Statin Use and Risk of Prostate Cancer: Results from a Population-based Epidemiological Study

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Abstract

Background: Epidemiological studies of statin use in relation to prostate cancer risk have been inconclusive. Recent evidence, however, suggests that longer-term use may reduce risk of more advanced disease.

Methods: We conducted a population-based study of 1,001 incident prostate cancer cases diagnosed in 2002-2005 and 942 age-matched controls from King County, WA, to evaluate risk associated with statin use. Logistic regression was used to generate odds ratios (OR) for ever, current and duration of use.

Results: There was no overall association between statin use and prostate cancer risk (OR=1.0, 95% CI 0.8, 1.2 for current use; OR=1.1, 95% CI 0.7, 1.8 for $\geq$ 10 years use), even in cases with more advanced disease. Risk related to statin use, however, was modified by body mass index (BMI) (interaction p= 0.04). Obese men (BMI $\geq$ 30 kg/m^2) who used statins had an increased risk (OR=1.5; 95% CI 1.0, 2.2) relative to obese non-users, with a stronger association for longer-term use (OR=1.8, 95% CI 1.1, 3.0 for $\geq$ 5 years use).

Conclusions: Statin use was not associated with overall prostate cancer risk. Our finding of an increased risk associated with statin use among obese men, particularly use for extended durations, warrants further investigation.

Key words: statins, HMG-CoA reductase inhibitors, prostate cancer, obesity, case-control study, odds ratio

INTRODUCTION

Statin drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that controls the conversion of HMG-CoA to mevalonate, an essential precursor of cholesterol (1-3). Statins are used to treat hypercholesterolemia and have been shown to reduce cardiovascular disease incidence and mortality (4-7). Thus, use of statins has increased exponentially in the U.S. over the last decade (8).

Statin use in relation to prostate cancer etiology is of interest because: 1) these drugs inhibit the synthesis of cholesterol, a precursor of androgens that also plays a role in cell signaling pathways (9); 2) mevalonate is necessary for the prenylation of proteins involved in signal transduction cascades downstream of membrane receptors that are crucial in cell growth and apoptosis (10, 11); and 3) statins inhibit cell proliferation, inflammation, oxidative stress, angiogenesis and metastasis in experimental models (2, 3, 11, 12).

Some studies suggest that statins may alter prostate cancer risk. Randomized clinical trials of statin use for the prevention of cardiovascular disease reported no associations with prostate cancer incidence (13-15), but such trials were limited by the short durations of use and brief follow-up periods (16, 17). Several observational studies showed an inverse association between statin use and risk of prostate cancer (18-23), although others found no association (24, 25, 27, 28). The inverse association observed in some studies was limited to subgroups of men with advanced stage disease (20, 23), current, $\geq$ 5 year users with advanced disease (21), or regular users of nonsteroidal anti-inflammatory drugs (NSAIDs) (22). An increase in overall prostate cancer risk was observed for statin users in two studies (23, 26). To further examine the potential relationship between these widely used medications and risk of prostate cancer, we conducted a population-based case-control study.

MATERIALS AND METHODS

Study population

Subjects were Caucasian and African American men residing in King County, WA, aged 35 to 74 years. Incident cases were diagnosed with histologically confirmed adenocarcinoma of the prostate from January 1, 2002 through December 31, 2005 and were identified via the Seattle-Puget Sound SEER cancer registry. Caucasian cases 50-74 years were randomly sampled (30% of cases); 100% of eligible Caucasian cases 35-49 years and 100% of African American cases 35-74 years were selected. The SEER registry provided information on Gleason score, tumor stage, and serum prostate-specific antigen (PSA) level at diagnosis. Of the 1,327 eligible cases ascertained, 1,001 (75.4%) were interviewed. Reasons for non-response were: patient refusal (14.9%), physician refusal to allow patient contact (1.8%), inability to locate the patient (2.3%), patient moved (1.3%), patient was too ill or had other problems (2.6%), or death (1.7%).

