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Inflammation is an Independent Risk Factor for Colonic Neoplasia in Patients with Ulcerative Colitis: a Case–Control Study

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Author Contributions:

Author Responsibilities and Contributions

Author	Study Concept and Design	Data Acquisition	Analysis and Interpretation of Data	Drafting of the Manuscript	Critical Revision of the Manuscript for Important Intellectual Content	Statistical Analysis	Material Support	Study Supervision
Rubin	X	X	X	X	X			X
Huo	X		X		X	X		
Kinnucan		X		X				
Sedrak		X	X					
McCullom		X					X	
Bunnag		X	X				X	
Raun-Royer			X	X	X			
Cohen		X			X			
Hanauer		X			X			
Hart		X	X		X			
Turner	X	X	X		X			X

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Abstract

Background & Aims—An association between inflammatory activity and colorectal neoplasia (CRN) has been documented in patients with ulcerative colitis (UC). However, previous studies did not address the duration of inflammation or the effects of therapy on risk for CRN. We investigated the effects of inflammation, therapies, and characteristics of patients with UC on their risk for CRN.

Methods—We collected data from 141 patients with UC without CRN (controls), and 59 matched patients with UC who developed CRN (cases), comparing disease extent and duration and patients' ages. We used a new 6-point histologic inflammatory activity (HIA) scale to score biopsy fragments (n=4449). Information on medications, smoking status, primary sclerosing cholangitis (PSC), and family history of CRN were collected from the University of Chicago Inflammatory Bowel Disease Endoscopy Database. Relationships between HIA, clinical features, and CRN were assessed by conditional logistic regression.

Results—Cases and controls were similar in numbers of procedures and biopsies, exposure to steroids or mesalamine, smoking status, and family history of CRN. They differed in proportion of men vs women, exposure to immune modulators, and PSC prevalence. In univariate analysis, HIA was positively associated with CRN (odds ratio [OR], 2.56/ per unit increase; $P=.001$), whereas immune modulators (including azathioprine, 6-mercaptopurine, and methotrexate) reduced the risk for CRN (OR, 0.35; $P<.01$). HIA was also associated with CRN in multivariate analysis (OR, 3.68; $P=.001$).

Conclusion—In a case-control study, we associated increased inflammation with CRN in patients with UC. Use of immune modulators reduced the risk for CRN, indicating that these drugs have chemoprotective effects. Based on these data, we propose new stratified surveillance and treatment strategies to prevent and detect CRN in patients with UC.

Keywords

IBD; AZA; 6MP; 5-ASA; colorectal cancer; chemoprevention; dysplasia

Introduction

The association between UC and colorectal cancer (CRC)^{1,2} has been linked to disease duration and extent, primary sclerosing cholangitis (PSC), family history of CRC.³⁻⁵ Additional potential risk factors include , age at diagnosis, backwash ileitis. pseudopolyps, degree of inflammatory activity.³⁻⁷

Although incompletely understood, inflammatory processes are thought to contribute to UC-associated colorectal neoplasia (CRN) pathogenesis.⁸ In support of this idea, a study from St. Mark's Hospital used an IBD surveillance database to retrospectively assess the degree of histological and endoscopic inflammation as independent risk factors for CRN. They found that the degree of histological, but not endoscopic, inflammation was an independent risk factor for CRN. [ENREF 7](#)⁷ [ENREF 7](#) Similarly, a retrospective cohort analysis at Mt. Sinai Medical Center found that increasing histologic inflammation was associated with high grade dysplasia or CRC, but not with low grade dysplasia.⁶

Despite the advances above, the relationship between CRN risk and a single episode of severe inflammation, relative to multiple distinct relapses of milder inflammation over

longer periods of time, has not been explored. This is critical for development of strategies that incorporate inflammation control into long-term risk reduction. Unfortunately, no retrospective studies of UC therapies and potential chemoprotective effects to reduce CRN risk considered degree of inflammation as a confounding variable.^{1,9,10} Thus, the aim of this study was to comprehensively evaluate the risk of CRN in UC by measuring the degree of histologic inflammation over time and adjusting for therapy exposures and other known risk factors.

