

# Similarity of colorectal cancer in Crohn's disease and ulcerative colitis: implications for carcinogenesis and prevention

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## Abstract

**Colorectal cancer is the most frequent malignant complication in patients with inflammatory bowel disease. Eighty patients with colorectal cancer complicating Crohn's disease (CD) or ulcerative colitis (UC) with median ages at diagnosis of colorectal cancer of 54.5 years and 43.0 years respectively were studied. The median duration of disease to the diagnosis of cancer was long (CD 15 years; UC 18 years). Most cancers developed after more than eight years of disease (CD 75%; UC 90%). Patients with multiple carcinomas at diagnosis were equally common (CD 11%; UC 12%). Carcinoma occurred in the area of macroscopic disease in most patients (CD 85%; UC 100%). Mucinous and signet ring histological features were equally common (CD 29%; UC 21%). Dysplasia was present with similar frequency in both diseases (CD 73%; UC 79%). The overall five year survival rates were also similar (CD 46%; UC 50%). These findings show that carcinomas complicating CD and UC have strikingly similar clinicopathological features and suggest that a common underlying process, such as chronic inflammation, maybe important in the pathogenesis of colorectal carcinoma.**

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Colorectal cancer is the most frequent malignant complication of inflammatory bowel disease. Since the initial description of this complication in 1925,<sup>1</sup> much has been learned about colorectal cancer in ulcerative colitis (UC). Thus, the increased cancer risk in long standing UC is now well established, and is thought to be dependent on the duration and extent of disease.<sup>2-8</sup> Periodic colonoscopic surveillance with multiple biopsies is currently recommended as a method of identifying high risk patients. Our recent study<sup>9</sup> suggests that surveillance colonoscopy can improve cancer related mortality in patients with long standing UC.

In comparison, colorectal cancer in Crohn's disease (CD) has not been as well studied. In fact, until recently the detection of colorectal carcinoma in inflammatory bowel disease was considered diagnostic of UC.<sup>10</sup> However, subsequent studies<sup>11-13</sup> have shown that the risk of developing colorectal cancer in CD is significant, and may be comparable to that in UC. The implications of these studies on the

specific management of cancer risk in patients with CD are not yet clear, particularly since only limited information is available on clinical and pathological features of this complication. Studies<sup>14</sup> suggesting a rising incidence of CD in the general population places a greater number of patients at increased risk of developing carcinoma. Therefore, an understanding of this problem is becoming critical.

Unfortunately, the basis for the increased risk of colorectal cancer in patients with either CD or UC remains even less well understood. Clearly, a better understanding of the aetiopathogenesis of cancer in inflammatory bowel disease would be extremely helpful in defining patients at highest risk and in developing an improved cancer risk management plan.

In this study, we have compared directly the features of colorectal cancer in CD and UC. We show that the clinicopathological characteristics of colorectal cancer in the two diseases are strikingly similar. We discuss evidence supporting the importance of inflammatory activity in carcinogenesis and its implication for cancer prevention in patients with inflammatory bowel disease.

## Methods

The computerised medical record system at the Lahey Clinic Medical Center was used to identify patients with the diagnosis of inflammatory bowel disease or colorectal cancer, or both, (using the International Classification of Diseases 7-9) who had been seen between 1957 and 1991. There were 6217 patients with inflammatory bowel disease, 3124 patients with CD and 3093 patients with UC. Among these patients, 80 had concomitant colorectal cancer. During this period 5266 patients with colorectal cancer but without a known history of inflammatory bowel disease were seen at the same institution among the 1 020 765 patients without inflammatory bowel disease.

