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Original Article

Nested Case-Control Study on Associations between Lung Function, Smoking and Mortality in Japanese Population

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Abstract

Objectives: Only a few long-term follow-up studies with a focus on the association between lung function and mortality in the Japanese population have been undertaken. In this study, we examined the associations of lung function, smoking and the results of allergy skin tests with mortality in a longitudinal study of the Japanese population.

Methods: Baseline measurements were performed on residents of Fukui, Japan in 1972, and a follow-up survey was conducted in 2002. By employing a nested case-control design, 596 cases (deaths) and 596 age and sex-matched controls (survivals) were selected. Lung function was assessed using forced vital capacity (FVC) expressed as the normal percent predicted (FVC %pred) and the ratio of forced expiratory volume in 1 second (FEV_1) to FVC (FEV_1/FVC). Allergy skin tests were performed with extracts of house dust, candidia and mixed fungal samples (bronchomycosis). The Brinkman index was used to assess smoking intensity. The Cox proportional hazards model was used to evaluate whether lung function was associated with mortality after adjustment for other potential confounding variables.

Results: Those categorized into the first- or second-lowest quartile of FVC %pred had a higher mortality [hazard ratios (HRs) and 95% confidence intervals (CIs): 2.01 (1.26–3.19) and 1.84 (1.11–3.05)], respectively. On top of these, heavy smoking (BI≥400) was associated with a higher mortality [HR and 95%CI: 1.73 (1.18–2.53)]. There were only weak of associations between the results of allergy skin tests and mortality.

Conclusions: These results suggest that FVC %pred of lung function and smoking can serve as long-term independent predictors of mortality.

Key words: forced vital capacity, mortality, smoking status, allergy skin tests, Japanese population

Introduction

Impaired lung function is a significant predictor of mortality (1–14). However, most of the studies showing this have focused mainly on forced expiratory volume in 1 second (FEV_1) (4–7, 12–14) and a smaller number of such studies have focused on forced vital capacity (FVC), including FVC %perd. (1, 2, 8). Cigarette smoking is a major cause of impaired lung function (15, 16). In the general Japanese population, high smoking rates have been reported; 45.8% of men and 13.8% of women were reported to smoke in 2005 (Ministry of Health, Labor and Welfare 2005). Investigating the smoking-lung functions-mortality associations will be helpful in establishing various health promotion initiatives. To our knowledge, only a limited number of studies have examined the relationship between lung function and mortality in the Japanese population (17). The most cited study, the Honolulu Heart Program study (undertaken in Hawaii, 1965) investigated the above-mentioned aspects among Japanese Americans (5, 6). In one cohort study, it was found that the mortality in a poor lung function group was significantly higher than that in a good lung function group (33.6% vs 9.4%) of females in Kyushu, Japan (3).

Furthermore, apart from aging and smoking, other factors with possible effects on lung function have been examined infrequently, particularly among the older population. One of these factors, the results of allergy skin tests, presents a strong

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association with lung function (18, 19). However, the association between the results of allergy skin tests and mortality remains controversial; some researchers report that the results of allergy skin tests are not good predictors of subsequent mortality (20). In contrast, others maintain that positive allergy skin test results carry an increased risk of all causes of mortality in subjects with an FEV_1<80% of that predicted (21). However, some researchers consider that positive allergy skin test results are associated with a significantly increased risk of cardiovascular mortality only in obese and smoking subjects, but show an association with reduced cardiovascular mortality in nonsmoking subjects of normal weight and lung function (22).

Nevertheless, the long-term (over several decades) associations between lung function, smoking and mortality in the Japanese population have been examined in only a few studies, even though mortality from lung diseases is a serious concern among aged Japanese (Ministry of Health, Labor and Welfare 2004). The purpose of this study is to investigate the effects of lung function, smoking and allergy skin tests on mortality by undertaking a 30-year follow-up study on the Japanese population.

