# Statin Use in Prostate Cancer: An Update

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**ABSTRACT:** 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, known as statins, are commonly prescribed for the treatment of hypercholesterolemia and cardiovascular disease. A systematic review was conducted using the keywords "statin and prostate cancer" within the title search engines including PubMed, Web of Science, and the Cochrane Library for relevant research work published between 2004 and December 2015. Although still premature, accumulating clinical evidence suggests that statin use may be beneficial in the prevention and/or treatment of prostate cancer. These human studies consist of meta-analyses of secondary endpoints obtained from randomized, controlled cardiovascular disease clinical trials of statins, patient database, observational studies, and a few, small case–control studies, directly addressing statin use on prostate cancer pathology and recurrence. This review summarizes and discusses the recent clinical literature on statins and prostate cancer with a recommendation to move forward with randomized, placebo-controlled clinical trials, investigating the use of statins. Additional preclinical testing of statins on prostate cancer cell lines and in vivo models is needed to elucidate pathways and determine its efficacy for prevention and/or treatment of prostate cancer, more specifically, the difference in the effectiveness of lipophilic versus hydrophilic statins in prostate cancer.

**KEYWORDS:** statins, prostate cancer, chemoprevention, prostate-specific antigen, cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme

## Introduction

Statins are a family of drugs that directly inhibit the catalytic active site of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that catalyzes the conversion of HMG-CoA into mevalonate within the cholesterol biosynthesis pathway.[1] Used by an estimated 24 million adults alone in the United States,[2] statins are widely prescribed in the primary treatment of hypercholesterolemia and cardiovascular disease.[3] Accumulating clinical and preclinical evidence suggests that statins may also prevent prostate carcinogenesis by (i) lowering serum and tissue cholesterol levels, which can disrupt cellular lipid rafts leading to reduced raft-dependent signaling and reduced prostate cancer cell proliferation and survival;[4] (ii) inhibiting isoprenoid synthesis, preventing anchorage to the plasma membrane and activation of small GTPase proteins, which play a pivotal role in cellular proliferation, differentiation, apoptosis, and migration;[5] and (iii) reducing the secretion of pro-inflammatory cytokines.[6]

## Clinical Studies on Statins and Prostate Cancer

The majority of clinical data evaluating the use of statins on the inhibition of prostate cancer development and progression stem from observational (case–control or cohort) studies utilizing large databases or meta-analyses of statin randomized clinical trials (RCTs). Results from these observational studies and meta-analyses have been mixed, likely due to the limitations of these types of studies. Meta-analyses of randomized, controlled cardiovascular disease clinical trials on statins are not well suited to address potential effects of long-term use on prostate cancer incidence. The primary endpoint of these RCTs was to evaluate the effect of statin treatment on primary or secondary prevention of cardiovascular disease; the effect of statin treatment on overall cancer or prostate cancer risks was evaluated as secondary endpoints. The number of these RCTs evaluating statins is a limiting factor, and the clinical trials were underpowered to detect any significant effect on prostate cancer risk. Additionally, the duration of statin administration and follow-up periods may have been too short to suffice any clinically significant effect on prostate cancer prevention and any relationship between statin use and different prostate cancer stage or Gleason grade has not been evaluated. Not surprisingly, all but one of these meta-analyses detected no significant effect of statin use on prostate cancer risk.[7–11] The meta-analysis performed by Bonovas et al[12] was the only study

to ascertain a significantly reduced incidence of advanced prostate cancer in subjects prescribed with statins; however, no relationship between statin use and overall prostate cancer risk was demonstrated in these earlier studies. Because of their significant disadvantages, meta-analyses of the statin RCTs should not be considered confirmatory evidence of an insignificant role of statins in the prevention of prostate carcinogenesis.

