

Published in final edited form as:

Clin Gastroenterol Hepatol. 2013 February ; 11(2): 109–e14. doi:10.1016/j.cgh.2012.08.037.

Statins and colorectal cancer

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Abstract

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, more commonly referred to as statins, comprise a family of lipid-lowering drugs that are prescribed on a global scale on account of their demonstrated safety and efficacy in reducing mortality from cardiovascular disease. Beyond their potent pharmacologic inhibition of cholesterol biosynthesis, statins appear to have pleiotropic effects, including modulation of cell growth, apoptosis, and inflammation. Through modulation of these pathways, statins have the potential to influence a wide range of disease processes, including cancer. Much attention has focussed on the association between statins and colorectal cancer, raising the prospect that these well-tolerated compounds could form the basis of future chemopreventive strategies. Herein we review the epidemiologic, clinical, and pre-clinical data relevant to statins and colorectal neoplasia, and discuss the current status and future potential of statins as chemopreventive agents.

INTRODUCTION: STATINS AND CANCER

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, more commonly referred to as statins, were first identified in the 1970s by Japanese biochemist Akira Endo,¹ and received market approval for the treatment of hypercholesterolemia in the late 1980's.² As a result of their proven efficacy in the primary and secondary prevention of cardiovascular mortality and stroke,³ statins have become one of the most widely-prescribed medications in the world. Approximately 11% of the U.S. population use statins, with prevalence rising to 44% in those over 65 years of age.⁴ Statins competitively inhibit HMG-CoA reductase, which catalyses the rate-limiting step in the mevalonate pathway.⁵ By preventing the conversion of HMG-CoA to mevalonate, statins potently reduce endogenous cholesterol synthesis, leading to a decrease in circulating low density lipoprotein (LDL)-cholesterol.⁵ Independent of their lipid-lowering properties, statins appear to possess a variety of pleiotropic effects, including inhibition of cell proliferation, enhanced apoptosis, and modulation of inflammation, endothelial function, and angiogenesis.^{6,7} Indeed, some of

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Conflicts of interest: Dr Chan has consulted for Bayer Healthcare, Millennium Pharmaceuticals, and Pfizer Inc.

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these additional actions are thought to contribute to their demonstrated cardioprotective benefit.^{6,8,9} Through these diverse mechanisms, statins have been hypothesized to influence a wide range of additional disease processes, including cancer.

A significant body of evidence suggests that statins might have a role in cancer chemoprevention.^{10,11} However, the association between statins and cancer risk has a rather chequered history. Following the market approval of statins, concerns were raised regarding the long-term safety of pharmacological cholesterol-lowering in humans, based largely upon observational data suggesting that non-cardiovascular mortality, including cancer, may be increased by low serum cholesterol levels.^{12,13} In retrospect, this association was probably largely explained by uncontrolled confounding and reverse causality, with low cholesterol being a consequence of occult malignancy.^{14,15} Anxieties over long-term statin use were further compounded by pre-approval studies that suggested statins were carcinogenic in rodents.¹⁶ Data from an early cardiovascular randomized controlled trial (RCT) of pravastatin,¹⁷ demonstrating an increased incidence of breast cancer in the treatment arm, and findings of a later case-control study, suggesting increased risk of breast and prostate cancer among statin users,¹⁸ did little to allay fears over statin safety.

A number of subsequent RCTs have, reassuringly, suggested a neutral effect of statin use on overall cancer risk.^{19–22} Furthermore, some, but not all, observational studies have raised the possibility of inverse associations between statins and overall cancer risk,^{23–25} and risks of specific cancers, including colorectal cancer.^{26–29} In this article, we review the experimental, epidemiologic, and clinical data relevant to statins and colorectal neoplasia, and discuss the current status and future potential of statins as chemopreventive agents.

