

Risk of Colorectal Cancer in Self-Reported Inflammatory Bowel Disease and Modification of Risk by Statin and NSAID Use

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BACKGROUND: Statins and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with reduced risk of colorectal cancer (CRC) in some studies. The objective of this study was to quantify the relative risk of inflammatory bowel disease (IBD) as a risk factor for CRC and to estimate whether this risk may be modified by long-term use of NSAIDs or statins. **METHODS:** The Molecular Epidemiology of Colorectal Cancer study is a population-based, case-control study of incident colorectal cancer in northern Israel and controls matched by age, sex, clinic, and ethnicity. Personal histories of IBD and medication use were measured by structured, in-person interview. The relative risk of IBD and effect modification by statins and NSAIDs were quantified by conditional and unconditional logistic regression. **RESULTS:** Among 1921 matched pairs of CRC cases and controls, a self-reported history of IBD was associated with a 1.9-fold increased risk of CRC (95% confidence interval [CI], 1.12-3.26). Long-term statin use was associated with a reduced risk of both IBD-associated CRC (odds ratio [OR] = 0.07; 95% CI, 0.01-0.78) and non-IBD CRC (OR = 0.49; 95% CI, 0.39-0.62). Stratified analysis suggested that statins may be more protective among those with IBD (ratio of OR = 0.14; 95% CI, 0.01-1.31; $P = .51$), although not statistically significant. NSAID use in patients with a history of IBD was suggestive of reduced risk of CRC but did not reach statistical significance (OR = 0.47; 95% CI, 0.12-1.86). **CONCLUSIONS:** The risk of CRC was elevated 1.9-fold in patients with IBD. Long-term statin use was associated with reduced risk of CRC in patients with IBD. *Cancer* 2011;117:1640-8. © 2010 American Cancer Society.

KEYWORDS: inflammatory bowel disease (IBD), colorectal cancer, statins, chemoprevention.

The first reports of intestinal cancer occurrence in inflammatory bowel disease (IBD) were published 80 years ago.¹ The IBD-associated cancer risk has been identified in both referral center studies²⁻⁶ and population-based studies.⁷⁻¹¹ The magnitude of risk observed in studies from referral centers generally exceeds the risk reported in population-based studies. Thus, the true risk for malignancy in IBD remains imprecisely estimated. Additional evidence from population-based studies can help quantify the risk of colorectal cancer (CRC) in IBD patients, offer prognostic information, and determine appropriate surveillance algorithms based on level of risk.

Research investigating the role of potential chemopreventive agents as a means to reduce the complications and deaths due to colorectal cancer has identified aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), calcium,^{12,13} hormone replacement therapy,¹⁴⁻¹⁶ and statins as potentially active drugs.¹⁷⁻²⁴ Balancing potential risks and benefits of chemoprevention can be dramatically influenced by the risk of the disease, and the equation is not demonstrably in favor of chemoprevention for average-risk patients at this point in time. However, high-risk populations such as those with IBD might benefit from chemoprevention if specific agents that reduce the risk of CRC in these patients can be identified and validated. Studies in high-risk populations such as those with IBD can be difficult to execute, in part due

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to the smaller study populations at risk, making it hard to study several variables simultaneously and to adjust for potential confounders.

The aims of the current study were to determine the prevalence of IBD in a population-based, case-control study of CRC in Israel, quantify the relative risk of IBD as a risk factor for CRC, evaluate the influence of aspirin, NSAID, or statin use on the relative risk of IBD-associated CRC.

MATERIALS AND METHODS

Participants

The Molecular Epidemiology of Colorectal Cancer (MECC) study is a population-based, case-control study of incident colorectal cancer in northern Israel. Patients were eligible for participation in this analysis if they had received a diagnosis of colorectal cancer between March 31, 1998 and July 11, 2004, lived in a geographically defined area of northern Israel, and provided written informed consent at the time of enrollment. Controls were identified from the same source population with the use of the Clalit Health Services (CHS) database. CHS is the largest health-care provider in Israel and covers approximately 70% of the older population (persons at least 60 years of age). Health-care coverage in Israel is mandated and is provided by 4 groups akin to health maintenance organizations. Thus, all study participants (patients and controls) had similar health insurance and similar access to health services. Controls were individually matched to patients according to the year of birth, sex, primary clinic locations, and ethnic group (Jewish vs non-Jewish). Potential controls were excluded if they had a history of colorectal cancer.

