Published in final edited form as:

Cancer Causes Control. 2014 April ; 25(4): 409–418. doi:10.1007/s10552-014-0343-0.

The association between circulating high-sensitivity C-reactive protein concentration and pathologic measures of colonic inflammation

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Abstract

Purpose—C-reactive protein (CRP), an inflammation marker, is associated with colorectal cancer (CRC) risk in some prospective studies. Whether increased CRP is indicative of colonic inflammation, a possible CRC cause, or of other sources of inflammation (e.g., adiposity), is unknown. Thus, we evaluated the association between CRP and colonic mucosal measures of inflammation.

Methods—151 adults undergoing colonoscopy provided a blood sample and random left and right side colonic mucosal biopsies. Height and weight were measured and lifestyle information was collected. hsCRP was measured by immunoturbidometric assay. A gastrointestinal pathologist evaluated biopsies for 7 colonic inflammation measures. Of 119 participants with complete information, 24 had an inflammatory bowel disease (IBD) history and were analyzed separately. We calculated number of colonic inflammation measures present in both biopsies, and separately for right and left biopsies. Adjusted geometric mean hsCRP was calculated using linear regression, overall, by demographic and lifestyle factors, and inflammation measures.

Results—Most participants had 1 colonic inflammation measure (0: 21%, 1: 39%, 2: 40%). Adjusted mean hsCRP did not increase with increasing number of inflammation measures (0: 1.67; 1: 1.33; 2: 1.01 mg/L; p-trend=0.21). Obese (2.03 mg/L) and overweight (1.61 mg/L)

Conflict of Interest: The authors have no conflicts of interest to disclose.

participants had higher adjusted mean hsCRP than normal weight participants (0.62 mg/L; p -trend<0.0001). Patterns were similar for IBD history.

Conclusions—hsCRP concentration was not associated with colonic inflammation, although hsCRP increased with adiposity. The hsCRP-CRC association may be explained by residual confounding by other risk factors, such as adiposity, rather than by CRP marking colonic inflammation.

Keywords

C-reactive protein; inflammation; colorectal cancer; obesity

Introduction

Chronic inflammation is hypothesized to be a cause of colorectal cancer. Considerable evidence supports this hypothesis, including the increased risk of colorectal cancer among those with inflammatory bowel disease [1, 2], and the decreased risk of colorectal cancer among regular aspirin users [3, 4]. Consequently, many circulating markers of inflammation have been investigated in relation to colorectal cancer, including C-reactive protein, a non-specific marker of systemic inflammation.

C-reactive protein (CRP) is an acute phase protein that is synthesized by the liver in response to both acute and chronic inflammatory conditions. Several prospective studies have evaluated circulating CRP in relation to future colorectal cancer risk; and though the findings were inconsistent, a meta-analysis found that increased circulating CRP concentration was weakly associated with an increased risk for colorectal cancer [5]. More recently, two prospective studies reported an increased risk of colorectal cancer with higher circulating CRP levels [6, 7], whereas several others reported no significant association [8–11].

While CRP appears to be associated with colorectal cancer, it remains unclear which causal process(es) circulating CRP may be capturing. Increased circulating CRP may be a marker of increased colonic mucosal inflammation, which may increase colorectal cancer risk. Beyond reverse causation (inflammatory response to undetected colorectal neoplasia), increased CRP may alternatively reflect other sources of inflammation; including sources, like obesity, that are, themselves, risk factors for colorectal cancer [12]. To address this gap, we evaluated the association between CRP and seven colonic mucosal measures of inflammation and damage assessed in random biopsies collected from adults undergoing colonoscopy at Johns Hopkins Hospital.

Methods

Study Population and Colonic Mucosal Biopsies

This study was embedded in a case-control study on the etiology of adenomatous polyps in which patients undergoing colonoscopy in the Endoscopy Unit at the Johns Hopkins Outpatient Center were recruited between December 2002 and June 2010. The Outpatient Center is part of tertiary care center and draws patients from Baltimore, MD and the greater geographic area. All patients referred for colonoscopy, including those for screening colonoscopy, diagnostic workup, and surveillance for inflammatory bowel disease (IBD), were eligible for recruitment. Participants completed a short interview, gave a blood sample, and consented to having endoscopy and pathology records reviewed. A trained interviewer asked participants to report their age, ethnicity, smoking status, and indicators for colonoscopy: age-appropriate screening; screening because of a positive family history of colorectal cancer; follow-up for a prior positive screen (e.g., fecal occult blood test, barium

enema); current symptoms; past symptoms; a history of polyps, and/or recent polyps (e.g. detected by sigmoidoscopy, and led to the need for a colonoscopy). The interviewer also measured the participant's weight and height, and body mass index (BMI) was calculated. Participants were classified as normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥ 30 kg/m²).