EXPERIMENTAL EVIDENCE: ANTICANCER MECHANISMS OF STATINS

The interest in statins as modifiers of cancer risk spawned a large number of experimental studies examining the anti-neoplastic effects of statins in cellular and animal models of human cancer.^{10,11} Inhibition of HMG-CoA reductase by statins leads not only to a decrease in cholesterol synthesis, but also to reduced generation of other intermediates of the mevalonate pathway, including the non-sterol isoprenoids, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP).⁵ FPP and GGPP are required for post-translational modification (isoprenylation), and biologic activity of a wide variety of cellular proteins, including the small GTPases RAS and RHO,¹¹ which are strongly implicated in carcinogenesis.^{30,31} Modulation of isoprenylation appears to be a central mechanism through which statins exert their antiproliferative and pro-apoptotic effects.^{7,11} In addition, dysregulation of the mevalonate pathway may be causally implicated as a driver of neoplastic transformation and tumor progression, and this may partly explain the tumor-selective effects of statins.^{32,33}

A number of HMG-CoA reductase-independent mechanisms have also been proposed to account for the pleiotropic effects of statins, including antioxidant activity,³⁴ and effects on cell adhesion,^{35,36} inflammation,^{8,37} immunoregulation,³⁸ and angiogenesis.³⁹ Experimental data support a role for statins as anti-neoplastic agents in the colon. Statins have been shown to exert growth inhibitory and pro-apoptotic effects in several human colorectal cancer cell lines in vitro, and in tumor xenograft models.^{40,41} The molecular mechanisms that account for the effect of statins on colorectal cancer cell growth and survival remain poorly understood; however, enhanced cellular oxidative stress,⁴² endoplasmic reticulum stress and autophagy,⁴³ altered expression of apoptotic and proliferative signalling molecules,^{44,45} and modulation of the bone morphogenic protein signalling pathway,⁴⁶ have all been implicated by experimental studies. In rodents, statins reduce the occurrence of azoxymethane-induced colonic neoplasia.^{40,47,48} Statins also appear to reduce polyp formation in the genetically-

predisposed Min mouse; either alone,⁴⁹ or synergistically with celecoxib.⁵⁰ *In vitro* data also support a role for statins as adjuncts to chemotherapy in colorectal cancer. Recent experimental evidence suggests that simvastatin may overcome resistance to EGFR inhibition with cetuximab in *KRAS*-mutated colon cancer cells,⁵¹ and lovastatin has been shown to act through epigenetic mechanisms to reduce cancer cell 'stemness' and enhance chemosensitivity to 5-fluorouracil.⁵² Considered together, experimental evidence provides biologically plausible roles for statins in

STATINS AND COLORECTAL CANCER RISK IN RANDOMIZED TRIALS

As a result of numerous large randomized controlled trials (RCTs) of lipid-lowering and major vascular events, a wealth of clinical data on statin use has accrued. Most statin RCTs have collected data on overall cancer incidence, while some studies have recorded site-specific incidence. Thus, cardiovascular RCTs represent a valuable resource for assessing differences in cancer incidence between groups where statin use has been randomly assigned. Several tabular meta-analyses of RCT data, performed using differing inclusion criteria and methodologies,^{19,20, 22,53} concur that statin use over follow-up periods of around 4–6 years is not associated with an increase in overall cancer incidence. Whilst this is obviously reassuring, aggregate cancer risk does not address the possibility of differential effects of statin use on the risks of specific cancer types. In the PROSPER trial,⁵⁴ for example, the observed reduction in cardiovascular risk was largely offset by an excess of gastrointestinal malignancies in those assigned to statin, compared to placebo. Although meta-analyses of colorectal cancer risk in cardiovascular RCTs face the limitation of a reduced number of studies with available site-specific cancer data, these metaanalyses have consistently failed to demonstrate an association between statins and colorectal cancer.^{20, 22, 53} Thus, the increased number of gastrointestinal cancers observed in the PROSPER trial may have arisen by chance. Most recently, the Cholesterol Treatment Trialists' (CTT) Collaboration published a meta-analysis of individual data from 175,000 participants in 27 statin RCTs, five of which were trials of more intensive vs. standard LDL-lowering.⁵⁵ Over a median follow up of 4.8 years, the number of incident colorectal cancers was not significantly different between those assigned to statin (or more statin) compared to controls (or less statin). Furthermore, there were no associations between overall cancer risk and duration of therapy, participant age, type of statin, or baseline LDL.⁵⁵

