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Risk of colorectal adenomas in patients with coeliac disease

B. Lebwohl*, E. Stavsky†, A. I. Neugut†,‡ & P. H. R. Green*

*Celiac Disease Center, Division of Digestive and Liver Diseases, Department of Medicine, Columbia University Medical Center, New York, NY, USA.
†Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, NY, USA.
‡Division of Medical Oncology, Department of Medicine, Columbia University Medical Center, New York, NY, USA.

Correspondence to:
Dr P. H. R. Green, Celiac Disease Center at Columbia University, 180 Fort Washington Avenue, Suite 936, New York, NY 10032, USA.
E-mail: pg11@columbia.edu

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SUMMARY

Background
Coeliac disease is associated with an increased risk of lymphoma and small bowel malignancy, but most studies have found no increased risk of colorectal cancer.

Aim
To compare the prevalence of colorectal adenomas in coeliac disease patients with that in non-coeliac disease controls.

Methods
We identified all coeliac disease patients who underwent colonoscopy at our institution during a 44-month period. We matched each patient with non-coeliac disease controls by age, gender and endoscopist. We compared the adenoma prevalence between these groups, and used multivariate analysis to assess the independent association of coeliac disease with adenomas.

Results
We identified 180 patients with coeliac disease and 346 controls. At least one adenoma was present in 13% of coeliac disease patients and 17% of controls ($P = 0.20$). On multivariate analysis, age (OR per year 1.04, 95% CI 1.02–1.07) and male gender (OR 2.33, 95% CI 1.36–3.98) were associated with adenomas, while the relationship between coeliac disease and adenomas remained null (OR 0.75, 95% CI 0.41–1.34).

Conclusions
Coeliac disease is not associated with an increased risk of colorectal neoplasia. The lack of increased risk of colorectal cancer observed in population studies is related to a true average risk of colorectal neoplasia, rather than artifactually reflecting increased colonoscopy and associated polypectomies in the coeliac population.

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INTRODUCTION

Coeliac disease (CD) is a chronic autoimmune disease triggered by the ingestion of gluten in genetically susceptible individuals.[1] CD is associated with an increased risk of mortality,[2–6] and a number of malignancies, with lymphoma and adenocarcinoma of the small bowel carrying the greatest relative risk.[3, 7] Multiple investigations have also found that this elevated risk of malignancy declines with time after the diagnosis of CD,[2–5, 7–10] indicating that the institution of a gluten-free diet may diminish or nullify the increased cancer risk in these individuals.

Colorectal cancer is the most common gastrointestinal malignancy in the United States,[11] but its incidence in patients with CD compared with that in the general population is not elevated in those studies that evaluated this relationship.[7, 9, 12–14] The reason for this may be a true null relationship between CD and colorectal carcinogenesis, but may alternatively be attributed to increased health-care utilization among patients with known CD, particularly with gastroenterologists who are likely to perform screening colonoscopy. Given the potential for colonoscopy to decrease the incidence of colorectal cancer by virtue of the removal of precancerous adenomas during the procedure,[15] a possible underlying increased risk of colorectal cancer in patients with CD may be masked by the fact that such patients are generally followed by gastroenterologists.

We aimed to clarify the underlying risk of colorectal cancer in patients with CD by quantifying the relative prevalence of precancerous colorectal adenomas in these patients compared with patients without CD in a cohort of individuals undergoing colonoscopy. Therefore, to isolate the association of CD with colorectal adenomas, we controlled for three important predictors of adenoma detection on colonoscopy: endoscopist, patient age and patient gender.[16]

METHODS

We designed a retrospective cohort study at Columbia University Medical Center, a large academic medical centre in northern Manhattan, New York. The medical centre maintains an electronic endoscopy database which catalogues all procedures since 21 March 2006. We identified all patients age ≥ 40 years with biopsy-confirmed CD followed at the Celiac Disease Center at Columbia University who had undergone colonoscopy at the medical centre since the inception of the endoscopy database. We matched each CD patient with up to two non-CD controls from the endoscopy database who met the following three matching parameters: age decile, gender and endoscopist. If more than two control subjects were available for matching to a given CD subject, the two subjects with the closest age to the CD subject were included. If more than one colonoscopy was performed on a given individual, the earliest chronological colonoscopy in the database was included. The following exclusion criteria applied to all subjects: personal history of inflammatory bowel disease, colorectal cancer, familial adenomatous polyposis and hereditary non-polyposis colon cancer. In addition to the three matching parameters noted above, we elicited the following data from each procedure: indication for colonoscopy, depth of colonoscope insertion, bowel preparation quality and all neoplastic findings.

