complication.[9,15,28,29] In the present study, capsule retention rate in patients with eCD was 7.4%, the value of which is similar to those reported from Western countries.[9,15,28,29] In addition, capsule retention rate in patients with sCD was as high as that in eCD in the present study. This observation contradicts to the OMED-ECCO consensus statement showing less incidence of capsule retention in sCD than in eCD.[15] Such a discordant result may be a consequence of the difference in the definition of sCD. Nevertheless, the present survey strongly suggests that pre-examination with the use of a patency capsule should be seriously considered when applying CE for Japanese patients with sCD.

The present survey has several limitations. First, we could not assess precise characteristics of CE findings including distribution, severity, and alignment of mucosal injuries because the aim of the study was to assess overall diagnostic yield of CE and complication rate. Second, the priority of CE in the diagnosis of CD was subjectively determined. With the introduction of patency capsule, a more objective and comprehensive role of CE for CD would be expected to be analyzed in the near future.

In summary, the present survey demonstrated favorable diagnostic yield of CE in Japanese patients with suspected and eCD, although endoscopists had been reluctant to the use of CE in consideration of the risk of capsule retention and of the lower diagnostic value of typical mucosal injuries in eCD. Therefore, cautious application of CE seems to be a useful tool for the diagnosis of CD, and this may be especially the case for sCD. Appropriate diagnostic criteria of CD by means of CE seem mandatory.

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References

1 Triester SL, Leighton JA, Leontiadis GI *et al.* A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure GI bleeding. *Am. J. Gastroenterol.* 2006; **101**: 954–64.
2 Marmo R, Rotondano G, Piscopo R, Bianco MA, Cipolletta L. Meta-analysis: capsule endoscopy vs. conventional modalities in diagnosis of small bowel diseases. *Aliment. Pharmacol. Ther.* 2005; **22**: 595–604.
3 Mergener K, Ponchon T, Gralnek I *et al.* Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy* 2007; **39**: 895–909.
4 Gastineau S, Viala J, Caldari D *et al.* Contribution of capsule endoscopy to Peutz-Jeghers syndrome management in children. *Dig. Liver Dis.* 2012; **44**: 839–43.
5 Günther U, Bojarski C, Buhr HJ, Zeitz M, Heller F. Capsule endoscopy in small-bowel surveillance of patients with hereditary polyposis syndrome. *Int. J. Colorectal Dis.* 2010; **25**: 1377–82.
6 Rokkas T, Niv Y. The role of video capsule endoscopy in the diagnosis of celiac disease: a meta-analysis. *Eur. J. Gastroenterol. Hepatol.* 2012; **24**: 303–8.
7 Rondonotti E, Villa F, Saladino V, de Francis R. Enteroscopy in the diagnosis and management of celiac disease. *Gastrointest. Endosc. Clin. N. Am.* 2009; **19**: 389–407.
8 de Melo SW Jr, Di Palma JA. The role of capsule endoscopy in evaluating inflammatory bowel disease. *Gastroenterol. Clin. North Am.* 2012; **41**: 315–23.
9 Lewis BS. Expanding role of capsule endoscopy in inflammatory bowel disease. *World J. Gastroenterol.* 2008; **14**: 4137–41.
10 Hara AK, Leighton JA, Heigh RI *et al.* Crohn disease of the small bowel: preliminary comparison among CT enterography, capsule endoscopy, small-bowel follow-through, and ileoscopy. *Radiology* 2006; **238**: 128–34.
11 Solem CA, Loftus EV Jr, Fletcher JG *et al.* Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. *Gastrointest. Endosc.* 2008; **68**: 255–66.
12 Voderholzer WA, Beinhoelzl J, Rogalla P *et al.* Small bowel involvement in Crohn's disease: a prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. *Gut* 2005; **54**: 369–73.
13 Marmo R, Rotondano G, Piscopo R *et al.* Capsule endoscopy versus enteroclysis in the detection of small-bowel involvement in Crohn's disease: a prospective trial. *Clin. Gastroenterol. Hepatol.* 2005; **3**: 772–6.
14 Dionisio PM, Gurudu SR, Leighton JA *et al.* Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. *Am. J. Gastroenterol.* 2010; **105**: 1240–8.
15 Bourreille A, Ignjatovic A, Aabakken L *et al.* Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009; **41**: 618–37.

16 Yao T, Matsui T, Hiwatashi N. Crohn's disease in Japan: diagnostic criteria and epidemiology. *Dis. Colon Rectum* 2000; **43**: S85–93.
17 Matsumoto T, Iida M, Matsui T, Yao T. Chronic nonspecific multiple ulcers of the small intestine: a proposal of the entity from Japanese gastroenterologists to Western enteroscopists. *Gastrointest. Endosc.* 2007; **66** (Suppl. 3): S99–107.
18 Baumgart DC, Sandborn WJ. Inflammatory bowel: clinical aspect and established and evolving therapies. *Lancet* 2007; **369**: 1641–57.
19 Gay GJ, Delmotte JS. Enteroscopy in small intestinal inflammatory diseases. *Gastrointest. Endosc. Clin. N. Am.* 1999; **9**: 115–23.
20 Mehdizadeh S, Chen GC, Barkodar L *et al.* Capsule endoscopy in patients with Crohn's disease: diagnostic yield and safety. *Gastrointest. Endosc.* 2010; **71**: 121–7.
21 Efthymiou A, Viazis N, Mantzaris G *et al.* Does clinical response correlate with mucosal healing in patients with Crohn's disease of the small bowel? A prospective, case-series study using wireless capsule endoscopy. *Inflamm. Bowel Dis.* 2008; **14**: 1542–7.
22 Tukey M, Pleskow D, Legnani P, Cheifetz AS, Moss AC. The utility of capsule endoscopy in patients with suspected Crohn's disease. *Am. J. Gastroenterol.* 2009; **104**: 2734–9.
23 Jensen MD, Nathan T, Kjeldsen J. Inter-observer agreement for detection of small bowel Crohn's disease with capsule endoscopy. *Scand. J. Gastroenterol.* 2010; **45**: 878–84.
24 Casciani E, Masselli G, Di Nardo G *et al.* MR enterography versus capsule endoscopy in paediatric patients with suspected Crohn's disease. *Eur. Radiol.* 2011; **21**: 823–31.
25 Jensen MD, Nathan T, Rafaelsen SR, Kjeldsen J. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. *Clin. Gastroenterol. Hepatol.* 2011; **9**: 124–9.
26 Doherty GA, Moss AC, Cheifetz AS. Capsule endoscopy in suspected Crohn's disease: "yield" does not equal "diagnosis". *Am. J. Gastroenterol.* 2010; **105**: 2111–2.
27 Mow WS, Lo SK, Targan SR *et al.* Initial experience with wireless capsule enteroscopy in the diagnosis and management of inflammatory bowel disease. *Clin. Gastroenterol. Hepatol.* 2004; **2**: 31–40.
28 Hartmann D. Capsule endoscopy and Crohn's disease. *Dig. Dis.* 2011; **29** (Suppl. 1): 17–21.
29 Doherty GA, Moss AC, Cheifetz AS. Capsule endoscopy for small-bowel evaluation in Crohn's disease. *Gastrointest. Endosc.* 2011; **74**: 167–75.

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Pre-Illness Isoflavone Consumption and Disease Risk of Ulcerative Colitis: A Multicenter Case-Control Study in Japan

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Abstract

Introduction: Previous studies have suggested that estrogens play a role in the development of ulcerative colitis (UC). Because isoflavones have a similar structure to 17β-estradiol, dietary consumption of isoflavones may have similar influences on the development of UC. We examined the association between pre-illness isoflavone consumption and the risk of UC.

Materials and Methods: We conducted a hospital-based case control study, and compared the dietary habits of 126 newly diagnosed UC cases with those of 170 age- and gender-matched hospital controls. Information on dietary factors was collected using a self-administered diet history questionnaire. To consider potential changes in dietary habits due to disease symptoms, the habits were assessed separately during the previous 1 month and at 1 year before the recruitment.

Results: In the assessment of dietary habits during the previous 1 month, the highest tertile of isoflavone consumption revealed an increased odds ratio (OR) for UC (OR = 2.79; 95% confidence interval (CI), 1.39–5.59; Trend P = 0.004). A significant association was also observed for the dietary assessment at 1 year before, when most UC cases had not yet experienced their first disease symptoms (OR = 2.06; 95% CI, 1.05–4.04; Trend P = 0.04). Associations were more pronounced in females (OR in highest tertile of isoflavone consumption at 1 year before = 4.76; 95% CI, 1.30–17.5; Trend P = 0.02) but were obscured in males (corresponding OR = 1.21; 95% CI, 0.49–3.01; Trend P = 0.63).

Conclusions: Dietary isoflavone consumption may be associated with an increased risk of UC, particularly in females. Prospective cohort studies are warranted to confirm these findings.

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Introduction

In Japan, the prevalence of ulcerative colitis (UC) has been increasing over the last two decades [1,2] and the age-standardized prevalence of UC was 63.6 per 100,000 persons in 2005 [3]. However, the etiology and pathogenesis of UC have remained largely unclear. Although several studies have confirmed an important role of genetic predisposition in UC [4], the number of UC patients with a family history of inflammatory bowel disease remains low [5], and the rising incidence against a background of stable prevalence of the genetic predisposition [5,6] has suggested the importance of environmental factors in the disease etiology.