The diagnoses of CD and UC were confirmed by standard clinical, roentgenographic, endoscopic, and histological criteria for these 80 patients. The onset of disease was defined as the time when the patient first experienced symptoms consistent with inflammatory bowel disease.<sup>6</sup> The anatomical location of the colorectal cancer and its relationship to the location and macroscopic extent of inflammatory bowel disease were determined by roentgenography or colonoscopy examination.<sup>15 16</sup> Tumour histology and associated dysplasia were analysed in patients in whom

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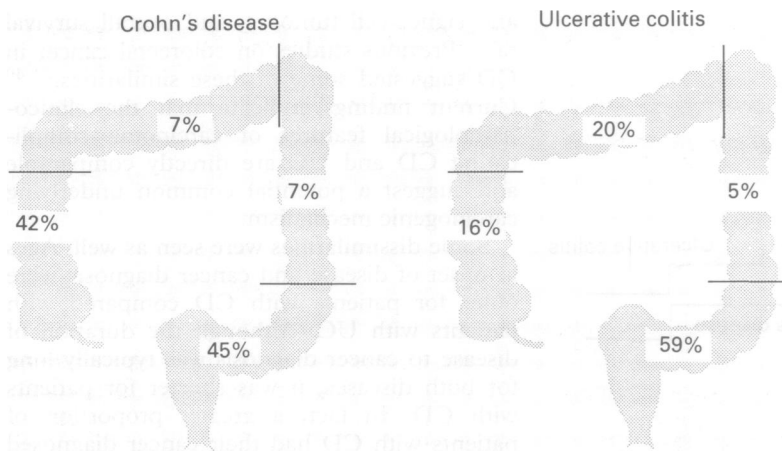


Figure 1: Anatomical distribution of cancer in patients with associated Crohn's disease and ulcerative colitis.  $p=0.04$ .

this information was available. Complete data were not available for all patients. Dysplasia was not subcategorised into low grade and high grade dysplasia because of the small sample size. The Dukes's stage was confirmed pathologically in all but one patient with CD.

Medical records were reviewed to determine the patients' current condition. For patients whose follow up records were not up to date, telephone calls were used to determine the current status. For deceased patients, the cause of death was determined to be related to the underlying malignancy in all patients by autopsy reports or medical records, or both.

Statistical analysis was performed using the BMDP-1L statistical program (BMDP Statistical Software Inc, Los Angeles, CA). Survival distributions were calculated by the product-limit method of Kaplan and Meier.<sup>17</sup> The statistical significance of differences between distributions were analysed by the Tarone-Ware method. Probability values are two tailed with  $p < 0.05$  regarded as statistically significant.<sup>18 19</sup>

## Results

Eighty of the 6217 patients with either CD or UC had colorectal cancer. Of these 80 patients, 28 had CD and 52 UC. The median age at diagnosis of CD of 35.5 years (range, 14–72 years) was older than the median of 25.0 years (range, 5–68 years) in patients with UC ( $p=0.001$ ). The median age at diagnosis of colorectal cancer in patients with CD of 54.5 years (range, 32–76 years) was older than the median of 43.0 years (range, 17–75 years) found in patients with UC ( $p=0.005$ ). The median duration of disease to the time of the diagnosis of cancer was 15 years for patients with CD compared with 18 years for patients with UC ( $p=0.12$ ). For reference, the median age at diagnosis of sporadic colorectal cancer during the period studied was 65.0 years (range, 7–99) for 5266 patients without inflammatory bowel disease. Thus, cancer developed at a relatively younger age in patients with CD ( $p < 0.001$ ) and UC ( $p < 0.001$ ).

Colorectal cancer was diagnosed in seven of 28 (25%) patients with CD within the first

eight years of disease. In comparison, five of 52 (10%) patients with UC were diagnosed with cancer within the first eight years of disease ( $p=0.08$ ). In patients with Crohn's disease, 86% of those who developed cancer within the first eight years of disease were older than 50 years of age (median age, 65; range, 35–72), compared with 57% of those with a disease duration of greater than eight years (median age, 52; range, 32–76;  $p=0.21$ ). In comparison, 40% of patients with UC who developed cancer within the first eight years of disease were older than 50 years of age (median age, 36; range, 19–65), compared with 34% of those with UC duration of greater than eight years (median age, 43; range, 17–75;  $p=0.79$ ).

Mucinous carcinomas were seen in 22% of patients with CD and 15% of patients with UC ( $p=0.51$ ). Signet ring carcinoma was detected in 7% of patients with CD and 6% of patients with UC ( $p=0.81$ ). Pathology specimens were available for analysis of dysplasia in 40 patients (CD 11; UC 29). Dysplasia was detected in 73% of patients with CD and 79% of patients with UC ( $p=0.67$ ).

