Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n–6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan1–3

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ABSTRACT We examined the correlation between the incidence of Crohn disease and dietary change in a relatively homogeneous Japanese population. The incidence and daily intake of each dietary component were compared annually from 1966 to 1985. The univariate analysis showed that the increased incidence of Crohn disease was strongly \( (P < 0.001) \) correlated with increased dietary intake of total fat \( (r = 0.919) \), animal fat \( (r = 0.880) \), n–6 polyunsaturated fatty acids \( (r = 0.883) \), animal protein \( (r = 0.908) \), milk protein \( (r = 0.924) \), and the ratio of n–6 to n–3 fatty acid intake \( (r = 0.792) \). It was less correlated with intake of total protein \( (r = 0.482, P < 0.05) \), was not correlated with intake of fish protein \( (r = 0.055, P > 0.1) \), and was inversely correlated with intake of vegetable protein \( (r = -0.941, P < 0.001) \). The multivariate analysis showed that increased intake of animal protein was the strongest independent factor with a weaker second factor, an increased ratio of n–6 to n–3 polyunsaturated fatty acids. The present study in association with reported clinical studies suggests that increased dietary intake of animal protein and n–6 polyunsaturated fatty acids with less n–3 polyunsaturated fatty acids may contribute to the development of Crohn disease. Am J Clin Nutr 1996;63:741–5.

KEY WORDS n–6 Polyunsaturated fatty acid, n–3 polyunsaturated fatty acid, pathogenesis of Crohn disease, dietary change, Japanese population

INTRODUCTION

The incidence of Crohn disease in Japan has been increasing steadily during recent decades (1). Because the genetic background of the Japanese people is relatively homogeneous and has not changed, its increased incidence could be explained by environmental changes such as alterations in eating habits. Increased intake of Western foods in recent years in Japan (2) could be a factor because the incidence of Crohn disease is significantly higher in the Western industrial nations than in Japan (3).

It has been accepted generally that nutritional interventions, such as total parenteral nutrition and total enteral feeding with an elemental diet, are the primary therapy for active Crohn disease (4, 5). We reported previously that elemental enteral alimentation at home is effective in maintaining the remission of Crohn ileitis and ileocolitis (6). The working hypothesis of these nutritional treatments is advocated to be the reduction of dietary fat (7) and the elimination of antigenic dietary protein (8). Moreover, the quality of dietary fat, mainly the fatty acid composition, as well as its quantity has been focused on recently (9). Administration of the n–3 polyunsaturated fatty acid (PUFA) eicosapentaenoic acid has been shown to control active ulcerative colitis (10) as well as many other inflammatory disorders, like rheumatoid arthritis (11).

These epidemiologic and clinical observations led us to investigate whether the recent increasing incidence of Crohn disease in Japan is related to dietary changes.

METHODS

Vital statistics for Crohn disease in Japan

The incidence of Crohn disease in Japan was obtained from recent data collected by the research committee for inflammatory bowel disease in the Ministry of Health and Welfare of Japan (12). The data are based on a nationwide multicenter survey of the annual numbers of new patients with Crohn disease. Patients were enrolled in the same year that they first experienced symptoms that suggested the diagnosis of Crohn disease. The diagnostic criteria used in this study were those of the Japanese Research Committee for Inflammatory Bowel Disease. The criteria were based on a double-contrast barium study of the small and large intestines and/or a colonoscopic examination with histopathologic study of biopsied specimens. The criteria were as follows: 1) discontinuity of lesion, 2) cobblestone appearance and/or longitudinal ulcer, 3) transmural inflammation (mass formation or stenosis), 4) noncaseous granuloma, 5) fissure and/or fistula, and 6) anal lesion (pro-

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tracted ulcer, atypical anal fistula, or anal fissure). Positive findings of 1, 2, 3, and 5; 1, 2, 3, and 6; 1, 2, and 4; 1, 3, and 4; or 2, 3, and 4 indicate definite Crohn disease. Disease with 1, 2, and 3 is diagnosed as indefinite. Moreover, the following diseases should be ruled out to establish the diagnosis: intestinal tuberculosis, ulcerative colitis, ischemic colitis, radiation colitis, intestinal Behcet, simple (nonspecific) ulcer, atypical multiple small intestinal ulcers, and acute terminal ileitis.

Analysis of the food intake in Japan

The chronologic change in intake of dietary elements from 1966 to 1985 was surveyed from the data by the Ministry of Health and Welfare of Japan (2). Briefly, 16,500-68,000 people from 4200 to 16,500 families were interviewed individually for 5 consecutive days every year about precise dietary intake. The average daily intake of each nutrient, such as total fat, animal protein, or n-6 PUFAs, was calculated annually with a conversion table (13), which was assembled by food composition in 1985.

