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Men with Low Serum Cholesterol Have a Lower Risk of High-Grade Prostate Cancer in the Placebo Arm of the Prostate Cancer Prevention Trial

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Abstract

Background: **Several prospective studies suggest that use of cholesterol-lowering statin drugs is inversely associated with advanced stage and possibly high-grade prostate cancer. One study reported that men with low cholesterol had a lower risk of high-grade prostate cancer. Given these findings, we investigated the association between low serum cholesterol and prostate cancer risk in the Prostate Cancer Prevention Trial.**
Methods: **We conducted a cohort study of 5,586 men ages ≥55 years who were randomized to the placebo arm of the Prostate Cancer Prevention Trial between 1993 and 1996. Serum cholesterol was measured enzymatically at entry. By the end of follow-up, 1,251 prostate cancer cases were confirmed. We used logistic regression to calculate the multivariable odds ratio (OR) of total, and Gleason 2 to 6 (n = 993), 7 (n = 199), and 8 to 10 (n = 59) prostate cancer comparing low serum (normal, <200 mg/dL) to high-serum (borderline and elevated cholesterol, ≥200 mg/dL) cholesterol.**
Results: **Men with low cholesterol had a lower risk of Gleason 8 to 10 prostate cancer [OR, 0.41; 95% confidence interval (CI), 0.22-0.77] than men with high cholesterol. No association was present for prostate cancer overall (OR, 0.97; 95% CI, 0.85-1.11), Gleason 2 to 6 disease (OR, 1.03; 95% CI, 0.89-1.18), or Gleason 7 disease (OR, 0.93; 95% CI, 0.69-1.24).**
Conclusion: **These prospective results support that men with low cholesterol have a reduced risk of high-grade prostate cancer. These and other contemporary data that suggest that cholesterol metabolism should be investigated further in the etiology of prostate cancer.** (Cancer Epidemiol Biomarkers Prev 2009;18(11):2807–13)

Introduction

Five recent, large prospective cohort studies support inverse associations between use of statin drugs and advanced stage prostate cancer (1-5). Two other studies that evaluated this association by stage and grade, a hospital-based case-control study (6), and a retrospective cohort study (7), were not in agreement. The association between statin drugs and prostate cancer overall has not been consistent (8). An earlier clinic-based case-control study observed a stronger inverse association for high-grade than for low-grade prostate cancer (9), a result also observed for longer-term statin use in a cohort study (1).

One mechanism by which statin drugs might influence the development of prostate cancer with a more aggressive phenotype is cholesterol lowering. Freeman (10) proposed that because prostate cancer cells exhibit cholesterol feedback dysregulation, they may be particularly susceptible to cholesterol lowering. A nested case-control study investigating low-circulating cholesterol as a possible mechanism underlying the statin findings reported that men with low plasma cholesterol had a lower risk of high-grade prostate cancer and possibly advanced stage disease, but not organ-confined or low-grade disease (11). The inverse associations for high-grade disease persisted after excluding users of cholesterol-lowering drugs, suggesting that cholesterol itself may be playing a role. Previous studies on circulating cholesterol concentration and prostate cancer (12-18) did not systematically evaluate associations by stage or histologic grade.

Given this promising hypothesis, we evaluated the association between serum cholesterol and prostate cancer, in particular, high-grade disease, in the placebo arm of the Prostate Cancer Prevention Trial (PCPT). Unlike standard cohort studies, the PCPT protocol called for annual prostate-specific antigen (PSA) screening and prostate

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digital-rectal examination (DRE); all cases were biopsy detected; all diagnoses and Gleason score determinations were confirmed centrally; and men not diagnosed with prostate cancer during the trial were recommended for biopsy at the end of the trial in accordance with the trial protocol. Because of this latter feature of the trial, the opportunity to detect prostate cancer was less influenced by factors that may be associated with serum cholesterol concentration than in other studies. Also, unlike prior studies, the number of high-grade cases in the placebo arm of the PCPT was sufficiently large to allow estimation of the association for Gleason 8 to 10 disease, which has a substantially worse prognosis than other grades of prostate cancer.

