Two approaches were used to evaluate the effects of air pollution.[4] First, dummy variables for the study area were included, using the least polluted area, namely, Wakuya/Tajiri towns, as the reference category. Multivariate-adjusted HRs for each of the 6 areas were plotted against the average pollution levels in those areas. Second, area-specific concentrations of each pollutant were included directly in the models, and multivariate-adjusted HRs were estimated according to a 10-unit increase in air pollution levels. The average concentrations during the 10-year exposure time window (1974–1983) before the baseline survey were used for the analysis, and the subsequent 10-year average concentrations (1984–1993) corresponding to the follow-up period of our cohort were also analyzed. We only applied single-pollutant models because the number of measurement stations was small and the concentrations of different pollutants were spatially correlated (>0.80).

In the analysis of deaths from respiratory diseases, the HRs by 10-unit increase in air pollution levels were calculated after adjustment for sex, age (continuous), smoking status (current, former, never), pack-years (<10, 10–19, ≥20), smoking status of family members living together (current smoking/no current smoking), use of indoor charcoal or briquette braziers for heating (yes/no), and occupation (experience in occupations with potential exposure to gases, fumes, or dust or not). Participants with a previous diagnosis of pneumonia, asthma, chronic bronchitis, emphysema, or pneumoconiosis were excluded from the analysis ($n = 4970$). Analyses stratified by sex and smoking status were also performed. In all analyses, SAS version 8.02 (SAS Institute Japan Ltd.) was used to estimate HRs and CIs.

RESULTS

Air pollution data

The 10-year average concentrations (1974–1983) of SPM, $PM_{2.5}$, SO_2, and NO_2 across the 6 study areas were 24.0 to 59.9 μg/m^3, 16.8 to 41.9 μg/m^3, 2.4 to 19.0 ppb, and 1.2 to 33.7 ppb, respectively (inter-area range). The average concentrations of these 4 air pollutants during the subsequent 10-year period (1984–1993) were 21.9 to 45.0 μg/m^3, 15.3 to 31.5 μg/m^3, 2.3 to 10.6 ppb, and 2.6 to 33.0 ppb, respectively (inter-area range). The area-specific air pollution levels during the 2 consecutive 10-year periods are shown in Table 1. The concentrations of all pollutants were highest in Osaka city and lowest in Wakuya/Tajiri towns for both 10-year periods. In all 6 study areas, the concentration of SO_2 was lower by 0.1 to 8.4 ppb during the second 10-year period as compared with the first 10-year period. In all the study areas, excluding Nose/Kanan/Kumatori towns, the concentration of SPM was lower by 2.1 to 15.8 μg/m^3 during the second period as compared with the first period. The concentrations of NO_2 during the first and second periods were similar; the differences ranged from −2.2 to 3.6 ppb (second period minus first period).

Figure 2 shows the annual trends for the 3 air pollutants. The concentrations of SPM decreased during the early 1980s, especially in heavily polluted areas such as Sendai city, Nagoya city, and Osaka city. SO_2 concentrations markedly decreased in the late 1970s, especially in Sendai city and Osaka city, and continued to decrease slowly thereafter. NO_2 concentrations remained stable throughout the observation period. Significant temporal correlations were observed between the area-pooled concentrations of SO_2 and NO_2 within the exposure time window (1974–1983) (Pearson correlation coefficient = 0.76, $P = 0.01$). The temporal correlations between the concentrations of SPM and SO_2 and between SPM and NO_2 were weak (Pearson correlation coefficient: 0.47 [$P = 0.17$] and 0.26 [$P = 0.48$] respectively).

Baseline characteristics

Area-specific baseline characteristics are shown in Table 1. The prevalence of current smokers ranged from 29% to 36%, and the prevalence of former smokers ranged from 9% to 17%. Pack-years were distributed within small ranges: 32 to 35 for current smokers and 28 to 30 for former smokers. Approximately half of the participants were exposed to passive smoking from current family members, and over 70% of the participants had been exposed to passive smoking from parents during childhood. The prevalence of the use of charcoal or briquette braziers for heating was over 40% in Wakuya/Tajiri towns, which are located in a cold rural region, and 10% or lower in the other study areas.

Association between air pollution and lung cancer

The number of cause-specific deaths and person-years of follow-up for the 6 study areas are shown in Table 1. In total, 6687 deaths were observed, including 518 deaths from lung cancer, during an average follow-up of 8.7 years. Figure 3 shows the adjusted HRs of lung cancer mortality relative to the least polluted area, plotted against the 10-year average concentration levels of the air pollutants (1974–1983). For men and women combined, a significant increase in risk was observed in Nagoya city and Osaka city at a level of 50 μg/m^3 or higher for SPM (equivalent to 35 μg/m^3 or higher for $PM_{2.5}$) and at a level of 20 ppb or higher for NO_2. The HR point estimates for these 2 areas were approximately 1.5.

When stratified by sex, the results for men were similar to those for the entire population. Among women, although HRs were not significantly higher even in the most polluted area, there was a gentle concentration-response gradient regardless of whether the analysis was or was not limited to never smokers. For male current smokers, a significant increase in risk was observed even in the second least polluted area at an SPM level of approximately 36 μg/m^3 (equivalent to 25 μg/m^3 for $PM_{2.5}$), an SO_2 concentration of 10 ppb, and an NO_2 concentration of 14 ppb, with HR point estimates of

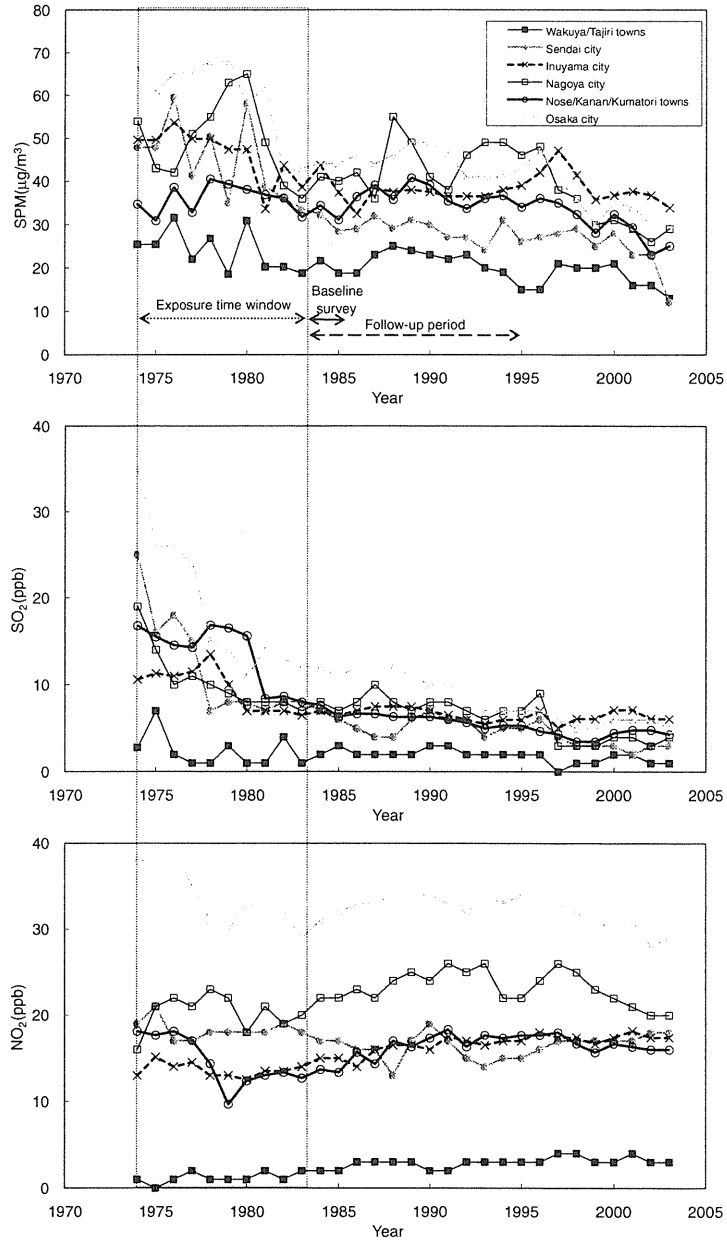

Figure 2. Annual trends in air pollutant levels from 1974 through 2003 in the 6 study areas. NO_2, nitrogen dioxide; SO_2, sulfur dioxide; SPM, suspended particulate matter.

approximately 1.5. The highest HR point estimate for male current smokers was close to 2.5.

