Research Article

Cancer Epidemiology, Biomarkers & Prevention

Cholesterol Levels in Blood and the Risk of Prostate Cancer: A Meta-analysis of 14 Prospective Studies

Liu YuPeng[1], Zhang YuXue[2], Li PengFei[3], Cheng Cheng[4], Zhao YaShuang[1], Li DaPeng[1], and Du Chen[5]

Abstract

Background: As a neutral lipid and prominent component of the Western diet, cholesterol levels might be a risk factor for prostate cancer. However, current evidence has been inconsistent. This meta-analysis aimed to evaluate the association between blood cholesterol levels and the risk of prostate cancer.

Methods: An extensive search was performed in MEDLINE and EMBASE for prospective studies that have reported the association between total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) levels in blood and risk of prostate cancer. Random-effects models were used to summarize the study-specific results.

Results: Fourteen studies were included in this meta-analysis. In the meta-analysis, the summarized risk ratios (RR) for the highest to lowest cholesterol levels were as follows: 1.05 [95% confidence interval (CI), 0.97–1.14; $P = 0.21$] for TC, 0.93 (95% CI, 0.80–1.10; $P = 0.40$) for HDL, and 1.17 (95% CI, 0.88–1.55; $P = 0.51$) for LDL. When restricting to high-grade prostate cancer, the pooled RR was 1.32 (95% CI, 0.93–1.87; $P = 0.13$) for TC. In dose–response analyses, a 1 mmol/L increment in blood TC, HDL, and LDL level conferred an RR of 1.01 (95% CI, 0.99–1.02; $P = 0.38$), 0.98 (95% CI, 0.91–1.07; $P = 0.72$), and 1.04 (95% CI, 0.98–1.10; $P = 0.24$), respectively.

Conclusion: In this meta-analysis of 14 large prospective studies, blood TC, HDL, and LDL levels were not associated with the risk of either overall prostate cancer or high-grade prostate cancer.

Impact: Our findings did not appear to support the hypothesis that hypercholesterolemia increases the risk of prostate cancer.
Cancer Epidemiol Biomarkers Prev; 24(7); 1086–93. ©2015 AACR.

Introduction

Cholesterol, a modified steroid lipid that makes up about one third of the lipid content of the plasma membrane, is an essential structural component of cell membranes (1). Cholesterol is the principal sterol synthesized in the human liver. Major food sources of cholesterol include cheese, egg yolks, beef, pork, poultry, fish, and shrimp (2). Western diets of excess cholesterol may cause hypercholesterolemia in developed countries. Hypercholesterolemia presents with high cholesterol levels in the blood (3). Hypercholesterolemia is not a disease, but a metabolic derangement that can be secondary to many diseases, and can contribute to many types of disease, most notably cardiovascular disease.

Prostate cancer is the second-most frequently diagnosed cancer and the sixth-leading cause of cancer-related death in men (4). Although the causes of prostate cancer are not understood, it is apparent that both genetic factors and environmental factors play important roles in risk of prostate cancer. Geographically, prostate cancer has a high incidence in Western Europe and North America, but a low incidence in Asia (4), which suggests that the Western lifestyle or environment might have a causal role in the incidence of prostate cancer in these areas. In addition, the prevalence of elevated blood total cholesterol (TC) levels was highest in the WHO Region of Europe (54% for both sexes) followed by the WHO Region of the Americas (48% for both sexes); the prevalence of high TC levels was the lowest in the WHO African Region (22.6%) and the WHO South East Asian Region (29.0%; ref. 5). Hence, prostate cancer risk has been suggested to be related to the high levels of circulating cholesterol concentrations.

According to studies of mechanisms and epidemiologic studies, some reviews have proposed that a high blood cholesterol level might be a risk factor for prostate cancer (6–8), and some studies have suggested that high TC level might increase the risk of high-grade or advanced prostate cancer rather than total prostate cancer (6, 9). Some epidemiologic studies and preclinical models also suggest that high levels of cholesterol in blood may be associated with the risk of prostate cancer (6). However, the findings from these epidemiologic studies are inconsistent (10–23), as some studies have reported that high levels of

[1]Department of Epidemiology, School of Public Health, Harbin Medical University, Harbin, China. [2]Department of Preventive Medicine, School of Public Health, Harbin Medical University, Harbin, China. [3]Department of Medical Oncology, The third Affiliated Hospital, Harbin Medical University, Harbin, China. [4]Laboratory Center, Heilongjiang Entry-Exit Inspection and Quarantine Bureau, Harbin, China. [5]Department of Urology Oncology, The third Affiliated Hospital, Harbin Medical University, Harbin, China.

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

Corresponding Authors: Du Chen, The third Affiliated Hospital, Harbin Medical University, 150 Haping Road, Harbin, Heilongjiang 150086, China. Phone: 86-0-451-8629-8072; Fax: 86-0-451-8750-2885; E-mail: duchenharbin@163.com; and Li DaPeng, School of Public Health, Harbin Medical University, 157 Baojian Road, Harbin 150086, China. E-mail: ldroc1987@gmail.com

doi: 10.1158/1055-9965.EPI-14-1329

AACR

cholesterol increased risk of prostate cancer (15, 16, 18), and some studies have reported no association between cholesterol and risk of prostate cancer (10–14, 17, 19, 21–23). Moreover, high cholesterol has been proposed to be closely associated to late-stage prostate cancer, and cholesterol may play a promotional role in late-stage prostate cancer development and progression (11, 15, 18, 19). Therefore, this meta-analysis comprehensively summarized the results of prospective studies that focused on the association between blood cholesterol level and risk of prostate cancer.