One major criticism of cancer risk estimates from meta-analyses of statin RCTs is duration of follow up. The longest average follow-up in the cited meta-analyses was 5.9 years,⁵³ with some meta-analyses including individual RCTs with only two years of follow-up, or less.^{19,20,22} Individually, a small number of studies have accumulated longer post-trial follow-up. The WOSCOPS primary prevention study, which randomized participants to pravastatin or placebo for 5 years, found no difference in colorectal cancer incidence between groups 10 years after the completion of the trial.⁵⁶ Similarly, the Heart Protection Study found no difference in colorectal cancer incidence between those assigned to five years of simvastatin or placebo after cumulative follow-up of 11 years.⁵⁷ The adenoma-carcinoma sequence is postulated to take at least 10 years, and the initiation of colorectal neoplasia from normal mucosa may take even longer. Unless the effects of statins are restricted to advanced stages of colorectal neoplasia, it is likely that the majority of RCTs have insufficient follow-up to assess fully the potential beneficial or adverse effects of statins on colorectal carcinogenesis. Additionally, as secondary endpoints, data on cancer incidence and mortality are not systemically collected in cardiovascular RCTs, and may thus be subject to ascertainment bias. Given that many cardiovascular trials have been conducted in high-risk populations, competing risks also becomes an important potential source of bias; individuals randomized to placebo may die from major vascular events before they have had time to develop cancer.

OBSERVATIONAL STUDIES OF STATINS AND COLORECTAL CANCER

Case-control studies are generally able to efficiently examine associations between remote exposures and risk of disease, while cohort studies can be valuable in dissecting time-dependent associations between exposures and outcomes. A large number of observational studies have assessed the association between statin use and colorectal cancer (Table 1). Perhaps the most publicised and highly cited of these studies is the analysis by Poynter and colleagues, based on the Molecular Epidemiology of Colorectal Cancer study.²⁶ This was the first well-powered case-control study of statins and colorectal cancer, including 1,953 cases and 2,015 controls derived from the population of northern Israel. Following adjustment for multiple potential confounders, Poynter and colleagues observed an impressive 43% reduction in colorectal cancer risk associated with at least 5 years of self-reported statin use. Interestingly, a subsequent genetic association study, performed in the same parent case-control study, demonstrated that a polymorphism in the HMG-CoA reductase gene modified the association between statins and colorectal cancer and was associated with lower LDL-cholesterol in both cases and controls.⁵⁸ A nested case-control study in veterans with diabetes, including 6,080 colorectal cancer cases and 24,320 controls, demonstrated a more modest reduction in colorectal cancer risk (9%) associated with statin use, but without significant dose or duration-dependent relationships.²⁹ Furthermore, the protective association was limited to colon (not rectal) cancer in patients older than 65 years without a history of previous polyps.²⁹ A German population-based case-control study, comprising 540 cases and 614 controls, demonstrated an inverse association between colorectal cancer risk and statin use of 1–4 years duration, but, interestingly, no additional risk reduction was observed for use beyond 5 years.²⁷ In contrast, at least 12 case-control studies from the U.S., Europe, and Asia have reported no significant associations between statin use and colorectal cancer risk.^{23, 24, 59–68} Indeed, in a study conducted in the United Kingdom, using an electronic general practice prescribing database, an increased risk of colorectal cancer was associated with statin use of greater than 4 years.⁶⁷ A limitation of these data is that case-control studies are particularly susceptible to recall bias, or biases arising from the selection of cases and controls. Moreover, in the case-control study of Poynter and colleagues, over two thirds of cases and controls were Ashkenazi Jews,²⁶ potentially limiting the generalizability of the findings to other populations.²⁰

