The Role of Statins for Primary Prevention in Non-elderly Colorectal Cancer Patients

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Abstract. *Background: There is conflicting evidence for the role of statins in the primary prevention of colorectal cancer (CRC). We conducted a case control study (N=357,702) in the non-elderly adult US population (age=18-64 years) with the primary objective to examine the association between CRC and statin use. Patients and Methods: MarketScan® databases were used to identify patients with CRC. A case was defined as having an incident diagnosis of CRC. Up to ten individually matched controls (age, sex, region and date of diagnosis) were selected per case. Statin exposure was assessed by prescription tracking in the 12 months prior to the index date. Conditional logistic regression was used to adjust for multiple potential confounders and calculate adjusted odds ratios (AOR). Results: The mean age of participants was 54 years; 52% males and 48% females. In a multivariable model, any statin use was associated with 26% reduced odds of CRC (AOR, 0.74, 95% confidence interval (CI), 0.72-0.77, p<0.001). Age-stratified analyses showed a stronger effect of statins on CRC in participants aged 55 years or younger (AOR, 0.67, 95% CI, 0.63-0.71, p<0.001) than in participants aged above 55 years (AOR, 0.79, 95% CI, 0.76-0.82, p<0.001); the age-by-statin interaction was statistically significant (p<0.001). The dose-response analyses performed with simvastatin only showed a trend towards significance between the duration of simvastatin exposure and odds of developing CRC (p=0.06). Conclusions: Statins appears to reduce the risk of CRC in non-elderly US population. Chemoprevention with statin might be more effective in non-elderly US population.*

Colorectal cancer (CRC) has a high worldwide incidence and mortality. It is the second most commonly diagnosed cancer in females and third most commonly diagnosed cancer in males. Over 1.2 million incident cases and 608,700 deaths were recorded globally in 2008 (1). Recent epidemiology data have shown that incidence and mortality of CRC are decreasing in the United States. This is particularly due to CRC screening and detection of pre-neoplastic lesions (2). However, current knowledge about the risk factors for various cancers is good enough to prevent at least 50% of cancer cases (3). Besides lifestyle modifications (4), chemoprevention with aspirin has shown to be effective in reducing the incidence as well as mortality without significant adverse effects (5). Additional drugs that are safe and efficacious, and can be widely prescribed show promise in further expanding the role of chemoprevention in cancer control and prevention.

The 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, have the potential to be effective chemoprevention drugs. Statins usage has been reported to be about 11% in the overall US population and as high as 44% in people above 65 years (6). Moreover statins are relatively safe and well-tolerated (7, 8). The interest in the potential chemopreventive role of statins largely emerged from the pre-clinical experiments showing anti-neoplastic actions through a variety of pleiotropic effects (9, 10). Besides inhibiting cholesterol synthesis through HMG-CoA inhibition, statins also inhibit several other intermediates of the mevalonate pathway leading to a number of pleiotropic effects including anti-inflammatory, anti-

Abbreviations: CRC, colorectal cancer; AOR, adjusted odds ratio; CI, confidence interval; DM, diabetes mellitus; IBD, inflammatory bowel disease; CAD, coronary artery disease; PCOD, polycystic ovary disease; SU, sulfonylurea; TZD, thiazolidinediones; and NSAID, non-steroidal anti-inflammatory drugs.

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antigeogenic, anti-oxidant, immunoregulation and modulation of cell adhesion and proliferation (6). Due to these actions, statins have been thought to be a promising anti-neoplastic and chemopreventive agent.

A decade of observational studies and *post-hoc* analyses of randomized controlled trials (RCT) from cardiovascular literature has shown inconsistent results. These studies are criticized for methodological problems. The *post-hoc* analyses of RCT are criticized due to insufficient follow-up duration, potential death from competing cardiovascular risk in placebo arm leading to undetected cancer cases and ascertainment bias due to cancer incidence being a secondary endpoint and lack of systematic data collection for cancer incidence (6). The observational studies largely illustrate the problems of confounding due to sampling bias, recall bias and inability to account for certain variables that may predict outcome (11). Moreover, most studies were performed using data that were not specifically collected for evaluating the effect of statins but rather were a part of large epidemiological datasets (12). Lastly and most importantly, several studies were underpowered to detect the association due to small sample size (13). This concern is especially supported by the meta-analyses of these studies, which have shown a consistent but modest reduction in CRC with statin use (14, 15).

