REVIEW

Influence of serum total cholesterol, LDL, HDL, and triglyceride on prostate cancer recurrence after radical prostatectomy

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Purpose: The clinical impacts of serum lipid levels on prostate cancer recurrence after radical prostatectomy have been evaluated by several observational studies with conflicting results. We performed the present meta-analysis to summarize the evidence evaluating the role of serum lipid profile in prostate cancer patients.

Methods: We comprehensively searched the PubMed database for potentially relevant studies through January 2019. Pooled hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) for the highest versus the lowest level of serum lipid levels were calculated with the DerSimonian and Laird random-effects model.

Results: A total of 12 eligible studies with 10,978 prostate cancer cases were included in this study. The pooled HRs of prostate cancer recurrence after racial prostatectomy were 0.92 (95% CI 0.73–1.16, $P=0.462$), 0.87 (95% CI 0.56–1.35, $P=0.535$), 1.09 (95% CI 0.92–1.30, $P=0.320$), and 1.01 (95% CI 0.78–1.31, $P=0.938$) for serum total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride, respectively. Sensitivity analysis was conducted by excluding each study sequentially and the results showed that all the summary risk estimates were stable and not influenced by any single study.

Conclusion: The present meta-analysis indicated that serum lipid levels in patients undergoing radical prostatectomy were not associated with prostate cancer recurrence.

Keywords: serum lipids, prostate cancer, recurrence, radical prostatectomy, meta-analysis

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer and the second most common cause of cancer-related mortality in men in developed countries.[1] Radical prostatectomy remains the gold-standard treatment for clinically localized prostate cancer.[2] However, 20–40% of the patients undergoing radical prostatectomy will experience biochemical recurrence within 10 years.[3,4] Well-established risk factors to predict prostate cancer recurrence include prostate-specific antigen (PSA) levels at diagnosis, tumor stage, Gleason score, and surgical margin status.[5,6]

Hyperlipidemia, a condition strongly related to obesity, currently affects about 20% of the adult population in the United States.[7] Cholesterol is hypothesized to participate in prostate cancer pathogenesis as it plays a crucial role in the differentiation and growth of the prostate gland.[8] The impact of dyslipidemia on the risk of prostate cancer recurrence has been evaluated by various epidemiologic studies. Some studies reported positive associations between elevated cholesterol,[9] low-density lipoprotein (LDL),[10] or triglyceride[9] and the risk of prostate cancer

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recurrence, while others reported no associations[11,12] or even inverse associations.[13–15] Therefore, we aimed to investigate the effects of serum lipid levels, including total cholesterol, LDL, high-density lipoprotein (HDL), and triglyceride, on the prostate cancer recurrence after radical prostatectomy based on a meta-analysis of all eligible studies.

Materials and methods
Search strategy
We comprehensively searched PubMed database for potentially relevant studies through January 2019 using the following keywords: (Lipid level or cholesterol or high-density lipoprotein or HDL or low-density lipoprotein or LDL or triglyceride or dyslipidemia) and prostatectomy and (prospective or follow-up or followed up or cohort or longitudinal or nested case-control or case-cohort). In addition, we manually examined the reference lists of retrieved articles and related reviews for additional eligible studies. There was no limitation on publication date or language. We attempted to perform this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16]

Inclusion criteria
Studies included in this meta-analysis met all the following criteria: (i) It was a cohort study in prostate cancer patients after radical prostatectomy; (ii) the exposure of interest was serum lipid profile, including total cholesterol, HDL, LDL, or triglyceride; (iii) the endpoint of interest was prostate cancer recurrence; and (iv) the study provided the hazard ratios (HRs) with their 95% confidence intervals (CIs) for the highest compared with the lowest category of serum lipids. If multiple publications used the same study population, the study with the largest sample size was included in our meta-analysis.

Data extraction
The following information were extracted independently by two investigators (SC and QZ) using a standardized data-collection form: the first author's last name, publication year, study location, study design (prospective or retrospective), length of follow-up, number of participants, rate of recurrence, age of participants, types of exposure, the HRs with their corresponding 95% CIs from the most fully adjusted model, and adjusted variables in the multivariate analysis.

Assessment of study quality
The study quality and risk of bias were evaluated by two independent investigators (SC and QZ) using the Newcastle–Ottawa Scale (NOS). NOS is a 9-star instrument designed to assess the characteristics of the study population, the comparability of the groups, and ascertainment of endpoint of interest. A study with no less than 7 stars was considered as a high-quality study.

Statistical analysis
The study by Allott et al (2016)[9] assessed the association between serum cholesterol and prostate cancer recurrence in black and non-black men separately, which was considered as two independent studies. Risk estimates and their corresponding 95% CIs were not directly available in the study by Ohno et al,[17] which were calculated from the data reported in the articles using the methods proposed by Parmar et al.[18]

Combined risk estimates with their corresponding 95% CIs for the highest versus the lowest level of total cholesterol, LDL, HDL, or triglyceride were calculated with the DerSimonian and Laird random-effects model,[19] which takes into account both within-study and between-study variation. Heterogeneity across studies was tested by Q statistics (significance level set at $P<0.10$) and I^2 statistic (a quantitative measure of inconsistency across studies). Prespecified subgroup analyses and meta-regression models were performed to investigate the potential sources of between-study heterogeneity.

