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Statins and Prostate Cancer Diagnosis and Grade in a Veterans Population

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Background	Although prostate cancer is commonly diagnosed, few risk factors for high-grade prostate cancer are known and few prevention strategies exist. Statins have been proposed as a possible treatment to prevent prostate cancer.
Methods	Using electronic and administrative files from the Veterans Affairs New England Healthcare System, we identified 55 875 men taking either a statin or antihypertensive medication. We used age- and multivariable-adjusted Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer incidence among patients taking statins (n = 41 078) compared with patients taking antihypertensive medications (n = 14 797). We performed similar analyses for all lipid parameters including total cholesterol examining each lipid parameter as a continuous variable and by quartiles. All statistical tests were two-sided.
Results	Compared with men taking an antihypertensive medication, statin users were 31% less likely (HR = 0.69, 95% CI = 0.52 to 0.90) to be diagnosed with prostate cancer. Furthermore, statin users were 14% less likely (HR = 0.86, 95% CI = 0.62 to 1.20) to be diagnosed with low-grade prostate cancer and 60% less likely (HR = 0.40, 95% CI = 0.24 to 0.65) to be diagnosed with high-grade prostate cancer compared with antihypertensive medication users. Increased levels of total cholesterol were also associated with both total (HR = 1.02, 95% CI = 1.00 to 1.05) and high-grade (HR = 1.06, 95% CI = 1.02 to 1.10) prostate cancer incidence but not with low-grade prostate cancer incidence (HR = 1.01, 95% CI = 0.98 to 1.04).
Conclusions	Statin use is associated with statistically significantly reduced risk for total and high-grade prostate cancer, and increased levels of serum cholesterol are associated with higher risk for total and high-grade prostate cancer. These findings indicate that clinical trials of statins for prostate cancer prevention are warranted.
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In 2010, it is estimated that 217 730 men will be diagnosed with prostate cancer and 32 050 men will die of prostate cancer (1). Prostate cancer is the most commonly diagnosed cancer among men, excluding nonmelanoma skin cancer, and is the second most common cause of cancer-related mortality (1). Although prostate cancer is prevalent and a common cause of cancer-related mortality, few prevention strategies for prostate cancer currently exist.

One potential prevention strategy for prostate cancer is taking a statin, 3-hydroxy-3-methyl-glutaryl-coenzyme reductase inhibitor. Several recent published studies have reported that statin use may be associated with a decreased risk for advanced prostate cancer (2–5). Platz et al. (2) found a statistically significant inverse relationship between statins and metastatic prostate cancer. Other studies (3–5) have shown that statin use was associated with a decreased Gleason score at prostate cancer diagnosis. However, most recently, one study (6) did not find that statin use was associated with decreased risk for advanced prostate cancer. Unfortunately, a limitation of several of these studies is the potential

healthy user bias (7,8). Compared with nonusers, patients who use statins may have a different risk profile for prostate cancer. For example, statin users may have different access to health care, including use of preventive health services such as prostate-specific antigen (PSA) testing (8,9); different competing risks; and different diet and exercise habits compared with nonusers. This bias may result in statin users appearing to have a decreased risk for advanced prostate cancer when in fact something else that is associated with statin use and different from the comparison population may be responsible for the decrease in risk.

A recent study has shown that low serum cholesterol is associated with a decreased risk for advanced prostate cancer compared with high serum cholesterol (10). Platz et al. (10) found a statistically significant direct relationship between higher levels of serum cholesterol and increased risk for high-grade prostate cancer, which supports the hypothesis that taking a medicine to lower cholesterol levels may prevent advanced prostate cancer. However, several questions remain about the relationship between statins,

cholesterol, and prostate cancer. After attempting to control for a potential healthy user bias, is statin use associated with decreased incidence of high-grade prostate cancer? Is there a dose response between statins and the incidence of high-grade prostate cancer? Are lipid parameters such as high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C associated with the incidence of high-grade prostate cancer or is total cholesterol (TC) alone associated with the incidence of high-grade prostate cancer? Therefore, we built on our previously published analysis of statins and cancer diagnosis to specifically examine the relationship between statins and pathology-confirmed prostate cancer diagnosis and grade. Furthermore, we examined the relationship between several different lipid parameters and pathology-confirmed prostate cancer diagnosis and grade.