The primary outcome of interest was the proportion of CD patients compared with controls with ≥1 adenoma identified on colonoscopy. We also compared CD patients and controls with regard to the size, number, location and histology of adenomas. For this secondary analysis, we considered advanced lesions to be those lesions which were greater than 10 mm in diameter and/or exhibited tubulovillous or villous features or high grade dysplasia.

Due to the possibility that other differences between CD patients and controls may account for the findings of adenoma prevalence, and to identify all variables independently associated with the presence of adenomas, we employed multivariate analysis which included age, gender, provider, clinical indication for colonoscopy, preparation quality and the presence of CD. All statistical calculations were performed using SAS 9.1 (Cary, NC, USA). The Institutional Review Board at Columbia University Medical Center approved this study.

RESULTS

We identified 180 CD patients who underwent colonoscopy at Columbia University Medical Center during a 44-month period (21 March 2006–30 November 2009). An exact date of diagnosis of CD was known in 114 of the 180 patients (63%). Among these 114 patients, all were diagnosed with CD prior to the colonoscopy, and 110 of the 114 patients (96%) were diagnosed with CD more than 1 year prior to the colonoscopy. We identified at least one control patient for every CD patient, and two control patients for 166 CD patients (92%), yielding a total of 346 controls and a total sample size of 526 individuals who underwent colonoscopy by 11 endoscopists during the prespecified time period.

Characteristics of the CD patients and controls are listed in Table 1. The cohort was predominantly (71%)

Table 1 | Characteristics of the cohort of CD patients and controls undergoing colonoscopy at Columbia University Medical Center

Characteristic	All patients (n = 526)	Coeliac disease (n = 180)	Noncoeliac disease (n = 346)	P value
Mean (s.d.) age*	58.8 (11.1)	58.7 (11.2)	58.8 (11.1)	0.91
Age (years)*				
40–49	118 (22)	44 (24)	74 (21)	0.96
50–59	162 (31)	54 (30)	108 (31)	
60–69	147 (28)	49 (27)	98 (28)	
70–79	84 (16)	28 (16)	56 (16)	
≥80 years	15 (3)	5 (3)	10 (3)	
Gender*				
Male	153 (29)	51 (28)	102 (29)	0.78
Female	373 (71)	129 (72)	244 (71)	
Indication				
Screening	144 (27)	45 (25)	99 (29)	<0.0001
Surveillance	83 (16)	19 (11)	64 (19)	
Diarrhoea	94 (18)	56 (31)	38 (11)	
Anaemia/haem positive stool	148 (28)	45 (25)	103 (30)	
Other	57 (11)	15 (12)	42 (8)	
Depth of insertion†				
Caecum/ileum	506 (97)	175 (98)	331 (96)	0.34
Did not reach caecum	17 (3)	4 (2)	13 (4)	
Preparation quality†				
Poor	34 (7)	12 (7)	22 (7)	0.61
Excellent/good/fair	458 (93)	156 (93)	302 (93)	

* Matched variables.

† Sums do not add up to the total sample size due to missing data values.

women, and the mean age was 58.8 (s.d. 11.1) years. The distribution of clinical indications differed significantly between CD patients and controls; a greater proportion of CD patients underwent colonoscopy for the indication of diarrhoea (31% vs. 11% of controls), and a lesser proportion underwent colonoscopy for the indication of anaemia/haem positive stool (25% vs. 30% of controls) or surveillance of prior adenomas (11% vs. 19% of controls, overall $P < 0.0001$). CD patients did not differ from controls with regard to caecal intubation rates (98% vs. 96% of controls, $P = 0.34$) or the proportion of patients with poor bowel preparation (7.1% vs. 6.8% of controls, $P = 0.61$).

With regard to neoplastic findings, at least one adenoma was identified in 16% of all patients (Table 2). The prevalence of at least one adenoma was not significantly different between CD patients (13%) and controls (17%, $P = 0.20$). CD patients and controls did not significantly differ with regard to the number of adenomas per patient ($P = 0.12$), the size of adenomas ($P = 0.43$) or the relative proportions of histological categories ($P = 0.80$). An advanced histological lesion was identified in 5.0% of CD patients and 5.2% of controls ($P = 0.92$). Adenocarcinoma was identified in two patients (0.4%), both in the control group.

