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Association between plasma total cholesterol concentration and incident prostate cancer in the CLUE II cohort

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Abstract Statin drugs appear to protect against advanced and possibly high-grade prostate cancer, perhaps through cholesterol-lowering. Thus, we evaluated the association between plasma cholesterol and prostate cancer. We conducted a prospective study in the CLUE II cohort of Washington County, MD. Included were 6,816 male county residents aged 35+ years old who did not have a cancer diagnosis at baseline in 1989. Plasma cholesterol, measured enzymatically at baseline, was categorized by clinical cutpoints. Cox proportional hazards regression was used to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for total ($n = 438$) and high-grade (Gleason sum ≥ 7, $n = 137$) prostate cancer. Compared to men with high cholesterol (≥ 240 mg/dl), men with desirable (<200 mg/dl) or borderline (200 to <240 mg/dl) levels were less likely to develop high-grade prostate cancer, particularly when restricting to organ-confined cases (HR: 0.68, 95% CI 0.40–1.18; P trend $= 0.12$) and among men with higher BMI (HR: 0.36, 95% CI 0.16–0.79; P trend $= 0.02$). Results were unchanged after excluding cholesterol-lowering drug users. Cholesterol was not associated with total prostate cancer. Our study supports two prior ones suggesting that cholesterol influences risk of high-grade prostate cancer, and indirectly supports the hypothesis that cholesterol-lowering is a mechanism by which statins are protective.

Keywords Cohort studies · Prostatic neoplasms · Cholesterol

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Introduction

In a previous study, Platz et al. observed that statins (HMG-CoA reductase inhibitors), a class of drugs commonly used to lower serum cholesterol, were inversely associated with advanced and possibly high-grade prostate cancer risk [1]. Among men with similar screening histories undergoing radical prostatectomy for prostate cancer, those who took statins at the time of their surgery were less likely to have extraprostatic extension of their prostate tumor than those who did not take statins [2]. These findings have been supported by other prospective studies [3–7]. The mechanism by which statins may exert their protective effect is unclear: lowering cholesterol, the primary indication for taking a statin, may be explanatory or statins may reduce cancer risk through other pathways [8]. Given that prostate cancer cells are known to exhibit cholesterol dysregulation and recent studies show that Akt cell survival signaling is cholesterol-

sensitive, it is plausible that cholesterol-lowering could influence prostate carcinogenesis [8]. Thus, we focus on cholesterol and prostate cancer in this study, rather than other possible pathways.

In the early 1980s there was growing concern that a low circulating cholesterol concentration, while beneficial for cardiovascular health, might increase the risk of non-cardiac outcomes, particularly risk of incident or fatal cancer [9]. Several studies, both prospective and case–control, designed to address this concern provided estimates of organ-site specific associations, some of which included prostate [10–22]. However, the results from these studies were inconsistent for prostate cancer, some showed a positive [22], some showed an inverse [10, 12, 13, 19], and some showed no association [11, 14–18, 20, 21]. Most of these studies included relatively small numbers of prostate cancer cases, and importantly, none examined high-stage or high-grade prostate cancer specifically, although the stage distribution of the cases in those studies published before PSA testing was available is likely shifted toward higher stage.

Platz et al. recently found, in two different populations, the Health Professionals Follow-up Study and the Prostate Cancer Prevention Trial, that men with a lower plasma cholesterol concentration were less likely to develop high-grade prostate cancer, especially if organ confined, subsequently than men with a higher concentration [23, 24]. In the present study, we sought to further address whether low cholesterol might be a mechanism by which statins protect against prostate cancer with a poor prognosis in a community-based cohort. Thus, we examined the association between plasma cholesterol concentration and prostate cancer in the CLUE II cohort, a large prospective cohort study conducted in Washington County, Maryland.

