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# High Body Mass Index After Age 20 and Diabetes Mellitus Are Independent Risk Factors for Ossification of the Posterior Longitudinal Ligament of the Spine in Japanese Subjects

## A Case-Control Study in Multiple Hospitals

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**Study Design.** A sex- and age-matched case-control study was carried out.

**Objectives.** To facilitate early prediction, prevention, and treatment of ossification of the posterior longitudinal ligament of the spine, the authors analyzed histories of past illness, past body mass indexes, and body pliableness by nature, adjusted for other factors considered to be risk factors.

**Summary of Background Data.** The cause of ossification of the posterior longitudinal ligament of the spine has not yet been elucidated in detail, although many possible causative factors have been suggested, including gender, diabetes mellitus, trauma, hormonal imbalance, and dietary habits.

**Methods.** A self-administered questionnaire was obtained from 69 patients with ossification of the posterior longitudinal ligament of the spine and 138 sex- and age-matched control participants who were free of spinal disease, randomly selected from participants in a health checkup in a town. After univariate analysis, a stepwise method was applied to select significant factors in multivariate analysis.

**Results.** A multivariate analysis revealed that the following three indicators were independent potent risk factors for ossification of the posterior longitudinal ligament of the spine: history of diabetes mellitus, history of lumbago, and maximum body mass index before manifestation ≥25, after adjustment for other possible lifestyle risk factors.

**Conclusion.** Excessive weight gain between 20 and 40 years of age, diabetes mellitus, and lumbago were found to be independent risk factors for ossification of the posterior longitudinal ligament of the spine. Follow-up studies, including the addition of hospital-based control participants and analysis of genetic polymorphisms, will be needed in the future. [Key words: ossification of the posterior longitudinal ligament of the spine, case-control study, body mass index, diabetes mellitus, body pliableness] **Spine 2004;29:1006–1010**

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Ossification of the posterior longitudinal ligament of the spine (OPLL) is an intractable disease in Japan. It has been called a Japanese disease, because many cases have been reported mainly in Japan as well as in other Asian peoples, more than in races. However, the relation of diffuse idiopathic skeletal hyperosteosis (DISH) to OPLL reported by Resnick *et al*[1] has recently attracted attention, and many cases of complication of the two diseases have been reported.[2] Now, OPLL is recognized as an important disease occurring not only in the Japanese but also in peoples in Europe and in the United States.[3] The frequency is approximately 1.9% to 4.3% in the Japanese general population.[4] It has also been reported that men are three times more likely to have OPLL than women, and that the peak of OPLL prevalence occurs in the 60s.[5]

It is manifested in the cervical vertebrae and causes a range of disease conditions varying from near-normality to quadriplegia. The cause of OPLL has not yet been elucidated in detail, although it is thought to be a multifactorial disease in which complex environmental and genetic factors interact. Although many possible causative factors have been suggested, including gender, diabetes mellitus (DM), trauma, hormonal imbalance, and dietary habits, the cause of the disease has not yet been clarified.[6-8] Regarding dietary factors, previous epidemiologic studies carried out in Japan and Taiwan suggest that both a high-salt diet and low consumption of animal protein are risk factors for OPLL, although this issue has not yet been fully settled.[8,9] By contrast, a hospital-based study revealed that both glucose intolerance and high body mass index (BMI) are significantly associated with OPLL, although few adjustments for confounding factors were carried out in that study.[10] In any case, in order to facilitate the early prediction, prevention, and treatment of OPLL, it will be necessary to elucidate the specific etiologic role of environmental factors that can be regulated by appropriate interventions, as well as possible genetic markers, which were reported recently.[11-16]

We are currently carrying out a case-control study at multiple hospitals in several areas in Japan, in order to identify both genetic and environmental risk factors for OPLL. In the present report, we describe the results of an age- and sex-matched case-control analysis, in which we analyzed histories of past illness, past BMI, and body pliableness by nature, adjusted for other factors considered to be risk factors.

## ■ Materials and Methods

**Design of Case-Control Study.** Patients with a diagnosis of OPLL in the previous 3 years and sex- and age-matched (±3 years) control participants who did not have any spinal disorders, including hospital participants obtained from 12 hospitals in various areas (9 in Hokkaido, 1 in Aichi, 1 in Fukuoka, and 1 in Saga) in Japan, and population control participants obtained from participants in a health checkup in a town in Hokkaido, were recruited to the study. The diagnosis of OPLL was carried out by the specialists on the basis of clinical symptoms and radiologic examinations by using radiographs of the cervical and thoracic spines, tomograph, computed tomograph, and magnetic resonance imaging, being classified according to the criteria of the Investigation Committee on the Ossification of the Spinal Ligaments, Japanese Ministry of Public Health and Welfare.[4] All the patients were symptomatic and required medical consultation, and many of them underwent spinal surgery before or during the present study. The answers to a self-administered questionnaire and a 2-mL sample of whole blood in a blood-collecting vessel containing ethylenediaminetetraacetate were obtained from the subjects, along with written informed consent of cooperation with the study.

The blood samples were stored at −20° C until use for DNA extraction and genotyping of the candidate genes of OPLL. The contents of the questionnaire were (1) present and past body height and weight, (2) history and family history of the diseases, (3) past food consumption (in the period 5 years before the present), (4) occupation and work environment (in the prime of life), (5) sleep, rest, mental stress, and physical exercise (in the prime of life), (6) drinking and smoking, (7) body pliableness by nature, and (8) type A character tendency.

The present study was approved by the institutional review boards of Hokkaido University School of Medicine and of each collaborating hospital.

**Subjects and Methods.** A self-administered questionnaire was obtained from 69 patients who had received diagnoses of OPLL manifested in 1998 to 2001 in collaborating hospitals in Hokkaido, and 138 sex- and age-matched control participants who were without spinal diseases, randomly selected from participants in a health checkup in a town in Hokkaido. The factors analyzed in the present report were (1) present and past history of illness, (2) present and past BMI, and (3) body pliableness. In univariate analysis, the differences were analyzed statistically by the $\chi^2$ test ($df = 1$). The Yates correction for continuity was used when an observed number was ≤5. A stepwise method was applied to select significant ($P < 0.05$) factors in multivariate analysis for 7 factors that were significantly associated with OPLL in univariate analysis, *ie* with a history of DM, with a history of whiplash injury, with a history of lumbago, BMI at age 40 years ≥25, maximum BMI before manifestation ≥25, and lack of body pliableness, adjusted for the other factors that appeared to be associated with OPLL in the present study, such as high consumption of Japanese pickles, high consumption of rice, low consumption of hams and sausages, low consumption of tofu and fermented soybeans, insufficient sleep (<5 hours/day), and irregular sleeping time (Washio and Okamoto, unpublished data) obtained from the questionnaire. A multiple logistic model was applied to evaluate the odds ratios of the major risk factors. All statistical analyses were conducted by use of a statistical analysis system package (SAS Institute Inc., Cary, NC, USA).

## ■ Results

The characteristics of the 69 patients with of OPLL and 138 control participants are shown in Table 1. No significant differences were found in present age, age at graduation, or age at menarche (in females) between OPLL patients and control participants. The present BMI was significantly higher in OPLL patients than in control participants in both men (25.8 ± 0.6 (mean ± SE) in OPLL *vs* 23.3 ± 0.3 in control participants, $P < 0.001$) and in women (25.9 ± 0.9 in OPLL *vs* 23.4 ± 0.4 in control participants, $P < 0.05$), and the frequency of having a history of DM was also significantly higher in OPLL patients than in control participants in both men (20.0% *vs* 5.0%, $P < 0.05$) and women (27.6% *vs* 1.7%, $P < 0.001$). In men, the frequencies of having a history of whiplash injury and a history of lumbago were significantly higher in OPLL patients (12.5% in the former, 42.5% in the latter) than in control participants (1.3% in the former, 20.0% in the latter) ($P < 0.05$, $P < 0.01$, respectively).

