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The associations between statin use and prostate cancer screening, prostate size, high-grade prostatic intraepithelial neoplasia (PIN), and prostate cancer.

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Abstract

Objective—Prior studies report statins may reduce the risk of advanced prostate cancer. This study investigates the association between statin use and the likelihood of having a PSA or DRE test, blood PSA levels, prostate volume, and the severity of lower urinary tract symptoms. We also describe the association between statin use and prostate cancer and high-grade prostatic intraepithelial neoplasia (PIN) before and after controlling for prostate cancer screening indices associated with statin use.

Methods—The Nashville Men's Health Study used a multicenter, rapid recruitment protocol to collect clinical, biological, behavioral and body measurement data from 2,148 men 40 years or older scheduled for diagnostic prostate biopsy. Medication use and other data were ascertained by research survey, clinical interview, and chart review.

Results—Approximately 37% of participants were taking a statin. Statin use was significantly associated with a 12% lower PSA levels and 8% smaller prostate volume after controlling for age, race, BMI, WHR, aspirin use, other comorbidity. Simvastatin was more strongly associated with prostate volume, while atorvastatin was associated with PSA. Statin use was marginally associated with increasing PSA test frequency among men with undiagnosed cancer. Statin use was not associated with the frequency or results of digital rectal exams, lower urinary tract symptom severity, high-grade (Gleason >6) prostate cancer (OR=0.95 (0.73, 1.24)), low-grade (Gleason = 6) prostate cancer (OR=1.11 (0.86, 1.42)) or PIN (OR=0.82, (0.57, 1.17)). Additional control for the number of prior PSA tests, PSA levels, and prostate volume did not alter these results.

Conclusion—These results suggest selective referral for biopsy associated with statin use is an essential element to address in further understanding the potential for statins to prevent prostate cancer.

Keywords

prostate cancer; PSA; Statin; prostate volume; bias

Introduction

Prior reports that men with lower cholesterol levels have a lower risk of prostate cancer have suggested that small molecule inhibitors of 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase, known as statins, may reduce prostate cancer risk(1,2). Statins inhibit prenylation and the activity of several key cellular regulatory elements, blocking cholesterol synthesis (3), but also affecting regulatory mechanisms of apoptosis, cell proliferation, cell migration, and the inflammatory response (4). Several recent studies, including prospective analyses from the Health Professionals Follow-up Study and the Cancer Prevention Study II, reported that extended statin use lowered the risk of advanced, aggressive, or clinically relevant forms of prostate cancer (5-10). The California Men's Health Study reported a non-significant protective association between statin use and advanced prostate cancer (11), while analysis of the Kaiser Permanente Medical Care Program in northern California found statin use was associated with a decrease in advanced disease but also an increased in localized prostate cancer (12). The European Randomized Study of Prostate Cancer Screening, with few advanced cases, found statin use reduced the risk of early-stage prostate cancer (13). In contrast, an analysis of 236 prostatectomy patients within the Veteran's Administration found simvastatin use was associated with detection of high-grade prostate cancer at biopsy (14), while a population-based case-control analysis found statin use increased prostate cancer risk among obese men (15).

Increasing utilization of the prostate-specific antigen test (PSA) within a population leads to a dramatic increase in the detection of localized prostate cancer. This has raised the concern that previously observed stage-specific associations between statins and prostate cancer may derive from differential prostate cancer detection between statin users and nonusers. Indeed, several studies now report statin use is associated with an increase in PSA testing (7,9), lower PSA levels (9,16,17), and fewer prostate biopsies (10). With increasing PSA testing, there is the potential for increasing the detection of localized disease at the expense of advanced cancer, lending the appearance of a protective association between statin use and advanced prostate cancer. Furthermore, lower PSA levels may prevent referral for a diagnostic prostate biopsy, also lending to the appearance of a reduced cancer risk. Beyond the impact on clinical referral for biopsy, any relationship between statin use and prostate size may also affect the stage/grade at diagnosis, as analyses from the Prostate Cancer Prevention Trial suggest that a smaller prostate size improves the efficiency of prostate biopsy to detect small, high-grade, prostate cancer foci (18). Although a recent randomized trial found atorvastatin administration for six months was insufficient to reduce prostate size among men with normal to borderline LDL levels(19), the possible effects of statin on prostate size among men at risk for prostate cancer is not understood.