Statistical analysis

STATVIEW (version 4.0; Abacus Concepts, Inc, Berkeley, CA) for Macintosh was used for analysis. The correlation between the logarithmic numbers of the new patients with Crohn disease and the average intake of each nutrient per day was examined annually in the same year by the univariate analysis. Multivariate analysis was also done for those nutrients for which there had been a significant difference after univariate analysis of fat and/or protein. Finally, multivariate analysis was used to evaluate a correlation between the incidence of Crohn disease and principle nutrients for the exposure-onset interval of 0–12 y annually. A P value < 0.05 was considered significant.

RESULTS

Vital statistics for Crohn disease in Japan

Absolute as well as standardized numbers (per 10,000 population) of newly diagnosed patients with Crohn disease have increased in Japan. Reported numbers of patients of both sexes increased as shown in Figure 1 (12). The age distribution of newly diagnosed patients did not change, the peak being at 20–24 y of age. Of the 242 newly diagnosed patients in 1975–1979, 123 had ileocolitis (50.8%), 51 had colitis (21.1%), and 68 had ileitis (26.6%) (12).

Changes in dietary habits in Japan

Although total energy intake changed only slightly, from 9180 to 8740 kJ/d (2193 to 2088 kcal/d), total fat intake increased drastically from 1966 to 1985 (from 39.7 to 56.9 g/d) (2). Total protein intake increased modestly (from 74.8 to 79.0 g/d) and total carbohydrate intake decreased (from 378 to 298 g/d) during this period. Nutrients from animal sources increased and those from vegetable sources decreased. Intake of fish did not change significantly.

Incidence of Crohn disease and fat intake

The univariate analysis showed that the recently increased incidence of Crohn disease was strongly correlated with increased average daily intake of total fat, animal fat, and n-6 PUFAs with r values of 0.919, 0.880, and 0.883, respectively (P < 0.001; Figure 2). It was also strongly correlated with the ratio of n-6 to n-3 PUFAs intake (r = 0.792, P < 0.001; Figure 3) but less correlated with fish-oil intake (r = 0.598; P < 0.005). Among these nutrients, an increased intake of animal fat and an increased ratio of n-6 to n-3 PUFAs were the independent factors by the multivariate analysis.

Incidence of Crohn disease and protein intake

The univariate analysis indicated that the increased incidence of Crohn disease had only a weak correlation with the intake of total protein (P < 0.05, r = 0.482). However, it was strongly correlated with the increased intake of animal protein and milk protein (r = 0.908 and 0.924, respectively; P < 0.001; Figure 4). It had an inverse correlation with intake of vegetable protein (r = -0.941, P < 0.001) and no correlation with intake of fish protein (r = 0.055; P > 0.1; Figure 5). Of these proteins, animal protein was the independent and strongest factor correlated with the increased incidence of Crohn disease by mul-

![FIGURE 1. Incidence of Crohn disease in Japan, which increased from 1966 to 1985 in the total population (▲) and in both males (△) and females (●).](https://academic.oup.com/ajcn/article-abstract/63/5/741/4651425/FIGURE1)

![FIGURE 2. Correlation between incidence of Crohn disease and daily fat intake examined annually from 1966 to 1985 by univariate analysis. Daily intakes of total fat (□), animal fat (●), and n-6 polyunsaturated fatty acid (△) all correlated significantly with the number of Crohn disease patients.](https://academic.oup.com/ajcn/article-abstract/63/5/741/4651425/FIGURE2)
tivariate analysis. The multivariate analysis indicated that animal protein is the strongest nutrient correlated with the increased incidence of Crohn disease of all the above-mentioned nutrients, including fat and protein.

**Analysis for exposure-onset interval**

The multivariate analysis indicated that the best correlation, the highest \( r \) value and adjusted \( r^2 \) value, was observed between the incidence of Crohn disease and intake of principal nutrients (animal fat, ratio of \( n-6 \) to \( n-3 \) PUFAs, and animal protein, which were independent by the above-mentioned multivariate analysis) at the exposure-onset interval of 3 y. The second peak of the correlation was found at the interval of 9 y. The adjusted \( r^2 \) and \( r \) values were constantly high enough to have significantly positive correlations up to 10 y (Figure 6).