Table 2 summarizes information about BMI and body pliableness before manifestation of OPLL. The BMI at age 40 years was significantly higher in OPLL patients than in control participants in both men (25.5 ± 0.6 in OPLL *vs* 23.0 ± 0.2 in control participants, $P < 0.001$)

**Table 1. Characteristics of Patients with Ossification of the Posterior Longitudinal Ligament of the Spine (OPLL) and Control Participants: no. (%)**

| | Male | | Female | |
|---|---|---|---|---|
| | OPLL (n = 40) | Control (n = 80) | OPLL (n = 29) | Control (n = 58) |
| Present age | 63.1 ± 1.5 | 63.2 ± 1.1 | 59.8 ± 1.8 | 59.8 ± 1.3 |
| Present body mass index* | 25.8 ± 0.6 | 23.3 ± 0.3† | 25.9 ± 0.9 | 23.4 ± 0.4‡ |
| Age at graduation (yr) | 16.6 ± 0.5 | 17.4 ± 0.3 | 16.4 ± 0.3 | 16.5 ± 0.3 |
| Age at menarche (yr) | — | — | 13.9 ± 0.3 | 13.9 ± 0.2 |
| With past history of | | | | |
| Cancer | 2 (5.0) | 5 (6.3) | 1 (3.5) | 1 (1.7%) |
| Stroke | 1 (2.5) | 0 (0) | 0 (0) | 0 (0%) |
| Myocardial infarction | 0 (0) | 0 (0) | 0 (0) | 0 (0%) |
| Angina | 0 (0) | 1 (1.3) | 1 (3.5) | 0 (0%) |
| Arrhythmia | 3 (7.5) | 8 (10.0) | 2 (6.9) | 1 (1.7%) |
| Diabetes mellitus | 8 (20.0) | 4 (5.0)‡ | 8 (27.6) | 1 (1.7%)† |
| Hypertension | 7 (17.5) | 14 (17.5) | 10 (34.5) | 11 (19.0%) |
| Renal disease | 5 (12.5) | 2 (2.5)§ | 0 (0) | 2 (3.5%) |
| Hypercholesterolemia | 2 (5.0) | 3 (3.8) | 3 (10.3) | 8 (18.8%) |
| Gout | 1 (2.5) | 3 (3.8) | 0 (0) | 1 (1.7%) |
| Head injury | 1 (2.5) | 1 (1.3) | 1 (3.5) | 1 (1.7%) |
| Neck injury | 3 (7.5) | 0 (0)§ | 3 (10.3) | 0 (0%)† |
| Back injury | 3 (7.5) | 4 (5.0) | 2 (6.9) | 2 (3.5%) |
| Whiplash injury | 5 (12.5) | 1 (1.3)‡ | 1 (3.5) | 1 (1.7%) |
| Lumbago | 17 (42.5) | 16 (20.0)¶ | 9 (31.0) | 13 (22.4%) |
| With family history of | | | | |
| Cancer | 14 (35.0) | 27 (33.8) | 6 (20.7) | 21 (36.2%) |
| Stroke | 7 (17.5) | 19 (23.8) | 4 (13.8) | 8 (13.8%) |
| Myocardial infarction | 1 (2.5) | 2 (2.5) | 3 (10.3) | 3 (5.2%) |
| Diabetes mellitus | 6 (15.0) | 10 (12.5) | 9 (31.0) | 8 (13.8%)† |
| Hypertension | 11 (27.5) | 20 (25.0) | 12 (41.9) | 12 (20.7%)* |
| Rheumatic arthritis | 2 (5.0) | 5 (6.3) | 2 (6.9) | 2 (3.5%) |

*P* values *versus* OPLL
* mean ± SE.
† $P < 0.001$.
‡ $P < 0.05$.
§ $P < 0.1$.
¶ $P < 0.01$.

and women (24.7 ± 0.8 in OPLL *vs* 22.5 ± 0.3 in control participants, $P < 0.05$), and maximum BMI before manifestation was also significantly higher in OPLL patients than in control participants in both men (28.2 ± 0.7 in OPLL *vs* 24.9 ± 0.3 in control participants, $P < 0.001$) and women (28.9 ± 1.0 in OPLL *vs* 24.8 ± 0.4 in control participants, $P < 0.001$), although there were no significant differences between OPLL patients and control par-

**Table 2. Factors of Body Mass Index and Body Pliableness in Patients with, Ossificaiton of the Posterior Longitudinal Ligament of the Spine (OPLL) (Before Manifestation) and in Control Participants**

| | Male | | Female | |
|---|---|---|---|---|
| | OPLL (n = 40) | Control (n = 80) | OPLL (n = 29) | Control (n = 58) |
| BMI at age 20 yr* | 22.7 ± 0.4 | 22.2 ± 0.2 | 22.5 ± 0.8 | 21.4 ± 0.3 |
| BMI at age 40 yr* | 25.5 ± 0.6 | 23.0 ± 0.2§ | 24.7 ± 0.8 | 22.5 ± 0.3¶ |
| Maximum BMI before manifestation*† | 28.2 ± 0.7 | 24.9 ± 0.3§ | 28.9 ± 1.0 | 24.8 ± 0.4§ |
| Lack of body pliableness by nature‡ | 28 (70.0%) | 47 (61.9%) | 26 (89.7%) | 32 (55.2%)§ |

* mean ± SE
† Age with maximum BMI (mean ± SD); 47.08 ± 14.40 (OPLL, male), 45.32 ± 15.92 (controls, male), 41.38 ± 14.45 (OPLL, female), 45.22 ± 15.96 (controls, female)
‡ Body pliableness by nature had four choices: a, pliable; b, somewhat pliable; c, somewhat nonpliable; d, nonpliable, with c and d considered risk factors.
§ $P < 0.001$.
¶ $P < 0.05$.
** $P < 0.01$.
*P* values *versus* OPLL.

**Table 3. Odds Ratios (OR) of Selected Risk Factors for Ossification of the Posterior Ligament of the Spine**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR | (95% CI) | OR* | (95% CI) |
| With a past history of | | | | |
| diabetes mellitus | 8.03 | (2.80–23.03)† | 11.78 | (2.39–58.10)‡ |
| whiplash injury | 6.48 | (1.28–33.00)§ | — | — |
| lumbago | 2.27 | (1.20–4.29)§ | 4.07 | (1.59–10.40)‡ |
| BMI at age 40 yr ≥25 | 4.11 | (2.04–8.29)† | — | — |
| Maximum BMI before manifestation ≥25 | 3.52 | (1.86–6.68)† | 3.49 | (1.48–8.26)‡ |
| Lack of body pliableness by nature | 2.69 | (1.38–5.22)‡ | — | — |

Odds ratios and 95% confidence intervals are shown only if the factors were significant ($P < 0.05$) in univariate analysis, except for "with a past history of whiplash injury," because the number of subjects who possessed this factor was too small for the analyses.
In multivariate analysis, odds ratios and 95% confidence intervals are shown only if the factors were significant ($P < 0.05$) when screened by a stepwise procedure.
* Adjusted by other significant factors for OPLL, such as high consumption of Japanese pickles, high consumption of rice, low consumption of ham and sausages, tofu and fermented soybeans, sleep time <5 hr/day, and irregular sleeping time.
† $P < 0.001$.
‡ $P < 0.01$.
§ $P < 0.05$.
*P* values *versus* OPLL.

ticipants in BMI at age 20 years. Lack of body pliableness by nature was significantly higher in OPLL patients than in control participants in women (89.7% *vs* 55.2%, $P < 0.001$) but not in men (70.0% *vs* 61.9%).

Multivariate analysis revealed that the following three factors were potent independent risk factors for OPLL: history of DM, history of lumbago, and maximum BMI before manifestation ≥25, after adjustment for the other factors that appeared to be associated with OPLL in the present study (see Subjects and Methods). The odds ratios of these three factors were 11.78 (2.39–58.10, 95% CI), 4.07 (1.59–10.40), and 3.49 (1.48–8.26), respectively, in a multiple logistic model (Table 3).

## ■ Discussion

Few studies have concerned OPLL because the disorder is not very common except in Asians. Some studies have suggested a close association between OPLL and DISH.[17,18] An association with obesity or DM has been reported with DISH in Hungarian subjects as well as with OPLL in Japanese subjects.[6,19] In the present study, we first showed that obesity and DM are potent independent risk factors for OPLL in multivariate analysis adjusted for other factors considered to be risk factors, such as food consumption, sleep, and rest, in a sex- and age-matched case-control study.

In the present analysis, excessive weight gain between 20 and 40 years old was found to be an independent risk factor for OPLL. It was reported previously that obesity at age 25 years is a risk factor for DISH.[19] The prevention of obesity by lifestyle interventions, such as diet control or exercise from youth, is thus suggested to be one of the ways to prevent the future manifestation of OPLL.

