

The Effect of Lycopene on Reducing the Risk of Prostate Cancer: A Systematic Review and Meta-Analysis

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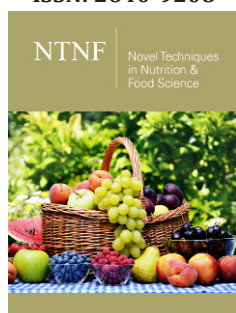
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Abstract

Background: Prostate cancer is a major cause of cancer-related death in men globally. Lycopene, a carotenoid found in tomatoes and related products, has strong antioxidant properties and may reduce prostate cancer risk. **Methods:** A systematic review and meta-analysis were conducted using PubMed, Scopus, Cochrane Library and ScienceDirect up to September 2024. Twenty-three observational studies involving 414,128 participants and 33,552 prostate cancer cases. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-and fixed-effects models.

Results: High dietary lycopene intake was significantly associated with reduced prostate cancer risk (OR=0.91, 95% CI: 0.84-0.99, P=0.03), especially at >10 mg/day. Lycopene intake also reduced advanced prostate cancer risk (OR=0.88, 95% CI: 0.78-0.99, P=0.04), notably at >15 mg/day. Serum lycopene levels were associated with prostate cancer risk (OR = 0.83, 95% CI: 0.73-0.96, P = 0.009). Greater risk reduction was seen in studies with >10 years follow-up (OR=0.92, P = 0.003).

Conclusion: Higher lycopene intake and serum levels are associated with reduced prostate cancer risk. Notably, lycopene intake also appears to decrease the risk of advanced prostate cancer. These findings highlight its potential as a preventive dietary factor.

Keywords: Lycopene; Prostate cancer; Meta-analysis; Antioxidant

Abbreviations: CI: Confidence Interval; OR: Odds Ratio; PCA: Prostate Cancer; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; REVMAN: Review Manager; NOS: Newcastle-Ottawa Scale; PCA: Prostate Cancer; NCC: Nested Case-Control; CC: Case-Control; FFQ: Food Frequency Questionnaire; Q: Quantile; FHPC: Family History of Prostate Cancer; BMI: Body Mass Index; NA: Not Applicable; CLUE I: Give us a CLUE to Cancer Study I; CLUE II: Give us a CLUE to Cancer Study II; NSAIDS: Non-Steroidal Anti-Inflammatory Drugs; RCTs: Randomized Controlled Trials

Introduction

Prostate cancer is a significant public health issue and ranks among the most frequently diagnosed malignancies in men globally. It is the second most common cancer and the fifth leading cause of cancer related death among men worldwide, accounting for an estimated 1.4 million new cases and approximately 375,000 deaths annually [1]. While early-stage prostate cancer often has an excellent prognosis, advanced stages are associated with poorer outcomes and significantly diminished quality of life. Current treatment modalities, including

androgen deprivation therapy, chemotherapy and radiation, may offer disease control but are frequently accompanied by substantial adverse effects, recurrence, or resistance [2,3]. These limitations underscore the need for preventive strategies that are both effective and minimally invasive. Over the past two decades, the role of dietary factors in modulating cancer risk has gained increasing attention, particularly the consumption of fruits, vegetables and plant-derived compounds known as phytochemicals. Lycopene, a non-provitamin A carotenoid found predominantly in tomatoes and tomato-based products, has emerged as one of the most extensively studied phytochemicals in the context of prostate cancer [4,5]. Unlike beta-carotene, lycopene does not convert into vitamin A but exhibits potent antioxidant properties through its ability to scavenge Reactive Oxygen Species (ROS) [6-8]. These oxidative species contribute to DNA damage, lipid peroxidation and protein dysfunction, processes that are central to carcinogenesis. Furthermore, chronic inflammation, a recognized driver of prostate cancer progression, may be attenuated by lycopene's anti-inflammatory effects [9]. Biochemically, lycopene exerts multifaceted protective effects through both antioxidant dependent and independent mechanisms. It enhances intracellular gap junction communication, induces cell cycle arrest in the G0/G1 phase, promotes apoptosis and modulates several key molecular pathways, including NF- κ B, IGF-1 and androgen receptor signaling. Additionally, lycopene influences gene expression by downregulating oncogenes and upregulating tumor suppressor genes such as p53 and PTEN. Its bioavailability is improved by food processing and the presence of dietary fats, making cooked tomato products a more efficient source of lycopene than raw tomatoes [10].

