Increased risk of colorectal cancer in ulcerative colitis patients diagnosed after 40 years of age

Constantine J Karvellas MD FRCPC, Richard N Fedorak MD FRCPC, John Hanson MSc, Clarence KW Wong MD FRCPC

BACKGROUND: The association between ulcerative colitis (UC) and colorectal cancer (CRC) is well established. Retrospective data show a 5.4% CRC incidence rate among patients with pancolitis and suggest that cancer surveillance should be provided to patients following eight to 10 years of extensive UC.

AIM: To identify premalignant risk factors for UC patients and to determine whether current recommendations for cancer surveillance need reviewing.

PATIENTS AND METHODS: A retrospective audit was conducted of adult patients with UC who were diagnosed with CRC between 1991 and 2002 in five hospitals in Edmonton, Alberta.

RESULTS: Thirty-one cases of CRC (68% male) were identified. In this group, the mean ages at diagnosis were 44.4 years for UC patients and 60.1 years for CRC patients. For patients in whom the initial data of diagnosis of UC could be determined (n=29), the median duration of UC at the time of CRC diagnosis was 16 years. Patients diagnosed with UC after 40 years of age (n=15, mean age 64 years) progressed more rapidly to CRC than patients diagnosed before 40 years of age (n=14, mean age 23 years). The median durations of UC before development of CRC were 22 years and 10 years, respectively, for patients with a diagnosis of UC before and after 40 years of age (OR 11.5, 95% CI 2.41 to 20.16; P=0.00029). Only four patients (13%) were enrolled in an appropriate cancer-screening program. Nine of these UC patients (29%) who were older than 40 years of age developed CRC before the 10-year point.

CONCLUSIONS: In the present study, patients diagnosed with UC after 40 years of age developed CRC more rapidly than those diagnosed before 40 years of age. This finding suggests that patients who are diagnosed with UC after 40 years of age should undergo CRC surveillance earlier than current recommendations.

Key Words: Colorectal cancer; Dysplasia; Surveillance colonoscopy; Ulcerative colitis

The association between long-standing, extensive ulcerative colitis (UC) and an increased risk of colorectal cancer (CRC) is well established. Many studies have investigated this risk, although the reported rates of incidence vary. A recent meta-analysis (1) of 116 studies from the United States, Great Britain and Europe estimated the overall incidence of CRC among all UC patients to be 3.7%. For patients with pancolitis, the rate increased to 5.4%. For all patients with UC, the incidence rates were 2% at 10 years, 8% at 20 years and 18% at 30 years. In comparison, incidence rates for children were 5.5% at 10 years, 11% at 20 years and 16% at 30 years (1).

Several independent risk factors for malignancy in UC patients have been identified. These factors include duration of disease, extent of inflammation, history of concurrent primary sclerosing cholangitis and family history of CRC (2). However, recent controlled studies (3) have suggested that treatment with chemoprotective agents such as 5-aminosalicylic

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acid (5-ASA) may be beneficial in preventing malignant transformations in UC patients.

Currently, Canadian practice guidelines suggest providing surveillance colonoscopy for patients with either pancolitis, extensive left-sided colitis. Based on retrospective data (2), it has been recommended that screening colonoscopy be given to UC patients following eight to 10 years of active UC. However, no major clinical trials have been able to unequivocally determine the survival benefit or the cost-effectiveness of surveillance (4). The purpose of the present study was to identify premalignant risk factors in UC patients and determine whether current surveillance guidelines need reviewing.

PATIENTS AND METHODS

Patient selection

For the present study, a retrospective audit was conducted of adult patients with UC who developed CRC between 1991 and 2002. Patient information was retrieved electronically, using the International Classification of Diseases, Ninth Revision codes from the databases of two academic tertiary care centres (University of Alberta Hospital and Royal Alexander Hospital) and two community hospitals (Grey Nuns Hospital and Misericordia Community Hospital) in Edmonton, Alberta. All cases were correlated with charts from the WW Cross Cancer Institute in Edmonton, Alberta, to which all cases of colon cancer in the region are reported. Two independent ethics review boards (Alberta Cancer Board and Capital Health Authority) approved the review of patient files. The charts for the selected patients were then audited by one reviewer (CJK). Patients were excluded from the study if the diagnosis of CRC was made before the diagnosis of UC.