Although confounding is a difficult problem to control in observational studies, sample size can certainly be increased to have enough power to detect a real difference between groups. Therefore, we conducted a large case control study (N=357,702) in non-elderly adult US population (mean age 54 years; range 18-64 years) to investigate the role of statins in primary prevention of CRC. Our study is unique as we are not aware of any other large study in the current literature that has addressed the role of statin on the risk of CRC in a non-elderly US population. It is theoretically possible that statins might be more effective for chemopreventive purposes in a younger population as colorectal cancer has a long latency period (16).

Materials and Methods

Patients and eligibility criteria. We used MarketScan® (Truven Health Analytics, Ann Arbor, MI, USA) Commercial Claims and Encounters Database to identify patients with CRC above the age of 18 years using the International Classification of Disease (9th revision, clinical modification; ICD9-CM) between 2004 and 2010. These data are a longitudinal database that contains de-identified, individual-level employer-sponsored insurance claims data of nearly 150 million individuals from all geographic areas of the United States. The study was approved by the Institutional Review Board of the University of Chicago, IL, USA. The primary objective was to assess the odds of developing CRC in statin users and nonusers. To ensure completeness of claims for the identification of statin use, only patients with continuous enrollment in the 12 months period prior to the earliest diagnosis date of CRC were included in the study.

Cases and controls. All patients above the age of 18 years diagnosed with CRC from 2004 to 2010 were identified in the MarketScan® database using the International Classification of Disease (9th revision, clinical modification; ICD9-CM) codes (153.0 to 153.9, 154.0, 154.1 and 154.8). To reduce the false positive rate of CRC cases, only patients with at least two or more claims of ICD-9 codes indicating CRC on different dates within a period of 3 months were included. For the purpose of this study, a CRC case was considered incident if there were no claims indicative of CRC in the previous year so as to ensure statin use prior to the development of CRC. Therefore, a case was defined as a patient having an incident diagnosis of CRC and a control was defined as a patient without a diagnosis of CRC. Up to ten controls individually matched for age, sex, geographical region (*i.e.,* Northeast, North Central, South, West and unknown) and date of diagnosis were selected per case. The purpose of having ten matched controls *per* case was to increase statistical power and ensure adequate exposure of statins and other possible confounders in the control group.

Exposure ascertainment. The statins' exposure was estimated by tracking the prescriptions in the 12 months prior to the index date. For cases, index date was defined as the earliest date of CRC diagnosis and for controls, index date was defined as the date of diagnosis of the case that was used to find the matched controls. We used simvastatin as the representative statin and calculated a detailed exposure to only simvastatin (but not for lovastatin, atorvastatin, rosuvastatin or pravastatin) by estimating the dose and duration for each study participant. We used simvastatin as the representative statin as it was the single most commonly prescribed statin in our dataset and is one of the most commonly used statins in United States (17). Similarly, the exposure to other drugs, including prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), metformin, sulfonylureas (SU), thiazolidinediones (TZD) and insulin, was ascertained by tracking prescriptions. The exposure assessment in the year prior to CRC diagnosis ensured inclusion of only incident cases of CRC to the best extent possible for this study.

Potential confounders. We collected data on multiple potential confounders of patient-related variables and concurrent medications 12 months prior to the index date. The patient-related variables for this purpose included diabetes mellitus (DM; ICD-9 codes 250.0 to 250.9), obesity (ICD-9 codes 278.00 and 278.01), polycystic ovary disease (PCOD; ICD-9 code 256.4), inflammatory bowel disease (IBD; ICD-9 codes 556.0 to 556.9, 555.0 to 555.2 and 555.9), coronary artery disease (CAD; ICD-9 codes 410.0 to 410.9, 414.0 to 414.4, 414.8, 414.9, and 429.2), age, sex, geographic region and comorbidity scores. The comorbidity scores were calculated using the modified Charlson algorithm available from the SEER-Medicare website (18) and revised to fit the data structure in MarketScan®. Medications being used concurrently in the last 1 year (including the index date), for which statistical model adjustments were made, included prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), metformin, SU, TZD, and insulin. We also gathered data on healthcare utilization by counting the number of outpatient visits and number of hospitalizations during the 12 months prior to the index date.