Although *in-vitro* and *in-vivo* studies have consistently demonstrated lycopene's anticancer potential [11,12], evidence from epidemiological studies remains inconclusive [13]. Some observational studies suggest a significant inverse association between lycopene intake or serum levels and prostate cancer risk, while others report no statistically significant relationship. These discrepancies may stem from methodological differences, including variations in dietary assessment tools, the use of Food Frequency Questionnaires (FFQs), heterogeneous study populations and differences in study design, such as cohort versus case-control or nested case-control studies [14]. Furthermore, variations in follow-up duration and the extent of statistical adjustment for confounding variables may influence reported outcomes [15]. Given these inconsistencies, a comprehensive synthesis of the available evidence is warranted. Systematic reviews and meta-analyses serve as valuable tools for integrating findings across studies, enhancing statistical power and generating more robust conclusions. By pooling data from multiple sources, these methods can clarify the extent and nature of the association between lycopene exposure and prostate cancer risk. This study aims to conduct a systematic review and meta-analysis of observational studies to examine the relationship between lycopene consumption (both dietary and serum levels) and the risk of prostate cancer. Specifically, the

analysis will evaluate dose-response relationships, the potential protective effect against advanced prostate cancer. This evidence-based synthesis will contribute to a more refined understanding of lycopene's role in prostate cancer prevention and may support its inclusion in dietary recommendations for at-risk populations.

Materials and Methods

Protocol and registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The study protocol was prospectively registered in PROSPERO (International Prospective Register of Systematic Reviews) under the registration number CRD420251053002.

Search strategies

A comprehensive literature search was performed across four electronic databases: PubMed, Scopus, Cochrane Library and ScienceDirect, covering studies published up to 30 September 2024. Search terms included combinations of (1) "Lycopene" or "Tomato" (2) "Prostate cancer" were employed to optimize search precision. Search queries were tailored to the indexing system of each database. In addition, the reference lists of all included studies and relevant systematic reviews were manually screened to identify any eligible trials not captured in the initial search. No language restrictions were applied during the search process. All records were independently screened by two reviewers (W.S. and C.S.) and discrepancies were resolved through discussion or adjudication by a third reviewer.

Eligibility criteria and study selection

The study included observational studies (cohort, nested case-control and case-control) published in English that met the following eligibility criteria:

- A. Population/participants: Men aged 40 years or older.
- B. Intervention: Lycopene with no restrictions on type, formulation, dose, frequency, or duration of therapy.
- C. Comparison/control group: Participants who did not engage in lycopene. They may have performed usual care.
- D. Outcomes: clearly defined diagnosis of prostate cancer.

Data extraction

Data was independently extracted by two reviewers (W.S. and C.S.) using a predesigned standardized data extraction form. Extracted data included: study characteristics (author, year and country), participant demographics (age and sample size), Assessment method (FFQ or serum lycopene) and outcome assessment (diagnosed with confirmed prostate cancer). Discrepancies between reviewers were resolved through discussion and a third reviewer was consulted if consensus could not be reached. When data were missing or unclear, corresponding

authors were contacted for clarification. If no response was received, only available data from the publication were used in the analysis.

Quality assessment

The risk of bias for each included observational studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS) [17]. This tool evaluates three domains: (1) Selection of study groups, (2) Comparability of groups based on design or analysis, (3) Outcome/exposure ascertainment. Each study could score up to 9 points. Studies scoring 7-9 were considered high quality, 5-6 moderate quality and < 5 low quality.

Statistical analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.4. Meta-analyses were conducted based on the degree of heterogeneity among studies. If $I^2 < 50\%$, a fixed-effects model was used; if $I^2 \geq 50\%$, a random-effects model (Der Simonian and Laird method) was applied to account for between-study variability. The pooled effect estimate was calculated as the Odds Ratio (OR) with 95% Confidence Interval (CI), comparing the highest vs. lowest lycopene exposure categories. For studies reporting Relative Risk (RR) or Hazard Ratios (HR), these were considered approximately equivalent to OR, based on the rare disease assumption (prostate cancer incidence < 10%) [18].

