Risk factors for colorectal neoplasia in patients with underlying inflammatory bowel disease: a multicenter study

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Abstract

Background: This study sought to evaluate the risk factors for the development of colitis-associated neoplasia (CAN) in Chinese patients with inflammatory bowel disease (IBD).

Methods: IBD patients who developed CAN between 1999 and 2016 were identified from eight medical centers. In addition to initial pathology evaluation, a CAN diagnosis was confirmed by two expert pathologists. Patients with CAN (n = 29) were compared with non-CAN controls (n = 87). Matching was performed for gender and IBD type with a ratio of three controls to one subject.

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**Results:** Of the 29 patients with CAN, 8 (27.6%) had colorectal cancer (CRC), 20 (69.0%) had a final diagnosis of low-grade dysplasia and 1 (3.4%) had high-grade dysplasia. Multivariate analysis revealed that an older age at the time of IBD diagnosis and a longer IBD duration were independent risk factors for the development of CAN, with odds ratios of 1.09 [95% confidence interval (CI): 1.04–1.14, \( P < 0.001 \)] and 1.14 (95% CI: 1.03–1.27, \( P = 0.013 \)), respectively. Comparison between IBD patients with CRC and those with dysplasia indicated that the former were older at the time of IBD diagnosis (\( P = 0.012 \)) and had longer IBD durations (\( P = 0.019 \)).

**Conclusions:** Older age at the time of IBD diagnosis and longer IBD duration were found to be associated with the development of CAN in IBD patients.

**Key words:** Colorectal neoplasia; inflammatory bowel disease; risk factor

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**Introduction**

Patients with long-standing inflammatory bowel disease (IBD) who suffer from either ulcerative colitis (UC) or Crohn’s disease (CD) have an increased risk of developing colorectal neoplasia [1–3]. Although IBD-associated colorectal cancer (CRC) only accounts for 1–2% of patients with CRC in the general population, it constitutes 10–15% of deaths in IBD patients [4]. When compared to sporadic CRC, IBD-associated CRC is frequently detected at both late stages and at younger ages [5, 6]. Moreover, there are overall poorer long-term prognoses for patients diagnosed with IBD-associated CRC [7–9]. Colonoscopy surveillance has been widely accepted as an effective method in reducing the risk of IBD-associated CRC [5, 10, 11]. However, it is crucial to identify risk factors related to the development of colorectal neoplasia in patients with underlying IBD. This allows earlier and more effective diagnosis and treatment of colorectal dysplasia and CRC using surveillance colonoscopy [12–14] together with biopsy and chemoprevention [15–17].

The risk factors for colorectal neoplasia in patients with underlying IBD have been well defined in Western populations. Previous studies have shown that disease extension [18] and duration [1] are the two major drivers for high CRC risk in patients with underlying IBD. Concomitant primary sclerosing cholangitis (PSC) [19], family history of CRC [20] and active intestinal inflammation [21–23] have also been reported as other established risk factors. However, whether Eastern and Western IBD populations share similar risk factors remains unknown.

The past decade has seen a rapid growth in the incidence of IBD in both China and other Asian countries [24–26]. Critically, IBD etiology and disease course in China may not overlap with the patterns seen in Western countries. To this end, the risk factors and disease course of colitis-associated neoplasia (CAN) in China have not yet been defined. If the current trend continues, China and other Asian countries will continue to see a growing number of IBD patients. As such, the surveillance, management and follow-up of colorectal neoplasia in patients with underlying IBD will pose a great challenge to gastroenterologists, colorectal surgeons, pathologists and other healthcare professionals. Given these problems, we designed the following case-controlled study to investigate risk factors for the development of colorectal neoplasia in Chinese patients with underlying IBD.

**Patients and methods**

**Patients**

This study was approved by each participating institution’s Institutional Review Board (IRB) and/or ethics committee. All IBD patients who developed colorectal neoplasia between 1999 and 2016 were identified from eight tertiary-care hospitals throughout China. To ensure the accuracy and objectivity of our study, IBD patients initially identified were reconfirmed both clinically and histologically. All patients included in this study have demographic and clinic-pathological variables as well as outcomes prospectively maintained in the Registry. Both paper charts and electronic medical records were carefully reviewed when necessary.

**Study and Control groups**

Two groups—Study and Control—were used in our case-matched study. The characteristics of each were as follows: Study group (IBD patients with colorectal neoplasia) and Control group (IBD patients without colorectal neoplasia). IBD patients without colorectal neoplasia were matched with study cases for gender (male vs female) and type of IBD (UC or CD). The control-to-case ratio was 3:1.

