence of lung cancer have become a

Table 4. Correlation coefficients between standardized mortality ratios (SMRs) for lung cancer and the amounts of dust fall.

Lag years	Total			Northern district			Southern district		
	r	p	N	r	p	N	r	p	N
Males									
15	0.025	0.911	22	−0.390	0.073	22	0.278	0.210	22
16	0.062	0.785	22	−0.361	0.099	22	0.304	0.169	22
17	0.108	0.634	22	−0.305	0.168	22	0.311	0.159	22
18	0.165	0.463	22	−0.210	0.348	22	0.308	0.163	22
19	0.180	0.422	22	−0.136	0.545	22	0.273	0.219	22
20	0.179	0.425	22	−0.040	0.860	22	0.190	0.398	22
21	0.132	0.559	22	0.060	0.791	22	0.084	0.712	22
22	0.150	0.505	22	0.223	0.319	22	−0.002	0.994	22
23	0.155	0.492	22	0.377	0.084	22	−0.113	0.616	22
24	0.250	0.261	22	0.576	0.005	22	−0.231	0.302	22
25	0.274	0.230	21	0.601	0.004	21	−0.336	0.136	21
26	0.262	0.264	20	0.610	0.004	20	−0.428	0.060	20
27	0.019	0.939	19	0.429	0.067	19	−0.531	0.019	19
28	−0.129	0.611	18	0.383	0.117	18	−0.597	0.009	18
29	−0.145	0.579	17	0.304	0.235	17	−0.522	0.032	17
30	0.140	0.606	16	0.371	0.157	16	−0.381	0.145	16
Females									
15	0.130	0.563	22	0.496	0.019	22	−0.042	0.852	22
16	0.114	0.614	22	0.522	0.013	22	−0.103	0.648	22
17	0.109	0.631	22	0.475	0.026	22	−0.082	0.717	22
18	0.194	0.386	22	0.421	0.051	22	−0.023	0.920	22
19	0.316	0.152	22	0.319	0.148	22	0.085	0.706	22
20	0.483	0.023	22	0.252	0.258	22	0.225	0.315	22
21	0.587	0.004	22	0.210	0.349	22	0.366	0.094	22
22	0.574	0.005	22	0.278	0.210	22	0.431	0.045	22
23	0.499	0.018	22	0.329	0.135	22	0.448	0.036	22
24	0.392	0.071	22	0.338	0.124	22	0.456	0.033	22
25	0.290	0.202	21	0.317	0.161	21	0.447	0.042	21
26	0.290	0.215	20	0.321	0.167	20	0.440	0.052	20
27	0.387	0.102	19	0.311	0.195	19	0.389	0.100	19
28	0.572	0.013	18	0.259	0.299	18	0.318	0.199	18
29	0.771	0.000	17	0.366	0.148	17	0.150	0.567	17
30	0.847	0.000	16	0.463	0.071	16	−0.050	0.854	16

The SMRs for lung cancer and the amounts of dust fall are shown by lag years.

major concern (Nawrot *et al.*, 2007; Laden *et al.*, 2006; Pope *et al.*, 2002). However, the concentrations of fine particles were not measured in the 1960s. In the present analysis, the amounts of sulfur oxides and dust fall that had been measured in the 1960s were used as the indices of air pollution. The concentrations and constituents of fine particles should be further evaluated. In Amagasaki City, an asbestos cement factory had also been located, and the risk of mesothelioma was reported to be high among residents around the factory (Kurumatani and Kumagai, 2008). However, it is presumed that the affected area was limited to about 2 km from the factory. On the other hand, this study showed an increased risk of lung cancer mortality in a rather wide area covering the entire city.

Fourth, we calculated expected deaths using national data on mortality for lung cancer, which has consistently increased during the past several decades. The concentrations of air pollution were very high in the 1960s and 1970s not only in Amagasaki City, but also in other industrial cities in Japan. Therefore, the comparison of lung cancer mortality with all Japanese who died due to lung cancer may lead to underestimation of the risk of air pollution.

It has been recognized that air pollution is associated with an increased prevalence of bronchial asthma and chronic obstructive pulmonary disease (COPD) (Committee on Japan's Experience in the Battle against Air Pollution; Chairman: Sawa, 1997; Imai *et al.*, 1986). In Yokkaichi, an industrial city with a severe level of air pollution in the 1960s, as in Amagasaki, the mortality of bronchial asthma and COPD increased as a result of worsening air pollution. The mortality due to bronchial asthma decreased promptly in response to

decreased air pollution, but the mortality due to COPD decreased with a time lag of 4 or 5 years (Imai *et al.*, 1986). A recent study (Guo *et al.*, 2008) showed that mortality and life expectancy in patients with these diseases were still affected, despite the fact that the level of air pollution had already improved. In addition, the present study showed the association between the level of air pollution and lung cancer after considering the lag time of 20-30 years, especially in the southern district of Amagasaki City where the levels of air pollution were markedly higher. Thus, severe air pollution might produce prolonged effects on human health after the level had decreased.

