Inflammation Is an Independent Risk Factor for Colonic Neoplasia in Patients With Ulcerative Colitis: A Case–Control Study

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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, 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 primary sclerosing cholangitis 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; $P = .001$).**

CONCLUSIONS: **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. On the basis of these data, we propose new stratified surveillance and treatment strategies to prevent and detect CRN in patients with UC.**

Keywords: IBD; AZA; 6MP; Mesalamine; Colorectal Cancer; Chemoprevention; Dysplasia.

The association between ulcerative colitis (UC) and colorectal cancer (CRC)[1,2] has been linked to disease duration and extent, primary sclerosing cholangitis (PSC), and family history of CRC.[3–5] Additional potential risk factors include age at diagnosis, backwash ileitis. pseudopolyps, and 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 inflammatory bowel disease (IBD) surveillance database to retrospectively assess the degree of histologic and endoscopic inflammation as independent risk factors for CRN. They found that the degree of histologic, but not endoscopic, inflammation was an independent risk factor for CRN.[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 these advances, the relationship between CRN risk and a single episode of severe inflammation, relative to multiple distinct relapses of milder inflammation during 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.

Abbreviations used in this paper: AOR, adjusted odds ratio; CI, confidence interval; CRC, colorectal cancer; CRN, colorectal neoplasia; HIA, histologic inflammatory activity; IBD, inflammatory bowel disease; 6-MP, 6-mercaptopurine; OR, odds ratio; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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Methods

A case–control study design was used to study UC patients drawn from IBD Endoscopy Database and IBD Registry, 2 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 discrete 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) histologic 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, 1–4 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 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 before 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 mesalamine, 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 was 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 3 individuals to ensure accuracy.

Duration and dosage of azathioprine, 6-mercaptopurine (6-MP), and methotrexate were recorded. Because nonuniform 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–tumor necrosis factor agents were not yet available for UC patients at the time of this retrospective review.[11]

Pathology Review

Pathology reports and hematoxylin-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 histologic 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 0 was given to normal tissue completely uninvolved by disease with no architectural distortion or inflammatory infiltrates. An HIA score of 1 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 2. An HIA score of 3 denoted intraepithelial granulocytes without crypt abscesses, whereas the presence of crypt abscesses in less than 50% of crypts rated an HIA score of 4. If crypt abscesses were present in more than 50% of crypts or erosion or ulceration was present, an HIA score of 5 was assigned (Supplementary Figure 1).

Non-study biopsies were reviewed by 2 pathologists to develop the HIA scale and clarify interpretation. Samples from the first, second, and third sets 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 1 of the 2 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 were assessed by using a multivariate conditional logistic regression. Kappa statistics were calculated to assess interobserver agreement between the 2 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 ratio (OR) or adjusted odds ratio (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 by 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, 5 had high-grade dysplasia, 33 had low-grade dysplasia, and 6 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 men than controls (Table 1).

Histologic Inflammatory Activity Scores

The 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 interobserver variability. Interobserver agreement improved with review; the kappa value was 0.49, 0.54, and 0.60 for the first, second, and third sets of 10 procedures reviewed. This indicates moderate agreement without training and improvement to substantial agreement after training[12] and shows that our novel scale is reproducible. Similar proportions of cases and controls were examined by each pathologist ($P = .59$).

Mean HIA scores of CRN cases were greater than those of controls ($P = .001$, Table 2). On the basis of 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 ($P = .03$, 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 with a single severe episode of inflammation, the mean HIA score remained statistically significant ($P = .013$). However, the maximum HIA score was no longer significant ($P = .99$). In particular, the average score of 0–1 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, $P < .0001$), mean scores were used in subsequent analyses.

Table 1. Characteristics of Cases and Controls

Characteristics	Cases (n = 59) Mean	Cases (n = 59) Standard deviation	Controls (n = 141) Mean	Controls (n = 141) Standard deviation	*P* value[a]
Age (*y*)	47.1	11.9	46.7	11.5	.80
Age at UC diagnosis (*y*)	27.7	12.1	28.2	11.3	.66
Years of UC	19.4	10.1	18.5	10.1	.72
Sex, n (%)					
Female	13	22	73	52	<.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 (%)					.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)	.20

[a]From conditional logistic regression.