A longitudinal study design and mixed model analysis was conducted by Algotar et al,[13] and the results were inconclusive; neither a positive nor a negative correlation was found between prostate cancer risk and statin use. This study was conducted only for 3.5 years, and it did not address other medicines taken, comorbidities, or examine and standardize dosages of statin. However, a population-based retrospective cohort study that looked more specifically at the usage of statins after prostate cancer diagnosis did find a statistically significant reduction in prostate cancer mortality.[14] Comorbidities were taken into account, and a dose- and time-dependent relationship was observed, with a greater risk reduction found in patients who used statins before diagnosis as well as throughout their treatment. This study did not examine serum prostate-specific antigen (PSA) concentration or grade of cancer; rather, it focused on prostate cancer mortality in relationship to post-diagnosis statin use. Longer and higher dosages led to a lower incidence in mortality, as well as distant site metastasis, with a 23% decreased risk with lipophilic statins and a 35% decreased risk with hydrophilic statins.[14] Another retrospective cohort study by Nordström et al[15] found a significantly increased risk of finding prostate cancer and high-grade tumor when compared to men who did not take statin. The PSA levels measured after diagnosis was, on average, 8% lower in men who used statins when compared to nonusers. This study did not account for comorbidities, although it did acknowledge them. A regression model adjusted for coexisting medication, but did not account for preexisting conditions, such as obesity, hypertension, and diabetes, which are conditions that can often increase the risk for prostate cancer. A 10-year retrospective cohort study by Farwell et al[16] compared statin use in veteran population taking antihypertensive medications and found that, on average, statin users had a 31% lower risk of prostate cancer incidence. More specifically, men were 14% less likely to be diagnosed with low-grade prostate cancer and 60% less likely to be diagnosed with high-grade prostate cancer. The study by Platz et al[17] indicated no statistically significant difference in prostate cancer risk between statin users and non-statin users, whereas another study by Moon et al[18] adjusted for serum PSA levels noted an association between statin use and reduced risk of diagnosis of prostate cancer, as well as a reduced risk of aggressive and fatal prostate cancer. Observational studies have the advantages of large sample size and minimal information bias; however, the number of prostate cancer cases is small compared to total sample size and the study can be biased if not statistically adjusted for PSA testing

and serum PSA levels. PSA, a protease produced and secreted by the prostate gland, is used as a serum biomarker for the early detection of prostate cancer and other prostatic disorders.[6] In clinical studies, statin use is associated with an increase in PSA testing, lower PSA levels, and fewer prostate biopsies.[19] Therefore, statistical adjustment for PSA testing and serum PSA levels is critical for the credibility of results from observational studies evaluating the effect of statins on prostate cancer incidence. Studies not controlled for PSA testing did not detect a significant reduction in prostate cancer risk,[20–23] or they even reported an increased risk,[24–27] whereas the vast majority of observational studies with statistical adjustment for PSA testing reported an inverse association between statin use and either overall prostate cancer incidence[28–33] or advanced prostate cancer risk[28,34–36] (only a handful of PSA-adjusted observational studies demonstrated no effect between statin use and prostate cancer incidence) (Table 1).[2,19,37] In an effort to eliminate bias caused by opportunistic PSA testing and fluctuations in PSA level, an observational study by Murtola et al[32] used patients from the Finnish Prostate Cancer Screening Trial, a population of men frequently and systematically screened for prostate cancer, eliminating any detection bias between statin users and nonusers. This study reported a dose-dependent, significant inverse association between overall prostate cancer incidence and statin use, with the strongest inverse association for early-stage prostate cancer.

Results obtained from observational studies suggest that patients using statins may have a different risk profile for prostate cancer compared to nonusers. Statin users may have different access to health care, leading to more frequent PSA testing.[19] This creates the potential for increased detection of localized disease at the expense of advanced prostate cancer, potentially lending the appearance of an increased risk of localized disease or a protective effect against advanced-stage prostate cancer. As demonstrated by a recent simulation study by Mondul et al,[38] detection bias due to medical practices may explain the positive association between statin use and total prostate cancer incidence, especially in populations with low prevalence of PSA screening, such as in many European countries; however, this bias is unlikely the cause of the inverse association between statin use and advanced-stage disease observed in several cohort and case–control studies.[28,34–36] Statin users are more likely to be overweight and obese compared to nonusers;[6,19] therefore, the association between statin use and reduced serum PSA may be due to hemodilution. Lower PSA levels may delay referral for prostate biopsy,[3,19,39,40] leaving statin users underdiagnosed with prostate cancer and creating the appearance of reduced prostate cancer risk. Patients prescribed statins usually have elevated serum cholesterol levels.[41] Increased levels of serum cholesterol are associated with higher risk of total and high-grade prostate cancer (Table 1);[33,41,42] therefore, increased serum and tissue cholesterol levels may be promoting prostate carcinogenesis in patients taking statins, leading some observational