Materials and Methods

Search strategy

We systematically reviewed MEDLINE and EMBASE through March 2014 to identify all relevant articles. We used the following MeSH terms for exposure: lipid level, cholesterol, high-density lipoprotein, HDL, low-density lipoproteins, LDL. We combined these terms with the following terms using corresponding free-text words for the outcomes: prostate neoplasm, prostate neoplasms, prostatic neoplasm, prostatic neoplasms, prostate cancer, prostate cancers, prostatic cancer, and prostatic cancers. Moreover, we reviewed reference lists from retrieved articles to identify any potentially relevant studies. This systematic review was planned, conducted, and reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE; Supplementary Table S1; ref. 24).

Inclusion criteria

We included studies if they met the following criteria: (i) studies published in English; (ii) studies designed as a prospective method (including cohort, case–cohort, and nested case–control); (iii) exposure factors were levels of cholesterol (TC, LDL, or HDL) in blood serum or plasma; (iv) the outcome of interest was prostate cancer; (v) relative risk (RR), odds risk (OR), or HR estimates with 95% confidence intervals (CI; or sufficient information to calculate these data) for more than three categories of cholesterol levels were reported; and (vi) when duplicated reports were published from the same population, we included the most recent or complete publications.

Data extraction

Data abstraction was conducted independently by two authors (D. Chen and Z. YaShuang) according to the standard forms specifically created for this systematic review and meta-analysis, and any disagreement was resolved by consensus. The following information was extracted for each retrieved article: name of the first author, publication year, study design, study period or follow-up time, country, mean age or age range of participants at baseline, number of prostate cancer cases, sample size, variables that were adjusted for or matched in each retrieved article, and effect estimates with corresponding 95% CIs for the highest versus the lowest categories of blood TC, LDL, or HDL cholesterol levels.

Quality assessment

We chose to use the 9-star Newcastle-Ottawa Scale (NOS) to assess the studies' quality (Supplementary Table S2; ref. 25). The NOS consists of three parts of quality: selection, comparability, and outcome. The maximum points for four points for selection, two points for comparability, and three points for outcome were assigned, respectively. Quality assessment was conducted independently by two authors (D. Chen and Z. YaShuang), and discrepancies were resolved by consensus.

Statistical analysis

The maximally adjusted effect estimates with 95% CIs were used in this meta-analysis. Of the included studies, some calculated ORs or RRs using logistic regression analysis to estimate the risk of prostate cancer; other studies calculated HRs using Cox proportional hazard models. Because the prostate cancer incidence was low, we used both HRs and ORs to approximate RRs. Study-specific effect estimates were pooled using a random-effect model meta-analysis. We first separately pooled RRs with the corresponding 95% CIs for the highest versus the lowest categories of blood TC, LDL, and HDL cholesterol levels. The pooled RRs between cholesterol levels and high-grade prostate cancer were also calculated.

To evaluate the dose–response relationship between the levels of blood TC, HDL or LDL and the risk of prostate cancer, we used the method described by Orsini and colleagues (26) using all available category points from each study. In linear dose–response analysis, the generalized least-square (GLST) regression model was used to evaluate the study-specific linear trends. The GLST model included a fixed-effects model and a random-effects model. In our analysis, we observed obvious heterogeneity after accounting modifiers, random-effects model was necessary to estimate summary trend according to Orsini and colleagues opinion. Because the included studies used two different measurement units of mmol/L and mg/dL for blood cholesterol, we converted these into mmol/L (blood TC, HDL, and LDL, 1 mg/dL = 0.026 mmol/L). As only a few studies reported the HDL and LDL, we only performed subgroup analysis for TC by study population (American, European, and Asian), study design (cohort study versus others), duration of follow-up (<10 years vs. ≥10 years), number of patients with prostate cancer (<1,000 vs. ≥1,000), and adjustment for body mass index (BMI; yes vs. no). Sensitivity analyses were repeated using a fixed-effect model and were used to evaluate whether the results could have been markedly changed by removing the most relatively weighted study from each subgroup analysis.

The statistical heterogeneity of the risk estimates was assessed by using the Q and I^2 statistics. For I^2 statistics, we considered low, moderate, and high degrees of heterogeneity to be I^2 statistics below 25%, 25% and 75%, and above 75%, respectively. The publication bias was evaluated with a funnel plot and was further examined quantitatively using the Begg's rank correlation and Egger's linear regression tests for funnel plot asymmetry. All statistical analyses were performed using Stata statistical software version 12 (StataCorp.); all P values were two-sided, and P values <0.05 were chosen for significance.