Between February 2007 and July 2008, random colonic biopsies were obtained from a convenience sample of 151 of the study participants, including participants undergoing surveillance for IBD (Table 1); these patients were additionally consented. Patients who currently had a polyp of any type or colon cancer were not included. Four random colonic biopsies were obtained, two from the right side (e.g. proximal to the splenic flexure) and two from the left side (e.g. distal to the splenic flexure) of the colon. One biopsy from each side was fixed in formalin and embedded in paraffin. Participants were excluded if they were missing paraffin embedded biopsies from both sides of the colon (n=9), a blood sample (n=8), or relevant demographic or lifestyle information (n=15). A total of 119 participants were included in the final analysis. A subset of participants (n=24) had a history of IBD, only 2 participants had active IBD as determined by pathology reports. Participants with a history of IBD were used as a putative “positive control” group; expecting that colonic inflammation causes higher circulating C-reactive protein. This study was approved by the Institutional Review Boards at the Johns Hopkins School of Medicine and at the Johns Hopkins Bloomberg School of Public Health.

Measures of colonic inflammation

Colonic biopsies were fixed in formalin, paraffin embedded, stained with H&E, sectioned, and analyzed by a gastrointestinal pathologist (C. I-D.). Mucosal biopsies were evaluated for 7 measures of colonic inflammation: chronic epithelial inflammation (increased or normal), lymphoid aggregates (present or absent), lamina propria chronic inflammation (increased or normal), goblet cells (reduced/absent or normal), acute epithelial inflammation (increased or normal), crypt epithelium damage (present or absent), and surface epithelium damage (present or absent). All scores were performed blinded to patient demographics.

Given that the colonoscopy preparation could lead to acute inflammation, we also divided the measures into those associated with chronic or acute inflammation. The measures of chronic inflammation included increased chronic epithelial inflammation, the presence of lymphoid aggregates, increased lamina propria chronic inflammation, and/or a reduction or absence of goblet cells. The measures of acute inflammation included increased acute epithelial inflammation, the presence of crypt epithelium damage, and/or the presence of surface epithelium damage.

Measure of C-reactive protein

High-sensitivity C-reactive protein (hsCRP) was measured using an automated latex-enhanced immunoturbidometric assay performed on a Behring BN II nephelometer (Dade Behring, Deerfield, IL) in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA). Ten masked quality control samples were aliquotted for 10 participants, and the duplicate samples were assayed adjacently. The mean intra-pair coefficient of variation for the quality control samples was 0.95% (range: 0% to 6.15%). The lower limit of detection was 0.03 mg/L; all samples had concentrations above the limit of detection.

Statistical Analysis

The total number of the 7 measures of colonic inflammation was calculated for each participant in both biopsies, and separately by location; the total counts were then categorized as 0, 1 or ≥ 2. The total number of measures of chronic inflammation was

calculated in both biopsies, and separately by location; the total counts were then categorized as 0, 1 or 2. The total number of measures of acute inflammation was calculated in both biopsies, and separately by location; the total counts were then categorized as 0 or 1.

The means and proportions for demographic and other factors were calculated by the total number of measures of colonic inflammation (0, 1, or 2) in both biopsies, and by tertile of hsCRP. Proportions were compared with the chi-square test, and means were compared with the F-test. We also calculated the proportion of individual and total of measures of colonic inflammation. Because the distribution of the concentrations of the hsCRP was not normal, unadjusted and adjusted geometric mean concentrations and 95% confidence intervals from linear regression models were calculated, overall, by demographic and lifestyle factors, and by individual and totals of measures of colonic inflammation. Means were adjusted for (1) age and sex, and (2) age, sex, body mass index (continuous), smoking status (current or former/never). To test for trend, we assigned each participant the median hsCRP value within their demographic, lifestyle or inflammation category. The median values were modeled and the coefficient was tested with the Wald test. All analyses were stratified by participant history of IBD and conducted in SAS version 9.2 (Cary, NC).