Data collection

All endoscopy and pathology reports for the study participants were reviewed. Each medical record-defined case was cross-referenced with pathology records. The date of case diagnosis was determined according to the earliest pathological or endoscopic evidence of UC. All data from pathology reports, the four hospitals and the WW Cross Cancer Institute, as well as any out-of-region data were examined as much as possible. Disease collection criteria were determined a priori. Disease extent of UC was recorded as the longest extent on any colonoscopy. Patients were then classified as having either proctitis (less than 10 cm), left-sided colitis (between 10 cm and 60 cm) or pancolitis (greater than 60 cm). Biopsy findings from each endoscopy were recorded according to the following categories: normal, inflammatory, low-grade dysplasia, high-grade dysplasia, dysplasia-associated lesion or mass, or carcinoma. Where possible, the type of cancer surveillance program (ie, colonoscopy, sigmoidoscopy or other) was determined. Mean duration from the time of diagnosis of UC to diagnosis of CRC was determined using the earliest pathological or endoscopic confirmation of UC and the date of biopsy confirming CRC.

Patients were stratified into two groups: one for diagnosis of UC before 40 years of age and one for diagnosis of UC after 40 years of age. The rationale for this was based on data from Bernstein et al (5) from the Manitoba Inflammatory Bowel Disease database, which showed that the peak incidence of UC occurred in patients between 20 and 29 years of age (incidence rate of 20.4 per 100,000 people) and 50 and 59 years of age (incidence rate of 19.5 per 100,000 people).

Data obtained from each chart also included identification of initial and subsequent therapy (either medical or surgical), long-term use of 5-ASA and long-term use of immunomodulatory therapy. Further data were obtained on smoking history, family history of CRC and evidence of concomitant primary sclerosing cholangitis (diagnosed on endoscopic retrograde cholangiopancreatography). Patient postdiagnosis survival times were also determined.

Statistics

Kaplan-Meier analyses were used for statistical analysis; the diagnoses of UC and CRC were the start and end points. Mean duration of disease before UC was determined from the 50% point on the respective curves. The nonparametric log rank test was used to determine the differences between the two curves, ORs, 95% CIs and P values.

RESULTS

Patient demographics

An epidemiological profile of the case series of selected patients is presented in Table 1. Of the 31 patients with UC who had been subsequently diagnosed with CRC, 24 patients had active colitis at the time of diagnosis with CRC. Twenty patients had pancolitis, nine had left-sided colitis and two patients had indeterminate diagnoses. Only three patients had a positive family history for a first-degree relative with CRC. Nine patients had been on 5-ASA therapy for longer than three months, while only one patient was on long-term immunosuppressive therapy. Thirteen patients had a history of smoking. Three patients had endoscopically confirmed primary sclerosing cholangitis.

CRC

Thirty-one patients with UC who had been subsequently diagnosed with CRC were identified. Sixty-eight per cent of the investigative group was male, and 32% was female. In 29 of 31 patients in whom the initial date of UC diagnosis could be determined, the mean age at diagnosis of UC was 44.4 years, and for CRC, it was 60.1 years.

Figure 1 shows the Kaplan-Meier survival analysis of the 29 patients for whom the initial date of diagnosis was determined through chart analysis (two patients with indeterminate diagnoses). From the Kaplan-Meier curve, the median duration of UC at the time of CRC diagnosis was presented in Table 1. Of the 31 patients with UC who had been subsequently diagnosed with CRC, 24 patients had active colitis at the time of diagnosis with CRC. Twenty patients had pancolitis, nine had left-sided colitis and two patients had indeterminate diagnoses. Only three patients had a positive family history for a first-degree relative with CRC. Nine patients had been on 5-ASA therapy for longer than three months, while only one patient was on long-term immunosuppressive therapy. Thirteen patients had a history of smoking. Three patients had endoscopically confirmed primary sclerosing cholangitis.

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### Table 1: Patient demographics (n=31)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Results</th>
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<tbody>
<tr>
<td>Ratio of male to female, n</td>
<td>21:10</td>
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<tr>
<td>Patients with a history of smoking, n</td>
<td>13</td>
</tr>
<tr>
<td>Patients on 5-ASA therapy for longer than 3 months, n</td>
<td>9</td>
</tr>
<tr>
<td>Patients on immunomodulatory therapy for longer than 3 months, n</td>
<td>1</td>
</tr>
<tr>
<td>Patients with active UC disease at diagnosis of CRC, n</td>
<td>24</td>
</tr>
<tr>
<td>Patients with a family history of CRC, n</td>
<td>3</td>
</tr>
<tr>
<td>Mean age at diagnosis of UC (n=29), years*</td>
<td>44.4</td>
</tr>
<tr>
<td>Mean age at diagnosis of CRC (n=29), years*</td>
<td>60.1</td>
</tr>
<tr>
<td>Median duration of UC, years*</td>
<td>16</td>
</tr>
<tr>
<td>Patients with primary sclerosing cholangitis, n</td>
<td>3</td>
</tr>
<tr>
<td>Patients with pancolitis (&gt;60 cm), n</td>
<td>20</td>
</tr>
<tr>
<td>Patients with left-sided colitis, n†</td>
<td>9</td>
</tr>
</tbody>
</table>

