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Statins and the Risk of Colorectal Carcinoma: A Nested Case – Control Study in Veterans With Diabetes

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Abstract

OBJECTIVES—Experimental data indicate a possible preventive effect for statins in colorectal cancer (CRC). However, the available epidemiological data are conflicting.

METHODS—We conducted a nested case –control study of veterans with diabetes in national databases of the Department of Veterans Affairs (VA) and Medicare-linked files. Cases were defined as incident CRC during January 2001 –December 2002, sampled on incidence density. VA pharmacy benefits management (PBM) files were used to identify filled prescriptions for statins. Multivariable conditional logistic regression models were used to estimate odds ratios (ORs) after adjusting for potential confounding variables. Stratified analyses were conducted for potential effect modifiers.

RESULTS—A total of 6,080 cases and 24,320 controls were examined. The mean age was 74 years, and the majority of patients were Caucasian (88 %) and male (99 %). Filled prescriptions of statins were recorded less frequently in cases (49 %) than in controls (52 %; OR: 0.88; 95 % confidence interval (95 % CI): 0.83 –0.93). This inverse association remained significant after adjusting for inflammatory bowel disease, diabetes severity, cholecystectomy, liver disease, filled prescriptions for sulfonylurea, aspirin or NSAID use, or colorectal evaluation. Simvastatin comprised the majority (87 %) of statin-filled prescriptions, and the association with risk of CRC

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CONFLICT OF INTEREST

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with simvastatin was very similar to that of any statin. No significant associations were observed between the risk of CRC and nonstatin cholesterol (OR: 1.02; 95 % CI 0.88 –1.18) or triglyceride-lowering medications (OR: 0.96; 95 % CI: 0.87 –1.05). The significant inverse association was limited to Caucasians, patients without history of polyps, patients aged 65 years and older, and patients with colon cancer (excluding rectum).

CONCLUSIONS—The use of statins was associated with a small reduction in the risk of colon cancer in patients with diabetes. However, the causal link is not clear.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer and the second most common cause of death in the United States. As the development of CRC is a multistep process, pharmacologic chemoprevention has potential implications for primary and secondary prevention (1). During the past decade, statins have consistently been the most widely prescribed drug category in the United States (2), and experimental studies indicate a potential cancer prevention effect for statins. This positions statins to be a formidable force for CRC chemoprevention if a benefit is proven.

Statins inhibit the synthesis of mevalonic acid, an essential precursor of cholesterol synthesis involved in the synthesis of Ras and Rho proteins, which are critical proteins for tumorogenesis (3) that are present in approximately 50 % of CRC (4). Statins may also play a role in chemoprevention through inhibition of the increased expression of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase that occurs in human colon adenocarcinoma cells (4,5) or in inducing apopotosis and inhibiting the metastatic potential of colon cancer cell lines (6,7) .

In humans, secondary analyses from large randomized controlled studies indicate a possible statin-related reduction in overall cancer mortality, but there is insufficient data from these trials to allow specific examination of individual cancer types (8,9). The available epidemiological data for CRC are conflicting with some studies reporting no significant association (10–14), and a few other studies reporting moderate reductions in the risk of CRC in statin users (15–17). Only five of these studies have specifically examined CRC as a primary outcome (10,12,15,16,18). Some of these studies were limited by short exposure time, recall bias (10,15), and insufficient accounting for confounders or effect modifiers because of inadequate power (16). In addition, the association of statins with high-risk populations (i.e., African Americans, patients with polyps) has not been well characterized in these studies.

Given the widespread use of statins (19) and the high prevalence of CRC, their potential association is important to examine further. Therefore, we sought to examine the risk of CRC associated with the use of statins in a pharmaco epidemiological study using a matched case - control design nested within a well-characterized cohort of patients with diabetes. Furthermore, we examined the potential determinants of association including type, dose, and duration of statin use, and its interaction with other known potential determinants of CRC.

METHODS

This study was approved by the Institutional Review Boards of Baylor College of Medicine and the Michael E. DeBakey VA Medical Center in Houston, TX.

