

Racial Differences in the Association Between Preoperative Serum Cholesterol and Prostate Cancer Recurrence: Results from the SEARCH Database

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Abstract

Background: Black men are disproportionately affected by both cardiovascular disease and prostate cancer. Epidemiologic evidence linking dyslipidemia, an established cardiovascular risk factor, and prostate cancer progression is mixed. As existing studies were conducted in predominantly non-black populations, research on black men is lacking.

Methods: We identified 628 black and 1,020 non-black men who underwent radical prostatectomy and never used statins before surgery in the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Median follow-up was 2.9 years. The impact of preoperative hypercholesterolemia on risk of biochemical recurrence was examined using multivariable, race-stratified proportional hazards. In secondary analysis, we examined associations with low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, overall and among men with dyslipidemia.

Results: High cholesterol was associated with increased risk of recurrence in black [HR_{per10 mg/dL} 1.06; 95% confidence

interval (CI), 1.02–1.11] but not non-black men (HR_{per10 mg/dL} 0.99; 95% CI, 0.95–1.03; $P_{\text{interaction}} = 0.011$). Elevated triglycerides were associated with increased risk in both black and non-black men (HR_{per10 mg/dL} 1.02; 95% CI, 1.00–1.03 and 1.02; 95% CI, 1.00–1.02, respectively; $P_{\text{interaction}} = 0.458$). There were no significant associations between LDL or HDL and recurrence risk in either race. Associations with cholesterol, LDL, and triglycerides were similar among men with dyslipidemia, but low HDL was associated with increased risk of recurrence in black, but not non-black men with dyslipidemia ($P_{\text{interaction}} = 0.047$).

Conclusion: Elevated cholesterol was a risk factor for recurrence in black but not non-black men, whereas high triglycerides were associated with increased risk regardless of race.

Impact: Significantly contrasting associations by race may provide insight into prostate cancer racial disparities. *Cancer Epidemiol Biomarkers Prev*, 25(3); 547–54. ©2016 AACR.

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Introduction

Relative to non-black men, black men are almost twice as likely to be diagnosed with prostate cancer, and more than twice as likely to die of their disease (1). Although nonbiologic mechanisms such as access to care and socioeconomic status contribute to prostate cancer racial disparities (2), racial differences in host and tumor biology may also play a role (3).

Strong biologic rationale supports a role for cholesterol in prostate cancer pathogenesis via multiple mechanisms including Akt pathway activation (4) and intratumoral steroid biosynthesis (5), resulting in increased cellular proliferation and migration (6). However, although some epidemiologic evidence supports a positive association between cholesterol and risk of aggressive prostate cancer (7–9), not all studies have reported this finding (10–13). Similarly, the impact of hypercholesterolemia on prostate cancer recurrence and mortality is unclear. One prospective study reported that elevated cholesterol was associated with increased risk of prostate cancer-specific mortality (14), but other large prospective studies did not replicate this finding (15, 16). However, these studies were

conducted in predominantly non-black populations, and therefore the impact of race on associations between cholesterol and prostate cancer is unknown.

We examined the impact of preoperative serum lipid levels on risk of recurrence using a retrospective cohort of black and non-black prostate cancer patients who never used statins prior to radical prostatectomy from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Previously in this cohort, we reported that elevated triglycerides were associated with increased risk of prostate cancer recurrence among all men, whereas high cholesterol, high low-density lipoprotein (LDL), and low high-density lipoprotein (HDL) were associated with increased risk of recurrence only among men with dyslipidemia (17). However, due to limited numbers of patients in our prior study, we were unable to test whether associations differed between black and non-black men. Using an updated and larger cohort, the aim of the current analysis was to test for racial differences in the association between cholesterol and risk of prostate cancer recurrence. In secondary analysis, we explored associations between LDL, HDL, and triglycerides and risk of prostate cancer recurrence in black and non-black men.