Several potential environmental or external risk factors have been reported to date, including oral contraceptive use [7–9]. Two meta-analyses have provided evidence for a modest association between the use of oral contraceptive agents and the development of UC [10,11]. Another study indicated that hormone-replacement therapy increased the risk of UC among postmenopausal women [12]. Such findings suggest that pathways related to estrogens might mediate the pathogenesis of UC.

Isoflavones have a similar structure to 17β-estradiol. Daidzein and genistein are the main isoflavones present in soybeans, and possess the ability to bind to estrogen receptors [13,14]. Dietary consumption of isoflavones has therefore been suggested to potentially exert a similar influence to estrogens on the development of UC. In addition, extensive animal studies showing the effect of isoflavones on immune parameters have suggested the feasibility of genistein and daidzein exerting immunological effects in humans [15]. However, these possible associations have yet to be evaluated.

We therefore sought to examine the association between isoflavone consumption and risk of UC development, using a multicenter case-control study in Japan. Since UC patients are likely to change dietary habits following the onset of disease symptoms, pre-illness dietary habits would be important to examine in considering issues of causality. Thus, the present hospital-based case-control study enrolled newly diagnosed UC patients as cases, and dietary habits both during the previous 1 month and at 1 year before recruitment were assessed separately as candidate pre-illness dietary habits.

Materials and Methods

Selection of Cases and Controls

Between September 2008 and March 2014, a multicenter case-control study was conducted in Japan, to investigate risk factors for the development of UC. Newly diagnosed cases of UC were recruited at 38 collaborating hospitals, in which the gastroenterologists were members of the Research Committee of Inflammatory Bowel Disease. Eligible cases were patients who were newly diagnosed with UC in those hospitals and whose age at diagnosis was less than 80 years. In the case of UC patients referred from neighboring associated hospitals, patients who had been diagnosed within the preceding 3 months were regarded as eligible. Collaborating gastroenterologists were responsible for UC diagnosis, in accordance with the following diagnostic criteria proposed by the Research Committee of Inflammatory Bowel Disease in 2008: patients should have symptoms (or episodes) of persistent/repetitive bloody diarrhea or mucous bloody stool and also characteristic findings of the disease on endoscopy, barium enema study, or histological study; infectious, radiation-induced, ischemic, or granulomatous colitis should be excluded [16]. These patients were asked to participate in the present study as soon as possible after diagnosis.

Two matched controls for each case with UC were sought in the same hospital as the enrolled case of UC. We encouraged collaborating hospitals to select two controls: one from the department of digestive diseases, and the other from another department (i.e., orthopedic surgery, internal medicine, ophthalmology, dermatology, otolaryngology, etc.). Conditions for matching were gender and age (within the same 5-year age group, as follows: 10–14 years, 15–19 years, 20–24 years, 25–29 years, and so on). Exclusion criteria were follows: presence of malignant neoplasm; lasting symptoms of diarrhea and/or abdominal pain for more than 1 week; or history of inflammatory bowel disease. Each collaborating hospital was asked to provide two sets of these cases and controls every year.

The study protocol was approved by the ethics committees at Osaka City University Faculty of Medicine and Tokyo Medical and Dental University, and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to participation. In cases where the subject was less than 20 years old, written informed consent was obtained from the subject's legal representative.

Information Collection

The following clinical findings of UC patients were reported by the gastroenterologists-in-charge using a standardized questionnaire: date at symptom onsets; date at first visit to the hospital; disease severity at diagnosis (mild, moderate, severe, or fulminant); location of disease at diagnosis (rectum, colon, cecum, or ileum); and parenteral complications. Afterwards, age at symptom onset, duration from symptom onset to recruitment, and duration from first visit to the hospital to recruitment were calculated from the date of birth, date at symptom onset, date at first visit to the hospital and recruitment date. Disease severity, based on the criteria proposed by the Research Committee of Inflammatory Bowel Disease, was regarded as "mild" when the frequency of defecation was 4 times/day or less, bloody diarrhea or mucous bloody stool was absent or minimal, and systemic symptoms were absent, as "severe" when the frequency of defecation was 6 times/day or more, severe bloody diarrhea or mucous bloody stool was present, and systemic symptoms (fever, tachycardia, anemia, etc.) were apparent, and as "moderate" when the features were intermediate between "mild" and "severe". In particular, patients with "severe" disease and those showing extremely severe symptoms (bloody stools of about 15 times/day or more, persistent high fever of 38°C or higher, increase in leukocyte count to 10,000/mm^3 or more, and severe abdominal pain) were classified as having "fulminant" disease [16].

In addition, study subjects were asked to fill out a set of 2 self-administered, mail-back questionnaires. One questionnaire was used to obtain information about demographic factors, past medical history including appendicitis, family history of UC, smoking (never, ever, or current), alcohol drinking (never, ever, or current), and, for females, menopausal status and use of exogenous female hormones including oral contraceptives and hormone-replacement therapy.

The other questionnaire was a validated self-administered diet-history questionnaire (DHQ), which assessed dietary habits during the previous 1 month. In this instrument, estimates of daily consumption for a total 150 food items, energy, and selected nutrients were calculated using an ad hoc computer algorithm for the DHQ. Detailed descriptions of the methods used for calculating dietary consumption and the validity of the DHQ have been published elsewhere [17–20]. In this questionnaire, the frequencies of intake for 6 soy products (tofu, tofu products such as deep-fried tofu and fried bean curd, fermented soybeans, boiled soybeans, miso, and miso soup) were asked, and daily consumptions for each food item were estimated. Total consumption of soy products was considered as the sum of these 6 food items. Isoflavone consumption from these soy products, which included daidzein and genistein, was estimated according to previously published studies [21,22]. In the present study, the sum of daidzein and genistein consumptions was regarded as the isoflavone consumption. If study subjects answered that they had changed their dietary habits within 1 year, we asked for further information about their dietary habits at 1 year before recruitment using the same questionnaire. Previous studies have demonstrated that retrospective recall of dietary intake for the distant past using a self-administered food frequency questionnaire yielded moderate correlation coefficients with the original reports at that time, in terms of both dietary and nutrient consumptions [23,24].

Statistical Analysis

Energy-adjusted intake by the density method was used for the analyses. The chi-square test, Wilcoxon rank-sum test and Student's t-test were used to compare characteristics between cases and controls. Intakes of selected foods and nutrients were

Table 1. Clinical characteristics in patients with newly diagnosed ulcerative colitis (N = 126).*

Characteristics		n (%)
Age (years)	Mean (SD)	41.2 (14.6)
	<30	30 (24)
	30–39	33 (26)
	40–49	31 (25)
	50+	32 (25)
Age at symptom onsets (years)	Mean (SD)	41.2 (14.8)
	<30	24 (27)
	30–39	20 (22)
	40–49	23 (26)
	50+	23 (26)
	Unknown	36
Duration from symptom onsets (months)	Median (range)	2.4 (0–276)
	<4	59 (66)
	4–11	21 (23)
	12+	10 (11)
	Unknown	36
Duration from first visit to the hospital (months)	Median (range)	1.2 (0–651.6)
	<4	104 (85)
	4–11	14 (11)
	12+	4 (3)
	Unknown	4
Disease severity	Mild	35 (40)
	Moderate	37 (42)
	Severe	16 (18)
	Fulminant	0 (0)
	Unknown	38
Location of disease	Rectum	19 (22)
	Colon	39 (44)
	Cecum	27 (31)
	Ileum	3 (3)
	Unknown	38
Parenteral complications	Present	1 (1)
	Unknown	40

SD, standard deviation.
*Data expressed as n (%) unless otherwise indicated.
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categorized into tertiles according to the distribution of control subjects. Logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for UC development. Trends for association were assessed by assigning ordinal scores to a single dietary variable. Variables showing p-values less than 0.1 or that seemed likely to correlate with isoflavone consumption were considered as potential confounders for adjustment.

In addition, to examine gender-specific associations between isoflavone consumption and UC development, stratified analyses by gender were also conducted. When we assessed associations in females, menopausal status and use of exogenous female hormones were also considered as potential confounders.

All tests were two-sided. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

Results

Among the 150 UC cases and 206 controls enrolled, 126 cases and 170 controls responded to the questionnaire (response rates, 84% for cases and 83% for controls). The voluntary participation of study subjects thus resulted in some variations in matched status. Although 44 sets (44 cases and 88 controls) maintained the initial matching condition, 38 cases had only one matched control each, and 44 cases and 44 controls had no corresponding counterparts for pairing. Thus, to increase the statistical power, further main analyses were conducted in all 126 cases and 170 controls who responded to the questionnaire, using unconditional logistic regression model with adjustment for matching factors (age categories and gender).

Table 1 shows the clinical characteristics of the newly diagnosed UC cases. Mean age at recruitment was 41.2 years. About 90% of

Table 2. Characteristics of the 126 cases and 170 controls.

