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Lycopene and Risk of Prostate Cancer

A Systematic Review and Meta-Analysis

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Abstract: Prostate cancer (PCa) is a common illness for aging males. Lycopene has been identified as an antioxidant agent with potential anticancer properties. Studies investigating the relation between lycopene and PCa risk have produced inconsistent results. This study aims to determine dietary lycopene consumption/circulating concentration and any potential dose–response associations with the risk of PCa. Eligible studies published in English up to April 10, 2014, were searched and identified from Pubmed, Sciencedirect Online, Wiley online library databases and hand searching. The STATA (version 12.0) was applied to process the dose–response meta-analysis. Random effects models were used to calculate pooled relative risks (RRs) and 95% confidence intervals (CIs) and to incorporate variation between studies. The linear and nonlinear dose–response relations were evaluated with data from categories of lycopene consumption/circulating concentrations. Twenty-six studies were included with 17,517 cases of PCa reported from 563,299 participants. Although inverse association between lycopene consumption and PCa risk was not found in all studies, there was a trend that with higher lycopene intake, there was reduced incidence of PCa ($P = 0.078$). Removal of one Chinese study in sensitivity analysis, or recalculation using data from only high-quality studies for subgroup analysis, indicated that higher lycopene consumption significantly lowered PCa risk. Furthermore, our dose–response meta-analysis demonstrated that higher lycopene consumption was linearly associated with a reduced risk of PCa with a threshold between 9 and 21 mg/day. Consistently, higher circulating lycopene levels significantly reduced the risk of PCa. Interestingly, the concentration of circulating lycopene between 2.17 and 85 μg/dL was linearly inversed with PCa risk whereas there was no linear association >85 μg/dL. In addition, greater efficacy for the circulating lycopene concentration on preventing PCa was found for studies with high quality, follow-up >10 years and where results were adjusted by the age or the body mass index. In conclusion, our novel data demonstrates that higher lycopene consumption/circulating concentration is associated with a lower risk of PCa. However, further studies are required to determine the mechanism by which lycopene reduces the risk of PCa and if there are other factors in tomato products that might potentially decrease PCa risk and progression.

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Abbreviations: BMI = body mass index, CC = case-control, CI = confidence interval, HR = Hazard Ratio, MOOSE = Meta-analysis of Observational Studies in Epidemiology, NCC = nested case-control, OR = odd risk, PCa = prostate cancer, RO = risk ratio, RR = relative risk.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and fifth leading cause of death in men. There were 1.1 million patients diagnosed with PCa worldwide in 2012 accounting for 15% of the total diagnosed cancers in men and 307,000 deaths, representing 6.6% of the total male cancer mortality.[1] Diet, lifestyle, environment, and genetics are regarded as risk factors for PCa. A case-control study in Western Australia found that a Western dietary pattern with high intake of red or processed meats, fried fish, chips, high-fat milk and white bread was associated with a higher risk for PCa.[2] In recent decades, growth of the Chinese economy accompanied with a shift towards western lifestyle has been associated with an increased prevalence of PCa in China. The overall incidence of PCa in China increased from 3.80/100,000 in 2001 to 7.10/100,000 in 2011 and in urban areas from 4.49/100,000 to 10.06/100,000).[3,4] The World Cancer Research Fund has reported that a high intake of fruit and vegetable may be beneficial in reducing the risk of cancer including PCa.[5] Tomatoes and tomato products, which contain abundant lycopene, are in particular recommended for PCa prevention. Lycopene, a 40-carbon carotenoid molecule, has been identified as an antioxidant agent with potential anticancer properties and no obvious side effects.[6]

A number of studies have investigated lycopene in relation to PCa risk.[7–31] Some studies[12,20,25,28,31] supported an inverse association, whereas others[7–9,13–19,21–24,26,27,29,30] presented null findings. At present there are 2 meta-analyses studying the association between lycopene and PCa. In a meta-analysis[32] published in 2003, Etminan et al found an inverse association. However a study published in 2013 by Chen et al found no effect.[33] Moreover, these 2 meta-analyses did not evaluate the dose–response association with risk reduction or determine a beneficial range of consumption and both suggested a further study was needed to determine the type and quantity of tomato products for preventing PCa. In 2014, a high-quality 24-years follow-up nested case-control (NCC) study[20] including 51,529 US healthy men suggested a reduced odds of PCa for those with highest lycopene intake when compared to those with lowest

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All authors have fulfilled all conditions required for authorship. PC, WHZ, XHW and XHZ conceived and designed the study. XW, KKZ, DSN, ZL, and QM performed the electronic search, selected studies, extracted data and performed quality assessment. PC, WHZ and XHZ analyzed data and conducted meta-analysis. PC, XHZ, XW and WHZ supervised the research, edited and drafted revisions to the article.
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lycopene intake (hazard ratio [HR] 0.91, 95% confidential interval [CI] 0.84 to 1.00). As inconsistencies between studies may relate to different exposure levels, it is important to determine the shape of the dose–response curve. It is also possible that only those individuals with a low baseline lycopene intake or status may benefit from higher lycopene consumption. However, none of previous reviews have investigated these issues. Therefore we conducted an updated systematic review to clarify whether lycopene intake or serum concentration is inversely related to PCa, with particular emphasis on the shape of the dose–response curve.

METHOD

Search Strategy

Based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE),[34] we carried out and reported the present study. Case-control (CC) or NCC or prospective cohort studies that examined the associations of lycopene intake or circulating (plasma/serum) concentrations with the risk of PCa were analyzed. Databases, including PubMed (from 1950), Sciencedirect Online (from 1998), Wiley online library (from 1960) were searched for articles published up to 10 April 2014. The key search terms used were as follows: ''lycopene,'' ''intake,'' ''consumption,'' ''lycopene concentrations,'' ''prostate,'' ''neoplasm,'' ''humans,'' ''case-control studies,'' ''follow-up studies,'' ''prospective studies'' and their variants. Reference lists from published studies were manually searched to identify additional articles. The approval by an institutional review board is not required because this study was based on published studies.

Eligibility Criteria

Two independent investigators (WHZ, XW) conducted an initial screening of article titles and abstracts to remove duplicate references, letters, comments, reviews, ecological studies, animal studies, single case reports, and meta-analyses. Reviewers used prespecified guidelines to ensure a consistent approach. Then 2 independent investigators (PC and ZL) evaluated all potentially relevant articles based on full text reviews using a structured flow chart and detailed guidelines to determine eligibility for inclusion. Any disagreement was settled by a third reviewer (QM).

Studies were included if they meet the following criteria: first, patients in the case group must be diagnosed with PCa and free of PCa in the control group or the non-case group; second, there was documentation of lycopene intake or circulating concentrations; third, PCa was diagnosed by histology, pathology, biopsy, or histopathology; fourth, original research from observational studies, such as CC, NCC, or cohort studies; fifth, complete data was provided, such as relative risk (RR), risk ratio (RO), odd risk (OR) or HR, number of cases, controls or noncases or person years; finally, there were at least 3 quantitative categories of lycopene intake or circulating concentrations. Studies were excluded if they did not meet all criteria.

Multiple reports from the same cohort study were reviewed and papers with the longest follow-up for identical outcomes were included. If longer follow-up but insufficient data were presented, we chose those complete shorter follow-up ones. Different studies with sufficient data from one article were also included.

Data Extraction and Quality Assessment

Three reviewers (PC, KKZ and DSN) independently performed the data extraction by using a standardized data collection form. We extracted the information as follows: first author, cohort name, publication year, country, age, duration of follow-up, study design, clinical classification of PCa, numbers of cases, numbers of controls or noncases or person years, dose categories, adjusted or crude RR, OR or HR with 95% CI and adjusted variables that entered into the multivariable model as potential confounders. If studies already reported a linear dose–response trend with CI or standard error, they were used directly. For dose–response meta-analysis, the term RR will be used as a generic term for RO (cumulative incidence data), rate ratio (incidence-rate data), odds ratio (CC data) and HR.[35] The mean value or midpoint of the upper and lower boundaries of each category was used to estimate assigned dose. For the lowest quartile, lower boundary was assumed to be 0 if it was not provided. For the open-ended upper category, the assigned dose which was the cut point multiplied by 1.5 was evaluated.[36] Any potential inconsistencies were resolved through discussion.

Methodological quality of studies was evaluated using the Newcastle–Ottawa Scale.[37] Other aspects of study quality, such as follow-up duration, study types, study location, adjustment for various important confounders and clinical classification, were investigated through subgroup analysis.