Results

Literature search

Supplementary Fig. S1 shows the results of the literature search. We retrieved 1,276 articles (1051 in MEDLINE and 225 in EMBASE) in our initial searches. After screening titles and abstracts, 38 studies were considered to be potentially eligible; after retrieving full texts, there were 8 retrospective studies and 2 studies that reported RRs by per unit only. In addition, 2 prevalence studies and 12 duplicates were excluded. In total, 14 articles (1 nested case–control study, 3 randomized intervention studies,

Table 1. Characteristics of prospective studies on serum cholesterol and prostate cancer

Source	Study design	Location	Name of cohort	Follow-up years	Sample size	Age, y	Exposure	Range of exposure	Outcome (no. of cases)[a]	Study quality[b]
His et al. (10)	Randomized intervention trial	France	SU.VI.MAX Cohort	8–13	3,148	49.00 (mean)	TC&HDL&LDL	TC: Q1 (<5.53), Q4 (>6.80) mmol/L HDL: Q1 (<1.51), Q4 (>1.91) mmol/L LDL: Q1 (<3.39), Q4 (>4.35) mmol/L	PCa (128)	8
Häggström et al. (13)	Cohort study	Norway, Sweden, and Austria	the Metabolic Syndrome and Cancer (Me-Can) project	12 (mean)	2,89,886	43.9 (mean)	TC	TC: Q1 = 4.28,Q5 = 7.43 mmol/L	PCa (6,673)	8
Jacobs et al. (12)	Nest case–control study	USA	the Cancer Prevention Study II Nutrition Cohort	6–9	14,241	50–79	TC&HDL&LDL	TC: Q1 (<165), Q4(≥207) mg/dL HDL: Q1 (<36), Q4 (≥51) mg/dL LDL: Q1(<88), Q4 (≥128) mg/dL	Aggressive PCa (236) High grade (245)	8
Shafique et al. (11)	Cohort study	Scotland, UK	The Midspan studies	37	12,276	45–64	TC	TC: Q1(<5.05),Q5 (≥6.7) mmol/L	PCa (650) High grade (176)	8
Farwell et al. (18)	Rerospective cohort study	USA	Statins user of Veterans Affairs (VA) New England Healthcare System	2–11	55,875	66 (mean)	TC&HDL&LDL	TC: Q1 (<176),Q4 (>237) mg/dL HDL: Q1 (<37),Q4 (>51) mg/dL LDL: Q1 (<105), Q4 (>158) mg/dL	PCa (349) High grade (85)	8
Grundmark et al. (17)	Cohort study	Sweden	ULSAM	34	2,322	50 (mean)	TC	TC: Q1 (≤ 6.24), Q3 (>7.27) mmol/L	PCa (208)	7
Mondul et al. (2)	Randomized intervention trial	Finland	ATBC	21 (mean)	29,093	50–69	TC&HDL	TC: Q1 (<200), Q3 (≥240) mg/dL HDL: Q1 (<40), Q3 (≥60) mg/dL TC: Q1 (<5.1), Q4 (≥6.5) mmol/L	PCa (2,041) High grade (231)	8
Van Hemelrijck et al. (2)	Cohort study	Sweden	AMORIS	8.23 (mean)	2,00,660	>35	TC&HDL&LDL	HDL: Q1 (<1.13), Q4 (≥1.65) mmol/L LDL: Q1 (<3.19), Q4 (≥4.52) mmol/L	PCa (5,112)	7
Kitahara et al. (2)	Cohort study	Korea	Korean NHIC	11–14	53,944	45.08 (mean)	TC	TC: Q1 (<160), Q5 (≥240) mg/dL	PCa (2,480)	8
Mondul et al. (19)	Cohort study	USA	CLUE II cohort	11.9 (mean)	6,816	≥35	TC	TC: Q1 (<200), Q3 (≥240) mmol/L	PCa (443)	8
Iso et al. (22)	Cohort study	Japan	JPHC	10–14	33,368	40–69	TC	TC: Q1 (<5.0), Q4 (≥6.7) mmol/L	PCa (2,728)	8
Platz et al. (20)	Randomized intervention trial	USA	PCPT	6–9	5,586	≥55	TC	TC: Q1 (60–181), Q5 (241–408) mg/dL	PCa (1,251) High grade (258)	8
Martin et al. (22)	Cohort study	Norway	HUNT2	8–10	29,364	≥20	TC&HDL	TC: Q1 (<5.0), Q4 (≥6.7) mmol/L HDL: Q1 (<1.1), Q4 (≥1.5) mmol/L	PCa (687) High grade (86)	8
Steenland et al. (23)	Cohort study	USA	NHANES1	12–16	14,407	25–74	TC	TC: Q1(<190), Q4 (>246) mg/dL	PCa (156)	8

Abbreviations: Q, quartile or quintile; PCa, prostate cancer.

[a]High-grade, Gleason score of prostate cancer ≥7.

[b]Study quality was judged on the basis of the Newcastle-Ottawa Scale (range, 1–9 stars).