Statistical analyses. In the primary analyses, the odds of developing CRC for patients exposed to statins and those not

Table I. *Patient characteristics of the study population in case and control group.*

Variable name		Cases N=32,616	Controls N=325,086	*p*-Value*
Age, mean (±SD)		54.44 (±7.5)	54.43 (±7.5)	0.74 (t-test)
	Male	17,031 (52.2)	169,653 (52.2)	0.9
	Female	15,585 (47.8)	155,433 (47.8)	
Region	Northeast	2,899 (8.9)	28,906 (8.9)	1
	North Central	8,422 (25.8)	83,925 (25.8)	
	South	15,447 (47.4)	153,978 (47.4)	
	West	5,711 (17.5)	56,912 (17.5)	
	Unknown	137 (0.4)	1,365 (0.4)	
Year of diagnosis	2004	3,531 (10.8)	35,062 (10.8)	1
	2005	4,296 (13.2)	42,575 (13.1)	
	2006	3,374 (10.3)	33,594 (10.3)	
	2007	5,362 (16.4)	53,325 (16.4)	
	2008	5,094 (15.6)	50,940 (15.7)	
	2009	5,513 (16.9)	55,130 (16.9)	
	2010	5,446 (16.7)	54,460 (16.75)	
Obesity (BMI ≥30 kg/m^2)		683 (2)	4,604 (1.4)	<0.001
Diabetes mellitus		5182 (15.9)	40,087 (12.3)	<0.001
Inflammatory bowel disease		549 (1.7)	1564 (0.5)	<0.001
Coronary artery disease		2,077 (6.4)	19,091 (5.9)	<0.001
Polycystic ovary disease		22 (0.07)	105 (0.03)	0.001
Statins	All	5,704 (17.5)	62,757 (19.3)	<0.001
	Simvastatin	2,417 (7.4)	26,157 (8.0)	<0.001
Metformin		2,189 (6.7)	17,758 (5.46)	<0.001
NSAIDs		3,919 (12)	38,417 (11.8)	0.29
Sulfonylurea		1,285 (3.9)	9,267 (2.8)	<0.001
Insulin		1,027 (3.1)	7,462 (2.3)	<0.001
Thiazolidinedione		939 (2.9)	7,808 (2.4)	<0.001
Charlson comorbidity score		0.14±0.58	0.08±0.39	<0.001 (*t*-test)
Admissions (Mean±SD)		0.42±0.91	0.09±0.45	<0.001
Outpatient visits (Mean±SD)		7.94±8.86	4.2±6.3	<0.001

*Univariate *p*-value calculated with chi-square unless specified. BMI, Body mass index.

exposed to statins was calculated. Conditional logistic regression was used to estimate the adjusted odds ratios (AOR) and 95% CI, adjusting for patient-related variables, concomitant medications and health care utilization. In the secondary analyses, we did a stratified analysis for age. For the age-stratified analysis, we ran the interaction between age and statin exposure first and then conducted a subgroup analyses by dichotomizing the study participants into 2 groups (age ≤55 years and age >55 years). We also calculated the magnitude of effect of simvastatin's dose, duration and total exposure on CRC risk. To study dose response relationship, we collected data on dose and duration of simvastatin for the subset of study participants with at least one prescription claim of simvastatin in the past year. We divided the duration of use in four quartiles (1-90, 181-217, 218-303 and 304-365 days) and dose into 3 groups (10-20, 21-40 and 41-80 mg) for statistical analyses. We also calculated the total simvastatin exposure by multiplying the simvastatin dose with duration of use. The data management was done using SAS®, Enterprise Guide version 5.1 (SAS Institute Inc., Cary, NC, USA) and all statistical analyses were done using STATA®, version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Study participants. The mean age in both case and control group was 54 years, with 52% males and 48% females in each group. Any statin exposure was seen in 17.5% of patients in case group and 19.3% of patients in control group whereas simvastatin exposure was 7.4% and 8%, respectively. There were no significant differences in terms of age, sex, geographical region, date of diagnosis and prescribed NSAIDs use between the case and control group but the two groups were significantly different in terms of comorbidities (Obesity, DM, IBD, CAD, and PCOD) and concomitant medications [metformin, sulfonylureas (SU), thiazolidinediones (TZD), and insulin] with higher percentages in the case group compared to the control group (Table I). The Charlson comorbidity score, number of Hospital admissions and number of outpatient visits were also significantly higher in the case group compared to controls (Table I).