A sensitivity analysis was performed by repeating meta-analysis after omitting each study in turn to determine the influence of a single study. Publication bias was tested by Begg's funnel plot[20] and Egger's regression test.[21] We also used the trim-and-fill method to evaluate publication bias.[22] A two-tailed $P<0.05$ was considered significant, except where otherwise specified. All of the statistical analyses were performed using STATA 11.0 (StataCorp, College Station, TX).

Results
Study selection
Figure 1 presents a flow chart of the study selection process. Searches of the electronic databases yielded 156 potentially eligible studies. After carefully reading the titles/abstracts, most studies were excluded because they were reviews (n=11), non-human studies (n=6), or obviously not related with our topic (n=121). After
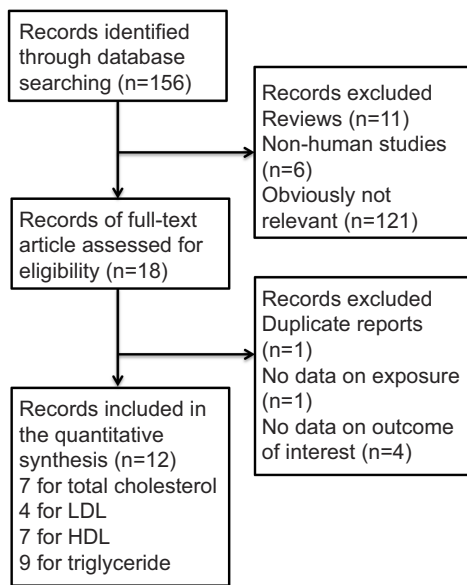
Figure 1 Flow diagram of literature search process. PubMed database was comprehensively searched for potentially relevant studies through January 2019. A total of 156 potentially eligible studies were identified and 12 eligible studies were finally included in this meta-analysis.

assessing the full-text of 18 potentially relevant articles, we identified 12 eligible studies,[9–15,17,23–26] including 13 data sets for analysis; 1 study[9] reported the results separately by racial differences. The main reasons for exclusion were as follows: duplicate reports (n=1), no data on exposure (n=1), and no data on outcome of interest (n=4).

Main characteristics of the included studies

The main characteristics of the 12 included studies are summarized in Table 1. These studies were published between 2010 and 2018, including 8 retrospective and 4 prospective cohort studies. Five studies were conducted in North America, 3 in Europe, and 4 in Asia. The total number of prostate cancer patients was 10,978. The length of the follow-up period ranged from 21 to 134.4 months. Total cholesterol was reported in 7 studies, LDL reported in 4 studies, HDL reported in 7 studies, and triglyceride reported in 9 studies. Definition of recurrence ascertainments was not consistent across studies; most studies used biochemical recurrence data, while some studies used either biochemical recurrence or receiving secondary treatment. NOS scores ranged from 6 to 9, with a mean of 7.75 (Table S1).

Quantitative synthesis

The pooled HRs of prostate cancer recurrence after racial prostatectomy were 0.92 (95% CI 0.73–1.16, P=0.462)

Table 1 Main characteristics of the included studies

Author	Year	Region	Design	Follow-up (months)	No. of cases	Age (years)	Exposure (no.)	Rate of recurrence
Allott et al (black)[9]	2016	USA	R	Median: 32.4	628	Mean: 59.7 (SD: 6.4)	TC (46), LDL (46), HDL (188), TG (92)	181 (29%)
Allott et al (non-black)[9]	2016	USA	R	Median: 36	1020	Mean: 62.3 (SD: 5.8)	TC (69), LDL (88), HDL (433), TG (182)	272 (27%)
Allott et al[23]	2018	USA	P	Median: 45.6	669	Range: 40–79	TC (425)	138 (21%)
Bhindi et al[24]	2016	Canada	P	Median: 31	1939	Mean: 61.5 (SD: 6.9)	HDL (NR), TG (NR)	NR
Kang et al[13]	2015	Korea	R	Median: 21	663	Median: 68 (IQR: 62–72)	TG (109)	66 (10%)
Komaru et al[12]	2010	Japan	R	Median: 35	173	Median: 65 (SD: 5.1)	TC (NR)	NR
Macleod et al[10]	2015	USA	R	Median: 41	1706	NR	LDL (440), HDL (1174), TG (736)	279 (16%)
Ohno et al[17]	2016	Japan	R	Median: 54.0	562	Mean: 65.9 (SD: 6.4)	TC (209)	168 (30%)
Post et al[26]	2011	USA	R	Mean: 49	383	Mean: 60.9	HDL (86), TG (159)	67 (17%)
Rantaniemi et al[14]	2018	Finland	P	Median: 134.4	1314	Median: 64/62	TC (275), LDL (188), HDL (48), TG (145)	435 (33%)
Sanchis-Bonet et al[11]	2015	Spain	R	NR	1319	Mean: 66 (SD: 7.1)	HDL (449), TG (317)	NR
Shiota et al[25]	2014	Japan	R	Median: 14.8	283	Median: 65 (range: 49–78)	TC (NR), TG (NR)	49 (17%)
Wettstein et al[15]	2017	Switzerland	P	Median: 28	319	Median: 63 (range: 41–78)	TC (211), LDL (188), HDL (38), TG (117)	49 (15%)

Abbreviations: R, retrospective; P, prospective; no., number; IQR, inter-quartile range; SD, standard deviation; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; NR, not reported.