When excluding all colonoscopies in which the indication for the procedure included a history of colorectal adenoma (remaining $n = 443$), the proportion of patients with ≥1 colorectal adenoma was 10% in CD patients and 15% in controls ($P = 0.16$). Among those subjects undergoing colonoscopy with a history of adenoma ($n = 83$), overall adenoma prevalence was greater (30%), and there was no significant difference in prevalence between CD patients and controls (37% and 28% respectively, $P = 0.47$). Likewise, there was no significant difference in the size, location or histological features of the adenomas

Table 2 | Neoplastic findings on colonoscopy among CD patients and controls

Characteristic	All patients (n = 526)	Coeliac disease (n = 180)	Noncoeliac disease (n = 346)	P value
One or more adenomas	82 (16)	23 (13)	59 (17)	0.20
Location				
Proximal only	39 (7)	10 (6)	29 (8)	0.52
Distal only	30 (6)	8 (4)	22 (6)	
Proximal and distal	13 (2)	5 (3)	8 (2)	
Number of adenomas				
1	65 (12)	16 (9)	49 (14)	0.12
2	6 (1)	1 (0.5)	5 (1.5)	
≥3	11 (2)	6 (3)	5 (1.5)	
Size of largest adenoma (mm)				
≤5	36 (7)	11 (6)	25 (7)	0.43
6–9	29 (6)	6 (3)	23 (7)	
≥10	17 (3)	6 (3)	11 (3)	
Histology				
Tubular	67 (13)	19 (11)	48 (14)	0.80
Tubulovillous	5 (1)	1 (0.6)	4 (1)	
Villous	1 (0.2)	0	1 (0.3)	
High-grade dysplasia	4 (0.8)	2 (1)	2 (0.6)	
Sessile serrated adenoma	3 (0.6)	1 (0.6)	2 (0.6)	
Adenocarcinoma	2 (0.4)	0	2 (0.6)	
Advanced neoplastic lesion	27 (5)	9 (5)	18 (5)	0.92

when comparing CD patients with controls in these subgroups.

On multivariate analysis (Table 3), the following variables were independently associated with significantly increased odds of adenoma detection: age (OR per year 1.04, 95% CI 1.02–1.07) and male gender (OR 2.33, 95% CI 1.36–3.98). After adjusting for the above variables as well as clinical indication, the null relationship between CD and adenoma detection persisted (OR 0.75, 95% CI 0.41–1.34). Adenoma detection did not vary significantly between providers (overall P value 0.29).

DISCUSSION

In this retrospective cohort study, the prevalence of colorectal adenomas among patients with CD was not significantly different from that among non-CD controls. This null association was observed in the crude analysis, in which CD patients were matched to controls by age decile, gender and endoscopist; the null association was maintained after adjusting for clinical indication.

This is the largest study to date to quantify the prevalence of adenomas in CD patients and the first such study designed primarily to measure adenoma detection. In a prior study of CD patients with iron deficiency anaemia undergoing colonoscopy (n = 98), adenoma prevalence was 8.2% compared to 11.3% in controls.[17] In another population of CD patients with altered bowel habits or iron deficiency anaemia (n = 69), the prevalence of colorectal neoplasia was 10%, and was comparable to the adenoma prevalence in non-CD patients with iron deficiency (12%).[18] To our knowledge, there are no published studies evaluating the relationship between positive CD serologies or the CD-associated HLA haplotypes and the prevalence of colorectal neoplasia.

Our finding that CD is not a risk factor for colorectal adenomas is congruent with the results of multiple analyses of cancer risk in CD. In these analyses, the risk of malignancy in general is elevated, but CD appears to have a variable relationship with different cancers. The relative risk of non-Hodgkin lymphoma and adenocarcinoma of the small bowel is greatly increased compared with that in the general population,[3, 4, 7] but the risk of breast and lung carcinoma appears to be reduced.[3] With one exception,[8] studies that evaluated a possible

Table 3 | Multivariate analysis of factors associated with the presence of ≥1 adenoma

	Odd Ratio (95% CI)	*P* value
Age (years)		
40–49	1.0 (reference)	0.0434
50–59	1.0 (0.44–2.91)	
60–69	1.42 (0.63–3.21)	
70–79	2.50 (1.10–5.68)	
≥80	3.80 (0.96–15.07)	
Gender (male)	2.33 (1.36–3.98)	0.002
Indication		
Screening	1.0 (reference)	0.05
Surveillance	1.77 (0.88–3.57)	
Diarrhoea	0.85 (0.37–1.96)	
Anaemia/haem positive stool	0.71 (0.34–1.48)	
Other	0.34 (0.09–1.22)	
Poor preparation	2.02 (0.71–5.77)	0.19
Coeliac disease	0.75 (0.41–1.34)	0.33

relationship between CD and colorectal cancer have not noted an association of these two diseases.[7, 9, 12–14] This null relationship may be understood by the fact that gastrointestinal mucosal inflammation in CD is classically a declining gradient starting from the proximal small bowel; indeed, the site of small bowel adenocarcinoma in CD patients demonstrates a similar distribution gradient, occurring more commonly proximally than distally.[19] Moreover, as has been posited previously,[20] the pathophysiology of CD may be protective against colorectal carcinogenesis, by means of malabsorption of ingested fat or putative dietary carcinogens. In addition, the inflammatory colonic condition most frequently associated with coeliac disease, microscopic colitis,[21] is not associated with an increased colon cancer risk.[22]