Materials and Methods

Study population

The SEARCH database is a retrospective cohort of prostate cancer patients undergoing radical prostatectomy at six Veterans Administration (VA) Medical Centers (West Los Angeles, CA; Palo Alto, CA; San Diego, CA; Durham, NC; Asheville, NC; and Augusta, GA; ref. 17). Institutional Review Board approval was obtained to abstract and analyze the data. SEARCH does not include patients treated with preoperative androgen deprivation or radiotherapy. Though data in SEARCH go back to 1988, preoperative cholesterol data were limited until 1999. Therefore, given that preoperative serum cholesterol level was our primary exposure of interest for the current analysis, we limited our analyses to men treated between 1999 and 2013 ($n = 3,553$). As previously described (17), patients who used statins before surgery were excluded ($n = 920$). We also excluded patients with missing data for any preoperative serum lipid levels ($n = 724$), preoperative PSA ($n = 11$), body mass index (BMI; $n = 107$), pathologic Gleason score ($n = 12$), other pathologic features ($n = 79$), and PSA follow-up ($n = 52$). These exclusions resulted in a study population of 1,648 men, of which 628 were black and 1,020 were non-black ($n = 907$ white and $n = 112$ other race).

Exposure assessment

Fasting serum cholesterol, LDL, HDL, and triglyceride levels, measured within the year prior to radical prostatectomy, were abstracted from VA computerized medical records. Recommended cut points for normal, borderline, and high serum levels (all in mg/dL) of total cholesterol (<200, 200–239, ≥ 240), LDL (<130, 130–159, ≥ 160), HDL (<40, 40–59, ≥ 60), and triglycerides (<150, 150–199, ≥ 200) were selected according to National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP) III guidelines (18). As previously described (17), we defined dyslipidemia (abnormal/borderline vs. normal levels) for each individual lipid independently of the others.

Outcome assessment

Follow-up protocols were at the discretion of the treating physicians. Biochemical recurrence was defined as a single PSA >0.2 ng/mL, two consecutive concentrations at 0.2 ng/mL, or secondary treatment for detectable postoperative PSA. Men receiving adjuvant therapy after surgery for an undetectable PSA were considered nonrecurrent at the time of adjuvant therapy, and their follow-up was censored at that point.

Statistical analysis

Differences in demographic, clinical, and pathologic factors between black and non-black patients, overall and stratified by serum cholesterol level (<200, 200–239, ≥ 240 mg/dL) were examined using *t* tests and χ^2 tests for continuous and categorical variables, respectively, and rank-sum tests for continuous variables not normally distributed. Fisher exact test was used for categorical variables when there was a cell count <5. Differences in these factors between our cohort and men excluded from our analysis due to preoperative statin use ($n = 920$) were also examined (Supplementary Table S1).

Cox proportional hazards analysis was used to examine the impact of hypercholesterolemia on risk of prostate cancer recurrence, stratified by race (black vs. non-black). We examined cholesterol levels both as categorical [<200 (reference), 200–239, ≥ 240 mg/dL] and continuous variables, with continuous cholesterol levels presented in 10 mg/dL increments to facilitate interpretation of the HRs. Cox models were adjusted for age at surgery (continuous), preoperative PSA (continuous, log-transformed), year of surgery, preoperative BMI (continuous, log-transformed), pathologic Gleason score [2–6, 7 (3+4), 7 (4+3)–10], positive surgical margins (yes vs. no), seminal vesicle invasion (yes vs. no), and surgical center. We also adjusted Cox models for postoperative statin use as a time-dependent covariate, as described previously (17). We tested for an interaction between serum cholesterol (continuous) and race in predicting risk of recurrence by incorporating a cross-product term into our models.

In secondary analysis, we examined associations between LDL, HDL, triglycerides, and risk of prostate cancer recurrence, stratified by race (black vs. non-black), using the same approach as described for cholesterol. In addition, given our previous findings that associations between serum lipids and risk of recurrence were stronger among men with dyslipidemia (17), we repeated all of our analyses among men with dyslipidemia, treating lipid levels as continuous variables. We conducted a sensitivity analysis by excluding men of other race ($n = 112$). Although cholesterol, LDL, and HDL levels were normally distributed, the distribution of triglycerides was slightly skewed and so we performed a sensitivity analysis using log-transformed triglycerides. Given that this did not impact associations with recurrence, we present the results for untransformed triglycerides to facilitate the interpretation of our findings. We also explored the impact of excluding men with any outlying lipid value from our analysis, using the formula $<Q1 - 1.5 \times IQR$ or $>Q3 + 1.5 \times IQR$ to identify outliers. This resulted in the exclusion of 191 men, but as results were similar, these data are not presented. Finally, given the established link between dyslipidemia and increased risk of death from causes other than prostate cancer (19), we repeated our main analyses using competing risks regression, treating nonprostate cancer death as a competing risk for biochemical recurrence.

