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Statin use is Associated With Reduced Risk of Colorectal Cancer in Patients with Inflammatory Bowel Diseases

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Abstract

Background & Aims—Inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis are associated with an increased risk of colorectal cancer (CRC).

Chemopreventive strategies have produced weak or inconsistent results. Statins have been inversely associated with sporadic CRC. We examined their role as chemopreventive agents in patients with IBD.

Methods—We collected data from 11,001 patients with IBD receiving care at hospitals in the Greater Boston metropolitan area from 1998 through 2010. Diagnoses of CRC were determined

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using validated ICD-9-CM codes. Statin use prior to diagnosis was assessed through analysis of electronic prescriptions. We performed multivariate logistic regression analyses, adjusting for potential confounders including primary sclerosing cholangitis, smoking, increased levels of inflammation markers, and CRC screening practices to identify independent association between statin use and CRC. We performed sensitivity analyses using propensity score adjustment and variation in definition of statin use.

Results—In our cohort 1376 of the patients (12.5%) received 1 or more prescriptions for a statin. Patients using statins were more likely to be older, male, white, smokers, and have greater comorbidity than non-users. Over a follow-up period of 9 years, 2% of statin users developed CRC compared to 3% of non-users (age-adjusted odds ratio, 0.35; 95% confidence interval, 0.24–0.53). On multivariate analysis, statin use remained independently and inversely associated with CRC (odds ratio, 0.42; 95% confidence interval, 0.28–0.62). Our findings were robust on a variety of sensitivity and subgroup analyses.

Conclusions—Statin use is inversely associated with risk of CRC in a large IBD cohort. Prospective studies on the role of statins as chemopreventive agents are warranted.

Keywords

Crohn's disease; ulcerative colitis; statin; colon cancer; HMG-CoA reductase inhibitors; lipid-lowering drug

INTRODUCTION

Colorectal cancer (CRC) is an important source of morbidity in inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC))^{1–6}. Patients with long-standing UC and colonic CD have a 2-fold increase in risk of CRC compared to the general population and a cumulative risk as high as 18% after 30 years of disease^{5, 7, 8} though population based studies have estimated this to be lower (2% after 25 years)⁹. Additionally, despite a decline in incidence of IBD-related CRC^{10, 11}, an excess risk persists in those with extensive colitis and prolonged disease. Other risk factors include co-existing primary sclerosing cholangitis (PSC), positive family history, male gender, and smoking⁶. Several mechanisms have been proposed to explain the development of IBD-related CRC and its distinction from sporadic cancer. These include early occurrence of p53 mutations in IBD-associated neoplasia, alteration in methylation profile in dysplastic and non-dysplastic mucosa and mutations in KRAS and CDKN2A contributing to a field defect, and alteration in the intestinal microflora which may be exacerbated by inflammation^{5, 12–16}.

Various chemopreventive approaches have been suggested to reduce the risk of IBD-related CRC. Recognizing the association between persistent colonic inflammation and cancer, a potential chemopreventive effect could be exerted by medications used to treat IBD. Indeed much initial enthusiasm surrounded the use of 5-aminosalicylates for this role with initial studies showing a reduced risk of CRC with sulfasalazine or mesalamines^{5, 17–19}. However, subsequent studies failed to support this benefit, directing attention to therapies with other mechanisms of effect^{20, 21}.

Statins are a class of medications that exert their primary action by inhibition of 3-hydroxy 3-methylglutaryl-coenzyme A (HMG-CoA). They are among the most commonly used drugs for treatment of hypercholesterolemia and reduction of cardiovascular risk²². However studies have suggested an intriguing potential benefit by reducing cancer incidence, in particular, colorectal cancer^{22–25}. Most prior studies have focused on sporadic colon cancer with only one prior study demonstrating an inverse association between statin use and IBD-related neoplasia²⁶. However, this study was limited by a small number of IBD patients and inability to adjust for several key disease-related covariates. The aim of the present study was to use a well characterized multi-center large IBD cohort to examine whether use of statins modified risk of CRC in patients with IBD. Additionally, we analyzed if this effect remained robust adjusting for the effect of inflammatory burden, disease severity, and differences in healthcare behavior between statin users and non-users.

METHODS

Study Population

The population for this study consisted of a cohort of patients with CD or UC receiving care at one of two referral hospitals serving the Greater Boston metropolitan area. The development of this cohort has been described previously^{27–30}. We identified all eligible patients with at least 1 International Classification of Diseases, 9th Edition, clinical modification (ICD-9-CM) codes for CD (555.x) or UC (556.x). Using a combination of ICD-9-CM codes for disease complications and procedures, electronic prescriptions for medications, and narrative free text data identified using natural language processing, we developed and validated a case-finding algorithm to classify patients as having UC or CD with a positive predictive value (PPV) of 97%. This yielded a final cohort of 11,001 IBD patients.

