occupational agents, smoking habits, moulds in the house, indoor domestic pets and residential municipality. Employment data focused on type of job held for the longest period of time during the subject's work life and years of exposure were requested regarding the job and occupational agents, respectively. Occupational agents were defined as present if the subject reported ⩾10 h of exposure per week. Neither the questionnaire nor a telephone interview requested a full occupational history or gave any information to help responders recall possible exposures to occupational agents that they may otherwise have overlooked in relation to their particular occupation.

The other self-administered questionnaire was a validated self-administered dietary history questionnaire that was used to assess dietary habits over a period of 1 month (Sasaki *et al.*, 1998, 2000). In the present study, data obtained from the dietary history questionnaire were not used.

Statistical analysis

Jobs held for the longest period of time were coded using the Japanese Standard Occupational Classification and stratified into 11 major groups (professional and technical; managers and officials; clerical and related fields; sales; service; protective service; farming, fishing and forestry; transport and communication; production; materials handling; and construction and extraction). Included in this analysis were eight specific occupational agents to which three or more subjects had been exposed for more than a year. Age was classified into four categories (<50, 50–59, 60–69 and 70+ years); region into five (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu); cigarette smoking into three (never smoked, former smoker and current smoker); pack-years of smoking into five (none, 0–19.9, 20.0–39.9, 40.0–59.9, and 60.0+); and residential municipality into two (city and town or village). Multiple logistic regression analysis was used to estimate the adjusted ORs and 95% confidence intervals (CIs) of IPF for single factors with adjustment for age, sex and region. The reference category for all occupational factors, moulds in the house and indoor domestic pets was based on the comparison of those exposed to a single agent with all those unexposed, including potential subjects who were exposed to other etiologic factors. All computations were performed using version 8.2 of the SAS software package (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Dyspnea on exertion was present at enrollment in 83 of the 104 cases (81.4%). The median (90% central range) of arterial O_2 pressure was 80.2 mmHg (57.2–97.0) and that of vital capacity expressed as percentage predicted values was 77.8% (41.0–116.3) in cases. The proportions of male subjects among cases and controls were 90.2% and 91.5%, respectively (Table 1). Compared with control subjects, cases were older and had a lower prevalence of residence in Chugoku-Shikoku.

Table 1. Characteristics of the study population

Variable	n (%)	
	Cases (*n* = 102)	Controls (*n* = 59)
Sex (male)	92 (90.2)	54 (91.5)
Age (years)		
<50	3 (2.9)	2 (3.4)
50–59	15 (14.7)	19 (32.2)
60–69	56 (54.9)	24 (40.7)
70+	28 (27.5)	14 (23.7)
Region		
Kanto-Koshinetsu	56 (54.9)	27 (45.8)
Tokai	11 (10.8)	10 (17.0)
Kinki	14 (13.7)	5 (8.5)
Chugoku-Shikoku	4 (3.9)	6 (10.2)
Kyushu	17 (16.7)	11 (18.6)

Table 2 presents adjusted ORs and 95% CIs for IPF in relation to occupational factors after controlling for age, sex and region. Because five female cases had never held a job, they were regarded as 'unexposed' in the occupational analyses. The median duration of the job held for the longest period of time was 35 years in cases and 31 years in controls. No marked difference was found in the risk of IPF among occupational groups ($P = 0.50$, Wald $\chi^2 = 9.38$ with 10 degrees of freedom for homogeneity of OR for each occupational group). None of the occupational groups was related to the risk of IPF with statistical significance, although at least a 2-fold increase in OR was observed among managers and officials and production workers, and there was a <0.5-fold decrease in OR among those in clerical and related fields, protective service and materials handling. Further adjustment for pack-years of smoking slightly strengthened associations with two major occupational groups: managers and officials, and clerical and related occupations (adjusted ORs were 6.06, 95% CI: 0.97–118.6 and 0.42, 95% CI: 0.18–0.95, respectively). Overall, 25 cases and three controls were exposed to only one of the occupational agents being studied, and four cases and two controls were exposed to two agents. Only three and one cases were exposed to three and six occupational agents, respectively. Exposure to any of the eight kinds of dust being studied was significantly associated with an increased risk of IPF. In particular, exposure to metal dust was related to an ∼10-fold increased risk of IPF. No association

Table 2. Adjusted odds ratios for idiopathic pulmonary fibrosis in relation to occupational factors

Factor	*n* (%)		Adjusted odds ratio[a]	95% confidence interval
	Cases (*n* = 102)	Controls (*n* = 59)		
Job held for the longest period of time				
Professional or technical	9 (8.8)	7 (11.9)	0.71	0.23–2.25
Manager or official	9 (8.8)	1 (1.7)	4.26	0.74–80.88
Clerical or related occupation	18 (17.7)	18 (30.5)	0.49	0.22–1.08
Sales	11 (10.8)	6 (10.2)	1.29	0.44–4.18
Service	6 (5.9)	3 (5.1)	1.02	0.23–5.46
Protective service	2 (2.0)	3 (5.1)	0.33	0.04–2.19
Farming, fishing or forestry	7 (6.9)	7 (11.9)	0.55	0.16–1.89
Transport or communication	4 (3.9)	2 (3.4)	1.10	0.19–8.73
Production	18 (17.7)	5 (8.5)	2.56	0.91–8.54
Materials handling	2 (2.0)	2 (3.4)	0.46	0.05–4.34
Construction or extraction	11 (10.8)	5 (8.5)	1.37	0.42–4.44
Occupational agents				
Any dust[b]	33 (32.4)	5 (8.5)	5.61	2.12–17.89
Metal	12 (11.8)	1 (1.7)	9.55	1.68–181.12
Wood	5 (4.9)	0 (0.0)		
Asbestos	3 (2.9)	0 (0.0)		
Coal	3 (2.9)	0 (0.0)		
Stone or sand	11 (10.8)	4 (6.8)	1.75	0.52–7.01
Solvents	4 (3.9)	0 (0.0)		
Pesticides	6 (5.9)	2 (3.4)	1.46	0.30–10.61
Chalk	4 (3.9)	0 (0.0)		

[a]Adjusted for age (<50, 50–59, 60–69 or 70+ years), sex and region (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu).
[b]Eight cases and two controls were exposed to two or more occupational agents.

of exposure to stone, sand or pesticides with the risk of IPF was found. None of the control subjects reported exposure to wood, asbestos, coal, solvents or chalk. Additional adjustment for pack-years of smoking did not change the association with IPF of exposure to any of the dusts being studied and metal dust. When exposures to metal dust, stone, sand and pesticides were included in the same model with age, sex and region, a positive association between metal dust exposure and IPF was slightly attenuated but remained statistically significant (adjusted OR 9.25, 95% CI: 1.59–176.7).

Results for environmental factors are shown in Table 3. More cases than control subjects were former smokers, whereas current smoking was more prevalent in controls than in cases, although differences between groups were not statistically significant. Adjusted OR for the comparison of having smoked with never having smoked was 1.91 (95% CI: 0.71–5.15). A significantly increased risk of IPF was observed for smokers with 20.0–39.9 pack-years, but there was no dose–response association with cumulative consumption of cigarettes. Although not statistically significant, moulds in the living room and the presence of indoor hamsters were associated with a >50% decreased risk of IPF. Moulds in the bathroom, kitchen or closets and the presence of indoor birds, cats or dogs were not measurably related to the risk of IPF. There was no clear difference between cases and controls in terms of residential municipality.

DISCUSSION

The present study demonstrated that, compared with control subjects, cases were more likely to have been managers and officials or production workers and less likely to have been protective service workers or materials handling workers, although none of the effects reached significance. Workers in clerical and related fields had a significantly decreased risk of IPF independent of age, sex, region and smoking status. Exposure to metal dust was significantly associated with an increased risk of IPF, but exposure to stone, sand or pesticides was not materially related to IPF. There was no statistically significant relationship between the environmental factors under study and IPF, although 20.0–39.9 pack-years of smoking was significantly associated with an increased risk of IPF.