Materials and Methods

Study Design and Population. Included in this prospective cohort study were participants in the multisite PCPT (19). The PCPT investigated whether finasteride, an inhibitor of 5α-reductase type II, the enzyme that catalyzes the conversion of testosterone to the more potent androgen dihydrotestosterone, prevents prostate cancer. Starting in 1993, 18,882 men ages ≥55 y who had a normal DRE and a serum PSA of ≤3.0 ng/mL were randomized to 5 mg/d finasteride or placebo for 7 y. Because finasteride reduces serum PSA concentration, PSA concentration was adjusted upward for men in the finasteride arm to keep the proportion of biopsies triggered by PSA testing during the trial comparable between the arms; blinding of the investigators and the men and their physicians was maintained (19). Additionally because of finasteride's influence on PSA, all men not diagnosed with prostate cancer during the trial were recommended to undergo biopsy at the end of the trial irrespective of their PSA concentration or DRE result to determine prostate cancer status. The trial was stopped early by the Data Safety and Monitoring Board because the reduction in the period prevalence of prostate cancer reached statistical significance (19). Ultimately, 58% (n = 10,979) of the men, 5,615 in the placebo arm and 5,364 in the finasteride arm, were eligible for cohort analyses on prostate cancer etiology because they were diagnosed with prostate cancer based on an abnormal PSA and/or abnormal DRE by 6 mo after the end of the trial, or they underwent biopsy at the end of the trial and were found to be free of prostate cancer. We excluded men who had a diagnosis of any cancer except nonmelanoma skin cancer before the date of blood draw at entry into the trial, and men with a missing serum cholesterol concentration (29 otherwise eligible men). *A priori*, we restricted the primary analysis to men who were randomized to the placebo arm of the trial to limit any modifying effect of the study drug on the association between cholesterol and prostate cancer. The primary analysis included 5,586 men.

The PCPT was approved by the Institutional Review Boards at the participating sites, the Southwest Oncology Group (San Antonio, TX), and the Southwest Oncology Group Data and Statistical Center (Fred Hutchinson Cancer Research Center, Seattle, WA). The secondary data analysis to address the cholesterol hypothesis was approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

At the entry visit and then annually, nonfasting blood samples were collected for measurement of serum PSA. After collection, the entry blood sample was shipped on ice to a contract laboratory for processing and long-term storage at −80°C. As part of the trial, serum cholesterol was measured enzymatically at a central commercial facility (20). At entry, the men completed an exposure questionnaire and at the subsequent annual visit they completed a food frequency questionnaire at the majority of the participating sites. Height was measured at baseline, weight was measured annually, and waist and hip circumferences were measured one year after randomization.

Prostate Cancer Ascertainment. Diagnosis of adenocarcinoma of the prostate based on a biopsy prompted by an elevated PSA and/or abnormal DRE or on the end-of-study biopsy was made in 1,264 men in the placebo arm. Of these, 1,251 had a serum cholesterol measurement available. The diagnosis was based on an end-of-study biopsy for 53.9%. The diagnosis made at the study site was confirmed and determination of Gleason score was made centrally at the Prostate Diagnostic Laboratory, University of Colorado (Denver, CO); the pathologists were blinded to trial arm and serum cholesterol concentration. Gleason sum was available for all 1,251 cases, and of these, stage was available for 1,153.

Statistical Analysis. We calculated age-adjusted means and prevalences of participant characteristics by quintiles of serum cholesterol and by subsequent prostate cancer status as least squares means from linear regression models. Because the date of prostate cancer diagnosis for more than half of the cases was arbitrarily determined by the scheduled date of the end-of-study biopsy, a time-to-event statistical analysis typically used in cohort studies was not appropriate. Instead, we used logistic regression to calculate the odds ratio (OR), as an estimate of the cumulative incidence ratio, and its 95% confidence interval (CI) for total prostate cancer, organ-confined disease (n = 1,124), and for Gleason 2 to 6 (n = 993), 7 (n = 199), 7 to 10 (n = 258), and 8 to 10 (n = 59) disease. Because of the low PSA eligibility criterion and annual screening, the vast majority of cases were diagnosed at an organ-confined stage (T1 or T2, and N0 and M0), precluding analysis of advanced-stage disease (17 T3N0M0, 6 N+M0, and 6 M+). Based on the findings of a previous study (11), for high and low Gleason score cases, we performed subanalyses in which we excluded cases with clinical stage T3 or worse. We also classified the T1a-T1c cases as potentially clinically significant based on the Epstein criteria of a PSA density of ≥0.10 to 0.15 ng/mL, Gleason sum of >6, cancer in ≥3 biopsy cores, or cancer present in >50% of the area of any positive core (21).

