

Serum Lipid Profile and Risk of Prostate Cancer Recurrence: Results from the SEARCH Database

Emma H. Allott^{1,2,3}, Lauren E. Howard^{1,3,4}, Matthew R. Cooperberg⁵, Christopher J. Kane⁶, William J. Aronson^{7,8}, Martha K. Terris^{9,10}, Christopher L. Amling¹¹, and Stephen J. Freedland^{1,3,12}

Abstract

Background: Evidence for an association between total cholesterol, low- and high-density lipoproteins (LDL and HDL, respectively), triglycerides, and prostate cancer is conflicting. Given that prostate cancer and dyslipidemia affect large proportions of Western society, understanding these associations has public health importance.

Methods: We conducted a retrospective cohort analysis of 843 radical prostatectomy (RP) patients who never used statins before surgery within the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Multivariable Cox proportional hazards analysis was used to investigate the association between cholesterol, LDL, HDL, and triglycerides and biochemical recurrence risk. In secondary analysis, we explored these associations in patients with dyslipidemia, defined using National Cholesterol Education Program guidelines.

Results: Elevated serum triglycerides were associated with increased risk of prostate cancer recurrence [HR_{per 10 mg/dl}, 1.03; 95% confidence interval (CI), 1.01–1.05] but associations between total cholesterol, LDL and HDL, and recurrence risk were null. However, among men with dyslipidemia, each 10 mg/dl increase in cholesterol and HDL was associated with 9% increased recurrence risk (HR, 1.09; 95% CI, 1.01–1.17) and 39% reduced recurrence risk (HR, 0.61; 95% CI, 0.41–0.91), respectively.

Conclusions: Elevated serum triglycerides were associated with increased risk of prostate cancer recurrence. Cholesterol, LDL, or HDL were not associated with recurrence risk among all men. However, among men with dyslipidemia, elevated cholesterol and HDL levels were associated with increased and decreased risk of recurrence, respectively.

Impact: These findings, coupled with evidence that statin use is associated with reduced recurrence risk, suggest that lipid levels should be explored as a modifiable risk factor for prostate cancer recurrence. *Cancer Epidemiol Biomarkers Prev*; 23(11); 2349–56. ©2014 AACR.

¹Division of Urology, Department of Surgery, Duke University School of Medicine, Durham, North Carolina. ²Cancer Prevention, Detection, and Control Program, Duke Cancer Institute, Durham, North Carolina. ³Division of Urology, Veterans Affairs Medical Center Durham, Durham, North Carolina. ⁴Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina. ⁵Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California. ⁶Urology Department, University of California San Diego Health System, San Diego, California. ⁷Urology Section, Department of Surgery, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California. ⁸Department of Urology, UCLA School of Medicine, Los Angeles, California. ⁹Section of Urology, Veterans Affairs Medical Center, Augusta, Georgia. ¹⁰Section of Urology, Medical College of Georgia, Augusta, Georgia. ¹¹Division of Urology, Oregon Health and Science University, Portland, Oregon. ¹²Department of Pathology, Duke University School of Medicine, Durham, North Carolina.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

Corresponding Author: Stephen J. Freedland, Duke University School of Medicine, DUMC 2626, 571 Research Drive, Durham, NC 27710. Phone: 919-668-8361; Fax: 919-668-7093; E-mail: steve.freedland@duke.edu

doi: 10.1158/1055-9965.EPI-14-0458

©2014 American Association for Cancer Research.

Introduction

Prostate cancer is the most commonly diagnosed non-cutaneous cancer in U.S. males and the second most common cause of cancer-related deaths (1). Approximately two thirds of the U.S. population are overweight or obese (2), a metabolic disorder associated with increased risk of aggressive prostate cancer and prostate cancer mortality (3). Hypercholesterolemia, a condition strongly related to obesity, currently affects approximately 20% of the U.S. adult population (4). Cholesterol is hypothesized to contribute to prostate cancer progression due to its established role as a signaling molecule in prostate growth and differentiation (5), in addition to evidence from laboratory studies suggesting that cholesterol may drive prostate cancer growth via multiple biologic mechanisms, including Akt signaling (6) and *de novo* steroidogenesis (7). Given the high prevalence of hypercholesterolemia in Western society, understanding the potential association between this modifiable risk factor and prostate cancer progression is of great public health importance.