(Figure 2), 0.87 (95% CI 0.56–1.35, *P*=0.535) (Figure 3), 1.09 (95% CI 0.92–1.30, *P*=0.320) (Figure 4), and 1.01 (95% CI 0.78–1.31, *P*=0.938) (Figure 5) for serum total cholesterol, LDL, HDL, and triglyceride, respectively.

In the subgroup analysis by study design and geographical region, significant associations were observed for total cholesterol in prospective studies and in Asia studies, for LDL in prospective studies, in retrospective studies, in North America studies, and in Europe studies, and for triglyceride in prospective studies and in Asia studies. There were no significant associations in the rest of the subgroups. Interaction analyses based on meta-regression models indicated that study design and geographical region were the significant sources of heterogeneity for LDL analysis (*P*=0.025) (Table 2). We also performed subgroup analyses by duration of follow-up, number of total patients, and NOS score. The results have been summarized in Table S2. A significant inverse association was
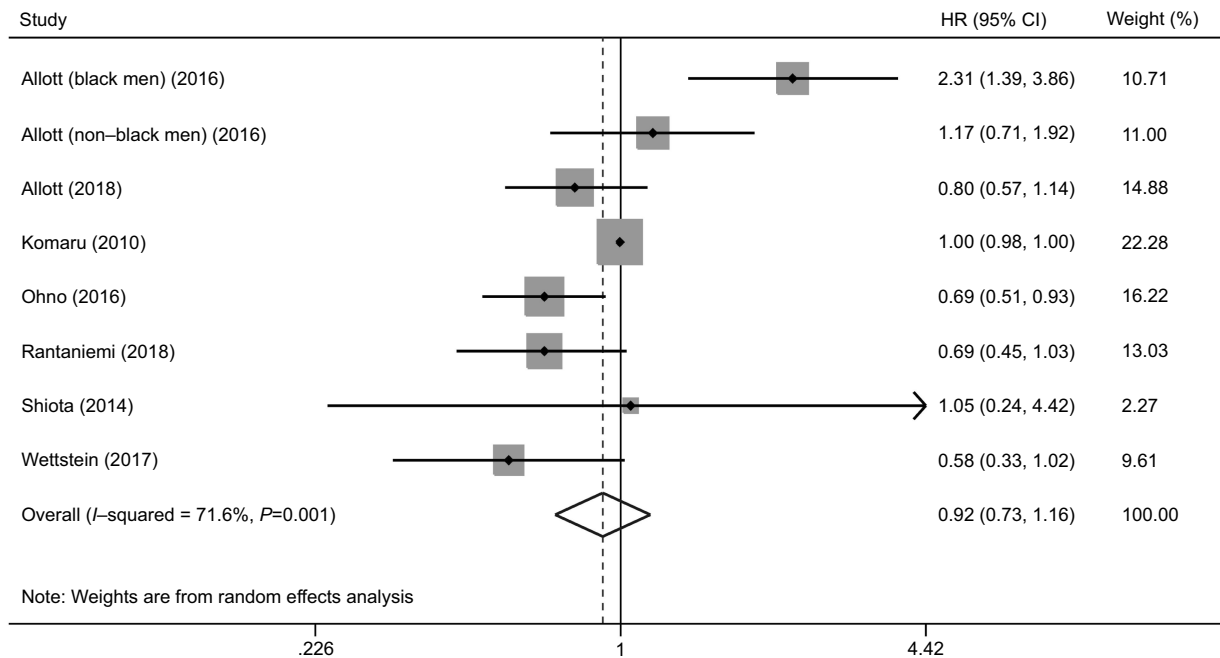

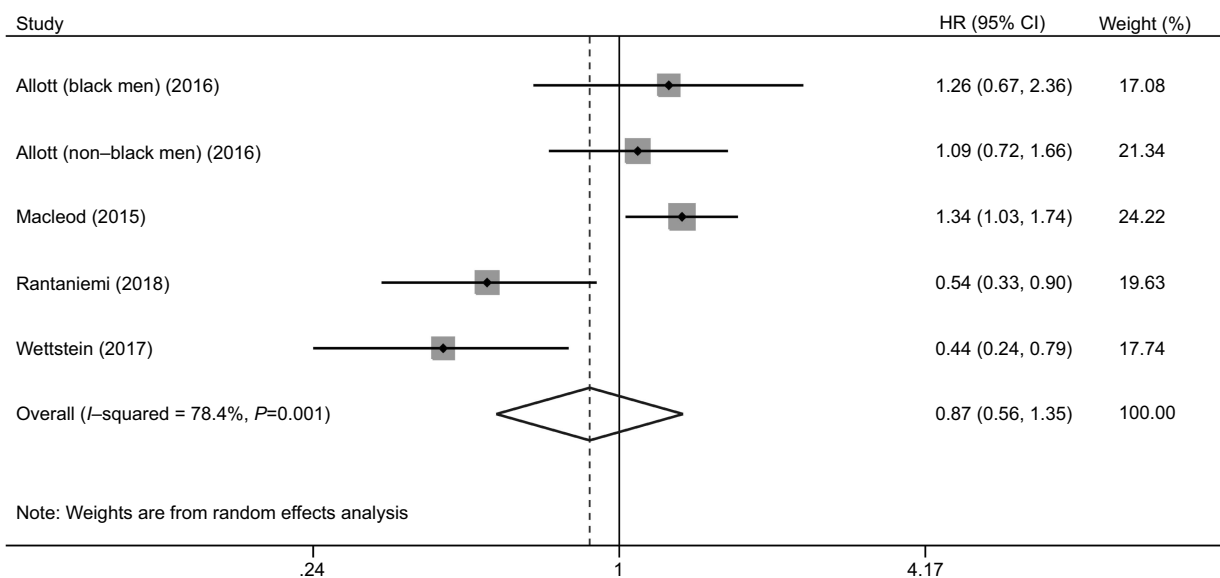**Figure 2** A forest plot of hazard ratio for total cholesterol, which was reported in 7 studies (8 data sets).

