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Risk factors for developing colorectal cancer in Japanese patients with ulcerative colitis: a retrospective observational study—CAPITAL (Cohort and Practice for IBD total management in Kyoto-Shiga Links) study I

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ABSTRACT

Background and Aims: Patients with ulcerative colitis (UC) are at risk for developing colorectal cancer (CRC), despite the development of new therapeutic agents. Stratification of the individual UC-patient's risk would be helpful to validate the risk factors for CRC. The aim of this study was to evaluate the risk factors for the development of CRC in a large cohort of patients with UC.

Methods: Data were obtained from 12 hospitals in the Kyoto-Shiga region during 2003–2013. We performed a retrospective cohort study of 2137 patients with UC.

Results: In total, 60 lesions of CRC were detected in 43 (2.0%) of 2137 patients. 30 of the 43 patients were male. The median age was 53 years. The median duration of disease was 13 years, and 67.4% of these patients had a disease duration >10 years. Of the 43 patients, 34 (79.1%) had extensive colitis. Primary sclerosing cholangitis was detected in 2 patients (4.7%). The median corticosteroids (CS) dose was 6.4 g, and 4 patients were treated with a total of more than 10 g of CS. 18 of these patients underwent more than 1 year CS treatment. Of all 60 CRC lesions, 43 (71.7%) were located in the distal colon and 35 (58.3%) were of the superficial type. Moreover, the stage of CRC was stage 0 or I in 55.8% of the 43 patients with CRC. Multivariate analysis suggested that extensive colitis could be a risk factor for the development of advanced CRC in patients with UC.

Conclusions: Our findings indicated that male, extensive colitis, long-term duration of UC and family history of CRC, but not concomitant primary sclerosing cholangitis, are important factors for predicting CRC in Japanese patients with UC. Moreover, long-standing extensive colitis might contribute to the progression of CRC. Further studies are required to establish CRC surveillance in Japanese patients with UC.

Summary box

What is already known about this subject?

- Colorectal cancer (CRC) surveillance is very important for patients with ulcerative colitis (UC).
- Previous papers reported that early-age onset of UC, family history of CRC, sulfa allergy, concomitant primary sclerosing cholangitis, clinical activity and backwash ileitis are predictive factors of CRC in Western countries.
- CRC surveillance, however, has not yet been established.

What are the new findings?

- Our data indicated that male, extensive colitis, long-term duration of UC and family history of CRC, but not concomitant primary sclerosing cholangitis, are important factors for predicting CRC in Japanese patients with UC.
- Moreover, patients with UC with extensive colitis were at high risk for developing advanced CRC.
- No difference in time to the previous colonoscopy was found between patients with UC with advanced CRC and those with non-advanced CRC.

How might it impact on clinical practice in the foreseeable future?

- To detect CRC at an early stage, colonoscopic surveillance based on the individual risk for CRC should be established imperatively. Colonoscopic surveillance alone, however, might be not enough to detect CRC at an early stage. Therefore, monitoring molecular markers involved in developing CRC in patients with UC should be incorporated into colonoscopic surveillance in the future.

BACKGROUND

The increasing number of Japanese patients with ulcerative colitis (UC) has brought to light several clinically important issues, such as refractoriness to conventional therapy, escalation of medical costs due to long-term treatment, and the appearance of colorectal cancer (CRC).[1 2] CRC is a particularly clinically important issue of UC management because it accounts for ~10–15% of all deaths in patients with inflammatory bowel disease (IBD).[3 4] In addition, a population-based study demonstrated that the mean age of patients with UC at CRC diagnosis is 15–20 years younger than that in a control group.[5–8] To detect CRC at an early stage, therefore, surveillance for CRC is required. However, the promising surveillance strategy for CRC has not yet been established.

To establish the optimal surveillance system for CRC, several predictive and protective factors associated with the development of CRC should be investigated, and patients with UC at high risk for developing CRC should be identified. Many studies from Western countries, including meta-analyses and case–control studies, reported that early-age onset of UC, family history of CRC, sulfa allergy, concomitant primary sclerosing cholangitis (PSC), clinical activity and backwash ileitis are predictive factors of CRC.[9–13] Those risk factors for CRC based on Western data, however, are not necessarily suitable for Asian patients with UC, because the clinical and genetic characteristics of patients with UC in Asian countries differ from those in Western countries.[14–16] Thus, an Asian-origin surveillance strategy for CRC in patients with UC should be established.