**Inclusion and exclusion criteria**

To be included in the study, patients had to meet all the following inclusion criteria: (i) all patients had been diagnosed with underlying IBD; (ii) Study group patients had one of the following complications: indefinite for dysplasia (IND), low-grade dysplasia (LGD), high-grade dysplasia (HGD) or adenocarcinoma; and (iii) Control group patients had a routine follow-up with diagnostic/surveillance colonoscopy two or more times. Patients were excluded if they did not have IBD or if they had inadequate follow-up.

**Definition of variables**

Demographic and clinic-pathological variables were defined as follows: general information (gender, age and ethnicity); age at the time of IBD diagnosis; active smoking (consumption of more than seven cigarettes per week for at least 6 months prior to data entry); ex-smoker (cessation of smoking 6 months prior to data entry); active drinking (consumption of alcoholic beverages at least once a week for a minimum of 1 year prior to data entry); ex-drinker (cessation of drinking for more than 6 months prior to data entry); family history of IBD [having one or more of first-degree (parents, offspring or siblings of the index patient) or second-degree relatives who had IBD]; family history of CRC [having one or more of first-degree (parents, offspring or siblings of the index patients) or second-degree relatives who had CRC]; significant comorbidities (including congestive heart failure, coronary artery bypass surgery, chronic obstructive pulmonary diseases, renal stone or insufficiency, non-gastrointestinal cancer, stroke and/or liver failure); autoimmune disorders (including asthma, psoriasis, type 1 diabetes, rheumatoid arthritis, Grave’s disease, Hashimoto’s thyroiditis, psoriasis, systemic lupus
Risk factors for colorectal neoplasia

Risk factors associated with colorectal neoplasia in IBD patients

Univariate analysis showed that colorectal neoplasia was significantly associated with age at the time of IBD diagnosis [odds ratio (OR), 1.07; 95% confidence interval (CI): 1.03–1.11, \( P = 0.001 \)] and IBD duration (OR, 1.09; 95% CI: 1.0007–1.18, \( P = 0.034 \)) (Table 2). No other clinical factors were found to be correlated with risk for colorectal neoplasia, including ethnicity, smoking history, alcohol history, family history of CRC, body mass index (BMI), significant comorbidities, autoimmune disorders, EIM, extent of colitis or medication use.

The factors detected in our univariate analysis that were associated with the development of colorectal neoplasia were then included in a multivariate analysis model. Results indicated that both age at the time of IBD diagnosis (OR, 1.09; 95% CI: 1.04–1.14, \( P < 0.001 \)) and IBD duration (OR, 1.14; 95% CI: 1.03–1.27, \( P = 0.013 \)) were confirmed to be independent risk factors for colorectal neoplasia (Table 3).

Comparison between IBD patients with dysplasia and those with CRC

Of the 29 patients with a CAN diagnosis, 20 (69.0%) had a final diagnosis of LGD, 1 (3.4%) had HGD and 8 (27.6%) had CRC. Of the CRC patients, 75% (6/8) were diagnosed at an advanced tumor stage (AJCC stage III). A comparison between IBD patients with a final diagnosis of CRC and those with dysplasia indicated that patients with CRC had an older age at the time of IBD diagnosis (54.3 ± 14.4 vs 38.5 ± 12.9 years, \( P = 0.012 \)) and a longer IBD duration (10.4 (IQR: 3.0–18.6) years vs 1.2 (IQR: 0.1–8.1) years, \( P = 0.019 \)) (Table 4).

Discussion

CRC is a potentially lethal and adverse sequela for patients with underlying IBD. Carcinoma of the colon arising in a patient with UC was initially described by Crohn and Rosenberg in 1925 [27]. Since then, there has been a general agreement that patients with IBD have increased risk of developing CRC. A landmark meta-analysis from 2001 showed that the cumulative risks of CRC among those with long-standing UC were 1.6% at 10 years, 8.3% at 20 years and as high as 18.4% at 30 years [1]. A subsequent meta-analysis 5 years later suggested that the cumulative risk of CRC in CD patients approached 3% after 10 years, 6% after 20 years and 8% after 30 years, and was similar to that of UC [28]. Recently, a multicenter study from China reported that the cumulative risk of CRC was 1.5% at 10 years, 3.6% at 20 years and 14.4% at 30 years after UC diagnosis [29]. The risk of CRC in long-term IBD patients has become concerning. As such, it is critical that additional risk factors for neoplastic progression be identified, permitting closer observation of high-risk patients with underlying IBD.