Methods

Study population

This study was conducted using a nested case-control design. The subjects were drawn from participants of the First Population Health Examination Survey (May 1972) in Awara-machi (Fukui prefecture) in northwestern Japan. In total, 4,470 participants aged 20–69 years agreed to take part in the lung function examination, and the participation rate was 79.2%. A follow-up survey was performed in April and May of 2002 on persons who had taken parting in the initial survey. However, 47 people had moved out of the area and information on the living status for 117 people was not available. We confirmed the deaths of 760 persons (excluding 4 accidental deaths). Subsequently, we selected 596 cases (deaths) and an equal number of controls (survivals) nest-matched for sex and age (±5 years) as the study subjects. The remaining deaths (164 people) were not included in this study, as between the two surveys, the number of survivals older than 55 at the time of the initial survey had been decreasing markedly and we were unable to find respective nest-matched controls for the remaining deaths.

Lung function measurements

After receiving informed consent for lung function measurements, spirometry was carried out three times by trained examiners using the Spirometer PM-80 (Fukuda Electrical Co., Tokyo) (23). Before the measurement procedure, the lung function examination was explained to all the participants. The highest values of all the subjects in three measurements were recorded. FEV_1 and FVC were also measured. FVC %pred and FEV_1/FVC were calculated using FVC, FEV_1 and predicted FVC. Predicted FVC values were calculated using Baldwin's formula (24):

$$\text{Male: } (27.63 - 0.112 \times \text{age}) \times \text{height (cm) and}$$
$$\text{Female: } (21.78 - 0.101 \times \text{age}) \times \text{height (cm)}$$

Lung function values for forced vital capacity (FVC) expressed as the normal percent predicted (FVC %pred) and FEV_1/FVC ratios were calculated. For FVC %pred, the subjects were categorized into quartiles as follows: (1) <80.0%, (2) 80.0–89.5%, (3) 89.6–98.7%, and (4) ≥98.8%. For the FEV_1/FVC ratio, the subjects were classified into quartiles as follows: (1) <70.0% and (2) ≥70.0%.

Mortality data

For the participants who undertook the first health examination survey on lung function in Awara-machi, Fukui prefecture, the mortality data was collected from mortality reports in the town's obituary lists issued by the Awara-machi hall and health visitor's information in the town.

Allergy skin tests

Many studies have reported that the results of allergy skin tests are associated with respiratory diseases, lung function and mortality (18, 19, 21, 22). Skin-prick tests are widely used in large population surveys because the procedure is simple and well documented. Allergy skin tests were randomly performed on participants living in the given districts. One-quarter of the districts were randomly selected for the tests. The examination procedure consisted of prick tests in which an allergic flare reaction to house dust, candidia and a mixed fungal extract of bronchomycosis (Hollistwer-Stier Labs) greater than 5 mm (25) were considered to be positive.

Respiratory symptoms and past history

Using the BMRC questionnaire (British Medical Research Council's Committee on Research into Chronic Bronchitis) (26) interview schedule, information on respiratory symptoms (e.g., presence or absence of cough, sputum and shortness of breath) was collected. The subjects also confirmed or denied a past history of the following: pneumonia, pulmonary tuberculosis, bronchitis, heart disease, heart operation, asthma or chest emphysema.

Body mass index

Height and weight were measured using a stadiometer and a weight scale to the nearest 0.1 centimeter and 0.1 kilogram, respectively. The body mass index was calculated by dividing each subject's weight in kilograms by the square of height in meters. According to the World Health Organization's recommendation, the subjects were classified into four categories: (1) <18.5 (underweight), (2) 18.5–24 (normal weight), (3) 25–29 (overweight), and (4) ≥30 (obese).

Smoking habits and Brinkman index (BI)

The subjects were asked to answer questions regarding their smoking habits (current, never or ex-smoker). For the current and ex-smoker categories, the respondents completed a smoking history, including the duration of smoking and number of cigarettes smoked per day. On the basis of the answers to those questions, cumulative cigarette consumption was expressed using BI (the average number of cigarettes per day multiplied by the number of years of smoking). The subjects were categorized into four groups: (1) never smoker, (2) ex-smoker,

(3) <400 cigarette year (light to moderate smoker), and (4) ≥400 cigarette year (heavy smoker).

