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Effect of Medications on Risk of Cancer in Patients with Inflammatory Bowel Diseases: A Population-based Cohort Study from Olmsted County, Minnesota

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Abstract

Objective—To estimate the overall risk of cancer in a population-based cohort of patients with inflammatory bowel diseases (IBD), and how IBD-related medications modify this risk.

Methods—We identified all incident cancers (excluding non-melanoma skin cancer) after IBD diagnosis in a cohort of 839 patients diagnosed between January 1, 1940 and December 31, 2004 in Olmsted County, Minnesota, and followed over a median 18 years through December 31, 2011 (122 patients on biologic agents at last follow-up). We calculated standardized incidence ratios (SIR) with 95% confidence intervals (CIs) of all cancers, and compared cancer risk in patients treated with immunomodulators (IMM) and biologics with that of patients not exposed to these medications, using an incidence rate ratio (IRR).

Results—One hundred nine patients developed 135 cancers. The 10-year cumulative probability of cancer was 3.8%. Patients with CD (SIR, 1.6; 95% CI, 1.2–2.1), but not UC (SIR, 1.1; 95% CI, 0.8–1.4), had an increased overall risk of cancer, as compared to the general population. Patients

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treated with IMM (relative to IMM-naïve patients) had an increased risk of melanoma (IRR 5.3; 95% CI, 1.1–24.8) (and a numerically higher risk of hematological malignancies [IRR, 4.2; 95% CI, 0.9–19.2]), although this risk returned to baseline on discontinuation of IMM. Patients treated with biologics (relative to biologic-naïve patients) had a numerically higher risk of hematological malignancies (IRR, 5.3; 95% CI, 0.7–40.5). There was no significant increase in the risk of gastrointestinal malignancies in IBD patients, as compared to the general population.

Conclusions—We observed an increased risk of melanoma in IMM-treated patients with IBD, and this risk returned to baseline after discontinuation of medications.

Keywords

Cancer; immunomodulators; anti-tumor necrosis factor; inflammatory bowel disease; ulcerative colitis; Crohn's disease

INTRODUCTION

Chronic gastrointestinal inflammation in inflammatory bowel disease (IBD) has been associated with increased risk of colitis-associated colorectal cancer (CRC).[1] Besides CRC, IBD may also be associated with an increased risk of extra-intestinal cancers, in particular hematological malignancies and melanoma.[2–6] However, results have been conflicting, in part due to different settings in which these studies have been conducted. Clinic-based studies are prone to selection and detection bias, and may over-estimate cancer risk. On the other hand, population-based studies from unselected cohorts of patients are more representative of the true cancer risk in patients with IBD, and are useful for prognostic information and life insurance estimates.

Predisposing factors for extra-intestinal cancers in patients with IBD are poorly understood. Besides gut-specific changes, IBD is also associated with systemic immune dysregulation leading to impairment of tumor surveillance.[7,8] Besides the primary disease process, lifestyle changes and immunosuppressive therapy may modify cancer risk.[9] The effect of immunosuppressive medications on cancer risk is of particular interest. Thiopurines have been associated with an increased risk of lymphomas and non-melanoma skin cancers (NMSC);[4,10–12] it is unclear whether anti-tumor necrosis factor-α (anti-TNF) agents modify the risk of cancer, with conflicting evidence.[13–15]

Hence, the aims of this study were: (a) to estimate the cumulative incidence and relative risk of intestinal and extra-intestinal solid organ cancers, hematological malignancies and melanoma by IBD phenotype (UC and Crohn's disease [CD]), as compared to the general population; and (b) to assess whether the use of medications used to treat IBD (5-aminosalicylates [5-ASA], corticosteroids, immunomodulators [IMM] in particular thiopurines, and anti-TNF agents) modifies the risk of cancer, in a population-based inception cohort of IBD patients from Olmsted County, Minnesota. We hypothesized that patients treated with thiopurines, but not those treated with 5-ASA or anti-TNF agents, would have an increased risk of hematological malignancies.

METHODS

Setting

Olmsted County, in southeastern Minnesota, has a population of 144,260.[16] Eighty-three percent of the population is non-Hispanic white, and a substantial proportion is of North European ancestry. Residents of Olmsted County are socioeconomically comparable to the US white population, although a higher proportion are employed in health care services and have a higher level of education.[17,18]

Healthcare providers in Olmsted County are connected through a unique medical recordlinkage system (Rochester Epidemiology Project [REP]).[19] The central diagnostic index of the REP comprises all diagnoses generated from outpatient evaluations, hospitalizations, emergency room evaluations, nursing home visits, surgical procedures, autopsy reports, and death certificates. It is therefore possible to identify all cases of a disease for which patients sought medical attention over a particular period of time.

