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Statin Use and Cancer Risk: A Comprehensive Review

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Abstract

Importance of the Field—HMG-CoA inhibitors (statins), a class of drugs that reduce cholesterol, are used to manage and prevent coronary heart disease. They are among the most commonly prescribed drugs worldwide. Contrary to early concerns over the carcinogenicity of statins, a growing body of evidence suggests statins may in fact have a chemopreventive potential against cancer.

Areas Covered in This Review—In this paper, we review evidence on the association between statin use and cancer risk. Specifically, we report on clinical trials and observational studies that measured all cancer or site-specific cancers of the breast, colorectal, lung, prostate, and reproductive organs associated with statin use.

What the reader will gain—An understanding of the evidence, including strengths and limitations, to support an association between statins and cancer. Information on the current state of the field and future directions are also discussed.

Take Home Message—Few strong or consistent associations between statins and cancer incidence overall or for any of the sites reviewed were detected. Data is lacking for any effects of statins on cancer prognosis and secondary prevention; with the exception of consistent evidence that statins are associated with reduced risk of advanced/aggressive prostate cancer. Statins appear safe in relation to cancer risk but any chemopreventive effect in humans remains to be established and should not be recommended outside the context of clinical trials. It is encouraging that numerous trials are on-going. The prospect of reducing the incidence and burden of some of the most prevalent cancers with a safe, affordable, and tolerable medication that already reduces the risk of the leading cause of death, cardiovascular disease, warrants further exploration in clinical trials and observational studies of prognosis and survival.

Keywords

statins; HMG-CoA inhibitors; cancer; prevention; treatment; drug safety

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I. Introduction

HMG-CoA inhibitors (statins), a therapeutic class of drugs that reduce plasma cholesterol levels, are used to manage and prevent coronary heart disease.[1] Numerous large-scale randomized controlled trials (RCTs) demonstrate the beneficial effects of statins on cardiovascular morbidity and mortality among patients with proven coronary artery disease (CAD) and patients with high cholesterol who are at increased risk for heart disease.[2–5] As such, statins are among the most commonly prescribed drugs worldwide.[6] Their use has increased dramatically in the past decade and is likely to continue rising, especially with their new over-the-counter status in the United Kingdom.

There are currently six statins on the US market: lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin. Pravastatin is extremely hydrophilic compared to the other statins, except for fluvastatin which has intermediate physiochemical properties. Differences in hydrophilicity may have clinical significance with respect to factors such as cancer risk.

Early studies in animal models raised concerns that statins may have carcinogenic properties. A review of findings on rodent carcinogenicity of lipid-lowering drugs reported that all statins available in 1994, initiate or promote cancer in rodents at concentrations equivalent to those commonly prescribed in humans.[7]

Contrary to concerns over the carcinogenicity of statins, a growing body of evidence suggests statins may in fact have a chemopreventive potential against cancer.[8–10] HMG-CoA reductase is the major rate-limiting enzyme of the mevalonate pathway. Statins' inhibition of HMG-CoA reductase prevents the conversion of HMG-CoA to mevalonate, and thereby reduce levels of mevalonate and its downstream products.[8] Many products of the mevalonate pathway are necessary for critical cellular functions such as membrane integrity, cell signaling, protein synthesis, and cell cycle progression.[8,9] Disruptions of these processes in neoplastic cells by statins may result in control of tumor initiation, growth, and metastasis,[9] which has been shown to inhibit cancer cell growth and lead to apoptotic cell death.[11–13] Inhibition of the mevalonate pathway by statins has the potential to reduce the risk of cancer and improve the recurrence of aggressive cancers, although other mechanisms are also suggested.[10] Most recently, the possible tumor suppressive activity of statins was linked to downregulating or inhibiting matrix metalloproteinases (MMPs) through prolonged lowering of circulating cholesterol.[14] MMPs degrade almost all extracellular matrix components involved in processes such as tumor growth, invasion, and metastasis. Interestingly, they may have antitumorigenic and protumorigentic functions depending on the stage of cancer, genotype, and type of MMP.[14] However, many laboratory studies demonstrate that statins induce apoptosis (programmed cell death) and reduce cell invasiveness.[9] This characteristic has been studied in cell lines derived from mammary carcinoma,[15,16] lung,[17] colorectal,[18] pancreatic,[12] and prostate carcinoma.[19]

The clinical relevance of animal and mechanistic studies on statins and cancer in humans remains unclear. For example, statins are selectively localized to the liver and less than 5% of a given dose reaches the circulatory system. Such selective hepatic uptake and low systemic availability casts doubt on the usefulness of statins as chemopreventive agents. Regardless, the animal and mechanistic data compels us to research such effects in human populations.

In this article, we review the current evidence on the association between statin use and cancer risk. Specifically, we report on clinical trials and observational studies that measured

all cancer or site-specific cancers of the breast, colorectal, lung, prostate, and reproductive organs associated with statin use.

2. Clinical Trials

Several RCTs of statin use and coronary heart disease events reported on incident cancers, but most results were equivocal because of inadequate power. However, pravastatin was associated with an increase in breast cancer risk in one clinical trial lasting 5 years (12 breast cancer cases among pravastatin users vs. 1 case in the placebo group - p=0.002),[2] and total cancer and gastrointestinal cancer risk in another clinical trial.[20] However, no other large RCTs of statins demonstrated an altered risk of incident cancer.[21–23] All results should be considered, but trials are generally not powered to assess secondary and rare safety outcomes such as cancer and follow-up periods were relatively short compared to the long latency period (e.g., ten plus years) of cancer. In addition, the eligibility criteria of trials often results in study subjects who are not representative of the real-world population treated with statins.

Six meta-analyses of RCTs and two meta-analyses of RCTs and observational studies found no association between statin use and overall incident cancer risk. [24–31] One meta-analyses also evaluated the association between statin-mediated reductions in low-density cholesterol (LDL) and cancer risk and found an inverse relationship between on-treatment LDL levels and cancer risk but no effect of statins on cancer risk once adjusted for decreases in LDL.[30] However, limitations such as relatively short follow-up times, short duration of statin use, no evaluation of dose-duration response, highly selected groups of patients in RCTs, and failure to account for multiple types of statins must be considered when interpreting results of all the meta-analyses. Cancer is an endpoint that needs to be followed-up for at least 10 years and mean follow-up in statin RCTs is generally 4–6 years. Meta-analyses of overall cancer risk are unlikely to be very sensitive as it is unlikely that statins alter the risk of all cancers, and any true change in the risk of specific cancers may be masked by the random variation in the association of statins with other cancers. The meta-analyses that evaluated site-specific cancers [26,28,29,31] mostly reported null findings but a recent meta-analysis of 17 RCTs, 10 cohort studies, and 15 case-control studies found no evidence of differences in lung, breast, or prostate cancer risk by statin use, but a protective effect was noted for stomach cancer, liver cancer, and lymphoma and an increased risk for both melanoma and non-melanoma skin cancers.[31]

The different pharmacokinetic properties of hydrophilic statins (e.g., pravastatin) versus hydrophobic statins (e.g., lovastatin, simvastatin) support opposing effects on cancer risk, [32,33] and may explain the increased risk of cancer found among pravastatin users in two of the large RCTs. Studies and meta-analyses that pool hydrophilic and hydrophobic statins ignore any differential effect on cancer. Only two published meta-analyses reported on statin type and found no difference in risk by hydrophilic versus hydrophobic statins.[28,29] Of note, one observational study examined the occurrence of all types of cancer among a cohort of only hydrophobic statin users.[34] The adjusted HR associated with high-dose hydrophobic statin use versus non-use was 0.75 (0.60–0.95), whereas the adjusted HR for low-dose hydrophobic statin use versus non-use was 0.89 (0.75–1.07).