Methods

A case-control study design was used to study UC patients drawn from IBD Endoscopy Database and IBD Registry, two databases that include all IBD patients seen at the University of Chicago. Patients with CRN, including flat low-grade dysplasia, high-grade dysplasia or adenocarcinoma, were selected as cases. Patients with discreet polypoid dysplasia proximal to the area of colitis were excluded.

Controls without CRN were selected from the same databases by matching CRN cases on 1) histological extent of disease, 2) age at diagnosis, and 3) duration of disease (within 5 years). The index date for cases was defined as the date of CRN diagnosis, and UC duration was defined as the number of years between UC diagnosis and index date. This approach also ensured that the ages at diagnosis (UC) were similar between cases and controls. Controls were only included if they did not have surgery during a duration of disease that was at least as long as their matching CRN case. Depending on availability, 1 to 4 controls were identified for each case.

Medical Record Abstraction

All electronic records as well as original paper records were reviewed for patients in this study. The latter included original records from referring physicians and detailed prior medication history collected on initial consultation in our center. Only patients with complete records were included in this study.

Patients were classified as current smokers if they had smoked since the onset of UC; ex-smokers were defined as patients with smoking cessation prior to onset of disease. PSC required confirmation by biopsy or imaging studies and liver function tests. Family history was defined as Crohn's disease or UC in first or second-degree relatives or CRC in first-degree relatives.

Duration and dosage of 5-aminosalicylic acid (5-ASA), including sulfasalazine and nonsulfasalazines, were converted to mesalamine equivalents.⁹ Average mesalamine intensity (grams per day) and the total combined mesalamine intensity (total mesalamine equivalents, calculated by multiplying the number of days by the dose taken) were determined. If dosage was unknown but duration known, the calculated average mesalamine intensity was used as total combined mesalamine intensity. When exact date of dosage changes was unknown, it was assumed to have occurred halfway between the clinic visits. Calculations were performed and independently reviewed by three individuals to ensure accuracy.

Duration and dosage of AZA, 6MP, and methotrexate were recorded. Because non-uniform tapering schedules prevented accurate calculation of total steroid exposure, the number of discrete episodes of exposure to oral prednisone or rectal steroids was recorded. Folate supplementation was also recorded. Anti-TNF agents were not yet available for UC patients at the time of this retrospective review.¹¹

Pathology Review

Pathology reports and hematoxylin and eosin-stained slides from all diagnostic, screening and surveillance endoscopy biopsies were retrieved for cases and controls between May 1994 and July 2005. Each colonoscopy was considered a unique episode of assessment and each biopsy fragment was assessed as an individual specimen. Available colectomy specimens were reviewed to confirm UC and CRN diagnoses, but not to assess histological inflammatory activity (HIA).

A novel 6-point HIA scale was developed for this study. Because previous studies suggested that low grade chronic inflammation was associated with increased CRN risk,^{6,7} this scale was designed to expand the low range of the scale. A score of zero was given to normal tissue completely uninvolved by disease with no architectural distortion or inflammatory infiltrates. An HIA score of one was given to tissue with quiescent disease exhibiting architectural distortion and increased lamina propria mononuclear infiltrates. Tissue with increased numbers of granulocytes in the lamina propria, but no intraepithelial granulocytes, was assigned an HIA score of two. An HIA score of three denoted intraepithelial granulocytes without crypt abscesses, while the presence of crypt abscesses in less than 50% of crypts rated an HIA score of four. If crypt abscesses were present in greater than 50% of crypts or erosion or ulceration was present an HIA score of five was assigned (See supplemental figure 1).

Non-study biopsies were reviewed by two pathologists to develop the HIA scale and clarify interpretation. Samples from the first, second and third set of 10 surveillance endoscopy procedures were then reviewed independently by both pathologists and reviewed together to develop consensus. Agreement improved over these sets and remaining tissue samples were reviewed by only one of the two study pathologists.

