Gastroenterology Report, 7(1), 2019, 67–73

doi: 10.1093/gastro/goy039
Advance Access Publication Date: 13 December 2018
Original article

ORIGINAL ARTICLE

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

Xian-Rui Wu[1,2,†], Xiao-Bin Zheng[1,2,†], Yan Huang[2,3], Qian Cao[4], Hong-Jie Zhang[5], Ying-Lei Miao[6], Kai-Fang Zou[7], Min Chen[8], Fa-Ming Zhang[9], Qiao Mei[10], David Gonzalo[11], Daniela Allende[12], Pin-Jin Hu[2,13], Bo Shen[14], Xiu-Li Liu[11,†] and Ping Lan[1,2,*,†]

[1]Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China, [2]Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China, [3]Department of Pathology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China, [4]Department of Gastroenterology, Sir Run Run Shaw Hospital of Zhejiang University School of Medicine, Hangzhou, China, [5]Department of Gastroenterology, Jiangsu Province Hospital, Nanjing, China, [6]Department of Gastroenterology, The First Affiliated Hospital of Kunming Medical University, Kunming, China, [7]Department of Gastroenterology, Wuhan Union Hospital, Wuhan, China, [8]Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China, [9]Medical Center for Digestive Diseases, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China, [10]Department of Gastroenterology, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [11]Department of Pathology and Laboratory Medicine, University of Florida, Gainesville, FL, USA, [12]Department of Anatomic Pathology, The Cleveland Clinic Foundation, Cleveland, OH, USA, [13]Department of Gastroenterology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China and [14]Department of Gastroenterology/Hepatology, The Cleveland Clinic Foundation, Cleveland, OH, USA

*Corresponding author. Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, Guangdong 510655, China. Tel: +86-20-38254009; Fax: +86-20-38254166; Email: lanping@mail.sysu.edu.cn

†These authors contributed equally to this work.

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.

Submitted: 31 March 2018; **Revised:** 14 July 2018; **Accepted:** 13 August 2018

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

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

erythematosus, celiac disease, autoimmune hemolytic anemia, vitiligo, pernicious anemia, multiple sclerosis and/or idiopathic thrombocytopenic purpura); extra-intestinal manifestations (EIM) (including the presence of PSC, arthralgia or arthropathy, erythema nodosum, pyoderma gangrenosum, thromboembolic events and/or IBD-related ocular lesions); extensive colitis (endoscopic, macroscopic or microscopic disease extending proximal to the splenic flexure).

Duration of IBD was also included: for the Study group, it was defined as the time interval from the date of IBD diagnosis (i.e. diagnosis of UC or CD) to the date of colorectal neoplasia detection (i.e. LGD, HGD, dysphasia unclassified, adenocarcinoma). For the Control group, it was defined as the time interval from the date of IBD diagnosis to the date of the most recent contact with the patients.

Outcome measurement

The primary study endpoint was to evaluate the risk factors for the development of CAN in a Chinese IBD patient population. In addition to the initial pathological evaluation, a diagnosis of CAN was confirmed via review by two expert pathologists (X.L.L. and Y.H.).

Statistical analysis

Descriptive statistics were computed for all variables. These included means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous factors and frequencies for categorical factors. Comparisons of the distribution of clinic-pathological characteristics between two groups were made by using the two-tail *t*-test (or Wilcoxon rank-sum test as appropriate) for continuous variables and chi-square test (or the Fisher exact test as appropriate) for categorical variables. Both univariate and multivariate analyses for risk factors associated with the development of neoplasia in IBD patients were constructed using a logistic regression analysis. All statistical analyses were performed with SPSS software (version 22; SPSS, Chicago, IL). *P*-values less than 0.05 were considered statistically significant.