We first divided the distribution of serum cholesterol in the analytic cohort into quintiles (<182, 182-200, 201-218, 219-240, and ≥241 mg/dL) and entered indicator terms for each of the bottom four quintiles into the model; the highest quintile was selected as the reference group based on the hypothesis that low cholesterol is protective. To test for trend across quintiles, we entered into the model a single ordinal variable with possible values corresponding to the median of the category into which a man's serum cholesterol fell. Next, we compared men with low serum cholesterol, which we defined as <200 mg/dL, the clinical cutpoint for normal cholesterol based on cardiovascular disease risk (22) and which corresponded to the bottom two quintiles in this analysis, to

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men with high serum cholesterol, which we defined as ≥200 mg/dL. To confirm that we captured the shape of the association using indicator variables for quintiles of the distribution of serum cholesterol and to obtain the *P* value for the test of association, we generated a smoothed plot for Gleason 8 to 10 prostate cancer using restricted cubic splines with three knots after truncating the cholesterol distribution at the 2.5 and 97.5 percentiles.

We report age- and multivariable-adjusted results. The final multivariable model included factors selected *a priori* based on their likely associations with prostate cancer and/or serum cholesterol: age (year, continuous), race (non-White versus White), first-degree family history of prostate cancer, body mass index (BMI, kg/m^2, continuous), and self-reported diagnosis of diabetes mellitus, regular aspirin use, and history of myocardial infarction. Other factors purported to be associated with prostate cancer and/or with serum cholesterol did not confound the serum cholesterol and prostate cancer association based on lack of notable change in the estimate: attained education, alcohol consumption, physical activity, cigarette smoking history, and intake of energy, saturated fat, fish, tomatoes, calcium, and vitamin E. We also considered adjustment for waist circumference or the combination of BMI and waist circumference; the results were similar to adjustment for BMI only.

We assessed whether the association between serum cholesterol and prostate cancer differed by age at diagnosis (<25th percentile, ≥25th percentile), family history of prostate cancer (yes, no), BMI (normal, <25; overweight/obese, ≥25 kg/m^2), regular aspirin use (yes, no), and history of diabetes mellitus (yes, no) by running stratified multivariable models. To test for interaction, we used the likelihood ratio test to compare nested multivariable models that included terms for cholesterol and the possible effect modifier and additionally a term for their product.

To directly assess the modifying effect of the study drug on the association between cholesterol and prostate cancer that we observed in the primary analysis, we ran key analyses for the 873 cases in 5,364 men randomized to the finasteride arm. To test for interaction, we used the same approach as described for the potential effect modifiers above.

Statistical analyses were conducted using SAS release 9.1 (SAS Institute) and the smoothed plot and accompanying test for association was generated using R statistical software. We report two-sided *P* values for hypothesis tests.

Results

Placebo Arm. Median age at prostate cancer diagnosis was 69 years (range, 56-87 years). Mean time between blood collection for serum cholesterol measurement and prostate cancer diagnosis was 5.5 ± 1.9 years. Men with low serum cholesterol were slightly older (Table 1). After age adjustment and compared with men with a moderate serum cholesterol, men with either low or high serum

Table 1. Entry characteristics of participants by quintile of serum cholesterol concentration, placebo arm of the PCPT