While the adenoma prevalence of patients with CD did not differ significantly from that of controls, overall adenoma prevalence was low, occurring in 16% of all patients. We attribute this finding to the fact that this cohort is younger than those patients included in prior studies of adenomas,[23, 24] and is predominantly female; moreover, none of the patients had a family history of colorectal cancer. Guidelines recommend that at ≥1 adenoma be identified in at least 15% of all women and 25% of all men aged 50 years and older undergoing colonoscopy.[25] When restricting this cohort to individuals aged ≥50 years, adenoma detection was 28% in men and 19% in women, meeting this quality benchmark.

This analysis has a number of limitations. As a single-institution study conducted at a major referral centre for individuals with CD, the generalizability of these findings is uncertain. As the colonoscopies included in the study were retrieved from a database that began its catalogue in 2006, individuals with CD who had an earlier colonoscopy only were not included, and colonoscopies that were included were not necessarily the first examination in each individual's lifetime. There may be significant differences between the CD patients and controls with regard to colonoscopic history; indeed, the control population had a higher proportion of examinations with the indication of adenoma surveillance. To minimize the potential bias resulting from differences between CD patients and controls with regard to colonoscopic history, we repeated the measurement of adenoma prevalence, eliminating those patients whose indication for the procedure included a history of colorectal neoplasia. In this repeat analysis, presumably dominated by first-time colonoscopies, the adenoma prevalence among CD patients and controls remained statistically nonsignificant. In another effort to minimize the potential confounding effect of colonoscopic history on the outcome of adenoma prevalence, we employed multivariate analysis in which clinical indication was a covariate; in this multivariate analysis, CD was not significantly associated with an increased or decreased odds of adenoma presence.

All of the CD patients in this cohort study underwent colonoscopy after the diagnosis of CD, and 96% were diagnosed more than 1 year prior to colonoscopy; presumably, many or most of these patients were following a gluten-free diet. That these CD patients probably have relatively quiescent disease activity is reflected by the fact that a lower proportion of CD patients had an indication of anaemia or haem positive stool as compared with controls. As patients with uncontrolled CD have high rates of haem positive stool,[26] the patient population in the current study may not reflect CD in the general population. It is therefore possible that there is an effect of untreated CD on colorectal neoplasia that is not detectable in this study. Indeed, the increased relative incidence of malignancy and/or mortality in CD declines in the years following diagnosis of CD,[2–5, 7–10] lending credence to the notion that a gluten-free diet can have a beneficial effect on the natural history of CD. As this study was performed at a major referral centre for CD, it is expected that a vast majority of patients with known CD who undergo colonoscopy at this institution already

having been diagnosed with CD. Thus, we cannot rule out a relationship between undiagnosed CD and colorectal adenomas. To assess for this relationship, a future study would require screening asymptomatic patients for CD at the time of screening colonoscopy.

In this study, the prevalence of adenomas among CD patients was 13%, whereas the prevalence of adenomas among controls was 17%. This difference was not statistically significant, but the possibility remains that CD patients actually have a lower prevalence of adenomas compared with non-CD patients. As mentioned above, malabsorption of fats and dietary carcinogens may provide a mechanistic explanation for this possible protective effect of CD on colorectal neoplasia.[20] However, it is premature to conclude that such an effect exists, as the sample size in our study was not sufficiently large to allow one to conclude that the observed difference in adenoma prevalence between CD patients and non-CD patients was not due to chance. It is nevertheless intriguing that in the two previous smaller reports of adenoma prevalence among CD patients, these patients had a lower (if not statistically significant) prevalence of adenomas compared with controls, as was the case in our study.[17, 18] *Post hoc* power analysis of our study shows that the smallest detectable difference of adenoma prevalence between CD and control patients that could be observed with 80% power was 8.6% (17% in controls vs. 8.4% in CD patients). To determine prospectively whether CD patients have a 4% lower prevalence of adenomas (as was observed in our study), such an analysis would require 2853 subjects: 951 CD patients and 1902 controls.

In conclusion, in this largest study of colorectal neoplasia in CD to date, the prevalence of adenomas in this population was not significantly different from that in controls. Future studies are warranted to evaluate a possible mild protective effect of CD on the development of colorectal adenomas, and to characterize better the mechanisms by which CD affects the individual patient's risk of malignancy.

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