Methods

Data Source and Definition of Outcome

We assembled a retrospective cohort of male patients aged 18 years and older in the Veterans Affairs (VA) New England Healthcare System between January 1, 1997, and December 31, 2007, using national and regional databases. The study protocol was reviewed and approved by the Institutional Review Board of the VA Boston Healthcare System, and the board granted our study a waiver from obtaining informed consent from the patients. We obtained patient level data from the VA National Patient Care Database and the VA Pharmacy Benefits Management System. Patient level data captured in the VA national database system include both inpatient and outpatient demographic characteristics, visits, diagnoses, procedures, medications, and laboratory test results. We defined the cohort entry date as the first recorded prescription fill date for the medication of interest. All patients with a cancer diagnosis were defined by *International Classification of Diseases* (*ICD*) codes. *ICD-Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 140.XX–208.XX or VA pathology-confirmed prostate cancer diagnosis, on or before the cohort entry date, were excluded from the study analyses. An observation period for each patient was defined as beginning 2 years after their entry date and continuing until 1) the first occurrence of a diagnosis of prostate cancer; 2) an *ICD-9-CM* code for a cancer other than prostate cancer or nonmelanoma skin cancer; 3) 1 year after the last fill date for a medication of interest; 4) death; or 5) the end of the cohort, December 31, 2007. To diminish any potential effects of latent cancer on our predictor variables, we excluded patients that were diagnosed with cancer within 2 years after their potential entry date. Because long-term exposure would likely be required for any medication to reduce prostate cancer incidence, we also excluded all patients who discontinued their medication of interest within 2 years after their potential entry date.

The primary outcomes of our analyses were prostate cancer incidence and Gleason grade. Patients with prostate cancer and the corresponding Gleason grade of their tumors were identified in the electronic medical record of the VA New England Healthcare System using the Automated Retrieval Console (11). Briefly, from a dataset of patients with an *ICD-9-CM* code for prostate cancer, Automated Retrieval Console identified pathology reports consistent with prostate cancer. Automated Retrieval Console was able to separate reports consistent with a biopsy from reports consistent a prostatectomy. We then used natural language processing to identify Gleason grade within these reports. If we identified a pathology report consistent with prostate cancer, we defined that patient as having been diagnosed with prostate cancer on the date of the pathology report. We further stratified our outcome by high- and low-grade prostate cancer. Low-grade prostate cancer was defined as a total Gleason score of less than or equal to 7 (3 + 4), and high-grade prostate cancer was defined as a total Gleason score of greater than or equal to 7 (4 + 3). Our method of identifying prostate cancer grade was found to have 97% recall and 95% precision (11).

Predictor Variables

Patients were selected among active users of the VA New England Healthcare System who 1) filled at least two prescriptions (generally a 90-day supply) for any antihypertensive medication or statin within 1 year, 2) continued filling at least yearly prescriptions for an identified medication of interest, and 3) were seen at least once per year in an outpatient VA clinic. Antihypertensive medication users were defined as patients who never filled a prescription for any cholesterol-lowering medication but filled prescriptions from the following classes of antihypertensive medications: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, alpha blockers, loop diuretics, thiazide diuretics, and centrally active antihypertensive medications. Statin users were defined as patients who filled prescriptions for

any of the following medications: atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin. Statin users may have been prescribed antihypertensive medication in addition to their cholesterol-lowering medication.