Ethical approval

This study was approved by the provincial and local (municipality) departments of inhabitants and health services in Awara-machi before enrollment were carried out. Because the survey was conducted at the same time as an annual medical examination, all the participants signed an informed consent document in upon undergoing baseline measurements. In addition, we treat the survey's data cautiously to protect the personal information in this study. Ethical approval was obtained from the Ethical Committee of the Toyama University of Health and Welfare.

Statistical analysis

Student's t test and the chi-square test were used to evaluate whether there were differences in variables between the case and control groups. We evaluated the associations of the characteristic variables and quartiles of FVC %pred or smoking status using the chi-square test and by analysis of covariance (ANCOVE). The Cox proportional hazards model was used to examine whether there were associations of mortality with lung function, smoking and the results of allergy skin tests. Lung function (FVC %pred and FEV_1/FVC ratio), age, sex, BMI, the results of allergy skin tests (house dust, candidia and a mixed fungal extract of bronchomycosis), respiratory symptoms (cough, sputum and shortness of breath), past history of chest disease, and smoking habits were simultaneously taken into account in the hazards model, and variables in the final model were selected by applying the stepwise method. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

The Pearson's correlation coefficients between variables entered in the model ranged from −0.24 to 0.27, implying that there was no multi-colinearity among the variables. All the statistical analyses were performed with a SPSS 10.0 J program package (SPSS Japan Inc., Tokyo), and a value of p<0.05 was considered as significant.

Table 1 Baseline characteristics of subjects according to case and control groups

	Case	Control	p value
	n=596	n=596	
Age (years)	52.2±10.5	52.4±10.6	0.800
Height (cm)	153.5±8.5	154.0±8.6	0.423
Weight (kg)	52.2±9.9	52.4±8.9	0.816
Sex			
Male	274 (46.0)	274 (46.0)	1.000
Female	322 (54.0)	322 (54.0)	
Body mass index (kg/m^2)	22.1±3.4	22.0±3.0	0.888
FVC %pred (%)	88.5±13.7	90.8±13.7	0.004
FEV_1/FVC ratio (%)	83.4±6.1	83.6±5.4	0.404
Smoking status			
Never smoker	241 (40.4)	282 (47.3)	0.075
Ex-smoker	46 (7.7)	44 (7.4)	
Current smoker 1 (BI<400)	145 (24.3)	138 (23.2)	
Current smoker 2 (BI≥400)	164 (27.5)	132 (22.1)	
Smoking BI			
0 (never smoker)	241 (40.5)	282 (47.6)	0.033
<400	174 (29.2)	164 (27.7)	
≥400	180 (30.3)	147 (24.8)	
Allergy skin tests (positive)	(n=178)	(n=178)	
House dust	8 (4.5)	17 (9.6)	0.065
Candidia	7 (3.9)	13 (7.3)	0.176
Mixed fungal extract (bronchomycosis)	16 (9.6)	16 (9.0)	1.000
Respiratory symptoms (yes)			
Cough	28 (4.7)	30 (5.0)	0.412
Sputum	47 (7.7)	52 (8.7)	0.699
Shortness of breath	157 (26.2)	167 (28.0)	0.431
History of chest disease (yes)	269 (46.4)	276 (45.2)	0.727
Follow-up period (years)	20.6±6.9	29.9±0.0	<0.001

Value indicates mean±SD or number (%).
FVC, forced vital capacity; FEV, forced expiratory volume in 1 second.
FVC %pred, FVC expressed as the normal percent predicted.
FEV_1/FVC ratio, the ratio of FEV_1 to FVC.
Brinkman index (BI): the average number of cigarettes per day multiplied by the number of years of smoking.
Data from the First Population Health Examination Survey in Awara-machi, Fukui, Japan, 1972, and follow-up in 2002.