Although epidemiologic evidence does not support an association between serum cholesterol levels and risk of total prostate cancer (8, 9), there is a suggestion that elevated cholesterol may be associated with increased risk of aggressive disease (8, 10–12), although not all studies have reported this finding (9, 13–15). There is mixed evidence for an association between serum cholesterol levels and risk of prostate cancer progression, with some studies reporting positive associations between elevated cholesterol and risk of prostate cancer recurrence (16) and mortality (17, 18), whereas another study reported no association with risk of prostate cancer mortality (19). Fewer studies examined the association between cholesterol subfractions—low- and high-density lipoprotein (LDL and HDL, respectively)—and prostate cancer. Although there is some evidence that elevated LDL (12, 20) and low HDL (10, 21) are associated with increased risk of aggressive prostate cancer, not all studies reported these findings (13, 15, 22), and the association between cholesterol subfractions and risk of prostate cancer recurrence has not been widely studied. Finally, evidence for an association between serum triglycerides and prostate cancer recurrence is mixed (14, 23). Thus, the impact of dyslipidemia on risk of prostate cancer recurrence is not well understood.

The aim of this study was to examine the association between serum lipid levels and risk of biochemical recurrence in a retrospective cohort of radical prostatectomy (RP) patients who never used statins before surgery, from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. We hypothesized that elevated serum cholesterol, triglycerides, and LDL would be associated with increased risk of prostate cancer recurrence, with a protective association between elevated HDL and risk of recurrence.

Materials and Methods

Study sample

After obtaining Institutional Review Board approval from each institution, data from patients undergoing RP ($n = 2,542$) between 1999 and 2013 at six VA Medical Centers (West Los Angeles, CA; Palo Alto, CA; San Diego, CA; Durham, NC; Asheville, NC; and Augusta, GA) were combined into the SEARCH database (24). SEARCH does not include patients treated with preoperative androgen deprivation or radiation therapy. Given that preoperative serum cholesterol level was our primary exposure of interest, patients who used statins before surgery were excluded ($n = 1,135$). We also excluded patients with missing data for serum lipid levels ($n = 482$), preoperative PSA ($n = 9$), body mass index (BMI; $n = 25$), pathologic Gleason score ($n = 11$), pathologic features ($n = 29$), and PSA follow-up ($n = 8$), resulting in a study sample of 843 men.

Exposure assessment and definitions

Fasting total serum cholesterol, LDL, HDL, and triglyceride levels measured within the year before RP were abstracted from VA-computerized medical records.

Recommended cutoffs for normal versus abnormal serum levels (all in mg/dl) of total cholesterol (<200 vs. ≥ 200), LDL (<130 vs. ≥ 130), HDL (≥ 40 vs. <40), and triglycerides (<150 vs. ≥ 150) were selected according to National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP) III guidelines (25). NCEP-ATPIII borderline and high lipid categories were combined to have adequate numbers of patients with abnormal lipid levels for the analysis. On the basis of the NCEP-ATPIII guidelines, we defined normal versus abnormal categories for each individual lipid independently of the others. For example, a patient could be included in the abnormal category for cholesterol but in the normal category for triglycerides if his cholesterol level was ≥ 200 mg/dl and his triglyceride level was <150 mg/dl.

Follow-up

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 post-operative 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

Given that our primary hypothesis was to test the association between total serum cholesterol levels and risk of biochemical recurrence, analysis of cholesterol was considered primary, whereas analysis of LDL, HDL, and triglyceride levels was considered secondary. Differences in demographic, clinical, and pathologic factors between patients with normal versus abnormal total serum cholesterol (<200 vs. ≥ 200 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.

Time from RP to biochemical recurrence was compared between normal versus abnormal serum cholesterol categories using Kaplan–Meier plots and the log-rank test. Cox proportional hazards analysis was used to test whether serum cholesterol levels (abnormal vs. normal, as well as continuous) independently predicted time to recurrence. Continuous lipid levels were presented in 10 mg/dl increments to facilitate interpretation of the HRs. The proportionality assumption was tested by examining the Schoenfeld residuals. Cox models were adjusted for age at surgery (continuous), race (black vs. non-black), preoperative PSA (continuous; log-transformed), year of surgery (continuous), BMI (continuous; log-transformed), pathologic Gleason score (2–6, 7 (3 + 4), 7 (4 + 3)–10), positive surgical margins (yes vs. no), extracapsular extension (yes vs. no), seminal vesicle invasion (yes vs. no), and surgical center. Models were also adjusted for post-RP statin use which was treated as a time-dependent variable to account for varying start dates and duration of post-RP statin use during follow-up, based upon our

previous findings that postoperative statin use affects biochemical recurrence risk (26). We did not have access to cardiovascular disease history. In secondary analysis using the same approach as described for serum cholesterol levels, we tested the association between LDL, HDL, and triglyceride levels and risk of recurrence. Although the distribution of triglyceride and HDL levels was slightly skewed, log transformation did not alter our results. Thus, to facilitate interpretation of HRs, analysis was conducted without log transformation of triglyceride and HDL levels. We tested for interaction between abnormal lipid levels and postoperative statin use in predicting risk of recurrence by treating postoperative statin use as a categorical variable and incorporating a product term into our multivariable analysis. We examined BMI as an effect modifier of the association between lipid levels and risk of recurrence by incorporating a product term into our multivariable analysis. Given the established link between abnormal serum lipid levels and increased risk of death from causes other than prostate cancer (27), we also conducted secondary analyses using a Cox proportional hazards analysis treating non-prostate cancer death as a competing risk for our primary outcome of biochemical recurrence.