Statistics Analysis

To derive a linear dose–response curve, the distribution of cases and person-years, or cases and non–cases with RRs and estimates of uncertainty (such as CIs) for at least 3 categories of quantified lycopene intake or circulating concentrations was required to be presented in the included studies. If the total number of cases or person-years was presented without distribution, we estimated the distribution on the basis of definitions of the quantiles. If the unit for circulating concentrations was μmol/L, it was multiplied by 536.85 (relative molecular weight of lycopene) and adjusted to μg/L.

STATA version 12.0 (StataCorp LP, College Station, TX) was applied to analyze the data. RR and 95% CI were used as a measure of the effect size for all studies, as HR and OR would be approximately regarded as RR for low incidence of diseases. The RR and relevant 95% CI of highest vs. lowest category of lycopene intake or circulating concentrations were pooled and an estimated dose–response trend was derived for each study with method recommended by Greenland and Longnecker.[38] These trends were then combined with using random effects meta-analysis, as a random effects model can provide more conservative results than a fixed one for variation between studies.[39] Based on data presented for each category of lycopene intake or circulating concentrations, study specific slopes (with 95% CIs) were generated.

In addition, we examined linear and nonlinear associations between lycopene intake or circulating concentrations and PCa by plotting linear and nonlinear dose–response curves using restricted cubic splines, with 3 knots at fixed centiles (10%, 50%, and 90%) of the distribution.[35,40] Considering the correlation between each published RR,[41] a restricted cubic spline model was estimated with a generalized least squares regression. Then study-specific estimates were combined with the restricted maximum likelihood method.[39]

Heterogeneity among studies was explored with Cochran's Q test and I^2 was applied to quantify the proportion of the total variation in study estimates resulted from that heterogeneity.[42] Sensitivity analyses and subgroup analysis were made to determine whether the results were robust and evaluate the sources of heterogeneity. In sensitivity analyses, the influence of

individual studies on the overall risk was carried out by sequentially omitting one study at each turn. Other methodological features were also evaluated through subgroup analysis, including geographical location (North America, Europe or others); follow-up duration (<10 years or ≥ 10 years); study quality scores (< 8 or ≥ 8), study type, clinical classification (advanced PCa or nonadvanced PCa) as well as confounders, such as age, family history, energy intake, and body mass index (BMI).

Potential publication bias was assessed by using contour-enhanced funnel plots[43] with Egger's linear regression test[44] and Begg's rank correlation test[45] of asymmetry. If evidence of asymmetry was indicated, the trim and fill method was used to recalculate the adjusted estimates with the addition of the missing studies.[46]

RESULTS

Search Results and Study Characteristics

Figure 1 depicts the literature search and the study selection process. We identified 319 articles from the PubMed database, 959 articles from the Sciencedirect database, and 1037 articles from Wiley online library. After excluding duplicates and papers that did not meet the inclusion criteria, 37 full articles of 38 potentially relevant studies were obtained. When full text was reviewed, we further excluded the following articles: 1 article[47] in which the unit for estimate of trend was g/1000 kcal; 3 random control trial[48–50] with different outcomes; 5 studies about lycopene and PCa progression;[51–55] 1 before-after study in which there was no control group;[56] and 2 studies[57,58] conducted by Giovannucci with shorter follow-up than the study conducted by Zu[20] in the same cohort. Since Huang's article[26] contains 2 different studies (CLUE I and CLUE II) in total we identified 25 articles containing 26 studies which met our criteria, with 9 CC studies,[7–15] 17 NCC or cohort studies.[16–31] Totally, 17,517 cases of PCa reported from 563,299 participants were analyzed.

These studies were performed primarily in 2 different regions: North America (18 studies)[9,10,12,15–17,20,21,23–29,31] and Europe (5 studies)[13,18,19,22,30] with other regions, such as New Zealand,[7] Uruguay,[8] Australia[14] and China[11] represented by only 1 study. The main characteristics were presented in Table 1. Table 2 and Table 3 describe detailed outcomes on lycopene intake and circulating concentrations with RRs of PCa risk, respectively.

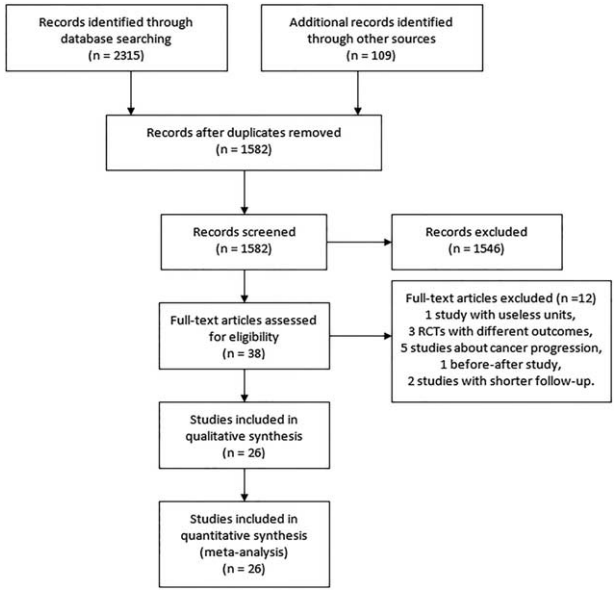

FIGURE 1. Flowchart of literature searches.

Quality Assess

The Newcastle–Ottawa Scale[37] was applied to assess the quality of included studies. As described in Table 4, the mean score was 7 (highest 8 and lowest 6) and 8 (highest 9 and lowest 6) for CC studies and cohort/NCC studies, respectively.

Lycopene Intake and Risk of PCa

A total of 13 studies[7–14,16–20] reported the relevant risk of PCa with lycopene supplementation, including 8 CC studies[7–14] and 5 NCC or cohort studies.[16–20] All of these studies provided complete data allowing dose–response meta-analysis.

As shown in Figure 2, the pooled RR of highest vs. lowest category of total lycopene intake was 0.910 (95% CI 0.819 to 1.011, $P = 0.078$) for all studies, 0.813 (95% CI 0.629 to 1.052, $P = 0.115$) for CC studies, 0.939 (95% CI 0.880 to 1.003, $P = 0.061$) for NCC or cohort studies. Although no statistical significance was found, higher lycopene intake showed a trend to reduce the incidence of PCa. We further carried out several sensitivity analyses. Heterogeneity between studies was mainly caused by 1 Chinese study.[11] After this study was excluded, there was no longer any evidence of significant heterogeneity for highest vs. lowest categories of total lycopene intake (I^2 changed from 45.5% to 0.0%). Moreover, the overall pooled estimates (RR 0.935, 95% CI 0.881 to 0.993, $P = 0.030$) became significant without this study (Figure 3). The heterogeneity test showed moderate heterogeneity ($I^2 = 45.5\%$, $P = 0.037$) among all studies, moderate heterogeneity ($I^2 = 60.6\%$, $P = 0.013$) among CC studies and little heterogeneity ($I^2 = 0.0\%$, $P = 0.504$) among NCC or cohort studies (Table 5).

Dose–response meta-analysis further showed each 5 mg/day increase of lycopene intake decreased the risk of PCa with RR 0.975 (95% CI 0.940 to 1.010, $P = 0.160$) for all studies, 0.894 (95% CI 0.774 to 1.032, $P = 0.126$) for CC studies and 0.979 (95% CI 0.961 to 0.997, $P = 0.023$) for NCC or cohort studies (Figure 4). The heterogeneity test showed moderate heterogeneity ($I^2 = 50.2\%$, $P = 0.020$) among all studies. Again, as shown in Figure 5, there was no longer any evidence of significant heterogeneity for each 5 mg/day increase of lycopene intake on decreasing risk of PCa (I^2 changed from 50.2% to 0.0%) when excluded the Chinese study[11] with pooled estimate (RR 0.979, 95% CI 0.962 to 0.996, $P = 0.017$) for all studies quite similar to the pooled estimate (RR 0.979, 95% CI 0.961 to 0.997, $P = 0.023$) for NCC or cohort studies or consistent with the pooled estimate (RR 0.975, 95% CI 0.995 to 0.995, $P = 0.013$) of high-quality studies (study quality score ≥ 8). Figure 5 also demonstrated that PCa incidence almost lowered by 2.1%. The linear test showed there was a linear relationship between each 5 mg/day increase of lycopene intake on decreasing PCa risk (chi-square = 6.29, $P = 0.012$) without any heterogeneity ($P = 0.109$). Accordingly, the nonlinear test showed there was no nonlinear relationship (chi-square = 0.00, $P = 0.953$). Compared with reference dose (0.1 mg), the approximate RRs of each dose of lycopene intake were as follows: 0.99 (95% CI 0.96 to 1.01) for 3 mg, 0.97 (95% CI 0.93 to 1.01) for 6 mg, 0.96 (95% CI 0.92 to 1.00) for 9 mg,

