STATINS REDUCE THE PROGRESSION OF NON-ADVANCED ADENOMAS TO COLORECTAL CANCER: A POST-COLONOSCOPY STUDY IN 187,897 PATIENTS

SHORT TITLE: STATIN AND POST-COLONOSCOPY COLORECTAL CANCER

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LIST OF ABBREVIATIONS

AF	Atrial fibrillation
ASD	Absolute standardised difference
CDARS	Clinical Data Analysis and Reporting System
cDDD	Cumulative defined daily dose
CHF	Congestive heart failure
COPD	Chronic pulmonary obstructive disease
COX-2	Cyclooxygenase-2
CRC	Colorectal cancer
CRF	Chronic renal failure
DM	Diabetes mellitus
HMG-CoA	Hydroxy-3-methylglutaryl coenzyme A
ICD-9	International Classification of Diseases, Ninth Revision
IHD	Ischemic heart disease
IQR	Interquartile range
NSAIDs	Non-steroidal anti-inflammatory drugs
NNT	Number-needed-to-treat
PCCRC	Post-colonoscopy colorectal cancer
PCCRC-3y	Post-colonoscopy colorectal cancer at 3 years
PCCRC-all	All post-colonoscopy colorectal cancer cases
PS	Propensity score
SHR	Subdistribution hazard ratio
WEO	World Endoscopy Organisation
WHO	World Health Organisation

ABSTRACT

Background & Aims: Post-colonoscopy colorectal cancer (PCCRC) accounts for up to 9% of all CRCs. Statins have been shown to be associated with a lower CRC risk. We aimed to investigate whether PCCRC risk was also lower among statin users.

Methods: This is a retrospective cohort study using a territory-wide electronic healthcare database in Hong Kong including patients aged 40 or above who had undergone colonoscopies between 2005 and 2013. Exclusion criteria included prior CRC, inflammatory bowel disease, prior colectomy and CRC detected within six months of index colonoscopy. We defined statin use as at least 90-day use before index colonoscopy. Medication use was traced up to five years before index colonoscopy**.** PCCRC-3y was defined as cancer diagnosed between 6 and 36 months after index colonoscopy. Sites of CRC were categorized as proximal (proximal to splenic flexure) and distal cancer. The subdistribution hazard ratio (SHR) of PCCRC-3y with statin use was derived by propensity score (PS) matching based on covariates (including patient factors, concurrent medication use and endoscopy center's performance).

Results: Of 187,897 eligible subjects, 854 (0.45%) were diagnosed with PCCRC-3y. Statin use was associated with a lower PCCRC-3y risk (SHR:0.72; 95% CI:0.55–0.95; p=0.018). Subgroup analysis shows that SHRs were 0.50 (95% CI:0.28–0.91;p=0.022) for proximal and 0.80 (95% CI:0.59–1.09;p=0.160) for distal cancer. Older (>60) patients, females, and those without diabetes mellitus or polyps appeared to benefit more from statins.

Conclusions: Statins were associated with a lower PCCRC risk, particularly for proximal cancer.

SIGNIFICANCE OF THIS STUDY

What is already known on this subject?

- Although the incidence and mortality of colorectal cancer (CRC) can be reduced by screening colonoscopy, CRC can still occur before the expected interval after an initial negative colonoscopy, which is named post-colonoscopy colorectal cancer (PCCRC).
- Meta-analyses of clinical studies report that statins are associated with a reduced CRC risk, but there are no studies that specifically explore its role in preventing PCCRC.

What are the new findings?

- Statin use was associated with a lower PCCRC risk.
- Older (>60) patients, females, and those without diabetes mellitus or polyps appeared to benefit more from statins.

How might it impact on clinical practice in the foreseeable future?

- Our study results help in the decision making process of commencing statins in patients at high risk for CRC with borderline indications for cardiovascular prevention.
- It prompts further studies on the potential role of statins in inhibiting the progression of advanced colorectal adenoma to cancer.

Introduction

Globally, colorectal cancer (CRC) is the third commonest cancer and the second leading cause of cancer-related death.[1] Although the incidence[2-4] and mortality of CRC [4-6] can be reduced by screening colonoscopy, CRC can still occur before the expected interval after an initial colonoscopy negative for CRC. These are named as interval cancer or more recently post-colonoscopy CRC (PCCCR) as proposed by the World Endoscopy Organization (WEO) consensus.[7] Specifically, the term "interval cancer" should be reserved for screening and surveillance colonoscopy programs only.[7] PCCRC accounts for up to 9% of all diagnosed CRCs,[8] with proximal colon more commonly involved than distal colon (2.4 times).[9] The majority of PCCRCs are due to missed lesions at index colonoscopy.[8] Other possible causes include residual lesions after polypectomy and CRC arising from sessile serrated pathway which tends to progress faster than the traditional adenoma-carcinoma sequence.[10-12]

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (an enzyme involved in cholesterol synthesis), and are used for primary and secondary prevention of cardiovascular diseases.[13] Besides, statins are proposed to have chemopreventive effect against solid organ tumours through induction of apoptosis,[14] inhibition of angiogenesis,[15] suppression of tumour growth,[16] and potentiation of anti-tumour effects of cytokines.[17] Meta-analyses of clinical studies reported that statins were associated with a reduced risk of CRC[18,19,20], but not adenoma.