Methods

Study population

Included in this analysis were men who participated in CLUE II, a prospective study of cancer and heart disease. During the summer and autumn of 1989, blood samples were collected and plasma cholesterol was measured, and a brief questionnaire was administered to 32,898 people, 43% of which were men. Participants were also asked to complete and return by mail an abbreviated Block food frequency questionnaire [25]. Beginning in 1996, follow-up questionnaires have been mailed to study participants every 2 to 3 years. Men were excluded from this analysis if at baseline they were not a resident of Washington County (24%), were younger than age 35 years (10%), had a prior cancer diagnosis (1.2%), or did not have a valid cholesterol measurement (0.3%). After these exclusions, 6,816 men remained the analytic cohort. Men in this cohort were followed for a mean of 11.9 ± 6.0 years.

Exposure and outcome assessment

Plasma total cholesterol concentration was measured enzymatically for all cohort members at baseline [26] by a clinical laboratory. All other factors were assessed on the baseline questionnaire except for family history of prostate cancer (father or brother) and history of PSA testing, which were first assessed on the 1996 questionnaire. A validly completed food frequency questionnaire (FFQ) was available for 58% of the analytic cohort at baseline.

Prostate cancer cases were ascertained by linkage to the Washington County Cancer Registry. Deaths from prostate cancer as the underlying cause were indentified based on death certificates.

Statistical analysis

Cox proportional hazards regression was used to estimate the association between clinical categories of plasma total cholesterol (desirable: <200, borderline high: 200 to <240, high: ≥240 mg/dl) [27] and prostate cancer overall ($n = 438$), by clinical stage (advanced: T3 and higher, $n = 113$; organ confined: <T3, $n = 189$), and by histologic grade (Gleason <7, $n = 188$; ≥7, $n = 137$). We further stratified organ-confined cases by histologic grade, but there were not enough cases in the high cholesterol category to obtain stable estimates for advanced/low grade ($n = 7$) and advanced/high grade ($n = 4$) disease. High cholesterol was chosen to be the reference group as done previously [23, 24], so that the results of our analyses would be interpretable in light of the findings from the statins and prostate cancer studies. Factors that have been associated with prostate cancer in previous CLUE II analyses or in other epidemiologic studies of prostate cancer were included in the multivariable model. Age in years was included as a continuous variable in all models; results did not differ when age was used as the time axis for the models. Multivariable models were further adjusted for the following baseline covariates: race (white vs. non-white), highest attained education level (not a high school graduate, high school graduate, some college or vocational school, college graduate or higher), cigarette smoking status (never, current, and former), and BMI (quintiles). Multivariable models were also adjusted for intake of meat, dairy products, and tomato products (quintiles of servings per day, missing), as well as, alcohol intake (nondrinker, less than weekly, weekly but less than five times per week, at least five times per week, missing); an indicator variable for a missing or invalid FFQ was included in the

multivariable model. In addition, family history of prostate cancer (yes, no) and history of PSA testing (yes, no, and missing) were included in the multivariable model with an indicator variable for not returning the 1996 questionnaire.

In order to assess the associations between very high and very low cholesterol and prostate cancer, we also estimated the association categorizing cholesterol into fifths of the distribution in the analytic cohort, and creating three categories of cholesterol: lowest tenth of the distribution, highest tenth of the distribution, and all others. The inferences were similar using each of these cutpoints, and so, we report the results by clinical categories of total cholesterol. Sub-analyses were conducted excluding men using cholesterol-lowering drugs, men using diabetes medications, men who never had a PSA test, and men with a family history of prostate cancer to rule out any influence of these factors on the association between cholesterol and prostate cancer. Analyses were conducted stratifying by age at diagnosis (<65, ≥65 years) and BMI (<26.5, ≥26.5 kg/m^2 (median)); statistical interaction was assessed using the likelihood ratio test.