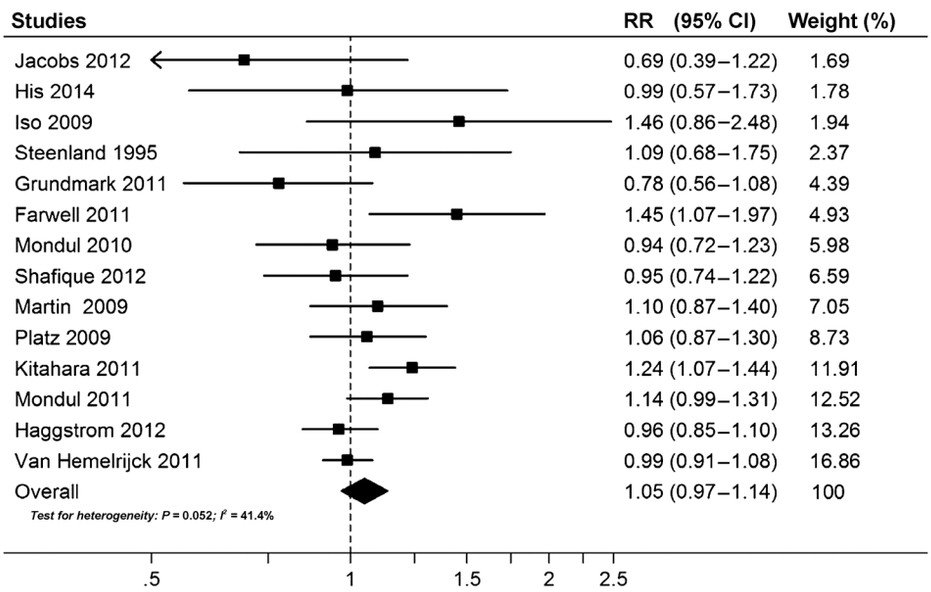

Figure 1.
Adjusted relative risks of prostate cancer for the highest versus lowest categories of TC level. The studies are ordered on the basis of their relative weight in the random-effect model.

and 10 cohort studies) were included in this analysis (10–23). In the 14 included studies, the retrospective cohort study by Farwell and colleagues (18) was also included because it prospectively measured serum cholesterol levels.

Study characteristics and quality assessment

The characteristics of the 14 included studies are summarized in Table 1. The additional information (levels of HDL and LDL, adjusted variables) are shown in Supplementary Table S3. The 14 included studies were published between 1995 and 2014. The follow-up duration ranged from 6 years up to 36 years. In the 14 included studies, 5 studies were conducted in the American population, 7 in the European population, and 2 in the Asian population. Most studies adjusted or controlled risk estimates by age (12 studies) or BMI (8 studies).

For TC, there were 23,142 prostate cancer cases from the 14 included studies across 737,217 total participants. As for HDL, 6 studies reported the association between blood HDL levels and the risk of prostate cancer. Only 4 studies reported the RRs of blood LDL levels relating to the prostate cancer risk.

Total cholesterol

Highest versus lowest of TC. The pooled results combined for the highest versus lowest TC levels are shown in Fig. 1. For the association between TC levels and risk of prostate cancer, the general studies reported null results with the exception of the two Asian studies. The overall pooled RR for the highest versus lowest levels of TC was 1.05 (95% CI, 0.97–1.14; $P = 0.21$). There was moderate heterogeneity in the results of the association between TC ($I^2 = 41.44\%$, P for heterogeneity = 0.05) and the risk of prostate cancer. When restricting to patients with prostate cancer of a high grade, there was still no obvious association between TC and risk of prostate cancer with a high cancer grade (RR, 1.32; 95% CI, 0.93–1.87; $P = 0.13$; Table 2).

Dose–response analysis. For the dose–response analysis, 12 studies were included to assess the dose–response relationship between TC and the risk of prostate cancer. The summary RR was 1.01 (95% CI, 0.99–1.02; $P = 0.38$; Supplementary Table S4) using two-stage random-effects dose–response model with heterogeneity ($P = 0.001$). We did not detect the potentially nonlinear dose–response relationship ($P = 0.19$; Fig. 2 and Supplementary Table S4).

Subgroup analyses. The stratified analyses were defined by the study population, study design, follow-up times, number of patients with prostate cancer, and adjustment for BMI (Table 2). The effects of TC on the risk of prostate cancer differed across different populations (Table 2). TC was not related to the risk of prostate cancer in the European population (RR, 1.01; 95% CI, 0.94–1.07; Table 2) and the American population (RR, 1.06; 95% CI, 0.88–1.29; Table 2), whereas TC significantly increased the risk of prostate cancer in the Asian population (RR, 1.25; 95% CI, 1.05–1.49; Table 2). For the heterogeneity of pooled results of TC, the subgroup analysis by study population showed that the heterogeneity was substantially reduced in different study populations (Table 2).

HDL and LDL cholesterol

Highest versus lowest of HDL and LDL. The pooled RRs of prostate cancer for the highest versus lowest of HDL and LDL levels were 0.93 (95% CI, 0.80–1.10; $P = 0.40$; Fig. 3) and 1.17 (95% CI, 0.88–1.55; $P = 0.51$; Fig. 3), respectively. There was statistically significant moderate heterogeneity among studies of HDL ($I^2 = 61.00\%$, P for heterogeneity = 0.03) and LDL ($I^2 = 63.8\%$, P for heterogeneity = 0.04). Neither HDL (RR, 1.21; 95% CI, 0.63–2.30; $P = 0.57$) and LDL (RR, 1.30; 95% CI, 0.35–4.80; $P = 0.69$) were related to the risk of high-grade prostate cancer. Because a relatively small number of studies reported the association between HDL, LDL, and the risk of prostate cancer, we did not perform subgroup analyses of HDL and LDL.