The bottom row of Figure 3 shows the results obtained when the exposure time window was shifted to the 10-year average concentration levels during the follow-up period (1984–1993). For SPM and SO_2, the distribution of 6 areas moved towards the lower half of the concentration ranges, and, accordingly, a significant increase in risk was observed for an SPM concentration of approximately 45 $\mu g/m^3$ (equivalent to 30 $\mu g/m^3$ for $PM_{2.5}$) and an SO_2 concentration of 7.5 ppb. By contrast, for NO_2, the concentration ranges in the 6 areas were similar to those in 1974–1983, and a significant increase in risk was observed at a concentration of approximately 25 ppb.

Table 2 shows the adjusted HR for lung cancer associated with a 10-unit difference in the 10-year average air pollution levels (1974–1983). A significant association with lung cancer mortality was observed for all 4 pollutants after adjustment for sex, age, smoking status, pack-years, smoking status of family members, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating (base model). The

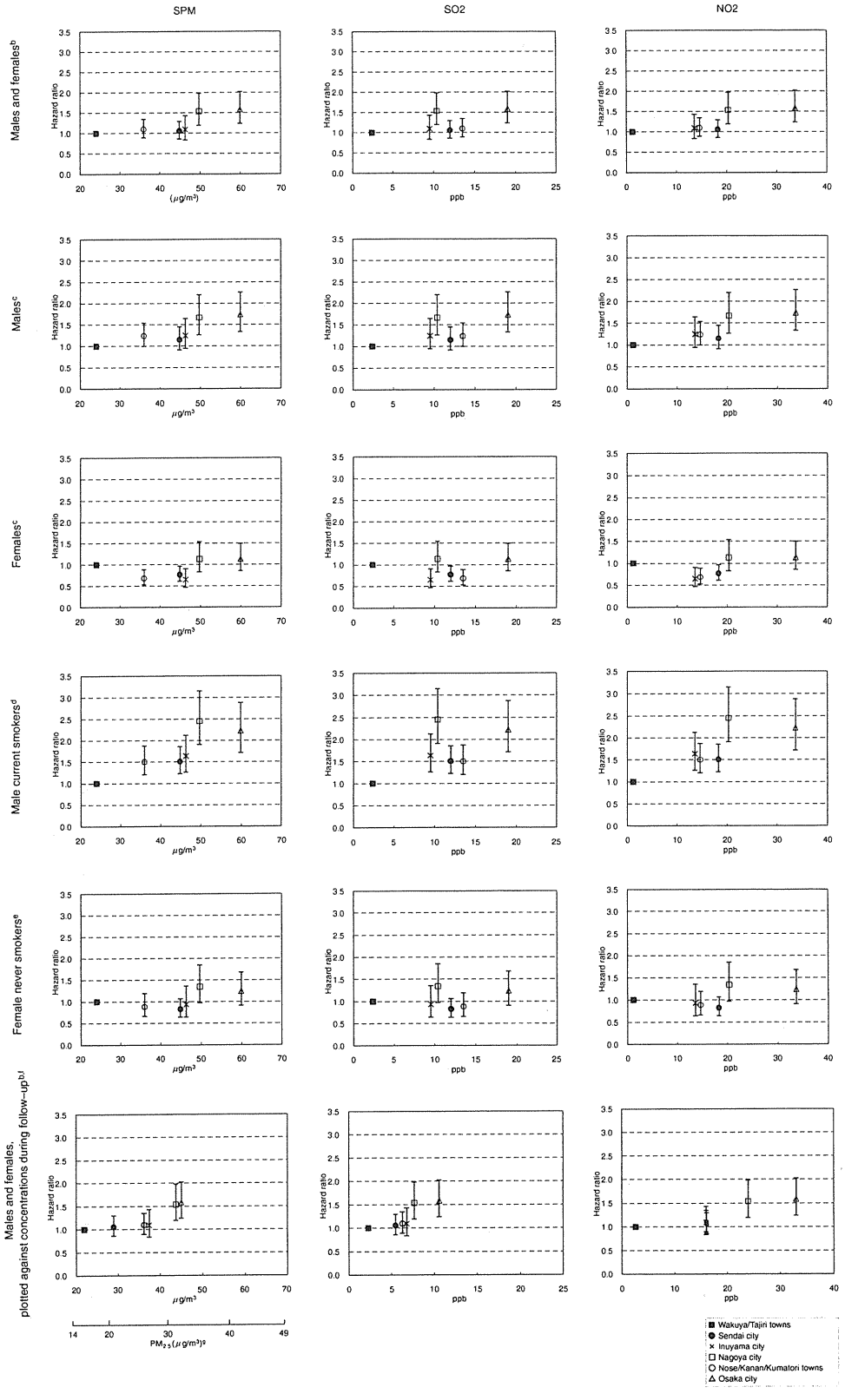

Figure 3. Continued on next page.

Figure 3. Adjusted hazard ratios for lung cancer mortality in the 6 study areas, plotted against average air pollutant concentrations.[a] NO2, nitrogen dioxide; PM2.5, particulate matter <2.5 μm in aerodynamic diameter; SO2, sulfur dioxide; SPM, suspended particulate matter. [a]10-year average concentrations (1974–1983) before the baseline survey are used as the horizontal axis, unless otherwise specified. Hazard ratios were calculated using Wakuya/Tajiri towns as a reference. Vertical bars indicate the 95% confidence intervals of the hazard ratios. [b]Adjusted for sex, age (continuous), smoking status (current, former, or never), pack-years (0 to <10, 10 to <20, ≥20), smoking status of family members (current smoking/no current smoking), daily green and yellow vegetable consumption (yes/no), daily fruit consumption (yes/no), and indoor charcoal or briquette braziers used for heating (yes/no). [c]Adjusted for age (continuous), smoking status (current, former, or never), pack-years (0 to <10, 10 to <20, 20 to <30, 30 to <40, ≥40 for men; 0 to <10, 10 to <20, ≥20 for women), smoking status of family members (current smoking/no current smoking), daily green and yellow vegetable consumption (yes/no), daily fruit consumption (yes/no), and indoor charcoal or briquette braziers used for heating (yes/no). [d]Adjusted for age (continuous), pack-years (0 to <10, 10 to <20, 20 to <30, 30 to <40, ≥40), smoking status of family members (current smoking/no current smoking), daily green and yellow vegetable consumption (yes/no), daily fruit consumption (yes/no), and indoor charcoal or briquette braziers used for heating (yes/no). [e]Adjusted for age (continuous), smoking status of family members (current smoking/no current smoking), daily green and yellow vegetable consumption (yes/no), daily fruit consumption (yes/no), and indoor charcoal or briquette braziers used for heating (yes/no). [f]10-year average concentration (1984–93) during the follow-up period was used as the horizontal axis. [g]Estimated by multiplying the level of SPM by 0.7.

Table 2. Adjusted HRs for lung cancer associated with a 10-unit increase in the average concentration of air pollutants[a]

Model description	Category	Number of deaths	Person-years	SPM (μg/m³)		$PM_{2.5}$ (μg/m³)[b]		SO_2 (ppb)		NO_2 (ppb)	
				HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Sex- and age-adjusted	(All)	518	550 339	1.18	(1.13–1.24)	1.27	(1.19–1.36)	1.36	(1.20–1.54)	1.20	(1.17–1.24)
Base model[c]	(All)	518	550 339	1.16	(1.08–1.25)	1.24	(1.12–1.37)	1.26	(1.07–1.48)	1.17	(1.10–1.26)
Full model[d]	(All)	421	472 762	1.16	(1.06–1.25)	1.23	(1.09–1.38)	1.19	(0.97–1.45)	1.15	(1.06–1.24)
By sex[e]	Male	407	257 120	1.17	(1.09–1.26)	1.26	(1.14–1.39)	1.30	(1.12–1.52)	1.18	(1.11–1.26)
	Female	111	293 219	1.12	(0.99–1.26)	1.17	(0.98–1.39)	1.11	(0.88–1.40)	1.13	(1.01–1.27)
By sex and smoking status[f]	Male current smokers	292	146 031	1.23	(1.14–1.34)	1.35	(1.20–1.52)	1.36	(1.06–1.75)	1.23	(1.12–1.35)
	Male former smokers	90	63 092	1.08	(0.83–1.39)	1.11	(0.77–1.60)	1.25	(0.75–2.10)	1.13	(0.88–1.44)
	Female never smokers	73	254 145	1.11	(1.01–1.22)	1.16	(1.02–1.33)	1.09	(0.92–1.29)	1.11	(1.02–1.20)
Base model, excluding participants with a history of respiratory diseases[c,g]	(No history of respiratory disease)	438	509 369	1.15	(1.06–1.26)	1.23	(1.08–1.39)	1.22	(1.02–1.45)	1.16	(1.07–1.25)
Base model, using average concentrations during the follow-up period[c,h]	(All)	518	550 339	1.27	(1.14–1.41)	1.41	(1.21–1.64)	1.97	(1.41–2.75)	1.21	(1.10–1.33)

CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; SO_2, sulfur dioxide; SPM: suspended particulate matter.