Figure 3 A forest plot of hazard ratio for low-density lipoprotein (LDL), which was reported in 4 studies (5 data sets).
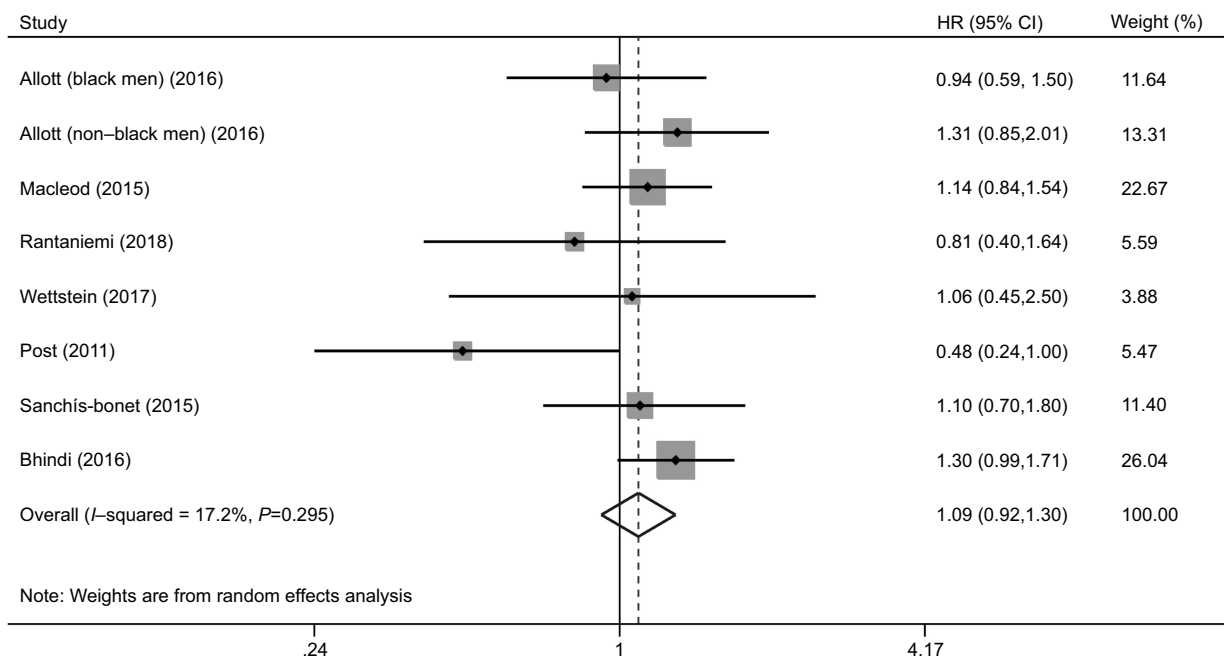
Study		HR (95% CI)	Weight (%)
Allott (black men) (2016)		0.94 (0.59, 1.50)	11.64
Allott (non–black men) (2016)		1.31 (0.85, 2.01)	13.31
Macleod (2015)		1.14 (0.84, 1.54)	22.67
Rantaniemi (2018)		0.81 (0.40, 1.64)	5.59
Wettstein (2017)		1.06 (0.45, 2.50)	3.88
Post (2011)		0.48 (0.24, 1.00)	5.47
Sanchís-bonet (2015)		1.10 (0.70, 1.80)	11.40
Bhindi (2016)		1.30 (0.99, 1.71)	26.04
Overall (*I*–squared = 17.2%, *P*=0.295)		1.09 (0.92, 1.30)	100.00

Note: Weights are from random effects analysis

.24   1   4.17

Figure 4 A forest plot of hazard ratio for high-density lipoprotein (HDL), which was reported in 7 studies (8 data sets).

