Statin use, high cholesterol and prostate cancer progression; results from HCaP-NC

Emma H. Allott[1,2,3], Laura Farnan[4], Susan E. Steck[5], Lixin Song[6], Lenore Arab[7], L. Joseph Su[8], Elizabeth T.H. Fontham[9], James L. Mohler[4,10,11], Jeannette T. Bensen[4,12]

[1]Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC

[2]Department of Histopathology and Morbid Anatomy, Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland

[3]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA

[4]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

[5]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC

[6]School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, NC

[7]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA

[8]Winthrop P Rockefeller Cancer Institute and College of Public Health, University of Arkansas for Medical Sciences, Little Rock, AR

[9]School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA

[10]Department of Urology, Roswell Park Comprehensive Cancer Center, Buffalo, NY

[11]Department of Urology, University of North Carolina at Chapel Hill, Chapel Hill, NC

[12]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC

Running title: Statins and prostate cancer progression

Corresponding author: Dr. Emma H. Allott, Department of Nutrition, CB 7461, University of North Carolina at Chapel Hill, 135 Dauer Drive, Chapel Hill, NC 27599, USA. Phone: +1 919-966-7230; Fax: +1 919-966-2089; E-mail: allott@email.unc.edu

Number of text pages: 18 (text pages, including title page and references); **Number of Tables:** 3; **Number of Figures:** 1

Financial support: This work was supported by the American Institute for Cancer Research (EHA) and the Irish Cancer Society John Fitzpatrick Fellowship (EHA). The North Carolina-Louisiana Prostate Cancer Project (PCaP) and the Health Care Access and Prostate Cancer Treatment in North Carolina (HCaP-NC) study are carried out as collaborative studies supported by the Department of Defense contract DAMD 17-03-2-0052 and the American Cancer Society award RSGT-08-008-01-CPHPS, respectively.

Conflicts of interest: The authors declare no conflicts of interest

Author Contributions: Conception and design (EHA, SES, JTB); data acquisition (LA, LJS, LF, ETHF, JLM, JTB, SES), analysis and interpretation of data (EHA, SES, JTB), manuscript writing (EHA), review and approval of manuscript (all authors).

Keywords: access to care, health literacy, high cholesterol, prostate cancer progression, race, radiation, radical prostatectomy, statin

Abstract

Background: Statin use is associated with lower advanced prostate cancer risk and reduced prostate cancer-specific mortality, but prior studies were conducted mainly in white men. We examined the effect of statin use on risk of prostate cancer progression in a population-based, minority-enriched cohort.

Methods: We used data from prostate cancer cases (45% African American) diagnosed between 2004 and 2007 who participated in the Health Care Access and Prostate Cancer Treatment in North Carolina cohort (HCaP-NC). We abstracted statin use at diagnosis. Men reported if they had ever been diagnosed with high cholesterol. Multivariable Cox proportional hazards analysis was used to examine associations between statin use and risk of prostate cancer progression (biochemical recurrence or secondary treatment), overall and by race. In secondary analysis, we examined the association between high cholesterol and risk of progression, overall and by statin use.

Results: Of 669 men, 244 (36%) were statin users at diagnosis. During 3.8 years median follow-up, 138 men experienced prostate cancer progression. There was no association between statin use and risk of progression, either overall (HR 1.03; 95% CI 0.72-1.46) or stratified by race. High cholesterol was inversely associated with risk of progression, particularly among statin users (HR 0.43; 95% CI 0.20-0.94; *p-interaction*=0.22) and in men with higher perceived access to care (HR 0.57; 95% CI 0.36-0.90; *p-interaction*=0.03).

Conclusions: Statin use at diagnosis was not associated with prostate cancer progression in the population-based, minority-enriched HCaP-NC. Greater healthcare engagement, including actively controlling serum cholesterol, may be linked to better prostate cancer-specific outcomes.

Introduction

Epidemiologic data strongly support an association between statin use and reduced risk of advanced prostate cancer [1, 2]. In addition, studies have shown that statin use in men diagnosed with prostate cancer is associated with a lower risk of prostate cancer recurrence [3] and decreased prostate cancer-specific mortality [4]. However, the vast majority of past research was conducted in white men, and studies exploring these associations in minority-enriched populations are few. Moreover, few prior studies of statin use and prostate cancer incorporated data for high serum cholesterol, a primary indication for use of the cholesterol-lowering statins.