Based on studies from Western populations, reported risk factors associated with colorectal neoplasia include PSC, disease extension and IBD duration [1, 18, 30–32]. However, there are scant data on risk factors in Eastern patient populations, including those in China. In this case-matched study, we identified an older age and a longer IBD duration as two independent risk factors for the development of CAN. These findings were based on data from patients enrolled from eight medical centers throughout China. Interestingly, IBD patients with CRC were also found to have an older age at the time of IBD diagnosis as well as a longer IBD duration than those who only had a final diagnosis of dysplasia.
### Table 1. Patient characteristics

|                                | All cases (n = 116) | Patients with CAN (n = 29) | Patients without CAN (n = 87) | P-value |
|--------------------------------|---------------------|-----------------------------|------------------------------|---------|
| **Age at IBD diagnosis, yrs**  | 40.2 ± 15.7         | 49.9 ± 15.5                 | 36.9 ± 14.5                  | <0.001  |
| **Gender**                     |                     |                             |                              | 1.0     |
| Female                         | 20                  | 5 (17.2)                    | 15 (17.2)                    |         |
| Male                           | 96                  | 24 (82.8)                   | 72 (82.8)                    |         |
| **Ethnicity**                  |                     |                             |                              | 0.25    |
| Han                            | 115                 | 28 (96.6)                   | 87 (100)                     |         |
| Others                         | 1                   | 1 (3.4)                     | 0 (0)                        |         |
| **Smoking, n (%)**             |                     |                             |                              | 0.51    |
| Never                          | 91                  | 24 (82.8)                   | 67 (77.0)                    |         |
| Ex or active                   | 25                  | 5 (17.2)                    | 21 (23.0)                    |         |
| **Alcohol, n (%)**             |                     |                             |                              | 0.44    |
| None                           | 90                  | 24 (82.8)                   | 66 (75.9)                    |         |
| Ex or active                   | 26                  | 5 (17.2)                    | 21 (24.1)                    |         |
| **Family history of IBD**      |                     |                             |                              | 1.0     |
| None                           | 115                 | 29 (100)                    | 86 (98.9)                    |         |
| UC or CD                       | 1                   | 0 (0)                       | 1 (1.1)                      |         |
| **Family history of CRC**      |                     |                             |                              | 0.57    |
| Significant comorbidities      | 17                  | 6 (20.7)                    | 11 (12.6)                    |         |
| Autoimmune disorders           | 8                   | 0 (0)                       | 8 (9.2%)                     | 0.20    |
| Extra-intestinal manifestations| 7                   | 2 (6.9%)                    | 5 (5.7%)                     | 1.0     |
| **Type of IBD**                |                     |                             |                              | 1.0     |
| UC                             | 80                  | 20 (69.0)                   | 60 (69.0)                    |         |
| CD                             | 36                  | 9 (31.0)                    | 27 (31.0)                    |         |
| **Extent of colitis**          |                     |                             |                              | 0.35    |
| Extensive colitis              | 68                  | 20 (71.4)                   | 48 (61.5)                    |         |
| Left colitis or proctitis      | 38                  | 8 (28.6)                    | 30 (38.5)                    |         |
| **Medications use (>3 months)**|                     |                             |                              |         |
| 5-aminosalicylic acid          | 95                  | 24 (82.8)                   | 71 (81.6)                    | 0.89    |
| Corticosteroids                | 30                  | 8 (27.6)                    | 22 (25.3)                    | 0.81    |
| Immunomodulators               | 28                  | 6 (20.7)                    | 22 (25.3)                    | 0.62    |
| Biologics                      | 10                  | 1 (3.4)                     | 9 (10.3)                     | 0.45    |
| Body mass index, kg/m²         | 20.3 ± 2.6          | 20.3 ± 3.3                  | 20.4 ± 2.3                   | 0.95    |
| **Duration of IBD, yrs**       | 2.3 [0.7–6.0]       | 3.4 [0.3–10.5]              | 2.1 [0.9–4.8]                | 0.35    |

Data are presented as mean ± standard deviation, median [interquartile ranges] or number (%).

CAN, colitis-associated neoplasia; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Chron’s disease; CRC, colorectal cancer.