Multiple tumours at the time of cancer diagnosis (synchronous cancer) were seen in 11% of patients with CD and 12% of those with UC ( $p=0.94$ ). The anatomical location of tumours in CD patients was evenly distributed between the right and rectosigmoid colon. This differed from patients with UC, in whom tumours were predominantly in the rectosigmoid area. Carcinoma of the descending and transverse colon was rare in both diseases. Overall, the anatomical distribution of colorectal cancer in two diseases was significantly different ( $p=0.04$ ; Fig 1).

Among 26 patients with CD whose extent of disease was known, 73% had ileocolitis and 27% colitis. Carcinoma was found within the area of macroscopic disease<sup>15 16</sup> in 22 (85%). No instance of colorectal cancer was found without concomitant colonic disease. In comparison, among 45 patients with UC whose extent of disease was known, 76% had pancolitis and 24% left sided disease. Cancer developed in the area of macroscopic disease in all 45 patients with UC (100%;  $p=0.05$ ). Thus, cancer developed in the left colon in all 11 patients with left sided disease.

For cancer stage and survival analyses, 20 patients with UC who had undergone cancer surveillance<sup>9</sup> were excluded to eliminate the intervention bias. In the remaining patients with cancer, the distribution of Dukes's stages in CD and UC were similar ( $p=0.91$ ; Table I). There were 32 deaths in these patients (CD 15; UC 17). The survival rates of the two groups were analysed using the Kaplan-Meier product-limit method to adjust for the difference in the duration of follow up.<sup>17</sup> The analysis showed a five year survival rate of mean (SD) 46.4 (10.1)% for patients with CD (median follow up time, 2.0 years; range, 0–13.0 years) compared with 50.1 (9.7)% for patients with UC (median follow up time, 3.6 years; range, 0–42.6 years). These results are shown in Figure 2 ( $p=0.97$ ) and are similar to previously reported survival data on our

### Dukes's stage in Crohn's disease (CD) and ulcerative colitis (UC) patients with colorectal cancer\*

Stage	CD No (%)	UC No (%)
A	4 (15)	6 (19)
B	9 (33)	9 (28)
C	14 (52)	17 (53)

$p=0.91$ .

\*One patient with CD whose stage was unknown and 20 patients with UC who were under colonoscopic surveillance were excluded from the cancer stage analysis.

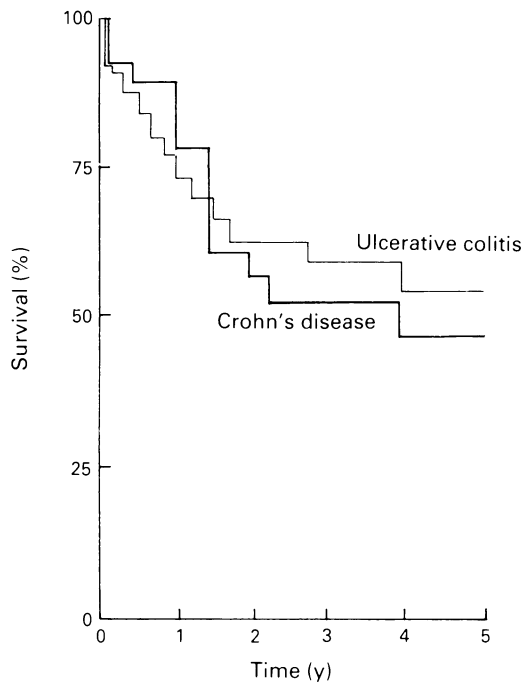


Figure 2: Overall five year survival. The mean (SD) five year survival rate was 50.1% (9.7%) for ulcerative colitis and 46.4% (10.1%) for Crohn's disease ( $p=0.97$ ).

patients with sporadic colorectal cancer.<sup>20 21</sup> No difference in the five year survival rates were found for each stage between the two diseases ( $p<0.05$ ; Fig 3). However, the five year survival rates between stages analysed for all patients with cancer were statistically significant ( $p<0.001$ ; data not shown).

