Cancer Risk in Patients with Inflammatory Bowel Disease

A Population-Based Study

Charles N. Bernstein, M.D.[1,2]
James F. Blanchard, M.D., Ph.D.[2,3,4]
Erich Kliewer, Ph.D.[4,5]
Andre Wajda, M.S.[4]

[1] Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

[2] University of Manitoba Inflammatory Bowel Disease Clinical and Research Centre, Winnipeg, Manitoba, Canada.

[3] Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada.

[4] Manitoba Epidemiology Unit, Winnipeg, Manitoba, Canada.

[5] Cancer Care Manitoba, Winnipeg, Manitoba, Canada.

Reported in part at the meeting of the American Gastroenterological Association, New Orleans, Louisiana, 1998.

Charles N. Bernstein is supported by a Manitoba Medical Services Foundation Clinical Research Professorship.

Address for reprints: Charles N. Bernstein, M.D., Section of Gastroenterology, University of Manitoba, John Buhler Research Centre, 804F-715 McDermot Avenue, Winnipeg, Manitoba, Canada R3E-3P4; Fax: (204) 789-3369; E-mail: cbernst@cc.umanitoba.ca

Received May 12, 2000; revision received October 2, 2000; accepted October 13, 2000.

BACKGROUND. The objective of the current study was to determine the incidence of cancer among persons with inflammatory bowel disease (IBD) and to compare these incidence rates with those of the non-IBD population using population-based data from the administrative claims data of Manitoba's universal provincial insurance plan (Manitoba Health).

METHODS. IBD patients were matched 1:10 to randomly selected members of the population without IBD based on year, age, gender, and postal area of residence. The incidence of cancer was determined by linking records from the IBD and non-IBD cohorts with the comprehensive Cancer Care Manitoba registry. Incidence rates and rate ratios (IRR) were calculated based on person-years of follow-up (Crohn's disease = 21,340 person-years and ulcerative colitis [UC] = 19,665 person-years) for 1984–1997.

RESULTS. There was an increased IRR of colon carcinoma for both Crohn disease patients (2.64; 95% confidence interval [95% CI], 1.69–4.12) and UC patients (2.75; 95% CI, 1.91–3.97). There was an increased IRR of rectal carcinoma only among patients with UC (1.90; 95% CI, 1.05–3.43) and an increased IRR of carcinoma of the small intestine only in Crohn disease patients (17.4; 95% CI, 4.16–72.9). An increased IRR of extraintestinal tumors was observed only for the liver and biliary tract in both Crohn disease patients (5.22; 95% CI, 0.96–28.5) and UC patients (3.96; 95% CI, 1.05–14.9). There was an increased IRR of lymphoma for males with Crohn disease only (3.63; 95% CI, 1.53–8.62), and this finding did not appear to be related to use of immunomodulatory therapy. Compared with controls, Crohn's disease was associated with an increased risk of cancer overall, but UC was not.

CONCLUSIONS. There appear to be similar increased risks for developing colon carcinoma and hepatobiliary carcinoma among patients with Crohn disease and UC. There is an increased risk of developing rectal carcinoma in UC patients, an increased risk of developing carcinoma of the small bowel in Crohn disease patients, and an increased risk of developing lymphoma among males with Crohn disease. ***Cancer* 2001;91:854–62.** © *2001 American Cancer Society.*

KEYWORDS: administrative databases, cancer, inflammatory bowel disease, population-based.

Ulcerative colitis (UC) is associated with an increased risk of colorectal carcinoma. This has been identified in both referral center studies[1–6] and population-based studies.[7–9] This risk is associated with an increased duration of disease and an increased extent of disease, and more recently has been associated with a concurrent diagnosis of primary sclerosing cholangitis.[10] A number of studies have reported increased rates of colon carcinoma in individuals with Crohn disease (CD),[11–13] but to our knowledge few have been popu-

lation-based.[14] There have been varied reports of extracolonic malignancies in both UC and CD patients, but again to our knowledge only a few reports have been population-based.[8,9,15,16] The risk of lymphatic malignancies in patients with inflammatory bowel disease (IBD) has become an increasingly important issue in view of the recent use of new biologic immunomodulatory therapies, such as antibody to tumor necrosis factor-α (TNF-α).[17]

We linked a population-based IBD database[18] to a comprehensive cancer registry to determine the incidence rates of various types of cancer among persons with IBD in a North American population for the years 1984–1997. We also compared these rates with those of a non-IBD population that was matched based on age, gender, and geographic location of residence.

MATERIALS AND METHODS

Overview

A matched cohort design was used. The site specific cancer incidence rates in a cohort of persons with IBD were compared with those of a non-IBD cohort that was matched (1:10) to the IBD cohort based on age, gender, and geographic location of residence.