Previously, we reported that statin use was inversely associated with prostate cancer aggressiveness in the population-based, minority-enriched North Carolina-Louisiana Prostate Cancer Project (PCaP) [5]. Herein, using data from the PCaP follow-up study, the Health Care Access and Prostate Cancer Treatment in North Carolina (HCaP-NC) cohort, we investigated the association between statin use at diagnosis and risk of prostate cancer progression, overall and by race. Further, we examined associations between high serum cholesterol and risk of prostate cancer progression, overall and stratified by statin use. We hypothesized that 1) statin use would be associated with reduced risk of prostate cancer progression, and 2) high serum cholesterol would be associated with increased risk of prostate cancer progression, particularly among non-statin-users.

Methods

Study population

The North Carolina-Louisiana Prostate Cancer Project (PCaP) is a population-based cohort of European American (EA) and African American (AA) men diagnosed with incident prostate cancer between July 2004 and October 2007 [6]. Briefly, eligible men were 40–79 years old at prostate cancer diagnosis, able to complete the study interview in English, did not live in an institution (i.e., nursing home), and were not cognitively impaired at the time of interview. Moreover, eligible men had to self-identify as AA/black or Caucasian/white (EA) in response to the open-ended question, “What is your race?” In 2008, North Carolina PCaP participants were invited to participate in the follow-up study, HCaP-NC, which involved completing follow-up questionnaires and providing permission for medical record release annually [7]. Follow-up questionnaires and medical records were received for a total of three years (2008 – 2011) for n=822 (80%) of baseline PCaP participants from North Carolina (n=1,031). Differences between those with and without follow-up medical records have been described [7].

Exposure and covariate assessment

PCaP nurses administered a series of structured questionnaires that included baseline characteristics, prostate cancer screening history and medication use during an in-home visit conducted approximately three months after diagnosis [6]. Height and weight were measured by the nurse during the in-home visit and used to calculate body mass index (BMI). Prostate cancer screening history was based on self-report and was defined as having at least one prostate-specific antigen (PSA) test or digital rectal exam (DRE) prior to the screening test that led to prostate cancer diagnosis. Clinical stage, biopsy Gleason sum, and serum PSA at diagnosis were abstracted from medical records, and high aggressive prostate cancer was defined as Gleason sum ≥8, or PSA >20 ng/ml, or Gleason sum ≥7 and clinical stage T3-T4,

consistent with prior PCaP studies [6]. Research subjects gathered all prescription medications used in the 2-week period prior to interview and presented them to the research nurse at the time of interview for documentation of statin use. Statin dose was converted to a simvastatin dose-equivalent, as previously described [8], and dichotomized as low/normal (≤20 mg simvastatin dose-equivalent) vs. high dose (>20 mg simvastatin dose-equivalent) [5]. Data regarding duration of statin use were not collected in this study.

Questionnaires administered in follow-up year 1 asked research subjects “Has a doctor or health professional EVER told you that you have or had high cholesterol?” In follow-up years 2 and 3, research subjects were asked this same question. If their response was “yes”, they had the option to indicate “I already had this at my last interview, but since then it has: A) gotten better, B) gotten worse, or C) stayed the same.” We recoded high cholesterol as ever vs. never. Among those ever told that they had high cholesterol, we further categorized this variable as those with cholesterol levels that improved during the follow-up period vs. those whose cholesterol levels stayed the same. We did not make a separate category for men with worsening cholesterol levels as numbers were few (n=12) and instead excluded them from the relevant analyses.

Health literacy was assessed using the Rapid Estimate of Adult Literacy in Medicine (REALM), a validated reading recognition test comprised of 66 health-related words to screen adult reading ability in medical settings, categorized as 0-18, 19-44, 45-60, >60 [9]. Since few research subjects fell into the lower categories, we dichotomized this variable as high (>60) vs. medium/low (≤60). Perceived access to care was measured using a nine-item questionnaire resulting in a normally-distributed summed score with values ranging from nine to 45 [10]; this variable was dichotomized above and below the mean score (<39 vs. ≥39).