Participants were interviewed to obtain demographic information and information about their personal and family history of cancer, reproductive history, medical history, medication use, and health habits. They also completed a dietary questionnaire. One pathologist confirmed diagnoses of colorectal cancer by means of a standardized pathologic review. The institutional review boards at the Carmel Medical Center, Haifa, and the University of Michigan, Ann Arbor, approved all procedures.

This was a secondary analysis of an existing data set (MECC) originally collected for another purpose.

Exposure Data

Participants were asked to recall each medication they had used for at least 5 years, and statin use was determined on the basis of this list. Statin use was defined as positive if the patient recalled use of medication for at least 5 years

and negative for never users or those with less than 5 years of use. Statin use was recorded from an in-person interview that asked participants to list all medications used for at least 5 years. Prior published work describes the correspondence between self-reported statin use and pharmacy records.²² Individual medications were separately recorded for all cases and controls but without corresponding data for duration of use. Specific exposure to simvastatin and pravastatin was measured based on the response to specify "other medications." The use of aspirin and other NSAIDs was also assessed; information gathered included dose, duration of use, and indication for use. For analyses of aspirin or other NSAIDs, exposure was defined as at least once weekly for greater than 3 years. A complete, 3-generation pedigree and information on the family history of cancer were also recorded for each participant. The report of colon or rectal cancer in at least one first-degree relative was considered to represent a family history of colorectal cancer.

Ethnic group was determined by assessing participants' religious affiliation, self-described ethnic group, and the country of birth of their parents and grandparents.

Ashkenazi Jewish heritage was determined as previously described.²⁵

A participant's history of inflammatory bowel disease was elicited by asking whether he or she had ever been diagnosed by a physician with Crohn disease, ulcerative colitis (UC), or had ever had bowel surgery for inflammatory bowel disease.

Statistical Analysis

Statistical analyses were performed with the use of SAS software (version 8.2; SAS Institute Inc, Cary, NC), and all reported *P*-values are 2-sided. Contingency table analysis was used to assess crude associations between inflammatory bowel disease and the risk of colorectal cancer.

To account for the study design, matched analyses were performed with the use of both contingency-table methods and conditional logistic regression. Because there were no differences in matched and unmatched analysis, we report the results of unmatched analysis with unconditional logistic regression models for increased power. These techniques were used to assess the main association between IBD and the risk of CRC, to adjust for confounding, and to identify potential effect modification.

RESULTS

Findings reported here are based on data from 1921 matched pairs for whom complete interview data were

Table 1. Demographic and Epidemiological Characteristics of the Study Population

Characteristic	Cases, n=1921 No. (%)	Controls, n=1921 No. (%)	P
Sex			1
Male	987 (51.4)	987 (51.4)	
Female	934 (48.6)	934 (48.6)	
Age, mean \pm SD	69.8 \pm 11.8	70.4 \pm 11.7	.10 (.77)
Ethnic group			.429
Jews	1680 (87.5)	1697 (88.3)	
Non-Jews	241 (12.6)	224 (11.7)	
Statin use \geq5 y			<.001
No	1805 (94.0)	1692 (88.1)	
Yes	116 (6.0)	229 (11.9)	
Statin type (any use)			<.001
Simvastatin	311 (16.2)	685 (35.7)	
Pravastatin	111 (5.8)	228 (11.9)	
No statin use	1563 (81.3)	1169 (60.8)	
Sports participation			<.001
No	1339 (69.7)	1137 (59.2)	
Yes	582 (30.3)	783 (40.7)	
First-degree relative with CRC			<.001
No	1701 (88.5)	1775 (92.4)	
Yes	220 (11.5)	146 (7.6)	
Aspirin or NSAID use at least once per week for >3 y			<.001
No	1606 (83.6)	1442 (75.1)	
Yes	315 (16.4)	479 (24.9)	
Vegetable consumption			<.001
Low	862 (44.9)	649 (33.8)	
Medium	543 (28.3)	671 (34.9)	
High	516 (26.8)	601 (31.3)	