### Table 2. Univariate analysis of risk factors associated with colorectal neoplasia in IBD patients

| Risk Factor                              | OR (95% CI) | P-value |
|------------------------------------------|-------------|---------|
| Age at IBD diagnosis, every 1-yr increase| 1.07 (1.03–1.11) | <0.001  |
| Ethnicity (others vs Han)                | 434.45 (0.00–8.95E+12) | 0.62    |
| Smoking (ever vs never)                  | 0.64 (0.19–2.12)  | 0.47    |
| Alcohol (ever vs never)                  | 0.62 (0.20–1.93)  | 0.41    |
| Family history of IBD (yes vs no)        | 0.03 (0.00–7.36E+6) | 0.73    |
| Family history of CRC (yes vs no)        | 0.002 (0.00–4.74E+7) | 0.62    |
| Body mass index, every 1-kg/m² increase  | 1.00 (0.84–1.19)  | 1.00    |
| Significant comorbidities (yes vs no)    | 1.96 (0.60–6.45)  | 0.27    |
| Autoimmune disorders (yes vs no)         | 0.023 (0.00–31.85) | 0.31    |
| Extra-intestinal manifestations (yes vs no)| 1.36 (0.16–11.62) | 0.78    |
| Extent of colitis (left colitis or proctitis vs extensive)| 0.53 (0.19–1.51) | 0.24    |
| Medications use (>3 months)              |             |         |
| 5-aminosalicylic acid                    | 1.09 (0.35–3.37)  | 0.89    |
| Corticosteroids                          | 1.20 (0.36–3.96)  | 0.76    |
| Immunomodulators                         | 0.65 (0.17–2.41)  | 0.52    |
| Biologics                                | 0.30 (0.035–2.51) | 0.27    |
| Duration of IBD, every 1-yr increase     | 1.09 (1.0007–1.18) | 0.034   |

IBD, inflammatory bowel disease; CRC, colorectal cancer; OR, odds ratio; CI, confidence interval.
from a 30-year study conducted by Rutter et al. indicated that patients who developed CRC had a higher median age of disease onset than those who did not develop cancer. Moreover, a nationwide, long-term survey from the Netherlands included 251 patients with IBD-CRC and found that IBD diagnosis at an older age was associated with early development of CRC [hazard ratio (HR) for 10 years older 2.25; 95% CI: 1.29–2.63]. In this multicenter study, we identified that an older age at the time of IBD diagnosis was an independent risk factor for the development of CAN. In a subsequent stratified analysis, we found that IBD patients with CRC had a significantly older age at the time of IBD diagnosis when compared with those with dysplasia only. One possible explanation might be that patients with late onset of IBD, similarly to the general population, accumulate malignant risk factors until the onset of IBD [37].

We also identified longer IBD duration as another independent risk factor for colorectal neoplasia in patients with IBD, which is in line with previous studies conducted based on Western patient populations [1, 38–40]. It has been suggested that intestinal chronic inflammation could invoke a cascade within the abnormal epithelial proliferative zone, progressing through dysplasia, adenoma and finally carcinoma [41]. This may offer a possible explanation for the higher CRC risk in longstanding IBD patients. Based on long-term follow-up in a subset of studies included in the landmark meta-analysis conducted by Eaden et al. [3], the cumulative risk of CRC in UC patients was estimated at 1.5% after 10 years, 8.3% after 20 years and 18.4% after 30 years of disease. A similar CRC risk was observed in Crohn’s colitis based on a separate population-based study [42]. Other subsequent studies observed lower incident rates in Western countries [40, 43, 44], which is likely a testament to the success of constant colonoscopic surveillance and improved medical therapies with chemoprevention. However, in Eastern countries including China, the incidence rate of IBD is still increasing [25]. Therefore, the occurrence of colitis-associated cancer is also anticipated to increase.

It has been widely accepted that patients with underlying IBD who have PSC are at an increased risk of developing colorectal neoplasia [1, 19, 45–47]. A recent meta-analysis of 16 observational studies indicated that IBD patients with concomitant PSC had a higher risk of developing CRC than IBD patients without PSC (OR, 3.24; 95% CI: 2.14–4.90) [48]. When dysplasia was excluded from the analysis, the risk for cancer was still increased by approximate 3-fold when compared with patients with IBD alone. Alterations in the bile salt pool and accumulation of bile acids in the colon may partially be responsible for the markedly increased colorectal neoplasia risk among IBD patients with PSC [49]. However, we could not identify IBD patients with concomitant PSC in this multicenter study, since the comorbidity of IBD and PSC is uncommon in the Chinese population [50]. Given this, caution is needed when interpreting the role of PSC in Chinese IBD patients.