[a]10-year average concentrations (1974–1983) before baseline survey were used, unless otherwise specified.

[b]Estimated by multiplying the level of SPM by 0.7.

[c]Adjusted for sex, age (continuous), smoking status (current, former, or never), pack-years (0 to <10, 10 to <20, ≥20), smoking status of family members (current smoking/no current smoking), daily green and yellow vegetable consumption (yes/no), daily fruit consumption (yes/no), and indoor charcoal or briquette braziers used for heating (yes/no).

[d]Base model, with additional adjustment for smoking status of parents in childhood (current smoking/no current smoking), daily consumption of vegetables other than green and yellow vegetables (yes/no), occupation (experience in occupation with potential exposure to gases, fumes, or dust or not), health insurance (4 categories). 9289 participants were excluded because of missing data for smoking status of parents, non-green/yellow vegetable consumption, occupation, and/or health insurance.

[e]Base model, excluding adjustment for sex. Pack-years were adjusted with different categories for males and females (0 to <10, 10 to <20, 20 to <30, 30 to <40, ≥40 for males, 0 to <10, 10 to <20, ≥20 for females).

[f]Base model, excluding adjustment for sex and smoking status. Pack-years were adjusted using 5 categories for male current or former smokers (0 to <10, 10 to <20, 20 to <30, 30 to <40, ≥40).

[g]4970 participants with a previous diagnosis of pneumonia, asthma, chronic bronchitis, emphysema, or pneumoconiosis were excluded.

[h]Base model, using the 10-year average concentrations (1984–1993) during the follow-up period.

Table 3. Adjusted HRs for respiratory diseases associated with a 10-unit increase in the average concentration of air pollutants[a]

Model description	Category	Number of deaths	Person-years	SPM (μg/m³)		$PM_{2.5}$ (μg/m³)[b]		SO_2 (ppb)		NO_2 (ppb)	
				HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Sex- and age-adjusted	(All)	677	509 369	1.08	(0.98–1.18)	1.11	(0.98–1.27)	1.38	(1.23–1.55)	1.13	(1.08–1.19)
Multivariate model[c]	(All)	677	509 369	1.11	(1.03–1.20)	1.16	(1.04–1.30)	1.43	(1.33–1.54)	1.16	(1.12–1.21)
By sex[e]	Male	417	236 047	1.07	(1.00–1.15)	1.11	(1.00–1.22)	1.30	(1.16–1.47)	1.11	(1.05–1.18)
	Female	260	273 322	1.19	(1.07–1.32)	1.28	(1.10–1.49)	1.68	(1.40–2.01)	1.25	(1.18–1.33)
By sex and smoking status[f]	Male current smokers	200	134 750	1.15	(1.03–1.28)	1.22	(1.05–1.42)	1.52	(1.35–1.71)	1.21	(1.11–1.31)
	Male former smokers	130	56 849	0.89	(0.79–1.01)	0.85	(0.71–1.01)	0.88	(0.66–1.18)	0.90	(0.80–1.01)
	Female never smokers	218	238 431	1.19	(1.09–1.30)	1.29	(1.14–1.46)	1.63	(1.44–1.84)	1.25	(1.20–1.30)
Pneumonia[c]	(All)	512	509 369	1.12	(1.03–1.21)	1.17	(1.04–1.32)	1.45	(1.34–1.57)	1.16	(1.12–1.21)
COPD[c]	(All)	64	509 369	0.92	(0.78–1.08)	0.89	(0.70–1.12)	1.32	(0.88–1.98)	1.03	(0.93–1.15)
Respiratory diseases, using average concentrations during the follow-up period[c,g]	(All)	677	509 369	1.08	(0.89–1.31)	1.12	(0.85–1.46)	1.62	(1.22–2.15)	1.14	(1.06–1.23)

CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; SO_2, sulfur dioxide; SPM, suspended particulate matter.

[a]10-year average concentrations (1974–1983) before the baseline survey were used, unless otherwise specified. 4970 participants with a previous diagnosis of pneumonia, asthma, chronic bronchitis, emphysema, or pneumoconiosis were excluded.

[b]Estimated by multiplying the level of SPM by 0.7.

[c]Adjusted for sex, age (continuous), smoking status (current, former, or never), pack-years (0 to <10, 10 to <20, ≥20), smoking status of family members (current smoking/no current smoking), indoor charcoal or briquette braziers used for heating (yes/no), and occupation (experience of occupation with potential exposure to gases, fumes, or dust or not).

[e]Multivariate model, excluding adjustment for sex. Pack-years were adjusted with different categories for males and females (0 to <10, 10 to <20, 20 to <30, 30 to <40, 40 for males, 0 to <10, 10 to <20, ≥20 for females).

[f]Multivariate model, excluding adjustment for sex and smoking status. Pack-years was classified into 5 categories for male current and former smokers (0 to <10, 10 to <20, 20 to <30, 30 to <40, ≥40).

[g]Multivariate model, using the 10-year average concentrations (1984–1993) during the follow-up period.

point estimates of the increased risk associated with a 10-unit increase in the concentrations were 16%, 24%, 26%, and 17% for SPM (μg/m³), $PM_{2.5}$ (μg/m³), SO_2 (ppb), and NO_2 (ppb), respectively. These increases in risk remained even after additional adjustment for the smoking status of parents during the participants' childhood, daily consumption of vegetables other than green and yellow vegetables, occupation, and health insurance (full model), although the association was not significant for SO_2. The significant associations with the 4 air pollutants were observed even after exclusion of participants with a history of respiratory diseases.

Men showed a significant increase in the risk for all 4 air pollutants, with point estimates ranging from 17% to 30%. For women, the corresponding increases in risk ranged from 11% to 17%, although the increase was significant only for NO_2. However, analyses limited to female never smokers revealed significant excess risk associated with SPM, $PM_{2.5}$, and NO_2. The increase in risk among male current smokers was significantly higher, with point estimates ranging from 23% to 36%, while no significant increase in risk was observed for male former smokers. The interactions between smoking status and air pollutant concentrations were not statistically significant in men or women ($P > 0.07$ for men and $P > 0.26$ for women).

When we incorporated the average air pollution levels during the follow-up period in the model (1984–1993), instead of those for the period before baseline (1974–1983), the excess risk associated with air pollution increased, with point estimates ranging from 21% to 97%.

Association between air pollution and respiratory diseases

Table 3 shows the adjusted HRs for mortality from respiratory diseases associated with 10-unit differences in the air pollution levels. A significant association was observed between mortality from respiratory diseases and the concentrations of all 4 pollutants. This association was observed in both sexes, and in male current smokers and female never smokers. The association was similar when the exposure time window was shifted to the 10-year average concentration levels during the follow-up period (1984–1993). In analysis stratified by disease, the association was significant for pneumonia, but not for chronic obstructive pulmonary disease (COPD).

DISCUSSION

This large-scale prospective cohort study demonstrated associations between long-term exposure to both particulate and gaseous ambient air pollution and an elevated risk of lung cancer mortality in the Japanese population, after controlling for potential confounding factors. The observed increase in risk ranged from approximately 16% to 26% for a 10-unit increase in air pollution levels. These values were generally comparable to those reported in previous studies conducted in the United States and European countries. For example, in previous studies, point estimates of the adjusted relative risks for a 10-$\mu g/m^3$ increase in $PM_{2.5}$ concentration ranged from 1.06 to 1.39 (calculated from published values, when necessary).[2,9,11,13,15] Our results suggest that the concentration-response gradient observed in US and European populations can also be applied to Japan, despite the differences in air pollution levels and constituents[17] and disease and risk distributions.[23,24]

Men, especially current smokers, had higher HRs for lung cancer associated with air pollution in the present study, even after controlling for smoking status and pack-years. Although the interactions between smoking status and air pollutant concentrations were not statistically significant, the stronger association for current smokers raises the question of whether the observed association between lung cancer and air pollution was confounded by unmeasured exposure to smoking. However, our results remained unchanged when we used a model that additionally controlled for age at initiation of smoking (data not shown), and a significant increase in risk was also observed for female never smokers. Although it is possible that active smoking and long-term exposure to air pollution have an additive or synergistic effect on lung cancer, previous studies are not consistent regarding the different effects of air pollution on lung cancer with respect to sex and smoking status. European studies showed weaker associations between air pollution and lung cancer for males[13] and current and former smokers.[2] These results cannot be interpreted in a straightforward manner because they were obtained without controlling for smoking status[13] or amount of smoking.[2] The American Cancer Society (ACS) study, which was controlled for active and passive smoking levels, reported stronger associations between air pollution and lung cancer in males, whereas the associations were more evident in former smokers.[15]

As compared with the effects of smoking, the excess risk of lung cancer associated with air pollution was small. In the present study, the multivariate-adjusted HR for lung cancer mortality in current smokers relative to never smokers was 4.8 (data not shown), which is consistent with the results of previous large-scale and meta-analytic studies conducted in Japan.[24,25] The maximum difference in $PM_{2.5}$ concentration during the 30-year observation period was 40 $\mu g/m^3$ (approximately 50 $\mu g/m^3$ in Osaka city versus 10 $\mu g/m^3$ in Wakuya/Tajiri towns). Similarly, the maximum differences in SO_2 and NO_2 concentrations were 35 ppb and 40 ppb, respectively. These differences in concentrations, combined with the observed relative risks for a 10-unit increase, correspond to a 1.9- to 2.4-fold increase in the risk of lung cancer.