Locally weighted regression (LOWESS), enabling flexible modeling of complex relationships based on the local data structure, was used to model the relationship between serum lipid levels and risk of recurrence. In secondary analysis based upon LOWESS modeling results, we explored the association between serum lipid levels and risk of recurrence after restricting our cohort to men with abnormal lipid levels. Cox proportional hazards analysis was used to examine the association between serum lipid levels (continuous) and risk of recurrence, adjusting for aforementioned demographic, clinical, and pathologic characteristics among men with abnormal lipid values. This analysis was repeated among men with normal lipid levels.

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

Results

Baseline characteristics

Patients excluded from the analysis due to preoperative statin use were older than those who never used statins before RP (Supplementary Table S1). As anticipated, preoperative statin users also had elevated BMI and higher prevalence of diabetes, but lower levels of cholesterol and LDL, relative to men who never used statins before RP. However, although preoperative statin users were less likely to have positive margins, no other pathologic features differed by preoperative statin use. Patients excluded from the analysis due to missing lipid levels had an earlier year of surgery (2002 vs. 2005; $P < 0.0001$) and longer median follow-up (86.7 vs. 74.4 months; $P = 0.0076$), but no other demographic or pathologic features differed by missing lipid status (data not shown).

Of the entire cohort of 843 men who never used statins before RP, 325 (39%) patients had abnormal preoperative cholesterol levels (≥ 200 mg/dl), as defined using NCEP-ATP III guidelines (Table 1; ref. 25). As anticipated, men with normal preoperative cholesterol levels (< 200 mg/dl) were significantly less likely to use statins after RP, relative to men with abnormal preoperative cholesterol ($P < 0.001$). However, there were no significant differences in age at surgery, race, preoperative PSA, diabetes status, BMI, or any pathologic features by cholesterol status (Table 1). With the exception of LDL and triglycerides, lipid levels were modestly intercorrelated, with the strongest correlation between cholesterol and LDL (Pearson correlation coefficient = 0.83). LDL and triglyceride levels were positively correlated with BMI, whereas HDL was negatively correlated with BMI (Supplementary Table S2).

Total serum cholesterol and risk of recurrence

A total of 293 (35%) men experienced biochemical recurrence. Median follow-up among men who did not recur was 74.3 months (Q1–Q3: 41.5–102.8). Patients with normal cholesterol levels were more recently treated than patients with abnormal cholesterol (2004 vs. 2005; $P < 0.001$; Table 1), but there was no significant difference in follow-up between groups ($P = 0.5$). Kaplan–Meier plots revealed no significant effect of cholesterol on risk of recurrence (log-rank $P = 0.334$; data not shown). Total serum cholesterol was not associated with risk of recurrence, either as a continuous or categorical variable, on multivariable analysis (both $P \geq 0.4$; Table 2). Competing risk analysis did not alter our results (Supplementary Table S3).

Serum lipids and risk of recurrence

Similar to our null findings for total cholesterol, neither LDL nor HDL were significantly related to risk of prostate cancer recurrence, either as continuous or categorical variables, on either univariable (log-rank $P = 0.824$ and $P = 0.339$, respectively) or multivariable analysis (all $P \geq 0.339$; Table 2). However, elevated triglycerides were associated with 35% increased risk of recurrence on multivariable analysis [abnormal vs. normal; HR, 1.35; 95% confidence interval (CI), 1.05–1.74; Table 2]. Furthermore, there was a significant 2% increased risk of recurrence for every 10 mg/dl increase in triglyceride level when treated as a continuous variable on both univariable (HR_{per 10 mg/dl}, 1.02; 95% CI, 1.02–1.03) and multivariable analyses (HR_{per 10 mg/dl}, 1.02; 95% CI, 1.02–1.04; Table 2). Given that abnormal serum triglycerides form part of the NCEP-ATPIII diagnostic panel for diabetes (25), we restricted our analysis to men without diabetes and found a similar association (abnormal vs. normal; HR, 1.46; 95% CI, 1.10–1.93). Given the strong correlation between LDL and cholesterol, we did not mutually adjust for LDL and cholesterol, but mutually adjusting for other combinations of lipids did not alter our results (data not shown). We found no significant interaction between BMI and any

Table 1. Demographic, clinical, and pathologic characteristics of patients by serum cholesterol status