3. Statins and Breast Cancer

Epidemiologic studies on the effects of statin use on breast cancer risk are numerous but in general do not lend strong support for a strong association between statin use and breast cancer risk (Table 1).[35–50] Some studies reported that statin use is inversely related to breast cancer and others reported no or positive associations. Six recently published large cohort studies, [41,43,46,48,50,51] and two small case-control studies [45,47] reported no

overall association between statin use and incident breast cancer risk. However, one of these large cohort studies by Cauley and colleagues found statin use was associated with an 18% lower risk of breast cancer when statin use was limited to hydrophobic statin users.[51] Other observational studies reported modest to large statistically significant reductions in the risk of breast cancer (30–74%) associated with overall use of statins.[38–40,42] Of the studies that evaluated duration of use, only two studies found a reduced risk with long term statin use (at least 4–5 years) compared to non-users[38,39] and three studies found no dose response with duration of statin use.[43,47,52]

Concomitant use of statin use and hormone therapy (HT) was especially prevalent in earlier years and estrogen may negate any effects of statins on cell cycle progression.[43,53] Most studies adjust for HT use but Cauley and colleagues reported no association between statin use and breastcancer risk among users of estrogen plus progestin or amongnever and past HT users, and a non-statistically significant reduced risk (22%) among users of estrogen alone. Cauley and colleagues were not powered to evaluate an interaction between HT and statins on breast cancer risk and, therefore, findings may be due to chance. In our previous work, we evaluated statin use and breast cancer risk separately by HT use, we found a suggestive difference in risk among non-users of HT (HR=1.29; 95% CI, 0.99–1.68) and estrogen plus progestin users (HR=0.83; 95% CI, 0.59–1.17).[43]

Many of the epidemiology studies on statin use and breast cancer risk lacked information on potential confounders such as diet, level of physical activity, and breast cancer screening behavior. Women prescribed and adherent to statins may differ from non-users by these health-seeking behaviors and/or preventive procedures and others not measured in the studies; possibly leading to residual confounding. Only one observational study by Setoguchi and colleagues compared statins to another preventive drug (i.e., glaucoma medications) in an attempt to achieve a reference group with similar characteristics as statin users.[44] A meta-analysis by Bonovas and colleagues attempted to address the issue of confounding by indication and small numbers by pooling results from seven large RCTs and nine observational studies.[54] Neither the meta-analysis (RR=1.03; 95% CI, 0.93–1.14) nor the study by Setoguchi et al. supported a protective effect of statins against breast cancer, but limitations such as relatively short statin exposure and follow-up periods remained. Bonovas and colleagues found similar results in their meta-analsis of RCTs and observational studies, which provide some confidence in the validity of observational studies in this area. Of the other meta-analyses that evaluated site-specific cancers, at least three found no relation between statin use and breast cancer risk [26,28,29] and one an increased risk with pravastatin only (RR=3.3; 95% CI, 1.7–6.3).[31]

While there are many observational studies and meta-analyses published on statin use and breast cancer risk, the current data are unsatisfactory for recommending statins for primary breast cancer prevention. Secondary prevention is not well studied. We found only one study of statin use and breast cancer recurrence, which showed promising results with post-diagnosis statin use associated with a suggested decreased risk of recurrence (HR=067; 95% CI, 0.39–1.13).[55]

There is strong laboratory evidence on statins anticancer effects in various cell lines including breast carcinoma cells, but RCTs in this area will be extremely insightful. There are numerous phase II RCTs registered in ClinicalTrials.gov to study questions such as effect of atorvastatin versus placebo for lowering mammography-defined breast density and other surrogate markers associated with breast cancer risk, the effects of atorvastatin on tumor proliferation in postmenopausal women undergoing treatment for breast cancer, fluvastatin's effect on biomarkers in women undergoing surgery for ductal carcinoma in situ or stage I breast cancer, how well simvastatin works in preventing new breast cancer in high

risk women after undergoing surgery for ductal carcinoma in situ or stage I–III breast cancer, and whether lovastatin results in a decrease in the rate of abnormal breast duct cytology among women at high risk for breast cancer. While these trials are small (<100 subjects), we anxiously await the results.

4. Statins and Colorectal Cancer

The risk of colorectal cancer following statin use was assessed by numerous observational studies in recent years (Table 2). Five large cohort studies[44,46,56–58] and seven case-control studies [47,59–64] did not find an association between statin use and colorectal cancer risk. However, two large observational studies reported a 35–43% reduction in colorectal cancer risk among statin users compared to non-users,[65,66] and one meta-analyses of observational studies showed a modest reduction (14%) in colorectal cancer risk with statin use.[28] A reduction in risk was not confirmed in other meta-analyses,[29,31] except when Bonovas and colleagues limited their analysis to case-control studies (RR = 0.91; 95% CI, 0.87–0.96).[67] A large case-control study examining clinical outcomes in patients with already existing colorectal cancer found a 30% decreased odds in metastasis among statin users compared to non-users.[68] Of note, two separate reviews of statin use in colorectal cancer concluded that long-term use of statins is associated with a decreased risk of disease, especially when used in combination with non-steroidal anti-inflammatory drugs (NSAIDs).[69,70] There is substantial evidence to indicate that aspirin and NSAIDs are associated with a decreased risk of colorectal cancer.[71,72] Almost all studies of statin use and colorectal cancer risk adjusted for NSAID use but residual confounding cannot be ruled out especially since over-the-counter medications such as aspirin and certain NSAIDs (e.g., ibuprofen) are difficult to capture in studies using administrative databases.