Controls without a history of prostate cancer were identified via random digit dialing, frequency matched to cases by five-year age groups, and recruited evenly throughout the ascertainment period for cases (29). Household census information was obtained for 81.4% of the 24,106 residential telephone numbers contacted. Of the 1,507 eligible controls identified, 942 (62.5%) were interviewed. Reasons for non-participation included: the person providing the household census data refused to provide information needed to send a recruitment letter to the eligible man in the household (10.5%), refusal (21.7%), illness (1.7%), language problem, moved or was lost to follow-up (3.3%), or death (0.3%).

Subjects completed a structured in-person interview administered by a trained male interviewer. The questionnaire collected demographic and lifestyle information, family history of cancer, medical history, medication use, and prostate cancer screening history prior to reference date (i.e., date of diagnosis for cases and a similar, randomly pre-assigned date for controls that approximated the distribution of diagnosis dates of cases). Participants were also asked to complete a self-administered food-frequency questionnaire (FFQ) and to provide a

blood sample and consent for access to medical records. The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and written informed consent was obtained from all study participants.

Use of statin medications

Information about statin use was obtained during the in-person interview, including ever use (use at least once a week for three months or longer), type of statin used (a show-card listing all brand names and generic names for FDA approved statin drugs was used to assist recall), dates of first and last use and total duration of use for each episode. Current use was defined as use within the year prior to reference date. Total duration of statin use was calculated as the sum of all episodes of use. Time since first use of a statin was defined as years elapsed from date of first use until reference date. In addition, statins were grouped into two classes: 1) lipophilic or fat soluble (lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin), which may be distributed at low levels throughout the body; and, 2) hydrophilic (pravastatin, rosuvastatin), which act primarily in the liver. Because all statins undergo hepatic first-pass metabolism, there is limited systemic bioavailability (30, 31).

Genotyping

Germline DNA was used to genotype variants in two cytochrome P450 genes, *CYP3A4* (rs2740574) and *CYP3A5* (rs776746). These single nucleotide polymorphisms (SNPs) were selected because they affect statin metabolism (32) and thereby may influence the statin-prostate cancer relationship. The Applied Biosystems SNPlex™Genotyping System was used for genotyping (www.appliedbiosystems.com). Quality control included genotyping 84 blind duplicate samples, which showed 100% agreement. Both SNPs were in Hardy-Weinberg equilibrium in controls (exact p-value >0.05).

Statistical analyses

Unconditional logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) (33). Potential confounding was assessed by fitting models including each main effect and then evaluating the change in parameter estimates when other variables entered the models one at a time. Covariates that changed the parameter estimates for statin use by > 10% were incorporated into the final model, and included age, race and prostate cancer screening history (none, DRE only, PSA test) within the five-year period prior to reference date. Further adjustment for family history of prostate cancer, smoking status, body mass index (BMI), alcohol consumption, income, education, physical activity and dietary intake (calories, fat) did not change risk estimates associated with statin use. Goodness of fit of statistical models was assessed by comparing the –2 Log Likelihood difference between nested models. Tests for trend were used to assess linear trends in risk estimates by duration of statin use.

We also examined the association between statin use and prostate cancer by stratifying cases on clinical characteristics such as Gleason score ($\leq$ 7, 3+4, vs. $\geq$ 7, 4+3), stage (localized vs. regional/distant) and a composite measure of disease aggressiveness (i.e., more aggressive = Gleason score of $\geq$ 7, 4+3 or regional/distant stage or PSA $\geq$ 20 ng/ml at diagnosis; less aggressive = Gleason score $\leq$ 7, 3+4 and localized stage and PSA level < 20 ng/ml). For these analyses, statin use in each group of cases was compared to that of controls using polytomous logistic regression. Lastly, we examined whether associations differed by age (< 60 vs. ≥ 60 years), race (Caucasian vs. African American), first-degree family history of prostate cancer (yes vs. no), BMI (< 30 vs. $\geq$ 30 kg/m^2), use of NSAIDs, and *CYP3A4* and *CYP3A5* gene variants. SAS Version 9.1 was used for statistical analyses (SAS Institute, Cary, NC).