Evaluation and Medication Use

All potential new cases of CD and UC were identified through the central diagnostic index.[20] A diagnosis of CD and UC was confirmed based on standard clinical, endoscopic, radiologic and/or histologic criteria. We abstracted data on medications commonly used to treat IBD, and estimated duration of use using the prescription start and stop dates, through review of individual medical records. Medications were categorized into: sulfasalazine and 5-ASA, corticosteroids, IMM (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus) and anti-TNF agents (infliximab, adalimumab, certolizumab pegol). We classified patients as: (a) current user, if a patient was on medication at time of cancer diagnosis (or had been on the medication within 2 months prior to cancer diagnosis) and had been on the medication for at least 6 months; (b) former user, if the patient had been exposed to that medication prior to cancer diagnosis (more than 2 months prior to cancer diagnosis), but was not on the medication at time of cancer diagnosis; or (c) non-user, if the patient had never been exposed to that medication (or, in case of corticosteroids, was only given that medication as a pre-medication with administration of infliximab).

Cancer Diagnosis

Using REP, we identified all incident cancers in patients with IBD, with confirmation through medical record review. Cancers were classified into 7 categories based on the primary site involved – intestinal cancer (CRC, small intestinal, biliary tract, hepatocellular, gallbladder, pancreatic, gastric, esophageal and anal cancer), tobacco-related cancers (lung, head and neck including oral, bladder, kidney, and ureter), female reproductive organ cancers (ovarian, endometrial, cervical, vaginal/vulvar and breast), male reproductive organ cancers (testicular and prostate cancer), miscellaneous extra-intestinal cancers (prostate, brain, spinal cord, thyroid, melanoma), hematological cancers (Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute and chronic leukemia, multiple myeloma) and melanoma.[21] We excluded NMSC from this analysis.

Statistical Analysis

Data were summarized as medians (range, interquartile range [IQR]) for quantitative variables and frequency for categorical variables. We recorded person-years at risk from the date of IBD diagnosis until the date of first cancer diagnosis (except NMSC), death, emigration or end of study period (December 31, 2011) for each individual in the cohort. We included only incident cancers occurring at least 30 days after IBD diagnosis to minimize the risk of detection bias and misclassification; patients with a history of cancer diagnosed prior to IBD diagnosis were still considered at risk of other organ cancers after IBD diagnosis. We estimated the risk of overall and site-specific cancer type, relative to the general population using SIR (observed/expected numbers) with 95% confidence intervals (CI) assuming a Poisson distribution; expected cancer risk was estimated using age- and sex-specific corresponding cancer rates from the Surveillance, Epidemiology, and End Results database (SEER) (white patients from Iowa, 1973–2000). The cumulative probability of any cancer from the diagnosis of CD or UC was estimated using the Kaplan–Meier survival method.

In order to estimate whether IBD-specific medications modify cancer risk, we calculated the incidence rate ratio (IRR) of cancer in current medication users as compared to non-users, by dividing the incidence rate of cancer among current users (number of cancers divided by person-years of follow-up on that medication) by the incidence rate of cancer among never users.[4] To assess whether there was any residual effect on cancer risk after discontinuation of medication, we calculated the IRR of cancer in former users as compared to non-users.[10] We also evaluated cancer risk among 5-ASA-treated, steroid-treated, IMM-treated and biologic-treated patients with IBD (ever use of medication), relative to the general population, using SIR with expected rates estimated from the SEER population.[9]

All statistical analyses were conducted using SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC). P-values <.05 were considered statistically significant.

Ethics

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. As per Minnesota state law, we did not include patients who had withdrawn authorization to review their medical records for research purposes.

RESULTS

Baseline Characteristics of the Entire IBD Cohort

We identified 839 patients with IBD (44.9% with CD). Baseline characteristics of these patients are reported in Table 1. Median age at diagnosis of patients with CD was 30.0 years (IQR, 22.2–45.2) and UC was 35.0 years (range, 25.0–48.5). Forty-one patients had a previous history of cancer, prior to IBD diagnosis (or within 30 days of IBD diagnosis). Of 686 patients with documented smoking status, 342 (50%) had ever smoked. One hundred eighty-four patients were treated with IMM (cumulative probability at 1 and 10 years, 7.5% and 17.1%, respectively), while 99 patients were treated with an anti-TNF agent (cumulative probability at 1 and 10 years, 1.6% and 8.3%, respectively).

