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Original Article

A Cross-Sectional Study of Primary Biliary Cirrhosis in Japan: Utilization of Clinical Data When Patients Applied to Receive Public Financial Aid

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BACKGROUND: There have not been many reports regarding primary biliary cirrhosis (PBC) in Asia. We conducted a cross-sectional study of PBC in Japan.
METHODS: In fiscal year 1999, 9,761 patients with symptomatic PBC were registered to receive public financial aid from the Ministry of Health, Labour and Welfare of Japan. For our cross-sectional study we chose 5,805 patients whose clinical data had been written between 1999 and 2000, and statistically analyzed the data, including sex, age, major symptoms, and laboratory data.
RESULTS: Our study estimated that the male-to-female ratio was 1:8.0. The median ages of male and female patients were 59 and 60 years, respectively. The major symptoms and physical findings were as follows: pruritus 53.3%, jaundice 11.3%, xanthomas 5.8%, splenomegaly 38.1%, and esophageal varices 19.1%. Antimitochondrial antibody (AMA) was positive in 86.6%, but its positive rate was lower among Japanese patients than among those in western countries. IgM levels were higher among AMA-positive patients than among AMA-negative patients. Regarding Sjögren's syndrome, rheumatoid arthritis, chronic thyroiditis, and scleroderma, patients had lower frequencies of complicated autoimmune diseases than those in western countries.
CONCLUSIONS: The male-to-female ratio, frequencies by age group, symptoms and physical findings among patients with PBC were consistent with previous reports in Japan and from other countries. However, positivity of AMA and the frequency of complicated autoimmune diseases were lower among patients in Japan than among those in western countries.
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Key words: Liver Cirrhosis, Biliary; antimitochondrial antibody (AMA); Cross-Sectional Studies; public financial aid.

Primary biliary cirrhosis (PBC) is a chronic cholestatic disorder characterized by progressive, nonsuppurative inflammation and destruction of small bile ducts, and the presence of antimitochondrial antibodies (AMA) in the sera. PBC is considered to be associated with disturbances in both cellular and humoral immunity, but the etiology is still uncertain. Although PBC has been described in virtually all parts of the world,[1,2] most of the epidemiologic data have been derived from Europe,[3,4] and there are not so many reports from Asia.

In Japan symptomatic PBC was specified as one of "the intractable diseases" from 1990. Patients with symptomatic PBC who want to receive public financial aid from the Ministry of Health, Labour and Welfare must sign agreements and write applications. Then they are registered and can receive the public financial aid. The recognition of patients with symptomatic PBC is conducted by each prefecture. In 1999, the Ministry of Health, Labour and Welfare permitted the use of clinical data from the recognized patients with symptomatic PBC. Most prefectures, but not all, provided clinical data to the research committee of intractable hepatic diseases. Therefore, the data was also available to the research committee on the epidemiology of intractable diseases.

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In the present study, we tried to elucidate the characteristics of patients with PBC in Japan by utilization of the clinical data when they applied to receive public financial aid, and compared the features of the patients in Japan with those in other countries.

METHODS

In the fiscal year 1999, 9,761 prevalent cases with symptomatic PBC were registered. For our cross-sectional study we used the clinical data of 6,305 patients because not all prefectures provided the data, and chose the cases of 5,805 patients whose clinical data were written between 1999 and 2000; the data from residual cases were not written during the time, for example written in 1998 or before.

Patients whose conditions met one of the criteria below were diagnosed as having PBC following the previous reports in Japan.[5-7]

1. Chronic non-suppurative destructive cholangitis (CNSDC) is histologically observed and laboratory data do not contradict PBC.
2. AMA is positive. CNSDC is not histologically observed but histological findings are compatible with PBC.
3. Histological examination is not performed, but AMA is positive and clinical findings and course indicate PBC.

For the patients with symptomatic PBC, the following information was collected from the records: sex, date of birth, date of diagnosis, estimated onset time, symptoms and physical findings, complicated autoimmune diseases, laboratory data including serum levels of bilirubin, alkaline phosphatase (ALP), γ -glutamyl transpeptidase (γ -GTP), total cholesterol (T-chole), IgM, and AMA. We evaluated symptoms and physical findings, laboratory data, and complicated autoimmune diseases according to sex. We also examined the association of IgM levels with the positivity of AMA. In the present study, frequencies of items in the clinical data were analyzed, excluding "unclear" or blank spaces.

Statistical analysis was performed using SPSS® version 10.0 (SPSS Inc.). The chi-squared test was used for comparing the proportions of two groups, and the Mann-Whitney test was used to evaluate differences in clinical variables. P values less than 0.05 were considered to be statistically significant.

Table 1. Demographic characteristics of the patients with primary biliary cirrhosis.

			both sexes	males	females
No. of patients			5,805	646	5,159
Age (year)	mean ±standard deviation		59±10.7	60±11.8	59±10.5
	median		60	62	59
	relative frequency (%)				
		<19 years	0.1	0.6	0.1
		20-29	0.6	0.6	0.6
		30-39	2.8	3.3	2.8
		40-49	15.8	13.8	16.1
		50-59	30.4	24.1	31.1
		60-69	34.1	35.1	34.0
		70-79	14.3	19.7	13.7
		80+	1.7	2.8	1.6
		total	100	100	100

Table 2. Symptoms and physical findings of the patients with primary biliary cirrhosis (%).*

	both sexes	males	females	p value†
Pruritus	53.3 (3,014/5,654)	57.5 (358/623)	52.8 (2,656/5,031)	0.03
Jaundice	11.3 (648/5,717)	15.4 (97/631)	10.8 (551/5,086)	<0.001
Xanthomas	5.8 (310/5,339)	6.4 (38/595)	5.7 (272/4,744)	0.58
Splenomegaly	38.1 (2,100/5,508)	37.8 (232/614)	38.2 (1,868/4,894)	0.89
Esophageal varices	19.1 (957/5,012)	17.3 (95/550)	19.3 (862/4,462)	0.27

* : Denominators are not equal because frequencies of items were analyzed, excluding "unclear" or blank spaces.
† : Chi-squared tests for males vs. females.

Table 3. Laboratory findings of the patients with primary biliary cirrhosis.

	both sexes				males				females				p value
	n	mean	SD	median	n	mean	SD	median	n	mean	SD	median	
Total bilirubin (mg/dL)	5,387	1.1	2.2	0.6	597	1.3	2.1	0.7	4,790	1.1	2.2	0.6	<0.01*
Alkaline phosphatase (ALP: IU/L)	5,655	486.8	702.4	364	643	537.7	595.9	406.5	5,021	480.3	714.6	359	<0.01*
γ -glutamyl transpeptidase (γ -GTP: IU/L)	5,638	165.1	246.4	86	629	292.1	345.5	178	5,009	149.1	226.0	79	<0.01*
Total cholesterol (mg/dL)	5,458	214.0	230.0	204	601	204.1	77.6	197	4,857	215.3	242.3	205	<0.01*
Immunoglobulin M (IgM: mg/dL)	4,450	444.6	395.2	349.5	477	426.8	316.0	342	3,973	446.7	403.6	350	<0.01*
Antimitochondrial antibody (AMA) positive (%)	86.6 (4,765/5,502)				90.9 (552/607)				86.1 (4,213/4,895)				<0.01†

* : Mann-Whitney tests for males vs. females
† : Chi-squared test for males vs. females
SD: standard deviation

RESULTS

Age and sex

Table 1 presents the demographic characteristics of the patients. Of 5,805 patients, 646 (11%) were males, and 5,159 (89%) were females, therefore the male-to-female ratio was approximately 1:8.0, showing a much greater frequency in females. The mean and median ages of all patients were 59 and 60 years, respectively. The median age appeared to be somewhat higher in males (62 years) than in females (59 years). The highest frequencies were in the 60s for both sexes (35.1% for males and 34.0% for females, respectively). We tried to estimate the age at the onset of the disease from the records, and found that the median age was 52 years (55 years for males, 52 years for females, respectively).

