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Abstract

Introduction—Patients with inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)) are at increased risk of colorectal cancer (CRC). Persistent inflammation is hypothesized to increase risk of CRC in patients with IBD; however the few studies in this area

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have been restricted to cross-sectional assessments of histologic severity. No prior studies have examined association between C-reactive protein or erythrocyte sedimentation rate (ESR) elevation and risk of CRC in an IBD cohort.

Methods—From a multi-institutional validated IBD cohort, we identified all patients with at least one measured CRP or ESR value. Patients were stratified into quartiles of severity of inflammation based on their median CRP or ESR, and subsequent diagnosis of CRC was ascertained. Logistic regression adjusting for potential confounders was used to identify the independent association between CRP or ESR elevation and risk of CRC.

Results—Our study included 3,145 patients with at least 1 CRP (CRP cohort) and 4,008 with at least 1 ESR (ESR cohort). Thirty-three patients in the CRP cohort and 102 patients in the ESR cohort developed colorectal cancer during a median follow-up of 5 years, at a median age of 55 years. On multivariate analysis, there was a significant increase in risk of CRC across quartiles of CRP elevation (P_{trend} 0.017, Odds ratio for Q4 vs. Q1: 2.72, 95% CI 0.95 – 7.76). Similarly higher median ESR was also independently associated with risk of CRC across the quartiles (OR 2.06, 95% CI 1.14 – 3.74) (P_{trend}=0.007).

Conclusions—An elevated CRP or ESR is associated with increased risk of CRC in patients with IBD.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), together referred to as inflammatory bowel diseases (IBD), are chronic, immunologically mediated illnesses that have an onset during young adulthood and a protracted course characterized by relapses[1, 2]. Patients with IBD are at increased risk for long-term complications related to their disease; one such morbidity is the occurrence of colorectal cancer (CRC)[3–7]. Early studies estimated the risk of CRC to be as high as 18% after 30 years of disease in UC with a similar risk in CD with colonic involvement[4, 5]. However, more recent estimates have suggested that the risk is significantly lower[8]. Professional societies and expert guidelines recommend colonoscopic surveillance for the identification of dysplasia and CRC beginning after 8 years of disease, and repeated every 1–3 years[6, 7, 9–11]. Given the decreasing incidence of CRC and the costs and morbidity associated with lifelong periodic colonoscopic surveillance, there is an important need to identify high-risk subgroups that may benefit from continued intensive surveillance strategies while allowing for less frequent colonoscopies in patients at low risk of CRC.

One such predictor that may be biologically relevant to stratify CRC risk is severity of inflammation. Prior studies have proposed an association between severity of histologic inflammation and risk of CRC in IBD patients[12–15]. However, none of the present guidelines stratify surveillance strategies by severity of inflammation, in part because of lack of use of widely acceptable scales of severity in routine clinical practice. Circulating markers of

inflammation have been associated with increased risk of sporadic colon cancer[16–18]. Whether such an association exists in CD and UC has not been examined previously.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are frequently measured serologic markers of inflammation in patients with CD and UC and correlate well with objective endoscopic and histologic inflammation[19, 20]. In addition, they predict risk of relapse and need for surgery[21–23]. However, they have not been examined longitudinally in association with risk of colon cancer. Demonstrating such a correlation would offer the ability to stratify intensity of surveillance strategies in patients with a cumulative history of repeated relapses while potentially allowing for less frequent surveillance in patients with a prolonged duration of quiescent disease and normal markers of inflammation. We performed this study to prospectively examine if severity of inflammation characterized by elevation of CRP and ESR predicts subsequent risk of CRC in a well-characterized multi-institutional cohort of patients with IBD.