Statistical analysis was performed using Stata, version 13.0 (Stata Corp.).

Results

Patient and tumor characteristics by race

In our cohort of 628 (38%) black and 1,020 (62%) non-black men who never used statins prior to radical prostatectomy, black men were younger at the time of surgery, but there were no differences in year of surgery or median follow-up by race (Table 1). Median PSA levels were higher in black men (6.6 vs. 6.2 ng/mL; $P = 0.001$). Although black men were more likely to have positive margins ($P = 0.003$), there were no differences in rates of extracapsular extension, seminal vesicle invasion, or lymph node status by race (Table 1). Black men had higher HDL but lower triglyceride levels than non-black men, but there were no differences in BMI, prevalence of diabetes, or mean levels of cholesterol or LDL by race. In this cohort of men who never used statins prior to radical prostatectomy, black and non-black men had similar rates of statin initiation after radical prostatectomy (19% and 18%, respectively; Table 1).

Patient and tumor characteristics by serum cholesterol level, stratified by race

The prevalence of hypercholesterolemia did not differ by race, with similar proportions of black and non-black men with borderline and high preoperative cholesterol. There were no differences in pathologic Gleason score, positive margin status, extracapsular extension, seminal vesicle invasion, or lymph node status by cholesterol level in either race (Tables 2 and 3). Although BMI and prevalence of diabetes did not differ by cholesterol level, men with high cholesterol had higher LDL, HDL, and triglycerides than men with normal cholesterol, regardless of race (all $P < 0.001$). Men with high cholesterol were more likely to initiate statin use after radical prostatectomy, regardless of race ($P \leq 0.001$, Tables 2 and 3).

Associations between serum cholesterol and risk of recurrence

During a median follow-up period of 2.9 years [interquartile range (IQR) 1.4–6.2 years], 181 (29%) black and 272 (27%) non-black men experienced biochemical recurrence. After adjusting for demographic, clinical, and pathologic characteristics, high cholesterol was associated with increased risk of recurrence in black men (≥ 240 vs. < 200 mg/dL; HR 2.31; 95% CI, 1.39–3.86), with a 6% increased risk of recurrence for every 10 mg/dL increase in cholesterol (HR_{per 10 mg/dL} 1.06; 95% CI, 1.02–1.11; Table 4). In contrast, there was no association between cholesterol and risk of recurrence in non-black men, treating cholesterol either as a categorical (≥ 240 vs. < 200 mg/dL; HR 1.17; 95% CI, 0.71–1.92) or continuous variable (HR_{per 10 mg/dL} 0.99; 95% CI, 0.95–1.03). The interaction between race and cholesterol in predicting risk of recurrence was significant ($P_{\text{interaction}} = 0.011$). Excluding men of other race did not substantially impact our findings (Supplementary Table S2).

Associations between LDL, HDL, and triglycerides and risk of recurrence

There was no significant association between HDL levels and risk of recurrence in either race, treating HDL either as a categorical or continuous variable. Although there were no significant associations between LDL levels and risk of recurrence, there was a suggestion that elevated LDL was associated with increased risk of recurrence in black men (HR_{per 10 mg/dL} 1.04; 95% CI, 0.99–1.10; Table 4). Conversely, there was a suggestion of an opposite direction of association in non-black men (HR_{per 10 mg/dL} 0.98; 95% CI, 0.94–1.02), with a significant interaction between race and LDL in association with risk of recurrence ($P_{\text{interaction}} = 0.028$).

Relative to normal triglyceride levels, elevated triglycerides were associated with increased risk of recurrence in black men (≥ 200 vs. < 150 mg/dL; HR 1.75; 95% CI, 1.22–2.52), with an attenuated but similar direction of association in non-black men (HR 1.27; 95% CI, 0.94–1.72; Table 4). Treating triglycerides as a continuous variable, each 10 mg/dL increase in triglycerides was accompanied by a 2% increased risk of recurrence in both black

Table 1. Demographic, clinical, and pathologic characteristics of prostate cancer cases by race