Symptoms and physical findings

Pruritis was present in 53.3%, jaundice in 11.3%, xanthomas in 5.8%, splenomegaly in 38.1%, and esophageal varices in 19.1% of all patients (Table 2). Pruritus and jaundice were found significantly more frequently among males than among females.

Laboratory data

Key laboratory data are summarized in Table 3. Levels of total bilirubin, ALP, and γ -GTP were significantly higher among males than among females, whereas levels of T-Chole and IgM were significantly higher among females than among males. AMA was positive in 86.6% of all cases, and its positive rate was significantly higher among males than among females (90.9% for males, 86.1% for females, respectively). Table 4 shows a significant association of IgM levels with the positivity of AMA, i.e., a higher IgM level, and a higher rate of AMA-positive patients (P for trend <0.001).

Complicated autoimmune diseases

Complications such as Sjögren's syndrome, rheumatoid arthritis, chronic thyroiditis, and scleroderma including CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectases) were found in 13.5%, 7.3%, 4.4%, and 2.0% of patients, respectively (Table 5). All these complicated diseases were found significantly more frequently among females than among males.

DISCUSSION

The patients with PBC were characterized by a high proportion of females, especially of middle age. It has been reported that 90% to 95% of patients with PBC are females, with a median age at the time of diagnosis in the early 50s.[8,9,10]. In Japan, the Research Committee on the Epidemiology of Intractable Diseases conducted two rounds of nationwide surveys of PBC.[11,12] These surveys reported that the male-to-female ratio was 1:8.3-9.1, and that for males the percentage of patients gradually increased from their 40s, reaching the highest frequency age group between 60 and 70

Table 4. Association between serum IgM level and positivity of antimitochondrial antibody (AMA) among patients with primary biliary cirrhosis.

	Immunoglobulin M (IgM: mg/dL)			
	-299	300-599	600-899	900+
AMA (+)	2,430 (82.4)	1,456 (90.2)	540 (91.8)	332 (96.8)
AMA (-)	520 (17.6)	158 (9.8)	48 (8.2)	11 (3.2)

Parcentages in parentheses
P for trend <0.001

Table 5. Parcentages of patients with primary biliary cirrhosis complicated with selected autoimmune diseases (%).*

	both sexes	males	females	p value†
Sjögren's syndrome	13.5 (683/5,041)	4.5 (25/555)	14.7 (658/4,486)	<0.001
Rheumatoid arthritis	7.3 (390/5,373)	2.5 (15/596)	7.9 (375/4,777)	<0.001
Chronic thyroiditis	4.4 (258/5,805)	0.8 (5/646)	4.9 (253/5,159)	<0.001
Scleroderma	2 (117/5,805)	0.6 (4/646)	2.2 (113/5,159)	0.011

* : Denominators are not equal because frequencies of items were analyzed, excluding "unclear" or blank spaces.
† : Chi-squared tests for males vs. females.

years old, while for females the former increased from their 30s and the latter was between 50 and 60 years old. Regarding the male-to-female ratio and age distributions of the highest frequencies for both sexes, our results approximately agreed with the two reports from the previous nationwide surveys. Inoue et al. also reported that the male-to-female ratio was 1: 7.9, and the peak incidence was in the 50s.[7]

It is still uncertain why females are more susceptible to autoimmune diseases, including PBC, than males. However, a sex-linked genetic influence and hormonal effect for females is one possible explanation.[13] Females are considered to have the higher absolute number of CD4+ lymphocytes than males, and it is suggested that cytokine secretion is enhanced in the presence of estrogen.[14] Moreover, androgens have been found to suppress the activity of autoimmune disease such as systemic lupus erythematosus in animal experiments.[15] Gonadal steroids are likely to play important roles in modulating autoimmune diseases.

Pruritus, jaundice, and xanthomas are usually found in 55%, 10%, and less than 10% of the patients with PBC, respectively.[1,2] Our results for pruritus, jaundice and xanthomas were similar to our theses values. The percentage of splenomegaly among patients with PBC is reported to be 15%,[2] but in the present study splenomegaly was observed in more patients than previously reported. The recent progress of diagnostic imaging techniques such as ultrasonography and computed tomography may be one possible explanation for this. Frequencies of jaundice and biliary enzyme levels were higher among males than among females. Further studies are required to clarify the association between sex and jaundice and biliary enzymes levels.

In Western countries it has been reported that AMA in PBC occurs in 90% to 95% of patients,[8,16] but the positivity of AMA was lower (86.6% of total patients). This may be one of the reasons that Japanese patients with PBC have lower frequency of certain types of AMA (e.g. anti-PDC-E2) than Europeans.[13] More precise laboratory examinations for various types of AMA might resolve this issue.

Lacerda et al. reported that IgM levels were higher in AMA-positive than AMA- negative patients.[17] Our results also showed an association of a higher IgM level with a higher frequency of AMA-positive patients.

It is reported that Sjögren's syndrome, rheumatoid arthritis, thyroid diseases, and scleroderma are found in 75%, 10% to 20%, up to 15%, and 10% to 15% of patients with PBC, respectively.[8] Patients in the present study had lower frequencies of complicated autoimmune diseases than those in western countries. Other studies in Japan have also reported lower complications of these diseases,[5,6,7] but the difference in frequency of complicated autoimmune diseases between Japanese and Western people have not been clearly explained. Polymorphism of the human leukocyte antigen (HLA) might be related to the difference in races.[18,19] Our study found a higher frequency of complicated autoimmune diseases among females than among males. This fact also shows that gonadal steroids are likely to play important roles in modulating autoimmune diseases.

In conclusion, using established recorded data, we described the clinical and biochemical features of PBC in Japan. The male-to-female ratio, frequencies by age groups, symptoms and physical findings among patients with PBC were consistent with previous reports in Japan and from other countries. However, positivity of AMA and the frequencies of associated autoimmune diseases were lower among patients in Japan than among those in western countries.