Data Sources

The IBD cohort was created based on members of the population-based University of Manitoba IBD Database. The creation and characteristics of this database have been described previously.[18] Briefly, this database was developed using the Manitoba Health (Government of Manitoba) administrative databases. Manitoba Health provides comprehensive health care coverage for residents of the province of Manitoba, Canada (population of 1.14 million). Because Manitoba residents are not obliged to pay premiums for health care coverage, nonparticipation in the plan is rare. Manitoba Health maintains computerized databases of physician services (from medical billings to Manitoba Health) and hospitalizations for all persons registered with the Manitoba Health system. Each physician service record includes information regarding the identity of the patient, the date of service, services provided, and the diagnosis, which subsequently is coded to a three-digit International Classification of Diseases-9-Clinical Modification (ICD-9-CM) code. After each hospitalization, a detailed abstract is created that includes the identity of the patient, dates of hospitalization, procedures performed, and up to 16 diagnoses, which are coded according to 5-digit ICD-9-CM codes. In addition, Manitoba Health maintains a population registry that contains demographic information and coverage data, including dates of registration, emigration, and death.

By extracting physician service records and hospitalizations for all Manitoba residents between 1984–1997, we created a population-based database of all persons who had received a diagnosis of either CD (ICD-9-CM code 555) or UC (ICD-9-CM code 556). Based on a questionnaire survey and structured chart reviews, we refined our case definitions such that only persons with at least 5 separate physician contacts and/or hospitalizations for an IBD diagnosis ($\geq$ 3 contacts for those residing in Manitoba for $\leq$ 2 years) were designated as having IBD. The sensitivity and specificity of this IBD case definition were approximately 90% when compared with self-report or chart review.[18] By the end of 1997 (the final year of data collection for the current study) there were 6027 subjects with IBD in the database. This database includes both incident and prevalent cases because it is assumed that many of the cases who first appeared in the Manitoba Health administrative database prior to 1987 possibly may have been prevalent cases, and those that appeared for the first time after 1987 (with 3 prior years of no claims for IBD) more likely were incident cases.

The non-IBD cohort was created by randomly selecting 10 persons without IBD for each IBD subject from the Manitoba Health population registry. Non-IBD controls were matched with those with IBD based on age, gender, and postal area of residence (at the date of diagnosis of the index IBD case).

Cancer Care Manitoba (CCMB) maintains a registry for all individuals diagnosed with cancer in Manitoba. Ascertainment of cancer cases is high because not only is reporting of cancer mandated by law, but multiple sources of ascertainment are used. These include physician notifications, pathology and hematology reports, hospitalization, mortality, and autopsy records. We linked the IBD database and the non-IBD cohort database with the CCMB cancer registry to extract cancer diagnoses in each group.

We previously created longitudinal files for all our subjects within the IBD database and identified those who had concurrent diagnoses of primary sclerosing cholangitis.[19] Because primary sclerosing cholangitis has been identified as a risk factor for colorectal carcinoma[10] we determined how many of our cancer patients had this concurrent diagnosis.

Incidence Rates and Rate Ratios

We used ICD-9-CM codes to identify specific cancers. Only cancer diagnoses that occurred after the diagnosis of IBD or the diagnosis date of the IBD index case (for the matched non-IBD cohort members) were included in incidence rate calculations. Incidence rates were calculated based on person-years of follow-up

for 1984–1997 and standardized to the age and gender distribution of the combined IBD and non-IBD population using the direct method. Standardization was performed to account for differences in the age and gender distribution between CD and UC cohorts and for some residual confounding due to differential person-years of follow-up in the IBD and non-IBD cohorts. Incidence rate ratios (IRR) and 95% confidence intervals (95% CI) were calculated by comparing the standardized incidence rates in the IBD population with those of the matched population cohorts (version 6.0, STATA Corporation, TX).

The construction of the University of Manitoba IBD database and its use in clinical studies were approved by the University of Manitoba Research Ethics Board and by the Access and Confidentiality Committee of Manitoba Health.

Chart Review of Hematopoietic Cancer Cases

Once it was identified that there was an increased risk of lymphoma among patients with IBD and CD in particular, all CCMB charts were reviewed to determine whether subjects with lymphoma and IBD had been receiving any form of immunomodulatory therapy prior to the diagnosis of lymphoma.

RESULTS

Of the 6027 persons with IBD in the database, a full set of matched controls was available for 5529 (92%). There were 2857 CD cases with 21,340 person-years of observation. For UC, there were 2672 cases with a total of 19,665 person-years of observation. The mean age at the beginning of follow-up was 36.3 years for CD patients and 41.7 years for UC patients. The percentage of male cases was 41% for CD compared with 50% for UC.

The overall cancer incidence rate among IBD patients was 690.2 per 100,000. Compared with the non-IBD population, those with CD had a significantly increased incidence of cancer (all sites) (IRR = 1.29; 95% CI, 1.07–1.54). There was no significant difference between the UC cases and the non-IBD population (IRR = 1.10; 95% CI, 0.93–1.30). The site specific incidence rates are listed in Table 1.

Compared with the non-IBD population, there was an increased incidence rate of colon carcinoma for both CD patients (IRR = 2.64; 95% CI, 1.69–4.12) and UC patients (IRR = 2.75; 95% CI, 1.91–3.97) (Table 2). The IRR for colon carcinoma was greatest among IBD subjects age < 40 years and declined with advancing age (Table 3). The increased risk of colon carcinoma among those with IBD was more prominent among males (IRR = 3.17; 95% CI, 2.18–4.62) compared with females (IRR = 2.16; 95% CI, 1.39–3.36). Of 60 patients with colon carcinoma, only 3 had a concurrent diagnosis of primary sclerosing cholangitis.