Exposure, Covariates, and Outcomes

Our main outcome was development of CRC, determined by an ICD-9-CM code for colon or rectal cancer (153.x – 154.x). We have previously validated this on chart review with a PPV of 92%^{27, 30}. The main exposure was use of statins, defined as at least one electronic prescription for a statin (atorvastatin, simvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and fluvastatin). Statin users were defined as those who had prescription of statin at least 6 months prior to the diagnosis of colon cancer or end of follow-up.

Covariates ascertained from the medical record included gender, race, current age, and age at first contact with a diagnosis code for IBD. Non-IBD co-morbidity was quantified using the Charlson co-morbidity index³¹. Due to absence of reliable administrative data on smoking, a previously utilized method using narrative terms to define ever and never smokers was used^{32, 33}. Individuals with one or more narrative mentions of past or current smoking were considered ever smokers. Disease-related covariates included type of IBD (CD or UC), presence of co-existing primary sclerosing cholangitis (PSC)²⁸, and medical therapies (at least one electronic prescription) including use of 5-aminosalicylates (5-ASA), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and anti-tumor necrosis factor α biologic therapies (anti-TNF; infliximab, adalimumab, certolizumab).

As colonoscopy has been shown to be inversely associated with CRC in IBD patients²⁷, we assessed whether patients had undergone a colonoscopy within 6–36 months prior to development of CRC or end of follow-up. To adjust for burden of inflammation, patients with available C-reactive protein (CRP) levels (n=4,847) were classified as having normal or elevated values using a dichotomous cut-off of 8mg/L based on our laboratory ranges. For those with missing CRP, but available ESR (n=2,280), a threshold of 20mm/hr was used to define elevated inflammatory marker levels. Patients missing both CRP and ESR values were assigned the median values for the cohort.

Statistical Analysis

All analysis was carried out using Stata 13.2 (StataCorp, College Station, TX). Continuous variables were summarized using medians and interquartile ranges when skewed and means with standard deviation where normally distributed. Categorical variables were expressed as proportions and compared using the chi-square test. Univariate logistic regression was performed to identify potentially relevant covariates ($p < 0.1$) which were entered into a multivariable model to identify independent predictors at $p < 0.05$. *A priori* specified subgroup analyses were performed stratifying by gender, type of IBD, and smoking status.

We performed a number of sensitivity analyses to test the robustness of our findings. First, to account for non-random use of statins in our cohort, we adjusted for a propensity score defining likelihood of receiving a statin prescription that incorporated age, gender, smoking status, race, and non-IBD co-morbidity. To adjust for differing intensity of healthcare utilization between statin users and non-users, we adjusted for number of distinct healthcare contacts (laboratory tests, radiology procedures, office visits, hospital stays) per unit calendar year time (fact density). To minimize the effects of calendar time bias, we adjusted for earliest and latest date of follow-up in our system. Finally, we repeated our analysis lengthening the minimum required interval between statin use and CRC diagnosis to be classified a user to 2 years, and requiring at least 2 distinct prescriptions for statins within our healthcare system. The study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Our study consisted of 11,001 patients with IBD among whom 1,376 (12.5%) received one or more prescriptions for a statin (Table 1). Statin users were likely to be older, male, and white compared to non-users. They were also more likely to have UC (62% vs. 49%), while being less likely to require immunomodulator or anti-TNF biologic therapy use when compared to non-users. Statin use was also associated with lower rates of surgery (8% vs. 13%) and hospitalization (28% vs. 31%) ($p < 0.05$ for both). However, statin users has similar median C-reactive protein levels when compared to non-users (5mg/L vs. 4.4mg/L, $p=0.11$). As expected, patients prescribed statin were more likely to be ever smokers (86% vs. 55%) and had higher burden of non-IBD co-morbidity than non-users. Statin users were also modestly more likely to have a recent colonoscopy within 3 years when compared to non-users (40% vs. 35%).