	Black (n = 628)	Non-black (n = 1020)	P
Age, mean \pm SD	59.7 (6.4)	62.3 (5.8)	<0.001
Year of surgery, median (Q1–Q3)	2009 (2005–2011)	2009 (2004–2011)	0.407
Follow-up (years), median (Q1–Q3)	2.7 (1.2–6.0)	3.0 (1.5–6.3)	0.046
PSA (ng/mL), median (Q1–Q3)	6.6 (4.9–10.2)	6.2 (4.7–8.8)	0.001
Pathologic Gleason score, n (%)			
2–6	148 (24)	281 (28)	
7 (3+4)	284 (45)	369 (36)	0.001
7 (4+3)–10	196 (31)	370 (36)	
Positive margins, n (%)	273 (43)	369 (36)	0.003
Extracapsular extension, n (%)	109 (17)	209 (20)	0.117
Seminal vesicle invasion, n (%)	70 (11)	90 (9)	0.122
Positive lymph nodes, n (%)	20 (3)	21 (2)	0.297
BMI (kg/m ²), median (Q1–Q3)	27.7 (24.8–31.0)	28.1 (25.4–31.0)	0.122
Diabetes ^a , n (%)	65 (13)	75 (13)	0.912
Total cholesterol (mg/dL), mean \pm SD	186.3 (38.4)	186.6 (35.5)	0.855
LDL (mg/dL), mean \pm SD	111.6 (32.9)	114.1 (31.8)	0.121
HDL (mg/dL), mean \pm SD	50.0 (18.0)	44.5 (15.0)	<0.001
Triglycerides (mg/dL), mean \pm SD	124.6 (84.2)	144.2 (105.4)	<0.001
Statin use, n (%)			
Never use	509 (81)	839 (82)	0.538
Postoperative use	119 (19)	181 (18)	

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate-specific antigen; Q1, 25th percentile; Q3, 75th percentile.

^aMissing for n = 596 (36%) of cases.

Table 2. Characteristics of black men with low, borderline, and high levels of preoperative serum cholesterol

	Low cholesterol (<200 mg/dL) ($n = 416; 66\%$)	Borderline cholesterol ($200-239$ mg/dL) ($n = 166; 27\%$)	High cholesterol (≥ 240 mg/dL) ($n = 46; 7\%$)	P
Age, mean \pm SD	60.1 (6.4)	59.1 (6.4)	59.1 (6.0)	0.202
Year of surgery, median (Q1-Q3)	2009 (2005-2011)	2008 (2004-2011)	2010 (2005-2012)	0.057
Follow-up (years), median (Q1-Q3)	2.3 (0.8-4.9)	2.5 (0.8-4.4)	0.8 (0.4-2.8)	0.005
PSA (ng/mL), median (Q1-Q3)	6.4 (4.8-10.0)	6.9 (5.1-10.5)	7.5 (5.4-11.9)	0.167
Pathologic Gleason score, n (%)				
2-6	94 (23)	45 (27)	9 (20)	
7 (3+4)	179 (43)	84 (51)	21 (46)	0.071
7 (4+3)-10	143 (34)	37 (22)	16 (35)	
Positive margins, n (%)	182 (44)	71 (43)	20 (43)	0.977
Extracapsular extension, n (%)	77 (19)	24 (14)	8 (17)	0.507
Seminal vesicle invasion, n (%)	47 (11)	15 (9)	8 (17)	0.277
Positive lymph nodes, n (%)	13 (3)	5 (3)	2 (4)	0.232
BMI (kg/m^2), median (Q1-Q3)	27.5 (24.7-30.7)	27.6 (24.8-32.1)	29.1 (26.3-31.7)	0.251
Diabetes, n (%)	40 (12)	19 (15)	6 (18)	0.446
LDL (mg/dL), mean \pm SD	96.2 (22.7)	135.4 (21.7)	164.5 (38.3)	<0.001
HDL (mg/dL), mean \pm SD	47.7 (15.8)	54.6 (21.2)	54.2 (20.0)	<0.001
Triglycerides (mg/dL), mean \pm SD	115.4 (76.4)	131.8 (79.6)	181.1 (131.8)	<0.001
Statin use, n (%)				
Never use	354 (85)	121 (73)	34 (74)	0.001
Postoperative use	62 (15)	45 (27)	12 (26)	

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate-specific antigen; Q1, 25th percentile; Q3, 75th percentile.

(HR_{per 10 mg/dL} 1.02; 95% CI, 1.00-1.03) and non-black men (HR_{per 10 mg/dL} 1.02; 95% CI, 1.00-1.02), with no differences in these associations by race ($P_{\text{interaction}} = 0.458$).