Variables		Cases	Controls	P †
		n (%)*	n (%)*	
Age (years)	<30	30 (24)	36 (21)	0.39
	30–39	33 (26)	41 (24)	
	40–49	31 (25)	43 (25)	
	50+	32 (25)	50 (29)	
Gender	Male	73 (58)	89 (52)	0.34
	Female	53 (42)	81 (48)	
Body mass index (kg/m^2)	<21.0	67 (53)	58 (34)	0.001
	21.0–23.6	32 (25)	55 (32)	
	23.7+	27 (21)	57 (34)	
History of appendicitis	Present	8 (6)	29 (17)	0.006
Family history of ulcerative colitis	Present	9 (7)	5 (3)	0.09
Smoking habit	Never	63 (50)	98 (58)	0.003
	Ever	45 (36)	32 (19)	
	Current	18 (14)	40 (24)	
Drinking habit	Never	34 (27)	61 (36)	0.01
	Ever	25 (20)	14 (8)	
	Current	67 (53)	95 (56)	
Age at menarche (years)	Mean (SD)	12.7 (1.4)	12.7 (1.6)	0.76
Postmenopausal status	Present	13/53 (25)	26/81 (32)	0.35
Age at menopause (years)	Mean (SD)	50.2 (5.8)	48.3 (6.3)	0.24
	Unknown	0	2	
Use of exogenous female hormones	Ever	8/52 (15)	17/79 (22)	0.38
	Unknown	1	2	
Dietary intake during the previous 1 month[§]				
Total energy (kJ)	Mean (SD)	8590 (2761)	8541 (3314)	0.43
Total soy product (g/4184 kJ)	Mean (SD)	24.7 (17.8)	19.3 (14.8)	0.001
Tofu (g/4184 kJ)	Mean (SD)	13.7 (10.9)	9.9 (9.5)	0.001
Tofu product (g/4184 kJ)	Mean (SD)	0.9 (1.9)	1.0 (1.9)	0.15
Fermented soybeans (g/4184 kJ)	Mean (SD)	4.3 (6.2)	3.8 (6.2)	0.28
Boiled soybeans (g/4184 kJ)	Mean (SD)	1.7 (2.4)	1.7 (2.8)	0.66
Miso (g/4184 kJ)	Mean (SD)	1.3 (7.7)	0.4 (0.9)	0.71
Miso soup (g/4184 kJ)	Mean (SD)	2.9 (3.2)	2.5 (2.6)	0.40
Isoflavone (mg/4184 kJ)	Mean (SD)	13.6 (10.1)	11.1 (9.4)	0.005
Daidzein (mg/4184 kJ)	Mean (SD)	5.2 (3.8)	4.2 (3.5)	0.005
Genistein (mg/4184 kJ)	Mean (SD)	8.5 (6.3)	6.9 (5.8)	0.005
Dietary intake at 1 year before[§]				
Total energy (kJ)	Mean (SD)	8859 (2837)	8624 (3451)	0.12
Total soy product (g/4184 kJ)	Mean (SD)	22.8 (17.6)	19.3 (14.7)	0.04
Tofu (g/4184 kJ)	Mean (SD)	11.8 (10.4)	10.2 (9.9)	0.11
Tofu product (g/4184 kJ)	Mean (SD)	0.8 (1.5)	1.1 (1.9)	0.20
Fermented soybeans (g/4184 kJ)	Mean (SD)	4.4 (6.4)	3.5 (6.1)	0.13
Boiled soybeans (g/4184 kJ)	Mean (SD)	1.8 (2.6)	1.6 (2.6)	0.20
Miso (g/4184 kJ)	Mean (SD)	1.3 (7.7)	0.4 (0.9)	0.71
Miso soup (g/41841kJ)	Mean (SD)	2.7 (2.6)	2.5 (2.6)	0.36
Isoflavone (mg/4184 kJ)	Mean (SD)	13.0 (10.1)	10.9 (9.1)	0.02

Table 2. Cont.

Variables		Cases	Controls	P †
		n (%)*	n (%)*	
Daidzein (mg/4184 kJ)	Mean (SD)	4.9 (3.8)	4.1 (3.4)	0.02
Genistein (mg/4184 kJ)	Mean (SD)	8.1 (6.3)	6.7 (5.6)	0.02

SD, standard deviation.
*Data expressed as n (%) unless otherwise indicated.
†The χ^2 test or Wilcoxon rank-sum test were employed where appropriate.
‡Nutrient intake was adjusted for total energy intake using the density method.
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cases had experienced the first symptoms of disease within the preceding 11 months. About 40% suffered from mild disease, whereas 18% had severe disease.

As for controls, we confirmed that they were derived from the departments of digestive diseases and other departments, at a ratio of approximately 1 to 1. The most frequent digestive disease was liver diseases (n = 36), followed by upper digestive diseases (n = 24) and colon diseases (n = 19). The most frequent disease from other departments was orthopedic disease (n = 26), followed by ophthalmologic disease (n = 7), chronic renal disease (n = 7), and others (n = 51).

Table 2 shows the background characteristics of study subjects. Age and gender distributions were similar between cases and controls. However, cases had a lower body mass index, less frequent history of appendicitis, but more frequent family history of UC than controls. In addition, significant differences were identified in smoking and drinking habits. Regarding dietary intake, cases consumed a higher total amount of soy products than controls, for assessments of both the previous 1 month and at 1 year before recruitment. In addition, isoflavone consumption including daidzein and genistein was also higher in cases both during the previous 1 month and at 1 year before.

After adjustment for potential confounders, consumption of total soy products during the previous 1 month revealed a significantly increased OR in the highest tertile (Table 3). The association was significantly dose-respondent (Trend P = 0.007). Among individual soy products, only tofu consumption showed a significantly higher OR in the highest tertile (OR = 1.98; 95%CI, 1.06–3.70). As for nutrients, higher isoflavone consumption (both daidzein and genistein) was associated with increased ORs with a trend towards (OR in highest tertile = 2.79; 95%CI, 1.39–5.59; Trend P = 0.004). Associations with isoflavone remained significant even for the assessment of consumption at 1 year before recruitment, although the OR in the highest tertile of isoflavone consumption was somewhat lower than that during the previous 1 month (OR = 2.06; 95%CI, 1.05–4.04; Trend P = 0.04). To exclude the possibility of reverse causality even in the assessment of dietary habits at 1 year before, sensitivity analyses were conducted, with analyzed UC cases limited to those patients who experienced the first symptom within the preceding 11 months (80 cases, 170 controls). However, the results were almost unchanged (OR in highest tertile of isoflavone consumption at 1 year before = 2.66; 95%CI, 1.18–6.03; Trend P = 0.021). When we examined the association between isoflavone consumption and localization of UC, the association was more clearly observed for disease reaching the cecum or ileum (OR in highest tertile of isoflavone consumption at 1 year before = 4.60; 95%CI, 1.18–18.0; Trend P = 0.035), but was attenuated for disease located in the rectum only (OR in highest tertile of isoflavone consumption at 1 year before = 2.69; 95%CI, 0.73–9.93; Trend P = 0.110).

Table 4 shows the results of gender-stratified analyses regarding the association between isoflavone consumption and UC development. Increased ORs in highest tertiles were more clearly observed in females. In particular, an association with isoflavone consumption at 1 year before was obviously increased in females (OR in highest tertile = 4.76; 95%CI, 1.30–17.5; Trend P = 0.02) but was obscured in males (the corresponding OR = 1.21; 95%CI, 0.49–3.01; Trend P = 0.63). Increased ORs in females were unchanged even after adjusting for menopausal status and use of exogenous female hormones.

In addition, conditional logistic regression models were employed in which analyzed subjects were limited for the matched sets (82 cases and 126 controls). As a result, the increased ORs of isoflavone consumption at 1 year before were similarly observed, although lower statistical power brought about the broader confidence intervals (OR in highest tertile = 1.94; 95%CI, 0.76–4.98; Trend P = 0.16). In the gender-stratified analyses, we could not obtain meaningful ORs in females, since only 1 case fell into the lowest tertile of isoflavone consumption. When lowest and intermediate tertiles were combined to regard as a reference category, ORs in highest tertile of isoflavone consumption at 1 year before were 0.66 (95%CI, 0.19-2.35) in males and 4.90 (95%CI, 1.18–20.3) in females, respectively.

Discussion

The results of the present case-control study showed a possible association between higher isoflavone consumption and development of UC. The association was detected in dietary habits during the previous 1 month, as well as those at 1 year before. Since most UC cases had not experienced their first symptom of UC at 1 year before recruitment, isoflavone consumption at 1 year before seemed to represent an association with pre-illness dietary habits, although the association with dietary habits during the previous 1 month might have included some influence of changes in habits due to disease symptoms.

No previous studies have indicated associations between dietary isoflavone consumption and UC development. Since isoflavones, particularly genistein, show similar binding ability for estrogen receptor β to 17β-estradiol [13,14] and exert estrogenic activity in some organs [25,26], it is reasonable to consider that isoflavone consumption might be associated with UC development through similar mechanisms to estrogens. After an estrogen binds to estrogen receptor β in the gut, colonic barrier function is modified [27,28], which might trigger inappropriate mucosal immune responses. Higher estrogen doses might also cause gastrointestinal ischemia by increasing the tendency for intravascular coagulation [29]. In addition, mucosal inflammation in patients with UC is mediated by Th-2-related cytokines [30,31], which might offer another plausible biological mechanism for the effect of estrogen.

Table 3. Odds ratios of soy product intake and isoflavone intake for development of ulcerative colitis.

