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The current evidence on statin use and prostate cancer prevention: are we there yet?

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Abstract

An increasing amount of data supports an inverse association between statin use and cancer risk. The findings for prostate cancer, particularly advanced disease, are the most promising of all cancers studied. Use of these agents seems to also be associated with improved prostate-cancer-specific survival, particularly in men undergoing radiotherapy, suggesting usefulness of statins in secondary and tertiary prevention. Some study results might be influenced by increased PSA screening and health-conscious behaviour in statin users but these factors are unlikely to completely account for observed beneficial effects. The epidemiological evidence is supported by preclinical studies that show that statins directly inhibit prostate cancer development and progression in cell-based and animal-based models. The antineoplastic effect of statins might arise from a number of cholesterol-mediated and non-cholesterol-mediated mechanisms that affect pathways essential for cancer formation and progression. Understanding these mechanisms is

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The authors declare no competing interests.

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instrumental in drug discovery research for the development of future prostate cancer therapeutics, as well as in designing clinical trials to test a role for statins in prostate cancer prevention. Currently, sufficient data are lacking to support the use of statins for the primary prevention of prostate cancer and further research is clearly warranted. Secondary and tertiary prevention trials in men who have been diagnosed with prostate cancer might soon be performed.

Statins are a class of medications that effectively lower serum cholesterol levels by inhibiting 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme for cholesterol synthesis in the liver. Statins are becoming one of the most commonly prescribed medications in the USA, owing to the epidemic proportions of hyperlipidaemia in this country[1]. In 2012, more than one in four US adults aged ≥40 years reported using statins; simvastatin and atorvastatin were the two most commonly used agents (42% and 20% of all statin users, respectively)[2]. Unequivocal evidence exists that statins reduce the number of adverse cardiovascular events associated with hyperlipidaemia[3], but during the past decade several reports have highlighted the potential of statins in chemoprevention of other diseases[4–11]. For example, statin use has been linked to reduced risk of several cancer types. The most promising data relate to the prevention of prostate cancer — in particular advanced disease[6–11]. However, advocating that all men start taking statins as a chemopreventive measure against prostate cancer would currently be premature, as not all data agree on the potential benefits of statins, especially in reducing the risk of prostate cancer of any stage (referred to as total prostate cancer)[12,13]. In this Review, we present the current evidence supporting and opposing a role for statins in the chemoprevention of prostate cancer. We review cell-based and animal-based pre-clinical studies that examined the molecular mechanisms of inhibitory effects of statins on prostate cancer growth and examine the most current data from studies in humans on associations between statin use and prostate cancer, with an emphasis on the accumulating evidence that supports an effect of statin use in preventing advanced prostate cancer and prostate cancer progression. We also discuss the current gaps in our understanding of how statins might modify prostate cancer risk, which require further work to better guide future research and funding strategies.

Statin medications: the basics

The ability of statins to reduce the number of adverse cardiovascular events associated with hyperlipidaemia by lowering total serum cholesterol and LDL cholesterol levels is well established. The underlying mechanism is based on restricting cholesterol synthesis in the liver via inhibition of the rate-limiting hepatic HMG-CoA reductase[3]. Statins can be classified as either hydrophilic or lipophilic, depending on their solubility[14] (TABLE 1). Hydrophilic statins are more hepatoselective than lipophilic statins, as they are actively transported into the liver by members of the organic anion transporting poly-peptide family (also known as OATPs). By contrast, lipophilic statins enter the liver by passive diffusion. Relative to hydrophilic statins, lipophilic statins are taken up more easily by nonhepatic tissues that do not express dedicated transporters, such as the prostate[15]. Hence, lipophilic stat-ins have been hypothesized to have a greater influence on the prostate than hydrophilic statins, but this theory has not been corroborated by observational studies of statin use and

prostate cancer risk (TABLE 2), in part because the number of men taking hydrophilic statins was low[6,16–18].

Statins are generally well tolerated, with the most common adverse effects being hepatic dysfunction and muscle myopathies. A meta-analysis of 35 clinical trials in patients with hyperlipidaemia receiving a statin or a placebo drug concluded that statin therapy is associated with a small excess risk of hepatic dysfunction but not of myalgias, rhabdomyolysis or elevation of creatine kinase levels, which is a marker of myopathy[19]. Another meta-analysis of 13 clinical trials showed that statin use was associated with a slightly elevated risk of new-onset diabetes, but this risk was offset by the cardiovascular benefits of statins[20]. Owing to the good efficacy and safety profile of statins, following the FDA approval of lovastatin in 1987, market introduction of six other statins was not surprising and statin use has been increasing continuously[21,22] (FIG. 1). Interestingly, cardiovascular benefits of taking statins have also been observed in users who do not have elevated cholesterol levels[23], suggesting that statin use has non-cholesterol-mediated effects. These findings of pleiotropic effects of statins lend support to the rationale to examine whether statins might modify cancer risk.

Interestingly, early observations in rodents indicated that cholesterol-lowering drugs could cause cancer, albeit at doses exceeding those administered to humans[24]. Similar results in human populations were subsequently attributed to reverse causality, caused by accumulation of cholesterol from the serum in tumours, resulting in a drop in serum cholesterol levels[25]. Since the publication of these findings, the majority of epidemiological data have indeed shown a protective effect of statins against cancer[4–11].

Mechanisms of prostate cancer prevention

As evidence from studies in humans that supports a role for statins in modifying prostate cancer risk is accumulating, investigation of the underlying molecular mechanisms, using established cell-based and animal-based preclinical models becomes essential. Much data from these models have already been published, demonstrating that statins can inhibit prostate cancer growth through cholesterol-mediated and non-cholesterol-mediated mechanisms that affect many pathways essential for cancer formation and progression. Specifically, statins have been shown to inhibit prostate cancer inflammation[26], angiogenesis[27], cell proliferation[28], migration and/or adhesion[29] and invasion[30], and to promote apoptosis[31]. In addition, inhibition of HMG-CoA reductase by stat-ins lowers the concentration of mevalonate (FIG. 2) and, consequently, levels of downstream, isoprenylated intermediates believed to be essential in signalling pathways that support cancer formation and progression[32].

Cholesterol-mediated pathways

A positive correlation between cholesterol accumulation in prostatic tissues and the presence of prostate cancer was already reported in 1981 (REF. 33). Several mechanisms have since been shown to contribute to dysregulation of cholesterol homeostasis in prostate tumours. One study found that hypermethylation of the *ABCA1* promoter resulted in reduced expression of the encoded cholesterol efflux transporter, decreased cholesterol efflux rates

and elevated intracellular cholesterol levels in prostate cancer cell lines, and that the presence of this epigenetic alteration was associated with high-grade prostate cancer[34]. In addition, the mTOR pathway is important in regulating sterol-regulatory-element-binding proteins (also called SREBPs), which are transcription factors that control lipid and cholesterol homeostasis[35]. One study reported that intracellular accumulation of cholesteryl ester in lipid droplets was driven by loss of expression of the tumour suppressor PTEN and subsequent activation of the PI3K–AKT–mTOR signalling pathway, and that intracellular accumulation of cholesteryl ester was associated with high-grade prostate cancer in humans[36].