Results

Table 1 shows the characteristics of the subjects. There were no significant differences in the mean values of age, sex, height, weight or BMI between the cases and controls. FVC %pred was significantly (p=0.004) higher in the controls than it was in the cases. The cases showed more evidence of a smoking habit (p=0.075). No significant differences were found for FEV_1/FVC ratio or the prevalence of respiratory symptoms (i.e., cough, sputum, shortness of breath) between the cases and controls. In addition, cases were more likely to be positive to allergy skin tests for house dust (p=0.065).

Table 2 presents patients characteristics according to the quartiles of FVC %pred (1 with the lowest and 4 with the highest values). There were associations of FVC %pred with FVC %pred cutoff, other anthropological indices (age, height, weight and sex), and some respiratory symptoms, but none with the results of allergy skin tests and smoking status.

The associations between cigarette smoking status, gender, lung functions, respiratory symptoms and the results of allergy skin tests are presented in Table 3. The Brinkman index of smoking was significantly higher in the male group. FVC %pred did not show significant association with smoking status. Instead, we found that FEV_1/FVC ratio was significantly lower in heavy smokers (BI≥400). Heavy smokers showed a significantly higher prevalence of respiratory symptoms. In the case of allergic reactions, only house dust presented significance in current smokers.

Table 4 shows the hazard ratios (HR) and 95% confidence intervals (CI) for FVC %pred and smoking habits obtained using the Cox proportional hazards model. Compared with the highest quartile of FVC %pred (≥98.8%), the lowest quartile of FVC %pred (<80.0%) presented a high mortality risk [HR=2.01; 95%CI=1.26–3.19; p=0.003]. The second-lowest quartile of FVC %pred (80.0–89.5%) also presented a relatively high mortality risk [HR=1.84; 95%CI=1.11–3.05; p=0.019]

Table 2 Characteristics of subjects according to quartile of FVC %pred at baseline survey

	Quartile of relative FVC %pred				p value
	1	2	3	4	
FVC %pred cutoff (%)	<80.0	80–89.5	89.6–98.7	≥98.8	
Numbers	300	294	296	301	
FVC %pred (%)	72.4±6.7	84.9±3.0	94.1±2.7	107.0±6.9	<0.001
FEV_1/FVC ratio (%)	83.2±7.3	83.9±5.1	83.6±5.5	83.1±4.7	0.350
Age (years)	55.4±9.0	54.0±9.2	51.0±10.5	48.8±12.0	<0.001
Height (cm)	150.7±7.6	152.7±8.6	155.2±8.3	156.4±8.6	<0.001
Weight (kg)	50.4±10.0	52.3±10.1	52.9±8.7	53.1±8.4	0.001
Body mass index (kg/m^2)	22.1±3.7	22.4±3.4	21.9±2.7	21.7±2.7	0.083
Sex					
Male	109 (19.8)	128 (23.4)	162 (29.6)	149 (27.2)	<0.001
Female	191 (29.8)	166 (25.8)	134 (20.8)	152 (23.6)	
Respiratory symptoms (yes)					
Cough	30 (52.6)	12 (21.1)	9 (15.8)	6 (10.5)	<0.001
Sputum	30 (30.3)	28 (28.3)	20 (20.2)	21 (21.2)	0.343
Shortness of breath	119 (36.8)	78 (24.1)	61 (18.9)	65 (20.1)	<0.001
Allergy skin tests (positive)	(n=135)	(n=78)	(n=67)	(n=70)	
House dust	7 (28.0)	9 (36.0)	3 (12.0)	6 (24.0)	0.263
Candidia	5 (25.0)	4 (20.0)	7 (35.0)	4 (20.0)	0.278
Mixed fungal extrat (bronchomycosis)	11 (28.0)	8 (36.0)	5 (12.0)	8 (24.0)	0.815
History of chest disease (yes)	156 (28.7)	133 (24.4)	137 (25.2)	118 (21.7)	0.023
Smoking status					
Never smoker	138 (26.4)	137 (26.4)	122 (23.4)	125 (23.9)	0.155
Ex-smoker	27 (30.0)	22 (24.4)	19 (21.1)	22 (24.4)	
Current smoker 1 (BI<400)	63 (22.3)	64 (22.6)	67 (23.7)	89 (31.4)	
Current smoker 2 (BI≥400)	72 (24.3)	71 (24.0)	88 (29.7)	65 (22.0)	

Value indicates mean±SD or number (%).