Our multivariate analysis also revealed that a history of DM was a potent independent risk factor for OPLL, after adjustment for other factors considered to be risk factors. In the present population control participants, the prevalence of DM was found to be about 4%, which is lower than that in the general Japanese population. A selection bias caused by the fact that the people with DM who are receiving hospital treatment tend not to participate in the annual health checkup in their towns is thought to be responsible for the low prevalence of DM in our control population. It was impossible to clarify whether there is an association of status of DM treatment with OPLL, because we could not obtain laboratory data such as $HbA_1$ or $HbA_{1C}$ for our subjects. Furthermore, questions about dietary factors in our questionnaire referred to the period 5 years before the present, which was before the onset of OPLL but not necessarily before the onset of DM. These are thought to be limitations of this study. However, it was previously reported that OPLL is associated with non-insulin dependent diabetes mellitus (NIDDM), among several kinds of DM. Furthermore, activation of nuclear factor kappa B, which is stimulated by environmental factors involving cytokines and growth factors in ligament cells, was reported to be associated with the onset of OPLL or DISH, particularly in the cases complicated by NIDDM.[20] Further analysis using genetic markers of NIDDM as well as OPLL or DISH will be important for gaining insights into this association.

Lumbago, a selected risk factor in the analysis, appeared to be one of the predictive symptoms for OPLL. However, lumbago may have various causes and may reflect the process of ossification or may be an effect of the lack of body pliableness rather than simply a causal factor of OPLL. In any case, the present questionnaire study revealed body pliableness to be a significant factor in univariate analysis, which is in accord with the clinical impression and recent reports about an association of OPLL with collagen gene polymorphism,[13,15] suggesting that further analyses of this issue should be performed.

In summary, excessive weight gain between 20 and 40 years of age, DM, and lumbago were found to be inde-

pendent risk factors for OPLL. Follow-up studies, including the addition of hospital-based control participants and analysis of genetic polymorphisms, will be needed in the future.

## ■ Key Points

- A sex- and age-matched case-control study with 69 OPLL patients and 138 sex- and age-matched control participants was carried out.
- History of diabetes mellitus, history of lumbago, and maximum body mass index before manifestation ≥25 were found to be independent potent risk factors for OPLL, after adjustment for other possible lifestyle risk factors.
- Follow-up studies, including the addition of hospital-based control participants and analysis of genetic polymorphisms, will be needed in the future.

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# Environmental Factors and Risk of Idiopathic Dilated Cardiomyopathy

## —— A Multi-Hospital Case–Control Study in Japan ——

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**Background** Detailed epidemiological investigations on the relationship of environmental factors, especially occupational and microbiological factors, to the development of idiopathic dilated cardiomyopathy (IDC) are scarce.

**Methods and Results** A multi-hospital case–control study was conducted in 38 hospitals throughout Japan in order to survey IDC cases and age, sex-matched outpatient controls at each hospital. Crude and adjusted odds ratios (ORs) by various environmental factors were calculated in 135 pairs of cases and controls. Univariate analyses revealed significantly increased ORs for lower education, passive smoking in the workplace, cold and/or hot workplace, symptoms of fatigue and history of bacterial infection; in contrast, decreased ORs were associated with a history of rubella and gastroduodenal diseases. Based on multivariate adjusted analyses, lower education (OR 1.96, 95% confidence interval (CI) 1.13–3.40), cold or hot workplace (OR 1.84, 95%CI 1.08–3.12) and history of measles (OR 1.78, 95%CI 1.01–3.08) exhibited a significant positive relationship with IDC risk. History of rubella (OR 0.17, 95%CI 0.06–0.52) and gastroduodenal diseases (OR 0.14, 95%CI 0.07–0.29) were inversely related to the risk.

**Conclusions** Some occupational and microbiological factors appear to relate independently to the development of IDC and further investigation is required to establish their respective mechanisms. (*Circ J* 2004; **68:** 1011–1017)

**Key Words:** Dilated cardiomyopathy; Epidemiology; Risk factors

Idiopathic dilated cardiomyopathy (IDC) is a primary myocardial disease of unknown etiology characterized by left ventricular or biventricular dilatation and impaired myocardial contractility[1] Its incidence and prevalence rates in Japan are nearly the same as those of Western countries, despite the rate of coronary heart disease being much lower[2,3] Several risk factors have been documented in observational epidemiological studies: male sex, black race, hypertension, smoking, heavy alcohol consumption and lower socioeconomic and educational status[4–10] Recent investigations into its pathogenesis have focused on genetic factors, viral myocarditis, immune abnormalities or metabolic abnormalities[1,11–16] In our previous case–control study, susceptibility to the common cold or diarrhea appeared to increase the disease risk[17]

However, detailed epidemiological investigations regarding the relationship of environmental factors, including occupational and microbiological factors, to the development of IDC are scarce, so we conducted a case–control study, using 40 departments in 38 participating hospitals throughout Japan.

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## Methods

*Case Ascertainment*

IDC patients in Japan receive financial aid for treatment from the Japanese government. From the total of 1,024 hospitals throughout Japan registered to participate with respect to government aid, 190 hospitals in which 5 or more IDC patients were treated were selected for participation in this study and 38 hospitals (40 departments of internal medicine or cardiology) agreed to collect both cases and controls (Fig 1). Among the 40 departments, 20 were in university hospitals and the remainder were in general hospitals. In 1995 a questionnaire survey for cases and controls was performed in which the cases were restricted to IDC patients diagnosed within the past 3 years. The survey asked subjects to recall lifestyle and environment prior to diagnosis. Each hospital surveyed between 1 and 11 cases, and 175 cases in total were surveyed (4.4 cases on average at each hospital).

The diagnostic criteria of IDC, which are based on the report of the WHO/ISFC task force regarding the definition and classification of cardiomyopathies[18] were prepared by the Research Committee on Idiopathic Cardiomyopathy, Japan[19] Specific heart muscle disease, which was defined

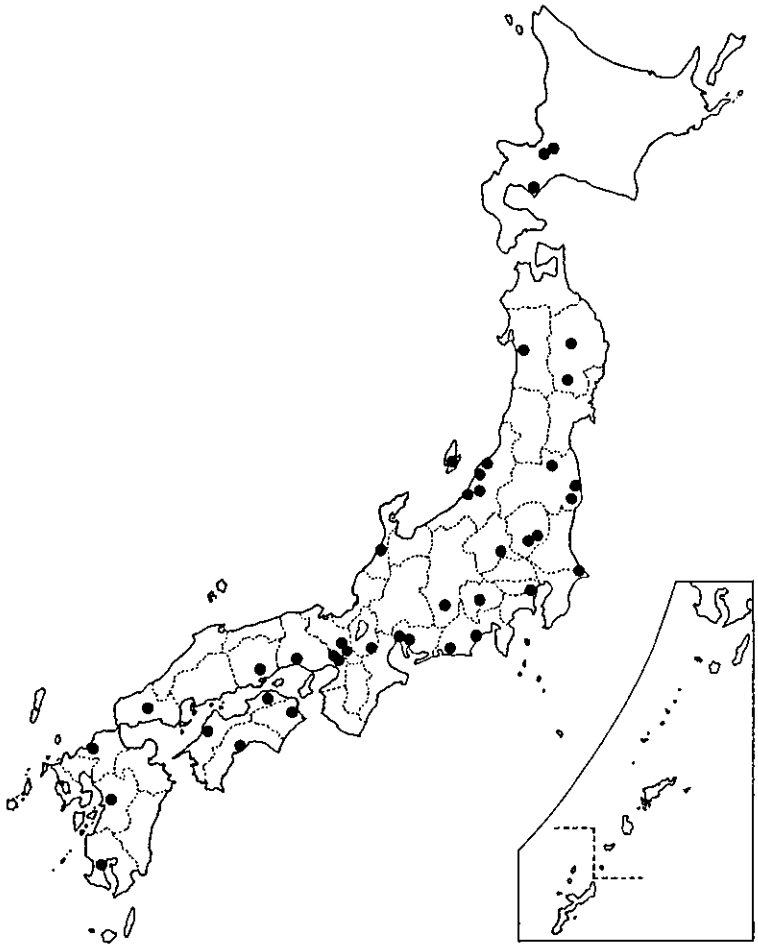

Fig 1. Location of the 38 hospitals (40 departments) participating in the questionnaire survey (cases and controls).

as heart muscle disease of known etiology or associated with disorders of other systems, was excluded.

*Control Selection*

Controls, who were matched on 5-year age intervals and sex for each case, were selected from outpatients of the same hospital. The age of each control was matched to that of a case at the time of diagnosis. Outpatients diagnosed with other types of cardiomyopathy, myocarditis, ischemic heart diseases, heart failure, valvular heart diseases, hypertensive heart diseases, congenital heart disease and severe arrhythmia were not selected as controls. Patients displaying essential hypertension, hyperlipidemia and mild arrhythmia were not excluded from control selection.