	All	Quintile of serum cholesterol concentration					*P*
		1	2	3	4	5	
Median (range) serum cholesterol (mg/dL)	209 (60-408)	167 (60-181)	191 (182-200)	208 (201-218)	227 (219-240)	257 (241-408)	
n	5,586	1,098	1,072	1,164	1,099	1,153	
Mean age (y)	62.8	63.1	63.1	62.9	62.9	62.2	0.0013
Non-White (%)	6.6	8.1	5.1	5.7	6.4	7.7	0.02
Mean BMI (kg/m^2)	27.3	27.4	27.2	27.1	27.5	27.6	0.04
Mean height (inches)	69.9	70.0	70.2	69.8	69.8	69.6	<0.0001
Education (%)							
<High school	1.2	0.9	0.6	1.5	1.3	1.4	0.49
High school	16.4	14.9	16.8	15.9	17.0	17.5	
>High school	82.4	84.3	82.6	82.7	81.7	81.0	
Cigarette smoking (%)							
Never	34.5	37.9	36.4	34.9	34.2	29.3	<0.001
Former	58.7	54.6	57.1	59.5	57.8	64.2	
Current	6.8	7.5	6.5	5.6	8.0	6.5	
Physical activity (%)							
Sedentary	16.7	17.1	16.5	14.1	16.9	19.2	0.41
Light	41.8	42.0	40.7	42.3	42.6	41.6	
Moderate	31.4	30.8	32.4	32.8	30.7	30.1	
Active	9.7	9.8	9.9	10.5	9.6	8.9	
Family history of prostate cancer (%)	16.9	17.6	15.8	16.5	16.9	17.6	0.78
Mean PSA (ng/mL)	1.26	1.20	1.26	1.26	1.25	1.31	0.02
History of diabetes (%)	5.0	8.5	4.9	3.8	4.0	4.0	<0.0001
History of heart attack (%)	4.2	5.8	4.3	4.4	2.9	3.7	0.02
Regular aspirin use (%)	50.0	47.7	49.6	53.2	48.5	50.5	0.08
Vasectomy (%)	34.0	35.9	35.0	31.1	33.5	34.5	0.14
Alcohol intake (g/d)	9.8	8.8	8.7	9.3	11.6	10.4	<0.0001
Red meat intake (servings/d)	0.61	0.60	0.59	0.59	0.63	0.62	0.03
Energy-adjusted cholesterol intake (mg/d)	281	285	282	276	281	282	0.30
Calcium intake, diet and supplements (mg)	926	938	936	953	933	872	<0.0001

NOTE: All characteristics (except for age) are age adjusted and were calculated as least squares means from linear regression models.

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cholesterol were more likely to be non-White and to have higher BMI and lower calcium intake. Compared with men with high serum cholesterol, men with a low concentration were taller and more likely to have a history of diabetes and heart attack, but were less likely to have ever smoked, they drank less alcohol, ate less red meat, and they had a lower entry PSA concentration. Men subsequently diagnosed with prostate cancer were older at entry than men found to be free of prostate cancer (Table 2). After adjusting for age, men subsequently diagnosed with prostate cancer were more likely to have a family history of prostate cancer, to be shorter, to use aspirin, and to have a higher entry PSA, but were less likely to be diabetic or to have ever smoked. Intake of energy, fish, tomatoes, cholesterol, and saturated fat did not differ across serum cholesterol concentration or by subsequent prostate cancer diagnosis (data not shown).

Mean serum cholesterol did not differ ($P = 0.77$) between men subsequently diagnosed with prostate cancer (211 ± 36 mg/dL) and men found to be free of prostate cancer (211 ± 36 mg/dL). After age adjustment, there still was no difference (cases, 212; 95% CI, 210-214; noncases, 211; 95% CI, 210-212; $P = 0.53$). There was no association between quintile of serum cholesterol and total, organ-confined, or Gleason 2 to 6 prostate cancer after age or multivariable adjustment (Table 3). However, after age and multivariable adjustment, risk of Gleason 7 to 10 prostate cancer decreased with decreasing quintiles of serum cholesterol ($P_{trend} = 0.07$), which was attributable to a strong association for Gleason 8 to 10 disease ($P_{trend} = 0.01$). The results based on quintiles of the distribution of serum cholesterol for Gleason 8 to 10 (Fig. 1) prostate cancer were supported by smoothed plot of the associations ($P = 0.015$). After restricting cases to those with clinically organ-confined disease, risk of Gleason 7 to 10 prostate cancer was lowest in the bottom two quintiles of serum cholesterol when compared with the highest quintile, again a finding that mainly was due to Gleason 8 to 10 disease (data not shown).

We next compared men with serum cholesterol in the reference range (<200 mg/dL) to men with borderline or high cholesterol (≥200 mg/dL). No association was observed for total, organ-confined, Gleason 2 to 6, or Gleason 7 prostate cancer (Table 3) or for T1a-T1c cases that were clinically insignificant (OR, 1.06; 95% CI, 0.81-1.38) or significant (OR, 0.91; 95% CI, 0.77-1.08) cancer based on the Epstein criteria. In contrast, men with normal serum cholesterol had a statistically significantly lower risk of Gleason 8 to 10 prostate cancer (OR, 0.41; 95% CI, 0.22-0.77), especially when the disease was also organ confined (OR, 0.32; 95% CI, 0.15-0.66). The associations were unchanged when restricting to White men only ($n = 4,068$; data not shown). None of the associations between normal serum cholesterol and any of the prostate cancer end points differed by age, family history, BMI, diabetes, or aspirin use (all P interaction > 0.20); the ORs of total and Gleason 2 to 6 prostate cancer were close to the null in both strata of these factors, but the ORs of Gleason 8 to 10 disease were generally less than one in both strata.