Before recommending statins for the prevention of prostate cancer, the relationship between statin use and the range of individual and clinical factors involved in detecting and diagnosing prostate cancer needs to be determined. Here, we investigate the association between cholesterol-lowering medications, including statins, and PSA testing frequency, blood PSA levels, DRE results, prostate volume, LUTS severity, and the risk of PIN, low-grade prostate cancer, and high-grade prostate cancer, while controlling for body size (15,20), aspirin use (21), and comorbidity such as diabetes and cardiovascular disease (CVD) (22). Our results may identify prostate cancer screening and detection factors that most influence an association between statin use and prostate cancer risk, and ultimately may serve to better target statin use to those men most likely to benefit.

Materials and Methods

Study Population

All participants provided written informed consent with guarantees of confidentiality prior to data collection in accordance with the Vanderbilt University IRB. Men scheduled for a diagnostic prostate biopsy between 2002 and 2010 at a Vanderbilt University Medical Center (Nashville, TN), the Tennessee Valley Veteran's Administration Hospital (Nashville, TN), or Urology Associates, a private urology clinic in Nashville, were approached for recruitment. Eligible participants were 40 years of age or older and had no prior prostate cancer diagnosis. Approximately 95% of eligible men approached for recruitment agree to participate, and the study population included 2,509 eligible consenting subjects.

Data Collection

Measures of body size and weight were collected by a trained research staff member at the time of recruitment using standardized protocols. Participants wore a hospital gown or other light clothing, and did not wear shoes. Chart review included age, race, PSA history, DRE history, and prostate needle-biopsy result (cancer, PIN, negative, or a suspicious, atypical, or other diagnosis). Gleason scores at biopsy were also ascertained for subjects diagnosed with cancer following pathology review of the biopsy specimen, and high-grade cancer was defined by a biopsy Gleason sum score of 7 or higher. A suspicious DRE included a report of nodularity, firmness, induration, or asymmetry at the most recent DRE relative to the biopsy. Prostate volume (mls) was measured by transrectal ultrasound (TRUS) during the prostate biopsy procedure. PSA density was calculated ($\text{PSA (ng/ml)} / \text{volume (mls)}$) as an index of PSA produced per unit of prostate. Family history of prostate cancer was ascertained from the surgical chart and by a structured research questionnaire administered to each participant at recruitment. Subjects with a family history recorded on the medical chart or reporting a family history by questionnaire were considered positive for a family history. Severity of lower urinary tract symptoms (LUTS) was initiated in 2008 using the International Prostate Symptom Score, and 379 participants provided LUTS severity scores.

As a part of the pre-biopsy clinic visit, all subjects record all current medications on a medication record form. Subjects are instructed to make a list of all current medications at home or to bring their medications to this clinic visit. Medications reported on the medication record form were entered into the subject's computerized medical record. However, duration of drug use was not recorded. Prior to biopsy, the surgeon reviews responses with the subject to confirm current medication status for the listed drugs. Additionally, the surgeon makes specific queries for drugs that might affect bleeding, blood pressure, or clotting during the biopsy procedure. In addition to the statins, prescription and non-prescription medications to treat CVD, diabetes, hyperlipidemia, and benign prostatic hyperplasia were ascertained, as well as regular use of aspirin and other prescription and non-prescription non-steroidal anti-inflammatory drugs (NSAIDs). Drugs formulated as a combination of two or more active drugs were re-classified by the component drugs.

Data Analysis

From the 2,509 consenting subjects, we excluded men with atypia or uncertain pathology findings ($n=44$), or taking exogenous testosterone ($n=24$) or a steroid reductase inhibitor (finasteride, dutasteride, $n=156$). We also excluded 11 men with a BMI less than 18.5 to reduce any influence of severe morbidity, and 126 participants were excluded because prostate volume or PSA data were missing from the medical record. The analytic study population involved 2,148 participants, including 844 cancer cases, 185 PIN cases, and 1119 controls without cancer or PIN at biopsy.

The association between statin use and the number of prior PSA tests or DREs was first evaluated using a Mantel-Haenszel chi-square test. Ordinal logistic regression was also used to calculate odds ratios and 95% confidence intervals summarizing the association between statin use and an increasing number of prior screening tests while adjusting for age (continuous), race (black, white, other), family history (Y/N), prostate volume (continuous), BMI (categorized as 18.5-<25, 25-<30, 30-<35, 35 or more) aspirin use (Y/N), treatment for BPH (Y/N), treatment for diabetes (Y/N), treatment for CVD (Y/N), waist-hip ratio (WHR: categorized at quartiles), and height (categorized at quartiles). A similar approach using standard multivariable logistic regression was used to determine the association between statin use and DRE frequency and results.