5. CONCLUSIONS

Past severe air pollution in an industrial city appears to be related to the subsequent increase in lung cancer mortality. In many industrial cities, the levels of air pollution had been high in the past. Since lung cancer might occur several decades after exposure to risk factors, the effects of air pollution should be evaluated over a long period after the levels have decreased.

ACKNOWLEDGEMENTS

Most of vital statistics and air pollution data in the past were available from the Amagasaki Municipal Archives, Japan. The authors thank the staffs of the archive for their helpful supports.

REFERENCES

Annesi-Maesano I., N. Agabiti, R. Pistelli, M.F. Couilliot, and F. Forastiere (2003) Subpopulations at increased risk of adverse health outcomes from air pollution. Eur. Respir. J. Suppl., 40, 57s-63s.

Archer V.E. (1990) Air pollution and fatal lung disease in three Utah counties. Arch. Environ. Health, 45(6), 325-334.

Barbone F., M. Bovenzi, F. Cavallieri, and G. Stanta (1995) Air pollution and lung cancer in Trieste, Italy. Am. J. Epidemiol., 141(12), 1161-1169.

Buffler P.A., S.P. Cooper, S. Stinnett, C. Contant, S. Shirts, R.J. Hardy, V. Agu, B. Gehan, and K. Burau (1988) Air pollution and lung cancer mortality in Harris County, Texas, 1979-1981. Am. J. Epidemiol., 128(4), 683-699.

Cohen A.J. and C.A. Pope, 3rd (1995) Lung cancer and air pollution. Environ. Health Perspect., 103 Suppl 8, 219-224.

Department of Environment, Amagasaki City (1961-1993) Reports on environment of Amagasaki City in 1960-1992 [in Japanese], Amagasaki City Printing Office, Amagasaki.

Dockery D.W., C.A. Pope, 3rd, X. Xu, J.D. Spengler, J.H. Ware, M.E. Fay, B.G. Ferris, Jr., and F.E. Speizer (1993) An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med., 329(24), 1753-1759.

Doll R., R. Peto, K. Wheatley, R. Gray, and I. Sutherland (1994) Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ, 309, 901-911.

Filleul L., V. Rondeau, S. Vandentorren, N. Le Moual, A. Cantagrel, I. Annesi-Maesano, D. Charpin, C. Declercq, F. Neukirch, C. Paris, D. Vervloet, P. Brochard, J.F. Tessier, F. Kauffmann, and I. Baldi (2005) Twenty five year mortality and air pollution: results from the French PAARC survey. Occup. Environ. Med., 62, 453-460.

Gallus S., E. Negri, P. Boffetta, J.K. McLaughlin, C. Bosetti, and C. La Vecchia (2008) European studies on long-term exposure to ambient particulate matter and lung cancer. Eur. J. Cancer Prev., 17(3), 191-194.

Greenland S. and J. Robins (1994) Invited commentary: ecologic studies-biases, misconceptions, and counterexamples. Am. J. Epidemiol., 139(8), 747-760.

Guo P., K. Yokoyama, M. Suenaga, and H. Kida (2008) Mortality and life expectancy of Yokkaichi asthma patients, Japan: late effects of air pollution in 1960-70s. Environ. Health, 7:8, doi:10.1186/1476-069x-7-8.

Health and Welfare Bureau, Amagasaki City (1985-2008) Vital statistics of Amagasaki City in 1983-2006 [in Japanese], Amagasaki Public Health Center, Amagasaki.

Health and Welfare Bureau, Amagasaki City (2003) A survey on health promotion of an Amagasaki citizen [in Japanese], Amagasaki City Printing Office, Amagasaki.

Henderson B.E., R.J. Gordon, H. Menck, J. Soohoo, S.P. Martin, and M.C. Pike (1975) Lung cancer and air pollution in southcentral Los Angeles County. Am. J. Epidemiol., 101(6), 477-488.

Hirayama T. (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br. Med. J., 282, 183-185.

Hitosugi M. (1968) Epidemiological study of lung cancer with special reference to the effect of air pollutiuon and smoking habit. Bulletin of the Institute of Public Health, 17, 237-256.