Data source

We conducted a nested case - control study within a large cohort of patients with diabetes mellitus (DM), identified between calendar year (CY) 1997 and 2002 in the national databases of the Department of Veterans Affairs (VA). These databases included the patient treatment file (PTF), outpatient clinic (OPC) file, pharmacy benefits management (PBM) file, and beneficiary identification records locator system (BIRLS) death file. The PTF contains demographic data, date of admission, and discharge, and up to 10 discharge diagnoses (by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) codes) for all hospitalizations in over 150 VA hospitals in the United States (20). The OPC file contains similar data for all outpatient encounters. In the OPC and PTF, we identified patients with ICD-9 codes for DM (250.0 –250.9, 357.2, 362.0, and 366.41). We employed an additional measure to define the DM cohort by searching the VA PBM files (CY 1999 –2002) for prescriptions for oral diabetes medications (HS502), insulin (HS501), or blood glucose monitoring supplies. Each patient was assigned an entry date into the DM cohort based on their earliest qualifying inpatient or outpatient encounter. The VA DM cohort was linked with Medicare claims files (CY 1999 –2002) to maximize the probability of capturing health care encounters among dual VA - Medicare users (21) .

Study population

We excluded from the sampling frame patients who had a diagnosis of cancers of the pancreas (157.0 –157.9), stomach (151.0 –151.9), lung (162.0 –162.9), esophagus (150.0 –150.9), liver (155.0, 155.2), and breast (174.0 –175.0, 175.9) before index CRC diagnosis date. To maximize the completeness of exposure and risk factor information, cases were excluded if they had any Health Maintenance Organization (HMO) enrollment or had enrollment in Medicare for less than 75 % of the time they were eligible. Therefore, all patients were dually enrolled in both the VA and Medicare healthcare systems.

Case subjects were selected from patients with incident CRC defined by ICD-9 codes, which included colon or rectal cancer (153.0 –153.9, 154.0 –154.1, 154.8, 230.3, 230.4) recorded in VA or Medicare files at least 6 months following the entry date into the DM cohort. We limited eligible cases to those diagnosed between 1 January 2001 and 12 December 2002 to have at least 2 years of exposure before CRC diagnosis with complete VA PBM and Medicare data.

Control subjects were eligible patients who remained at risk at the date of the CRC diagnosis for the case. Each case was matched with up to four controls on sex and year of birth (± 1 year), and sampled on incidence density, where matching was performed for both enrollment date in the diabetic cohort (± 30 days) as well as CRC diagnosis date. Controls were selected randomly with replacement, such as one subject could be a control for more than one case, and any one control could become a case later by developing CRC.

Exposure

Statin exposure was obtained from filled outpatient prescriptions between 1 January 1999 and the date of CRC diagnosis (or corresponding date for controls). We collected the dates of filled or refilled prescriptions and the daily dose per prescription. In the case of overlapping prescriptions, exposure days were calculated as the sum of the day's supply of prescriptions if the overlap was ≤ 30 days. If the overlap was > 30 days, we only considered the more recent prescription, and assumed that the new prescription had replaced the previous one. We collected similar prescription information on nonstatin lipid-lowering medications (cholestyramine, colesevelam, colestipol, ezetimibe, and niacin), and triglyceride-lowering medications (clofibrate, fenofibrate, and gemfibrozil).

Statistical analyses

Cases and controls were compared with regard to differences in covariate distribution using χ^2 -tests for categorical variables and *t* -tests for continuous variables. Odds ratios (ORs) as estimates of the relative risk for CRC, defined as combined colon or rectal cancer, associated with statin use, and 95 % confidence intervals (CIs) were estimated using conditional logistic regression. In addition to matching variables, adjustment was carried out for potential confounding factors, including inflammatory bowel disease (555 and 556), severity of diabetes (retinopathy (250.5 and 362.0), nephropathy (250.4), neuropathy (250.6, 357.2)), liver disease (570.X–573.X, 794.8), and cholecystectomy (51.21 –51.24, and CPT codes 47600, 47605, 47610, 47612, 47620, 49310, and 49311). These variables were defined based on the presence of one inpatient or two outpatient ICD-9 codes before CRC index. We ascertained colorectal evaluation by imaging, endoscopy, or fecal occult blood testing, excluding those recorded within 6 months of CRC index date. Potential effect modifiers that were examined in stratified analyses included the presence of previous colorectal polyps, cancer site (colon vs. rectal), race, and age. We also ascertained filled prescriptions before index date for diabetes medications (insulin, sulfonylurea, thioglitazone, or other diabetes medication), aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). The distribution of at least one filled prescription of exposures listed above was compared between cases and controls. In a separate analysis, we excluded statin prescriptions recorded in the year preceding the index date, to reduce the possibility of confounding by indication. To examine duration - response associations, we evaluated the effect of cumulative duration of filled prescriptions categorized as 0 –180, 181 –360, 361 –540, 541 –720, and >720 days.