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Dietary Risk Factors for Inflammatory Bowel Disease

A Multicenter Case-Control Study in Japan

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Abstract: To evaluate the role of dietary factors in the etiology of inflammatory bowel disease (IBD), we conducted a multicenter hospital-based case-control study in a Japanese population. Cases were IBD patients aged 15 to 34 years [ulcerative colitis (UC) 111 patients; Crohn's disease (CD) 128 patients] within 3 years after diagnosis in 13 hospitals. One control subject was recruited for each case who was matched for sex, age, and hospital. A semiquantitative food frequency questionnaire was used to estimate preillness intakes of food groups and nutrients. All the available control subjects (n = 219) were pooled, and unconditional logistic models were applied to calculate odds ratios (ORs). In the food groups, a higher consumption of sweets was positively associated with UC risk [OR for the highest versus lowest quartile, 2.86; 95% confidence interval (CI), 1.24 to 6.57], whereas the consumption of sugars and sweeteners (OR, 2.12; 95% CI, 1.08 to 4.17), sweets (OR, 2.83; 95% CI, 1.38 to 5.83), fats and oils (OR, 2.64; 95% CI, 1.29 to 5.39), and fish and shellfish (OR, 2.41; 95% CI, 1.18–4.89) were positively associated with CD risk. In respect to nutrients, the intake of vitamin C (OR, 0.45; 95% CI, 0.21 to 0.99) was negatively related to UC risk, while the intake of total fat (OR, 2.86; 95% CI, 1.39 to 5.90), monounsaturated fatty acids (OR, 2.49; 95% CI, 1.23 to 5.03) and polyunsaturated fatty acids (OR, 2.31; 95% CI, 1.12 to 4.79), vitamin E (OR, 3.23; 95% CI, 1.45 to 7.17), and n-3 (OR, 3.24; 95% CI, 1.52 to 6.88) and n-6 fatty acids (OR, 2.57; 95% CI, 1.24 to 5.32) was positively associated with CD risk. Although this study suffers from the shortcoming of recall bias, which is inherent in most retrospective studies (prospective studies are warranted to confirm the associations between diet and IBD risk), the present findings suggest the importance of dietary factors for IBD prevention.

Key Words: case-control study, Crohn's disease, diet, inflammatory bowel disease, ulcerative colitis

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The incidence of inflammatory bowel disease (IBD), namely, ulcerative colitis (UC) and Crohn's disease (CD), is far lower in Japan than in Western Europe and North America.[1] However, surprisingly, the rate has been increasing and the gap has become smaller over the past decade.[2] This increasing incidence in Japan cannot be attributed to genetic factors.[3,4]

Potential environmental factors affecting IBD include early appendectomy,[5] some nonsteroidal anti-inflammatory drugs,[6] and dietary[7–10] and smoking habits.[11,12] Among these factors, changes in the Japanese diet (e.g., taking in more fats

and fast foods) may provide an explanation for the increasing incidence of IBD.[13,14] The etiology of IBD is assumed to be the dysregulated activation of the mucosal immune system, which may in part be related to dietary factors. For example, the recent increase in the incidence of CD in Japan has been related to increased dietary fat intake, including n-6 fatty acids, which are metabolized to immunomodulatory leukotrienes and prostaglandins.[15]

Epidemiologically, some case-control studies have suggested that vegetables and fruit are protective factors,[7,8] while refined sugar[9,10] and fat[10] are risk factors for IBD. However, as only a few studies[10] have quantified nutrient or food intake using a validated questionnaire, it is possible that there have been inconsistent results.

Thus, we focused on preillness dietary risk factors for IBD and assessed them in a case-control study in a Japanese population, in which the incidence of IBD is rapidly growing, using a food frequency questionnaire (FFQ).

MATERIALS AND METHODS

Study Subjects

We conducted this study in 13 hospitals from September 2000 to November 2001, using a self-administered questionnaire. To be eligible as cases for the present study, patients had to have received diagnoses of UC or CD within the past 3 years and to be 15 to 34 years old. We enrolled patients who presented to the participating hospitals when a coinvestigator was available. The diagnostic criteria for UC and CD were in accordance with the criteria proposed by the Research Committee on Inflammatory Bowel Disease in Japan.[16] To elucidate the role of diet in IBD development, particularly that of dietary fat, we focused on patients 15 to 34 years of age, because fat intake is highest in this age group in the Japanese population.[17]

Control subjects, with a wide variety of clinical diagnoses, were recruited from among other patients in the hospitals. Patients with cancers (other than those of lymphohematopoietic tissues), chronic bowel disease, acute appendicitis, allergic diseases, and anal fistulas were excluded. Patients with the latter 3 diseases were excluded because we also attempted to clarify the association of the history of these diseases with IBD. We also excluded control subjects who had reported symptoms of irritable bowel syndrome or anal fistula up to 5 years before the survey in the questionnaire. Study centers were asked to provide one control subject for each case, matching gender and age (within the same 5-year age group, as follows: 15–19, 20–24, 25–29, or 30–34 years).

Data Collection

A self-administered questionnaire was used to obtain information on demographic factors, medical history, lifestyle in childhood, smoking and drinking habits, and dietary habits. Participating investigators or supervised physicians distributed and collected the questionnaire, and unanswered questions were filled in by interview. One of the authors (N.S.) reviewed the questionnaire before data analysis occurred. The reviewer was not blinded to the patient's disease but checked all unanswered questions irrespective of case-control status. If unanswered questions were found, the questionnaire was returned to the relevant participating investigator. The investigator or supervised doctors posed the unanswered questions to the patient and completed the questionnaire. Unanswered questions were completed in accord with the patient's replies.

Subjects were asked to report their behavior and characteristics 5 years before the time of the study. To facilitate the recall of lifestyles, including dietary habits, 5 years before the study, we inserted into the questionnaire some questions about their familial and social backgrounds at that time.

The dietary component of the questionnaire inquired about the average intake frequency of 97 items of Japanese foods or dishes. This FFQ was specifically developed to estimate the average daily intakes of nutrients and food groups.[18] Nutrient intakes were computed using the Japanese food composition tables[19,20] with a supplemental database.[21] The FFQ was validated in a healthy Japanese population by referring to 16-day dietary records as a standard, and was proved to be adequately valid for most of the nutrients and food groups.[18,22] The ranges of correlation coefficients between the FFQ and dietary records were 0.16 to 0.83 (median, 0.57) for the food groups and 0.42 to 0.83 (median, 0.58) for the nutrients under study. Nutrient intake from supplements was not considered in the present study.

Statistical Methods

We compared the background characteristics of UC or CD case patients with those of control subjects by the χ^2 test or the Mantel-Haenszel test.[23] Odds ratios (ORs) and their 95% confidence intervals (CIs) were computed to assess the strength of the associations between the intake of selected food groups or nutrients and the risk of UC or CD. In this analysis, we pooled all the control subjects and compared them with both UC and CD case patients to make the most of the data and to obtain more stable estimates of ORs than those using only the control subjects originally matched to cases of UC or CD. Thus, we employed unconditional logistic regression analysis[24] to compute the ORs adjusted for age, gender, study area, and other confounding covariates.

Energy-adjusted intakes of food groups or nutrients were calculated by the method of Willett and Stampfer.[25] Natural logarithms of food and nutrient intakes were used to improve the normality of their distribution. The energy-adjusted intake in control subjects was compared between genders, study areas, and education levels using the *t* test or one-way analysis of variance to describe the effect of these background factors.