Several potential confounders were documented before or at the start of the observation period. Diabetes mellitus was coded present or absent in the analysis on the basis of the presence or absence of ICD-9-CM code, 250.XX, and a filled prescription for a medication from any of the following classes of medications: insulin, sulfonylurea, biguanide, thiazolidinedione, alpha-glucosidase inhibitor, and meglitinide. Cardiovascular disease was coded present or absent in the analysis on the basis of the presence or absence of ICD-9-CM codes, 410.XX–412.XX, 414.XX, 428. XX–438.XX, or 441.XX–444.2X. We defined aspirin use (yes or no) as an active prescription at the cohort entry date for any of the following agents: aspirin, aspirin buffered oral, aspirin oral enteric coated, and aspirin suppository. We defined finasteride use (yes or no) as an active prescription for finasteride at the cohort entry date. We defined PSA testing (yes or no) as having had a PSA test within 1 year before the cohort entry date and within the 2-year observation period. We defined having had a prostatectomy as the presence or absence of a surgical pathology report consistent with a prostatectomy after a diagnosis of prostate cancer. We extracted information from the electronic medical record on smoking history (yes, no, or unknown), age (years), weight (in kilograms), and height (in meters) at entry into the observation period. We identified measured serum values for TC, LDL-C, and HDL-C within 6 months before each patient's cohort entry date. We calculated non-HDL-C by subtracting HDL-C from TC among those patients who had both lipid parameters measured on the same day.

Statistical Analysis

We constructed age- and multivariable-adjusted Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer incidence among statin users compared with the referent group, antihypertensive medication users. A Kaplan–Meier curve was created and reviewed to confirm the assumption of proportionality. Multivariable models for prostate cancer incidence among statin users compared with antihypertensive medication users included age, race, smoking history, prescription for aspirin, prescription for finasteride, PSA testing, diabetes mellitus, and total serum cholesterol. We also calculated a propensity score for being prescribed a statin using a logistic regression model with the same variables as listed above for the multivariable model. The c-statistic for the propensity score model was 0.79. We constructed models to predict prostate cancer incidence that included the propensity score among our entire cohort and the population within the fifth and 95th percentile of propensity score.

To further investigate the relationship between statin dose and prostate cancer incidence, we defined groups of patients by statin use within categories of equivalent simvastatin dosages, the most commonly used statin in our cohort (antihypertensive medication users, ≤10 mg equivalent simvastatin dose, 20 mg equivalent simvastatin dose, and ≥40 mg equivalent simvastatin dose) as previously described (12,13). Briefly, to allow time for a patient to achieve a stable statin dose, categories of equivalent simvastatin dosages

were calculated on the basis of the dose and type of statin prescribed at 1 year after treatment initiation. Equivalent simvastatin dosages were calculated by dividing lovastatin and pravastatin doses by 2, dividing the fluvastatin dose by 4, and multiplying the atorvastatin dose by 2. We then determined the hazard ratio and 95% confidence interval of each tertile of equivalent simvastatin dose compared with our referent group for prostate cancer incidence. We controlled for the same potential confounders listed for our models described above. We calculated tests of trend across categories of equivalent simvastatin dose with the median dose in each category acting as an ordinal variable.

We also examined the relationship between serum lipid parameters at baseline and prostate cancer incidence. We constructed age- and multivariable-adjusted Cox proportional hazard models to calculate the hazard ratios and 95% confidence intervals for prostate cancer incidence by continuous measures and quartiles of each lipid parameter. Multivariable models contained all of the previously mentioned variables except that for each lipid parameter, the lipid parameter of interest was exchanged for TC. We calculated tests of trend across quartiles of each lipid parameter with the median value in each quartile acting as an ordinal variable. Quartiles of TC were defined as: <176, 176–206, 207–237, and > 237 mg/dL. Quartiles of HDL-C were defined as: <37, 37–42, 43–51, and >51 mg/dL. Quartiles of non-HDL-C were defined as: <131, 131–160, 161–192, and >192 mg/dL. Quartiles of LDL-C were defined as: <105, 105–131, 132–158, and >158 mg/dL. We created similar models to those listed above to examine the relationship between statin use and each lipid parameter with low- and high-grade prostate cancer incidence.