SD indicates standard deviation; CRC, colorectal cancer; NSAID, nonsteroidal anti-inflammatory drug.

available at the time of a planned analysis. Sixty patients were identified with a self-reported history of IBD. Ashkenazi Jews constituted the largest fraction of patients, a finding corresponding to the demographic distribution in Israel and the known increased risk of colorectal cancer among Ashkenazi compared with non-Ashkenazi Jews. As previously reported in these data, statin use of at least 5 years' duration was recorded in 6% of patients and 12% of controls. The vast majority of these patients and controls used simvastatin. A summary of demographic data is presented in Table 1.

The overall prevalence of self-reported IBD among persons with colon cancer was 2.0%. Compared with the control population, those with colorectal cancer had a sig-

Table 2. Crude Analysis Between Crohn Disease or Ulcerative Colitis and CRC

	Cases No. (%)	Controls No. (%)	OR (95% CI) P=
IBD	39 (2.0)	21 (1.1)	1.91 (1.12-3.26)
No IBD	1882 (98.0)	1900 (98.9)	P=.018
Crohn disease	2 ^a (0.1)	2 (0.1)	1.0 (0.14-7.11)
No Crohn disease	1919 (99.9)	1919 (99.9)	P=1.00
UC	35 ^a (1.8)	16 (0.8)	2.21 (1.22-4.01)
No UC	1886 (98.2)	1905 (99.2)	P=.0074

CRC indicates colorectal cancer; OR, odd ratio; CI, confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis.

^aCrohn disease and UC columns do not add up to 39 IBD cases because this definition also included a few respondents who had surgery for IBD but did not specify subtype.

Table 3. Unadjusted and Adjusted Analysis Between IBD Status and CRC

	Unadjusted		Adjusted ^a	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
IBD	1.91 (1.12-3.26)	.018	1.88 (1.08-3.26)	.025
Statin	0.48 (0.38-0.61)	<.001	0.55 (0.43-0.7)	<.001
NSAID/ASA	0.60 (0.51-0.70)	<.001	0.62 (0.53-0.74)	<.001
IBD	2.25 (1.25-4.06)	.007	2.19 (1.2-3.97)	.010
Statin	0.49 (0.39-0.62)	<.001	0.56 (0.44-0.72)	<.001
IBD * statin	0.17 (0.02-1.62)	.124	0.19 (0.02-1.86)	.154
IBD	1.93 (1.06-3.51)	.032	1.90 (1.04-3.50)	.038
NSAID/ASA	0.59 (0.51-0.7)	<.001	0.62 (0.53-0.74)	<.001
IBD * NSAID/ASA	0.79 (0.2-3.17)	.743	0.93 (0.22-3.89)	.920

IBD indicates inflammatory bowel disease; CRC, colorectal cancer; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; ASA, acetylsalicylic acid.

^aAnalyses adjusted for age, ethnicity, vegetable consumption, history of colorectal cancer in first-degree relative, sports participation and smoking status.

* Indicates an interaction term.

nificantly increased prevalence of IBD (2.0% vs 1.1%). Thus, in patients with a self-reported history of IBD, the unmatched odds ratio (OR) of colorectal cancer was 1.91 (95% confidence interval [CI], 1.12-3.26) (Table 2). The majority of this risk was in patients with self-reported ulcerative colitis where the unmatched odds ratio of colorectal cancer was 2.21 (95% CI, 1.22-4.01) and not increased in Crohn disease (Table 2). Remaining analyses were restricted to the broader definition of IBD and not subtypes (Crohn or ulcerative colitis). After adjustment for potential confounders (including age, ethnic group, presence or absence of sports participation, level of vegetable consumption, smoking status, and history of colorectal cancer in a first-degree relative), the association between IBD and elevated risk of colorectal cancer remained significantly elevated (Table 3).