METHODS

Study Cohort and Outcomes

Our study cohort consisted of patients with UC or CD identified from a multi-institutional electronic medical record (EMR) cohort. The development and validation of our cohort have been described in detail in previous publications[24, 25]. In brief, we created a "data mart" of all patients with at least 1 International Classification of Diseases, 9th edition, clinical modification (ICD-9-CM) code for CD (555.x) or UC (556.x) (n=24,182) from patients attending two large teaching hospitals and affiliated medical centers in the Greater Boston metropolitan area. We then developed a classification algorithm using codified data (ICD-9-CM codes for disease-related complications, procedures), treatments captured using the electronic prescription feature of our EMR, and free-text concepts identified using natural language processing. The final classification algorithm had a positive predictive value (PPV) of 97% for both CD and UC which was validated in an independent sample of patients from our data mart. The final cohort consisted of 5,506 patients with CD and 5,522 patients with UC.

The primary outcome of our study was development of CRC, determined as the date of first diagnosis code for colon (ICD-9-CM 153.x) or rectal cancer (ICD-9-CM 154.x). Chart review was performed on a random sample of 50 patients with at least 1 ICD-9-CM code for CRC and confirmed the PPV to be 90%, consistent with published data[26, 27]. For non-CRC controls, to avoid misclassification due to incomplete information or healthcare occurring outside of our system, we required a follow-up within our healthcare system of at least 12 months after the first diagnosis code for CD or UC, and at least one sigmoidoscopy or colonoscopy.

Covariates

Information was obtained on age, age at first diagnosis code for CD or UC, gender, race (white, black, other) and duration of follow-up for IBD in our healthcare system. Medication exposure was modeled as ever or never use (prior to diagnosis of CRC or end of follow-up)

based on the electronic prescription function of our EMR and included 5-aminosalicylates (5ASA), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and monoclonal antibodies against tumor necrosis factor α (anti-TNF) (infliximab, adalimumab, certolizumab pegol). Primary sclerosing cholangitis (PSC) is a well-recognized risk factor for CRC in patients with IBD; however identification of this is hampered by the lack of a distinct ICD-9-CM code[28]. Consequently, to identify patients with PSC, we adopted a method using codified and free-text NLP data similar to that used in the development of our IBD cohort. In brief, we identified all potential patients with PSC using the presence of 1 ICD-9-CM code for cholangitis, cholangiocarcinoma, endoscopic retrograde cholangio-pancreatography (ERCP), liver biopsy, liver transplantation, prescription of ursodiol or narrative mention of "sclerosing cholangitis" "primary sclerosing cholangitis" or "PSC" within their medical chart. We developed a classification algorithm with a final 95% PPV and NPV that was validated by chart review of an independent sample. This yielded a total of 224 patients with PSC, comprising 2% of our IBD cohort.

Measurement of CRP and ESR

All measures of CRP and ESR were obtained as part of routine clinical care. To estimate cumulative severity of inflammation, we calculated the median CRP and ESR value for each patient. To minimize skew from clustered measurement around a single hospitalization, we included only those CRP or ESR measurements at least 1 week apart. For patients who developed CRC, only those values that were obtained after the first diagnosis code for CD or UC and prior to the first code for CRC were included. For other patients, we included all measures of CRP and ESR following diagnosis of CD or UC to the end of follow-up. CRP and ESR were modeled as quartiles; statistical significance of the trend across quartiles was examined using the median CRP or ESR for each quartile. Patients with 1 CRP or ESR measure were likely to be younger (44 vs. 48 years), have longer duration of follow-up after their first IBD diagnosis code (6 vs. 5 years), more likely to have CD (57% vs. 44%), and require anti-TNF biologic or immunomodulator therapy than those with no measured inflammatory markers.

Statistical Analysis

All statistical analysis was performed using Stata 12.0 (StataCorp, College Station, TX). Continuous variables were summarized using medians and interquartile ranges; categorical variables were expressed in proportions. The t-test was used to compare continuous variables. The chi-square test with Fisher's exact correction where appropriate was used to compare categorical variables. We performed univariate logistic regression to identify the association between median CRP or ESR level and risk of CRC. All significant variables in the univariate analysis at $p < 0.1$ were included in our multivariate model. Variables were considered independently significant in the final multivariate model at $p < 0.05$. We also performed a lag analysis by excluding CRP or ESR values measured within 6 months of the diagnosis of CRC or end of follow-up. The study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Study cohort