*Questionnaire Survey*

A self-administered questionnaire survey was provided to all cases and controls. A physician at each hospital explained the purpose of the study and verbal informed consent was obtained from each participant. The questionnaire included 37 questions regarding lifestyle (mainly related to drinking and active and passive smoking), occupation, education, living environment and past history. Cases were asked about these items prior to diagnosis; controls were asked about them immediately prior to the survey. Cases and controls were asked about the past occupation in which they were involved for the longest period: the questions included physical intensity, shift work, stress, and the chemical and physical environment. Questions regarding past history included 29 infectious diseases and infection-related diseases. Having a past history of 1 or more of measles, mumps, rubella, and varicella was categorized as a past history of any viral infection, whereas a past history of 1 or more of pneumonia, paranasal sinusitis, cystitis, pyelonephritis, cholecystitis, appendicitis, and repeated tonsillitis was categorized as a past history of any bacterial infection. Having a past history of 1 or more of chronic gastritis, gastric ulcer, and duodenal ulcer was categorized as a past history of gastroduodenal disease. Height and previous maximum weight were used to calculate previous maximum body mass index (BMI, kg/m$^2$). Men less than 160 cm in height and women less than 145 cm in height were categorized as being short. Subjects who had difficulty with reading or writing were interviewed by a physician, a nurse, or their family.

*Exclusions*

Of the 175 pairs of cases and controls, 40 pairs were excluded for the following reasons: cases were initially diagnosed more than 3 years prior to the survey (13 pairs); cases were pregnant less than 6 months before diagnosis (2 pairs); age difference of case and control exceeded 5 years (5 pairs); controls had ischemic heart disease (4 pairs); controls were selected from paramedical staff associated with each hospital (16 pairs). Thus, this report is based on 135 pairs of cases and controls.

**Table 1 Crude Odds Ratios for Idiopathic Dilated Cardiomyopathy by Basic Characteristics and Occupational Factors**

| Characteristics | Controls (n=135)* | | Cases (n=135)* | | Crude odds ratio | 95% confidence interval |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| *Short height*† | | | | | | |
| *Yes* | 15 | 11.5 | 26 | 19.5 | 1.88 | 0.90–3.96 |
| *No* | 116 | 88.5 | 107 | 80.5 | | |
| *Previous maximum body mass index* | | | | | | |
| *≥25 kg/m²* | 60 | 46.9 | 72 | 55.4 | 1.41 | 0.84–2.37 |
| *<25 kg/m²* | 68 | 53.1 | 58 | 44.6 | | |
| *Years of education* | | | | | | |
| *<9 years* | 35 | 27.3 | 59 | 45.7 | 2.24 | 1.29–3.90 |
| *≥10 years* | 93 | 72.3 | 70 | 54.3 | | |
| *Cigarettes/day* | | | | | | |
| *None* | 64 | 47.4 | 52 | 38.8 | 1.00‡ | |
| *1–19* | 27 | 20.0 | 24 | 17.9 | 1.09 | 0.34–2.23 |
| *≥20* | 44 | 32.6 | 58 | 43.3 | 1.62 | 0.92–2.88 |
| *Smoking of spouse* | | | | | | |
| *Yes* | 26 | 20.3 | 28 | 22.0 | 1.11 | 0.58–2.11 |
| *No* | 102 | 79.7 | 99 | 78.0 | | |
| *Passive smoking in workplace* | | | | | | |
| *Yes* | 77 | 57.0 | 96 | 71.1 | 1.85 | 1.09–3.17 |
| *No* | 58 | 43.0 | 39 | 28.9 | | |
| *Ethanol consumption/week* | | | | | | |
| *0–99 g* | 76 | 56.3 | 71 | 55.5 | 1.00‡ | |
| *100–299 g* | 33 | 24.4 | 27 | 21.1 | 0.88 | 0.46–1.67 |
| *≥300 g* | 26 | 19.3 | 30 | 23.4 | 1.24 | 0.64–2.40 |
| *Intensity of labor* | | | | | | |
| *Heavy* | 14 | 10.4 | 22 | 16.3 | 1.68 | 0.78–3.66 |
| *Moderate or light* | 121 | 89.6 | 113 | 83.7 | | |
| *Cold workplace* | | | | | | |
| *Yes* | 30 | 22.4 | 53 | 39.3 | 2.24 | 1.27–3.96 |
| *No* | 104 | 77.6 | 82 | 60.7 | | |
| *Hot workplace* | | | | | | |
| *Yes* | 35 | 26.1 | 56 | 41.5 | 2.01 | 1.16–3.47 |
| *No* | 99 | 73.9 | 79 | 58.5 | | |
| *Cold or hot workplace* | | | | | | |
| *Yes* | 43 | 32.1 | 67 | 49.5 | 2.09 | 1.23–3.53 |
| *No* | 91 | 67.9 | 68 | 50.4 | | |
| *Chemical use in workplace* | | | | | | |
| *Yes* | 26 | 20.3 | 27 | 22.9 | 1.16 | 0.61–2.23 |
| *No* | 102 | 79.7 | 91 | 77.1 | | |
| *Shift work or night work* | | | | | | |
| *Yes* | 24 | 17.8 | 18 | 13.3 | 0.71 | 0.35–1.45 |
| *No* | 111 | 82.2 | 117 | 86.7 | | |
| *Chronic overnight fatigue* | | | | | | |
| *Yes* | 48 | 35.8 | 74 | 56.5 | 2.33 | 1.38–3.93 |
| *No* | 86 | 64.2 | 57 | 43.5 | | |
| *Sleep disturbance because of failure* | | | | | | |
| *Yes* | 29 | 21.8 | 57 | 44.2 | 2.84 | 1.60–5.05 |
| *No* | 104 | 78.2 | 72 | 55.8 | | |
| *Job stress* | | | | | | |
| *Great* | 11 | 8.9 | 15 | 12.1 | 1.41 | 0.58–3.47 |
| *Mild or moderate* | 113 | 91.1 | 109 | 87.9 | | |

**Numbers of cases and controls vary because of missing data.*
*†Men less than 160 cm in height and women less than 145 cm in height.*
*‡Reference level.*

*Statistical Analysis*

Cases and their matched controls were initially compared by obtaining unmatched estimates of odds ratios (OR). Approximate 95% confidence intervals (CI) were determined with Woolf's method[20] Multivariate analysis with conditional logistic regression methods was used to determine adjusted OR and assess statistical significance[20,21] Statistical analyses were performed with the Statistical Analysis System (SAS Institute Inc, Cary, NC, USA).

## Results

The age range of the cases at the time of diagnosis was 19–84 years (mean, 57.6 years) and that of the controls at the time of the survey was 17-84 years (mean, 56.3 years). Of the 135 pairs, 98 (73%) were men and 37 (27%) were women. The clinical diagnoses of the controls were: hypertension (55), hyperlipidemia (9), gastroduodenal ulcer (8), gastritis (8), diabetes mellitus (7), common cold (7), mild arrhythmia (7), liver disease (7) and others (27).

Crude OR for IDC with respect to basic characteristics, including anthropometric indices, education and lifestyle, and occupational factors, are presented in Table 1. Previous