An increased risk of rectal carcinoma was evident only among patients with UC (IRR = 1.90; 95% CI, 1.05–3.43) and there was an increased risk of carcinoma of the small intestine only in CD patients (IRR = 17.4; 95% CI, 4.16–72.9). There were no diagnoses of carcinoma of the small intestine identified in patients with UC and no diagnoses of anal carcinoma were identified in any IBD patient. Of 18 patients with rectal carcinoma, only 2 had a concurrent diagnosis of primary sclerosing cholangitis.

With regard to extraintestinal tumors an increased rate was observed only for liver and biliary tract malignancies in both CD patients (IRR = 5.22; 95% CI, 0.96–28.5, $P = 0.06$) and UC patients (IRR = 3.96; 95% CI, 1.05–14.9), and for lymphoma among patients with CD only (IRR = 2.40; 95% CI, 1.17–4.97). Of the five patients with carcinoma of the liver or biliary tract, two had concurrent diagnoses of primary sclerosing cholangitis. In fact a significant increase in the rate of lymphoma in CD patients was observed only among males (IRR = 3.63; 95% CI, 1.53–8.62) and not among females (IRR = 1.09; 95% CI, 0.25–4.67). Chart review of all hematologic malignancies in IBD patients revealed that no patient had received any immunomodulatory therapy other than corticosteroids (i.e., purine analogs or methotrexate) prior to the development of their cancer.

The incidence rates of breast, prostate, and respiratory carcinomas were not significantly different compared with the general population. There were no significant gender differences for any tumors other than those of the colon and lymphoma.

DISCUSSION

The results of the current study have corroborated previous findings regarding the increased risk of colon carcinoma in both UC and CD patients in a North American population. Strengths of these findings include the use of a population-based study and the use of a matched non-IBD cohort. By matching based on geographic location of residence, our methodology likely reduced confounding that may be present due to differences in socioeconomic status between those with IBD and the general population.

The risk of colorectal carcinoma in UC patients is estimated to be approximately 7–14% after 25 years of disease.[1–3] Actuarial data suggest that rates may be as high as 30% when disease duration is > 35 years.[4,7] The relative risk of colon carcinoma in UC patients from Swedish population-based data was higher (5.7; 95% CI, 4.6–7.0)[7] than found in the current study. The higher IRR noted in that study might reflect their

TABLE 1
Site Specific Incidence (Per 100,000 Person-Years) of Cancer Among Persons with Inflammatory Bowel Disease in Manitoba, Canada, 1984–1997

	Crohn disease		Ulcerative colitis		Total IBD	
Cancer site	Cases	Crude (adjusted)[a] incidence per 100,000 pyrs	Cases	Crude (adjusted)[a] incidence per 100,000 pyrs	Cases	Crude incidence per 100,000 pyrs
Lip, tongue, other oral	1	4.7 (5.4)	4	20.3 (17.0)	5	12.2
Esophagus	1	4.7 (5.1)	2	10.2 (8.6)	3	7.3
Stomach	3	14.1 (14.3)	4	20.3 (17.8)	7	17.1
Small intestine	5	24.2 (24.9)	0	0.0 (0.0)	5	12.2
Colon	24	112.5 (134.4)	36	183.1 (161.1)	60	146.3
Rectum	5	23.4 (31.2)	13	66.1 (56.7)	18	43.9
Liver and biliary tract	2	9.4 (10.1)	3	15.3 (13.9)	5	12.2
Pancreas	0	0.0 (0.0)	3	13.0 (12.3)	3	7.3
Trachea, bronchus, lung	21	98.4 (124.9)	17	86.4 (73.9)	38	92.7
Bone	1	8.0 (7.2)	0	0.0 (0.0)	1	2.4
Melanoma	3	14.1 (16.4)	4	20.3 (16.7)	7	17.1
Breast (female)	18	142.2 (156.4)	16	166.9 (147.0)	34	152.8
Cervix	1	7.9 (9.4)	2	20.9 (17.7)	3	13.5
Uterus	2	15.8 (17.3)	1	10.4 (7.4)	3	13.5
Ovary	2	15.8 (17.7)	3	31.3 (29.4)	5	22.5
Prostate	7	80.6 (108.7)	19	188.5 (154.6)	26	138.6
Bladder	5	23.4 (27.2)	4	20.3 (16.5)	9	21.9
Kidney	3	14.1 (16.4)	3	15.3 (13.3)	6	14.6
Brain	1	4.7 (5.4)	0	0.0 (0.0)	1	2.4
Thyroid	2	9.4 (9.7)	0	0.0 (0.0)	2	4.9
Lymphoma	9	42.2 (47.2)	7	35.6 (29.8)	16	39.0
Hodgkin disease	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0
Leukemia/multiple myeloma	3	14.1 (18.0)	4	20.3 (19.6)	7	17.1
Other and ill-defined	12	56.2 (61.3)	7	35.6 (30.1)	19	46.3
Total	131	613.9 (730.6)	152	772.9 (653.7)	283	690.2