To our knowledge, there are currently no studies that specifically explore the role of pharmacological agents in preventing PCCRC. In this territory-wide study based on

the Hong Kong population, we determined the potential effect of statins in reducing PCCRC risk.

METHODS

Study design and data source

This is a retrospective cohort study based on data retrieved from Clinical Data Analysis and Reporting System (CDARS), an electronic healthcare database under the management of Hong Kong Hospital Authority. Being the only provider of public healthcare services, Hong Kong Hospital Authority covers 90% of all primary, secondary and tertiary care services of Hong Kong with 7.3 million population.[21] Each patient is assigned a unique reference key to ensure confidentiality in the CDARS. CDARS retains all essential but anonymized clinical data including patient's demographics, death, hospitalization, outpatient visits, diagnoses, investigations, drug prescription and dispensing history. All drug prescription and dispensing history were electronically recorded in CDARS. The prescription record generally matches with the dispensing record, as prescribed medications are dispensed by hospital pharmacy at a very low cost (US$2 per item for 16 weeks). The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (reference no: UW 18-253). Multiple descriptive and analytic population-based studies were conducted based on CDARS.[22-28] The International Classification of Diseases, Ninth Revision (ICD-9) coding was used, showing a high degree of coding accuracy (90–100 %).[22, 23, 29, 30]

Outcome definition and study subjects

All patients (aged 40 years or above) who had undergone colonoscopy between 2005 and 2013 were identified. Exclusion criteria included history of CRC, inflammatory bowel disease, prior colectomy and detected CRC (**Figure 1**). We followed recent World Endoscopy Organization (WEO) consensus of PCCRC rate for an interval of 3

years (PCCRC-3y) for benchmarking purposes[7]. PCCRC-3y was defined as CRC cases with prior colonoscopy performed between 6 and 36 months in which no CRC was diagnosed. This duration was also commonly adopted by previous studies to define interval cancer.[31-35] Detected CRC was defined as cancer diagnosed within 6 months of index colonoscopy, as CRCs suspected at index procedure were likely confirmed within this period.[31] Secondary outcomes of interest were (1) PCCRC-all (i.e. all PCCRC cases except detected CRC), and (2) PCCRC beyond 3 years (i.e. subsequent CRC cases that developed >36 months after index colonoscopy by excluding detected CRC and PCCRC-3y cases), and (3) CRC-all (i.e. all CRC cases including detected CRC and PCCRC-all cases) (**eFigure 1**). CRC location was categorized into proximal and distal colon. Proximal cancer encompassed cancer from caecum to transverse colon, while cancer from splenic flexure to rectum was classified as distal cancer (**eTable 1**).

For the primary outcome, patients were observed from date of index colonoscopy till PCCRC-3y diagnosis, death or 36 months from index colonoscopy. For the secondary PCCRC outcomes, patients without detected cancer were observed from date of index colonoscopy and observed till CRC diagnosis, death or 31 December 2017.

To characterize the effects of statins on colorectal adenoma development, we also compared adenoma development (including any adenoma, non-advanced adenoma and advanced adenoma) after index colonoscopy between statin users and non-users. Any adenoma encompassed both non-advanced and advanced adenoma (defined as adenoma with severe dysplasia or villous component). The number of adenomas was also compared between statin users and non-users.

Data validation

As patient identity is anonymized in the CDARS, we could only retrieve data from our own center, Queen Mary Hospital (n=137), for validation. The coding accuracy was 97.1%.

Study covariates

The exposure of interest was statin use before index colonoscopy. Other risk factors for PCCRC-3y included patient's factors and endoscopy centres' performance.[31, 33, 34, 36] Patient's factors included age at index colonoscopy, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking, heavy alcohol consumption, other comorbidities (diabetes mellitus [DM], hypertension, dyslipidaemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin,[37] non-steroidal anti-inflammatory drugs [NSAIDs][38] and cyclooxygenase [COX]-2 inhibitors[38]). The details of the ICD coding were listed in **eTable 1**. Endoscopy centres' performance included annual endoscopy volume and annual polypectomy rate.

We traced prescription records for up to five years before index colonoscopy. In the primary analysis, statin use was defined as at least 90-day use as described by Coogan et al.[39] The treatment duration of each prescription of statins was derived by the difference between prescription start date and end date, and total treatment duration was subsequently calculated. Exposure to other medications was defined similarly. To study the dose-response relationship of statins, we quantified statin use based on the defined daily doses (DDDs) as per World Health Organization (WHO)

recommendation.[40] Cumulative DDD (cDDD) was subsequently calculated by summing dispensed DDDs within five years before index colonoscopy.