	Cholesterol < 200 mg/dl (n = 518; 61%)	Cholesterol ≥ 200 mg/dl (n = 325; 39%)	P
Age, mean ± SD	60.4 ± 6.3	60.6 ± 6.4	0.664 ^a
Race, n (%)			0.106 ^b
Black	222 (43)	121 (37)	
Non-black	296 (57)	204 (63)	
Year of surgery, median (Q1–Q3)	2005 (2003–2008)	2004 (2002–2007)	<0.001 ^c
Follow-up, median (Q1–Q3)	74.7 (41.3–99.0)	73.4 (41.5–108.1)	0.501 ^c
PSA, median (Q1–Q3)	6.3 (4.8–9.4)	7.2 (5.0–10.5)	0.071 ^c
Statin use, n (%)			<0.001 ^b
Never	308 (59)	108 (33)	
Started after RP	210 (41)	217 (67)	
BMI, median (Q1–Q3)	27.4 (24.7–30.5)	27.5 (24.9–30.6)	0.936 ^c
Diabetes, n (%)	84 (21)	48 (20)	0.687 ^c
LDL, mean (SD)	101.9 (21.6)	141.9 (25.4)	<0.0001
HDL, mean (SD)	43.8 (13.7)	51.2 (20.3)	<0.0001
Triglycerides, mean (SD)	126.0 (83.2)	150.0 (83.9)	0.0001
Pathologic Gleason score, n (%)			0.276 ^b
2–6	177 (34)	125 (39)	
7 (3+4)	214 (41)	134 (41)	
7 (4+3)–10	127 (25)	66 (20)	
Positive margins, n (%)	228 (44)	141 (43)	0.857 ^c
Extracapsular extension, n (%)	87 (17)	66 (20)	0.198 ^c
Seminal vesicle invasion, n (%)	44 (8)	30 (9)	0.713 ^c
Positive lymph nodes, n (%)	12 (2)	9 (3)	0.919 ^c

NOTE: P values calculated by ^at test, ^bχ² test, or ^cWilcoxon rank-sum test.

Abbreviations: Q1 = 25th percentile; Q3 = 75th percentile.

lipid for predicting risk of recurrence (data not shown). Treating death as a competing risk did not materially affect the associations between HDL, LDL, and triglycerides and recurrence (Supplementary Table S3). Given that

preclinical disease may affect serum lipid levels, we repeated our analysis after excluding the first year of follow-up and found that none of the HRs were appreciably altered (data not shown).

Table 2. HRs for serum lipid levels predicting risk of biochemical recurrence after radical prostatectomy

Total cholesterol	< 200 mg/dL	≥ 200 mg/dL	Continuous^a
Unadjusted	Ref.	1.13 (0.90–1.43), P = 0.294	1.02 (0.98–1.05), P = 0.365
Adjusted ^b	Ref.	1.09 (0.85–1.39), P = 0.493	1.02 (0.98–1.05), P = 0.407
LDL	< 130 mg/dL	≥ 130 mg/dL	Continuous^a
Unadjusted	Ref.	1.03 (0.81–1.31), P = 0.824	1.00 (0.96–1.03), P = 0.832
Adjusted ^b	Ref.	1.01 (0.78–1.30), P = 0.944	0.99 (0.95–1.04), P = 0.768
HDL	≥ 40 mg/dL	< 40 mg/dL	Continuous^a
Unadjusted	Ref.	1.12 (0.89–1.41), P = 0.339	0.99 (0.92–1.07), P = 0.854
Adjusted ^b	Ref.	1.11 (0.87–1.41), P = 0.402	0.97 (0.89–1.04), P = 0.378
Triglycerides	< 150 mg/dL	≥ 150 mg/dL	Continuous^a
Unadjusted	Ref.	1.15 (0.91–1.46), P = 0.250	1.02 (1.01–1.03), P = 0.006
Adjusted ^b	Ref.	1.35 (1.05–1.74), P = 0.020	1.02 (1.01–1.04), P < 0.001

NOTE: Cells display HR (95% CI), P value.

^aHRs are for every 10 mg/dL increase.