Study		HR (95% CI)	Weight (%)
Allott (black men) (2016)		1.75 (1.22, 2.52)	12.82
Allott (non–black men) (2016)		1.27 (0.94, 1.72)	13.89
kang (2015)		0.22 (0.05, 0.91)	2.67
Macleod (2015)		0.92 (0.68, 1.25)	13.85
Rantaniemi (2018)		0.91 (0.57, 1.46)	10.93
Shiota (2014)		2.09 (0.28, 11.53)	1.73
Wettstein (2017)		0.69 (0.37, 1.26)	8.72
Post (2011)		1.10 (0.64, 1.70)	10.63
Sanchís-bonet (2015)		1.40 (0.80, 2.20)	10.34
Bhindi (2016)		0.67 (0.51, 0.88)	14.40
Overall (*I*–squared = 68.2%, *P*=0.001)		1.01 (0.78, 1.31)	100.00

Note: Weights are from random effects analysis
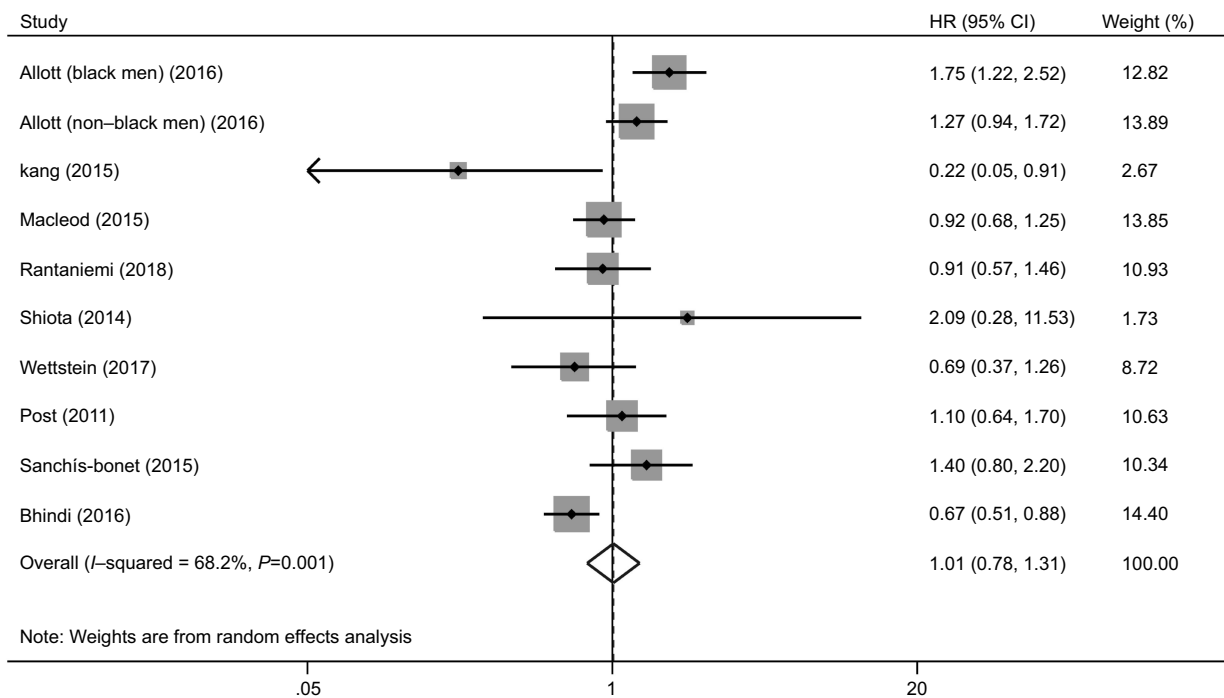
.05   1   20

Figure 5 A forest plot of hazard ratio for triglyceride, which was reported in 9 studies (10 data sets).

observed between total cholesterol and prostate cancer recurrence in studies with long follow-up (≥36 months).

Obvious between-study heterogeneity was observed for total cholesterol (P=0.001, I^2 = 71.6%), LDL (P=0.001, I^2 = 78.40%), and triglyceride (P=0.001, I^2 = 68.20%), except for HDL (P=0.295, I^2 = 17.20%). Sensitivity analysis was conducted by excluding each study sequentially. As shown in Figure 6, all the summary risk estimates for total cholesterol, LDL, HDL, and triglyceride were stable and not influenced by any single study. There was no evidence of significant publication bias based on Begg's test or Egger's test for total cholesterol, LDL, and triglyceride, but not for

Table 2 Subgroup analyses stratified by study design and region

	Total cholesterol			Low-density lipoprotein			High-density lipoprotein			Triglyceride		
	N[a]	HR (95% CI)	P_for interaction	N[a]	HR (95% CI)	P_for interaction	N[a]	HR (95% CI)	P_for interaction	N[a]	HR (95% CI)	P_for interaction
Overall	7	0.92 (0.73–1.16)		4	0.87 (0.56–1.35)		7	1.09 (0.92–1.30)		9	1.01 (0.78–1.31)	
Study design			0.160			0.025			0.494			0.051
Prospective	2	0.72 (0.56–0.91)		2	0.50 (0.34–0.73)		3	1.21 (0.95–1.54)		3	0.72 (0.58–0.90)	
Retrospective	5	1.09 (0.79–1.51)		2	1.26 (1.03–1.56)		4	1.03 (0.80–1.32)		6	1.19 (0.91–1.57)	
Geographical region			0.321			0.025			0.630			0.423
North America	2	1.27 (0.68–2.35)		2	1.26 (1.03–1.56)		4	1.09 (0.85–1.39)		4	1.07 (0.77–1.50)	
Europe	2	0.87 (0.64–1.18)		2	0.50 (0.34–0.73)		3	1.10 (0.70–1.80)		3	0.98 (0.67–1.44)	
Asia	3	0.65 (0.47–0.91)		0	-		0	-		2	0.63 (0.07–5.67)	

Note: [a]The number of studies included.
Abbreviations: HR, hazard ratio; CI, confidence interval.