Outcome assessment

Our primary outcome was prostate cancer progression. Research subjects treated initially with radical prostatectomy (RP, n=482; 72%) were categorized as having a prostate cancer progression event if they had biochemical persistence, biochemical recurrence (BCR), or received secondary treatment. Persistence was defined as not achieving undetectable PSA within 6 months after surgery. Men with persistence were recorded as having prostate cancer progression at 90 days after surgery, since RP typically produces undetectable PSA within 90 days. BCR was defined according to the American Urological Association (AUA) as undetectable PSA after RP that was followed by a PSA ≥0.2 ng/ml, confirmed with a second PSA ≥0.2 ng/ml. BCR was recorded at the date of first PSA ≥0.2 ng/ml. Secondary treatment included radiation, androgen deprivation therapy (ADT), or chemotherapy. Neoadjuvant radiation or neoadjuvant ADT, defined as radiation or ADT initiated ≤6 months after RP, was not considered secondary treatment. Research subjects were recorded as having a progression event on the date the secondary treatment began.

Research subjects treated initially with radiation (external beam or brachytherapy, n=244; 28%) were categorized as having a prostate cancer progression event if they had BCR or received secondary treatment. BCR was determined using the Phoenix definition and was defined as nadir (lowest PSA achieved after radiation) + 2 ng/ml [11]. Men with BCR were recorded as having prostate cancer progression at the first PSA that was 2 ng/ml above nadir. Secondary treatment for prostate cancer included ADT or chemotherapy. Neoadjuvant ADT, defined as ADT initiated ≤1 year after start of radiation, was not considered secondary treatment. Research subjects were recorded as having a prostate cancer progression event on the date the secondary treatment began.

Prostate cancer progression was not determined for men if they: (i) received no treatment or only watchful waiting (n=59); (ii) received ADT as the primary treatment (n=31); (iii) underwent radical prostatectomy but no PSAs were measured within 6 months of surgery (n=33); or (iv)

information essential to determine progression status was missing, including missing treatment date or PSA values (n=24). Ultimately, prostate cancer progression was determined for 672 (82%) research subjects in HCaP-NC.

Statistical analysis

Of 672 men with progression data, we excluded three men who were missing BMI data, leaving 669 research subjects included in our analysis. We examined differences in baseline characteristics according to statin use and high cholesterol status 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.

We conducted Cox proportional hazards analysis to test the association between statin use and dose at diagnosis and risk of prostate cancer progression, overall and stratified by race. For multivariable models, covariates were selected based on known confounders in the literature. We performed backwards selection (using $p<0.1$ as the criteria to retain covariates) to build our final model, which included age at diagnosis (continuous), race (EA, AA; except for analyses stratified by race) and obesity status (BMI <30, ≥30 kg/m^2). We examined log-log plots and assessed Schoenfeld residuals to confirm that none of our exposure variables or covariates violated the proportional hazards assumption. Given data supporting radio-sensitizing properties of statins [12], we conducted exploratory analysis stratified by primary treatment type (RP vs. radiation), but this produced similar findings (data not shown). We explored sensitivity analyses where models were further adjusted for tumor aggressiveness (low/medium, high) and prostate cancer treatment (RP, radiation). In addition, we further adjusted statin models for self-reported history of high cholesterol. As this did not substantially alter our results, these findings are not presented. We also examined whether changes in cholesterol levels during the follow-up period modified the association between statin use at diagnosis and risk of prostate cancer progression.

In secondary analysis, using the same approach as described for statins, we examined the association between high cholesterol and risk of prostate cancer progression, overall and stratified by statin use at diagnosis. We explored health literacy and perceived access to care as effect modifiers of the association between self-reported high cholesterol and prostate cancer progression. We tested for interaction between these variables and high cholesterol for predicting risk of progression by incorporating a cross-product term into the model and testing its significance using the Wald test.

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

Results

Characteristics of the HCaP-NC cohort by statin use and high cholesterol status

Statin users comprised 36% of the HCaP-NC cohort, and were older at diagnosis than non-users ($p<0.001$; Table 1). Neither race nor tumor characteristics (clinical stage, biopsy Gleason sum, prediagnosis PSA or tumor aggressiveness) differed by statin use (all $p\geq0.17$). However, statin users were more likely to report a history of prostate cancer screening than non-users ($p=0.017$). Relative to non-users, statin users were more likely to receive radiation as primary treatment for prostate cancer ($p<0.001$). There were no differences in first-degree family history of prostate cancer, education, income level, or smoking status by statin use. However, relative to non-users, statin users were more likely to be obese ($p<0.001$) and more likely to have at least one comorbid condition ($p<0.001$), including diabetes (27% vs. 14%; $p<0.001$) and high cholesterol (91% vs. 48%; $p<0.001$; Table 1). Relative to statin users who reported high cholesterol, statin users who did not report a history of high cholesterol (n=22; 9%) were more likely to have diabetes (41% vs. 25%), another indication for statin use [13].