TABLE 1. Characteristics of the Identified Studies Included in the Meta-Analyses on the Lycopene Status and Prostate Cancer

Author and year	Country	Study Name	Study Type	Age	Follow-up	Measure of Associations	Assessment Method	Endpoints	Case/control
Lycopene intake studies									
Norrish 2000[4]	New Zealand	Auckland Prostate study	PB-CC	40–80	N/A	OR	FFQ	Histology	281/442
Deneo-Pellegrini 1999[5]	Uruguay	N/A	HB-CC	40–89	N/A	OR	FFQ	Histology	175/233
Jain 1999[6]	Canada	Nutrient intake in Canada	PB-CC	69.8	N/A	OR	validated FFQ	Histology	617/636
Cohen 2000[7]	America	N/A	HB-CC	40–64	N/A	OR	FFQ	Histology	654/625
Jian 2005[8]	China	N/A	HB-CC	>45	N/A	OR	validated FFQ	Pathology	130/270
Lu 2001[9]	America	MSKCC	HB-CC	59.98	N/A	OR	HHHQ dietary questionnaire	Pathology	65/132
Key 1997[10]	Britain	EPIC	PB-CC	68.1	N/A	OR	EPIC FFQ	Histology	328/328
Hodge 2004[11]	Australia	N/A	PB-CC	N/A	N/A	OR	FFQ	Histopathology	858/905
Kirsh 2006[13]	America	PLCO	Cohort	63.3	4.2	RR	validated FFQ	Pathology	1338/29361
Agalliu 2011[14]	Canada	CSDLH	NCC	66.2	7	HR	validated FFQ	Pathology	661/1864
Kristal 2010[15]	America and Canada	PCPT	NCC	63.6	10	OR	validated FFQ	Histology or pathology	1703/17415
Schuurman 2002[16]	Netherlands	NLCS	Cohort	55–69	6.3	RR	validated FFQ	Histology or microscopy	642/58179
Zu 2014[17]	America	HPFS	NCC	40–75	24	HR	semiquantitative FFQ	Histology	5728/47898
Circulating concentration									
Kristal 2011[18]	America	PCPT	NCC	63.6	10	OR	validated FFQ	Pathology	1683/1751
Vogt 2002[12]	America	N/A	PB-CC	40–79	N/A	OR	N/A	Histology	209/228
Key 2007[19]	8 European countries	EPIC	Cohort	60.4	8	RR	validated FFQ	Histology	966/1064
Nomura 1997[20]	America	N/A	NCC	62	21	OR	N/A	Pathology	142/142
Peters 2007[21]	America	PLCOCS	NCC	64.7	8	OR	N/A	Histology	692/844
Gann 1999[22]	America	Physicians' Health Study	NCC	60.7	13	OR	N/A	Pathology	578/1294
Huang 2003[23]	America	CLUE I	NCC	45–64	22	OR	N/A	Histology	182/361
Huang 2003[23]	America	CLUE II	NCC	45–64	22	OR	N/A	Histology	142/284
Hsing 1990[24]	America	N/A	NCC	71	12	OR	N/A	Histology	103/103
Wu 2004[25]	America	HPFS	NCC	40–75	5	OR	N/A	Histology	450/450
Beilby 2010[26]	Australia	N/A	NCC	69.8	14	OR	N/A	Histology	96/225
Lu 2001[9]	America	MSKCC	HB-CC	59.98	2	OR	N/A	Pathology	65/132
Karppi 2009[27]	Finland	KIHDRF	NCC	56.2	12.6	RR	N/A	Histology	55/856
Goodman 2003[28]	America	CARET	NCC	45–69	5	OR	N/A	Biopsy	205/205

CARET = β-Carotene and Retinol Efficacy Trial, CC = case-control study, CLUE II = Campaign Against Cancer and Heart Disease, CSDLH = Canadian Study of Diet, Lifestyle and Health, EPIC = European Prospective Investigation into Cancer and Nutrition, FFQ = food frequency questionnaire; HB-CC = population-based case–control study, HPFS = Health Professionals Follow-up Study, HR = hazard ratio, KIHDRF = Kuopio Ischaemic Heart Disease Risk Factor cohort, MSKCC = Memorial Sloan-Kettering Cancer Center, N/A = Not Applicable, NCC = nested case-control study, NLCS = Netherlands Cohort Study, OR = odd risk, PB-CC = population-based case-control study, PCPT = Prostate Cancer Prevention Trial, PLCO = Prostate, Lung, Colorectal, and Ovarian, PLCOCS = Prostate, Lung, Colorectal, and Ovarian Cancer Screening, RR = relative risk.

TABLE 2. Detailed Outcomes on Lycopene Intake and RRs of Prostate Cancer

Author and Year	Country	Study Type	Dose (mg/d)	RR (95%CI)	RR (95%CI) Advanced	RR (95%CI) Nonadvanced	Confounders
Key 1997[13]	Britain	CC	<0.402	1	NA	NA	Social class
			0.402–0.717	0.90 (0.63–1.29)	NA	NA	
			> 0.717	0.99 (0.68–1.45)	NA	NA	
Deneo-Pellegrini 1999[8]	Uruguay	CC	<1.301	1	NA	NA	Age, residence, urban/rural status, education, family history of prostate cancer, body mass index and total energy intake
			1.301–2.501	1.6 (0.9–2.8)	NA	NA	
			2.502–3.300	0.8 (0.4–1.4)	NA	NA	
			> 3.300	1.2 (0.7–2.2)	NA	NA	
Jain 1999[9]	Canada	CC	<2.103	1	NA	NA	Total energy, vasectomy, age, ever-smoked, marital status, study area, BMI, education, ever-used multivitamin supplements
			2.103–5.251	0.90 (0.68–1.19)	NA	NA	
			5.252–12.681	0.90 (0.68–1.19)	NA	NA	
			> 12.681	1.01 (0.76–1.35)	NA	NA	
Cohen 2000[10]	America	CC	<4.900	1	NA	NA	Fat, energy, race, age, family history of prostate cancer, body mass index, prostate-specific antigen tests in previous 5 years, and education
			4.900–6.599	0.93 (0.64–1.35)	NA	NA	
			6.600–9.900	1.23 (0.86–1.76)	NA	NA	
			> 9.900	0.89 (0.60–1.31)	NA	NA	
Norrish 2000[7]	New Zealand	CC	< 0.662	1	1	NA	Age, height, total nonsteroidal anti-inflammatory drugs, and socioeconomic status
			0.662–1.212	0.77 (0.50–1.19)	0.77 (0.50, 1.19)	NA	
			1.213–1.994	0.86 (0.56–1.32)	0.86 (0.56, 1.32)	NA	
			> 1.994	0.76 (0.50–1.17)	0.76 (0.50, 1.17)	NA	
Lu 2001[12]	America	CC	< 1.458	1	NA	NA	Age, race, education, alcohol drinking, pack-years of smoking, family history of prostate cancer, and total dietary caloric intake
			1.458–2.370	1.14 (0.36–3.62)	NA	NA	
			2.371–3.450	0.91 (0.27–3.11)	NA	NA	
			> 3.450	0.69 (0.23–2.08)	NA	NA	
Schuurman 2002[19]	Netherlands	Cohort	0.1	1	1	NA	Age, family history of prostate cancer, socioeconomic status, and alcohol from white or fortified wine
			0.4	0.79 (0.57–1.09)	0.80 (0.49–1.31)	NA	
			0.7	1.08 (0.80–1.47)	1.09 (0.69–1.71)	NA	
			1.1	0.99 (0.72–1.36)	0.94 (0.59–1.50)	NA	
			2.0	0.98 (0.71–1.34)	0.92 (0.57–1.47)	NA	
Hodge 2004[14]	Australia	CC	< 4.092	1	NA	NA	Atate, age group, year, country of birth, socioeconomic group, and family history of prostate cancer
			4.092–5.848	0.9 (0.6–1.2)	NA	NA	
			5.849–8.224	0.8 (0.6–1.0)	NA	NA	
			8.225–11.088	0.9 (0.6–1.2)	NA	NA	
			> 11.088	0.8 (0.6–1.2)	NA	NA	