Results

Participants with no history of IBD

There was no difference in the unadjusted geometric mean concentration of hsCRP by the total number of measures of colonic inflammation (Table 1). Fewer women were in the highest category of colonic inflammation than men. Participants did not significantly differ in other demographic or lifestyle factors, or reasons for colonoscopy by category of colonic inflammation. When compared by tertile of hsCRP, participants were similar on most factors (Table 1). However, there was a higher proportion of overweight and obese participants in the second and third tertiles of hsCRP as compared to the first tertile.

Adjusted hsCRP concentrations were significantly higher among obese and overweight participants compared with normal weight participants (Table 2). Adjusted hsCRP concentrations were also non-statistically significantly higher among men compared with women, and current smokers compared with former and never smokers (Table 2).

The majority of participants had at least one measure of colonic inflammation; inflammation was more common on the right side than on the left (Table 3), likely a measure of the normal baseline levels of lymphoplasmatic cell infiltrates in the proximal colon [13]. Measures of chronic inflammation were also more common than measures of acute inflammation. Lamina propria chronic inflammation and lymphoid aggregates were the most common measures of inflammation, whereas acute epithelial inflammation and reduced or absent goblet cells were these least common measures of inflammation.

Mean concentration of hsCRP did not increase with increasing number of measures of colonic inflammation, overall or by right or left side (Table 3). Similarly, the mean concentration of hsCRP did not increase with increasing number of measures of chronic colonic inflammation or with increasing number of measures of acute colonic inflammation. The only measure associated with an increased mean hsCRP concentration was the presence of acute epithelial inflammation; those with this measure had a significantly higher mean hsCRP concentration than those without, though this was based on small numbers.

Participants with a history of IBD

The patterns we observed for participants with a history of IBD were similar to those observed for participants without IBD. There was no difference in the unadjusted geometric mean concentration of hsCRP by the total number of measures of colonic inflammation (Table 1). Participants did not significantly differ in other demographic or lifestyle factors, or reasons for colonoscopy by category of colonic inflammation. When compared by tertile of hsCRP, participants were similar on most factors (Table 1). However, there were non-statistically significant higher proportions of obese participants and current smokers in the third tertile of hsCRP as compared to the first and second tertiles.

Adjusted hsCRP concentrations were non-statistically significantly higher among men compared with women, obese participants compared with normal weight participants, and current smokers compared with former and never smokers (Table 2).

The majority of participants had at least one measure of colonic inflammation; inflammation was more common in the right side of the colon than the left (Table 3). Measures of chronic inflammation were more common than measures of acute inflammation. Lamina propria chronic inflammation and lymphoid aggregates were the most common measures of inflammation, whereas, acute epithelial inflammation and reduced or absent goblet cells were these least common measures of inflammation.

Mean concentration of CRP did not increase with increasing number of measures of colonic inflammation, overall, or with increasing number of measures of acute inflammation (Table 3). There was a non-statistically significant increase in mean CRP with increasing number of measures of chronic inflammation. There was also a non-statistically significant increase in mean CRP with increasing number of measures of inflammation on the left side; this pattern was similar for left-sided chronic and left-sided acute inflammation.

Discussion

In this study, no association between circulating C-reactive protein concentration and pathologic measures of colonic inflammation was observed. Thus, these findings do not support circulating CRP as a marker of colonic inflammation in patients without active IBD. As previously reported by others [14, 15], we observed that C-reactive protein was significantly higher among overweight and obese participants as compared to those of normal weight. Regarding the observation that higher circulating CRP is associated with an increased risk of colon cancer, our results suggest that this association may be explained by residual confounding by other risk factors for colon cancer, such as body fatness, rather than by CRP marking colonic inflammation.