HDL (Figure 7 and Table 3). The trim-and-fill analysis suggested that no trimming was performed and thus data were unchanged for HDL.

Discussion

The present meta-analysis included 12 cohort studies with a total of 10,978 prostate cancer cases. The results indicated that serum lipid profile, including total cholesterol, LDL, HDL, and triglyceride, was not related with the prostate cancer recurrence after radical prostatectomy. To the best of our knowledge, this is the first meta-analysis aimed to evaluate the impact of dyslipidemia on oncologic outcomes in prostate cancer patients.

Several laboratory studies have investigated the impact of cholesterol levels on the growth of prostate tumors. Zhuang et al[27] found that cholesterol-rich lipid rafts mediated epidermal growth factor (EGF)-induced AKT signaling activation, which promoted the survival of prostate cancer cells. Mostaghel et al[28] reported that hypercholesterolemia increased intratumoral de novo steroidogenesis and thus was able to drive the growth of prostate tumors. Murtola et al[29] proposed that cholesterol metabolism in prostate cancer had been reprogrammed to accelerate the cell growth of prostate cancer. However, epidemiologic evidence for the potential association between serum cholesterol and prostate cancer recurrence was mixed as discussed earlier. Considering that dyslipidemia was a modifiable risk factor and thus potentially had an important role in secondary prevention strategy for prostate cancer recurrence, we performed the present meta-analysis.

The role of serum lipid profile on other human cancers' development has been assessed by various observational studies. A meta-analysis of prospective cohort studies by Lin et al[30] indicated that serum total cholesterol and HDL were inversely associated with lung cancer risk, while triglyceride was positively associated with lung cancer risk. Touvier et al[31] found that there was a modest but statistically significant inverse association between total cholesterol and more specifically HDL and breast cancer risk. As for prognosis analysis, a recent meta-analysis included 26 studies with a total of 24,655 individuals, which suggested that serum total cholesterol and HDL were significantly negatively associated with cancer survival.[32] By contrast, two previous meta-analyses aimed to evaluate the association between blood lipid concentrations and prostate cancer risk did not support the hypothesis that dyslipidemia was related with the risk
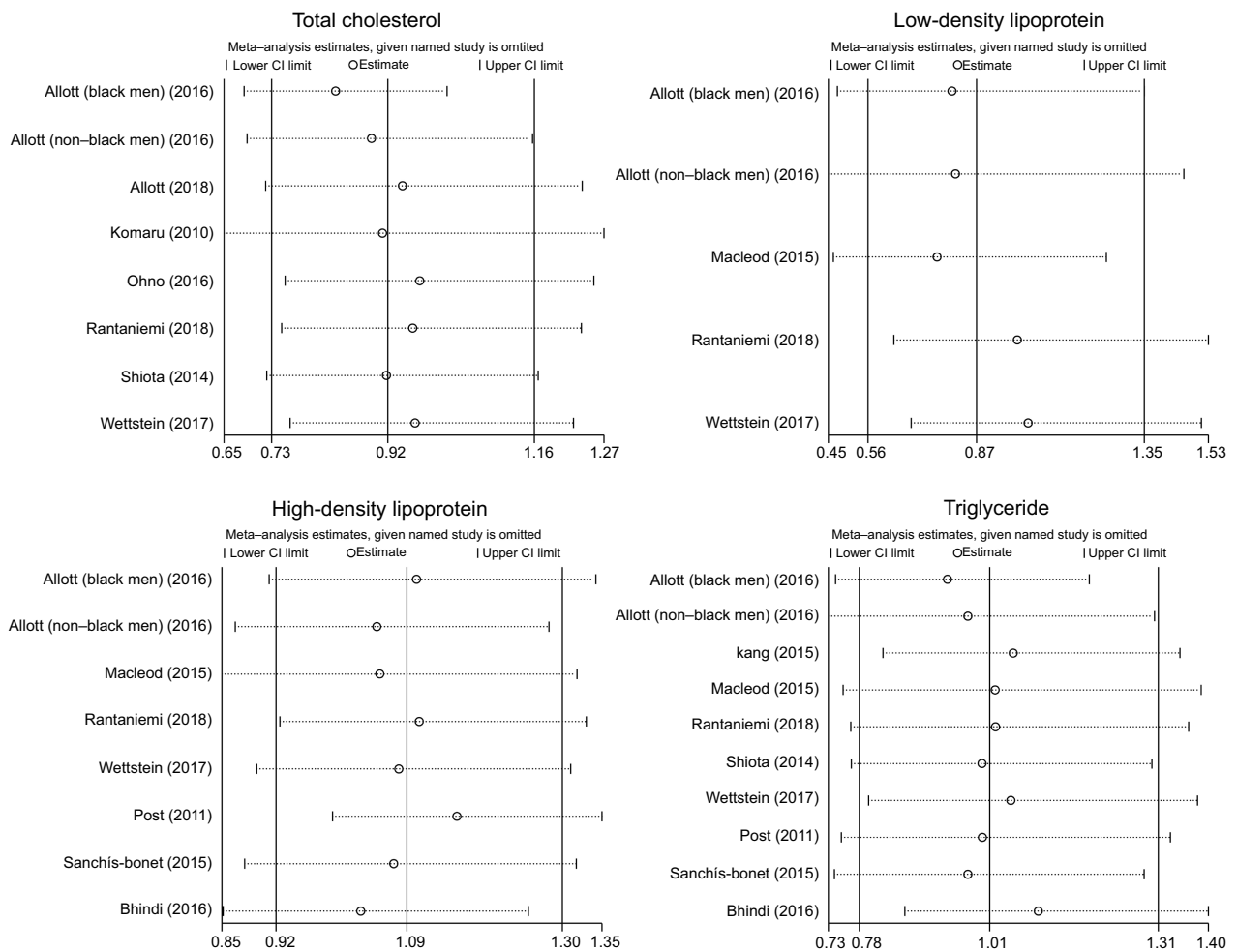
Figure 6 Sensitivity analysis was conducted by excluding each study sequentially and then repeating the meta-analysis to determine the influence of a single study.