Statistical Analysis

Two summative inflammation scores were calculated. The average inflammation of each procedure was calculated from the biopsy fragments in that procedure, and the average of all procedure scores was then calculated as the “mean score” for each patient. The maximum HIA score for any single biopsy fragment was reported as the “maximum score.” To assess whether CRN risk is associated with a single episode of severe inflammation or multiple episodes of milder disease, the independent effects of mean and maximum HIA score on the risk of CRN was assessed using a multivariate conditional logistic regression. Kappa statistics were calculated to assess inter-observer agreement between the two pathologists.¹²

Conditional logistic regression was used to examine the relationship of inflammation score and other clinical parameters to the risk of CRN. The effect was expressed as odds ratios (OR) or adjusted odds ratios (AOR) with a 95% confidence interval (CI). Potential confounding variables were controlled in multiple logistic regression models. Factors that correlated with inflammation score among patients without CRN were assessed using t-test or Spearman correlation.

Results

Patient Characteristics

We identified 59 eligible cases of UC-related CRN between 1994 and 2005; 15 had CRC, five had high-grade dysplasia, 33 had low-grade dysplasia, and six were indefinite for dysplasia. The mean age of cases and controls at index date of CRN diagnosis was 47.1 years with mean disease duration of 18.8 years. Cases were matched with 141 controls (2.4 controls per case). Cases and controls were similar in age and years since UC diagnosis, and

were perfectly matched in extent of disease. However, CRN cases included a greater proportion of males than controls (Table 1).

Histological inflammatory activity scores

4449 biopsy specimens obtained in 335 procedures were reviewed. Numbers of procedures and specimens per patient were similar in cases and controls (Table 1). The first 30 procedures (429 biopsies) were reviewed by both study pathologists to evaluate the inter-observer variability. Inter-observer agreement improved with review: the kappa was 0.49, 0.54 and 0.60 for the first, second, and third set of 10 procedures reviewed. This indicates moderate agreement without training and improvement to substantial agreement after training¹² and shows that our novel scale is reproducible. Similar proportions of cases and controls were examined by each pathologist ($p=0.59$).

Mean HIA scores of CRN cases were greater than those of controls ($p=0.001$; Table 2). Based on mean scores, patients were classified as no inflammatory activity (scores 0-1), mild inflammatory activity (score 2), or moderate to severe inflammatory activity (scores 3-5). A dose-response relationship was observed between mean HIA score and CRN risk (Figure 1). The maximum HIA scores of CRN cases were also greater than controls ($p=0.03$; Table 2), indicating that CRN cases had more intense inflammatory episodes than controls. These differences remained significant when the analyses were limited to patients with pancolitis (Table 2).

In multivariate conditional regression assessment of the effect of multiple mild inflammatory episodes compared to a single severe episode of inflammation, the mean HIA score remained statistically significant ($p=0.013$). However, the maximum HIA score was no longer significant ($p=0.99$). In particular, the average score of 0 to 1 was not predictive of an elevated risk of CRN even when there were separate episodes of more severe inflammation (Table 3). Because the mean and maximum HIA scores and CRN risk were highly correlated (Spearman correlation coefficient = 0.70, $p<0.0001$), mean scores were used in subsequent analyses.

Sensitivity analysis for single colonoscopies

Given the potential bias of patients who had only one colonoscopy during which neoplasia and degree of inflammation was measured, a sensitivity analysis was performed after removing the 27 cases with only one colonoscopy that included the diagnosis of neoplasia. In this analysis the odds ratio for 1 unit change in mean inflammation score was 3.96 ($p=0.014$), similar to odds ratio of 3.68 ($p=0.001$) for all patients. We therefore included these patients in subsequent analyses.

Univariate analysis of other risk factors for CRN

Univariate analysis of the relationship between CRN and other patient characteristics demonstrated that PSC increased CRN risk (Table 4). Conversely, treatment with immune modulators (AZA, 6MP, and methotrexate) and mesalamine (non-sulfasalazine 5-ASA) were protective. However, patients treated with sulfasalazine were not protected relative to patients who had never received sulfasalazine (OR=0.72, CI 0.35-1.52; $p=0.39$). In contrast, patients treated with non-sulfasalazines were protected CRN compared relative to those who had never received non-sulfasalazines (OR=0.32, CI 0.76-2.95 $p=0.003$).

