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

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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*

L'accroissement du risque de cancer colorectal chez les personnes atteintes de colite ulcéreuse diagnostiquées après 40 ans

HISTORIQUE : L'association entre la colite ulcéreuse (CU) et le cancer colorectal (CCR) est bien établie. Des données rétrospectives indiquent un taux d'incidence de 5,4 % de cas de CCR chez les personnes atteintes d'une pancolite et laissent supposer qu'il faudrait leur fournir la surveillance du cancer lorsqu'elles sont atteintes d'une CU importante depuis huit à dix ans.
OBJECTIF : Dépister les facteurs de risque prémalins chez les personnes atteintes de CU et déterminer si les recommandations courantes à l'égard de la surveillance du cancer méritent d'être analysées.
PATIENTS ET MÉTHODOLOGIE : On a mené une vérification rétrospective de patients adultes atteints de CU chez qui un CCR avait été diagnostiqué entre 1991 et 2002 dans cinq hôpitaux d'Edmonton, en Alberta.
RÉSULTATS : On a repéré 31 cas de CCR (68 % d'hommes). L'âge moyen des personnes de ce groupe au diagnostic était de 44,4 ans pour les patients atteints de CU, et de 60,1 ans pour ceux atteints de CCR. Chez les patients pour qui on pouvait déterminer les données diagnostiques initiales de CU (n=29), la durée médiane de la CU au moment du diagnostic de CCR était de 16 ans. L'état des personnes atteintes d'une CU diagnostiquée après l'âge de 40 ans (n=15 ans, âge moyen de 64 ans) s'est détérioré plus rapidement en CCR que celui des personnes diagnostiquées avant l'âge de 40 ans (n=14, âge moyen de 23 ans). Les durées médianes de CU avant l'apparition du CCR étaient de 22 ans et de dix ans, respectivement, pour les personnes ayant reçu un diagnostic avant et après l'âge de 40 ans (RC 11,5, 95 % IC 2,41 à 20,16; P=0,00029). Seulement quatre personnes (13 %) ont été inscrites à un programme pertinent de dépistage du cancer. Neuf de ces personnes atteintes de CU (29 %) qui avaient plus de 40 ans ont développé un CCR avant le délai de dix ans.
CONCLUSIONS : Dans la présente étude, les personnes ayant reçu un diagnostic de CU après l'âge de 40 ans ont développé un CCR plus rapidement que celles qui avaient été diagnostiquées avant l'âge de 40 ans. D'après ces observations, les personnes chez qui on diagnostique un CU après l'âge de 40 ans devraient se soumettre à une surveillance du CCR plus rapidement que ce que les recommandations actuelles préconisent.

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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TABLE 1
Patient demographics (n=31)*

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

**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*

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 or 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 Alexandra 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. Data 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. Median 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

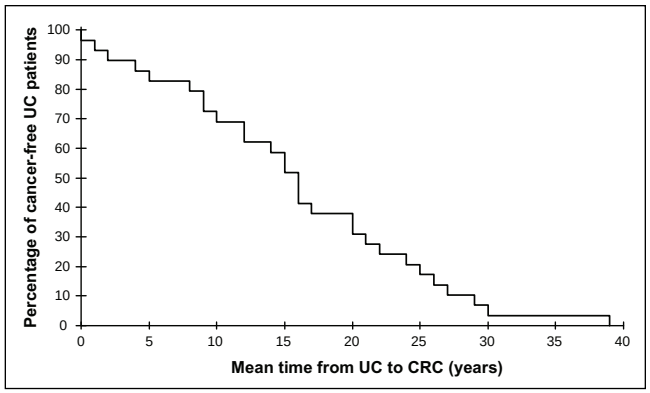

Figure 1) *Kaplan-Meier analysis showing the mean time from diagnosis of ulcerative colitis (UC) to colorectal cancer (CRC), using CRC as the end point. Diagnoses of UC and CRC were confirmed both histologically and endoscopically (a total of 29 patients for whom initial date of diagnosis of UC was determined)*