Over a median follow-up of 18.4 years, 109 patients with IBD developed 135 cancers. The cumulative probability of first cancer was 3.8% by 10 years, 9.1% by 20 years, and 16.3% by 30 years.

Overall and Site-Specific Cancer Risk in Crohn's Disease

Over a total follow-up of 7487 person-years, 47 patients with CD developed 58 cancers. The 10-year cumulative probability of cancer after the diagnosis of CD was 3.6% (Figure 1A). Overall, patients with CD had a 57% higher risk of cancer as compared to an age- and sex-matched general population (SIR, 1.6; 95% CI, 1.2–2.1). This increased risk was statistically significant in females (SIR, 1.7; 95% CI, 1.1–2.6) but not in males (SIR, 1.4; 95% CI, 0.9–2.2).

On category-specific analysis, a 3-fold higher risk of hematological malignancies (SIR, 3.0; 95% CI, 1.2–6.9) and a non-significant 2.7-fold higher risk of melanoma (SIR, 2.7; 95% CI, 0.9–6.2) was observed (Table 2A). On site-specific analysis, CD was associated with increased risk of small intestinal cancer (SIR, 9.4; 95% CI, 1.1–33.9), biliary tract cancer (SIR, 21.2; 95% CI, 4.4–61.8), Hodgkin's lymphoma (SIR, 11.3; 95% CI, 2.3–33.1) and brain cancer (SIR, 4.9; 95% CI, 1.0–14.4); the risk of other solid-organ cancers was not significantly increased, including CRC (SIR, 0.6; 95% CI, 0.1–1.7) (Supplementary Table 1).

Overall and Site-Specific Cancer Risk in Ulcerative Colitis

Over a total follow-up of 9822 person-years, 62 patients with UC developed 77 cancers. The 10-year cumulative probability of cancer after the diagnosis of UC was 4.9% (Figure 1B). Overall, patients with UC did not have a higher risk of cancer than an age- and sex-matched general population (SIR, 1.1; 95% CI, 0.8–1.4). On sex-specific analysis, females with UC had a 59% higher risk of cancer as compared to females in the general population (SIR, 1.6; 95% CI, 1.1–2.3); there was no increase in the overall risk of cancer in males with UC (SIR, 0.9; 95% CI, 0.6–1.2).

On category-specific analysis, we observed a 2.7-fold higher risk of hematological malignancies (SIR, 2.7; 95% CI, 1.2–5.3) in patients with UC; the risk of melanoma was numerically, but not statistically, higher than expected (SIR, 2.0; 95% CI, 0.7–4.4) (Table 2B). On site-specific analysis, UC was associated with increased risk of biliary tract cancer (SIR, 11.4; 95% CI, 2.4–33.2) and decreased risk of lung cancer (SIR, 0.3; 95% CI, 0.1–0.9); the risk of other solid-organ cancers was not significantly increased, including CRC (SIR, 0.7; 95% CI, 0.2–1.4) (Supplementary Table 2).

Risk of Cancer by Medications Used to Treat IBD

We did not find any increase in the overall risk of cancer in patients treated with 5-ASA (vs. 5-ASA-naïve patients; IRR, 1.0; 95% CI, 0.5–1.8), corticosteroids (vs. corticosteroid-naïve patients; IRR, 1.4; 95% CI, 0.5–3.4), IMM (vs. IMM-naïve patients; IRR, 0.9; 95% CI, 0.3–2.3) or anti-TNF agents (vs. anti-TNF-naïve patients; IRR, 0.6; 95% CI, 0.1–4.5) (Table 3A). On category-specific analysis, we observed an increased risk of melanoma in corticosteroid-treated (IRR, 8.2; 95% CI, 1.4–49.2) or IMM-treated patients (IRR, 5.3; 95%

CI, 1.1–24.8); no cases of melanoma were observed in anti-TNF treated patients. There was a numerically, but not statistically, higher risk of hematological malignancies in patients treated with corticosteroids (IRR, 4.9; 95% CI, 0.9 –25.1), IMM (IRR, 4.2; 95% CI, 0.9–19.2) and anti-TNF agents (IRR, 5.3; 95% CI, 0.7–40.5). Hematological malignancies observed in IMM-treated patients were Hodgkin's (1 patient) and non-Hodgkin's lymphoma (1 patient); 4 patients had EBV-positive lymphoma.