RESULTS

Demographic and lifestyle characteristics of cases and controls are presented in Table 1. Cases were more likely than controls to report a first-degree family history of prostate cancer (23% vs. 12%) and to have had PSA screening in the five years before reference date (71% vs. 58%). Cases and controls were similar with respect to BMI, smoking status, alcohol consumption, education, and recent exercise frequency. The prevalence of hypercholesterolemia for which statins are primarily prescribed was similar between cases and controls, 43% vs. 40%, respectively (age-adjusted OR=1.07; 95% CI 0.89, 1.29). With respect to clinical characteristics of prostate cancer, 31% of the cases were classified as having "more aggressive" disease.

The prevalence of any statin use among controls was 28%. Table 2 shows comparisons between users and non-users in the control group. Statin users were older, more likely to be Caucasian, have a higher BMI, be former smokers, and have undergone PSA screening. There were no differences, however, with respect to first-degree family history of prostate cancer. Users of statin medications had a higher prevalence of self-reported hypercholesterolemia, diabetes mellitus, hypertension, myocardial infarction or stroke in comparison to non-users (all p-values <0.0001).

The prevalence of statin use was similar in prostate cancer cases and controls (OR = 0.98, 95% CI 0.80, 1.21) (Table 3). No associations were observed with other measures of statin use (current use, duration of use, age at first use, time since first use). In relation to the type of statin used, most cases and controls reported using atorvastatin (18.3% and 17.8%, respectively), followed by simvastatin (9.1% and 9.2%, respectively), pravastatin and lovastatin (4.2% and 4.0% respectively for each drug). The prevalence of use of other types of statins was low (< 2%). Statins were also grouped as hydrophilic or lipophilic, but no association was found for either group.

Next, we examined statin use and prostate cancer risk according to clinical features (Table 4). There were no associations between statin use and Gleason score (≤7, 3+4 vs. ≥7, 4+3), tumor stage (local vs. regional/distant) or prostate cancer aggressiveness status (less vs. more). In a subset analysis of metastatic or fatal prostate cancer (n= 27 cases), we found an OR of 0.24 (95% CI 0.05, 1.02) for ever use; however, only two cases who used a statin < 12 months contributed to this observation.

Lastly, we examined statin use in relation to prostate cancer in analyses stratified by age (< 60 vs. ≥ 60 years), race (Caucasian vs. African American), first-degree family history of prostate cancer (yes vs. no), BMI (< 30 vs. ≥ 30 kg/m^2), use of NSAIDs, and *CYP3A4* and *CYP3A5* gene variants. No differences in risk estimates were observed for any of these other factors, except for BMI (Table 5). A statistically significant statin use by BMI interaction was observed for ever use (interaction p= 0.03) and for duration of use (interaction p= 0.04). No association was observed among non-obese men, but in obese men (BMI ≥ 30 kg/m^2) statin use increased risk (OR = 1.5) relative to no use. The relative risk was higher in obese, long-term users (OR = 1.8; 95% CI 1.1, 3.0 for ≥ 5 years of use).

Discussion

In this study there were no associations between detailed measures of statin use and either risk of prostate cancer overall or of more aggressive disease. Interestingly, analyses stratified by BMI showed that obese men (BMI ≥ 30 kg/m^2) who reported current use of a statin had an increased relative risk of prostate cancer (OR = 1.5, 95% CI 1.0, 2.1), which was stronger in those with extended durations of use (OR = 1.8 for ≥ 5 years of use).

Several randomized clinical trials of cardiovascular disease (13-15) as well as observational studies (19-28) have examined risk of prostate cancer in relation to statin use. The randomized trials data revealed no associations (13-15), but the trials were not designed to test the statin-prostate cancer hypothesis. Moreover, these trials involved short durations of

statin use and limited periods of follow-up, which are likely inadequate for assessing statin use in relation to cancer occurrence (16).