A total of 4,726 IBD patients had at least 1 available CRP level measured prior to diagnosis of CRC or end of follow-up. The median number of CRP measures per patient in each quartile was 3 (interquartile range 1–6) and was similar across quartiles. After excluding patients younger than age 18 years, those with no lower gastrointestinal endoscopic evaluation in our healthcare system or duration of follow-up of less than 12 months after first diagnosis code for CD or UC, we arrived at our final study cohort of 3,145 patients. Table 1 compares the characteristics of the patient across the quartiles of median CRP. There was no significant difference in age or race between the groups. Patients in the highest quartile of CRP were more likely to be female, have CD, and have a concomitant diagnosis of PSC. Patients in the highest quartile were also more likely to have ever required anti-TNF therapy compared to the lowest quartile (31% vs. 23%, p=0.004). The median CRP across the quartiles ranged from 0.8mg/L to 32.8 mg/L.

Supplementary Table 1 compares the characteristics of the 4,008 patients who fulfilled our inclusion criteria, across quartiles of ESR. The median number of ESR measurements was 6 (IQR 1–10) and was similar across quartiles. Patients in the highest quartile of median ESR were likely to be older, female, have a longer duration of follow-up, and have CD. The median ESR across the quartiles ranged from 7 mm/hr to 50 mm/hr.

Characteristics of patients with colorectal cancer

There were 33 patients in the CRP cohort who developed colorectal cancer. The median age at CRC diagnosis was 55 years (interquartile range (IQR) 41 – 62 years) after a median duration of follow-up in our system of 5 years. Fourteen patients (42%) were women and the majority (n=29, 88%) were Caucasian. Twenty-one patients (63%) had CD, all of whom had colonic involvement, and two (6%) had concomitant PSC. For the analysis examining the correlation between ESR and CRC, there were 102 patients who developed CRC at a median age of 55 years and median duration of follow-up in our system of 5 years (supplemental table 2). Just over half were male (n=56, 54%), and five (5%) had concomitant PSC. Half the patients (n=46, 45%) had UC. The median duration of follow-up after first diagnosis code for IBD in patients who did not develop CRC was 7.6 years.

Association between inflammatory markers and CRC

Compared to patients in the lowest quartile of median CRP, those in the highest quartile had a three-fold increase in risk for CRC (Odds ratio (OR) 3.27, 95% confidence interval (CI) 1.10 – 10.32) (P_{trend} 0.009) (Table 2). After adjusting for age, gender, race, IBD type, presence of PSC, and duration of follow-up, the trend for increase in colorectal cancer risk across the quartiles of CRP remained significant (P_{trend} 0.017, OR for Q4 vs. Q1: 2.72, 95% CI 0.95 – 7.76). In subgroup analyses, the strength of association was similar in men and women, and in those with CD and UC. Adjusting for number of colonoscopies within our EMR to account for the fact that patients with elevated CRP may be more likely to undergo a colonoscopic evaluation also did not affect our results. Adjusting for the intensity of healthcare utilization quantified as number of office visits, hospitalizations, laboratory visits,

radiology tests or procedures also did not influence our findings. Adjusting for use of corticosteroids also did not change our association with CRP or ESR measurements.

Higher median ESR values were similarly associated with increased risk of colorectal cancer. Compared to those in the lowest quartile of ESR, patients in the highest quartile had a significantly increased risk of CRC (OR 2.51, 95% CI 1.44 – 4.37) (P_{trend} < 0.001) (Table 2). This difference remained statistically significant on multivariate analysis (OR 2.06, 95% CI 1.14 – 3.74, P_{trend} 0.007). The median ESR more strongly correlated with CRC risk in patients with UC (OR 3.33, 95% CI 1.44 – 7.76; P_{trend} 0.001) than CD (OR 1.65, 95% CI 0.75 – 3.63; P_{trend} 0.08), and in men (P_{trend} < 0.001) than women (P_{trend} 0.36).