IBD: inflammatory bowel disease; pyrs: person-years.
[a] Adjusted to the age distribution of the total inflammatory bowel disease population using the direct method.

longer follow-up period of approximately 50 years. It also may be due to the lack of control for socioeconomic status because both IBD and colorectal carcinoma reportedly are more common in those with higher socioeconomic status. Another population-based Swedish study encompassing the years 1955–1989 revealed a relative risk of 4.1 (95% CI, 2.7–5.8).[9] The current study database covers 14 years and we suspect that with more extended follow-up we will find an increase in the number of cases of colon carcinoma in UC as patients have increased durations of disease. Unfortunately, because we have at a maximum only 14 years of potential patient follow-up, we cannot accurately comment on the impact of disease duration on colorectal carcinoma risk. Because we are relying on administrative data and not chart review we also cannot analyze the data accurately by extent of disease. However, the greatest IRR was evident for patients with IBD who were age $<$ 40 years. Thus, those remaining in the cohort are "survivors," which may diminish somewhat a small source of bias regarding the statistically significantly increased IRRs for those patients age $>$ 40 years. A population-based study from Denmark encompassing 13 years (1977–1989) found a risk ratio of 1.8 for colorectal carcinoma in UC patients (95% CI, 1.3–2.4). In the current study there was a similarly increased relative risk of colon carcinoma (1.7) and rectal carcinoma (1.9).[8]

It recently has been suggested that patients with primary sclerosing cholangitis have an increased risk of developing colorectal carcinoma.[10] Overall, only 5 of 78 IBD patients (6.4%) who subsequently developed colorectal carcinoma also received a diagnosis of primary sclerosing cholangitis. With such small numbers, it is difficult for us to assess whether the presence of primary sclerosing cholangitis was associated with an increased risk of colorectal carcinoma. However, even if it was, it would not contribute much to the excess risk among persons with IBD.

The Swedish group's data regarding colon carcinoma risk in CD patients for the years 1965–1983 revealed a standardized incidence ratio (SIR) of 2.5

TABLE 2
Site Specific Cancer Incidence Rate Ratios Comparing Cohorts with IBD with Non-IBD Cohorts Matched by Age, Gender, and Postal Area of Residence, Manitoba, Canada, 1984–1997

Cancer site	Crohn disease IRR (95% CI)	Ulcerative colitis IRR (95% CI)	Total IBD IRR (95% CI)
Lip, tongue, other oral	0.34 (0.05–2.49)	1.06 (0.38–2.96)	0.74 (0.30–1.84)
Esophagus	1.53 (0.19–12.5)	1.40 (0.32–6.11)	1.44 (0.43–4.82)
Stomach	1.44 (0.43–4.80)	1.02 (0.36–2.84)	1.16 (0.53–2.54)
Small intestine	17.4 (4.16–72.9)	Undefined	10.4 (3.02–36.1)
Colon	2.64 (1.69–4.12)	2.75 (1.91–3.97)	2.71 (2.04–3.59)
Rectum	1.08 (0.43–2.70)	1.90 (1.05–3.43)	1.56 (0.95–2.57)
Liver and biliary tract	5.22 (0.96–28.5)	3.96 (1.05–14.9)	4.38 (1.54–12.4)
Pancreas	Undefined	0.87 (0.27–2.83)	0.51 (0.16–1.63)
Trachea, bronchus, lung	1.40 (0.89–2.21)	0.82 (0.50–1.34)	1.06 (0.76–1.48)
Bone	11.0 (0.69–177)	Undefined	3.48 (0.36–33.5)
Melanoma	1.06 (0.32–3.50)	1.11 (0.40–3.13)	1.09 (0.50–2.38)
Breast (female)	0.97 (0.60–1.56)	0.91 (0.54–1.51)	0.94 (0.66–1.33)
Cervix	0.69 (0.09–5.26)	1.08 (0.25–4.62)	0.91 (0.28–2.97)
Uterus	0.50 (0.12–2.09)	0.24 (0.03–1.77)	0.37 (0.12–1.18)
Ovary	0.63 (0.15–2.64)	1.03 (0.31–3.38)	0.82 (0.33–2.05)
Prostate	0.65 (0.30–1.40)	0.97 (0.61–1.55)	0.86 (0.57–1.28)
Bladder	1.30 (0.51–3.30)	0.67 (0.24–1.85)	0.92 (0.47–1.82)
Kidney	1.02 (0.31–3.34)	0.80 (0.25–2.58)	0.89 (0.39–2.06)
Brain	0.78 (0.10–5.99)	Undefined	0.43 (0.06–3.15)
Thyroid	2.85 (0.59–13.7)	Undefined	1.34 (0.31–5.87)
Lymphoma	2.40 (1.17–4.97)	1.03 (0.47–2.24)	1.52 (0.90–2.57)
Hodgkin disease	Undefined	Undefined	Undefined
Leukemia/multiple myeloma	0.79 (0.24–2.54)	1.02 (0.37–2.86)	0.91 (0.42–1.96)
Other and ill-defined	1.94 (1.05–3.58)	0.69 (0.32–1.49)	1.17 (0.73–1.88)
Total	1.29 (1.07–1.54)	1.10 (0.93–1.30)	1.18 (1.05–1.34)

IBD: inflammatory bowels; IRR: incidence rate ratios; 95% CI: 95% confidence interval.