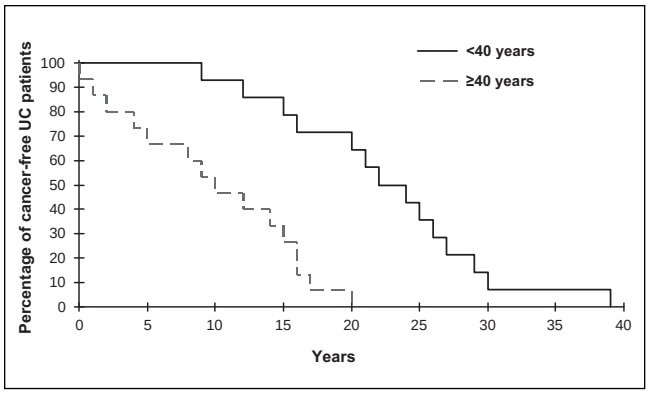

Figure 2) *Age-stratified times from diagnosis of ulcerative colitis (UC) to diagnosis of colorectal cancer (CRC). Twenty-nine patients were stratified based on whether the diagnosis of UC was made before 40 years of age (solid line, n=14) or after 40 years of age (dashed line, n=15). Kaplan-Meier analysis was performed using diagnosis of CRC as the end point. Both diagnosis of UC and CRC were confirmed histologically and endoscopically. The median duration of UC before the development of CRC (50% cancer-free points on the graph), were 22 years and 10 years, respectively, for patients with diagnoses of UC before and after 40 years of age. Using the log rank test, the difference between the curves was found to be statistically significant (OR 11.5, 95% CI 2.41 to 20.16; P=0.00029)*

(50% cancer-free point) was 16 years. However, nine patients (29%) developed CRC before the 10-year point.

Figure 2 demonstrates the Kaplan-Meier analysis of two sets of patients: those diagnosed with UC before 40 years of age, and those diagnosed after 40 years of age. Patients diagnosed with UC after 40 years of age (n=15, mean age 64 years) progressed more rapidly to CRC than patients diagnosed with UC before 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. Our study was not designed to address this question. Rather, our initial findings suggest that, regardless of the mechanism responsible for the increased rapidity, the standard practice of commencing cancer surveillance 10 years after UC diagnosis may lead practitioners to miss the development of a significant number of cancers among those patients diagnosed with UC after 40 years of age.

Another goal of the present audit was to identify premalignant risk factors for UC patients. We found that pancolitis and active inflammation were prevalent at the time of diagnosis of CRC, likely reflecting a larger burden of uncontrolled disease. This finding is in keeping with those of previous studies that have suggested that cancer risk is proportional to the burden and extent of inflammation (8). Indeed, compared with age-matched members of the general population, the RR of cancer is 20-fold for those with extensive colitis and fourfold for those with left-sided colitis (9). However, a family history of CRC, smoking, the use of immunomodulatory therapy and primary sclerosing cholangitis did not appear to be as prevalent among our patients.

Overall, we found that 29% of UC patients developed CRC before the 10-year mark, the point when current guidelines generally recommend commencing surveillance. Only four of 31 patients were in an adequate cancer surveillance program; of these four patients, three patients survived. We suspect that the inadequate screening practices found in the present study likely reflect standards of care from 10 to 20 years ago, when these patients were initially identified with UC.

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 *p53*, *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.

The main limitation of the present study was accounting for patients who had diagnoses in different provinces. For this reason, we cannot claim that this is an all-inclusive population study; it only represents the catchment of our audit. Because all cases of CRC in northern Alberta are reported to the WW Cross Cancer Institute (Alberta Cancer Board), we were able to account for patients who were diagnosed with CRC in Alberta, and we attempted to get out-of-province data to confirm the initial diagnosis of UC. However, we could not account for UC patients who were diagnosed with CRC in a different province. Furthermore, the rates of cancer observed likely reflected practice and treatment patterns of 20 years ago, when most of these patients were originally diagnosed with UC. While our sample size was small (31 patients), it was similar to a study performed in Stockholm, Sweden, where 31 cases were retrieved between 1951 and 1998 (24).

