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Statin use and prostate cancer aggressiveness: results from the population-based North Carolina-Louisiana Prostate Cancer Project

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Abstract

Background: While statin use has been associated with reduced prostate cancer (PC) aggressiveness, the impact of race and other patient characteristics on this association is not well understood. We examined the association between statin use and PC aggressiveness in Caucasians (CA) and African Americans (AA), and explored effect modification by health-seeking behaviors associated with statin use.

Methods: Of 1,955 cases from the North Carolina-Louisiana Prostate Cancer Project (PCaP), 345 (18%) were classified as aggressive based on clinical criteria. Logistic regression was used to examine the association between statin use and PC aggressiveness, overall and stratified by race. Smoking and PSA screening were examined as effect modifiers of this association.

Results: There was an inverse association between statin use and PC aggressiveness (OR 0.70; 95%CI 0.54-0.91), with comparable effect estimates in both races. Statin use was associated with reduced odds ratios for aggressive PC in never-screened men (OR 0.71; 95%CI 0.43-1.18) and in men screened at low/recommended frequency (≤once/year; OR 0.62; 95%CI 0.42-0.91), with no association in men screened at high frequency (>once/year; OR 1.19; 95%CI 0.54-2.62). The inverse association between statins and aggressive PC was strongest in never smokers (OR 0.43; 95%CI 0.25-0.74), attenuated in former smokers (OR 0.77; 95%CI 0.54-1.09), and absent in current smokers (OR 1.27; 95%CI 0.67-2.41).

Conclusions: Statin use was associated with reduced PC aggressiveness, with strongest inverse associations in non-smokers and in men following screening recommendations.

Impact: Health-seeking behaviors associated with statin use should be considered when examining the impact of statins on PC aggressiveness.

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous cancer type in US males, and the second most common cause of male cancer deaths [1]. Aggressive disease characteristics at diagnosis, defined by biopsy Gleason sum, clinical stage and PSA level, are associated with increased prostate cancer-specific mortality [2]. As such, there is a need to identify factors which may impact the risk of aggressive prostate cancer.

Statins, a class of cholesterol-lowering drugs, are used by approximately one in every four adult males in the US population [3]. While statin use is not associated with overall prostate cancer incidence [4-7], two meta-analyses have reported an inverse association between statin use and risk of aggressive prostate cancer [5, 8]. However, many of the studies contributing to these meta-analyses were limited by incomplete assessment of type and dose of statin and use of other cholesterol-lowering drugs, as well as patient characteristics including dietary cholesterol and saturated fat intake, smoking status and PSA screening history. In addition, these prior studies were conducted in predominantly Caucasian populations, and therefore the impact of race on these associations is unknown.

Using the population-based North Carolina-Louisiana Prostate Cancer Project (PCaP), we examined associations between statin use, dose and type, and prostate cancer aggressiveness, overall and stratified by race. We explored PSA screening history as both a confounder and an effect modifier of the association between statin use and prostate cancer aggressiveness. In addition, we tested whether associations differed by smoking status, given that smoking is a known modifier of serum lipid levels.

Methods

Study population

The North Carolina-Louisiana Prostate Cancer Project (PCaP) is a population-based study of incident prostate cancer in two southern US states [9]. Men with a first diagnosis of histologically confirmed prostate cancer on or after July 1, 2004 were eligible to participate in PCaP if they were 40-79 years of age at diagnosis, could complete the study interview in English, did not live in an institution or nursing home, and were not cognitively impaired. Eligibility criteria also required men to self-identify as either African American/black (AA) or Caucasian/white (CA) in response to an open-ended question "what is your race?" Research protocols were approved by the institutional review boards at University of North Carolina, Louisiana State University Health Services Center, and Department of Defense CaP Research Program.