Statistical analyses

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as mean (±1 SD [standard deviation]) or median (interquartile range [IQR]). Mann-Whitney U-test was used to compare continuous variables of two groups. Chi-square test or Fisher's exact test was applied for categorical variables. We used propensity score (PS) matching as primary analysis to calculate the risk of PCCRC-3y with statin compared to non-statin use.[41, 42] Details of PS matching were described in supplementary material. Death was a competing risk for CRC as statin users had higher cardiovascular risk (**Table 1**) and thus mortality. Competing risk regression model was used to estimate the subdistribution hazard ratio (SHR).[43] Stratified analysis was performed according to CRC location (proximal or distal). The PS-adjusted absolute risk difference was calculated, with number-needed-to-treat (NNT) subsequently derived.

Sensitivity analyses were conducted by (1) PS adjustment with and without trimming of extreme PS strata (with all covariates included into competing risk regression model) and (2) examination of the effect of post-colonoscopy statin use (defined as statin use for at least 90 days between the date of index colonoscopy and end of observation) with PS adjustment with trimming to show the robustness of study results. For secondary outcomes, SHR was derived by competing risk regression model using PS adjustment with trimming. The odds ratio (OR) of colonic adenoma

with statins was derived by logistic regression model using PS adjustment with trimming. A two-sided p-value of < 0.05 was used to define statistical significance.

RESULTS

Patient Characteristics

A total of 234,827 patients underwent colonoscopies during the 9-year study period and 187,897 eligible patients were included in this analysis (**Figure 1**). The baseline characteristics of whole cohort and subgroups according to statin use are shown in **Table 1**. Males accounted for 48.9% and the mean age at index colonoscopy was 62.1±12.3 years. The total follow-up duration was 560,471 person-years.

Risk of PCCRC-3y

There were 854 (0.45%) PCCRC-3y with 707 (82.8%) distal and 147 (17.2%) proximal cancers. The overall incidence rate of PCCRC-3y was 15.2 per 10,000 person-years. The median age at diagnosis of PCCRC-3y was 75.9 years (IQR:65.5–83.8), and median time from index colonoscopy to PCCRC-3y diagnosis was 1.2 years (IQR:0.8–1.9).

Association between statins and PCCRC-3y

There were 25,447 (13.5%) statin users (simvastatin:17,744 [69.7%]; atorvastatin:1847 [7.3%]; rosuvastatin:542 [2.1%]; changing from one statin to another statin: 5314 [20.9%]), and the median cDDD was 245.0 (IQR:181.6–323.2). Among statin users, 114 (0.5%) developed PCCRC-3y (incidence rate:15.0 per 10,000 person-years).

A total of 17,662 statin users and 30,304 non-statin users were included for PS matching, with all covariates being balanced between the two groups (ASD<0.2) (**Table 1**). Statin users had a lower risk of PCCRC-3y (SHR:0.72, 95% CI:0.55–0.95)

(**Table 2**). Sensitivity analyses by PS adjustment with and without trimming showed similar results **(eTable 2)**. The PS adjusted absolute reduction in PCCRC-3y risk for statin use was 0.20% (95% CI:0.09%–0.31%), and NNT to prevent one PCCRC-3y was 498. Stratified analysis showed that statins were associated with a lower PCCRC-3y risk in proximal (SHR:0.50, 95% CI:0.28–0.91) but not distal colon (SHR:0.80, 95% CI:0.59–1.09). Compared with non-statin use, statins were associated with a dose-dependent lower risk of PCCRC-3y (SHR: 0.93, 95% CI:0.87–0.99; for every 100 increase in cDDD; p=0.023).

Sensitivity analysis on investigating the post-colonoscopy statin use on PCCRC-3y risk showed a consistent result (SHR:0.37, 95% CI:0.28–0.47; p<0.001)

Subgroup analysis

Subgroup analysis showed that statins were associated with a lower PCCRC-3y risk in certain subgroups (**Table 3**). These include patients aged ≥60 years (SHR:0.72, 95% CI:0.56–0.92), females (SHR:0.35, 95% CI:0.22–0.58), non-diabetic patients (SHR:0.59, 95% CI:0.42–0.81) and those without history of polyps and/or polypectomy (SHR:0.58, 95% CI:0.41–0.83).

Statins and PCCRC-all, PCCRC beyond 3 years or CRC-all

There were a total of 11,295 CRC cases (CRC-all) including 10,005 cases of detected CRC (diagnosed within 6 months of index colonoscopy) and 1,290 PCCRC-all (all PCCRC that developed 6 months after index colonoscopy). The SHR for CRC-all and PCCRC-all with statin use was 1.06 (95% CI: 0.99–1.14; p=0.082) and 0.75 (95% CI:0.61– 0.93; p<0.001), respectively.

For those patients who were not found to have cancer within 3 years of index colonoscopy (n=187,043), the median follow up was 8.1 years (IQR: 6.0–10.4 years). Among them, 436 (0.2%) patients were diagnosed with PCCRC beyond 3 years and the adjusted SHR with statins was 1.05 (95% CI:0.73–1.50).