For CRC surveillance, scheduled colonoscopic surveillance based on individual risk for CRC is very important.[17 18] Recent papers reported that chromoendoscopy and colonoscopy using a narrow band imaging system could be useful for the early diagnosis of CRC in patients with UC.[19–22] Although it is well recognised that colonoscopic surveillance is effective for detecting CRC, it remained unclear whether surveillance colonoscopy could prolong survival in patients with UC. Despite performing scheduled colonoscopic surveillance at a short interval, advanced CRC was detected in patients with UC in a clinical practice.[23] According to that clinical experience, the colonoscopic surveillance alone is not enough to detect CRC at an early stage in patients with UC. Some clinical factors might be involved in the progression of CRC in patients with UC, and identifying those factors would be useful for establishing the optimal CRC surveillance in patients with UC.

Hence, we evaluated the clinical characteristics of CRC in Japanese patients with UC and the difference in those factors between the advanced and non-advanced CRC groups to establish an Asian-origin surveillance of CRC.

METHODS

Patients

We retrospectively analysed 2137 patients with UC treated as inpatients or outpatients between 2003 and 2013 at Kyoto University Hospital, University Hospital, Kyoto Prefectural University of Medicine, Shiga University of Medical Science Hospital, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto Second Red Cross Hospital, Oki Clinic, Obata Medical Clinic, Japanese Red Cross Otsu Hospital, National Hospital Organization of Kyoto Medical Center, Kyoto Katsura Hospital, National Hospital Organization of Higashi-Ohmi Medical Center and Kogawa Internal Medicine Clinic in the Kyoto-Shiga region. The diagnosis of UC was based on clinical features, as well as endoscopic and histopathological findings. In all hospitals, surveillance colonoscopy was scheduled at 1–2 year intervals. At surveillance colonoscopy, performing targeting biopsy or non-targeting biopsy was the physician's independent decision.

Evaluation of clinical characteristics of patients with UC with CRC

Data on clinical characteristics including demographics and disease characteristics were collected from the patient's clinical records in a cross-sectional analysis. The disease onset and estimated onset of disease were defined as the timing of diagnosing UC and the onset of clinical symptoms related to UC retrospectively. In addition, data regarding colitis-related proctocolectomy and grade of CRC were collected. We classified patients with UC with CRC into two groups based on the American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) staging seventh edition, a non-advanced group (stage 0–I), and an advanced group (stage II A–IV B).[24] We compared the patients' characteristics between these two groups.

Ethics

This retrospective multicentre study was conducted in accordance with the principles of the Declaration of Helsinki, and reviewed and approved by the Institutional Review Board of Kyoto University Hospital (E2292). The other hospital institutional review boards relied on this approval. Owing to the retrospective multicentre cohort study over a decade, we could not obtain informed consent from all patients for their clinical records to be used in this study. Therefore, the clinical records of patients were anonymised and de-identified prior to analysis.

Statistical analysis

Statistical analysis was performed using StatView software (SAS, Cary, North Carolina, USA). Categorical and continuous data were compared using a two-tailed Fisher exact test, χ^2 test and Mann-Whitney U test. To perform multivariate analysis of risk factors for developing advanced CRC, 'age', 'disease duration' and 'extensive

colitis', which were suggested by univariate analysis, were analysed by logistic regression. A p value of <0.05 was considered statistically significant.