Research subjects reporting a history of high cholesterol comprised 64% of our cohort (Supplementary Table 1). Age, race and tumor characteristics did not differ by self-reported history of high cholesterol, and neither did primary treatment type, education, income, health literacy or perceived access to care. However, men with high cholesterol were more likely to be obese (42% vs. 31%) and have at least one co-morbid condition, including diabetes (23% vs. 11%). Just over half (52%) of men reporting a history of high cholesterol were statin users at diagnosis (Supplementary Table 1).

Statin use and risk of prostate cancer progression

Of 669 research subjects, 138 (21%) experienced prostate cancer progression. Median follow-up among men who did not progress was 3.8 years. Kaplan Meier curves showed no

association between statin use at diagnosis and risk of prostate cancer progression (log-rank p=0.892; Figure 1A). In multivariable analysis, there was no association between statin use at diagnosis and risk of prostate cancer progression (HR 1.03; 95% CI 0.72-1.46; Table 2). Neither was there any significant association between higher statin dose and risk of prostate cancer progression. Similar null associations were observed in both EA and AA men. Further adjusting our models for tumor aggressiveness and prostate cancer treatment did not substantially alter these findings (data not shown). Analyses stratified by change in cholesterol levels during follow-up produced similarly null findings (Supplementary Table 2).

High cholesterol and risk of prostate cancer progression

High cholesterol was not associated with risk of prostate cancer progression on univariable analysis (log-rank p=0.245; Figure 1B). High cholesterol remained unassociated with risk of progression after adjusting for age, race and obesity status (HR 0.80; 95% CI 0.57-1.14; Table 3). However, stratification by statin use revealed a significant inverse association among statin users (HR 0.43; 95% CI 0.20-0.94) but not non-users (HR 0.86; 95% CI 0.56-1.36), though no significant interaction was found between cholesterol and statin use in association with prostate cancer progression (p-interaction=0.22). The inverse direction of association between cholesterol and risk of progression contradicted our hypothesis. Therefore, we conducted exploratory analyses stratified by surrogates of healthcare engagement in an attempt to better understand this relationship. We found a suggestion of a stronger inverse association between self-reported high cholesterol and risk of prostate cancer progression among men with high versus low/medium health literacy (Supplementary Table 3). Furthermore, analyses stratified by perceived access to care revealed that self-reported high cholesterol was inversely associated with risk of prostate cancer progression only among men with greater perceived access to care (p-interaction=0.03; Supplementary Table 3).

Discussion

Mounting epidemiologic evidence links statins with reduced risk of advanced prostate cancer diagnosis, lower risk of prostate cancer progression, and decreased prostate cancer-specific mortality [1, 2]. However, the majority of prior studies were conducted in white men, and thus this association has not been well tested in AAs. Herein, using data from the HCaP-NC population-based study comprising 42% AAs, we found that statin use at the time of diagnosis was unrelated to risk of prostate cancer progression. As such, our results do not support an association between statin use and risk of prostate cancer progression in this minority-enriched population.

Only two prior studies, to our knowledge, examined associations between statin use and prostate cancer risk or progression in AAs. The prospective Southern Community Cohort Study, comprised of 67% AAs, reported no significant association between statin use and risk of either overall or advanced prostate cancer, with no differences by race [14]. An analysis of the Veterans Administration-based SEARCH database, comprised of 44% AAs, reported a significant inverse association between post-diagnosis statin use and risk of biochemical recurrence in non-AA, but not in AA men [3]. In the present study, race-stratified analyses did not support an association between statin use and risk of progression overall, or in EAs or AAs. If future studies find that associations between statin use and prostate cancer-specific outcomes are weaker in AAs, this may help to explain the lack of association between statin use and prostate cancer progression in the present analysis which contained large numbers of AAs. Possible racial differences in associations between statin use and prostate cancer-specific outcomes, if confirmed by future studies, could be attributable to as yet undefined biologic (e.g. racial differences in molecular tumor subtype [15]) and/or non-biologic (e.g. racial differences in adherence to statin therapy, health-seeking behaviors) mechanisms [16].