Variables	During the previous 1 month				1 year before			
	Tertile			P for trend	Tertile			P for trend
	1 (lowest)	2	3 (highest)		1 (lowest)	2	3 (highest)	
Total soy product								
Daily intake (g/4184 kJ)*	<11.3	11.3–21.8	21.9+		<11.1	11.1–22.2	22.3+	
No. cases/controls	27/57	37/56	62/57		30/57	45/56	51/57	
Crude OR (95%CI)	1.00	1.40 (0.75–2.59)	2.30 (1.28–4.11)	0.004	1.00	1.53 (0.85–2.76)	1.70 (0.95–3.04)	0.08
Multivariate OR (95%CI)†	1.00	1.32 (0.67–2.60)	2.45 (1.25–4.79)	0.007	1.00	1.51 (0.79–2.89)	1.80 (0.92–3.53)	0.09
Tofu								
Daily intake (g/4184 kJ)*	<4.68	4.68–10.85	10.86+		<4.6	4.6–11.4	11.5+	
No. cases/controls	31/57	32/56	63/57		35/57	43/56	48/57	
Crude OR (95%CI)	1.00	1.05 (0.57–1.95)	2.03 (1.16–3.58)	0.01	1.00	1.25 (0.70–2.23)	1.37 (0.78–2.42)	0.28
Multivariate OR (95%CI)†	1.00	0.89 (0.45–1.75)	1.98 (1.06–3.70)	0.02	1.00	1.12 (0.59–2.11)	1.29 (0.69–2.43)	0.43
Tofu product								
Daily intake (g/4184 kJ)*	0	0.001–1.66	1.67+		0	0.01–1.62	1.63+	
No. cases/controls	84/94	18/38	24/38		80/91	20/39	26/40	
Crude OR (95%CI)	1.00	0.53 (0.28–0.99)	0.71 (0.39–1.28)	0.12	1.00	0.58 (0.32–1.08)	0.74 (0.42–1.32)	0.18
Multivariate OR (95%CI)†	1.00	0.59 (0.30–1.17)	0.66 (0.34–1.27)	0.13	1.00	0.70 (0.36–1.37)	0.69 (0.36–1.32)	0.20
Fermented soybeans								
Daily intake (g/4184 kJ)*	0	0.01–3.47	3.48+		0	0.01–3.12	3.13+	
No. cases/controls	39/67	46/51	41/52		36/67	47/51	43/52	
Crude OR (95%CI)	1.00	1.55 (0.88–2.72)	1.36 (0.77–2.39)	0.28	1.00	1.72 (0.97–3.02)	1.54 (0.87–2.73)	0.14
Multivariate OR (95%CI)†	1.00	1.53 (0.83–2.83)	1.41 (0.75–2.67)	0.27	1.00	1.65 (0.89–3.06)	1.61 (0.85–3.06)	0.13
Boiled soybeans								
Daily intake (g/4184 kJ)*	0	0.01–1.72	1.73+		0	0.01–1.604	1.605+	
No. cases/controls	48/67	35/51	43/52		40/64	38/53	48/53	
Crude OR (95%CI)	1.00	0.96 (0.54–1.69)	1.15 (0.67–2.00)	0.62	1.00	1.15 (0.65–2.04)	1.45 (0.83–2.53)	0.19
Multivariate OR (95%CI)†	1.00	0.93 (0.49–1.75)	1.12 (0.60–2.09)	0.74	1.00	1.12 (0.59–2.10)	1.51 (0.80–2.83)	0.21
Miso								
Daily intake (g/4184 kJ)*	0	0.01–1.374	1.375+		0	0.01–1.374	1.375+	
No. cases/controls	97/134	15/18	14/18		97/134	15/18	14/18	
Crude OR (95%CI)	1.00	1.15 (0.55–2.40)	1.07 (0.51–2.27)	0.76	1.00	1.15 (0.55–2.40)	1.07 (0.51–2.27)	0.76
Multivariate OR (95%CI)†	1.00	1.62 (0.73–3.60)	1.28 (0.54–3.02)	0.35	1.00	1.62 (0.73–3.60)	1.28 (0.54–3.02)	0.35
Miso soup								
Daily intake (g/4184 kJ)*	<1.009	1.009–2.97	2.98+		<0.98	0.98–2.80	2.81+	
No. cases/controls	33/57	52/56	41/57		31/57	51/56	44/57	
Crude OR (95%CI)	1.00	1.60 (0.91–2.84)	1.24 (0.69–2.24)	0.50	1.00	1.68 (0.94–2.99)	1.42 (0.79–2.56)	0.27
Multivariate OR (95%CI)†	1.00	1.42 (0.76–2.66)	1.23 (0.64–2.38)	0.54	1.00	1.33 (0.70–2.50)	1.47 (0.76–2.84)	0.25
Isoflavone								
Daily intake (mg/4184 kJ)*	<6.0	6.0–12.2	12.3+		<6.01	6.01–12.06	12.07+	
No. cases/controls	25/57	42/56	59/57		28/57	45/56	53/57	
Crude OR (95%CI)	1.00	1.71 (0.92–3.17)	2.36 (1.30–4.28)	0.005	1.00	1.64 (0.90–2.98)	1.89 (1.05–3.40)	0.04
Multivariate OR (95%CI)†	1.00	1.78 (0.91–3.50)	2.79 (1.39–5.59)	0.004	1.00	1.75 (0.91–3.38)	2.06 (1.05–4.04)	0.04
Daidzein								
Daily intake (mg/4184 kJ)*	<2.28	2.28–4.66	4.67+		<2.26	2.26–4.5	4.6+	
No. cases/controls	25/57	42/56	59/57		28/57	45/56	53/57	
Crude OR (95%CI)	1.00	1.71 (0.92–3.17)	2.36 (1.30–4.28)	0.005	1.00	1.64 (0.90–2.98)	1.89 (1.05–3.40)	0.04
Multivariate OR (95%CI)†	1.00	1.74 (0.89–3.42)	2.73 (1.37–5.46)	0.005	1.00	1.73 (0.90–3.36)	2.04 (1.04–4.01)	0.04
Genistein								

Table 3. Cont.

Variables	During the previous 1 month				1 year before			
	Tertile			P for trend	Tertile			P for trend
	1 (lowest)	2	3 (highest)		1 (lowest)	2	3 (highest)	
Daily intake (mg/4184 kJ)*	<3.7	3.7–7.6	7.7+		<3.7	3.7–7.45	7.46+	
No. cases/controls	25/57	43/56	58/57		28/57	45/56	53/57	
Crude OR (95%CI)	1.00	1.75 (0.95–3.24)	2.32 (1.28–4.21)	0.006	1.00	1.64 (0.90–2.98)	1.89 (1.05–3.40)	0.04
Multivariate OR (95%CI)†	1.00	1.83 (0.94–3.59)	2.72 (1.36–5.46)	0.005	1.00	1.75 (0.91–3.37)	2.06 (1.05–4.07)	0.04

OR, odds ratio; CI, confidence interval.
*Tertiles were based on intake in g/4184 kJ or mg/4184 kJ adjusted for energy intake using the density method.
†Adjusted for age, gender, body mass index, history of appendicitis, family history of ulcerative colitis, smoking and alcohol drinking status.
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Although the precise pathophysiology of UC remains largely unknown, these estrogen-mediated pathways might play roles in the association between isoflavone consumption and development of UC.

In the present study, gender-stratified analyses indicated that the association with isoflavone consumption was more pronounced in females, but was obscured in males, suggesting that the influence of isoflavone consumption on UC differs across gender. In light of previous studies, one experimental study also demonstrated that perinatal exposure to exogenous estrogens promoted the development of severe intestinal inflammation, particularly among adult female offspring, but not among male offspring [27]. Estrogen-mediated pathways might thus act to promote the development of intestinal inflammation, specifically among females. However, isoflavones exert a wide range of effects as demonstrated in ex vivo model systems and in animals. This already complex picture is further complicated by the fact that pathogenetically relevant in vitro or ex vivo findings do no correlate with the effects of isoflavones in animal models of inflammation [32]. Further epidemiological and experimental studies are thus needed to confirm these findings.

The present study design offered several methodological advantages. First, cases were identified using strict diagnostic criteria and thus the possibility of misclassification of UC was negligible. Second, use of incident cases (newly diagnosed UC patients) minimized the probability of poor recall about pre-illness dietary habits. In addition, to assess the association with pre-illness dietary habits as precisely as possible, we collected information regarding: 1) dietary information on both the previous 1 month and at 1 year before; and 2) the time of first symptom occurrence. This information allowed us to consider the association from several aspects, and sensitivity analyses, in which analyzed UC cases were limited to patients who experienced their first symptom within the preceding 11 months, provided results in which any positive association with isoflavone consumption would be free from reverse causality. Third, the large variation in isoflavone consumption among Japanese individuals allowed the examination of associations between isoflavones and UC, although generalizability to other ethnic groups is uncertain. In fact, daily isoflavone consumption at 1 year before among the present study subjects ranged from 0.01 mg to 138.9 mg (mean daily consumption, 23.6 mg), representing a wider range than seen in other ethnic groups, including US adults (mean daily consumption, 2.6 mg) [33].

However, the following limitations might have influenced the study results. Although response rates among cases and controls were high (84%), non-respondents brought about some variation in matched status, and then provided results with lower power when using conditional logistic regression models limited to matched sets. However, the proportion of non-respondents was similar in both cases and controls, and was considered unrelated to isoflavone consumption. This selection bias might thus have attenuated the association between isoflavone consumption and UC. Second, information bias resulting from imperfect recall of past consumption of soy products might have occurred. However, the hypothesis that soy products are related to UC or inflammatory bowel disease was not recognized by study participants. Thus, all subjects would have received similar recall stimuli about past consumption of soy products. Misclassification due to such information bias, if any, is probably non-differential and would not affect the plausibility of the results. Third, it is also conceivable that other life style characteristics might account for the increasing effects of isoflavone consumption. Although the present results were obtained after adjusting for potential confounders (e.g., body mass index, smoking, and menopausal status) according to the previous study [34], other uncontrolled factors might have affected the validity of our results.