In order to evaluate whether the increased risk of cancer persisted after discontinuing medications, we compared overall and category-specific cancer risk in patients previously exposed to those medications with IBD patients never exposed to those medications (former users vs. never users). On this analysis, we observed that the overall risk of cancer was not significantly different in former users of 5-ASA, corticosteroids, IMM or anti-TNF agents, compared to patients with IBD who had never been treated with these agents, respectively (Table 3B). The increased risk of melanoma observed in current users of corticosteroids and IMM decreased back to baseline off-treatment. Risk of hematological malignancies in former users of corticosteroids (IRR, 1.3; 95% CI, 0.4–4.2) and IMM (IRR, 2.7; 95% CI, 0.6–12.5) was comparable to the risk observed in patients with IBD never exposed to these patients.

On comparing cancer risk in patients treated with IBD-related medications to the general population, we did not find any significant increase in overall or category-specific cancer risk in 5-ASA, corticosteroid, IMM or anti-TNF treated patients with IBD, except an increase in the risk of hematological malignancies in IMM-treated patients with IBD (Supplementary Table 3).

DISCUSSION

In our population-based cohort study of 839 patients with IBD followed over a median 18 years, we made several key observations. First, we confirmed a modest increase in the overall risk of cancer in patients with CD, but not in UC, as compared with the general population. Second, we observed a 3-fold higher risk of hematological malignancies, both in patients with CD and UC, as compared to the general population, although the overall incidence was low (<0.1% annually); the risk of melanoma was also numerically higher in patients with IBD. Third, we observed an increased risk of melanoma in current users of corticosteroids and IMM; there was a numerically, but not statistically, higher risk of hematological malignancies in corticosteroid-, IMM- and anti-TNF-treated patients. Finally, the relatively increased risk of melanoma and hematological malignancies observed while on specific IBD-related medications returned to baseline after discontinuation of the implicated treatment.

A modestly increased risk of overall cancer incidence[3,9,21,22] and mortality[23] has been observed in patients with CD, and not in patients with UC. In their recent Danish population-based cohort study, Jess and colleagues observed a 55% higher risk of cancer after CD diagnosis, but no similar increase in cancer risk in patients with UC.[9] Systemic immune dysregulation and more prevalent use of immunosuppressive therapy in CD may impair tumor surveillance and predispose these patients to extra-intestinal cancers. We also

observed a lower risk of lung cancer in patients with UC compared to the general population, similar to previous observations,[22] which may be related to a lower proportion of smokers in patients with UC.

We observed that patients with IBD treated with IMM (primarily thiopurines) had an increased risk of melanoma (and a numerically higher risk of hematological malignancies). Melanoma is an immunogenic tumor;[24] systemic IMM may drive the growth of dysplastic nevi, which are strong risk factors for melanoma, by down-regulating tumor surveillance mechanisms, increasing susceptibility to infection with oncogenic viruses such as melanoma-associated retroviruses, or through a direct pharmacologic effects on DNA metabolism.[24,25] Although thiopurine analogs have been associated with an increased risk of NMSC, there are only a limited number of studies assessing the risk of melanoma in patients with IBD treated with thiopurines. In a large US administrative database, Long et al did not find an increased risk of melanoma in thiopurine-exposed patients.[4] However, follow-up in their cohort was short, and all patients ever-exposed to thiopurines (current or former users) were grouped together. In contrast, in our cohort, the increased risk of melanoma was only seen in current users of thiopurines, and this risk decreased to baseline upon discontinuation of medications. The increased risk of hematological malignancies with thiopurines, particularly EBV-positive lymphoma, has been reported in multiple previous cohort studies, as well as meta-analysis.[10–12,26] Importantly, we observed that this increased risk of hematological malignancies decreased back to baseline (comparable to hematological malignancy risk in IMM-naïve patients) after stopping medication, similar to previous findings;[10,11] we acknowledge that these observations were not statistically significant.

Patients treated with corticosteroids were also at an increased risk of melanoma (and had a numerically, but not statistically, higher risk of hematological malignancies), as compared to corticosteroid-naïve patients. Corticosteroids have pleiotropic immunosuppressive effects,[27] and by impairing tumor surveillance, it is possible that prolonged prednisone use may directly increase the risk of immunogenic tumors. Alternatively, it is possible that this increased malignancy risk observed in corticosteroid-treated patients may not be a direct effect of corticosteroids, but rather represents confounding by severity. In our practice, IMM were used primarily in steroid-dependent patients with IBD, and hence, corticosteroid-treated patients were more likely to have concomitantly received IMM as steroid-sparing agents; the observed malignancy risk may be attributable to increased risk afforded by thiopurine use.