Author and Year	Country	Study Type	Dose (mg/d)	RR (95%CI)	RR (95%CI) Advanced	RR (95%CI) Nonadvanced	Confounders
Jian 2005[11]	China	CC	< 1.609	1	NA	NA	Age at interview, locality, education, family income, marital status, number of children, family history, BMI, tea drinking, caloric intake, fat intake
			1.609–3.081	0.50 (0.27–0.91)	NA	NA	
			3.081–4.917	0.41 (0.21–0.77)	NA	NA	
			> 4.917	0.18 (0.08–0.41)	NA	NA	
Kirsh 2006[16]	America	Cohort	5.05	1	1	1	Age, BMI, education and family history of prostate cancer
			7.56	1.10 (0.93–1.30)	1.25 (0.96–1.63)	0.99 (0.78–1.25)	
			9.65	1.06 (0.89–1.25)	0.98 (0.74–1.31)	1.13 (0.90–1.41)	
			12.27	1.07 (0.90–1.27)	1.11 (0.84–1.47)	1.01 (0.80–1.27)	
			17.59	0.95 (0.79–1.13)	1.11 (0.83–1.47)	0.82 (0.64–1.05)	
Kristal 2010[18]	America and Canada	NCC	< 3.999	1	1	1	Age, race/ethnicity, treatment arm, and body mass index.
			3.999–6.646	1.11 (0.96–1.27)	1.22 (0.73–2.04)	1.13 (0.97–1.32)	
			6.647–10.918	1.01 (0.87–1.16)	1.50 (0.90–2.51)	1.00 (0.85–1.18)	
			> 10.918	1.04 (0.90–1.20)	1.33 (0.76–2.34)	1.06 (0.89–1.26)	
Agalliu 2011[17]	Canada	NCC	2.451	1	1	1	Age at baseline, race, BMI, exercise activity, and education
			4.868	0.71 (0.53–0.96)	0.96 (0.59–1.57)	0.66 (0.46–0.95)	
			6.769	0.77 (0.58–1.03)	0.67 (0.40–1.12)	0.86 (0.61–1.21)	
			9.614	0.77 (0.57–1.03)	0.74 (0.44–1.24)	0.82 (0.58–1.17)	
			15.871	0.82 (0.61–1.10)	0.71 (0.42–1.20)	0.86 (0.61–1.23)	
Zu 2014[20]	America	NCC	0–3.687	1	1	NA	Age, height, body mass index, race, family history of prostate cancer, vigorous activity, smoking status, dietary intakes total calories
			3.688–5.301	1.00 (0.95–1.10)	0.90 (0.72–1.10)	NA	
			5.302–7.062	0.96 (0.89–1.00)	0.84 (0.66–1.10)	NA	
			7.063–10.130	0.96 (0.88–1.00)	0.99 (0.78–1.20)	NA	
			10.131–115.012	0.91 (0.84–1.00)	0.72 (0.56–0.94)	NA	

CC = case-control study, CI = confidence interval, NA = Not Applicable, NCC = nested case-control study, RR = relative risk.

0.95 (95% CI 0.90 to 0.99) for 12 mg, 0.94 (95% CI 0.89 to 0.99) for 15 mg, 0.92 (95% CI 0.86 to 0.98) for 18 mg and 0.91 (95% CI 0.84 to 0.99) for 21 mg, which were summarized in Figure 6 presenting the trend of simulative dose–response effect and demonstrated that higher lycopene consumption (9 to 21 mg/d) was inversely associated with a reduced risk of PCa.

Circulating Lycopene Concentrations and Risk of PCa

Totally, 14 studies[12,15,21–31] (2 CC studies[12,15] and 12 NCC or cohort studies)[21–31] reported the association between circulating concentrations and risk of PCa. Figure 7 describes the pooled RR and relevant 95% CI of highest vs. lowest categories was 0.821 (95% CI 0.711 to 0.949, $P = 0.008$) for all studies, 0.399 (95% CI 0.112 to 1.412, $P = 0.154$) for case-control studies and 0.850 (95% CI 0.748 to 0.965, $P = 0.012$) for NCC or cohort studies. A heterogeneity test showed little heterogeneity ($I^2 = 16.9\%$, $P = 0.269$) among all studies, middle heterogeneity ($I^2 = 63.2\%$, $P = 0.099$) among CC studies and little heterogeneity ($I^2 = 0.0\%$, $P = 0.490$) among NCC or cohort studies (Table 6). Sensitivity analyses showed the overall evaluation was robust by removing each study.

As depicted in Figure 8, dose–response meta-analysis of 11 studies included in 10 articles[12,21,22,24–27,29–31] further showed the RR and relevant 95% CI of each 10 μg/dL increase of circulating concentrations was 0.970 (95% CI 0.943 to 0.997, $P = 0.030$) with a middle heterogeneity ($I^2 = 43.7\%$, $P = 0.059$). Consistent with lycopene intake, higher circulating concentrations significantly reduced the risk of PCa by 3.0%. The nonlinear test showed a nonlinear relationship (chi-square = 3.88, $P = 0.049$) between circulating concentrations and the risk of PCa without any heterogeneity ($P = 0.260$). Compared with reference dose (2.15 μg/dL), Figure 9 showed the approximate RRs of each dose of circulating concentration were as follows: 0.95 96 (95% CI 0.93 to 0.99) for 10 μg/dL, 0.92 (95% CI 0.86 to 0.97) for 20 μg/dL, 0.88 (95% CI 0.80 to 0.96) for 30 μg/dL, 0.86 (95% CI 0.77 to 0.95) for 40 μg/dL, 0.85 (95% CI 0.76 to 0.94), 0.85 (95% CI 0.76 to 0.94) for 60 μg/dL, 0.86 (95% CI 0.77 to 0.94) for 70 μg/dL, 0.87 (95% CI 0.76 to 0.99) for 80 μg/dL, 0.88 (95% CI 0.76 to 1.01) for 90 μg/dL, 0.88 (95% CI 0.75 to 1.05) for 100 μg/dL and 0.89 (95% CI 0.74 to 1.08) for 110 μg/dL. It was observed a range from 2.15 to 85 μg/dL circulating concentrations which could decrease PCa incidence.

TABLE 3. Detailed Outcomes on Plasma/Serum Lycopene Concentration and RRs of Prostate Cancer