Relative to normal lipid levels, there were no associations between borderline lipid levels in any lipid measure and risk of recurrence in either race (Table 4). Competing risk analysis did not substantially alter our findings (Supplementary Table S3).

Associations between serum lipids and risk of recurrence among men with dyslipidemia

Restricting analyses to men with dyslipidemia produced similar findings to those reported among all men. There was a 22% increase in risk of recurrence for every 10 mg/dL increase in cholesterol above 200 mg/dL in black men (HR_{per 10 mg/dL}

1.22; 95% CI, 1.13-1.31), with no evidence for any association in non-black men (HR_{per 10 mg/dL} 0.99; 95% CI, 0.90-1.09; Table 4). The interaction between race and serum cholesterol for predicting recurrence in men with high cholesterol levels was significant ($P_{\text{interaction}} = 0.001$).

Whereas HDL was unrelated to recurrence risk among all men, when we restricted analysis to men with low HDL (<40 mg/dL), each 10 mg/dL increase in HDL was significantly associated with reduced risk of recurrence in black (HR_{per 10 mg/dL} 0.40; 95% CI, 0.23-0.70), but not non-black men (HR_{per 10 mg/dL} 0.75, 95% CI, 0.51-1.12). The interaction between race and HDL in predicting recurrence risk was significant ($P_{\text{interaction}} = 0.047$). Although there were no significant associations between increasing LDL and risk of recurrence, the direction of the associations differed by

Table 3. Characteristics of non-black men with low, borderline, and high levels of preoperative serum cholesterol

	Low cholesterol (<200 mg/dL) ($n = 669; 65\%$)	Borderline cholesterol ($200-239$ mg/dL) ($n = 282; 28\%$)	High cholesterol (≥ 240 mg/dL) ($n = 69; 7\%$)	P
Age, mean \pm SD	62.5 (5.6)	62.1 (6.2)	62.2 (5.7)	0.671
Year of surgery, median (Q1-Q3)	2009 (2005-2011)	2007 (2003-2011)	2008 (2003-2011)	<0.001
Follow-up (years), median (Q1-Q3)	2.4 (0.9-4.5)	2.7 (0.8-6.2)	2.5 (1.5-6.2)	0.166
PSA (ng/mL), median (Q1-Q3)	6.0 (4.6-8.3)	6.9 (5.1-10.5)	6.1 (4.3-8.0)	0.001
Pathologic Gleason score, n (%)				
2-6	170 (25)	90 (32)	21 (30)	
7 (3+4)	244 (36)	94 (33)	31 (45)	0.067
7 (4+3)-10	255 (38)	98 (35)	17 (25)	
Positive margins, n (%)	236 (35)	104 (37)	29 (42)	0.517
Extracapsular extension, n (%)	125 (19)	70 (25)	14 (20)	0.101
Seminal vesicle invasion, n (%)	60 (9)	26 (9)	4 (6)	0.651
Positive lymph nodes, n (%)	12 (2)	9 (3)	0 (0)	0.301
BMI (kg/m^2), median (Q1-Q3)	28.3 (25.5-31.2)	28.0 (25.4-30.9)	27.1 (24.2-30.4)	0.147
Diabetes, n (%)	50 (14)	21 (13)	4 (11)	0.937
LDL (mg/dL), mean \pm SD	98.8 (21.8)	135.8 (21.3)	174.2 (26.8)	<0.001
HDL (mg/dL), mean \pm SD	42.4 (12.3)	48.2 (17.8)	50.6 (21.2)	<0.001
Triglycerides (mg/dL), mean \pm SD	131.3 (77.4)	157.9 (86.4)	214.2 (263.2)	<0.001
Statin use, n (%)				
Never use	580 (87)	209 (74)	50 (72)	<0.001
Postoperative use	89 (13)	73 (26)	19 (28)	

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate-specific antigen; Q1, 25th percentile; Q3, 75th percentile.