Several observational studies have examined the association between statin use and prostate cancer (19-28). Most of these studies utilized hospital- or clinic-based populations or computerized pharmacy data for analyses. The prevalence of statin use varied widely across studies, ranging from 5% to 49%, and in some studies increased over time. Two studies reported an overall inverse association between any statin use and prostate cancer risk (18, 19), while others reported no association (24, 25, 27, 28) or a positive association (23, 26). Shannon and colleagues (19) conducted a study within a Veterans Administration hospital population and reported an OR of 0.4 (95% CI 0.2, 0.7) for prostate cancer in relation to ever use of a statin and an OR of 0.3 for > 2 years duration of use. Graaf et al. (18) used a pharmacy database to define exposure and observed a similar reduction in risk (OR = 0.4) of prostate cancer in relation to statin prescriptions. However, both of these studies had small sample sizes. Recently, Flick and colleagues (22) used data from the California Men's Health Study cohort to evaluate statin exposure and also reported an inverse association between ≥ 5 years of statin use and overall prostate cancer risk (RR = 0.72; 95% CI 0.53, 0.99). The remaining studies reported no associations with overall prostate cancer risk, with the exception of two studies. Data from the United Kingdom GPRD database (26) revealed a modest increase in prostate cancer risk (OR = 1.3; 95% CI 1.0, 1.9) associated with use of a statin drug, and a large population-based study from Finland (23) also reported an elevated risk estimate in statin users (OR = 1.07; 95% CI 1.0, 1.2).

With respect to clinical features of prostate cancer, Shannon and colleagues (19) reported an OR of 0.3 (95% CI 0.1, 0.5) in men with a Gleason score of $\geq$ 7 in relation to ever use of a statin. In another recent analysis based on the Health Professionals Follow-up Study, Platz et al. (20) reported a significant reduction in risk of advanced stage disease (RR = 0.5; 95% CI 0.3, 0.9) and metastatic or fatal prostate cancer (RR = 0.4; 95% CI 0.2, 0.8) among

users of cholesterol-lowering medications. An inverse association between statin use and advanced prostate cancer was also noted in some other studies (21-23). In the Cancer Prevention Study II Nutrition Cohort, long-term (≥ 5 years) statin use was associated with a reduction in risk of advanced prostate cancer (stage III, IV or fatal; RR = 0.60; 95% CI 0.36, 1.00) (21). Similar findings were observed in the California Men's Health Study Cohort for risk of regional/distant stage disease in relation to statin use lasting for ≥ 5 years (RR = 0.57; 95% CI 0.2, 1.4), although this result was not statistically significant. In a third study that included 24,723 prostate cancer cases identified via the Finnish Cancer Registry, Murtola and colleagues (23) also reported an inverse association between statin use that was limited to advanced stage disease (OR = 0.75; 95% CI 0.62, 0.91), with a dose-response relationship (p trend=0.001).

In our study we evaluated several measures of statin use (ever, current, duration of use) in relation to clinical features of prostate cancer such as Gleason score, tumor stage and a composite measure of more aggressive disease, but found no associations. In the subset of cases with regional or distant stage, there was a non-significant reduction in risk in current statin users relative to non-users (OR = 0.73; 95% CI 0.5, 1.1). We also analyzed data according to distant stage or fatal prostate cancer and found an inverse association between ever use of a statin medication (OR = 0.24; 95% CI 0.05, 1.02) and metastatic or fatal disease, but there were only two exposed cases in this analysis and both had used a statin for less than one year. These findings, however, are consistent with the hypothesized anti-metastatic activitiy of statins (3, 11).

In relation to BMI, the Cancer Prevention Study II Nutrition Cohort investigators reported an interaction between long-term use of cholesterol-lowering drugs and BMI (p=0.02) for advanced prostate cancer, but not for overall prostate cancer (21). However, in that study there were no obese cases with advanced disease among long-term users of cholesterol-lowering drugs. In our study, there were 74 obese cases with more aggressive disease features, and of these, 13 (18%) had used a statin for ≥ 5 years. The prevalence of long-term (≥ 5 years) statin

use in the obese, more aggressive disease subgroup was not markedly different in comparison to the prevalence of long-term use (22%, p=0.3) in obese men with less aggressive disease. There is no clear biological mechanism to explain why statin use may preferentially increase risk of prostate cancer in obese men. Data from our control group show that statin users have higher BMIs and are more likely to have co-morbid conditions that may be indications for statin use. These medical conditions may also be associated with altered hormone levels that could affect prostate cancer risk. Of interest in this regard is a recently published study that found no difference in circulating levels of androgens between statin users compared to non-users (34), but levels of sex hormone-binding globulin (SHBG) were significantly lower in statin users. With respect to the latter finding, a recent meta-analysis of studies of endogenous sex hormones and prostate cancer revealed that men with lower levels of SHBG are at higher risk for developing prostate cancer (35). Another potential mechanism described by Goldstein et al. (36) is the ability of statin medications to increase the level of regulatory T cells, which may suppress anti-tumor T cell response and thereby enhance cancer risk.