Mean PSA levels, PSA density, and prostate volume were compared between statin users vs. statin non-users within a multivariable linear model. The distributions of PSA level and prostate volume data were natural log transformed prior to analysis. We compared PSA and volume scores between statin users and non-users while adjusting for age, race, family history, number of prior PSA tests, BMI, WHR, height, treatment for BPH, diabetes, or CVD, and the diagnosis of PIN, low-grade cancer, or high-grade cancer following biopsy. Models may also include PSA levels or prostate volume, as indicated within the text. PSA and prostate volume scores were back-transformed and geometric mean values and percent differences are reported. Separate analyses were developed to investigate the consistency of associations between statin use and PSA or prostate volume by diagnostic category. Tests for interaction were determined by a cross-product term between statin use and diagnosis in the presence of each main-effect and other covariates.

Multivariable logistic regression was used to investigate the association between statin use and the risk of high-grade prostate cancer, low-grade prostate cancer, or PIN. Participants without cancer or PIN at biopsy served as controls, allowing equal data collection and recruitment protocols across case and control participants while reducing the prevalence of latent disease in the control series as much as possible. The impact of prostate screening factors on these associations was evaluated by re-running the analyses after including covariates for the number of prior PSA tests, prostate volume, PSA levels and other parameters.

Results

Study Population

Participants included men between 40 and 94 years of age, with an average age of 65.1 years (Table 1). Approximately 34% had a BMI of 30 or more, 11% were of non-white race/ethnicity, and 52% were without cancer or PIN at biopsy. The majority of participants were taking medications for the treatment of CVD, including amlodipine (n=201), atenolol (n=137), enalapril (n=38), hydrochlorothiazide (n=231), lisinopril (n=365), or other medications. Approximately 13% were being treated for diabetes, including thiazolidinediones (n=71), metformin (n=165), insulin (n=52), sulfonoureas (n=124), or other medications. Almost 20% of participants were being treated for BPH symptoms with alfuzosin (n=36), tamsulosin (n=236), or similar medications.

Statin Use

Almost 40% of participants were taking a cholesterol lowering medication. Statin use (n=783, 36.5%) included simvastatin (n=314), atorvastatin (n=275), lovastatin (n=77), rosuvastatin (n=66), pravastatin (n=36), and fluvastatin (n=15). There were 74 participants taking a non-statin lipid medication, including ezetimibe (n=25), fenofibrate (n=21), gemfibrozil (n=8), cholestyramine (n=5), and niacin (n=24) (not mutually exclusive). Statin

users tended to be older than non-statin users, and also had a higher BMI and WHR, were more likely to take aspirin regularly, and were more likely to be treated for diabetes or CVD (Table 1).

Statins and Frequency of PSA or DRE

The likelihood of having an additional PSA tests moderately increased 13% among men taking any cholesterol lowering medication (OR=1.13 (0.96, 1.32); statin use: OR=1.12 (0.95, 1.32); age-adjusted). This association was seen only among men later diagnosed with cancer (any tx: OR=1.27 (0.99, 1.64); statin use: OR=1.24 (0.96, 1.61)). Further adjustment for factors potentially related to screening frequency reduced the strength of the association between cholesterol lowering medication and PSA testing frequency, while age, PSA level, WHR, and treatment for CVD remained significantly associated with the number of prior PSA tests (all $p < 0.05$). Cholesterol lowering medication was not significantly associated with the number of prior DREs, a suspicious DRE (OR=1.00 (0.81, 1.23)), or the likelihood of moderate or severe LUTS (IPSS > 7: OR =1.25 (0.79, 1.99); $n=315$ participants not under treatment for BPH, and adjusted for age and diagnostic group).

Statins in Association with PSA and Prostate Volume

Cholesterol-lowering medication use was associated with an approximately 8% smaller prostate volume ($p < 0.001$) and a 12% lower PSA level ($p < 0.001$) (Table 3). Cholesterol-lowering medication use was not significantly associated with PSA density. A similar pattern was seen among statin users and among men taking a non-statin medication, although the number of non-statin users was limited and associations were not statistically significant.

We further explored the effects of each statin on PSA and prostate volume. Simvastatin was significantly associated with a smaller prostate volume, but was not significantly associated with PSA levels. Atorvastatin, in contrast, was significantly associated with lower PSA levels. Rosuvastatin was marginally associated with prostate volume and PSA levels, while fluvastatin, lovastatin, and pravastatin uses were rare and not associated with prostate volume or PSA. Additional exclusion of participants using other types of lipid lower medications did not substantially affect the results.