Table 4. Impact of race on associations between preoperative lipid levels and risk of prostate cancer recurrence

	Black			Non-black			<i>P</i> _{interaction}
	<i>n</i> , total (recurrences)	HR ^a (95% CI)	<i>P</i> value	<i>n</i> , total (recurrences)	HR ^a (95% CI)	<i>P</i> value	
Total cholesterol							
<200 mg/dL	416 (111)	1.00 (ref)		669 (169)	1.00 (ref)		
200–239 mg/dL	165 (52)	0.95 (0.67–1.34)	0.763	282 (85)	0.96 (0.73–1.27)	0.781	
≥240 mg/dL	46 (18)	2.31 (1.39–3.86)	0.001	69 (18)	1.17 (0.71–1.92)	0.541	
			<i>P</i> _{trend} = 0.063			<i>P</i> _{trend} = 0.827	
Per 10 mg/dL increase	628 (181)	1.06 (1.02–1.11)	0.006	1,020 (272)	0.99 (0.95–1.03)	0.557	0.011
Per 10 mg/dL increase in men with high cholesterol ^b	212 (70)	1.22 (1.13–1.31)	<0.001	351 (103)	0.99 (0.90–1.09)	0.883	0.001
LDL							
<130 mg/dL	451 (122)	1.00 (ref)		728 (188)	1.00 (ref)		
130–159 mg/dL	130 (48)	1.19 (0.84–1.67)	0.331	204 (57)	1.01 (0.74–1.38)	0.941	
≥160 mg/dL	46 (11)	1.26 (0.67–2.36)	0.479	88 (27)	1.09 (0.72–1.66)	0.675	
			<i>P</i> _{trend} = 0.263			<i>P</i> _{trend} = 0.722	
Per 10 mg/dL increase	628 (181)	1.04 (0.99–1.10)	0.079	1,020 (272)	0.98 (0.94–1.02)	0.331	0.028
Per 10 mg/dL increase in men with high LDL ^b	177 (59)	1.09 (0.97–1.24)	0.157	292 (84)	0.96 (0.85–1.08)	0.479	0.051
HDL							
≥60 mg/dL	134 (33)	1.00 (ref)		123 (31)	1.00 (ref)		
40–59 mg/dL	305 (85)	0.85 (0.56–1.31)	0.467	464 (117)	1.06 (0.69–1.62)	0.805	
<40 mg/dL	188 (63)	0.94 (0.59–1.50)	0.797	433 (124)	1.31 (0.85–2.01)	0.226	
			<i>P</i> _{trend} = 0.821			<i>P</i> _{trend} = 0.136	
Per 10 mg/dL increase	628 (181)	0.96 (0.87–1.05)	0.360	1,020 (272)	0.96 (0.88–1.05)	0.357	0.719
Per 10 mg/dL increase in men with low HDL ^b	188 (63)	0.40 (0.23–0.70)	0.001	433 (124)	0.75 (0.51–1.12)	0.159	0.047
Triglycerides							
<150 mg/dL	469 (126)	1.00 (ref)		660 (174)	1.00 (ref)		
150–199 mg/dL	66 (13)	0.67 (0.37–1.20)	0.180	178 (41)	0.86 (0.61–1.23)	0.415	
≥200 mg/dL	92 (42)	1.75 (1.22–2.52)	0.003	182 (57)	1.27 (0.94–1.72)	0.123	
			<i>P</i> _{trend} = 0.012			<i>P</i> _{trend} = 0.218	
Per 10 mg/dL increase	628 (181)	1.02 (1.00–1.03)	0.061	1,020 (272)	1.01 (1.00–1.02)	0.043	0.458
Per 10 mg/dL increase in men with high triglycerides ^b	158 (55)	1.02 (0.99–1.05)	0.268	360 (98)	1.01 (1.00–1.03)	0.074	0.488

^aHRs are adjusted for age, preoperative PSA, year of surgery, BMI, surgical center, postoperative statin use, pathologic Gleason score, positive surgical margins, extracapsular extension, and seminal vesicle invasion.

^bHigh lipid levels are defined as ≥200 mg/dL for cholesterol, ≥130 mg/dL for LDL, and ≥150 mg/dL for triglycerides, whereas low HDL levels are defined as <40 mg/dL.

race (suggestively positive in blacks but suggestively inverse in non-blacks), with a borderline significant interaction between race and LDL in predicting risk of recurrence in men with high LDL (*P*_{interaction} = 0.051).

Finally, similar to our findings among all men, each 10 mg/dL increase in triglycerides above 150 mg/dL was associated with increased risk of recurrence in both black (HR_{per 10 mg/dL} 1.02; 95% CI, 0.99–1.05) and non-black men (HR_{per 10 mg/dL} 1.01; 95% CI, 1.00–1.03; Table 4), although these associations were slightly attenuated compared with our estimates among all men. There was no significant interaction between race and triglycerides (*P*_{interaction} = 0.488).