Among patients using statins, 30 developed CRC on follow-up (2%) when compared to 287 among statin non-users (3%) (age-adjusted OR 0.35, 95% CI 0.24 – 0.53). Among users, the mean interval between statin prescription and CRC diagnosis was 4 years. On adjustment for age, gender, race, duration of follow-up, smoking status, type of IBD, recent colonoscopy, immunomodulator, and anti-TNF biologic exposure, statin use demonstrated a statistically significant and independent inverse association with CRC (OR 0.42, 95% CI 0.28 – 0.62). Other significant risk factors for CRC included age (OR 1.04 for every 1 year increase in age), a diagnosis of PSC (OR 3.37, 95% CI 1.93 – 5.88), smoking (1.85, 95% CI 1.42 – 2.41) and elevated inflammatory markers (OR 1.82, 95% CI 1.31 – 2.53) while female gender, non-white race, and recent colonoscopy within 3 years (OR 0.52, 95% CI 0.37 – 0.73) were inversely associated with risk of CRC. Use of 5-aminosalicylates did not modify risk of CRC on univariate analysis and was not included in the multivariable model.

We then compared characteristics of CRC patients stratified by statin use (Table 3). Statin users who developed CRC were likely to be older, had a longer interval between first contact for IBD and a diagnosis of CRC, and more likely to have UC than statin non-users who developed CRC. There was no difference in overall mortality among CRC patients based on prior statin use ($p=0.74$).

Sensitivity Analyses

In a multivariable model additionally adjusting for the propensity score outline above, there was no alteration in the association between statin use and CRC (OR 0.30, 95% CI 0.19 – 0.45). Adjusting for intensity of healthcare utilization yielded a similarly robust inverse association (OR 0.36, 95% CI 0.24 – 0.55). Adjusting the multivariable model for date of earliest contact or most recent follow-up identified no modification of our effect sizes. Requiring at least 2 distinct prescriptions for statins did not significantly modify our findings. Requiring a minimum of 2 year interval between statin prescription and diagnosis of CRC to be considered a user further strengthened our association (OR 0.21, 95% CI 0.13 – 0.35). On subgroup analysis, statin use was associated with a similarly lower risk of CRC in those with UC as CD, in men and women, and smokers and non-smokers (Table 4). To account for the intensity of a surveillance program, in addition to whether a colonoscopy was performed within 3 years, we adjusted for the number of colonoscopies over their duration of follow-up within our system and found no alteration in the association between statin use and CRC (OR 0.39, 95% CI 0.25 – 0.59). Recognizing that both CRP and ESR may not adequately predict inflammatory burden in all patients, we repeated the analysis adjusting for number of corticosteroid prescriptions and found no difference in our findings (OR 0.33, 95% CI 0.21 – 0.51). Restricting the analysis to those with a listed Partners primary care provider, and consequently the highest likelihood of receiving their care primarily within our system yielded similar results (OR 0.34, 95% CI 0.21 – 0.55).

DISCUSSION

Colorectal cancer is an important cause of morbidity and mortality in patients with inflammatory bowel diseases^{1–6}. Efficacy of chemopreventives in reducing this risk has been weak and inconsistent, limited by the quality of data, much of which are from small cohorts

or inadequately adjust for confounding disease-related factors^{5, 6, 34}. In this study, we used a large cohort of IBD patients with long follow-up to demonstrate a strong and robust inverse association between use of statins and risk of CRC.

Support for the potential chemopreventive effect of statins against colon cancer is derived from both experimental data in animal models and large epidemiologic cohorts^{22, 23}. In two large prospective cohort studies, current use of statins was associated with a reduced risk for rectal but not colon cancer³⁵. In a large population-based study of colorectal cancer from Northern Israel that included nearly 2,000 patients with colorectal cancer, use of statins for at least five years was associated with a 50% reduction in the risk of colorectal cancer compared to non-users³⁶. Using this cohort, Samadder *et al.* examined the effect on colorectal neoplasia specifically in IBD²⁶. Disease diagnosis and medication use was by recall, and analysis lacked information on important disease-related confounders including duration of disease, extent, coexisting PSC, and treatments used. In an analysis that included 60 IBD patients, long-term statin use was associated with a significant reduction of risk of colon cancer (OR 0.07), an effect that was larger in magnitude than among the participants without IBD²⁶. However, as outlined above, the many limitations in the study design and sample size limited the generalizability of the findings. In the general population, other prospective cohorts have yielded non-statistically significant trends towards a reduced risk of colon cancer with statin use^{37, 38}. This effect was recently confirmed in a meta-analysis demonstrating a weak effect among both cohort and case control studies³⁹.