Author and year	Country	Study	Lycopene Measures	Lycopene Concentration (μg/dL)	RR (95%CI)	RR (95%CI) Advanced	RR (95%CI) Nonadvanced	Confounders
Gann 1999[25]	America	NCC	Plasma	< 26.17	1	1	NA	Exercise frequency, body mass index, plasma total cholesterol, alcohol.
				26.17–35.36	0.89 (0.64–1.23)	0.64 (0.40, 1.03)	NA	
				35.36–44.29	0.90 (0.65–1.24)	0.71 (0.44, 1.15)	NA	
				44.29–58.01	0.87 (0.63–1.19)	0.70 (0.44, 1.10)	NA	
				> 58.01	0.75 (0.54–1.06)	0.56 (0.34, 0.92)	NA	
Huang 2003[26]	America	NCC	Plasma	< 21.7	1	NA	NA	Age, gender, race, date of blood donation, totallipid levels in the blood, hours since last meal, and education, body mass index at age 21y
				21.7–31.1	0.86 (0.51–1.47)	NA	NA	
				31.1–41.1	0.74 (0.41–1.33)	NA	NA	
				41.1–54.9	0.96 (0.55–1.67)	NA	NA	
				> 54.9	0.83 (0.46–1.48)	NA	NA	
Huang 2003[26]	America	NCC	Plasma	< 24.3	1	NA	NA	Age, gender, race, and date of blood donation, totallipid levels in the blood, hours since last meal, and education, body mass index at age 21 y
				24.3–35.2	0.88 0.45–1.70	NA	NA	
				35.2–48.8	0.77 0.40–1.47	NA	NA	
				48.8–62.8	0.83 0.42–1.62	NA	NA	
				> 62.8	0.79 0.41–1.54	NA	NA	
Key 2007[22]	8 European countries	Cohort	Plasma	< 15.04	1	1	1	BMI, smoking status, alcohol intake, physical activity level, marital status, and educational level.
				15.04–24.32	1.36 (1.02–1.83)	1.35 (0.67, 2.74)	1.31 (0.87, 1.97)	
				24.32–34.75	1.25 (0.93–1.68)	1.19 (0.62, 2.29)	1.36 (0.90, 2.05)	
				34.75–49.37	1.11 (0.83–1.49)	0.93 (0.47, 1.85)	1.05 (0.69, 1.59)	
				> 49.37	0.97 (0.70–1.34)	0.40 (0.19, 0.88)	1.40 (0.89, 2.21)	
Peters 2007[24]	America	NCC	Serum	30.5	1	1	NA	Age, time since initial screening, year of blood draw, and study center.
				46.8	1.00 (0.72–1.40)	0.74 (0.45, 1.20)	NA	
				62.2	0.93 (0.66–1.31)	0.95 (0.59, 1.52)	NA	
				78.5	1.16 (0.84–1.61)	1.22 (0.78, 1.91)	NA	
				108.4	1.14 (0.82–1.58)	0.99 (0.62, 1.57)	NA	
Kristal 2011[21]	America	NCC	Serum	< 26.3	1	1	1	Age, race, diabetes, serum cholesterol, and BMI
				26.3–36.0	0.82 (0.64–1.04)	1.10 (0.77, 1.56)	0.64 (0.48,0.86)	
				36.0–46.6	0.70 (0.55–0.91)	0.84 (0.58, 1.23)	0.58 (0.43,0.79)	
				> 46.6	0.78 (0.61–1.01)	0.99 (0.68, 1.45)	0.65 (0.48,0.88)	
				Continuous 10	0.94 (0.88–0.99)	0.98 (0.89, 1.06)	0.91 (0.84,0.98)	
Hsing 1990[27]	America	NCC	Serum	< 20	1	NA	NA	Effects of cigarette smoking, hours since last meal, and years of education
				20–32	0.81 (0.38–1.73)	NA	NA	
				32–47	0.55 (0.23–1.34)	NA	NA	
				> 47	0.50 (0.20–1.29)	NA	NA	
Goodman 2003[31]	America	NCC	Serum	< 22.9	1	NA	NA	Exposure population, study center, age within 5-year intervals, sex, smoking status.
				22.9–32.1	0.65 (0.36–1.15)	NA	NA	
				32.1–41.7	0.47 (0.26–0.87)	NA	NA	
				> 41.7	1.04 (0.61–1.77)	NA	NA	
Lu 2001[12]	America	CC	Serum	< 0.179	1	NA	NA	Age, race, education, alcohol drinking, smoking, family history, and total dietary caloric intake
				0.179–0.275	0.64(0.23–1.75)	NA	NA	
				0.275–0.401	0.29(0.09–0.90)	NA	NA	

Author and year	Country	Study	Lycopene Measures	Lycopene Concentration (μg/dL)	RR (95%CI)	RR (95%CI) Advanced	RR (95%CI) Nonadvanced	Confounders
				> 0.401	0.17(0.04–0.78)	NA	NA	
				Continuous 10	0.67(0.49–0.92)	NA	NA	
Beilby 2010[29]	Australia	NCC	Serum	0–0.19	1	NA	NA	Age, administered vitamin A supplement
				0.20–0.30	0.55 (0.30–0.99)	NA	NA	
				0.31–1.30	0.77 (0.40–1.47)	NA	NA	
Karppi 2009[30]	Finland	NCC	Serum	< 0.08	1	NA	NA	Age, alcohol, family history, physical activity, waist-to-hip ratio, education, smoking
				0.08–0.19	1.10 (0.58–2.08)	NA	NA	
				> 0.19	0.78 (0.37–1.66)	NA	NA	
Nomura 1997[23]	America	NCC	Serum	Q1	1	NA	NA	NA
				Q2	1.0 (0.5–2.0)	NA	NA	
				Q3	1.0(0.5–1.8)	NA	NA	
				Q4	1.1 (0.5–2.2)	NA	NA	
Vogt 2002[15]	America	CC	Serum	0.5–10.7	1	NA	1	Age, race, study center, and month of blood draw
				10.8–17.1	0.97 (NA)	NA	1.05(NA)	
				17.2–24.7	0.74 (NA)	NA	0.72(NA)	
				24.8–57.4	0.65(0.36–1.15)	NA	0.79(NA)	
Wu 2004[28]	America	NCC	Plasma	Q1	1	NA	NA	Cholesterol levels, selenium, vitamin E, family history of prostate cancer, height, vigorous exercise, body mass index, vasectomy and current smoking
				Q2	0.63 (0.37–1.07)	NA	NA	
				Q3	0.51 (0.29–0.92)	NA	NA	
				Q4	0.66 (0.37–1.15)	NA	NA	
				Q5	0.48 (0.26–0.89)	NA	NA	

CC = case-control study, CI = confidence interval, NA = not applicable, NCC = nested case-control study, Q1, Q2, Q3, Q4 and Q5 Cannot be quantified, RR = relative risk.

Subgroup Analyses

As shown in Table 5, subgroup analyses found lycopene intake and the risk of PCa did not differ substantially according to location, study type, duration of follow-up, clinical classification, adjustment for various important confounders such as age, family history, energy intake, BMI. However, it became statistically different with the overall pooled estimate 0.927 (95% CI 0.866 to 0.992, $P = 0.029$) when stratifying by study quality. We also found an inverse association between each 5 mg/day increase of lycopene intake and decreased risk of PCa only for high-quality studies (RR 0.975, 95% CI 0.955 to 0.995, $P = 0.013$). Similarly, Table 6 shows subgroup analyses of circulating concentrations and risk of PCa. There was no significant difference when stratified by location, clinical classification, and adjustment for family history or energy intake. But significant difference was found when classified by study quality, study type, follow-up duration, and adjustment for age or BMI. The inverse associations between circulating concentrations and decreased risk of PCa were indicated for high-quality studies (RR 0.805, 95% CI 0.692 to 0.936, $P = 0.005$), NCC or cohort studies (RR 0.850, 95% CI 0.748 to 0.965, $P = 0.012$), studies in which follow-up duration $\geq$ 10 years (RR 0.801, 95% CI 0.681 to 0.942, $P = 0.007$), studies adjusted by age (RR 0.828, 95% CI 0.696 to 0.984, $P = 0.032$) and studies adjusted by BMI (RR 0.792, 95% CI 0.679 to 0.925, $P = 0.003$).

Publication Bias

For dose–response meta-analysis of each 5 mg/day increase of lycopene intake and the risk of PCa, Begg's rank correlation test ($P = 0.200$) and Egger's linear regression test ($P = 0.220$) indicated no publication bias. For dose–response meta-analysis of each 10 μg/dL increase of circulating concentrations and the risk of PCa, Begg's rank correlation test ($P = 0.350$) also indicated no publication bias whereas Egger's linear regression test ($P = 0.026$) indicated publication bias existed. Trim and fill methods were used to recalculate our pooled risk estimate and found the imputed risk estimate was 0.970 (95% CI 0.943 to 0.997) in the random model and 0.980 (95% CI 0.963 to 0.997) in the fixed model, which is identical to our original risk estimate. No missing studies were imputed in the contour enhanced funnel plot.

DISCUSSION

To our knowledge, this is the first dose–response meta-analysis to systematically and quantitatively evaluate the association of lycopene intake or circulating concentrations and PCa risk. Our novel data demonstrates lycopene could significantly reduce the incidence of PCa with a linear and nonlinear dose–response effect for its intake and circulating concentration, respectively.