**Table 1.** Studies on statin use in prostate cancer.

| REFERENCE | DATA SOURCE | FOLLOW UP (YEARS) | AGE | SUBJECTS N | STATIN DOSAGE | PSA LEVELS | TUMOR STAGE/ GLEASON SCORE | RESULTS |
|---|---|---|---|---|---|---|---|---|
| Bonovas et al,[12] | Meta-analysis of epidemiological studies; 19 studies; 6 RCT, 6 cohort, 7 case-control | | | | | | | Negative |
| Algotar et al,[13] | Negative biopsy trial- randomized double blind, placebo-controlled phase 3 trial | 3.5 | 1. 66 (6.7) 2. 65 (8.0) | 1. 171 2. 520 | | 1. 6.9 (6.2) 2. 6.9 (6.2) Mean (sd) | | Inconclusive |
| Yu et al,[14] | – United Kingdom National Cancer Registry – Clinical Practice Research Datalink – Hospital Episode Statistics Database – Office for National Statistics Database – Population based retrospective cohort study | 4.4 (2.9) | 1. 71.9 (7.5) 2. 71.1 (9.3) | 1. 3407 2. 8365 | | 1. >10: 54.6% 2. >10: 57.0% | 1. >7: 58.0% 2. >7: 54.3% | Negative |
| Nordström et al,[15] | – Retrospective cohort – All PSA tested men in Stockholm, Sweden | 4 | 1. 64.1 (10.7) 2. 54.0 (12) | 1. 26432 2. 147134 | | 1. 1.2 (1.91) (ng/mL) 2. .98 (1.2) median (IQR) | 1. >7: 29% 2. >7: 23% | Negative |
| Farwell et al,[16] | Veterans affairs New England Healthcare System – Retrospective Cohort | 5.6 | 1. 66.3 (10.4) | 1. 41078 | Mean = 26.2 mg (22.2) | | 1. >7: 45.1 | Negative |
| Platz et al,[17] | – Cohort – Prostate Cancer Prevention Trial | 7 | 1. 63.3 2. 63.3 | 1. 2249 2. 7208 | | 1. 1.19 (ng/mL) 2. 1.24 | | Inconclusive |
| Moon et al,[18] | Analysis of epidemiological studies | N/A | N/A | N/A | N/A | N/A | N/A | Negative |
| Fowke et al,[19] | Nashville Mens Health Study | | 65.1 years | 1. 783 2. 1365 | | 1. 6.1 ng/mL 2. 6.8 ng/mL | 1. >7: 19% 2. >7: 18.7% | Inconclusive |
| Blais et al,[20] | Régie de l'Assurance-Maladie du Québec | 2.7 years | | 6721 | | | | Inconclusive |
| Graaf et al,[21] | PHARMO record linkage system | 7.2 years | | 3789 | | | | Negative |
| Friis et al,[22] | Pharmacoepidemiological Prescription Database of North Jutland | 3.3 years | 1. 60.7 2. 53.9 | 12251 | | | | Negative |
| Coogan et al,[23] | Patients admitted to participating hospitals in New York, Philadelphia, and Baltimore | | | | | | | Inconclusive |
| Kaye et al,[24] | General Practice Research Database | | | 1. 62 2. 204 | | | | Positive |
| Murtola et al,[25] | Finnish Cancer Registry | 7 years | 69 years | 25,029 | | | | Positive |

(Continued)