When cancers of the colon[35,45,48–50,[59],61,63,65,73] and rectum[45,48,50,59,63,65] were evaluated separately, only the case-control study conducted in Israel by Poynter and colleagues observed a similar 45% reduction in colon cancer risk and an even stronger reduction of 62% in rectum cancer risk with statin use compared to non-use.[65] Another case-control study by Coogan et al. found a 30% reduction in rectum cancer risk but no effect on colon cancer risk with statin use.[59] A meta-analysis of six case-control studies also showed an association between statin use and decreased risk of colon cancer (OR=0.89; 95% CI=0.82–0.97).[74]

Several observational studies evaluated the duration of statin use and none found any association between length of statin use and risk of colorectal cancer (Table 2). One large cohort study of a veteran population found a reduced risk in colorectal cancer at various statin dosages and a bigger reduction was observed with increasing dose.[66] Cancer risk by type of statin use was also evaluated, and one study found a 56% decrease in colorectal cancer risk with pravastatin [65] and two studies found a 17–51% reduction in colorectal cancer risk with simvastatin.[60,65]

Similar to breast cancer, it is important to note that any observed reductions in colorectal cancer risk associated with statin use may be at least partially attributable to more healthy behaviors, including diet, exercise, and colorectal cancer screening among statin users as compared to non-users.[75,76] Higher screening rates among statin users than non-users could result in a greater opportunity to identify pre-malignant lesions (i.e., protective effect) and/or earlier stage diagnoses. The latter is supported by at least two studies.[65,68] Several observational studies were able to collect and adjust for diet, exercise, socioeconomic status, and/or colorectal screening history which are potential confounders of the association between statin use and colorectal cancer risk. Further adjustment for colorectal cancer screening, smoking status and vitamin supplementation yielded similar cancer risk reduction

following statin use (OR=0.54; 95% CI=0.41–0.72).[65] In addition, a study conducted among patients with diabetes reported a reduced risk of colorectal carcinoma associated with statin use compared to non-users (OR=0.88; 95% CI, 0.83–0.93) and no association with nonstatin cholesterol lowering medications.[77]

The NCI first sponsored a phase II trial of atorvastatin use in preventing cancer among patients with an increased risk of colorectal neoplasia in 2005.[75] According to ClinicalTrials.gov, the trial completed in April of 2009 but results are not yet published. Other on-going trials according to ClinicalTrials.gov include: a phase III study of rosuvastatin versus placebo in the occurrences of adenomatous polyp of the colon or rectum, colorectal carcinoma, or colon cancer recurrence among patients with resected stage I or II colon cancer, and a phase II study to assess the tolerability and efficacy of simvastatin plus chemotherapy in metastatic colorectal cancer patients.

5. Statins and Lung Cancer

Four case-control studies that evaluated the association between statin use and lung cancer risk did not find any evidence that supported the association (Table 3).[35,45,47,49] All of these studies had small number of cancer cases among statin users. In contrast, a large case-control study of a veteran population with almost 2000 lung cancer cases among statin users that was conducted by Khurana et al. found a 45% reduction in lung cancer risk among statin users when compared to non-users.[78] Defining use as at least 6 months of statin use increased the association with a protective effect on lung cancer to 55%. At least two cohort studies found no association between statin use and risk of lung cancer (Table 3).[44,46] Friedman performed separate analyses by gender and found an increased risk of lung cancer among female statin users (HR=1.16; 95% CI=1.06–1.28) but not among male users (HR=1.02; 95% CI=0.94–1.11) compared to a non-user group.[48] A retrospective cohort study of another veteran population by Farwell and colleagues reported a 30% reduction in risk of lung cancer among statin users.[66] Both studies in the veteran population consisted of predominantly men and therefore, the study result may not be generalizable to female populations. A recently published study of statins and numerous site specific cancers found a lower incidence of lung cancer among statin users compared to non-users (RR=0.81; 95% CI, 0.77–0.86) but only age and sex were adjusted for in the regression analysis.[50] One study conducted analyses of hydrophobic statins and concluded no difference from the non-significant overall results on the association between statins and lung cancer risk.[44] Two meta-analyses of observational studies found no association between statin use and risk of lung cancer (OR=0.75; 95% CI=0.50–1.11 and OR=1.07; 0.89–1.28).[28,74]

Among the five studies that investigated the duration of statin use and the risk of lung cancer, only two reported a statistically significant finding. In the study conducted by Khurana and colleagues, the investigators evaluated various duration of statin use: 0–6 months, 6–12 months, 1–2 years, 2–4 years and >4 years of use.[78] Except for the shortest duration of 0–6 months, all durations of use were associated with a reduced risk of lung cancer compared to non-users (Table 3). The authors' hypothesis is that the statistically significant odds ratio of 2.3 for the 0–6 months statin use was attributed to those lung cancer cases that "may represent an old diagnosis or recording issue at the time of entry into the VA Health Care System". It was thus, concluded that increasing duration of statin use was associated with a protective effect on lung cancer risk. Friedman also assessed the duration of <3 years, 3–5 years and >5 years of statin use and the risk of lung cancer, but only the estimates for >5 years of use were reported: an 18% reduction in lung cancer risk was found among men who used statin for >5 years but no significant association was found among women.[48]

Farwell and colleagues conducted the only study to date that assessed the association between dose of statin use and risk of lung cancer.[66] They evaluated tertiles of simvastatin equivalent doses: 10 mg or lower, 11–39 mg, and at least 40 mg, and the adjusted HRs (95% CI) compared to non-users were 0.70 (0.58–0.84), 0.70 (0.57–0.86), and 0.73 (0.54–0.97). Although the range of the HRs by dose was narrow, the trend was statistically significant (p-value <0.001).

Most studies evaluating statin use and lung cancer risk attempted to adjust for smoking status as a confounder. Cigarette smoke is the largest risk factor of lung cancer, [79] and a factor considered in the risk assessment tool for estimating risk of developing coronary heart disease (CHD) and thus whether to use statins in preventing CHD.[80] However, smoking information is not uniformly collected in health care electronic databases or medical records, and thus, it may be difficult to fully adjusted for this strong risk factor of lung cancer. Among the observational studies of statin use and risk of lung cancer, only the study by Coogan, et al. was able to ascertain smoking status by interviewing cases and controls.[47] In a study of the VA population, 36% of patients were missing information on smoking status but subgroup analyses showed that statin use was associated with a 53% reduction in the odds of lung cancer among smokers and 60% reduction in non-smokers compared to non-users of statins.[78] Farwell and colleagues who studied a different VA population also used smoking information from the electronic medical record in their analyses but it was not available for 56% of statin users and 63% of non-users.[66] Another two cohort studies did not have smoking information on their subjects and thus, they attempted to adjust for smoking status by using external data to estimate the prevalence of smoking in a similar population and the association between smoking and risk of lung cancer.[44,48] The bias due to smoking and thus, the corrected association between statin use and lung cancer risk (only slightly lower than the observed) were then calculated.

Statin use and lung cancer risk was studied by many investigators in recent years, but more evaluations on different types of statins, duration of use, dose, and more complete adjustment of strong risk factors such as cigarette smoking and asbestos exposure are needed to better understand any effects of statins on lung cancer risk. Because lung cancer is relatively rare in non-smokers, one could argue that prevention is only relevant in smokers. RCTs will be especially helpful in advancing this field and overcoming some of the limitations of observational studies. Currently, there are at least two RCTs of statin use and lung cancer registered in ClinicalTrials.gov and they include 1) a phase III trial of adding pravastatin to a 1st line chemotherapy regimen in treating patients with small cell lung cancer; and 2) a phase II trial comparing gefitinib plus simvastatin to gefitinib alone in patients with previously treated advanced non-small cell lung cancer.