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

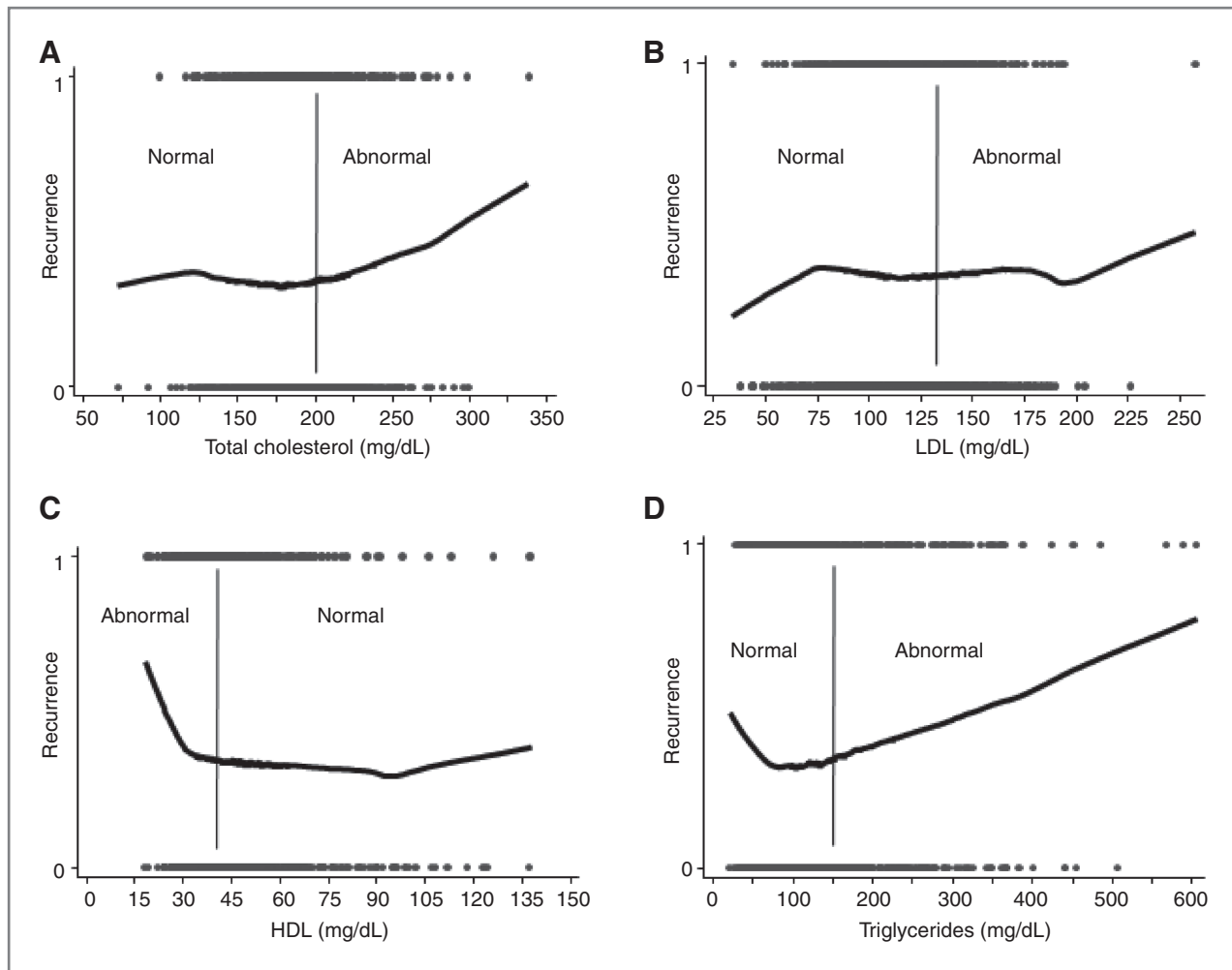


Figure 1. LOWESS plots depicting the relationship between prostate cancer recurrence and A) total cholesterol, B) LDL, C) HDL, and D) triglyceride levels. Bars, cutoff for normal versus abnormal lipid levels, as per NCEP-ATPIII guidelines (25).

Risk of recurrence among men with abnormal lipid levels

Given these null overall findings for cholesterol, LDL, and HDL, we further explored the association between serum lipid levels and risk of prostate cancer recurrence by modeling these relationships using LOWESS plots (Fig. 1). Because these plots suggested a possible relationship between lipid levels and risk of recurrence when lipid values were in the abnormal range, we performed secondary analyses restricted to patients with abnormal lipid levels. On multivariable analysis of men with abnormal lipid levels, there was a significant association between higher cholesterol levels and risk of recurrence, with each 10 mg/dl increase in cholesterol above 200 mg/dl associated with 9% increased risk of recurrence ($HR_{\text{per } 10 \text{ mg/dl}}, 1.09$; 95% CI, 1.01–1.17; Table 3). Furthermore, increasing HDL within the abnormal range was significantly protective, with each 10 mg/dL increase associated with 39% reduced risk of recurrence ($HR_{\text{per } 10 \text{ mg/dl}}, 0.61$; 95% CI, 0.41–0.91), while the association between LDL and risk of

recurrence was null ($HR_{\text{per } 10 \text{ mg/dl}}, 1.05$; 95% CI, 0.94–1.17). In line with our analysis among all men, elevated triglycerides within the abnormal range remained associated with increased risk of recurrence ($HR_{\text{per } 10 \text{ mg/dl}}, 1.03$; 95% CI, 1.01–1.05). There were no significant interactions between abnormal levels of any lipid and post-operative statin use in predicting risk of recurrence (data not shown). Treating death as a competing risk did not materially affect the associations between HDL, LDL, and triglycerides and recurrence (Supplementary Table S4). Among men with normal lipid levels, total cholesterol, LDL, HDL and triglycerides were not associated with risk of recurrence (data not shown).