Table II. *Results of statin exposure and colorectal cancer risk in multivariate regression model.*

Variable	COR (95% CI)	*p*-Value	AOR* (95% CI)	*p*-Value
Associated with increased odds of CRC (based on AOR)				
Diabetes	1.35 (1.30-1.39)	<0.001	1.10 (1.05-1.16)	<0.001
Metformin	1.24 (1.19-1.30)	<0.001	1.13 (1.06-1.20)	<0.001
Polycystic ovary disease	2.10 (1.32-3.32)	0.002	1.78 (1.11-2.86)	0.017
Inflammatory bowel disease	3.53 (3.20-3.89)	<0.001	2.35 (2.11-2.61)	<0.001
Sulfonylurea use	1.40 (1.31-1.48)	<0.001	1.14 (1.06-1.19)	0.001
Number of outpatient visits	1.05 (1.04-1.06)	<0.001	1.03 (1.03-1.04)	<0.001
Hospital admissions	2.03 (2.00-2.06)	<0.001	1.76 (1.73-1.79)	<0.001
Associated with decreased odds of CRC (based on AOR)				
Statins	0.88 (0.85-0.90)	<0.001	0.74 (0.72-0.77)	<0.001
Coronary artery disease	1.09 (1.04-1.14)	<0.001	0.68 (0.65-0.72)	<0.001
Prescribed NSAIDs	1.01 (0.98-1.05)	0.285	0.83 (0.80-0.86)	<0.001
Charlson Comorbidity Index	1.22 (1.20-1.24)	<0.001	0.84 (0.82-0.87)	<0.001
Insulin	1.38 (1.29-1.48)	<0.001	0.87 (0.80-0.94)	<0.001
No significant association (based on AOR)				
Obesity	1.49 (1.37-1.61)	<0.001	1.06 (0.97-1.15)	0.20
Thiazolidinedione	1.20 (1.12-1.29)	<0.001	1.02 (0.96-1.05)	0.75

Abbreviations: COR, Crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval. *Adjusted for obesity, polycystic ovary disease, inflammatory bowel disease, sulfonylurea use, coronary artery disease, prescribed NSAIDs, diabetes, insulin, metformin, Thiazolidinedione, Charlson comorbidity index, number of hospital admission and number of outpatient visits.

Statins and risk of colorectal cancer. In a multivariable model, any statin use was associated with 26% reduced odds of CRC (AOR 0.74, 95% CI, 0.72-0.77, $p<0.001$). We controlled for all the patient-related variables, concomitant medications, Charlson comorbidity score, and health-care utilization in our multivariable model (Table II). We found that obesity and thiazolidinediones showed no significant association with CRC risk whereas coronary artery disease, insulin, Charlson comorbidity index and prescribed NSAIDs were associated with significantly decreased CRC risk. Inflammatory bowel disease, polycystic ovary disease, diabetes, metformin, sulfonylurea, number of outpatient visits and Hospital admissions were associated with significantly increased CRC incidence. Stratified by age, we found the effect of statin on CRC was stronger in participants aged 55 years or younger (AOR, 0.67, 95% CI, 0.63-0.71, $p<0.001$) than in participants aged above 55 years (AOR, 0.79, 95% CI, 0.76-0.82, $p<0.001$); the age-by-statin interaction was statistically significant ($p<0.001$).

Dose response analysis with simvastatin. The overall effect of simvastatin on the CRC risk was similar to the effect of statins in the multivariable model (AOR, 0.79, 95% CI, 0.75-0.83, $p<0.001$). No significant dose response relationship was found between simvastatin dose or total exposure (dose x duration) and CRC risk, although the relationship between duration of simvastatin exposure and odds of developing CRC showed a trend towards significance (p=0.06) (Table III).

Discussion

There is growing interest in the role of statin for chemoprevention given the experimental evidence in support of statins as anti-cancer drugs (6). In a large case control study, we found a statistically significant reduced risk of CRC by 26% with any statin use. The dose-response calculations conducted with simvastatin did not show any significant relationship between dose, duration or total exposure of simvastatin and CRC, however, there appeared to be a trend towards more benefit with increasing duration of simvastatin. The stratified analysis by age showed a greater benefit in those ≤55 years age compared to those >55 years of age. It is possible that statins are more effective in the younger population as adenoma progression into carcinoma takes several years (16). Our study is unique due to the relatively younger population with a mean age of 54 years (range 18-64 years) and we are not aware of any large studies in the current statin literature assessing the effect of statins for CRC prevention in non-elderly population.