RESULTS

Patient's characteristics

In 43 (2.0%) of 2137 patients with UC, 60 CRCs were observed. The CRC detection rate in each hospital was as follows: Kyoto University (2.13%), Kyoto Prefectural University (2.67%), Shiga University of Medical Science Hospital (2.7%), Japanese Red Cross Kyoto Daiichi Hospital (2.0%), Kyoto Second Red Cross Hospital (2.27%), Oki Clinic (0%), Obata Medical Clinic (0%), Japanese Red Cross Otsu Hospital (2.0%), Kyoto Medical Center (1.82%), Kyoto Katsura Hospital (0.63%), Higashi-Ohmi Medical Center (0%) and Kogawa Internal Medicine Clinic (3.26%). Table 1 summarises the data on age, gender and stage at time of CRC diagnosis for the 43 patients with UC with CRC. Of these 43 patients with UC, 28 were male. The median age was 53 years (range 28–74 years), and the median age at diagnosis of UC was 33 years (15–72 years). The median duration of disease was 13.0 years (0–40 years), and 29 (67.4%) of the 43 patients had UC for more than 10 years. Of the 43 patients with UC with CRC, 34 (79.1%) had extensive colitis and 8 (18.6%) had left-sided colitis; 5 (11.6%) had a family history of UC, 3 (7.0%) had a family history of CRC, 37 (86.0%) had no family history of CRC, and 3 (7.0%) had an unclear family history. The number of current smokers, past smokers and never smokers was 3 (7.0%), 12 (27.9%) and 22 (51.2%), respectively. The smoking history of the remaining six patients (14.0%) was unclear. Two patients had PSC (4.7%).

Of the 43 patients with CRC, 37 (86.0%) were treated with 5-aminosalicylic acid (5-ASA). Of those 37, 24 (64.9%) were treated with 5-ASA for more than 10 years. Of the 43 patients, 26 (60.5%) had received corticosteroid (CS) therapy, and of these 26, 18 (69.2%) were treated with CS for more than 1 year. The median total dosage of CS was 6.4 g (0–30 g). Among the 18 patients treated with CS for more than 1 year, 4 (22.2%) received more than 10 g of CS. Of the 43 patients, 10 (23.3%) had a history of treatment with immunomodulators. Five (50.0%) of the 10 patients were treated with immunomodulator for more than 4 years. Four patients (9.3%) were treated with biologics. Four (9.3%) received non-steroidal anti-inflammatory drugs.

Characteristics of CRC

More than half of all CRCs were located at the distal side of the colon (sigmoid colon: 18 (30.0%), rectum: 17 (28.3%); table 2). The number of CRCs located at the caecum, ascending colon, transverse colon and descending colon were 5 (8.3%), 6 (10.0%), 6 (10.0%) and 8 (13.3%), respectively. With regard to the

Table 1 Patient's characteristics

Gender (male/female)	28/15
Age (median)	53 (28–74)
Age at diagnosis of UC (median)	33 (15–72)
Disease duration (year) (median)	13.0 (0–40)
The number of patients who had disease duration of more than 10 years	29 (67.4%)
Time to previous colonoscopy (months) (median)	14.0 (1–72)
Extent of disease (%)	
Extensive colitis	34 (79.1)
Left-sided colitis	8 (18.6)
Unclear	1 (2.3)
Family history of UC (%)	
Yes	5 (11.6)
None	36 (83.7)
Unknown	2 (4.7)
Family history of CRC	
Yes	3 (7.0)
None	37 (86.0)
Unknown	3 (7.0)
Tobacco	
Current smoker	3 (7.0)
Past smoker	12 (27.9)
Never smoker	22 (51.2)
Unknown	6 (14.0)
Concomitant PSC (%)	2 (4.7)
Duration of treatment with 5-ASA (%)	
Naïve	3 (7.0)
Within 1 year	2 (4.7)
From 1 to 5 years	5 (11.6)
From 6 to 10 years	6 (14.0)
Over 10 years	24 (55.8)
Unknown	3 (7.0)
Duration of treatment with CS (%)	
None	11 (25.6)
Within 1 year	8 (18.6)
Over 1 year	18 (41.9)
Unknown	6 (14.0)
Dose of CS (g) (median)	6.4 (0–30)
The number of patients treated with more than 10 g CS (%)	4 (9.3)
Duration of treatment with immunomodulator (%)	
None	18 (41.9)
From 1 to 2 years	2 (4.7)
From 2 to 4 years	3 (7.0)
Over 4 years	5 (11.6)
Unknown	15 (34.9)
Duration of treatment with an anti TNF-α agent (%)	
None	27 (62.8)
From 1 to 2 years	3 (7.0)
Over 2 years	1 (2.3)
Unknown	12 (27.9)
The number of patients treated with NSAIDs (%)	
None	37 (86.0)
Yes	4 (9.3)
Unclear	2 (4.7)