Table 2. Entry characteristics of men subsequently diagnosed with prostate cancer and men found to be free of prostate cancer, placebo arm of the PCPT

	Subsequent prostate cancer diagnosis		*P*
	No	Yes	
n	4,335	1,251	
Mean age (y)	62.6	63.6	<0.0001
Non-White (%)	6.5	7.0	0.52
Mean BMI (kg/m^2)	27.4	27.2	0.11
Mean weight (pounds)	192.0	190.9	0.27
Mean height (inches)	69.8	67.0	0.07
Mean waist circumference (cm)	100.2	100.0	0.65
Education (%)			
<High school	1.1	1.4	0.29
High school	16.8	15.0	0.12
>High school	82.1	83.5	0.26
Cigarette smoking (%)			
Never	33.9	36.7	0.07
Former	59.4	56.4	0.06
Current	6.7	6.9	0.80
Physical activity (%)			
Sedentary	16.7	16.9	0.87
Light	42.1	40.6	0.34
Moderate	30.8	33.5	0.07
Active	10.0	8.8	0.21
Family history of prostate cancer (%)	15.7	21.2	<0.0001
Mean PSA (ng/mL)	1.2	1.5	<0.0001
History of diabetes (%)	5.2	4.1	0.10
History of heart attack (%)	4.1	4.4	0.65
Regular aspirin use (%)	49.0	53.5	0.005
Vasectomy (%)	34.0	33.8	0.90
Alcohol intake (g/d)	9.7	9.9	0.77
Red meat intake (servings/d)	0.61	0.60	0.31
Energy-adjusted cholesterol intake (mg/d)	281	281	0.91
Calcium intake, diet and supplements (mg/d)	922	939	0.23

NOTE: All characteristics (except for age) are age adjusted and were calculated as least squares means from linear regression models.

Effect Modification by Finasteride. Finasteride treatment modified the association between low serum cholesterol and Gleason 8 to 10 prostate cancer ($P_{interaction} = 0.02$): the inverse association present in the placebo arm was not observed in the finasteride arm (Table 4).

Discussion

Consistent with a previous nested case-control study and with the recent observations on cholesterol-lowering statin drugs and prostate cancer, in the placebo arm of the PCPT, we observed that men with low serum cholesterol had a lower risk of high-grade prostate cancer. We did not observe associations between low cholesterol and total, organ-confined, or low-grade prostate cancer. We also extended the previous observations by showing that the association was restricted to the highest grade cases, Gleason 8 to 10. No association was observed between serum cholesterol and prostate cancer in the men randomized to finasteride. The plausibility that cholesterol may influence prostate cancer cell survival has been reviewed recently (23). Our findings add to the literature supporting a role for cholesterol in the etiology of prostate cancer with a worse prognosis.

There is a large literature indicating that low serum cholesterol is associated with a higher risk of all-cause cancer incidence and mortality, which may be due to reverse causation; that is, cancer influencing serum cholesterol. Despite this literature, the association between circulating cholesterol and prognostic characteristics of prostate cancer is largely unexplored, aside from the

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Table 3. Association between serum cholesterol concentration and prostate cancer, placebo arm of the PCPT