With regard to respiratory mortality, previous findings regarding the effect of long-term exposure to ambient air pollution have been somewhat inconsistent. The Harvard Six Cities Study, the Adventist Health Study of Smog (AHSMOG), and several European studies reported positive associations for $PM_{2.5}$,[1,2,9,11,13] but only some of these associations were significant.[13] For SO_2, many studies showed a relative risk close to unity.[1,2,14] For NO_2, both significant[2,13] and null[1] associations have been reported. Some of those reports should be interpreted with caution, however. The AHSMOG was limited to nonsmoking males and females belonging to a specific religious group,[1,11] and 2 European studies did not adjust for smoking status[13] or amount of smoking.[2] In the present study, we controlled for potential confounding factors for respiratory diseases and observed significant increases in risk due to particulate and gaseous air pollution.

Respiratory diseases represent a variety of medical conditions that have different etiologies. The present study observed a significant effect of air pollution on pneumonia, but not COPD. However, data on disease-specific mortality were limited. The majority of the observed deaths from respiratory diseases were from pneumonia (76%); COPD accounted for only 9% of deaths. Although we only extracted respiratory diseases as the underlying cause of death, this category might have included respiratory complications of other underlying diseases or might have failed to identify underlying chronic respiratory diseases. Many of the studies cited above used the same broad definition of respiratory diseases as that of the present study (ie, ICD-9: 460–519).[1,2,11,14] Indeed, the AHSMOG adopted an even broader outcome, namely, "any mention of respiratory mortality," which included the contributing cause of death as well as the underlying cause of death.[1,11] In contrast, a Norwegian study focused on COPD mortality and observed a significant association with PM and NO_2.[13] Similar disease-specific studies need to be accumulated to address the question of whether long-term exposure to air pollution affects chronic respiratory mortality.

The major strength of the present study is its prospective cohort design, which allowed for direct control of individual risk factors, particularly smoking status and level of exposure to smoking. The participants of the present study were enrolled on a population basis, and the response rate was high. Furthermore, our long-term exposure data allowed us to use the pre-baseline time window of ambient air pollution data.

There are several sources of uncertainty in the present study. First, we used mean ambient concentrations in or nearby each study area, instead of individual exposure levels. As was the case in many studies using the same exposure assessment, there could be spatial variability within an area, as well as differences among individuals in time spent outdoors.[26]

Second, it is difficult to determine which time period was most important in relation to health effects, because there were no substantial changes in relative air pollution levels in the study areas over the observation period. This difficulty is also true of previous studies; the ranking of cities from low to high pollution levels changed little across different time windows in the ACS study[15] and the Harvard Six Cities Study.[27] As illustrated in Figure 2, air pollution levels sharply differed before and after the baseline survey. When we shifted the exposure time window from the 10-year period before the baseline survey (1974–1983) to the subsequent 10-year period (1984–1993), the HRs for lung cancer mortality increased, especially in relation to SPM, $PM_{2.5}$, and SO_2 levels. This is because the absolute levels of these air pollutants decreased over time, while the relative levels for these 2 periods remained almost constant (the values for the spatial correlation between the 2 time periods for each pollutant were >0.85). The difficulty in distinguishing between the effects of past and recent exposure is also relevant to identification of the latency period. The observed increase in risk associated with air pollution levels during the 10 years before the baseline survey suggests that the effects occurred after a certain lag period. However, we cannot exclude the possibility of the effect occurring within a shorter lag period of 1 or 2 years.[28]

A third source of uncertainty is that we estimated $PM_{2.5}$ concentrations by converting SPM concentrations using a single ratio (0.7), as in previous studies.[2,19] As mentioned above, in our partial monitoring data, the $PM_{2.5}$/SPM ratio ranged from approximately 0.6 to 0.8. If we assume that between-area variations in the ratio were within this range, there would be no substantial differences in the ordering of the study areas, because the concentrations of SPM were distributed over a wide range. At selected European sites, high correlations were found between coarse and fine PM concentrations ($PM_{2.5}$ and PM_{10}; $R^2 > 0.98$),[29] and $PM_{2.5}$/PM_{10} ratios were uniform.[30] However, a slight tendency towards higher ratios at rural background sites as compared with urban traffic sites was also reported.[30] In the United States, $PM_{2.5}$/PM_{10} ratios in the eastern part of the country were double those in the Southwest, and a poor correlation was observed between $PM_{2.5}$ and PM_{10} concentrations in the West (eg, $r < 0.5$ in the upper Midwest).[31] The components of PM may also vary by time.[31] In our study areas, the concentration of substances such as SO_2 decreased during and after the exposure window (Figure 2), which could have affected the components of PM and the coarse and fine fractions of PM. Because we had limited data on the concentrations of different particulate sizes in our study areas, it remains uncertain how well the SPM concentration represented the variability of the $PM_{2.5}$ concentration. As mentioned in the Methods above, SPM concentration was measured differently in 2 study areas of Miyagi prefecture. Although this might be another source of uncertainty, excluding those 2 areas did not change our results substantially: the HR for a 10-unit increase in SPM concentration was 1.17 (95% CI, 1.12–1.24) for lung cancer and 1.09 (0.92–1.29) for respiratory diseases.

Fourth, pollutant concentrations were correlated with each other. The spatial correlation between different air pollutants within the exposure time window was very high (>0.80). In addition, SO_2 and NO_2 are potential constituents of ambient PM, and their concentration levels vary over time. Therefore, it is very difficult to isolate the health effects of individual pollutants. To understand the biologic mechanisms underlying the increased risk of a specific disease, or to specify potential determinant substances, additional toxicological research is needed.

Finally, our results could have been affected by the exclusion of participants with missing data. We confirmed that the unadjusted HRs were similar when these data were included and excluded from the analysis. Smoking status was unknown among approximately two thirds of the participants whose data were excluded. However, we performed a sensitivity analysis that defined the participants with unknown smoking status as either current or never smokers and confirmed that the effect of the exclusion was negligible. Although there were participants who had moved out of the study areas during the follow-up period, this was considered to have occurred in an unselective way because the characteristics of disease-specific mortality in our analytic cohort were consistent with the reported vital statistics of the study areas.[32]

In conclusion, our large-scale prospective cohort study revealed an association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan.

ACKNOWLEDGMENTS

This work was supported by the Japanese Ministry of the Environment. The authors thank the staff in each of the study areas for the collection and processing of the data.

Conflicts of interest: K Katanoda, T Sobue, H Satoh, T Suzuki, T Nakayama, H Nitta, K Tanabe, and S Tominaga are members of the review panel on the effects of long-term exposure to ambient particulate matter, which was established by the Japanese Ministry of the Environment in 2007. T Sobue, H Satoh, H Nitta, and S Tominaga are members of the review panel on the effects of fine particulate matter, which was established by the Japanese Ministry of the Environment in 2007.