Table 3. Adjusted odds ratios for idiopathic pulmonary fibrosis in relation to environmental factors

Factor	*n* (%)		Adjusted odds ratio[a]	95% confidence interval
	Cases (*n* = 102)	Controls (*n* = 59)		
Smoking status				
Never smoked	18 (17.6)	14 (23.7)	1.00	
Former smoker	80 (78.4)	34 (57.6)	2.21	0.82–6.04
Current smoker	4 (3.9)	11 (18.6)	0.50	0.10–2.24
Pack-years of smoking				
None	18 (17.7)	14 (23.7)	1.00	
0.6–19.9	10 (9.8)	11 (18.6)	0.87	0.25–3.10
20.0–39.9	30 (29.4)	10 (17.0)	3.23	1.01–10.84
40.0–59.9	29 (28.4)	15 (25.4)	2.22	0.70–7.23
60.0+	15 (14.7)	9 (15.3)	1.59	0.46–5.64
Moulds				
Any place[b]	56 (54.9)	36 (61.0)	0.98	0.48–2.01
Living room	5 (4.9)	8 (13.6)	0.36	0.10–1.20
Bathroom	51 (50.0)	28 (47.5)	1.38	0.69–2.82
Kitchen	12 (11.8)	11 (18.6)	0.61	0.24–1.57
Closets	17 (16.7)	9 (15.3)	1.25	0.50–3.30
Indoor domestic pets				
Any pets[c]	40 (39.2)	25 (42.4)	0.94	0.47–1.86
Birds	17 (16.7)	9 (15.3)	1.16	0.47–3.03
Cats	14 (13.7)	8 (13.6)	1.24	0.45–3.58
Dogs	15 (14.7)	10 (17.0)	0.85	0.33–2.26
Hamsters	2 (2.0)	3 (5.1)	0.27	0.03–1.80
Residential municipality				
Village or town	15 (14.7)	12 (20.3)	1.00	
City	87 (85.3)	47 (79.7)	1.35	0.56–3.28

[a]Adjusted for age (<50, 50–59, 60–69 or 70+ years), sex and region (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu).
[b]Overall, 22 cases and 13 controls were exposed to moulds in two or more places.
[c]Overall, 8 cases and 3 controls had two or more types of indoor domestic pets.

These findings are in agreement with previous observations showing a positive relationship between exposure to metal dust and the risk of IPF (Scott *et al.*, 1990; Iwai *et al.*, 1994; Hubbard *et al.*, 1996b; Baumgartner *et al.*, 2000), but they are at variance with a case–control study that reported positive associations between farming and stone/sand dust exposure and IPF (Baumgartner *et al.*, 2000). The mechanisms underlying the positive association between metal dust exposure and the risk of IPF are still obscure. Recent experimental research has demonstrated that particulate nickel promotes pulmonary fibrosis by inhibiting the fibrinolytic cascade (Andrew and Barchowsky, 2000). Potolicchio *et al.* reported that susceptibility to hard metal lung disease is associated with binding of cobalt by HLA-DP molecules (Potolicchio *et al.*, 1997, 1999). Managers, officials and those working in clerical and related fields are not likely to be potentially exposed to metal dust. The first Whitehall study showed that mortality rates from lung cancer, chronic bronchitis and respiratory diseases were markedly increased with a decrease in employment grade (van Rossum *et al.*, 2000). The present findings partially contradict this observation. In our current study, nine cases were managers and officials: six presidents of a company, two department managers of a company and one director of a union. One of the controls was an executive director of a company. None had been exposed to any of the occupational agents under investigation. A non-significant increased risk of IPF among managers and officials may be ascribed to unrecognized factors that are related to job grade. A case–control study in Lithuania found that the main risk factors of myocardial infarction for managers were hypertension and stress (Malinauskiene *et al.*, 2002). Their stressful work life may have contributed to the manifestation of IPF. The excess IPF risk among managers and officials was not likely to be explained by overdiagnosis in the higher employment grades. All Japanese are covered by universal medical care insurance and all are provided with completely free access to the same medical care.

A case–control study in the USA reported that being a former smoker and 21–40 pack-years of smoking were significantly related to an increased risk of IPF, whereas there was no association of current smoking and more than 40 pack-years of smoking with IPF (Baumgartner *et al.*, 1997). Our results are generally in agreement with these findings, although a positive relationship between having previously smoked and IPF was not statistically significant in this study. A history of having ever smoked was associated with a 1.6-fold increased risk of IPF in the above-cited US study (Baumgartner *et al.*, 1997) and a study in the UK (Hubbard *et al.*, 1996b). The present findings, although not statistically significant, are similar to these observations. Overall, 34 cases and 14 controls quit smoking within 3 years of data collection. It is possible that cases were more likely to quit smoking because of diagnosis or the progression of their disease. When these subjects who stopped smoking within 3 years were considered to be current smokers, adjusted ORs (95% CIs) were 2.11 (0.72–6.19) and 1.73 (0.60–5.03) for former and current smoking, respectively. Additional adjustment for pack-years of smoking slightly affected the association with IPF in managers and officials and workers in clerical and related fields, although the interaction with pack-years of smoking was not statistically significant for those occupational groups. On the other hand, adjustment for smoking did not measurably influence the effects of metal dust exposure. Thus, smoking and metal dust exposure were likely to be independent factors. A case–control study of 17 cases and 94 controls in the USA reported that patients with interstitial lung disease were 16.0 times more likely to be exposed to mould than were controls in their workplace (Mullen *et al.*, 1998). The present results are not consistent with this finding. To our knowledge, no study has assessed the relationship between domestic pets and the risk of IPF. Our findings contradict a previous epidemiologic study in Japan showing a positive association between residence in an agricultural area and the risk of IPF (Iwai *et al.*, 1994).

Selection and information bias are methodological issues that need careful consideration. We attempted to identify and recruit all eligible cases seen at each participating hospital during the specified study period according to the most recent diagnostic criteria. Only three eligible patients did not take part in this study. Thus, it was unlikely that selection bias for the cases occurred. It is difficult to ensure that control subjects are drawn from the same study population as the cases. This disadvantage is likely to be diluted by controlling for region. Almost all controls were hospitalized patients with acute bacterial pneumonia. Therefore, control subjects may not have been representative of the general population that generated the cases. The prevalence values of having ever smoked in the present controls were not likely to differ from those reported elsewhere, although the prevalence values of current smoking were relatively low in this study. In a population-based case–control study of acute myocardial infarction in Fukuoka, Japan, the proportions of people who had never smoked, had formerly smoked and currently smoked were 25%, 23% and 52%, respectively, among 260 male controls below 65 years old, and 24%, 41% and 35%, respectively, among 212 male controls aged 65 years or over (Miyake and Fukuoka Heart Study Group, 2000). The corresponding figures in this study were 14%, 55% and 31%, respectively, among 29 male controls below 65 years old, and 24%, 68% and 8%, respectively, among 25 male controls aged 65 years or over. If acute bacterial pneumonia shared risk factors with IPF, the reported OR would have been underestimated. The ratio of controls to cases was below 1:1. Eligible control subjects with acute bacterial pneumonia were not likely to arise during the summer months because of seasonal variation in this disease. Moreover, eligible control patients who received treatment at the non-respiratory ward of 50 hospitals were not recruited. The statistical power of this study was extremely low, although a statistically significant association was observed. Cases may have been more likely than controls to remember specific exposures under study. However, subjects would not have been aware of the possible ill effects of occupational and environmental factors under investigation because the etiology of IPF is unknown. Thus, a difference in recall between cases and controls was not likely to have occurred. We did not collect data for a detailed occupational history. However, the impact of job activities, other than the job held for the longest period of time, on IPF was likely to be negligible and unlikely to differ between cases and controls because the median duration of the job held for the longest period of time was 30 years or more in both cases and controls. The consequence could be a minor underestimation of values in our results.

Despite these potential limitations, the present results appear to confirm data from previous epidemiologic studies. Exposure to metal dust is a particularly important risk factor for IPF in Japan, as well as in the UK and the USA. Larger studies with more precise and detailed exposure measurements are needed to assess the impact of occupational and environmental factors on the development of IPF. Investigations regarding biological mechanisms are also required.

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ORIGINAL ARTICLE

Case-control study of medical history and idiopathic pulmonary fibrosis in Japan

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Objectives: A few epidemiological studies have indicated that a patient's past medical history may contribute to the risk of developing idiopathic pulmonary fibrosis (IPF). A relationship between a history of selected disorders and the risk of IPF was assessed in a multicentre hospital-based case-control study in Japan.