One of the major cholesterol-mediated mechanisms through which statins inhibit tumour growth involves specialized cholesterol-rich regions of the cell membrane known as lipid rafts[37]. These domains facilitate membrane-initiated signalling events in the cell through compartmentalization of signalling pathways, which can enhance tumour growth. Cell signalling pathways implicated in prostate cancer development and progression that might be affected by lipid raft cholesterol composition include pathways involving the androgen receptor[38], the epidermal growth factor receptor (EGFR)[39] and the luteinizing hormone receptor[40]. Statins, through their effect on intracellular cholesterol homeostasis, are thought to disrupt the organization of lipid rafts and, thus, interfere with these or other downstream intracellular signalling pathways[41].

The EGFR pathway is one example of the direct effect that reduced cholesterol content of the rafts can have on membrane-initiated signalling. EGFR is a cell-membrane-bound receptor that associates with lipid rafts in prostate cancer cells[39]. EGFR activation leads to activation of protein kinase B (AKT, encoded by *AKT1*), which promotes the growth of several solid tumour types, including prostate cancer[42]. Treatment of prostate cancer cells with cholesterol binders can disrupt lipid raft organization and interfere with EGFR signalling[39].

In addition, one study found that activation of cholesterol efflux through treatment with a liver X receptor agonist induced apoptosis through disruption of lipid rafts and subsequent downregulation of AKT signalling in LNCaP *in vitro* and *in vivo* models[43]. Other signalling pathways implicated in the development of prostate cancer and castration resistance, such as IL-6-activated JAK–STAT3 (Janus kinase–signal transducer and activator of transcription 3) signalling, have also been found to be affected by lipid raft organization and are, therefore, potentially influenced by lipid raft cholesterol concentrations[44]. The importance of cholesterol in prostate cancer development has also been seen in a mouse model. In one study, mice were either fed a high-fat, high-cholesterol diet or a low-fat, low-cholesterol diet[45]. After subcutaneous injection of LNCaP cells, elevated cholesterol levels in the serum of mice that were fed the high-fat, high-cholesterol diet promoted xenograft tumour growth and reduced apoptosis, in part by increasing activity of AKT. Inhibition of cholesterol synthesis with a statin disrupted lipid rafts in the tumours and induced apoptosis via attenuation of AKT signalling[45].

In addition, cholesterol levels might also affect prostate cancer development via androgen signalling pathways, as cholesterol is the precursor of androgens. Lowering cholesterol

levels using statins might reduce prostate cancer growth by reducing serum or intratumoural levels of androgens. However, the effect of statins on serum androgen levels is unclear. Some studies have suggested that statins reduce serum testosterone levels[46–48], but these reductions were small or caused by statin doses that were higher than commonly used in clinical practice. Other observational studies[49,50] and two clinical trials[51,52] found no association between statin use and serum androgen levels. A study in 1,812 men in the Boston Area Community Health Survey cohort of which 237 men were statin users found no association between statin use and serum androgen levels[53]. Emerging evidence suggests that intratumoural levels of androgens remain high even when castrate levels of androgens are reached in the serum of patients with prostate cancer, possibly owing to *de novo* androgen synthesis in the tumour cell[54–56]. Thus, statins might conceivably be able to lower intratumoural androgen levels by lowering intratumoural cholesterol levels. Indeed, a study in noncastrated mice with hyper-cholesterolaemia induced by a high-fat, high-cholesterol diet found increased intratumoural levels of androgens in LNCaP xenografts without an effect on androgen levels in serum, suggesting that hypercholesterolaemia induces intratumoural *de novo* steroidogenesis[57].

Non-cholesterol-mediated pathways

Statins inhibit the conversion of HMG-CoA to mevalonate, thereby reducing cellular mevalonate concentrations. Mevalonate is a precursor for a class of compounds called isoprenoids, such as farnesyl pyrophosphate and geranyl pyrophosphate (FIG. 2). Farnesyl pyrophosphate and geranyl pyrophosphate facilitate the recruitment of signalling proteins, such as G-proteins of the Ras and Rho superfamilies, by bridging their attachment to the plasma membranes, where their signalling activities can promote prostate cancer cell survival and proliferation[58,59]. Thus, statins, by reducing mevalonate and downstream isoprenoids, might inhibit cancer cell proliferation.

Furthermore, statins seem to directly induce apoptosis in cancer cells independently of their effect on cholesterol levels[32]. For example, in prostate cancer, statins can inhibit cyclin-dependent kinase 2 and stimulate cell cycle arrest[60], or activate specific proteases that themselves can activate apoptosis[61]. Statins also have direct anti-inflammatory and antiangiogenic properties that, conceivably, might also inhibit cancer growth and progression[32]. One study in a cohort of men undergoing radical prostatectomy found that statin users were 69% less likely to have inflammation within their prostate tumours than nonusers (P=0.047), as assessed by pathological evaluation of tumour sections stained with haematoxylin and eosin[62].

Epidemiological evidence

In the past few years, interest in the use of statins for prostate cancer prevention has increased[63]. It has even been suggested in a study by Colli and Amling[64] that stat-ins might be partially responsible for the steep decline in the prostate cancer death rate in the USA during the past 15 years (see the American Cancer Society Cancer Facts & Figures 2016), as it paralleled the market introduction and distribution of statins (FIG. 1). Evaluation of epidemiological studies and secondary analyses of randomized controlled trials seems to

show that most evidence supports the hypothesis that statin use reduces prostate cancer risk, with the strongest evidence to date supporting that statins might selectively lower the risk of advanced prostate cancer. In addition to data supporting an inverse association between statin use and risk of advanced prostate cancer, evidence also exists that statins might affect prostate cancer progression at multiple stages of the disease course, including biochemical recurrence after primary therapy, development of castration resistance following androgen deprivation therapy, as well as prostate cancer-specific mortality (FIG. 3).

Total prostate cancer

More than 30 observational studies have examined the link between statin use and total prostate cancer risk with encouraging though conflicting results (TABLE 2). A number of case-control studies reported no associations[7,16,65–67], but three reported an elevated risk of total prostate cancer in statin users[10,68,69]. The investigators of one of these studies suggested that the positive association between statin use and total prostate cancer risk is potentially attributable to bias arising from increased surveillance in men initiating statin treatment[10]. Indeed, one study in Finland found that the elevated prostate cancer risk in new statin users disappeared with increasing duration of statin use, supporting this possible explanation[69]. Other case-control studies have reported inverse associations between statin use and risk of total prostate cancer[6,18,70], including one study in 4,204 men undergoing prostate biopsy that reported a significant 8% reduced risk of total prostate cancer in statin users in comparison with nonusers (RR 0.92; 95% CI 0.85–0.98)[70]. The largest population-based case-control study to date, a Danish study that included >40,000 patients with any stage of prostate cancer and >200,000 controls, reported a significant 6% reduction in risk of total prostate cancer in statin users (adjusted OR 0.94; 95% CI 0.91–0.97)[18].