Few studies have evaluated CRP in relation to bowel inflammation in those without IBD. Poullis and colleagues evaluated the association between a surrogate measure of bowel inflammation, fecal calprotectin level, and CRP, and lifestyle factors in participants without IBD [16]. CRP was not associated with increased fecal calprotectin levels in models adjusted for age, sex and other factors. In our study, the only measure of colonic inflammation associated with a significant increase CRP in participants without IBD was the presence of acute inflammation, though this estimate was based on a small sample size (e.g. ~2% of participants without IBD). Several investigators have evaluated CRP as a marker of IBD and IBD severity. CRP has been more consistently associated with the presence of Crohn's disease than the presence of ulcerative colitis, though the reason for this heterogeneity between conditions is unknown [17, 18]. Two larger studies that evaluated the association between CRP and degree of intestinal inflammation among those with IBD yielded inconsistent results [18, 19]. Further, Henriksen and colleagues observed that a

substantial proportion of study participants with IBD had CRP levels well within the clinically normal range [18]. These studies are consistent with our observation that CRP level was not associated with pathologic measures of bowel inflammation.

The CRP values in our study were consistent with estimated population averages. Clinical cut points for high sensitivity CRP have been defined based on cardiovascular disease risk (<1 , $1-3$, >3 mg/L) [20]. These cut points are based on approximate tertiles of CRP in the US population, which were estimated using several large cohorts of apparently health US men and women [21]. The mean hsCRP values within each tertile of our study population fell within the estimated population tertiles, irrespective of IBD status. When evaluated by demographic factors, lifestyle factors, and measures of colonic inflammation, only obese participants with a history of IBD had a CRP level in the highest risk category. All other values were in the middle or lowest risk categories. The median value estimated for the US population was approximately 1.5 mg/L [21]. In our study, virtually all mean CRP values fell at or below 1.5 mg/L, irrespective of demographic factors, presence and type of bowel inflammation, or IBD status. Among those without IBD, the only exceptions were obese participants, those with reduced goblet cells, or the presence of acute inflammation; and the latter two CRP values were based on small sample sizes. The exceptions among participants with IBD were those with two or more measures of inflammation in the left colon or those who currently smoked cigarettes. In sum, the only consistent influence on CRP value in our study population was obesity.

Studies in humans and animal models support the role of chronic inflammation in colorectal carcinogenesis, though the exact mechanisms of action are not known [22]. CRP has also been associated with colorectal cancer risk in most [5–7], but not all studies [8–11], and hypothesized to be a marker of colonic inflammation. The purpose of this study was to investigate whether CRP level is reflective of inflammation in the colon; and more specifically, to identify whether CRP was higher in those with greater pathologic inflammation, but otherwise normal, colons. In our study population, increased bowel inflammation was not associated with increased CRP, irrespective of IBD history. This suggests that the association between CRP and colorectal cancer risk is not due to colonic inflammation, but rather is reflective of other processes, or due to residual confounding across the spectrum of CRC risk factors that investigators have adjusted for in their analyses. For example, in our study obesity, a risk factor for colorectal cancer [23, 24], was associated with increased CRP. This observation is consistent with other studies in which obesity was associated with elevated circulating CRP in national samples [14, 15], and also shown to increase with weight gain over time [25]. The association between CRP and colorectal risk observed in many studies may be a consequence of residual confounding or misspecification, especially as commonly used measures of body fatness (e.g. body mass index, waist circumference) are imperfect.

We assessed one circulating measure of inflammation, hs-CRP, and seven measures of bowel inflammation in a convenience sample of patients undergoing colonoscopy. It is possible that our sample did not reflect CRP levels and bowel inflammation in the general population, though the prevalence of characteristics known to influence CRP level (e.g. obesity and current smoking) in our study were similar to the prevalence of those characteristics in the general population. Though the sample size was too small for subgroup analyses, participation was acceptable, given participants agreed to random biopsy without indication. Biopsy collection was not standardized, though biopsy processing followed standard procedures. To our knowledge, there is no established pathologic scoring system for colonic inflammation in people without IBD. Thus, one gastrointestinal pathologist evaluated biopsies using common features of acute and chronic inflammation in the normal colon compartments. The extent of bowel inflammation was low in this study

population. We measured only one circulating marker of inflammation, because we sought specifically to determine whether circulating CRP was associated with bowel inflammation. CRP was measured one time, concurrent with biopsies, using a high sensitivity assay; this was necessary to address our study question. In response to challenge, CRP peaked at 24 hours in normal participants [26]. Thus, in our study, had the participants been experiencing ongoing, chronic colonic inflammation, measuring CRP levels concurrent with tissue biopsy should have captured the resultant higher CRP. In addition, our use of a single CRP measure is comparable to the colorectal cancer risk literature, which has evaluated one CRP measure with future colorectal cancer risk. Because participants were not followed prospectively for future colorectal cancer, we were unable to directly test the alternative hypothesis that the association between CRP and colorectal cancer risk is due to residual confounding or misspecification of other risk factors, like obesity.