Methodology: Included in the study were 104 patients of IPF, aged 40 years or over, who had been diagnosed within the previous 2 years, in accordance with the most recent criteria. Control subjects, aged 40 years or over, consisted of 56 hospitalized patients diagnosed as having acute bacterial pneumonia and four outpatients with the common cold. Adjustment was made for age, gender, region, pack-years of smoking, employment status, occupational exposure and BMI.

Results: Medical histories of hypertension, hyperlipidaemia, coronary heart disease, diabetes mellitus, hepatitis C virus infection, tuberculosis, asthma, atopic dermatitis and allergic rhinitis were not statistically significantly associated with the risk of IPF, although cases were more likely to have suffered from allergic rhinitis and less likely to have been asthmatics than control subjects. Having a child with a history of allergic rhinitis, but not of asthma or atopic dermatitis, was significantly related to an increased risk of IPF.

Conclusions: These findings suggest that a genetic predisposition to allergic rhinitis may be associated with an increased risk of IPF.

Key words: case-control studies, hay fever, Japan, pulmonary fibrosis.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and usually fatal lung disease characterized by fibroblast proliferation and extracellular matrix remodelling, leading to irreversible distortion of the lung architecture.[1] Patients with IPF are often between 40 and 70 years of age and approximately two-thirds are over the age of 60 years at the time of presentation.[2] Although the aetiology is unknown, factors relating to aging may be implicated in the pathogenesis of IPF. For example, a few epidemiological studies have indicated that a patient's medical history may contribute to the risk of developing IPF. A recent case-control study in Japan demonstrated that diabetes mellitus was significantly associated with a fourfold increased risk of IPF.[3] A case-control study in the UK suggested that atopy may be an important determinant of susceptibility to IPF.[4] An increased prevalence of antibodies to hepatitis C virus was observed in both Japanese and Italian patients with IPF,[5,6] while Irving *et al.* failed to confirm these findings in a British series of patients with IPF.[7]

To confirm these reported findings, we examined the relationship between a history of selected disorders and the risk of IPF, based on data from a multicentre hospital-based case-control study in Japan.

METHODS

Subjects

Eligible cases were patients aged 40 years or over, who had been diagnosed within the previous 2 years and who were identified among the 21 collaborating hospitals and their 29 affiliated hospitals during the period from 1 June to 30 November 2001. The diagnosis of IPF by the collaborating respiratory disease specialists was based on clinical history, clinical examination and high-resolution CT (HRCT) of the chest. Results of video-assisted thoracoscopic lung biopsy, transbronchial lung biopsy and/or BAL, corresponding to the international consensus statement on IPF of the American Thoracic Society and European Respiratory Society,[8] were also used when available, either alone or in combination, to assist diagnosis. All patients had basal fine crackles on auscultation and predominantly peripheral, subpleural, bibasal fine reticular shadows and/or honeycombing, occasionally with traction bronchiectasis and bronchiolectasis on HRCT. There was no evidence of either coexisting collagen-vascular disease or a history of known occupational exposure to agents that might produce a clinical picture similar to that of IPF in any of the patients. The physicians-in-charge asked eligible patients to participate in this study, and 104 patients were cooperative in answering the questionnaires, while three patients refused.

Control subjects were aged 40 years or over, had no prior respiratory diseases and were prospectively selected from individuals who received treatment at the respiratory ward of the recruiting hospitals, during the same time period as the cases. Fifty-six hospitalized patients, diagnosed as having acute bacterial pneumonia, and four outpatients with common cold served as controls by answering the same questionnaires as the cases. Controls were not, individually or in larger groups, matched with cases. Patients with acute infectious or common diseases are unlikely to receive treatment at a specialized medical institution. Fourteen of the 21 collaborating hospitals were university hospitals with doctors who exclusively treated patients with serious illnesses. Thus, 95 of the 104 cases were recruited from the 21 collaborating hospitals, while 34 of the 60 controls were selected from the 29 hospitals that were affiliated with the collaborating hospitals.

The study subjects were originally restricted to males, but included in the analysis were 10 female cases and five female controls, whose treatment was provided at six of the collaborating hospitals and one affiliated hospital. A total of 104 cases and 60 control subjects who gave their fully informed consent remained in the present study.

Questionnaires

The physicians handed a set of two self-administered questionnaires to the cases and the controls. The subjects filled out the questionnaires and mailed them to the data management centre. A telephone interview was conducted by a trained research technician in order to complete missing or illogical data.

One of the self-administered questionnaires was used to ascertain age, gender, weight, height, smoking habits, type of job held for the longest period of time, occupational exposure, personal medical history and a history of asthma, atopic dermatitis and allergic rhinitis (including cedar pollinosis) in the subject's children. Hypertension, hyperlipidaemia, coronary heart disease, diabetes mellitus, tuberculosis, asthma, atopic dermatitis and allergic rhinitis (including cedar pollinosis) were defined as being present when subjects had received medication, or in the case of diabetes mellitus, if they were receiving dietary therapy. Hepatitis C virus was considered to be present if the subject had been diagnosed by a physician as being infected with hepatitis C virus or being its carrier. A child's history of asthma, atopic dermatitis and allergic rhinitis (including cedar pollinosis) was considered to be confirmed if one or more of the study subject's children had been treated for these conditions with medications at any time since birth. Occupational exposure was defined as being present if the subject had been exposed to any of eight specific occupational agents (metal, wood, asbestos, coal, stone and sand, solvents, pesticide or chalk) for 10 or more hours per week for more than 1 year. BMI was calculated by dividing self-reported body weight (kg) by height (m) squared.

The other self-administered questionnaire was a validated diet history questionnaire that was used to assess dietary habits over a period of 1 month.[9,10] Data obtained from this diet history questionnaire were not used in the present study.

Table 1 Clinical features of idiopathic pulmonary fibrosis cases

Lung function	Mean	SD	Minimum	Median	Maximum
Arterial O_2 pressure (mmHg)	79.6	11.4	50.0	80.6	102.0
Vital capacity (% predicted)	77.4	22.0	19.8	77.6	128.0

Arterial O_2 pressure: 8-values missing. Vital capacity: 5-values missing.

Statistical analysis

Multiple logistic regression analysis was used to estimate adjusted odds ratios (OR) and their 95% confidence intervals (CI) for IPF relative to selected medical histories. Covariates included in the multivariate models were age, gender, region, pack-years of smoking, employment status, occupational exposure and BMI, which was used as a continuous variable. Age was classified into four categories (<50, 50–59, 60–69 and ≥70 years); region into five (Kanto-Koshinetsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu); employment status into two (high employment status as represented by professionals, technical workers, managers and officials, and other); and pack-years of smoking into five (never, 0 < –19.9, 20.0–39.9, 40.0–59.9 and ≥60.0). In two cases and one control, data on smoking were missing and they were regarded as never having smoked. All computations were performed using the SAS software package version 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Dyspnoea on exertion was present at enrollment in 84 of the 104 cases (80.8%). The median (90% central range) arterial O_2 pressure was 80.2 mmHg (57.2–98.0 mmHg) and the median vital capacity in the cases, expressed as per cent predicted value, was 78.0% (42.1–113.5%) (Table 1). About 90% of both cases and controls were male (Table 2). In comparison with controls, cases were older, fewer were resident in Chugoku-Shikoku and had never smoked, and more cases had high employment status, occupational exposure and were overweight.

In Table 3, adjusted OR for associations between selected medical histories and IPF are presented. After controlling for gender and age, hypertension, hyperlipidaemia, coronary heart disease, diabetes mellitus and hepatitis C virus infection were not significantly associated with the risk of IPF. Further adjustment for region, pack-years of smoking, employment status, occupational exposure and BMI did not materially modify these results. Tuberculosis tended to be related to a decreased risk of IPF after adjusting for gender and age, but the relationship was almost completely attenuated in the multivariate model. There was a tendency for an inverse association between asthma and the risk of IPF: the multivariate OR was 0.22 (95% CI 0.04–1.09). Atopic dermatitis did not appear to be related to IPF. Allergic rhinitis was associated with a twofold increased risk of IPF, although the 95% CI included the null hypothesis value.