REFERENCES

1. Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Lawrence Beeson W, et al. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med. 1999;159:373–82.
2. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, et al. Long-term effects of traffic-related air

pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ Health Perspect. 2008;116:196–202.
3. Chen LH, Knutsen SF, Shavlik D, Beeson WL, Petersen F, Ghamsary M, et al. The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk? Environ Health Perspect. 2005;113:1723–9.
4. Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med. 1993;329:1753–9.
5. Enstrom JE. Fine particulate air pollution and total mortality among elderly Californians, 1973–2002. Inhal Toxicol. 2005;17:803–16.
6. Filleul L, Rondeau V, Vandentorren S, Le Moual N, Cantagrel A, Annesi-Maesano I, et al. Twenty five year mortality and air pollution: results from the French PAARC survey. Occup Environ Med. 2005;62:453–60.
7. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet. 2002;360:1203–9.
8. Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, et al. Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. A Special Report of the Institute's Particle Epidemiology Reanalysis Project: Health Effects Institute, 2000.
9. 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;173:667–72.
10. Lipfert FW, Perry HM Jr, Miller JP, Baty JD, Wyzga RE, Carmody SE. Air pollution, blood pressure, and their long-term associations with mortality. Inhal Toxicol. 2003;15:493–512.
11. McDonnell WF, Nishino-Ishikawa N, Petersen FF, Chen LH, Abbey DE. Relationships of mortality with the fine and coarse fractions of long-term ambient PM10 concentrations in nonsmokers. J Expo Anal Environ Epidemiol. 2000;10:427–36.
12. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med. 2007;356:447–58.
13. 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;165:435–43.
14. Nafstad P, Håheim LL, Wisløff T, Gram F, Oftedal B, Holme I, et al. Urban air pollution and mortality in a cohort of Norwegian men. Environ Health Perspect. 2004;112:610–5.
15. Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA. 2002;287:1132–41.
16. Pope CA 3rd, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med. 1995;151:669–74.
17. Sivertsen B. 2. Global ambient air pollution concentrations and trends. Air Quality Guidelines Global Update 2005: World Health Organization; 2006. p. 31–59.
18. Marugame T, Sobue T, Satoh H, Komatsu S, Nishino Y, Nakatsuka H, et al. 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. 2005;96:120–6.
19. Dockery DW, Pope CA 3rd. Acute respiratory effects of particulate air pollution. Annu Rev Public Health. 1994;15:107–32.
20. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. Stat Med. 1994;13:2233–47.
21. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective: World Cancer Research Fund/American Institute for Cancer Research, 2007.
22. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans 95. Household Use of Solid Fuels and High-temperature Frying. Lyon: World Health Organization International Agency for Research on Cancer, 2010.
23. Centers for Disease Control and Prevention (CDC). Annual smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 1997–2001. MMWR Morb Mortal Wkly Rep. 2005;54:625–8.
24. Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. J Epidemiol. 2008;18:251–64.
25. Wakai K, Inoue M, Mizoue T, Tanaka K, Tsuji I, Nagata C, et al. Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. Jpn J Clin Oncol. 2006;36:309–24.
26. Janssen N, Mehta S. 3. Human exposure to air pollution. Air Quality Guidelines Global Update 2005: World Health Organization; 2006. p. 31–59.
27. Villeneuve PJ, Goldberg MS, Krewski D, Burnett RT, Chen Y. Fine particulate air pollution and all-cause mortality within the Harvard Six-Cities Study: variations in risk by period of exposure. Ann Epidemiol. 2002;12:568–76.
28. Schwartz J, Coull B, Laden F, Ryan L. The effect of dose and timing of dose on the association between airborne particles and survival. Environ Health Perspect. 2008;116:64–9.
29. Dingenen R, Racs F, Putaud J, Baltensperger U, Charron A, Facchini M, et al. A European aerosol phenomenology—1: physical characteristics of particulate matter at kerbside, urban, rural and background sites in Europe. Atmos Environ. 2004;38:2561–77.
30. Second Position Paper on Particulate Matter: CAFE Working Group on Particulate Matter, 2004.
31. Review of the National Ambient Air Quality Standards for Pariculate Matter: Policy Assessment of Scientific and Technical Information OAQPS Staff Paper. (Publication No. EPA-425/R-05-005a): United States Environmental Protection Agency, 2005.
32. Special Report of Vital Statistics—Vital Statistics by Municipalities and Public Health Center Areas in 1988–1992 [Japanese]. Tokyo: Health and Welfare Statistics Association; 1994.

ISSN 1881-1965

CT検診

The Journal of the Japanese Society of CT Screening

C T S

VOL.18
NO.2
2011

日本CT検診学会

第19回 日本CT検診学会会告

原　著

「公的」肺癌CT検診（対策型検診）の実現への諸課題

西井研治

2010年11月4日にNational Cancer Institute（NCI）がNational Lung Screening Trial（NLST）研究は第一義的目的であるCT検診の死亡率減少効果を認めたので、研究自体を終了すると発表した。このようにCT検診による肺癌死亡率低下に対する有効性が証明されつつあるが、わが国では公的検診（対策型検診）に取り入れられている例はまだ一部である。公的検診（対策型検診）に取り入れにくい原因とその対策を検討した。①国のがん検診ガイドラインで推奨されていないことに対しては、NLSTの結果を踏まえて、推奨度をIからBまたはCに変更してもらうよう働きかける。②検診用のらせんCT車の不足に対しては、レンタル検診車の活用も考える。③検診条件や精検基準の未統一については、CT検診学会のガイドラインの徹底を働きかけるとともに、認定技師および認定医師制度の普及に努める。④CT読影医の不足に対しては、自動診断システム（CAD）や認定技師の読影参加を検討する。⑤検診実施主体（企業や市町村）の負担、受診者の費用負担についても、議論を深める必要がある。⑥精密検査および治療担当医療機関の地方での不足には遠隔診断システムの活用が考えられる。

CTによる検診システムを構築するのに参考になるのは、やはり現行のレントゲン検診システムの経験ではなかろうか。

キーワード：　肺がんCT検診、NLST、公的検診（対策型検診）、コスト
J Thorac CT Screen 2011; 18: 95-100

はじめに

わが国の肺がん死亡数は7万人に迫ろうとしており[1]、がん対策のなかでも重要な課題の一つである。治療の進歩は著しいが、救命のためには早期発見が必要であることに異論はない。そのために肺がん検診の役割は重要であるが、検診受診率や受診者数は全国的に減少傾向にある。その原因の一つには、現在でも肺癌検診方法の主流が結核検診から発展した間接X-Pであることがあげられる。その果たしてきた役割は非常に大きいが、医療機器の進歩が著しいなかで、CTのような画期的デバイスが検診に採用されてこなかったため、肺癌発見率の飛躍的向上につながらず、住民の検診意欲を低下させる原因の一つになったのかもしれない。このような状況のなかで、わが国で開発されたらせんCTを住民の肺がん検診に導入しようという試みが先駆的な地域で1996年から始まっている[2]。しかし、公的検診に取り入れられている例はまだ一部である。海外で行われたCT検診の有効性評価の研究で良好な成績も出始めており[3]、この機会にCT検診の公的検診への導入のための問題点と対策を検証したい。

*1 岡山県健康づくり財団附属病院
〒700-0952　岡山市北区平田408-1
e-mail: nkenji@okakenko.jp

1. がん検診ガイドラインで推奨されていない問題（Table 1）

現在わが国で肺がん検診に対する公式な推奨度を公表しているのは、国立がん研究センター祖父江らによるガイドラインである[4]。このガイ

ドラインに準拠して国の検診政策が決定されており、その影響度は大きい。平成18年度版のガイドラインによれば、低線量CT検診の推奨度はIとなっており、「死亡率減少効果の有無を判断する証拠が不十分であるため、公的検診（対策型検診）として実施することは勧められない」という判断である。その根拠としては、低線量CT検診による死亡率減少効果を検討した直接証拠が乏しく、胸部X線による従来検診との間に有意差が認められなかったことを挙げている。たとえばSwensenらの論文[5]では、シングルアームで行われたCT検診の肺がん死亡率と70年代に行われたMayo Lung Project[6]の単純X線検診の肺がん死亡率を比較して、有意差を検出するにいたらなかったと結論している。ガイドラインの判断をせめてB（死亡率減少効果を示す相応な証拠があるので、実施することを勧める）に変更するには、肺がん死亡率減少効果と不利益が利益を下回るというエビデンスの集積が必要であり、今回のNLSTの発表[3]は大きな期待を集めている。さらにわが国独自のコホート研究（中山富雄ら：厚生科学研究　CT肺がん検診有効性コホート研究・喀痰細胞診有効性症例対照研究）の成績や現在計画中の無作為化試験[7]の結果が待たれる。

Table 1　肺がん検診の推奨レベル

祖父江友孝他：平成18年度厚生労働省がん研究助成金「がん検診の適切な方法とその評価法に関する研究」班．有効性評価に基づく肺がん検診ガイドラインより

検査方法	証拠	推奨	
非高危険群に対する胸部X線検査、及び高危険群に対する胸部X線検査と喀痰細胞診併用法	2+	B	死亡率減少効果を示す相応な証拠があるので、対策型検診及び任意型検診として、非高危険群に対する胸部X線検査、及び高危険群に対する胸部X線検査と喀痰細胞診併用法による肺がん検診を実施することを勧める。ただし、死亡率減少効果を認めるのは、二重読影、比較読影などを含む標準的な方法[注1)]を行った場合に限定される。標準的な方法が行われていない場合には、死亡率減少効果の根拠はあるとはいえず、肺がん検診としては勧められない。また、事前に不利益に関する十分な説明が必要である。
低線量CT	2-	I	死亡率減少効果の有無を判断する証拠が不十分であるため、対策型検診として実施することは勧められない。任意型検診として実施する場合には、効果が不明であることと不利益について適切に説明する必要がある。なお、臨床現場での撮影条件を用いた非低線量CTは、被曝の面から健常者への検診として用いるべきではない。