**DISCUSSION**

The incidence of Crohn disease is reported to be steadily increasing in Japan (1). Because the Japanese population is relatively homogeneous, the increased incidence of Crohn disease could be explained by environmental changes. Among them, dietary change is suspected to be the most important factor because clinical investigations indicate that nutritional treatments like total parenteral nutrition and total elemental enteral almentation are able to induce and maintain remission in patients with Crohn disease (4–6). Because enteral feeding with a polymeric diet may be less effective than that with an elemental diet to control active Crohn disease (14), elimination of whole protein and reduction of fat from the diet may contribute to the efficacy of these nutritional interventions. In addition to the quantity of dietary fat, the quality of fat has received more attention recently because \( n-3 \) PUFAs have been shown to have an antiinflammatory effect (10, 11, 15).

Although several epidemiologic studies have shown clear geographic features of Crohn disease (3, 8, 16), its etiologic factors are still an enigma (17). Genetic factors indeed contribute to the development of Crohn disease (18, 19). However, the increased incidence of Crohn disease in the racially homoge-
were registered with the Ministry of Health and Welfare and their characteristics were well-documented. Although it is impossible to detect all the patients with Crohn disease, we believe that our patient population reasonably reflects the real increased incidence of the disease.

The exact reason for this drastically increased incidence of Crohn disease in Japan is unknown. However, possible explanations are as follows. First, drastic dietary changes may have had an influence. For example, dietary fat intake increased sixfold from 1945 to 1985. Diet could have major effects on the incidence of Crohn disease if the disease increases only when fat and/or protein intakes exceed certain amounts. Second, the biologic effect of dietary change itself might exponentially affect the incidence of Crohn disease. Third, it is impossible to rule out the possibility that factors other than these dietary changes are responsible for the great increase of Crohn disease in Japan. However, nutritional manipulation such as enteral alimentation with an elemental diet, which has no protein and has a negligible amount of fat, can induce remission of Crohn disease. This fact again suggests that the importance of dietary factors should not be ignored in the development of Crohn disease despite the above-mentioned possible nondietary factors.

Exposure-onset-diagnosis intervals can also be problematic in this type of epidemiologic study. It was suggested that the exposure-onset interval might be 3 y in the present study. However, r values at the exposure-onset intervals of 0 and 3 y still had similar ranges and were also significant for all nutrients (total fat, 0.910; n-6 PUFAs, 0.917; ratio of n-6 to n-3 PUFAs, 0.837; animal protein, 0.813; and milk protein, 0.895 by univariate analysis), except for total protein intake (0.092) at the 3-y interval. Moreover, there is no definite clinical consensus in this exposure-onset-diagnosis issue. We, therefore, did not take exposure-onset-diagnosis intervals into account in the present analysis.

Almost all epidemiologic analyses have been conducted as case-control studies to investigate the correlation between dietary pattern and the development of Crohn disease (23).

Case-control studies of pre- and postillness dietary habits were preferentially used to overcome biases like changes in diagnostic criteria, maldistribution of medical care, and change in physicians' interest. Despite these advantages, disadvantages included uncertainties about the patients' memory concerning previous dietary habits, and the small size of the patient population (24), which is particularly unavoidable in an epidemiologic study of Crohn disease in Japan because of its rarity (1). Moreover, some authors emphasized recently the importance of correlation studies, which had traditionally been considered to be weak (25). In this study, therefore, we used a simple secular trend to analyze the relation between the incidence of the disease and dietary change despite the above-mentioned biases and exposure-onset-diagnosis intervals.

Consumption of certain types of food elements such as more refined sugar (26, 27) and less dietary fiber (28) have been reported to be closely correlated with the development of Crohn disease in several epidemiologic studies. There are, however, no definite supportive clinical or other epidemiologic findings (29, 30). Consumption of refined sugar had two peaks in 1955 and 1971, and has been increasing subsequently in Japan (2). Even exposure-onset-diagnosis intervals are unlikely to explain the steadily increasing incidence of Crohn disease in the present study.

It has been shown that milk proteins aggravate Crohn disease (8) and that there is a good correlation between disease activity and antibody titers against some milk proteins in Crohn disease patients (31). These clinical observations also support our results. Some investigators, however, suggested that other foodstuffs such as cereals, vegetables, and fruit can induce flare-ups of Crohn disease (32). Further investigations are required to confirm the correlation between consumption of these foodstuffs and the development of Crohn disease.

In conclusion, the present study showed that the increased incidence of Crohn disease correlated closely with the increased intake of dietary fat, especially n-6 fatty acids, with a relatively decreased intake of n-3 fatty acids, and with an
increased intake of animal protein in Japan. These results are supported by clinical observations, such as a dramatic improvement in Crohn intestinal lesions after total elemental enteral alimentation. Japan has had large changes in the incidence of Crohn disease and in dietary patterns in its genetically homogeneous, stable population. Therefore, this study provides fundamental information for further epidemiologic and clinical investigations despite the substantial limitations of this type of epidemiologic study.

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REFERENCES