of prostate cancer.[33,34] Therefore, the biological role of serum lipid profile played in tumorigenicity may be varied in human cancers.

This present study had several limitations that should be acknowledged. First, obvious heterogeneity was observed across included studies. Heterogeneity was generally caused by the inconsistency of study population, study design, methods of exposure (ie, the methods used to measure the serum metabolites) and outcome assessment, and so on. This can also explain why some studies demonstrated a positive association while others showed a negative association with total cholesterol, LDL, or HDL. Our subgroup analysis and interaction analysis suggested that study design and geographical region were the potential sources of heterogeneity. Second, the number of eligible studies for LDL analysis was relatively limited. In addition, the results of these studies were opposite, which made the summary risk estimate toward null. Further studies are needed to evaluate the role of LDL in

the prognosis of prostate cancer. Third, a certain degree of publication bias was found for HDL analysis. Gray literature (eg, conference abstract) was hard to be found and small studies with null results were less likely to be published. Fourth, the cutoff points for highest versus lowest level of serum lipids varied across included studies, which might distort the summary analysis. Fifth, most of the included studies did not provide the risk estimates according to the patients' Gleason score or tumor stage. Therefore, we were not able to investigate the hazard ratio of lipids with prostate cancer recurrence in context of the Gleason score and tumor stage. Finally, the length of follow-up in part of the included studies was relatively too short to identify enough number of recurrence cases, which reduced the statistical power.

This study also had some strengths. The sample size was relatively large with a total of 12 cohort studies and more than 10,000 prostate cancer patients, which improved the statistical power and reliability of pooled
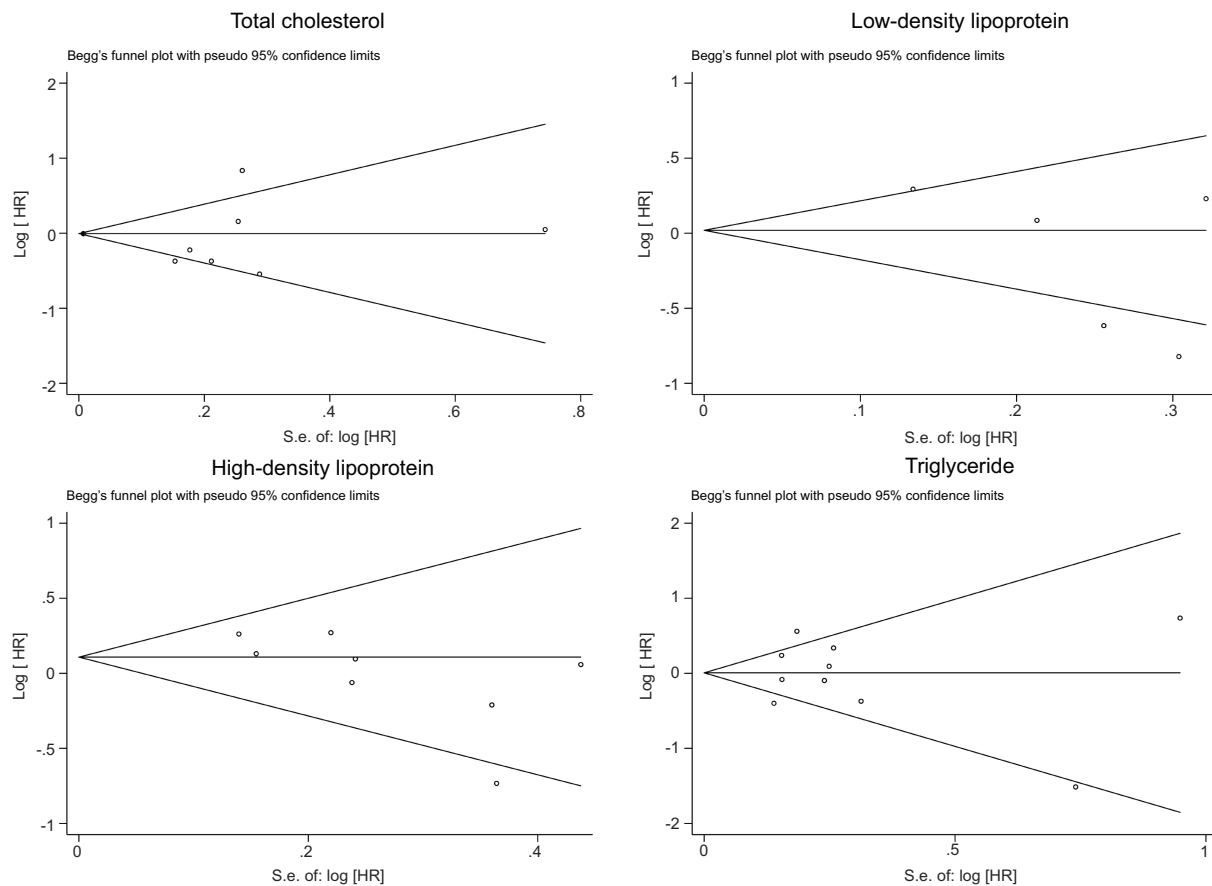
Figure 7 Begg's funnel plots for publication bias. If publication bias is present, the plot will be asymmetrical.