**Table 1.** (*Continued*)

| REFERENCE | DATA SOURCE | FOLLOW UP (YEARS) | AGE | SUBJECTS N | STATIN DOSAGE | PSA LEVELS | TUMOR STAGE/ GLEASON SCORE | RESULTS |
|---|---|---|---|---|---|---|---|---|
| Haukka et al,[26] | | | | | | | | Positive |
| Chang et al,[27] | Taiwan National Health Insurance Program | | Prostate cancer cases-71.98 Controls-71.95 | Prostate cancer cases-388 Controls-1552 | | | | Positive |
| Shannon et al,[28] | | | | | | | | Negative |
| Flick et al,[29] | Northern and Southern California Kaiser Permanente (KP) members | 2.3 years | 58 years | 84,170 | | | | Negative |
| Farwell et al,[30] | Veterans affairs New England Healthcare System | 5 years | 1. 66.6 2. 66.3 | 1. 37248 2. 25594 | | | | Negative |
| Breau et al,[31] | Olmsted County, Minnesota | 1. 15.7 years 2. 15.2 years | 1. 38.6%—40—49 years 33.4%—50–59 years 22.1% 60—69 years 5.8% 70+ 2. 49.5% 40–49 years; 21.4% 50–59 years; 17% 60–69 years; 12.1% 70+ years | 1. 634 2. 1813 | | 1. >4.0 ng/mL = 12.8% >2.5 ng/mL = 15.2% 2. >4.0 ng/mL = 12.8% >2.5 ng/mL = 25.5% | 1. prostate biopsy = 13.7% prostate cancer = 6% High grade prostate cancer = 1.1% 2. prostate biopsy = 23.6% prostate cancer = 10.3% High grade prostate cancer = 2.8% | Negative |
| Murtola et al,[32] | The finnish prostate cancer screening trial | 1. 6.92 years 2. 6.92 years | 55–67 years | 1. 6692 2. 16516 | | Baseline PSA: 1. 1.05 2. 1.10 | 1. 2–6 = 75% 7–10 = 22.6% 2. 2–6 = 75% 7–10 = 25% | Negative |
| Farwell et al,[33] | Veterans Affairs (VA) New England Healthcare System | 5.6 years | 66.0 years | 1. 41078 2. 14797 | Mean equiv simvastatin dose = 26.2 mg (SD = 22.2 mg) | | 1. >7 = 45.1% 2. >7 = 52% | Negative |
| Platz et al,[34] | Health professionals follow-up study | 5 years | 1. 63.2 years 2. 60.9 years | 1. 2847 2. 27796 | | | | Negative |
| Tan et al,[36] | Cleveland Clinic | | 1. 65.7 2. 63.5 | 1. 1022 2. 3182 | | 1. 5.13 2. 5.98 | 1. >8 14.9% 2. >8 14.5% | Negative |
| Friedman et al,[37] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Inconclusive |
| Mondul et al,[38] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Positive |
| Mener et al,[39] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Negative |
| Morote et al,[40] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Negative |
| Mondul et al,[41] | NHANES | | 1. 60.0 2. 53.5 | 1. 483 2. 2091 | | 1. .88 (.82–.94) 2. .95 (.92–.99) | | Positive |
| Mondul et al,[42] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Positive |