Table 2 Characteristics of the study population

Variable	No. (%) or mean (SD) Cases (n = 104)	Controls (n = 60)	P-value
Gender (% male)	94 (90.4)	55 (91.7)	0.78
Age (% years)			0.10
<50	3 (2.9)	2 (3.3)	
50–59	16 (15.4)	19 (31.7)	
60–69	56 (53.9)	25 (41.7)	
≥70	29 (27.9)	14 (23.3)	
Region (%)			0.21
Kanto-Koshinetsu	57 (54.8)	27 (45.0)	
Tokai	12 (11.5)	10 (16.7)	
Kinki	14 (13.5)	5 (8.3)	
Chugoku-Shikoku	4 (3.9)	7 (11.7)	
Kyushu	17 (16.4)	11 (18.3)	
Pack-years of smoking (%)			0.26
Never	20 (19.2)	15 (25.0)	
0 < –19.9	10 (9.6)	11 (18.3)	
20.0–39.9	30 (28.9)	10 (16.7)	
40.0–59.9	29 (27.9)	15 (25.0)	
≥60.0	15 (14.4)	9 (15.0)	
High employment status (%)[†]	18 (17.3)	8 (13.3)	0.50
Occupational exposure (%)[‡]	33 (31.7)	5 (8.3)	0.0006
BMI (kg/m^2)	23.3 (3.1)	21.9 (3.0)	0.005

[†]Subjects considered to have a high employment status were those who were professionals, technical workers, managers or officials for the longest period within their working years.
[‡]Exposure to metal, wood, asbestos, coal, stone and sand, solvents, pesticide, or chalk for 10 or more hours per week for more than 1 years.

We further examined the relationship between an allergic history in at least one child and the risk of IPF. The multivariate OR for having a child with a history of asthma was 1.82 (95% CI 0.54–7.04), of atopic dermatitis, 0.91 (95% CI 0.30–2.77) and of allergic rhinitis, 2.49 (95% CI 1.01–6.54).

DISCUSSION

The present study demonstrated that having a child with a history of allergic rhinitis, but not asthma

Table 3 Odds ratios for idiopathic pulmonary fibrosis in relation to selected items from personal and child's medical history

Variable	No. (%) Cases	No. (%) Controls	Gender and age adjusted Odds ratio	Gender and age adjusted 95% confidence interval	Multivariate adjusted† Odds ratio	Multivariate adjusted† 95% confidence interval
Personal history						
Hypertension	28 (26.9)	15 (25.0)	1.00	0.48–2.14	0.56	0.23–1.35
Hyperlipidaemia	10 (9.6)	4 (6.7)	1.63	0.50–6.37	1.35	0.34–6.39
Coronary disease	10 (9.6)	3 (5.0)	1.58	0.45–7.39	1.31	0.32–6.76
Diabetes mellitus	13 (12.5)	7 (11.7)	0.95	0.36–2.74	1.43	0.46–4.76
Hepatitis C virus	7 (6.7)	4 (6.7)	0.85	0.22–3.60	0.80	0.15–4.27
Tuberculosis	7 (6.7)	9 (15.0)	0.35	0.12–1.03	0.58	0.17–1.94
Asthma	4 (3.9)	6 (10.0)	0.39	0.09–1.48	0.22	0.04–1.09
Atopic dermatitis	2 (1.9)	1 (1.7)	1.31	0.12–29.99	1.76	0.12–46.06
Allergic rhinitis	12 (11.5)	4 (6.7)	1.96	0.62–7.58	2.00	0.53–9.19
Child's history						
Asthma	12 (11.5)	5 (8.3)	1.56	0.53–5.33	1.82	0.54–7.04
Atopic dermatitis	9 (8.7)	9 (15.0)	0.56	0.20–1.56	0.91	0.30–2.77
Allergic rhinitis	30 (28.9)	11 (18.3)	1.94	0.89–4.49	2.49	1.01–6.54

†Adjusted for age, gender, region, pack-years of smoking, employment status, occupational exposure and BMI.

or atopic dermatitis, was significantly related to an increased risk of IPF. Hypertension, hyperlipidaemia, coronary heart disease, diabetes mellitus, hepatitis C virus infection, tuberculosis, asthma, atopic dermatitis and allergic rhinitis were not significantly associated with the risk of IPF after adjustment for potential confounders, although cases were more likely to have suffered from allergic rhinitis and were less likely to have been asthmatic than control subjects.

The prevalence of allergic disorders has been increasing in Japan.[11] In particular, the prevalence of allergic rhinitis was likely to be underestimated in the present study because the disorder was defined as being present when subjects had been under medical treatment. The prevalence of seasonal rhinitis, which was defined as having symptoms from February to May, was 28.8% among Japanese male railway employees.[12] The consequence of such a hypothetical misclassification would have been to introduce a bias toward the null hypothesis. A previously cited study also demonstrated an inverse association between advancing age and the prevalence of allergic rhinitis.[12] A significant positive relationship between having a child with a history of allergic rhinitis and the risk of IPF, as identified in this study, may support the causality. Genetic predisposition to allergic rhinitis or the joint effect of the genetic background and environmental factors such as exposure to metal dust and smoking, may be associated with the development of IPF.

Our results are in contradiction to a recent Japanese case-control study showing a significant positive association between diabetes mellitus and the risk of IPF.[3] In the present investigation, the definition of diabetes mellitus was crude because only individuals who had been receiving dietary or drug treatment were considered to be diabetics and results of fasting blood sugar or glycosylated haemoglobin testing were not available. Thus, latent or untreated diabetics were missed, and such misclassification may have masked a true positive association. Matsuse *et al.* found that all lung tissue samples obtained from seven necropsy cases with IPF showed strong advanced glycation end-product expression on alveolar macrophages.[13] Advanced glycation end-product modification may be involved in the pathogenesis of IPF. An animal experiment demonstrated that the morphological grade of fibrosis in mice with streptozotocin-induced diabetes was more severe than that in mice treated with bleomycin alone.[14] Lack of a positive relationship between hypertension or hyperlipidaemia and the risk of IPF in this study is in agreement with a previously cited study in Japan.[3] However, caution is needed in interpreting our findings because hypertension and hyperlipidaemia were defined by the use of drugs. The reported OR associated with such diseases may have been underestimated.

With regard to hepatitis C virus infection, our findings are in agreement with a UK observation,[7] but at variance with previous Japanese and Italian studies that showed an increased prevalence of hepatitis C virus infection in patients with IPF.[5,6] The discrepancy between our results and those from the previous Japanese study might be ascribed to the high false-positive rates from the first generation ELISA tests used in the previous Japanese study.[5] Eight of 60 patients with IPF were, however, hepatitis C virus-RNA positive in the previously cited Italian study.[6] The prevalence of hepatitis C virus positivity is high in Japan as well as in Italy. Egan *et al.* suggested that it is most likely that the relationship between hepatitis C virus infection and IPF is spurious and reflects the background rate of hepatitis C virus infection.[15]

The present study had methodological advantages. Cases were selected according to the most recent diagnostic criteria and extensive information on potential confounding factors was incorporated. Weaknesses of this study should be borne in mind. Although selection bias in the choice of cases was not likely to have occurred because of the high response rate (only three eligible patients refused), control subjects may not have been representative of the general population from which the cases arose, because almost all controls were hospitalized patients with acute bacterial pneumonia. In fact, the prevalences of hypertension and diabetes mellitus were relatively high in the present study. In a population-based case-control study of acute myocardial infarction in Fukuoka, Japan, the proportions of persons with hypertension and diabetes mellitus, using the same definitions as in this study, were 13% and 10%, respectively, among 260 male controls less than 65 years of age, and 21% and 8%, respectively, in 212 male controls aged 65 years or over.[16] The corresponding figures for hypertension and diabetes mellitus in the present study were 27% and 10%, respectively, in 30 male controls less than 65 years old, and 28% and 16%, respectively, in 25 male controls aged 65 years or over. Our control subjects may have been likely to have had histories of medical conditions such as hypertension and diabetes mellitus. Such a hypothesis would give rise to an underestimation of our results. If acute bacterial pneumonia shared risk factors with IPF, the reported OR would have been underestimated. Eligible control subjects with acute bacterial pneumonia were not likely to be recruited during the summer months because of seasonal variation in this disease. The ratio of controls to cases was below 1:1 and our investigation did not have substantial statistical power. In the present study, the percentages of atopic dermatitis sufferers among cases and controls were 1.9% and 1.7%, respectively. A case-control study is not suitable for studying rare exposures.