TABLE 3
Incidence Rate Ratios by Age and Gender for Colon Carcinoma Comparing a Cohort with IBD with a Non-IBD Cohort, Manitoba, Canada, 1984–1997

Age group (yrs)	Male IRR (95% CI)	Female IRR (95% CI)	All IRR (95% CI)
Birth–39	17.3 (5.20–65.6)	7.64 (1.52–35.5)	12.4 (5.04–31.7)
40–59	3.37 (1.54–6.80)	1.62 (0.56–3.85)	2.44 (1.35–4.17)
60+	2.12 (1.16–3.67)	2.05 (1.07–3.66)	2.09 (1.36–3.11)
Total	3.17 (2.18–4.62)	2.16 (1.39–3.36)	2.71 (2.04–3.59)

IBD: inflammatory bowel disease; 95% CI: 95% confidence interval.

(95% CI, 1.3–4.3), which is comparable to our result.[14] The risk in their study was similar among males and females. Patients with ileal disease alone did not have an increased risk, such that assessing only patients who had colonic disease yielded an SIR of 5.6 (95% CI, 2.1–12.2).[14] There was increased risk for those diagnosed prior to age 30 years but no affect on risk based on disease duration was noted. We were not able to define disease site in our database. Curiously, data from Sweden encompassing the years of diagnosis from 1955–1984 did not reveal an increased risk of colon carcinoma in CD patients.[16]

Others also have found an increased risk of colon carcinoma for patients with CD.[6,11,12] In 1 study the risk was 4.3 (95% CI, 2.0–8.2), with a relative risk as high as 23.8 among those patients with CD only.[12] An update of these data in the 1990s revealed a relative risk of colon carcinoma in CD patients of 3.4, with a prevailing increased risk in those who were diagnosed prior to age 30 years.[13] The highest reported risk for developing colon carcinoma in CD appears to be in patients whose disease is diagnosed prior to age 25 years and who have extensive CD (relative risk = 57.2; 95% CI, 15.4–146.3).[13] This study also showed an increased risk with increased years of disease duration. Thus, patients with CD with increased years of at-risk mucosa and increased extent of at-risk mucosa are at increased risk for colon carcinoma. Having only ileal disease, a previous substantial colonic resection, or a relatively new diagnosis is likely to reduce the risk in patients with CD.

Some studies refute the possibility that CD is associated with an increased risk of colon carci-

noma.[16,20–22] One study from Denmark included a small number of patients with colonic CD and a mean follow-up period of 5.5 years.[20] This group revisited this issue and still found a low risk of colon carcinoma among CD patients, although their series had a high number of patients who underwent surgical resections, which might have biased their result.[21] When patients with CD of > 10 years' duration were analyzed, the relative risk for colon carcinoma was 4.8 (95% CI, 1.7–10.9) and was 8.3 for those patients with CD for at least 10 years and no surgery within the first 10 years (95% CI, 3.2–17.3). Thus, even among this reportedly negative study, when variables such as disease duration and possibly disease extent (based on no surgery) are analyzed, the relative risk is elevated. Two other negative studies either had a small number of patients with a lengthy follow-up period[22] or had a large number of patients who previously underwent large bowel resection.[23]

The similar rates of colon carcinoma in our database among UC and CD patients might suggest a similar tumor biology in both diseases. One study has shown that colon carcinoma complicating UC is quite similar clinicopathologically to that complicating CD. Colon carcinoma complicating both diseases was associated with long disease duration (median of at least 15 years), multiple carcinomas were apparent in 11–12% of cases, and there was associated dysplasia in 73–79% of cases that occurred in macroscopic areas of inflammation in 85–100% of cases. Finally, colon carcinoma associated with CD shared a 5-year survival rate similar to colon carcinoma occurring in UC (46% vs. 50%).[24] Others also have shown similarities clinically and with regard to incidence for colon carcinoma occurring in CD compared with that occurring in UC.[25]

It has been shown elsewhere that the risk of rectal carcinoma in CD patients is not significantly different from control populations.[13,14] Although based on a small number of cases, the increased relative risk of adenocarcinoma of the small intestine in patients with ileal CD typically has been reported to be very large (range, 15.6–114.5), mostly due to the rarity of these lesions in the general population.[6,13,16,22] Because we are relying on administrative data and not chart review we cannot analyze the data accurately by disease location to determine whether all our cases of adenocarcinoma of the small intestine occurred in the setting of ileal CD, as expected.