The cumulative dose for simvastatin was calculated as the total duration for filled prescriptions multiplied by dosage and summed across all prescriptions. The average daily dose was calculated as the cumulative dose divided by the total number of days used. We compared the distribution of dose quartiles as well as a variable indicating ≥ 1.5 × mean cumulative dose (vs. < 1.5 × mean).

Finally, to examine potential effect modifiers, we conducted analyses stratified by the presence of previous colorectal polyps (ICD-9 codes: 211.3, 211.4, 569.0, and V12.72), cancer site as delineated by a colon cancer alone that excluded rectal cancer (ICD-9 codes: 153.0 –153.9, and 230.3), rectal cancer (ICD-9 codes: 154.0, 154.1, 154.8, and 230.4), race (African American), and age (65 years and older).

RESULTS

The cohort consisted of 763,807 veterans diagnosed with DM during CY 1997 –2002. There were 6,080 CRC cases and 24,320 controls who fulfiled the inclusion and exclusion criteria. Given the incidence density sampling, the case - control ratio was close, but not exactly 1 – 4; 672 unique controls were each matched to two different cases, 13 controls were each matched to three different cases, and 97 controls became cases at a later time. Thus, the final analysis was conducted on 6,080 cases and 24,320 controls.

Table 1 shows the demographic features of cases and controls. The mean age of patients was 74 years and the majority were Caucasian (84 %) and male (99 %) with no difference between cases and controls. The mean duration between date of entry into DM cohort and date of CRC index was 842 days.

Filled prescriptions for any statin were documented in 51 % of the study population, and simvastatin comprised the majority (87 %) of statin use.

The mean duration of statin use was statistically shorter in cases than controls before CRC index (274 and 296 days, respectively ($P < 0.0001$)). Table 2 shows the comparisons between controls and cases with regard to potential confounders and effect modifiers. As expected, cases were more likely than controls to have a history of colorectal polyps and inflammatory bowel disease. Controls had significantly more colorectal evaluation by imaging, endoscopy, or fecal occult blood testing. Cases were also more likely than controls to have markers of serious or prolonged diabetes, including diabetic nephropathy or sulfonylurea-filled prescriptions. Finally, cases were significantly less likely to have filled aspirin/NSAID prescriptions.

The presence of a filled prescription for any statin was inversely associated with CRC risk in the unadjusted regression model (OR: 0.88; 95 % CI: 0.83 –0.93; Table 3). Similar risk reductions were observed when we excluded filled statin prescriptions in the 1 year before the CRC index date. The inverse association was attenuated but remained significant (OR: 0.91; 95 % CI: 0.86 –0.96) after adjusting for inflammatory bowel disease, diabetic nephropathy, colorectal evaluation before CRC diagnosis, cholecystectomy, liver disease, and filled prescriptions of sulfonylurea, aspirin, or NSAIDs. Adjustment for these variables was performed because they were significantly associated with CRC in unadjusted analyses (Table 2). Regular use of statin as indicated by filled prescription greater than 80 % of the time in the 3 years preceding the index date was associated with significant CRC risk reduction in unadjusted (OR: 0.79; 95 % CI: 0.72 –0.86) and adjusted models (OR: 0.83; 95 % CI: 0.76 –0.91; data not shown).