	Quintile of serum cholesterol concentration					P_{trend}	Serum cholesterol concentration <200 versus ≥200 mg/dL
	1	2	3	4	5		
Total prostate cancer (*n*)	245	232	252	262	260		
$OR_{age\text{-}adjusted}$ (95% CI)	0.93 (0.76- 1.13)	0.89 (0.73-1.09)	0.90 (0.74-1.09)	1.02 (0.84-1.24)	1.00 (Reference)	0.37	0.96 (0.85-1.10)
$OR_{multivariable\text{-}adjusted}$* (95% CI)	0.94 (0.77-1.15)	0.90 (0.74-1.10)	0.90 (0.74-1.09)	1.03 (0.85-1.25)	1.00 (Reference)	0.43	0.97 (0.85-1.11)
Organ-confined disease (*n*)	215	209	222	233	245		
$OR_{age\text{-}adjusted}$ (95% CI)	0.87 (0.71-1.06)	0.85 (0.70-1.05)	0.84 (0.69-1.03)	0.97 (0.79-1.18)	1.00 (Reference)	0.14	0.95 (0.83-1.08)
$OR_{multivariable\text{-}adjusted}$* (95% CI)	0.88 (0.72-1.08)	0.86 (0.70-1.06)	0.83 (0.68-1.02)	0.97 (0.80-1.19)	1.00 (Reference)	0.17	0.96 (0.84-1.10)
Gleason 2-6 (*n*)	204	185	196	204	204		
$OR_{age\text{-}adjusted}$ (95% CI)	0.99 (0.80-1.22)	0.91 (0.73-1.13)	0.89 (0.72-1.10)	1.01 (0.82-1.25)	1.00 (Reference)	0.85	1.01 (0.88-1.17)
$OR_{multivariable\text{-}adjusted}$* (95% CI)	1.00 (0.81-1.24)	0.91 (0.73-1.13)	0.88 (0.71-1.09)	1.02 (0.82-1.26)	1.00 (Reference)	0.94	1.03 (0.89-1.18)
Gleason 7-10 (*n*)	41	47	56	58	56		
$OR_{age\text{-}adjusted}$ (95% CI)	0.72 (0.48-1.09)	0.86 (0.57-1.28)	0.94 (0.64-1.37)	1.07 (0.74-1.57)	1.00 (Reference)	0.07	0.79 (0.60-1.03)
$OR_{multivariable\text{-}adjusted}$* (95% CI)	0.70 (0.46-1.07)	0.88 (0.59-1.31)	0.95 (0.65-1.39)	1.08 (0.74-1.58)	1.00 (Reference)	0.07	0.78 (0.60-1.02)
Gleason 7 (*n*)	34	41	45	37	42		
$OR_{age\text{-}adjusted}$ (95% CI)	0.80 (0.51-1.27)	1.00 (0.64-1.55)	1.01 (0.66-1.55)	0.91 (0.58-1.43)	1.00 (Reference)	0.50	0.93 (0.69-1.24)
$OR_{multivariable\text{-}adjusted}$* (95% CI)	0.79 (0.49-1.25)	1.02 (0.66-1.59)	1.01 (0.66-1.56)	0.92 (0.59-1.44)	1.00 (Reference)	0.49	0.93 (0.69-1.24)
Gleason 8-10 (*n*)	7	6	11	21	14		
$OR_{age\text{-}adjusted}$ (95% CI)	0.48 (0.19-1.20)	0.43 (0.17-1.14)	0.73 (0.33-1.62)	1.55 (0.78-3.08)	1.00 (Reference)	0.01	0.42 (0.22-0.77)
$OR_{multivariable\text{-}adjusted}$* (95% CI)	0.46 (0.18-1.16)	0.45 (0.17-1.17)	0.75 (0.33-1.66)	1.53 (0.77-3.05)	1.00 (Reference)	0.01	0.41 (0.22-0.77)

*Adjusted for age, race, family history of prostate cancer, BMI, diabetes, regular aspirin use, and history of heart attack.

recently published nested case-control study on cholesterol and prostate cancer in the Health Professionals Follow-up Study (HPFS). In the HPFS, the OR of Gleason 7 to 10 disease (n = 247) was 0.61 (95% CI, 0.39-0.98) when comparing low (<25th percentile in controls) with high plasma cholesterol, and the association was modestly stronger in cases that were also organ confined (OR, 0.54; 95% CI, 0.29-0.99); these associations were unchanged after excluding men who used cholesterol-lowering drugs (11). Too few men in the HPFS were diagnosed with Gleason 8 to 10 prostate cancer to evaluate the cholesterol association in this subgroup. Low cholesterol was not associated with prostate cancer overall, organ-confined, or Gleason 2 to 6 cases in the HPFS. We noted the same patterns of association in PCPT. Earlier studies, most of which had a small number of prostate cancer cases, reported no association between circulating cholesterol and prostate cancer (14, 16, 17, 24, 25) or that risk was lower among men with higher cholesterol (12, 13). The majority of the prostate cancer cases diagnosed in PCPT and HPFS were clinically organ confined because of high PSA screening intensity in both cohorts, and additionally in the PCPT because of the low PSA eligibility criterion and the recommendation of a biopsy at the end of the trial. In contrast, some of the prior studies were conducted before or early in the PSA era during which time a greater proportion of cases were diagnosed later in their natural history. The discrepancy in the findings between the past studies and the HPFS and PCPT may be, in part, due to a lack of consideration of pathologic characteristics of the tumor, including differentiation status. In addition, our findings may differ from past findings of a higher risk of prostate cancer incidence or death in men with low cholesterol because in HPFS and PCPT prostate cancer was diagnosed early in its natural history, and thus unlikely to have influenced circulating cholesterol concentrations.