Sensitivity Analysis for Single Colonoscopies

Because of the potential bias of patients who had only 1 colonoscopy during which neoplasia and degree of

Table 2. Inflammation Severity Score and Risk of CRC and Dysplasia

Inflammation score	Cases		Controls		OR[a]	95% CI	*P* value
In all patients (n = 171)							
	Mean	**Standard deviation**	**Mean**	**Standard deviation**			
Mean score	2.00	0.89	1.55	0.68	2.56	1.45–4.54	.001
Maximum score	3.70	1.22	3.25	1.32	1.41	1.03–1.91	.03
Mean score	**n**	**%**	**n**	**%**			
0–1	19	35	68	59	1.00	Reference	.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	Reference	.04
3	14	25	36	31	1.44	0.53–3.87	
4–5	32	58	50	43	2.69	1.00–7.24	
In pancolitis patients (n = 142)							
	Mean	**Standard deviation**	**Mean**	**Standard deviation**			
Mean score	1.96	0.76	1.57	0.69	2.31	1.26–4.23	.007
Maximum score	3.70	1.10	3.21	1.32	1.46	1.03–2.07	.033
Mean score	**n**	**%**	**n**	**%**			
0–1	15	32	55	58	1.00	Reference	.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	Reference	.054
3	13	28	29	31	1.72	0.61–4.88	
4–5	27	57	40	42	2.82	0.97–8.20	

[a]OR was calculated per 1-unit change in the score if no reference group is specified.

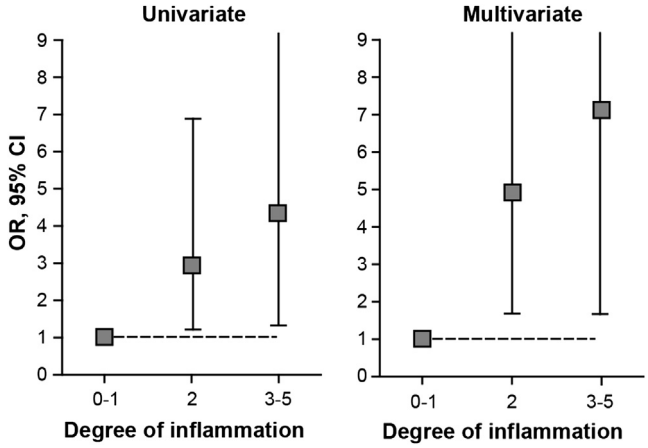

Figure 1. ORs and 95% CIs of CRC and dysplasia by inflammation score calculated in the univariate and multivariate conditional logistic regressions. The multivariate ORs were adjusted by immune modulator, nonsulfasalazine mesalamine use, and sex.

inflammation were measured, a sensitivity analysis was performed after removing the 27 cases with only 1 colonoscopy that included the diagnosis of neoplasia. In this analysis the OR ratio for a 1-unit change in mean inflammation score was 3.96 ($P = .014$), similar to the OR of 3.68 ($P = .001$) for all patients. We therefore included these patients in subsequent analyses.

Univariate Analysis of Other Risk Factors for Colorectal Neoplasia

Univariate analysis of the relationship between CRN and other patient characteristics demonstrated that PSC increased CRN risk (Table 4). Conversely, treatment with immune modulators (azathioprine, 6-MP, and methotrexate) and mesalamine (nonsulfasalazine mesalamine) was 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; $P = .39$). In contrast, patients treated with nonsulfasalazines were protected from CRN compared to those who had never received nonsulfasalazines (OR = 0.32; CI, 0.76–2.95; $P = .003$).