We evaluated whether circulating C-reactive protein concentration, which has been associated with colorectal cancer risk, was associated with pathologic colonic inflammation. We observed no association between circulating CRP and colonic inflammation. CRP was significantly higher among overweight and obese participants compared with those of normal weight. Taken together, our findings do not support the hypothesis that CRP is a marker of colonic inflammation, and indicate that the association between CRP and future colorectal cancer risk may be due to residual confounding by other risk factors, like obesity.

Acknowledgments

Financial Support: Seraph Foundation; Frederik B. Bang Award for Student Research in Pathobiology, Johns Hopkins Bloomberg School of Public Health; Maryland Cigarette Restitution Fund at Johns Hopkins; and the National Cancer Institute (T32 CA009314). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the NIH.

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Table 1

Demographic and lifestyle factors by total number of measures of colonic inflammation, tertile of concentration of C-reactive protein, and history of inflammatory bowel disease (IBD).

	No History of IBD (n=95)				
	Total Number of Measures of Colonic Inflammation ^a				
	0 (n=20)	1 (n=37)	2 (n=38)	p-value	Tertile of CRP
					1st 2nd 3rd p-value
Geometric Mean hsCRP, mg/L (SD)	1.78 (1.30)	1.23 (1.21)	1.06 (1.21)	0.28	0.32 (1.09) 1.33 (1.09) 4.44 (1.09) <0.0001
Mean Age, yrs (SD)	59.3 (7.45)	57.4 (6.91)	57.7 (9.57)	0.69	57.1 (8.15) 56.5 (7.89) 60.1 (8.16) 0.18
Female, %	45.0	64.9	31.6	0.02	64.5 28.1 50.0 0.01
White, %	55.0	67.6	68.4	0.55	67.7 71.9 56.3 0.40
Body Mass Index ^b , %				0.64	
Normal	30.0	37.8	34.2		64.5 25.0 15.6
Overweight	40.0	21.6	34.2		22.6 34.4 34.4
Obese	30.0	40.5	31.6		12.9 40.6 50.0
Current Smokers, %	20.0	5.4	13.2	0.24	6.5 15.6 12.5 0.61
Reason for Colonoscopy ^c , %					
Screening	0.0	2.7	5.3	0.80	3.2 3.1 3.1 1.00
Family History	5.0	21.6	18.4	0.26	22.6 15.6 12.5 0.55
Screening Age	70.0	46.0	55.3	0.22	45.2 56.3 62.5 0.38
Current Symptoms	15.0	32.4	26.3	0.36	35.5 15.6 28.1 0.19
Past Symptoms	5.0	5.4	10.5	0.69	3.2 12.5 6.3 0.49
Recent polyps ^d	0.0	5.4	0.0	0.19	0.0 0.0 6.3 0.33
Past polyps	20.0	32.4	21.1	0.44	29.0 21.9 25.0 0.81

	History of IBD (n=24)				
	Total Number of Measures of Colonic Inflammation ^a				
	0 (n=3)	1 (n=6)	2 (n=15)	p-value	Tertile of CRP
					1st 2nd 3rd p-value
Geometric Mean hsCRP, mg/L (SD)	0.96 (2.09)	2.08 (1.69)	1.06 (1.39)	0.52	0.30 (1.22) 1.33 (1.22) 4.67 (1.22) <0.0001
Mean Age, yrs (SD)	46.8 (2.75)	59.2 (8.95)	50.5 (9.99)	0.11	49.0 (10.22) 53.6 (11.14) 53.9 (8.63) 0.56
Female, %	100.0	66.7	73.3	0.82	100.0 62.5 62.5 0.18
White, %	100.0	83.3	73.3	1.00	75.0 87.5 75.0 1.00