| Study | Institution | Follow-up | Age | N (1. statin, 2. non-statin) | Dose | PSA | Gleason | Result |
|---|---|---|---|---|---|---|---|---|
| Loeb et al,[43] | Northwestern University | | 1. 61 years 2. 58 years | 1. 504 2. 847 | | 1. 4.8 ng/mL 2. 5.0 ng/mL | 1. >7 = 31.5% 2. >7 = 31.4% | Inconclusive |
| Mondul et al,[44] | Johns Hopkins Hospital | | 1. 57.7 years 2. 56.0 years | 1. 386 2. 2012 | | 1. 6.3 ng/mL 2. 7.1 ng/mL | 1. >7 = 9.0% 2. >7 = 10.3% | Positive |
| Chao et al,[45] | Kaiser Permanente Southern California Kaiser Permanente Southern California Cancer Registry | 5 years | 1. 61 years 2. 59 years | 1. 446 2. 738 | | 1. 6.7 ng/mL 2. 7.1 ng/mL | 1. >7 = 48% 2. >7 = 44% | Inconclusive |
| Ishak-Howard et al,[46] | University of Michigan prostate Cancer Genetic Project | 4.2 years | 1. 66.5 2. 62.6 | 1. 258 2. 281 | | 1. 1.37 (SD = 13.4) 2. 2.8 (SD = 23) | 1. >7 = 50.4% 2. >7 = 51.3% | Inconclusive |
| Allot et al,[47] | Shared Equal Access Regional Cancer Hospital Database | 1. 7.7 years 2. 5 years | 1. 60.7 years (SD = 6.5) 2. 60.6 years (SD = 6.3) | 1. 400 2. 746 | | 1. 5.9 ng/mL 2. 7.1 ng/mL | 1. >7 = 29% 2. >7 = 40% | Negative |
| Moyad et al,[48] | | 5.4 years | 1. 66.4 years 2. 66.0 years | 1. 191 2. 747 | | 1. 7.9 (SD = 4.6) 2. 8.6 (SD = 6.1) | 1. 6.7 (SD = .9) 2. 6.7 (SD = 1.0) | Negative |
| Gutt et al,[49] | University of Chicago Pritzker School of Medicine | 4.2 years | 1. 69 2. 68 | 1. 189 2. 502 | | 1. 7.2 ng/mL 2. 8.78 ng/mL | 1. >7 = 44% 2. >7 = 37% | Negative |
| Hamilton et al,[50] | Shared Equal Access Regional Cancer Hospital Database (SEARCH) | 1. 2 years 2. 3.2 years | 1. 62.6 (SD = 5.6) years 2. 60.6 (SD = 6.6) years | 1. 236 2. 1083 | <20 mg (simvastatin equiv) = 33% =20 mg = 35% >20 mg = 32% | 1. 6.2 2. 6.9 | | Negative |
| Kollmeier et al,[51] | Memorial Sloan-Kettering Cancer Center | 5.9 years | 1. <65 = 26% >65 = 74% 2. <65 = 27% >65 = 73% | 1. 382 2. 1299 | | 1. >10 = 27% 2. >10 = 39% | 1. >7 = 52% 2. >7 = 55% | Negative |
| Soto et al,[52] | University of Michigan Cancer Center | 3.9 years | 1. 68 (7.2) 2. 68.2 (7.3) | 1. 220 2. 748 | | 1. 6.5 ng/mL 2. 8.2 ng/mL | 1. >7 = 15.5% 2. >7 = 13.7% | Inconclusive |
| Bansal et al,[53] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Negative |
| Melvin et al,[54] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Inconclusive |
| Brown et al,[55] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Negative |

**Notes:** 1. statin users, 2. non-statin users.

studies to report a positive association between statin use and prostate cancer incidence. Statin users often have other comorbidities, such as diabetes and metabolic syndrome, known to promote prostate cancer development and progression.[6] Patients receiving statins may also be advised to implement changes to diet and exercise habits to prevent CVD that may also affect prostate cancer incidence.[6] Additionally, statin users more frequently take nonsteroidal anti-inflammatory drugs (NSAIDs) for the prevention of cardiovascular disease;[6] NSAIDs have been found to significantly reduce prostate cancer risk[29] and may act synergistically with statins to prevent prostate cancer. These biases may result in statin users appearing to have decreased risk for prostate cancer, where in fact adjustments in lifestyle factor(s) associated with cardiovascular disease prevention may be responsible for the decreased risk of prostate cancer.