6. Statins and Prostate Cancer

There are numerous published studies on the association between statin use and risk of prostate cancer but, taken together, they do not provide a definitive answer (Table 4). [35,36,45–47,[49],52,66,81–89][90] At least two studies, including a small clinic-based case-control study within Oregon Veterans Affairs (VA) Medical Center,[81] and a large case-control study within 10 VA Medical Centers [82] report a reduced risk (54%–65%) of prostate cancer among statin users compared to non-users. A large cohort study conducted within a health plan found a reduced risk of prostate cancer among long-term users of statins (28%) compared to non-users, and the association was strongest among regular users of NSAIDs.[84] Another large cohort study conducted using health plan data evaluated type of statin use but found no association between use of hydrophobic statins and prostate cancer risk.[87] Only one epidemiologic study found a moderate increase in risk [49] but other observational studies[35,36,46,47,[52],83,85–89,91], meta-analyses[28,29,31], and a review of

the evidence between statins and prostate cancer risk [85] do not support an association between statin use and overall prostate cancer risk. However, numerous recent studies consistently reported that statins are associated with a reduction in advanced and metastatic/fatal prostate cancer,[83,85,86] and aggressive disease.[81] At least two studies reported improved biochemical progression free survival among statin users compared to non-statin users following brachytherapy for clinically localized prostate cancer,[92,93] but this result was not confirmed in a subsequent study.[94] The reasons for the differences in the findings between advanced disease and organ-confined disease are unknown but prevention of cancer, in general, can occur at different stages of disease and/or disease progression. For example, Platz and colleagues reported a decreased risk of advanced prostate cancer with any statin use and an even lower risk with use for 5 years or longer, which remained after adjusting for prostate-specific antigen (PSA) screening history.[83] However, they found no association between statin use and risk of total prostate cancer. Loeb and colleagues found an association between statins and numerous factors predictive of improved prostate cancer prognosis, such as lower risk of positive surgical margins, tumor volume, and percentage cancer at radical prostatectomy in multivariate models adjusted for tumor and stage.[95] It should also be noted that the long-term follow-up, ten years after completion of the trial, of the West of Scotland Coronary Prevention Study recently reported a trend toward an increased risk of prostate cancer among the pravastatin group compared with placebo, [96] but a meta-analysis of 6 RCTs and 13 observational studies found no association between statin use and overall prostate cancer risk (RR = 1.06, 95% CI: 0.93–1.20 for RCTs and RR=0.93, 95% CI: 0.77–1.13 for observational studies) and a protective association in studies that examined advanced prostate cancer risk (RR = 0.77, 95% CI: 0.64–0.93).[97]

To make conclusions about the effect of statins on prostate cancer prevention, mechanistic data suggests that the type, dose, and potency of statin used and the serum concentrations achieved need to be considered in observational studies.[32,98] The most recently published studies on advanced disease are promising but many of the specifics on statin use (e.g., individual statins, potency) are not adequately addressed in relation to prostate cancer, and the influence of detection bias,[99] as well as other confounders such as socioeconomic status, lifestyle factors, and PSA testing history need further study. PSA screening to detect and treat prostate cancer at earlier stage began in the mid-1980s and, although controversial, the test is commonly performed. While many of the observational studies adjusted for PSA, the possibility that statins decrease PSA levels[100–102] complicates prostate cancer detection (i.e., detection bias if lower PSA results in deferred referral for biopsy) and modeled associations between statin use and prostate cancer risk (e.g., confounder or part of the biologic pathway in reducing prostate cancer risk). However, statins remain associated with a reduced overall risk of prostate cancer in studies that included men who underwent comprehensive PSA screening[81,90] and in studies that controlled for PSA testing.[83,84] In addition, Krane and colleagues showed that pre-operative statin use is associated with reduced PSA levels among men presenting for radical prostatectomy, which may result in improved outcomes.[103]

There is only one on-going clinical trial of statin use and prostate cancer registered in clinicaltrials.gov. The trial aim is to measure the effect of pre-operative simvastatin versus placebo on the mevalonate pathway synthesis and target activation in benign and malignant prostate tissue among men undergoing prostatectomy as their primary treatment for prostate cancer.

7. Statins and Female Reproductive Organ Cancer

There are only six observational studies evaluating statin use and risk of female reproductive organ cancer (Table 5).[35,46–49,104] The most recent study published by Yu, et al.

evaluated a cohort of women within an integrated healthcare delivery system in the United States. A non-significant but clinically meaningful reduction in risk of endometrial (HR=0.67; 95% CI, 0.39–1.17) and ovarian (HR=0.69; 95% CI, 0.32–1.49) cancers among statin users compared to non-users was observed.[87] In another cohort study of women 20+ years conducted by Friedman et al., the HR was 1.1 (95% CI, 1.0–1.3) for endometrial cancer and 0.8 (95% CI, 0.7–1.1) for ovarian cancer among statin users compared to non-users.[48] When they compared statin users of 5+ years to non-users, the HR for ovarian cancer was reduced to 0.54 (95% CI, 0.27–1.09). Coogan and colleagues also evaluated endometrial cancer risk in a hospital-based case-control study of women 40–79 years of age and reported that regular statin users and non-users had similar risk of endometrial cancer (OR=1.3; 95% CI, 0.7–2.4).[47] Another cohort study conducted in Denmark by Friis et al. also did not find an overall association between statin use and female genital cancer (RR=0.9; 95% CI, 0.6–1.4), although the definition of genital cancer was not specified in the article.[46] In a matched case-control study using the General Practice Research Database in the United Kingdom, Kaye and colleagues reported a RR of 1.0 (95% CI, 0.4–2.7) for ovarian cancer and a RR of 0.5 (95% CI, 0.1–1.9) for endometrial cancer.[49]

The only study that found a statistically significant reduction in risk of cancer in the uterus among statin users compared with bile acid-sequestrant users was conducted in Canada.[35] In this nested case-control study, 26 cancer cases of uterus (defined as cervix, endometrium, and ovary) between 1988 and 1994 were included, and statin users were 70% less likely than bile acid-sequestrant users to develop incident cancers of the uterus. The study did not evaluate the difference in cancer risk between statin users and non-users since the study population was all lipid-lowering medications users. The number of cancer cases was small and included cancers in different parts of the uterus which may have different etiologies and thus, associations with statin.

Among the six studies, only the study by Coogan et al. evaluated the type (hydrophobic vs hydrophilic) of statin use.[47] They did not find any difference in endometrial cancer risk between hydrophobic (simvastatin, lovastatin, and fluvastatin) statin users and non-users or hydrophilic (pravastatin and rosuvastatin) statin users and non-users. However, these analyses were based on only 8 and 5 endometrial cancer cases among hydrophobic and hydrophilic statin users, respectively.

Almost all of these six studies were based on very small number of cancer cases among statin users, and thus, the 95% confidence intervals for the risk estimates were relatively wide. Due to lingering questions regarding the association between statin use and cancer risk and the limited studies evaluating endometrial and ovarian cancers, a large study with more statistical power to assess duration and type of statin may be warranted. It may also be worthwhile to conduct a meta-analysis that combines results from all of these studies to increase statistical power.

Of note, there is a small (n<15) phase II study registered with clinical trials.gov of the synergistic interaction of lovastatin and paclitaxel for patients with refractory or relapsed ovarian cancer that is currently recruiting patients.