Statins in Association with PSA and Prostate Volume; by Diagnostic Group

Age-adjusted mean PSA levels were highest among high-grade cancer cases (8.5 ng/ml), but similar among low-grade cancer cases (5.5 ng/ml), PIN cases (5.5 ng/ml), and controls (4.8 ng/ml). High-grade cancer cases also had the smallest prostate size (age-adjusted mean = 33.5 mls), followed by low-grade cases (39.0 mls), PIN cases (44.3 mls), and controls (46.6 mls). Statin use was associated with lower PSA levels and a smaller prostate volume within participants found to have cancer, PIN, or a negative biopsy (Table 4). Tests for interaction between statin use and diagnostic group were not significant. Differences in PSA levels were larger with atorvastatin use, and atorvastatin use was significantly associated with lower PSA levels among high-grade cancer cases and within control participants with a negative biopsy. Simvastatin use was associated with prostate volume across diagnostic groups, with statistically significant differences among cancer cases.

Statins and Prostate Cancer

Statin use was similar between cases and controls (Gleason 8-10 cancer (35.0%); Gleason 7 cancer (38.0%); Gleason 6 cancer (38.6%), PIN (31.9%), and Controls (36.2%), $p=0.57$). Use of cholesterol lowering medication or a statin was not significantly associated with prostate cancer or PIN (Table 5). Controlling for prostate volume, an increasing number of

PSA tests, and PSA levels had little substantive effect on these relationships. Since atorvastatin and simvastatin had separate relationships with PSA or prostate volume, we explored the separate associations between atorvastatin and simvastatin with cancer and PIN. Atorvastatin was significantly associated with increased risk of low-grade prostate cancer (OR=1.50 (1.08, 2.08)), while simvastatin was associated with reduced risk of PIN (OR=0.43 (0.24, 0.78)).

Discussion

Statin use was significantly associated with lower PSA levels and a smaller prostate volume, marginally associated with increased PSA testing frequency, but not associated with DRE or LUTS severity. Statin-specific analyses found atorvastatin use was significantly associated with PSA levels, while simvastatin was significantly associated with prostate volume. Statin use was not significantly associated with prostate cancer or PIN, although exploratory analyses found simvastatin was associated with a reduced risk of PIN while atorvastatin was associated with an increased risk of Gleason 6 prostate cancer.

PSA

We confirmed and further generalize the results from several recent studies reporting lower PSA levels among statin users in the U.S. general population (16), a Veteran's Administration hospital (17), or in study populations of men with or without prostate cancer (10,13,14,23,24). Thus, while statins seem to affect blood PSA levels to some extent, the mechanisms mediating such an affect remain unclear. Statin use may limit steroid hormone synthesis by limiting the production of lipid precursors, however statin use has not been associated consistently with androgen levels (25). Nevertheless, prior studies suggest that the effect of statins may be mediated through lower blood lipid levels (2,17), and our observation that statin and non-statin cholesterol medications had similar associations with PSA levels may support a mediating role for blood lipids. Statins also may alter the activity of Ras and Ras-like proteins, CEBPE/F, p21, p27, and elements of the MAPK and PI3K-ATK pathways (26), further affecting NF-kB activation and the inflammatory response (4) and possibly preventing PSA escape to the vasculature.

Prostate Volume

Prostate enlargement is common as men age (27), and clinical BPH and prostate enlargement have, to varying degrees, been associated with obesity (28), hypertension (29) and serum LDL levels (30). We found that statin use was associated with an 8% smaller prostate volume, independent of diagnostic group, BMI, or aspirin use. Higher cholesterol levels have been associated with prostate tissue inflammation (14), and inflammatory infiltrates within the prostate may generate a tissue microenvironment conducive to prostate enlargement, BPH, or prostate cancer (31). The cholesterol precursor squalene was also associated with a diagnosis of prostate cancer (32). Thus, perhaps cholesterol lowering medications sufficient to control hyperlipidemia are also able to reduce tissue inflammation, avoiding inflammation-induced cell damage and proliferation, and delaying prostate cancer or BPH progression. We considered the possibility that a smaller prostate size improves biopsy efficiency to detect high-grade prostate cancer (18), but the effects of statins on prostate size were consistent across Gleason grades and we did not see substantive differences in cancer Gleason scores between statin users and non-users.