Data from cohort studies are more limited. A retrospective cohort study conducted in a large U.S. veterans population, containing over 37,000 statin users, reported a 35% reduction in colorectal cancer risk associated with statin use, and also found a significant decrease in risk with increasing statin dose.²⁸ In combined analysis of prospectively-collected data from the Health Professionals Follow-up Study and Nurses' Health Study, statin use was not associated with overall colorectal cancer risk, although an inverse association was observed for rectal cancer risk (RR = 0.59).⁶⁹ Analysis of incident colorectal cancers over almost 11 years of follow up in the Women's Health Initiative revealed no difference in incidence according to statin use, but did report risk reduction of borderline statistical significance specifically associated with lovastatin use.⁷⁰ Eight additional large cohort studies reported neither beneficial nor harmful associations between statins and colorectal cancer.^{25,71–77} Compared to case-control analyses, cohort studies are generally less vulnerable to recall and selection biases, but can be limited by sample size and insufficient follow-up time for incident cancers. Some cohort studies encompass less follow-up time than several of the statin RCTs.^{71,72,75}

Among four meta-analyses that have included data from case-control and cohort studies,^{20,22,53, 78} one found no association between statin use and colorectal cancer risk,²² while three reported risk reductions of more modest magnitude (risk estimates 0.86–0.91).^{20,53,78} In two of these meta-analyses, a significant association between statin use and

colorectal cancer risk was observed only in fixed effects models but not random effects models.^{20,53} The study by Poynter and colleagues²⁶ appears to have been a major source of inter-study heterogeneity in the metaanalysis by Bonovas and colleagues,⁵³ suggesting that it may represent an outlier. The Poynter study also appears to have been the driver of the protective association observed in the metaanalysis by Browning and colleagues;²⁰ when this case-control study was excluded, the association between statin use and colorectal cancer was null.

The main limitation of both case-control and cohort studies is that they are prone to residual confounding by unmeasured exposures or behaviors that are associated with both statin use and colorectal cancer incidence. Indeed, evidence suggests that statin use is associated with higher socioeconomic status,⁷⁹ NSAID use,⁶² and health conscious behaviors, such as multivitamin use and screening colonoscopy.⁶² While most observational studies adjust for use of aspirin and NSAIDs, which are consistently associated with lower colorectal cancer risk, information on cancer screening and other risk modifiers, such as physical activity, are not universally collected. Furthermore, residual confounding is impossible to exclude, even in the best-designed studies.

STATINS AND POLYP PREVENTION

Even short-term statin use may be sufficient to influence the evolution or progression of colorectal adenomas, the precursors to the vast majority of colorectal cancers (Table 2). In a retrospective analysis conducted in over 2,500 veterans with a history of colonoscopic polypectomy for adenomas, Siddiqui and colleagues demonstrated a 49% reduction in the incidence of recurrent adenomas, and a 29% reduction in the incidence of advanced adenomas, associated with continuous statin use over 3–5 years.⁸⁰ In a subsequent analysis of 231 individuals from the same population,⁸¹ significantly fewer adenomas, of smaller size, were observed at follow-up colonoscopy in individuals who had achieved 30% reduction in LDL-cholesterol, compared to those who had not, suggesting that lipid-lowering, rather than statin use per se, may partly be responsible for the effect of statins on adenoma development and progression.⁸¹ An independent case-control study of 197 patients, also from a veterans population, found no association between statin use and adenoma recurrence over a median 3.4 years.⁸² Furthermore, a secondary analysis of data from three large colorectal adenoma chemoprevention trials, with a combined total of 2,915 subjects, failed to demonstrate any association between statin use, recurrent adenomas, multiple adenomas, or advanced adenomas.⁸³ The prevalence of self-reported statin use was, however, low (8.1%) across the three chemoprevention trials, limiting power for the post-hoc analysis.⁸³ Statin users comprised a much larger proportion (37%) of participants in the Adenoma Prevention with Celecoxib (APC) trial.⁸⁴ However, in a secondary analysis of APC trial data, Bertagnolli and colleagues found no evidence to support a chemopreventive effect of statin use over 5 years of follow-up. On the contrary, statin use of >3 years was associated with a 39% increased risk of adenomas.⁸⁴ Although these data are derived from a RCT, statin use was self-selected. Nonetheless, this analysis represents the largest prospective study of statin use and incident adenomas. Furthermore, assessment of the association between statin use and study endpoints was a planned secondary analysis.⁸⁴