8. Conclusion

In general, few strong or consistent associations between exposure to statins and cancer incidence overall or for any of the sites reviewed were detected. Statins appear safe in relation to cancer risk but any chemopreventive effect in humans remains to be established and should not be recommended outside the context of clinical trials. There does, however, appear to be a consistent relationship between statin use and reduced risk of aggressive

prostate cancer. The relationship between statins and cancer is complex and further research on biologic and clinical endpoints is needed in both primary and secondary/tertiary prevention. To date, the majority of published results are from observational studies on risk of incident cancers or RCTs reporting on cancer only as a secondary endpoint. Observational studies are imperative in pharmacoepidemiology but given the remaining level of controversy and unanswered questions amidst an already large body of observational studies, it is appropriate that specific questions in defined populations are being moved into the clinical trial setting.

9. Expert Opinion

As stated in the conclusion, results of RCTs and observational studies on the association between statin use and the site-specific cancers reviewed were varied. Differences in study methods and study populations are likely responsible for some of the variation in the observational study results that we reviewed. Findings from many of the observational studies in this area need to be interpreted with caution due to factors such as residual confounding and crude exposure assessment (ever versus never use of statins). There was few clear dose or duration response relationships between statin use and risk of any of the site specific cancers reviewed here. Exposure time to statins and follow-up time in the majority of studies were relatively short given the long latency period of cancer and therefore, it is likely that any observed associations are due to changes in tumor growth rates (i.e., statins as a mediator) as opposed to effects on initiation of a tumor.

The indication for a prescription medication is one of the most important confounding factors in pharmacoepidemiology research.[105] For indication to be a confounder, it must be associated with both statin use and the site specific cancer under study, and not be in the causal pathway. Studies of pharmacologic and dietary cholesterol lowering are unable to address whether or not reducing total serum cholesterol, as opposed to having low cholesterol, may increase the risk of cancer.[106–110] While epidemiologic studies in the 1980s documented an association between low cholesterol and higher overall cancer incidence and mortality, this is now attributed to reverse causation (i.e., cholesterol levels decline before cancer diagnosis) although an increased risk cannot be ruled out.[109,110] Few studies reported on the association between high-density cholesterol (HDL or “good” cholesterol) and cancer risk, but a recently published large cohort study reported statins were associated with a decreased risk of overall cancer incidence (RR= 0.89; 95% CI, 0.83–0.97).[110] The observed decreased risk was mostly attributable to small, non-significant decreases in incident lung and prostate cancer cases. Confounding by hypercholesterolemia cannot be ruled out but any effects are likely weak. Importantly, other risk factors for CHD such as diabetes, obesity, smoking, and hypertension should be considered when evaluating confounding by indication with statin use.

Comparisons between statin users and other cholesterol-lowering drugs is one way to control for confounding, but use of non-statin cholesterol-lowering drugs greatly diminished once statins were introduced to the market. In addition, non-statin cholesterol lowering drugs are a heterogeneous group with varied mechanisms of action. Few studies evaluated other cholesterol-lowering drugs and, in general, they are not associated with risk of cancer. Adjustment for hypercholesterolemia, diabetes, and smoking did not significantly alter results for many of the reviewed observational studies including our previously published studies in breast, prostate, and reproductive organ cancers.[43,87] However, it is probable that statin users differ in cancer risk factors from non-users. Adherence to drug therapy is known to be associated with higher educational status and health seeking behavior, especially if the drug is treating an asymptomatic condition, such as hypercholesterolemia in the case of statins.[111] This phenomenon, known as the healthy user effect, is a type of

selection bias that not only limits generalizability in clinical research but may also lead to confounding of study results. Confounding is of particular concern in observational research; because adherent users may be inherently different from non-adherent users, therapeutic effects may be misrepresented where information is not available to control for patient characteristics that are closely associated with adherence. Similarly, therapeutic effects seen in clinical research may not reflect those observed in the general population, as those patients who voluntarily enroll in trials are likely to be proactive with regard to health issues.

Several studies have examined the relationship between adherence to drug therapy and other health-related behaviors. A recent study sought evidence of the health user bias by examining statin adherence and risk of accidents and other negative health outcomes.[112] Using data from a large prospective cohort study, the investigators found that patients more adherent to statin therapy were less likely to have a number of negative outcomes such as motor vehicle accidents and workplace accidents, and were more likely to use screening services. Adherent users were also less likely to develop other diseases unlikely to be related to a biological effect of statins. Finally, Brookhart and colleagues examined the association between adherence to statin therapy and the use of preventive health services.[76] Their results suggested that patients who adhere to chronic therapies are more likely to seek out preventive health services, such as screening tests and vaccinations, supporting the notion of a possible health user effect in studies of preventive therapies. In order to examine the potential for confounding by the healthy user effect, Setoguchi and colleagues investigated the association between statin therapy and the risk of lung, breast, and colorectal cancers, using glaucoma medications as a comparator.[44] Because glaucoma medications are another type of preventive therapy and their users are likely to have health-related characteristics similar to users of statins, glaucoma drug users from the same study population served as a reference group for comparing cancer outcomes. Adjusted HRs for colorectal, lung, and breast cancer failed to demonstrate any clinically significant decrease or increase in cancer risk among statin users compared to users of glaucoma medication users.

According to ClinicalTrials.gov, there are 27 ongoing studies examining associations between statin therapy and cancer risk or outcomes. Two additional studies—one in colorectal cancer and one in multiple myeloma—were recently completed, but results are not yet available. Nine of the 27 ongoing studies are in breast cancer, seven are in hematological malignancies, and the remaining trials involve lung, prostate, pancreatic, colorectal, skin, ovarian, and renal cell carcinomas. Several ongoing studies explore the addition of statin therapy to enhance effects of current cancer treatment therapies, such as anastrazole in breast cancer, gefitinib in non-small cell lung cancer, and gemcitabine in pancreatic cancer, with only four studies examining prevention of incident cancers (three in breast cancer and one in colorectal cancer prevention).

Only a few observational studies reported on the association between statin use and cancer prognosis and survival in patients already diagnosed and treated for cancer. A study among men undergoing brachytherapy for localized prostate cancer reported a trend of improvement in 9-year biochemical progression free survival with statin use.[93] Similar promising results were presented for decreased risk of breast cancer recurrence with statin use.[55] Cancer recurrence and progression have important negative consequences for patients and their families, often requiring a variety of palliative treatments and often leading to death. While risk of incident cancers is important, progression (including secondary/tertiary prevention) should not be overlooked. Learning more about preventable factors that influence the sequelae of outcomes will help with the secondary prevention of cancer and could ultimately lead to a reduction in cancer morbidity and mortality. In

addition to clinical trials, observational studies of the association between statins and cancer prognosis are an area of research that warrants study in the future.

Statins cannot be recommended for the prevention of any site specific cancer or for the improvement of cancer endpoints among patients with already diagnosed cancers until effects are demonstrated in RCTs. It is encouraging that numerous trials, although most small, are ongoing. Results of these on-going trials will be a major contribution to the field and hopefully, will lead to large prevention trials with adequate follow-up in high risk populations or in patients already diagnoses with tumors that are responsive to statin therapy. Such trials and epidemiologic studies are more feasible for cancer prognosis than incident risk due to the long latency period of cancer and thus, the long follow-up periods required. However, the prospect of reducing the incidence and burden of some of the most prevalent cancers with a safe, affordable, and tolerable medication that already reduces the risk of the leading cause of death, cardiovascular disease, warrants further exploration.

