Similarities and differences in clinical and pathologic features of inflammatory bowel disease-associated colorectal cancer in China and Canada

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Abstract

Background: Colorectal cancer (CRC) has become one of the major life-threatening complications in patients with inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD). This study aimed to explore the clinical-pathologic similarities and differences in the IBD-associated CRC (IBD-CRC) between patients in China and Canada.

Methods: Data of 78 patients with IBD-CRC retrospectively retrieved from two representative medical institutions in Beijing (China) and Calgary (Canada) over the same past 13 years, including 25 (22 UC-associated and three CD-associated) from Beijing group and 53 (32 UC-associated and 21 CD-associated) from Calgary group, were compared with regards to their clinical and pathologic characteristics.

Results: Several known features of IBD-CRC were seen in both groups, including long duration and large extent of colitis, active inflammation background, multifocal lesions, and advanced tumor-node-metastasis stage. Beijing group showed a significantly higher percentage of UC (88.0% *vs.* 60.4%, $P = 0.018$), younger age at diagnosis of CRC (48.6 ± 12.8 years *vs.* 61.6 ± 14.7 years, $P < 0.001$), lower ratio of mucinous adenocarcinoma (7.1% *vs.* 42.4%, $P = 0.001$) compared with Calgary group. None of the Beijing group had concurrent primary sclerosing cholangitis, while 5.7% of Calgary group did. Surveillance colonoscopy favored the detection rate of precancerous lesions (41.4% *vs.*17.0%, $P = 0.002$).

Conclusions: As compared with patients from the Calgary group, the IBD-CRC patients in Beijing group were younger, less CD-associated and had less mucinous features, otherwise they were similar in many common features.

Keywords: Colitis-associated colorectal cancer; Comparative study; Crohn's disease; Inflammatory bowel disease; Ulcerative colitis

Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), has become a global disease, with a plateauing incidence in western countries and an increasing incidence in newly industrialized countries.[1] Colorectal cancer (CRC) is one of the major long-term complications of IBD, especially in patients with long disease duration, large extent of colitis, uncontrolled inflammation, and concurrent primary sclerosing cholangitis (PSC).

With the increasing incidence of IBD in Asia, the IBD-associated CRC (IBD-CRC) has become a challenge subsequently. A recent meta-analysis of UC-associated CRC (UC-CRC) in Asian UC patients found that the overall prevalence of CRC was 0.85% and the risks for CRC were 0.02% at 10 years, 4.81% at 20 years, and 13.91% at 30 years.[2] The data is comparable with the findings from western countries in recent years.[3,4]

It has been known that, as compared with the sporadic CRC, the IBD-CRC tends to present with younger age of onset, multifocal involvement, higher prevalence of mucinous or signet-ring cell carcinoma in histology, advanced tumor-node-metastasis (TNM) stage, and worse prognosis. Frequent surveillance colonoscopy and effective medical treatment to achieve sustainable remission of mucosal inflammation help reduce the risk of colitis-associated

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colorectal neoplasia, which has contributed to the recent decrease of IBD-CRC in western countries.[5]

Interestingly, it is being appreciated that between the western and eastern patients with IBD, their disease phenotypes, care protocols, medication use, and prognosis are not entirely the same.[6,7] Additionally, western countries have a much longer history and more experience in IBD patient care. However, little is known so far about whether the IBD-CRC patients in the two populations show any similarities and differences in the clinic-pathologic features based on comparative study. To explore the possible differences, we have conducted a retrospective comparative study on the clinical and pathologic features of IBD-CRC encountered in two large tertiary medical centers in China and Canada over the past decade.

Methods

Ethical approval

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (No. SK-558) and the Conjoint Health Research Ethics Board of the University of Calgary, respectively. Given the retrospective nature of the study, the requirement of written informed consent was waived.

Patients

The study was initially conducted by two independent groups in Beijing (China) and Calgary (Canada). Data of the patients were retrieved from almost the same period of time, although by different means, as shown in Figure 1.