Discussion

In this retrospective cohort of prostate cancer patients treated with radical prostatectomy, we show that the association between serum cholesterol and prostate cancer recurrence differed significantly by race, with hypercholesterolemia associated with increased risk of recurrence in black, but not non-black men. In contrast, although LDL and HDL levels were not significantly associated with risk of prostate cancer recurrence, elevated triglycerides were associated with increased risk of recurrence regardless of race. Secondary analyses among men with dyslipidemia did not substantially impact associations between cholesterol, LDL, or triglycerides and risk of recurrence, but revealed that low HDL was associated with increased risk of recurrence in black, but not non-

black men with dyslipidemia. If confirmed, these findings suggest that hypercholesterolemia may disproportionately increase risk of prostate cancer recurrence in black men, thereby providing some mechanistic insight into prostate cancer racial disparities.

Previously, we reported null associations between cholesterol and its subfractions, LDL and HDL, and risk of prostate cancer recurrence in a smaller subset of the present cohort which combined data from black and non-black men (17). Given the smaller sample size, we were unable to test for interactions by race in this prior study. Few other studies have explored associations between lipid levels and risk of prostate cancer recurrence, with no consistent findings (13,20). However, several large prospective studies in non-black populations have examined the association between dyslipidemia and prostate cancer–specific mortality. The UK Whitehall study, consisting of approximately 18,000 men and 600 prostate cancer deaths occurring during 40 years of follow-up, reported that high cholesterol was associated with a modestly elevated risk of prostate cancer–specific mortality (14). In contrast, the Metabolic Syndrome and Cancer Project, comprising almost 300,000 men from Northern Europe and over 1,000 prostate cancer deaths, reported similar rates of prostate cancer–specific mortality in men with normal versus elevated triglyceride and cholesterol levels (15). Finally, the findings of a large prospective study in the Asian-Pacific region were suggestive of a positive association between high cholesterol and increased prostate cancer–specific mortality, though associations did not reach statistical significance (16). Thus, although data are somewhat

sparse and largely represent non-black men, together these findings suggest a weak to null association between dyslipidemia and prostate cancer recurrence and mortality. However, in the current analysis, we show that when stratified by race, hypercholesterolemia was associated with a significantly increased risk of prostate cancer recurrence in black but not non-black men. Our null results in non-black men are consistent with previous studies in non-black populations, which also reported largely null findings. However, our positive findings among black men may provide rationale for future studies to explore racial differences in these associations.

Despite lower rates of visceral obesity (21, 22), and a more favorable lipid profile [including lower triglycerides (23) and higher HDL (24)], the prevalence of cardiovascular disease is higher in black, relative to non-black populations (25, 26). However, although many cardiovascular risk factors have also been implicated in prostate cancer pathogenesis (27), racial differences in associations between obesity, dyslipidemia, and prostate cancer progression have not been widely explored. In addition to evidence from the current analysis that the association between cholesterol and prostate cancer recurrence varies by race, on secondary analysis we also observed a suggestion of racial differences in associations between cholesterol subfractions, LDL and HDL, and risk of recurrence. To our knowledge, no studies have examined racial differences in associations between lipid levels and prostate cancer recurrence. However, one prior study reported that high LDL levels were associated with increased risk of prostate cancer on biopsy in black, but not non-black men (28), whereas a case-control study reported racial differences in the association between metabolic syndrome, a cluster of conditions including low HDL and high triglyceride levels, and prostate cancer risk (29). In the current study, although associations between LDL and risk of recurrence were not significant in either race, the directions of association were significantly contrasting, with LDL showing a positive association with recurrence in blacks, but an inverse association in non-blacks. Finally, we found that each 10 mg/dL increase in HDL levels among men with low HDL was significantly protective in black, but not non-black men. Although future studies are required to validate these results, our findings of racial differences in the association between dyslipidemia and prostate cancer recurrence, in particular, our primary findings for cholesterol which showed a strong racial interaction ($P = 0.001$), suggest that dyslipidemia may be a mechanism contributing to racial disparities in prostate cancer.