The findings of the current study have several clinical implications. To the best of our knowledge, there have been few studies evaluating the risk factors for colorectal neoplasia in patients with underlying IBD in a Chinese patient population. This multicenter study included eight medical centers throughout China and may provide a reference point for colorectal surgeons and gastroenterologists regarding care programs and screening for colorectal neoplasia in Chinese IBD patients. In addition, since colonoscopic surveillance is both labor-intensive and expensive, our findings contribute to further refinement of high- and low-risk subgroups of patients, thus allowing a more appropriate allocation of resources. This fine-tuned approach would reduce unnecessary procedures for those at a low risk of

### Table 3. Multivariate Analysis of Risk Factors Associated with Colorectal Neoplasia in Patients with Underlying Inflammatory Bowel Diseases

| Characteristics                        | OR (95% CI)       | P value |
|----------------------------------------|-------------------|---------|
| Age at IBD diagnosis, every 1-yr increase | 1.09 (1.04–1.14) | <0.001  |
| Duration of IBD, every 1-yr increase    | 1.14 (1.03–1.27) | 0.013   |

IBD, inflammatory bowel disease; OR, odds ratio; CI, confidence interval.

### Table 4. Comparisons of characteristics between inflammatory bowel disease (IBD) patients with dysplasia and those with colorectal cancer

| Characteristic                  | Patients with dysplasia (n = 21) | P-value | Patients with colorectal cancer (n = 8) |
|--------------------------------|----------------------------------|---------|---------------------------------------|
| Age at IBD diagnosis, yrs      | 38.5 ± 12.9                      | 0.012   | 54.3 ± 14.4                           |
| Gender                         |                                  |         |                                       |
| Female                         | 4 (19.0)                         |         | 1(12.5)                               |
| Male                           | 17 (81.0)                        |         | 7 (87.5)                              |
| Ethnicity                      |                                  | 1.0     |                                       |
| Han                             | 20 (95.2)                        | 1.0     |                                       |
| Others                          | 1 (4.8)                          |         |                                       |
| Smoking, Ex or active          | 5 (23.8)                         | 0.28    | 0 (0)                                 |
| Alcohol, None                  | 16 (76.2)                        | 0.28    | 8 (100)                               |
| Type of IBD                    |                                  | 1.0     |                                       |
| Ulcerative colitis             | 14 (66.7)                        |         | 6 (75.0)                              |
| Crohn’s disease                | 7 (33.3)                         |         | 2 (25.0)                              |
| Extent of colitis              |                                  | 1.0     |                                       |
| Extensive colitis              | 14 (70.0)                        |         | 6 (75.0)                              |
| Left colitis or proctitis      | 6 (30.0)                         | 0.60    |                                       |
| Medications use (> 3 months)   |                                  | 0.65    |                                       |
| 5-aminosalicylic acid          | 18 (85.7)                        | 1.0     |                                       |
| Steroids                       | 5 (23.8)                         | 1.0     |                                       |
| Immunomodulators               | 4 (19.0)                         |         |                                       |
| Biologics, None                | 0 (0)                            | 0.28    |                                       |
| Body mass index, kg/m²         | 20.1 ± 2.6                       | 0.50    | 21.0 ± 4.9                           |
| Duration of IBD                | 1.2 [0.1–8.1]                    | 0.019   | 10.4 [3.0–18.6]                      |

Data are presented as mean ± standard deviation, median [interquartile ranges] or number (%). IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; 5-ASA, 5-aminosalicylic acid. Continuous factors are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR), and categorical factors are described as frequencies.
developing colorectal neoplasia, and enable more intensive surveillance for those who are most likely to benefit.

The results of the present study should be interpreted against the background of potential limitations, particularly its retrospective study design. A prospective study enrolling large numbers of Chinese IBD patients with long-term follow-up is ongoing, but results will be unavailable for quite some time. Moreover, since the overall capacity for early diagnosis and treatment of IBD patients in China lags that of Western countries, the mean age at IBD diagnosis was older than that in studies from Western countries [22, 31, 38, 51]. While this likely introduced some bias, it is present in both groups of the study. As such, it likely did not interfere with study outcomes and conclusions.

In conclusion, we have demonstrated that both an older age at the time of IBD diagnosis as well as a longer IBD duration were independent risk factors for colorectal neoplasia in Chinese patients with underlying IBD. IBD patients with CRC had a significantly older age at the time of IBD diagnosis and a longer IBD duration when compared with those with dysplasia only. These results may help form a first step toward the development of a risk-prediction model, which can be applied in daily clinical practice for an individualized approach to CAN surveillance in Chinese IBD patients.

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