Association between statins and colorectal adenoma

Among the 27,104 patients who had at least one repeat colonoscopy, 8,817 had at least one adenoma, including 1,255 with at least one advanced adenoma. There was no significant association between statins and development of any adenoma (OR:1.08; 95% CI:0.97–1.20), including non-advanced adenoma (OR:1.04; 95% CI:0.82–1.30) and advanced adenoma (OR:1.09; 95% CI:0.98-1.22) (**Table 4**). Statin users had fewer advanced adenomas than non-statin users (3[IQR:2–3] vs 3[IQR:2–4];p=0.017). There was however no significant difference in the number of any adenomas (median number=3[IQR:2–4] vs 3[IQR:2–4];p=0.440 or non-advanced adenomas (median number=3[IQR:2–4] vs 3[IQR:2–4];p=0.550) between statin and non-statin users.

DISCUSSION

PCCRC could account for up to 9% of all diagnosed CRCs.[8] Although current evidence suggests that statins are associated with a reduced risk of CRC,[18, 19, 44] studies on the potential role of statins in PCCRC are lacking. To our knowledge, this is the first epidemiological study involving more than 180,000 subjects to demonstrate the potential dose-related chemopreventive effect of statins in PCCRC-3y (overall 28% lower risk and 7% reduction for every 100 increase in cDDD of statin uses).

Interestingly, this demonstrated beneficial effect is larger than pooled result from previous meta-analysis that reported only a modest reduction (10%) in overall CRC risk.[19, 20, 44] It is important to note that previous findings were based on all CRCs without stratified analysis into detected and PCCRC. Specifically, we found that the beneficial effect of statins was mainly limited to PCCRC-3y, but not PCCRC beyond 3 years and CRC-all risk, which is consistent with the previous findings of modest beneficial effect of statins on overall CRC risk[19, 20, 44]. This observation further supports that statins preferentially affect the later stage of adenoma-carcinoma progression.[18] Inhibition of HMG-CoA reductase leads to reduced expression of carcinogenic intermediates from mevalonate pathway which is involved in neoplastic transformation of adenomas and cancer progression rather than adenoma development.[45] As a period of about ten years is required for pre-existing adenomas to become invasive cancer,[46] we speculate that missed lesions (which are later diagnosed as PCCRC) are more likely the lesions on which statins exert the greatest effect (i.e. inhibiting progression from advanced adenoma to cancer). This is also supported by

our findings that statins were not associated with a reduced risk of any adenoma development after colonoscopy.

The protective effect of statins on PCCRC-3y appears to be more pronounced for proximal than distal cancers (OR 0.50 vs 0.80). While potential difference in the beneficial effect of chemopreventive agent for proximal and distal CRC has been scarcely reported, it is plausible that statins have differential effect on carcinogenesis of proximal and distal cancer.[19] In particular, it remains to be determined whether statins have a larger effect on the sessile serrated pathway (hence greater benefit on proximal CRC prevention) than the adenoma-carcinoma sequence. It should be acknowledged that the majority of sessile serrated polyps were simply reported as hyperplastic polyps during the study period when awareness of this pathology was still low, and hence the effect of statins on sessile serrated polyps could not be further studied in this study.

Subgroup analysis shows that beneficial effect of statins on PCCRC-3y was limited to those with advanced age (≥ 60 years), female patients, those without DM and history of polyps. While younger patients generally have fewer colonic polyps (both adenomatous[47] and serrated polyps[48]), subgroup analysis may be underpowered to detect a beneficial effect of statins in younger subjects. As DM can lead to a higher CRC risk via hyperinsulinemia,[49, 50] it is not surprising that statins are non-beneficial as they do not target at this pathway. Male patients and those with a history of polyps represent individuals with a higher underlying risk of CRC. The effect of these risk factors may overwhelm beneficial effect of statins.

The strength of our study is the use of a territory-wide healthcare database which addresses potential biases (selection, information and recall biases) inherent to traditional observational studies. Biases from unmeasured confounding was further reduced by PS matching with well balance of major characteristics including smoking, alcoholism, other cardiovascular risk factors and diseases. However, it should be noted that residual/unmeasured confounding is always possible in observational studies. Furthermore, we minimized potential competitive risks from death among statin users by using SHR as statin users were more likely to die from comorbid diseases that mandate statin use. Given the potential large number of PCCRC, a NNT of 498 for statins (≥ 90 days) to prevent one PCCRC could still have significant public health benefit. This may also contribute to the decision making process of commencing statins in patients with borderline indications for cardiovascular disease prevention but high risk of CRC, especially older age groups (≥ 60 years). However, men and diabetic patients may benefit less from statin for prevention of PCCRC than expected from cardiovascular diseases as in our subgroup analysis.

