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

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Abstract

Background and Aims—Statins and non-steroidal anti-inflammatory drugs (NSAIDs) are associated with reduced risk of CRC in some studies. Our objective was to quantify the relative risk of IBD as 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% CI, 1.12-3.26). Long-term statin use was associated with a reduced risk of both IBD-associated CRC (OR= 0.07, 95% CI, 0.01-0.78) and non-IBD CRC (OR = 0.49, 95% CI 0.39–0.62). Stratified analysis suggests that statins maybe more protective among those with IBD (ratio of OR = 0.14, 95% CI, 0.01–1.31, p=0.51), although not statistically significant. NSAID use in patients with a history of IBD was suggestive of

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reduced risk of CRC, but did not reach statistical significance (odds ratio, 0.47, 95% CI, 0.12-1.86).

Conclusions—The risk of CRC is elevated 1.9-fold in patients with IBD. Long term statin use is associated with reduced risk of CRC in patients with IBD.

Keywords

Inflammatory Bowel Disease (IBD); Colorectal cancer; Statins; Chemoprevention

INTRODUCTION

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 studies (2-6) 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 be due to the smaller study populations at risk, making it difficult to study several variables simultaneously and to adjust for potential confounders.

The aims of the present study were to determine the prevalence of IBD in a population based case control study of colorectal cancer (CRC) in Israel, quantify the relative risk of IBD as risk factor for CRC and evaluate the influence of aspirin or NSAID and statin use on the relative risk of cancer.

METHODS

Participants

The Molecular Epidemiology of Colorectal Cancer study is a population-based case-control study of incident colorectal cancer in northern Israel. Patients were eligible for participation if they had received a diagnosis of colorectal cancer between May 31, 1998 and 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 four 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 versus 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 pathological 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 dataset (MECC) originally collected for another purpose.

Exposure data

Participants were asked to recall each medication they had used for at least five years, and statin use was determined on the basis of this list. Statin use was defined as positive if 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, three-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's disease, ulcerative colitis, 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), and all reported P values are two-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. Since 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 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 as 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 significantly increased prevalence of IBD (2.0% versus 1.1%). Thus, in patients with a self-reported history of IBD, the unmatched odds ratio of colorectal cancer was 1.91 (95% 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's disease (Table 2). Remaining analyses were restricted to the broader definition of IBD and not subtypes (Crohn's or UC). 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.

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 location of tumor and IBD (Table 4). 17.2% of IBD patients had tumors showing high microsatellite instability (MSI-H) as compared to 10.8% of sporadic tumors, (OR = 1.73, 95% CI, 0.65-4.59). Colorectal cancer was somewhat more likely to be microsatellite instable in patients with self-reported IBD, although this difference was not significant (P=0.267) (Table 4). IBD patients also had a similar distribution of tumors by stage compared to 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 (odds ratio, 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). Importantly, 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 maybe more protective among those with IBD (ratio of OR = 0.14, 95% CI, 0.01–1.31, p=0.51), although not statistically significant. When statin use was subdivided by type, simvastatin was associated with a profoundly reduced risk of IBD associated CRC (odds ratio, 0.05, 95% CI, 0.004-0.54, P=0.014) compared to non-statin users. Pravastatin use was similarly associated with a reduced risk of CRC versus non-statin users, but was not statistically significant (odds ratio, 0.11, 95% CI, 0.004-3.0, P=0.164). The use of NSAID and/or aspirin in patients with a history of IBD was also associated with reduced risk of CRC, however was not statistically significant (odds ratio, 0.47, 95% CI, 0.12-1.86, P=0.283) (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 to 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 1955-1989 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 CD patients for the years 1965-1983 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). While a population based study from Manitoba, Canada (11) found an incidence rate ratio for UC of 2.75 (95% CI: 1.91-3.97), CD of 2.64 (1.69-4.12) and for IBD of 2.71 (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 is 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 Israel (31) 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-aminoslicylates 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 two populations may be due to maintenance treatment with mesalamine, high proctocolectomy rates or other factors.

Colonic inflammation is felt 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 tumorgenesis 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. Karlen (10) had shown that of UC patients with CRC 94% had total colitis and with rectal cancer 74% had total colitis. Jess (28) 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 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 to 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 Europe (32-34) and New Zealand (35) 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 heterozygositiy, 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) as compared to 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 study (45) reports a prevalence of MSHI-H in IBD neoplasia between 15-17% 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, though 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 five years was associated with a profoundly reduced risk of IBD-associated CRC (odds ratio, 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 five 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 1-4 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 non-significant protective effect of long term statin use among patients with colorectal cancer (IRR: 0.89; 95% CI: 0.70-1.13) (48). Similarly, two nested case-control studies from Quebec, Canada (23) and the Netherlands (24) showed a non-significant 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 Womens Health Study and a secondary analysis of the Physicians' Health Study did not observe any association with colorectal cancer after 5-10 years of treatment (53,54). IBD patients are often counseled to avoid NSAIDs since 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, since 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 could therefore not assess the data for dose response relationship, however statin type was assessed. Limitations associated with all studies of this design are intrinsic differences between the cases and controls (such as healthy behaviour) 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 suggest 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.