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Table 1

Epidemiologic studies of the association between statin use and incident breast cancer risk.

Author, year	Design*	Number of cases		Results (point estimate (95% CI))**
		User	Non-user	
Blais, 2000[35]	CC	65		OR=0.67 (0.33–1.38)
Coogan, 2002[36]	CC	33	828	OR=1.5 (1.0–2.3)
Kaye, 2002[37]	CC	31	102	OR=1.0 (0.6–1.6)
Beck, 2003[39]	Cohort	188	691	Ever use: OR=1.09 (0.93–1.28) Age <55 yrs: OR=0.81 (0.53–1.24) Age >55 yrs: OR=1.15 (0.97–1.37) Use ≥4 yrs: OR=0.26 (0.12–0.55)
Cauley, 2003[40]	Cohort	6	234	RR=0.28 (0.09–0.86)
Boudreau, 2004[38]	CC	112	849	Ever use: OR=0.9 (0.7–1.2) Use> 5 yrs: OR=0.7 (0.4–1.0)
Graaf, 2004[45]	CC	467		OR=1.07 (0.65–1.74)
Kaye, 2004[49]	CC	40		OR=0.9 (0.6–1.3)
Kochhar, 2005[42]	CC	556		OR=0.49 (0.38–0.62)
Eliassen, 2005[41]	Cohort	152	1,472	Current use: RR=0.91 (0.76–1.08)
Friis, 2005[46]	Cohort	48	3,093	RR=1.02 (0.76–1.36)
Cauley, 2006[51]	Cohort	297	4,086	Ever use: HR=0.91 (0.80–1.05) Hydrophobic statin use: HR=0.82 (0.70, 0.97)
Setoguchi, 2007[44]	Cohort	203	65	HR=0.99 (0.74–1.33)
Boudreau and Yu, 2007[43]	Cohort	130	2,577	Ever use: HR=1.07 (0.88–1.29) Use ≥5 yrs: HR=1.27 (0.89–1.81) Hydrophobic use: HR=1.01 (0.80–1.26)
Coogan and Rosenberg, 2007[47]	CC	69 cases and controls	1101 cases and controls	Ever use: OR=1.2 (0.8–1.8) Duration Use ≤1 year: OR=1.0 (0.5–2.1) Use 1–5 year: OR=1.2 (0.7–2.1) Use ≥5 years: OR=1.5 (0.7–3.2) P for trend in duration: 0.1 Hydrophobic statin use: OR=1.0 (0.6–1.6)
Friedman, 2007[52]	Cohort	881	-	Ever use: HR=0.99 (0.92–1.06) Use >5 yrs: HR=1.02 (0.86–1.21)
Smeeth, 2008[89]	Cohort	324	2880	HR=1.17 (0.95–1.43)
Haukka, 2010[50]	Cohort	-	-	RR=1.01 (0.96–1.06)

* CC=case control

** OR=odds ratio; RR= relative risk; HR=hazard ratio; CI=confidence interval; relative to non-users

Table 2

Epidemiologic studies of the association between statin use and incident colorectal cancer risk.

Author, year	Design*	Number of cases		Results (point estimate (95% CI))**
		User	Non-User	
Blais, 2000[35]	CC	56		Colon: OR=0.83 (0.37–1.89)
Graaf, 2004[45]	CC	292 colon, 148 rectum		Colon: OR=0.87 (0.48–1.57) Rectum: OR=0.48 (0.16–1.48)
Kaye, 2004[49]	CC	25 colon, 23 rectum		Colon, current use: OR=1.0 (0.6–1.7) Rectum, current use: OR=1.6 (0.9–2.8)
Khurana, 2004[73]	CC	2453	2886	Colon: OR=0.94 (0.89–1.00)
Friis, 2005[46]	Cohort	55	2951	Colorectal: RR=0.85 (0.65–1.11)
Poynter, 2005[65]	CC	120	1833	Colorectal: OR=0.57 (0.44–0.73) Colon: OR=0.55 (0.38–0.80) Rectum: OR=0.38 (0.19–0.73) Statin type Simvastatin: OR=0.49 (0.36–0.67) Pravastatin: OR=0.44 (0.31–0.63)
Jacobs, 2006[56]	Cohort	183 current 31 former	601	Colorectal Former use: RR=0.79 (0.55–1.15) Current use: RR=1.03 (0.85–1.26) Current use <5 years: RR=1.00 (0.80–1.25) Current use ≥5 years: RR=1.09 (0.83–1.43)
Setoguchi, 2007[44]	Cohort	190	59	Colorectal HR=0.96 (0.70–1.31) Duration Use <3 years: HR=0.93 (0.57–1.51) Use ≥3 years: HR=0.97 (0.65–1.46)
Coogan and Rosenberg, 2007[47]	CC	35 cases and controls	691 cases and controls	Colorectal Regular use: OR=0.8 (0.5–1.2) Duration Use ≤1 year: OR=0.7 (0.3–1.5) Use 1–5 year: OR=0.7 (0.4–1.3) Use ≥5 years: OR=1.1 (0.6–2.2) P for trend in duration: 0.5
Coogan and Smith, 2007[59]	CC	457	523	Colorectal Regular use: OR=0.92 (0.78–1.09) Recent regular use: OR=1.08 (0.71–1.65) Duration Use <1 year: OR=0.57 (0.27–1.24) Use 1–4 year: OR=0.94 (0.77–1.15) Use 5–9 years: OR=0.95 (0.71–1.27) Use ≥10 years: OR=0.86 (0.51–1.45) P for trend in duration: 0.19 Average daily dose score*** Use ≤1: OR=1.32 (0.86–2.03) Use >1 & <2: OR=0.67 (0.40–1.13) Use 2: OR=0.84 (0.63–1.11) Use >2: OR=0.76 (0.57–1.03) P for trend in dose: 0.11 Statin type Atorvastatin: OR=0.93 (0.76–1.14) Simvastatin: OR=0.81 (0.59–1.12) Pravastatin: OR=0.94 (0.60–1.46) Lovastatin: OR=1.73 (1.03–2.88) Colon Regular use: OR=1.07 (0.87–1.32) Rectum Regular use: OR=0.70 (0.51–0.95)
Vinogradova, 2007[60]	CC	538	5148	Colorectal Ever use: OR=0.93 (0.83–1.04) Duration Use 1–12 months: OR=0.84 (0.71–1.00)