Results

Characteristics of the men by clinical cutpoints of plasma cholesterol concentration are shown in Table 1. Men with the lowest plasma cholesterol concentration tended to be slightly older and have a lower BMI than men with the highest cholesterol concentration (Table 1). Further, men with the lowest cholesterol concentration were less likely to have ever smoked, were more likely to be college graduates, and were more likely to have had a PSA test than men with the highest cholesterol concentration (Table 1). Men who subsequently became cases differed ($P < 0.05$) from the rest of the cohort on race, cigarette smoking status, family history of prostate cancer, and PSA screening, although it should be noted that information on family history and PSA screening was collected after diagnosis for men diagnosed before 1996.

There was no association between cholesterol concentration and incidence of total, advanced, or organ-confined prostate cancer (Table 2). The possible positive association between cholesterol and low-grade prostate cancer was attenuated after restricting to cases that were organ confined.

In contrast, men with a desirable or borderline high cholesterol were slightly less likely, although not statistically significantly so, to develop high-grade prostate cancer than men with a high cholesterol concentration (Table 2). When restricted to organ-confined cases, the inverse association between lower cholesterol and high-grade prostate cancer was stronger for both desirable and borderline high cholesterol (Table 2). These associations were the same after both age- and multivariable-adjustment, and did not appreciably differ when we excluded cholesterol-lowering drug users ($n = 259$) (Table 2), diabetes medication users ($n = 256$; high-grade/organ confined, vs. high, desirable: 0.56, and borderline: 0.67), men who never had a PSA test ($n = 1{,}401$; vs. high, desirable: 0.57, and borderline: 0.84), or men with a family history of prostate cancer ($n = 265$; vs. high, desirable: 0.53, and borderline: 0.70). Excluding the first two years of follow-up also did not change the results (vs. high, desirable: 0.60, and borderline: 0.67).

The association between cholesterol and high-grade prostate cancer differed by BMI (Table 3). Among men with high BMI, men with desirable cholesterol were less likely to develop high-grade prostate cancer, particularly when restricted to organ-confined cases (Table 3); these men were somewhat more likely to develop low-grade prostate cancer, although the result was not statistically significant (Table 3). However, among men with low BMI, there was a suggestion of an increased risk of both advanced stage and high-grade prostate cancer among men with desirable cholesterol, although the confidence intervals were wide (Table 3). The possible increased risk of high-grade disease was attenuated when we restricted to organ-confined cases (Table 3). These associations did not change when we further adjusted for BMI as a continuous variable, restricted to men with a BMI between 18 and 35 kg/m^2, or excluded the first 2 years of follow-up. There was no evidence that the association between cholesterol and high-grade prostate cancer varied by younger (vs. elevated, desirable: 0.51, and borderline: 0.68) or older (desirable: 0.59 and borderline 0.68) age at diagnosis (P interaction = 0.94).

Discussion

In this community-based prospective cohort study, men with lower cholesterol were less likely to develop high-grade disease, particularly when we restricted to clinically organ-confined cases; these findings were not explained by the use of cholesterol-lowering drugs. These results are consistent with two previous prospective studies that observed men with lower cholesterol are less likely to develop high-grade disease, especially among organ-confined cases [23, 24]. We cannot compare our findings with those from earlier studies because they did not examine the cholesterol association by histologic subtypes of prostate cancer. These findings suggest that cholesterol may be important in the development of prostate cancer with a poorer prognosis and, indirectly, suggest that cholesterol-lowering may be one of the mechanisms by which statins may exert a protective effect on prostate cancer.

One observation from our study that has not, to our knowledge, been reported previously is that the inverse

Table 1 Age-adjusted[a] characteristics of men by clinical cutpoints of total cholesterol, CLUE II, 1989