All statistical tests were two-sided and considered statistically significant if P is less than .05. Statistical tests were performed using SAS, version 9.1 (SAS, Cary, NC).

Results

We identified a cohort of 55 875 male patients who met our entry criteria. The mean age was 66.0 years (SD = 11.0 years) and median total follow-up time of 5.6 years (range = 2.0–11.0 years) in the overall cohort (median total follow-up time of 5.2 and 5.6 years was observed among antihypertensive medication users and statin users, respectively). The following is the proportion of each different statin agent in the statin user group 1 year after statin initiation: simvastatin, 54.6%; lovastatin, 43.9%; atorvastatin, 1.2%; pravastatin, 0.2%; and fluvastatin, 0.1%. The mean equivalent simvastatin dose among statin users was 26.2 mg (SD = 22.2 mg). Several characteristics of statin users and users of antihypertensive medications are presented in Table 1.

Among the referent group, 187 (1.3%) of 14 797 patients developed VA pathology-confirmed prostate cancer during their observation period compared with 359 (0.9%) of 41 078 patients taking statins. Overall, Gleason grade was reported in more than 99% of biopsy reports consistent with prostate cancer, and the most common total Gleason grade was 6 (Table 2).

Compared with patients taking antihypertensive medications, the risk of prostate cancer incidence was 31% less among patients taking statins (HR = 0.69, 95% CI = 0.52 to 0.90) after adjusting for age and other potential confounders (Table 3). Statin users

Table 1. Characteristics of patients taking an antihypertensive medication or statin (N = 55 875)

Characteristic	Antihypertensive users (n = 14 797)	Statin users (n = 41 078)
Age, y		
Mean (SD)	65.2 (12.7)	66.3 (10.4)
Race, No. (%)		
White	7853 (53.1)	27 319 (54.3)
Black	604 (4.1)	1007 (2.5)
Other	51 (0.3)	74 (0.2)
Missing	6289 (42.5)	17 678 (43.0)
Smoker, No. (%)	3573 (24.2)	9039 (22.0)
Aspirin use, No. (%)	4310 (29.1)	15 571 (37.9)
Finasteride use, No. (%)	1424 (9.6)	3733 (9.1)
Diabetes mellitus, No. (%)	1321 (8.9)	9299 (22.6)
Cardiovascular disease, No. (%)	4697 (31.7)	24 469 (59.6)
Prostate-specific antigen test, No. (%)	6516 (44.0)	19 131 (46.6)
Total cholesterol, mg/dL		
Mean (SD)	183.7 (35.4)	213.8 (47.8)
High-density lipoprotein cholesterol, mg/dL		
Mean (SD)	47.8 (15.1)	44.1 (11.2)
Non–high-density lipoprotein cholesterol, mg/dL		
Mean (SD)	136.4 (32.8)	168.7 (46.5)
Low-density lipoprotein cholesterol, mg/dL		
Mean (SD)	108.8 (28.8)	136.1 (39.1)

were 14% less likely (HR = 0.86, 95% CI = 0.62 to 1.20) to be diagnosed with low-grade prostate cancer and 60% less likely (HR = 0.40, 95% CI = 0.24 to 0.65) to be diagnosed with high-grade prostate cancer compared with use of antihypertensive medication. The trend for prostate cancer incidence across categories of equivalent simvastatin dose was non-statistically significant (slope = −0.01, P_{trend} = .09), but the risk of prostate cancer incidence was statistically significantly reduced in each category of equivalent simvastatin dose compared with patients taking antihypertensive medications. No apparent dose response among statin users compared with antihypertensive medication users was observed for low-grade prostate cancer incidence (slope = −0.00, P_{trend} = .83). However, for high-grade prostate cancer incidence, the trend across categories was statistically significant (slope = −0.03,