Table 2　CT検診車コスト

CT検診車年間運用コスト							
固定費		準固定費		準変動費		変動費	
CT検診車*	20581740	保守費		光熱費	291360	人件費	4484000
車検費用	185065	読影システム	2000000			燃料費	378000
自動車税	30000	CT装置	4800000			読影料	6000000
車両整備費	60000	（X線管球代込）				通信費	1000000
読影システム	4000000					雑費	1000000
計	24,856,805		6,800,000				12,862,000

合計　　¥44,518,805

＊16chマルチスライスCT,3.5MHUの管球を想定

5年償却　年100日稼動　2000人受診とすると1人当たり¥22,259

年100日稼働　5000人受診とすると1人当たり　¥8,904

2. 検診用のらせんCT車の不足の問題 (Table 2)

肺がん検診専用のらせんCT検診車は、1台7,000から9,000万円程度の導入費用とかなりのランニングコストが発生する。守谷の概算[8]によると、検診機関が購入して利益をだすためには、1日50人、年間100日稼働と仮定して、一人当たり総費用は10,000円と高額になる。レンタルCT検診車はシングルスライスの場合、一人当たり5,000円と設定されており、読影料や事務費用を加味しても8,000円程度に収まり、現時点では民間のレンタル業者の利用が現実的である。しかし、全国の検診機関が大量に同一規格の検診車を発注するようになれば、コストは大幅に下がる可能性があり、独自に購入しても、一人当たりの費用は半減できると思われる。なお中山の平成21年の集計によれば、現在稼働している検診車車載型CTは15台であり、大幅な増車にはかなりの時間と費用が必要であろう。現在、施設据え置き型CTも56台検診用に稼働しているが、ほとんどは人間ドックなど任意型健診での利用である。

3. 検診対象の選定

現行の肺がん検診の対象者は40歳以上のすべての住民となっているが、CT検診の対象者については統一された基準はない。NLSTの対象者は50～74歳の喫煙者、松本市では40歳以上の松本市在住者で3年に1回、鹿児島県では50歳以上で鹿児島県在住者などとなっており、実施主体によってまちまちである。全国的に実施する場合には、統一が必要であるが、基準となるエビデンスがまだないため困難な問題である。なお、参考として平成16年に中山らが発表している【CT検診精度管理ガイドライン】の記載を示す (Table 3)。

4. 検診条件や精検基準の未統一の問題

検診条件や精検基準については、当学会肺がん診断基準部会がガイドラインを発表しているが、必ずしも検診実施機関で遵守されておらず、低線量撮影も徹底されていない (Table 4)。現在、NPO肺がん検診認定機構 (http://www.ct-kensin-nintei.jp/) で認定医師・認定技師の認定が順次行われ、平成23年5月現在、認定医師851名、認定技師458名となっているが、今後、公的検診を普及させるために必要な基準の統一を考えると、検診施設の認定制度の創設も早急に取り組むべきである。

5. CT読影医の不足

CT読影医の不足の問題は深刻であり、現在の任意型、一部公的検診の読影ですら放射線科医の過重労働を招いているとの批判がある。全国的に公的検診となった場合、読影数は数十倍になり、しかもMDCTが主体となれば読影の負担は計り知れない。CADの精度向上と普及は当然

Table 3　検診対象をどうするか

【CT検診精度管理ガイドライン】 (平成16年7月　中山ら)
対象①：50歳以上75歳未満の高危険群 (喫煙指数600以上の喫煙者で過去喫煙も含む)
対象②：50歳以上で非高危険群
対象③：40歳以上50歳未満の男女
対象④：75歳以上男女

Table 4　検診条件

平成21年度日本ＣＴ検診学会全国集計　精度管理部会
中山富雄

撮影管電流について		
固定式　41(最小　15mAs　最大　200mAs)		
	25mAs以下	32%
	25< ≦50mAs	61%
	70mAs以上	7%
可変式　19* (auto MAとのみ記載が4施設) 最大管電流の記載なし(当施設は30～40mA)		
記載無し　8		

であるが、認定放射線技師による一次スクリーニングを議論する必要がある。

一つの実験事業であるが、総務省のICTふるさと元気事業として「地域における肺がんCT検診の普及と在宅医師の活用事業」が平成22年度開始されており、現在家庭の事情で在宅勤務しかできない医師の戦力化が大いに期待できる（Fig. 1）。（http://www.soumu.go.jp/main_content/000067924.pdf）

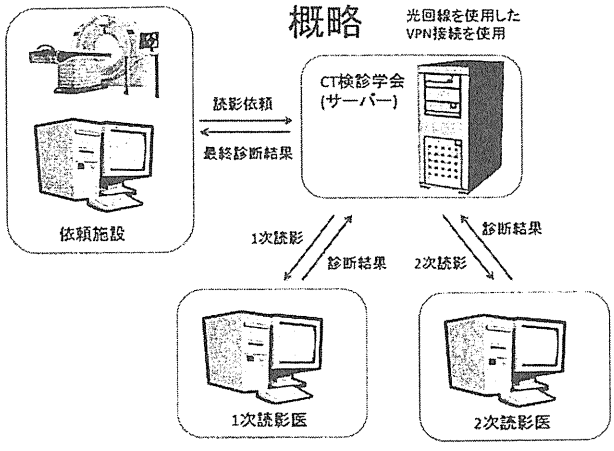

Fig. 1　地域における肺がんCT 検診の普及と在宅医師の活用事業

6. 検診料金および検診経費負担の問題

住民あるいは職員の健康管理上、当然必要な経費であるが、どの程度まで許容できるのか、実施主体の考え方により大きく異なっている。胸部X-Pなら一人当たり1,300円程度でほとんどの自治体では自己負担はないが、CT検診になると松本市のように7,000円の検診費用のうち5,000円を市が負担し、本人負担を2,000円に設定しているところや、愛媛県のように自己負担を6,000円としているなど大きなばらつきがある。公的検診として全国一律に行うのであれば、一律の負担額の設定が求められる。費用負担軽減と読影医師の負担軽減のため、公的検診では数年に1度のCT検診の導入から始めるのが現実的ではなかろうか。実際に松本市では3年に1度実施され、

Table 5　検診料金

検診費用　1件あたり	
施設検診	
11,731円	岡山県健康づくり財団では8,400円
最小5,250 - 最大45,000円（中央値10,000円）	
車載型検診	
8,276円	
最小　450 - 最大16,000円（中央値 7,380円）	

CT検診学会全国調査より（中山富雄ら）

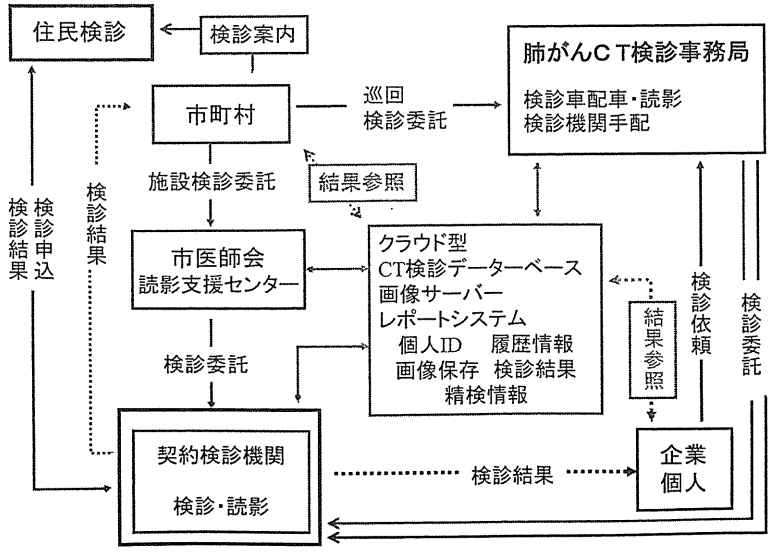

Fig. 2　岡山県での胸部CT 検診システム

岡山では5年に1度のCT検診を企画している。

都市部では、集団検診ではなく、個別医療機関実施の検診が普及してきている。医師会と協力してそのような施設でも実施可能なシステムや検診料金体系を考える必要がある。

7. 精検施設の問題

CT検診での肺癌発見率は初回受診では胸部X-P検診の8～10倍と飛躍的に向上する。しかも陰影は1cm前後と非常に早期のものが発見される。しかし、小さい陰影が多数発見されるため、その確定診断は極めて難しくなる。気管支内視鏡検査、CTガイド下生検、VATSなどに熟達した専門医のいる施設が精密検査を担当しなければならない。しかし、多くの地方ではそのような専門病院は限られており、要精検者が殺到すれば、病院機能は麻痺してしまう恐れがある。経過観察にしても特定の病院に集中すれば、一般診療でのCT予約がパンクしてしまうだろう。優秀なCT撮影装置を備えてはいるが、あまり稼働率のよくない地方病院でも精査あるいは経過観察ができるように、専門医による遠隔診断支援システムはどうしても必要になるであろう。