We also observed that patients treated with anti-TNF agents had a numerically, but not statistically, higher risk of hematological malignancies. Prospective cohort studies have reported an increased risk of lymphoproliferative disorders with combination anti-TNF and IMM therapy, but not with anti-TNF monotherapy.[12,26,28,29] In our cohort, only one patient (out of 14) was on anti-TNF monotherapy at time of diagnosis of lymphoma. In a recent Danish nationwide cohort study of 56,146 patients with IBD, anti-TNF use (as compared to non-use) was not associated with increased risk of hematological malignancies, after adjusting for age, disease duration, baseline propensity scores and use of IBD-related medications (5-ASA, corticosteroids and IMM) (relative risk, 0.90; 95% CI, 0.42–1.91).[30]

Our study has several strengths. First, ours represents a well-characterized population-based inception cohort of IBD patients, in a defined geographic area with a stable population, over an extended period of time, and hence is truly representative of the general population. Second, complete and long follow-up over 2 decades allows better assessment of rare outcomes such as cancer. Third, our medical records linkage system allowed pathological confirmation of each cancer case, minimizing the risk of misclassification. Finally, we were able to study the effect of medications on cancer risk in patients with IBD, examining the risk both on-treatment and after discontinuation of treatment, and comparing it to patients with IBD who had never been exposed to these agents.

Our study also has certain limitations that merit discussion. First, our sample size was fixed due to the population-based nature of this study, and hence, may have been underpowered for some detailed pharmacoepidemiological analyses; we did not correct for multiple statistical comparisons. Second, caution must be exercised in interpreting the independent effect of each IBD-related medication on cancer risk. A significant proportion of patients were concomitantly on multiple medications, especially corticosteroids and IMM. Due to the small number of events, multivariate analysis after adjusting for concomitant use of other medications was not possible. Third, duration of follow-up on each medication was variable, with shorter follow-up in patients treated with anti-TNF agents, and this may have influenced the observed cancer risk with these medications. Finally, due to small sample size, we were limited in stratified analyses based on covariates that may modify cancer risk, such as cigarette smoking, duration of IBD, disease location or phenotype and past history of cancer.

Conclusion

In our population-based inception cohort of patients with IBD in Olmsted County from 1940–2011 with median follow-up of 18 years, we observed a modest increase in overall risk of cancer in patients with CD, but not in patients with UC. This observed increase in risk was due to high incidence of hematological malignancies and melanoma, although the overall incidence was low (<0.1% annually). Besides inherent disease-specific processes predisposing to these cancers, immunosuppressive therapy with corticosteroids, IMM or anti-TNF agents may also contribute to this risk. Importantly, this risk reverses to baseline levels after discontinuation of these medications. Future prospective studies evaluating the effect of combination immunosuppressive therapy versus monotherapy are warranted to clarify the impact of dual- or triple-immunosuppression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

5-ASA	5-aminosalicylate
Anti-TNF	Anti-tumor necrosis factor-α agents
CD	Crohn's disease
CRC	Colorectal Cancer
IBD	Inflammatory bowel diseases
IMM	Immunomodulator
IRR	Incidence Rate Ratio
NMSC	Non-melanoma skin cancer
REP	Rochester Epidemiology Project
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized Incidence Ratio
UC	Ulcerative colitis