By searching the patient registration database of the Peking Union Medical College Hospital, a tertiary medical center with over 2000 beds in Beijing, China, we retrieved data of 31 hospitalized patients admitted for surgical treatment for CRC secondary to IBD during the period of January 2004 to May 2017. The patients were largely from regions in northern China, and all were Han Chinese in ethnicity. Chart review was conducted to confirm the diagnoses and the IBD-CRC sequence. In addition to the review of the carcinomas in the surgical resection specimens, the archived patients' past colonoscopy reports and images as well as the related pathologic materials (archived glass slides) were retrospectively reviewed to confirm the pre-existing inflammatory status of bowel (background colitis) and precancerous lesions, with focus in the bowel regions where the cancers occurred. Four patients (three UC, one CD) were excluded later for their lack of evidence of chronic colitis in the background mucosa, and other two UC-CRC patients with clinical TNM staging IVb were excluded because they did not accept colectomy and so the exact pathological staging was not available. In the end, 22 patients with UC-CRC and three with CD-CRC formed the Beijing group for the study.

Meanwhile, by using the Anatomic Pathology database of the Calgary Laboratory Services, the sole pathology laboratory serving the entire Calgary region (Calgary Health Region/Alberta Health Services Calgary Zone) in Canada over the past 30 years, all cases of surgically resected IBD-CRC during the period of January 2004 to December 2017 were searched. The patients were mostly from Calgary and the surrounding regions in Alberta province. Fifty-seven patients in total, hospitalized in three tertiary medical centers (including Foothills Medical Centre, Peter Lougheed Centre, and Rockyview General Hospital, with >2000 beds together) were retrieved. Confirmatory clinical-pathological review of charts, colonoscopic reports, and pathologic materials was also conducted in a similar way. Four patients (two UC, two CD) were excluded due to their lack of evidence of colitis ever found in the regions where the cancers arose. The remaining 53 patients (32 with UC-CRC, 21 with CD-CRC) comprised the Calgary group. Five patients were Hispanics, and the others were all Caucasians.

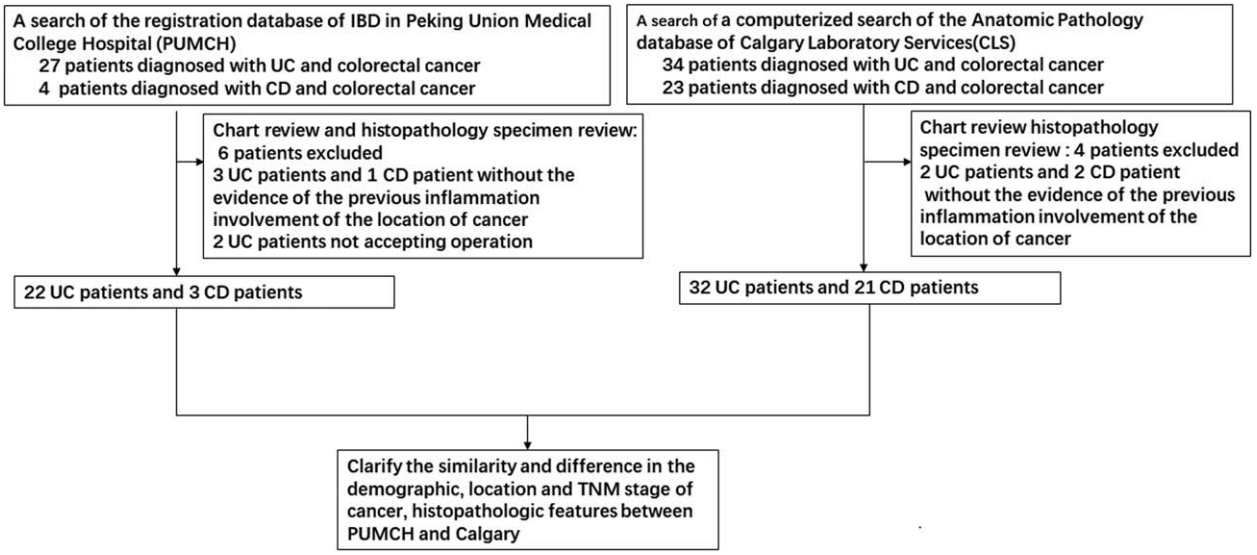

Figure 1: The flowchart of patient enrollment from two medical centers. CD: Crohn's disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

Clinical and pathologic features

For both groups, the demographic characteristics, IBD classification, disease duration (ie, the interval between the time when the diagnosis of IBD was established to the time when the diagnosis of colorectal carcinoma was made for the first time), disease extent by Montreal classification, and concurrence of PSC were collected. The endoscopic findings of previous diagnostic colonoscopies were reviewed by local gastroenterologists. Examples of some representative colonoscopic figures of IBD-CRC were shown in Figure 2.