STATIN USE AFTER A DIAGNOSIS OF COLORECTAL CANCER

Another high-risk group, in whom it may be possible to demonstrate benefit from statin use in shorter term studies, are individuals who have already developed colorectal cancer. In a retrospective cohort study of 1,309 male veterans with colorectal cancer,⁸⁵ compared to non-users, >3 years of pre-diagnosis statin use was associated with lower tumor stage, lower prevalence of metastases, and a higher frequency of proximal cancers. Survival analysis

demonstrated more favorable 5-year cancer-specific survival in statin users compared to non-users. A significant limitation of this study was the inability to control for pre-diagnosis colorectal screening. In a randomized trial of adjuvant chemotherapy involving 842 patients with stage III colorectal cancer, prospective observational analysis of post-diagnosis statin use did not reveal any association with improved disease free, recurrence free, or overall survival.⁸⁶ A randomized phase II trial of chemoprevention with atorvastatin, sulindac, or dietary fiber, conducted in individuals with resected colorectal cancer or advanced adenomas, also failed to demonstrate a protective effect of statin therapy.⁸⁷ This study, which used rectal aberrant crypt foci as a surrogate endpoint, was, however, underpowered, with only 85 subjects randomized to each of the three interventions, or placebo.⁸⁷

The safety of simvastatin as an adjunct to conventional chemotherapy for metastatic colorectal cancer has been demonstrated by a completed phase II trial,⁸⁸ and a number of additional phase II and III studies are currently recruiting.⁸⁹ The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-5 study is actively enrolling patients with resected stage I and II colon cancer. Participants will be randomized to receive rosuvastatin or placebo for five years, and the effect of statin therapy on the incidence of adenomas, metachronous cancer, and colon cancer recurrence will be evaluated.⁹⁰

STATINS AND COMBINATION CHEMOPREVENTION

Even if statins, when used alone, are judged to be ineffective at reducing the risk of colorectal neoplasia, their use in combination with other agents, such as NSAIDs or aspirin, may still prove to be a successful chemopreventive strategy.⁹¹ Experimental evidence suggests that statins act synergistically with NSAIDs, and cyclooxygenase-2 (COX-2) inhibitors, to induce cell cycle arrest and apoptosis in human colorectal cancer cell lines.^{40,92} In an animal model, statins, in combination with NSAIDs or aspirin, markedly reduce the incidence and multiplicity of azoxymethane-induced colon tumors.^{47,93} In addition, atorvastatin greatly enhances the chemopreventive efficacy of celecoxib in the Min mouse model of familial adenomatous polyposis.⁵⁰

In the German population-based case-control study,²⁷ combined use of statins and low-dose aspirin for at least 5 years was associated with a striking 62% reduction in the risk of colorectal cancer. However, five other case-control studies,^{26,60,62,63,65} and two large prospective cohort studies,^{69,77} reported a lack of interaction between NSAIDs, aspirin, or COX-2 inhibitors and statin use. Furthermore, in the secondary analysis of data from three large adenoma chemoprevention trials, no differences in the risk ratios were observed between strata of aspirin or NSAID use.⁸³ The ongoing NSABP P-5 study clinical trial permits entry of patients already on aspirin, and a planned secondary analysis is assessment of potential effect modification of rosuvastatin by aspirin.⁹⁰

SUMMARY AND FUTURE PERSPECTIVES

An abundance of experimental data has provided a variety of biologically plausible mechanisms through which statins might affect the initiation or evolution of colorectal neoplasia. Evidence from clinical studies is, however, conflicting. Studies supporting a chemopreventive role for statins in colorectal neoplasia are relatively few in number and are almost exclusively of retrospective observational design. While the magnitude of risk reduction observed in the case-control study of Poynter and colleagues was impressive, collective analysis of observational studies by meta-analysis suggests a more modest effect size.^{53,78} Collectively, the influence of statin use on colorectal cancer in cardiovascular RCTs appears neutral. Taken together with the null observational analysis of statin use in the APC trial, this has certainly dampened enthusiasm for statins as chemopreventive agents. It remains conceivable, however, that statin use for longer periods, at higher doses, in

combination with other agents, or in genetically defined subgroups (such as those with HMG-CoA reductase gene polymorphisms), may influence the risk of colorectal neoplasia.