Our exploration of statin sub-types found the decrease in prostate size associated with simvastatin use, and that controlling for the effects of simvastatin on prostate volume accounted for somewhat lower PSA levels among simvastatin users. In contrast, atorvastatin use was not significantly associated with prostate volume. These statin-specific associations

were not hypothesized prior to the study, but if true may be related to differences in drug lipophilicity, binding affinity to targeted proteins, or alternatively there could be underlying differences between atorvastatin and simvastatin users that were not controlled in our analyses. Interestingly, the Finnish section of the ERSPCS found hydrophilic statins similar to atorvastatin were more strongly associated with prostate cancer prevention than other statins, while Moyad and colleagues reported that atorvastatin improved biochemical progression-free survival following brachytherapy (33). Gene expression and protein expression profiles within prostate tissue are needed to characterize the effects of specific statins.

PSA Testing Frequency

Several studies now report that statin use is associated with having at least one PSA test (7-9,11,15). Differences in health-seeking behaviors between statin users vs. non-users may involve the willingness to attend more frequent healthcare visits and routine blood collection over an extended period of time to monitor blood lipid levels among men treated for dyslipidemia. There was a marginally significant increase in the number of PSA tests among men receiving cholesterol lower medication, such that the age-adjusted likelihood of having a follow-up PSA test increased about 13% among men taking cholesterol lowering medications. This pattern was similar among statin users, although not as strong. Furthermore, these relationships were specific to participants harboring as yet undiagnosed prostate cancer. In our study, statin use was significantly associated with treatment for comorbidities, aspirin use, and obesity, and an association between cholesterol lowering medication use and PSA testing practices may reflect some fundamental differences in healthcare practice patterns between men receiving routine medical care to monitor lipid profiles. Controlling for factors related to comorbidity status reduced the association with PSA testing somewhat, although not completely. Enhanced PSA testing was somewhat greater among men diagnosed with low grade disease (not shown), and may suggest a more frequent screening procedures among statin users with marginal PSA levels. A DRE would not be routinely performed during clinical follow-up for dyslipidemia, and we found no association between statin use and DRE frequency or DRE results.

Statins, Prostate Cancer, and PIN

Protective associations between statin use and advanced prostate cancer were reported in the HPFS and the CPS-II (8,9). These studies collected PSA test history data from study participants and concluded that differences in the likelihood of a prior PSA test with statin use did not substantially affect their results. The Olmsted County study reported statin use was associated with a decreased risk of prostate cancer and high-grade prostate cancer after controlling for diabetes, CVD, BPH treatment, and NSAID use (10). Interestingly, the CMHS also found extended statin use was associated with decreased prostate cancer risk, although the majority of men had been screened and most prostate cancer was diagnosed as localized disease (11). Perhaps the strongest control for preferential prostate cancer detection, however, was within a recent analysis from the Finnish arm of the European Randomized Study of Prostate Cancer Screening (13). PSA test administration was standardized within the intervention design, and statin use was associated with a lower risk of early-stage or low-grade prostate cancer and a suggested but non-significant protective association with advanced prostate cancer. In contrast to the above, we found cholesterol-lowering medications were not significantly associated with prostate cancer or PIN. Our analysis shares components of the CMHS and ERSPCS analyses in that the study population had access to healthcare and prostate cancer screening. We were also able to control for potential sources of detection bias associated with PSA testing frequency, PSA levels, and prostate size, hypothesizing that the any protective association may develop once we controlled for differences in screening and detection. However adjusting for these factors did

not substantially change the associations, or somewhat attenuated the association. It is possible that statins inhibit prostate carcinogenesis during an earlier phase than we were able to observe, and a protective association between simvastatin and PIN may support this possibility. Also, an association may have developed if we had data regarding duration of statin use. It may also be possible that statin users with latent cancer were selectively referred for biopsy, independent of PSA testing frequency, PSA levels, and prostate size. To produce a 'null' association, statin users with latent cancer need to be preferentially biopsied up to a level almost identical to controls without latent cancer (see Results). To the extent that such a selective referral by undiagnosed disease could also be selective for specific statins, this could also contribute to the observed significant increased risk of Gleason 6 prostate cancer associated with atorvastatin. Prostate size differed between diagnostic groups, and prostate enlargement may be a contributing factor toward LUTS severity and thus perhaps biopsy referral. However, consistent with a prior study (19) we did not find an association between statin use and LUTS severity. Prior case-control and cohort analyses have reported a modest increase in risk of prostate cancer associated with statin use (12,15). However, a positive association between atorvastatin and Gleason 6 prostate cancer may also be a chance finding, and this is first investigation of statin use and PIN risk. As such, replication of statin-specific associations is required.