5-ASA, 5-aminosalicylic acid; CRC, colorectal cancer; CS, corticosteroid; NSAIDs, non-steroidal anti-inflammatory drugs; PSC, primary sclerosing cholangitis; TNF-α, tumour necrosis factor-α; UC, ulcerative colitis.

morphological findings, 35 (58.3%) of 60 CRCs were classified as type 0. The number of type 4 and 5 tumours was 11 (18.3%) and 3 (5.0%), respectively. Moreover, the number of type 1, 2 and 3 tumours was 2 (3.3%), 5 (8.3%) and 4 (6.7%), respectively. The median tumour size was 26 mm in diameter. Based on histological findings, 34 (56.7%) of 60 CRCs were classified as well-differentiated carcinoma. The number of moderately and poorly differentiated carcinoma was 12 (20.0%) and 8 (13.3%), respectively. The number of papillary, mucinous and signet ring cell carcinomas was 1 (1.7%), 2 (3.3%) and 1 (1.7%), respectively. According to the stage of cancer by AJCC TNM staging seventh edition, finally, 12 (17.9%) and 12 (17.9%) of 43 patients with CRC were diagnosed with stage 0 and I, respectively. Of the remaining 19 patients, 6 patients with CRC (14.0%) had stage II A–C, 5 (11.6%) had stage III A–C, and 7 (16.3%) had stage IV B. Of the seven patients with distant metastasis, four had peritoneal dissemination. Liver metastasis and lung metastasis were found in 3 and 1 of the 7 patients, respectively. Moreover, one patient had metastasis at the vagina and pelvic wall, and another patient had metastasis at the omentum, seminal vesicle and duodenum.

Table 2 Clinical characteristics of colorectal cancer (CRC)

Location (%)	
Caecum	5 (8.3)
Ascending colon	6 (10.0)
Transverse colon	6 (10.0)
Descending colon	8 (13.3)
Sigmoid colon	18 (30.0)
Rectum	17 (28.3)
Macroscopic findings CRC (%)	
Type 0	35 (58.3)
Type 1	2 (3.3)
Type 2	5 (8.3)
Type 3	4 (6.7)
Type 4	11 (18.3)
Type 5	3 (5.0)
The major axis of CRC (mm) (median)	26 (2–800)
Histological findings of CRC (%)	
Well differentiated	34 (56.7)
Moderately differentiated	12 (20.0)
Poorly differentiated	8 (13.3)
Papillary adenocarcinoma	1 (1.7)
Mucinous adenocarcinoma	2 (3.3)
Signet ring cell carcinoma	1 (1.7)
Unclear	2 (3.3)
TNM classification	
Tumour	
Tx	1 (2.3)
Tis	12 (27.9)
T1	7 (16.3)
T2	7 (16.3)
T3	6 (14.0)
T4a	3 (7.0)
T4b	6 (14.0)
Unclear	1 (2.3)
Nodes	
Nx	2 (4.7)
N0	30 (69.8)
N1	5 (11.6)
N2	5 (11.6)
Unclear	1 (2.3)
Metastasis	
M0	35 (81.4)
M1a	0 (0)
M1b	7 (16.3)
Unclear	1 (2.3)
Stage	
0	12 (17.9)
I	12 (17.9)
II A	4 (9.3)
II B	1 (2.3)
II C	1 (2.3)
III A	1 (2.3)
III B	2 (4.7)
III C	2 (4.7)
IV A	0 (0)
IV B	7 (16.3)
Unclear	1 (2.3)

Difference in the patient characteristics between the non-advanced and advanced groups

We classified 42 patients with CRC based on TNM staging into the following two groups: a non-advanced group (stage 0–I; n=24) and an advanced group (stage II A–IV B; n=18). The remaining one patient was excluded because staging of CRC was unclear. Age at diagnosis of CRC in the non-advanced group was significantly higher than that in the advanced group (table 3, p=0.023). Disease duration was longer and the percentage of patients with UC with extensive colitis was higher in the advanced group than in the non-advanced group, although the difference between the non-advanced and advanced groups was not statistically significant (disease duration: p=0.284, extensive colitis: p=0.055). Moreover, the time to previous colonoscopy for detecting CRC was not significantly different between the non-advanced and advanced groups. To investigate whether or not these clinical variables are risk factors for developing advanced CRC in patients with UC, we analysed the risk factors with multivariate analysis. As shown in table 4, multivariate analysis suggested that extensive colitis could be a risk factor for developing advanced CRC in patients with UC, although there was no statistical significance (relative risk 6.695, p=0.101, 95% CI 0.689 to 65.058).