Table 3 *P*-values of Begg's test and Egger's test

	Total cholesterol	**Low-density lipoprotein**	**High-density lipoprotein**	**Triglyceride**
Begg's test	0.902	0.462	0.035	1.000
Egger's test	0.943	0.203	0.029	0.903

results. Sensitivity analyses performed by repeating meta-analysis after omitting each single study in turn indicated that the summary risk estimates were robust and not dominated by any individual study.

Conclusion

The present meta-analysis indicated that serum lipid levels in patients undergoing radical prostatectomy were not associated with prostate cancer recurrence.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Newcastle–Ottawa Scale scores of each included study

Study[a]	Representativeness of the cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability[b]	Outcome assessment	Enough follow-up[c]	Adequacy of follow-up[d]	Total scores
Allott et al (2016)[9]	*	*	*	*	**	*	*	*	9
Allott et al (2018)[23]	*	*	*	*	*	*	*	*	8
Bhindi et al (2016)[24]	*	*	*	*	**	*	*	*	9
Kang et al (2015)[13]	*	*	*	*	*	*	-	*	7
Komaru et al (2010)[12]	*	*	*	*	-	*	*	*	7
Macleod et al (2015)[10]	*	*	*	*	**	*	*	*	9
Ohno et al (2016)[17]	*	*	*	*	-	*	*	*	7
Post et al (2011)[26]	*	*	*	*	**	*	*	*	9
Rantaniemi et al (2018)[14]	*	*	*	*	**	*	*	*	9
Sanchis-Bonet et al (2015)[11]	*	*	*	*	-	*	-	*	6
Shiota et al (2014)[25]	*	*	*	*	-	*	-	*	6
Wettstein et al (2017)[15]	*	*	*	*	-	*	*	*	7

Notes: [a]A study can be awarded a maximum of one star for each item except the item 'Comparability'. [b]A maximum of two stars can be awarded for this item. [c]A cohort study with a follow-up time more than 24 months was assigned one star. [d]A cohort study with a follow-up rate more than 75% was assigned one star.

Table S2 Subgroup analyses stratified by duration of follow-up, No. of patients, and NOS score

	Total cholesterol		Low-density lipoprotein		High-density lipoprotein		Triglyceride	
	N[a]	HR (95% CI)	N[a]	HR (95% CI)	N[a]	HR (95% CI)	N[a]	HR (95% CI)
Follow-up								
≥ 36 months	4	0.78 (0.64–0.96)	3	0.96 (0.58–1.58)	4	0.97 (0.67–1.39)	4	1.06 (0.88–1.27)
<36 months	4	1.10 (0.65–1.85)	2	0.74 (0.26–2.08)	3	1.19 (0.95–1.49)	5	0.85 (0.45–1.59)
No. of patients								
≥ 1000	2	0.88 (0.53–1.48)	3	0.96 (0.58–1.58)	5	1.19 (1.01–1.41)	5	0.98 (0.74–1.29)
<1000	6	0.93 (0.70–1.24)	2	0.74 (0.26–2.08)	3	0.80 (0.51–1.24)	5	1.00 (0.57–1.75)
NOS score								
≥ 7	7	0.91 (0.72–1.16)	5	0.87 (0.56–1.35)	7	1.07 (0.88–1.32)	8	0.96 (0.72–1.27)
<7	1	1.05 (0.24–4.51)	0	-	1	1.10 (0.69–1.76)	2	1.44 (0.88–2.34)

Note: [a]The number of data sets included.
Abbreviations: No., number; NOS, Newcastle–Ottawa Scale; HR, hazard ratio; CI, confidence interval.