In contrast to the strong epidemiologic evidence linking statins and prostate cancer, data from human studies supporting a role for serum cholesterol in prostate cancer are less clear. Results from a large consortium showed a weak association between high serum cholesterol and increased risk of high-grade prostate cancer [17], and several large studies examining the effect of high serum cholesterol on prostate cancer-specific mortality reported null to weakly positive findings [18-20]. However, a recent analysis of data from a series of RP patients in Switzerland found that high levels of low-density lipoprotein (LDL), measured the day before surgery, were associated with a reduced risk of BCR [21]. Another RP series from Japan also found that high serum cholesterol levels, measured shortly after diagnosis, were associated with reduced risk of BCR [22]. These authors acknowledged that their findings could be explained by reverse causation, where cholesterol uptake by the growing tumor can lower serum levels thereby producing a spurious inverse association between high cholesterol and more aggressive disease [23]. Our findings from the present study also showed an inverse direction of association between a self-reported history of high cholesterol and risk of prostate cancer progression. However, we do not expect that self-reported history of high cholesterol would be affected by tumor aggressiveness, and therefore our findings cannot be explained by reverse causality. Instead, we found that the inverse association between high cholesterol and risk of progression was more pronounced in statin users as well as in men with higher health literacy levels and greater perceived access to care. Only 55% of the 78 million US adults with high cholesterol are taking medication to control cholesterol levels [24], as reflected in the present study where 52% of men with high cholesterol were taking statins. Therefore, it may be that men who self-reported a history of high cholesterol but who were taking statins to control cholesterol levels were more engaged in their healthcare, and that this and other related behaviors contributed to improved prostate cancer-specific outcomes in these men.

Our findings should be considered in the context of study limitations. Statin use was assessed roughly three months after prostate cancer diagnosis, and we do not have data on duration of statin use before diagnosis nor were we able to assess whether statin users continued on statins during follow-up. Any misclassification of statin use would be expected to be non-differential with regard to the progression outcome and would likely bias associations towards the null. Second, with a median follow-up of 3.8 years, we were unable to examine the effect of statin use on risk of longer-term outcomes including prostate cancer-specific mortality. Finally, our sample size was somewhat limited and we may have had insufficient power to detect significant associations, particularly for stratified analyses. These limitations are balanced by a number of important strengths, which include the racial and socioeconomic diversity of HCaP-NC and its population-based study design. We were able to incorporate data regarding health literacy and perceived access to care as potential effect modifiers of associations between self-reported high cholesterol and prostate cancer progression, whereas many observational studies do not have access to these data. Moreover, previous studies have mostly been limited to a single treatment modality (e.g. RP [3]), whereas this study includes men treated with RP or radiation and thus may be more generalizable to all prostate cancer patients.

In conclusion, our study does not support an inverse association between statin use and prostate cancer progression in a minority-enriched cohort. Future studies, potentially incorporating biomarkers to classify prostate cancer subtypes with distinct biology, are required to identify specific populations that could benefit from statin use with respect to prostate cancer-specific outcomes.

Acknowledgements: The authors thank the staff, advisory committees and research subjects participating in the PCaP and HCaP-NC studies for their important contributions.

References

1. Alfaqih MA, Allott EH, Hamilton RJ, Freeman MR, and Freedland SJ. The current evidence on statin use and prostate cancer prevention: are we there yet? Nat Rev Urol 2017;14:107-119.
2. Mucci LA and Kantoff PW. Is the Evidence Sufficient to Recommend Statins for All Men With Prostate Cancer? J Clin Oncol 2017;35:3272-3274.
3. Allott EH, Howard LE, Cooperberg MR, et al. Postoperative statin use and risk of biochemical recurrence following radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. BJU Int 2014.
4. Yu O, Eberg M, Benayoun S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol 2014;32:5-11.
5. Allott EH, Farnan L, Steck SE, et al. Statin use and prostate cancer aggressiveness: results from the population-based North Carolina-Louisiana Prostate Cancer Project. Cancer Epidemiol Biomarkers Prev 2016.
6. Schroeder JC, Bensen JT, Su LJ, et al. The North Carolina-Louisiana Prostate Cancer Project (PCaP): methods and design of a multidisciplinary population-based cohort study of racial differences in prostate cancer outcomes. Prostate 2006;66:1162-76.
7. Khan S, Cai J, Nielsen ME, et al. The Association of Diabetes and Obesity With Prostate Cancer Progression: HCaP-NC. Prostate 2017;77:878-887.
8. Hamilton RJ, Banez LL, Aronson WJ, et al. Statin medication use and the risk of biochemical recurrence after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) Database. Cancer 2010;116:3389-98.
9. Davis TC, Crouch MA, Long SW, et al. Rapid assessment of literacy levels of adult primary care patients. Fam Med 1991;23:433-5.
10. Ellis SD, Blackard B, Carpenter WR, et al. Receipt of National Comprehensive Cancer Network guideline-concordant prostate cancer care among African American and Caucasian American men in North Carolina. Cancer 2013;119:2282-90.
11. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965-74.
12. Hutchinson J and Marignol L. Clinical Potential of Statins in Prostate Cancer Radiation Therapy. Anticancer Res 2017;37:5363-5372.
13. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
14. Kantor ED, Lipworth L, Fowke JH, Giovannucci EL, Mucci LA, and Signorello LB. Statin use and risk of prostate cancer: Results from the Southern Community Cohort Study. Prostate 2015;75:1384-93.
15. Faisal FA, Sundi D, Tosoian JJ, et al. Racial Variations in Prostate Cancer Molecular Subtypes and Androgen Receptor Signaling Reflect Anatomic Tumor Location. Eur Urol 2015.
16. Lewey J, Shrank WH, Bowry AD, Kilabuk E, Brennan TA, and Choudhry NK. Gender and racial disparities in adherence to statin therapy: a meta-analysis. Am Heart J 2013;165:665-78, 678 e1.
17. Bull CJ, Bonilla C, Holly JM, et al. Blood lipids and prostate cancer: a Mendelian randomization analysis. Cancer Med 2016;5:1125-36.