Strengths and Limitations

Strengths of this study include ability to ascertain PSA testing history, blood PSA levels, DRE results, LUTS, and prostate volume in a single study population. We also were able to ascertain prostate cancer screening data and the types of statins used through medical chart review, minimizing error and avoiding potential reporting biases. The usual concerns of response bias derived from missing data on medication reporting forms are minimized because all patients must complete these forms prior to biopsy. All drug intakes were captured prior to biopsy or subject's knowledge of disease status, removing the potential for recall bias. Furthermore, evaluation of subjects seeking a diagnostic biopsy provided a means to control for selective biopsy referral and PSA testing practices previously shown to be associated with statin use and known to determine stage at diagnosis. We were also able to identify PIN cases and subjects without latent cancer or PIN at biopsy, reducing a null bias that can occur when cancer cases or PIN cases are included in the control group. Our investigation of PIN cases also allowed us to consider a pre-cancer phenotype and evaluate an earlier phase of prostate carcinogenesis. Body size was measured by trained staff and standardized protocols. Participants taking finasteride or dutasteride were removed from the analysis, and we controlled for the use aspirin, BMI, WHR, and other treatment for BPH, diabetes, or CVD.

An important limitation of this analysis is that we were unable to capture with confidence data regarding duration or dose of statin use. Prior studies report a weaker association, or no association, between current statin use and prostate cancer (9,11), and it is possible that we might have seen a stronger association among those participants with extended statin use. As discussed above, a null-bias or spurious positive association between statin use and prostate cancer could occur if statin users with latent cancer selectively receive biopsy beyond controlling for PSA, prostate volume, PSA testing frequency, aspirin, obesity, and comorbidity.

Conclusions

Statin use was significantly associated with lower PSA levels and a smaller prostate volume, and marginally associated with an increasing frequency of PSA testing among men suspected of harboring latent cancer. Among men referred for prostate biopsy, statin use was not consistently associated with a diagnosis of prostate cancer, although exploratory

analyses found simvastatin and atorvastatin were associated with PIN or low-grade cancer, respectively. Selective referral for biopsy associated with statin use is an essential element to address in future evaluations of statins and prostate cancer prevention.

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Table 1

Study Population Description (n=2148)

Factor	Level	No Statin Use		Statin Use		p
		n	%	n	%	
Age (years)	40 – <50	65	4.8%	11	1.4%	
	50 – <60	359	26.3%	146	18.7%	
	60 – <70	527	38.6%	357	45.6%	
	70 – <80	340	24.9%	228	29.1%	
	80 – ≤94	74	5.4%	41	5.2%	<0.001
BMI	18.5 - < 25	305	22.3%	121	15.4%	
	25 - < 30	627	45.9%	365	46.6%	
	30 - < 35	327	24.0%	212	27.1%	
	35 or more	106	7.8%	85	10.9%	<0.001
	Less than 0.97	356	26.1%	158	20.2%	
WHR	0.97 - < 1.00	184	13.5%	88	11.2%	
	1.00 - < 1.05	437	32.0%	257	32.8%	
	1.05 or more	388	28.4%	280	35.8%	<0.001
	Less than 170	289	21.2%	184	23.5%	
	170 - < 175	375	27.5%	225	28.7%	
Height (cm)	175 - <179	300	22.0%	173	22.1%	
	179 or more	401	29.3%	201	25.7%	0.267
	African American	149	10.9%	80	10.2%	
	White	1204	88.2%	699	89.3%	
	Other*	12	0.9%	4	0.5%	0.549
Family	Yes	288	21.1%	165	21.1%	
History	No / Unsure	1077	78.9%	618	78.9%	0.989
Non-Statin	Yes	74	5.4%	140	17.9%	<0.001
Cholesterol Tx	No	1291	94.6%	643	82.1%	
Aspirin	Yes	363	26.6%	421	53.8%	
	No	1002	73.4%	362	46.2%	<0.001
BPH Tx	Yes	258	18.9%	170	21.7%	

Factor	Level	No Statin Use			Statin Use			p
		n	%	n	%	n	%	
Diabetes Tx	No	1107	81.1%	613	78.3%	0.117		
	Yes	120	8.8%	161	20.6%			
CVD Tx	No	1245	91.2%	622	79.4%	<0.001		
	Yes	628	46.0%	581	74.2%			
Diagnosis	No	737	54.0%	202	25.8%	<0.001		
	Cancer (Gleason 8-10)	95	7.0%	51	6.5%			
	Cancer (Gleason 7)	160	11.7%	98	12.5%			
	Cancer (Gleason 6)	270	19.8%	170	21.7%			
	PIN	126	9.2%	59	7.5%			
	Negative for cancer and PIN	714	52.3%	405	51.7%	0.557		

* Other includes self-defined race/ethnicity as Hispanic (10), Asian (4) and Muslim (2).