History of IBD (n=24)								
Total Number of Measures of Colonic Inflammation ^a					Tertile of CRP			
	0 (n=3)	1 (n=6)	2 (n=15)	p-value	1st	2nd	3rd	p-value
Body Mass Index ^b , %				0.25				0.09
Normal	0.0	33.3	60.0		62.5	62.5	12.5	
Overweight	66.7	50.0	20.0		25.0	37.5	37.5	
Obese	33.3	16.7	20.0		12.5	0.0	50.0	
Current Smokers, %	0.0	33.3	6.7	0.17	0.0	12.5	25.0	0.75
Reason for Colonoscopy ^c , %								
Screening	0.0	0.0	0.0	NE	0.0	0.0	0.0	NE
Family History	33.3	0.0	6.7	0.29	25.0	0.0	0.0	0.30
Screening Age	0.0	16.7	6.7	0.62	12.5	0.0	12.5	1.00
Current Symptoms	100.0	33.3	26.7	0.11	50.0	12.5	50.0	0.26
Past Symptoms	66.7	83.3	60.0	0.82	75.0	62.5	62.5	1.00
Recent polyps ^d	0.0	0.0	0.0	NE	0.0	0.0	12.5	1.00
Past polyps	33.3	33.3	20.0	0.82	25.0	25.0	25.0	1.00
Standard deviation (SD), Not Estimable (NE).								

^aTotal number of 7 measures of colonic inflammation present: chronic epithelial inflammation (increased or normal), the presence of lymphoid aggregates (present or absent), lamina propria chronic inflammation (increased or normal), goblet cells (reduced/absent or normal) acute epithelial inflammation (increased or normal), crypt epithelium damage (present or absent), and surface epithelium damage (present or absent).

^bNormal: BMI < 25 kg/m², Overweight: 25 kg/m² BMI < 30 kg/m², Obese: BMI ≥ 30 kg/m².

^cPercentages were calculated by dividing the number of participants who reported the specific reason divided by the total number of participants within the category, and then multiplied by 100. Participants reported all of the reasons for their colonoscopy, because participants could report more than one reason, percentages do not add up to 100% within each category.

^dRecent polyps are those that were detected by sigmoidoscopy and led to the need for colonoscopy.

Table 2

Geometric mean C-reactive protein (hsCRP; mg/L) concentration by history of inflammatory bowel disease (IBD), demographic and lifestyle characteristics

	No IBD (n=95)		IBD (n=24)	
	Model 1	Model 2	Model 1	Model 2
Overall	1.19 (0.94–1.51)	1.17 (0.95–1.45)	1.52 (0.93–2.48)	1.60 (1.03–2.48)
Sex^a				
Men	1.45 (1.05–1.99)	1.37 (1.02–1.83)	1.56 (0.57–4.22)	1.11 (0.39–3.21)
Women	1.06 (0.76–1.49)	1.13 (0.83–1.54)	1.15 (0.66–1.99)	1.28 (0.73–2.24)
p-value	0.20	0.39	0.64	0.83
Race/Ethnicity				
White	1.17 (0.87–1.56)	1.25 (0.96–1.63)	1.05 (0.60–1.85)	1.19 (0.67–2.08)
Non-white	1.43 (0.96–2.13)	1.25 (0.87–1.80)	2.30 (0.73–7.30)	1.45 (0.41–5.16)
p-value	0.42	0.99	0.26	0.79
Body Mass Index^b				
Normal	0.63 (0.43–0.91)	0.62 (0.43–0.90)	0.89 (0.42–1.88)	0.89 (0.43–1.83)
Overweight	1.57 (1.06–2.34)	1.61 (1.08–2.40)	1.11 (0.44–2.81)	1.05 (0.43–2.61)
Obese	2.05 (1.42–2.94)	2.03 (1.41–2.91)	3.01 (0.97–9.39)	3.32 (1.09–10.12)
p-value	<0.0001	<0.0001	0.23	0.17
Smoking Status				
Current	1.56 (0.77–3.16)	1.52 (0.81–2.86)	2.85 (0.63–12.98)	2.92 (0.71–11.92)
Former/Never	1.21 (0.95–1.56)	1.22 (0.97–1.52)	1.10 (0.64–1.88)	1.09 (0.67–1.80)
p-value	0.51	0.52	0.27	0.22

Model 1: Adjusted for age and sex. Model 2: Mutually adjusted for age, sex, body mass index (continuous), smoking status (current or former/never).

^aModel 1 is not adjusted for sex.

^bNormal: BMI < 25 kg/m², Overweight: 25 kg/m² BMI < 30 kg/m², Obese: BMI ≥ 30 kg/m².