Table 3 Associations between cigarette smoking status, gender, lung functions, respiratory symptoms and allergic tests at baseline in baseline survey

	Never smoker	Ex-smoker	Current smoker		p value
			(1) BI<400	(2) BI≥400	
	n=523	n=90	n=283	n=296	
Sex					
Male	49 (8.9)	66 (12.0)	178 (32.5)	255 (46.5)	<0.001
Female	474 (73.6)	24 (3.7)	105 (16.3)	41 (6.4)	
Age (years)	53.0±10.7	54.1±10.1	49.0±11.9	53.7±8.2	<0.001
FVC %pred (%)	89.2±13.4	87.8±15.3	91.2±14.5	89.3±12.8	0.117
FEV_1/FVC ratio (%)	84.8±5.2	82.7±6.2	83.6±6.3	81.4±5.5	<0.001
Respiratory symptoms (yes)					
Cough	19 (32.8)	5 (8.6)	6 (10.3)	28 (48.3)	<0.001
Sputum	15 (15.2)	17 (17.2)	26 (26.3)	41 (41.4)	<0.001
Shortness of breath	178 (54.9)	27 (8.3)	57 (17.6)	62 (19.1)	<0.001
Allergy skin tests (positive)	(n=131)	(n=31)	(n=99)	(n=90)	
Housedust	4 (16.0)	—	11 (44.0)	10 (40.0)	0.017
Candidiasis	3 (15.0)	2 (10.0)	9 (45.0)	6 (30.0)	0.162
Mixed fungal extrat (bronchomycosis)	6 (18.8)	5 (15.6)	11 (34.4)	10 (31.3)	0.112
History of chest disease (yes)	238 (43.7)	49 (9.0)	121 (22.2)	137 (25.1)	0.307

Value indicates mean±SD or number (%).

after adjustment for age, sex, BMI, the results of allergy skin tests, respiratory symptoms, past history of chest diseases and smoking habits. Compared with never smokers, heavy smokers (BI≥400) presented a high mortality risk [HR=1.73; 95%CI= 1.18–2.53; p=0.005]. Interestingly, separate analyses by gender (results not presented here) revealed the same results in men subjects only.

Figure 1 shows the cumulative survival curves for subjects stratified by quartile of relative FVC %pred. We found a significant negative relationship between FVC %pred and mortality.

Figure 2 shows the cumulative survival curves for subjects stratified by smoking status. A dose-response relationship between smoking habits and mortality was found.

Table 4 Associations of lung function and smoking status with causes of mortality in Cox proportional hazards regression model*

Variable	Hazards ratio	95%CI	p value
Age (years)			
20–39	1.00		
40–49	0.89	0.47–1.69	0.719
50–59	1.53	0.83–2.82	0.176
≥60	2.79	1.50–5.18	0.001
FVC %pred (%)			
<80.0	2.01	1.26–3.19	0.003
80.0–89.5	1.84	1.11–3.05	0.019
89.6–98.7	1.24	0.71–2.15	0.446
≥98.8	1.00		
Smoking status			
Never smoker	1.00		
Ex-smoker	1.13	0.66–1.94	0.655
Current smoker 1 (BI<400)	1.29	0.87–1.93	0.211
Current smoker 2 (BI≥400)	1.73	1.18–2.53	0.005

* Lung function (FVC %pred, FEV_1/FVC ratio), age, sex, body mass index, smoking status, allergy skin test results (house dust, candida, fungal mix of bronchomycosis), respiratory symptoms (cough, sputum and shortness of breath) and history of chest disease were simultaneously entered into the proportional hazards model, and the final model was chosen with a stepwise elimination procedure.
CI, confidence interval.