Our findings suggest that a genetic predisposition to allergic rhinitis may be associated with an increased risk of IPF. Further investigations with more precise and detailed exposure measurements are required to confirm whether allergic rhinitis is an independent risk factor for IPF, and to clarify our results that showed lack of a relationship between diabetes mellitus and IPF, which was in disagreement with previous reports.

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Behçet病の最近の疫学像の動向

A recent trend of epidemiological feature of Behçet's disease

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◎Behçet病の全国疫学調査は1972年にはじめて実施された．以後5～7年間に1回の頻度で行われているが，今回の第5回目の調査は前回(1991)から11年目を経て実施された．本調査は患者数を推計する一次調査と臨床疫学像を明らかにする二次調査からなり，厚生労働省難治性克服研究事業特定疾患の疫学に関する研究班，ベーチェット病に関する調査研究班が共同で実施した．その結果，2002年1年間にBehçet病で受診した患者数は15,000人(95%信頼区間14,000～16,000)と推計された．1972年以降，患者数推計値，受療患者数ともに増加していたが，今回はじめて減少に転じた．臨床疫学像としては30年間で完全型Behçetの割合が段階的に減少しており，とくに男性での減少が顕著であった．重症度分類では女性より男性，とくに若年で発症した男性に重症・中等度者が多かった．

Key word：Behçet病，全国疫学調査，患者数推計，臨床疫学像

厚労省難治性克服研究事業特定疾患の疫学に関する研究班(主任研究者：稲葉　裕)とベーチェット病に関する調査研究班(主任研究者：金子史男)は，2002年1年間にBehçet病で受療した患者を対象に全国疫学調査を実施した．難治性克服研究事業対象疾患の全国疫学調査は患者数を推計する一次調査と臨床疫学像を明らかにする二次調査からなり，上記疫学班と該当疾患の臨床班との共同研究として実施されているものである．Behçet病の全国疫学調査は1972年にはじめて実施され，以後5～7年間に1回の頻度で行われているが，今回第5回目の調査は前回(1991)から11年目を経て実施された．本稿では今回の全国疫学調査結果とこれまでに実施された調査結果を比較し，Behçet病の最近の疫学像の動向について述べる．

2003年に実施した全国疫学調査の概要

疫学班で作成された全国疫学調査マニュアル[1]に基づき，一次調査の対象を2002年1月1日～12月31日の1年間の受療患者，調査対象科を内科(含膠原病科，リウマチ科)，眼科，皮膚科とし，特別階層を20床以上の眼科，皮膚科病院として全国の病院から病床規模別に層化無作為抽出された計2,914科(表1)を対象医療施設とし，2003年1月に患者数推計のための一次調査票を郵送した．一次調査でBehçet病患者ありと回答のあった施設を二次調査対象とした．一次調査で得られた報告患者数をもとに二次調査結果より不適格率，重複率を考慮して患者数の推計を行った．二次調査の実施計画は，主任研究者所属施設の倫理審査委員会の承認を得，2003年11月に調査を開始した．

一次調査結果(患者数推計)と30年間の患者数の推移

病床規模別の対象数，抽出率，抽出数，各疾患の報告患者数を表1に示す．一次調査の回収数は1,674診療科(回収率57.4%)，報告患者数は7,652例であった．二次調査票より対象期間外や診断基準を満たさない不適格率は4.6%，重複率は調査票が匿名であるため求められないが，同施設内の明らかな重複(2.5%)を考慮して1年間の受療患者数を15,000人(95%信頼区間14,000～16,000)，男

表 1　Behçet病全国疫学調査一次調査の対象数，抽出率，報告患者数

対象科	規模	対象数	抽出率	抽出数	返送数	合計
皮膚科	20～99 床	897	6.2	56	29	6
	100～199 床	597	9.9	59	25	6
	200～299 床	359	19.8	71	36	26
	300～399 床	330	39.7	131	78	88
	400～499 床	176	80.1	141	77	208
	500 床以上	229	100.0	229	151	604
	特別階層	2	100.0	2	2	1
	大学病院	115	100.0	115	89	601
小計		2,705		804	487	1,540
内科	20～99 床	3,280	5.0	164	101	22
	100～199 床	1,542	9.8	151	70	24
	200～299 床	622	19.9	124	54	73
	300～399 床	406	39.9	162	83	141
	400～499 床	205	80.0	164	79	168
	500 床以上	243	100.0	243	119	539
	特別階層	0		0	0	0
	大学病院	235	100.0	235	177	1,676
小計		6,533		1,243	683	2,643
眼科	20～99 床	443	12.6	56	28	6
	100～199 床	538	10.0	54	30	16
	200～299 床	414	20.0	83	41	46
	300～399 床	346	39.9	138	82	171
	400～499 床	180	80.0	144	91	263
	500 床以上	231	100.0	231	123	583
	特別階層	38	100.0	38	27	137
	大学病院	123	100.0	123	82	2,247
小計		2,313		867	504	3,469
合計		11,551		2,914	1,674	7,652

表 2　過去に実施した全国調査推計患者数と医療費受給者数の推移

調査年	全国調査	受給者数
1972	8,500	—
1979	11,500	4,766
1984	13,000	7,921
1991	18,400	12,987
2002	15,000(14,000～16,000)	16,834

性 7,000 人(95% 信頼区間 6,500～7,500)，女性 8,000 人(95%信頼区間 7,500～8,500)と推計した．

過去に実施した全国調査推計患者数と医療費受給者数の推移を表 2[2-4]に示す．1991 年の推計患者数は不適格率を考慮していないが 18,400 人で，今回の推計患者数はそれより数千人少なかった．推計患者数減少の理由は不明であるが，医療費受給者数も 2001 年をピークに減少している．今回の全国調査二次調査結果などから Behçet 病患者は軽症者の割合が増加していることが考えられ，それが今回の推計値に影響した可能性もある．

二次調査(臨床疫学像)結果と過去の調査結果との比較

回収された二次調査票は不適格例，重複例，性別不明を除いた 1,884 例(一次調査報告患者数の 24.6%)について分析した．性別は男性 906 例(48.1%)，女性 978 例(51.9%)，男性は 30～50 歳