Exposure assessment

PCaP nurses administered a series of structured questionnaires that included baseline characteristics, PSA screening history, diet and medications, during an in-home visit conducted approximately 3 months after diagnosis [9]. PSA screening history was dichotomized as ever vs. never screened, with the never screened category including men who underwent PSA screening only within one year of diagnosis, in order to ensure that diagnostic PSA tests were not misclassified as PSA screening history. Among the ever screened, PSA screening frequency was calculated as the total number of PSA tests in the patient's lifetime divided by the number of years since the first PSA test. PSA screening frequency was dichotomized as ≤1 PSA test per year versus >1 PSA test per year, given that prostate cancer screening guidelines in place at the

time of PCaP recruitment recommended annual PSA screening. The dietary assessment instrument was a modified National Cancer Institute (NCI) Diet History Questionnaire to which numerous Southern US foods were added. Men were asked to report dietary intake during the 12 month period prior to prostate cancer diagnosis. Dietary cholesterol intake (mg per day) and the average percentage of calories obtained from saturated fat were calculated using NCI Diet Calc. Study participants gathered all prescription and non-prescription medications and supplements used in the two week period prior to interview and presented them to the nurse at the time of interview for documentation of current medication use, including type and dose. For the present analysis, we abstracted statin use [atorvastatin (lipitor, caduet), simvastatin (zocor, vytorin), rosuvastatin (crestor), lovastatin (altoprev, advicor), pravastatin (pravachol), fluvastatin (lescol)] and non-statin cholesterol-lowering drug use [niacin (niaspan, niacor), fibrate (gemfibrozil, tricor) and ezetimibe (ezetimibe, vytorin)]. Statin type was classified as hydrophilic (rosuvastatin, pravastatin) or lipophilic (atorvastatin, simvastatin, lovastatin, fluvastatin) [10]. Statin dose was converted to a simvastatin dose-equivalent, as previously described [11], and dichotomized as low/normal (≤20 mg simvastatin dose-equivalent) vs. high dose (>20 mg simvastatin dose-equivalent).

Outcome assessment

Clinical stage, biopsy Gleason sum, and PSA at diagnosis were abstracted from medical records. Prostate cancer aggressiveness was defined using these three variables as follows i) high aggressive (Gleason sum ≥8, or PSA >20 ng/ml, or (Gleason sum ≥7 and clinical stage T3-T4)), ii) low aggressive (Gleason sum <7 and clinical stage T1-T2 and PSA <10 ng/ml), ii) intermediate aggressive (all other cases), as described previously for PCaP [9]. Complete prostate cancer aggressiveness data were missing for 85 men, and these men were excluded from

our analysis. We also excluded men who were missing body mass index (BMI; n=21), smoking status (n=1) and PSA screening history (ever/never; n=196), resulting in 1,955 research subjects (n=1,037 CA and n=918 AA) eligible for the present analysis.

Statistical analysis

We examined differences in patient and tumor characteristics between CA and AA men, and between statin users and non-users, using chi-square tests for categorical variables, student's t-tests for continuous, normally-distributed variables and rank sum tests for continuous non-normally distributed variables.

Multivariable logistic regression was used to examine the association between statin use, dose and type, and prostate cancer aggressiveness (high vs. low/intermediate). We utilized a directed acyclic graph to select covariates and then performed backwards selection to build our final model which included age (continuous), race (AA, CA), site (NC, LA), BMI (continuous, log-transformed), cholesterol intake (continuous, log-transformed), percent calories from saturated fat (continuous), smoking status (never, former, current), and PSA screening history (never, ever). When examining associations between hydrophilic statins and prostate cancer aggressiveness, we excluded lipophilic statin users, and *vice versa*. We conducted a sensitivity analysis excluding men who used non-statin cholesterol-lowering drugs (22% of statin users and 7% of statin non-users). We also explored the effect of additionally adjusting models for frequency of PSA screening (never, ≤one PSA test per year, >one PSA test per year (in place of PSA screening history ever/never)), education level (less than high school, high school graduate, college graduate or some college), annual household income (<$20,000, $20,000-$50,000, $50,000-$80,000, >$80,000), and family history of prostate cancer in a first degree relative (yes,

no), in the subset of men for whom all of these data were available (n=1,507). In order to examine smoking status and PSA screening frequency as potential effect modifiers of the association between statin use and prostate cancer aggressiveness, we conducted stratified analysis by each of these health-seeking behaviors. We tested for interaction between smoking status and statin use for predicting prostate cancer aggressiveness by incorporating a cross product term into the logistic regression model, and testing its significance using the Wald test.

Statistical analyses were performed using Stata 13.1 (Stata, Corp., College Station, TX, USA). Statistical significance was two-sided with $p < 0.05$.