Subgroup analysis for cancer and dysplasia

In univariate subgroup analysis, cancer and dysplasia patients were evaluated separately. Similar to the primary analysis, a one-unit increase in HIA was associated with a 2.64-fold

increased risk of CRC (n=15, p=0.16) (Table S1) and a 2.54-fold increased risk of dysplasia (n= 44, p=0.004) (Table S2).

Multivariate analysis

In multivariate analysis mean HIA score remained significantly associated with CRN risk; the adjusted odds ratio for one-unit HIA increase was 3.68 (95% CI 1.69-7.98; p=0.001) (Table 5). Adjusting for PSC or removing PSC patients entirely did not change the results (OR 3.44 or 3.04, respectively). Male gender was also a significant risk for CRN (AOR 5.45, 1.79-16.6). After adjusting for HIA, the protective effect of immune modulators remained significant (AOR 0.25, 0.08-0.73) and mesalamine remained suggestive of benefit (AOR 0.37, 0.13-1.04).

Correlates for inflammation score

In analyses of patients without CRN (controls) (Tables S1-S3), we found that female colitis patients tended to have higher HIA scores than males (p=0.057). Patients who ever used AZA/6-MP also had higher HIA, but longer disease duration trended with lower HIA. While, patients who ever used non-sulfa aminosalicylates also tended to have higher HIA than those who did not, longer exposure durations corresponded with lower HIA. This paradoxical finding may reflect more frequent use of anti-inflammation agents in patients subjects with severe inflammation, but greater efficacy of longer treatment durations or “survival bias,” with colectomy removing patients with the most severe inflammation or treatment failure from the risk pool.

Discussion

In this case-control study we confirm the association between increased degree of inflammation and subsequent neoplasia in patients with UC. This confirmation was achieved through our systematic approach, using one of the largest patient cohorts to date, blinded re-reading of pathology, comprehensive assessments of risk factors and variables for each case, and elimination of confounders using a matched case-control design. Our study also confirmed previous conclusions that male patients with UC are at higher risk for CRN and provides new information about the chemoprotective roles of aminosalicylates and thiopurines.¹⁶

The first major study of the relationship between inflammation and CRN in UC was based on the St. Mark's Hospital cancer surveillance database.¹³ Using a retrospective review employing categorical grading for endoscopic and histologic degrees of inflammation in 68 CRN cases and 136 controls, univariate analysis found that CRN was indeed increased in UC patients with greater grades of endoscopic or histologic inflammation. However, only histologic degree of inflammation remained significantly associated with CRN on multivariate analysis.⁷ [ENREF 7](#) Similarly, a retrospective review of 418 UC patients, of whom 65 had CRN, at Mt. Sinai Medical Center found that inflammation was associated with high grade dysplasia or cancer.⁶ [ENREF 6](#) While these studies have contributed significantly to understanding of the relationship between inflammation and CRN in UC, both suffer from limitations. Among these is the purely retrospective nature of these studies, involvement of multiple endoscopists and pathologists over the time period of review, and incomplete adjustment for known or suspected confounding variables such as dose or duration of medication exposure. Importantly, the endoscopists and pathologists were not blinded to the clinical care or current status of the patient when they performed their original exams, and correlation between observers was not assessed.

Our study is unique in several important ways, most notably in the re-review and grading of all pre-existing biopsies by expert gastrointestinal pathologists who were blinded to patient outcomes as well as prior pathology reports. It is a strength of this study that the pathologists were trained, given feedback, and demonstrated substantial inter-observer agreement. Given the large number of patients and samples and the many years of data required to perform such an analysis, another strength of our study design that all tissue was reviewed and scored using a single scale. This eliminated concerns of retrospective chart review and potential bias introduced by clinical information during tissue diagnosis. We also quantified detailed exposure to medical therapies in all patients throughout their history, prior to developing CRN, and thus minimized the effect of recall bias. Finally, cases were matched to controls based on known risk factors, including age at diagnosis and duration and extent of disease. Further, multivariable conditional logistic regression was used to remove confounding due to these factors. Using our novel University of Chicago HIA scale, multivariate analysis related one-unit increase in mean HIA to a greater than three-fold increase in CRN risk. CRN risk was increased up to 7-fold in patients with higher degrees of inflammation