Although we did not find an inverse association between lycopene consumption and the risk of PCa incidence for all studies, there was a trend for higher lycopene levels to reduce the incidence of PCa with a P value of 0.078. After removing one Chinese study[11] in sensitivity analyses or recalculating only high-quality studies in subgroup analysis, it indeed significantly lowered PCa risk. Our dose–response meta-analysis further

TABLE 4. Quality Assessment of Studies Included in Meta-Analyses, Using the Newcastle-Ottawa Scale for Assessing Cohort Studies

Authors Year	Year	Quality Indicators From Newcastle-Ottawa Scale									Score
CC		1	2	3	4	5	6	7	8	9	
Norrish 2000[7]	2000	*	*	*	*	*	*	*	*	–	8
Deneo-Pellegrini 1999[8]	1999	*	*	–	*	*	–	*	*	–	6
Jain 1999[9]	1999	*	*	*	*	*	–	*	*	–	7
Cohen 2000[10]	2000	*	*	*	*	*	*	*	*	–	8
Jian 2005[11]	2005	*	*	–	*	*	–	*	*	–	6
Lu 2001[12]	2001	*	*	–	*	*	*	*	*	–	7
Key 1997[13]	1997	*	*	–	*	–	*	*	*	–	7
Hodge 2004[14]	2004	*	*	*	*	*	*	*	*	–	8
Vogt 2002[15]	2002	*	*	*	*	*	–	*	–	–	6
cohort or NCC											
Kirsh 2006[16]	2006	*	*	*	*	*	*	*	–	–	7
Agalliu 2011[17]	2011	*	*	*	*	*	*	*	*	–	8
Kristal 2010[18]	2010	*	*	*	*	*	*	–	*	*	8
Schuurman 2002[19]	2002	*	*	*	*	*	*	*	*	–	8
Zu 2014[20]	2014	*	*	*	*	*	*	*	*	*	9
Kristal 2011[21]	2011	*	*	*	*	*	*	*	*	*	9
Key 2007[22]	2007	*	*	*	*	–	*	*	–	–	6
Nomura 1997[23]	1997	*	*	*	*	–	–	*	*	*	7
Peters 2007[24]	2007	*	*	*	*	*	*	*	*	–	8
Gann 1999[25]	1999	*	*	*	*	–	*	*	*	*	8
Huang (CLUE I) 2003[26]	2003	*	*	*	*	*	*	*	*	*	9
Huang (CLUE II) 2003[26]	2003	*	*	*	*	*	*	*	*	*	9
Hsing 1990[27]	1990	*	*	*	*	–	*	*	*	*	8
Wu 2004[28]	2004	*	*	*	*	*	*	*	*	–	8
Beilby 2010[29]	2010	*	*	*	*	*	*	*	*	*	9
Karppi 2009[30]	2009	*	*	–	*	*	*	*	*	*	8
Goodman 2003[31]	2003	*	*	–	*	*	*	*	*	–	7

* For case-control studies, 1 indicates cases independently validated; 2, cases are representative of population; 3, community controls; 4, controls have no history of prostate cancer disease; 5, study controls for age; 6, study controls for additional factor(s); 7, ascertainment of exposure by blinded interview or record; 8, the same method of ascertainment used for cases and controls; and 9, non-response rate the same for cases and controls. For cohort studies, 1 indicates exposed cohort truly representative; 2, non-exposed cohort drawn from the same community; 3, ascertainment of exposure; 4, outcome of interest not present at start;5, study controls for age; 6, study controls for any additional factor(s); 7, quality of outcome assessment; 8, follow-up long enough for outcomes to occur; and 9, complete accounting for cohorts.

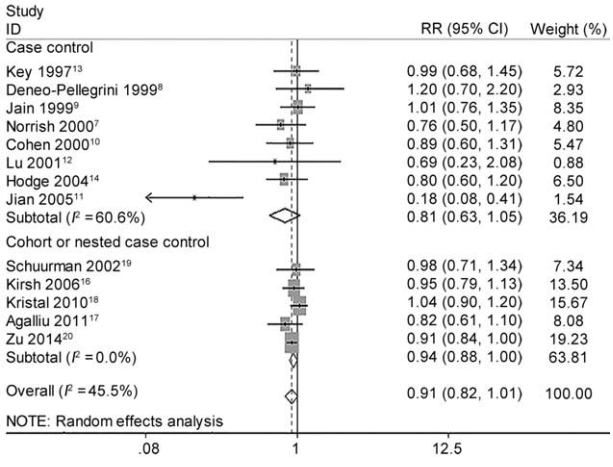

FIGURE 2. Forest plot for the association of highest vs. lowest categories of dietary lycopene consumption and the risk of prostate cancer (PCa). The association was indicated as relative risk (RR) estimate with the corresponding 95% confidence interval (CI). The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR <1 indicates decreased risk of PCa.

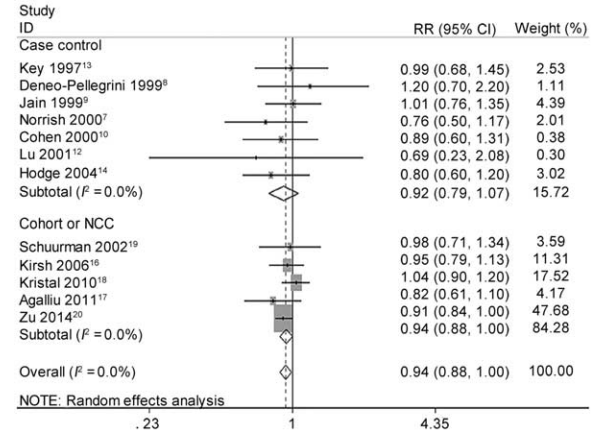

FIGURE 3. Forest plot for dose–response association of highest vs. lowest categories of dietary lycopene consumption and the risk of prostate cancer (PCa) after sensitivity analysis and removing one Chinese study. The association was indicated as relative risk (RR) with the corresponding 95% confidence interval (CI). The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR <1 indicates decreased risk of PCa.

TABLE 5. Study Subgroup Pooled Risk Estimates for Lycopene Intake and Prostate Cancer

	Highest vs. Lowest					Each 5 mg per day increase				
	No.	OR (95% CI)	P^*	$P^\#$	I^2	No.	RR [95% CI]	P^*	$P^\#$	I^2
Overall	13	0.910 [0.819–1.011]	0.078	0.037	45.5%	13	0.975 [0.940–1.010]	0.160	0.020	50.2%
Location:										
North America	7	0.939 [0.880–1.001]	0.053	0.692	0.0%	7	0.981 [0.963–0.998]	0.030	0.748	0.0%
Europe	2	0.984 [0.772–1.255]	0.897	0.968	0.0%	2	1.056 [0.598–1.866]	0.850	0.816	0.0%
Others	4	0.655 [0.377–1.137]	0.132	0.002	79.2%	4	0.692 [0.411–1.165]	0.116	0.001	82.5%
Study type										
CC	8	0.813 [0.629–1.052]	0.115	0.013	60.6%	8	0.894 [0.774–1.032]	0.126	0.003	67.7%
NCC or Cohort	5	0.939 [0.880–1.003]	0.061	0.504	0.0%	5	0.979 [0.961–0.997]	0.023	0.681	0.0%
Follow-up time (years):										
≥10	2	0.960 [0.819–1.011]	0.539	0.120	58.7%	2	0.982 [0.949–1.015]	0.276	0.165	48.0%
<10	11	0.869 [0.745–1.014]	0.075	0.040	47.4%	11	0.958 [0.898–1.022]	0.192	0.014	54.9%
Study quality score:										
≥8	6	0.927 [0.866–0.992]	0.029	0.423	0.0%	6	0.975 [0.955–0.995]	0.013	0.669	0.0%
<8	7	0.858 [0.661–1.114]	0.251	0.009	64.9%	7	0.919 [0.795–1.063]	0.258	0.012	74.6%
Adjusted for age										
Yes	12	0.903 [0.807–1.010]	0.074	0.025	49.8%	12	0.974 [0.939–1.011]	0.165	0.012	54.3%
No	1	0.990 [0.678–1.446]	0.959	–	–	1	0.833 [0.105–6.604]	0.863	–	–
Adjusted for family history										
Yes	8	0.866 [0.729–1.029]	0.103	0.016	59.3%	8	0.954 [0.896–1.016]	0.142	0.005	65.1%
No	5	0.978 [0.877–1.091]	0.692	0.481	0.0%	5	0.996 [0.964–1.029]	0.820	0.694	0.0%
Adjusted for energy intake										
Yes	3	0.996 [0.804–1.234]	0.971	0.692	0.0%	3	1.010 [0.940–1.084]	0.780	0.727	0.0%
No	10	0.885 [0.781–1.004]	0.058	0.013	56.8%	10	0.968 [0.929–1.009]	0.126	0.007	62.2%
Adjusted for BMI										
Yes	8	0.912 [0.792–1.051]	0.203	0.006	64.9%	8	0.979 [0.940–1.020]	0.312	0.003	67.3%
No	5	0.882 [0.738–1.054]	0.168	0.782	0.0%	5	0.927 [0.842–1.020]	0.121	0.837	0.0%
Clinical classification:										
Advanced	6	0.936 [0.774–1.134]	0.501	0.354	9.7%	6	0.977 [0.924–1.032]	0.404	0.286	19.5%
Non-advanced	3	0.936 [0.783–1.118]	0.463	0.204	37.1%	3	0.984 [0.943–1.027]	0.456	0.572	0.0%

BMI = body mass index, CC = case-control study, CI = confidence interval, NCC = nested case-control study, No. = means number, P^* = significance within each subgroup, $P^\#$ = Heterogeneity within each subgroup, RR = relative risk.