Our results are similar to the results of several other observational studies (Table IV) (17, 19-24). The mean age in these studies range from 66 to 74 years, except a small study (23) (N=603) with a mean age of 60 years. The first study on statins and risk of CRC was published by Poytner *et al*. in 2005, which showed about 50% lower risk of developing colorectal cancer with over 5 years of statin use (19). However, some consider this study to be an outlier due to a dramatic benefit seen with statin use. Additionally, the

Table III. *Dose-response analyses for CRC risk in persons who used simvastatin.*

Statins	Cases N (%)	Controls N (%)	AOR (95% CI)*	*P* for trend
Simvastatin duration	2,338 (8.45)	25,332 (91.55)		
Q1 (1-90 days)	673 (28.79)	6,544 (25.83)	1.00	0.06
Q2 (91-217 days)	559 (23.91)	6, 490 (25.62)	0.77 (0.62-0.95)	
Q3 (218-303 days)	590 (25.24)	6,590 (26.01)	0.83 (0.67-1.02)	
Q4 (304-365 days)	516 (22.07)	5,708 (22.53)	0.80 (0.65-0.99)	
Simvastatin dose	2,374 (8.45)	25,736 (91.55)		
5-20 mg	1057 (44.52)	11956 (46.46)	1.00	0.29
21-40 mg	1042 (43.89)	10703 (41.59)	0.98 (0.84-1.15)	
41-80 mg	275 (11.58)	3077 (11.96)	0.87 (0.68-1.12)	
Simvastatin total dose (dose x duration)	2,409 (8.45)	26,085 (91.55)		
Q1 (5-2,420 mg)	673 (27.94)	6478 (24.83)	1.00	0.13
Q2 (2,421-5,600 mg)	544 (22.58)	6611 (25.34)	0.65 (0.53-0.80)	
Q3 (5,601-10,280 mg)	582 (24.16)	6560 (25.15)	0.75 (0.61-0.92)	
Q4 (10,281-29200 mg)	610 (25.32)	6436 (24.67)	0.76 (0.62-0.94)	

*Adjusted in conditional logistic regression models for obesity, polycystic ovary disease, inflammatory bowel disease, sulfonylurea use, coronary artery disease, prescribed NSAIDs, diabetes, insulin, metformin, thiazolidinediones, Charlson comorbidity index, number of hospital admission and number of outpatient visits.

generalizability of this study is limited as the majority of participants were Ashkenazi Jews. From 2007-2010, four other studies showed the beneficial effect of statin use in reducing the incidence of CRC with the effect size of 9-35% relative risk reduction. Interestingly, two case control studies published in 2012 showed a very dramatic and significant benefit with statin use similar to the study by Poytner *et al*. (23, 24). The first study by Broughton *et al*. showed that any statin use was associated with 57% reduced incidence of CRC (OR, 0.43, 95% CI, 0.25-0.80, $p<0.01$) (24). Similarly, the second study by Lakha *et al*. found a 63% reduced risk of CRC with any statin use (OR, 0.33, 95% CI, 0.15-0.69, $p<0.004$) (23). However, a number of other case control studies (22, 25-35), cohort studies (13, 36-44) and secondary analysis of randomized clinical trials (45-53) have shown no significant relationship between statin use and CRC incidence.

Two large meta-analyses, including case control, cohort and RCTs, have shown a statistically significant modest reduction (approximately 8-9%) in CRC risk with combined analyses of all study designs and analysis of only case control studies but no significant association with analyses of only cohort studies or only RCT (14, 15). The authors of these meta-analyses concluded that further studies are required to test the hypothesis of statin use in CRC prevention.

Our study has many strengths. First, the large sample size of our study provided sufficient power to address the impact of statin use on CRC risk. Second, a computerized prescription database was used for assessing the exposure to drugs of interest, thereby minimizing the recall bias. Third, several attempts were made to avoid misclassification bias, such as, using a stringent case definition (as described in methods) and using only patients with at least 12 months of continuous enrollment prior to the date of diagnosis. Forth, we controlled for many potential confounders including diseases and concomitant medications during the prior 12 months prior to the date of diagnosis. Fifth, we adjusted for health care utilization by estimating the number of outpatient visits and hospital admissions. An unequal health-care utilization can induce a potential bias in a case control study, for example, if patients in the case group are using more health care resources compared to the control group it can erroneously result in better outcomes in case group.