Our study has several strengths and limitations that should be considered when interpreting these results. Strengths are its population-based approach, sample size and the fact that it was designed to test the association between statin use and risk of prostate cancer. In addition, we had detailed information about statin use that allowed us to evaluate duration of use, time since first use, time since last use, age at first use and type of statin used. One concern in observational studies is the accuracy of self-reported exposures. In an attempt to address this issue, we compared self-reported use of statins (162 cases, 162 controls) with data from a computerized pharmacy database maintained by Group Health Cooperative of Puget Sound. There was 87% agreement for any use of a statin (90% and 85% agreement for cases and controls, respectively).

Another issue is that of potential confounding by prostate cancer screening, which is correlated with statin use and prostate cancer diagnosis. We evaluated the statin-prostate

cancer relationship after adjusting for various measures of prostate cancer screening: 1) any tests (none, DRE only, PSA) done within the five-year period before reference date; 2) the number of PSA tests (0, 1-2, 3-4, 5+) done within the five-year period before reference date; and 3) the time interval since the most recent PSA test and reference date. Prostate cancer screening questions were asked in such a way so as to excluded diagnostic tests, and only 25 cases and 38 controls reported having a PSA screening test within four months of reference date. We also analyzed our data excluding men (84 cases, 46 controls) who reported that they "had a problem or symptom" at the time of the most recent PSA test prior to reference date, and performed separate analyses in men who reported having a PSA screening test within the five years before reference date and in men who reported no such screening. Results from these analyses were similar to the risk estimates presented, which are adjusted for any prostate cancer screening tests within the five years prior to reference date.

Other concerns include potential selection bias and recall bias. There is a possibility that men who did not participate had a different prevalence of statin use than those who joined the study. Although we have no data on non-participants, it is reassuring that the prevalence of statin use in our control group (28%) is similar to the prevalence estimates of 25% (21) and 27% (22) for statin use reported from other recently studies. Standardized interviews, medication show cards and trained interviewers were used to enhance reporting of drug use. Lastly, the prevalence of long-term statin use (> 10 years) is low (4% in controls) since these medications only became available in the U.S. in 1987. Thus, our study as well as other studies reported to date was underpowered to address the relationship between extended periods of statin use (> 10 years) and risk of developing prostate cancer.

In conclusion, results of this study suggest that statin use is not associated with overall prostate cancer risk. However, obese men who use statin medications, particularly for longer durations, have an increased risk of prostate cancer relative to obese non-users. This latter

observation warrants further investigation, particularly given the high prevalence of both statin use and of obesity in the general population.

Table 1. Selected demographic, lifestyle and clinical characteristics of population-based prostate cancer cases and controls, King County, WA, 2002-2005