Results

We initially identified 155 patients with listed IBD-related colorectal neoplasia (56 females, 99 males) and a total of 126 cases were excluded after chart and pathology review. Reasons for exclusion were as follows: missing paraffin-embedded samples ($n = 18$), ambiguous pathological diagnosis ($n = 64$), diagnoses of non-IBD or IBD without colorectal neoplasia ($n = 39$), discordant diagnoses between pathologists ($n = 3$) and missing major clinical data ($n = 2$). IBD patients without colorectal neoplasia were matched with cases for gender and type of IBD with a ratio of three controls to one subject. In total, 29 cases and 87 controls were included for further analysis.

Patient demographics

Of the 29 patients with confirmed CAN, 20 (69.0%) had UC and 9 (31.0%) had CD. Patients with CAN were found to be older at the time of IBD diagnosis (49.9 ± 15.5 vs 36.9 ± 14.5 years, $P < 0.001$) than controls. They also had longer durations of IBD [3.4 (IQR: 0.3–10.5) years vs 2.1 (IQR: 0.9–4.8) years], although this did not reach statistical significance ($P = 0.35$). There were no significant differences in all other clinicopathological characteristics between the two groups (Table 1).

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 IBD, 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	3	0 (0)	3 (3.4)	0.57
Significant comorbidities	17	6 (20.7)	11 (12.6)	0.36
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/m^2	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

	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/m^2 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.

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 ($n=21$)	Patients with colorectal cancer ($n=8$)	*P*-value
Age at IBD diagnosis, yrs	38.5 ± 12.9	54.3 ± 14.4	0.012
Gender			1.0
Female	4 (19.0)	1(12.5)	
Male	17 (81.0)	7 (87.5)	
Ethnicity			1.0
Han	20 (95.2)	8 (100)	
Others	1 (4.8)	0 (0)	
Smoking,			0.28
None	16 (76.2)	8 (100)	
Ex or active	5 (23.8)	0 (0)	
Alcohol			0.28
None	16 (76.2)	8 (100)	
Ex or active	5 (23.8)	0 (0)	
Significant comorbidities	4 (19.0)	2 (25.0)	1.0
Extra-intestinal manifestations	2 (9.5%)	0 (0)	1.0
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)	2 (25.0)	
Medications use (>3 months)			
5-aminosalicylic acid	18 (85.7)	6 (75.0)	0.60
Steroids	5 (23.8)	3 (37.5)	0.65
Immunomodulators	4 (19.0)	2 (25.0)	1.0
Biologics	0 (0)	1 (12.5)	0.28
Body mass index, kg/m^2	20.1 ± 2.6	21.0 ± 4.9	0.50
Duration of IBD	1.2 [0.1–8.1]	10.4 [3.0–18.6]	0.019

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.

It still remains controversial whether an older age at the time of IBD diagnosis is an independent risk factor for CAN. Some studies have shown an increased risk of CAN in patients diagnosed at a younger age [33, 34]. To this end, Ekbom *et al.* [18] conducted a population-based cohort study in Sweden of 3117 patients who were diagnosed with UC between 1922 and 1983. They found that a younger age at the time of IBD onset (<15 years old) was an independent risk factor for the development of CRC. However, other studies have reached contrary conclusions. For example, Greenstein *et al.* [35] found that patients diagnosed with IBD above 30–40 years of age were at a higher risk for the development of CRC when compared with those diagnosed below 20 years of age. Data from a 30-year study conducted by Rutter *et al.* [36] 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 long-standing IBD patients. Based on long-term follow-up in a subset of studies included in the landmark meta-analysis conducted by Eaden *et al.* [1], the cumulative risk of CRC in UC patients was estimated at 1.6% 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

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.

Acknowledgments

X.R.W. and X.B.Z. contributed to the study concept and design; acquisition, analysis and interpretation of the data; and drafting of the manuscript. Y.H., Q.C., H.J.Z., Y.L.M., K.F.Z., M.C., F.M.Z., Q.M., D.H.G., D.A., P.J.H., B.S., X.L.L. and P.L. contributed to the study concept and design, analysis and interpretation of the data, and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Funding

This work was supported by National Key Clinical Discipline, National Natural Science Foundation of China (No. 81870383), Guangdong Natural Science Foundation (No. 2017A030313785), Science and Technology Planning Project of Guangzhou City (No. 201804010014), and Science and Technology Planning Project of Guangdong Province (No. 2015B020229001).