Several limitations of this study should be noted. First, a few risk factors for CRC like family history and lifestyle factors such as dietary habits were not available in CDARS. Dietary fibre intake is a major risk factor for CRC[51], but their association with PCCRC and statins can be biased in both directions. One may argue that without adjusting for dietary factor, beneficial effect of statins may be attenuated as statin users, usually with concomitant cardiovascular risk factors, may have an adverse lifestyle. Alternatively, healthy user bias may exaggerate beneficial effect of statins. Second, drug adherence could not be ascertained from CDARS. This was however unlikely to be a significant problem in Hong Kong as medications are prescribed and

dispensed together in the same hospital at a very affordable price. In addition, non-adherence will usually attenuate the result towards null. Third, as around 70% of the patients were prescribed simvastatin, the result may not apply to other statins. Fourth, use of diagnostic coding will likely underestimate true prevalence of smoking and alcoholism which are risk factors for CRC. Differential follow-up based on statin use is another concern. However, as explained above, PS matching would likely minimize these biases, as reflected by the well balance of cardiovascular risk factors and other factors between the two groups after matching (**Table 1**). Fifth, data on the indications of index colonoscopy, individual endoscopist's adenoma detection rate, quality of bowel preparation, and size of colonic polyps were unavailable in CDARS. In particular, indications of index colonoscopy could partly reflect future risk of CRC. Lastly, as the majority of our patients are ethnic Chinese, our study results may not be generalizable to other ethnic groups with genetic variation in HMG-CoA reductase activity.[52] In particular, it is interesting to note that majority of PCCRC-3y in our study were distal cancers rather than proximal cancer as reported in western literature.[9] Despite this difference in tumour location with more distal PCCRC, statin users were still found to have a significantly lower risk of PCCRC-3y, particularly for proximal cancer.

CONCLUSION

This territory-wide cohort study shows a significantly lower risk of PCCRC-3y for statin use in a dose-response manner, particularly for proximal cancer. Further studies are necessary to confirm our findings in other populations.

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FIGURE LEGEND

Figure 1: Study patient selection flow diagram

CRC, colorectal cancer; CLN, colonoscopy

Table 1. Baseline characteristics of study cohort before and after propensity score matching

		Before PS Matching			After PS Matching *		
	All (n=187,897)	Statin (n=25,447)	Non-statin (n=162,450)	ASD#	Statin (n=17,662)	Non-statin (n=30,304)	ASD#
Age at index colonoscopy (years)*	62.1 +/- 12.3	68.0 +/- 10.5	61.2 +/- 12.3	0.50	61.7 +/- 11.0	63.6 +/- 13.8	0.09
Male sex (n, %)	91961 (48.9%)	13319 (52.3%)	78642 (48.4%)	0.05	8935 (50.6%)	15024 (49.6%)	0.01
History of colonic polyps (n, %)	39066 (20.8%)	6754 (26.5%)	32312 (19.9%)	0.09	4344 (24.6%)	7530 (24.8%)	0.01
Polypectomy at index colonoscopy (n, %)	28724 (15.3%)	3663 (14.4%)	25061 (15.4%)	0.02	2519 (14.3%)	4875 (16.1%)	0.02
Smoking (n, %)	3874 (2.1%)	699 (2.7%)	3175 (2.0%)	0.06	450 (2.5%)	974 (2.6%)	0.02
Alcohol (n, %)	1065 (0.6%)	101 (0.4%)	964 (0.6%)	0.002	77 (0.4%)	127 (0.4%)	0.002
DM (n, %)	17935 (9.5%)	7448 (29.3%)	10487 (6.5%)	0.35	3486 (19.7%)	5684 (18.8%)	0.04
Hypertension (n, %)	28982 (15.4%)	10104 (39.7%)	28982 (15.4%)	0.38	4968 (28.1%)	7925 (26.2%)	0.03
Dyslipiemia (n, %)	9557 (5.1%)	6828 (26.8%)	9557 (5.1%)	0.28	1573 (8.9%)	1622 (5.4%)	0.05
AF (n, %)	5673 (3.0%)	1712 (6.7%)	3961 (2.4%)	0.15	1030 (5.8%)	1833 (6.0%)	0.03
IHD (n, %)	13266 (7.1%)	8094 (31.8%)	5172 (3.2%)	0.40	2919 (16.5%)	3203 (10.6%)	0.06
CHF (n, %)	6302 (3.4%)	2442 (9.6%)	3860 (2.4%)	0.18	1163 (6.6%)	1777 (5.9%)	0.01
Stroke (n, %)	7638 (4.1%)	3385 (13.3%)	4253 (2.6%)	0.28	1591 (9.0%)	2461 (8.1%)	0.02
CRF (n, %)	3924 (2.1%)	1718 (6.8%)	2206 (1.4%)	0.15	753 (4.3%)	1174 (3.9%)	0.01
Cirrhosis (n, %)	1250 (0.7%)	113 (0.4%)	1137 (0.7%)	0.23	82 (0.5%)	149 (0.5%)	0.006
Dementia (n, %)	1258 (0.7%)	269 (1.1%)	989 (0.6%)	0.05	173 (1.0%)	322 (1.1%)	0.02
Parkinsonism (n, %)	779 (0.4%)	129 (0.5%)	650 (0.4%)	0.02	82 (0.5%)	160 (0.5%)	0.01
Aspirin (n, %)	28569 (15.2%)	14224 (55.9%)	14345 (8.8%)	0.68	7181 (40.7%)	10838 (35.8%)	0.02