The association between statins and CRC was modified by the presence of previous colorectal polyps as defined by ICD-9 codes. There was no consistent decrease in CRC risk in the subgroup with previous polyps (Table 3), whereas a 14 % risk reduction was noted with any statin prescription in the subgroup without known polyps. This reduced risk persisted in models adjusted for inflammatory bowel disease, diabetic nephropathy colorectal evaluation, cholecystectomy, filled prescriptions of sulfonylurea, NSAIDs, and liver disease. Race was also a potential effect modifier; there was no significant association

between statins and CRC for any duration or dose duration of statins in African Americans (data not shown).

We examined the effect of cumulative duration of statin prescriptions. We found no consistent duration - response relationship, with both short (< 6 months) and long duration (>24 months) significantly associated with decreased CRC risk, and the other periods not significantly associated with CRC risk (Table 4). There was also no duration - response relationship (data not shown) in an analysis that excluded filled statin prescriptions in the 1 year before CRC diagnosis. Similar findings were noted for simvastatin (data not shown).

To examine the possibility of a medication class effect, we analyzed the data for simvastatin and observed similar results in both direction and magnitude as those for any statin (Table 5). Simvastatin was associated with a small but significant reduction in CRC risk in unadjusted and adjusted models but with no duration - response relationship. On the other hand, nonstatin lipid- and triglyceride-lowering medications (Table 6) showed no association with CRC in unadjusted and adjusted conditional logistic regression models as well as in analysis stratified by the presence of previous polyps.

In an analysis limited to patients aged 65 years and older, similar risk reductions to the whole population were noted for filled prescriptions for any statin (adjusted OR: 0.90; 95 % CI 0.85 –0.96) or simvastatin (adjusted OR: 0.90; 95 % CI: 0.85 −0.97). No consistent duration - response relationship was seen (data not shown).

In a subgroup analysis based on filled insulin prescription, there was a decreased risk of CRC with statin use in patients with filled insulin prescriptions (adjusted OR: 0.79; 95 % CI: 0.66 –0.94), as well as in those with no insulin use (adjusted OR: 0.93; 95 % CI: 0.86 –0.99) as compared with no statin use (full analyses not shown).

In another analysis restricted to patients with rectal cancer alone (1,417 cases and 5,668 controls), no significant risk reduction was noted with any statin (Table 7) or simvastatin in the unadjusted or adjusted models (data not shown). However, the power of the analysis was limited due to small numbers.

DISCUSSION

This study indicates that statin use may be associated with a small but significant reduction in the risk of CRC in patients with diabetes. This risk reduction was seen with statins as a group, as well as simvastatin-only filled prescriptions. However, it was not seen with triglyceride- or nonstatin cholesterol-lowering medications. The risk reduction observed may be more important for colon cancer, as there was no significant risk reduction with statin use when analyzing rectal cancer separately.

Furthermore, the possible statin effect was limited to subgroups of patients with no previous colorectal polyps, aged 65 years and older, and Caucasians. However, there was no consistent significant dose or duration - response relationship. Of note, the significant risk reduction observed among the relatively few patients exposed to statin use >24 months suggests that longer duration of exposure may be necessary for the assessment of a

significant reduction of CRC with statin use. This is in agreement with a previous case - control study that found a reduced risk of CRC associated with statins, specifically simvastatin, especially with use greater than 5 years (OR: 0.53; 95 % CI: 0.38 –0.74) (15). However, another population-based study from Germany indicated a 64 % CRC risk reduction occuring within 1 –4 years of statin use, with no further risk reduction beyond 5 years (16). Neither study characterized dose or duration of statins in detail, and both studies defined statin use by recall. Our results, however, conflict with a recent case - control study (1,809 cases and 1,809 controls) that found no significant decreased risk of CRC associated with regular statin use (OR: 0.92; 95 % CI: 0.78 –1.1) (10). In that study, atorvastatin was the most commonly used statin. The disparate results between simvastatin and atorvastatin may arise because individual statins have shown differences in specificities for HMG-CoA reductase, metabolism, and volumes of distribution (22,21). In another population-based nested case - control study (5,686 cases and 24,982 controls) from the United Kingdom, there was no significant risk reduction in CRC with any statin use; however, similar to our study, a 17 % risk reduction ($P = 0.01$) was shown with simvastatin use (18). It is unclear whether the type of statin plays a role in the potential effect of statins in CRC risk, and this should be explored further.