Table 3. Independent Effect of Mean and Maximum Inflammation Severity Score on Risk of CRC and Dysplasia

Inflammation score	AOR[a]	95% CI	*P* value
As continuous variables			
Mean score	2.57	1.22–5.39	.013
Maximum score	1.00	0.67–1.49	.99
As categorical variables			
Mean score			
0–1	1.00	Reference	.044
2	2.75	0.98–7.74	
3–5	3.96	0.95–16.5	
Maximum score			
1–2	1.00	Reference	.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

[a]AOR per 1-unit change in the score if no reference group is specified; it is calculated from conditional logistic model including both mean and maximum inflammation scores.

Subgroup Analysis for Cancer and Dysplasia

In univariate subgroup analysis, cancer and dysplasia patients were evaluated separately. Similar to the primary analysis, a 1-unit increase in HIA was associated with a 2.64-fold increased risk of CRC (n = 15, $P = .16$) (Supplementary Table 1) and a 2.54-fold increased risk of dysplasia (n = 44, $P = .004$) (Supplementary Table 2).

Multivariate Analysis

In multivariate analysis mean HIA score remained significantly associated with CRN risk; the AOR for a 1-unit HIA increase was 3.68 (95% CI, 1.69–7.98; $P = .001$) (Table 5). Adjusting for PSC or removing PSC patients entirely did not change the results (OR, 3.44 or 3.04, respectively). Male sex was also a significant risk for CRN (AOR, 5.45; CI, 1.79–16.6). After adjusting for HIA, the protective effect of immune modulators remained significant (AOR, 0.25; CI, 0.08–0.73), and mesalamine remained suggestive of benefit (AOR, 0.37; CI, 0.13–1.04).

Correlates for Inflammation Score

In analyses of patients without CRN (controls) (Supplementary Tables 1–3), we found that female colitis patients tended to have higher HIA scores than male patients ($P = .057$). Patients who ever used azathioprine/6-MP also had higher HIA, but longer disease duration trended with lower HIA. Whereas 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 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 confirmed the association between increased degree of inflammation and subsequent neoplasia in patients with UC. This confirmation was achieved through our systematic approach, which used 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 by using a matched case-control design. Our study also confirmed previous conclusions that male patients with UC are at higher risk for CRN and provided new information about the chemoprotective roles of aminosalicylates and thiopurines.[13]

The first major study of the relationship between inflammation and CRN in UC was based on the St Mark's Hospital cancer surveillance database.[14] By using a retrospective review that used categorical grading for endoscopic and histologic degrees of inflammation in 68 CRN cases and 136 controls, univariate