DISCUSSION

Our cohort data, based on 2137 patients with UC from the Kyoto-Shiga region in Japan collected over a decade, demonstrated that CRC was detected in 2.0% of patients with UC. In accordance with previous Western cohort studies, the current data also demonstrated that male, extensive colitis, long-term disease duration (>10 years), total dose of CS (>10 g) and

Table 3 The difference of clinical factors between non-advanced and advanced group

	Non-advanced group (stage 0 and I) n=24	Advanced group (stage II A–IV B) n=18	p Value
Gender (male/female)	17/7	11/7	0.741
Age (year) (median)	53	50.5	0.023
Disease duration (year) (median)	13	24.5	0.284
Extensive colitis (%)	16 (66.7)	17 (94.4)	0.055
Family history of CRC	1 (4.2)	2 (11.1)	0.387
Concomitant PSC (%)	1 (4.2)	1 (5.5)	0.834
Medication			
Duration of treatment with 5-ASA (%)			
Naïve	1 (4.2)	2 (11.1)	0.489
Within 1 year	0 (0)	2 (11.1)	
From 1 to 5 years	5 (20.8)	0 (0)	
From 6 to 10 years	4 (16.7)	2 (11.1)	
Over 10 years	11 (45.8)	12 (66.7)	
Unknown	3 (12.5)	0 (0)	
Duration of treatment with CS (%)			
None	4 (16.7)	7 (38.9)	0.458
Within 1 year	6 (25.0)	2 (11.1)	
Over 1 year	10 (41.7)	7 (38.9)	
Unknown	4 (16.7)	2 (11.1)	
Dose of CS (g) median (range)	4.3 (1.79–17.0)	16.15 (2.3–30)	0.28
Immunomodulator use (%)	8 (33.3)	4 (22.2)	0.657
Anti TNF-α agents use (%)	3 (12.5)	1 (5.6)	0.623
NSAIDs use (%)	1 (4.2)	2 (11.1)	0.567
Time to previous colonoscopy (months) (median)	13	16	0.735

5-ASA, 5-aminosalicylic acid; CRC, colorectal cancer; CS, corticosteroid; NSAIDs, non-steroidal anti-inflammatory drugs; PSC, primary sclerosing cholangitis; TNF-α, tumour necrosis factor-α.

Table 4 Multivariate analysis of risk factors for developing advanced CRC in patients with UC

	RR	p Value	95% CI	
Age	0.944	0.073	0.885	1.005
Disease duration	1.035	0.333	0.965	1.109
Extensive colitis	6.695	0.101	0.689	65.058

CRC, colorectal cancer; RR, relative risk; UC, ulcerative colitis.

family history of CRC are associated with higher risk of CRC development.

In Western countries, the prevalence rates of CRC in patients with UC range from 0.7% to 3.3%.[25–29] The trend in Asia, which has not been fully investigated, also indicates that the likelihood of CRC is low, ranging from 0.8% to 1.8%.[4 30–33] The difference in the incidence of CRC might be due to several variables, such as geographic, racial differences and therapeutic differences. Our study indicated a CRC incidence of 2.0% in patients with UC whose median duration of disease was 13 years. Judging from a meta-analysis by Eaden *et al* that the cumulative risk of CRC was 2% by 10 years,[6] the incidence of CRC in Japan is likely to be similar to that in Western countries because of (1) the increasing number of patients with UC in Japan and (2) CRC surveillance in patients with UC with a high degree of recognition.