Between-study heterogeneity was quantified using the I^2 statistic. The degree of heterogeneity was categorized into three levels: low ($I^2 < 25\%$), moderate ($I^2 = 25\% - 75\%$) and high ($I^2 > 75\%$). Subgroup analyses were conducted according to exposure type (dietary VS serum lycopene), lycopene dose categories (<5mg/day, 5-10mg/day and >10mg/day), duration of follow-up (<10 years vs. ≥ 10 years). Potential publication bias was assessed through funnel plot visualization and quantitatively using Egger's test, with $p < 0.05$ indicating statistically significant bias.

Results

Search results

The initial database search retrieved a total of 1,653 records: 617 from PubMed, 456 from Scopus, 313 from the Cochrane Library and 267 from ScienceDirect. After removing 359 duplicates, 1,294 records remained for title and abstract screening. Following this, 769 articles were excluded for not addressing prostate cancer risk and 29 non-English studies were removed. Of the remaining 496 articles, 6 full-text articles were not retrievable. A further 464 studies were excluded for being editorials, reviews, or non-human studies. Ultimately, 26 studies met the eligibility criteria, of which 3 were conducted in overlapping populations. After excluding these, 23 primary studies [19-41] were included in the systematic review and meta-analysis. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

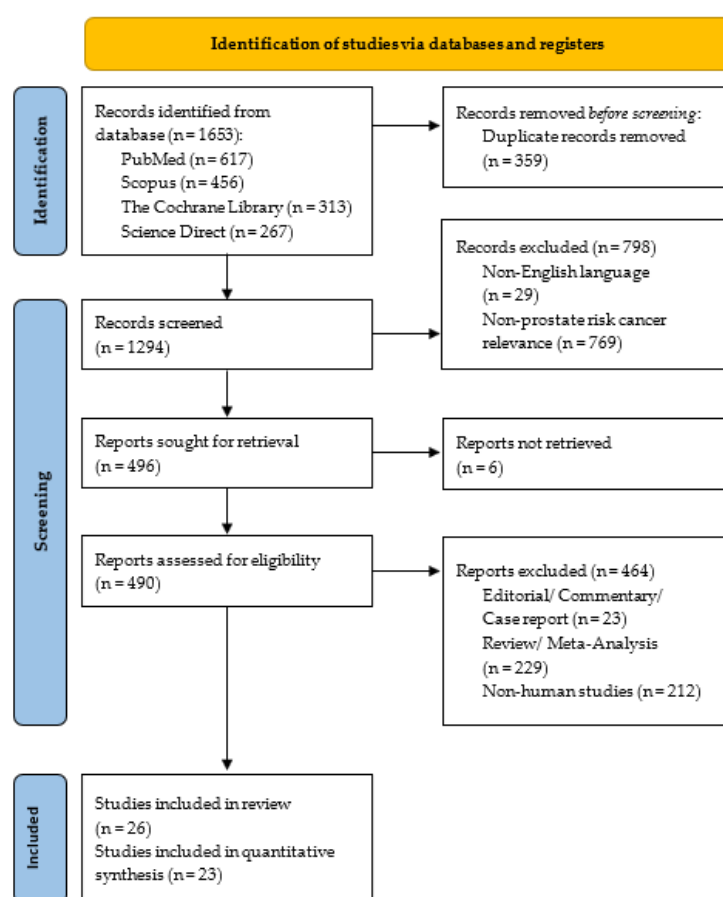


Figure 1: PRISMA flow diagram of literature search and study selection.

Study characteristics

The 23 included studies comprised 9 cohort studies, 9 nested case-control studies and 5 case-control studies, conducted between 1995 and 2022. The study population comprised 414,128 male participants aged over 40 years, of whom 33,552 were diagnosed with confirmed prostate cancer. Lycopene exposure was assessed either via dietary intake using validated Food Frequency Questionnaires (FFQs) or through serum lycopene levels. Most studies used histologically or clinically confirmed diagnoses of prostate cancer as the outcome of interest. Detailed study characteristics, including location (Specifies the country or region where the study was conducted e.g., USA, Netherlands, Finland or 8 European countries), study design (cohort, nested case-control or case-control), follow-up duration, studied population, assessment method and outcome assessment. This table highlights the methodological diversity across studies, which is essential for interpreting pooled results in Table 1. The detailed outcomes of

lycopene intake and its associated odds ratio for prostate cancer risk presenting a comparative analysis of various studies evaluating the association between different levels of dietary lycopene intake (measured in mg/day) and odds ratio for overall, advanced and non-advanced prostate cancer. For each study, showing lycopene doses is categorized into quantiles. The reference category (Q1) is used as the baseline. The odds ratios and their corresponding 95% CI for higher quantiles (Q2-Q5) are presented relative to this baseline in Table 2. The detailed outcomes of serum lycopene and its associated odds ratios for prostate cancer risk presenting a comparative analysis of various studies evaluating the association between different levels of serum lycopene (measured in µg/dl) and odds ratio for overall, advanced and non-advanced prostate cancer. For each study, serum lycopene levels are categorized into quantiles. The reference group (Q1) represents the lowest exposure and serves as the baseline. The odds ratios and their corresponding 95% CI for higher quantiles (Q2-Q5) are presented relative to this baseline in Table 3.