Here, it is important to note that while higher consumption of isoflavones may increase the risk of UC development, the benefits of isoflavones to females may still remain substantial. Several reports have indicated favorable effects of isoflavone intake for decreasing the incidences of breast cancer [35], lung cancer [36] and cerebral or myocardial infarctions [37] and the prevalence of periodontal disease [38]. A major issue is thus the balance between positive and negative health effects of isoflavones. The level of UC risk associated with isoflavone consumption might be rather low. We think that it may be important for clinicians to discuss the possible risks and benefits of isoflavone consumption, especially for females with a family history of UC.

In conclusion, pre-illness isoflavone consumption might be associated with UC development, particularly in females. Prospective cohort studies are needed to confirm these findings.

Table 4. Odds ratios of isoflavone intake for development of ulcerative colitis, stratified by gender.

Variables	During the previous 1 month				1 year before			
	Tertile			P for trend	Tertile			P for trend
	1 (lowest)	2	3 (highest)		1 (lowest)	2	3 (highest)	
Isoflavone								
OR (95%CI) in male*	1.00	1.50 (0.66–3.38)	2.15 (0.86–5.38)	0.099	1.00	1.27 (0.57–2.87)	1.21 (0.49–3.01)	0.63
OR (95%CI) in female*	1.00	2.44 (0.61–9.67)	4.43 (1.21–16.3)	0.02	1.00	3.29 (0.85–12.7)	4.76 (1.30–17.5)	0.02
OR (95%CI) in female†	1.00	2.53 (0.64–10.1)	4.61 (1.26–16.9)	0.02	1.00	3.06 (0.79–11.8)	4.44 (1.20–16.4)	0.03
Daidzein								
OR (95%CI) in male*	1.00	1.54 (0.68–3.47)	2.05 (0.83–5.08)	0.11	1.00	1.17 (0.51–2.65)	1.16 (0.47–2.90)	0.72
OR (95%CI) in female*	1.00	2.19 (0.56–8.65)	4.08 (1.14–14.6)	0.02	1.00	3.64 (0.95–14.0)	5.03 (1.38–18.3)	0.02
OR (95%CI) in female†	1.00	2.25 (0.57–8.93)	4.21 (1.18–15.1)	0.02	1.00	3.41 (0.89–13.1)	4.71 (1.29–17.2)	0.02
Genistein								
OR (95%CI) in male*	1.00	1.57 (0.70–3.53)	2.01 (0.80–5.09)	0.13	1.00	1.23 (0.55–2.77)	1.27 (0.51–3.20)	0.58
OR (95%CI) in female*	1.00	2.44 (0.61–9.67)	4.43 (1.21–16.3)	0.02	1.00	3.48 (0.90–13.4)	4.56 (1.25–16.7)	0.03
OR (95%CI) in female†	1.00	2.53 (0.64–10.1)	4.61 (1.26–16.9)	0.02	1.00	3.25 (0.84–12.6)	4.24 (1.15–15.6)	0.04

OR, odds ratio; CI, confidence interval.

*Adjusted for age, body mass index, history of appendicitis, family history of ulcerative colitis, smoking and alcohol drinking status.

†Further adjusted for menopausal status and use of exogenous female hormones.

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References

1. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A (2011) Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 140:1785–1794.
2. Japan Intractable Diseases Information Center (2013) The number of inflammatory bowel disease patients authorized to receive financial aid by prefectural governments in Japan from 1975 to 2008. Available: http://www.nanbyou.or.jp/entry/62. Accessed 2013 Aug 27.
3. Asakura K, Nishiwaki Y, Inoue N, Hibi T, Watanabe M, et al. (2009) Prevalence of ulcerative colitis and Crohn's disease in Japan. J Gastroenterol 44:659–665.
4. Podolsky DK (2002) Inflammatory bowel disease. N Engl J Med 347:417–429.
5. Kuwahara E, Asakura K, Nishiwaki Y, Inoue N, Watanabe M, et al. (2012) Effects of family history on inflammatory bowel disease characteristics in Japanese patients. J Gastroenterol 47:961–968.
6. Kitahora T, Utsunomiya T, Yokota A (1995) Epidemiological study of ulcerative colitis in Japan: incidence and familial occurrence. The Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan. J Gastroenterol 30:S5–8.
7. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S (2006) Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 81:1462–1471.
8. Koutroubakis IE, Vlachonikolis IG (2000) Appendectomy and the development of ulcerative colitis: results of a metaanalysis of published case-control studies. Am J Gastroenterol 95:171–176.
9. Loftus EV Jr (2004) Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 126:1504–1517.
10. Godet PG, May GR, Sutherland LR (1995) Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. Gut 37:668–673.
11. Cornish JA, Tan E, Simillis C, Clark SK, Teare J, et al. (2008) The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. Am J Gastroenterol 103:2394–2400.
12. Khalili H, Higuchi LM, Ananthakrishnan AN, Manson JE, Feskanich D, et al. (2012) Hormone therapy increases risk of ulcerative colitis but not Crohn's disease. Gastroenterology 143:1199–1206.
13. Nikov GN, Hopkins NE, Boue S, Alworth WL (2000) Interactions of dietary estrogens with human estrogen receptors and the effect on estrogen receptor-estrogen response element complex formation. Environ Health Perspect 108:867–872.
14. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, et al. (1998) Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β. Endocrinology 139:4252–4263.
15. Cooke PS, Selvaraj V, Yellayi S (2006) Genistein, estrogen receptors, and the acquired immune response. J Nutr 136:704–708.
16. Hibi T, Ueno F, Matsuoka K, Lee TC, Research Group for Intractable Inflammatory Bowel Disease 2006 (2010) Guidelines for the management of ulcerative colitis in Japan-Developed through integration of evidence and consensus among experts-. IBD Research 4:189–239.
17. Sasaki S, Yanagibori R, Amano K (1998) Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. J Epidemiol 8:203–215.
18. Sasaki S, Ushio F, Amano K, Morihara M, Todoriki T, et al. (2000) Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. J Nutr Sci Vitaminol 46:285–296.
19. Kobayashi S, Murakami K, Sasaki S, Okubo H, Hirota N, et al. (2011) Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16d dietary records in Japanese adults. Public Health Nutr 14:1200–1211.
20. Kobayashi S, Honda S, Murakami K, Sasaki S, Okubo H, et al. (2012) Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. J Epidemiol 22:151–159.
21. Arai Y, Watanabe S, Kimira M, Shimoi K, Mochizuki R, et al. (2000) Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr 130:2243–2250.
22. Miyake Y, Sasaki S, Ohya Y, Miyamoto S, Matsunaga I, et al (2005) Soy, isoflavones, and prevalence of allergic rhinitis in Japanese women: the Osaka Maternal and Child Health Study. J Allergy Clin Immunol 115:1176–83.
23. Wu ML, Whittemore AS, Jung DL (1988) Errors in reported dietary intakes. Am J Epidemiol 128:1137–1145.
24. Byers T, Marshall J, Anthony E, Fiedler R, Zielezny M (1987) The reliability of dietary history from the distant past. Am J Epidemiol 125;999–1011.
25. Messina MJ (1999) Legumes and soybeans: overview of their nutritional profiles and health effects. Am J Clin Nutr 70:439S–450S.

26. Bingham SA, Atkinson C, Liggins J, Bluck L, Coward A (1998) Phyto-oestrogens: where are we now? Br J Nutr 79:393–406.
27. Braniste V, Jouault A, Gaultier E, Polizzi A, Buisson-Brenac C, et al. (2010) Impact of oral bisphenol A at reference doses on intestinal barrier function and sex differences after perinatal exposure in rats. Proc Natl Acad Sci USA 107:448–453.
28. Looijer-van Langen M, Hotte N, Dieleman LA, Albert E, Mulder C, et al. (2011) Estrogen receptor-β signaling modulates epithelial barrier function. Am J Physiol Gastrointest Liver Physiol 300:G621–626.
29. Gomes MP, Deitcher SR (2004) Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. Arch Intern Med 164:1965–1976.
30. Fuss IJ, Heller F, Boirivant M, Leon F, Yoshida M, et al. (2004) Nonclassical CD 1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. J Clin Invest 113:1490–1497.
31. Heller F, Florian P, Bojarski C, Richter J, Christ M, et al. (2005) Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. Gastroenterology 129:550–564.
32. Oswald E, Sesarman A, Franzke CW, Wolfle U, Bruckner-Tuderman L, et al. (2012) The flavonoid luteolin inhibits Fcγ-dependent respiratory burst in granulocytes, but not skin blistering in a new model of pemphigoid in adult mice. PLoS One 7:e31066.
33. Nechuta SJ, Caan BJ, Chen WY, Lu W, Chen Z, et al. (2012) Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am J Clin Nutr 96:123–132.
34. Wu AH, Stanczyk FZ, Seow A, Lee HP, Yu MC (2002) Soy intake and other lifestyle determinants of serum estrogen levels among postmenopausal Chinese women in Singapore. Cancer Epidemiol Biomarkers Prev 11:844–851.
35. Yamamoto S, Sobue T, Kobayashi M, Sasaki S, Tsugane S for the Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Diseases (JPHC Study) Group (2003) Soy, isoflavones, and breast cancer risk in Japan. J Natl Cancer Inst 95:906–913.
36. Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Sawada N, et al for the JPHC Study Group (2011) Plasma isoflavones and the risk of lung cancer in women: a nested case-control study in Japan. Cancer Epidemiol Biomarkers Prev 20:419–427.
37. Kokubo Y, Iso H, Ishihara J, Okada K, Inoue M, et al. (2007) Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation 116:2553–2562.
38. Tanaka K, Sasaki S, Murakami K, Okubo H, Takahashi Y, et al for the Freshmen in Dietetic Courses Study II Group (2008) Relationship between soy and isoflavone intake and periodontal disease: the Freshmen in Dietetic Courses Study II. BMC Public Health 8:39.