This study is also unique in that it uses maximum and mean HIA scores over time to ask if a short period of severe disease confers the same CRN risk as a longer period of milder relapsing or chronically-active inflammation? The data indicate that mean inflammation over time is more important than a single maximum HIA score. Although there are acknowledged limitations, this suggests that reduced inflammation and stable maintenance of disease may lessen CRN risk. This suggests that active inflammation should be considered a marker of increased CRN risk and should trigger more intensive prevention strategies.

Impact of Aminosalicylates on CRN in UC

There has been great interest in the chemopreventive properties of aminosalicylates in chronic UC with studies suggesting that exposure to this therapy may prevent CRN,¹⁴ [ENREF 17](#) and other notable studies finding no protective effect.^{7,10, 15} [ENREF 11](#) In a meta-analysis of cohort and case-control studies of 5-ASA and CRN in UC, Velayos and colleagues described a significantly reduced risk of CRN in UC patients exposed to 5-ASAs (OR 0.51, 95% CI (0.4-0.7)).¹⁴ [ENREF 17](#) However, Bernstein and colleagues performed population based studies of this association and reported no association between the development of CRC and 5-ASA use (HR 1.04, 95% CI (0.67-1.62)) and when studying those patients who did develop CRC, they found no difference in 5-ASA use compared to controls. Similar to findings in other studies related to gender, they did note an increased risk of CRC in male patients.¹⁰ [ENREF 10](#) However, most studies of chemoprevention have not accounted for degree of inflammation as a confounding variable. The St. Mark's multivariate analysis controlling for degree of inflammation was included in the Velayos meta-analysis, and did not find a statistically significantly reduced risk of CRN associated with 5-ASAs, but reported a nonsignificant trend for non-sulfasalazine aminosalicylates towards reduced neoplasia rates with increasing years of exposure.⁷ [ENREF 7](#)

The present study, which controlled for degree of inflammation and added the additional detail of dose of 5-ASA therapies, provides a possible explanation for the findings and discrepancies of prior studies, including our own.⁹ [ENREF 9](#) In the univariate analysis of 5-ASA use and CRN, we identified a chemoprotective effect of any 5-ASA exposure (OR 0.08, CI 0.01-0.68), but when controlling for type of 5-ASA and adjusting for other risks including inflammation, the benefit maintained an odds ratio of protection, but had a wider confidence interval and p value (AOR for non-sulfasalazine 5-ASA 0.37, CI 0.132-1.04, p=0.056).

Impact of Azathioprine and 6-mercaptopurine on CRN in UC

Our study provides strong evidence of a protective effect of immunomodulators against UC-associated CRN. Because we controlled for degree of inflammation and all other known risk factors, this result suggests that these therapies may have unique chemopreventive properties. The mechanism of such an interaction is not known, but may be related to cytotoxicity towards aberrant epithelial cells or other stop signals in mutated DNA replication. Clearly more work is needed in this area. It would be of interest to compare the risk of lymphoma associated with thiopurine exposure¹⁶ [ENREF 25](#) to the potential benefit identified in this study.

Limitations

As with any retrospective analysis, inaccuracies in data collection may have affected our results. However, the use of overlapping data sources (electronic records, pathology reports and review of biopsy and colectomy specimens) make this limitation less likely. There also may have been a selection bias for patients who have more frequent sigmoidoscopies or colonoscopies based on their disease activity or adherence to office visits and prevention programs. This limitation is minimized by the concordance between number of procedures and biopsies in CRN patients and controls. While efforts were made to exclude pathology from uninvolved colon in patients with distal disease, another potential bias is the possible inclusion of non-diseased mucosa in the study. However, analysis of pancolitis-only patients also demonstrated a significant increase in CRN risk with inflammation, suggesting that inclusion of non-diseased mucosa did not significantly affect the results.