**Discussion**

These findings show that the clinicopathological features of carcinoma complicating CD and UC are strikingly similar. Similarities include typical long duration of disease before the diagnosis of cancer, relatively young age at diagnosis of cancer compared with sporadic colorectal cancer, frequent multiple tumours at presentation, usual predominance of cancer in the area of macroscopic disease, prevalence of associated dysplasia, frequency of mucinous

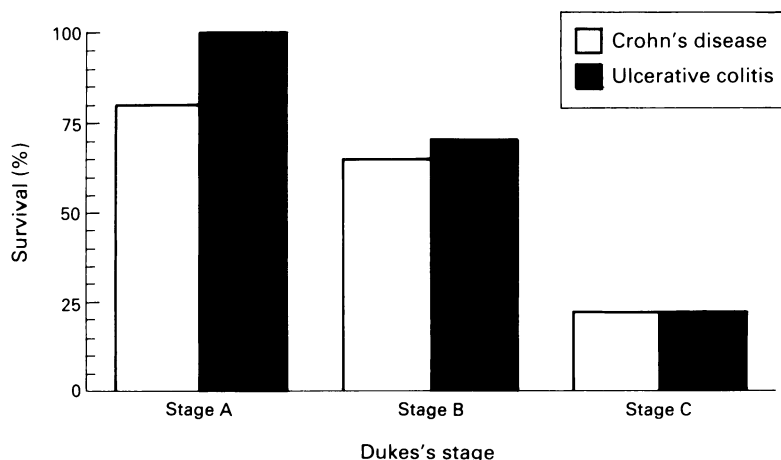


Figure 3: Five year survival in relation to Duke's stage. The five year survival rate by each Duke's stage between Crohn's disease and ulcerative colitis showed no significant difference ( $p>0.05$ ).

and signet cell tumours, and overall survival rate. Previous studies on colorectal cancer in CD suggested some of these similarities.<sup>22 40</sup> Current findings indicate that the clinicopathological features of carcinoma complicating CD and UC are directly comparable and suggest a potential common underlying carcinogenic mechanism.

Some dissimilarities were seen as well. Ages at onset of disease and cancer diagnosis were older for patients with CD compared with patients with UC. Although the duration of disease to cancer diagnosis was typically long for both diseases, it was shorter for patients with CD. In fact, a greater proportion of patients with CD had their cancer diagnosed within the first eight years of the onset of disease, a tendency previously noted.<sup>22</sup> Paradoxically, the age at cancer diagnosis of patients with CD of shorter duration was older than that of the patients with a longer duration of disease.

Although these findings may be explained by sampling and referral biases, a review of the published reports showed nearly identical findings. Of 72 analysable patients (median age, 50; range, 26-77) in more than 100 reported cases,<sup>22 40</sup> colorectal cancer developed in 18 (25%) within the first eight years of CD. The vast majority of these patients (78%) were older than 50 years (median age, 59; range, 27-72) compared with only 39% of the remaining 54 patients with a duration of disease longer than eight years (median age, 47.5; range, 26-77;  $p=0.005$ ). Thus, a chance occurrence of sporadic colorectal cancer related to age may partly explain the shorter duration of disease before the diagnosis of cancer in these older patients.

In addition, a high proportion (57%) of our patients with CD whose diagnosis of cancer was made within the first eight years of disease had an antecedent history of poorly characterised bowel symptoms, such as frequent loose bowel movements and vague abdominal pain, or a diagnosis of irritable bowel syndrome. It is possible that these patients had, in fact, subclinical CD. In contrast, none of the patients with a short duration of UC before the diagnosis of cancer had such a history.

Another difference was that the anatomical distribution of colorectal carcinoma differed between CD and UC (Fig 1). However, cancers tended to occur in areas affected by inflammatory bowel disease. In all patients with UC, cancer developed in the area of macroscopic disease, and therefore none of those with left sided colitis developed cancer in the proximal unaffected colon. Similarly, most patients with CD developed cancer in the area of macroscopic disease. Colorectal cancer did not develop in patients with small bowel CD only. Because CD often starts in the rectosigmoid and ileocaecal region, and UC invariably begins from the rectum and extends proximally,<sup>41</sup> it seems that the anatomical distribution of cancer followed these respective sites of disease involvement.