Our findings should be considered in light of the study's strengths and limitations. First, serum lipid measurements were obtained in the year prior to radical prostatectomy and therefore may be impacted by the presence of preclinical disease (30). However, the presence of preclinical disease would be expected to lower serum lipid levels (31), thereby biases our estimates toward the null. As such, our analyses may have underestimated the strength of the association between serum lipid levels and reduced risk of recurrence. Furthermore, bias due to reverse causation is less likely in screened populations such as ours where prostate cancer is diagnosed early in the natural history of the disease. Indeed, in our prior study in a subset of the current patient cohort, we tested the impact of excluding recurrence events within 1 year of diagnosis and found that this did not alter our findings (17). Second, given that we lacked sufficient numbers of events to explore racial differences in the association between dyslipidemia and prostate cancer-specific mortality, we examined biochemical recurrence as a

surrogate endpoint. Although time to biochemical recurrence is informative for predicting risk of prostate cancer-specific mortality, the natural history of prostate cancer following biochemical recurrence can vary greatly between individuals (32). Therefore, studies with longer follow-up are required to assess the impact of dyslipidemia on longer-term prostate cancer outcomes. Third, we did not adjust for multiple testing, and so our findings from secondary analyses of associations between triglycerides, LDL, and HDL and risk of recurrence should be interpreted with caution. Finally, we made two main sets of exclusions in this article: patients with missing lipid levels and patients who used statins prior to surgery. We previously showed that demographic, clinical, and pathologic features of patients with missing lipid levels did not differ from those without missing lipid data (17). Therefore, our missing lipid data appear to be missing at random, thereby alleviating concerns about selection bias. We acknowledge that excluding patients who used statins prior to surgery likely truncates our range of exposure by excluding many patients with high cholesterol from our analysis, thereby potentially introducing bias into our study. However, we argue that exclusion of preoperative statin users from our analysis strengthens our exposure assessment for the following reasons. First, date of preoperative statin initiation and duration of preoperative statin use are not available in this dataset. As such, we do not have access to data that would be informative in our efforts to adjust lipid levels to account for preoperative statin use. Second, inter-individual variability in the degree to which statins lower lipid levels further hampers our ability to select a constant value to add to the lipid levels of preoperative statin users. Finally, the "window of susceptibility" for serum lipids to impact prostate cancer recurrence is unknown. As such, we do not know whether lipid levels are most relevant at the time of tumor initiation or at the time of diagnosis when the tumor comes to clinical attention. Given that we only know statin use status at the time of diagnosis and not before, it may be inappropriate to add a constant value to lipid levels of statin users if their tumor developed in a lower lipid environment (i.e., if the patient was a long-term statin user). For these reasons, we believe that adjusting lipid levels to account for preoperative statin use would lead to uncertainty in the accuracy of our lipid data, and we decided instead to exclude preoperative statin users. As shown in Supplementary Table S1, men excluded from our analysis due to preoperative statin use were older at diagnosis and less likely to be black. Preoperative statin users had lower PSA and lower pathologic Gleason score, but there were no differences in other pathologic features between preoperative statin users and nonusers. Although cholesterol or LDL levels did not differ, preoperative statin users had higher BMI, higher prevalence of diabetes, lower HDL, and higher triglycerides, relative to nonusers. Given these differences between the characteristics of preoperative statin users and those of our cohort, the exclusion of these patients may have given rise to selection bias and may limit the generalizability of our findings. However, the exclusion of men using statins prior to radical prostatectomy strengthens our exposure assessment by ensuring that our assessment of preoperative serum lipid levels was unaffected by statin use. Furthermore, we adjusted our models for postoperative statin use as a time-dependent covariate, enabling us to account for varying start dates and duration of statin use during the follow-up period. Finally, SEARCH represents a racially diverse sample population and enables examination of biologic contributors to prostate cancer racial disparities in the context of equal access to care.

In summary, hypercholesterolemia was associated with increased risk of recurrence in black, but not non-black men, whereas elevated triglycerides were associated with increased risk of prostate cancer recurrence regardless of race. Significantly contrasting associations by race may provide some mechanistic insight into prostate cancer racial disparities, and should be explored in future studies. Given that hypercholesterolemia may be a shared risk factor for cardiovascular disease and prostate cancer, two common causes of mortality in prostate cancer patients, understanding the mechanisms linking cholesterol and prostate cancer progression has high clinical and public health relevance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.H. Allott, M.K. Terris, S.J. Freedland

Development of methodology: E.H. Allott, S.J. Freedland

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