Conclusions

This large U.S. study confirms that increased histological degree of inflammation is associated with a greater risk for neoplasia in patients with UC and, importantly, adds to the understanding that risk increases with mean activity over time rather than with a single severe episode of disease. We also demonstrate that male gender is an important risk factor and thiopurine exposure is associated with a significantly decreased CRN risk in UC. Furthermore, our data may explain discrepancies between prior 5-ASA chemoprotection study results. The implications of this information are significant and include the need to stratify patients for CRN risk in a variety of new ways. In the emerging era of “individualized medicine,” we suggest that this comprehensive study of neoplasia risk in UC patients provides compelling information about customizing discussions and the incorporation of existing cancer prevention guidelines. More severe disease should also prompt consideration of intensive surveillance strategies and assist in rational distribution of health care resources to those at highest risk.

Finally, these data demand that we to revise treatment endpoints and therapeutic goals from a focus on “symptomatic improvement” to one of sustained control of inflammation. Such a recommendation has already been incorporated into the British Society of Gastroenterology guidelines for UC management.¹⁷ [ENREF 14](#) [ENREF 16](#) Our study provides evidence that supports this approach and indicates that “control” should be defined histologically or by validated biomarkers of histologic inflammation. Prospective trials of therapies and measurements of outcomes must incorporate these findings into a concept of the longitudinal health of UC patients. By doing so, we will move into an era in which we can successfully modify long-term outcomes for our UC patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Odds ratios and 95% confidence intervals of colorectal cancer and dysplasia by inflammation score calculated in the univariate and multivariate conditional logistic regressions. The multivariate odds ratios were adjusted, immune modulator, nonsulfasalazine mesalamine use, and gender.

Table 1

Characteristics of cases and controls

Characteristics	Cases (n=59)		Controls (n=141)		p*
	Mean	(SD)	Mean	(SD)	
Age	47.1	(11.9)	46.7	(11.5)	0.80
Age at ulcerative colitis diagnosis	27.7	(12.1)	28.2	(11.3)	0.66
Years of ulcerative colitis	19.4	(10.1)	18.5	(10.1)	0.72
Gender, n (%)					
Female	13	(22)	73	(52)	<0.001
Male	46	(78)	68	(48)	
Extent, n (%)					
Pancolitis	50	(85)	115	(82)	1.00
Left sided	8	(14)	25	(18)	
Proctitis	1	(2)	1	(1)	
Total no. of procedures	111		224		
No. of procedures per patient, n (%)					0.37
1	27	(49)	70	(60)	
2	14	(25)	23	(20)	
3+	14	(25)	23	(20)	
Total no. of inflammation scores	1565		2884		
Median no. of scores per patient (range)	24	(4-103)	16	(5-123)	0.20

*
p-value from conditional logistic regression

Table 2

Inflammation severity score and the risk of colorectal cancer and dysplasia

Inflammation score	Cases		Control		OR [†]	(95% CI)	p-value
<i>In all patients (n=171)</i>							
	<i>Mean</i>	<i>(SD)</i>	<i>Mean</i>	<i>(SD)</i>			
Mean score	2.00	(0.89)	1.55	(0.68)	2.56	(1.45-4.54)	0.001
Maximum score	3.70	(1.22)	3.25	(1.32)	1.41	(1.03-1.91)	0.03
Mean score	<i>n</i>	<i>(%)</i>	<i>n</i>	<i>(%)</i>			
0-1	19	(35)	68	(59)	1.00	(ref.)	0.005
2	23	(42)	35	(30)	2.90	(1.23-6.85)	
3-5	13	(24)	13	(11)	4.35	(1.33-14.3)	
Maximum score							
1-2	9	(16)	30	(26)	1.00	(ref.)	0.04
3	14	(25)	36	(31)	1.44	(0.53-3.87)	
4-5	32	(58)	50	(43)	2.69	(1.00-7.24)	
<i>In pancolitis patients (n=142)</i>							
	<i>Mean</i>	<i>(SD)</i>	<i>Mean</i>	<i>(SD)</i>			
Mean score	1.96	(0.76)	1.57	(0.69)	2.31	(1.26-4.23)	0.007
Maximum score	3.70	(1.10)	3.21	(1.32)	1.46	(1.03-2.07)	0.033
Mean score	<i>n</i>	<i>(%)</i>	<i>n</i>	<i>(%)</i>			
0-1	15	(32)	55	(58)	1.00	(ref.)	0.017
2	22	(47)	30	(32)	3.14	(1.26-7.79)	
3-5	10	(21)	10	(11)	3.34	(0.95-11.8)	
Maximum score							
1-2	7	(15)	26	(27)	1.00	(ref.)	0.054
3	13	(28)	29	(31)	1.72	(0.61-4.88)	
4-5	27	(57)	40	(42)	2.82	(0.97-8.20)	