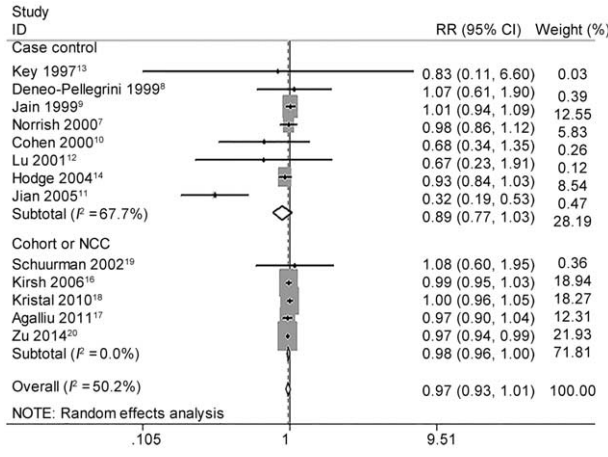

FIGURE 4. Forest plot for dose–response association of each 5 mg/day increase of lycopene intake with the risk of prostate cancer (PCa). The association was indicated as relative risk (RR) with the corresponding 95% confidence interval (CI). The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR <1 indicates decreased risk of PCa.

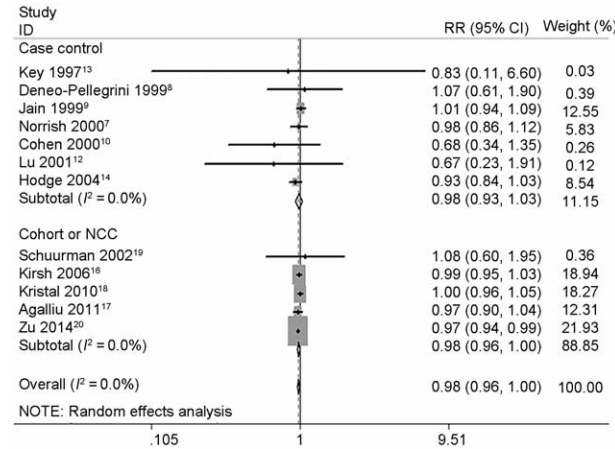

FIGURE 5. Forest plot for dose–response association of each 5 mg/day increase of lycopene intake with the risk of prostate cancer (PCa) after sensitivity analysis and removing one Chinese study. The association was indicated as relative risk (RR) with the corresponding 95% confidence interval (CI). The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR <1 indicates decreased risk of PCa.

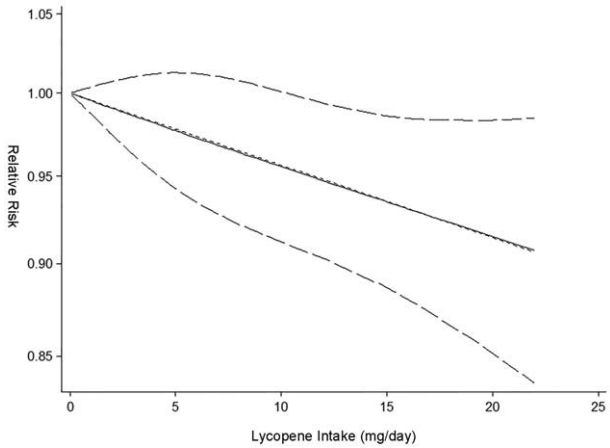

FIGURE 6. Dose–response analysis of lycopene consumption and risk of prostate cancer. The solid black line and 2 dotted black lines are the restricted cubic spline for the published relative risks (RR) and 95% confidence intervals (CIs); the short dash straight line is the linear fitting curve used for linear and nonlinear analysis.

demonstrated that higher lycopene consumption (9 to 21 mg/d) was linearly associated with a reduced risk of PCa by 2.1%. A randomized controlled trial (RCT) with 40 participants conducted by Mohanty et al[59] found that 8 mg/d lycopene intake for 1 year was not inversely associated with PCa risk (RR 0.33, 95% CI 0.08 to 1.46). The ideal daily intake of lycopene is unknown, although it has been suggested that a daily intake of 6 mg may be sufficient.[60]

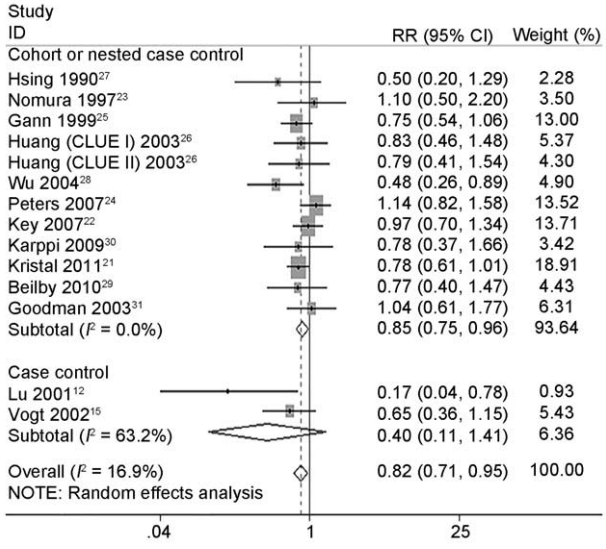

FIGURE 7. Forest plot for dose–response association of highest vs. lowest categories of circulating lycopene concentrations and the risk of prostate cancer (PCa). The association was indicated as relative risk (RR) with the corresponding 95% confidence interval (CI). The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR <1 indicates decreased risk of PCa.

Moreover, the association did not differ substantially between subgroups stratified by location, study type, duration of follow-up, or clinical classification. For various important confounders such as age, family history, energy intake, and BMI, there was no statistical difference if they were adjusted. The heterogeneity could contribute to the insignificance. When one Chinese study was excluded or just high-quality studies were analyzed, lycopene intake was observed to significantly decrease the risk of PCa.

As variations of lycopene content in food, long-term dietary intake of lycopene cannot be accurately estimated via food–frequency questionnaire, diet records, or diet history, circulating concentrations might provide a more accurate estimation of intake. Indeed, little heterogeneity was found for all studies on circulating lycopene levels and PCa risk. Consistently, higher circulating lycopene levels significantly reduced the risk of PCa. Interestingly, our dose–response meta-analysis further proved higher circulating concentrations had a nonlinear association with the decreased PCa incidence by 3.0% for each 10 μg/dL rise of its circulating levels with a threshold around 2.17 to 110 μg/dL. The concentration of circulating lycopene between 2.17 and 85 μg/dL was linearly inversed with PCa risk whereas there was no linear association >85 μg/dL. The value effect for doses > 85 μg/dL was hampered because there were only 3 different doses >85 μg/dL (87.02, 94.20, and 108.40) in the current analysis. After these 3 doses removed, a linear inverse association existed within the threshold 2.17 to 85 μg/dL (chi-square = 6.06, $P = 0.014$) without any heterogeneity ($P = 0.177$), completely consistent with the curve of lycopene consumption described above. In addition, more evidence for the efficacy of circulating concentrations of lycopene on preventing PCa was found for high-quality studies including NCC or cohort studies, studies following-up >10 years and studies adjusted by age or BMI. Thus, age and BMI were assumed as independent risk factors for PCa, which is consistent to a clinical investigation conducted by Jose et al[61] and a recent dose-response meta-analysis conducted by Hu et al.[62] Jose et al depicted that prevalence of PCa was estimated to increase on average from 16% in men aged 50–59 years to 69% in men aged 90–99 years. Hu et al observed a 5 kg/m^2 increase in BMI was associated with a 15% higher risk of PCa detection (OR, 1.15; 95% CI, 0.98–1.34). As there was only 6 (advanced) and 3 (nonadvanced) studies reported RR of lycopene and PCa, the null effect of lycopene on PCa progression could resulted from the limited studies.