There were no significant risk reductions in groups with high risk for CRC, such as African Americans and patients with previous coloerectal polyps. Although relatively limited power might have played a role in these subgroups, it is possible that the modest preventive action of statins is unlikely to be prominent in the presence of other strong risk factors. Multiple studies have shown increased incidence and mortality rates from CRC in the African American population (23,24) and in patients with previous colorectal polyps (25) with high prevalence for dyslipidemia in both of these populations (26,27). Our subgroup analysis of patients with known previous colorectal polyps contained 2,078 cases and 4,252 controls. An earlier study of 2,638 patients found no benefit for preventing the recurrence of colorectal adenomas, multiple adenomas, or advanced adenomas with over 4 years of statin use (28). It is possible that polypectomy lowers the risk to a large extent, obscuring any additional advantage of statins. Our study defined previous colorectal polyps by ICD-9 codes and lacked pathological confirmation. It is possible that polyps that do not pose a higher risk for CRC (e.g., isolated hyperplastic polyps) were included. Irrespective of the nature of the polyp, the presence of these codes was more common in cases than controls (34 vs. 17 %). Finally, although the observed lack of association between statins and rectal cancer could be a true effect, the power of the study was relatively limited, especially for examining long duration of statin use.

The findings need to be interpreted within other limitations of the study. Several differences between cases and controls were modest although, given the large sample size statistically significant. However, we had a focused hypothesis regarding the possible effect of statins, and thus we did not adjust for multiple testing. In addition, the study was limited to mostly male veterans with diabetes, and may not be generalizable to women, nonveterans, or patients without diabetes. The choice for the diabetes cohort for this study was made both for convenience, given the availability of this well-characterized cohort, as well as for the potential of better detection of small effects. Diabetes has been suggested as a modest risk

factor for colorectal polyps as well as CRC (29,30). Therefore, it is possible that it was easier to show benefit in this study owing to the generally elevated risk in patients with diabetes. Earlier studies evaluating the association between statins and cancer in patients with diabetes included a Chinese population-based cohort study that reported that patients with type 2 diabetes, who were statin users, were less likely to develop all-site cancer during a median follow-up of 4.9 years (5.5 vs. 2.6 %; $P < 0.001$) (25). Other studies reported a possible protective effect of statins in patients with diabetes on lung (adjusted OR: 0.43; 95 % CI: 0.38 –0.49) (31) and pancreatic cancer (adjusted OR: 3.03; 95 % CI: 2.46 –3.71) (32). However, no earlier studies have specifically evaluated the effect of statins on CRC in a diabetic population. In addition, we were able to assess the effects of statins in diabetic subgroups (insulin vs. noninsulin users), and found a consistent risk reduction of CRC with statin use irrespective of the diabetes treatment subgroup.

Given the nature of the administrative data, we were not able to capture all potential confounding variables for CRC risk, including alcohol or tobacco use, family history of colon cancer, dietary or exercise history, and socioeconomic status. However, the study dealt with a mostly low-income group (veterans who use VA services), hence we do not expect major variations in socioeconomic status, as reflected by income and education.

Moreover, although it is reasonable to assume that fecal occult blood testing (FOBT) was performed for CRC screening, we were not able to determine the purpose of the imaging or colonoscopy as to screening, surveillance, or diagnosis.

Furthermore, incident CRC diagnosis was based on first time appearance of ICD-9 codes for CRC during 1999 –2002. The use of ICD-9 codes can be erroneous, but in this study, we performed a chart review in a sample of cases and found a PPV of 83 % for CRC ICD-9 codes. Also, an earlier Spanish study validated ICD-9 codes for CRC and showed a sensitivity of 80 % and a positive predictive value of 75 % of hospital administrative data when compared with a cancer registry as a gold standard (33). Exposure was based on filled statin prescriptions and may not accurately capture intake. The potential for missed statin prescriptions received in non-VA facilities may underestimate our findings; however, these errors are likely to occur at random. In addition, we have previously shown that among VA and Medicare dual users, most veterans use VA for their pharmacy services for the majority of their medications (22). Finally, like other observational studies, residual confounding cannot be completely excluded. For example, statin use might be associated with weight reduction or better diabetic control, and these other measures might be related to CRC risk.