Conflict of interest statement: none declared.

References

1. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;**48**:526–35.
2. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012;**10**:639–45.
3. Jess T, Gamborg M, Matzen P *et al*. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005;**100**:2724–9.
4. Munkholm P. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;**18**:1–5.
5. Rogler G. Chronic ulcerative colitis and colorectal cancer. *Cancer Lett* 2014;**345**:235–41.
6. Grivennikov SI. Inflammation and colorectal cancer: colitis-associated neoplasia. *Semin Immunopathol* 2013;**35**:229–44.
7. Jensen AB, Larsen M, Gislum M *et al*. Survival after colorectal cancer in patients with ulcerative colitis: a nationwide population-based Danish study. *Am J Gastroenterol* 2006;**101**:1283–7.
8. Peyrin-Biroulet L, Lepage C, Jooste V *et al*. Colorectal cancer in inflammatory bowel diseases: a population-based study (1976-2008). *Inflamm Bowel Dis* 2012;**18**:2247–51.
9. Watanabe T, Konishi T, Kishimoto J *et al*. Ulcerative colitis-associated colorectal cancer shows a poorer survival than sporadic colorectal cancer: a nationwide Japanese study. *Inflamm Bowel Dis* 2011;**17**:802–8.
10. Collins PD. Strategies for detecting colon cancer and dysplasia in patients with inflammatory bowel disease. *Inflammatory bowel diseases* 2013;**19**:860–3.
11. Zhen Y, Luo C, Zhang H. Early detection of ulcerative colitis-associated colorectal cancer. *Gastroenterol Rep (Oxf)* 2018;**6**:83–92.
12. Cairns SR, Scholefield JH, Steele RJ *et al*. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010;**59**:666–89.
13. Farraye FA, Odze RD, Eaden J *et al*. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010;**138**:746–74.
14. Farraye FA, Odze RD, Eaden J *et al*. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010;**138**:738–45.
15. Subramanian V, Logan RF. Chemoprevention of colorectal cancer in inflammatory bowel disease. *Best Pract Res Clin Gastroenterol* 2011;**25**:593–606.
16. Jess T, Lopez A, Andersson M *et al*. Thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2014;**12**:1793–800.e1.
17. O'connor A, Packey CD, Akbari M *et al*. Mesalamine, but not sulfasalazine, reduces the risk of colorectal neoplasia in patients with inflammatory bowel disease: an agent-specific systematic review and meta-analysis. *Inflamm Bowel Dis* 2015;**21**:2562–9.
18. Ekbom A, Helmick C, Zack M *et al*. Ulcerative colitis and colorectal cancer: a population-based study. *N Engl J Med* 1990;**323**:1228–33.
19. Torres J, Pineton de Chambrun G, Itzkowitz S *et al*. Review article: colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;**34**:497–508.
20. Askling J, Dickman PW, Karlen P *et al*. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. *Gastroenterology* 2001;**120**:1356–62.
21. Rutter M, Saunders B, Wilkinson K *et al*. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;**126**:451–9.
22. Gupta RB, Harpaz N, Itzkowitz S *et al*. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007;**133**:1099–105; quiz 340–1.
23. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology* 2011;**140**:1807–16.
24. Zhiqin W, Palaniappan S, Raja Ali RA. Inflammatory bowel disease-related colorectal cancer in the Asia-Pacific region: past, present, and future. *Intest Res* 2014;**12**:194–204.
25. Ye L, Cao Q, Cheng J. Review of inflammatory bowel disease in China. *Sci World J* 2013;**2013**:1.