Results

Characteristics of study participants by race

Incident prostate cancer cases in this study included 1,037 CAs (n=487 from NC and n=550 from LA) and 918 AAs (n=424 from NC and n=494 from LA; Table 1). AAs were younger at diagnosis than CAs (62 vs. 64 mean years of age; p<0.0001). While clinical stage did not differ by race (p=0.863), AAs had a higher median PSA level than CAs (6.3 vs. 5.2 ng/ml; p<0.0001; Table 1) and were more likely to have a high biopsy Gleason sum (≥4+3; 22% vs. 18%; p=0.025) and aggressive prostate cancer (20% vs. 15%; p=0.003).

AAs were less likely than CAs to have a history of PSA screening (64% vs. 85%; p<0.0001), although the frequency of PSA screening among screened men did not differ by race (p=0.267). While the prevalence of family history of prostate cancer in a first degree relative did not differ by race (p=0.131), AAs were less highly educated (p<0.0001), reported a lower annual household income (p<0.0001) and were more likely to be current smokers than CAs (22% vs. 9%; p<0.0001; Table 1).

The prevalence of obesity, defined as BMI≥30 kg/m^2, did not differ by race (p=0.473). However, despite lower prevalence of cardiovascular disease (13% vs. 19%; p<0.0001), AAs were more likely than CAs to have co-morbid health conditions (Charlson index ≥1; 54% vs. 47%; p=0.001), including diabetes (27% vs. 17%; p<0.0001). In addition, AAs had higher dietary cholesterol intake (302 vs. 262 mg/day; p<0.0001), although the percentage of calories obtained from saturated fat was higher in CAs (11.2% vs. 10.0%; p<0.0001; Table 1).

Characteristics of study participants by statin use

Of a total of 1,955 patients, 729 (37%) were statin users at the time of interview, with the majority of statin users taking either simvastatin (38%) or atorvastatin (34%), and the remainder using rosuvastatin (10%), pravastatin (9%), lovastatin (5%) or fluvastatin (2%). Statin type or dose did not differ by race (data not shown). Statin users were older than non-users (65 vs. 62 mean years of age at diagnosis; $p<0.0001$), and were more likely to be CA (57% vs. 43%; $p=0.006$). While there were no significant differences in biopsy Gleason sum or clinical stage by statin use ($p=0.105$ and $p=0.089$, respectively), statin users had lower median PSA level (5.3 vs. 5.8 ng/ml; $p=0.0001$) and a lower frequency of aggressive prostate cancer (15% vs. 19%; $p=0.016$; Table 2).

Statin users were more likely to report a history of PSA screening, relative to non-users (85% vs. 72%; $p<0.0001$), although the frequency of PSA screening among screened men did not differ by statin use ($p=0.198$). While there was no difference in the prevalence of family history of prostate cancer, level of education or annual household income by statin use (all $p>0.198$), statin users were less likely to be current smokers (11% vs. 18%; $p<0.0001$; Table 2).

Relative to non-users, statin users were more likely to be obese (BMI$\geq$30 kg/m^2; 44% vs. 34%; $p<0.0001$) and have a co-morbid condition (Charlson index $\geq$1; 62% vs. 42%; $p<0.0001$), including diabetes (31% vs. 15%, $p<0.0001$) and cardiovascular disease (29% vs. 8%; $p<0.0001$). However, statin users had lower dietary cholesterol intake (269 vs. 288 mg/day; $p=0.0002$), although there was no difference in the percentage of calories obtained from saturated fat between statin users and non-users ($p=0.564$). Use of non-statin cholesterol-lowering drugs (niacin, fibrates or ezetimibe) was higher among statin users, relative to non-users (22% vs. 7%; $p<0.0001$).

We also examined differences in statin users vs. non-users stratified by race, and found that these aforementioned differences in tumor and patient characteristics between statin users and non-users were observed in both CAs and AAs (Supplementary Table 1).