[†]Odds ratio was calculated per 1 unit change in the score if no reference group is specified.

Table 3

Independent effect of mean and maximum inflammation severity score on the risk of colorectal cancer and dysplasia

Inflammation score	AOR [†]	(95% CI)	p-value
<i>As continuous variables</i>			
Mean score	2.57	(1.22-5.39)	0.013
Maximum score	1.00	(0.67-1.49)	0.99
<i>As categorical variables</i>			
Mean score			
0-1	1.00	(ref.)	0.044
2	2.75	(0.98-7.74)	
3-5	3.96	(0.95-16.5)	
Maximum score			
1-2	1.00	(ref.)	0.70
3	0.92	(0.31-2.74)	
4-5	1.12	(0.31-3.97)	

	Mean score 0-1		Mean score 2		Mean score 3-5	
Maximum score	Case	Control	Case	Control	Case	Control
1-2	9	29		1		
3	6	24	6	10	2	2
4-5	4	15	17	24	11	11

[†] Adjusted odds ratio per 1 unit change in the score if no reference group is specified; calculated from conditional logistic model including both mean and maximum inflammation scores.

Table 4

Other risk factors of colorectal neoplasia: Univariate analysis

Risk factor	Cases (n=59)		Control (n=141)		OR	(95% CI)	p-value
Smoking, n (%)							
Never	41	(69)	105	(75)	1.00	(ref.)	0.63
Ex	10	(17)	19	(14)	1.54	(0.63-3.74)	
Current	8	(14)	16	(11)	1.15	(0.45-2.99)	
Family history of colorectal cancer, n (%)							
No	53	(90)	131	(94)	1.00	(ref.)	
Yes	6	(10)	8	(6)	2.25	(0.74-6.89)	0.15
Primary sclerosing cholangitis, n (%)							
No	51	(86)	135	(96)	1.00	(ref.)	
Yes	8	(14)	5	(4)	3.62	(1.16-11.3)	0.026
Azathioprine, n (%)							
No	54	(92)	107	(76)	1.00	(ref.)	
Yes	5	(8)	33	(24)	0.33	(0.12-0.90)	0.031
6-MP, n (%)							
No	52	(88)	112	(80)	1.00	(ref.)	
Yes	7	(12)	28	(20)	0.38	(0.12-1.15)	0.087
Azathioprine/6-MP, n (%)							
No	49	(83)	84	(60)	1.00	(ref.)	
Yes	10	(17)	56	(40)	0.28	(0.12-0.65)	0.003
Duration of azathioprine/6-MP, n (%)							
Never	49	(83)	84	(60)	1.00	(ref.)	0.001
< 2 years	3	(5)	24	(17)	0.19	(0.05-0.70)	
2 years	5	(9)	32	(23)	0.27	(0.09-0.78)	
Dose of azathioprine/6-MP, mean (SD)	91	(71)	77	(37)			1.0
Methotrexate, n (%)							
No	56	(95)	138	(99)	1.00	(ref.)	
Yes	3	(5)	2	(1)	2.51	(0.40-15.6)	0.32
Immune modulators, n (%)							
No	47	(80)	84	(60)	1.00	(ref.)	
Yes	12	(20)	56	(40)	0.36	(0.17-0.77)	0.009
Number of steroids exposure *, median (IQR)	2	(1-4)	2	(1-3)	1.05	(0.88-1.26)	0.58
Folate supplement, n (%)							
No	31	(53)	74	(53)	1.00	(ref.)	
Yes	28	(47)	66	(47)	1.13	(0.60-2.13)	0.71
NSAID							
No	49	(83)	127	(91)	1.00	(ref.)	