A separate review of five small bowel cancers

in our patients with inflammatory bowel disease also showed a similar tendency for cancer to develop in the region affected by inflammatory bowel disease. For example, in three patients with CD, small bowel cancer developed in the area of ileal disease (unpublished observation). This agrees with previous studies on the pattern of small bowel carcinoma in CD.<sup>42</sup> No instance was found of small bowel cancer complicating CD that affected only the colon. In addition, cancer developed at the site of the ileostomy in two previously reported patients with UC who had undergone colectomy.<sup>43</sup> Interestingly, the pre-colectomy barium enema study had shown evidence of 'backwash' ileitis in both patients.

The exact comparative risks of colorectal cancer in our patients with inflammatory bowel disease is difficult to determine on the basis of current analysis, because of well described potential biases.<sup>44,45</sup> It is nevertheless notable that the crude cumulative rate of colorectal cancer seen in our patients with CD was less than that seen in those with UC (0.9% v 1.7%). This is similar to results from two of the largest population based studies<sup>13,46</sup> in which the overall cumulative rate of colorectal cancer for their inflammatory bowel disease population, which included both low and high risk patients over a 26 year period, was 0.6% in patients with CD and 2.9% for those with UC.

This apparent difference in cancer risks may be a reflection of the different pattern of bowel involvement in the two diseases. For example, segmental involvement of disease, frequent small bowel disease without colonic involvement, and common surgical resection in CD<sup>47,48</sup> signify less absolute length of colon at risk. The decreased length of bowel affected by the disease process probably played a role in the decreased rate of colorectal cancer in patients with CD.

These findings suggest a common underlying carcinogenic mechanism in inflammatory bowel disease. One likely candidate is the underlying chronic inflammation<sup>49,50</sup> shared by both diseases. Findings including the predominance of cancer in the area affected by the chronic inflammatory process, an apparent dose dependent relationship between the risk of developing cancer and the duration and extent of colonic inflammation, and the similarity of pathological features of neoplasia developing in two distinct chronic inflammatory conditions of the bowel, indicate that the increased cancer risk seen in inflammatory bowel disease may be related to the underlying chronic inflammation rather than to an undefined carcinogenic mechanism unique to either CD or UC. Results seen with other chronic inflammatory conditions such as Barrett's oesophagus<sup>51</sup> and experimental colitis<sup>52-54</sup> also support this conclusion. These observations, in turn, provide an explanation for recent studies<sup>55-60</sup> showing the efficacy of anti-inflammatory agents in the prevention of colorectal cancer and suggest their potential role as a chemopreventive measure in patients with inflammatory bowel disease.

These results also suggest a potential

method of improving the current technique of colonoscopic surveillance with random biopsies at fixed interval in patients with UC. For example, these results suggest that cancer is less likely to develop in an unaffected bowel. Thus, surveillance biopsies of the proximal colon in patients with well documented, left sided UC may not be as important. On the other hand, a separate analysis<sup>61</sup> showed that the rectosigmoid in UC is at the highest risk for the development of dysplasia and carcinoma, probably because of the invariable involvement of this region by the chronic inflammation.<sup>41</sup> Thus, the current biopsy regimen may benefit from an increased sampling of the distal colon.

Cancer surveillance in patients with CD at increased risk should probably be considered too. It is likely that patients with extensive CD of long duration without prior surgical resection would benefit from a surveillance programme that emphasises biopsies in the area of macroscopic disease. These results suggest that a periodic surveillance should probably start after eight years of disease. In a few people who present with CD after 50 years of age, surveillance starting at the time of the diagnosis of disease may be appropriate.

In conclusion, these results indicate that clinicopathological features of colorectal cancer complicating CD and UC are strikingly similar. These findings indicate a common underlying process, such as chronic inflammation, may be important in colon carcinogenesis and suggest potential methods of improving current approaches to cancer prevention in patients with inflammatory bowel disease.

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