These case-control studies reported varying findings for associations between statin use and total prostate cancer risk, but a number of cohort studies have also been conducted. A retrospective study of data from a cohort of >55,000 men in the Veterans Affairs New England Healthcare System found that statin users were 31% less likely to be diagnosed with total prostate cancer than men who did not use statins[71]. Two prospective cohort studies including 6,692 and 634 men taking statins and undergoing PSA screening found a 25% and 64% reduced prostate cancer risk, respectively[72,73]. A retrospective cohort study in Israel of 37,645 men taking statins found a 74% reduced risk of total prostate cancer in long-term statin users, defined as >5 years of statin use, in comparison with nonusers[74]. Other studies found weaker but still inverse associations between statin use and total prostate cancer risk[75,76], including a population-based study in Washington, USA, that found that statin users had a nonsignificant 12% lower prostate cancer risk[17].

Despite these promising data, other observational studies found no link between statin use and total prostate cancer risk, including a secondary analysis of a randomized trial in men with a negative prostate biopsy who underwent repeat biopsies at 2 years and 4 years[77], in addition to several cohort studies[5,8,9,11,78–82]. Overall, individual case-control and cohort studies had conflicting findings, but the most recent meta-analysis of these studies from 2012 reported a significant 7% reduction in risk of total prostate cancer in statin users in comparison with nonusers (P= 0.03)[83].

Three meta-analyses of randomized controlled trials of statin use for the primary and secondary prevention of adverse cardiovascular outcomes reported no association between statin use and total prostate cancer risk[84–86]. However, trial participants do not represent the general population. For example, all trials of statin use incorporated dietary interventions in both statin and placebo groups and all trial participants had a history of cardiovascular disease[3]. Furthermore, although the most commonly used statin in the USA is simvastatin[2] (TABLE 1), participants in the majority of clinical trials were randomized to receive pravastatin, which inhibits HMG-CoA reductase more weakly than simvastatin and has reduced cholesterol-lowering efficacy[87]. Finally, randomized controlled trials have relatively short follow-up periods: the median follow-up duration was 4.8 years for the 27 statin trials performed to date[84]. Together, these factors could explain differences in associations between statin use and total prostate cancer risk reported by observational studies and randomized trials.

Advanced prostate cancer

Overall, the data from studies examining associations between statin use and total prostate cancer are inconclusive, with the majority of studies showing no effect of statin use on total prostate cancer risk. However, increasing data indicate that statin use might selectively lower the risk of advanced prostate cancer (defined using varying levels of Gleason grade, clinical stage or a combination of both variables; TABLE 2).

Six large, prospective studies all found that statin users had a reduced risk of advanced prostate cancer without any reduction, or with an attenuated reduction, in total prostate cancer risk[8,9,11,76,80,82]. In all six studies, bias was minimized by controlling for potential confounding variables, for example, concomitant diseases, such as diabetes, use of antidiabetic drugs or other treatments and cardiovascular risk factors that are associated with prostate cancer risk, such as age, race and body mass index.

In a report from The Health Professionals Follow-up Study, data on cholesterol-lowering drug use for the period 1990–2002 from 34,989 men without a cancer diagnosis in 1990 were analysed[8]. Statin use was significantly associated with a 49% reduced risk of advanced prostate cancer (RR 0.51; 95% CI 0.30–0.86) and a 61% reduced risk of metastatic or fatal prostate cancer (RR 0.39; 95% CI 0.19–0.77), but it was not associated with a reduced risk of total prostate cancer. In men who took statins for ≥5 years, the risk of advanced prostate cancer was significantly reduced by 74% (RR 0.26; 95% CI 0.08–0.83). Investigators of another prospective cohort, using data from the Cancer Prevention Study II Nutrition Survey (n= 55,454)[9], found that men who took statins for ≥5 years had a 40% reduced risk of advanced prostate cancer but these findings were only just statistically significant (RR 0.60; 95% CI 0.36–1.00) and did not reach significance in a follow-up analysis of this data-set[80]. Analyses of data from the California Men's Health Study (n= 69,047)[11], Southern Community Cohort Study (n = 32,091)[76] and Kaiser Permanente Medical Care Program (n= 2,097,474)[82] found 20%, 38% and 17% reductions, respectively, in the risk of advanced prostate cancer among statin users; however, only the findings from Kaiser Permanente, the largest of these studies, were statistically significant (HR 0.83; 95% CI 0.72–0.96).

Three small prospective studies have also been conducted, one of which found a 75% significantly reduced risk of advanced prostate cancer among daily statin users (HR 0.25; 95% CI 0.11–0.58)[73]; findings of the other two studies were not significant[81,88]. A large retrospective cohort study[71] that included men in the Veterans Affairs New England Healthcare System found a significant 60% reduction in risk of advanced prostate cancer among statin users (HR 0.40; 95% CI 0.24–0.65), but results from two other retrospective cohorts were not significant[17,75].

Among published case-control studies, some reported no associations between statin use and risk of advanced prostate cancer[7,65,66,68,69,89], but one small study[6] and two large studies[70,18] reported a significantly reduced risk of advanced prostate cancer in statin users (76%, 24% and 10%, respectively).

In summary, despite some contradicting reports, the majority of evidence supports an inverse association between statin use and risk of advanced prostate cancer. This finding is also demonstrated by the most recent meta-analysis, conducted using data from 27 observational studies published before 2012, which found that statin use was associated with only a modest reduction in total prostate cancer risk (7%; $P = 0.03$) but a more pronounced reduction in advanced disease risk (20%; RR 0.80; 95% CI 0.70–0.90; $P<0.001$) [83]. Eight studies were published in 2012 or later[18,74–77,81,88,90] and were, therefore, not included in this meta-analysis. Seven of these studies did not find statin use to be associated with reduced risk of advanced prostate cancer[74–77,81,88,90]. However, the study[18] including the highest number of men with advanced prostate cancer of all studies to date ($n = 12,412$) reported a 10% significantly reduced risk of advanced prostate cancer in statin users (OR 0.90; 95% CI 0.85–0.96), in line with the findings of the meta-analysis[83].

Prostate cancer mortality

Understanding associations between statin use and prostate-cancer-specific mortality is important, as not all men with advanced prostate cancer die from their disease. An analysis of 1,001 men with prostate cancer of whom 289 men were statin users reported a hazard ratio of 0.19 (95% CI 0.06–0.56) for prostate-cancer-specific death in statin users compared with nonusers[91]. A registry-based study in a Danish population of 27,752 men with prostate cancer of whom 10,542 died of this disease, and who commenced statin use before diagnosis of any type of cancer, found that statin users had significantly lower prostate-cancer-specific mortality than nonusers (HR 0.81; 95% CI 0.75–0.88)[92]. A study that had been designed to assess the association between β-blocker use and prostate-cancer-specific mortality and analysed use of statins as a potential confounding factor found that statin use was inversely associated with lethal prostate cancer among 3,561 men with the disease with a median follow-up period of 39 months (HR 0.70; 95% CI 0.56–0.88; $P= 0.03$)[93]. Finally, an analysis of a population-based electronic database in the UK, containing data from 11,772 men with prostate cancer and 1,791 deaths from prostate cancer during a mean follow-up period of 52 months, found that use of statins was associated with a lower risk of death from prostate cancer. The reduction in risk was larger in men who had commenced statin use before prostate cancer diagnosis (HR 0.55; 95% CI 0.41–0.74) compared with those who started taking statins after diagnosis (HR 0.82; 95% CI 0.71–0.96)[94].