*For two of 31 patients, the initial date of diagnosis of ulcerative colitis (UC) could not be determined. †Two of nine patients had indeterminate diagnoses. 5-ASA 5-Aminosalicylic acid; CRC Colorectal cancer
which affects the expression of oncogenes in the colonic populations. It has been shown that DNA hypermethylation, explanation involves altered immunosurveillance in older UC patients diagnosed with UC after 40 years of age. Patients diagnosed with UC before 40 years of age are likely to have had undiagnosed colitis for a longer period of time, or progress more rapidly to CRC than patients diagnosed with UC after 40 years of age. Patients diagnosed with UC before 40 years of age (n=15, mean age 64 years) progressed more rapidly to CRC than patients diagnosed with UC after 40 years of age (n=14, mean age 23 years). From the Kaplan-Meier curves, the median durations of UC before the development of CRC (50% cancer-free point) were 22 years and 10 years, respectively, for patients with a diagnosis of UC before and after 40 years of age. Using the nonparametric log rank test, the difference between the curves was statistically significant (OR 11.5, 95% CI 2.41 to 20.16; P=0.00029).

Of the 31 patients diagnosed with CRC, nine were diagnosed as stage I (29%, mean age 58 years), 10 as stage II (32%, mean age 65 years), six as stage III (19%, mean age 60 years) and six as stage IV (19%, mean age 55 years). At the time of diagnosis, 38% of patients had nodal disease. By the end of the review period, 15 patients survived, 13 had died due to complications of CRC and three had died due to nongastrointestinal-related causes.

Only four patients (13%) were enrolled in an appropriate cancer-screening program at the time of CRC diagnosis; of this small group, three patients survived. Seventeen patients had been diagnosed with dysplasia. Of these, only five (16%) were diagnosed more than three months before the diagnosis of CRC.

**DISCUSSION**

In the present study, we found that patients diagnosed with UC after 40 years of age progressed more rapidly to CRC than patients diagnosed with UC before 40 years of age. Indeed, similar findings have been previously published in the Japanese literature (6). It has not yet been determined whether this finding reflects an epidemiological lead-time bias, such that patients diagnosed with UC after 40 years of age are likely to have had undiagnosed colitis for a longer period of time, or whether this is a true pathological phenomenon. One possible explanation involves altered immunosurveillance in older UC populations. It has been shown that DNA hypermethylation, which affects the expression of oncogenes in the colonic neoplasia cascade (7), increases with cancer, UC and older age.

Researchers are currently debating on the efficacy and cost-effectiveness of surveillance programs, as well as the optimal management of dysplasia. In terms of endoscopic surveillance, Bernstein et al (2) have estimated that 64 biopsies are required to have a 95% certainty of finding the highest grade of neoplastic lesion when dysplasia is present. Newer fecal DNA assays, which can detect multiple mutations in the colon
cancer cascade, have been recently assessed (10,11), as well as a multitarget DNA assay panel for specific mutations of \( \text{p53}, \text{K-ras} \) and adenomatous polyposis coli, and microsatellite instability (12,13). Modern advances in genetic fingerprinting of colonic epithelia may improve risk prediction of colitis-associated cancer at an early stage (14-16). Other endoscopic technologies, such as chromoendoscopy, have been shown to more accurately diagnose the extent and severity of inflammatory activity in UC, as well as detect dysplasia or neoplasia in patients with active UC (17,18). Currently, it is also recommended that patients with long-standing UC who show periodic high-grade dysplasia should undergo prophylactic colectomy. More study is necessary to determine what the ideal surveillance technique is and what the appropriate treatment strategy should be. Nonetheless, the earlier the detection, the more treatment possibilities there are and likely the outcomes are better.

Currently, there is also a great deal of interest in chemoprotective agents, such as folic acid (19,20) and, in particular, 5-ASA for patients with increased risk of colonic malignancy, although the results of several studies have been contradictory (21-23). In our cohort, only nine of 31 patients were on 5-ASA-based medications for more than three months. Clearly more robust, prospective, randomized studies are required to provide answers about treatment with these agents.

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