	Plasma total cholesterol concentration (mg/dl)			*P* value
	Desirable <200	Borderline high 200 to <240	High ≥240	
N (%)	2,895 (42.5%)	2,737 (40.2%)	1,184 (17.4%)	
Age (years)				
Mean	54.8	54.7	53.9	0.10
Race (%)				
White	97.9	98.5	98.3	
Black	1.7	1.1	1.0	
Other/missing	0.3	0.4	0.7	0.09
BMI (kg/m^2)				
Mean	26.6	27.1	27.3	<0.0001
Cigarette smoking (%)				
Never	38.7	36.9	33.8	
Former	44.0	45.1	45.1	
Current	17.3	18.0	21.1	0.007
Attained education (%)				
<High School	22.5	22.5	22.4	
High school graduate	41.1	41.5	42.4	
Some college	15.0	14.9	16.4	
≥College graduate	21.3	21.2	18.8	0.58
Marital status (%)				
Never married	4.0	3.9	2.2	
Currently married	84.2	85.0	84.3	
Other/missing	11.8	11.1	13.5	0.02
Intake[b]				
Meat (servings/day)				
Mean	1.2	1.3	1.4	0.10
Dairy (servings/day)				
Mean	1.6	1.6	1.5	0.003
Tomato products (servings/day)				
Mean	0.31	0.32	0.34	0.17
Alcohol (drinks/day)				
Mean	0.18	0.22	0.27	<0.0001
Family history (%)[c]	7.4	5.6	5.8	0.13
PSA test (%)[c]	61.3	59.1	58.8	0.50

[a] Directly standardized to the age distribution of the analytic cohort

[b] Among 58% of the analytic cohort who returned a valid baseline FFQ

[c] Among 61% of the analytic cohort who returned the 1996 questionnaire

association between cholesterol and high-grade prostate cancer was more pronounced among men with higher BMI. Heavier men with lower circulating cholesterol were less likely to develop high-grade and, possibly, advanced disease. Conversely, there was a suggestion that leaner men with lower circulating cholesterol were more likely to develop advanced stage disease. Although the suggestion of increased risk of advanced disease with low cholesterol among the leaner men did not change when we excluded either the first two years of follow-up time or men with very low BMI (<18 kg/m^2), we cannot rule out the possibility that these results are due to reverse causation. Another possibility is that these results may be consistent with older, pre-PSA era studies that found an increased risk of overall prostate cancer incidence [10, 13] and with one study which found an increased risk of prostate cancer mortality [19] among men with lower total cholesterol concentrations. The case distribution was likely shifted toward more advanced cases in the pre-PSA era, and because obesity has been increasing in the US population over time [28] the study populations in those older studies were likely comparable to the leaner group in our BMI stratified analyses. As the number of advanced prostate cancer cases was limited in this study, an alternative explanation for these results may be due to chance.

Our prospective design, large sample size, and population-based cohort are strengths of this study. We adjusted for many potential confounding factors and conducted

Table 2 Association between serum total cholesterol by clinical cutpoints and prostate cancer, CLUE II 1989-2007