Our data suggested that Japanese patients with UC with CRC were clinically characterised by male, extensive colitis and long-term duration of disease, which is consistent with previous reports.[10 13 29] On the other hand, age, history of smoking, duration of 5-ASA therapy and immunomodulatory drug therapy were not associated with clinical characteristics of patients with UC with CRC. In particular, extensive colitis is a very important factor for risk of developing CRC in patients with UC. The meta-analysis by Eaden *et al* reported that the prevalence rate of CRC in patients with UC with extensive colitis is high compared with the overall prevalence rate of CRC in patients with UC.[6] Several clinical studies demonstrated that the risk of CRC in patients with UC with extensive colitis is high compared with that in those with proctitis.[6 31 34 35] A previous paper also demonstrated that 40% of UC-associated CRC develop in the proximal colon.[31] Our cohort data demonstrated that CRC was located in the distal colon and in the proximal colon. Therefore, colonoscopic surveillance of the total colon should be required for patients with UC with extensive colitis.

The presence of PSC has been suggested to increase the risk of dysplasia and CRC in patients with UC.[36 37] In the initial report from Sweden, the cumulative risk for CRC including dysplasia in patients with UC with concomitant PSC after 10, 20 and 25 years of disease duration was 9%, 31% and 50%, respectively.[36] Recently,

Boonstra *et al* also reported that the cumulative risk for CRC in patients with IBD with concomitant PSC at 10, 20 and 30 years after an IBD diagnosis was 1%, 6% and 13%, respectively.[38] Moreover, a recent paper by Baars *et al* reported that the prevalence rate of concomitant PSC in patients with UC with CRC was 8%.[39] On the other hand, our data showed that the ratio of patients with UC with PSC was only 4.7% of patients with UC with CRC, and the median disease duration of patients with UC with concomitant PSC was 5 years. These data are similar to those of a previous nationwide study from Korea.[31] Compared with recent data from Western countries, the prevalence rate of concomitant PSC was low in Asian patients with UC. Although the incidence ratio of PSC in this cohort could not be directly compared with the previous data in Caucasians, the PSC ratio of patients with UC with CRC in our cohort might reflect the difference in the prevalence of PSC between Asian and Western countries. PSC occurs in ~3–7% of patients with UC,[40–44] and approximately two-thirds of patients with PSC have UC in Western countries,[36 45] while PSC occurs in 2.5% of patients with UC and 34–37% of patients with PSC have IBD in Japan.[46 47] The low prevalence rate of PSC in Japanese patients with UC, however, does not diminish the importance of concomitant PSC as a risk factor for developing CRC in Japanese patients with UC. Despite the low prevalence of PSC in Japanese patients with UC, concomitant PSC should be kept in mind as a risk factor related to development of CRC in patients with UC. To clarify the importance of concomitant PSC in Asian patients with UC as a risk factor for CRC, further prospective cohort data from Asia are needed.

Regarding the stage of CRC in patients with UC, a previous paper reported that more than half of the CRC in patients with CRC was classified as Dukes' A.[48] Moreover, the cumulative 5-year survival rate of patients with UC with Dukes' A CRC was 90.6%. Our cohort study also demonstrated that, as similar to Western data, 57.1% of UC patients with CRC were classified as stage 0–I. In 16.3% of patients with UC with CRC, however, metastasis of CRC was detected. These data are similar to those of previous nationwide studies.[31 49] Although more than half of the CRC in patients with UC was detected at an early stage, ~15% of those were detected at an advanced stage. Therefore, how to detect CRC at an early stage in patients with UC is a clinically important issue for our gastroenterologists.

The recent European Crohn's and Colitis Organisation guidelines proposed that, based on an individual risk profile, CRC surveillance colonoscopy should be performed either every 1–2 years for high-risk cases or every 3–4 years for low-risk cases, beginning 8 years after disease onset in cases of extensive or left-sided UC.[50] In our cohort, we evaluated the differences in the clinical characteristics between patients with UC with non-advanced and advanced CRC. Mean age at CRC diagnosis was younger in the advanced CRC group compared with the non-advanced CRC group. This finding might reflect the previously suggested notion that patients with an onset of UC at a younger age have an increased risk of CRC.[29] Moreover, our multivariate analysis suggested that patients with UC with extensive colitis were at high risk of developing advanced CRC. Of note, there was no difference in time to the previous colonoscopy between the two groups. A recent report from the Netherlands suggested that an inadequate surveillance interval could be a risk factor for CRC.[23] In that report, however, one-third of all CRC cases were found during an adequate surveillance interval.[23] According to our findings and a recent report, colonoscopic surveillance alone might not be satisfactory for detecting CRC at an early stage in patients with UC.