Associations between statin use and prostate cancer aggressiveness

Of 345 (18%) incident cases of aggressive prostate cancer, 109 (32%) occurred in statin users and 236 (68%) occurred in non-users. For comparison, of 1,610 (82%) incident cases of non-aggressive prostate cancer, 620 (39%) occurred in statin users and 990 (61%) occurred in non-users. After adjusting for potential confounders, statin use was associated with a significantly reduced odds ratio (OR) for aggressive prostate cancer (OR 0.70; 95% CI 0.54-0.91; Table 3), with similar effect estimates in CAs (OR 0.66; 95% CI 0.45-0.96) and AAs (OR 0.75; 95% CI 0.51-1.09), although the association in AAs was not statistically significant. We observed similar inverse associations in men taking a low/normal statin dose (OR 0.68; 95% CI 0.47-0.99) and in men taking a high statin dose (OR 0.72; 95% CI 0.52-0.98), with no evidence for a dose-response relationship. Finally, while there was a suggestion of a stronger protective effect with hydrophilic relative to lipophilic statins (OR 0.49; 95% CI 0.27-0.88 and OR 0.74; 95% CI 0.56-0.98, respectively), these estimates were somewhat imprecise due to low numbers of men using hydrophilic statins and should be interpreted cautiously. Excluding men using non-statin cholesterol-lowering drugs or additionally adjusting our models for PSA screening frequency, education level, annual household income and family history of prostate cancer did not alter our findings (Supplementary Tables 2 and 3, respectively).

Impact of health-seeking behaviors on the association between statin use and prostate cancer aggressiveness

In order to further explore possible PSA screening-related detection biases, we examined PSA screening frequency as an effect modifier of the association between statins and prostate cancer aggressiveness. We observed an inverse association between statin use and prostate cancer aggressiveness in men who were screened annually or less frequently (OR 0.62; 95% CI 0.42-0.91) and a similar, albeit slightly attenuated, inverse association in men who had never undergone PSA screening (OR 0.71; 95% CI 0.43-1.18; Table 4). However, there was no evidence for an association between statin use and prostate cancer aggressiveness in men who were screened more frequently than once a year (OR 1.19; 95% CI 0.54-2.63).

Smoking increases low-density and total cholesterol levels and decreases high-density cholesterol levels [12, 13], potentially offsetting the cholesterol-lowering effect of statin use. Indeed, we found no association between statin use and prostate cancer aggressiveness in current smokers (OR 1.27; 95% CI 0.67-2.41). In contrast, there was a strong inverse association between statin use and prostate cancer aggressiveness in never smokers (OR 0.43; 95% CI 0.25-0.74), with a slightly attenuated protective effect in former smokers (OR 0.77; 95% CI 0.54-1.09; Table 5), and a significant interaction between smoking status and statin use in predicting prostate cancer aggressiveness (Wald test; p=0.0003).

Discussion

Using data from the population-based North Carolina-Louisiana Prostate Cancer Study, we report an inverse association between statin use and aggressive prostate cancer. These findings are in agreement with the ~20-25% reduced risk of aggressive prostate cancer in statin users relative to non-users reported by two meta-analyses [5, 8]. As such, our findings strengthen existing rationale to explore a role for statins in aggressive prostate cancer prevention.

One important consideration when studying the impact of statin use on prostate cancer aggressiveness is that detection bias arising from higher rates of PSA screening in statin users could produce an inverse association with aggressive disease, irrespective of a causal relationship [14, 15]. In the present study, we found that adjusting our models for PSA screening frequency did not substantially impact our estimates. However, analyses stratified by PSA screening frequency showed a null association between statin use and prostate cancer aggressiveness in men who were screened more often than once a year, potentially attributable to underlying health issues which may have driven the higher-than-recommended frequency of PSA screening in this group. On the other hand, we observed a similar magnitude of inverse association between statin use and prostate cancer aggressiveness in men screened at low or recommended frequency (i.e., annually) and in unscreened men, suggesting that the association between statin use and prostate cancer aggressiveness cannot be completely explained by PSA screening-related detection bias. In support of these findings, inverse associations between statin use and aggressive prostate cancer have been reported both in European populations with very low screening rates [16] and in US populations with higher screening rates [17]. Moreover, an analysis of simulated datasets with different PSA screening frequencies suggested that detection bias is unlikely to explain the association between statin use and reduced risk of aggressive

prostate cancer [15]. As such, while the potential for detection bias should be considered, our findings, in addition to those from populations with different PSA screening frequencies [19], support a true association between statin use and aggressive prostate cancer.