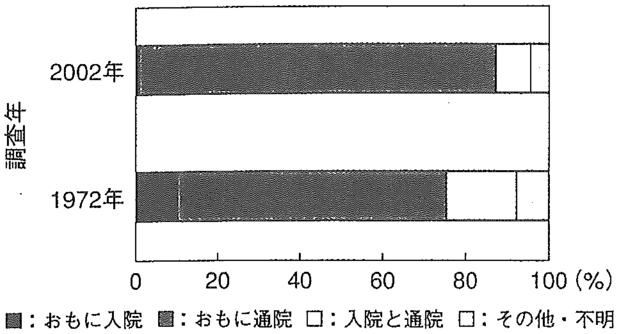

図 1　最近 1 年間の受療状況——1972年と2002年の比較

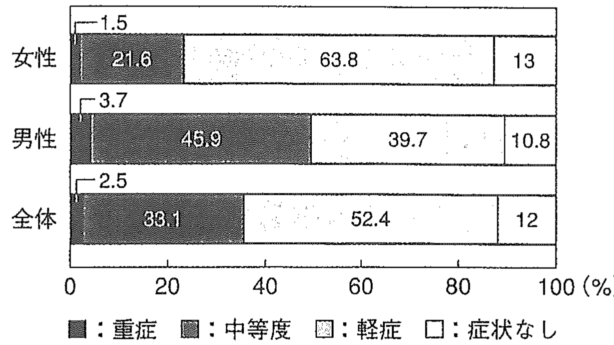

図 2　性別にみた重症度割合

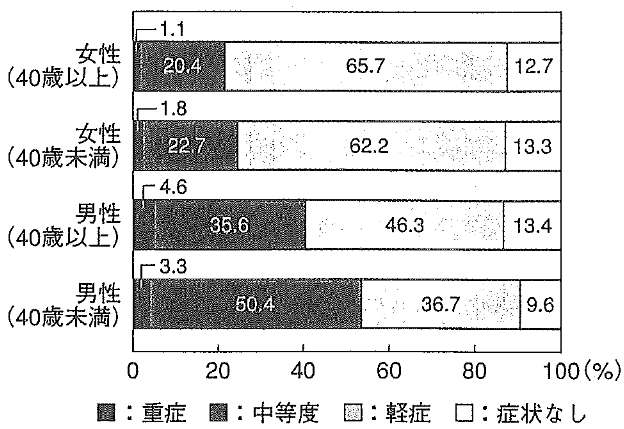

図 3　性別発症年齢別重症度割合

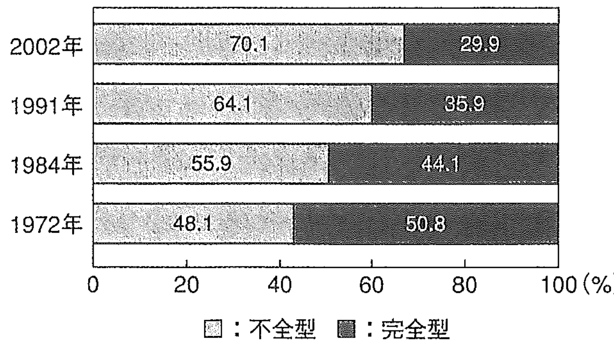

図 4　病型（完全型と不全型）別割合の推移（男性）

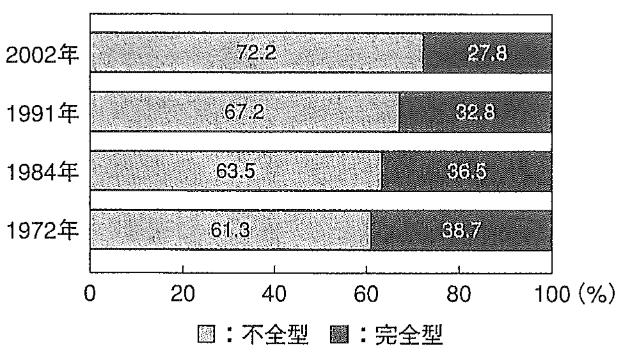

図 5　病型（完全型と不全型）別割合の推移（女性）

代が多く，女性は 50〜60 歳代が多かった．1997 年度の Behçet 病医療受給者[3]の年齢分布と比べると，本調査対象者は若年男性の報告がやや多かった．二次調査票の性比は 0.93 で，一次調査の性比 0.88，2002 年度の Behçet 病医療受給者[5]の性比 0.74 と比べるとやや男性の報告が多かった．平均年齢は男性 47.8 歳，女性 51.3 歳で，1972 年調査結果[2]より約 10 歳高くなっていた．発症年齢のピークは，男性 30〜35 歳，女性 35〜45 歳，平均発症年齢は男性 35.0 歳，女性 38.1 歳で，1972 年調査結果[2]と比べると男女とも 4 歳高くなっていた．

本調査結果で家族歴を有するのは 1.9%で，1972 年の 1.8%[6]とほぼ同じ結果であった．最近 1 年間の受療状況（図 1）は，30 年前と比べると大きく変化している．1972 年には“おもに入院”が約 10%，“入院と通院”が約 17%いたが，2002 年の調査では“おもに入院”は 0.7%に減少し，“入院と通院”も 8%に減少しており，通院（86.5%）の割合が多くなっていた．

今回調査項目に加わった重症度（図 2）は，重症・中等度の割合が男性 49.7%，女性 23.1%と男性での割合が高く（$p<0.001$），重症度には性差が顕著に認められた．また，性別発症年齢別（図 3）にみると重症・中等度者の割合は 40 歳未満の男性で高く，半数以上を占めていた．

病型については疑い例，分類不能例を除く完全型，不全型のみの割合の推移を性別に図 4，5 に示す．1972 年の男性の完全型 Behçet の割合は 50.8%と半数を超えていたが，その後段階的に減少[7,8]しており，2002 年には 29.9%まで減少してい

表 3　主症状別性別有病割合の推移

症状		調査年			
		1972	1984	1991	2002
口腔内アフタ	男性	97.9%	—	98.0%	87.6%
	女性	98.8%	—	98.0%	92.1%
皮膚症状	男性	89.8%	—	87.0%	70.1%
	女性	90.4%	—	87.0%	78.3%
眼症状	男性	86.3%	66.4%	71.4%	70.0%
	女性	67.8%	35.0%	35.7%	45.3%
外陰部潰瘍	男性	76.8%	47.1%	32.2%	43.8%
	女性	83.8%	77.8%	71.5%	64.6%

た(図 4)．同じく 1972 年の女性の完全型の割合は男性より少ない 38.7%であったが，それ以降徐々に減少し，2002 年には 27.8%に減少していた(図 5)．完全型 Behçet の減少はとくに男性に顕著であった．

これまでに出現した主症状(口腔内アフタ，皮膚症状，眼症状，外陰部潰瘍)の割合の推移[6,9]を性別に表 3 に示す．1972 年から 30 年間に口腔内アフタは男性が約 10%減少，女性もやや減少していた．同じく皮膚症状は男性が約 20%，女性は 10%強減少していた．眼症状は性差が大きいが，1972 年から 1984 年にかけて男性は 20%，女性は 30%以上減少し，その後はほとんど変化が認められない．外陰部潰瘍は 30 年間で女性は約 20%減少しているが，男性は 1972 年から 1984 年にかけて約 30%減少し有病割合は 47.1%となった．さらに 1991 年に有病割合は 32%まで減少したが，今回の調査では 43.8%まで上昇していた．今回の調査結果のみであるが，虹彩毛様体炎，網膜ぶどう膜炎有の割合は若年発症者で高く，皮下の血栓性静脈炎有は女性の高齢発症者に高いという特徴があった．HLA-B51 陽性率は 71.4%(1972)，58.1%(1984)，54.9%(1991)，48.7%(2002)と推移していたが，HLA-B51 は毎回二次調査対象者の約 30%しか測定されておらず，測定者は重症者や悪化している人に多いなどの偏りがあるため，陽性率の変化についての解釈は慎重にする必要がある．

今回，過去 30 年間に実施された全国調査結果を比較し，Behçet 病の患者数の推移や臨床像の変化を示し最近の疫学像を示した．今後は平成 14 年(2002)度より全都道府県から厚生労働省にオンラインで集積される臨床調査個人票の分析[10]によって臨床像やその推移をより詳細に把握することが期待される．

謝辞：本研究の一部は厚生労働科研難治性疾患克服研究事業特定疾患の疫学に関する研究班およびベーチェット病研究班の補助を得た．本研究は西部明子，金子史男(福島県立医科大学医学部皮膚科学)，玉腰暁子(名古屋大学大学院医学系研究科健康社会医学専攻)，川村　孝(京都大学保健管理センター)，松葉　剛(順天堂大学医学部衛生学)の各先生と共同で行ったものである．また，調査にご協力いただいた対象医療機関担当医の皆様に深謝いたします．

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ORIGINAL ARTICLE

Changes in the incidence of amyotrophic lateral sclerosis in Wakayama, Japan

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Abstract
In the 1960s, the incidence of amyotrophic lateral sclerosis (ALS) in the Kozagawa and Koza areas in Wakayama prefecture was much higher than that in other areas of the world. However, between 1980 and 1993, a gradual decrease in the incidence of the disease in these areas was reported. To ascertain whether the decreased incidence has persisted, we conducted a retrospective epidemiological study, and determined the average annual incidence of ALS in Wakayama prefecture from 1998 to 2002. The number of ALS cases encountered during the period was 134 (male 79, female 55). The crude average annual incidence in Wakayama prefecture in total was 2.50 (male 3.08, female 1.99) per 100,000. In the Kozagawa and Koza areas in Wakayama prefecture, where the senility rate rapidly increased in recent years, the average annual incidence of ALS in the present research was 10.56 (male 14.14, female 7.66). When the crude rate was standardized for both age and sex to the Japanese population in 1990, the expected value was 5.24 (male 7.34, female 3.18), which was lower than that of our previous survey. The prevalence in Wakayama prefecture at 31 December 2002 was 11.31 (male 14.40, female 8.53). In Kozagawa and Koza areas, the crude prevalence was 52.81 (male 70.70, female 38.28). These results indicated that the incidence of ALS in Wakayama prefecture, especially for females, steadily decreased compared to that in previous reports. However, a high incidence of ALS persisted among males in Wakayama prefecture, especially in the Kozagawa and Koza areas. Some environmental factors and gender specificity may be related to the decreased incidence of ALS in focus areas.