8. 精度管理システム

公的検診として機能するためには、検診対象者の把握から受診勧奨、検診実施方法および精密検査やその結果の把握などの均てん化が必要である。精密検査の結果把握はがん登録との照合が不可欠であるが、地方自治体が個別に行うのは困難であり、また検診機関が行うことにも問題がある。公的検診を全県的に実施する場合には、Fig. 2に示すような組織を岡山県で立ち上げたいと考えている。

結　語

以上、現時点で公的CT検診導入に向けての問題点と対策を列挙してみた。まだまだ多くのハードルが存在すると思われるが、CT検診の有用性が明らかになってきたことを踏まえて、公的検診がいつでも実施できるように準備をしておくことは本学会に課せられた使命であると思われるので、今後も建設的な議論を重ねていく必要がある。

文　献

[1] Matsuda T, Marugame T, Kamo KI, Katanoda K, Ajiki W, Sobue T; The Japan Cancer Surveillance Research Group. Cancer Incidence and Incidence Rates in Japan in 2005: Based on Data from 12 Population-based Cancer Registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Japanese Journal of Clinical Oncology, 41: 139-47, 2011

[2] Sone S, Takashima S, Li F et al: Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998; 351: 1242-1245

[3] http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease：2010年11月

[4] 厚生労働省「がん検診の適切な方法とその評価法の確立に関する研究」班：有効性評価に基づく肺がん検診ガイドライン．厚生労働省，2006

[5] Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002; 165: 508-13

[6] Robert S. Fontana MD, David R. Sanderson MD, et al. Screening for lung cancer. A critique of the mayo lung project. Cancer 67; 1155-1164, 1991

[7] 佐川元保、祖父江友孝、江口研二ほか．肺がんCT検診の有効性評価のための無作為化比較試験計画．CT検診 2009; 16: 102-107

[8] 守谷欣明：肺癌CT検診－新しい胸部検診の構築－．複十字290 (3)：12-17. 2003

Problems to achieve lung cancer screening with CT as population based screening

Kenji Nishii

Okayama Health Foundation Hospital

Abstract

On November 4, 2010, the National Cancer Institute announced that the National Lung Screening Trial (NLST) was ending, because independent experts came to the conclusion that the study's primary objective, benefit for the group screened by LDCT, was proven.

In consideration of this report, we have to figure out how to widespread CT screening as population based screening over Japan. To achieve this, there are several problems that need to be overcome.

The first thing is that CT screening is "I" recommendation in Japanese Guideline for Lung Cancer Screening. We will need to change "B" or "C" recommendation from "I" on the ground of NLST. The second thing is severely deficient in CT screening examination car and radiologist. CAD and accredited Radiological Technologists need to be explored. The third thing is the unsaturation of knowledge of low dose CT and detected pulmonary nodules management rule. All medical screening facilities must adhere to the criterion of the Japanese society of CT screening (JSCTS). Fourth, how much cost can screenees of having CT afford? Finally, we confront a severe shortage of doctors that can perform diagnostic workup and treatment of lung cancer in local areas.

In conclusion, we need to discuss for solutions to these problems at the JSCTS meeting, and I think to draw on a breakthrough from existing chest X-ray screening system.

Key words: CT screening for early detecting of lung cancer, NLST, population based screening, screening cost
J Thorac CT screen 2011; 18: 95-100

肺がん検診は受けたほうがよいですか？また，体への影響はないのでしょうか？

ご存じのように，肺がんは死亡者の最も多いがんで，早期に発見しなければ助からないがんの代表です．ほとんどの肺がんは症状出現時にはすでに進行がんで，治癒が望める切除を受けることが困難です．ただ，症状の出現するかなり前から，胸部X-Pでは陰影が認められます．胸部X-Pによる年1回の検診はぜひ受けてほしいと思います．最近は胸部X-Pもデジタル化され，画質も向上しています．低線量らせんCTによる検診も行われており，超早期の肺がんも発見されています．一部の肺がんは胸部X-Pに写る前に，痰のなかにがん細胞を認めるものがあり，このようなタイプの肺がんは喫煙者に多いため，喫煙指数(一日喫煙本数×喫煙年数)600以上の方は胸部X-P検診と同時に喀痰細胞診が推奨されています．検診の体への影響としては放射線の被曝がありますが，デジタル化された胸部X-Pでは1枚の撮影で0.05mSv以下，CT検診でも低線量で行われるので1mSvと影響を心配しなくてもよいレベルです．

西井研治
岡山県健康づくり財団附属病院　院長

解　説

臨床家は個別の症例をみているので，胸部X-P検診で無症状のうちに早期発見することが，肺がん死を減らすためには当然重要だと考えるが，残念ながら検診でも進行がんでみつかるケースもある．700万人が毎年検診を受けている国レベルで考えた場合は別の見方もある．20年以上続いている肺がん検診有効・無効の論争である．個人で受ける検診(人間ドックなど任意型検診)は推奨するのに何ら躊躇する必要はないが，公的検診として税金を投入して行われる集団検診(対策型検診)の場合は，受診者全体の死亡率低減効果がなければ行政施策として行うべきではないという意見である．長い論争の末，わが国で行われた複数の症例対照研究など[1,2]を根拠に，2006年「有効性評価に基づく肺がん検診ガイドライン」[3](班長　祖父江友孝　国立がんセンターがん予防・検診研究センター)での推奨レベルB決定と2007年に厚生労働省が組織した「がん検診に関する検討会」(座長　垣添 忠生 国立がんセンター名誉総長)報告書で，「わが国で行われている肺がん検診は，死亡率減少効果を示す相応な証拠があるので，対策型検診および任意型検診として推奨される」とやっと結論が出された(**表1**)．「**肺がん検診は受けたほうがいいです**」と勧めるべき根拠を得たわけで，患者・家族から質問を受けた際に自信をもって答えればよいと思われる．ただし，精度の高い検診を受けることが条件とされており，二重読影や比較読影が行われ，精密検査結果や肺がん発見率が公表されている施設を勧めるべきであろう．推奨される検診機関については，多くの県では生活習慣病管理指導協議会肺がん部会がホームページなどで公表しており，その資料を利用するのが適切である．

むしろ最近大きな関心を集めているのは，らせ

表1　肺がん検診の推奨レベル

検査方法	証　拠	推　奨	
非高危険群に対する胸部X線検査および高危険群に対する胸部X線検査と喀痰細胞診併用法	2＋	B	死亡率減少効果を示す相応な証拠があるので，対策型検診および任意型検診として，非高危険群に対する胸部X線検査，および高危険群に対する胸部X線検査と喀痰細胞診併用法による肺がん検診を実施することを勧める．ただし，死亡率減少効果を認めるのは，二重読影，比較読影などを含む標準的な方法*を行った場合に限定される．標準的な方法が行われていない場合には，死亡率減少効果の根拠はあるとはいえず，肺がん検診としては勧められない．また，事前に不利益に関する十分な説明が必要である．
低線量CT	2－	I	死亡率減少効果の有無を判断する証拠が不十分であるため，対策型検診として実施することは勧められない．任意型検診として実施する場合には，効果が不明であることと不利益について適切に説明する必要がある．なお，臨床現場での撮影条件を用いた非低線量CTは，被曝の面から健常者への検診として用いるべきではない．

＊：標準的な方法とは，「肺癌取扱い規約」の「肺癌集団検診の手引き」に規定されているような機器および方法に則った方法を意味している．したがって，撮影電圧が不足したもの，二重読影を行わないもの，比較読影を行わないものなどは，ここでいう標準的な肺がん検診の方法ではない．