Hepatobiliary carcinoma previously has been reported to be increased in UC.[5,8] One Swedish population-based study did not find an increased risk in either UC or CD patients,[15] whereas a later study found an increased risk of 6.0 (95% CI, 2.8–11.1) in UC patients.[9] Only two of five liver and/or biliary tumor cases had a concurrent diagnosis of primary sclerosing cholangitis. It might be assumed that all cholangiocarcinomas in IBD patients would arise in the setting of primary sclerosing cholangitis, but this may not invariably be the case and some of these cases actually may have been primary hepatocellular carcinoma. Because of our concern for any administrative data confusion regarding distinct coding of liver and biliary malignancies (or even a definite clinical distinction between these entities) we grouped these entities together.

There have been several case studies linking IBD with hematologic malignancies. Case series from referral centers have suggested an association between CD and lymphoma and between UC and leukemia and lymphoma.[5,26–30] One case series from Cleveland reported an increase in leukemia among patients with UC (SMR = 5.3; 95% CI, 1.7–12.3), but no significant increase in lymphoma.[5] A case series from New York reported an increase of leukemia in UC patients (relative risk = 8.7; 95% CI, not stated) and an increased risk of lymphoma in UC patients (relative risk = 8.82) and in CD patients (relative risk = 4.69).[28] This series reported no patients with hematologic malignancies who were receiving purine analog therapy. An updated study by this group found nine cases of lymphoma in IBD patients followed until 1983.[29] Of the four cases that occurred in CD patients, all occurred in males. Four of nine lymphoma cases had associated colon carcinoma, a finding not evident in our population. None of these patients received purine analog therapy. A recent review of studies examining leukemias and IBD suggested a significantly positive association.[30] However, all 30 reviewed studies were reported anecdotally and to our knowledge none of the conclusions of this article were drawn from population-based studies. None of the studies involved cases in which purine analog therapy was used.

A population-based Danish study found no increased risk of either leukemia or lymphoma in UC patients.[8] In one population-based study from Sweden, patients with CD or UC were found to have no increased risk of leukemia or lymphoma.[15] This later was corroborated in a report on CD alone.[16] Another population-based Swedish study found no increased risk of developing leukemia or lymphoma in patients with UC.[9] The current study was performed in a North American population, among patients of a more recent era. The era of the cases may be significant because there has been a trend toward increasing rates of lymphoma overall in the North American population.[31] To our knowledge, our data represent the first population-based data to substantiate an increased

risk of developing hematologic malignancies among patients with IBD. However, we have found this to be the case only for lymphoma among males with CD. It is possible that this may be a finding specific to patients in our geographic area.

To our knowledge, the reason why individuals with CD are at increased risk for lymphoma is unknown. It is unlikely to occur secondary to chronic inflammation as might be postulated for colon carcinoma in the setting of IBD because to our knowledge intestinal lymphomas arising in CD are rare.[32] Non-Hodgkin lymphoma has been associated with immune deficiency states such as after transplantation,[33,34] but to our knowledge a direct effect of purine analogs has not been determined.[34] Another chronic inflammatory disease, rheumatoid arthritis, also has been associated with an increased risk of lymphoma.[35]

Once we discovered an increased risk of lymphomas among males with CD, we attempted to determine whether these cases were related to the use of immune modulating therapy by reviewing the charts of these patients. We found that no patients had received immune modulating therapy other than corticosteroids prior to the onset of their malignancies. Immune modulating therapy may contribute to an increased risk of hematologic malignancies in any patient with an immunocompromised state and this also might be true in CD patients treated with these drugs. Several series have reported leukemia and lymphoma development in the absence of immune modulating therapy.[29,30,36] Patients treated with purine analogs for IBD have been found not to be at increased risk of developing extraintestinal malignancies including lymphoma if the drug was used for < 5 years.[37] However, although based on small numbers, there was a suggestion of increased risk among patients who used purine analogs for > 5 years. In reports of long-term use of purine analog therapy and its associated toxicity, two patients were identified as having developed cerebral lymphomas.[38,39] In a recent review of a large series of patients with IBD using 6-mercaptopurine, some cases of cancer, including lymphoma, were reported.[40] Elsewhere, two recent case reports of lymphoma[41] and leukemia[42] in patients treated with long-term purine analog therapy continue to raise fears among patients and some clinicians regarding the prescription of these drugs. These anecdotal reports underscore the need for population-based data.

We recently reported that 7.8% of the Manitoba IBD population in 1997 were receiving immunomodulatory therapy (including 6-mercaptopurine, azathioprine, methotrexate, or cyclosporine).[43] Thus only a small percentage of our patients use these agents (and likely an even smaller percentage through the earlier years of the study), suggesting that they are unlikely to be important as risk factors for the development of malignancy. Furthermore, our chart review in the lymphoma cases identified confirmed that none of these patients was receiving any immunomodulatory therapy. However, it remains possible that in populations with a much higher use of immunomodulatory therapy, an increased incidence of cancer in relation to immunomodulatory therapy may occur.

Recently, novel immune modifier therapies for CD have emerged. One in particular is antibody to TNF-α.[17] A major concern regarding this drug is whether it would lead to the development of malignancy, particularly lymphoma.[17] Thousands of Americans were prescribed TNF-α in its first year on the market. Any concerns regarding the development of lymphoma among patients with CD who are receiving this drug also must be viewed with the knowledge that these patients now have been proven to be at increased risk for this complication in the absence of any immune modulating therapy.