Dose–response analysis. For the dose–response analysis between HDL and prostate cancer risk, 6 studies that reported on ≥ 3 categories of HDL levels were included. The summary RR associated with a 1 mmol/L increase in HDL levels was 0.99 (95% CI, 0.91- 1.07; $P = 0.72$; Supplementary Table S4) using a two-stage random-effects dose–response model with heterogeneity ($P =$

Table 2. Subgroup analysis and publish bias analysis

	No. of studies	RR (95% CI)	P	Heterogeneity P	Heterogeneity I^2 (%)	$P_{interaction}$	Publish bias (P) For Begg's rank correlation test	Publish bias (P) For Egger's linear regression test
TC and PCa risk	14	1.05 (0.97–1.14)	0.21	0.05	41.44	NA	0.83	0.84
High grade	6	1.32 (0.93–1.87)	0.13	0.02	63.56	NA	1.00	0.98
Study population								
European	7	1.01 (0.94–1.07)	0.87	0.35	11.06	0.02	1.00	0.74
American	5	1.06 (0.88–1.29)	0.53	0.14	42.83		0.81	0.69
Asian	2	**1.25 (1.05–1.49)**	**<0.001**	0.56	0.00		NA	NA
Study design								
Cohort study	10	1.05 (0.95–1.16)	0.33	0.03	51.06	0.65	0.59	0.48
Others	4	1.09 (0.97–1.22)	0.15	0.38	1.73		0.09	0.14
Follow-up time (years)								
<10	5	1.06 (0.93–1.22)	0.39	0.10	49.31	0.85	0.46	0.63
≥10	9	1.05 (0.94–1.16)	0.82	0.09	42.40		0.92	0.68
Adjustment for BMI								
Yes	8	1.05 (0.95–1.16)	0.22	0.03	60.30	0.94	0.55	0.77
No	6	1.05 (0.91–1.20)	0.52	0.22	26.11		0.71	0.85
No. of PCas								
<1,000	8	1.01 (0.87–1.16)	0.95	0.16	33.92	0.45	0.39	0.56
≥1,000	6	1.07 (0.98–1.18)	0.13	0.05	55.66		0.26	0.20
HDL and PCa risk	6	0.93 (0.80–1.10)	0.40	0.03	61.00	NA	1.00	0.59
High-grade	3	1.21 (0.63–2.30)	0.57	0.001	85.60	NA	1.00	0.58
LDL and PCa risk	4	1.17 (0.88–1.55)	0.29	0.04	63.83	NA	1.00	0.61
High-grade	2	1.30 (0.35–4.80)	0.69	0.003	88.40	NA	NA	NA

Abbreviations: NA, not available; PCa, prostate cancer.

0.02). We did not detect a potentially nonlinear dose–response relationship ($P = 0.06$; Fig. 4 and Supplementary Table S4). When examining LDL, 4 studies were included to assess the dose–response relationship between LDL and risk of prostate cancer. A 1 mmol/L increment in LDL level conferred an RR of 1.04 (95% CI, 0.98–1.10; $P = 0.24$; Supplementary Table S4) using the two-stage random-effects dose–response model with heterogeneity ($P = 0.03$). We found no evidence of a statistically significant departure from a nonlinear dose–response relationship ($P = 0.49$; Fig. 4 and Supplementary Table S4).

Sensitivity analyses and published bias

The sensitivity analyses by repeating the analysis with fixed-effect models showed that all of the pooled results were consistent (Supplementary Table S5) with the exception of the subgroup of TC by high-grade prostate cancer and the pooled results between HDL and the risk of prostate cancer. In addition, the sensitivity analyses showed that none of the individual studies substantially affected the pooled results for any of the outcomes (Supplementary Table S5). No evidence of publication bias was found by using funnel plots (Supplementary Fig. S2), the Begg's rank correlation test, or the Egger's regression test (Table 2).

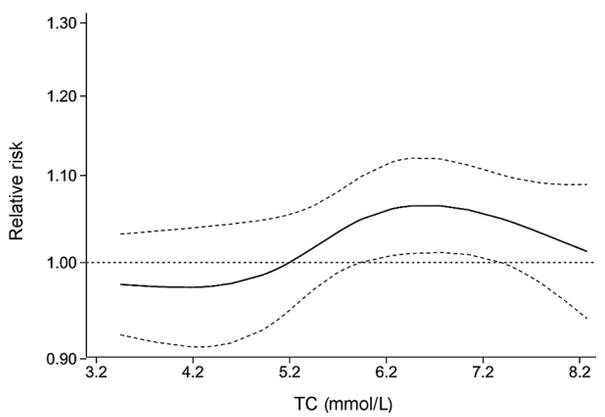

Figure 2.
Dose–response relationship between TC level and relative risk of prostate cancer. Dotted lines represent the 95% CIs for the fitted trend.