Discussion

Although obesity is an established risk factor for aggressive prostate cancer and prostate cancer mortality (3), the mechanisms contributing to this obesity–prostate cancer link are not well understood. On the basis of biologic evidence supporting an important role for cholesterol in

Table 3. HRs for abnormal lipid levels predicting risk of biochemical recurrence after radical prostatectomy

Total cholesterol	Continuous; \geq 200 mg/dL
Unadjusted	1.06 (0.97–1.15), $P = 0.206$
Adjusted ^a	1.09 (1.01–1.19), $P = 0.027$
LDL	Continuous; \geq 130 mg/dL
Unadjusted	1.01 (0.90–1.13), $P = 0.860$
Adjusted ^a	1.05 (0.94–1.17), $P = 0.356$
HDL	Continuous; $<$ 40 mg/dL
Unadjusted	0.73 (0.51–1.04), $P = 0.085$
Adjusted ^a	0.61 (0.41–0.91), $P = 0.016$
Triglycerides	Continuous; \geq 150 mg/dL
Unadjusted	1.04 (1.02–1.06), $P < 0.001$
Adjusted ^a	1.03 (1.01–1.05), $P = 0.004$

NOTE: Cells display HR (95% CI), P value.

All HRs are for every 10 mg/dL increase.

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

prostate cancer, we hypothesized that serum lipid levels, a potentially modifiable factor, may influence risk of prostate cancer recurrence. In contrast to this hypothesis, we found a null association between total cholesterol, LDL and HDL, and risk of recurrence. However, each 10 mg/dl increase in serum triglyceride levels was associated with 2% increased risk of prostate cancer recurrence, with elevated serum triglycerides (≥ 150 mg/dl vs. < 150 mg/dl, as defined by NCEP-ATPIII guidelines) significantly associated with 35% increased risk of recurrence. Given the scarcity of studies examining the association between triglycerides and prostate cancer progression, future studies are required to confirm these findings.

Secondary analysis, guided by modeling the relationship between serum lipid levels and risk of recurrence using LOWESS plots, examined these associations in men with dyslipidemia. We found that each 10 mg/dl increase in total cholesterol above the abnormal cutoff value of 200 mg/dl was significantly associated with a 9% increased risk of prostate cancer recurrence, while each 10 mg/dl increase in HDL below the abnormal cutoff value of 40 mg/dl was significantly associated with a 39% decreased risk of recurrence. These findings, which require confirmation in other studies, may highlight the importance of controlling total cholesterol and HDL levels in patients with prostate cancer with dyslipidemia, not only for cardiovascular disease risk reduction but also for potentially reducing risk of prostate cancer recurrence.

In contrast to the only previous study to examine the impact of LDL on risk of recurrence in patients with prostate cancer which found a positive association (16), we found a null association between LDL and risk of

recurrence in our cohort. It is noteworthy that although the previous study was limited by sparse LDL data ($n = 169$), more than half of which came from statin users (16), we had complete LDL data for our entire cohort of 843 men, none of whom were statin users at the time of LDL measurement. Although future studies are required to examine the impact of elevated LDL levels on risk of recurrence, our results from this current study do not support this association.

Relative to other organs of the body, normal prostate epithelial cells have high cholesterol content and these levels increase further during progression to prostate cancer (5), suggesting that cholesterol accumulation may be advantageous to prostate cancer progression. Cholesterol promotes prostate cancer cell line growth both *in vitro* and in xenograft models via lipid raft-mediated Akt signaling (6). Moreover, reduction of serum cholesterol, the precursor for sex steroid synthesis, has been demonstrated to lower tumor androgen levels and slow tumor growth in xenograft models of human prostate cancer (7). However, epidemiologic evidence for an association between cholesterol and prostate cancer progression is mixed. One retrospective study reported a protective association between low cholesterol and risk of recurrence in radiation-treated patients with prostate cancer (16), and two large studies found that elevated cholesterol levels were associated with increased risk of prostate cancer mortality (17, 18). In contrast, another study reported a null association between cholesterol and prostate cancer mortality, although this study was conducted in a predominantly Asian population (19). Of note, in contrast to total cholesterol, we found no association between LDL and recurrence even among men with abnormal LDL levels. Although LDL levels are important for estimating cardiovascular disease risk, it is unknown which cholesterol subfractions are most important for tumor growth, and this requires further study. Although the primary mechanism by which HDL reduces cardiovascular disease risk is via reverse cholesterol transport (28), it is not known whether this same mechanism may affect prostate cancer growth. HDL has also been demonstrated to have antiinflammatory, antiproliferative, and antioxidant properties (29), which may slow prostate cancer growth and progression, although epidemiologic evidence has been inconclusive (22). Finally, high triglycerides have been associated with elevated levels of reactive oxygen species and oxidative stress, in addition to development of insulin resistance, all of which have been associated with prostate tumorigenesis (30). Thus, the possible association between dyslipidemia and increased risk of prostate cancer recurrence is supported by these multiple biologic pathways by which serum lipids may affect prostate cancer growth and progression.