NSAIDs (n, %)	21757 (11.6%)	3786 (14.9%)	17971 (11.1%)	0.85	2574 (14.6%)	4595 (15.2%)	0.02
COX-2 inhibitors (n,%)	378 (0.2%)	86 (0.3%)	292 (0.2%)	0.02	52 (0.3%)	127 (0.4%)	0.02
Center endoscopy volume	2683 +/- 953	2712 +/- 988	2678 +/- 947	0.04	2704 +/- 986	2717 +/- 961	<0001
Center polypectomy rate	24.9% +/- 4.5%	25.7% +/- 4.3%	24.8% +/- 4.5%	0.05	25.5 +/- 4.3%	25.5 +/- 4.4%	0.004

Continuous variables were expressed as mean (years) +/- 1 standard deviation
Categorical variables were expressed as number (%)
Drug use was defined as use for more than 90 days, and expressed as number (%)
Abbreviations: PS, propensity score; ASD, absolute standardised difference; DM, diabetes mellitus; IHD, ischemic heart disease; AF, atrial fibrillation; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2
* PS matching was performed after trimming of the extreme PS strata (5th and 95th percentiles). Non-statin users were matched to statin users on PS within a caliper width of 0.1. All variables were included in the model for PS estimation
# Variables with an ASD > 0.20 is considered to be imbalanced

Table 2. Association between statin use and risk of PCCRC-3y for the whole cohort and according to the cancer site (proximal and distal CRC) after propensity score matching

	No. of patients	No. of CRC	Person-years of follow-up	SHR	95% CI	p-value
All PCCRC-3y	**47,966**	**253**	**142,957**			
Non-statin use	30,304	178	90,244	Ref	-	-
Statin use (≥ 90 days)	17,662	75	52,713	0.72	0.55 – 0.95	0.018
Proximal PCCRC-3y	**47,775**	**62**	**142,704**			
Non-statin use	30,174	48	90,076	Ref	-	-
Statin use (≥ 90 days)	17,601	14	52,628	0.50	0.28 – 0.91	0.022
Distal PCCRC-3y	**47,904**	**191**	**142,876**			
Non-statin use	30,256	130	90,181	Ref	-	-
Statin use (≥ 90 days)	17,648	61	52,695	0.80	0.59– 1.09	0.16

PCCRC-3y, post-colonoscopy colorectal cancer within 3 years; CRC, colorectal cancer; SHR, subdistribution hazard ratio; 95% CI, 95% confidence interval; PS, propensity score

Table 3. Subgroup analysis of the association between statin use and risk PCCRC-3y (PS adjustment with trimming)

	No. of patients	CRC cases	Person-years of follow-up	Adjusted SHR	95% CI	p-value
Age ≥ 60	**87,472**	**631**	**259,992**			
Non-statin use	72,452	549	215,230	Ref	-	-
Statin use (≥ 90 days)	15,020	82	44,762	0.72	0.56 – 0.92	0.009
Age < 60	**82,849**	**151**	**248,050**			
Non-statin use	79,399	148	237,719	Ref	-	-
Statin use (≥ 90 days)	3,450	3	10,332	0.54	0.18 – 1.66	0.28
Male	**82,764**	**469**	**246,525**			
Non-statin use	73,246	412	218,158	Ref	-	-
Statin use (≥ 90 days)	9,518	57	28,367	0.88	0.64 – 1.22	0.44
Female	**86,343**	**315**	**257,851**			
Non-statin use	77,685	296	213,975	Ref	-	-
Statin use (≥ 90 days)	8,658	19	25,876	0.35	0.22 – 0.58	<0.001
Presence of DM	**16,141**	**79**	**48,080**			
Non-statin use	9,588	47	28,543	Ref	-	-
Statin use (≥ 90 days)	6,553	32	19,537	1.17	0.75 – 1.81	0.49
Absence of DM	**152,964**	**684**	**456,302**			
Non-statin use	140,874	640	420,205	Ref	-	-
Statin use (≥ 90 days)	12,090	44	36,097	0.59	0.42 – 0.81	<0.001
History of polyp and/or polypectomy	41,128	294	122,406			
Non-statin use	35,477	252	105,591	Ref	-	-
Statin use (≥ 90 days)	5,651	42	16,815	0.75	0.52 – 1.10	0.14
No history of polyp and/or polypectomy	**127,979**	**498**	**381,952**			
Non-statin use	115,462	461	344,549	Ref	-	-
Statin use (≥ 90 days)	12,517	37	37,403	0.58	0.41 – 0.83	0.003

PCCRC-3y, post-colonoscopy colorectal cancer within 3 years; PS, propensity score; SHR, subdistribution hazard ratio; 95% CI, 95% confidence interval; DM, diabetes mellitus

Table 4. A. Association between statin use and risk of colonic adenoma development (PS adjustment with trimming); B. Comparison of the number of adenomas between statin and non-statin users