18. Batty GD, Kivimaki M, Clarke R, Davey Smith G, and Shipley MJ. Modifiable risk factors for prostate cancer mortality in London: forty years of follow-up in the Whitehall study. Cancer Causes Control 2011;22:311-8.
19. Haggstrom C, Stocks T, Nagel G, et al. Prostate cancer, prostate cancer death, and death from other causes, among men with metabolic aberrations. Epidemiology 2014;25:823-8.
20. Huxley R. The impact of modifiable risk factors on mortality from prostate cancer in populations of the Asia-Pacific region. Asian Pac J Cancer Prev 2007;8:199-205.
21. Wettstein MS, Saba K, Umbehr MH, et al. Prognostic Role of Preoperative Serum Lipid Levels in Patients Undergoing Radical Prostatectomy for Clinically Localized Prostate Cancer. Prostate 2017;77:549-556.
22. Ohno Y, Ohori M, Nakashima J, et al. Association between preoperative serum total cholesterol level and biochemical recurrence in prostate cancer patients who underwent radical prostatectomy. Mol Clin Oncol 2016;4:1073-1077.
23. Law MR and Thompson SG. Low serum cholesterol and the risk of cancer: an analysis of the published prospective studies. Cancer Causes Control 1991;2:253-61.
24. Mercado C, DeSimone AK, Odom E, Gillespie C, Ayala C, and Loustalot F. Prevalence of Cholesterol Treatment Eligibility and Medication Use Among Adults--United States, 2005-2012. MMWR Morb Mortal Wkly Rep 2015;64:1305-11.

Table 1: Demographic and tumor characteristics of HCaP-NC research subjects according to statin use at diagnosis

	Statin non-users	Statin users	*p value*
N (%)	425 (64)	244 (36)	
Age at diagnosis, mean (SD)	60.8 (7.8)	63.3 (7.0)	<0.001
Race, n (%)			
African American	198 (47)	102 (42)	0.231
European American	227 (53)	142 (58)	
Clinical stage, n (%)			
T1	266 (63)	149 (61)	0.587
T2-T4	155 (37)	95 (39)	
missing	4	0	
PSA, median (IQR)	5.5 (4.3-8.3)	5.2 (4.2-7.4)	0.170
Biopsy Gleason grade, n (%)			
≤3+4	355 (84)	203 (84)	0.844
≥4+3	67 (16)	40 (16)	
missing	3	1	
Aggressive prostate cancer, n (%)			
Low/Intermediate	368 (87)	213 (87)	0.795
High	57 (13)	31 (13)	
Prostate cancer screening history, n (%)			
No	57 (14)	19 (8)	0.017
Yes	348 (86)	223 (92)	
missing	20	2	
Primary treatment, n (%)			
Radical prostatectomy	324 (76)	158 (65)	0.001
Radiation	101 (24)	86 (35)	
Family history of prostate cancer in a first-degree relative, n (%)			
No	307 (74)	179 (77)	0.509
Yes	107 (26)	55 (24)	
missing	11	10	
Education, n (%)			
Less than high school	66 (15)	27 (11)	
High school graduate	101 (24)	60 (25)	0.309
College graduate or some college	259 (61)	157 (64)	
Income, n (%)			
<$20,000	60 (15)	27 (12)	
$20,000-$50,000	135 (34)	80 (34)	0.509
$50,000-$80,000	84 (21)	58 (25)	
>$80,000	123 (30)	69 (29)	
missing	23	10	
Smoking status, n (%)			
Never	160 (38)	76 (31)	
Former	205 (48)	140 (57)	0.075
Current	60 (14)	28 (11)	
Obesity status, BMI (kg/m^2), n (%)			
<30	284 (67)	130 (53)	0.001
≥30	141 (33)	114 (47)	
Charlson co-morbidity index, n (%)			
0	269 (63)	111 (45)	<0.001
≥1	156 (37)	133 (55)	
Diabetes, n (%)			
No	367 (86)	177 (73)	<0.001