The records of patients' post-diagnostic colonoscopies over their clinical course until the diagnosis of carcinoma were collected. The colonoscopic surveillance in this study was defined by regular colonoscopies with multiple biopsies every 1 to 2 years at least during the mid and late course of disease prior to the discovery of cancer, which represented the most common practice in the pre-chromoendoscopy era and was basically in principle with the earlier recommendations from an international expert panel and the British Society of Gastroenterology and American Gastroenterology Association,[8-10] although it may not be stringent enough to follow any particular guideline. Those who had never had any, or only occasional colonoscopy between the diagnosis of IBD and CRC, or had multiple colonoscopies with the interval more than 2 years during the mid and late course of disease before the discovery of cancer were categorized into the non-surveillance group.

The pathologic features of both colitis and CRC on colectomy specimens and prior colonoscopic biopsies were reviewed by two experienced gastrointestinal pathologists (WZ in Beijing and XG in Calgary) who communicated to keep consistency in their criteria in the histological assessments. The CRCs were analyzed with regards to the location, histologic type and grade/differentiation, and TNM staging. The regional bowel mucosa with chronic and active inflammation was defined as chronic active colitis in the background. Otherwise, the mucosa with only cytoarchitectural features of chronicity was defined as chronic quiescent colitis. Examples of some representative histopathologic findings were shown in Figure 3. The precancerous lesions detected previously at or adjacent to the cancer sites and elsewhere were also reviewed and analyzed.

Statistical analysis

The continuous variables with normalized distribution were presented as the mean ± standard deviation, and continuous variables with non-normal distribution were presented as median (P25, P75). Differences in the quantitative data between these two groups were statistically examined through univariate analysis using the unpaired Student's *t* test and Mann-Whitney *U* test for normal and non-normal distribution variables, respectively. Categorical variables were presented as numbers and proportions. Fisher exact probability test was conducted to reveal the difference between these two groups for categorical variables. *P* values were two-tailed, and $P < 0.05$ was considered to be statistically significant. All analyses were performed with Statistical Package for Social Sciences (SPSS) version 19 (SPSS Inc., Chicago, IL, USA).

Results

Overall and common features of IBD-CRCs in both groups

As shown in Table 1, 78 patients in total, including 54 UC and 24 CD, were included in the combined groups. Fifty (64.1%) were male. The mean age at diagnosis of CRC was 57.4 ± 15.3 years. The median disease duration was 13.0 years (15.0 years in the Beijing group, and 12.0 years in the Calgary group, in median length). The 3/78 (3.8%) patients had concurrent PSC, and they were all seen in Calgary group (3/53, 5.7%). The 9/78 (11.5%) patients had more than one cancer at different locations. In total 87 cancer lesions were analyzed and all were adenocarcinoma in histology. The 56/87 (64.4%) occurred in left-side colon (including descending colon and sigmoid colon) and rectum. Although the number of cancers in right-side colon (including cecum, ascending colon, and transverse colon) in Calgary group appeared higher than that in Beijing group, the difference did not reach the statistical significance (of note, in Calgary group 3 carcinomas that seemingly arose in terminal ileum but also involved cecum were included into right-side cancers in our analysis). The proportion of well, moderate, and poor differentiation of the adenocarcinomas were 25/87 (28.7%), 45/87 (51.7%), and 17/87 (19.5%), respectively. The 27/87 (31.0%) cancers had mucinous features, and 8/87 (9.2%) showed mixed signet-ring cell