Limited clinical studies have directly addressed the relationship between statin use and prostate cancer. Two studies analyzed preoperative statin use in a population of patients who underwent radical prostatectomy to determine the influence of statin use on the pathological characteristics of the prostate tumor in prostatectomy specimens.[43,44] Statin users in the study by Mondul et al[44] were statistically significantly more likely to have organ-confined disease than nonusers, whereas no association between preoperative statin use and organ-confined disease was reported. In the study by Loeb et al,[43] statin users were shown to have significantly fewer positive surgical margins and a smaller tumor volume than nonusers;[43] however, it was acknowledged that this could be due to increased access to health care and surveillance of statin users, leading to earlier diagnosis. Both studies demonstrated a trend of inverse association between statin use and incidence of Gleason grade ≥7 (4 + 3) prostate cancer in radical prostatectomy specimens;[43,44] yet, this trend was only statistically significant in the Mondul et al[44] study for men with serum PSA concentrations ≥10 ng/mL. One study showed no association between statin use and freedom from biochemical recurrence (BCR).[17] Another study also examined the probability of BCR after radical prostatectomy and postoperation statin use. There was no dose–response relationship found for statins and prostate cancer BCR,[45] but the follow-up time was only after five years, and the authors suggested a longer follow-up time to better determine distant metastatic effect of statins. This was supported by another study conducted by Ishak-Howard et al,[46] who also found no association between statin use and BCR when compared to nonusers. The authors did acknowledge that BMI could mediate the relationship between prostate cancer and statin use, which could be a source of confounding and explain the lack of association found between duration of statin use and BCR. Allott et al[47] compiled results from the SEARCH database to determine BCR and postoperative statin use and found a significant 36% decreased risk. However, the dose was not recorded, so there is likely a significant amount of variability

in type and dosages used after surgery. Additionally, seven studies have investigated the effect of statin use on incidence of prostate cancer recurrence after curative radiation therapy.[44,48–53] Five of these clinical studies demonstrated that statin use was associated with significant improvement in freedom from biochemical failure, based upon serum PSA levels (Table 1).[44,48–53] Soto et al[52] demonstrated that statin use significantly increased progression-free survival time versus nonusers overall; however, when the clinical analysis was limited to the years 1996–2006, when statins were more readily available and prescribed, this association disappeared. Bansal et al[53] conducted an analysis of 27 observational studies conducted from 1993 through 2011 and found a 7% reduction in total prostate cancer risk when compared to nonusers, but this was a nonsignificant decreased risk, which they attributed to varying patterns of statin use and major confounding variables, such as PSA levels, BMI, and lifestyle factors.

Melvin et al[54] examined the use of population-based data to establish a relationship between statins and cancer, and they determined that there was sizable confounding, and attempts to reduce variability only increased this. The authors determined that there was a need for clinical trials, and causal inference methods cannot make clear associations between statins and the risk of prostate cancer from population-based data. This explains much of the variability seen among population studies done throughout the years and why there cannot be a clear-cut answer regarding the chemopreventative and treatment potential of statins.

## Preclinical Studies on Statins and Prostate Cancer

Studies conducted in cell culture have provided information on the potential mechanisms of action by which statins can impart protective effect in prostate cancer. Brown et al[55] treated PC-3 cells with lipophilic and hydrophilic statins to determine the relationship between statin use and invasion toward bone marrow stroma. Lipophilic statins significantly reduced the number of colonies in clonogenic assays and bone marrow stroma (BMS) coculture and changed the morphology of cells by inhibiting formation of lamellipodia and distorting trailing edges. Although similar results were not observed with hydrophilic statins, such as pravastatin, this is likely due to its need for active transport in order to cross the cell membrane. This study suggests that the reduction in cholesterol synthesis is not the reason why statins have shown preventative and treatment potential for prostate cancer.[55] In vitro studies have further confirmed that statins were active in prostate cancer cells, inducing cell apoptosis, G1 cell cycle arrest, autophagy, and the degradation of androgen receptors. Costa et al[56] found that PC-3 cell necrosis could be induced by simvastatin at 10 μM concentrations; however, simvastatin is toxic to humans at that pharmacological dose level. Because simvastatin is lipophilic in nature, it can accumulate into cells as a function of time, supporting the fact that long-term use of statins is warranted in order to determine its chemopreventive effects.