Key words: *Focus ALS, Kii-ALS, environmental factor, incidence*

Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating disease affecting the upper and lower motor neurons, causes of which are unknown. Retrospective studies reported that the incidence of ALS in the world varied from 0.6 to 2.6 per 100,000 of the population and the prevalence from 1.6 to 8.5 per 100,000 of the population. In the southern part of the Kii Peninsula of Japan as well as on the island of Guam, the incidence and prevalence rates of ALS in the 1960s were 100 to 150 times higher than those of other countries in the world (1,2). However, over 30 years' follow-up studies in Kii Peninsula foci (Kozagawa in Wakayama prefecture and Hobara in Mie prefecture) demonstrated a marked decline in the incidence of ALS. A previous study during the period 1989 to 1993 in Wakayama prefecture also indicated that the incidence rate of the disease decreased steadily except in the Kozagawa area, where the crude incidence rate was reported to be 9.54 (two ALS cases within five years: 4193 base population) (3). The environmental or socioeconomic changes over 30 years probably played some roles in the decline in ALS occurrence in Kii Peninsula (4,5). This study documented the incidence and prevalence of ALS in Wakayama prefecture of the Kii Peninsula during five recent years and investigated whether a continuous decline in the occurrence of the disease persisted.

Methods

Area of investigation

The Kii Peninsula is located in the central southern part of the Japanese mainland, facing the western Pacific Ocean with a rugged coast and steeply

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mountainous regions about 1000 m above sea level (Kumano mountains) (Figure 1). Wakayama prefecture covers the southwest side of the Kii Peninsula, and includes seven cities, 36 towns, seven villages and eight public health districts with a resident population of 1,069,912 (male 506,882, female 563,030, in the 2000 census). Demographic data of Wakayama prefecture are shown in Table I. In the Kozagawa and Koza areas, immigrant influx and emigration rate to other areas have been very low. The proportion of people over 65 years old in Wakayama prefecture increased 3 times in the past 40 years. In Kozagawa and Koza areas, the senility rate rapidly increased in recent years. With regard to the proportion of the employed population, there was no difference between Wakayama prefecture in total and the focus areas (Table I). From south to north, the province includes three different geographic and economic regions (mountainous, level, and urban areas). The area of investigation was divided into these three regions (from region A to region C as shown in Figure 1). Region A is in the most northern section of the prefecture and is an economically developing region with a flat and mildly mountainous area; region B includes the prefecture's capital and urban area; region C is predominantly rural area with a rugged coast and steep mountains. Region C covers a geographically large part of the Wakayama prefecture, and includes the high incident area of ALS (Kozagawa and Koza areas) which is subdivided as region C (f). Each region has several main hospitals and public health centers.

Case collection and ascertainment

First, two mail survey questionnaires at 589 clinics and hospitals where ALS would be potentially diagnosed were conducted from 1 January 1998 to 31 December 2002. Physicians in these medical facilities were asked to register all patients diagnosed with ALS during that period according to the modified El Escorial diagnostic criteria (6). Second, the Wakayama Prefecture's List of Patients with Intractable Disease (WPLPID, as certified by the Ministry of Health and Welfare of Japan) were used for ascertainment. All cases of progressive bulbar palsy (PBP) and primary lateral sclerosis (PLS) were included among the incident

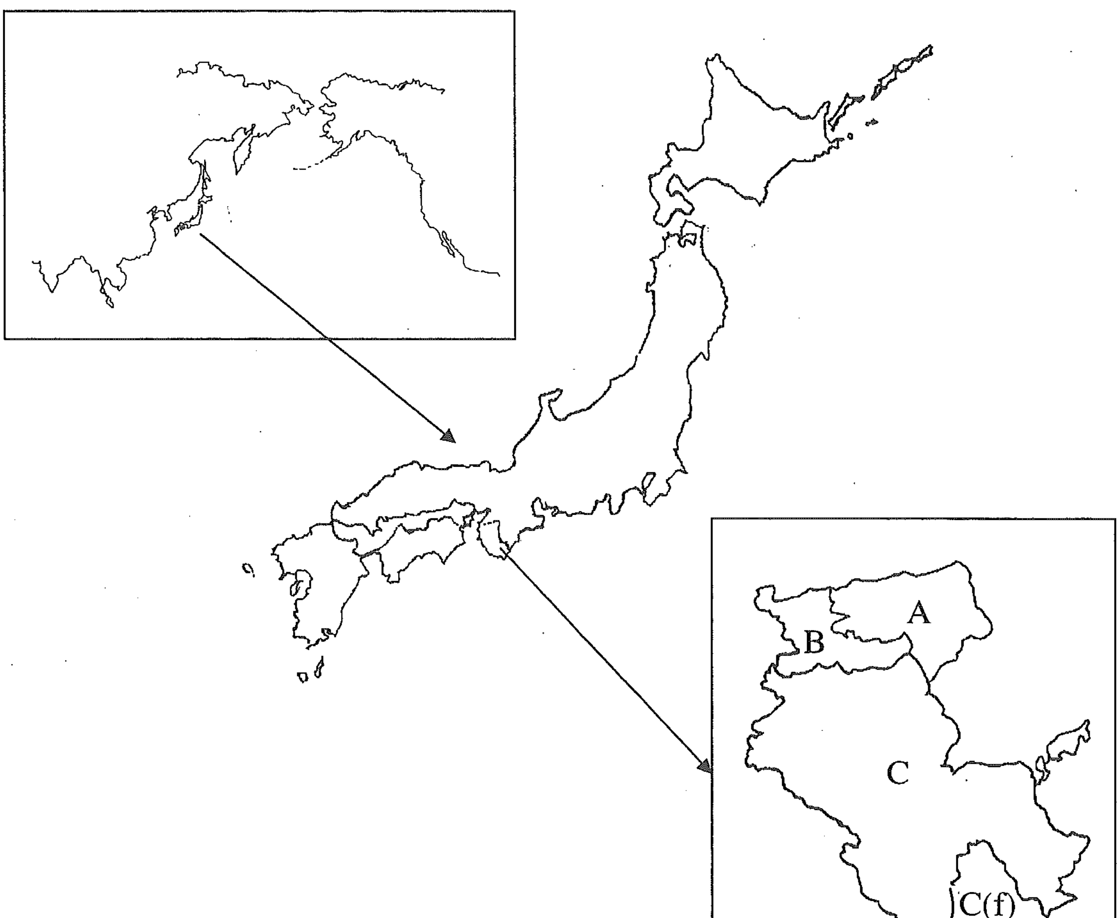

Figure 1. Wakayama prefecture, covering level and mountainous areas of 4725 km^2, is situated in the middle of the Japan mainland between 33°25′ and 34°23′N and 136°0′ and 134°59′E. Subdivisions into regions in Wakayama prefecture are shown as A, B, C and C(f). Sources: Statistics Bureau, MIC and Statistical Handbook of Japan, Statistics Bureau, MIC.

Table I. Demographic data in Wakayama Prefecture.

	Population in the 2000 census			Emigrations		Immigrations		Proportion of old people			Occupations in 1995		
	Total(A)	Male	Female	Number of emigrants	To other Prefectures (B)(B/A%)	Number of immigrants	From other Prefectures (C)(C/A%)	1960 (%)	1990/1995* (%)	2000 (%)	Agriculture, forestry and fishing (%)	Secondary industries (%)	Tertiary industries (%)
Wakayama Prefecture	1,069,912	506,882	563,030	37,345	21,204 (1.98)	33,454	17,213 (1.61)	7.3	15.3/18.10*	21.2	11.7	28.2	59.5
Kozagawa area	3,726	1,662	2,064	91	50 (1.34)	98	47 (1.26)	un	37.08*	42.62	13.1	28.2	58.8
Koza area	5,742	2,581	3,161	176	69 (1.20)	190	84 (1.46)	un	28.25*	32.97	12.7	23.3	64

Sourse: Tokei nennkan 2003 from Wakayama Prefecture

un: unknown

cases for this study, but familial progressive muscular atrophy was excluded. All cases were diagnosed by neurologists (registered with Societas Neurologica Japonica: Japanese Association of Neurology) at the main hospitals in Wakayama prefecture (Wakayama Laborer's Hospital, Japan Red Cross Hospital, Wakayama Medical University, and other public hospitals) and were verified for this survey by the authors. ALS patients were registered using the initials of their name, gender, date of birth, and residence area as well as their clinical data. To maintain the confidentiality of each personal record, we used the patient's initials and municipality of residence rather than full names and detailed addresses. The protocol of this study was approved by the Wakayama Medical Ethics Association.