**Table 2 Crude Odds Ratios for Idiopathic Dilated Cardiomyopathy by History of Infection and Other Diseases**

| Past history | Controls (n=135)* | | Cases (n=135)* | | Crude odds ratio | 95% confidence interval |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| *Measles* | | | | | | |
| *Yes* | 48 | 35.6 | 62 | 45.9 | 1.54 | 0.92–2.59 |
| *No* | 87 | 64.4 | 73 | 54.1 | | |
| *Mumps* | | | | | | |
| *Yes* | 34 | 25.2 | 27 | 20.0 | 0.74 | 0.40–1.37 |
| *No* | 101 | 74.8 | 108 | 80.0 | | |
| *Rubella* | | | | | | |
| *Yes* | 20 | 14.8 | 5 | 3.7 | 0.22 | 0.07–0.65 |
| *No* | 115 | 85.2 | 130 | 96.3 | | |
| *Varicella* | | | | | | |
| *Yes* | 23 | 17.0 | 22 | 16.3 | 0.95 | 0.48–1.89 |
| *No* | 112 | 83.0 | 113 | 83.7 | | |
| *Any viral infection*† | | | | | | |
| *1 or more* | 60 | 44.4 | 73 | 54.1 | 1.47 | 0.89–2.45 |
| *No* | 75 | 55.6 | 62 | 45.9 | | |
| *Appendicitis* | | | | | | |
| *Yes* | 29 | 21.5 | 38 | 28.1 | 1.43 | 0.79–2.59 |
| *No* | 106 | 78.5 | 97 | 71.9 | | |
| *Pecurrent tonsilitis* | | | | | | |
| *Yes* | 12 | 8.9 | 19 | 14.1 | 1.68 | 0.74–3.87 |
| *No* | 123 | 91.1 | 116 | 85.9 | | |
| *Any bacterial infection*‡ | | | | | | |
| *1 or more* | 48 | 35.6 | 65 | 48.1 | 1.68 | 1.00–2.83 |
| *No* | 87 | 64.4 | 70 | 51.9 | | |
| *Common cold* | | | | | | |
| *≥twice/year* | 59 | 49.2 | 75 | 60.5 | 1.58 | 0.92–2.72 |
| *<twice/year* | 61 | 50.8 | 49 | 39.5 | | |
| *Candida albicans* | | | | | | |
| *Yes* | 44 | 32.6 | 36 | 26.7 | 0.75 | 0.43–1.31 |
| *No* | 91 | 67.4 | 99 | 73.3 | | |
| *Chronic gastritis* | | | | | | |
| *Yes* | 17 | 12.6 | 3 | 2.2 | 0.16 | 0.04–0.59 |
| *No* | 118 | 87.4 | 132 | 97.8 | | |
| *Gastric ulcer* | | | | | | |
| *Yes* | 15 | 11.1 | 9 | 6.7 | 0.57 | 0.22–1.45 |
| *No* | 120 | 88.9 | 126 | 93.3 | | |
| *Duodenal ulcer* | | | | | | |
| *Yes* | 16 | 11.9 | 5 | 3.7 | 0.29 | 0.09–0.87 |
| *No* | 119 | 88.1 | 130 | 96.3 | | |
| *Gastro duodenal diseases*§ | | | | | | |
| *1 or more* | 43 | 31.9 | 15 | 11.1 | 0.27 | 0.13–0.53 |
| *No* | 92 | 68.1 | 120 | 88.9 | | |
| *Chronic liver disease* | | | | | | |
| *Yes* | 9 | 6.7 | 3 | 2.2 | 0.32 | 0.07–1.32 |
| *No* | 126 | 93.3 | 132 | 97.8 | | |
| *Bronchial asthma* | | | | | | |
| *Yes* | 7 | 5.2 | 11 | 8.1 | 1.62 | 0.56–4.80 |
| *No* | 128 | 94.8 | 124 | 91.9 | | |
| *Drug allergy* | | | | | | |
| *Yes* | 13 | 11.0 | 8 | 7.0 | 0.61 | 0.22–1.66 |
| *No* | 105 | 89.0 | 106 | 93.0 | | |

**Numbers of cases and controls vary because of missing data.*
*†Any past history of measles, mumps, rubella, and varicella.*
*‡Any past history of pneumonia, paranasal sinusitis, cystitis, pyelonephritis, cholecystitis, appendicitis tonsillitis.*
*§Any past history of chronic gastritis, gastric ulcer or recurrent duodenal ulcer.*

obesity and shorter height did not exhibit a significant association. Fewer years (less than 10 years) of education demonstrated a significantly higher OR. An association with smoking 20 or more cigarettes per day was of borderline significance; however, a significant increase in OR was observed with passive smoking in the workplace. In terms of occupational factors, physical intensity did not increase the risk; however, a hot and/or cold workplace environment significantly related to the risk of IDC. Other occupational factors (eg, type of occupation, exposure to vibration, noise and dust) did not have a significant relationship (data not shown). Significantly higher OR were found for subjects reporting chronic overnight fatigue and sleep disturbance because of fatigue; however, feelings related to job stress showed no relationship. Living environment, whether natural (sea, forest etc) or artificial (traffic, factory, farmland, house etc), was also surveyed, but no significant relationship was observed (data not shown).

Crude OR based on past histories of infectious and other diseases are shown in Table 2. A positive association with a history of measles was of borderline significance, whereas a significant inverse association was observed with history

**Table 3 Adjusted Odds Ratios for Idiopathic Dilated Cardiomyopathy From Conditional Logistic Regression**

| Covariate | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted odds ratio | 95% confidence interval | Adjusted odds ratio | 95% confidence interval | Adjusted odds ratio | 95% confidence interval | Adjusted odds ratio | 95% confidence interval |
| *Years of education (9 years or less/10 years or more)* | *1.64* | *0.91–2.98* | *1.89* | *1.08–3.31* | *1.81* | *1.03–3.18* | *1.96* | *1.13–3.40* |
| *Passive smoking in workplace (yes/no)* | *1.00* | *0.63–1.58* | *1.13* | *0.73–1.75* | *1.04* | *0.66–1.64* | | |
| *Cold or hot workplace (yes/no)* | *1.75* | *0.98–3.14* | *1.86* | *1.06–3.27* | *1.72* | *0.96–3.06* | *1.84* | *1.08–3.12* |
| *Sleep disturbance because of fatigue (yes/no)* | *2.12* | *1.13–3.95* | | | | | | |
| *Measles (yes/no)* | | | | | *1.57* | *0.87–2.83* | *1.78* | *1.01–3.08* |
| *Rubella (yes/no)* | *0.18* | *0.06–0.53* | *0.20* | *0.07–0.58* | *0.16* | *0.05–0.50* | *0.17* | *0.06–0.52* |
| *Any bacterial infection (1 or more/no)* | *1.43* | *0.84–2.46* | *1.60* | *0.94–2.70* | *1.47* | *0.86–2.52* | | |
| *Gastroduodenal diseases (1 or more/no)* | *0.14* | *0.06–0.29* | *0.14* | *0.06–0.28* | *0.13* | *0.06–0.27* | *0.14* | *0.07–0.29* |

*Model 1 includes 7 covariates that revealed significant relationships based on univariate analyses. Because of the possibility that sleep disturbance attributable to fatigue is a symptom caused by the development of IDC, this covariate was excluded in model 2. Past history of measles showed borderline significance based on univariate analysis; consequently, this covariate was incorporated into model 3. Two covariates (passive smoking in the workplace and any bacterial infection) demonstrating weaker relationships were removed in model 4.*

of rubella. A significantly high OR was apparent with a past history of any bacterial infection, but a positive association with common colds 2 or more times per year was of borderline significance. Significant inverse associations were detected for a past history of chronic gastritis and duodenal ulcer, and with a past history of 1 or more of these 3 gastroduodenal diseases. A history of bronchial asthma failed to display a significant association.

For the factors displaying significant relationships in the univariate analyses, independent relationships adjusted for one another were determined using conditional logistic regression (Table 3). Model 1 included 7 covariates, which revealed significant relationships based on univariate analyses; 'cold or hot workplace' was included in the model because of the strong correlation between 'cold workplace' and 'hot workplace' (r=0.61); 'chronic overnight fatigue', which correlated with 'sleep disturbance because of fatigue' (r=0.44), was not included. In model 1, a positive association with 'sleep disturbance because of fatigue' remained significant and inverse associations with past histories of rubella and gastroduodenal diseases remained significant. Education and a cold or hot workplace were of borderline significance; additionally, passive smoking in the workplace was no longer associated. Because of the possibility that sleep disturbance attributable to fatigue is a symptom caused by the development of IDC, this covariate was excluded in model 2. In model 2, education and a hot or cold workplace exhibited significant positive associations, whereas a past history of any bacterial infection was of borderline significance.

Because a past history of measles showed borderline significance in the univariate analysis, it was incorporated into model 3, where it displayed a tendency toward positive correlation. Following the removal of 2 covariates that demonstrated weaker relationships (passive smoking in the workplace and any bacterial infection), the relationship of a past history of measles gained strength and significance (model 4).

## Discussion

The results from the present multi-hospital case–control study regarding the development of IDC in Japan suggest the importance of several environmental factors, mainly occupational and microbiological factors, in terms of increased or decreased risk of the disease; these factors have not been fully investigated. Among the occupational factors, a cold or hot workplace appeared to increase the risk and among the infectious factors, a history of rubella appeared to exert a protective effect, whereas measles and bacterial infection possibly increased the risk. Moreover, a history of gastroduodenal diseases was suggested to exert a protective effect.

Several previous epidemiological investigations have demonstrated a relationship between risk of IDC and lower socioeconomic status, such as lower income and less education;[4,5,9] however, the etiology of this association remains unclear. In the present study also, lower education level was related to risk; furthermore, the relationship was independent of occupational, infectious and other aspects of the living environment that might coexist with a lower socioeconomic status. The results suggest that the relation between IDC and lower socioeconomic status is attributable to other factors not examined in this study (eg, nutritional factors, psychological factors, etc) and additional investigations are necessary.