The current review of 26 studies with 563,299 participants found both lycopene supplementation and circulating concentrations exhibited a preventive effect on PCa. Also, the meta-analysis of 21 observational studies from 1950 s to 2003 by Etminan et al[32] demonstrated both the highest category of lycopene intake (RR 0.89, 95% CI 0.81 to 0.98) and circulating concentrations (RR 0.74, 95% CI 0.59 to 0.92) were associated with a significant lower risk of PCa, although no dose-effect was analyzed. In contrast, a recent meta-analysis of 17 studies published in 2013 by Chen et al[33] reported the highest category of lycopene intake or circulating concentrations did not prevent PCa risk (OR 0.93, 95% CI 0.86 to 1.01 and OR 0.97, 95% CI 0.88 to 1.08, respectively). This study did not include the case control studies nor perform dose–response analysis. However, Chen et al still concluded that tomatoes do play a modest role in the prevention of PCa and suggested further research would be needed. Indeed, a 24-years follow-up high-quality NCC study[20] including 51,529 US healthy men was published in 2014 and suggested reduced odds of PCa for those with highest lycopene

TABLE 6. Study Subgroup Pooled Risk Estimates for Plasma/Serum Lycopene Concentration and Prostate Cancer

	Highest vs. Lowest					Each 10 μg/dL increase				
	No.	OR (95% CI)	P^*	$P^\#$	I^2	No.	OR (95% CI)	P^*	$P^\#$	I^2
Overall	14	0.821 [0.711–0.949]	0.008	0.269	16.9%	11	0.970 [0.943–0.997]	0.030	0.059	43.7%
Location:										
North America	11	0.793 [0.659–0.955]	0.015	0.148	31.4%	8	0.964 [0.928–1.001]	0.056	0.014	60.2%
Europe	2	0.937 [0.696–1.263]	0.670	0.601	00%	2	0.980 [0.934–1.029]	0.419	0.725	0.0%
Others	1	0.770 [0.402–1.476]	0.431	–	–	1	0.973 [0.898–1.055]	0.513	–	–
Study type:										
CC	2	0.399 [0.112–1.412]	0.154	0.099	63.2%	1	0.700 [0.521–0.879]	0.005	–	–
NCC or Cohort	12	0.850 [0.748–0.965]	0.012	0.490	0.0%	10	0.980 [0.963–0.998]	0.035	0.289	16.7%
Follow-up time (years):										
≥10	8	0.801 [0.681–0.942]	0.007	0.901	0.0%	6	0.958 [0.934–0.982]	0.001	0.907	0.0%
<10	6	0.757 [0.538–1.064]	0.109	0.030	59.6%	5	0.977 [0.919–1.038]	0.448	0.024	68.3%
Study quality score:										
≥8	9	0.805 [0.692–0.936]	0.005	0.404	3.7%	8	0.974 [0.947–1.001]	0.060	0.148	35.2%
<8	5	0.848 [0.599–1.199]	0.351	0.146	43.7%	3	0.930 [0.827–1.046]	0.228	0.035	70.3%
Adjusted for age:										
Yes	11	0.828 [0.696–0.984]	0.032	0.195	26.1%	8	0.970 [0.933–1.009]	0.129	0.037	53.0%
No	3	0.765 [0.571–1.024]	0.072	0.420	0.0%	3	0.967 [0.937–0.999]	0.044	0.379	0.0%
Adjusted for family: history										
Yes	3	0.495 [0.261–0.936]	0.031	0.186	40.5%	2	0.790 [0.602–1.037]	0.090	0.178	44.9%
No	11	0.862 [0.758–0.980]	0.024	0.642	0.0%	9	0.977 [0.955–0.999]	0.040	0.211	25.1%
Adjusted for energy intake:										
Yes	1	0.170 [0.038–0.751]	0.019	–	–	0	–	–	–	–
No	13	0.839 [0.741–0.950]	0.006	0.509	0.0%	11	0.970 [0.943–0.997]	0.030	0.060	43.7%
Adjusted for BMI:										
Yes	6	0.792 [0.679–0.925]	0.003	0.524	0.0%	6	0.959 [0.937–0.982]	0.012	0.185	33.5%
No	8	0.837 [0.634–1.105]	0.209	0.162	33.3%	5	0.994 [0.958–1.031]	0.744	0.328	13.5%
Clinical classification:										
Advanced	4	0.739 [0.501–1.088]	0.126	0.068	58.0%	4	0.960 [0.905–1.018]	0.168	0.045	62.8%
Non-advanced	2	0.848 [0.689–1.044]	0.121	0.299	7.4%	2	0.982 [0.963–1.001]	0.061	0.234	29.3%

BMI = body mass index, CC = case-control study, CI = confidence interval, NCC = nested case-control study, No. = means number, $P^\#$ = heterogeneity within each subgroup, P^* = significance within each subgroup, RR = relative risk.

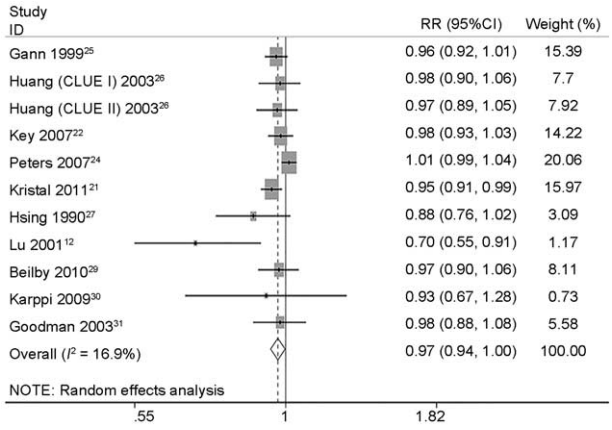

FIGURE 8. Forest plot for dose–response association of each 10 μg/dL increase of circulating lycopene concentrations with the risk of prostate cancer (PCa). The association was indicated as relative risk (RR) with the corresponding 95% confidence interval (CI). The RR estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. RR <1 indicates decreased risk of PCa.

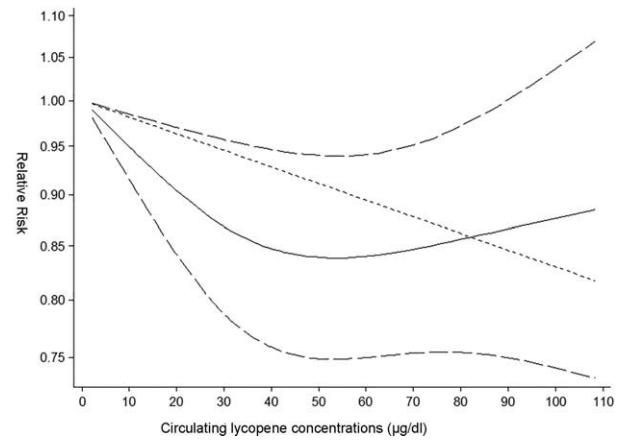

FIGURE 9. Dose–response analysis of circulating lycopene concentrations and risk of prostate cancer. The solid black line and 2 dotted black lines are the restricted cubic spline for the published relative risks (RRs) and 95% confidence intervals (CIs); the short dash straight line is the linear fitting curve used for linear and nonlinear analysis.

intake when compared to those with lowest lycopene intake (HR 0.91, 95% CI 0.84 to 1.00). Current review incorporated this latest study, which further improved our meta-analysis.

As a powerful antioxidant agent with potential anticancer properties,[6] lycopene has many biochemical actions of which antiproliferative insulin-like growth factor-1 inhibition, differentiation and apoptosis, connexin and gap junctional intercellular communication are identified as the most relevant in preventing carcinogenesis. Additionally, Zu et al[20] evaluated tumor biomarkers and found that high lycopene intake can suppress the neoangiogenesis in the tumor based on the vessel size and shape by regulating vascular endothelial growth factor.[63] Elgass et al[64] reported lycopene inhibited angiogenesis *in vitro* by using human umbilical vein endothelial cells. Chen et al[65] showed the mechanism for antiangiogenic activity of lycopene may involve PI3K-Akt and ERK/p38 signaling pathways.

Strengths and Limitations

Generating dose–response curves along with comparisons of high and low lycopene intake or circulating concentrations strengthened the quality of this meta-analysis. The pooled estimates for adjusted models were used to reduce the heterogeneity. Sensitivity analyses and subgroup analyses were conducted to examine the sources of heterogeneity and evaluate robustness. However, several limitations should also be concentrated. Errors in measurement were inevitable for lycopene intake being assessed by food frequency questionnaires in different countries. In addition, the association between lycopene and PCa risk could be impacted for only several studies adjusted for family history. Furthermore, different classifications of lycopene from fruit and vegetables were used across studies.

CONCLUSIONS

In summary, our dose–response meta-analysis indicates a significant linear dose–response association between lycopene intake and PCa risk, but a significant nonlinear dose–response association between circulating concentrations and PCa risk. Further high-quality research data are required to substantiate these conclusions in populations with high lycopene intake and circulating concentrations.

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