Table 2

Treatment with Statins and the number of prior PSA tests or DREs

		# PSA tests			Any Cholesterol Tx			Statin		
		n	%		n	%		n	%	
All	1	823	38.3%		315	38.3%		286	34.8%	
	2	652	30.4%		259	39.7%		240	36.8%	
	3 or more	673	31.3%		283	42.1%		257	38.2%	
			P*			0.14			0.17	
Cancer			OR (95% CI)**		1.13 (0.96, 1.32)			1.12 (0.95, 1.32)		
			OR (95% CI)***		1.01 (0.84, 1.21)			1.01 (0.85, 1.21)		
	1	349	41.4%		132	37.8%		120	34.4%	
	2	247	29.3%		102	41.3%		95	38.5%	
PIN	3 or more	248	29.3%		116	46.8%		104	41.9%	
			P			0.09			0.17	
			OR (95% CI)		1.27 (0.99, 1.64)			1.24 (0.96, 1.61)		
			OR (95% CI)		1.18 (0.89, 1.57)			1.15 (0.87, 1.53)		
Controls	1	57	30.8%		18	31.6%		16	28.1%	
	2	57	30.8%		24	42.1%		22	38.6%	
	3 or more	71	38.4%		24	33.8%		21	29.6%	
			P			0.46			0.42	
Controls			OR (95% CI)		1.02 (0.59, 1.78)			0.98 (0.55, 1.73)		
			OR (95% CI)		0.87 (0.45, 1.69)			0.76 (0.39, 1.48)		
	1	417	37.3%		165	39.6%		150	35.9%	
	2	348	31.1%		133	38.2%		123	35.3%	
Controls	3 or more	354	31.6%		143	40.4%		132	37.3%	
			P			0.84			0.86	
			OR (95% CI)		0.98 (0.78, 1.22)			1.00 (0.80, 1.25)		
			OR (95% CI)		0.91 (0.71, 1.17)			0.94 (0.74, 1.21)		

* p-value from Mantel-Haenszel chi-square testing for trend across ordered categories.

** Odds ratio and 95% confidence interval for cumulative logit model, with odds ratio representing the age adjusted likelihood of treatment associated with the next higher category of PSA test number.

also adjusted for race, biopsy outcome (all only), family history, BMI, WHR, prostate volume, PSA levels, aspirin use, treatment for diabetes, BPH, or CVD.

Table 3

Adjusted Mean PSA and Prostate Volume by Statin Use

Cholesterol Treatment	Use	n	Volume (mls)	PSA (ng/ml)	PSA density
Any Tx	No	1291	41.4	6.8	0.164
	Yes	857	38.3	6.0	0.158
Statin (any)			7.9%	12.5%	4.2%
			% **		
	No	1365	41.3	6.8	0.164
	Yes	783	38.4	6.1	0.158
Non-Statins Tx *			7.6%	11.7%	3.8%
			%		
	No	1291	40.8	7.1	0.174
	Yes	74	38.8	6.3	0.163
Simvastatin			5.1%	12.1%	6.6%
			%		
	No	1834	36.7	5.9	0.160
	Yes	314	33.4	5.4	0.163
Atorvastatin			10.0%	8.6%	1.3%
			%		
	No	1872	36.1	6.2	0.172
	Yes	275	34.1	5.1	0.151
Rosuvastatin			5.9%	20.9%	14.2%
			%		
	No	2081	36.8	6.1	0.165
	Yes	66	33.3	5.2	0.156
Fluvastatin			10.4%	16.7%	5.7%
			%		
	No	2132	35.2	5.4	0.154
	Yes	15	34.8	5.9	0.168
			1.2%	7.8%	8.9%
			%		
			0.910	0.698	0.643
			P		

Cholesterol Treatment	Use	n	Volume (mls)	PSA (ng/ml)	PSA density
Lovastatin	No	2070	35.5	5.5	0.154
	Yes	77	34.5	5.8	0.169
			%	6.8%	9.9%
Pravastatin			p	0.441	0.263
	No	2111	35.1	5.5	0.154
	Yes	36	34.9	5.8	0.169
			%	4.1%	3.5%
			p	0.931	0.786

Prostate volume and PSA levels were log-transformed prior to statistical analysis. Geometric mean values are reported, adjusted for age, race, biopsy outcome, family history, BMI, WHR, height, number of prior PSA tests, aspirin use, treatment for diabetes, BPH, or CVD. Analyses of specific statins also adjusted for use of other statins and use of non-statin cholesterol lowering medications

* Excludes all statin users.

