REVIEW

Biologic and epidemiologic evidence assessing if statins prevent prostate cancer

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Introduction: *During their lives, 1 in 8 men will be diagnosed with prostate cancer. Several drugs have been shown to decrease prostate cancer risk, but have not been widely used in prostate cancer prevention because of concerns about side-effects and cost-effectiveness. Statins are indicated for prevention of cardiovascular disease, have an excellent benefit to risk profile, and some studies suggest that statins may reduce the risk of prostate cancer.*

Materials and methods: *We performed a systematic search of Medline (Ovid), EMBASE (Ovid), and PubMed. This search informed a narrative review of the biological rationale for why statins may reduce prostate cancer risk and an evaluation of the existing epidemiological evidence to determine whether further studies are needed to assess the true impact of statins on prostate cancer risk.*

Results: *Statins may help prevent the development of prostate cancer through inhibition of sustained proliferative signals (androgen and Ras/Rho), sensitizing potentially malignant cells to programmed cell death, minimizing inflammation, reducing angiogenesis, and impeding invasiveness by blocking adhesion molecules. The epidemiologic literature examining the effect of statin use on overall prostate cancer diagnosis is highly heterogeneous, with relative risks of 0.26 to 2.94. Out of 33 published studies, 5 show an increased risk of prostate cancer with statin use, 10 demonstrate a decreased risk, and 18 suggest no effect.*

Conclusion: *There is a compelling pre-clinical rationale for statins as potential chemopreventive agents. However, large, population-based studies with long pre-diagnosis drug exposure data are needed to investigate the impact of statin exposure on prostate cancer incidence.*

Key Words: statins, prostate cancer, epidemiology, chemoprevention, review

Introduction

Prostate cancer is a significant public health problem. It is the most common non-cutaneous malignancy in men living in developed countries, with an estimated 758,700 newly diagnosed cases in 2012, and the third leading cause of death from cancer.[1] During their lives, 1 in 8 men will be diagnosed with prostate cancer.[2] Even before the advent of prostate specific antigen (PSA) screening, the age-adjusted incidence rates for prostate cancer were steadily increasing both worldwide and in Canada.[3] This trend, coupled with an aging population and increasing treatment costs, suggests that the clinical and economic burden of prostate cancer will continue to grow in the future.[4]

These burdens emphasize the need for strategies to prevent the development of prostate cancer. Several drugs, including the 5-alpha-reductase inhibitors finasteride[5] and dutasteride,[6] were found to reduce the risk of prostate cancer. However, using 5-alpha-reductase inhibitors preventatively may increase the risk of aggressive or advanced prostate cancer.[7] A protective effect of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)[8,9] has been confirmed in a pooled analysis of relevant clinical trials.[10] However, these drugs have not been widely used in prostate cancer prevention because of concerns about side-effects and cost-effectiveness.[11,12]

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Evidence from laboratory and animal studies suggests that statins may reduce the risk of prostate cancer.[13-15] Statins — inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway of cholesterol synthesis — are among the most commonly prescribed medications in North America. Canadian studies demonstrate that statins were used by 8.3% of adults in 2002 and 46.6% of seniors in 2012.[16,17] As cholesterol-lowering drugs, statins are indicated for the treatment of hypercholesterolemia and for the primary and secondary prevention of cardiovascular disease.[18-20] For these indications, they have an excellent benefit-to-risk profile, and can be taken over the long term.[18,19]

Despite the public health problem posed by prostate cancer, little is known about its causes. In a detailed review of the literature,[21] only three established risk factors were found: aging, African-American ethnicity,[22,23] and family history of prostate cancer;[24] none of which are modifiable. The search for highly penetrant candidate genes has been largely unsuccessful.[25] Migrant studies show that risk increases among men who move from low risk to high risk areas,[26] but studies of lifestyle factors such as smoking, dietary habits, alcohol intake, and physical activity have produced inconsistent results and failed to validate modifiable risk factors.[27-31]

While no modifiable risk factors have been identified for prostate cancer, certain biologic capabilities and conditions are necessary for carcinogenesis. These requirements include: evading growth suppression, avoiding immune destruction, enabling replicative immortality, resisting cell death, sustained proliferative signaling, inducing angiogenesis, genome instability, tumor-promoting inflammation, dysregulated cellular energetics, and the activation of invasion and metastasis.[32] Any potential chemopreventive agent would need to interfere with one or more of these processes to prevent prostate cancer.