Sensitivity analysis

We performed a number of sensitivity analyses. Introducing a lag interval of at least 180 days between last CRP or ESR measurement and colorectal cancer did not significantly modify the strength of our association (P_{trend} < 0.05 for both CRP and ESR). Excluding patients with PSC-related colon cancer, and adjusting for immunosuppressive therapies in our multivariate model also did not influence the results. Our effect sizes were robust to excluding patients with extreme values of CRP or ESR (highest 1%). Restricting the analysis to patients with at least 2 measured CRP or ESR values also did not alter our measures of association. To account for the fact that a subgroup of patients may not mount an elevation in their CRP levels in response to inflammation, we repeated our analysis including only patients who had at least one measured CRP > 1mg/dL. This further strengthened our effect sizes (OR for quartile 4 vs. quartile 1: 8.33, 95% CI 1.08 – 64.33, P_{trend} 0.009). To exclude the possibility that we are observing an association solely due to more frequent healthcare follow-up in patients with elevated CRP/ESR, and consequently an ascertainment bias, we performed analyses adjusting for number of colonoscopy performed prior to CRC detection (or end of follow-up), number of IBD related hospitalizations, or office visits. In all such analyses, the association between the CRP or ESR quartiles and risk of CRC remained statistically significant and unchanged in magnitude (p < 0.05 for all). We repeated the analysis in a subset of patients who were noted to have a primary care provider within our healthcare system. This resulted in unaltered positive association with elevated CRP (Q4 vs. Q1: 5.16, 95% CI 1.09 – 24.35, P_{trend} 0.012) and ESR (Q4 vs. Q1 3.45, 95% CI 0.84 – 14.21, P_{trend} 0.03).

DISCUSSION

Using a large multi-institutional cohort of patients with CD and UC, we demonstrate that higher median CRP or ESR is associated with an increased risk of CRC. This is consistent with prior literature suggesting an association between severity of colonic inflammation on histology and risk of CRC, and further suggests the need to examine whether treatment to normalization of circulating inflammatory markers is associated with reduction in long-term risk of CRC in patients with IBD.

While colonic inflammation is felt to be an important factor driving the excess risk of CRC in patients with IBD[3, 4, 10, 12–14, 29], incorporation of severity of inflammation into surveillance guidelines has been challenging because of lack of universally accepted

objective measures. Correlation between severity of histologic activity and risk of CRC has been examined previously, albeit mostly with cross-sectional assessments of severity of inflammation on histology. In a case-control study, Nieminen *et al.* compared histologic activity at most recent colonoscopy for 183 IBD patients with neoplasia matched to IBD controls and found an increased CRC risk in patients with moderate (OR 2.6) or severe (OR 31.8) histologic inflammation[14]. Using a similar design, Gupta *et al.* demonstrated that histologic inflammation was associated with three-fold increase in risk for progression to advanced neoplasia in a cohort of 418 UC patients[12]. Rutter *et al.* identified an association with both endoscopic and histologic activity, but only severity of histologic inflammation was found to be an independent predictor[13]. A more recent study by Rubin et al. demonstrated an association between colorectal neoplasia and both maximum and mean histologic disease activity[15]. However, the study was limited by small numbers of patients, case-control design, and bias introduced by indication for the colonoscopy (to obtain biopsies). Furthermore, the use of histologic severity of inflammation to stratify CRC risk is challenging for a few reasons. There is no universally accepted scale for assessment of histologic severity with considerable practice variation between pathologists, and indeed even in the published literature on this topic. Furthermore, such tools are not routinely used in clinical practice making it difficult to assign cumulative severity scores outside of the research setting.

In contrast, CRP and ESR are readily obtained markers of inflammation, correlating strongly with clinical and endoscopic severity in both CD and UC[19, 20, 23]. There has been only limited examination of the longitudinal implications of elevated inflammatory markers. In a small prospective study of 101 CD patients by Boirivant *et al.*, disease relapse at 2 years was more common in those with persistently raised CRP[21]. A larger study from the IBSEN group demonstrated that an elevated CRP at diagnosis was associated with increased risk of surgery in both UC and CD, particularly at CRP levels above 10mg/L in those with UC and 53mg/L in patients with CD[22]. Elevated CRP at clinical remission is also associated with increased risk of relapse after therapy withdrawal[30].