Hoek G., B. Brunekreef, S. Goldbohm, P. Fischer, and P.A. van den Brandt (2002) Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet, 360, 1203-1209.

Imai M., K. Yoshida, and M. Kitabatake (1986) Mortality from asthma and chronic bronchitis associated with changes in sulfur oxides air pollution. Arch. Environ. Health, 41(1), 29-35.

Iwai K., S. Mizuno, Y. Miyasaka, and T. Mori (2005) Correlation between suspended particles in the environmental air and causes of disease among inhabitants: cross-sectional studies using the vital statistics and air pollution data in Japan. Environ. Res., 99, 106-117.

Jedrychowski W., H. Becher, J. Wahrendorf, and Z. Basa-Cierpialek (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. J. Epidemiol. Community Health, 44(2), 114-120.

Katsouyanni K., D. Trichopoulos, A. Kalandidi, P. Tomos, and E. Riboli (1991) A case-control study of air pollution and tobacco smoking in lung cancer among women in Athens. Prev. Med., 20, 271-278.

Kurumatani N. and S. Kumagai (2008) Mapping the risk of mesothelioma due to neighborhood asbestos exposure. Am. J. Respir. Crit. Care Med., 178, 624-629.

Laden F., J. Schwartz, F.E. Speizer, and D.W. Dockery (2006) Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am. J. Respir. Crit. Care Med., 173, 667-672.

Marugame T. and T. Sobue (2004) Mortality trend of mouth and pharynx, esophagus, stomach, larynx and lung cancer in Japan by birth cohort. Jpn. J. Clin. Oncol., 34(7), 432-434.

Marugame T., T. Sobue, H. Satoh, S. Komatsu, Y. Nishino, H. Nakatsuka, T. Nakayama, T. Suzuki, T. Takezaki, K. Tajima, and S. Tominaga (2005) Lung cancer death rates by smoking status: comparison of the Three-Prefecture Cohort study in Japan to the Cancer Prevention Study II in the USA. Cancer Sci., 96(2), 120-126.

Ministry of Health, Labor, and Welfare, Japan (2004) The National Nutrition Survey, 2002 [in Japanese], Daiichi Shuppan Press, Tokyo.

Naess O., P. Nafstad, G. Aamodt, B. Claussen, and P. Rosland (2007) 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., 165(4), 435-443.

Nafstad P., L.L. Haheim, B. Oftedal, F. Gram, I. Holme, I. Hjermann, and P. Leren (2003) Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. Thorax, 58(12), 1071-1076.

Nawrot T.S., K. Nackaerts, P.H. Hoet, and B. Nemery (2007) Lung cancer mortality and fine particulate air pollution in Europe. Int. J. Cancer, 120(8), 1825-1826; author reply 1827.

Nyberg F., P. Gustavsson, L. Järup, T. Bellander, N. Berglind, R. Jakobsson, and G. Pershagen (2000) Urban air pollution and lung cancer in Stockholm. Epidemiology, 11(5), 487-495.

Parodi S., E. Stagnaro, C. Casella, A. Puppo, E. Daminelli, V. Fontana, F. Valerio, and M. Vercelli (2005) Lung cancer in an urban area in Northern Italy near a coke oven plant. Lung Cancer, 47(2), 155-164.

Pope C.A., 3rd, R.T. Burnett, M.J. Thun, E.E. Calle, D. Krewski, K. Ito, and G.D. Thurston (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA, 287(9), 1132-1141.

Sawa T. (Committee on Japan's Experience in the Battle against Air Pollution: Chairman) (1997) Japan's Experience in the Battle against Air Pollution, The Pollution-Related Health Damage Compensation and Prevention Association, Tokyo.

Shimizu H., S. Tominaga, N. Nakagawa, and T. Kuroishi (1979) An epidemiological study on lung cancer. The relationship between the lung cancer mortality and air pollution by ward in a large city [in Japanese]. Journal of Japan Society of Air Pollution, 14, 324-333.

Stevens R.G. and S.H. Moolgavkar (1984) A cohort analysis of lung cancer and smoking in British males. Am. J. Epidemiol., 119(4), 624-641.

Thun M.J., C. Day-Lally, D.G. Myers, E.E. Calle, W.D. Flanders, B.P. Zhu, M.M. Namboodiri, and C.W. Heath (1997) Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959 through 1965) and II (1982 through 1988). National Cancer Institute, Smoking and Tobacco Control, Monograph 8: Changes in Cigarette-Related Disease Risks and their Implication for Prevention and Control., NIH Publication, Washington D.C., pp. 305-382.