Discussion

In this meta-analysis of 23,142 prostate cancer cases, we did not observe any association between risk of prostate cancer and blood levels of TC, HDL, or LDL. When restricting to those patients with a high-grade of prostate cancer, blood TC, HDL, and LDL levels were not associated with the risk of high-grade prostate cancer. All of the subgroup analyses also showed no association between blood TC levels and risk of prostate cancer, with exception of a subgroup of Asian participants from only 2 studies.

This meta-analysis showed that higher levels of TC, HDL, or LDL in the blood were not associated with the risk of prostate cancer or high-grade prostate cancer. However, some retrospective studies and preclinical studies have recently proposed that blood cholesterol might play an important role in the progression of prostate cancer. A range of different biologic mechanisms have been proposed, including effects on cell proliferation, inflammation, membrane organization, and steroidogenesis, and it has been proposed that high cholesterol increases the risk of prostate cancer. Some preclinical studies reported that cholesterol levels might affect prostate cell growth and/or survival. Using a xenograft model, Zhuang and colleagues (27) and Solomon and colleagues (28) found that hypercholesterolemia accelerated the growth of prostatic tumors, whereas hypocholesterolemia had the opposite effect and retarded tumor growth. Using the TRAMP mouse model, an autochthonous model of prostate cancer, hypercholesterolemia was shown to result in increased tumor volume and progression as well as increased tumor incidence and metastases to the lung (29). Some experimental studies also

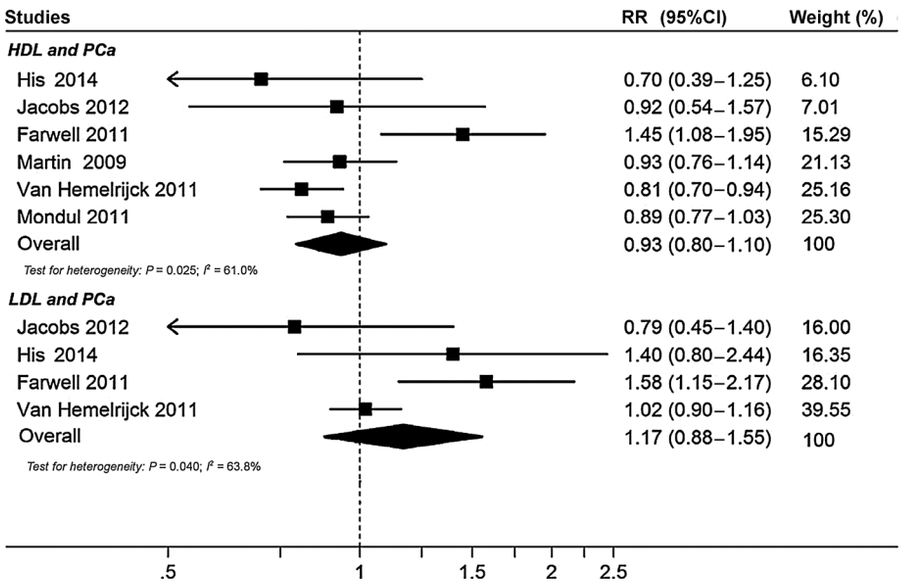

Figure 3.
Adjusted relative risks of prostate cancer for the highest versus lowest categories of HDL and LDL level. The studies are ordered on the basis of their relative weight in the random-effect model.

showed that cholesterol was an important element controlling signaling events in prostate cancer cells (27, 30, 31). Some case–control studies were conducted to assess the role of cholesterol in prostate cancer incidence and progression. A hospital-based case–control study involving 312 prostate cancer patients found a significant association between TC and prostate cancer risk (OR, 1.58; 95% CI, 1.11–2.24; ref. 32). In another case–control study that included 1,294 prostate cancer cases using self-reported history, Bravi and colleagues (33) reported that men with hypercholesterolemia had a higher risk of prostate cancer (OR, 1.51; 95% CI, 1.23–1.85). Nevertheless, case–control studies have some obvious limitations, such as recall bias, selection bias, or survivor bias. In contrast, prospective studies, which have a clear time sequence from causes to diseases, start from exposures and observe the occurrence of the outcome prospectively over time. Moreover, the results from the 14 included prospective studies with large sample sizes have notable clinical and public health implications to general population. Taken together, prospective studies provide stronger statistical power and demonstrability for causality than retrospective studies to detect a potential relationship between blood cholesterol levels and risk of prostate cancer. However, further study is still needed to explore why the results of retrospective studies and preclinical models differed from the null results of our meta-analysis based on prospective studies. Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors), as a type of cholesterol-lowering drug, have contrasting effects (including reduced intratumoral steroidogenesis, reduced inflammation, reduced proliferation, and changes in lipid rafts) to cholesterol on prostate cancer progression. In addition, the association between use of statins and the risk of prostate cancer has been assessed in several epidemiologic studies. In a recent meta-analysis of 27 observational studies by Bansal and colleagues (34), statin use significantly reduced the risk of both total prostate cancer by 7% (RR, 0.93; 95% CI, 0.87–0.99) and clinically important advanced prostate cancer by 20% (RR, 0.80; 95% CI, 0.70–0.90). In fact, in the subgroup analysis of cohort studies (RR, 0.93; 95% CI, 0.87–1.01) and case–control studies (RR, 0.87; 95% CI, 0.72–1.05), there was no significant association between