Among persons with self-reported IBD, 50% of colorectal cancers were left sided, 30% were right sided, and 20% were rectal cancers. No strong association was seen between tumor location and IBD (Table 4). A total of 17.2% of IBD patients had tumors showing high microsatellite instability (MSI-H) compared with 10.8% of sporadic tumors (OR = 1.73; 95% CI, 0.65-4.59). Colorectal cancer was somewhat more likely to be micro-

satellite instable in patients with self-reported IBD, although this difference was not significant ($P = .267$) (Table 4). IBD patients also had a similar distribution of tumors by stage compared with non-IBD cases (Table 4).

Effect modification was assessed for use of NSAIDs, aspirin, or statins. As previously reported,²² the long-term use of statins (vs never use of statins) was associated with a significantly reduced risk of CRC overall (OR = 0.49; 95% CI, 0.39-0.62), which remained significant after adjustment for potential confounders (including age, ethnic group, presence or absence of sports participation, level of vegetable consumption, and history of colorectal cancer in a first-degree relative). Statin use was associated with a profoundly reduced risk of IBD-associated CRC (OR = 0.07; 95% CI, 0.01-0.78). After adjustment for potential confounders, the odds ratio remained strongly suggestive of reduced risk of colorectal cancer, although not statistically significant (OR = 0.10; 95% CI, 0.01-1.31) (Table 5). Stratified analysis suggested that statins may be more protective among those with IBD (ratio of OR = 0.14; 95% CI, 0.01-1.31; $P = .51$), although not statistically significant. When statin use was subdivided by type, simvastatin was associated with a profoundly reduced risk of IBD associated CRC (OR = 0.05; 95% CI, 0.004-0.54; $P = .014$) compared with non-statin users. Pravastatin use was similarly associated with a reduced risk of CRC versus non-statin users but was not

Table 4. Tumor Location, Microsatellite Instability, and Tumor Stage and Self-Reported IBD Among Cases

	IBD Cases	Non-IBD Cases	OR (95% CI)	P
	No. (%)	No. (%)		
CRC Site				
Rectum	6 (20.0)	444 (27.0)	1.0	—
Left	15 (50.0)	571 (34.7)	1.94 (0.75-5.05)	.165
Right	9 (30.0)	630 (38.3)	1.06 (0.37-2.99)	.917
Microsatellite instability				
High	5 (17.2)	158 (10.8)	1.73 (0.65-4.59)	.267
Stable and low	24 (82.8)	1310 (89.2)		
Tumor stage	29	1643		
I	2 (6.9)	307 (18.7)	1.0	—
II	15 (51.7)	660 (40.2)	3.48 (0.79-15.4)	.111
III	8 (27.6)	450 (27.4)	2.73 (0.58-12.94)	.331
IV	4 (13.8)	226 (13.8)	2.72 (0.49-14.96)	.410

IBD indicates inflammatory bowel disease; OR, odds ratio; CI, confidence interval; CRC, colorectal cancer.

Table 5. Analysis of Statin and NSAID or Aspirin Use and Odds of Colorectal Cancer Stratified by IBD

Variable	Cases No. (%)	Controls No. (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)^{a,b}
No IBD				
Statin use			0.49 (0.39-0.62)	0.56 (0.44- 0.72)
Yes	115 (6.1)	224 (11.8)	$P < .001$	$P < .001$
No	1767 (93.9)	1676 (88.2)		
NSAID/ASA use			0.60 (0.51-0.71)	0.62 (0.53-0.73)
Yes	310 (16.5)	474 (24.9)	$P < .001$	$P < .001$
No	1572(83.5)	1426 (75.1)		
IBD				
Statin use			0.07 (0.01-0.78)	0.10 (0.01-1.31)
Yes	1 (2.6)	5 (23.8)	$P = .029$	$P = .080$
No	38 (97.4)	16 (76.2)		
NSAID/ASA use			0.47 (0.12-1.86)	0.49 (0.07-3.32)
Yes	5 (12.8)	5 (23.8)	$P = .283$	$P = .461$
No	34 (87.2)	16 (76.2)		

NSAID indicates nonsteroidal anti-inflammatory drug; IBD, inflammatory bowel disease; OR, odds ratio; CI, confidence interval; ASA, acetylsalicylic acid.