There are several strengths to our study, including large samples with a relatively long duration of potential exposure to statins. We had virtually complete capture of VA pharmacy data through the VA - PBM records, and CRC through the linked VA - Medicare records. We also had the additional advantage of evaluating large numbers of patients, underrepresented in other studies, with a substantial African American and elderly patient population. We performed several sensitivity analyses of exposure within subgroups to examine the robustness of findings. Finally, our results confirmed the earlier findings indicating protective benefit of NSAID use and CRC screening in reducing CRC risks. These features increase the internal validity of our study.

In conclusion, there is a significant reduction in the risk of CRC in patients with diabetes, although the risk reduction is small (~ 10 %) and likely to be limited to colon cancer. However, there is not a clear dose - response or duration - response relationship between filled statin prescriptions and CRC risk.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Patients with diabetes appear to be at increased risk for colorectal cancer.
- ✓ Colorectal cancer is a multistep process with potential for pharmacologic chemoprevention by statins.
- ✓ Earlier studies are conflicted on whether statins are associated with a reduced risk of colon or rectal cancer.

WHAT IS NEW HERE

- ✓ Statins are associated with a reduction in the risk of colorectal cancer in patients with diabetes.
- ✓ The risk reduction was most evident in subgroups: those with no previous colorectal polyps, those aged 65 years and older, and Caucasians.
- ✓ There was no clear dose –or duration –response relationship between statin use and the risk of colorectal cancer.

Table 1

Distribution of demographic characteristics and duration of follow-up in cases with colon or rectal cancer and controls without CRC matched on age and sex, and sampled on incidence density

	Cases ***n*** **= 6,080**	**Controls** ***n*** **= 24,320**
Age (mean)	74	74
Sex (men) %	6,002 (98.7%)	24,008 (98.7%)
Race		
White, non-Hispanic	4,985 (82.0%)	20,453 (84.1%)
Black	864 (14.2%)	2,960 (12.1%)
Asian	23 (0.4%)	108 (0.4%)
Hispanic	151 (2.5%)	532 (2.2%)
Native American	20 (0.3%)	96 (0.4%)
Other	31 (0.5%)	144 (0.6%)
Unknown	6 (0.1%)	27 (0.1%)
Days between entry into diabetes mellitus cohort and colorectal cancer (CRC) index (mean; standard deviation)	842 (355)	842 (355)

Table 2

Comparison between cases with colon or rectal cancer and controls without CRC

	Cases ***n*= 6,080**	**Controls** ***n*= 24,320**
Lipid-lowering medications, filled prescription (%)		
Any statin*	2,987 (49.1%)	12,706 (52.3%)
Simvastatin*	2,271 (37.4%)	9,596 (39.5%)
Nonstatin cholesterol- lowering drugs	228 (3.8%)	896 (3.7%)
Triglyceride-lowering drugs	544 (9.0%)	2,267 (9.3%)
Diabetes medications, filled prescription (%)		
Insulin	1,460 (24.0%)	5,567 (22.9%)
Sulfonylurea*	3,995 (65.7%)	15,371 (63.2%)
Thioglitazone	488 (8.0%)	1,914 (7.9%)
Severity of diabetes, n *(%)*		
Retinopathy	1,363 (22.4%)	5,122 (21.1%)
Nephropathy*	550 (9.1%)	1,877 (7.7%)
Neuropathy	1,320 (21.7%)	5,145 (21.2%)
Potential CRC risk factors, n *(%)*		
History of colonic polyps*	2,078 (34.1%)	4,252 (17.5%)
Colorectal evaluation* [a]	3,977 (65.4%)	16,359 (67.3%)
Inflammatory bowel disease*	112 (1.8%)	238 (0.8%)
NSAID (filled prescription)*	3,864 (63.6%)	16,242 (66.8%)
Cholecystectomy*	133 (2.2%)	399 (1.6%)
Liver disease*	659 (10.8%)	1,831 (7.5%)

* $P < 0.05$.

[a] Imaging, endoscopy, fecal occult blood testing.