Epidemiological studies have repeatedly shown that smoking increases the IDC risk.[6–8,17] Although the present study found that daily cigarette smoking tended to increase the risk, the relationship diminished following adjustment for education and other factors (data not shown). A positive relationship was also observed with respect to passive smoking in the workplace, but this correlation disappeared after multivariate adjustment. One possible mechanism of this association is related to damage to the small coronary arteries;[7] therefore, the association might be weaker in Japan, where coronary heart disease is less common than in Western counties. In the present study, IDC risk was not

significantly associated with a history of bronchial asthma, despite documentation of a relationship with asthma in studies conducted in the United States[4,9,10] As one explanation for the association has been the use of $\beta$-agonists for the treatment of asthma[10] the discrepancy might relate to differences in the use of these drugs among countries.

To the best of our knowledge, few investigations have examined the relationship between IDC risk and occupational factors. Interestingly, in the present study, both hot and cold temperature in the workplace displayed a positive correlation to risk in a manner independent of other factors; other physical and chemical occupational factors and types of occupation were not related. It is possible that greater and frequent temperature change relates to IDC development through activation of the sympathetic nervous system, a mechanism that has been suggested as one form of pathogenesis[1,22] It is not clear that exposure to cold or hot temperature causes the disease; however, this factor, at the very least, may accelerate the development of the disease. Because the validity of the questionnaire on temperature in workplace could be relatively low, further investigations, both experimental and epidemiological, are required.

It is believed that IDC is a sequel of viral myocarditis in some patients, especially with respect to Coxsackie virus B[1,14,23] Other infectious agents are suspected causative factors of IDC (ie, cytomegalovirus, human immunodeficiency virus, hepatitis C virus and some bacteria);[1,15] however, these hypotheses remain controversial. In our previous case-control study in Japanese, susceptibility to the common cold or diarrhea increased the risk, which suggested some viral or bacterial infections as risk factors[17] The present investigation examined the subjects' histories of relatively common infectious diseases and having a history of measles and bacterial infectious diseases indicated increased risk. More interestingly, the data suggested that a history of rubella was associated with decreased risk independently of other factors, including education. There are case reports regarding myocarditis and pericarditis associated with rubella[24,25] but the reason for this inverse relationship between IDC and rubella is unclear. In contrast, documentation of cardiomyopathy or myocarditis associated with measles is scarce[26] and the long-term effects of measles infection on the heart have not been examined; thus, additional investigation of the effects of these viruses is necessary, particularly case-control studies using serological examinations to determine past infection.

An inverse association between IDC risk and gastroduodenal diseases (ie, chronic gastritis, gastric and duodenal ulcer) has not been reported previously. A direct mechanism involving protection against IDC by gastroduodenal diseases is difficult to theorize; the association might be mediated by the factors that cause peptic ulcer or gastritis. Previous reports suggest that the risk factors for peptic ulcer are Helicobacter pylori infection, use of non-steroidal anti-inflammatory drugs, tobacco smoking, stress, use of minor tranquilizers and low levels of physical activity[27,28] It is possible that some of these factors relate to IDC risk. However, this inverse correlation might be somewhat overestimated as some of the hospital controls sought medical advice in reference to gastroduodenal disease. Studies employing controls derived from a general population are necessary.

A major strength of the present study is that both cases and controls were obtained from many hospitals throughout Japan. To examine the varying environmental factors in terms of relation to the disease, a study in a single hospital or in a small area would be inadequate because the examined factors would tend toward uniformity in such a small sample. We surveyed many factors pertaining to infections, and the occupational and living environments across a broad area of Japan. Moreover, although collection of hospital controls tends to be biased in case-control studies, this bias would be smaller in the present investigation because of the control collection from many hospitals by many physicians. However, limitations remain when using hospital controls. For example, the physicians are cardiologists and a large number of controls had hypertension. Therefore, the risk of some environmental factors that also relate to hypertension could be underestimated. Also, selection bias in using hospital controls might overestimate the relationship of lower education, gastroduodenal diseases, and some other infectious and occupational factors, because people who agreed to participate as hospital controls might belong to a somewhat higher social class.

In conclusion, the results of this multi-hospital case-control study in Japan suggest that a cold or hot workplace and, possibly, measles infection increase the IDC risk, in addition to a lower education level. Moreover, rubella infection and a history of gastroduodenal disease are related to a lower IDC risk. Additional investigations are essential in order to establish the mechanisms governing these relationships.

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# Vegetable, Fruit, and Cereal Intake and Risk of Idiopathic Pulmonary Fibrosis in Japan

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**Key Words**
Antioxidants · Dietary fiber · Pulmonary fibrosis

**Abstract**
***Aims:*** There has been little interest in the role of nutrition in prevention of idiopathic pulmonary fibrosis (IPF). We investigated the relationship between dietary intake of vegetables, fruit, cereals, antioxidants, and fiber and the risk of IPF in Japan. ***Methods:*** Included were 104 cases aged 40 years or over who were within 2 years of the diagnosis in accordance with the most recent criteria. Controls aged 40 years or over comprised 56 hospitalized patients diagnosed as having acute bacterial pneumonia and 4 outpatients with common cold. Information on dietary factors was collected using a validated self-administered diet history questionnaire. Adjustment was made for age, sex, region, pack-years of smoking, employment status, occupational exposure, saturated fatty acid intake, and body mass index. ***Results:*** Consumption of fruit in the second and third quartiles was associated with a statistically significant reduced risk of IPF. Although not statistically significant, a beneficial association between soluble fiber intake and IPF was found. No statistically significant dose-response relationship was observed between intake of green and yellow vegetables, other vegetables, cereals, β-carotene, vitamins C and E, or insoluble fiber and the risk of IPF. ***Conclusion:*** Our findings suggest that fruit intake may confer protection against the development of IPF.

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## Introduction

Despite advances in the diagnosis and management of idiopathic pulmonary fibrosis (IPF), which is defined as a specific form of chronic fibrosing interstitial pneumonia

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limited to the lung, the condition is fatal in the majority of affected patients [1]. Median survival of US cases was 4.2 years [2]. In a US study, the incidence was estimated to be 10.7 cases per 100,000 per year for males and 7.4 cases per 100,000 per year for females and increased markedly with age [3]. Mortality from IPF has increased in the UK and other countries [4]. Prevention therefore remains the key to reducing IPF mortality in the near future.

Occupational exposure to metal or wood dust has been identified as a potential risk factor for IPF [5]. Three case-control studies reported a significantly elevated risk for ever smokers [6–8]. Other potential etiologic factors proposed include exposure to antidepressants [9], atopy [10], and viral infection [11]. Although dietary factors have been implicated as a cause of several important diseases, there has been little interest in the role of nutrition in IPF prevention. A Japanese case-control study found no relationship between vegetable intake and IPF [8]. Evidence has accumulated that diet may be preventive against the development of chronic obstructive pulmonary disease. A high intake of antioxidants [12–23] and foods rich in these [21–30] was protectively associated with pulmonary function or chronic obstructive pulmonary disease symptoms. In the MORGEN study, whole grain intake showed a beneficial association with chronic obstructive pulmonary disease independent of potential confounders and alcohol, fruit, vegetable, and fish consumption [29]. To our knowledge, no study examined a relation of fiber intake to chronic obstructive pulmonary disease.

To assess the impact of diet on the development of IPF, we investigated the relationship between dietary intake of vegetables, fruit, cereals, antioxidants, and fiber and the development of IPF in Japan, based on a multicenter hospital-based case-control study.

## Methods

*Subjects*

Eligible cases aged 40 years or over were patients who were within 2 years of the diagnosis of IPF and who received treatment at one of the 21 collaborating hospitals or their 29 affiliated hospitals during the period from June 1 to November 30, 2001. The collaborating respiratory disease specialists were responsible for the diagnosis of IPF, which was based on clinical history, clinical examination, and high-resolution computerized tomography (HRCT) of the chest. Results of video-assisted thoracoscopic lung biopsy, transbronchial lung biopsy, and/or bronchoalveolar lavage, corresponding to the international consensus statement on IPF of the American Thoracic Society and European Respiratory Society [31], were also used when available, either alone or in combination, to assist diagnosis. All cases had basal fine crackles through 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 cases. The physicians in charge asked eligible patients to participate in this study, and 104 patients consented to join the study while 3 patients refused.