Table 2. Percentages of Gleason scores (N = 546)

Gleason score	Antihypertensive users No. (%)	Statin users No. (%)
2	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)
4	2 (1.1)	1 (0.3)
5	4 (2.1)	12 (3.3)
6	84 (44.9)	184 (51.3)
7 (3 + 4)	42 (22.5)	87 (24.2)
7 (4 + 3)	22 (11.8)	34 (9.5)
8	19 (10.2)	32 (8.9)
9	13 (7.0)	8 (2.2)
10	1 (0.5)	1 (0.3)

P_{trend} = .005) and the risk in each category was statistically significantly reduced. Patients in the highest category of equivalent simvastatin dose were found to have a 73% decreased risk (HR = 0.27, 95% CI = 0.11 to 0.67) for high-grade prostate cancer compared with patients taking antihypertensive medications. Results from the overall cohort and between the fifth and 95th percentile of propensity score adjusted for the propensity score did not differ markedly from the results of our multivariable model (data not shown).

Increased levels of baseline TC appeared to increase the risk of total and high-grade prostate cancer incidence (Table 4). Every 10 mg/dL increase of baseline TC was associated with 2% increased risk of total prostate cancer (HR = 1.02, 95% CI = 1.00 to 1.05) and 6% increased risk of high-grade prostate cancer (HR = 1.06, 95% CI = 1.02 to 1.10). The highest quartile of TC at baseline was associated with a 45% increased risk of total prostate cancer (HR = 1.45, 95% CI = 1.07 to 1.97) and a 204% increased risk of high-grade prostate cancer (HR = 3.04, 95% CI = 1.65 to 5.60). TC was not associated with low-grade prostate cancer. Every 10 mg/dL increase of HDL-C at baseline was associated with 10% increased risk of total prostate cancer (HR = 1.10, 95% CI = 1.02 to 1.19) and 11% increased risk of low-grade prostate cancer (HR = 1.11, 95% CI = 1.02 to 1.21). The highest quartile of HDL-C at baseline was associated with a 45% increased risk of total prostate cancer (HR = 1.45, 95% CI = 1.08 to 1.95) and 157% increased risk of high-grade prostate cancer (HR = 2.57, 95% CI = 1.49 to 4.42). The highest quartile of LDL-C at baseline was associated with a 58% increased risk of total prostate cancer (HR = 1.58, 95% CI = 1.15 to 2.17) and 154% increased risk for high-grade prostate cancer (HR = 2.54, 95% CI = 1.34 to 4.81).

Discussion

Among patients in the New England VA Healthcare System, our study found that statin users were at lower risk for total and specifically high-grade prostate cancer incidence compared with users of antihypertensive medications. Furthermore, there was an inverse relationship between the dose of statin achieved at 1 year and the incidence of high-grade prostate cancer. We also found a strong direct relationship between baseline TC and total and high-grade prostate cancer. These findings are all consistent with the hypothesis that cholesterol plays an important role in total and high-grade prostate cancer incidence and medications that lower cholesterol, specifically statins, may reduce the risk of total and high-grade prostate cancer.

Previous observational studies have not clarified the relationship between statins and prostate cancer. Most of these studies only examined the relationship between statins and total prostate cancer and did not specifically investigate the relationship between statins and high-grade prostate cancer. Platz et al. (2) did examine the relationship between advanced prostate cancer patient statin use and metastasis and death and found a statistically significantly decreased risk for advanced prostate cancer among patients taking statins. To date, there are no reports of clinical trials of statins for prostate cancer prevention. One multicenter randomized placebo controlled clinical trial is examining the relationship between statins and prostate cancer biomarkers among men with Gleason

Table 3. Prostate cancer outcomes by use of antihypertensives, statins, and categories of equivalent simvastatin doses*