In addition to differences in PSA screening behaviors, characteristics of statin users differ from those of non-users in a variety of ways. Data from the present study show that obesity and diabetes, both associated with increased prostate cancer-specific mortality [20, 21], were more prevalent among statin users. On the other hand, we observed that statin use was associated with health-seeking behaviors, as indicated by the higher prevalence of PSA screening, lower prevalence of smoking and reduced dietary cholesterol intake, relative to non-users. These health-seeking behaviors themselves have been associated with reduced risk of aggressive prostate cancer [14, 22-26], potentially giving rise to a "healthy-user" bias whereby the association between statin use and prostate cancer aggressiveness could be explained by the health-seeking behaviors of statin users, and not statin use *per se* [27]. In the present analysis, we found that adjusting our models for these health-seeking behaviors did not substantially impact our estimates. However, analyses stratified on smoking status revealed a strong inverse association between statin use and prostate cancer aggressiveness in never smokers, a slightly attenuated effect in former smokers, and no association in current smokers. Given that the impact of statins on prostate cancer may be mediated at least in part via their cholesterol-lowering properties [18], a smoking-related increase in cholesterol level [12, 13] could potentially offset the protective effect of statins on prostate cancer aggressiveness. If confirmed in future studies, these findings may highlight the importance of smoking cessation to maximize the protective effect of statins on prostate cancer aggressiveness, in addition to the established role of smoking cessation in cardiovascular disease risk reduction.

Our findings should be considered in light of the strengths and limitations of this study. First, statin use was captured at the time of interview, with no information regarding the timing of statin initiation relative to prostate cancer diagnosis. However, given that the majority of our study population was interacting with the health care system prior to prostate cancer diagnosis (75% of individuals had a history of PSA screening), it is likely that the majority of men indicated for statin therapy would have initiated statins before diagnosis. Indeed, a previous study reported similar rates of statin use before and after prostate cancer diagnosis [28], suggesting that the majority of post-diagnosis statin users were also users prior to diagnosis. Moreover, any potential misclassification of unexposed individuals (i.e., pre-diagnosis non-users who initiated statin use after diagnosis) as exposed individuals (i.e., pre-diagnosis statin users) would likely bias our estimates towards the null. As such, our study may have underestimated the strength of the association between pre-diagnosis statin use and prostate cancer aggressiveness. In addition, while we did not have access to data for duration of use or adherence to statin therapy, the type and dose of statin and non-statin cholesterol-lowering drugs was documented by a trained nurse, thus improving the accuracy of our exposure data. Second, while serum cholesterol measurements were unavailable, dietary cholesterol and saturated fat intake was available for all study participants, and these dietary factors are important determinants of serum cholesterol level [29]. Third, observational studies examining the association between statin use and prostate cancer are susceptible to confounding by indication, given that statin use is not randomized. However, an important strength of this study is our comprehensive assessment of clinical and demographic characteristics, in addition to health-seeking behaviors of statin users and non-users, and adjustment for these potential confounders in our analysis.

In summary, we report an inverse association between statin use and aggressive prostate cancer in both Caucasians and African Americans. Differences in patient characteristics and health-seeking behaviors by statin use should be an important consideration for future observational studies of statin use and prostate cancer, although our findings suggest that detection bias arising from higher rates of PSA screening in statin users does not entirely explain the inverse association between statin use and prostate cancer aggressiveness. The stronger protective effect of statin use in non-smokers requires confirmation in other studies, but suggests that increased efforts to reduce smoking rates in this population are warranted. Statins are well-tolerated, cost-effective and widely-prescribed cholesterol-lowering drugs, with proven benefits for cardiovascular disease prevention [30]. Given that cardiovascular disease and cancer are the two most common causes of mortality in the US [31], with prostate cancer the second most common cause of cancer death in US men [1], understanding the role of statins in aggressive prostate cancer prevention will have important public health impact.

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Table 1: Demographic and tumor characteristics of Caucasian and African American prostate cancer cases in the North Carolina-Louisiana Prostate Cancer Project