Table 3

Odds ratios (and 95% CIs) for filled prescriptions for statins in cases with colon or rectal cancer and controls without CRC

	Unadjusted All	Adjusted [a]		
		All	Patients with polyps	Patient without polyps
Filled prescription duration	(6,080 cases, 24,320 controls)	(6,080 cases, 24,320 controls)	(2,078 cases, 4,252 controls)	(4,002 cases, 20,068 controls)
Any duration	0.88 (0.83,0.93)	0.91 (0.86,0.96)	0.89 (0.75,1.06)	0.86 (0.80,0.93)
Any duration, excluding 1 year before index date	0.89 (0.84,0.94)	0.92 (0.86,0.97)	0.88 (0.74,1.05)	0.89 (0.82,0.96)
At least 6 months	0.89 (0.84,0.94)	0.92 (0.86,0.98)	0.92 (0.77,1.10)	0.86 (0.80,0.93)
At least 6 months (excluding 1 year before index date)	0.87 (0.82,0.93)	0.91 (0.85,0.97)	0.82 (0.68,1.00)	0.89 (0.82,0.97)

Results of conditional logistic regression models.

[a] Adjusted for the following variables: inflammatory bowel disease, diabetic nephropathy, colorectal evaluation, cholecystectomy, sulfonylurea prescription, nonsteroidal anti-inflammatory drug prescription, and liver disease.

Table 4

Odds ratios (and 95% CIs) for filled prescriptions for statins in cases with colon or rectal cancer and controls without CRC

	Unadjusted All	Adjusted [a]		
		All	Patients with polyps	Patients without polyps
Filled prescription duration	(6,080 cases, 24,320 controls)	(6,080 cases, 24,320 controls)	(2,078 cases, 4,252 controls)	(4,002 cases, 20,068 controls)
< 6 months	0.85 (0.76,0.95)	0.86 (0.77,0.95)	0.78 (0.57,1.08)	0.86 (0.75,0.99)
	(459 cases, 2,031 controls)		(144 cases, 328 controls)	(315 cases, 1,703 controls)
6 –12 months	0.97 (0.88,1.07)	0.98 (0.89,1.09)	1.11 (0.83,1.50)	0.90 (0.79,1.03)
	(585 cases, 2,277 controls)		(225 cases, 377 controls)	(360 cases, 1,900 controls)
12 –18 months	0.90 (0.81,1.00)	0.91 (0.82,1.02)	0.93 (0.67,1.27)	0.86 (0.74,0.99)
	(469 cases, 1,957 controls)		(180 cases, 374 controls)	(289 cases, 1,583 controls)
18 –24 months	0.90 (0.81,1.00)	0.93 (0.84,1.04)	0.85 (0.62,1.16)	0.85 (0.74,0.97)
	(513 cases, 2,145 controls)		(201 cases, 378 controls)	(312 cases, 1,767 controls)
>24 months	0.83 (0.76,0.90)	0.87 (0.80,0.95)	0.84 (0.66,1.07)	0.85 (0.76,0.95)
	(961 cases, 4,296 controls)		(366 cases, 911 controls)	(595 cases, 3,385 controls)

Results of conditional logistic regression models.

[a] Adjusted for the following variables: inflammatory bowel disease, diabetic nephropathy, colorectal evaluation, cholecystectomy, sulfonylurea prescription, nonsteroidal anti-inflammatory drug prescription, and liver disease.

Table 5

Odds ratios (and 95% CIs) for filled prescriptions for simvastatin in cases with colon or rectal cancer and controls without CRC

	Unadjusted All	Adjusted [a]		
		All	Patients with polyps	Patients without polyps
	(6,080 cases, 24,320 controls)	(6,080 cases, 24,320 controls)	(2,078 cases, 4,252 controls)	(4,002 cases, 20,068 controls)
Any duration	0.89 (0.83,0.94)	0.91 (0.86,0.97)	0.91 (0.76,1.09)	0.85 (0.79,0.92)
Any duration, excluding 1 year before index date	0.90 (0.84,0.96)	0.93 (0.87,0.99)	0.90 (0.75,1.09)	0.89 (0.81,0.96)
At least 6 months	0.90 (0.84,0.96)	0.93 (0.87,0.99)	0.93 (0.77,1.13)	0.85 (0.78,0.93)
At least 6 months (excluding 1 year before index date)	0.88 (0.82,0.95)	0.91 (0.85,0.95)	0.84 (0.67,1.04)	0.88 (0.80,0.97)

Results of conditional logistic regression models.