Statin use and PSA levels

PSA testing is the most widely used method for prostate cancer screening. If statin use affects PSA levels, a systematic bias would be inherent in all studies that evaluated participants with PSA-based prostate cancer diagnoses (TABLE 2). Indeed, a pilot study in 15 men demonstrated that statin use caused a 42% decline in PSA levels over a period of 5 years[95].

One cross-sectional study in 323,426 men aged ≥65 years who had a screening PSA test in 2003 investigated how statin use affects PSA levels at the time of prostate cancer screening. Statin use was associated with a reduced probability of having an abnormal screening PSA result for each of the commonly-used PSA thresholds of >2.5 ng/ml, >4.0 ng/ml and >6.5 ng/ml (REF. 96). Another study examined the effect of use of statins, thiazide diuretics and nonsteroidal anti-inflammatory drugs on PSA levels in a cohort of 1,864 men ≥40 years of age from the National Health and Nutrition Examination Survey that had no history of prostate cancer, prostatitis or recent prostate manipulations. The investigators found that statin use was inversely correlated to PSA levels ($P = 0.01$) and that men who had been using statins for ≥5 years had a 13% reduction in PSA levels[97].

The observation that statin use results in reduced PSA levels at screening seems to indicate that these reduced PSA levels would diminish biopsy rates in statin users and use of statins would, therefore, be associated with a decreased incidence of total prostate cancer. If this hypothesis was true, prostate cancer diagnoses would be delayed and statin users would have an increased incidence of advanced prostate cancer. However, as the vast majority of studies found a reduced risk of advanced disease in statin users, a substantial bias introduced by the effect of statins on PSA levels is unlikely.

One could also argue that statin users might be more health conscious and might make more frequent visits to their health care provider compared with nonusers. This behaviour might make statin users more likely to be diagnosed with prostate cancer of an early stage compared with nonusers. Early detection of prostate cancer and subsequent early treatment is associated with less frequent progression to advanced disease stages. Overall, these relationships might explain the reduced risk of advanced prostate cancer observed in statin users. However, a number of studies reported that adjusting for the intensity of PSA screening did not affect the association between statin use and risk of advanced disease[76,98,99]. The most recent meta-analysis, published in 2012, reported that the findings of studies which controlled statistical models for potential confounding introduced by differing rates of PSA screening between statin users and nonusers did not greatly differ from the findings of studies that did not consider differences in PSA screening[83] In addition, PSA testing is performed much more rarely in Europe compared with the USA, which makes the case-control studies set in Denmark[18] and Finland[10] relatively free from this potential bias[100]. Yet, these studies also observed a significant reduction in the risk of advanced prostate cancer, similar to the studies from the USA. Hence, although the potential for screening-related detection biases should be considered, studies taking into account differences in PSA screening frequency between statin users and nonusers (in addition to

studies in populations with coherently different PSA screening frequencies) support a true association between statin use and reduced risk of advanced prostate cancer.

Combination with prostate cancer therapies

In addition to the potential chemopreventive effect of statins, investigators are beginning to study whether statin use can improve the outcome of patients receiving established prostate cancer therapies.

One study in 938 men treated with brachytherapy compared the outcomes of 191 men taking statins with those of nonusers[101]. Statin users had smaller prostate volumes, lower PSA values and lower tumour volume in their biopsy specimens compared with nonusers. A trend was found that statin use was associated with improved prostate-cancer-specific and overall survival, but this association was not statistically significant. A different study in 1,171 men with stage T1–3 prostate cancer treated with radiotherapy included 382 men who were taking a statin at the time of diagnosis and found that statin use was a significant predictor of improved 5-year PSA-failure-free survival (P= 0.002)[102]. Oh *et al.*[103] retrospectively examined the association between use of statins and risk of biochemical recurrence in 247 men with prostate cancer treated with permanent ^{125}I brachy-therapy, with a median follow-up period of 51 months. In this study, statin use was associated with a significant delay in biochemical disease recurrence (P= 0.03). Furthermore, a meta-analysis of 13 studies that examined the effect of statin use on biochemical recurrence following local treatment with radical prostatectomy or radiotherapy found that statin use was associated with a statistically significant improvement in recurrence-free survival in patients who underwent radiotherapy (six studies; HR 0.68; 95% CI 0.49–0.93), but not in patients who underwent radical prostatectomy (seven studies; HR 1.05; 95% CI 0.90–1.24)[104].

Taken together, these results suggest that statin use slows the progression of prostate cancer in men undergoing radiation treatment, possibly by sensitizing the cells to radiotherapy, but further research is needed to confirm these findings. One hypothesis states that statins might radiosensitize prostate tumour cells by causing cell cycle arrest in the late G_1 phase, which is the stage at which cells are most sensitive to radiation-induced cell death[105].

In addition, some evidence suggests that a beneficial effect of statin use in men who have received treatment might not be limited to radiotherapy. A retrospective study with a median follow-up period of 76 months in a cohort of 1,146 men that had never received statins before radical prostatectomy found that postoperative use of statins was associated with a 36% reduction in the risk of PSA recurrence (P=0.004)[106]. Furthermore, a study comparing pre-operative and postoperative use of statins in 2,137 Korean men who underwent radical prostatectomy between 1998 and 2011 found that postoperative statin use prolonged recurrence-free survival over a median follow-up period of 32 months, especially in patients with high-risk disease (Gleason score ≥7; HR 0.27; 95% CI 0.13–0.59; P= 0.001), but preoperative statin use did not change pathological outcomes[107]. Finally, one study with a median follow-up time of 70 months reported that statin use significantly prolonged time to progression in 926 men receiving androgen deprivation therapy, even after adjusting for known prognostic factors such as biopsy-based Gleason score, type of primary therapy and

presence of metastases at initiation of androgen deprivation (HR 0.83; 95% CI 0.69–0.99; P= 0.04)[108].