A.	No. of patients	Adjusted OR	95% CI	p-value
Any adenoma				
Non-statin use	22,446	Ref	-	-
Statin use	1,946	1.08	0.97 – 1.20	0.14
Non-advanced adenoma				
Non-statin use	16,258	Ref	-	-
Statin use	1,328	1.04	0.82 – 1.30	0.76
Advanced adenoma				
Non-statin use	21,434	Ref	-	-
Statin use	1,829	1.09	0.98 – 1.22	0.12
B.	**No. of patients**	**Median no. of adenomas**	**IQR**	**p-value**
Any adenoma				
Non-statin use	7,752	3	2 – 4	
Statin use	1,065	3	2 – 4	0.44
Non-advanced adenomas				
Non-statin use	7,316	3	2 – 4	
Statin use	1,014	3	2 – 4	0.55
Advanced adenomas				
Non-statin use	1,096	3	2 – 4	
Statin use	159	3	2 – 3	0.017

PS, propensity score; OR, odds ratio; IQR: interquartile range

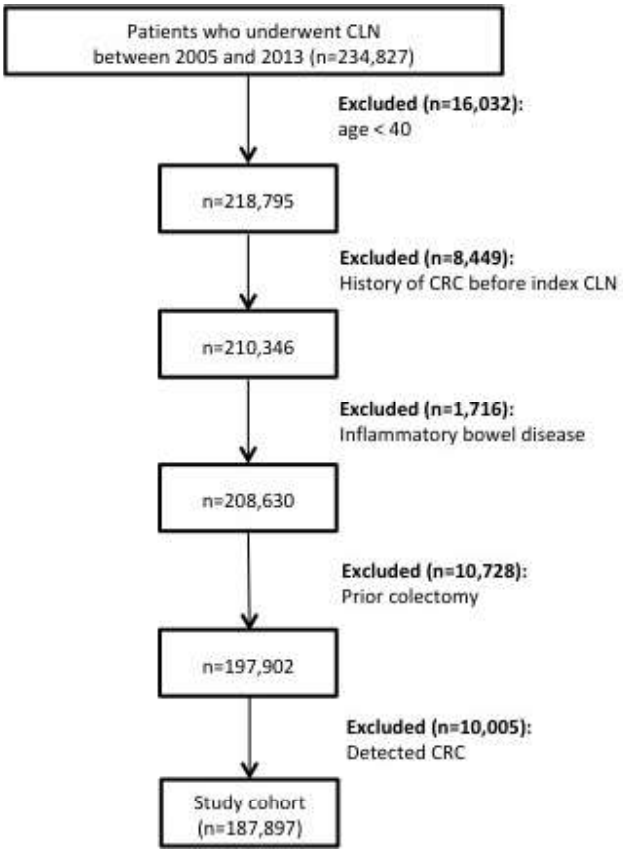

Figure 1: Study patient selection flow diagram
CRC, colorectal cancer; CLN, colonoscopy

148x152mm (72 x 72 DPI)

Description of propensity score matching

Propensity score was derived from logistic regression to represent the probability of statin prescription conditional on the 22 aforementioned covariates. Before PS matching, subjects in the extreme ends of the PS distribution were excluded to reduce bias from unmeasured confounding.[1] Twenty categories of 5% each for the PS distribution were created, followed by trimming of the first and 20th PS categories. Statin users were matched to non-statin users in a 1:2 ratio without replacement using a greedy distance-based matching algorithm with the logit of the PS within 0.1 standard deviation. The balance of the covariates between the two groups was then assessed by absolute standardized difference (ASD), which was derived from the absolute difference in means or proportions divided by the pooled standard deviation. An ASD of < 0.20 indicates good balance for that particular variable. Imbalanced variables with ASD > 0.20 after matching were adjusted for in the regression model.[2]

References

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eTable 1. ICD-9 codes for outcome and covariates

Outcome	
Colorectal cancer	Proximal cancer: 153.4, 153.6, 153.0, 153.1 Distal cancer: 153.2, 153.3, 153.7, 154.0, 154.1 Unspecified site: 154
Covariates	
Smoking*	491, 492, 496, V15.82
Alcohol*	291, 303, 305.0, 571.0, 571.1, 571.2, 571.3, 980.8, 980.9
Diabetes mellitus	249, 250
Hypertension	401-405
Dysplipidemia	272.0-272.4
Atrial fibrillation	427.3
Ischemic heart disease	410-413, 414.0, 414.8, 414.9, 429.7
Congestive heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Stroke	430-432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 437.0, 437.1
Chronic renal failure	585
Cirrhosis	571.2, 571.5, 571.6, 572.2-572.4, 573.5
Dementia	290, 291.2, 292.82, 294.1-294.2
Parkinsonism	332
Crohn's disease	555
Ulcerative colitis	556
Colectomy	45.8, 45.81, 45.82, 45.83, V45.89

* Smoking was identified by the ICD-9 code of V15.82 and chronic obstructive pulmonary disease (COPD) indicating heavy smoking. Heavy alcohol consumption was identified by the presence of alcohol-related disorders, including hepatic, gastrointestinal, neurological and psychiatric diseases.