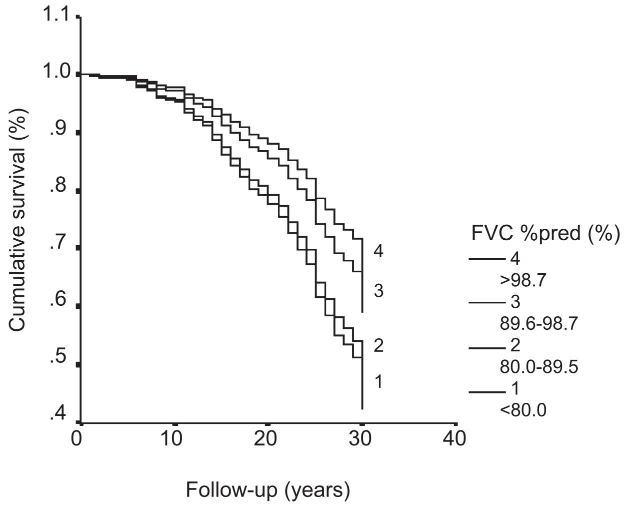

Fig. 1 Cumulative survival curves for subjects stratified by quartiles of relative FVC %pred in baseline survey in follow-up period.

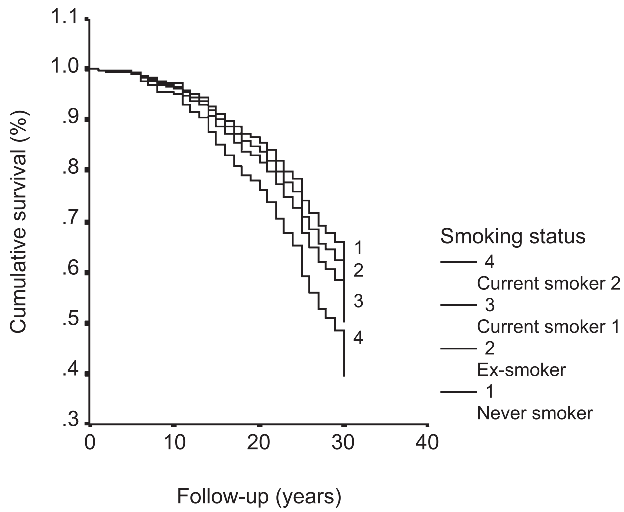

Fig. 2 Cumulative survival curves for subjects stratified by smoking status in baseline survey in follow-up period.

Discussion

The findings of this case-control study indicate that FVC %pred is significantly associated with mortality, after adjustment for associated confounding factors, in a 30-year follow-up study of the Japanese population. The study confirmed that the lowest and second lowest-quartiles of FVC %pred are associated with higher mortality, independent of smoking habits. In previous studies, similar findings have been presented—low spirometric values predicted a higher mortality due to all causes, which were independent of smoking habits (1). Impaired lung function (determined by FEV_1 and FVC) was also reported as an important independent predictor of mortality rate due to all causes, in addition to smoking habits and dyspnea, in an 11-year follow-up study (2). Furthermore, it was reported that a lower level of ventilatory function (50% decrease in FVC %pred and FEV_1 %pred) strongly predicted mortality due to all causes among never smokers in both sexes over a follow-up period of 10 years (8): relative risks of death were 1.8 for FVC %pred and 1.6 for FEV_1 %pred. Only a few studies have reported on the relationship between restrictive lung diseases with a lower FVC %pred and all-cause mortality in follow-up studies of 22 and 11 years (9, 10): the relative risks (HRs) were 1.7 and 2.3, respectively. A linear association between the percentage of predicted mortality due to all causes and FVC (RR 1.1) was observed in a sample of US adults (11). Two previous studies have shown a significant relationship between peak expiratory flow rate (PEFR) and all-cause mortality in American and Australian populations (27, 28). Therefore, the findings of this study are consistent with previous data. In addition, severely impaired lung function is a significant predictor of lung cancer and this fact is still under appreciated among some medical professionals (29).