Table 3

Geometric mean C-reactive protein (hsCRP; mg/L) concentration by measures of colonic inflammation stratified by history of inflammatory bowel disease (IBD)

		No IBD (n=95)		IBD (n=24)	
		Prevalence (%)	Model 1	Prevalence (%)	Model 1
		Model 2	Model 2	Model 2	Model 2
Total Number ^a					
0	21.05%	1.70 (1.02–2.84)	1.67 (1.06–2.65)	12.50%	1.20 (0.26–5.49)
1	38.95%	1.33 (0.91–1.95)	1.33 (0.94–1.87)	25.00%	1.68 (0.55–5.16)
2	40.00%	1.00 (0.69–1.46)	1.01 (0.72–1.42)	62.50%	1.10 (0.56–2.15)
p-value		0.25	0.21		0.78
Total for Right Side ^b					
0	27.37%	1.60 (1.03–2.50)	1.47 (0.98–2.21)	16.67%	0.97 (0.27–3.53)
1	41.05%	1.36 (0.94–1.97)	1.39 (1.00–1.94)	33.33%	1.81 (0.73–4.45)
2	31.58%	0.90 (0.59–1.37)	0.94 (0.65–1.37)	50.00%	1.04 (0.50–2.18)
p-value		0.16	0.21		0.48
Total for Left Side ^c					
0	53.68%	1.45 (1.06–1.99)	1.39 (1.04–1.86)	25.00%	1.87 (0.63–5.55)
1	32.63%	0.88 (0.59–1.32)	0.99 (0.68–1.44)	45.83%	0.96 (0.43–2.14)
2	13.68%	1.61 (0.85–3.04)	1.42 (0.80–2.54)	29.17%	1.30 (0.49–3.45)
p-value		0.12	0.34		0.65
Measures of Chronic Inflammation					
Total Number					
0	27.37%	1.64 (1.05–2.57)	1.59 (1.06–2.38)	12.50%	1.21 (0.26–5.59)
1	52.63%	1.18 (0.85–1.63)	1.15 (0.86–1.54)	58.33%	1.35 (0.66–2.78)
2	20.00%	1.01 (0.60–1.71)	1.12 (0.69–1.80)	29.17%	1.04 (0.38–2.86)
p-value		0.35	0.41		0.93
Total for Right Side					
0	33.68%	1.57 (1.05–2.34)	1.44 (1.00–2.09)	25.00%	1.18 (0.40–3.53)
1	49.47%	1.23 (0.88–1.72)	1.24 (0.92–1.68)	54.17%	1.38 (0.67–2.88)
2	16.84%	0.83 (0.47–1.47)	0.96 (0.57–1.61)	20.83%	0.98 (0.31–3.08)
					1.06 (0.36–3.14)