** % difference: for log transformed data: % difference = $100(e^{\text{diff}} - 1)$

Table 4
Association between Statins, Simvastatin, and Atorvastatin with prostate volume and PSA; by Diagnostic Group

Any Statin	n		PSA (ng/ml)				Volume (mls)			
	No Statin	Any Statin	No Statin	Any Statin	% diff**		No Statin	Any Statin	% diff	
Cancer (G1>6)	255	149	9.3	7.9	17.0% *		34.9	32.5	7.3%	
Cancer (G1=6)	270	170	5.5	5.2	5.3%		40.7	38.1	6.7%	
PIN	126	59	5.2	4.7	10.1%		44.6	43.9	1.6%	
Negative	714	405	4.3	4.1	4.5%		48.3	44.6	8.3% *	
Simvastatin	No Simvas	Yes Simvas	No Simvas	Yes Simvas	% diff	p-int	No Simvas	Yes Simvas	% diff	0.78
Cancer (G1>6)	340	64	8.1	6.9	18.6%		34.4	30.5	12.8% *	
Cancer (G1=6)	376	64	5.2	5.1	1.9%		39.5	35.1	12.5% *	
PIN	171	14	4.8	4.6	4.5%		46.5	37.2	25.1%	
Negative	947	172	4.0	4.0	0.04%		46.2	43.8	5.4%	
Atorvastatin	No Atorvas	Yes Atorvas	No Atorvas	Yes Atorvas	% diff	p-int	No Atorvas	Yes Atorvas	% diff	0.42
Cancer (G1>6)	354	50	8.5	6.6	28.0% *		32.9	31.9	3.2%	
Cancer (G1=6)	368	72	5.4	4.8	13.2%		38.7	35.8	7.9%	
PIN	161	24	5.0	4.4	11.8%		40.2	43.0	7.1%	
Negative	990	129	4.3	3.6	18.6% *		46.6	43.5	7.2%	
				p-int						0.55

adjusted for age, race, family history, simvastatin or atorvastatin as appropriate, high-grade cancer, low-grade cancer, PIN, number of prior PSA tests, BMI, WHR, height, use of non-statin medications, treatment for CVD, diabetes, or BPH. PSA levels also adjusted for prostate volume.

* p<0.05

** % difference: for log transformed data: % difference = 100(e^{diff} - 1)

Table 5

Association between statin use and high-grade prostate cancer, low-grade prostate cancer, or PIN.

Treatment	Model*	Cancer (GI>6)		Cancer (GI=6)		PIN	
		OR	95% CI	OR	95% CI	OR	95% CI
Any Tx	1	0.97	0.75, 1.26	1.14	0.89, 1.46	0.87	0.61, 1.24
	2	0.90	0.67, 1.20	1.06	0.82, 1.36	0.86	0.60, 1.23
Any Statin	1	0.95	0.73, 1.24	1.11	0.86, 1.42	0.82	0.57, 1.17
	2	0.90	0.67, 1.21	1.03	0.80, 1.33	0.80	0.56, 1.15
Non-Statin Tx	1	1.14	0.59, 2.23	1.38	0.73, 2.61	1.34	0.56, 3.22
	2	1.02	0.48, 2.16	1.27	0.66, 2.43	1.40	0.58, 3.38
Simvastatin	1	1.04	0.74, 1.45	0.92	0.66, 1.26	0.45	0.25, 0.80
	2	0.97	0.67, 1.42	0.87	0.62, 1.20	0.43	0.24, 0.78
Atorvastatin	1	1.08	0.75, 1.56	1.54	1.12, 2.13	1.17	0.72, 1.89
	2	1.14	0.75, 1.72	1.50	1.08, 2.08	1.17	0.72, 1.90

* Model 1: age, race, family history, BMI, WHR, height, aspirin use, and treatment for CVD, diabetes, or BPH.
 Model 2: Model 1 and PSA (continuous), prostate volume (continuous), and number of prior PSA tests (1, 2, > 2)