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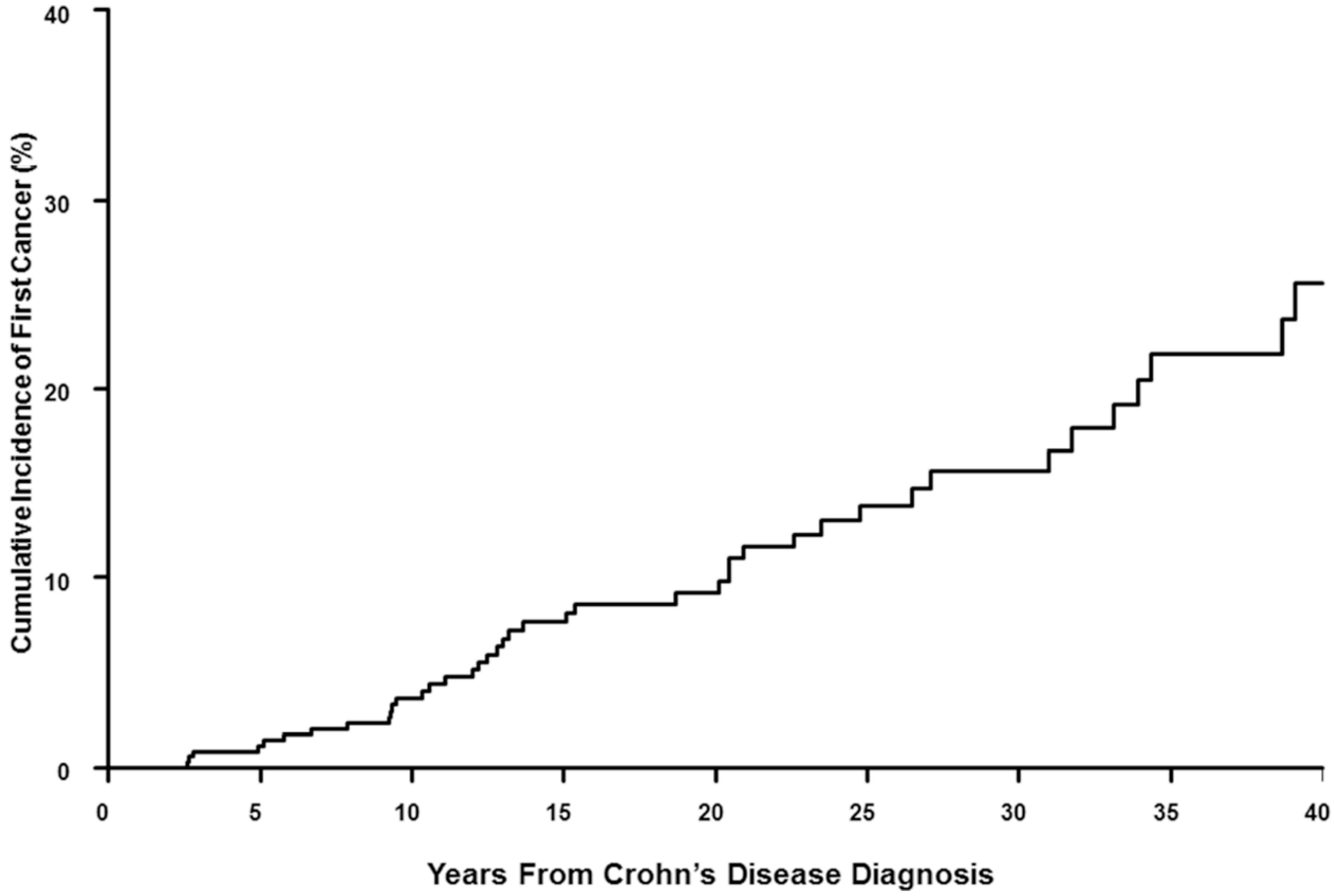