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Table 1

Demographic & Epidemiological Characteristics of the Study Population (1921 Matched Pairs)

Characteristic		Case	Control	P Value
All subjects: matched pairs – no.		1921	1921	
Sex – no. (%)				1
	Male	987(51.4)	987(51.4)	
	Female	934(48.6)	934(48.6)	
Age – year		69.8±11.8	70.4±11.7	0.10 (0.77)
Ethnic group – no. (%)				0.429
	Jews	1680 (87.5)	1697 (88.3)	
	Non Jews	241 (12.6)	224 (11.7)	
Statin use ≥ 5yrs – no. (%)				<0.001
	No	1805(94.0)	1692(88.1)	
	Yes	116(6.0)	229(11.9)	
Statin Type (any use) – no. (%)				<0.001
	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				<0.001
	No	1339(69.7)	1137(59.2)	
	Yes	582(30.3)	783(40.7)	
First Degree Relative with CRC - no. (%)				<0.001
	No	1701(88.5)	1775(92.4)	
	Yes	220(11.5)	146(7.6)	
Aspirin or NSAID use at least once per week for greater than 3 years- no. (%)				<0.001
	No	1606(83.6)	1442(75.1)	
	Yes	315(16.4)	479(24.9)	
Vegetable Consumption - no. (%)				<0.001
	Low	862(44.9)	649(33.8)	
	Medium	543(28.3)	671(34.9)	
-	High	516(26.8)	601(31.3)	-

Table 2

Crude Analysis between Crohn's Disease or Ulcerative Colitis and CRC

	Case	Control	OR
IBD	39 (2.0)	21 (1.1)	**1.91 (1.12-3.26)**
No IBD	1882 (98.0)	1900 (98.9)	**p=0.018**
Crohn's	2 (0.1)	2 (0.1)	1.0 (0.14-7.11)
No Crohn's	1919 (99.9)	1919 (99.9)	p=1.00
UC	35 (1.8)	16 (0.8)	**2.21 (1.22-4.01)**
No UC	1886 (98.2)	1905 (99.2)	**p=0.0074**

UC and CD columns do not add up to 39 IBD cases since 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

Table 3a	Unadjusted		Adjusted*	
	Odds Ratio(CI)	p-value	Odds Ratio(CI)	p-value
IBD	**1.91(1.12,3.26)**	**0.018**	**1.88(1.08,3.26)**	**0.025**
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**

Table 3b	Unadjusted		Adjusted*	
	Odds Ratio (CI)	p-value	Odds Ratio(CI)	p-value
IBD	**2.25(1.25, 4.06)**	**0.007**	**2.19(1.2, 3.97)**	**0.010**
Statin	**0.49(0.39, 0.62)**	**<.001**	**0.56(0.44, 0.72)**	**<.001**
IBD * statin	0.17(0.02, 1.62)	0.124	0.19(0.02, 1.86)	0.154
IBD	**1.93(1.06, 3.51)**	**0.032**	**1.90(1.04, 3.50)**	**0.038**
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)	0.743	0.93(0.22, 3.89)	0.920

*Analyses adjusted for age, ethnicity, vegetable consumption, history of colorectal cancer in first-degree relative, sports participation and smoking status. CI denotes 95% confidence interval.

Table 4

Tumor Location and Self-reported IBD among cases

CRC Site	IBD Case	Non-IBD Case	OR (95% CI)	P
Rectum	6 (20.0)	444 (27.0)	1.0	-
Left	15(50.0)	571 (34.7)	1.94(0.75-5.05)	0.165
Right	9 (30.0)	630 (38.3)	1.06(0.37-2.99)	0.917

Microsatellite Instability and Self-reported IBD among cases

	IBD Case	Non-IBD Case	OR (95% CI)	P
MSI High	5 (17.2)	158(10.8)	1.73 (0.65-4.59)	0.267
MSI Stable & Low	24 (82.8)	1310 (89.2)		

Tumor Stage and Self-reported IBD among cases

	IBD Case	Non-IBD Case	OR (95% CI)	P
Stage	N=29	N=1643		
I	2 (6.9)	307(18.7)	1.0	-
II	15(51.7)	660(40.2)	3.48(0.79-15.4)	0.111
III	8(27.6)	450(27.4)	2.73(0.58-12.94)	0.331
IV	4(13.8)	226(13.8)	2.72(0.49-14.96)	0.410

Table 5

Analysis of Statin and NSAID or Aspirin use and Odds of Colorectal Cancer Stratified by IBD

Variable	Case	Control	Unadjusted OR	Adjusted OR*#
No IBD				
Statin use:			**0.49 (0.39, 0.62)**	**0.56 (0.44, 0.72)**
Yes	115 (6.1)	224 (11.8)	**P<0.001**	**P<0.001**
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<0.001**	**P<0.001**
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=0.029**	P=0.080
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=0.283	P=0.461
No	34 (87.2)	16 (76.2)		

*Unmatched analysis.

#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	Case[+]	Control[+]	Unadjusted OR	Adjusted OR[*#]
No IBD			**0.35 (0.30-0.40)**	**0.36 (0.30-0.42)**
Simvastatin use:				
Yes	308	676	**P<0.001**	**P<0.001**
No Statin	1528	1158		
Pravastatin use:			**0.37(0.29-0.47)**	**0.41(0.31-0.52)**
Yes	109	226	**P<0.001**	**P<0.001**
No Statin	1528	1158		
IBD				
Simvastatin use:			**0.11 (0.024-0.46)**	**0.05 (0.004-0.54)**
Yes	3	9	**P=0.003**	**P=0.014**
No Statin	35	11		
Pravastatin use:			0.31 (0.039-2.5)	0.11 (0.004-3.0)
Yes	2	2	P=0.274	P=0.164
No Statin	35	11		

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

[*]Unmatched analysis.

[#]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.