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RAPID COMMUNICATION

The 2nd edition of consensus statements for the diagnosis and management of intestinal Behçet's disease: indication of anti-TNFα monoclonal antibodies

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Abstract
Background Clinical evidence regarding intestinal Behçet's disease (BD) management is lacking and intestinal lesions are a poor prognostic factor. In 2007, the Japan consensus statement for diagnosis and management of intestinal BD was developed. Recently, the efficacy of anti-tumor necrosis factor (TNF)α monoclonal antibodies (mAbs), and infliximab (IFX) was reported and adalimumab (ADA) was approved for intestinal BD in Japan. This study renewed consensus-based practice guidelines for diagnosis and treatment of intestinal BD focusing on the indication of anti-TNFα mAbs.
Methods An expert panel of Japanese gastroenterology and rheumatology specialists was involved. Clinical statements for ratings were extracted from the literature, a professional group survey, and by an expert panel discussion, which rated clinical statements on a nine-point scale. After the first round of ratings, a panelist meeting discussed areas of disagreement and clarified areas of uncertainty. The list of clinical statements was revised after the panelist meeting and a second round of ratings was conducted.
Results Fifteen relevant articles were selected. Based on the first edition consensus statement, improved clinical statements regarding indications for anti-TNFα mAbs use were developed. After a two-round modified Delphi approach, the second edition of consensus statements was finalized.
Conclusions In addition to standard therapies in the first edition, anti-TNFα mAbs (ADA and IFX) should be considered as a standard therapy for intestinal BD. Colchicines, thalidomide, other pharmacological therapy,

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endoscopic therapy, and leukocytapheresis were deemed experimental therapies.

Keywords Intestinal Behçet's disease · Anti-TNFα mAb · Consensus statements

Abbreviations

ADA	Adalimumab
BD	Behçet's disease
CRP	C-reactive protein
IFX	Infliximab
mAb	Monoclonal antibody
TNF	Tumor necrosis factor

Introduction

Behçet's disease (BD) is a chronic relapsing disease with multiple organ system involvement characterized clinically by oral and genital aphthae, cutaneous lesions, and ophthalmological, neurological, or gastrointestinal manifestations [1, 2]. Approximately 3–16 % of patients with BD have gastrointestinal tract involvement. Gastrointestinal disease typically affects the ileocecal area, although involvement of the esophagus and small intestine has been reported [3]. The most common gastrointestinal symptoms are abdominal pain, diarrhea, and bleeding. Deep ulcers are responsible for the most common intestinal complications, such as severe bleeding and perforation [4]. Various drugs, such as 5-aminosalicylic acid (5-ASA), systemic corticosteroids, and immunosuppressive agents have been used anecdotally to treat intestinal BD. However, the clinical evidence regarding the management of intestinal BD is very limited. In 2007, the Japanese Inflammatory Bowel Disease Research Group, supported by the Japanese Ministry of Health, Labour and Welfare, proposed consensus statements for the management of intestinal BD for the first time [5]. In this consensus, infliximab (IFX) was described as an optional therapy for intestinal BD. In recent years, accumulating evidence on the efficacy of anti-TNFα agents for the management of Crohn's disease and Behçet's uveitis have encouraged the use of anti-TNFα agents for management of intestinal BD. Although clinical studies with high-quality evidence have not been available, several cases of intestinal BD successfully treated by anti-TNFα agents have been reported [6–14]. These case reports mainly showed clinical efficacy in the short term, although some reports showed mid- and long-term efficacy and improved endoscopic findings [15, 16]. Furthermore, on May 16 2013, adalimumab (ADA) was approved as a therapeutic option for intestinal BD in Japan. Currently, the Research Committee for small bowel inflammation of unknown etiology operated by the Health Labour Sciences Research Grant, titled "Research on Measures for Intractable Diseases", was concerned that the approval of anti-TNFα mAb could dramatically change the therapeutic strategy for intestinal BD. Furthermore, the first edition does not contain information regarding anti-TNFα mAbs and is, therefore, outdated. Therefore, consensus statements for the management of intestinal BD should be adjusted to the current clinical settings, especially regarding the indication of anti-TNFα agents (Table 1).

Methods

An overview of the study

The development of the second edition of consensus statements for the diagnosis and management of intestinal BD consisted of three phases. In brief, in the first phase, literature that reported the efficacy of anti-TNFα monoclonal antibodies (mAbs) in intestinal BD were collected by survey using PubMed with the following key words: "intestine", "Behçet's disease", "anti-TNF", "infliximab" and "adalimumab". In addition, results of a questionnaire-based investigation on the actual treatment situation of intestinal BD by infliximab performed by the Japanese Study Group for a project on Research on Measures for BD operated by the Japanese Ministry of Health, Labour and Welfare in 2012 were referred to. During the second phase, expert panelists discussed areas of disagreement and areas of uncertainty regarding improvements of statements from the first edition and revised some of the clinical statements. During the third phase, the revised clinical statements were rated. Ratings of appropriate methods were developed using a modified Delphi approach, where members of the expert panel rated each part of the statements using a nine-point scale from 9 to 1 (9, strongly agree; 1, strongly disagree). Consensus was defined as a median score of ≥ 7, if the difference between the highest score and lowest score

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Table 1 Consensus statements for the diagnosis and management of intestinal Behçet's disease (second edition), by Research Committee for small bowel inflammation of unknown etiology, and Behçet's Disease Research Committee, Ministry of Health, Labour, and Welfare, Japan

Concept of the second edition of consensus statements

According to increased use of anti-TNFα mAb in inflammatory bowel disease, many cases of intestinal Behçet's disease in which anti-TNFα mAb (infliximab, IFX) showed efficacy also have been reported in Japan. The same tendency was observed in foreign countries that have a high prevalence of Behçet's disease, such as Korea. In 2013, adalimumab, humanized anti-TNFα mAb was approved for intestinal Behçet's disease in Japan. In the second edition, statements have focused on where we should place anti-TNFα mAb for the treatment of intestinal Behçet's disease based on relevant literature and expert panel discussion.[a]

Diagnosis

1. Diagnosis of intestinal Behçet's disease can be made if

   A. There is a typical oval-shaped large ulcer in the terminal ileum, OR

   B. There are ulcerations or inflammation in the small or large intestine, and clinical findings meet the diagnostic criteria of Behçet's disease.[b]

2. Acute appendicitis, infectious enteritis, tuberculosis, Crohn's disease, nonspecific colitis, drug-associated colitis and other diseases that mimic intestinal Behçet's disease should be excluded by clinical findings, radiology, and endoscopy before diagnosis of intestinal Behçet's disease is made.

Assessment of severity

Disease severity should be comprehensively assessed by systemic symptoms (e.g., fever, extra-intestinal manifestations), physical examinations of abdomen (e.g., pain, inflammatory mass, rebound tenderness), depth of ulcers and intestinal complications (e.g., bleeding, stricture, fistula), inflammatory mediators (e.g., CRP, WBC, ESR), and anemia.

Treatment objectives

In the treatment of intestinal Behçet's disease, as well as the improvement of abdominal and extra-intestinal symptoms, the achievement of negative levels of CRP could be desirable. In the long-term prognosis, the prevention of progression to disability and poly-surgery is important.

A. Standard treatment

1. In patients with severe symptoms (i.e., abdominal pain, diarrhea, gastrointestinal bleeding) and complications with deep ulcers confirmed by radiology or endoscopy, corticosteroids should be considered for induction therapy. The initial dose of corticosteroids is 0.5–1 mg/kg per day of prednisolone for l–2 weeks. When clinical improvement is observed, prednisolone should be tapered by 5 mg every week and finally stopped. ADA (approved on May 16, 2013 in Japan) could be considered for induction therapy [160 mg at 0 w, 80 mg at 2 w, 40 mg at 4 w, sub-cutaneously (s.c.)]. In responders, scheduled maintenance therapy should be considered (40 mg s.c. every other week). IFX (not approved yet) could also be considered for induction therapy (5 mg/kg at week 0, 2, and 6). In responders, scheduled maintenance therapy every 8 weeks should be considered. In patients with mild to moderate activity, mesalasine (5-ASA) could be effective for induction therapy. In patients treated with corticosteroids, anti-TNFα mAbs and immunomodulators, infectious disease and neoplasm should be surveyed. After initiation of these therapies, the risk of infectious disease and neoplasm should be monitored continuously.
2. In patients who are induced to clinical remission, 5-ASA and colchicine could be used for maintenance therapy. The optimal dose of 5-ASA for adult patients is 2.25–3 g/day. When sulfasalazine (SASP) is used, the optimal dose is 3–4 g/day.
3. Immunosuppressive agents such as azathioprine (AZA)[c] are indicated when patients are corticosteroid-dependent, corticosteroid-resistant, or anti-TNFα mAb-resistant. The initial dose of AZA is 25–50 mg/day. In patients treated with AZA, adverse effects (e.g., neutropenia and liver dysfunction) should be monitored.
4. Total parenteral nutrition (TPN) is indicated for patients with severe systemic symptoms such as fever and for patients with intestinal complications such as stenosis, fistula, bleeding, and impending perforation. TPN is also indicated for patients who cannot orally intake drugs due to severe oral or upper gastro intestinal lesions. It is usually used for a limited period of time considering the risk of catheter infection and thrombosis. After the patient's condition is improved by TPN, enteral nutrition (EN) could be considered.
5. EN using an elementary diet could be effective for induction therapy. It is indicated in particular for patients with refractory disease, severe activity, and disability such as stricture lesions. When EN is introduced, adherence and quality of life of the patients should be considered.
6. Surgery is indicated for patients in whom improvement is not expected by medications. Patients with severe stricture lesions, perforations, large abscesses, and massive gastrointestinal bleedings have an absolute indication. Patients refractory to medications, and with a low quality of life due to intestinal complications such as fistula, have a relative indication of surgery. Minimum length of resection surgery should be considered.
7. Risk of post-operative recurrence is high in patients with volcano shape deep ulcers and fistulas. Post-operative recurrence often occurs at anastomosis. Although a treatment strategy has not been established that can reduce the risk of post-operative recurrence, considering the high risk of post-operative recurrence and poly surgeries, medication by 5-ASA, immunomodulators, metronidazole, anti-TNFα mAb and EN could be considered for post-operative management.
8. In patients with intestinal Behçet's disease complicated with eye lesions, consultation with ophthalmologists is necessary for their management

B. Optional treatment

- Since there are some case reports showing that spraying of absolute ethanol via endoscope has efficacy for ulcers of intestinal Behçet's, it could be considered in refractory patients.