It has been argued that the duration of chemoprevention trials should be at least as long as the latency period of many cancers.⁹⁴ Follow-up duration is a major shortcoming of prospective analyses of statins and colorectal neoplasia to date, and attempting to address the latency period of colorectal cancer represents a logistic and financial challenge to future studies. In addition, given that the prevalence of statin use is high among those likely to be target subjects for future statin chemoprevention trials, establishing and maintaining a statin-free control arm is likely to become increasingly difficult.

From a clinical practice perspective, at present, there is insufficient evidence to recommend the use of statins for colorectal cancer chemoprevention. However, follow-up will continue to accrue for statin users in prospective cohorts and participants of completed intervention studies. Future analyses, benefitting from more lengthy exposure to statins, and increased time at risk of colorectal cancer, may prove enlightening. The outcome of ongoing clinical studies of statins in high-risk populations for polyp prevention, and as adjuvant therapeutic agents, will be eagerly awaited.

Acknowledgments

Funding Support: Dr Lochhead is supported by a clinical academic fellowship from the Chief Scientist Office of the Scottish Government. Dr Chan is a Damon Runyon Clinical Investigator.

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Table 1

Observational studies of statins and colorectal cancer risk

Author, ^{ref} year	Study design ^a	Study description/population	Findings: point estimate (95% CI) ^b
Blais, ²³ 2000	CC	Canadian administrative health database. Statin use compared to use of bile acid-binding resins in 56 colon cancer cases and 560 controls	Colon cancer: OR=0.83 (0.37–1.89)
Graaf, ²⁴ 2004	CC	Dutch dispensing database. Nested study containing 292 colon cancer cases and 148 rectal cancer cases.	Colon cancer: OR=0.87 (0.48–1.57) Rectal cancer: OR=0.48 (0.16–1.48)
Kaye, ⁵⁹ 2004	CC	UK General Practice Research Database study containing 25 colon, and 23 rectal cancer cases, and 115 and 49 controls, respectively.	Colon cancer: OR=1.0 (0.6–1.7) Rectal cancer: OR=1.6 (0.9–2.8)
Friis, ²⁵ 2005	RC	Danish population-based cohort. Cancer incidence compared among 12,251 statin users and non-users in a base population of 334,754.	Colorectal cancer: RR=0.85 (0.65–1.11)
Poynter, ²⁶ 2005	CC	Molecular Epidemiology of Colorectal Cancer study conducted in northern Israel and comprising 953 colorectal cancer cases and 2,015 controls.	Colorectal cancer: Any use, OR=0.53 (0.38–0.74) Use for 5 years, OR=0.55 (0.40–0.74) Colon cancer: Any use, unadjusted OR=0.55 (0.38–0.80) Rectal cancer: Any use, unadjusted OR=0.38 (0.19–0.73)
Jacobs, ⁷¹ 2006	PC	Association of statin use and cancer in 132,136 participants of the Cancer Prevention Study II Nutrition Cohort.	Colorectal cancer: Current use, RR=1.03 (0.85–1.26) Current use of 5 years, RR=1.09 (0.83–1.43)
Setoguchi, ⁷¹ 2007	RC	Study of drug prescribing records for an elderly population in Pennsylvania. Cancer incidence in 24,439 statin initiators compared to 7,284 initiators of glaucoma medications.	Colorectal cancer: HR=0.96 (0.70–1.31)
Hoffmeister, ²⁷ 2007	CC	German population-based colorectal cancer study. Statin and low dose aspirin use assessed in 540 cases and 614 controls.	Colorectal cancer: Statin use, OR=0.65 (0.43–0.99) Aspirin use, OR=0.77 (0.55–1.07) Use of both drugs for 5 years, OR=0.38 (0.15–0.97)
Coogan, ⁶¹ 2007	CC	U.S. population-based study of 10 cancers containing 734 colorectal cancer cases and 3,900 controls.	Colorectal cancer: OR=0.8 (0.5–1.2) Colon cancer: OR=0.7 (0.4–1.1) Rectal cancer: OR=1.1 (0.6–2.0)
Coogan, ⁶² 2007	CC	Massachusetts population-based study of colorectal cancer with 1,809 cases and 1,809 controls.	Colorectal cancer: Any use, OR=0.92 (0.78–1.09) Use for 10 years, OR=0.86 (0.51–1.45)
Vinogradova, ⁶⁰ 2007	CC	Nested study in UK QResearch general practice database. Statin use compared among 5,686 colorectal cancer cases and 24,982 controls.	Colorectal cancer: Any use, OR=0.93 (0.83–1.04) Use for >25 months, OR=0.99 (0.84–1.16)
Farwell, ²⁸ 2008	RC	New England Veterans Affairs healthcare database. Cancer incidence compared among 37,248 statin users and 25,594 anti-hypertensive drug users not taking statins.	Colorectal cancer: Any dose, HR=0.65 (0.55–0.78) Low dose, HR=0.66 (0.54–0.82) Medium dose, HR=0.63 (0.50–0.81) High dose, HR=0.59 (0.41–0.85)
Friedman, ⁷³ 2008	RC	Northern California health care program database. Cancer incidence in 361,859 statins users compared to non-users.	Colon cancer: Any use, HR=0.97 (0.85–1.11) Use >5years, HR=1.02 (0.75–1.38) Rectal cancer: Any use, HR=0.97 (0.76–1.25) Use for >5years, HR=1.15 (0.66–2.01)