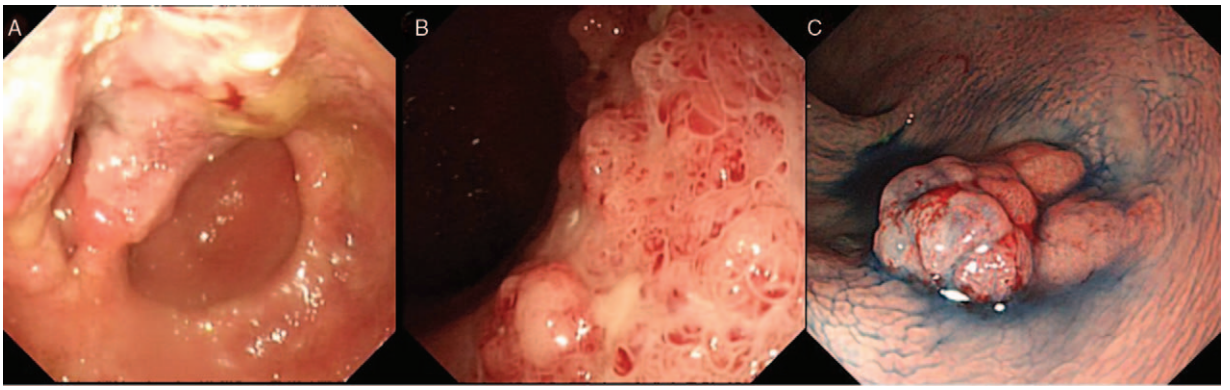

Figure 2: Representative endoscopic appearances of concurrent ulcerated mass lesions in ileocecal valve (A) and rectum (B) in a ulcerative colitis patient; and a mass in sigmoid colon (C), with indigo stained carmine in a Crohn's disease patient.

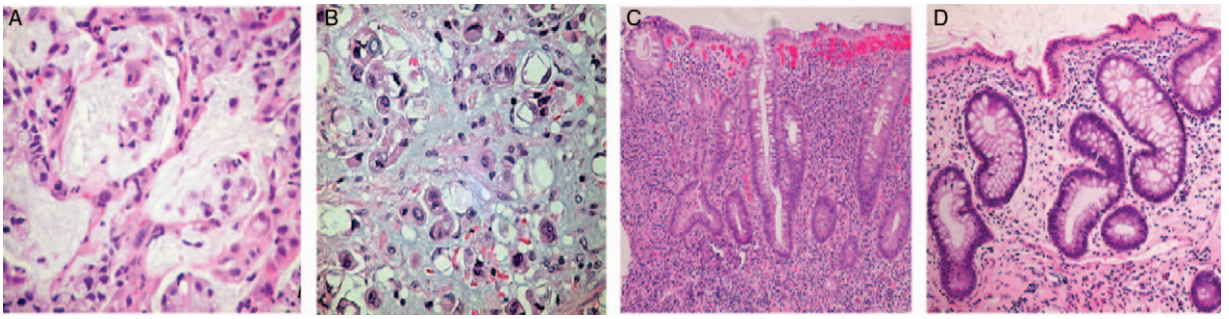

Figure 3: Representative histopathologic micrographs: (A) mucinous carcinoma (hematoxylin-eosin staining, original magnification ×400); (B) signet cell carcinoma (hematoxylin-eosin staining, original magnification ×400); (C) chronic active colitis in background mucosa (hematoxylin-eosin staining, original magnification ×100); and (D) chronic quiescence colitis in background mucosa (hematoxylin-eosin staining, original magnification ×200).

Table 1: Comparison of clinical and histopathologic features of IBD-associated colorectal cancers between Beijing and Calgary patients.

Items	Total ($n=78$)	Beijing group ($n=25$)	Calgary group ($n=53$)	Statistical value	*P*
Male, *n* (%)	50 (64.1)	14 (56.0)	36 (67.9)	1.050*	0.324
Age (years), mean ± SD	57.4 ± 15.3	48.6 ± 12.8	61.6 ± 14.7	–3.798†	<0.001
Disease duration (years), median (P25, P75)	13.0 (6.5, 16.0)	15.0 (7.5, 19.0)	12.0 (6.0, 16.0)	–1.286‡	0.202
Multifocal cancers, *n* (%)	9 (11.5)	3 (12.0)	6 (11.3)	0.008*	1.000
Location of cancer, *n*	87	28	59	3.741*	0.154
Right side colon, *n* (%)	31 (35.6)	6 (21.4)	25 (42.4)		
Left side colon, *n* (%)	32 (36.8)	12 (42.9)	20(33.9)		
Rectum	24 (27.6)	10 (35.7)	14 (23.7)		
Tumor size (cm), mean ± SD	4.9 ± 3.2	4.0 ± 2.4	5.2 ± 3.3	–1.579†	0.120
Differentiation, *n*	87	28	59	0.983*	0.621
Well, *n* (%)	25 (28.7)	10 (35.7)	15 (25.4)		
Moderate differentiated, *n* (%)	45 (51.7)	13 (46.4)	32 (54.2)		
Poorly differentiated, *n* (%)	17 (19.5)	5 (17.9)	12 (20.3)		
Mucinous, *n*/N (%)	27/87 (31.0)	2/87 (7.1)	25/87 (42.4)	11.011*	0.001
Signet-ring cell, *n*/N (%)	8/87 (9.2)	1/87 (3.6)	7/87 (11.9)	1.564*	0.428
TNM stage, *n*	78	25	53	27.003*	<0.001
I, *n* (%)	18 (23.1)	5 (20.0)	13 (24.5)		
IIa, *n* (%)	21 (26.9)	4 (16.0)	17 (32.1)		
IIb, *n* (%)	8 (10.3)	8 (32.0)	0		
IIC, *n* (%)	3 (3.9)	0	3 (5.7)		
IIIa, *n* (%)	2 (2.6)	2 (8.0)	0		
IIIb, *n* (%)	14 (18.0)	4 (16.0)	10 (18.9)		
IIIc, *n* (%)	10 (12.8)	1 (8.0)	9 (17.0)		
IV, *n* (%)	2 (2.6)	1 (8.0)	1 (1.9)		
Background active colitis, *n* (%)	60 (76.9)	16 (64.0)	44 (83.0)	3.461*	0.085
Surveillance, *n* (%)	19 (24.4)	7 (28.0)	12 (22.6)	0.265*	0.778
Complicated with PSC, *n* (%)	3 (3.8)	0	3 (5.7)	1.472*	0.547