^a Unmatched analysis.

^b Analyses adjusted for age, sex, ethnic group, presence or absence of sports participation, level of vegetable consumption, smoking status, and history of colorectal cancer in a first-degree relative.

Table 6. Analysis of Simvastatin or Pravastatin Use and Odds of Colorectal Cancer Stratified by IBD

Variable	Cases ^a	Controls ^a	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^{b,c}
No IBD				
Simvastatin use				
Yes	308	676	0.35 (0.30-0.40) <i>P</i> < .001	0.36 (0.30-0.42) <i>P</i> < .001
No statin	1528	1158		
Pravastatin use				
Yes	109	226	0.37 (0.29-0.47) <i>P</i> < .001	0.41 (0.31-0.52) <i>P</i> < .001
No statin	1528	1158		
IBD				
Simvastatin use				
Yes	3	9	0.11 (0.024-0.46) <i>P</i> = .003	0.05 (0.004-0.54) <i>P</i> = .014
No statin	35	11		
Pravastatin use				
Yes	2	2	0.31 (0.039-2.5) <i>P</i> = .274	0.11 (0.004-3.0) <i>P</i> = .164
No statin	35	11		

IBD indicates inflammatory bowel disease; OR, odds ratio; CI, confidence interval.

^a There were 225 patients (64 cases and 161 controls) who used both simvastatin and pravastatin and are included in the analysis of both groups.

^b Unmatched analysis.

^c Analyses adjusted for age, sex, ethnic group, presence or absence of sports participation, level of vegetable consumption, smoking status, and history of colorectal cancer in a first-degree relative.

statistically significant (OR = 0.11; 95% CI, 0.004-3.0; *P* = .164). The use of NSAID and/or aspirin in patients with a history of IBD was also associated with reduced risk of CRC but was not statistically significant (OR = 0.47; 95% CI, 0.12-1.86; *P* = .283) (Tables 5 and 6).

DISCUSSION

In this population-based study, we have corroborated and quantified the increased risk of colorectal carcinoma in IBD patients. Among patients with a self-reported history of IBD, the risk for CRC was increased by 1.9-fold compared with the control population. The majority of this risk was in patients with a self-reported history of ulcerative colitis, where the risk of CRC was increased 2.2-fold.

A number of studies have reported elevated rates of CRC in patients with IBD. A Swedish population-based study spanning the years 1955 to 1989 found a relative risk of 4.1 (95% CI, 2.7-5.8) for CRC in UC patients.¹⁰ Swedish data regarding colorectal carcinoma risk in Crohn disease (CD) patients for the years 1965 to 1983 revealed a standardized incidence ratio (SIR) of 2.5 (95% CI, 1.3-4.3).⁸ A Danish population-based study spanning 13 years (1977-1989) found a risk ratio of 1.8 (95% CI, 1.3-2.4) for CRC in UC patients.²⁶ A population-based study from Manitoba, Canada¹¹ found an incidence rate ratio for UC of 2.75 (95% CI, 1.91-3.97), for CD of 2.64

(95% CI, 1.69-4.12), and for IBD of 2.71 (95% CI, 2.04-3.59). These studies all report elevated risk ratios for CRC in patients with IBD. Several studies have also confirmed similar incidence rates of CRC amongst UC and CD.^{4,6,27} The only American data are from a population-based study from Olmstead County, which observed a trend toward increased CRC risk in the CD cohort (SIR 1.9; 95% CI, 0.7-4.1).²⁸

Other studies from Europe,²⁹ North America,³⁰ and Israel³¹ refute the association between UC or CD and CRC. The conflicting results may be owing to differences in local treatment policies. In the Denmark and Olmstead County studies, maintenance treatment with 5-aminosalicylates and surgical resection rates are high. Proctocolectomy rates in Copenhagen were approximately 20% after 20 years for both UC and CD patients, which are higher than those in Israel and many other jurisdictions. Low cancer risk in these 2 populations may be due to maintenance treatment with mesalamine, high proctocolectomy rates, or other factors.