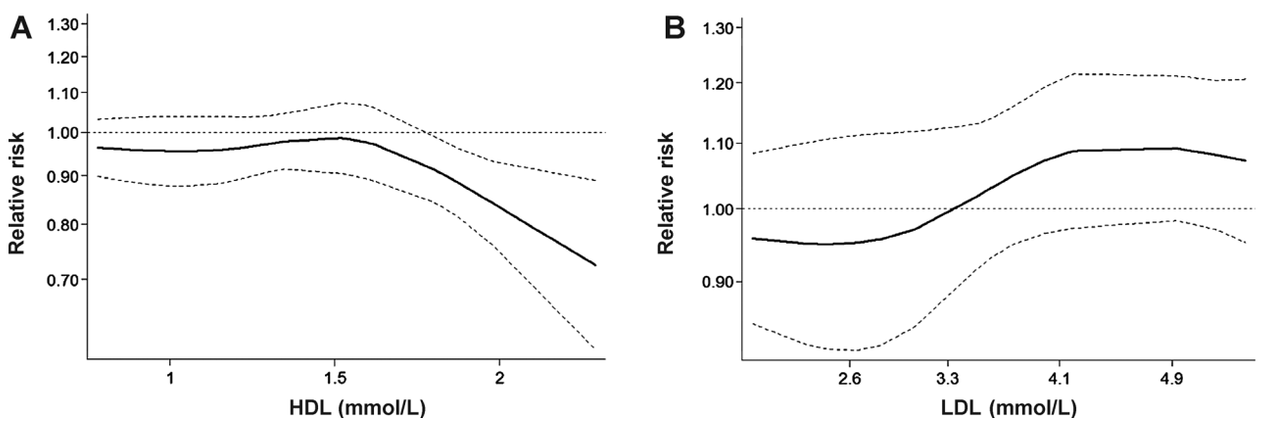

Figure 4.
Dose–response relationship between (A) HDL and (B) LDL level and relative risk of prostate cancer. Dotted lines represent the 95% CIs for the fitted trend.

stain use and prostate cancer risk. Moreover, long-term statin use did not significantly affect the risk of total prostate cancer (RR, 0.94; 95% CI, 0.84–1.05). Hence, those findings from Bansal and colleagues meta-analysis (34) provided evidence that partly supported our results. In addition, a meta-analysis of 27 randomized controlled trials published in the *Lancet* in 2012 reported that there was no association between lowering LDL-C with statins compared with lowering LDL-C with control therapy and total cancer incidence risk (35).

In subgroup analyses of TC, we noted that high TC concentrations only significantly increased the risk of prostate cancer in the Asian population. Explaining the different effects of TC on the risk of prostate cancer in different populations is difficult. However, the incidence of prostate cancer in Asians was significantly lower than the population in developed countries, and there are obvious differences in the diets between Asians and populations in developed countries. Specifically, Western diets have more excess cholesterol than Asian diets. Moreover, there are differences in genetic susceptibility, culture, and lifestyles. Taken together, these reasons may partly explain the inconsistent results. It cannot be ruled out that the reason for the significant effect of TC on risk of prostate cancer was caused by the limited numbers of included studies (only 2 studies).

Regarding HDL, we could not draw a definite conclusion for the nonsignificant association between HDL and prostate cancer risk, based on the currently available evidence in this meta-analysis. The sensitivity analysis showed an inverse association using a fixed-effect model (RR, 0.90; 95% CI, 0.83–0.98; Supplementary Table S5). Meanwhile, there was an inverse association (RR, 0.95; 95% CI, 0.91–0.99; Supplementary Table S4) between HDL levels and prostate cancer risk using linear fixed-effect dose–response analysis and the result ($P = 0.06$; Supplementary Table S4) of nonlinear dose–response analysis was close to the artificial threshold for statistical significance. More relevant studies are warranted to assess the potential effect of HDL on prostate cancer risk.

Strengths and limitations

This meta-analysis had several strengths. First, this meta-analysis is designed to quantitatively summarize the results from only quantitative prospective studies, which could partly eliminate selection bias and recall bias. Second, we included a large sample size of participants (23,142 prostate cancer cases from a total of 737,217 participants) involving different general populations throughout the world. However, this study also has several limitations. First, although the included studies adjusted or controlled for various risk factors (e.g., age, BMI, and physical activity), the unmeasured residual confounders cannot be excluded. Second, blood cholesterol levels were only assessed at baseline in the 14 included studies, which could lead to the loss of information about the change in blood cholesterol levels on the development and progression of prostate cancer. In addition, because of the limited number of included studies that focused on HDL and LDL, we could not use subgroup analyses to evaluate the effect of HDL and LDL on risk of prostate cancer in different subgroups. In addition, we summarized the effect estimates and 95% CIs for the highest versus lowest levels of cholesterol in this meta-analysis, in which different groups were pooled together. Finally, caution is required that the nonsignificant association for high-grade prostate cancer may be due to the limited studies and future well-designed studies are required to clarify this issue.