Author, year	Design*	Number of cases		Results (point estimate (95% CI))**
		User	Non-User	
				Use 13–24 months: OR=0.99 (0.80–1.22) Use ≥25 months: OR=0.99 (0.84–1.16) P for trend in duration=0.69 Statin type Atorvastatin: OR=1.11 (0.95–1.30) Simvastatin: OR=0.83 (0.72–0.96) Pravastatin: OR=0.84 (0.55–1.28) Fluvastatin: OR=1.21 (0.85–1.74) Cerivastatin: OR=1.34 (0.97–1.86)
Hoffmeister, 2007[61]	CC	58	482	Colorectal Regular use: OR=0.69 (0.45–1.06) Regular use 1–4 years: OR=0.58 (0.33–1.04) Regular use ≥5 years: OR=0.71 (0.39–1.28) Statin type: Atorvastatin: OR=0.84 (0.46–1.53) Simvastatin: OR=0.50 (0.24–1.02) Pravastatin: OR=0.61 (0.21–1.81) Colon, regular use: OR=0.64 (0.39–1.04) Rectum, regular use: OR=0.69 (0.37–1.28)
Farwell, 2008[66]	Cohort	316	371	Colorectal Ever use: HR=0.65 (0.55–0.78) Dose Use ≤10mg: HR=0.66 (0.54–0.82) Use 11–39mg: HR=0.63 (0.50–0.81) Use ≥40mg: HR=0.59 (0.41–0.85) P for trend in dose: 0.001
Friedman, 2008[48]	Cohort	Men: 292 colon, 129 rectum Women: 243 colon, 69 rectum		Men, colon Ever use: HR=0.88 (0.78–1.00) Use >5 years: HR=1.00 (0.78–1.30) Men, rectum Ever use: HR=0.93 (0.77–1.12) Use >5 years: HR=1.09 (0.74–1.61) Women, colon Ever use: HR=0.97 (0.85–1.11) Use >5 years: HR=1.02 (0.75–1.38) Women, rectum Ever use: HR=0.97 (0.46–1.25) Use >5 years: HR=1.15 (0.66–2.01)
Yang, 2008[62]	CC	140	4292	Colorectal Ever use ≥5 years: OR=1.1 (0.5–2.2) Duration Use 5 years OR=1.1 (0.8–1.6) Use 6 years: OR=1.2 (0.8–1.8) Use 7 years: OR=1.2 (0.7–2.0) Use 8 years: OR=1.2 (0.7–2.2) Use 9 years: OR=1.3 (0.7–2.4) Use 10 years: OR=1.3 (0.6–2.7) Defined daily dose (DDD) Use ≤129: OR=1.0 (0.7–1.4) Use 129–342: OR=0.7 (0.5–1.1) Use 342–715: OR=1.0 (0.7–1.4) Use ≥715: OR=1.2 (0.9–1.7) Average daily dose (ADD) Use ≥1.5 ADD: OR=0.4 (0.1–1.2) Use ≥1.5 ADD for 1 year: OR=0.2 (0.02–1.3)
Boudreau, 2008[87]	CC	Colorectal 60	Colorectal 297	Colorectal Ever use: OR=1.02 (0.65–1.59) Use <2 years: OR=0.80 (0.40–1.59) Use ≥2 years: OR=1.22 (0.70–2.12) Colon Ever use: OR=0.91 (0.55–1.50) Use <2 years: OR=0.78 (0.37–1.65) Use ≥2 years: OR=1.06 (0.57–1.98) Rectum Ever use: OR=1.47 (0.50–4.29) Use <2 years: OR=1.04 (0.36–2.98) Use ≥2 years: OR=1.69 (0.77–3.70)

Author, year	Design*	Number of cases		Results (point estimate (95% CI))**
		User	Non-User	
Flick, 2009[57]	Cohort	Colorectal 56 Regional/ distant 32 Colon 42 Rectal 14	Colorectal 115 Regional/distant 63 Colon 81 Rectal 34	Colorectal Ever use: HR=0.89 (0.61–1.30) Use 101 days to <5 years: HR=0.91 (0.61–1.34) Use ≥5 years: HR=0.83 (0.43–1.63) Regional/distant CRC Ever use: HR=1.08 (0.65–1.79) Use 101 days to <5 years: HR=1.13 (0.68–1.89) Use ≥5 years: HR=0.83 (0.31–2.20) Colon Ever use: HR=0.90 (0.58–1.40) Use 101 days to <5 years: HR=0.92 (0.59–1.45) Use ≥5 years: HR=0.80 (0.37–1.76) Rectum Ever use: HR=0.86 (0.41–1.78) Use 101 days to <5 years: HR=0.84 (0.39–1.81) Use ≥5 years: HR=0.94 (0.26–3.37)
Shadman, 2009[64]	CC	36	453	Ever use: OR=1.17 (0.74–1.85) Former use: OR=1.93 (0.56–6.06) Current use: OR=1.09 (0.67–1.78)
Siddiqui, 2009[68]	CC	326	983	Metastasis Use ≥3 years: OR=0.7 (0.4–0.9) All cause mortality at 5 years Use ≥3 years: OR= 0.7 (0.6–0.9)
Singh, 2009[58]	Cohort	402	6,235	Regular use: RR=1.03 (0.93–1.14) Use ≥5 years: RR=1.10 (0.75–1.37) for low dose and RR=0.75 (0.51–1.10) for high dose
Haukka, 2010[50]	Cohort	-	-	Colon RR=0.99 (0.92–1.06) Rectum RR=1.07 (0.98–1.17)

* CC=case control

** OR=odds ratio; RR=relative risk; HR=hazard ratio; CI=confidence interval; relative to non-users of statin

*** Standardized dose scores: 1 = 10 mg of simvastatin, 20–40 mg of fluvastatin, 10–20 mg of lovastatin, 10–20 mg of pravastatin, or any dose of cerivastatin; 2 = 10 mg of atorvastatin, 20 mg of simvastatin, 80 mg of fluvastatin, 40 mg of lovastatin, or 40 mg of pravastatin; 3 = 20–40 mg of atorvastatin, 40–80 mg of simvastatin, or any dose of rosuvastatin.

Table 3

Epidemiologic studies of the association between statin use and incident lung cancer risk.

Author, year	Design*	Number of cases		Results (point estimate (95% CI))**
		User	Non-User	
Blais, 2000[35]	CC	70		OR=0.94 (0.43–2.05)
Graaf, 2004[45]	CC	449		OR=0.89 (0.56–1.42)
Kaye, 2004[49]	CC	43		Current use: RR=0.9 (0.6–1.3)
Friis, 2005[46]	Cohort	73	3326	RR=0.92 (0.72–1.16) Use ≥10 years: RR=0.80 (0.36–1.79)
Setoguchi, 2007[44]	Cohort	179	37	Ever use: HR=1.11 (0.77–1.60) Duration Use <3 years: HR=1.18 (0.72–1.92) Use ≥3 years: HR=1.02 (0.59–1.74)
Coogan and Rosenberg, 2007[47]	CC	31 cases and controls	424 cases and controls	Regular use: OR=0.7 (0.4–1.1) Duration Use ≤1 year: OR=0.3 (0.1–1.1) Use 1–5 year: OR=0.8 (0.4–1.5) Use ≥5 years: OR=0.9 (0.4–2.1) P for trend in duration: 0.8
Khurana, 2007[78]	CC	1994	161,668	Ever use: OR=0.55 (0.52–0.59) Use >6 month: OR=0.45 (0.42–0.48) Duration Use 0–6 months: OR=2.32 (2.05–2.63) Use 6–12 months: OR=0.75 (0.63–0.89) Use 1–2 years: OR=0.70 (0.61–0.79) Use 2–4 years: OR=0.49 (0.44–0.55) Use >4 years: OR=0.23 (0.20–0.26) No trend test for duration use
Farwell, 2008[66]	Cohort	436	431	Ever use: HR=0.70 (0.60–0.81) Dose Use ≤10mg: HR=0.70 (0.58–0.84) Use 11–39mg: HR=0.70 (0.57–0.86) Use ≥40mg: HR=0.73 (0.54–0.97) P for trend in dose: 0.002
Friedman, 2007[52]	Cohort	Men: 614 Women: 482	Did not report Did not report	Men Ever use: HR=1.02 (0.94–1.11) Use >5 years: HR=0.82 (0.68–0.99) Women Ever use: HR=1.16 (1.06–1.28) Use >5 years: HR=0.88 (0.70–1.10)
Haukka, 2010[50]	Cohort	-	-	RR=0.81 (0.77–0.86)

*CC=case control

**OR=odds ratio; RR=relative risk; HR=hazard ratio; CI=confidence interval; relative to non-users of statin

Table 4

Epidemiologic studies of the association between statin use and incident prostate cancer risk.