Yes	58 (14)	65 (27)	
missing	0	2	
Ever diagnosed with high cholesterol, n (%)			
No	222 (52)	22 (9)	<0.001
Yes	203 (48)	222 (91)	
Serum cholesterol change during follow-up, n (%)			
Stayed the same	52 (34)	86 (47)	
Got worse	7 (5)	5 (3)	0.043
Improved	95 (62)	92 (50)	

Table 2: Hazard ratios and 95% confidence intervals for associations between statin use at diagnosis and risk of prostate cancer progression in HCaP-NC

	Overall			European American			African American		
	N, total	**N (%), progressed**	**HR[a] (95% CI)**	**N, total**	**N (%), progressed**	**HR[a] (95% CI)**	**N, total**	**N (%), progressed**	**HR[a] (95% CI)**
Statin use									
No use	425	86 (20)	1.00 (Ref)	227	39 (17)	1.00 (Ref)	198	47 (24)	1.00 (Ref)
Use	244	52 (21)	1.03 (0.72-1.46)	142	25 (18)	0.93 (0.55-1.57)	102	27 (26)	1.12 (0.69-1.82)
Statin dose[b]									
No use	425	86 (20)	1.00 (Ref)	227	39 (17)	1.00 (Ref)	198	47 (24)	1.00 (Ref)
Low/normal	94	25 (27)	1.31 (0.83-2.05)	60	13 (22)	1.15 (0.60-2.18)	34	12 (35)	1.43 (0.75-2.73)
High	150	27 (18)	0.86 (0.55-1.33)	82	12 (15)	0.78 (0.40-1.50)	68	15 (22)	0.95 (0.52-1.72)

[a]adjusted for age, race, and obesity status (except for analyses stratified by race which are adjusted for age and obesity only)
[b]Low/normal dose ≤20 mg simvastatin or equivalent; high dose >20 mg simvastatin or equivalent

Table 3: Hazard ratios and 95% confidence intervals for high serum cholesterol in association with risk of prostate cancer progression, overall and stratified by statin use at diagnosis in HCaP-NC

	Overall			Statin non-users			Statin users		
	N, total	**N (%), progressed**	**HR[a] (95% CI)**	**N, total**	**N (%), progressed**	**HR[a] (95% CI)**	**N, total**	**N (%), progressed**	**HR[a] (95% CI)**
High cholesterol									
Never	244	55 (23)	1.00 (Ref)	222	47 (21)	1.00 (Ref)	22	8 (36)	1.00 (Ref)
Ever	425	83 (20)	0.80 (0.57-1.14)	203	39 (19)	0.86 (0.56-1.32)	222	44 (20)	0.43 (0.20-0.94)

[a]adjusted for age, race, and obesity status

Supplementary Table 1: Demographic and tumor characteristics of HCaP-NC research subjects according to history of high cholesterol