Colonic inflammation is thought to be the primary risk factor for CRC in patients with IBD.⁸ In our study, we could not confirm if patients with self-reported CD had colonic or small bowel inflammation, whereas patients with UC by definition have involvement of the large bowel. Thus our finding of elevated risk of CRC in UC is consistent with the theory of colonic inflammation

as the risk factor for CRC. Patients with CD in our study may have had small bowel involvement, which is not believed to be a significant risk factor for CRC.

We show a nearly equal distribution of cancers throughout the colon in persons with IBD, similar to those without a history of IBD. This is consistent with our understanding of tumorigenesis in IBD patients. IBD patients at greatest risk of CRC are those with pancolitis, and one would expect tumors to be evenly distributed throughout the colon. Karlen¹⁰ had shown that of UC patients with CRC 94% had total colitis and those with rectal cancer 74% had total colitis. Jess²⁸ had reported CRC distribution throughout the colon in both UC and CD patients. In their 6 patients with UC, CRC was located in the rectum (2 cases), sigmoid (1 case), and ascending colon (1 case). In their 6 patients with CD, CRC was located in the rectum (2 cases), descending colon (1 case), and cecum (2 cases).

Stage of colon cancer denotes the extent of disease at time of diagnosis and correlates with prognosis. Persons with IBD and CRC had a similar distribution of lesions by stage compared with non-IBD persons. Since patients with IBD are expected to undergo regular endoscopic surveillance, we would potentially expect tumors to be identified at an earlier stage. This is in contrast to our observation of a CRC stage distribution that closely approximates those without IBD. This suggests the possibility that patients with IBD either did not adhere to the recommended endoscopic surveillance guidelines or that surveillance is not effective at identifying earlier stage tumors in IBD. The literature supports the hypothesis that inadequate adherence may be a more likely explanation than ineffective endoscopic surveillance. Several studies from Europe³²⁻³⁴ and New Zealand³⁵ found that less than 50% of gastroenterologists adhere to national surveillance guidelines.

In patients with IBD, CRC arises in a field of chronically inflamed mucosa, characterized by aneuploidy, loss of heterozygosity, hypermethylation, and p53 mutations. Chronic inflammation has been proposed to constitute a risk factor for the development of MSI-H cancers.³⁶⁻³⁸ We report that 17% of self-reported IBD patients had tumors showing high microsatellite instability (MSI-H) compared with 11% of sporadic tumors, yielding an odds ratio of 1.73 (0.65-4.59). Previous studies have reported a wide range of MSI-H frequency in IBD-associated neoplasia (1%-45%).^{36,37,39-44} Several factors contribute to this discrepancy, including differing microsatellite marker panels, number of microsatellite

markers used, and classifications of MSI among the different studies. A more recent study⁴⁵ reports a prevalence of MSHI-H in IBD neoplasia from 15% to 17% in a largely Caucasian US-based population, consistent with our results. A slightly lower frequency of MSI-H (8.3%) in IBD neoplasia was found in a French population study in 2007.³⁸ Our results suggest that chronic inflammation may be worth investigating as a risk factor for development of MSI-H CRC in IBD, and that the biologic behavior of IBD-associated cancers may differ from sporadic CRC.

Previous research has suggested the risk of CRC is related to duration, extent, and severity of IBD, although this has not been shown consistently in all studies. We were not able to define IBD duration, extent, or severity in our database.