Table 4. Other Risk Factors of CRN: Univariate Analysis

Risk factor	Cases (n = 59)		Controls (n = 141)		OR	95% CI	*P* value
Smoking, n (%)							
Never	41	(69)	105	(75)	1.00	Reference	.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 CRC, n (%)							
No	53	(90)	131	(94)	1.00	Reference	
Yes	6	(10)	8	(6)	2.25	0.74–6.89	.15
PSC, n (%)							
No	51	(86)	135	(96)	1.00	Reference	
Yes	8	(14)	5	(4)	3.62	1.16–11.3	.026
Azathioprine, n (%)							
No	54	(92)	107	(76)	1.00	Reference	
Yes	5	(8)	33	(24)	0.33	0.12–0.90	.031
6-MP, n (%)							
No	52	(88)	112	(80)	1.00	Reference	
Yes	7	(12)	28	(20)	0.38	0.12–1.15	.087
Azathioprine/6-MP, n (%)							
No	49	(83)	84	(60)	1.00	Reference	
Yes	10	(17)	56	(40)	0.28	0.12–0.65	.003
Duration of azathioprine/6-MP, n (%)							
Never	49	(83)	84	(60)	1.00	Reference	.001
<2 y	3	(5)	24	(17)	0.19	0.05–0.70	
≥2 y	5	(9)	32	(23)	0.27	0.09–0.78	
Dose of azathioprine/6-MP, mean (standard deviation)	91	(71)	77	(37)			1.0
Methotrexate, n (%)							
No	56	(95)	138	(99)	1.00	Reference	
Yes	3	(5)	2	(1)	2.51	0.40–15.6	.32
Immune modulators, n (%)							
No	47	(80)	84	(60)	1.00	Reference	
Yes	12	(20)	56	(40)	0.36	0.17–0.77	.009
No. of steroids exposure,[a] median (interquartile range)	2	(1–4)	2	(1–3)	1.05	0.88–1.26	.58
Folate supplement, n (%)							
No	31	(53)	74	(53)	1.00	Reference	
Yes	28	(47)	66	(47)	1.13	0.60–2.13	.71
Nonsteroidal anti-inflammatory drug							
No	49	(83)	127	(91)	1.00	Reference	
Yes	10	(17)	13	(9)	1.84	0.75–4.50	.18
Sulfasalazine, n (%)							
Never	18	(31)	34	(24)	1.00	Reference	
Ever	41	(69)	106	(76)	0.72	0.35–1.52	.39
Years of sulfasalazine, n (%)							
Never	18	(31)	34	(24)	1.00	Reference	.62
<10	19	(32)	56	(40)	0.67	0.30–1.50	
≥10	22	(37)	50	(36)	0.82	0.34–1.99	
Dose of sulfasalazine, n (%)							
<1.2 g daily	32	(54)	86	(61)	1.00	Reference	
≥1.2 g daily	27	(46)	54	(39)	1.49	0.76–2.95	.25
Nonsulfasalazine mesalamine, n (%)							
Never	27	(46)	35	(25)	1.00	Reference	
Ever	32	(54)	105	(75)	0.32	0.15–0.68	.003
Years of nonsulfasalazine mesalamine use, n (%)							
Never	27	(46)	35	(25)	1.00	Reference	.002
<10	26	(44)	76	(54)	0.38	0.17–0.86	
≥10	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	Reference	.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	.052
All mesalamine, n (%)							
Never	7	(12)	2	(1)	1.00	Reference	
Ever	52	(88)	138	(99)	0.08	0.01–0.68	.02

Table 4. Continued

Risk factor	Cases (n = 59)		Controls (n = 141)		OR	95% CI	*P* value
Years of all mesalamine,[a] median (interquartile range)	11	(6–21)	12	(6–19)	1.00	0.95–1.04	.86
Dose of all mesalamine, n (%)							
<1.2 g daily	15	(25)	27	(19)	1.00	Reference	.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	.47

[a]OR is for 1-unit change.

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] 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] Although 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 during 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 preexisting 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 interobserver agreement. Because of 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 is that all tissue was reviewed and scored by 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, before developing CRN, and thus minimized the effect of recall bias. Finally, cases were matched to controls on the basis of known risk factors, including age at diagnosis and duration and extent of disease. Furthermore, multivariable conditional logistic regression was used to remove confounding that was due to these factors. By using our novel University of Chicago HIA scale, multivariate analysis related a 1-unit increase in mean HIA to a greater than 3-fold increase in CRN risk. CRN risk was increased up to 7-fold in patients with higher degrees of inflammation.

Table 5. Multivariate Analysis of CRN

Risk factor	AOR (95% CI)[a]	*P* value	AOR (95% CI)[a]	*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

[a]Adjusting for variables in the table.

This study is also unique in that it uses maximum and mean HIA scores over time to ask whether 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 Colorectal Neoplasia in Ulcerative Colitis

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,[15] and other notable studies finding no protective effect.[7,10,16] In a meta-analysis of cohort and case–control studies of mesalamine and CRN in UC, Velayos et al[15] described a significantly reduced risk of CRN in UC patients exposed to mesalamines (OR, 0.51; 95% CI, 0.4–0.7). However, Bernstein et al[10] performed population-based studies of this association and reported no association between the development of CRC and mesalamine use (hazard ratio, 1.04; 95% CI, 0.67–1.62), and when studying those patients who did develop CRC, they found no difference in mesalamine use compared with controls. Similar to findings in other studies related to sex, they did note an increased risk of CRC in male patients. 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 meta-analysis by Velayos et al and did not find a statistically significantly reduced risk of CRN associated with mesalamines but reported a nonsignificant trend for nonsulfasalazine aminosalicylates toward reduced neoplasia rates with increasing years of exposure.[7]

The present study, which controlled for degree of inflammation and added the additional detail of dose of mesalamine therapies, provides a possible explanation for the findings and discrepancies of prior studies, including our own.[9] In the univariate analysis of mesalamine use and CRN, we identified a chemoprotective effect of any mesalamine exposure (OR, 0.08; CI, 0.01–0.68), but when controlling for type of mesalamine and adjusting for other risks

including inflammation, the benefit maintained an OR of protection but had a wider CI and *P* value (AOR for nonsulfasalazine mesalamine, 0.37; CI, 0.132–1.04; $P = .056$).