The mechanisms of effect of statins may be through HMG-CoA reductase inhibition as well as non HMG-CoA related effects^{22, 23}. Through inhibition of HMG-CoA reductase, statins reduce the production of farnesyl pyrophosphate and geranylgeranyl pyrophosphate (GGPP) which are required for post-translational modification (isoprenylation) and activation of various proteins including the *Ras* and *Rho* proteins^{22, 23, 40}. These proteins are over-expressed in CRC and are associated with tumor invasion²². In rat intestinal epithelium, this inhibition of isoprenylation by lovastatin was associated with induction of apoptosis which could be reversed by administration of GGPP. Induction of apoptosis has been described in several different mice models with various statins, suggesting a class effect²⁴. In addition, statins may reduce formation of aberrant crypt foci and polyps, and reduce tumor metastasis²². Non HMG-CoA reductase mediated effects of statins may be through their inhibition of cell adhesion and angiogenesis, an antioxidant effect, and through inhibition of inflammation^{22, 23}. While we did not see a difference in the median C-reactive protein levels between statin users and non-users, statin users were less likely to require immunomodulator or biologic therapy for their IBD supporting a potential anti-inflammatory role for statins.

There are several implications to our findings. The majority of the studies examining chemopreventives in IBD have focused on IBD-related medications, primarily aminosalicilate therapy. Initial studies by Moody *et al.*¹⁸ and Eaden *et al.*¹⁹ suggested a reduction in risk of colorectal cancer among regular users of sulfasalazine and other aminosalicilates. Similar findings were reported from larger population-based analysis from the United Kingdom (UK) General Practice database⁴¹. In contrast, other studies from the United States, UK, and Canada failed to show an inverse association between aminosalicilate use and colon cancer, and indeed even a weak effect suggesting increased

risk among users for 5 years or longer^{20, 21, 42–44}. Under the same hypothesis that more effective treatment of IBD may reduce risk of colorectal cancer, other studies suggested a weak inverse association between azathioprine⁴³ or anti-TNF biologic therapy⁴⁵ and colon cancer though not all have yielded statistically significant effects⁵. Among agents unrelated to treatment of IBD, folic acid supplementation was not associated with a reduced risk of CRC⁴⁶ while ursodeoxycholic acid had variable benefit with a trend towards increased risk at high doses^{47, 48}. Our findings add to the literature in this field suggesting the need for further studies examining a potential inverse association between statin use and colorectal neoplasia, particularly supported by strong experimental evidence in support of this hypothesis. Prospective controlled trials of statins for prevention of colorectal cancer are likely to be prohibitively large and impractical. Consequently, consistent findings from other epidemiologic cohorts may serve as sufficient evidence base to consider use of statin therapy for chemoprevention in patients with IBD. Additionally, there is a need to study the effect of statins on IBD patients at high risk such as prior dysplasia or those with PSC.

We readily acknowledge the limitations of our study. The population for the study consisted primarily of patients receiving care at two tertiary referral hospitals, and consequently may have greater severity of disease than a population-based cohort. Additionally, some but not all prior meta-analyses have suggested that a stronger chemopreventive effect appears apparent in referral center studies without a similar effect in population-based cohorts^{49–51}. A reason that has been proposed for such a difference is bias introduced by treatment practices of gastroenterologists recruiting into referral center studies, particularly those utilizing a case-control analysis. However, as our population was under the care of a wide spectrum of gastroenterologist, this is less likely to be an explanation for these findings. As in any observational study, our findings do not confirm causality in the effect of statins and our findings may be subject to measured and unmeasured confounders. We did not have information on extent or duration of disease as these are not reliably obtained from the administrative data. However, we adjusted for a number of relevant confounders including burden of inflammation and colonoscopic screening, supporting the robustness of our results. Additionally, the confirmation of previously identified risk factors including smoking, PSC, elevated markers of inflammation, and male gender support the validity of our findings. We were not able to examine the individual type of statin or examine effect of duration of therapy or past use. For patients receiving their primary care outside of our health system, there is potential for misclassification as non-users, though one would expect such misclassification to bias towards the null. There is also the potential for missing cancer outcomes in patients who receive care outside our health system.

In conclusion, using a large, well characterized cohort of patients with IBD, we demonstrate an inverse association between statin use and risk of colorectal cancer. There is need for mechanistic studies on the role of statins in colitis-associated cancer to supplement the existing data on sporadic colon cancer. Further confirmation from other cohorts may provide support for the use of statins as a chemopreventive in patients with IBD.