Statins have also been evaluated for their ability to reduce common adverse effects of local prostate cancer treatment, such as erectile dysfunction. Investigators prospectively examined the effect of statins on recovery of erectile function after radical retropubic prostatectomy in a randomized controlled trial including 50 men without hypercholesterolaemia who never used statins[109]. They found that postoperative treatment with a statin resulted in accelerated recovery of erectile function. Statin users had a significantly improved score in the 5-item International Index of Erectile Function (IIEF-5) tool at 6 months after surgery compared with nonusers (P = 0.003), and 55% of statin users versus 26% of nonusers had recovered erectile function by this time point[109]. This result is in agreement with a meta-analysis published in 2014 of 11 prospective randomized clinical trials that found that randomization of men without prostate cancer to receive statins resulted in a clinically relevant improvement in erectile function, indicated by a 3.4-point improvement on the IIEF-5 scale (P = 0.0001), even after adjusting for two potential confounding factors (average age of study participants and level of LDL cholesterol)[110].

Future perspective

Successful completion of the Prostate Cancer Prevention Trial (PCPT), the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) and the Selenium and Vitamin E Cancer Prevention Trial (SELECT) demonstrates that participants can be recruited for large prostate cancer primary prevention trials. Evidence is accumulating that supports a role for statins in reducing prostate cancer risk, especially advanced prostate cancer. Thus, the question arises whether a trial of similar size should be launched to test the efficacy of statins in the primary prevention of prostate cancer. We strongly believe that a trial of this nature should not yet be initiated.

First, our understanding of the many potential molecular mechanisms through which statins might prevent development and progression of cancer is still far from complete. Deciphering these mechanisms will help guide statin clinical trials with appropriate intermediate end points, as well as enable us to identify novel anticancer pathways that could inform the development of next-generation prostate cancer therapeutics. In addition, understanding the mechanisms that link cholesterol and prostate cancer will lead to the identification of tumour biomarkers that can indicate response to statins and enable clinicians to prescribe statin therapy to those patients who are predicted to show a tumour response.

Second, which type of statin would be most appropriate for use in a clinical trial is currently unclear. Simvastatin is the most commonly used statin in the vast majority of epidemiological studies that report an inverse association between statin use and risk of advanced prostate cancer, potentially supporting the use of simvastatin in prostate cancer trials. Future epidemiological studies with sufficient sample size should investigate the effects of different statin types on prostate cancer risk and progression or, at least, report the frequency of the use of different statin types in their populations.

Two major obstacles to a primary prevention statin trial are readily foreseeable. First, as the prevalence of statin use is so great, finding eligible nonusers who would enrol in such a trial and stay in the placebo arm without becoming statin users at later stages would be a considerable challenge. Second, diagnosis of advanced prostate cancer is a relatively rare occurrence in the current era of PSA screening. As statins seem to be most strongly linked with a reduced risk of this form of the disease, the number of men that would need to be randomized and the duration of follow-up monitoring required to detect a difference in advanced disease incidence would be very high.

Much can be learned without launching an expensive, large and time-consuming primary prevention trial. For example, a strong impetus exists to begin analysing the role of statins in secondary and tertiary prevention. Whether statin use improves outcomes in men who have already been diagnosed with prostate cancer is not fully elucidated. Statin use seems to not affect the risk of localized prostate cancer. However, epidemiological evidence supports an effect of statin use in delaying disease recurrence and reducing prostate-cancer-specific mortality, regardless of disease characteristics at diagnosis. These findings provide a rationale for secondary prevention trials in all men with prostate cancer. Late stage castration-resistant or metastatic prostate cancer is a disease of short duration and outcome events occur in a time span of a few months to 1–2 years. Accordingly, from an epidemiological standpoint, more meaningful results from much smaller sample sizes and after shorter trial durations can be extrapolated from studying the effect of statin use at this disease stage in comparison with early-stage prostate cancer. In this setting, much could be learned about the biological actions of statins.

Earlier in the development of prostate cancer, studying men who undergo primary treatment would also yield information on how statins interact with current treatment modalities and might identify factors that predict response, for example, changes in lipid profiles following the start of statin use. In men on active surveillance protocols, particularly those at highest risk of disease progression, statins could be tested as an adjuvant therapy to reduce or delay the need for subsequent treatment, and tumour response could be monitored using tumour imaging[111]. Indeed, targeting cancer prevention at populations at high-risk of disease has been suggested as a way to improve the risk:benefit ratio of giving medications with potential adverse effects as preventive agents[112]; however, statins are considered to be well tolerated drugs with few major adverse effects.

Future drugs against prostate cancer could be used separately or in combination with statins to reduce prostate cancer mortality and/or morbidity. Clinical trials to investigate treatment with statins in combination with other agents are warranted, particularly combinations with compounds that show synergy with statins in animal models and whose mechanism of synergistic activity is known. Indeed, a study published in 2015 in 767 diabetic men with prostate cancer undergoing radical prostatectomy found that combined treatment with statins and metformin, but neither statin nor metformin use alone, resulted in a significantly reduced risk of biochemical recurrence during a follow-up period of 27 months ($P = 0.037$ for combined statin and metformin use, $P = 0.676$ for statin use alone and $P = 0.117$ for metformin use alone)[113]. Liver X receptor agonists are a group of other potential candidates for combination treatments with statins. These agents stimulate cholesterol efflux from

cancer cells, thus, reducing intracellular cholesterol levels and inducing apoptosis[43]. Through this mechanism, these agents might act synergistically with statins to inhibit prostate cancer growth.

Conclusions

Increasing evidence is being published that supports the hypothesis that statin use is associated with a reduced risk of advanced prostate cancer. Determining causality from observational studies is difficult, but these epidemiological data are also supported by a multitude of preclinical studies that show that statins directly inhibit prostate cancer development and progression in cell-based and animal-based models. Thus, ample justification exists to proceed with further population-based and basic research. The results from these studies will bolster the current rationale for a primary prevention trial as well as targeted clinical trials with mechanistic end points. At present, we still need to further elucidate the benefits of statins before we can advocate that all men at risk of prostate cancer start statins regardless of their cholesterol profile. However, the use of statins in secondary and tertiary prevention to improve therapeutic outcomes in men who have already been diagnosed with prostate cancer might become reality in the not too distant future.

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Key points

- Statins are a commonly prescribed class of medications that lower serum cholesterol levels by inhibiting HMG-CoA reductase, the rate-limiting enzyme for cholesterol synthesis in the liver
- Preclinical research shows that statins can inhibit prostate cancer growth through cholesterol-mediated and non-cholesterol-mediated mechanisms (for example, lipid-raft-mediated and Ras signalling, respectively) that affect pathways essential for cancer formation and progression
- Of >30 observational studies on statin use and prostate cancer risk published to date, most support the hypothesis that statin use reduces the risk of advanced prostate cancer
- Increased PSA screening and health-conscious behaviour in statin users might bias some findings but are unlikely to fully explain the inverse association between statin use and prostate cancer risk
- Statin use also seems to be associated with improved prostate-cancer-specific survival, particularly in men undergoing radiotherapy, suggesting a role for statins in secondary and tertiary prostate cancer prevention
- Before conducting primary prevention trials, further research into the mechanisms contributing to reported inverse associations is required; however, secondary and tertiary prevention trials in men diagnosed with prostate cancer might soon be performed