	Plasma total cholesterol concentration (mg/dl)			*P* trend
	Desirable <200	Borderline high 200–<240	High ≥240	
Total				
# cases	200	165	73	
Person-years	33,824	33,044	14,206	
HR (95% CI)[a]	1.08 (0.83–1.41)	0.93 (0.71–1.22)	1.0 (ref)	0.36
HR (95% CI)[b]	1.06 (0.81–1.39)	0.93 (0.70–1.22)	1.0 (ref)	0.47
HR (95% CI)[c]	0.98 (0.75–1.30)	0.87 (0.66–1.15)	1.0 (ref)	0.79
Organ confined				
# cases	84	69	36	
Person-years	33,824	33,044	14,206	
HR (95% CI)[a]	0.92 (0.62–1.36)	0.79 (0.53–1.18)	1.0 (ref)	0.93
HR (95% CI)[b]	0.92 (0.62–1.36)	0.80 (0.54–1.21)	1.0 (ref)	0.88
HR (95% CI)[c]	0.83 (0.55–1.23)	0.74 (0.49–1.12)	1.0 (ref)	0.53
Advanced				
# cases	54	41	18	
Person-years	33,824	33,044	14,206	
HR (95% CI)[a]	1.16 (0.68–1.99)	0.93 (0.53–1.61)	1.0 (ref)	0.41
HR (95% CI)[b]	1.13 (0.66–1.94)	0.91 (0.52–1.59)	1.0 (ref)	0.47
HR (95% CI)[c]	1.14 (0.66–1.97)	0.91 (0.52–1.62)	1.0 (ref)	0.46
Gleason sum < 7				
# cases	87	75	26	
Person-years	33,824	33,044	14,206	
HR (95% CI)[a]	1.35 (0.87–2.09)	1.20 (0.77–1.87)	1.0 (ref)	0.17
HR (95% CI)[b]	1.35 (0.87–2.09)	1.22 (0.78–1.91)	1.0 (ref)	0.19
HR (95% CI)[c]	1.24 (0.79–1.93)	1.11 (0.71–1.75)	1.0 (ref)	0.32
Gleason sum <7/organ confined				
# cases	66	61	22	
Person-years	33,824	33,044	14,206	
HR (95% CI)[a]	1.21 (0.75–1.96)	1.15 (0.71–1.88)	1.0 (ref)	0.47
HR (95% CI)[b]	1.23 (0.75–2.00)	1.19 (0.73–1.94)	1.0 (ref)	0.45
HR (95% CI)[c]	1.10 (0.68–1.81)	1.07 (0.65–1.76)	1.0 (ref)	0.70
Gleason sum ≥7				
# cases	60	49	28	
Person-years	33,824	33,044	14,206	
HR (95% CI)[a]	0.86 (0.55–1.35)	0.73 (0.46–1.16)	1.0 (ref)	0.75
HR (95% CI)[b]	0.83 (0.53–1.30)	0.72 (0.45–1.14)	1.0 (ref)	0.62
HR (95% CI)[c]	0.79 (0.50–1.24)	0.67 (0.42–1.07)	1.0 (ref)	0.51
Gleason sum ≥7/organ confined				
# cases	36	29	21	
Person-years	33,824	33,044	14,206	
HR (95% CI)[a]	0.72 (0.42–1.23)	0.60 (0.34–1.05)	1.0 (ref)	0.37
HR (95% CI)[b]	0.68 (0.40–1.18)	0.58 (0.33–1.02)	1.0 (ref)	0.28
HR (95% CI)[c]	0.65 (0.38–1.12)	0.55 (0.31–0.97)	1.0 (ref)	0.12

[a] Adjusting for age (continuous)

[b] Adjusting for age (continuous), race, BMI, education level, smoking status, intake of meat, dairy, tomato products, and alcohol, family history of prostate cancer, PSA screening, and use of diabetes medications

[c] Excluding men taking cholesterol-lowering medications ($n = 259$ men and 17 total cases), adjusting for age (continuous), race, BMI, education level, smoking status, intake of meat, dairy products, tomato products, and alcohol, family history of prostate cancer, PSA screening, and use of diabetes medications

Table 3 Association between serum total cholesterol by clinical cutpoints and prostate cancer, stratified by BMI, CLUE II 1989–2007