Materials and methods

We performed a systematic search of Medline (Ovid), EMBASE (Ovid), and PubMed from inception to March 7, 2016. We planned a narrative review and therefore only included a representative selection of biologic mechanism articles. However, all epidemiologic studies that focused on statin use and prostate cancer incidence were included. We excluded studies focused on prostate cancer mortality, aggressiveness, or recurrence.

Results

Biological rationale

The postulated anticancer effects of statins are biologically plausible. The enzyme HMG-CoA reductase is upregulated in several cancers, including prostate cancer.[33-35] The downstream products of the mevalonate pathway, including cholesterol, retinoids and the isoprene moieties, are involved in steroid hormone production, cell cycle regulation and numerous signal transduction pathways,[36] and could, therefore, influence the processes leading to tumor initiation, progression and spread.[37]

Inhibition of HMG-CoA reductase may reduce the risk of cancer via both cholesterol-mediated and cholesterol-independent pathways. Cholesterol is a precursor of androgens,[38] which are required for prostatic carcinogenesis by inducing a sustained proliferative response.[39] While statins were found to lower serum androgens in some studies,[40,41] others showed no effect.[42,43] It has been proposed that lowering blood cholesterol may hinder carcinogenesis by reducing intraprostatic androgen levels,[44] or by altering cell membrane signaling.[45] However, epidemiologic studies that examined the relationship between serum cholesterol levels and prostate cancer risk have found no consistent associations.[46-49]

Numerous animal and experimental studies suggest that statins have potent anti-tumor effects, independent of their cholesterol-lowering effects, including pro-apoptotic, anti-proliferative, anti-inflammatory and anti-angiogenic effects.[37] Statins induced apoptosis (programmed cell death) in several cell lines derived from prostate cancer, possibly by activating multiple caspases,[50,51] and inhibiting pro-survival *Akt*-mediated signalling.[33] These pro-apoptotic effects may be reversed by the addition of mevalonate.[50] Furthermore, there is evidence that statins are more effective in inducing apoptosis in tumor cells than in normal cells.[52] Such effects suggest an ability to circumvent the ability of malignant cells to resist cell death.

Statins, in particular lipophilic statins, were found to decrease the proliferation of prostate cancer cells *in vitro* and tumor growth rate *in vivo*, likely due to their ability to block G_1-S transition in the cell cycle through stabilization of the cell cycle inhibitor kinases p21 and p27.[53] Also, several small G-proteins in the *Ras*, *Rho*, and *Rac* signaling pathways, essential for cancer cell survival and proliferation, are activated via post-translational modifications involving the geranylgeranyl and farnesyl isoprene units – other downstream products of the

mevalonate pathway blocked by statins.[36] Therefore, statins may reduce proliferative signaling both through reduction of androgens and blocking of isoprene moieties.

Like NSAIDs,[8,9] statins can suppress the production of several inflammatory mediators including interleukins and TNFα.[54] A growing body of evidence implicates inflammation in prostatic carcinogenesis.[21,55,56] This raises the possibility that statins could act, independently or synergistically with NSAIDs, to inhibit prostatic carcinogenesis. In one experiment, the combination of aspirin and simvastatin inhibited the growth of early prostate cancer but not advanced prostate cancer cell lines.[57] However, the combination of atorvastatin and the COX2-selective NSAID celecoxib was found to inhibit the growth of LnCAP cells derived from advanced androgen-sensitive prostate cancer both *in vitro* and when implanted in animals.[58]

Statins, especially at higher doses,[59] may also inhibit angiogenesis (the formation of new blood vessels), a process involved in later stages of tumor development and migration.[60] This effect appears to be mediated by activation of the endothelial protein kinase *Akt/PKB*, and suppression of the release of vascular endothelial growth factor (VEGF) in response to cellular hypoxia.[59] Statins also inhibit tumor invasiveness, likely by blocking the release of matrix metalloproteinases,[61] and by suppressing the expression of endothelial adhesion molecules.[13] Taken together, these observations suggest that statins may reduce the metastatic potential of prostate cancer cells.