Author, ^{ref} year	Study design ^a	Study description/population	Findings: point estimate (95% CI) ^b
Yang, ⁶³ 2008	CC	Population-based study nested in UK general practice research database, containing 4,432 colorectal cancers and 44,292 controls.	Colorectal cancer: Use for >5 years, OR=1.1 (0.5–2.2) Use for 10 years, OR=1.3 (0.6–2.7)
Boudreau, ⁶⁴ 2008	CC	Western Washington SEER cancer registry used to identify 665 colorectal cancer cases and 665 controls.	Colorectal cancer: OR=1.02 (0.65–1.59) Colon cancer: OR=0.91 (0.55–1.50) Rectal cancer: OR=1.47 (0.50–4.29)
Flick, ⁷⁵ 2009	PC	Statin use and colorectal cancer risk evaluated in 65,115 participants in the California Men's Health Study.	Colorectal cancer: Any use, HR=0.89 (0.61–1.30) Use for 5 years, HR=0.93 (0.43–1.63)
Hachem, ²⁹ 2009	CC	Nested case-control study of veterans with diabetes. Frequency of filled statin prescriptions compared between 6,080 colorectal cancer cases and 24,320 controls.	Colorectal cancer: Any use, OR=0.91 (0.86–0.96) Use for 6 months, OR=0.92 (0.86–0.98)
Shadman, ⁶⁵ 2009	CC	Population-based study of 669 females with colorectal cancer identified from Wisconsin cancer reporting system, and 1,375 community controls.	Colorectal cancer: Any use, OR=1.17 (0.74–1.85) Use for 3 years, OR=1.27 (0.68–2.38)
Singh, ⁷⁴ 2009	RC	Manitoba's prescribing database used to compare colorectal cancer incidence among 35,739 individuals regularly dispensed statins and 377,532 non-users.	Colorectal cancer: Any use, IRR=1.13 (1.02–1.25) Low dose 5 years, IRR=0.90 (0.54–1.49) High dose 5 years, IRR=0.69 (0.37–1.28)
Haukka, ⁷⁶ 2010	RC	Finnish record linkage study using national prescribing database. Incidence of cancer in 472,481 individuals prescribed statins compared to an equal number of statin non-users.	Colon cancer: RR=1.01 (0.94–1.08) Rectal cancer: RR=1.07 (0.98–1.17)
Robertson, ⁶⁶ 2010	CC	Danish National Registry of Patients study. Statin use assessed in 9,979 colorectal cancer cases and 99,790 controls.	Colorectal cancer: Use for 0–3 years, OR=0.84 (0.75–0.95) Use for 3–5 years, OR=0.88 (0.74–1.04) Use for >5 years, OR=0.95 (0.80–1.12)
Jacobs, ⁷⁷ 2011	PC	Association of long-term use of cholesterol-lowering drugs and 10 cancers evaluated in Cancer Prevention Study II Nutrition Cohort (N=133,255).	Colorectal cancer: Former use, RR=1.09 (0.87–1.36) Current use of <5 years, RR=0.93 (0.80–1.07) Current use of 5 years, RR=0.96 (0.82–1.12)
Lee, ⁶⁹ 2011	PC	Association of statin use and colorectal cancer evaluated in the Nurses' Health Study (121,700 women) and Health Professionals Follow-up Study (51,529 men). There were 1818 incident colorectal cancers during follow-up.	Colorectal cancer: Current use, RR=0.97 (0.84–1.12) Use for 6 years, RR=0.97 (0.75–1.10) Colon cancer: Current use, RR=1.10 (0.94–1.29) Rectal cancer: Current use, RR=0.59 (0.41–0.84)
Vinogradova, ⁶⁷ 2011	CC	Risk of common cancers in relation to statin use assessed using 88,125 cases and 362,254 controls in the UK general practice QResearch database.	Colorectal cancer: Any use, OR=1.07 (1.00–1.15) Use for <12 months, OR=1.05 (0.95–1.17) Use for 49 months, OR=1.23 (1.10–1.38)
Cheng, ⁶⁸ 2011	CC	Taiwanese population-based study comprising 1156 colorectal cancer cases and 4624 controls selected from a national health insurance database.	Colorectal cancer: Any use, OR=1.09 (0.94–1.30) Low cumulative use, OR=0.99 (0.78–1.27) Medium cumulative use, OR=1.07 (0.78–1.49) High cumulative use, OR=1.30 (0.96–1.75)
Simon, ⁷⁰ 2012	PC	Association of statin use and colorectal cancer in 159,219 women enrolled in Women's Health Study, where there were 2000 incident colorectal cancers.	Colorectal cancer: Any use, HR=0.99 (0.83–1.20) Use for 3 years, HR=0.79 (0.56–1.11) Lovastatin use, HR=0.62 (0.39–0.99)