We conducted the primary analysis among men randomized to the placebo arm of the trial. Unlike in the placebo arm, in the finasteride arm, we did not find an association between serum cholesterol and high-grade prostate cancer. In other ongoing analyses, we have observed effect modification by finasteride as well. Several articles have been published describing differences in the detectability and the pathologic characteristics of the high-grade cases in the finasteride compared with placebo arm (26-28). The finding of a lower risk of prostate cancer in men with low cholesterol in the placebo arm but no difference in risk in the finasteride arm could not be explained by the imperfect sensitivity of detecting high-grade prostate cancer if in the placebo arm the sensitivity were the same in men with low and high cholesterol or higher in men with low than high cholesterol. The pattern that we observed, in theory, could be explained by the sensitivity being lower in men with low than high cholesterol, but this is not the expectation. Men with low cholesterol on average have a lower prostate volume (29), and thus, a greater proportion of the total prostate would be sampled by needle biopsy increasing the sensitivity of detection of high-grade cancers. Other possible explanations for the difference in the association for high-grade disease between the two arms of the trial might include that finasteride prevented the same subset of high-grade cases that low cholesterol would have prevented, or a difference in the accuracy of the detection of high-grade prostate cancer in those with low cholesterol in the placebo versus finasteride arms of the trial.

Important strengths of this study are its prospective design; large size; central pathology confirmation of diagnosis, stage, and grade; rich information on covariates; and

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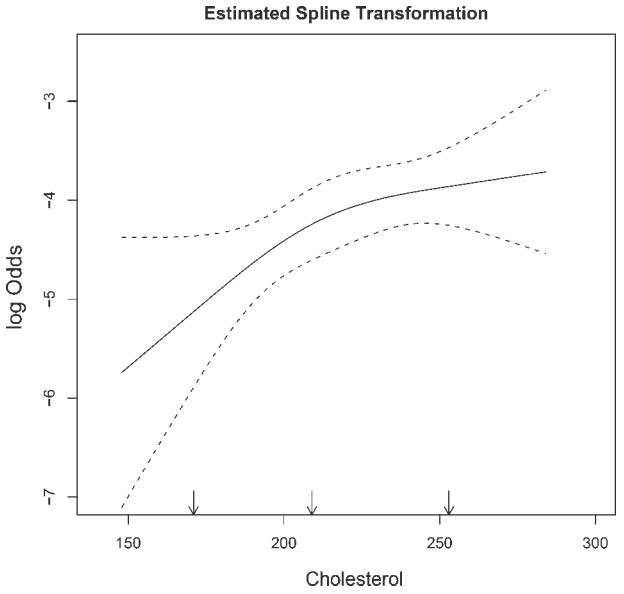

Figure 1. Association between serum cholesterol concentration (mg/dL) and Gleason 8 to 10 prostate cancer, placebo arm of the PCPT. The association was estimated using restricted cubic splines with three knots (*arrows*), truncating at the 2.5 percentile and 97.5 percentile, and adjusting for age, race, family history, BMI, diabetes, regular aspirin use, and history of heart attack. The *P* value for the test of association was 0.015.