Myelodysplastic syndromes also have been associated anecdotally with CD,[44–46] but we did not find any statistically significant association.

Some studies have found IBD patients to be at a significantly increased risk of other tumors relative to control populations. For CD, these include squamous skin cancers[15] and bladder tumors.[16] In patients with UC there have been reports of an increased risk of connective tissue malignancies and brain tumors,[15] nonmelanoma skin cancers,[8] squamous skin malignancies,[9] and bone and endometrial carcinomas.[5] To our knowledge there are no readily apparent explanations for these types of associations with IBD. For some extraintestinal tumors, such as hepatobiliary carcinoma, there may be an underlying chronic inflammatory process such as primary sclerosing cholangitis,[9,10] but for other malignancies, such as skin cancer, the higher risk may reflect increased diagnoses resulting from more medical attention. An increase in respiratory tumors in CD patients and a significant decrease in UC patients reported in a small Italian study may reflect the smoking habits of the individual disease populations.[20] The current study did not show any statistically significant association between CD or UC and any of these cancers.

The results of the current study report similar increased risks for developing colon carcinoma and hepatobiliary carcinoma among patients with CD and UC, an increased risk of developing rectal carcinoma among patients with UC and an increased risk of developing lymphoma among males with CD. It previously has been widely reported that there is an increased risk of developing colorectal and biliary car-

cinomas in patients with IBD although the findings of the current study with regard to lymphoma are somewhat novel. Although it might be argued that the increased risk of lymphoma among males with CD may be due to chance (in view of multiple comparisons), it should be pointed out that none of the 20 other cancers studied were found to be increased in IBD patients, all of which had less plausible connections for increased risk in IBD than lymphoma. The strength of the current study is that it is population-based and the control group was an age-matched, gender-matched, and geographically matched cohort. Population-based data are required to substantiate possibilities put forward in case reports or in case series from specialized centers.

REFERENCES

1. Gyde SN, Prior P, Allan RN, Stevens A, Jewell DP, Truelove SC, et al. Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. *Gut* 1988;29: 206–17.
2. Lennard-Jones JE, Melville DM, Morson BC, Ritchie JK, Williams CB. Precancer and cancer in extensive ulcerative colitis: findings among 401 patients over 22 years. *Gut* 1990; 31:800–6.
3. Lofberg R, Brostrom O, Karlen P, Tribukait B, Ost A. Colonoscopic surveillance in long-standing total ulcerative colitis–a 15 year follow-up study. *Gastroenterology* 1990;99:1021–31.
4. Lindberg B, Persson B, Veress B, Ingelman-Sundberg H, Granqvist S. Twenty years' colonoscopic surveillance of patients with ulcerative colitis. Detection of dysplastic and malignant transformation. *Scand J Gastroenterol* 1996;31: 1195–204.
5. Mir-Madjlessi SH, Farmer RG, Easley KA, Beck GJ. Colorectal and extracolonic malignancy in ulcerative colitis. *Cancer* 1986;58:1569–74.
6. Greenstein AJ, Sachar DB, Smith H, Janowitz HD, Aufses AH Jr. A comparison of cancer risk in Crohn's disease and ulcerative colitis. *Cancer* 1981;48:2742–5.
7. Ekbom A, Helmick C, Zack M, Adami-H-O. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990;323:1228–33.
8. Mellemkjaer L, Olsen JH, Frisch M, Johansen C, Gridley G, McLaughlin JK. Cancer in patients with ulcerative colitis. *Int J Cancer* 1995;60:330–3.
9. Karlen P, Lofberg R, Brostrom O, Leijonmarck C-E, Hellers G, Persson P-G. Increased risk of cancer in ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 1999; 94:1047–52.
10. Kornfeld D, Ekbom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. *Gut* 1997;41:522–5.
11. Weedon DD, Shorter RG, Ilstrup DM, Huizenga KA, Taylor WF. Crohn's disease and cancer. *N Engl J Med* 1973;289: 1099–103.
12. Gyde SN, Prior P, Macartney JC, Thompson H, Waterhouse JAH, Allan RN. Malignancy in Crohn's disease. *Gut* 1980;21: 1024–9.
13. Gillen CD, Andrews HA, Prior P, Allan RN. Crohn's disease and colorectal cancer. *Gut* 1994;35:651–5.
14. Ekbom A, Helmick C, Zack M, Adami H-O. Increased risk of large bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990;336:357–9.
15. Ekbom A, Helmick C, Zack M, Adami H-O. Extracolonic malignancies in inflammatory bowel disease. *Cancer* 1991; 67:2015–9.
16. Persson P-G, Karlen P, Bernell O, Leijonmarck C-E, Brostrom O, Ahlblom A, et al. Crohn's disease and cancer: a population-based cohort study. *Gastroenterology* 1994;107: 1675–9.
17. Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, et al. Efficacy and safety of retreatment with anti-Tumor Necrosis Factor antibody (Infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; 117:761–9.
18. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. The epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol* 1999;149:916–24.
19. Bernstein CN, Kliewer E, Rawsthorne P, Doig W, Blanchard JF. Diagnoses of extraintestinal manifestations and cancers in IBD in large population-based databases. *Gastroenterology* 1998;114:A930.
20. Binder V, Hendriksen C, Kreiner S. Prognosis in Crohn's disease-based on results from a regional patient group from the country of Copenhagen. *Gut* 1985;26:146–50.
21. Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993;105:1716–23.
22. Gollop JH, Phillips SF, Melton LJ III, Zinsmeister AR. Epidemiologic aspects of Crohn's disease. *Gut* 1988;29:49–56.
23. Kvist N, Jacobsen O, Norgaard P, Ockelmann HH, Kvist HK, Schou G, et al. Malignancy in Crohn's disease. *Scand J Gastroenterol* 1986;21:82–6.
24. Choi PM, Zelig MP. Similarity of colorectal cancer in Crohn's disease and ulcerative colitis: implications for carcinogenesis and prevention. *Gut* 1994;35:950–4.
25. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut* 1994;35: 1590–2.
26. Fabry TL, Sachar DB, Janowitz HD. Acute myelogenous leukemia in patients with ulcerative colitis. *J Clin Gastroenterol* 1980;2:225–7.
27. Bargen JA. Chronic ulcerative colitis associated with malignant disease. *Arch Surg* 1928;17:561–76.
28. Greenstein AJ, Gennuso R, Sachar DB, Heimann T, Smith H, Janowitz HD, et al. Extraintestinal cancers in inflammatory bowel disease. *Cancer* 1985;56:2914–21.
29. Greenstein AJ, Mullin GE, Srauchen JA, Heimann T, Janowitz HD, Aufses AH Jr., et al. Lymphoma in inflammatory bowel disease. *Cancer* 1992;69:1119–23.
30. Caspi O, Polliack A, Klar R, Ben-Yehuda D. The association of inflammatory bowel disease and leukemia-coincidence or not? *Leuk Lymphoma* 1995;17:255–62.
31. Weisenburger DD. Epidemiology of non-Hodgkin's lymphoma: recent findings regarding an emerging epidemic. *Ann Oncol* 1994;5(Suppl 1):S19–S24.
32. Perosio PM, Brooks JJ, Saul SH, Haller DG. Primary intestinal lymphoma in Crohn's disease: minute tumor with a fatal outcome. *Am J Gastroenterol* 1992;87:894–8.
33. Penn I. The occurrence of cancer in immune deficiencies. *Curr Probl Cancer* 1982;6:28–43.