CONCLUSIONS

In the present retrospective study, patients diagnosed with UC after 40 years of age developed CRC more rapidly, a median of 10 years after diagnosis, than those patients diagnosed with UC before 40 years of age, in whom CRC was not observed until a median of 22 years afterwards. The present findings suggest that patients who are diagnosed with UC after 40 years of age should be enrolled in a CRC surveillance program before the currently recommended 10-year point.

REFERENCES

1. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: A meta-analysis. Gut 2001;48:526-35.
2. Bernstein CN. Cancer surveillance in inflammatory bowel disease. Curr Gastroenterol Rep 1999;1:496-504.
3. Bus PJ, Nagtegaal ID, Verspaget HW, et al. Mesalazine-induced apoptosis of colorectal cancer: On the verge of a new chemopreventive era? Aliment Pharmacol Ther 1999;13:1397-402.
4. Delco F, Sonnenberg A. The unsolved problem of surveillance for colorectal cancer in ulcerative colitis. Can J Gastroenterol 1999;13:655-60.
5. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: A population-based study. Am J Epidemiol 1999;149:916-24.
6. Bamba T, Nishiyama Y. [Clinical features and management of the elderly patients with ulcerative colitis.] Nippon Rinsho 1999;57:2598-602.
7. Issa JP, Ahuja N, Toyota M, Bronner MP, Brentnall TA. Accelerated age-related CpG island methylation in ulcerative colitis. Cancer Res 2001;61:3573-7.
8. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004;126:451-9.
9. Connell W. PRO: Endoscopic surveillance minimizes the risk of cancer. Am J Gastroenterol 2004;99:1631-3.
10. Ahlquist DA, Shuber AP. Stool screening for colorectal cancer: Evolution from occult blood to molecular markers. Clin Chim Acta 2002;315:157-68.
11. Ahlquist DA. Stool-based DNA tests for colorectal cancer: Clinical potential and early results. Rev Gastroenterol Disord 2002;2:S20-6.
12. Brand RE, Ross ME, Shuber AP. Reproducibility of a multitarget stool-based DNA assay for colorectal cancer detection. Am J Gastroenterol 2004;99:1338-41.
13. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME; Colorectal Cancer Study Group. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004;351:2704-14.
14. Fujii S, Fujimori T, Chiba T. Usefulness of analysis of *p53* alteration and observation of surface microstructure for diagnosis of ulcerative colitis-associated colorectal neoplasia. J Exp Clin Cancer Res 2003;22:107-15.
15. Fujii S, Fujimori T, Kashida H. Ulcerative colitis-associated neoplasia. Pathol Int 2002;52:195-203.
16. Fujii S, Fujimori T, Kawamata H, et al. Development of colonic neoplasia in *p53* deficient mice with experimental colitis induced by dextran sulphate sodium. Gut 2004;53:710-6.
17. Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124:880-8.
18. Dekker E, Fockens P. New endoscopic tools for the IBD physician. Inflamm Bowel Dis 2004;10:S7-10.
19. Lashner BA. Red blood cell folate is associated with the development of dysplasia and cancer in ulcerative colitis. J Cancer Res Clin Oncol 1993;119:549-54.
20. Lashner BA, Provencher KS, Seidner DL, Knesebeck A, Brzezinski A. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. Gastroenterology 1997;112:29-32.
21. Eaden J, Abrams K, Ekbom A, Jackson E, Mayberry J. Colorectal cancer prevention in ulcerative colitis: A case-control study. Aliment Pharmacol Ther 2000;14:145-53.
22. Croog VJ, Ullman TA, Itzkowitz SH. Chemoprevention of colorectal cancer in ulcerative colitis. Int J Colorectal Dis 2003;18:392-400.
23. Bernstein CN, Blanchard JF, Metge C, Yogendran M. Does the use of 5-aminosalicylates in inflammatory bowel disease prevent the development of colorectal cancer? Am J Gastroenterol 2003;98:2784-8.
24. Rubio CA, Befrits R, Ljung T, Jaramillo E, Slezak P. Colorectal carcinoma in ulcerative colitis is decreasing in Scandinavian countries. Anticancer Res 2001;21:2921-4.