With regard to each dietary variable, subjects were divided into four groups according to the quartile of energy-

adjusted intake in the distribution of control subjects. The power calculation assuming linearly increasing or decreasing risk showed that our study should have detected ORs of 3 or 0.33 in the highest quartile versus the lowest one, with statistical significance ($P < 0.05$) with >80% probability (for UC 84%; for CD 88%).[26] The trend of the association was assessed by assigning ordinal scores (i.e., 0, 1, 2, or 3) to a single dietary variable.[27] All statistical analyses were performed by the Statistical Analysis System (SAS Institute, Cary, NC).[28]

Ethical Considerations

All of the participants provided written informed consent. The Ethical Board of the Hyogo College of Medicine approved the protocol of this study.

RESULTS

By November 2001, 131 patients with UC, 160 patients with CD, and 273 control subjects had been surveyed. The number of patients who were approached during recruitment for the study was not formally documented, but almost all of the patients who were asked to participate completed the questionnaire. For 18 IBD case patients, matching control subjects could not be set up.

We excluded 42 subjects (UC, 14 patients; CD, 10 patients; and control subjects, 18 subjects) outside the age range (15 to 34 years). Six patients with UC and 22 patients with CD were additionally excluded because they did not fulfil the eligibility criteria for disease duration, and 36 control subjects turned out to be ineligible because of their disease criteria or previous symptoms. Furthermore, 3 UC cases, 2 CD cases, and 8 control subjects showed implausibly low or high values of estimated energy intake (i.e., <800 or >5000 kcal/d) and were therefore excluded from the analyses. Thus, 108 UC case patients, 126 CD case patients, and 211 control subjects remained in the present study.

Of the patients with UC, 45.4% (n = 49) completed the questionnaire within 1 year of diagnosis, 30.6% (n = 33) in the second year, and 24.1% (n = 26) in the third year. The corresponding figures for CD patients were 43.7% (n = 55), 30.2% (n = 38), and 26.2% (n = 33), respectively. The numbers of control subjects by clinical diagnosis were as follows: respiratory diseases (n = 56, including 18 with a common cold and 11 with acute bronchitis); digestive diseases (n = 48, including 15 with anal prolapses and 12 with gastritis); malignant neoplasm of the lymphohematopoietic tissues (n = 16); circulatory diseases (n = 15, including 11 with hemorrhoids); infectious diseases (n = 14); injury (n = 11); orthopedic diseases other than injury (n = 8); diseases of the skin and subcutaneous tissue (n = 7); genitourinary diseases (n = 6); and other diagnoses (n = 30).

Table 1 presents the background characteristics of the UC and CD case patients and the control subjects. Ages were distributed similarly among the 3 groups, while the proportion of women was higher among the UC patients and slightly lower among the CD patients than among the control subjects. The distribution of the study areas showed some differences among the groups. UC patients tended to be less educated than control subjects. As expected,[8] current smoking was negatively associated with UC. Current smokers accounted for 7.4% of UC cases compared to 29.9% of control subjects. We treated the above-mentioned factors as confounding variables and included them in the following multivariate analyses. The strata specified in Table 1 were used in the logistic models.

Among control subjects, the energy-adjusted intake of most nutrients, except for carbohydrates, was higher in women than in men, as was the energy-adjusted consumption of most food groups, excluding alcoholic beverages and rice. This is in line with the findings from the National Nutrition Survey in Japan.[17] Study area and education level had much less impact than gender but were still associated with dietary intake. Control subjects who had finished only high school or less showed a lower intake of vitamin E, sugars and sweeteners, and vegetables. The energy-adjusted consumption of sugars and sweeteners was high in the northern area of Japan (Hokkaido) and low in the southern area (Kyushu and Okinawa), while that of green-yellow vegetables was high in the Kinki region but low in Tokyo (data not shown).

The more frequent the consumption of sweets, the higher the risk of UC (Table 2; trend $P = 0.012$). Those patients in the highest quartile of intake had a 3-fold higher risk than those in the lowest quartile (OR, 2.86; 95% CI, 1.24 to 6.57). ORs for the higher consumption of vegetables or fruit were smaller than unity but did not reach statistical significance.

When the CD patients were compared with control subjects (Table 3), we found an increasing trend in the risk of CD with the increasing consumption of sugars and sweeteners, sweets, fats and oils, and fish and shellfish (trend $P < 0.05$). ORs for the highest quartile of intake versus the lowest were 2.12 (95% CI, 1.08 to 4.17) for sugars and sweeteners, 2.83 (95% CI, 1.38 to 5.83) for sweets, 2.64 (95% CI, 1.29 to 5.39) for fats and oils, and 2.41 (95% CI, 1.18 to 4.89) for fish and shellfish.

Table 4 summarizes the ORs for UC by daily nutrient intake. ORs were smaller with a higher intake of vitamin C. ORs for the second, third, and fourth quartiles were 0.46, 0.44, and 0.45 (95% CI, 0.21 to 0.99; trend $P = 0.053$), respectively. For fat, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), cholesterol, and vitamin E, significantly higher ORs were found in the second or top quartile of intake. There was no dose-response relationship for either total fat or different types of fat.

Fat intake was positively associated with the risk of CD, with a clear dose-response relationship (Table 5). The risk was about 3-fold greater in those in the highest quartile of intake. ORs from the second to the highest quartile, were 1.31, 1.86, and 2.86 (95% CI, 1.39 to 5.90; trend $P = 0.002$), respectively.

TABLE 1. Background Factors in UC Cases (n = 108), CD Cases (n = 126), and Controls (n = 211)

	UC Cases		CD Cases		Controls		*P* for Difference	
	N	%	N	%	N	%	UC versus Controls	CD versus Controls
Age (yr)								
15–19	30	27.8	30	23.8	43	20.4		
20–24	24	22.2	41	32.5	63	29.9	0.46	0.44
25–29	31	28.7	25	19.8	55	26.1		
30–34	23	21.3	30	23.8	50	23.7		
Gender								
Men	56	51.9	91	72.2	135	64.0	0.037	0.12
Women	52	48.1	35	27.8	76	36.0		
Study area								
Hokkaido	7	6.5	2	1.6	9	4.3		
Tohoku	25	23.1	17	13.5	43	20.4		
Tokyo	22	20.4	69	54.8	78	37.0	0.039	0.033
Kanto	21	19.4	9	7.1	22	10.4		
Kinki	21	19.4	16	12.7	39	18.5		
Kyushu and Okinawa	12	11.1	13	10.3	20	9.5		
Education								
High school or less	39	36.1	44	35.2	69	32.7		
Junior college or technical school	38	35.2	31	24.8	51	24.2	0.076	0.57
College, university or more	31	28.7	50	40.0	91	43.1		
Smoking habits								
Nonsmokers	87	80.6	79	62.7	127	60.2		
Ex-smokers	13	12.0	20	15.9	21	10.0	3.0×10^{-5}	0.11
Current smokers	8	7.4	27	21.4	63	29.9		

UC: ulcerative colitis; CD: Crohn's disease.