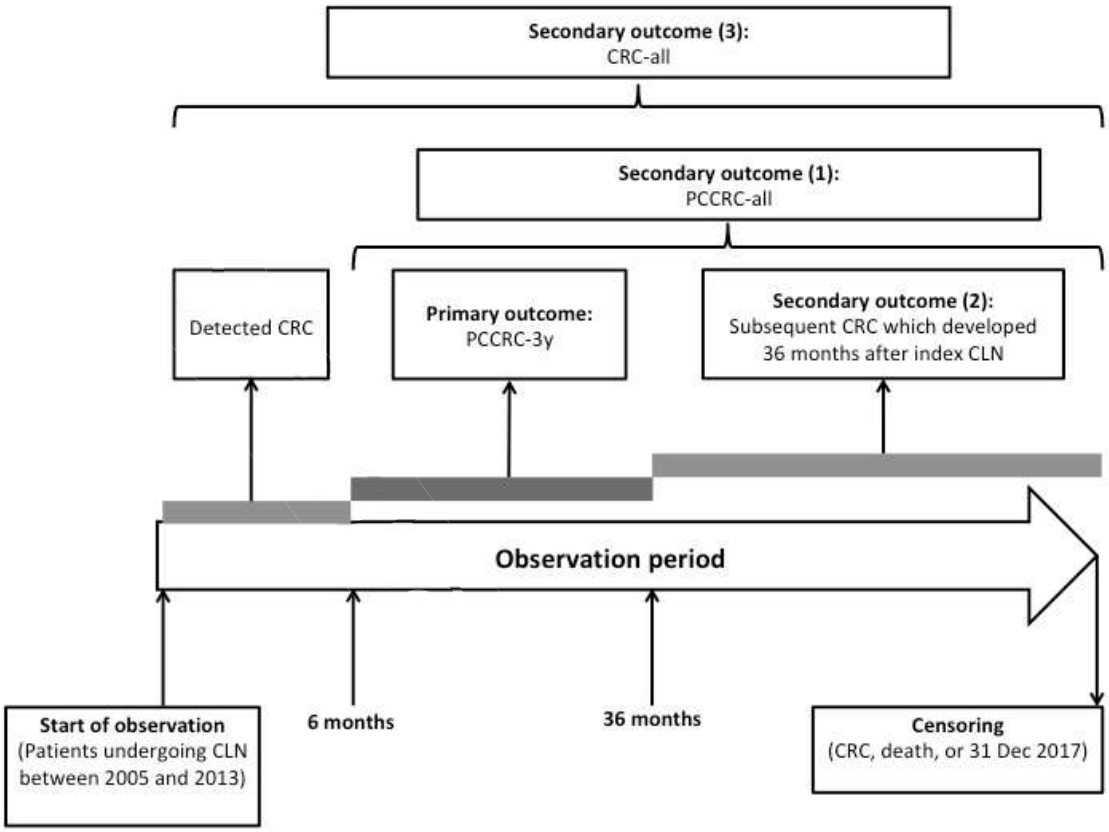
eTable 2. Sensitivity analysis on the association between statin use and risk of PCCRC-3y for the whole cohort and according to the cancer site (proximal and distal CRC) by PS adjustment with and without trimming

		PS adjustment without trimming (n=187,897, CRC=854)			PS adjustment with trimming (n=169,107, CRC=790*)	
All PCCRC-3y	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**
Non-statin use	Ref	-	-	Ref	-	-
Statin use (≥90 days)	0.74	0.58 – 0.93	0.012	0.64	0.49– 0.83	<0.001
		(n=187,190, CRC=147)			**(n=168,471, CRC=140*)**	
Proximal PCCRC-3y	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**
Non-statin use	Ref	-	-	Ref	-	-
Statin use (≥90 days)	0.44	0.22 – 0.88	0.020	0.43	0.23 – 0.83	0.011
		(n=187,750, CRC=707)			**(n=168,974, CRC=649*)**	
Distal PCCRC-3y	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**
Non-statin use	Ref	-	-	Ref	-	-
Statin use (≥90 days)	0.82	0.64 – 1.05	0.110	0.70	0.53 – 0.93	0.013

* For PS adjustment with trimming, the total number of all PCCRC-3y cases does not equate the sum of the number of proximal and distal PCCRC-3y cases as PS was derived for each stratified analysis according to CRC location

PCCRC-3y, post-colonoscopy colorectal cancer within 3 years; CRC, colorectal cancer; SHR, subdistribution hazard ratio; 95% CI, 95% confidence interval; PS, propensity score

eFigure 1. Study observation period



CRC, colorectal cancer; PCCRC-3y, post-colonoscopy colorectal cancer at 3 years; PCCRC-all, all post-colonoscopy colorectal cancer cases; CLN, colonoscopy
Detected CRC was defined as CRC diagnosed within 6 months after the index colonoscopy
PCCRC-3y was defined as CRC diagnosed between 6 to 36 months after the index colonoscopy
PCCRC-all was defined as CRC diagnosed beyond 6 months after the index colonoscopy