Outcome	Antihypertensive users	Statin users	Categories of equivalent simvastatin doses, mg			
			0	1–10	11–19	≥20
Total prostate cancer						
No. of patients	187	359	187	140	102	74
Person-years of follow-up	52 403	147 512	52 403	54 488	47 760	31 657
HR (95% CI)	1.0 (referent)†	0.69 (0.52 to 0.90)	1.0 (referent)	0.68 (0.51 to 0.89)	0.68 (0.50 to 0.92)	0.66 (0.46 to 0.95)
Low-grade prostate cancer‡						
No. of patients	132	284	132	113	78	60
Person-years of follow-up	52 257	147 313	52 257	54 398	47 689	31 631
HR (95% CI)	1.0 (referent)	0.86 (0.62 to 1.20)	1.0 (referent)	0.81 (0.58 to 1.12)	0.78 (0.55 to 1.12)	0.85 (0.57 to 1.29)
High-grade prostate cancer§						
No. of patients	55	75	55	27	24	14
Person-years of follow-up	52 403	147 512	52 403	54 488	47 760	31 657
HR (95% CI)	1.0 (referent)	0.40 (0.24 to 0.65)	1.0 (referent)	0.43 (0.25 to 0.74)	0.48 (0.26 to 0.86)	0.27 (0.11 to 0.67)

* Models were adjusted for the following variables: statin use (yes or no), finasteride use history (yes or no), age (years), serum total cholesterol (mg/dL), race (white, black, other, or missing), smoking history (yes or no), aspirin use (yes or no), heart disease (yes or no), diabetes mellitus (yes or no), history of prostate-specific antigen test (yes or no). CI = confidence interval; HR = hazard ratio.

† Referent defines the group that is the basis for the comparison.

‡ Low-grade prostate cancer is defined as a Gleason score ≤7 (3 + 4).

§ High-grade prostate cancer is defined as a Gleason score ≥7 (4 + 3).

grade 5 to 7 (3 + 4) prostate cancer who have been treated with a prostatectomy (14).

Measuring PSA has become the primary means of screening for prostate cancer incidence and progression. Several studies have found that men taking a statin may have a lower PSA (8,15,16). One explanation of our findings may be that decreased PSA levels secondary to taking a statin may have led to decreased PSA testing and therefore decreased incidence of prostate cancer. However, we found that more statin users had a PSA test than users of antihypertensive medications. If statin users were tested more frequently, perhaps another explanation of our results is lead-time bias. However, lead-time bias would result in a higher risk of low-grade prostate cancer among statin users. In fact, although non-statistically significant, we found statin users to be associated with a 14% reduced relative risk for low-grade prostate cancer.

One possible explanation for our findings could be a selection bias for cardiovascular disease that resulted in a difference in the competing risks between exposure groups. In our study, cardiovascular disease was more prevalent among statin users than antihypertensive users at baseline. Therefore, if statin users had more cardiovascular events and were not being tested for prostate cancer or died of cardiovascular events before being diagnosed for prostate cancer, statin users may have artificially appeared to be at lower risk for prostate cancer compared with antihypertensive medication users. However, we did not find any meaningful difference in the prevalence of PSA testing at baseline or follow-up time between exposure groups. Therefore, it is unlikely that the selection bias of cardiovascular disease would have resulted in a large enough difference in the competing risk of cardiovascular disease between exposure groups to explain our results.

Lipid rafts appear to be important for the development and progression of prostate cancer (17). Levels of caveolae have been associated with prostate cancer and aggressive prostate cancer (18). Caveolae are where HDL-C and the cell bind (19). Studies have shown that intracellular cholesterol plays a role in prostate cancer development and progression (20). However, to the best of our knowledge, few studies (10,21) have reported the relationship between various serum lipid parameters and prostate cancer incidence. It is interesting that we found a relationship between both serum TC and HDL-C, and high-grade prostate cancer, which was also independent of statin use.