An increased risk was also found in relation to the higher intake of several types of fats. ORs for the top quartile of intake relative to the bottom were 2.49 (95% CI, 1.23 to 5.03) for MUFAs, 2.31 (95% CI, 1.12 to 4.79) for PUFAs, 3.24 (95% CI, 1.52 to 6.88) for n-3 fatty acids, and 2.57 (95% CI 1.24–5.32) for n-6 fatty acids. We also found an increasing trend in risk with increasing the intake of vitamin E (OR for the highest quartile 3.23; 95% CI, 1.45 to 7.17; trend $P = 0.005$).

Pooling the control subjects may have influenced the data. We therefore recalculated the ORs without pooling; that is, by using only control subjects who were originally matched to UC or CD case patients. Although the CIs were widened due to lower numbers of control subjects, the major findings of our study were not essentially altered in this reanalysis.

For UC patients, the OR for the highest versus lowest quartile of sweet consumption was 2.82 (95% CI, 1.01 to 7.92). For CD patients, the corresponding ORs were 2.03 (95% CI, 0.96 to 4.33) for sugars and sweeteners, 3.38 (95% CI, 1.52 to 7.50) for sweets, 3.15 (95% CI, 1.45 to 6.80) for fats and oils, and 2.44 (95% CI, 1.12 to 5.31) for fish and shellfish. Regarding nutrient intake, the OR for UC (the top versus bottom quartile of intake) was found to be 0.41 (95% CI, 0.16 to 1.05) for vitamin C. The ORs for CD were 2.78 (95% CI, 1.24 to 6.22) for total fat, 2.81 (95% CI, 1.27 to 6.23) for MUFAs, 3.02 (95% CI, 1.36 to 6.70) for PUFAs, 3.96 (95% CI, 1.63 to 9.62) for vitamin E, 3.75 (95% CI, 1.67 to 8.46) for n-3 fatty acids, and 3.12 (95% CI, 1.37 to 7.07) for n-6 fatty acids.

DISCUSSION

In this case-control study, confections were associated with an increased risk for both UC and CD. Higher intakes of sugars and sweeteners, as well as of fats and oils, and fish and shellfish were associated only with an increased risk of CD. Regarding nutrient intake, vitamin C was related to a decreased risk of UC. On the other hand, total fat and fat-related nutrients, including MUFAs, PUFAs, vitamin E, and n-3 and n-6 fatty acids, increased the risk for IBD, particularly for CD.

A substantial proportion of subjects were removed from the analysis because they did not fulfill the eligibility criteria. We focused on patients aged 15 to 34 years and left out subjects who were outside this predefined age range. Therefore, the resultant ORs reflected the association of dietary intake

TABLE 2. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Ulcerative Colitis According to Daily Intake of Food Groups

	Cut Points (g)*			No. of Cases†				OR (95% CI)‡				Trend
	Q1/Q2	Q2/Q3	Q3/Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	P
Potatoes	11.1	16.2	22.3	21	26	20	41	1.00	1.11 (0.52–2.35)	0.68 (0.30–1.50)	1.30 (0.63–2.71)	0.63
Sugars and sweeteners	2.5	3.2	4.3	33	17	30	28	1.00	0.39 (0.18–0.84)	0.76 (0.37–1.56)	0.71 (0.35–1.45)	0.67
Confectioneries	3.0	6.8	12.0	12	22	31	43	1.00	1.66 (0.71–3.92)	2.11 (0.91–4.87)	2.86 (1.24–6.57)	0.012
Fats and oils	10.6	13.9	18.3	16	21	38	33	1.00	1.26 (0.56–2.85)	2.15 (1.02–4.54)	1.76 (0.82–3.77)	0.074
Nuts and seeds	0.1	0.4	0.9	19	31	28	30	1.00	1.36 (0.64–2.91)	1.20 (0.56–2.58)	1.06 (0.49–2.29)	0.93
Pulses	32.3	49.5	67.7	30	23	22	33	1.00	0.60 (0.29–1.27)	0.50 (0.24–1.05)	0.66 (0.32–1.35)	0.25
Fish and shellfish	26.1	42.0	64.8	21	20	31	36	1.00	0.84 (0.38–1.85)	1.07 (0.51–2.24)	1.21 (0.57–2.56)	0.48
Meats and poultry	54.8	72.9	94.6	22	23	31	32	1.00	0.93 (0.44–1.97)	1.27 (0.62–2.61)	1.35 (0.66–2.74)	0.29
Eggs	13.6	28.4	43.0	19	32	26	31	1.00	1.57 (0.74–3.31)	1.14 (0.53–2.46)	1.22 (0.56–2.65)	0.89
Milk and dairy products	54.3	158.1	259.8	23	24	28	33	1.00	0.71 (0.33–1.56)	0.91 (0.42–1.98)	0.79 (0.36–1.73)	0.76
Vegetables	96.1	148.7	197.2	24	30	25	29	1.00	0.93 (0.44–1.97)	0.65 (0.31–1.38)	0.75 (0.35–1.62)	0.32
Fruits	29.9	68.5	136.3	27	32	19	30	1.00	0.88 (0.43–1.79)	0.40 (0.18–0.91)	0.62 (0.29–1.32)	0.11
Mushrooms	2.0	3.9	10.1	23	35	27	23	1.00	1.50 (0.73–3.06)	0.87 (0.41–1.82)	0.69 (0.31–1.56)	0.18
Seaweeds	0.9	1.3	1.9	27	29	28	24	1.00	0.76 (0.37–1.56)	0.71 (0.34–1.48)	0.58 (0.27–1.22)	0.16
Alcoholic beverages	1.3	2.4	160.0	33	30	26	19	1.00	0.91 (0.46–1.80)	0.67 (0.31–1.47)	0.64 (0.27–1.55)	0.28
Rice	403.2	487.8	600.7	35	28	24	21	1.00	0.69 (0.35–1.37)	0.58 (0.28–1.19)	0.64 (0.30–1.36)	0.18
Breads	5.0	11.0	22.7	18	25	32	33	1.00	0.93 (0.42–2.03)	1.62 (0.75–3.50)	1.46 (0.68–3.13)	0.15
Noodles	61.5	103.3	144.8	24	31	20	33	1.00	1.29 (0.63–2.64)	0.75 (0.35–1.62)	1.31 (0.64–2.69)	0.78
Green-yellow vegetables	27.5	53.4	87.4	28	28	21	31	1.00	0.67 (0.32–1.39)	0.42 (0.19–0.93)	0.63 (0.30–1.34)	0.18
Other vegetables	59.7	84.6	111.0	23	31	21	33	1.00	1.21 (0.58–2.49)	0.59 (0.27–1.28)	1.03 (0.50–2.14)	0.69

*Adjusted to a mean energy intake of 2006 kcal/d (8394 kJ/d).

†Cases were classified into 4 groups according to the quartile (Q1–Q4) of energy-adjusted intake among controls. Each group therefore had almost the same number (52 for Q1 and 53 for Q2–Q4) of controls.