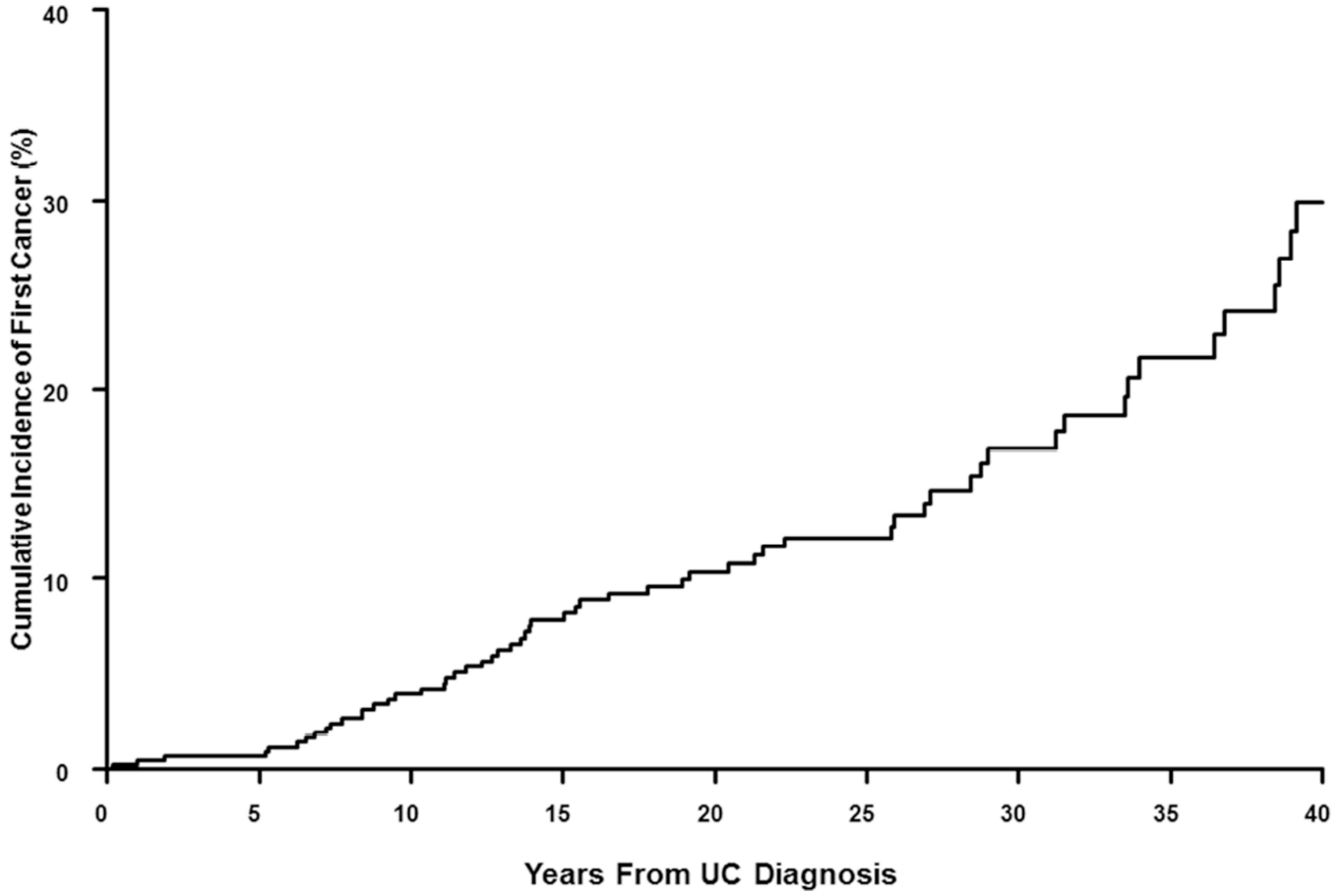

Figure 1.

Cumulative incidence of cancer after diagnosis of (A) Crohn's disease and (B) ulcerative colitis in a population-based inception cohort of 839 patients with IBD in Olmsted County, Minnesota, 1940–2011

Table 1

Baseline demographic and clinical characteristics of patients in 839 patients diagnosed with IBD in Olmsted County, Minnesota, 1940–2011

Baseline characteristics	Crohn's Disease (n=377)	Ulcerative Colitis (n=462)
Age at time of IBD diagnosis, in years (median, IQR)	30.0 (22.2–45.2)	35.0 (25.0–48.5)
• <40 years of age	255 (67.6%)	268 (58.0%)
• ≥40 years of age	122 (32.4%)	194 (42.0%)
Gender – Males (% total)	185 (49.1%)	264 (57.1%)
Follow-up, in years (median, IQR)	16.4 (10.0–28.4)	19.9 (11.0–29.2)
Duration of disease at time of last follow-up		
• <10 years	94 (24.9%)	100 (21.6%)
• 10–19 years	126 (33.4%)	132 (28.6%)
• 20–29 years	70 (18.6%)	123 (26.6%)
• ≥30 years	87 (23.1%)	107 (23.2%)
Smoking status		
• Current smokers	42 (13.8%)	19 (5.0%)
• Former smokers	97 (31.5%)	126 (33.3%)
Treatment at time of last follow-up (ever treated), n (cumulative probability of use at 1 year after diagnosis)		
• 5-aminosalicylates	279 (57.5%)	380 (67.7%)
• Corticosteroids	257 (37.1%)	295 (40.7%)
• Immunomodulators	184 (12.9%)	60 (3.1%)
• Anti-TNF agents	99 (3.0%)	23 (0.4%)
Number of patients with cancer (excludes NMSC)	47 (12.5%)	62 (13.4%)
Median age at time of cancer diagnosis, years (IQR)	61.7(50.5–71.8)	66.0(51.7–72.3)

IBD, inflammatory bowel disease; IQR, interquartile range; anti-TNF, anti-tumor necrosis factor; NMSC, non-melanoma skin cancer.

Table 2

Standardized incidence ratios of category-specific cancers in **(A)** 377 patients with CD and **(B)** 462 patients with UC, compared with expected numbers in a SEER-based age- and sex-matched general population, in Olmsted County, Minnesota, 1940–2011. Cancers were classified into 7 categories based on the primary site involved – intestinal cancer (including CRC, small intestinal, biliary tract, hepatocellular, gallbladder, pancreatic, gastric, esophageal and anal cancer), tobacco-related cancers (lung, head and neck including oral, bladder, kidney, and ureter), female reproductive organ cancers (ovarian, endometrial, cervical, vaginal/vulvar and breast), male reproductive organ cancers (testicular and prostate cancer), miscellaneous extra-intestinal cancers (prostate, brain, spinal cord, thyroid, melanoma), hematological cancers (Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute and chronic leukemia, multiple myeloma) and melanoma. Please note, figures in bold represent statistically significant results.