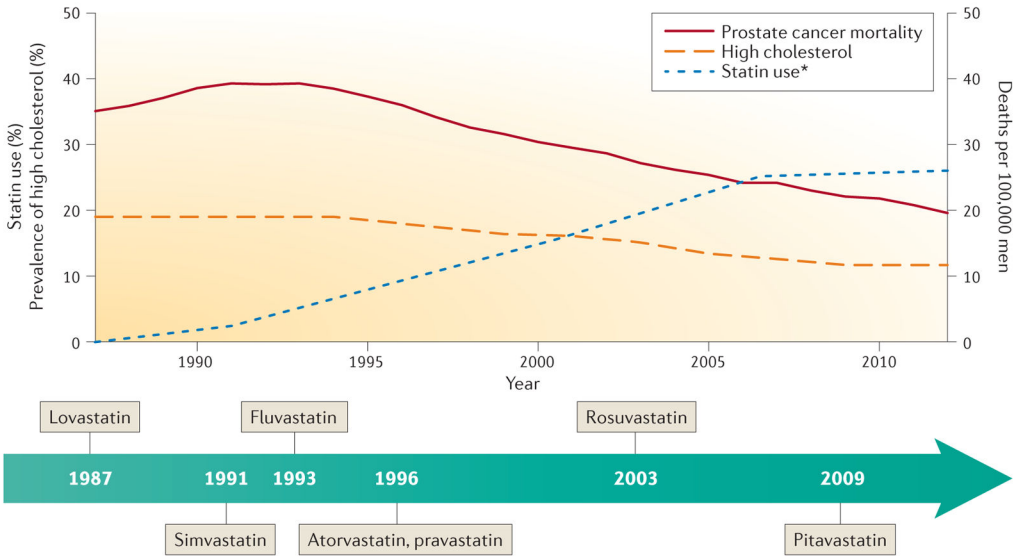

Figure 1. Statin use, high cholesterol and prostate cancer deaths in the USA

Age-adjusted US prostate cancer-specific mortality peaked in 1993 at 39 deaths per 100,000 men and has since been declining[114]. The percentage of US men ≥20 years of age with high total serum cholesterol (≥240 mg/dl per National Cholesterol Education Program guidelines[115]) has also declined, from 19% in 1987 to 12% in 2012(REFS 21,116). This reduction coincided with increasing prevalence of statin use (~26% of US adults ≥40 years of age in 2011–2012)[2,116]. Currently, seven statin drugs are being marketed in the USA. Lovastatin was the first agent to be approved by the FDA in 1987. The newest agent, pitavastatin, was approved in 2009. *Data of statin use before 2011–2012 relates to US adults aged ≥45 years[116], data for 2011–2012 relates to US adults aged ≥40 years[2].

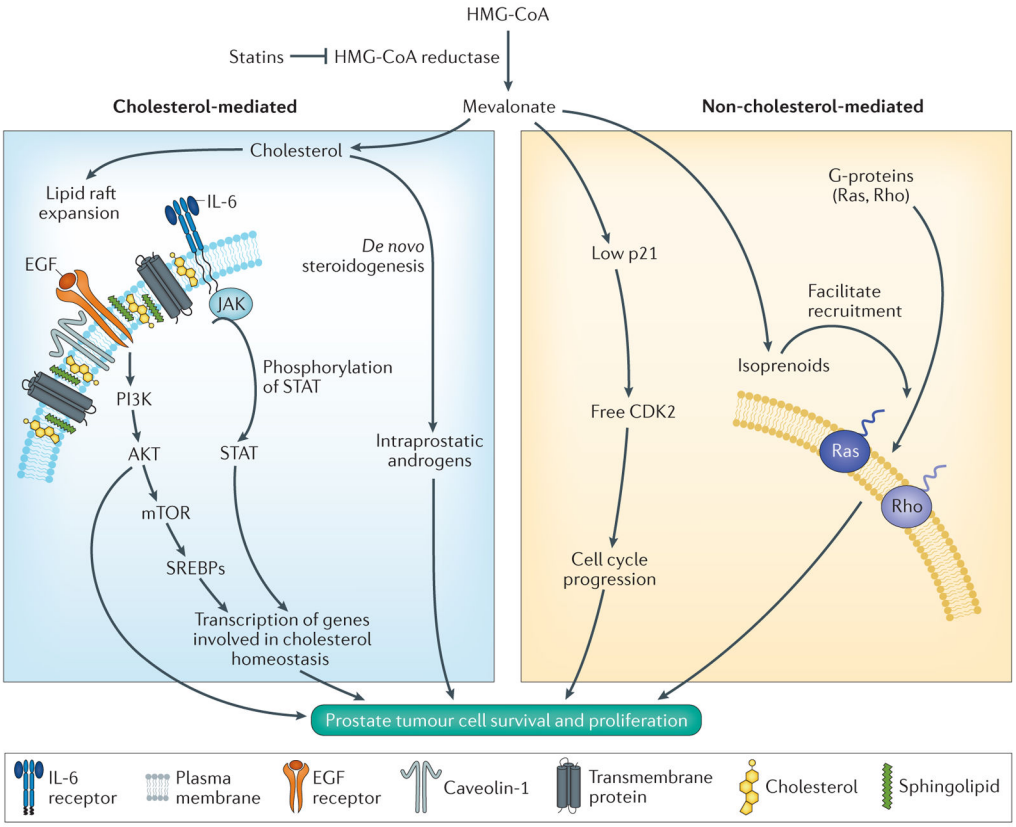

Figure 2. Mechanisms of prostate cancer growth affected by the mevalonate pathway

Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway that results in the synthesis of cholesterol and isoprenoids. Cholesterol is the sole precursor for sex steroid biosynthesis and has been shown to increase tumour androgen signalling and stimulate tumour growth in mouse models of prostate cancer. In addition, cholesterol is a key component of lipid rafts, which facilitate intracellular signalling processes by serving as organizing centres for the assembly of signalling molecules, such as the epidermal growth factor (EGF) and IL-6. EGF and IL-6 activate the PI3K AKT and JAK–STAT pathways, respectively, enhancing the transcription of genes involved in cholesterol homeostasis. The mevalonate pathway can also support prostate tumour growth via non-cholesterol-mediated mechanisms. For example, resulting isoprenoids, such as farnesyl pyrophosphate and geranyl pyrophosphate, facilitate recruitment of G-proteins Ras and Rho to the plasma membrane. High mevalonate levels suppress levels of the cyclin-dependent kinase inhibitor 1 (p21), thereby promoting cell cycle progression via activation of cyclin-dependent kinase 2 (CDK2) activity. SREBPs, sterol-regulatory-element-binding proteins.