^aCC, case-control; PC, prospective cohort; RC, retrospective cohort

^bCI, confidence interval; HR, hazard ratio; IRR, incidence risk ratio; OR, odds ratio; RR, relative risk. Point estimates are adjusted unless stated otherwise.

Table 2

Observational studies of statins and colorectal adenoma risk

Author, ^{ref} Year	Study description	Findings: point estimate (95% CI) ^a
Wei, ⁸³ 2005	Secondary analysis in a combined total of 2,638 participants of three large adenoma chemoprevention trials where 8% of participants used statins.	Any statin use: Any adenoma, HR=1.03 (0.87–1.23) Advanced adenom, HR=1.13 (0.70–1.81) Multiple adenomas, HR=1.25 (0.95–1.65)
Siddiqui, ⁸⁰ 2009	Endoscopy record-based retrospective study conducted in 2,626 veterans where the prevalence of continuous statin use was 35%.	Continuous statin use: Any adenoma, unadjusted OR=0.51 (0.43–0.60) Advanced adenoma, OR=0.71 (0.52–0.96)
Siddiqui, ⁸¹ 2009	Analysis of adenoma characteristics according to LDL reduction in 231 statin users with recurrent adenomas.	30% reduction in LDL vs. <30% reduction: Advanced adenoma: OR=0.47 (0.22–0.96)
Parker-Ray, ⁸² 2010	Retrospective cohort study using Veterans Affairs computerized patient record system. Of 197 eligible patients, 47% received statins during follow-up.	Any statin use: Any adenoma, HR=1.24 (0.15–10.4) Log cumulative statin use: Any adenoma, HR=0.90 (0.54–1.50)
Bertagnolli, ⁸⁴ 2010	Secondary analysis of self-reported statin use in Adenoma Prevention with Celecoxib (APC) trial. Statins were used by 36% of 2,035 participants.	Any statin use: Any adenoma, RR=1.24 (0.99–1.56) Statin use for >3 years: Any adenoma, RR=1.39, (1.04–1.86)

^a CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk. Point estimates are adjusted unless stated otherwise.