One should consider several strengths and limitations when interpreting our findings. Our data are from the electronic medical records and administrative files of patients in the VA New England Healthcare System. Although we were able to identify when medications were prescribed, we were unable to confirm that patients actually took the medication. Also, we were unable to account for prescriptions of our medications of interest that occurred outside the VA Healthcare System. Furthermore, we were unable to identify patients with prostate cancer diagnosed outside the VA Healthcare System. However, among veterans eligible for VA health care, approximately 60% use a VA facility for their only source of primary care and approximately 20% use both a VA and a non-VA facility for their primary care (22). Because we required both exposure groups to be routine users of the VA Healthcare System, it is unlikely that there was nonrandom misclassification in either the receipt of medications of interest or diagnosis of prostate

Table 4. Prostate cancer outcomes by lipid parameters*

Outcome	Continuous	Quartiles of lipid parameters			
		1	2	3	4
Total cholesterol	10 units	<176 mg/dL	176–206 mg/dL	207–237 mg/dL	>237 mg/dL
Total prostate cancer					
No. of patients	349	72	86	81	110
Person-years of follow-up	112178	24985	27644	28404	31145
HR (95% CI)	1.02 (1.00 to 1.05)	1.0 (referent)†	1.13 (0.84 to 1.54)	1.16 (0.85 to 1.58)	1.45 (1.07 to 1.97)
Low-grade prostate cancer‡					
No. of patients	264	55	61	68	80
Person-years of follow-up	111939	24937	27569	28369	31064
HR (95% CI)	1.01 (0.98 to 1.04)	1.0 (referent)	0.99 (0.69 to 1.42)	1.10 (0.78 to 1.56)	1.14 (0.80 to 1.63)
High-grade prostate cancer§					
No. of patients	85	17	25	13	30
Person-years of follow-up	112178	24984	27644	28404	31145
HR (95% CI)	1.06 (1.02, 1.10)	1.0 (referent)	1.66 (0.93, 2.98)	1.27 (0.62, 2.59)	3.04 (1.65, 5.60)
HDL-cholesterol	10 units	<37 mg/dL	37–42 mg/dL	43–51 mg/dL	>51 mg/dL
Total prostate cancer					
No. of patients	313	69	65	87	92
Person-years of follow-up	97911	23641	24927	23489	25853
HR (95% CI)	1.10 (1.02 to 1.19)	1.0 (referent)	1.19 (0.85 to 1.65)	1.51 (1.13 to 2.02)	1.45 (1.08 to 1.95)
Low-grade prostate cancer					
No. of patients	239	55	47	70	67
Person-years of follow-up	97714	25815	23439	24875	23586
HR (95% CI)	1.11 (1.02 to 1.21)	1.0 (referent)	0.98 (0.66 to 1.44)	1.48 (1.07 to 2.05)	1.18 (0.83 to 1.68)
High-grade prostate cancer					
No. of patients	74	14	18	17	25
Person-years of follow-up	97911	25853	23489	24927	23641
HR (95% CI)	1.10 (0.94 to 1.28)	1.0 (referent)	2.11 (1.13 to 3.95)	1.56 (0.81 to 3.01)	2.57 (1.49 to 4.42)
Non-HDL-cholesterol	10 units	<131 mg/dL	131–160 mg/dL	161–192 mg/dL	>192 mg/dL
Total prostate cancer					
No. of patients	240	56	50	62	72
Person-years of follow-up	78250	17157	18774	19646	22672
HR (95% CI)	1.02 (0.99 to 1.05)	1.0 (referent)	0.94 (0.66 to 1.34)	1.30 (0.95 to 1.79)	1.13 (0.80 to 1.60)
Low-grade prostate cancer					
No. of patients	183	41	40	48	54
Person-years of follow-up	78105	17129	18734	19614	22628
HR (95% CI)	1.00 (0.96 to 1.04)	1.0 (referent)	1.02 (0.69 to 1.52)	1.21 (0.84 to 1.75)	1.00 (0.67 to 1.48)
High-grade prostate cancer					
No. of patients	57	15	10	14	18
Person-years of follow-up	78250	17157	18774.4	19646	22672
HR (95% CI)	1.06 (1.02 to 1.09)	1.0 (referent)	0.68 (0.29 to 1.58)	1.63 (0.86 to 3.10)	1.72 (0.86 to 3.46)
LDL-cholesterol	10 units	<105 mg/dL	105–131 mg/dL	132–158 mg/dL	>158 mg/dL
Total prostate cancer					
No. of patients	279	58	64	71	86
Person-years of follow-up	84068	17891	20083	21775	24320
HR (95% CI)	1.02 (0.98 to 1.05)	1.0 (referent)	1.27 (0.92 to 1.76)	1.41 (1.03 to 1.93)	1.58 (1.15 to 2.17)
Low-grade prostate cancer					