		No IBD (n=95)			IBD (n=24)		
		Prevalence (%)	Model 1	Model 2	Prevalence (%)	Model 1	Model 2
p-value			0.21	0.46		0.88	0.95
Total for Left Side							
0		57.89%	1.45 (1.07–1.97)	1.41 (1.07–1.87)	33.33%	1.52 (0.60–3.82)	0.74 (0.28–1.97)
1		36.84%	0.97 (0.66–1.42)	1.05 (0.74–1.49)	58.33%	1.08 (0.52–2.23)	1.43 (0.73–2.83)
2		5.26%	1.50 (0.54–4.18)	1.10 (0.43–2.81)	29.17%	1.31 (0.29–5.93)	2.56 (0.61–10.73)
p-value			0.26	0.41		0.86	0.43
Chronic Epithelium Inflammation							
Absent		76.84%	1.27 (0.97–1.66)	1.25 (0.98–1.59)	54.17%	1.48 (0.71–3.07)	1.61 (0.81–3.22)
Increased		23.16%	1.20 (0.73–1.96)	1.27 (0.81–1.97)	45.83%	1.00 (0.45–2.23)	0.91 (0.42–1.95)
p-value			0.84	0.95		0.51	0.33
Lymphoid Aggregates							
Absent		52.63%	1.43 (1.04–1.97)	1.45 (1.08–1.95)	41.67%	1.33 (0.59–3.01)	1.08 (0.47–2.48)
Present		47.37%	1.08 (0.77–1.51)	1.06 (0.78–1.45)	58.33%	1.17 (0.59–2.33)	1.37 (0.69–2.70)
p-value			0.24	0.17		0.82	0.70
Lamina Propria Chronic Inflammation							
Absent		48.42%	1.47 (1.05–2.06)	1.43 (1.06–1.94)	37.50%	0.86 (0.36–2.03)	0.90 (0.40–1.99)
Present		51.58%	1.08 (0.78–1.49)	1.10 (0.82–1.48)	62.50%	1.54 (0.80–2.96)	1.50 (0.82–2.75)
p-value			0.20	0.23		0.32	0.35
Goblet Cells							
Normal		96.84%	1.23 (0.97–1.56)	1.23 (0.99–1.53)	87.50%	1.27 (0.73–2.19)	1.20 (0.72–2.00)
Reduced or Absent		3.16%	2.34 (0.61–9.04)	2.03 (0.60–6.91)	12.50%	1.04 (0.24–4.49)	1.52 (0.38–6.13)
p-value			0.36	0.43		0.81	0.76
Measures of Acute Inflammation							
Total Number							
0		68.42%	1.32 (0.99–1.75)	1.32 (1.02–1.71)	54.17%	1.45 (0.72–2.95)	1.35 (0.69–2.65)
1		31.58%	1.12 (0.73–1.70)	1.11 (0.76–1.62)	45.83%	1.02 (0.47–2.22)	1.11 (0.53–2.32)
p-value			0.53	0.46		0.53	0.72
Total for Right Side							
0		73.68%	1.36 (1.03–1.79)	1.36 (1.06–1.73)	54.17%	1.45 (0.72–2.95)	1.35 (0.69–2.65)

		No IBD (n=95)		IBD (n=24)			
		Prevalence (%)	Model 1	Model 2	Prevalence (%)	Model 1	Model 2
Total for Left Side							
1		26.32%	0.99 (0.63–1.57)	1.00 (0.66–1.51)	45.83%	1.02 (0.47–2.22)	1.11 (0.53–2.32)
p-value			0.25	0.22		0.53	0.72
Acute Epithelial Inflammation							
0		87.37%	1.21 (0.94–1.55)	1.20 (0.96–1.50)	66.67%	1.24 (0.65–2.38)	1.06 (0.58–1.95)
1		12.63%	1.59 (0.81–3.12)	1.69 (0.93–3.09)	33.33%	1.23 (0.47–3.21)	1.67 (0.68–4.13)
p-value			0.45	0.29		0.99	0.46
Crypt Epithelium Damage							
Absent		97.89%	1.22 (0.96–1.54)	1.21 (0.98–1.49)	91.67%	1.30 (0.76–2.22)	1.25 (0.76–2.06)
Present		2.11%	4.00 (0.78–20.57)	6.54 (1.52–28.02)	8.33%	0.71 (0.10–4.97)	1.08 (0.17–6.88)
p-value			0.16	0.03		0.57	0.89
Surface Epithelium Damage							
Absent		78.95%	1.31 (1.00–1.70)	1.30 (1.03–1.65)	70.83%	1.43 (0.76–2.71)	1.27 (0.69–2.33)
Present		21.05%	1.07 (0.64–1.78)	1.08 (0.68–1.71)	29.17%	0.87 (0.29–2.55)	1.16 (0.41–3.30)
p-value			0.50	0.49		0.48	0.90
Total for Right Side							
0		80.0%	1.35 (1.04–1.75)	1.33 (1.05–1.68)	58.33%	1.34 (0.68–2.65)	1.29 (0.68–2.44)
1		20.0%	0.92 (0.54–1.55)	0.98 (0.61–1.57)	41.67%	1.11 (0.49–2.50)	1.17 (0.54–2.49)
p-value			0.20	0.26		0.74	0.85

Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, body mass index (continuous), smoking status (current or former/never).

^aTotal number of 7 measures of colonic inflammation present across both biopsies: chronic epithelial inflammation (increased or normal), the presence of lymphoid aggregates (present or absent), lamina propria chronic inflammation (increased or normal), goblet cells (reduced/absent or normal) acute epithelial inflammation (increased or normal), crypt epithelium damage (present or absent), and surface epithelium damage (present or absent).

^bTotal number of 7 measures of colonic inflammation present in right biopsies only.

^cTotal number of 7 measures of colonic inflammation present in left biopsies only.