Statins have effects on pathways that regulate apoptosis, angiogenesis, and tumor invasions in vivo.[57–60] For example, dysregulation of the mevalonate pathway, involved in p53 expression and tumor promotion in many types of cancer, has been shown in mouse models to stimulate tumor proliferation. Other proposed mechanism(s) for the anticancer properties of statins is through the inhibition of Akt phosphorylation and prenylation of oncogenic proteins such as Ras, Rac, and Rho. These proteins play a role as mediators of tumor growth, mobility, and metastasis, and inhibition of the mevalonate pathway also limits their production. In murine models, statins have been shown to reduce cancer cell proliferation in breast, colon, liver, pancreatic, and ovarian cancers.[57–60] Particularly, in breast cancer, a review of prospective, case–control and randomized control trials involving 83,919 patients found significant negative associations between both pre-diagnosis statin use and breast cancer mortality, as well as post-diagnosis statin use and survival.[61] Similar large cohort studies are warranted in other types of human cancers as well.

## Conclusions

Clinical evidence on the protective effect of statins against prostate cancer is still weak and inconsistent. Several limitations should be taken into consideration when interpreting the results of this review. Data were taken from observational studies and through meta-analyses of major statin randomized control trials, which, upon analysis, have proven to have various disadvantages. The lack of statistical adjustment for PSA testing, serum PSA levels, and concomitant use of NSAIDs in observational studies, and the short duration of statin use and small number of prostate cancer cases leading to low statistical power in meta-analyses of statin RCTs impair results. Furthermore, limited data made it difficult to evaluate the effects of both pre-diagnostic and post-diagnostic statin use in prostate cancer. The strict population selection criteria of statin RCTs also render generalization of the results of meta-analyses implausible. Meta-analyses conducted examining statin use and prostate cancer risk and mortality have conflicting results, and until a way to reduce variability without increasing confounding can be found, conclusive directives cannot be made. More preclinical studies must be performed examining treatment of various prostate cancer cell lines with differing concentrations of statins to establish a dose- and time-dependent relationship. Despite a lack of conclusive evidence, there is a possibility that men receiving prescription statins may have a reduced risk for prostate cancer development. However, physicians should be aware of the potentially harmful effects of statins on prostate carcinogenesis suggested by some experimental studies; low doses of statins may promote angiogenesis, enhancing tumor growth,[6] and statins may increase the number of CD4+ CD25+ regulatory T-cells, suppressing tumor-specific T-cell immune responses.[6]

## Recommendations and Future Directions

Stains are a potentially promising class of agents with cholesterol-lowering properties, which could be a significant mechanism by which these drugs might inhibit the carcinogenic process. Statins have pleiotropic effects on other cancer-related processes such as angiogenesis and inflammation, and also on a number of novel molecular targets and complex signaling pathways. The use of statins is increasing, and there is a need to pinpoint the mechanism(s) that underlies the putative anticancer properties of statins, which will be a key in providing the rationale for prospective clinical trials of these drugs in prostate cancer. Although initial effort is needed to determine the class and optimal dose of statins that are sufficient to elicit chemopreventive effects, studies providing evidence that statins target premalignant lesions could be taken to the next level. Relatively small Phase I and II studies could be sufficient to provide information on the biological plausibility of statins in prostate cancer, and continued follow-up will be beneficial for the assessment of the effects of long-term statin use. In summary, statins may inhibit prostate carcinogenesis by suppressing cell growth, angiogenesis/invasion, and induction of apoptosis of prostate tumor cells. The focus now must be placed on preclinical trials to determine the direct relationship between prostate cancer and statin use. Additionally, the optimal timing of statin use is unclear; it can be used pre-diagnosis, post-diagnosis, or posttreatment. There also appears to be a difference between lipophilic and hydrophilic statin use in terms of prostate cancer chemoprevention. Further testing is needed to determine which is more effective. Hopefully, the role of statins in prostate cancer might be elucidated in future randomized, placebo-controlled clinical trials.

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## Author Contributions

Wrote the first draft of the manuscript: MAB. Contributed to the writing of the manuscript: MAB and SG. Contributed in putting new updates: JAM, AJ, and ES. Made critical revisions and approved the final version: SG. All the authors reviewed and approved the final version of the manuscript.

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