The major limitation of our study is its retrospective study design, which limits the ability to control for unknown potential confounders and sometimes known confounders when data is not available. It is possible that such confounders have affected our results as we explain below. First, we were unable to control for aspirin usage, as this is mainly an over-the-counter drug in the United States and this information is not available in the MarketScan® database. It is possible that the beneficial effect of statins observed in our study is merely because of higher over the counter use of aspirin in the statin-exposed group. Individuals with diabetes and coronary artery disease are more likely to take over the counter aspirin. Univariate analysis of our data does show a higher rate of diabetes and coronary artery disease in the case group, which implies that a higher proportion of individuals in the case group may be taking aspirin. However, since we adjusted for both diabetes and coronary artery disease in our multivariate model it is very unlikely that the results of our study are merely due to potential confounding by aspirin. Second, there is some evidence that the health conscious behavior such as

Table IV. *Selected statin observational studies assessing CRC incidence as the primary outcome and have results similar to our study.*

Study	Design	Total N	Study Description/Population	Mean age (Years)	OR/HR for developing outcome (95% CI) $p<0.05$ for all studies
Poynter et al. (19), 2005	Case Control	Cases 953 Controls 2015	Molecular Epidemiology of Colorectal Cancer study conducted in Northern Israel	70	Any use, OR, 0.53 (0.38-0.74) Use for >5 y, OR, 0.55 (0.40-0.74)
Hoffmeister et al. (21), 2007	Case Control	Cases 540 Controls 614	German population-based colorectal cancer study Statin and low-dose aspirin use assessed.	68 (Controls 67)	Statin use, OR, 0.65 (0.43-0.99) Aspirin use, OR, 0.77 (0.55-1.07) Use of both drugs for >5 y, OR, 0.38 (0.15-0.97)
Robertson *et al*. (22), 2010	Case Control	Cases 9,979 Controls 99,790	Danish National Registry of Patients	71	Use for 0-3 y, OR, 0.84 (0.75-0.95) Use for >5 y, OR, 0.95 (0.80-1.12)
Hachem et al. (17), 2009	Case Control	Cases 6,080 Controls 24,320	Veterans with Diabetes in the national databases of the Department of Veterans Affairs (VA) and Medicare-linked files	74	Any use, OR, 0.91 (0.86-0.96) Use for >6 mo, OR, 0.92 (0.86-0.98)
Lakha et al. (23), 2012	Case Control	Cases 309 Controls 294	Scottish Study of Colorectal Cancer	60 (Controls 61)	OR, 0.33 (0.15-0.69)
Broughton et al. (24), 2012	Case Control	Cases 101 Controls 132	Norwich University Hospital Gastroenterology Department	70 (Controls 64)	OR, 0.43 (0.25-0.80)
Farwell et al. (20), 2008	Cohort study	Statin users 37,248 Non-users 25,594	New England Veterans Affair health care database	66	HR, 0.65 (0.55-0.78)

Abbreviations: OR, odds ratio; HR, hazard ratio; y, years; mo, months.

screening colonoscopy is associated with increased statin usage (30). Therefore, it is possible that the reduced incidence of CRC in the case group is due to a higher likelihood of adhering to cancer screening guidelines among statin users. We could not adjust for screening colonoscopy in our study mainly because the guideline-recommended screening interval for colonoscopy is every 5-10 years and given our study duration of only 1 year we would have missed many screening colonoscopies done more than one year ago. However, we did adjust for overall health care utilization, which showed a higher utilization of healthcare resources in the case group compared to control. Therefore, it is possible that our results of beneficial effect of statins are due to excess healthcare utilization in the case group. Third, we could not adjust for lifestyle (diet and exercise) and socioeconomic factors in our analysis; however, we do not expect that these variables would be significantly different between the two groups to explain the findings of our study. Additionally, we matched for age, sex, geographical region and date of diagnosis that would have balanced any such differences between the case and control groups. Fourth, we could not adjust for smoking and alcohol consumption however the evidence of their relationship with CRC incidence is controversial. Lastly, our data was not linked to cancer registries and therefore, there may be ascertainment bias in the incident cohort identified from claims using ICD-9 codes.

In conclusion, despite large amounts of retrospective data and secondary data from cardiovascular RCTs, there is no convincing data to support clinical use of statin for colon cancer prevention. The results of our study suggest that statin may have potential beneficial effect in reducing the incidence of CRC. Our study is unique due to the non-elderly population (mean age of 54 years) and generates a new hypothesis of whether statins are more beneficial as chemopreventive agents for colorectal cancer if used at a younger age. However, due to inherent nature of study design, a causal relationship cannot be established. Prospective controlled studies are needed to answer the question of the efficacy of statin as a colon cancer chemopreventive agent in non-elderly population.

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