Author, year	Design*	Number of cases		Results (point estimate (95% CI))**
		User	Non-user	
Blais, 2000[35]	CC	78		OR=0.74 (0.36–1.51)
Coogan, 2002[36]	CC	71 9	1,292 230	All disease OR=1.2 (0.8–1.7) Advanced disease OR=0.9 (0.4–1.9)
Kaye, 2004[49]	CC	62		OR=1.3 (1.0–1.9)
Graaf, 2004[45]	CC	186		OR=0.37 (0.11–1.25)
Shannon, 2005[81]	CC	30 13	60 39	All disease Ever use: OR=0.35 (0.20–0.64) Use ≥2.8 years: OR=0.22 (0.08–0.66) Gleason score ≥7: Ever use: OR=0.24 (0.11–0.53) Use ≥2.8 years: OR=0.14 (0.03–0.67)
Friis, 2005[46]	Cohort	34	1,373	RR=0.87 (0.61–1.23)
Singal, 200[82]5	CC	26,139		OR=0.46 (0.45–0.48)
Platz, 2006[83]	Cohort	322 16	2,257 300	All disease Ever use: OR=0.96 (0.85–1.09 Use ≥5 yrs: 0.85 (0.71 to 1.03) Advanced disease Ever use: OR=0.51 (0.30–0.86) Use ≥5 yrs: OR=0.26 (0.08 to 0.83) Metastatic or fatal disease Ever use: OR=0.39 (0.19–0.77)
Flick, 2007[84]	Cohort	270	618	All disease Ever use: RR=0.92 (0.79–1.07) Use ≥5 years: RR=0.72 (0.53–0.99) Use ≥5 years and regular NSAID use: RR=0.64 (0.44–0.93) Advanced disease Ever use: RR=0.80 (0.53–1.19) Use ≥5 years: RR=0.57 (0.23–1.40)
Murtola, 2007[85]	CC	2,622	22,101	All disease OR=1.07 (1.00–1.16) Advanced disease OR=0.75 (0.62–0.91)
Jacobs, 2007[86]	Cohort	390 19	2,350 239	All disease Current use ≥5 years: RR=1.06 (0.93–1.20) Advanced disease Current use ≥5 years: RR=0.60 (0.36–1.00)
Coogan and Rosenberg, 2007[36]	CC	153 cases and controls	1027 cases and controls	Ever use: OR=1.2 (0.9–1.7) Duration Use ≤1 year: OR=1.1 (0.5–2.3) Use 1–5 year: OR=1.2 (0.8–1.9) Use ≥5 years: OR=1.2 (0.7–2.1) P for trend in duration: 0.1 Hydrophobic statin use: OR=1.29 (0.9–1.9)
Friedman, 2007[52]	Cohort	1,706	-	Ever use: HR=1.03 (0.98–1.08 Use >5 years: 1.04 (0.93–1.17)
Boudreau, 2008[87]	Cohort	246 43	2,286 415	All disease Ever use: HR=0.88 (0.76–1.02) Use ≥5 years: HR=1.06 (0.83–1.34) Hydrophobic use ≥5 yrs: HR=0.81 (0.56–1.16) Advanced disease Ever use: HR=1.22 (0.85–1.75) Use ≥5 years: HR=0.93 (0.45–1.92)

Author, year	Design*	Number of cases		Results (point estimate (95% CI))**
		User	Non-user	
Farwell, 2008[66]	CC	1164	1001	Ever use: HR=0.90 (0.81–0.99) Dose Use ≤10mg: HR=0.89 (0.79–1.01) Use 11–39mg: HR=0.89 (0.78–1.02) Use ≥40mg: HR=0.93 (0.77–1.12) P for trend in dose: 0.20
Smeeth, 2009[89]	Cohort	312	3213	Ever use: HR= 1.06 (0.86–1.30)
Agalliu, 2008[88]	CC	289	712	Ever use: OR=0.98 (0.80–1.21) Duration Use <5 years: OR=0.96 (0.74–1.23) Use 5–9.9 years: OR=0.97 (0.70–1.34) Use ≥10 years: OR=1.11 (0.70–1.75)
Haukka, 2010[50]	Cohort	-	-	RR=1.12 (1.08–1.17)
Murtola, 2010[90]	Cohort	268 22	1,326 111	All disease Current use: 0.75 (0.63–0.89) Use 4–5 yrs: HR=0.85 (0.65–1.11) Use ≥ 6 yrs: HR=0.70 (0.45–1.08) P trend for duration: 0.007 Advanced disease Current use: 0.93 (0.54–1.58) Use 4–5 yrs: HR=0.45 (0.11–1.85) Use ≥ 6 yrs: HR=2.02 (0.68–5.98) P trend for duration: 0.768

* CC=case control

** OR=odds ratio; RR= relative risk; HR=hazard ratio; CI=confidence interval; relative to non-users

Table 5

Epidemiologic studies of the association between statin use and female reproductive organ cancer risk.

Author, year	Design*	Endometrial Cancer			Ovarian Cancer		
		Number of Cases		Results (point estimate (95% CI))**	Number of Cases		Results (point estimate (95% CI))**
		User	Non-User		User	Non-User	
Blais, 2000[35]	CC	26		Cervix, endometrium, and ovary Ever use: OR=0.30 (0.11–0.81)	-	-	-
Kaye, 2004[49]	CC	3		Current use: OR=0.5 (0.1–1.9)	6		Current use: OR=1.0 (0.4–2.7)
Friis, 2005[46]	Cohort	24	1738	Genital cancer Ever use: RR=0.93 (0.62–1.40)	-	-	-
Coogan, 2007[47]	CC	19 cases and controls	194 cases and controls	Regular use: OR=1.3 (0.7–2.4)	-	-	-
Friedman, 2007[52]	Cohort	199	-	Ever use: HR=1.13 (0.98–1.31) Use >5 years: HR=1.10 (0.76–1.58)	79	-	Ever use: HR=0.83 (0.66–1.05) Use >5 years: HR=0.54 (0.27–1.09)
Yu, 2008[104]	Cohort	18	550	Ever use: HR=0.67 (0.39–1.17)	12	314	Ever use: HR=0.69 (0.32–1.49)

*CC=case control

**OR = odds ratio; RR = relative risk; HR = hazard ratio; CI = 95% confidence interval; relative to non-users