Table 1 continued

- Expecting the efficacy as an anti-rheumatoid arthritis drug, change from 5-ASA to SASP could be considered in patients with arthritis (especially peripheral arthritis).

The authors state that, (1) most of the consensus statements are based on expert opinions, (2) the consensus statements have not been endorsed by any organizations, (3) the consensus statements need to be prospectively reevaluated, (4) the consensus statements do not cover histopathological diagnosis, and (5) the consensus statements do not have any binding force.

[a] The majority of literature regarding anti-TNFα therapy in intestinal Behçet's disease that is referred to for establishment of the second edition described the efficacy of infliximab. On May 16 2013, ADA was approved for intestinal Behçet's disease. The clinical trial of infliximab in intestinal Behçet's disease is currently in progress in Japan.

[b] Diagnosis of Behçet's disease is according to the Japanese criteria proposed in 2003.

[c] Immunomodulators besides AZA, including 6-mercaptopurine, cyclosporine, tacrolimus and methotrexate could be considered, but consultations with specialists who have sufficient experience are required. When considering the use of these drugs, adverse effects should be monitored.

was <4. For the present study, an expert panel composed of gastroenterologists ($n = 6$), gastrointestinal surgeons ($n = 2$), and rheumatologists ($n = 2$) was established. In addition to the expert panel, a moderator (Hisamatsu, T.) and a professional adviser (Ueno, F.) were involved in the study. The moderator organized discussion by the expert panel and moderated the modified Delphi approach. The moderator searched and reviewed the literature and collected clinical statements. The professional adviser surveyed the process of the modified Delphi approach. The second edition of consensus statements proposed by the expert panel was discussed and then recognized by the Research Committee for small bowel inflammation of unknown etiology operated by a Health Labour Sciences Research Grant, Research on Measures for Intractable Diseases, Japan.

Results

Search for literature on intestinal BD and anti-TNFα mAbs

In the first phase, 15 relevant literature items were collected. This literature included 10 case reports, 3 retrospective analyses of more than one patient in a single institute, 1 letter to the editor, and 1 review article ("Appendix"). To date, no randomized controlled trials of anti-TNFα mAbs for the treatment of intestinal BD have been reported.

Development of the second edition of consensus statement

In the second phase, the expert panel discussed the place of anti-TNFα mAb for the treatment of intestinal BD. Based on the literature found, the clinical experience of experts and results of a questionnaire-based investigation, the expert panel agreed that anti-TNFα mAb treatment should be regarded as a standard therapy for intestinal BD, which was an optional treatment in the first edition. With the recognition of anti-TNFα mAb treatment as a standard therapy, the expert panel also discussed the therapeutic goal of intestinal BD. In the second edition, it was proposed that the achievement of negative levels of C-reactive protein (CRP) levels, in addition to the improvement of clinical symptoms, could be desirable as an objective therapeutic goal. The expert panel also proposed that improvement of long-term prognosis such as reducing the risk of surgery should be set as a final goal in the treatment of intestinal BD. Corticosteroid and anti-TNFα mAb were placed as standard therapies, while the expert panel deemed colchicines, thalidomide, endoscopic therapy, and leukocytapheresis to be experimental therapies.

In the first round of the modified Delphi approach, there were no statements with a median score <7. Although median scores were ≥7, three parts of statements did not obtain consensus because the difference between the highest and lowest score was 4. After discussion by the expert panel, the second round was performed, and then consensus was obtained for all statements. Thus, after a two-round modified Delphi approach, the second edition of consensus statements was finalized.

The authors' stated that limitations of the second edition included (1) most of the consensus statements are based on expert opinions, (2) the consensus statements have not been endorsed by any organizations, (3) the consensus statements need to be prospectively reevaluated, (4) the consensus statements do not cover histopathological diagnosis, and, (5) the consensus statements do not have any binding force.

Discussion

BD involves multiple organs, including the eye, nervous system, skin, genitalia, and gastrointestinal tract. About

3–16 % of patients with BD have gastrointestinal tract involvement [3], while most clinical studies of BD published to date concern the management of mucocutaneous lesions and ophthalmological lesions. However, intestinal BD often causes severe gastrointestinal complications, such as massive bleeding and perforation; therefore, intestinal lesions should be considered a poor prognostic factor. Even in high-prevalence areas such as Japan, Korea, the Middle East, and the Mediterranean region, intestinal BD has been treated empirically because data from the literature regarding management of this condition are scant. The consensus of expert opinion in a high-prevalence area should, therefore, be extremely helpful in daily practice. With this background, the first edition of a consensus for the management of intestinal BD was proposed for the first time in 2007 [5]. However, even after its proposal, conventional therapies have been insufficient for the management of intestinal BD. In the current clinical setting, anti-TNFα mAbs have been used to treat patients with intestinal BD. Reports demonstrating the efficacy of anti-TNFα mAbs for the management of intestinal BD are increasing. Furthermore, ADA was approved for intestinal BD in 2013 after an open-label clinical trial in Japan. With this in mind, it was considered that the first edition of the consensus statement should be updated.

The first edition was established in 2007 by the Japanese Inflammatory Bowel Disease Research Group. In 2011, the Research Committee for small bowel inflammation of unknown etiology was established independently from the Japanese Inflammatory Bowel Disease Research Group. To avoid changes in expert panel members affecting the results, some members of the first edition joined the expert panel of the second edition, which also had discussions with the Behçet's Disease Research Committee as well as the first edition expert panel. Finally, the second edition was evaluated and approved by the Research Committee for small bowel inflammation of unknown etiology composed of experts for gastrointestinal disorders including members of the first edition.

The modified Delphi approach used in the second edition also provided panelists with the opportunity to discuss their judgments between the rating rounds as well as in the first edition. Unfortunately, there is not much evidence for the management of intestinal BD. Therefore, the discussion by the expert panel must make practical consensus statements rather than be a simple rating method. In the process for improving the second edition of the consensus statement, several subjects were discussed. First, the expert panel discussed the validity of the efficacy of anti-TNFα mAb therapy in intestinal BD. To date, no clinical trial for anti-TNFα mAb therapy in intestinal BD with high-quality evidence such as a double-blind, randomized, placebo-controlled trial has been reported. Therefore, the expert panel relied on their clinical experience and clinical case reports. All members agreed that anti-TNFα mAb therapy is effective for intestinal BD. Second, the expert panel discussed where anti-TNFα mAb therapy should be placed in the treatment of intestinal BD. Although anti-TNFα mAb therapy was considered an option therapy in the first edition in 2007 [5], the expert panel recommended anti-TNFα mAb as a standard therapy in the second edition. Third, according to the recommendation of anti-TNFα mAb as a standard therapy, the expert panel discussed whether the goals for medication of intestinal BD should be addressed. The expert panel was concerned about the overuse of anti-TNFα mAb without any objective parameters. Unfortunately, practical clinical activity indexes for intestinal BD (e.g., Crohn's disease activity index for Crohn's disease) have not been established. Endoscopic mucosal healing was also discussed, but it was not agreed on because of the lack of evidence in the literature and an impractical setting. Although evidence that CRP is a practical biomarker to assess disease activity of intestinal BD is insufficient, several reports suggested that CRP could reflect disease activity and disease prognosis [17]. In addition, in Crohn's disease, negative CRP levels are considered a therapeutic goal as well as endoscopic mucosal healing by biologics therapy. In this context, the expert panel proposed "treatment objectives" that were not in the first edition and recommended the monitoring of CRP.

The problems that now confront us are the safety monitoring of anti-TNFα mAb use and the determination of whether anti-TNFα mAb treatment can improve the long-term prognosis of intestinal BD by prospective observation.

Conclusions

The second edition of consensus statements for the diagnosis and management of intestinal BD was established. In the second edition, anti-TNFα mAb treatment was recognized and recommended as a standard therapy for the treatment of intestinal BD.

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Conflict of interest Tadakazu Hisamatsu received a research grant from Ajinomoto Pharmaceuticals CO., LTD. and received lecture fees from Abbvie.