Characteristic	Cases (n=1,001)		Controls (n=942)		OR*	95% CI
Age (years)	n †	%	n †	%		
< 50	93	9.3	96	10.2		
50 - 54	108	10.8	113	12.0		
55 - 59	184	18.4	174	18.5		
60 - 64	218	21.8	187	19.9		
65 - 69	210	21.0	202	21.4		
70 - 74	188	18.8	170	18.0		
Race						
Caucasian	843	84.2	844	89.6	1.00	
African American	158	15.8	98	10.4	1.68	1.28, 2.21
First-degree family history of prostate cancer						
No	775	77.4	833	88.4	1.00	
Yes	226	22.6	109	11.6	2.24	1.75, 2.87
Body mass index (BMI, kg/m^2)						
< 25	287	28.7	259	27.5	1.00	
25.0 - 29.9	492	49.2	444	47.1	1.00	0.81, 1.24
≥ 30	222	22.2	239	25.4	0.84	0.66, 1.08
Smoking status						
Non-smoker	428	42.8	429	45.6	1.00	
Former smoker	462	46.2	394	41.9	0.95	0.71, 1.27
Current smoker	111	11.1	118	12.5	1.16	0.96, 1.40
Lifetime alcohol consumption (drinks/week)						
Non-drinker or <1 drink	222	22.2	234	24.8	1.00	
Low (1-7)	354	35.4	316	33.5	1.18	0.93, 1.50
Moderate (8-14)	222	22.2	205	21.8	1.15	0.88, 1.49
High (≥ 15)	203	20.3	187	19.9	1.16	0.88, 1.52
Recent exercise (times/week)						
None	262	26.2	246	26.1	1.00	
1 - 2	315	31.5	283	30.0	1.06	0.84, 1.35
3 - 4	251	25.1	244	25.9	0.98	0.76, 1.26
≥ 5	172	17.2	168	17.9	0.96	0.73, 1.26
Education						
High school or less	196	19.6	181	19.2	1.00	
Some college	241	24.1	210	22.3	1.08	0.82, 1.42
College degree	262	26.2	261	27.7	0.95	0.72, 1.24
Graduate degree	301	30.1	289	30.7	0.98	0.75, 1.27
Prostate cancer screening ‡						
None	133	13.3	136	14.4	1.00	
DRE only	159	15.9	263	27.9	0.62	0.45, 0.84
PSA	709	70.8	543	57.6	1.34	1.02, 1.75
NSAIDs use						

None	792	79.1	746	79.1	1.00	
Former use	78	7.8	70	7.4	1.07	0.76, 1.51
Current use	131	13.1	126	13.4	0.98	0.75, 1.28
CYP3A4 (rs2740574) genotype						
AA	665	82.4	663	85.3	1.00 §	
AG	100	12.4	94	12.1	0.83	0.58, 1.19
GG	42	5.2	20	2.6	1.19	0.59, 2.43
CYP3A5 (rs776746) genotype						
GG	624	76.2	623	79.5	1.00 §	
GA	143	17.5	134	17.1	0.95	0.71, 1.26
AA	52	6.3	27	3.4	1.17	0.62, 2.21
Hypercholesterolemia						
No	572	57.1	556	59.0	1.00	
Yes	425	42.5	380	40.3	1.07	0.89, 1.29
Gleason score						
2 - 6	525	52.4				
7 (3+4)	294	29.4				
7 (4+3)	78	7.8				
8 - 10	99	9.9				
Unknown	5	0.5				
Stage of cancer						
Local	818	81.7				
Regional	159	15.9				
Distant	22	2.2				
Unknown	2	0.2				
PSA value (ng/ml) at diagnosis						
< 4.0	134	13.4				
4.0 - 9.9	592	59.1				
10.0 - 19.9	143	14.3				
≥ 20.0	69	6.9				
Unknown	63	6.3				
Prostate cancer aggressiveness ¶						
Less aggressive	686	68.5				
More aggressive	315	31.5				

* Odds ratios (OR) are adjusted for age.
† Numbers may not add total due to missing data.
‡ Prostate cancer screening within the 5 year period before reference date.
§ Odds ratios are adjusted for age and race.
¶ More aggressive = Gleason score of 7(4+3) or 8-10 or regional or distant stage or a diagnostic PSA ≥ 20 ng/ml; Less aggressive = Gleason score of 2-6 or 7(3+4) and localized stage and a diagnostic PSA < 20 ng/ml.

Table 2. Distribution of selected demographic and lifestyle characteristics and medical conditions between users and non-users of statins among population-based controls, King County, WA, 2002-2005