Overall, statins may help prevent the development of prostate cancer through inhibition of sustained proliferative signals (androgen and *Ras/Rho*), sensitizing potentially malignant cells to programmed cell death, minimizing inflammation, reducing angiogenesis, and impeding invasiveness by blocking adhesion molecules. Interfering with five of the ten potential hallmarks of cancer provides a strong biological rationale for testing the chemopreventive potential of statins.

Epidemiologic evidence

Despite strong and consistent laboratory evidence, epidemiologic studies of the relationship between statin use and prostate cancer risk have reported conflicting results, Table 1.[38,47,53,62-91] A meta-analysis of three cardiovascular RCTs that included prostate cancer incidence as a safety endpoint, found no evidence of an association with prostate cancer incidence (relative risk [RR] = 0.98; 95%CI: 0.83-1.15).[14,15] These RCTs were limited by small sample size (only 300 patients), and by short follow up time (which averaged 3 years). Since prostate cancers are generally slow-growing,[28] any potential effects of medication use will likely involve a long latency period (10-15 years).[92] Statin use in the recent past may not be etiologically relevant for prostate cancer prevention, because exposure most likely took place after tumor initiation (although it could still influence disease progression and aggressiveness).

Initial observational studies examined multiple cancer sites (not just prostate cancer) and produced conflicting results.[47,63,70,71,93] Studies using Canadian,[63] Dutch[71] and Danish[70] pharmacy databases reported small, statistically non-significant inverse associations of prostate cancer risk with statin use, whereas a study using the British General Practice Research database[47] and a similar US study[93] reported no significant associations. More recently, similar studies from Britain,[91] Finland,[53] and the US[84] reported slightly increased risks (< 15%) among statin users. Issues of confounding (e.g., by use of other medications) and bias (e.g., detection bias) were not addressed in any of these studies.

Similarly, the observational studies designed to focus on the association of statins with prostate cancer have produced mixed results. Some studies found a reduced incidence of prostate cancer among statin users,[64,65,79,94] whereas others found no effect or even increased risks.[69,78,89,95] A systematic review of studies published up to February 2012 included 27 studies – 15 cohort and 12 case-control.[96] While there was heterogeneity among the studies, there did not appear to be any publication bias. Statin use was associated with a 7% reduction in the risk of prostate cancer diagnosis (RR 0.93, 95% CI 0.87-0.99). Subgroup analysis suggested similar trends when cohort and case-control studies or those adjusting or not for PSA testing were evaluated separately, but did not reach statistical significance. Heterogeneity of the studies also undermines the strength of these results.

Individual investigations highlight some of the challenges with this data. Breau et al reported the largest reduction in prostate cancer incidence with statin use in a prospective cohort study of 40- to 79-year-old white men with urinary symptoms started in 1990.[65] Drug exposure was ascertained at the baseline interview and biennially thereafter. After a median follow up time of 16 years, the RR for the effect of statin use on prostate cancer was 0.36 (0.25-0.53) and was even stronger for men who used statins for more than 9 years. However, all analyses, including the duration-response analyses, were based on just 38 exposed cases, which limited the investigators' ability to adjust for confounding in multivariate models and