*χ^2 value, †*t* value, ‡*Z* value. IBD: Inflammatory bowel disease; SD: Standard deviation; TNM: Tumor-node-metastasis; PSC: Primary sclerosing cholangitis.

morphology. Half of the cases were in TNM Stage I (18/78, 23.1%) and IIa (21/78, 26.9%). In 60/78 (76.9%) cases, the regional bowel mucosa had chronic active colitis in the background at the time of CRC diagnosed.

Both groups shared many clinical and pathologic features in common, including the male predominance, long disease duration, high proportion of multifocal lesions, distal location (ie, largely in left-side colon and rectum), mostly moderately and poorly differentiated adenocarcinomas and chronic active colitis in the background, and similar TNM staging.

Differences in clinical and pathologic features between the two groups

In comparison, between the Beijing and Calgary groups, several differences in both clinical and pathologic features were also noted. First, Beijing group showed a significantly higher percentage of UC compared with Calgary group (88.0% *vs.* 60.4%, $P=0.018$), Second, the patients' mean age at onset of CRC was significantly younger in the Beijing group (48.6 ± 12.8 years *vs.* 61.6 ± 14.7 years, $P<0.001$). Third, the Beijing group showed a significantly lower prevalence of mucinous adenocarcinoma (7.1% *vs.*

42.4%, $P = 0.001$). Fourth, the distribution of TNM stage in the Beijing group was significantly different from that in the Calgary group with more cases in IIb (32.0% *vs.* 0, $P < 0.001$).

Colonoscopic surveillance/follow-up for IBD-neoplasia in both groups

The 19/78 (24.4%) patients in the combined groups, including 7/25 (28.0%) of the Beijing group and 12/53 (22.6%) of the Calgary group, had gone through relatively regular surveillance colonoscopy over the course of IBD before the diagnosis of CRC. In 9/19 (47.4%) patients, some dysplastic lesions were reportedly found at some point. In the Beijing group, only one high-grade dysplasia was found in a UC patient and one adenoma (adenoma-like polyp) in a CD patient, which was in sigmoid, incompletely removed upon biopsy, and later increased in size and transformed to adenocarcinoma after 3 years, as shown in Figure 2C. In the Calgary group, three adenomas (adenoma-like polyps) and five endoscopically apparently non-adenoma-like colitis-associated dysplastic lesions (four with low-grade dysplasia, one with high-grade dysplasia) were found in eight patients from Calgary group. In three of them, the precursor lesions were found in the same regions where the carcinomas developed later.

Furthermore, there was a significantly higher detection rate of precancerous lesions in the surveillance group, compared with non-surveillance group (41.4% *vs.* 17.0%, $P = 0.002$). However, there was no significant difference of TNM staging, location of cancer, the percentage of mucinous or signet-ring pattern between two groups.

Discussion

IBD-CRC has been one of the major complications contributing to the mortality of IBD, and it has become a sub-population of CRC in Asian countries as well. Several recent studies in Asia, mostly based on hospitalization records, have suggested that the prevalence of CRC in Asian IBD patients was either a little lower than or similar to that in the western countries.[4,11] The present study did not allow us to compare the prevalence of IBD-CRC between east and west, since it was not entirely a population-based study and the number of subjects were small. We rather focused on the comparison for only the clinical-pathologic features. In summary, our study confirmed many common features of IBD-CRCs, such as long disease duration, active colitis in background, high proportion of multifocal lesions, left colon predominance, and high prevalence of moderate and poor differentiation. Meanwhile, our data revealed some differences between the patients in the two groups. The Beijing group somehow showed a much lesser number of CD-CRC, younger age of onset of cancer, lower prevalence of mucinous carcinoma, and different TNM staging distribution.