Appendix: literature list of intestinal Behçet's disease and anti-TNFα mAbs treatment

- Travis SP, Czajkowski M, McGovern DP, Watson RG, Bell AL. Treatment of intestinal Behçet's syndrome with chimeric tumour necrosis factor alpha antibody. Gut. 2001;49(5):725–8.
- Hassard PV, Binder SW, Nelson V, Vasiliauskas EA. Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behçet's disease: a case report. Gastroenterology. 2001;120(4):995–9.
- Kram MT, May LD, Goodman S, Molinas S. Behçet's ileocolitis: successful treatment with tumor necrosis factor-alpha antibody (infliximab) therapy: report of a case. Dis Colon Rectum. 2003;46(1):118–21.
- Pipitone N, Olivieri I, Cantini F, Triolo G, Salvarani C. New approaches in the treatment of Adamantiades-Behçet's disease. Curr Opin Rheumatol. 2006;18(1): 3–9. Review.
- Byeon JS, Choi EK, Heo NY, Hong SC, Myung SJ, Yang SK, Kim JH, Song JK, Yoo B, Yu CS. Antitumor necrosis factor-alpha therapy for early postoperative recurrence of gastrointestinal Behçet's disease: report of a case. Dis Colon Rectum. 2007;50(5):672–6.
- Ju JH, Kwok SK, Seo SH, Yoon CH, Kim HY, Park SH. Successful treatment of life-threatening intestinal ulcer in Behçet's disease with infliximab: rapid healing of Behçet's ulcer with infliximab. Clin Rheumatol. 2007;26(8):1383–5.
- Lee JH, Kim TN, Choi ST, Jang BI, Shin KC, Lee SB, Shim YR. Remission of intestinal Behçet's disease treated with anti-tumor necrosis factor alpha monoclonal antibody (infliximab). Korean J Intern Med. 2007;22(1):24–7.
- Ugras M, Ertem D, Celikel C, Pehlivanoglu E. Infliximab as an alternative treatment for Behçet disease when other therapies fail. J Pediatr Gastroenterol Nutr. 2008;46(2):212–5.
- Naganuma M, Sakuraba A, Hisamatsu T, Ochiai H, Hasegawa H, Ogata H, Iwao Y, Hibi T. Efficacy of infliximab for induction and maintenance of remission in intestinal Behçet's disease. Inflamm Bowel Dis. 2008;14(9):1259–64.
- Ariyachaipanich A, Berkelhammer C, Nicola H. Intestinal Behçet's disease: maintenance of remission with adalimumab monotherapy. Inflamm Bowel Dis. 2009;15(12):1769–71.
- Iwata S, Saito K, Yamaoka K, Tsujimura S, Nawata M, Suzuki K, Tanaka Y. Effects of anti-TNF-alpha antibody infliximab in refractory entero-Behçet's disease. Rheumatology (Oxford). 2009;48(8):1012–3.
- Kaneko U, Kishi T, Kikuchi M, Hara R, Shinoki T, Miyamae T, Imagawa T, Mori M, Yokota S. Two patients with childhood-onset Behçet's disease successfully treated by anti-tumor necrosis factor therapy. Nihon Rinsho Meneki Gakkai Kaishi. 2010;33(3): 157–61. (In Japanese).
- Donghi D, Mainetti C. Infliximab for the treatment of refractory Adamantiades-Behçet disease with articular, intestinal, cerebral and ocular involvement. Dermatology. 2010;220(3):282–6.
- Iwata S, Saito K, Yamaoka K, Tsujimura S, Nawata M, Hanami K, Tanaka Y. Efficacy of combination therapy of anti-TNF-α antibody infliximab and methotrexate in refractory entero-Behçet's disease. Mod Rheumatol. 2011;21(2):184–91.
- Maruyama Y, Hisamatsu T, Matsuoka K, Naganuma M, Inoue N, Ogata H, Iwao Y, Kanai T, Hibi T. A case of intestinal Behçet's disease treated with infliximab monotherapy who successfully maintained clinical remission and complete mucosal healing for six years. Intern Med. 2012;51(16):2125– 9.

References

1. Garton RA, Ghate JV, Jorizzo JL. Behçet's disease. In: Harris Jr ED, Budd RC, Genovese MC, Firestein GS, Sargent JS, Sledge CB, editors. Textbook of rheumatology. 7th ed. Philadelphia: Saunders; 2005.
2. Krause I, Weinberger A. Behçet's disease. Curr Opin Rheumatol. 2008;20(1):82–7 (Review).
3. Sakane T, Takeno M, Suzuki N, Inaba G. Current concepts: Behçet disease. New Eng J Med. 1999;341:1284–91.
4. Brandt LJ, Boley SJ. Intestinal ischemia. In: Feldman M, Friedman LS, Sleisenger MH, editors. Gastrointestinal and liver disease. 7th ed. Philadelphia: Saunders; 2002.
5. Kobayashi K, Ueno F, Bito S, Iwao Y, Fukushima T, Hiwatashi N, Igarashi M, Iizuka BE, Matsuda T, Matsui T, Matsumoto T, Sugita A, Takeno M, Hibi T. Development of consensus statements for the diagnosis and management of intestinal Behçet's disease using a modified Delphi approach. J Gastroenterol. 2007;42(9):737–45.
6. Travis SP, Czajkowski M, McGovern DP, Watson RG, Bell AL. Treatment of intestinal Behçet's syndrome with chimeric tumour necrosis factor alpha antibody. Gut. 2001;49(5):725–8.
7. Hassard PV, Binder SW, Nelson V, Vasiliauskas EA. Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behçet's disease: a case report. Gastroenterology. 2001;120(4): 995–9.
8. Kram MT, May LD, Goodman S, Molinas S. Behçet's ileocolitis: successful treatment with tumor necrosis factor-alpha antibody (infliximab) therapy: report of a case. Dis Colon Rectum. 2003;46(1):118–21.
9. Byeon JS, Choi EK, Heo NY, Hong SC, Myung SJ, Yang SK, Kim JH, Song JK, Yoo B, Yu CS. Antitumor necrosis factor-

alpha therapy for early postoperative recurrence of gastrointestinal Behçet's disease: report of a case. Dis Colon Rectum. 2007;50(5):672–6.
10. Lee JH, Kim TN, Choi ST, Jang BI, Shin KC, Lee SB, Shim YR. Remission of intestinal Behçet's disease treated with anti-tumor necrosis factor alpha monoclonal antibody (infliximab). Korean J Intern Med. 2007;22(1):24–7.
11. Ju JH, Kwok SK, Seo SH, Yoon CH, Kim HY, Park SH. Successful treatment of life-threatening intestinal ulcer in Behçet's disease with infliximab: rapid healing of Behçet's ulcer with infliximab. Clin Rheumatol. 2007;26(8):1383–5.
12. Ugras M, Ertem D, Celikel C, Pehlivanoglu E. Infliximab as an alternative treatment for Behçet disease when other therapies fail. J Pediatr Gastroenterol Nutr. 2008;46(2):212–5.
13. Naganuma M, Sakuraba A, Hisamatsu T, Ochiai H, Hasegawa H, Ogata H, Iwao Y, Hibi T. Efficacy of infliximab for induction and maintenance of remission in intestinal Behçet's disease. Inflamm Bowel Dis. 2008;14(9):1259–64.
14. Donghi D, Mainetti C. Infliximab for the treatment of refractory Adamantiades-Behçet disease with articular, intestinal, cerebral and ocular involvement. Dermatology. 2010;220(3):282–6.
15. Iwata S, Saito K, Yamaoka K, Tsujimura S, Nawata M, Hanami K, Tanaka Y. Efficacy of combination therapy of anti-TNF-α antibody infliximab and methotrexate in refractory entero-Behçet's disease. Mod Rheumatol. 2011;21(2):184–91.
16. Maruyama Y, Hisamatsu T, Matsuoka K, Naganuma M, Inoue N, Ogata H, Iwao Y, Kanai T, Hibi T. A case of intestinal Behçet's disease treated with infliximab monotherapy who successfully maintained clinical remission and complete mucosal healing for six years. Intern Med. 2012;51(16):2125–9.
17. Jung YS, Cheon JH, Park SJ, Hong SP, Kim TI, Kim WH. Clinical course of intestinal Behçet's disease during the first five years. Dig Dis Sci. 2013;58(2):496–503.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Long-term incidence and characteristics of intestinal failure in Crohn's disease: a multicenter study

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Abstract
Background The aim of this study was to clarify the risk and characteristics of intestinal failure (IF) in patients with Crohn's disease (CD).
Methods The present study was a retrospective study in 12 hospitals. CD patients who underwent initial surgery at any of the 12 hospitals between 1970 and 2009 were collected ($n = 1{,}703$). Those who developed IF were reviewed ($n = 68$), and the cumulative risk of IF was analyzed by the Kaplan–Meier method. In addition, IF patients who underwent initial surgery at other hospitals and were then treated at any of the 12 hospitals were also reviewed ($n = 33$). Thus, a total of 101 IF patients were collected, and the cumulative risk of IF-related death was analyzed.
Results The cumulative risk of IF after the initial surgery was 0.8 % (5 years), 3.6 % (10 years), 6.1 % (15 years), and 8.5 % (20 years). In CD patients with IF, mean age at initial surgery, IF occurrence, and present age at the time of the study were 28.2, 38.2, and 46.1 years, respectively. The mean number of surgeries per patient was 3.3. The mean length of the remnant small bowel was 163 cm. Twelve IF patients (12 %) had died and the cumulative risk of IF-related death by the time from the occurrence of IF was 1.1 % (3 years), 3.7 % (5 years), 6.5 % (7 years), and 8.9 % (10 years).

The present study was performed as a project study under the Surgical Research Group, the Research Committee of Inflammatory Bowel Disease, Ministry of Health, Labour and Welfare of Japan.

A portion of the data from the present study was presented as a symposium session at the 112th Annual Congress of Japan Surgical Society, April 12–14, 2012, Makuhari, Japan.

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