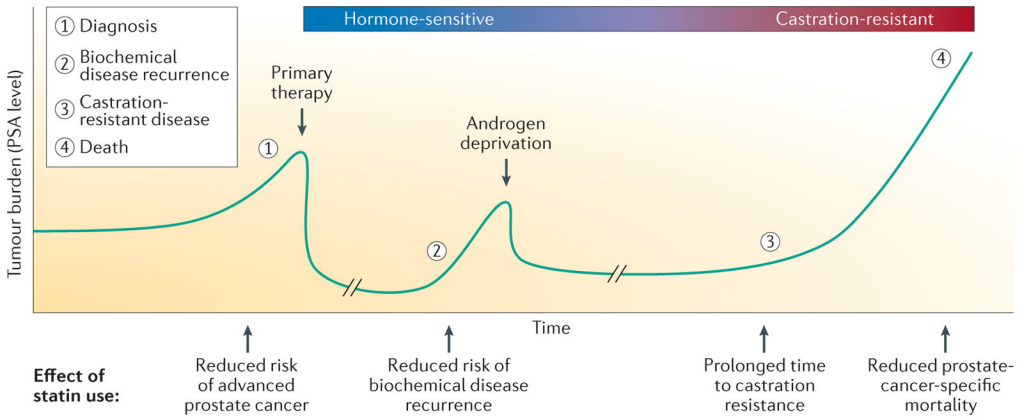

Figure 3. Effects of statin use during the clinical course of prostate cancer

The clinical course of prostate cancer can be followed using measurements of serum PSA levels, serving as a marker of tumour burden. Rising PSA levels indicate prostate cancer growth and clinical diagnosis. Primary therapy (for example, surgery or radiation) causes a rapid drop in PSA level, showing tumour removal or eradication. Prostate cancer recurrence is detected by rising PSA level after primary treatment. Subsequent androgen deprivation therapy initially results in a reduction in tumour burden and PSA level but most patients eventually develop castration-resistant prostate cancer. Currently, castration-resistant disease cannot be cured and these patients will eventually die of their disease. Statins have been shown to have a protective role at various stages of the clinical course of prostate cancer.

Table 1

Pharmacological characteristics of statin medications[2,14,15]

Statin type	Rate of use* (%)	Solubility	IC_{50} for HMG-CoA reductase (nM)	Systemic bioavailability (%)
Simvastatin	42.0	Lipophilic	11.2	<5
Atorvastatin	20.2	Lipophilic	8.2	~14
Pravastatin	11.2	Hydrophilic	44.1	17
Rosuvastatin	8.2	Hydrophilic	5.4	~20
Lovastatin	7.4	Lipophilic	2.7–11.1	<5
Pitavastatin	NR	Lipophilic	6.8	>60
Fluvastatin	NR	Lipophilic	27.6	24

*Rate of use in US adults aged ≥40 years reporting to take a cholesterol-lowering medication in the past 30 days (2011–2012).

IC_{50}, half maximal inhibitory concentration; NR, not reported.

Table 2

Observational studies of statin use and prostate cancer risk

Study	Design	Country	Participants (*n*)	Statin type	Follow-up duration	Exposure definition for primary analysis	Fully adjusted results	Definition of advanced disease
Case-control studies								
Shannon *et al.* (2005)[6]	Hospital-based case-control	USA	• 202 controls • 100 cases (57 advanced)	>97% simvastatin or lovastatin	NA	Statin use vs nonuse	• Total: OR 0.35 (95% CI 0.20–0.64) • Advanced: OR 0.24 (95% CI 0.11–0.53)	Gleason score ≥7
Graaf *et al.* (2004)[7]	Population-based nested case-control	Netherlands	• 16,976 controls • 186 cases	• 80% simvastatin • 7% pravastatin	Mean 7.2 years	Statin use vs nonuse	Total: OR 0.37 (95% CI 0.11–1.25)	NA
Murtola *et al.* (2007)[10]	Population-based case-control	Finland	24,723 case-control pairs (~3,700 advanced)	• ~50% simvastatin • ~25% atorvastatin • ~20% fluvastatin • ~20% lovastatin	NA	Statin use vs nonuse	• Total: OR 1.07 (95% CI 1.00–1.16) • Advanced: OR 0.75 (95% CI 0.62–0.91)	High disease stage (not defined)
Agalliu *et al.* (2008)[16]	Population-based case-control	USA	• 942 controls • 1,001 cases (181 advanced)	• ~20% atorvastatin • ~9% simvastatin	NA	Statin use vs nonuse	• Total: OR 0.98 (95% CI 0.80–1.21) • Advanced: OR 0.79 (95% CI 0.53–1.17)	High disease stage (not defined)
Jespersen *et al.* (2014)[18]	Population-based case-control	Denmark	• 212,400 controls • 42,480 cases (12,412 advanced)	• 72% simvastatin • 11% atorvastatin	NA	Current statin use vs nonuse	• Total: OR 0.94 (95% CI 0.91–0.97) • Advanced: OR 0.90 (95% CI 0.85–0.96)	Disease stage ≥3, N1, M1
Blais *et al.* (2000)[65]	Population-based nested case-control	Canada	• 780 controls • 78 cases	NR	Median 2.7 years	Statin use vs use of bile-acid-binding resins	Total: RR 0.74 (95% CI 0.36–1.51)	NA
Kaye *et al.* (2004)[66]	Case-control	UK	• 7,451 controls • 569 cases	NR	NA	Current statin use vs nonuse (in men without hyper-lipidaemia)	Total: RR 1.3 (95% CI 1.0–1.9)	NA
Coogan *et al.* (2010)[67]	Hospital-based case-control	USA	• 2,007 controls	Majority lipophilic	NA	Statin use vs nonuse	• Total: OR 1.1 (95% CI 0.9–1.5)	Disease stage ≥3

Study	Design	Country	Participants (*n*)	Statin type	Follow-up duration	Exposure definition for primary analysis	Fully adjusted results	Definition of advanced disease
			• 1,367 cases (*n* advanced NR)				• Advanced: OR 1.1 (95% CI 0.7–1.8)	
Chang *et al.* (2011)[68]	Population-based case-control	Taiwan	• 1,552 controls • 388 cases	NR	NA	Statin use vs nonuse	Total: OR 1.55 (95% CI 1.09–2.19)	NA
Haukka *et al.* (2010)[69]	Population-based nested case-control	Finland	235,830 pairs of statin users and nonuser (*n* cases NR)	• 53% simvastatin • 39% atorvastatin	Mean 8.8 years	Statin use vs nonuse	Total: RR 1.12 (95% CI 1.08–1.17)	NA
Tan *et al.* (2011)[70]	Case-control	USA	• 1,797 controls • 2,407 cases (1,681 advanced)	NR	NA	Current statin use vs nonuse	• Total: RR 0.92 (95% CI 0.85–0.98) • Advanced: RR 0.76 (95% CI 0.67–0.85)	Gleason score ≥7
Fowke *et al.* (2011)[89]	Cross-sectional case-control	USA	• 1,304 controls • 844 cases (404 advanced)	• 40% simvastatin • 35% atorvastatin • 10% lovastatin	NA	Current statin use vs nonuse	Advanced: OR 0.95 (95% CI 0.73–1.24)	Gleason score ≥7
Retrospective cohort studies								
Friis *et al.* (2005)[5]	Retrospective population-based cohort	Denmark	• 168,133 men • 1,626 cases	Majority simvastatin	Mean 4 years	Statin use vs nonuse	Total: RR 0.87 (95% CI 0.61–1.23)	NA
Boudreau *et al.* (2008)[17]	Retrospective cohort	USA	• 83,372 men • 2,532 cases (740 advanced)	Majority lovastatin and simvastatin	Median 5.7 years	Statin use vs nonuse	• Total: HR 0.88 (95% CI 0.76–1.02) • Advanced: HR 1.05 (95% CI 0.80–1.38)	Gleason score ≥8, or regional or distant stage
Farwell *et al.* (2011)[71]	Retrospective cohort	USA	• 55,875 men • 546 cases (130 advanced)	• 55% simvastatin • 44% lovastatin	Median 5.6 years	Statin use vs hypertension medication use	• Total: HR 0.69 (95% CI 0.52–0.90) • Advanced: HR 0.40 (95% CI 0.24–0.65)	Gleason score ≥4 + 3
Lustman *et al.* (2014)[74]	Retrospective population-based cohort	Israel	• 66,741 men • 1,813 cases	NR	NR	Long-term statin use (≥5 years) vs nonuse	Total: HR 0.26(95% CI 0.22–0.31)	NA