TABLE 1. **Statin use and prostate cancer**

Study	Study period	Cases	Controls	Relative risk	95% CI
Studies not adjusting for PSA testing					
Lovastatin groups 1993[62]	NR	5	499	2.94	0.95-6.86
Blais 2000[63]	1988-1994	78	780	0.74	0.36-1.51
Graaf 2004[71]	1995-1998	186	9599	0.37	0.11-1.25
Kaye 2004[47]	1990-2002	569	7451	1.3	1.00-1.90
Friis 2005[70]	1989-2002	1407	166726	0.87	0.61-1.23
Shannon 2005[79]	1997-2004	100	202	0.38	0.21-0.69
Flick 2007[69]	2002-2004	888	68159	0.92	0.79-1.07
Murtola 2007[78]	1995-2002	24723	24723	1.07	1.00-1.16
Boudreau 2008[64]	1990-2005	2532	80840	1	0.76-1.02
Breau 2010[65]	1990-2007	224	2223	0.36	0.25-0.53
Haukka 2010[53]	1996-2005	1051	9877	1.12	1.08-1.17
Hippisley 2010[72]	2002-2008	7129	983366	1.02	0.96-1.08
Coogan 2010[68]	1992-2008	1367	2007	1.1	0.90-1.50
Loeb 2010[74]	2003-2009	1351	0	0.71	0.51-0.98
Tan 2011[80]	2000-2010	1797	2407	0.92	0.85-0.98
Chang 2011[67]	2005-2008	388	1552	1.55	1.09-2.19
Mondul 2011[77]	1993-2006	683	1716	0.66	0.50-0.85
Chan 2012[66]	2000-2008	298	4120	1.07	0.82-1.40
Marcella 2012[76]	1997-2000	387	380	0.37	0.23-0.60
Jespersen 2014[73]	1997-2010	42,480	212,400	0.94	0.91-0.97
Lustman 2014[75]	2001-2009	1813	64928	0.26	0.22-0.31
Studies adjusting for PSA testing					
Platz 2006[89]	1990-2002	2579	32410	0.96	0.85-1.09
Friedman 2008[84]	1994-2003	1706	NR	1.03	0.98-1.08
Agalliu 2008[38]	2002-2005	1001	943	1	0.80-1.20
Smeeth 2009[91]	1995-2006	3525	361150	1.06	0.86-1.30
Murtola 2010[87]	1996-2004	1594	21614	0.75	0.63-0.89
Farwell 2011[81]	1997-2007	546	55329	0.69	0.52-0.90
Jacobs 2011[85]	1997-2007	NR	3913	0.98	0.90-1.06
Fowke 2011[82]	2002-2010	1029	1119	1.15	0.87-1.53
Freedland 2013[83]	2003-2005	1517	5212	1.05	0.89-1.24
Platz 2014[90]	1994-1997	574	8883	1.03	0.82-1.30
Kantor 2015[86]	2002-2010	570	31521	0.86	0.63-1.18
Nordstrom 2015[88]	2007-2012	7356	10144	1.16	1.04-1.29

PSA = prostate specific antigen; CI = confidence interval; NR = not reported

increased the risk of chance findings. Furthermore, all statin use data was based on self-reporting, which raises the concern of recall bias. Finally, only 55% of the cohort agreed to participate in completing the exposure questionnaire, increasing the risk of an inadvertent selection bias and jeopardizing generalizability.

At the opposite extreme, the study examining a cohort of patients observed after completing RCTs of lovastatin showed a dramatic increase in the risk of prostate cancer – (RR = 2.94, 0.95-6.86).[62] Interestingly, the investigators compared prostate cancer incidence in the cohort receiving lovastatin to the age-adjusted cancer rates from the Surveillance, Epidemiology, and End Results (SEER) registry. The increased number of cases could be explained by the inclusion of a digital rectal exam in the patient cohort, which was not yet being routinely completed in the community. There were also only 504 men, including five cases of prostate cancer in the study increasing the likelihood of a chance finding. In between these two studies, no association between statins and prostate cancer risk was reported by Agalliu et al (odds ratio (OR) = 1.0, 0.8-1.2) in their population-based study of 1,001 cases and 942 age-matched controls from King County, Washington.[38] Drug use was self-reported in this study, which raises the possibility of recall bias (cases being more likely to recall drug use) affecting results.

Boudreau et al eliminated the risk of recall bias by carrying out a retrospective cohort study among 83,372 male subscribers to a non-profit integrated health care plan in western Washington State.[64] Information on statin use, defined as using statins for 1 or more years, was obtained from plan databases. Men were monitored for prostate cancer using the SEER tumor registry. Users of lipophilic statins, but not non-lipophilic statins, had lower risk of prostate cancer (hazards ratio [HR] = 0.8; 0.7-0.9). This study was limited by short duration of follow up and statin use (3 years) and by limited power to examine the effect of hydrophilic statins (only 8 cases in about 2400 person-years of follow up).

None of the studies mentioned above adjusted for PSA screening. The first study to include this important factor used data from the Health Professionals Follow up Study.[89] A cohort of 34,989 men was followed from 1990 to 2001, and information on drug use and prostate cancer diagnosis was collected biennially using self-administered questionnaires. While no significant associations were evident for overall or organ-confined prostate cancer (HR = 1.0; 0.9-1.1), significant inverse associations between statin use and metastatic or fatal cancers were observed (HR = 0.4; 0.2-0.8). Unfortunately, this study had no information on type of statin used, dose, and minimal information on duration.