Since the crude incidence and mortality rate generally increase with age, it is difficult to compare those rates between two populations with different age distribution simply, e.g., an area with predominantly young population and that with predominantly elderly population. When comparing those rates in this study, we used age-adjusted rates that can be compared without the influence of age distribution.

Age-adjusted rates were calculated by direct methods using the population in 2000 and in 1990 in Japan as the standard.

Statistical analysis

The difference in proportions was assessed with the χ^2 test, and that in incidence and mortality rates was analysed by Z score. The differences were assessed with two-sided tests, with an alpha level of 0.05; 95% confidence intervals (95% CI) for incidence and mortality were calculated assuming a Poisson distribution.

Results

The questionnaire response rate was 58% on the first occasion, and 99% on the second. There were 215 Japanese cases registered as having MND in Wakayama prefecture. Of these, 134 (male 79, female 55) cases were newly diagnosed as possible, probable, or definite ALS during the five-year period between 1998 and 2002 (Table II). Of the 215 cases, 121 patients with ALS were living in Wakayama prefecture on 31 December 2002.

Clinical features

The clinical features of the 134 ALS cases are listed in Table III. The male/female ratio was 1.43:1, different from that of the general population of Wakayama prefecture (direct method) (χ^2=7.21, df=1,

Table II. Number of cases during the 5-year study period.

	Number of patients			Number of deaths		
Year	Total	Male	Female	Total	Male	Female
2002	20	8	12	2	1	1
2001	35	20	15	7	4	3
2000	19	16	3	9	8	1
1999	33	22	11	15	10	5
1998	27	13	14	13	5	8
Annual average	26.8	15.8	11	9.2	5.6	3.6
Total	134	79	55	46	28	18

Table III. Clinical characteristics of patients (1998~2002).

Total		134	%
Male/Female		79/55	1.43/1
Family history (+)		5	3.73
Clinical signs at onset	Bulbar	27	20.15
	Bulbar and upper limb	8	5.97
	Upper limb disturbance	41	30.60
	Lower limb disturbance	24	17.91
	Upper and lower limb disturbance	16	11.94
	Respiratory disturbance	6	4.48
	Primary lateral sclerosis	2	1.49
	Not defined	10	7.46
ALS associated with dementia		8	5.97

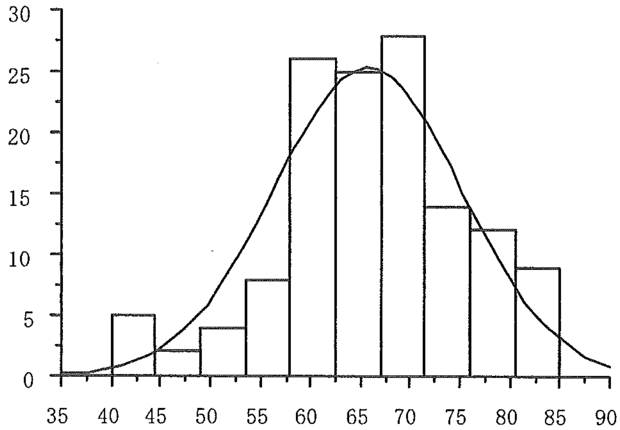

Figure 2. Ages at onset of 134 patients with ALS in Wakayama prefecture, 1998–2002.

$p<0.0073$). Five cases (3.73%) had familial ALS based on detailed family history. The most frequent clinical sign at onset was upper limb disturbance, and the second was bulbar sign. The mean age at onset was 65.7 ± 9.4 years (mean $\pm$ SD, range 40–85 years), 65.7 ± 9.6 for males (range 40–85 years), and 65.8 ± 9.3 for females (range 41–82) (Figure 2).

Incidence

Incidence rates based on the newly diagnosed 134 ALS cases are shown in Table IV. The average annual crude incidence in Wakayama prefecture was 2.50 (male 3.08, female 1.99) per 100,000 population. The incidence rates of ALS in Wakayama prefecture after adjustment for both age and gender to the 2000 or 1990 Japanese population (direct method) were 2.23 and 1.84 respectively (95% CI 1.33–3.21), 2.27 and 2.19 for male, and 1.79 and 1.51 for female. There was no significant difference in the age- and gender-adjusted incidence rates between males and females ($\chi^2=0.2$, df=1, $p<$NS). Regarding the age- and gender-adjusted incidence rates according to the three regions of Wakayama prefecture (regions A, B, and C), a low tendency of the incidence rate for females in the urban area (region B) of 1.43, when age-adjusted to the 2000 Japanese females was indicated, but there was no significant difference ($\chi^2=0.43$, df=3, $p<$NS). The highest age- and gender-adjusted incidence was for males in Kozagawa and Koza areas (region C (f)) (9.53 age-adjusted to the 2000 Japanese population) with significant difference ($\chi^2=3.77$, df=1, $p=0.05$). There were five ALS cases diagnosed during the survey period at Kozagawa and Koza areas (base population 4243 for males and 5225 for females). The average annual incidence for ALS was consistently higher for males than for females in all regions. There were no cases diagnosed before 39 years of age, and the incidence generally increased with advancing age. Regarding the incidence per 5-year age class, two peaks were found for males at 11.66 per 100,000 population between 60 and 64 years, and 14.41 per 100,000 population between 80 and 84 years. For females, a peak was found at 7.73 per 100,000 population between 70 and 74 years (Figure 3). The incidence at 80 to 84 years of age was significantly higher in males than in females ($\chi^2=5.56$, df=1, $p<0.01$).

Prevalence

There were 121 patients (male 72, female 49) with ALS residing in the community on the prevalence assessment date of 31 December 2002. The crude prevalence in Wakayama prefecture on the prevalence day was 11.31 (14.40 per 100,000 population for male, 8.53 per 100,000 population for female). Geographically, the prevalence rates were almost equivalent in these 3 blocks except for region C(f), where the rate was highest at 52.81 per 100,000 population (70.70 for males and 38.28 for females (Table V).

Mortality

The mortality rate was calculated based on deaths due to ALS each year. The crude annual mortality rate was 0.86 per 100,000 population (males 1.10, females 0.64). The age-specific mortality rate adjusted to the 1990 Japanese population was 0.58 per 100,000 population (males 0.72, females 0.44) (Table VI). The disease duration of all registered

Table IV. Number and average annual incidence per 100,000 population for ALS in Wakayama Prefecture, 1998–2002.

	Males			Females			Total			
District#	Number of cases	Crude rate	Age adjusted rate*(**)	Number of cases	Crude rate	Age adjusted rate*(**)	Number of cases	Crude rate	Age adjusted rate*(**)	95% CI
A	17	3.21	3.26 (2.66)	12	2.08	2.06 (1.66)	29	2.62	2.65 (2.16)	0.50–4.79
B	32	2.95	2.63 (2.02)	20	1.65	1.43 (1.21)	52	2.26	2.05 (1.66)	0.74–3.35
C	30	3.27	2.72 (2.28)	23	2.14	1.76 (1.52)	53	3.35	2.21 (1.87)	0.74–3.69
C(f)	3	14.14	9.53## (7.34)	2	7.66	4.16 (3.18)	5	10.56	6.57 (5.24)	
Total	79	3.08	2.72 (2.19)	55	1.99	1.79 (1.51)	134	2.50	2.23 (1.84)	1.33–3.12

* Rate adjusted to the Japanese 2000 population. ** Rate adjusted to the Japanese 1990 population.
#: District as shown in Fig. 1.
##: $\chi^2=3.77$, df=1, P=0.05.