Risk factor	Cases (n=59)		Control (n=141)		OR	(95% CI)	p-value
Yes	10	(17)	13	(9)	1.84	(0.75-4.50)	0.18
Sulfasalazine, n (%)							
Never	18	(31)	34	(24)	1.00	(ref.)	
Ever	41	(69)	106	(76)	0.72	(0.35-1.52)	0.39
Years of sulfasalazine, n (%)							
Never	18	(31)	34	(24)	1.00	(ref.)	0.62
< 10 years	19	(32)	56	(40)	0.67	(0.30-1.50)	
10 years	22	(37)	50	(36)	0.82	(0.34-1.99)	
Dose of sulfasalazine, n (%)							
< 1.2 g daily	32	(54)	86	(61)	1.00	(ref.)	
1.2 g daily	27	(46)	54	(39)	1.49	(0.76-2.95)	0.25
Nonsulfasalazine mesalamine, n (%)							
Never	27	(46)	35	(25)	1.00	(ref.)	
Ever	32	(54)	105	(75)	0.32	(0.15-0.68)	0.003
Years of nonsulfasalazine mesalamine use, n (%)							
Never	27	(46)	35	(25)	1.00	(ref.)	0.002
< 10 years	26	(44)	76	(54)	0.38	(0.17-0.86)	
10 years	6	(10)	29	(21)	0.18	(0.05-0.62)	
Dose of nonsulfasalazine mesalamine use, n (%)							
< 1.2 g daily	27	(46)	42	(30)	1.00	(ref.)	0.047
1.2-2.4 g daily	6	(10)	18	(13)	0.55	(0.19-1.57)	
2.4-3.6 g daily	15	(25)	32	(23)	0.76	(0.35-1.65)	
3.6 g daily	11	(19)	48	(34)	0.32	(0.13-0.79)	
1.2 vs. <1.2 g daily					0.52	(0.27-1.00)	0.052
All 5-ASA, n (%)							
Never	7	(12)	2	(1)	1.00	(ref.)	
Ever	52	(88)	138	(99)	0.08	(0.01-0.68)	0.02
Years of all 5-ASA *, median (IQR)	11	(6-21)	12	(6-19)	1.00	(0.95-1.04)	0.86
Dose of all 5-ASA, n (%)							
< 1.2 g daily	15	(25)	27	(19)	1.00	(ref.)	0.08
1.2-2.4 g daily	29	(49)	59	(43)	0.96	(0.42-2.19)	
2.4-3.6 g daily	12	(20)	32	(23)	0.70	(0.26-1.90)	
3.6 g daily	3	(5)	22	(16)	0.17	(0.03-0.90)	
1.2 vs. <1.2 g daily					0.75	(0.35-1.63)	0.47

OR, odds ratios; IQR, interquartile range

* Odds ratio is for 1 unit change.

Table 5

Multivariate analysis of colorectal neoplasia

Risk factor	AOR (95% CI)*	p-value	AOR (95% CI)*	p-value
Inflammation score				
Per 1 unit increase	3.68 (1.69-7.98)	.001		
2 vs. 0-1			4.91 (1.68-14.3)	.004
3-5 vs. 0-1			7.12 (1.70-29.8)	.007
Immune modulators	0.24 (0.08-0.74)	.013	0.25 (0.08-0.73)	.011
Nonsulfasalazine mesalamine	0.37 (0.13-1.04)	.06	0.36 (0.12-1.03)	.056
Male	5.45 (1.79-16.6)	.003	5.69 (1.89-17.1)	.002

AOR, adjusted odds ratio; CI, confidence interval.

* Adjusting for variables in the table