Control subjects, aged 40 years or over and without prior respiratory diseases, were prospectively selected from individuals who received treatment at the respiratory ward of the 21 collaborating hospitals or their 29 affiliated hospitals during the same time period as the cases. Control subjects were 56 hospitalized patients diagnosed as having acute bacterial pneumonia and 4 outpatients with common cold who cooperated by answering the questionnaires. Controls were not, individually or in larger groups, matched to cases. Few patients with acute infectious or common diseases 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 5 female controls whose treatment was provided at one of the 6 collaborating hospitals and 1 affiliated hospital. The analysis included the total study population of 104 cases and 60 control subjects.

*Questionnaires*

Sets of two self-administered questionnaires were handed to cases and controls by physicians. The subjects filled out the questionnaires and mailed them to the data management center. A trained research technician interviewed subjects by telephone to complete missing or illogical data. When the subjects were for any reason unable to provide the data required, their family members provided such information.

Dietary habits over a period of one month were assessed by use of a validated self-administered diet history questionnaire. In this instrument intake of 147 food items is calculated using an ad-hoc computer algorithm developed to analyze the questionnaire. The structure and validity of the questionnaire have been described in detail elsewhere [32, 33]. We adjusted for energy intake by using the residual method [34].

A second self-administered questionnaire yielded information on age, sex, weight, height, smoking habits, type of job held for the longest period of time, occupational exposure, and medical history. Occupational exposure was defined as present if the subject had been exposed to any of 8 specific occupational agents (metal, wood, asbestos, coal, stone and sand, solvents, pesticide, or chalk) 10 or more hours per week for more than 1 year. Body mass index was calculated by dividing self-reported body weight (kg) by the square of self-reported height (m).

*Statistical Analysis*

Intake of selected foods and nutrients was categorized at quartile points based on the distribution of all study subjects. 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 (professionals, technical workers, managers, and officials and other), and pack-years of smoking

**Table 1.** Characteristics of study population

| Variable | n (%) or mean (SD) | |
|---|---|---|
| | cases (n = 104) | controls (n = 60) |
| Sex, % male | 94 (90.4) | 55 (91.7) |
| Age, % years | | |
| <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, % | | |
| 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, % | | |
| 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, %[a] | 18 (17.3) | 8 (13.3) |
| Occupational exposure, %[b] | 33 (31.7) | 5 (8.3) |
| Body mass index, kg/m$^2$ | 23.3 (3.1) | 21.9 (3.0) |
| Daily nutrient intake[c] | | |
| Total energy, kcal | 1,937 (595) | 1,960 (587) |
| Green and yellow vegetables, g | 93.2 (66.8) | 88.9 (62.7) |
| Other vegetables, g | 174.3 (106.6) | 165.6 (90.8) |
| Fruit, g | 165.5 (148.6) | 203.7 (161.5) |
| Cereals, g | 506.3 (163.3) | 543.7 (168.1) |
| β-Carotene, mg | 2,089.7 (1,538.0) | 2,029.8 (1,359.6) |
| Vitamin C, mg | 141.9 (73.7) | 143.7 (71.1) |
| Vitamin E, mg | 8.9 (2.7) | 8.8 (3.1) |
| Soluble fiber, g | 2.3 (1.1) | 2.4 (1.1) |
| Insoluble fiber, g | 10.8 (4.0) | 10.9 (4.3) |

[a] 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.
[b] Exposure to metal, wood, asbestos, coal, stone and sand, solvents, pesticide, or chalk 10 or more hours per week for more than 1 year.
[c] Nutrients and food intake were adjusted for energy intake by the residual method.

into five (never, 0–19.9, 20.0–39.9, 40.0–59.9, and 60.0+). In 2 cases and 1 control, data on smoking were missing, and their smoking status was regarded as never smoked. Estimations of adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were carried out by means of multiple logistic regression analysis. Adjustment was made for age, sex, region, pack-years of smoking, employment status, occupational exposure, and body mass index in the multivariate models. Intake of saturated fatty acids was also controlled for because our previous findings showed a significantly positive association between a high saturated fatty acid intake and the development of IPF [Miyake et al., submitted]. Body mass index and saturated fatty acid intake were used as continuous variables. Trend of association was assessed by a logistic regression model assigning scores to the levels of the independent variable. Two-sided p values less than 0.05 were considered statistically significant. All computations were performed using the SAS software package version 8.2 (SAS Institute, Inc., Cary, N.C., USA).

## Results

Dyspnea on exertion was present at enrollment in 84 of 104 cases (80.8%). In cases, the median (90% central range) of arterial $O_2$ pressure was 80.2 mm Hg (57.2–98.0)

**Table 2.** Odds ratios for idiopathic pulmonary fibrosis by quartiles of vegetable, fruit, and cereal intake

| Variables[a] | n (%) | | Sex and age adjusted | | Multivariate adjusted[b] | |
|---|---|---|---|---|---|---|
| | cases | controls | odds ratio | 95% CI | odds ratio | 95% CI |
| Green and yellow vegetables | | | | | | |
| Q1 (32.6) | 22 (21.2) | 19 (31.7) | 1.00 | | 1.00 | |
| Q2 (63.3) | 33 (31.7) | 8 (13.3) | 3.56 | 1.32–10.33 | 7.06 | 2.00–27.91 |
| Q3 (95.3) | 22 (21.2) | 19 (31.7) | 0.87 | 0.35–2.14 | 1.02 | 0.34–3.09 |
| Q4 (162.8) | 27 (26.0) | 14 (23.3) | 1.35 | 0.53–3.52 | 1.62 | 0.48–5.59 |
| p for trend | | | 0.82 | | 0.68 | |
| Other vegetables | | | | | | |
| Q1 (81.9) | 28 (26.9) | 13 (21.7) | 1.00 | | 1.00 | |
| Q2 (134.9) | 25 (24.0) | 16 (26.7) | 0.65 | 0.25–1.67 | 0.61 | 0.20–1.78 |
| Q3 (175.4) | 26 (25.0) | 15 (25.0) | 0.65 | 0.25–1.69 | 0.59 | 0.18–1.91 |
| Q4 (256.8) | 25 (24.0) | 16 (26.7) | 0.62 | 0.24–1.60 | 0.77 | 0.25–2.35 |
| p for trend | | | 0.36 | | 0.72 | |
| Fruit | | | | | | |
| Q1 (37.9) | 33 (31.7) | 8 (13.3) | 1.00 | | 1.00 | |
| Q2 (108.5) | 23 (22.1) | 18 (30.0) | 0.29 | 0.10–0.80 | 0.17 | 0.05–0.56 |
| Q3 (181.5) | 23 (22.1) | 18 (30.0) | 0.24 | 0.08–0.66 | 0.13 | 0.03–0.44 |
| Q4 (312.5) | 25 (24.0) | 16 (26.7) | 0.26 | 0.08–0.75 | 0.28 | 0.07–1.01 |
| p for trend | | | 0.02 | | 0.06 | |
| Cereals | | | | | | |
| Q1 (361.3) | 28 (26.9) | 13 (21.7) | 1.00 | | 1.00 | |
| Q2 (470.5) | 29 (27.9) | 12 (20.0) | 1.00 | 0.38–2.65 | 0.96 | 0.30–3.02 |
| Q3 (540.7) | 27 (26.0) | 14 (23.3) | 0.75 | 0.28–1.97 | 0.99 | 0.31–3.12 |
| Q4 (668.5) | 20 (19.2) | 21 (35.0) | 0.42 | 0.16–1.07 | 0.75 | 0.21–2.64 |
| p for trend | | | 0.06 | | 0.70 | |

[a] Quartile medians in grams per day adjusted for energy intake with the residual methods given in parentheses.
[b] Odds ratios were separately calculated for each dietary variable adjusted for age, sex, region, pack-years of smoking, employment status, occupational exposure, saturated fatty acid intake, and body mass index.

and of vital capacity expressed as percent predicted values was 78.0% (42.1–113.5) in cases.

About 90% of both cases and controls were male (table 1). Compared with control subjects, cases were older, had a lower prevalence of residence in Chugoku-Shikoku and never smoking and a higher prevalence of high employment status, occupational exposure, and being overweight.

Table 2 shows the relation between vegetable, fruit, and cereal consumption and IPF risk, with adjustment for potential confounders. Compared with green and yellow vegetable intake in the first quartile, consumption of green and yellow vegetables in the second quartile, but not the third and fourth quartiles, was statistically significantly associated with an increased risk of IPF after controlling for sex and age. Further adjustment for region, pack-years of smoking, employment status, occupational exposure, saturated fatty acid intake, and body mass index notably strengthened the positive association. There was no statistically significant relationship between intake of other vegetables and IPF. After adjusting for sex and age, a clear inverse relation was observed between fruit intake and the risk of IPF (p for trend = 0.02), while in the multivariate model, the OR between extreme quartiles and the trend fell just short of the significance level. An inverse dose-response relationship between cereal intake and the risk of IPF was of borderline significance after controlling for sex and age ($p$ for trend = 0.06) but completely disappeared in the multivariate model.