Impact of Azathioprine and 6-Mercaptopurine on Colorectal Neoplasia in Ulcerative Colitis

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 toward 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 exposure[13] with 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) makes this limitation less likely. There also may have been a selection bias for patients who have more frequent sigmoidoscopies or colonoscopies on the basis of 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. Although efforts were made to exclude pathology from uninvolved colon in patients with distal disease, another potential bias is the possible inclusion of nondiseased mucosa in the study. However, analysis of pancolitis-only patients also demonstrated a significant increase in CRN risk with inflammation, suggesting that inclusion of nondiseased mucosa did not significantly affect the results.

Conclusions

This large U.S. study confirms that increased histologic 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 demonstrated that male sex 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 mesalamine 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 revise treatment end points 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] 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

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.06.023.

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Reprint requests

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Conflicts of interest

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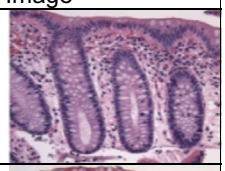
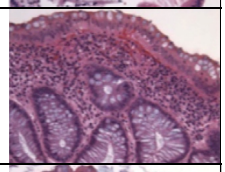
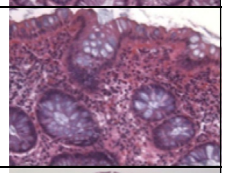
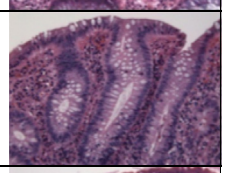
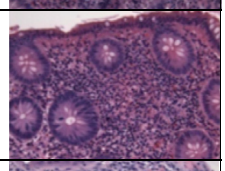
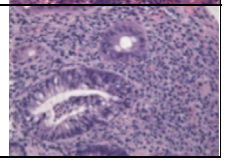
Inflammation Score	Inflammation Description	Inflammation Image
0	Normal (completely uninvolved, no architectural distortion, no infiltrates	
1	Quiescent (architectural distortion, increased lamina propria lymphs, but no activity)	
2	Increased lamina propria granulocytes without definite intraepithelial granulocytes	
3	Intraepithelial granulocytes (e.g. cryptitis) without crypt abscesses	
4	Crypt abscesses in less than 50% of crypts	
5	Crypt abscesses in greater than 50% of crypts, or erosion/ulceration	

Supplementary Figure 1. University of Chicago scale of histologic inflammation in colitis.

Supplementary Table 1. Factors Related to Inflammation Score in Controls

Risk factor	n	Mean inflammation score	Standard deviation	Spearman correlation coefficient	*P* value[a]
Sex					
Female	61	1.66	0.73		.057
Male	55	1.43	0.60		
PSC					
No	112	1.56	0.68		.51
Yes	4	1.37	0.58		
Smoking					
Never	89	1.54	0.59		.59
Ever	27	1.59	0.93		
Azathiopurine/6-MP					
Never	66	1.45	0.58		.06
Ever	50	1.68	0.77		
Duration	50			−0.21	.15
Daily dose	48			−0.04	.77
Steroid exposure	116			−0.11	.25
Nonsteroidal anti-inflammatory drug					
No	105	1.56	0.68		.62
Yes	11	1.46	0.67		
Folate supplement					
No	60	1.65	0.78		.31
Yes	56	1.44	0.54		
Sulfasalazine					
Never	27	1.73	0.77		.18
Ever	89	1.49	0.65		
Duration	89			−0.07	.53
Daily dose	89			−0.006	.95
Nonsulfasalazine mesalamine					
Never	28	1.39	0.48		.30
Ever	88	1.60	0.72		
Duration	88			−0.24	.025
Daily dose	88			−0.005	.96

[a]*P* values were calculated by using Wilcoxon rank-sum test or Spearman correlation.