Our study has several limitations which should be considered. First, all serum lipid measurements were obtained within the year before RP and thus may potentially be affected by the presence of preclinical disease (31). To address this, we explored the impact of excluding recurrences during the first year of follow-up, and found

that this did not alter our results. In addition, 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. Second, we lacked sufficient numbers to explore the impact of abnormal levels of all four lipids simultaneously on prostate cancer recurrence. Third, we did not have access to hypertension data and therefore could not assess the association between metabolic syndrome and risk of recurrence. Neither could we assess the impact of abnormal lipid levels within the context of metabolic syndrome. However, given the use of different definitions of the metabolic syndrome across epidemiologic studies (30), in addition to recent lack of certainty regarding its pathogenesis (32), it may be equally or more informative to estimate the effect of individual components of the metabolic syndrome on risk of prostate cancer recurrence. Finally, an important limitation of all observational biomarker studies is that causality cannot be inferred from these associations. These limitations are balanced by an important strength of this study. We excluded all men who were taking statins at the time of serum lipid measurement. Although exclusion of preoperative statin users limits the generalizability of our findings to men who do not use statins, we believe that this approach strengthens our exposure assessment as the preoperative lipid levels of statin users may not reflect the environment that their tumor developed in. Furthermore, we adjusted our multivariable models for post-RP statin use as a time-dependent variable. Thus, our serum lipid level measurements were obtained in the absence of any cholesterol-lowering medications and we were able to assess the association between serum lipid levels and risk of recurrence separately from statin use. Although we found no evidence for interaction between postoperative statin use and abnormal lipid levels in predicting risk of recurrence, future studies should assess whether beginning statin therapy after prostate cancer treatment could attenuate associations between abnormal lipid levels and risk of recurrence.

In summary, we found no strong evidence to support a link between serum lipid levels and risk of prostate cancer recurrence across the entire sample. However, among men with dyslipidemia, our findings suggest that normalization of serum lipid levels may be beneficial not only for cardiovascular disease prevention but also for prostate cancer recurrence risk reduction, though these results

require confirmation in future studies. Although it cannot be determined from this study if these observed associations are causal, given the biologic evidence supporting an important role of cholesterol in prostate cancer growth in addition to epidemiologic data demonstrating that statin use is associated with reduced risk of recurrence, we believe that serum lipid levels should be explored further as a risk factor for prostate cancer recurrence. Although the association between obesity and increased risk of prostate cancer recurrence is likely to be multifactorial (3), these findings suggest that dyslipidemia may be one of the mechanisms underlying this association. Given that 45% of deaths worldwide can be attributed to cardiovascular disease and cancer (15), with prostate cancer the second most common cause of male cancer deaths (1), understanding the role of dyslipidemia as a shared, modifiable risk factor for both of these common causes of mortality is of great importance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.H. Allott, W.J. Aronson, C.L. Amling, S.J. Freedland

Development of methodology: E.H. Allott, L.E. Howard, M.K. Terris, S.J. Freedland

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.J. Kane, M.K. Terris, C.L. Amling, S.J. Freedland

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.H. Allott, L.E. Howard, W.J. Aronson, C.L. Amling, S.J. Freedland

Writing, review, and/or revision of the manuscript: E.H. Allott, L.E. Howard, M.R. Cooperberg, C.J. Kane, W.J. Aronson, C.L. Amling, S.J. Freedland

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.J. Freedland

Study supervision: M.K. Terris, S.J. Freedland

Grant Support

This study was supported by grants from the NCI (5R25-CA126938-03; to E.H. Allott) and NIH (1-R01-CA131235-01A1 and 1K24CA160653; to S.J. Freedland).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 24, 2014; revised July 29, 2014; accepted August 6, 2014; published OnlineFirst October 10, 2014.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
2. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA* 2010;303:235–41.
3. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol* 2013;63:800–9.
4. Fryar CD, Chen TC, Li X. Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999–2010. *NCHS Data Brief* 2012;1–8.
5. Krycer JR, Brown AJ. Cholesterol accumulation in prostate cancer: a classic observation from a modern perspective. *Biochim Biophys Acta* 2013;1835:219–29.
6. Zhuang L, Lin J, Lu ML, Solomon KR, Freeman MR. Cholesterol-rich lipid rafts mediate akt-regulated survival in prostate cancer cells. *Cancer Res* 2002;62:2227–31.
7. Mostaghel EA, Solomon KR, Pelton K, Freeman MR, Montgomery RB. Impact of circulating cholesterol levels on growth and intratumoral androgen concentration of prostate tumors. *PLoS ONE* 2012;7:e30062.