Total cholesterol (mg/dl)	BMI <26.5 (median)				BMI ≥26.5 (median)				*P* interaction
	Desirable <200	Borderline high 200–<240	High ≥240	*P* trend	Desirable <200	Borderline high 200 to <240	High ≥240	*P* trend	
Total									
# cases	118	80	35	0.12	82	85	38	0.45	0.16
HR (95% CI)[a]	1.27 (0.87–1.86)	0.93 (0.62–1.38)	1.0 (ref)		0.89 (0.61–1.31)	0.93 (0.64–1.37)	1.0 (ref)		
HR (95% CI)[b]	1.25 (0.86–1.83)	0.93 (0.62–1.38)	1.0 (ref)		0.86 (0.58–1.27)	0.92 (0.62–1.35)	1.0 (ref)		
Advanced									
# cases	32	19	7	0.11	22	22	11	0.52	0.28
HR (95% CI)[a]	1.71 (0.75–3.87)	1.09 (0.46–2.60)	1.0 (ref)		0.81 (0.39–1.67)	0.83 (0.40–1.70)	1.0 (ref)		
HR (95% CI)[b]	1.72 (0.76–3.91)	1.08 (0.45–2.58)	1.0 (ref)		0.78 (0.37–1.62)	0.80 (0.38–1.65)	1.0 (ref)		
Gleason sum <7									
# cases	50	40	15	0.42	37	35	11	0.34	0.85
HR (95% CI)[a]	1.26 (0.71–2.25)	1.09 (0.60–1.97)	1.0 (ref)		1.45 (0.74–2.84)	1.35 (0.69–2.66)	1.0 (ref)		
HR (95% CI)[b]	1.27 (0.71–2.28)	1.09 (0.60–1.98)	1.0 (ref)		1.44 (0.73–2.83)	1.39 (0.70–2.75)	1.0 (ref)		
Gleason sum <7/organ confined									
# cases	36	32	14	0.83	30	29	8	0.28	0.51
HR (95% CI)[a]	0.98 (0.53–1.81)	0.93 (0.50–1.75)	1.0 (ref)		1.61 (0.74–3.52)	1.54 (0.70–3.37)	1.0 (ref)		
HR (95% CI)[b]	0.96 (0.52–1.79)	0.94 (0.50–1.76)	1.0 (ref)		1.66 (0.76–3.64)	1.64 (0.75–3.60)	1.0 (ref)		
Gleason sum ≥7									
# cases	39	22	10	0.22	21	27	18	0.03	0.03
HR (95% CI)[a]	1.50 (0.75–3.00)	0.90 (0.43–1.91)	1.0 (ref)		0.49 (0.26–0.93)	0.63 (0.35–1.15)	1.0 (ref)		
HR (95% CI)[b]	1.42 (0.71–2.87)	0.89 (0.42–1.89)	1.0 (ref)		0.46 (0.24–0.87)	0.60 (0.33–1.10)	1.0 (ref)		
Gleason sum ≥7/organ confined									
# cases	25	12	8	0.41	12	18	13	0.02	0.04
HR (95% CI)[a]	1.20 (0.54–2.67)	0.62 (0.25–1.51)	1.0 (ref)		0.40 (0.18–0.87)	0.59 (0.29–1.20)	1.0 (ref)		
HR (95% CI)[b]	1.16 (0.52–2.59)	0.61 (0.25–1.49)	1.0 (ref)		0.36 (0.16–0.79)	0.55 (0.27–1.13)	1.0 (ref)		

[a] Adjusting for age (continuous)

[b] Adjusting for age (continuous), race, education level, smoking status, intake of meat, dairy, tomato products, and alcohol, family history of prostate cancer, PSA testing, and use of diabetes medications

stratified analyses. This study was efficient in that serum total cholesterol was measured on all participants at baseline in CLUE. However, we could not evaluate low-density (LDL) and high-density lipoprotein (HDL) fractions with prostate cancer risk as these have not been measured for the majority of the participants in the CLUE II cohort. How LDL and HDL cholesterol relate to intraprostatic cholesterol concentration is unclear. Indeed, one possible limitation of our study is that circulating total cholesterol concentration may not accurately reflect cholesterol concentrations in the prostate. However, given that an association between circulating cholesterol concentration and prostate cancer has now been observed in three prospective studies, it seems plausible that circulating cholesterol concentration may be correlated with prostate biology. It is important to note that while we observed that men with low cholesterol might be less likely to develop high-grade prostate cancer, we were unable to directly assess whether cholesterol-lowering would reduce the risk of high-grade prostate cancer.

Conclusion

This study supports the findings from two recent prospective studies suggesting that cholesterol may be important in the development of high-grade prostate cancer. This observation indirectly supports the hypothesis that cholesterol-lowering may be one of the mechanisms by which statin drugs may protect against prostate cancer with a poorer prognosis.

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