Existing data supports an association between CRP and other circulating biomarkers of inflammation and sporadic colorectal cancer[16–18, 31, 32]. Whether a similar biologic effect exists in patients with inflammatory diseases who demonstrate a much wider range of fluctuation of CRP and ESR has not been examined previously. Additionally, the pathogenesis of colorectal neoplasia in patients with IBD is distinct from that of sporadic colorectal cancer with allelic deletions of the tumor suppressor gene P53 occurring earlier and more commonly in colitis-associated cancer, and less frequent APC gene deletions[10]. However, there exists considerable mechanistic plausibility supporting the pro-CRC effect of chronic inflammation. In animal models, defects in TNF-α signaling is associated with a reduction in both the burden of inflammation and tumor formation[10, 33]. Increased levels of inflammatory cytokines such as interleukin-6 (IL-6) have been observed in both peripheral blood and colonic tissue in patients with IBD-related CRC[34, 35]. Inhibitory cytokines like IL-10, transforming growth factor β (TGF β), and Toll-IL-1R8 inhibit neoplasia formation through suppression of inflammation[10, 29, 36–38].

There are several implications to our findings. To our knowledge, this is the first study examining the association between CRP and ESR in patients with inflammatory bowel disease and subsequent risk of CRC. This association adds another clinical variable to help stratify patients into risk categories for CRC in addition to existing predictors such as disease duration, extent, and presence of PSC. We have witnessed significant changes in the therapeutic endpoints in the management of patients with IBD. Current treatment strategies for both CD and UC focus on achieving objective healing rather than a focus on symptomatic remission[39, 40]. Treatment to mucosal healing reduces the need for hospitalizations and surgery, and may be cost-effective from a societal standpoint[41]. By demonstrating an association between elevated CRP and ESR and subsequent risk of CRC, our findings provide an additional data point suggesting that normalization of inflammatory markers should be an important treatment goal in the management of patients with CD and UC in order to reduce the risk of long-term disease related complications such as CRC. Since CRC fortunately remains a rare outcome in patients with IBD, we do not suggest a need to monitor CRP or ESR solely for the purpose of CRC risk stratification. However, a substantial literature already exists supporting the association between inflammatory markers and more common outcomes including IBD-related hospitalization and surgery suggesting a role of routine assessment of such inflammatory markers[20, 42, 43]. Since current guidelines for dysplasia screening offer wide ranges (every 1–3 years) for surveillance intervals, we believe that our findings, in conjunction with existing data on the association between histologic severity and CRC risk, suggest that an individual patient's severity of inflammation may be helpful in further personalizing surveillance recommendations.

We acknowledge several limitations to our findings. First, we readily acknowledge the likelihood of inter-provider variation in measurement and utilization of inflammatory markers. However, we believe that for several reasons that this bias is unlikely to influence our results. First, the median number of CRP or ESR measurements was also similar across the four quartiles of CRP/ESR suggesting that such measurement bias is unlikely. Second, since most patients usually seek care from a single provider over the course of their illness, for each patient the median value over their duration of follow-up with their treating physician takes into account the bias of the provider. Third, because the two major hospitals comprising this cohort are both academic referral centers, the majority of patients with IBD are under the care of a small subset of gastroenterologists specializing in the management of IBD, thereby reducing inter-provider variation in practices. Third, any misclassification in the measurement of CRP/ESR between the quartiles would likely be non-differential and bias towards the null, making our estimates more conservative than the true magnitude of the association. Finally, any bias in measurement is not likely to be differential based on subsequent development of colorectal cancer as all measurements were obtained prior to CRC diagnosis. Our next limitation is that not all patients underwent surveillance colonoscopies though we ensured that cases were not being misclassified as controls by requiring at least one colonoscopic examination. We could not examine the adequacy and quality of the colonoscopy as well as the surveillance biopsies in our study. As we used data from an EMR cohort, disease extent and duration were not available. However, we would expect such variables to be distributed similarly between cases and controls and do not expect a systematic bias from this missing information. We also did not have information on