34. Kinlen LJ, Sheil AGR, Peto J, Doll R. Collaborative United Kingdom-Australian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 1979;2:1461–6.
35. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am J Med* 1985;78:44–9.
36. Harewood GC, Loftus EV Jr., Sandborn WJ, Tremaine WJ. Concurrent inflammatory bowel disease and the leukemias [abstract]. *Gastroenterology* 1999;114:A992.
37. Connell WR, Kamm MA, Dickson M, Balkwill AM, Ritchie JK, Lennard-Jones JE. Long-term neoplasia risk after azathioprine treatment in inflammatory bowel disease. *Lancet* 1994;343:1249–52.
38. Present DH, Meltzer SJ, Krumholz MP, Wolke A, Korelitz BI. 6-mercaptopurine in the management of inflammatory bowel disease: short term and long-term toxicity. *Ann Intern Med* 1989;11:641–9.
39. Bouhnik Y, Lemann M, Mary J-Y, Scemama G, Tai R, Matuchansky C, et al. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996;347:215–9.
40. Korelitz BI, Mirsky FJ, Fleisher MR, Warman JI, Wisch N, Gleim GW. Malignant neoplasms subsequent to treatment of inflammatory bowel disease with 6-mercaptopurine. *Am J Gastroenterol* 1999;94:3248–53.
41. Larvol L, Soule J-C, Le Tourneau A. Reversible lymphoma in the setting of azathioprine therapy for Crohn's disease [letter]. *N Engl J Med* 1994;331:883–4.
42. Heizer WD, Peterson JL. Acute myeloblastic leukemia following prolonged treatment of Crohn's disease with 6-mercaptopurine. *Dig Dis Sci* 1998;43:1791–3.
43. Bernstein CN, Metge C, Blanchard JF, Peterson S. A population based study of the use of steroids and immunomodulatory therapy by IBD patients. *Gastroenterology* 2000;118: A784.
44. Eng C, Farraye FA, Shulman LN, Peppercorn MA, Krauss CM, Connors JM, et al. The association between the myelodysplastic syndromes and Crohn disease. *Ann Intern Med* 1992;117:661–2.
45. Hebbar M, Kozlowski D, Wattel E, Mastrini S, Dievart M, Duclos B, et al. Association between myelodysplastic syndromes and inflammatory bowel diseases. *Leukemia* 1997; 11:2188–91.
46. Bosch X, Bernadich O, Vera M. The association between Crohn disease and the myelodysplastic syndromes. Report of 3 cases and review of the literature. *Medicine (Baltimore)* 1998;77:371–7.