	Caucasian (n=1,037)	**African American (n=918)**	**p value**
Age at diagnosis, mean (SD)	64 (8)	62 (8)	<0.0001
Site			
North Carolina	487 (47)	424 (46)	0.732
Louisiana	550 (53)	494 (54)	
Clinical stage			
T1	580 (56)	517 (56)	0.863
T2-T4	457 (44)	401 (44)	
PSA (ng/ml), median (IQR)	5.2 (4.1-7.5)	6.3 (4.5-10.7)	<0.0001
Biopsy Gleason sum			
≤3+4	846 (82)	709 (78)	0.025
≥4+3	188 (18)	203 (22)	
Aggressive prostate cancer			
Low/Intermediate	879 (85)	731 (80)	0.003
High	158 (15)	187 (20)	
PSA screening history			
Never	158 (15)	328 (36)	<0.0001
Ever	879 (85)	590 (64)	
PSA screening frequency (among ever screened)[a]			
≤1 test per year	609 (78)	377 (75)	0.267
>1 test per year	171 (22)	123 (25)	
Family history of prostate cancer (first degree relative)[b]			
No	722 (75)	609 (72)	0.131
Yes	237 (25)	235 (28)	
Education			
Less than high school	96 (9)	263 (29)	
High school graduate	221 (21)	259 (28)	<0.0001
College graduate or some college	720 (69)	395 (43)	
Income[c]			
<$20,000	97 (10)	281 (33)	
$20,000-$50,000	281 (30)	323 (38)	<0.0001
$50,000-$80,000	231 (24)	137 (16)	
>$80,000	339 (36)	104 (12)	
Smoking status			
Never	382 (37)	279 (30)	
Former	561 (54)	439 (48)	<0.0001
Current	94 (9)	200 (22)	
BMI (kg/m^2)			
<30	644 (62)	568 (62)	0.917
≥30	393 (38)	350 (38)	
Charlson co-morbidity index			
0	557 (54)	436 (47)	0.006

≥1	480 (46)	482 (53)	
Cardiovascular disease			
No	840 (81)	795 (87)	<0.0001
Yes	192 (19)	114 (13)	
Diabetes			
No	863 (84)	676 (74)	<0.0001
Yes	170 (16)	238 (26)	
Dietary cholesterol intake (mg/day), median (IQR)	262 (180-355)	302 (209-447)	<0.0001
Percent saturated fat intake, mean (SD)	11.2 (2.7)	10.0 (2.6)	<0.0001
Non-statin cholesterol-lowering drug use			
None	868 (84)	850 (93)	<0.0001
Niacin/Fibrate/Ezetimibe	169 (16)	68 (7)	

[a]PSA screening frequency was missing for 99 Caucasian and 90 African American men; [b]Family history was missing for 78 Caucasian and 74 African American men; [c]Income was missing for 13 Caucasian and 30 African American men while 76 Caucasian and 43 African American men refused to answer this question

Table 2: Demographic and tumor characteristics of statin users and non-users in the North Carolina-Louisiana Prostate Cancer Project

	Statin non-users (n=1,226)	Statin users (n=729)	p value
Age at diagnosis, mean (SD)	62 (8)	65 (7)	<0.0001
Race			
Caucasian	621 (51)	416 (57)	0.006
African American	605 (49)	313 (43)	
Site			
North Carolina	592 (48)	319 (44)	0.052
Louisiana	634 (52)	410 (56)	
Clinical stage			
T1	706 (58)	391 (54)	0.089
T2-T4	520 (42)	338 (46)	
PSA, median (IQR)	5.7 (4.3-9.6)	5.3 (4.2-7.7)	0.0001
Biopsy Gleason sum			
≤3+4	961 (79)	594 (82)	0.105
≥4+3	259 (21)	132 (18)	
Aggressive prostate cancer			
Low/Intermediate	990 (81)	620 (85)	0.016
High	236 (19)	109 (15)	
PSA screening			
Never	365 (30)	121 (17)	<0.0001
Ever	861 (70)	608 (83)	
PSA screening frequency (among ever screened)[a]			
≤1 test per year	590 (79)	396 (75)	0.098
>1 test per year	160 (21)	134 (25)	
Family history of prostate cancer (first degree relative)[b]			
No	827 (73)	504 (76)	0.198
Yes	309 (27)	163 (24)	
Education			
Less than high school	293 (19)	120 (16)	
High school graduate	303 (25)	177 (24)	0.200
College graduate or some college	684 (56)	431 (59)	
Income[c]			
<$20,000	246 (22)	132 (20)	
$20,000-$50,000	368 (33)	236 (35)	0.403
$50,000-$80,000	225 (20)	143 (21)	
>$80,000	287 (25)	156 (23)	
Smoking status			
Never	417 (34)	244 (33)	
Former	593 (48)	407 (56)	<0.0001
Current	216 (18)	78 (11)	
BMI (kg/m^2)			
<30	807 (66)	405 (56)	<0.0001
≥30	419 (34)	324 (44)	