body weight or body mass index which has been shown to increase risk for sporadic CRC, but such variables have not been demonstrated to be a risk factor for colitis-associated cancer. Similarly, we also did not have information on family history of colon cancer or use of chemopreventive agents such as aspirin or non-steroidal anti-inflammatory drugs. However because of the frequent association of such agents with disease flares in patients with underlying IBD, we expect long-term chronic use of such therapies in our IBD cohort to be low. We were unable to adjust for ongoing immunosuppressive medication use as a time-varying covariate. However, none of the immunosuppressive medications have been associated with increased risk of CRC, and indeed there is some suggestion of reduced CRC risk with initiation of such therapies. Thus, the higher frequency of use of such medications in the group with elevated CRC likely makes our odds ratios a conservative estimate, suggesting a stronger true effect.

In conclusion, we demonstrated that elevation in CRP and ESR is associated with an increased risk of CRC in a large cohort of IBD patients. This supports incorporation of severity of inflammation into risk stratification and surveillance strategies in patients with IBD. Furthermore, treatment to objective resolution of inflammation as a treatment goal in patients with IBD may reduce likelihood of disease related complications such as CRC and improve long-term patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of inflammatory bowel disease patients in the study cohort, stratified by quartile of median C-reactive protein (CRP)

Characteristic	Quartile 1 %	Quartile 2 %	Quartile 3 %	Quartile 4 %	P-value
Median C-reactive protein (IQR) (mg/dL)	0.8 (0.5 − 1.1)	2.7 (2.1 − 3.5)	7.5 (5.9 − 10.2)	32.8 (20.9 − 57.9)	<0.001
Age [Median(IQR)] (years)	43 (31 − 55)	44 (32 − 59)	44 (32 − 60)	41 (29 − 58)	0.08
Age at first IBD code [Median(IQR)] (years)	33 (24 − 45)	37 (26 − 51)	36 (25 − 51)	35 (23 − 53)	0.19
Duration of follow-up after first IBD code [Median(IQR)] (years)	5 (3 − 9)	6 (3 − 10)	6 (2 − 10)	5 (2 − 9)	0.17
Sex					0.043
Female	52	53	58	57	
Male	48	47	42	43	
Race					0.16
White	88	90	87	86	
Black	7	7	9	10	
Other	5	4	5	4	
Type of IBD					0.001
Crohn's disease	49	54	57	58	
UC	51	46	43	42	
Primary Sclerosing Cholangitis	1	2	2	3	0.048
Ever IMM use	48	44	47	49	0.28
Ever biologic use	23	25	28	31	0.004

All figures represent percentages unless specified otherwise

IQR − Interquartile range; IBD − inflammatory bowel disease; UC − ulcerative colitis; IMM − immunomodulator (azathioprine, 6-mercaptopurine, methotrexate). Biologics include infliximab, adalimumab, and certolizumab pegol

Table 2

Association between quartile of median C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and risk of colorectal cancer in patients with inflammatory bowel diseases

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P(trend)
		OR (95% CI)	OR (95% CI)	OR (95% CI)	
C-reactive protein					
Unadjusted OR	1.0	0.95 (0.27 – 3.28)	1.96 (0.67 – 5.75)	3.09 (1.10 – 8.72)	0.009
Multivariate OR[†]	1.0	0.84 (0.24 – 2.93)	1.87 (0.63 – 5.54)	2.72 (0.95 – 7.76)	0.017
ESR					
Unadjusted OR	1.0	1.04 (0.55 – 1.97)	1.32 (0.72 – 2.43)	2.51 (1.44 – 4.37)	< 0.001
Multivariate OR[†]	1.0	1.14 (0.59 – 2.20)	1.40 (0.74 – 2.64)	2.06 (1.14 – 3.74)	0.007

ESR – erythrocyte sedimentation rate, OR – odds ratio, CI – confidence interval

[†] - Adjusted for age, gender, race, IBD type, duration of follow-up, presence of primary sclerosing cholangi