Study	Design	Country	Participants (*n*)	Statin type	Follow-up duration	Exposure definition for primary analysis	Fully adjusted results	Definition of advanced disease
Morote *et al.* (2014)[75]	Retrospective cohort	Spain	• 2,408 men • 848 cases (240 advanced)	NR	NR	Long-term statin use (≥3 years) vs nonuse	• Total: OR 0.88 (95% CI 0.73–1.06) • Advanced: OR 1.15 (95% CI 0.82–1.63)	Gleason score ≥8
Nordstrom *et al.* (2015)[90]	Retrospective cohort	Sweden	• 18,574 men • 8,430 cases (4,242 advanced)	NR	NR	Statin use vs nonuse	• Total: OR 1.16 (95% CI 1.04–1.29) • Advanced: OR 1.25 (95% CI 1.10–1.42)	Gleason score ≥7
Prospective cohort studies								
Platz *et al.* (2006)[8]	Prospective cohort	USA	• 34,989 men • 2,579 cases (316 advanced)	NR	376,939 person-years	Current statin use vs never or past statin use	• Total: RR 0.96 (95% CI 0.85–1.09) • Advanced: RR 0.51 (95% CI 0.30–0.86)	Disease stage ≥3b, N1, M1 or fatal
Jacobs *et al.* (2007)[9]	Prospective cohort	USA	• 55,454 men • 3,413 cases (317 advanced)	NR	NR	Long-term statin use (≥5 years) vs nonuse	• Total: RR 1.06 (95% CI 0.93–1.20) • Advanced: RR 0.60 (95% CI 0.36–1.00)	Disease stage ≥3 or fatal with unknown stage at diagnosis
Flick *et al.* (2007)[11]	Prospective cohort	USA	• 69,047 men • 888 cases (131 advanced)	• 64% lovastatin • 30% simvastatin	Median 2.3 years	Statin use vs nonuse	• Total: RR 0.92 (95% CI 0.79–1.07) • Advanced: RR 0.80 (95% CI 0.53–1.19)	Disease stage ≥2
Murtola *et al.* (2010)[72]	Prospective cohort	Finland	• 23,320 men • 1,594 cases (133 advanced)	• 45% simvastatin • 41% atorvastatin	Median 6.9 years	Statin use vs nonuse	• Total: HR 0.75 (95% CI 0.63–0.89) • Advanced: HR 0.93 (95% CI 0.54–1.58)	Disease stage ≥3, N1, M1
Breau *et al.* (2010)[73]	Prospective cohort	USA	• 2,447 men • 224 cases (56 advanced)	NR	Median 15 years	Daily statin use vs nonuse	• Total: HR 0.36 (95% CI 0.25–0.53) • Advanced: HR 0.25 (95% CI 0.11–0.58)	Gleason score ≥7
Kantor *et al.* (2015)[76]	Prospective cohort	USA	• 32,091 men	NR	Mean 5.2 years	Current statin use at baseline vs nonuse	• Total: HR 0.86 (95% CI 0.63–1.18)	Gleason score ≥4 + 3

Study	Design	Country	Participants (*n*)	Statin type	Follow-up duration	Exposure definition for primary analysis	Fully adjusted results	Definition of advanced disease
			• 570 cases (107 advanced)				• Advanced: HR 0.62 (95% CI 0.30–1.28)	
Smeeth *et al.* (2009)[78]	Prospective cohort	UK	• 364,675 men • 3,525 cases	>50% simvastatin or atorvastatin	Median 4.4 years	Statin use vs nonuse	Total: HR 1.06 (95% CI 0.86–1.30)	NA
Hippisley-Cox *et al.* (2010)[79]	Prospective cohort	UK	• 990,495 men • 7,129 cases	• 71% simvastatin • 22% atorvastatin	NR	Statin use vs nonuse	Total: HR 1.05 (95% CI 0.98–1.13)	NA
Jacobs *et al.* (2011)[80]	Prospective cohort	USA	• 60,059 men • 3,089 cases (324 advanced)	NR	NR	Long-term statin use (≥5 years) vs nonuse	• Total: RR 1.02 (95% CI 0.93–1.12) • Advanced: RR 0.86 (95% CI 0.62–1.18)	Disease stage ≥3 or fatal with unknown stage at diagnosis
Chan *et al.* (2012)[81]	Prospective cohort	USA	• 5,069 men • 356 cases (195 advanced)	NR	Mean 7 years	Current statin use at baseline vs nonuse	• Total: OR 1.07 (95% CI 0.82–1.40) • Advanced: OR 1.04 (95% CI 0.73–1.50)	Gleason score ≥7
Friedman *et al.* (2008)[82]	Prospective cohort	USA	• 2,097,474 men • 1,706 cases (217 advanced)	• 66% lovastatin • 29% simvastatin	Median 4.9 years	Statin use vs nonuse	• Total: HR 1.03 (95% CI 0.98–1.08) • Advanced: HR 0.83 (95% CI 0.72–0.96)	Disease stage ≥2
Platz *et al.* (2014)[88]	Prospective cohort	USA	• 9,457 men • 574 cases (156 advanced)	NR	7 years	Statin use vs nonuse	• Total: HR 1.03 (95% CI 0.82–1.30) • Advanced: HR 1.27 (95% CI 0.85–1.90)	Gleason score ≥7
Other study type								
Freedland *et al.* (2013)[77]	Secondary analysis of prospective trial	Multi-national	• 6,729 men • 1,517 cases (456 advanced)	NR	Prostate biopsy at 2 years and 4 years	Current statin use at baseline vs nonuse	• Total: OR 1.05 (95% CI 0.89–1.24) • Advanced: OR 1.11 (95% CI 0.85–1.45)	Gleason score ≥7

HR, hazard ratio; NA, not applicable; NR, not reported; OR, odds ratio; RR, relative risk ratio; vs, compared with.