(A)

Cancer Category	Males		Females		Overall	
	Observed	Expected	Observed	Expected	SIR	95% CI
Intestinal cancers	6	4.03	5	4.01	1.37	0.68–2.45
Tobacco-related cancers	7	6.06	5	4.40	1.15	0.59–2.00
Male reproductive organ cancers	7	6.00	NA	NA	1.17	0.47–2.40
Female reproductive organ cancers	NA	NA	12	9.65	1.24	0.64–2.17
Miscellaneous extra-intestinal solid organ cancers	2	0.92	3	0.97	2.64	0.86–6.15
Hematological malignancies	3	0.92	3	0.97	**3.17**	**1.16–6.89**
Melanoma	4	0.89	1	0.98	2.67	0.87–6.23

(B)

Cancer Category	Males		Females		Overall	
	Observed	Expected	Observed	Expected	SIR	95% CI
Intestinal cancers	6	9.08	7	5.51	0.89	0.47–1.52
Tobacco-related cancers	11	14.06	3	5.95	0.70	0.38–1.17
Male reproductive organ cancers	14	13.14	NA	NA	1.07	0.58–1.79
Female reproductive organ cancers	NA	NA	15	12.09	1.24	0.69–2.05
Miscellaneous extra-intestinal solid organ cancers	2	1.86	2	1.12	1.34	0.37–3.44
Hematological malignancies	5	1.86	3	1.12	**2.69**	**1.16–5.29**
Melanoma	4	1.84	2	1.13	2.02	0.74–4.40

SIR, standardized incidence ratio; 95% CI, 95% confidence interval.

Table 3

Incidence rate ratio of category-specific cancer risk in patients with IBD (A) on-treatment (current users v. never users) and (B) off-treatment (former users v. never users). Please note, figures in bold represent statistically significant results

(A) Cancer risk in patients with IBD on-treatment (current users v. never-users)								
	5 – aminosalicylates		Corticosteroids		Immunomodulators		Anti-TNF agents	
Cancer Category	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
All	0.97	0.52 – 1.8	1.37	0.54 – 3.45	0.85	0.31 – 2.31	0.63	0.09 – 4.52
Intestinal cancers	1.20	0.37 – 3.94	1.22	0.16 – 9.50	0.0	-	0.0	-
Tobacco-related cancers	1.05	0.33 – 3.29	2.76	0.60 – 12.79	0.87	0.12 – 6.44	0.0	-
Male reproductive organ cancers	0.73	0.13 – 3.98	0.0	-	1.11	0.15 – 8.26	0.0	-
Female reproductive organ cancers	0.82	0.24 – 2.82	0.0	-	0.85	0.11 – 6.25	0.0	-
Miscellaneous extra-intestinal solid organ cancers	0.72	0.07 – 7.96	0.0	-	0.0	-	0.0	-
Hematological malignancies	0.48	0.05 – 4.63	4.88	0.95 – 25.13	4.21	0.92 – 19.20	5.29	0.69–40.47
Melanoma	0.0	-	**8.23**	**1.38 – 49.25**	**5.26**	**1.12 – 24.77**	0.0	-

(B) Cancer risk in patients with IBD off-treatment (former users v. never-users)								
	5 – aminosalicylates		Corticosteroids		Immunomodulators		Anti-TNF agents	
Cancer Category	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
All	1.23	0.77 – 1.94	1.27	0.86 – 1.88	1.11	0.54 – 2.29	1.00	0.32 – 3.16
Intestinal cancers	0.98	0.37 – 2.57	1.23	0.54 – 2.82	1.22	0.29 – 5.18	0.0	-
Tobacco-related cancers	0.91	0.37 – 2.26	1.60	0.70 – 3.65	0.56	0.08 – 4.12	3.01	0.71 – 12.73
Male reproductive organ cancers	1.71	0.57 – 5.14	1.55	0.64 – 3.74	0.70	0.09 – 5.26	1.78	0.24 – 13.30
Female reproductive organ cancers	1.04	0.43 – 2.53	1.02	0.48 – 2.18	0.54	0.08 – 3.97	0.0	-
Miscellaneous extra-intestinal solid organ cancers	1.36	0.27 – 6.71	1.19	0.32 – 4.44	0.0		0.0	-
Hematological malignancies	1.51	0.42 – 5.48	1.33	0.42 – 4.2	2.74	0.60 – 12.52	0.0	-
Melanoma	1.21	0.32 – 4.57	1.92	0.48 – 7.66	1.69	0.21 – 13.49	0.0	-

IBD, inflammatory bowel disease; anti-TNF, anti-tumor necrosis factor; IRR, incidence rate ratio.