‡Adjusted for age, sex, study area, education, and smoking habits.

with IBD risk in relatively young populations. The major findings remained fundamentally unchanged even after including subjects who had been omitted due to disease duration, disease criteria, previous symptoms, or implausible values for estimated energy intake, although the associations of dietary intake with IBD risk were somewhat attenuated in some cases (data not shown).

Although we do not have data on regional differences regarding the incidence or severity of IBD, dietary intake did vary between study areas. To statistically adjust any potential confounding by area, we included the variable in the logistic models. Moreover, all the significant ORs for the highest quartile of intake of food groups or nutrients changed by <10% with this adjustment, indicating minimal effects from any regional differences in dietary intake.

Previously suggested dietary risk factors for IBD included high fat[10] and sugar[29,30] intake, whereas protective factors were the consumption of fruits and vegetables.[29–31] In our study, fat and sugars were also shown to be risk factors for IBD, particularly for CD.

The increase in CD incidence in Japan has been associated with the increased dietary fat intake. Our study also showed positive associations of total fat, and n-3 and n-6 fatty acids with risk for CD. The production of reactive oxygen species from inflammatory cells, such as activated neutrophils, may be altered by the plasma lipid status.[32] Reactive oxygen species produce various oxidant substances, such as lipid peroxides, and aggravate the disease.[33]

Diets containing high n-3 long-chain PUFA levels have been reported to ameliorate inflammation and mucosal damage in an experimental model of UC in rats,[34] and specific fatty acid intake is expected to be a therapeutic medication.[35] However, our study may warn against such thoughts, especially for CD. Increasing the intake of n-3 fatty acids by consuming oily

TABLE 3. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Crohn's Disease According to Daily Intake of Food Groups

	Cut Points (g)*			No. of Cases†				OR (95% CI)‡				Trend
	Q1/Q2	Q2/Q3	Q3/Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	*P*
Potatoes	11.1	16.2	22.3	24	27	31	44	1.00	0.96 (0.48–1.93)	1.14 (0.57–2.28)	1.69 (0.85–3.35)	0.097
Sugars and sweeteners	2.5	3.2	4.3	23	24	32	47	1.00	0.99 (0.48–2.05)	1.37 (0.68–2.76)	2.12 (1.08–4.17)	0.014
Confectioneries	3.0	6.8	12.0	20	30	29	47	1.00	1.42 (0.70–2.91)	1.44 (0.69–3.01)	2.83 (1.38–5.83)	0.005
Fats and oils	10.6	13.9	18.3	19	27	37	43	1.00	1.45 (0.70–3.01)	2.13 (1.05–4.33)	2.64 (1.29–5.39)	0.004
Nuts and seeds	0.1	0.4	0.9	21	39	31	35	1.00	1.86 (0.93–3.72)	1.56 (0.77–3.18)	1.92 (0.94–3.91)	0.15
Pulses	32.3	49.5	67.7	32	30	26	38	1.00	0.88 (0.45–1.72)	0.77 (0.38–1.54)	1.23 (0.63–2.40)	0.59
Fish and shellfish	26.1	42.0	64.8	21	28	34	43	1.00	1.36 (0.67–2.77)	1.52 (0.75–3.08)	2.41 (1.18–4.89)	0.015
Meats and poultry	54.8	72.9	94.6	20	33	35	38	1.00	1.63 (0.81–3.30)	1.61 (0.79–3.26)	1.90 (0.95–3.78)	0.10
Eggs	13.6	28.4	43.0	29	34	28	35	1.00	1.21 (0.63–2.34)	1.02 (0.52–2.04)	1.42 (0.72–2.83)	0.42
Milk and dairy products	54.3	158.1	259.8	39	38	24	25	1.00	0.90 (0.48–1.70)	0.54 (0.27–1.10)	0.50 (0.24–1.05)	0.031
Vegetables	96.1	148.7	197.2	24	49	20	33	1.00	2.19 (1.14–4.22)	0.90 (0.42–1.91)	1.55 (0.76–3.17)	0.78
Fruits	29.9	68.5	136.3	32	42	27	25	1.00	1.19 (0.62–2.28)	0.77 (0.38–1.59)	0.80 (0.38–1.66)	0.33
Mushrooms	2.0	3.9	10.1	31	37	25	33	1.00	1.21 (0.64–2.30)	0.84 (0.42–1.67)	1.29 (0.63–2.62)	0.76
Seaweeds	0.9	1.3	1.9	27	32	32	35	1.00	1.23 (0.62–2.42)	1.33 (0.67–2.65)	1.31 (0.66–2.60)	0.43
Alcoholic beverages	1.3	2.4	160.0	37	40	28	21	1.00	1.25 0.68–2.32)	0.73 (0.36–1.48)	0.50 (0.23–1.11)	0.094
Rice	403.2	487.8	600.7	43	28	22	33	1.00	0.58 (0.30–1.10)	0.49 (0.24–0.97)	0.62 (0.33–1.18)	0.12
Breads	5.0	11.0	22.7	25	24	42	35	1.00	1.00 (0.49–2.02)	1.89 (0.97–3.66)	1.49 (0.76–2.91)	0.093
Noodles	61.5	103.3	144.8	29	35	25	37	1.00	1.19 (0.62–2.29)	0.82 (0.41–1.63)	1.37 (0.71–2.66)	0.57
Green-yellow vegetables	27.5	53.4	87.4	29	41	30	26	1.00	1.45 (0.76–2.75)	1.13 (0.56–2.26)	1.02 (0.50–2.11)	0.84
Other vegetables	59.7	84.6	111.0	17	42	35	32	1.00	2.48 (1.22–5.03)	2.08 (1.00–4.33)	2.07 (0.98–4.37)	0.16

*Adjusted to a mean energy intake of 2006 kcal/d (8394 kJ/d).

†Cases were classified into 4 groups according to the quartile (Q1–Q4) of energy-adjusted intake among controls. Each group therefore had almost the same number (52 for Q1 and 53 for Q2–Q4) of controls.

‡Adjusted for age, sex, study area, education, and smoking habits.

fish would necessarily increase fat intake as a whole. The correlation between the intake of n-3 and n-6 fatty acids was as high as 0.88 among the control subjects (energy-adjusted values), and the n-6/n-3 fatty acid ratios did not give any information on IBD risk in our study. Some fish may have unknown elements that affect the activity and the initiation of IBD. Because our questionnaire cannot estimate the intake of specific kinds of fish, such effects could have been overlooked.

The intake of sugars and sweets increased the risk of IBD in this study. These foods contain sucrose, which has been associated with IBD risk.[8,31] Patients with CD had a higher dietary intake of sucrose and refined carbohydrates,[36] although a critical review of the literature on associations between the onset of CD and the intake of sugars or sugar-containing foods concluded that inconsistent results have arisen due to the lack of distinction between preillness intake and current intake.[37] Gastrointestinal permeability, assessed by the lactulose/mannitol ratio and sucrose excretion, is increased in patients with CD.[38] This phenomenon may be related to the intestinal disorder of CD, but small intestinal permeability is also increased in some healthy spouses of patients with CD,[39] who may share some dietary habits with the patients. Therefore, the increased permeability may be partially associated with environmental factors, such as the inappropriate intake of sugars and sweets, and may alter mucosal immune systems.