Vena J.E. (1982) Air pollution as a risk factor in lung cancer. Am. J. Epidemiol., 116(1), 42-56.

Vineis P., G. Hoek, M. Krzyzanowski, F. Vigna-Taglianti, F. Veglia, L. Airoldi, H. Autrup, A. Dunning, S. Garte, P. Hainaut, C. Malaveille, G. Matullo, K. Overvad, O. Raaschou-Nielsen, F. Clavel-Chapelon, J. Linseisen, H. Boeing, A. Trichopoulou, D. Palli, M. Peluso, V. Krogh, R. Tumino, S. Panico, H.B. Bueno-De-Mesquita, P.H. Peeters, E.E. Lund, C.A. Gonzalez, C. Martinez, M. Dorronsoro, A. Barricarte, L. Cirera, J.R. Quiros, G. Berglund, B. Forsberg, N.E. Day, T.J. Key, R. Saracci, R. Kaaks, and E. Riboli (2006) Air pollution and risk of lung cancer in a prospective study in Europe. Int. J. Cancer, 119(1), 169-174.

(Received 17 November 2008, accepted 5 April 2009)

「日本医事新報」別刷　第四四四二号（二〇〇九年六月一三日発行）

微小粒子状物質の健康影響

兵庫医科大学公衆衛生学
教授　島　正之

【研究報告】

微小粒子状物質の健康影響

兵庫医科大学公衆衛生学教授
島　正之（しま まさゆき）

はじめに

空気中には浮遊粉じん、エアロゾルなど、大きさや成分が異なる様々な粒子状物質が浮遊している。呼吸により人体に取り込まれた粒子の大部分は、鼻腔、咽頭、上気道に沈着し排出されるが、粒径が小さい粒子ほど空気中に比較的長く浮遊し、吸入されると細気管支や肺胞レベルまで到達して肺内に沈着しやすい。

我が国では大気中に浮遊する粒子状物質のうち粒径10㎛以下のものを浮遊粒子状物質（suspended particulate matter：SPM）として、1973年に環境基準が設定された。このうち、粒径が2・5㎛より大きい粒子は主に土壌、海塩粒子、花粉等の自然起源のものであるが、粒径2・5㎛以下の粒子は主に人工起源のものであり、燃焼により放出される1次粒子と、ガス状物質として排出され、光化学反応などによって凝集・転換した2次粒子からなっている（図1）[1]。こうした粒径2・5㎛以下のものは微小粒子状物質（$PM_{2.5}$）と呼ばれ、健康影響が国際的に懸念されており、我が国でも中央環境審議会で$PM_{2.5}$の環境基準を設定するための検討が進められている。

本稿では、$PM_{2.5}$の健康影響について、国内外で行われた疫学研究の知見を中心に紹介する。

欧米諸国における$PM_{2.5}$の健康影響と環境基準

1990年代から米国を中心に$PM_{2.5}$の健康影響に関する疫学研究の結果が相次いで報告されている。米国東部6都市の住民約8000人を14～16年間追跡したコホート研究では、年齢、性、喫煙、職業等を調整した死亡率は大気汚染レベルの高い都市ほど高く、各都市の$PM_{2.5}$濃度との間に強い関連が認められている[2]。観察期間を8年間延長しても同様であり、$PM_{2.5}$濃度10㎍／㎥増加当たりにおける総死亡の相対リスクは1・16倍、死因別に見ると肺癌は1・27倍、循環器系疾患は1・28倍であった[3]。全米50都市の約30万人を対象とした米国がん協会の研究でも、$PM_{2.5}$濃度と総死亡、心肺疾患・肺癌による死亡との関連が報告されている[4]。

$PM_{2.5}$濃度の日変動と1日単位の死亡数との関連を時系列的に解析した研究も数多く見られ、高濃度の$PM_{2.5}$への短期曝露が総死亡、循環器系・呼吸器系疾患による死亡を増加させるという影響が示されている[5]。このほかには、$PM_{2.5}$への曝露により、呼吸器系・循環器系疾患による救急受診や入院、呼吸器症状の増加、呼吸機能の低下、不整脈の増加、心拍変動の低下など、様々な影響が見出されている[6]。

このような$PM_{2.5}$の健康影響に関する知見を踏まえて、米国では1997年に$PM_{2.5}$の環境基準が設定され、その後の科学的知見を受けて2006年に強化された（年平均値15㎍／㎥、日平均値35㎍／㎥）[6]。世界保健機関（WHO）でも2006年に$PM_{2.5}$の大気質