Recent studies suggested that several molecular factors, such as genetic instability, epigenetic alteration, immune response, oxidative stress and microbiota, contribute to the pathogenesis of CRC in patients with UC.[51] Considering the mechanism of developing CRC in UC, molecular alterations in particular, such as genetic alteration including genetic mutations, microsatellite instability, DNA methylation and loss of heterozygosity of p53, would play an important role in the pathogenesis of CRC in patients with UC.[52 53] To detect CRC at an early stage certainly, therefore, those molecular alterations in biopsy specimens taken from colonic mucosa with a targeted biopsy method should be evaluated. There is still no consensus, however, regarding the detection of CRC at an early stage in the clinical management of patients with long-standing UC. Clinically, evaluating the expression of ki67 and p53 in colonic tissue is useful for detecting CRC and dysplasia in patients with UC.[54] Moreover, recent data suggested that an alteration of cyclin-dependent kinase inhibitor p16 is an important early molecular marker of carcinogenic progression in patients with UC.[51 55] Therefore, the combination of colonoscopy and monitoring molecular markers, such as p53, p16, microsatellite instability and alteration of mismatch repair proteins in biopsy specimens, should be considered as surveillance of CRC and dysplasia in patients with UC, although further studies to validate this surveillance are required.

Suppressing mucosal inflammation with anti-inflammatory treatment, such as CS, might be useful for preventing the developing CRC in patients with UC, because chronic inflammation contributes to the development of CRC. Unfortunately, however, a high dose of total lifetime CS was associated with many adverse events. In particular, irreversible side effects, such as cataract, idiopathic osteonecrosis of the femoral head and thoracolumbar compression fractures, have developed in cases administrated a total dose of 10 g of CS.[56 57] Although an excessive dose of CS could induce systemic adverse effects, the effect of CS in the development of CRC in patients with UC remains unclear. Our cohort study demonstrated that 41.9% of patients with

UC with CRC were treated with CS for over 1 year, and four of these patients were treated with more than 10 g of CS. Moreover, the administered dose of CS tended to be larger in patients with UC with advanced CRC compared with those with non-advanced CRC. These data suggested that long-term use of CS could be a risk factor for CRC, particularly the advanced phenotype. Previous papers reported that CS is a protective factor for CRC.[13 58 59] On the other hand, the necessity of steroid treatment reflects the refractoriness of UC with chronically sustained inflammation, which is related to the onset of CRC.[60] Thus, the exact association between the total dose of CS and cancer phenotype remains unclear. In general, many immune surveillance and immunosuppression systems are involved in cancer development.[61 62] CS could affect the development of CRC by changing the activity of CD8 T cells suppressing tumour growth in addition to induction of interleukin 10.[63] In this regard, we speculate that excessive use of CS could lead to the tumour invasion due to immune surveillance.

We deliberately designed this study investigating the overall epidemiology of IBD-related CRC to offset the limitations of a retrospective study. Unfortunately, all of the data could not be obtained from the clinical charts in the participating hospitals. To overcome this issue, further population-based prospective studies are required with a larger number of enrolled patients.

In conclusion, this retrospective study of the Kyoto-Shiga cohort of patients with UC revealed that male, extensive colitis, long-term duration of UC and family history of CRC are important factors for predicting the development of CRC in patients with UC, similar to Western countries. Moreover, long-standing extensive colitis might be involved in the progression of CRC, but colonoscopic surveillance alone could not detect CRC at an early stage. These data suggest that repeat colonoscopy within a short period of time alone is not satisfactory for detecting CRC at an early stage, particularly in a CRC high-risk group, such as those with extensive colitis. Although further studies are required, a new surveillance system incorporating monitoring molecular markers into surveillance colonoscopy for CRC in patients with UC should be established in the future.

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