In our study, the higher consumption of vegetables and fruits only slightly decreased the risk of UC, but a higher intake of vitamin C, which is concentrated in these foods, showed significantly lower ORs in UC patients. A relatively lower validity of our FFQ for vegetables may have led to the discrepant results.

Vitamins C and E are well-known antioxidant substances.[40] Circulating antioxidants are thought to prevent free

TABLE 4. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Ulcerative Colitis According to Daily Nutrient Intake

	Cut Points (g)*			No. of Cases†				OR (95% CI)‡				Trend
	Q1/Q2	Q2/Q3	Q3/Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	*P*
Protein (g)	61.6	68.1	74.2	16	22	31	39	1.00	0.88 (0.37–2.09)	1.13 (0.49–2.59)	1.36 (0.58–3.20)	0.31
Fat (g)	47.0	57.8	65.5	13	38	18	39	1.00	2.40 (1.07–5.36)	0.98 (0.40–2.36)	2.34 (1.02–5.39)	0.28
Carbohydrate (g)	254	275	300	35	21	33	19	1.00	0.56 (0.28–1.15)	0.74 (0.37–1.48)	0.66 (0.31–1.41)	0.37
Calcium (mg)	320	448	592	23	25	30	30	1.00	0.83 (0.38–1.81)	0.88 (0.41–1.92)	0.73 (0.33–1.64)	0.51
Iron (mg)	7.0	8.4	9.5	15	33	22	38	1.00	1.99 (0.88–4.48)	0.91 (0.39–2.15)	1.64 (0.72–3.77)	0.68
Potassium (mg)	1877	2192	2544	29	26	20	33	1.00	0.56 (0.27–1.18)	0.38 (0.17–0.84)	0.62 (0.29–1.32)	0.18
Vitamin A (IU)	1477	2065	2715	25	28	23	32	1.00	0.88 (0.42–1.83)	0.70 (0.33–1.49)	0.90 (0.44–1.87	0.69
Retinol (μg)	234.9	341.6	486.8	16	36	26	30	1.00	1.93 (0.90–4.13)	1.35 (0.62–2.96)	1.79 (0.82–3.89)	0.34
Carotene (μg)	845	1357	2025	23	26	24	35	1.00	0.72 (0.34–1.54)	0.61 (0.28–1.34)	0.86 (0.41–1.82)	0.73
Vitamin C (mg)	46	69	107	32	23	26	27	1.00	0.46 (0.21–0.97)	0.44 (0.21–0.92)	0.45 (0.21–0.99)	0.053
SFA (g)	12.9	16.3	19.0	16	32	24	36	1.00	1.65 (0.75–3.62)	1.21 (0.52–2.80)	1.56 (0.69–3.52)	0.51
MUFA (g)	16.9	21.0	24.4	10	39	26	33	1.00	3.33 (1.43–7.77)	1.85 (0.76–4.54)	2.61 (1.10–6.22)	0.22
PUFA (g)	11.3	13.8	16.3	11	39	32	26	1.00	2.59 (1.13–5.97)	2.07 (0.87–4.90)	1.66 (0.68–4.04)	0.72
Cholesterol (mg)	191	270	347	13	39	23	33	1.00	2.65 (1.20–5.86)	1.36 (0.58–3.20)	1.61 (0.69–3.74)	0.88
Vitamin E (mg)	6.3	7.6	8.8	13	39	22	34	1.00	2.79 (1.24–6.26)	1.15 (0.48–2.76)	1.82 (0.76–4.34)	0.82
Dietary fiber (g)	8.4	10.1	12.6	26	25	32	25	1.00	0.70 (0.34–1.46)	0.86 (0.42–1.77)	0.53 (0.24–1.15)	0.18
Magnesium (mg)	223	242	263	35	23	19	31	1.00	0.54 (0.26–1.13)	0.33 (0.15–0.71)	0.49 (0.24–1.01)	0.029
Zinc (μg)	7966	8879	9523	21	33	25	29	1.00	0.97 (0.44–2.14)	0.59 (0.26–1.36)	0.79 (0.35–1.81)	0.37
n-3 fatty acids (g)	2.1	2.7	3.2	13	33	31	31	1.00	1.92 (0.85–4.32)	1.86 (0.82–4.24	1.72 (0.75–3.96)	0.35
n-6 fatty acids (g)	9.0	10.9	12.9	12	34	35	27	1.00	2.14 (0.93–4.92)	2.02 (0.87–4.65)	1.62 (0.68–3.84)	0.54
n-6/n-3	3.73	4.14	4.56	26	32	22	28	1.00	1.17 (0.59–2.34)	0.96 (0.46–1.99)	1.25 (0.61–2.58)	0.68

SFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids.
*Adjusted to a mean energy intake of 2006 kcal/d (8394 kJ/d).
†Cases were classified into 4 groups according to the quartile (Q1–Q4) of energy-adjusted intake among controls. Each group therefore had almost the same number (52 for Q1 and 53 for Q2–Q4) of controls.
‡Adjusted for age, sex, study area, education, and smoking habits.

radical-mediated tissue injury. The circulating vitamin C level in IBD children was reported to be lower, although the vitamin E level was higher than that in control subjects, suggesting that there are changes in the circulating antioxidant defenses against oxidant stress.[41] On the other hand, plasma vitamin E levels were lower in adult patients with IBD than in control subjects with a lower intake of fruit and vegetables, as assessed by an FFQ.[42] The values for plasma vitamin E levels in IBD patients were inconsistent.

In the present study, vitamin C decreased UC risk, but vitamin E was found to be a risk factor for CD. These results may be related to their dietary sources. Vitamin C is contained mainly in fruit and vegetables, while vitamin E is present in vegetable oils or fatty foods.

Dietary factors were evaluated with a comprehensive and validated FFQ in relation to the risk of IBD. We think that there have only been a few such studies.[10] Our case groups reflect the typical gender and age composition of new IBD cases in Japan. The sex ratios in the nationwide registry[43] (UC patients, 1.18; CD patients, 2.35) were comparable with those found in our series (1.09 and 2.56, respectively). The number of patients peaked at ages 25 to 29 years for UC and 20 to 24 years for CD, in both the registry and the present study. To be more representative of the spectrum of UC and CD patients, however, further studies may need to be performed in a population-based setting.

A potential weakness of our study was that the control subjects were selected from among hospital patients. However, in a case-control study based on case patients from selected hospitals, a random sample of the general population does not necessarily correspond to a random sample of the source population that gives rise to the cases.[44] It is appropriate to select control subjects from among patients in the hospitals where the case patients were identified, because referral patterns should be taken into account.[44] The major limitation for the use of hospital control subjects is that the exposure in question might be associated with the control diseases.[44] Therefore, we attempted to exclude control subjects with conditions related to nutritional status, and to include patients with a variety of diagnoses as control subjects to dilute any biasing effects of including a specific diagnosis.