8. Platz EA, Till C, Goodman PJ, Parnes HL, Figg WD, Albanes D, et al. Men with low serum cholesterol have a lower risk of high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2009;18:2807–13.
9. Mondul AM, Clipp SL, Helzlsouer KJ, Platz EA. Association between plasma total cholesterol concentration and incident prostate cancer in the CLUE II cohort. *Cancer Causes Control* 2010;21:61–8.
10. Mondul AM, Weinstein SJ, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. *Cancer Causes Control* 2011;22:1545–52.
11. Shafique K, McLoone P, Qureshi K, Leung H, Hart C, Morrison DS. Cholesterol and the risk of grade-specific prostate cancer incidence: evidence from two large prospective cohort studies with up to 37 years' follow up. *BMC Cancer* 2012;12:25.
12. Farwell WR, D'Avolio LW, Scranton RE, Lawler EV, Gaziano JM. Statins and prostate cancer diagnosis and grade in a veterans population. *J Natl Cancer Inst* 2011;103:885–92.
13. Jacobs EJ, Stevens VL, Newton CC, Gapstur SM. Plasma total, LDL, and HDL cholesterol and risk of aggressive prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Causes Control* 2012;23:1289–96.
14. Martin RM, Vatten L, Gunnell D, Romundstad P, Nilsen TI. Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. *Cancer Causes Control* 2009;20:1181–92.
15. His M, Zelek L, Deschasaux M, Pouchieu C, Kesse-Guyot E, Hercberg S, et al. Prospective associations between serum biomarkers of lipid metabolism and overall, breast and prostate cancer risk. *Eur J Epidemiol* 2014;29:119–32.
16. Gutt R, Tonlaar N, Kunnavakkam R, Karrison T, Weichselbaum RR, Liauw SL. Statin use and risk of prostate cancer recurrence in men treated with radiation therapy. *J Clin Oncol* 2010;28:2653–9.
17. Colli JL, Amling CL. High cholesterol levels are associated with reduced prostate cancer mortality rates during periods of high but not low statin use in the United States. *Urol Oncol* 2009;27:170–3.
18. Batty GD, Kivimaki M, Clarke R, Davey Smith G, 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. 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.
20. Kok DE, van Roermund JG, Aben KK, den Heijer M, Swinkels DW, Kampman E, et al. Blood lipid levels and prostate cancer risk; a cohort study. *Prostate Cancer Prostatic Dis* 2011;14:340–5.
21. Magura L, Blanchard R, Hope B, Beal JR, Schwartz GG, Sahmoun AE. Hypercholesterolemia and prostate cancer: a hospital-based case-control study. *Cancer Causes Control* 2008;19:1259–66.
22. Kotani K, Sekine Y, Ishikawa S, Ikpot IZ, Suzuki K, Remaley AT. High-density lipoprotein and prostate cancer: an overview. *J Epidemiol* 2013;23:313–9.
23. Post JM, Beebe-Dimmer JL, Morgenstern H, Neslund-Dudas C, Bock CH, Nock N, et al. The metabolic syndrome and biochemical recurrence following radical prostatectomy. *Prostate Cancer* 2011;2011:245642.
24. Allott EH, Abern MR, Gerber L, Keto CJ, Aronson WJ, Terris MK, et al. Metformin does not affect risk of biochemical recurrence following radical prostatectomy: results from the SEARCH database. *Prostate Cancer Prostatic Dis* 2013;16:391–7.
25. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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.
26. Allott EH, Howard LE, Cooperberg MR, Kane CJ, Aronson WJ, Terris MK, et al. Postoperative statin use and risk of biochemical recurrence following radical prostatectomy: results from the SEARCH database. *BJU Int* 2014 Mar 3. [Epub ahead of print].
27. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS ONE* 2013;8:e65174.
28. McGrowder D, Riley C, Morrison EY, Gordon L. The role of high-density lipoproteins in reducing the risk of vascular diseases, neurodegenerative disorders, and cancer. *Cholesterol* 2011;2011:496925.
29. Toth PP. High-density lipoprotein as a therapeutic target: clinical evidence and treatment strategies. *Am J Cardiol* 2005;96:50K–58K; discussion 34K–35K.
30. Cowey S, Hardy RW. The metabolic syndrome: a high-risk state for cancer? *Am J Pathol* 2006;169:1505–22.
31. Ahn J, Lim U, Weinstein SJ, Schatzkin A, Hayes RB, Virtamo J, et al. Prediagnostic total and high-density lipoprotein cholesterol and risk of cancer. *Cancer Epidemiol Biomarkers Prev* 2009;18:2814–21.
32. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005;28:2289–304.