Characteristic	Statin Users (n = 265)		Statin Non-Users (n = 677)		P-value*
Age (years)	n †	%	n †	%	<0.0001
< 50	11	4.2	85	12.6	
50 - 54	15	5.7	98	14.5	
55 - 59	41	15.5	133	19.6	
60 - 64	65	24.5	122	18.0	
65 - 69	65	24.5	137	20.2	
70 - 74	68	25.7	102	15.1	
Race					0.04
Caucasian	246	92.8	598	88.3	
African-American	19	7.2	79	11.7	
First-degree family history of prostate cancer					0.45
No	231	87.2	602	88.9	
Yes	34	12.8	75	11.1	
BMI (kg/m^2)					0.01
< 25.0	55	20.8	204	30.1	
25.0 - 29.9	134	50.6	310	45.8	
≥ 30.0	76	28.7	163	24.1	
Smoking status					0.01
Non-smoker	104	39.2	325	48.0	
Former smoker	132	49.8	262	38.8	
Current smoker	29	10.9	89	13.2	
Lifetime alcohol consumption (drinks/week)					0.33
Non-drinker or <1	74	27.9	160	23.6	
Low (1-7)	87	32.8	229	33.8	
Moderate (8-14)	49	18.5	156	23.0	
High (≥ 15)	55	20.8	132	19.5	
Recent exercise (times/week)					0.63
None	71	26.8	175	25.9	
1 - 2	77	29.1	206	30.5	
3 - 4	63	23.8	181	26.8	
≥ 5	54	20.4	114	16.8	
Education					0.15
High school or less	47	17.7	134	19.8	
Some college or vocational	73	27.5	137	20.2	
Bachelors college degree	65	24.5	196	29.0	
Graduate school	80	30.2	209	30.9	
Prostate cancer screening ‡					<0.0001
None	19	7.2	117	17.3	
DRE only	59	22.3	204	30.1	
PSA	187	70.6	356	52.6	
Hypercholesterolemia					<0.0001
No	19	7.2	537	79.9	

Yes	245	92.8	135	20.1	
Diabetes mellitus					<0.0001
No	209	78.9	632	93.4	
Yes	56	21.1	45	6.6	
Hypertension					<0.0001
No	109	41.1	491	72.5	
Yes	156	58.9	186	27.5	
Myocardial infarction					<0.0001
No	202	76.2	660	97.5	
Yes	63	23.8	17	2.5	
Stroke					<0.0001
No	249	94.0	658	97.6	
Yes	16	6.0	16	2.4	

* Chi-square p-value.
† Numbers may not add to total due to missing data.
‡ Prostate cancer screening within the 5 year period before reference date.

Table 3. Associations between statin use and prostate cancer risk in a population-based case-control study, King County, WA, 2002-2005

	Cases (n = 1,001)		Controls (n = 942)		OR*	95% CI
Statin use	n	%	n	%		
None	712	71.1	677	71.9	1.00	
Ever use	289	28.9	265	28.1	0.98	0.80, 1.21
Current use	272	27.2	244	25.9	1.00	0.81, 1.24
Duration of use, yrs.						
< 5.0	154	15.4	146	15.5	0.96	0.74, 1.23
5.0 - 9.9	90	9.0	81	8.6	0.97	0.70, 1.34
≥ 10	45	4.5	38	4.0	1.11	0.70, 1.75
Continuous					1.01	0.98, 1.03
Age at first use						
< 59 †	166	16.6	138	14.6	1.11	0.86, 1.43
≥ 59	123	12.3	127	13.5	0.81	0.60, 1.07
Time since first use, yrs.						
< 5	145	14.5	133	14.1	0.96	0.74, 1.24
≥ 5	144	14.4	132	14.0	0.97	0.75, 1.27
Type of statin used ‡						
Hydrophilic	42	4.2	42	4.5	0.91	0.58, 1.44
Lipophilic	274	27.4	246	26.1	1.02	0.83, 1.27

* ORs are adjusted for age, race, and prostate cancer screening within the 5 year period before reference date.

† Age 59 was the median age at first use of a statin medication among controls.

‡ Hydrophilic statins = pravastatin, rosuvastatin; lipophilic statins = lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin; some cases (n=27) and controls (n=24) reported use of both types, so the analysis was also adjusted for the other type used.