Murtola et al linked data from the screening arm of the Finnish Prostate Cancer (PSA) Screening trial to national cancer registration and pharmacy databases to obtain information on prostate cancer incidence and use of statins and other cholesterol-lowering drugs.[87] Among men who had at least one PSA screen between 1996 and 2004, current statin users had lower risk of overall prostate cancer (RR = 0.75; 0.6-0.9), especially with longer (6 or more years) duration of use. The associations were much stronger for hydrophilic than for lipophilic statins. The cases group in this study overlapped with the cases included in a previous case-control study by the same team where no association with overall prostate cancer was observed.[78]

Trial populations, which standardize follow up and frequency of assessment for prostate cancer, have informed two other studies.[83,90] Freedland et al reported on patients in the REDUCE trial that investigated the chemopreventive potential of dutasteride, evaluating the risk of prostate cancer by statin use.[83] There were statistically significant differences in the baseline characteristics of the two groups, including in family history of prostate cancer. Multivariate analysis suggested that statin use does not impact risk of prostate cancer (OR 1.05, 95% CI 0.89-1.24). Platz et al completed a similar analysis of the placebo arm of the Prostate Cancer Prevention Trial (PCPT).[90] Statin use again did not impact risk of prostate cancer (HR 1.03, 95% CI 0.82-1.30). Both cohorts have the advantage of consistent prostate cancer screening practices, but suffer from limited length of follow up and brief, survey-based ascertainment of drug exposure.

Finally, Jespersen et al used Danish population-based data to examine the effect of statins in the largest group to date.[73] Statin users had a 6% lower risk of prostate cancer (OR 0.94, 95% CI 0.91-0.97), which did not differ by either duration or type of statin used. Conversely, Nordstrom et al examined men receiving their first prostate biopsy in Sweden and found that statin use increased the risk of prostate cancer (OR 1.16; 95% CI 1.04–1.29).[88] While both were large studies, benefited from population-based case identification, and had reliable exposure assessment during the study, both were only able to look at pre-exposure for 1-2 years.

In summary, epidemiologic data concerning the relationship between statin use and risk of prostate cancer are suggestive but inconclusive. The discrepancies between these studies may reflect their limitations. Most studies were limited by exposure data confined to the recent past, limited information on dose, timing and duration of statin use, and by the possibility of uncontrolled detection and recall biases. Very few studies have allowed for the long latency of any potential protective effects; the follow up periods of most studies may have been too short to detect an impact. None of these studies adjusted simultaneously (in the same model) for possible confounding by use of other drugs such NSAIDs, 5-alpha-reductase inhibitors

and non-statin cholesterol-lowering drugs. In most studies, analyses were not stratified by statin type or potency. Finally, many of these studies were carried out in the United States where very high levels of PSA screening could complicate the interpretation of their findings. For instance, intensive screening resulted in a paucity of advanced prostate cancer cases in most studies limiting their ability to detect clinically meaningful associations with advanced prostate cancer.

The limitations of our review include the lack of formal meta-analysis and the risk of publication bias in the literature as we did not seek out unpublished data. However, the intention of this article was to provide a narrative review of the mechanism through which statins may help prevent prostate cancer and summarize the existing epidemiologic literature. A meta-analysis would not have further facilitated this goal.

Conclusion

While the possibility of increased rates of aggressive prostate cancer has dampened enthusiasm for dutasteride and finasteride, chemoprevention remains an area of hope for prostate cancer. The need to prevent the development of prostate cancer has only been increasing due to the aging of the population. There is a compelling pre-clinical rationale for statins as potential chemopreventive agents, as they interfere with five of the ten hallmarks of cancer. However, the epidemiological literature investigating the effect of statin use on prostate cancer incidence has reported widely varying results and is often plagued by small sample sizes, short pre-diagnosis information on drug exposure, and potential biases. Large, population-based studies with long pre-diagnosis drug exposure data are needed to investigate the impact of statin use on prostate cancer incidence and determine if a definitive clinical trial is warranted.

Disclosures

Dr. Dawe reports attending advisory boards for Merck and AstraZeneca related to non-statin oncology products. Dr. Mahmud has received research funding from Merck, Sanofi, GlaxoSmithKline and Pfizer. □

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