(Table continues)

Table 4 (Continued).

Outcome	Continuous	Quartiles of lipid parameters			
		1	2	3	4
No. of patients	215	41	52	59	63
Person-years of follow-up	83 912	17 856	20 043	221 748	24 265
HR (95% CI)	1.01 (0.97 to 1.04)	1.0 (referent)	1.32 (0.92 to 1.90)	1.37 (0.96 to 1.95)	1.36 (0.94 to 1.97)
High-grade prostate cancer					
No. of patients	64	17	12	12	23
Person-years of follow-up	84 068	17 891	20 083	21 775	24 320
HR (95% CI)	1.01 (0.95 to 1.08)	1.0 (referent)	1.09 (0.54 to 2.24)	1.53 (0.77 to 3.02)	2.54 (1.34 to 4.81)

* Multivariable models were adjusted for the following variables: statin use (yes or no), finasteride use history (yes or no), age (years), serum total cholesterol (mg/dL), race (white, black, other, or missing), smoking history (yes or no), aspirin use (yes or no), heart disease (yes or no), diabetes mellitus (yes or no), and history of prostate-specific antigen test (yes or no). CI = confidence interval; HDL = high-density lipoprotein; HR = hazard ration; LDL = low-density lipoprotein.

† Referent defines the group that is the basis for the comparison.

‡ Low-grade prostate cancer is defined as a Gleason score ≤7 (3 + 4).

§ High-grade prostate cancer is defined as a Gleason score ≥7 (4 + 3).

cancer outside the VA Healthcare System. We attempted to limit any healthy user bias by comparing statin users to patients with similar risk profiles, access to health care, and lifestyles. Because we compared statin users to users of antihypertensive medications and not the general population, care should be taken before extrapolating our results to the general population. Furthermore, antihypertensive medications have been hypothesized and investigated as risk factors for prostate cancer (23,24). If antihypertensive medications are associated with increased risk for prostate cancer, our results would likely overestimate the potential decreased risk of prostate cancer among patients taking statins. However, patients in both groups were taking antihypertensive medications. We relied on unconfirmed *ICD-9-CM* codes and pharmacy codes for identification of some of our potential confounders. Any misclassification of our confounders would likely be random and bias our results toward the null hypothesis. Although we did not have information on lifestyle variables such as diet and exercise, it is unlikely that any difference in lifestyle variables between users of statins or antihypertensive medications would be large enough to account for our statistically significant findings. Another limitation of our study is that quantitative information on smoking was not available from the medical records and patient files. Also, the lipid values used in the analysis were from a single time point, and therefore, no inferences on the relationship between change in lipid parameters and risk of prostate cancer incidence can be made. Because of the limited numbers of minorities in our veteran population, our results were not analyzed in terms of race.

In conclusion, men who use statins appear to be at lower risk for prostate cancer and specifically high-grade prostate cancer than men who use antihypertensive medications. Furthermore, men with higher levels of TC appear to be at higher risk of prostate cancer and specifically high-grade prostate cancer than men with lower levels of TC. Clinical trials should investigate whether statins may prevent prostate cancer and specifically high-grade prostate cancer.

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Notes

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