Our study indicates that statin use is associated with a significant reduction in the risk of CRC in patients with a self-reported history of inflammatory bowel disease. Statins are a class of agents designed to inhibit HMG-CoA reductase, and they are effective in the management of hypercholesterolemia. It has been hypothesized that statins may have chemopreventive activity against several cancers, including colorectal cancer. Statin use has never been assessed specifically in the IBD patient population as a chemopreventive agent. We report that statin use for at least 5 years was associated with a profoundly reduced risk of IBD-associated CRC (OR = 0.07; 95% CI, 0.01-0.78). This association was seen with both simvastatin and pravastatin use. This is largely in agreement with previous studies assessing the impact of statins in average-risk patients. Previous results from our group assessed the use of statins in a population-based, case-control study of patients with a diagnosis of colorectal cancer in northern Israel. The use of statins for at least 5 years was associated with a significantly reduced relative risk of colorectal cancer (OR = 0.49; 95% CI, 0.39-0.62).²² Another population-based study from Germany indicated a 64% CRC risk reduction occurring within 1 to 4 years of statin use.⁴⁶ A nested case-control study of veterans with diabetes in the US national VA database showed a small but statistically significant reduction in CRC (OR = 0.91; 95% CI, 0.86-0.96).⁴⁷ A cohort study from Manitoba, Canada showed a nonsignificant protective effect of long-term statin use among patients with colorectal cancer (incidence rate ratio [IRR] = 0.89; 95% CI, 0.70-1.13).⁴⁸ Similarly, 2 nested case-control studies from Quebec, Canada²³ and the Netherlands²⁴ showed a nonsignificant protective effect of statin use among patients

with colorectal cancer (OR = 0.83; 95% CI, 0.37-1.89 and OR = 0.87; 95% CI, 0.48-1.57). In contrast, an analysis of data from the General Practice Research database found a minimally increased risk of colorectal cancer among patients using statins for greater than 60 months.⁴⁹

In our population, the use of NSAID and/or aspirin in patients with a self-reported history of IBD was associated with a reduced risk of CRC, although not statistically significant. Substantial evidence has shown that NSAIDs and selective COX-2 inhibitors can reduce the incidence and mortality of CRC.⁵⁰ Randomized studies have shown that aspirin usage decreases the recurrence of adenomas in high-risk patients.^{17,18} In a retrospective case-control study of UC patients with CRC at Mayo Clinic, the authors identified over-the-counter aspirin (OR = 0.3; 95% CI, 0.1-0.8) and NSAID (OR = 0.1; 95% CI, 0.03-0.5) use as protective factors.⁵¹ The point estimate for aspirin use is nearly identical to that found in our study for NSAID and/or aspirin use. NSAID use was also reported to reduce CRC mortality odds by 49% in a population of US military veterans with IBD.⁵² In contrast to these trials, both the Women's Health Study and a secondary analysis of the Physicians' Health Study did not observe any association with colorectal cancer after 5 to 10 years of treatment.^{53,54} IBD patients are often counseled to avoid NSAIDs because they may be associated with disease flares. However, in our study NSAID use was similar among controls with and without self-reported IBD.

The background prevalence of IBD was high in our population at 1%. Studies in Ashkenazi Jews have consistently reported elevated prevalence and incidence rates for both UC and CD, and this rate has increased over time.^{55,56}

Strengths of this study include the use of a population-based study design that takes advantage of age-, gender-, ethnicity- and geographically (clinic)-matched controls. By matching based on geographic location of residence, our methodology likely reduced confounding that may be present due to differences in socioeconomic status in other studies. Our study has several limitations. IBD diagnosis and medication exposure data were collected retrospectively by self-report and are therefore sensitive to recall bias. However, because participants are not likely to expect that the use of statins is related to the risk of colorectal cancer, any resulting misclassification is most likely nondifferential and therefore would only attenuate measured risks. Assessment of potential confounders was also self-reported. We also were not able to define IBD

duration, extent, or severity of disease and immunosuppressant medication use in our database as potential confounders. We did not have information on dose or duration of use of statins and therefore could not assess the data for a dose-response relation; however, statin type was assessed. Limitations associated with all studies of this design are intrinsic differences between the cases and controls (such as healthy behavior) that cannot be adjusted for and remain as confounders.

In conclusion, this population-based study showed that risk for CRC is elevated in older patients with IBD approximately 1.9-fold and suggested that statins are associated with reduced risk of CRC in these patients. Our findings are suggestive of an inverse association in a largely Ashkenazi Jewish population, which needs to be replicated in other populations to assess generalizability. These suggest potential for statins as a chemopreventative agent in patients with IBD.

CONFLICT OF INTEREST DISCLOSURES

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