TABLE 5. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Crohn's Disease According to Daily Nutrient Intake

	Cut Points (g)*			No. of Cases†				OR (95% CI)‡				Trend
	Q1/Q2	Q2/Q3	Q3/Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	P
Protein (g)	61.6	68.1	74.2	23	31	32	40	1.00	1.29 (0.64–2.60)	1.34 (0.65–2.74)	2.06 (0.99–4.28)	0.060
Fat (g)	47.0	57.8	65.5	20	27	33	46	1.00	1.31 (0.63–2.73)	1.86 (0.90–3.82)	2.86 (1.39–5.90)	0.002
Carbohydrate (g)	254	275	300	42	30	28	26	1.00	0.70 (0.37–1.31)	0.63 (0.32–1.23)	0.53 (0.27–1.03)	0.061
Calcium (mg)	320	448	592	39	36	22	29	1.00	0.85 (0.45–1.60)	0.53 (0.26–1.06)	0.67 (0.33–1.35)	0.14
Iron (mg)	7.0	8.4	9.5	23	34	33	36	1.00	1.43 (0.71–2.85)	1.55 (0.76–3.16)	1.86 (0.88–3.90)	0.11
Potassium (mg)	1877	2192	2544	38	37	24	27	1.00	0.94 (0.50–1.74)	0.62 (0.32–1.22)	0.72 (0.36–1.44)	0.20
Vitamin A (IU)	1477	2065	2715	26	40	26	34	1.00	1.41 (0.73–2.72)	1.02 (0.51–2.06)	1.49 (0.74–3.00)	0.45
Retinol (μg)	234.9	341.6	486.8	29	38	29	30	1.00	1.20 (0.63–2.30)	1.02 (0.52–2.01)	1.05 (0.54–2.06)	0.97
Carotene (μg)	845	1357	2025	25	40	25	36	1.00	1.59 (0.81–3.12)	1.00 (0.49–2.04)	1.69 (0.83–3.45)	0.37
Vitamin C (mg)	46	69	107	30	37	34	25	1.00	1.12 (0.58–2.14)	1.17 (0.60–2.29)	0.87 (0.42–1.82)	0.79
SFA (g)	12.9	16.3	19.0	27	35	28	36	1.00	1.32 (0.68–2.59)	1.04 (0.51–2.12)	1.46 (0.71–2.99)	0.44
MUFA (g)	16.9	21.0	24.4	21	27	33	45	1.00	1.18 (0.57–2.43)	1.79 (0.87–3.67)	2.49 (1.23–5.03)	0.005
PUFA (g)	11.3	13.8	16.3	20	19	48	39	1.00	0.84 (0.39–1.82)	2.93 (1.45–5.94)	2.31 (1.12–4.79)	0.002
Cholesterol (mg)	191	270	347	25	33	30	38	1.00	1.33 (0.68–2.62)	1.27 (0.63–2.56)	1.81 (0.88–3.69)	0.14
Vitamin E (mg)	6.3	7.6	8.8	17	35	36	38	1.00	2.14 (1.02–4.47)	2.89 (1.35–6.18)	3.23 (1.45–7.17)	0.005
Dietary fiber (g)	8.4	10.1	12.6	30	32	38	26	1.00	0.99 (0.51–1.92)	1.28 (0.66–2.47)	0.90 (0.43–1.86)	0.98
Magnesium (mg)	223	242	263	43	26	27	30	1.00	0.56 (0.29–1.08)	0.62 (0.32–1.18)	0.72 (0.36–1.43)	0.33
Zinc (μg)	7966	8879	9523	25	43	25	33	1.00	1.83 (0.93–3.59)	0.94 (0.44–2.00)	1.28 (0.61–2.68)	0.95
n-3 fatty acids (g)	2.1	2.7	3.2	17	29	39	41	1.00	1.75 (0.83–3.69)	2.62 (1.26–5.47)	3.24 (1.52–6.88)	0.001
n-6 fatty acids (g)	9.0	10.9	12.9	19	22	44	41	1.00	1.09 (0.51–2.35)	2.76 (1.34–5.67)	2.57 (1.24–5.32)	0.002
n-6/n-3	3.73	4.14	4.56	33	31	37	25	1.00	0.88 (0.46–1.70)	1.10 (0.58–2.07)	0.73 (0.37–1.45)	0.55

SFA = saturated fatty acids; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids.
*Adjusted to a mean energy intake of 2006 kcal/d (8394 kJ/d).
†Cases were classified into 4 groups according to the quartile (Q1–Q4) of energy-adjusted intake among controls. Each group therefore had almost the same number (52 for Q1 and 53 for Q2–Q4) of controls.
‡Adjusted for age, sex, study area, education, and smoking habits.

As we focused on patients in hospitals, we may have involved patients with more severe IBD, although in Japan a substantial proportion of the patients who visit a hospital are not admitted. The dietary risk or protective factors in the present study, therefore, may be related to rather severe IBD and could differ from those in mild IBD.

This study suffers from the shortcoming of recall bias, which is inherent in any retrospective study. It is very difficult to determine whether the observed changes in food intake were due to the disease and its related symptoms, or whether these changes were primary events. We did our best to accurately assess dietary intake before the onset of disease using a validated FFQ and, to facilitate the recall of lifestyles, including dietary habits, 5 years previously, some reminder questions were inserted into the questionnaire regarding familial and social background at that time. Nevertheless, it is difficult to ascertain whether the questionnaire correctly gathered information reflecting a time 5 years prior to the study. Prospective studies are warranted to confirm the associations between diet and IBD risk. However, in such low-incidence areas as Japan, such studies are extremely challenging to perform. Hence, we have initially conducted a case-control study.

The supplemental interviews by physicians to reduce missing data may have introduced some information bias since they had knowledge of the patients' disease. This bias, however, would be minimal because <10% of subjects underwent such interviews for <5% of the questions, on average.

Another methodological issue may be that we included patients with IBD within 3 years after receiving their diagnosis, which would have led to a larger recall bias.[44] Some patients may have undergone dietary education, and although we asked about the preillness diet 5 years before the study, patients' recall may have been influenced by their diet after the onset of disease. We reanalyzed the data limiting the cases to those patients who received a diagnosis of IBD within 1 year (UC, 49 patients; CD, 55 patients), and the results were similar to those derived from the whole data set (data not shown). Nevertheless, studies including only more recent cases may be required to confirm our results.

Some associations between dietary variables and IBD risk may have been missed due to the relatively small number of subjects. If the OR for the top quartile of intake compared with the bottom quartile had been 2.5 or 0.4, this study would have failed to detect significant associations with a 31% probability for UC or a 26% probability for CD.

Finally, the simultaneous examination of many foodstuffs and nutrients may have produced some chance findings. Consistencies of association between studies should be considered when interpreting the results of the present study.

In conclusion, our results indicated the importance of dietary factors in the development of IBD. Deleterious effects of fats and sugar were particularly stressed, whereas the protective effects of vitamin C on UC patients were suggested. Our findings, especially if they are confirmed in further studies, might be useful for preventing the recurrence of IBD by modifying a patient's diet in remission periods.

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