	Never had high cholesterol	Ever had high cholesterol	*p value*
N (%)	244 (36)	425 (64)	
Age at diagnosis, mean (SD)	61.1 (8.2)	62.1 (7.3)	0.097
Race, n (%)			
European American	125 (51)	244 (57)	0.122
African American	119 (49)	181 (43)	
Clinical stage, n (%)			
T1	144 (59)	271 (64)	0.169
T2-T4	100 (41)	150 (36)	
missing	0	4	
PSA, median (IQR)	5.6 (4.4-8.5)	5.2 (4.2-7.7)	0.124
Biopsy Gleason grade, n (%)			
≤3+4	203 (84)	355 (84)	0.989
≥4+3	39 (16)	68 (16)	
missing	2	2	
Aggressive prostate cancer, n (%)			
Low/Intermediate	211 (86)	370 (87)	0.830
High	33 (14)	55 (13)	
Prostate cancer screening history, n (%)			
No	35 (15)	41 (10)	0.052
Yes	198 (85)	373 (90)	
missing	11	11	
Primary treatment, n (%)			
Radical prostatectomy	179 (73)	303 (71)	0.566
Radiation	65 (27)	122 (29)	
Family history of prostate cancer (first degree relative), n (%)			
No	178 (74)	308 (75)	0.814
Yes	61 (26)	101 (25)	
missing	5	16	
Medical literacy, n (%)			
REALM ≤60	77 (32)	112 (26)	0.146
REALM >60	166 (68)	312 (74)	
missing	1	1	
Perceived access to care, n (%)			
<39	117 (48)	183 (43)	0.203
≥39	126 (52)	242 (57)	
missing	1	0	
Education, n (%)			
Less than high school	32 (13)	60 (14)	
High school graduate	57 (23)	104 (24)	0.859
College graduate or some college	155 (64)	261 (61)	
Income, n (%)			
<$20,000	34 (15)	53 (13)	
$20,000-$50,000	67 (29)	148 (37)	0.195
$50,000-$80,000	51 (22)	91 (22)	
>$80,000	79 (34)	113 (28)	
missing	13	20	
Smoking status, n (%)			
Never	80 (33)	156 (37)	0.586
Former	130 (53)	215 (51)	

Current	34 (14)	54 (13)	
Obesity status, BMI (kg/m^2), n (%)			
<30	169 (69)	245 (58)	0.003
≥30	75 (31)	180 (42)	
Charlson co-morbidity index, n (%)			
0	168 (69)	212 (50)	<0.001
≥1	76 (31)	213 (50)	
Diabetes, n (%)			
No	217 (89)	327 (77)	<0.001
Yes	27 (11)	96 (23)	
missing	0	2	
Statin use, n (%)			
No	222 (91)	203 (48)	<0.001
Yes	22 (9)	222 (52)	

Supplementary Table 2: Hazard ratios and 95% confidence intervals for statin use at diagnosis in association with risk of prostate cancer progression stratified by history of high cholesterol in HCaP-NC

	Never had high cholesterol			Ever had high cholesterol; cholesterol levels remained the same during follow up			Ever had high cholesterol; cholesterol levels improved during follow up		
	N, total	**N (%), progressed**	**HR[a] (95% CI)**	**N, total**	**N (%), progressed**	**HR[a] (95% CI)**	**N, total**	**N (%), progressed**	**HR[a] (95% CI)**
Statin use									
No	222	47 (21)	1.00 (Ref)	54	8 (15)	1.00 (Ref)	95	22 (23)	1.00 (Ref)
Yes	22	8 (36)	1.74 (0.82-3.72)	86	19 (22)	1.38 (0.58-3.26)	92	17 (18)	0.83 (0.44-1.60)

[a]adjusted for age, race, and obesity status

Supplementary Table 3: Hazard ratios and 95% confidence intervals for high serum cholesterol in association with risk of prostate cancer progression, stratified by health literacy and perceived access to care in HCaP-NC

	Low/medium health literacy[a]			High health literacy[a]			
	N, total	**N (%), progressed**	**HR[c] (95% CI)**	**N, total**	**N (%), progressed**	**HR[c] (95% CI)**	***p-interaction***
High cholesterol							
Never	77	16 (21)	1.00 (Ref)	166	39 (23)	1.00 (Ref)	
Ever	112	28 (25)	1.11 (0.60-2.07)	312	55 (18)	0.70 (0.46-1.06)	*0.37*
	Low perceived access to care[b]			**High perceived access to care[b]**			
	N, total	**N (%), progressed**	**HR[c] (95% CI)**	**N, total**	**N (%), progressed**	**HR[c] (95% CI)**	

High cholesterol							
Never	117	21 (18)	1.00 (Ref)	126	34 (27)	1.00 (Ref)	
Ever	183	42 (23)	1.24 (0.73-2.11)	242	41 (17)	0.57 (0.36-0.90)	*0.03*

[a]Health literacy classified as Rapid Estimate of Adult Literacy in Medicine (REALM) score >60 (high) vs. ≤60 (low/medium)
[b]Perceived Access To Care score classified as <39 (low) vs. ≥39 (high)
[c]adjusted for age, race, and obesity status