Table 4. Associations between statin use and clinical characteristics of prostate cancer in a population-based case-control study, King County, WA, 2002-2005

a. Gleason score

	Controls (n = 942)		Cases, Gleason score ≤ 7 (3+4) (n = 816)				Cases, Gleason score ≥ 7 (4+3) (n = 177)			
Statin use	n	%	n	%	OR*	95% CI	n	%	OR*	95% CI
None	677	71.9	584	71.6	1.00		120	67.8	1.00	
Ever use	265	28.1	232	28.4	0.96	0.77, 1.19	57	32.2	1.14	0.80, 1.63
Current use	244	25.9	220	27.0	0.99	0.79, 1.23	52	29.4	1.12	0.78, 1.62
Duration, yrs.										
< 5	146	15.5	127	15.6	0.96	0.73, 1.26	27	15.3	1.00	0.63, 1.58
≥ 5	119	12.6	105	12.9	0.97	0.72, 1.29	30	16.9	1.31	0.83, 2.07
Continuous					0.99	0.97, 1.03			1.02	0.98, 1.07

b. Tumor stage

	Controls (n = 942)		Cases, localized stage (n = 818)				Cases, regional/distant stage (n =181)			
Statin use	n	%	n	%	OR*	95% CI	n	%	OR*	95% CI
None	677	71.9	568	69.4	1.00		142	78.5	1.00	
Ever use	265	28.1	250	30.6	1.03	0.83, 1.27	39	21.5	0.79	0.53, 1.17
Current use	244	25.9	239	29.2	1.07	0.86, 1.33	33	18.2	0.73	0.48, 1.10
Duration, yrs.										
< 5	146	15.5	136	16.6	1.03	0.79, 1.34	18	9.9	0.65	0.38, 1.11
≥ 5	119	12.6	114	13.9	1.03	0.77, 1.37	21	11.6	0.96	0.58, 1.60
Continuous					1.00	0.97, 1.03			0.99	0.94, 1.04

c. Disease aggressiveness †

	Controls (n = 942)		Cases, less aggressive (n = 686)				Cases, more aggressive (n = 315)			
Statin use	n	%	n	%	OR*	95% CI	n	%	OR*	95% CI
None	677	71.9	478	69.7	1.00		234	74.2	1.00	
Ever use	265	28.1	208	30.3	1.01	0.81, 1.27	81	25.8	0.92	0.68, 1.23
Current use	244	25.9	199	29.0	1.05	0.83, 1.32	73	23.2	0.89	0.66, 1.22

Duration, yrs.										
< 5	146	15.5	116	16.9	1.04	0.78, 1.37	38	12.1	0.78	0.53, 1.15
≥ 5	119	12.6	92	13.4	0.98	0.73, 1.34	43	13.7	1.08	0.73, 1.59
Continuous					1.00	0.97, 1.04			1.00	0.96, 1.04

* ORs are adjusted for age, race, and prostate cancer screening within the 5 year period before reference date; respective analyses exclude cases with missing Gleason score (n=8) or stage (n=2).

† More aggressive = Gleason score of 7(4+3) or 8-10 or regional or distant stage or a diagnostic PSA ≥ 20 ng/ml; Less aggressive = Gleason score of 2-6 or 7(3+4) and localized stage and a diagnostic PSA < 20 ng/ml.

Table 5. Associations between statin use and prostate cancer risk stratified by body mass index (BMI), in a population-based case-control study, King County, WA, 2002-2005

BMI < 30 kg/m^2	Cases (n = 779)		Controls (n = 703)		OR*	95% CI
Statin use	n	%	n	%		
None	582	74.7	514	73.1	1.00	
Ever use	197	25.3	189	26.9	0.87	0.68, 1.11
Current use	187	24.0	176	25.0	0.89	0.69, 1.14
Duration of use, yrs.						
< 5	108	13.9	101	14.4	0.91	0.67, 1.23
≥ 5	89	11.4	88	12.5	0.83	0.59, 1.15
Continuous					0.99	0.96, 1.02

BMI ≥ 30 kg/m^2	Cases (n = 222)		Controls (n = 239)		OR*	95% CI
Statin use	n	%	n	%		
None	130	58.6	163	68.2	1.00	
Ever use	92	41.4	76	31.8	1.45	0.99, 2.13
Current use	85	38.3	68	28.5	1.50	1.00, 2.24
Duration of use, yrs.						
< 5	46	20.7	45	18.8	1.21	0.75, 1.96
≥ 5	46	20.7	31	13.0	1.80	1.06, 3.03
Continuous					1.05	1.00, 1.10

* ORs are adjusted for age, race, and prostate cancer screening within the 5 year period before reference date.

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