Conclusion

In conclusion, findings from this meta-analysis of 14 prospective studies suggest that higher levels of TC, HDL, or LDL were not associated with the risk of prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funding source had no involvement in study design, data collection, analysis, interpretation, writing of the report, or decision to submit for publication. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Authors' Contributions

Conception and design: L. YuPeng, L. DaPeng, D. Chen
Development of methodology: L. YuPeng, L. DaPeng, D. Chen
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. YuPeng, Z. YuXue, D. Chen
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. YuPeng, L. PengFei, C. Cheng, Z. YaShuang, D. Chen
Writing, review, and/or revision of the manuscript: L. YuPeng, L. DaPeng, D. Chen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Chen
Study supervision: Z. YaShuang, D. Chen

Grant Support

This work was supported by the Science and Technology Research Project of Department of Education of Heilongjiang Province, China (grant 12531338). L. YuPeng, L. PengFei, and C. Cheng had been awarded this grant.

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 December 4, 2014; revised March 27, 2015; accepted April 9, 2015; published OnlineFirst May 7, 2015.

References

1. Simons K, Vaz WL. Model systems, lipid rafts, and cell membranes. Annu Rev Biophys Biomol Struct 2004;33:269–95.
2. U.S. Department of Agriculture ARSI. USDA National Nutrient Database for Standard Reference-[cited 2014 October 27]. Available from: http://www.ars.usda.gov/ba/bhnrc/ndl.
3. Durrington P. Dyslipidaemia. Lancet 2003;362:717–31.
4. Ferlay J SH, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. [cited 2014 October 27]. Available from: http://globocan.iarc.fr.
5. WHO [Internet]. Global Health Observatory (GHO). [cited 2014 October 27]. Available from: http://www.who.int/gho/ncd/risk_factors/cholesterol_prevalence/en/.
6. Pelton K, Freeman MR, Solomon KR. Cholesterol and prostate cancer. Curr Opin Pharmacol 2012;12:751–9.
7. Krycer JR, Brown AJ. Cholesterol accumulation in prostate cancer: a classic observation from a modern perspective. Biochim Biophys Acta 2013;1835:219–29.
8. Hager MH, Solomon KR, Freeman MR. The role of cholesterol in prostate cancer. Curr Opin Clin Nutr Metab Care 2006;9:379–85.

9. Solomon KR, Freeman MR. The complex interplay between cholesterol and prostate malignancy. Urol Clin North Am 2011;38:243–59.
10. 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.
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. 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.
13. Haggstrom C, Stocks T, Ulmert D, Bjorge T, Ulmer H, Hallmans G, et al. Prospective study on metabolic factors and risk of prostate cancer. Cancer 2012;118:6199–206.
14. Van Hemelrijck M, Garmo H, Holmberg L, Walldius G, Jungner I, Hammar N, et al. Prostate cancer risk in the Swedish AMORIS study: the interplay among triglycerides, total cholesterol, and glucose. Cancer 2011;117: 2086–95.
15. 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.
16. Kitahara CM, Berrington de Gonzalez A, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol 2011;29:1592–8.
17. Grundmark B, Zethelius B, Garmo H, Holmberg L. Serum levels of selenium and smoking habits at age 50 influence long term prostate cancer risk; a 34 year ULSAM follow-up. BMC Cancer 2011;11:431.
18. 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.
19. 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.
20. 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.
21. 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.
22. Iso H, Ikeda A, Inoue M, Sato S, Tsugane S, Group JS. Serum cholesterol levels in relation to the incidence of cancer: the JPHC study cohorts. Int J Cancer 2009;125:2679–86.
23. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. Cancer Epidemiol Biomarkers Prev 1995;4:807–11.
24. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
25. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
26. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175: 66–73.
27. Zhuang L, Kim J, Adam RM, Solomon KR, Freeman MR. Cholesterol targeting alters lipid raft composition and cell survival in prostate cancer cells and xenografts. J Clin Invest 2005;115:959–68.
28. Solomon KR, Pelton K, Boucher K, Joo J, Tully C, Zurakowski D, et al. Ezetimibe is an inhibitor of tumor angiogenesis. Am J Pathol 2009;174: 1017–26.
29. Llaverias G, Danilo C, Wang Y, Witkiewicz AK, Daumer K, Lisanti MP, et al. A Western-type diet accelerates tumor progression in an autochthonous mouse model of prostate cancer. Am J Pathol 2010;177: 3180–91.
30. Graff JR, Konicek BW, McNulty AM, Wang Z, Houck K, Allen S, et al. Increased AKT activity contributes to prostate cancer progression by dramatically accelerating prostate tumor growth and diminishing p27Kip1 expression. J Biol Chem 2000;275:24500–5.
31. El Sheikh SS, Domin J, Abel P, Stamp G, Lalani el N. Phosphorylation of both EGFR and ErbB2 is a reliable predictor of prostate cancer cell proliferation in response to EGF. Neoplasia 2004;6:846–53.
32. 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.
33. Bravi F, Scotti L, Bosetti C, Talamini R, Negri E, Montella M, et al. Self-reported history of hypercholesterolaemia and gallstones and the risk of prostate cancer. Ann Oncol 2006;17:1014–7.
34. Bansal D, Undela K, D'Cruz S, Schifano F. Statin use and risk of prostate cancer: a meta-analysis of observational studies. PloS ONE 2012;7: e46691.
35. Cholesterol Treatment Trialists C. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–90.