（文献3）より改変）

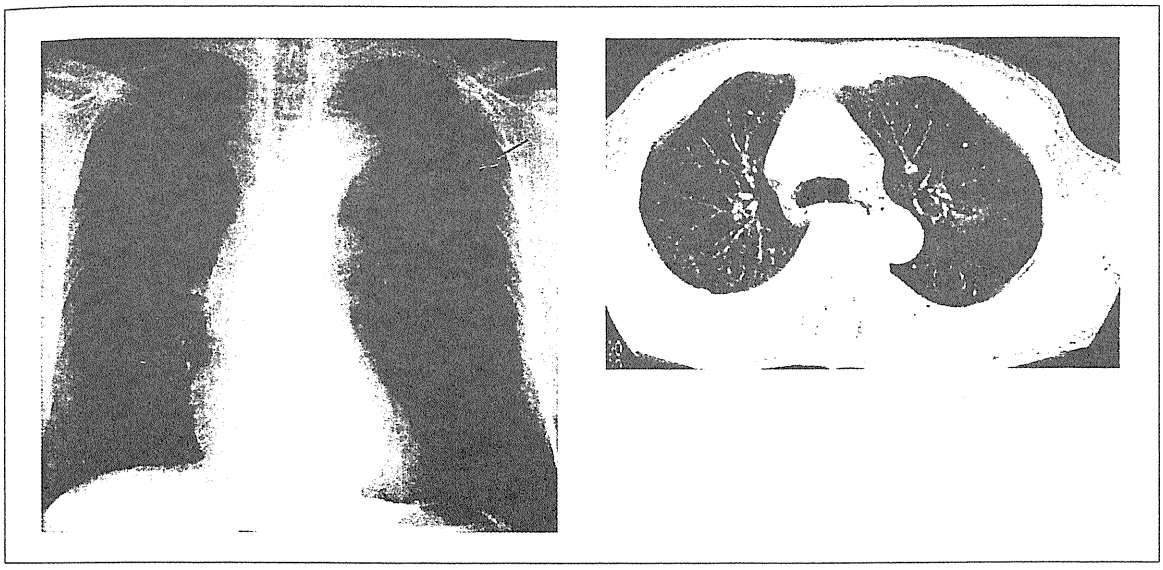

図1　CT検診で発見された肺胞上皮がん

んCTによる検診である．適切な方法で行っていると自負しているわれわれの施設でも，胸部X-P検診で発見される肺がんのうち，早期といわれるⅠ期は50～60％で5年生存率は50％にとどまっている．早期発見が困難な理由として，①ろっ骨や心臓，血管など既存の臓器に重なる肺がんの陰影を指摘するのが難しいこと，②肺胞上皮がんなど正常肺組織との違いが少ない，いわゆるすりガラス陰影は2cmを超えるような陰影でも指摘できないことがある（図1）．これらの弱点を克服する方法としてCT（低線量らせんCT）検診が注目されるようになっている．人間ドックではすでにオプションで選択できる施設が多いが，胸部X-P検診のときと同様に対策型検診として行った場合，CT検診によって本当に肺がん死亡減少効果があるのかについて，世界的に議論されている．高い肺がん発見率は生命予後に関与しないいわゆる「がんもどき」を多量に発見しているだけではないかという意見である．このような意見に反論するには，無作為化試験での肺がん死亡率低下の証明が必要である．低線量らせんCT検診はわが国の発明であるが，大規模な有効性評価研究は欧米が先行し

ている．その一つであるNCIが行っていたNLST(national lung screening trial)から2010年11月に有効性が証明されたとの発表があった[4]．このような研究成果を受けて，先の祖父江班ガイドラインや厚生労働省検討委員会の推奨度変更が期待される．

このようなエビデンスの集積から，質問に対する答えは「肺がん検診は受けたほうがいいですよ．機会があれば低線量らせんCTも受けることを勧めます」となる．

X線検診による不利益として，放射線被曝の問題を取り上げる報道もみられるが，胸部X-Pによる被曝線量は放医研の報告[5]ではわが国の平均で0.057mSv[注1)]とされており，国連科学委員会(UNSCEAR)の19ヵ国平均0.14mSvよりもかなり低い．低線量らせんCT検診も最近のMDCTでは，ファントムを使ったCT 線量指標(computed tomography dose index：CTDI)の検討などで，1mSvを切っていると推定されている．自然放射線(世界平均)2.4mSvに比べ，これらの値はかなり低く，被曝による障害を心配するレベルではないことを受診者に十分説明をして，不安に答えるべきであろう．

注1：Svとは線量当量のことで，人体が放射線を受けた場合の影響を表す単位．

参考文献

1) Nishii K, Ueoka H, Kiura K, et al：A case-control study of lung cancer screening in Okayama Prefecture, Japan. Lung Cancer, 34：325-332, 2001.
2) 佐川元保, 中山富雄, 塚田裕子, 他：肺がん検診の有効性評価：厚生省藤村班での4つの症例対照研究. 肺癌, 41 (6)：637-642, 2001.
3) 平成18年度厚生労働省がん研究助成金「がん検診の適切な方法とその評価法の確立に関する研究」班：有効性評価に基づく肺がん検診ガイドライン, 2006.
4) National Cancer Iistitute：Lung cancer trial results show mortality benefit with low-dose CT (www. cancer. gov/newscenter/pressreleases/NLSTresultsRelease).
5) 赤羽恵一：医療における放射線防護；医療被ばくの現状. INNERVISION, 25 (6)：6-9, 2010.

肺がんCT検診ランダム化比較試験のパイロットスタディにおける参加勧奨と研究応諾率

佐川元保，田中　良，水上　悟，西田耕造，
西井研治，薄田勝男，相川広一，町田雄一郎，
上野正克，佐久間　勉

金沢医科大学雑誌　第36巻　第1号　別刷
2011年6月

金医大誌（J Kanazawa Med Univ）36：25－32, 2011

肺がんCT検診ランダム化比較試験のパイロットスタディにおける参加勧奨と研究応諾率

佐川元保[1)]，田中良[1)]，水上悟[2)]，西田耕造[2)]，
西井研治[3)]，薄田勝男[1)]，相川広一[1)]，町田雄一郎[1)]，
上野正克[1)]，佐久間勉[1)]

要　約：目的：低線量CTによる肺がん検診の死亡減少効果を評価するため無作為化比較試験が計画された。試験のデザインは，参加者を無作為に2群に分けて，対照群では現行検診を10年間，研究群では喫煙者では低線量CT検診＋喀痰を10回，非喫煙者では低線量CT検診を3回，現行検診を7回行うというものである。この試験の実現可能性を検討するパイロット研究を行ったので，その参加勧奨と研究応諾率を中心に報告する。
方法：本年の肺がん検診を受診した羽咋市の50－64歳の国保加入者に対して，本試験の説明書を郵送した。その説明書で，効果はまだ不明なこと，無作為化して半分の人しかCTは受けられないこと，被曝や過剰診断などの不利益があることなどを説明した。
結果：329例に説明書を郵送し117例から返信があった。2例が不適格，1例が説明会参加不能で，残りの説明会参加114例中3例が研究に不参加となり，111例が研究参加した。
結論：研究参加応諾率は対象の1/3ときわめて高く，比較試験の実現可能性は高いと思われた。

キーワード：肺がん検診，早期発見，有効性評価，胸部CT検診

はじめに

厚生省藤村班の研究により，現行検診（胸部X線＋喀痰細胞診）を毎年受診することにより肺癌死亡リスクが有意に低下することが判明したが，一方でその効果が1年を超えては持続しないなどの限界も明らかとなった (1)。また，現行検診で効果を上げるには厳格な精度管理が必要で，そのため全国レベルでは肺癌による死亡率の減少は未だ充分に到達されていないのが現状である (2)。その点からも，現行検診を超えるパワーを持った検診方法の開発が必要とされている。低線量CTによる肺がん検診は小型末梢型肺癌の検出に大きな威力を発揮することから (3)，新しい肺がん検診として期待を集めているが，その死亡減少効果に関する評価はまだ確立していない (2)。

[1)]金沢医科大学医学部呼吸器外科学
石川県河北郡内灘町大学1-1
[2)]石川県成人病予防センター
[3)]岡山県健康づくり財団
平成23年1月25日受理

現在，本邦にて胸部CT検診の有効性評価のためのコホート研究が行われているが未だ結果は報告されていない。一方欧米では，すでにいくつかの無作為化比較試験が行われているが (4-6)，研究精度に問題がある可能性も指摘されており，結果に関しては楽観を許さないと考えられている。もし，欧米での無作為化比較試験で「CT検診は死亡率減少効果がない」という結果となった場合には，仮に本邦のコホート研究で「効果あり」となったとしても，CT検診の存続は危ういであろう。筆者らは，そのような状況になる前に本邦においても無作為化比較試験を遂行する必要があると以前から訴えており，本邦で実施可能な計画を提案した (7)。さらに2008年から厚労省がん研究助成金「がん検診の評価とあり方に関する研究」班（垣添班）において，より具体的な研究計画を立案・論文化するとともに (8)，2009年には金沢医科大学倫理委員会にて当該研究計画の実施が承認された。

当該研究計画は年間予算が2億円を超える大きなプロジェクトであるが，今回パイロット研究として，一部の市町（石川県羽咋市，岡山県里庄町）で先行して開始することになった。この論文では，石川県羽咋市での研究の実際の経過および参加応