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Table 1

Characteristics of statin users and non-users in patients with inflammatory bowel diseases

Characteristic	Statin users (n = 1,376)	Statin non-users (n = 9,625)	p-value
Current age (in years) [Median (IQR)]	67 (58 – 76)	42 (29 – 56)	< 0.001
Age at first IBD contact (in years) [Median (IQR)]	59 (50 – 68)	36 (24 – 50)	< 0.001
Duration since first IBD contact (in years) [Median (IQR)]	7 (3 – 11)	5 (2 – 9)	< 0.001
Female (%)	45	54	< 0.001
White race (%)	89	85	< 0.001
Type of IBD – ulcerative colitis (%)	62	49	< 0.001
Charlson score [Mean(SD)]	5.8 (3.7)	2.1 (2.7)	< 0.001
Co-existing PSC (%)	2	2	0.68
Medical therapies			
Immunomodulator (%)	20	25	< 0.001
Anti-TNF biologics (%)	6	13	< 0.001
Colonoscopy within 3 years (%)	40	35	< 0.001
C-Reactive protein [Median (IQR)] (in mg/L)	5 (2 – 16)	4.4 (2 – 14.4)	0.11
Ever smoker (%)	86	55	< 0.001

Table 2

Results of multivariable logistic regression analysis of predictors of risk of colorectal cancer in inflammatory bowel diseases

Characteristics	Odds ratio	95% confidence interval	p-value
Model 1[¶]			
Statin use	0.42	0.28 – 0.62	< 0.001
Colonoscopy within 3 years	0.52	0.37 – 0.73	< 0.001
Female gender	0.62	0.48 – 0.78	< 0.001
Non-white race	0.69	0.47 – 0.99	0.048
Duration of follow-up (for 1 year)	0.83	0.80 – 0.86	< 0.001
Ulcerative colitis	0.96	0.76 – 1.21	0.72
Anti-TNF biologic use	1.01	0.62 – 1.66	0.96
Immunomodulator use	1.15	0.83 – 1.59	0.41
Age (for 1 year)	1.04	1.03 – 1.05	< 0.001
Elevated inflammatory markers	1.82	1.31 – 2.53	< 0.001
Ever smoker	1.85	1.42 – 2.41	< 0.001
Primary sclerosing cholangitis	3.37	1.93 – 5.88	< 0.001
Sensitivity Analysis			
Statin use			
Model 2 [†]	0.30	0.19 – 0.45	< 0.001
Model 3 [‡]	0.36	0.24 – 0.55	< 0.001
Model 4 [¶]	0.36	0.24 – 0.54	< 0.001
Model 5 [*]	0.48	0.32 – 0.73	< 0.001
Model 6 ^{††}	0.31	0.13 – 0.35	< 0.001
Model 7 ⁺⁺	0.36	0.24 – 0.54	< 0.001

[¶] Mutually adjusted for all the covariates listed

[†] Adjusted for covariates listed in model 1 and propensity score

[‡] Adjusted for model 1 and density of facts (healthcare utilization)

[¶] Adjusted for covariates listed in model 1 and latest date of follow-up in our system

^{*} Adjusted for covariates listed in model 1 and requiring at least 2 distinct prescriptions for statins

^{††} Adjusted for covariates in model 1 and requiring at least a 2 year interval between statin use and colorectal cancer diagnosis or end-of follow-up

⁺⁺ Adjusted for calendar time (year of latest follow-up)

Table 3

Characteristics of colorectal cancer in statin users and non-users

Characteristic	Statin users (n = 30)	Statin non-users (n = 287)	p-value
Age at cancer diagnosis [Median(IQR)] (in years)	67 (63 – 73)	55 (45 – 65)	< 0.001
Age at first IBD contact [Median(IQR)] (in years)	64 (56 – 68)	53 (41 – 64)	< 0.001
Mean duration since first IBD contact (in years)	6	3	< 0.001
Female (%)	33	42	0.35
White (%)	93	89	0.48
Ulcerative colitis (%)	80	46	< 0.001
Co-existing PSC (%)	7	5	0.67
Medical therapies			
Immunomodulator (%)	23	16	0.31
Anti-TNF biologics (%)	0	7	0.14
C-Reactive protein [Median(IQR)] (in mg/L)	5.4 (0.5 – 11.8)	7.1 (3.7 – 29.4)	< 0.001
Ever smoker (%)	93	71	0.008
Died (%)	30	27	0.74

Table 4

Results of stratified analysis between statin use and risk of colorectal cancer in inflammatory bowel diseases

	Adjusted Odds ratio	95% Confidence interval
By type of inflammatory bowel disease		
Ulcerative colitis	0.57	0.35 – 0.93
Crohn's disease	0.15	0.06 – 0.35
By gender		
Female	0.36	0.18 – 0.75
Male	0.35	0.21 – 0.59
Smoking status		
Never smoker	0.20	0.05 – 0.87
Ever smoker	0.44	0.29 – 0.67

P (interaction) > 0.05 for all comparisons