[a] Adjusted for the following variables: inflammatory bowel disease, diabetic nephropathy, colorectal evaluation, cholecystectomy, sulfonylurea prescription, nonsteroidal anti-inflammatory drug prescription, and liver disease.

Table 6

Odds ratios (and 95% CIs) for filled prescriptions for non-statin and triglyceride lipid-lowering medications in cases with colon or rectal cancer and controls without CRC

	Number of patients All	Unadjusted All	Adjusted[a]		
			All	Patients with polyps	Patients without polyps
Number of patients		**(6,080 cases, 24,320 controls)**	**(6,080 cases, 24,320 controls)**	**(2,078 cases, 4,252 controls)**	**(4,002 cases, 20,068 controls)**
Filled prescription of patients of nonstatins					
Any duration	(228 cases, 896 controls)	1.02 (0.88,1.18)	1.04 (0.90,1.21)	1.19 (0.81,1.75)	1.00 (0.82,1.22)
Excluding 1 year before index date	(135 cases, 571 controls)	0.95 (0.78,1.14)	0.96 (0.80,1.17)	1.00 (0.62,1.60)	0.93 (0.72,1.20)
At least 6 months	(91 cases, 434 controls)	0.91 (0.73,1.13)	0.92 (0.74,1.15)	0.70 (0.38,1.29)	1.00 (0.75,1.34)
At least 6 months (excluding 1 year before index date)	(57 cases, 247 controls)	0.92 (0.69,1.23)	0.93 (0.70,1.25)	0.67 (0.31,1.44)	1.04 (0.71,1.50)
Filled prescription of triglycerides					
Any duration	(544 cases, 2,267 controls)	0.95 (0.87,1.05)	0.98 (0.89,1.08)	0.92 (0.69,1.22)	0.93 (0.82,1.06)
Excluding 1 year before index date	(409 cases, 1,731 controls)	0.94 (0.84,1.05)	0.96 (0.86,1.08)	0.93 (0.68,1.27)	0.90 (0.78,1.05)
At least 6 months	(389 cases, 1,619 controls)	0.96 (0.85,1.07)	0.99 (0.88,1.11)	0.88 (0.63,1.22)	0.94 (0.80,1.09)
At least 6 months (excluding 1 year before index date)	(260 cases, 1,124 controls)	0.92 (0.80,1.06)	0.95 (0.83,1.10)	0.78 (0.53,1.16)	0.92 (0.77,1.10)

lts of conditional logistic regression models.

[a]Adjusted for the following variables: inflammatory bowel disease, diabetic nephropathy, colorectal evaluation, cholecystectomy, sulfonylurea prescription, nonsteroidal anti-inflammatory drug prescription, and liver disease.

Table 7

Odds ratios (and 95% CIs) for filled prescriptions of any statin in cases restricted to rectal cancer and controls without colon or rectal cancer, excluding statin use 1 year before rectal cancer index date

Total	**1,417 cases 5,668 controls**	**Unadjusted**	**Adjusted** [a]
No statin use	**713 cases 2,746 controls**	**Reference**	
< 6 months	118 cases/518 controls	0.88 (0.70,1.09)	0.88 (0.71,1.10)
6 –12 months	116 cases/558 controls	0.79 (0.64,1.00)	0.80 (0.64,0.99)
12 –18 months	126 cases/548 controls	0.88 (0.71,1.09)	0.91 (0.73,1.12)
18 –24 months	110 cases/382 controls	1.13 (0.90,1.43)	1.17 (0.92,1.48)
>24 months	71 cases/271 controls	1.03 (0.77,1.38)	1.08 (0.81,1.45)

Results of conditional logistic regression models.

[a] Adjusted for the following variables: inflammatory bowel disease, diabetic nephropathy, colorectal evaluation, cholecystectomy, sulfonylurea prescription, nonsteroidal anti-inflammatory drug prescription, and liver disease.