Supplementary Table 2. Univariate Analysis for Cancer Cases and Controls

Risk factor	Cases (n = 15)		Controls (n = 37)		OR	95% CI	*P* value
Mean inflammation score							
Mean (standard deviation)	1.79	(0.51)	1.62	(0.60)	2.64[a]	0.69–10.2	.16
0–1	4	(31)	17	(52)	1.00	Reference	
2	8	(62)	13	(39)	2.94	0.77–20.2	
3–5	1	(8)	3	(9)	2.29	0.16–33.2	
Sex, n (%)							
Female	4	(27)	16	(43)	1.00	Reference	
Male	11	(73)	21	(57)	3.50	0.72–17.0	.12
Family history of CRC, n (%)							
No	14	(93)	36	(97)	1.00	Reference	
Yes	1	(7)	1	(3)	2.83	0.17–47.1	.47
PSC							
No	14	(93)	36	(100)			
Yes	1	(7)	0	(0)	—		
Smoking, n (%)							
Never	12	(80)	29	(81)	1.00	Reference	
Ever	3	(20)	7	(19)	1.22	0.26–5.91	.80
Immune modulators, n (%)							
No	14	(93)	21	(58)	1.00	Reference	
Yes	1	(7)	15	(42)	0.12	0.01–0.98	.05
Folate supplement, n (%)							
No	8	(53)	17	(47)	1.00	Reference	
Yes	7	(47)	19	(53)	0.88	0.22–3.51	.86
Sulfasalazine, n (%)							
Never	4	(27)	4	(11)	1.00	Reference	
Ever	11	(73)	32	(89)	0.36	0.08–1.69	.20
Nonsulfasalazine mesalamine, n (%)							
Never	7	(47)	11	(31)	1.00	Reference	
Ever	8	(53)	25	(69)	0.41	0.09–1.98	.27

[a]OR is for 1-unit increase in inflammation score.

Supplementary Table 3. Univariate Analysis for Dysplasia Cases and Controls

Risk factor	Cases (n = 44)		Controls (n = 104)		OR	95% CI	*P* value
Mean inflammation score							
Mean (standard deviation)	2.07	(0.97)	1.52	(0.71)	2.54[a]	1.35–4.78	.004
0–1	15	(36)	51	(61)	1.00	Reference	
2	15	(36)	22	(27)	2.56	0.93–7.02	
3–5	12	(29)	10	(12)	5.06	1.28–20.0	
Sex, n (%)							
Female	9	(20)	57	(55)	1.00	Reference	
Male	35	(80)	47	(45)	5.28	2.12–13.1	<.001
Family history of CRC, n (%)							
No	39	(89)	95	(93)	1.00	Reference	
Yes	5	(11)	7	(7)	2.16	0.64–7.30	.22
PSC							
No	37	(84)	99	(95)			
Yes	7	(16)	5	(5)	3.36	1.05–10.7	.04
Smoking, n (%)							
Never	29	(66)	76	(73)	1.00	Reference	
Ever	15	(34)	28	(27)	1.37	0.64–2.97	.42
Immune modulators, n (%)							
No	33	(75)	63	(61)	1.00	Reference	
Yes	11	(25)	41	(39)	0.47	0.20–1.10	.08
Folate supplement, n (%)							
No	23	(52)	57	(55)	1.00	Reference	
Yes	21	(48)	47	(45)	1.20	0.59–2.46	.61
Sulfasalazine, n (%)							
Never	14	(32)	30	(29)	1.00	Reference	
Ever	30	(68)	74	(71)	0.89	0.38–2.08	.79
Nonsulfasalazine mesalamine, n (%)							
Never	22	(50)	24	(23)	1.00	Reference	
Ever	22	(50)	80	(77)	0.23	0.09–0.56	.001

[a]OR is for 1-unit increase in inflammation score.