26. Kim ER, Chang DK. Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. *World J Gastroenterol* 2014;**20**:9872–81.
27. Marion JF. Colorectal cancer in colitis: a relic of the past? *Inflamm Bowel Dis* 2015;**21**:699–702.
28. Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006;**23**:1097–104.
29. Gong W, Lv N, Wang B *et al*. Risk of ulcerative colitis-associated colorectal cancer in China: a multi-center retrospective study. *Dig Dis Sci* 2012;**57**:503–7.
30. Jess T, Loftus EV Jr, Velayos FS *et al*. Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. *Am J Gastroenterology* 2007;**102**:829–36.
31. Baars JE, Looman CW, Steyerberg EW *et al*. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol* 2011;**106**:319–28.
32. Horvath B, Liu G, Wu X *et al*. Overexpression of p53 predicts colorectal neoplasia risk in patients with inflammatory bowel disease and mucosa changes indefinite for dysplasia. *Gastroenterol Rep (Oxf)* 2015;**3**:344–9.
33. Itzkowitz SH, Present DH. Consensus conference: colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;**11**:314–21.
34. Basseri RJ, Basseri B, Vassilaki ME *et al*. Colorectal cancer screening and surveillance in Crohn's colitis. *J Crohns Colitis* 2012;**6**:824–9.
35. Greenstein AJ, Sachar DB, Smith H *et al*. Cancer in universal and left-sided ulcerative colitis: factors determining risk. *Gastroenterology* 1979;**77**:290–4.
36. Rutter MD, Saunders BP, Wilkinson KH *et al*. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006;**130**:1030–8.
37. Brackmann S, Andersen SN, Aamodt G *et al*. Two distinct groups of colorectal cancer in inflammatory bowel disease. *Inflamm Bowel Dis* 2009;**15**:9–16.
38. Nieminen U, Jussila A, Nordling S *et al*. Inflammation and disease duration have a cumulative effect on the risk of dysplasia and carcinoma in IBD: a case-control observational study based on registry data. *Int J Cancer* 2014;**134**:189–96.
39. Beaugerie L, Svrcek M, Seksik P *et al*. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. *Gastroenterology* 2013;**145**:166–75.e8.
40. Lakatos L, Mester G, Erdelyi Z *et al*. Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study. *Inflamm Bowel Dis* 2006;**12**:205–11.
41. Murthy S, Flanigan A, Clearfield H. Colorectal cancer in inflammatory bowel disease: molecular and clinical features. *Gastroenterol Clin North Am* 2002;**31**:551–64.
42. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004;**287**:G7–17.
43. Winther KV, Jess T, Langholz E *et al*. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2004;**2**:1088–95.
44. Choi CH, Rutter MD, Askari A *et al*. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. *Am J Gastroenterol* 2015;**110**:1022–34.
45. Fevery J, Henckaerts L, Van Oirbeek R *et al*. Malignancies and mortality in 200 patients with primary sclerosering cholangitis: a long-term single-centre study. *Liver Int* 2012;**32**:214–22.
46. Thackeray EW, Charatcharoenwitthaya P, Elfaki D *et al*. Colon neoplasms develop early in the course of inflammatory bowel disease and primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2011;**9**:52–6.
47. Ananthakrishnan AN, Cagan A, Gainer VS *et al*. Mortality and extraintestinal cancers in patients with primary sclerosing cholangitis and inflammatory bowel disease. *J Crohns Colitis* 2014;**8**:956–63.
48. Zheng HH, Jiang XL. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis of 16 observational studies. *Eur J Gastroenterol Hepatol* 2016;**28**:383–90.
49. Lakatos PL, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. *World J Gastroenterol* 2008;**14**:3937–47.
50. Miao XP, Sun XN, Wei H *et al*. Crohn's disease and primary sclerosing cholangitis: a case report and review of the literature. *Intern Med* 2012;**51**:2077–81.
51. Mooiweer E, Baars JE, Lutgens MW *et al*. Disease severity does not affect the interval between IBD diagnosis and the development of CRC: results from two large, Dutch case series. *J Crohns Colitis* 2012;**6**:435–40.