Table 3 presents adjusted ORs of IPF in relation to β-carotene, vitamins C and E, and fiber intake. Dietary intake of β-carotene and vitamins C and E was not statis-

**Table 3.** Odds ratios for idiopathic pulmonary fibrosis by quartiles of β-carotene, vitamins C and E, and fiber intake

| Variables[a] | n (%) | | Sex and age adjusted | | Multivariate adjusted[b] | |
|---|---|---|---|---|---|---|
| | cases | controls | odds ratio | 95% CI | odds ratio | 95% CI |
| β-Carotene | | | | | | |
| Q1 (637.3) | 28 (26.9) | 13 (21.7) | 1.00 | | 1.00 | |
| Q2 (1417.8) | 26 (25.0) | 15 (25.0) | 0.74 | 0.28–1.91 | 0.93 | 0.31–2.85 |
| Q3 (2258.4) | 22 (21.2) | 19 (31.7) | 0.46 | 0.17–1.16 | 0.59 | 0.19–1.78 |
| Q4 (3485.8) | 28 (26.9) | 13 (21.7) | 0.81 | 0.30–2.16 | 1.03 | 0.32–3.32 |
| p for trend | | | 0.46 | | 0.85 | |
| Vitamin C | | | | | | |
| Q1 (65.8) | 27 (26.0) | 14 (23.3) | 1.00 | | 1.00 | |
| Q2 (111.6) | 28 (26.9) | 13 (21.7) | 0.77 | 0.28–2.07 | 1.05 | 0.32–3.38 |
| Q3 (158.7) | 25 (24.0) | 16 (26.7) | 0.54 | 0.20–1.44 | 0.62 | 0.19–1.97 |
| Q4 (220.9) | 24 (23.1) | 17 (28.3) | 0.49 | 0.18–1.33 | 0.69 | 0.20–2.40 |
| p for trend | | | 0.13 | | 0.42 | |
| Vitamin E | | | | | | |
| Q1 (5.9) | 25 (24.0) | 16 (26.7) | 1.00 | | 1.00 | |
| Q2 (8.0) | 28 (26.9) | 13 (21.7) | 1.28 | 0.50–3.32 | 1.23 | 0.38–4.04 |
| Q3 (9.3) | 26 (25.0) | 15 (25.0) | 1.05 | 0.41–2.70 | 0.80 | 0.23–2.70 |
| Q4 (12.0) | 25 (24.0) | 16 (26.7) | 0.93 | 0.37–2.35 | 0.69 | 0.21–2.19 |
| p for trend | | | 0.78 | | 0.38 | |
| Soluble fiber | | | | | | |
| Q1 (1.3) | 28 (26.9) | 13 (21.7) | 1.00 | | 1.00 | |
| Q2 (1.9) | 27 (26.0) | 14 (23.3) | 0.68 | 0.25–1.80 | 0.54 | 0.17–1.71 |
| Q3 (2.5) | 25 (24.0) | 16 (26.7) | 0.55 | 0.20–1.47 | 0.56 | 0.17–1.83 |
| Q4 (3.6) | 24 (23.1) | 17 (28.3) | 0.43 | 0.15–1.15 | 0.36 | 0.10–1.15 |
| p for trend | | | 0.09 | | 0.11 | |
| Insoluble fiber | | | | | | |
| Q1 (6.9) | 26 (25.0) | 15 (25.0) | 1.00 | | 1.00 | |
| Q2 (9.4) | 28 (26.9) | 13 (21.7) | 1.16 | 0.44–3.05 | 0.96 | 0.31–2.90 |
| Q3 (11.4) | 25 (24.0) | 16 (26.7) | 0.68 | 0.26–1.77 | 0.72 | 0.22–2.24 |
| Q4 (14.5) | 25 (24.0) | 16 (26.7) | 0.61 | 0.22–1.67 | 0.62 | 0.18–2.05 |
| p for trend | | | 0.22 | | 0.37 | |

[a] Quartile medians in grams (except for β-carotene and vitamins C and E; milligrams) per day adjusted for energy intake with the residual methods given in parentheses.

[b] Odds ratios were separately calculated for each dietary variable adjusted for age, sex, region, pack-years of smoking, employment status, occupational exposure, saturated fatty acid intake, and body mass index.

tically tically significantly associated with the risk of IPF after multivariate adjustment. There was a tendency for a protective relationship between soluble fiber intake and the risk of IPF by the multivariate model: the OR for the highest vs. lowest quartiles was 0.36 (95% CI: 0.10–1.15; p for trend = 0.11). We observed no statistically significant association for insoluble fiber intake.

## Discussion

A previous case-control study in Japan showed no association between vegetable intake and the risk of IPF [8]. Our results partially agree with this observation although we did find a significant positive association between intake of green and yellow vegetables and the risk of IPF when comparing the second with the first quartile. As far as we know, no epidemiological information is

available about the relationship between dietary intake of fruit, cereals, antioxidants, and fiber and IPF. An animal experiment demonstrated that dietary antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene exert inhibitory effects on proliferation of hyperplastic lesions associated with lung fibrosis induced by bleomycin in hamsters [35]. However, our investigation revealed no statistically significant association between intake of β-carotene and vitamins C and E and the risk of IPF. Dietary intake of antioxidants may not be preventive against the manifestation of IPF among human beings. Alternatively, dietary supplements that provide doses of antioxidants much higher than the average intake in this study may substantially reduce the risk of IPF.

We have no clear explanation as to underlying mechanisms for the observed inverse relationship between fruit intake and the risk of IPF. The beneficial association of fruit consumption with the development of IPF may to some extent be ascribed to soluble fiber or unknown factors in relation to soluble fiber intake. A meta-analysis of 67 controlled trials demonstrated that soluble fiber consistently lowered plasma total and low-density lipoprotein cholesterol levels [36]. Our previous findings showed that dietary intake of saturated fatty acids was significantly associated with an increased risk of IPF [Miyake et al., submitted]. High intake of saturated fatty acids was hypercholesterolemic [37]. Elevated levels of serum low-density lipoprotein cholesterol or unrecognized factors related to serum low-density lipoprotein cholesterol levels might be associated with the development of IPF although data on serum lipids and lipoproteins were not available in the present study. Alternatively, dietary fiber intake may play an important role in mediating the relation between diet and inflammation. Increased consumption of fiber was associated with a significantly lower likelihood of elevated C-reactive protein [38]. However, a recent review concerning IPF reported that inflammation is not a prominent histopathological finding and that epithelial injury in the absence of ongoing inflammation is sufficient to stimulate the development of fibrosis [39].

Our current investigation had methodological strengths in that cases were identified according to the most recent diagnostic criteria and that adjustment was made for extensive potential confounders. The dietary information was derived from a self-administered semiquantitative dietary assessment questionnaire. According to the validation studies, the correlation coefficients for nutrient intake between those estimated from the diet history questionnaire and those observed by a 3-day dietary record were 0.45 and 0.75 for vitamin C and saturated fatty acids, respectively, in women [32]; the correlation coefficients between intake and the corresponding concentrations in the serum phospholipid fraction were 0.40 and 0.60 in men and women, respectively, for β-carotene and −0.23 and −0.22 in men and women, respectively, for vitamin E [33]. However, our diet history questionnaire was designed to assess recent dietary intake, i.e. for the month prior to completing the questionnaire. Thus, the diagnosis of IPF could influence diet in some patients, leading to misclassification of their true long-term dietary exposure and a weakening of observed associations. Another limitation was that the control subjects were not derived from the general population but from hospital patients (acute bacterial pneumonia and common cold). Although the cases were unlikely to be a biased sample because of the high response rate (only 3 patients refused), hospital controls may have had diseases that are related to either low or high vegetable, fruit, or cereal intake. Alternatively, acute bacterial pneumonia may share risk factors with IPF, and this could lead to bias toward the null. Eligible control subjects with acute bacterial pneumonia were not likely to arise during the summer months because of seasonal variation in this disease. The control-to-case ratio was under 1:1 and our study did not have a substantial statistical power although a significant inverse association was detected.

## Conclusion

Our findings suggest that dietary intake of fruit may be associated with a reduced risk of IPF. Larger studies with more detailed information, such as that on serum lipids and lipoproteins, are needed to draw a conclusion as to the question of whether fruit intake confers protection against IPF in Japan. Further investigations of Western populations are also required to assess the effects of dietary factors on IPF.

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## Appendix

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