by its design, a reduced likelihood of detection bias. Studies in the PSA era are susceptible to detection bias: (*a*) if the exposure of interest is associated with the likelihood of PSA screening and thus diagnostic work-up for prostate cancer, or (*b*) if the exposure somehow influences the concentration of PSA in circulation. The likelihood of the first source of detection bias was limited in the PCPT because of the trial protocol that recommended annual PSA and DRE screening and biopsy at the end of the trial for men not diagnosed with prostate cancer during the trial, and because serum cholesterol was measured for all of the men at trial entry. Thus, the link between seeking medical care and being worked up for both elevated cholesterol and PSA was dissociated. The second source of detection bias was limited in the PCPT because elevated PSA was not the sole reason for biopsy; ~15% of the men without an elevated PSA or abnormal DRE were diagnosed with prostate cancer on the biopsy at the end of the trial. Further evidence that these biases are unlikely to be present is that the distribution of serum cholesterol was similar in men who did (211.1 ± 36.2; age-adjusted, 211.1; 95% CI, 210.0-212.3) and did not (210.9 ± 37.6; 210.9; 95% CI, 209.9-211.9) undergo biopsy at the end of the trial.

We cannot rule out that our results could be due to complex sources of selection bias related to the propensity to undergo the end of study biopsy per study protocol. Such a bias could occur if say, men with low cholesterol at baseline who had an occult high-grade prostate cancer present by the end of the trial were more likely to decline biopsy than men with low cholesterol at baseline who were free of prostate cancer at the end of the trial. To generate a bias in this scenario, the forces that would compel a man with low cholesterol to undergo the end of study biopsy dependent on whether he had a yet undetected high-grade prostate cancer would have to be strong risk factors for both undergoing biopsy and for high-grade disease. What these factors might be is unknown.

We used serum cholesterol as a biomarker of the possible availability of cholesterol to the prostate, whether derived from the prostate, made by the liver, or made by other organs, including the prostate. It is unknown the extent to which serum cholesterol would reflect intraprostatic concentration or whether intraprostatic cholesterol is the relevant etiologic factor. It is also unknown whether other measures of cholesterol, such as lipoprotein fractions, would better capture the mechanisms underlying the association between serum total cholesterol and prostate cancer that we observed. Men in PCPT had a comparable mean serum cholesterol (~211 mg/dL) to similarly aged men in the U.S. population during the same time interval (1988-1994: 216, 214, 205 in men ages 50-59, 60-74, and 75+ years; ref. 30). However, whether the size of the difference in serum cholesterol concentration across quintiles is adequately large to affect cholesterol-dependent biological processes that influence risk of prostate cancer, especially high-grade disease, is not known. We were unable to evaluate whether the association that we observed was explained by a higher prevalence of statin use in men with low compared with high serum cholesterol. However, based on the findings from the HPFS (11), this is unlikely to be explanatory.

Although the overall sample size was large, some subgroup analyses had a small number of cases. However, it should be noted that the small number of Gleason 8 to 10 cases in the low cholesterol group was not merely due to

Table 4. Association between low serum cholesterol concentration (<200 versus ≥200 mg/dL) and prostate cancer by treatment arm of the trial, PCPT

Treatment arm	No prostate cancer	Prostate cancer			
		Total	Gleason 2-6	Gleason 7-10	Gleason 8-10
Finasteride					
n (low/high cholesterol)	1,753/2,738	370/503	237/331	133/172	38/55
$OR_{multivariable\text{-}adjusted}$* 95% CI		1.13 (0.97-1.31)	1.11 (0.92-1.32)	1.16 (0.92-1.47)	1.03 (0.68-1.57)
Placebo					
n (low/high cholesterol)	1,693/2,642	477/774	389/604	88/170	13/46†
$OR_{multivariable\text{-}adjusted}$* 95% CI		0.97 (0.85-1.11)	1.03 (0.89-1.18)	0.78 (0.60-1.02)	0.41 (0.22-0.77)
$P_{interaction}$		0.12	0.52	0.03	0.02

*Adjusted for age, race, family history, BMI, diabetes, regular aspirin use, and history of heart attack.
†The expected number of Gleason 8-10 cases in the low cholesterol group is 30 based on the age- and race- adjusted proportion in the high cholesterol group.

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an insufficient sample size; the observed number of cases was 13, but 30 were expected based on the age- and race-adjusted proportion of Gleason 8 to 10 cases in men with high cholesterol. In addition, because of the intensive prostate cancer screening in the trial, we could not address the association for advanced stage prostate cancer.

In summary, our prospective findings support that men with low cholesterol have a reduced risk of high-grade prostate cancer. The results of the present study along with those for cholesterol from the HPFS, as well as recent findings for statin drugs, suggest that in-depth study of cholesterol in the etiology of prostate cancer is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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