CD patients with extensive colonic involvement were found to have similar risk for the development of CRC compared with UC patients. A meta-analysis focusing on studies from western countries revealed that the cumulative risk of developing CRC in CD patients with colonic involvement was similar to that in UC patients, with the risk ratio of 4.5 (1.3, 14.9) compared with general population.[12] However, the exact incidence of CRC in CD patients in Asia is still not known, largely due to the limited number of CD-CRCs. Two retrospective studies including 294 and 512 CD cases in Japan over a 20-year period found a total of 12 patients developed CRC, with the standardized incidence risk of 5.8 (2.13, 12.68) and 3.2 (1.2, 6.9), respectively.[13,14] In our study, the percentage of CD-CRC is significantly rare in the Beijing group, which we believe is mainly due to the relatively lower incidence/prevalence of CD in China so far. Our previous population-based study in a city in northern China revealed the age-adjusted incidence of CD and UC of 0.13 and 1.64 per 100,000, respectively,[15] which was significantly lower than that in Canada where the incidence of CD and UC were reportedly 20.2 and 19.2 per 100,000, respectively.[16,17]

Colonoscopic surveillance for colorectal neoplasia in longstanding and high-risk IBD patients, in an attempt to detect precancerous lesion and thus prevent cancer development, has been a standard of care for decades although the guideline was not universal and the methodology and techniques have been evolving.[18,19] The exact role of the surveillance in reducing the rate of cancer in IBD patients has been controversial though. Recently a meta-analysis included five observational study indicated that the surveillance endoscopy in IBD was associated with higher rate of early-stage CRC detection (odds ratio [OR] = 5.4, $P = 0.009$) and lower rate of CRC associated death (OR = 0.36, $P = 0.002$).[20] It is generally believed that the surveillance colonoscopy favors the detection of precancerous lesions and CRC in early stage, particularly with the current strategy using target biopsy guided by chromoendoscopy and high-definition endoscopy. Our findings did reveal the higher detection rate of precancerous lesions in surveillance group, compared with non-surveillance group.

Unfortunately, the patients' poor adherence to surveillance colonoscopy has been a common problem,[21] which is also reflected in our data. In both Calgary and Beijing groups, the rate of regular surveillance was low, only about a quarter of the patients had gone through some sort of surveillance, although it is possible that in some patients the records may not be complete. With the limitation of our data and study design, further analysis and discussion about the methodology and effectiveness of the surveillance colonoscopy are needed in future studies.

The majority of IBD-CRC lesions are moderately or poorly differentiated, and the patients have worse prognosis compared with sporadic CRCs.[22-24] Moreover, mucinous and/or signet-ring cell features and advanced TNM stage both would worsen the prognosis. A nationwide Japanese study reported 17% of mucinous and signet-ring cell carcinomas in their series of IBD-CRC, while there were only 4% in sporadic CRC.[24] Our own previous study in Chinese patients also revealed advanced TNM stage in UC-CRC as compared with sporadic CRC.[23] This study was also consistent with the previous findings. Furthermore, it showed younger age of onset of cancer, lower prevalence of mucinous adenocarcinoma and different

TNM stage distribution in the Beijing group, compared with the Calgary group. Different ethnics and medical systems might contribute partly to its difference. Additionally, considering this study was based on surgically resected cases, the selection criteria and timing for surgical treatment may also be slightly different between Calgary and Beijing. These preliminary data learned from this comparative study suggests that further analysis of the possible contributing role of each of the above factors in future studies would help us understand better about the additional co-factors in the carcinogenesis of IBD-CRCs.

In addition to the aforementioned limitations in this study, the data about past history of medical treatment and smoking status unfortunately could not be included in our analysis due to the incompleteness of these data in a significant number of patients. As we know, the different medical treatment has different effects on the disease activity of IBD which is one of the major risks for IBD-CRC. Cigarette smoking may also affect the disease course, especially in CD patients. Admittedly though, it is not our intention to further correlate the medication with the disease activity or with the later cancer development or to compare the difference of medication use between the two groups.

In conclusion, as compared with patients from Calgary, the IBD-CRC patients in Beijing group were younger, less CD-associated and had less mucinous features, otherwise they were similar in many common features.

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Conflicts of interest

None.

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