In American and European populations, FEV_1/FVC ratio and mortality often present significant relationships (2, 12–14), but in this study, we found no such relationship. This could be related to ratio and mortality differences, in addition to various anthropo-biological, social and cultural differences between Japanese and non-Japanese population. The relationship between FEV_1/FVC ratio and mortality risk has been presented but only for male subjects (8). Also, the prevalence of chronic obstructive pulmonary disease (COPD) with a FEV_1/FVC ratio <70% in Japan is far lower than those in Europe and America (30). The prevalence of the FEV_1/FVC ratio (<70%) was 1.7% in our study subjects. According to national survey results, the prevalence of COPD in Japan is only 0.2% (Ministry of Health, Labor and Welfare 1999). Similar results have been reported in other Asian populations (31, 32). However, in Europe and America, the proportion of COPD cases varies between 4% and 10% (30). This fact could serve as a possible explanation of our findings on the relationship between FEV_1/FVC ratio and mortality.

Concerning the association between smoking habits and mortality, we found that heavy smokers (BI≥400) presented a significant increase in mortality compared with nonsmokers after adjustment for confounding factors including lung function. This finding provided support for smoking habits as a significantly independent predictor of higher mortality. Several studies have presented the same relationship between smoking habits and mortality (6, 33–36). It has been reported, in a Japanese population, that smoking habits significantly increase the risk of premature death among middle-aged Japanese men and women, and that a substantial proportion of deaths, especially in men, is attributable to smoking (34). Regarding a specific cause of death, there is a strong association between cigarette smoking habits and an elevated mortality risk attributable to ischemic heart disease, cancer and chronic pulmonary diseases (35, 36).

With respect to the gender differences observed in this study, we found no significant relationship between males and females in relation to mortality in the case and control groups, because the subjects were matched in this study. Significant gender differences observed in smoking status and the quartile of FVC %pred in this survey are typical with respect to differences that have been reported repeatedly by numerous researchers, both in Japan and overseas (2, 34–36).

Since there have been studies on the association between the results of allergy skin tests and mortality, we decided to adopt the results of allergy skin tests as an indicator of longevity in this study. We found a significant association between positive allergy skin tests and smoking, but we could not detect a significant association between the results of allergy skin tests and mortality; in the end, only a weak association was found for house dust (p=0.065). The results of allergy skin tests have been shown to correlate with respiratory diseases and mortality, although the latter issue is still controversial. For example, Mensinga et al. (37) reported associations of positive allergy skin tests with persistent wheeze, asthma attacks and mortality. However, positive allergy skin tests have been reported to be associated with an increased risk of cardiovascular mortality only in obese and smoking subjects, and a negative association was found in nonsmoking subjects of normal weight and lung function (22). In contrast, Gergen et al. (20) reported that the results of allergy skin tests are not a predictor of all causes of subsequent mortality. Similarly, Arbes et al. (38) could not identify an association between the results of allergy skin tests and lung function. The results of allergy skin tests may be related to mortality through lung function, smoking and weight.

Some limitations of this study should be acknowledged. Firstly, the specific causes of death were not available because of privacy protection issues. Thus, we considered death due to risk-bearing causes and compensated for the lack of specific causes of death. Secondly, the current status of some subjects could not be ascertained in the follow-up survey. An explanation for this could be that subjects with a poorer lung function were less likely to be institutionalized out of town. Also, the proportion of chest-associated diseases was relatively high in both groups, but the range obtained has been reported to be usual for the time period studied (39). These limitations might lead to an underestimation of lung function as a risk factor. Thirdly, lung function was obtained only during the baseline examination; thus, we could not determine the decline in lung function over the years. In the same way, we were not able to evaluate changes in smoking habits over the follow-up period, which could have influenced the FEV_1/FVC ratio. Since the number current smokers is decreasing year by year, the attribution of smoking habits in the initial survey might be overestimated in the follow-up period. Fourthly, other potential confounding factors, such as drinking habits and physical activities, were not examined at the baseline. These factors are also associated with smoking behavior and mortality (40, 41). In summary, lung function (FVC %pred) and cigarette smoking can serve as long-term independent predictors of mortality in the Japanese population, but this association is not clear for the results of allergy skin tests. In addition to promoting a reduction in the number of current smokers, spirometry examinations should be recommended during general health assessments in the Japanese population.

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