Charlson co-morbidity index			
0	713 (58)	280 (38)	<0.0001
≥1	513 (42)	449 (62)	
Cardiovascular disease			
No	1,122 (92)	513 (71)	<0.0001
Yes	96 (8)	210 (29)	
Diabetes			
No	1,042 (85)	497 (69)	<0.0001
Yes	181 (15)	227 (31)	
Dietary cholesterol intake (mg/day)	288 (198-408)	269 (180-369)	0.0002
Percent saturated fat intake, mean (SD)	10.6 (2.7)	10.7 (2.8)	0.564
Non-statin cholesterol-lowering drug use			
None	1,146 (93)	572 (78)	<0.0001
Niacin/Fibrate/Ezetimibe	80 (7)	157 (22)	

[a]PSA screening frequency was missing for 111 statin non-users and 78 statin users; [b]Family history missing for 90 statin non-users and 62 statin users; [c]Income was missing for 28 statin non-users and 15 statin users, while 72 statin non-users and 47 statin users refused to answer this question

Table 3: Associations between statin use, dose and type and prostate cancer aggressiveness, overall and stratified by race

	All		Caucasian		African American	
	n, cases (aggressive)	**OR* (95% CI)**	**n, cases (aggressive)**	**OR* (95% CI)**	**n, cases (aggressive)**	**OR* (95% CI)**
Statin use						
No use	1,226 (236)	1.00 (ref)	621 (103)	1.00 (ref)	605 (133)	1.00 (ref)
Use	729 (109)	0.70 (0.54-0.91)	416 (55)	0.66 (0.45-0.96)	313 (54)	0.75 (0.51-1.09)
Statin dose[a]						
No use	1,226 (236)	1.00 (ref)	621 (103)	1.00 (ref)	605 (133)	1.00 (ref)
Low/normal	299 (43)	0.68 (0.47-0.99)	179 (25)	0.70 (0.43-1.15)	120 (18)	0.64 (0.37-1.13)
High	430 (66)	0.72 (0.52-0.98)	237 (30)	0.63 (0.40-1.10)	193 (36)	0.81 (0.53-1.26)
Statin type[b]						
No use	1,226 (236)	1.00 (ref)	621 (103)	1.00 (ref)	605 (133)	1.00 (ref)
Hydrophilic	129 (14)	0.49 (0.27-0.88)	82 (8)	0.42 (0.19-0.93)	47 (6)	0.57 (0.24-1.48)
Lipophilic	598 (94)	0.74 (0.56-0.98)	334 (47)	0.72 (0.48-1.07)	264 (47)	0.78 (0.52-1.15)

*****adjusted for age, race (except for analyses stratified by race), site, BMI, cholesterol intake, percent saturated fat intake, smoking status, PSA screening history

[a]low/normal dose≤20mg simvastatin or equivalent; high dose>20mg simvastatin or equivalent

[b]Hydrophilic=rosuvastatin, pravastatin; Lipophilic=atorvastatin, simvastatin, lovastatin, fluvastatin

Table 4: Associations between statin use and prostate cancer aggressiveness, stratified by PSA screening frequency

	Total cases, n	Aggressive, n (%)	OR* (95%CI)
Never screened			
Statin non-users	365	102 (28)	1.00 (ref)
Statin users	121	28 (23)	0.71 (0.43-1.18)
≤ 1 PSA tests per year			
Statin non-users	590	96 (16)	1.00 (ref)
Statin users	396	52 (13)	0.62 (0.42-0.91)
> 1 PSA tests per year			
Statin non-users	160	37 (10)	1.00 (ref)
Statin users	134	28 (13)	1.19 (0.54-2.62)

*adjusted for age, race, site, BMI, cholesterol intake, percent saturated fat intake, smoking status

Table 5: Associations between statin use and prostate cancer aggressiveness, stratified by smoking status

	Total cases, n	Aggressive, n (%)	OR* (95%CI)
Never smokers			
Statin non-users	417	68 (16)	1.00 (ref)
Statin users	244	23 (9)	0.43 (0.25-0.74)
Former smokers			
Statin non-users	593	113 (19)	1.00 (ref)
Statin users	407	65 (16)	0.77 (0.54-1.09)
Current smokers			
Statin non-users	216	55 (25)	1.00 (ref)
Statin users	78	21 (27)	1.27 (0.67-2.41)

*adjusted for age, race, site, BMI, cholesterol intake, percent saturated fat intake, PSA screening history