Table 1: Characteristics of included studies.

Author (Year)	Location	Study Design	Follow-up (y)	Studied Population		Assessment Method	Outcome Assessment
				Cohort size (cases) or Case/control	Age (y)		
Kirsh [19]	USA	Cohort	4.2	29,361 (1,338)	55-74	FFQ	Clinically confirmed PCA
Kristal [20]	USA & Canada	Cohort	10	9,559 (1,703)	>55	FFQ	Histologically confirmed PCA
Giovannucci [21]	USA	Cohort	12	47,365 (2,481)	40-75	FFQ	Diagnosed confirmed PCA
Schuurman [22]	Netherlands	Cohort	6.3	58,279 (642)	55-69	FFQ	Histologically confirmed PCA
Park [23]	USA	Cohort	13.9	75,216 (7,115)	45-75	FFQ	Histologically confirmed PCA
Zu [24]	USA	Cohort	24	49,898 (5,728)	40-75	FFQ	Histologically confirmed PCA
Graff [25]	USA	Cohort	23	46,719 (5,543)	40-75	FFQ	Histologically confirmed PCA
Stram [26]	USA	Cohort	8	82,486 (3,392)	45-75	FFQ	Diagnosed confirmed PCA
Karppi [27]	Finland	Cohort	12.6	997 (55)	Mean 56.2	Serum lycopene	Histologically confirmed PCA
Chadid [28]	USA	NCC	3	235/235	>55	Serum lycopene	Histologically confirmed PCA
Gann [29]	USA	NCC	13	578/1,294	40-84	Serum lycopene	Clinical confirmed PCA
Wu [30]	USA	NCC	5	450/450	40-75	FFQ, Serum lycopene	Diagnosed non-stage A PCA
Key [31]	8 European countries	NCC	8	966/1064	Mean 60.4 ± 5.82	Serum lycopene	Diagnosed incident PCA
Peters [32]	USA	NCC	8	692/844	Mean 64.7	FFQ, Serum lycopene	Histologically confirmed PCA
Nomura [33]	USA	NCC	21	142/142	52-74	Serum lycopene	Histologically confirmed PCA
Agalliu [34]	Canada	NCC	7	661/1,864	Mean 66.2	FFQ	Clinically confirmed PCA
Beilby [35]	Australia	NCC	14	96/225	Mean 69.8	Serum lycopene	Histologically confirmed PCA

Huang [36]	USA	NCC	22	CLUE I182/364CLUE II 142/284	45-64	FFQ, Serum lycopene	Histologically confirmed PCA
Jian [37]	China	CC	-	130/274	45	FFQ	Histologically confirmed PCA
Goodman [38]	USA	CC	-	77/174	45-69	FFQ	Histologically confirmed PCA
Norrish [39]	New Zealand	CC	-	281/442	40-80	FFQ	Histologically confirmed PCA
Lu [40]	USA	CC	-	65/132	59.98	FFQ, Serum lycopene	Histologically confirmed PCA
Hodge [41]	Australia	CC	-	858/905	<70	FFQ	Histologically confirmed PCA

Table Abbreviations: NCC: Nested Case-Control, CC: Case-Control, FFQ: Food Frequency Questionnaire, Pca, prostate cancer, CLUE I, give us a CLUE to Cancer Study I, CLUE II, Give us a CLUE to Cancer Study II.

Table 2: Detailed Outcomes on Lycopene Intake and Odds Ratio of Prostate Cancer.

Author (year)	Lycopene Dose (mg/d)	OR (95%CI)	OR (95%CI) Advanced Pca	OR (95%CI) Non-Advanced Pca	Adjusted for Confounders
Kirsh [19]	Q1 5.05	1	1	1	Age, BMI, education and FHPC
	Q2 7.56	1.10 (0.93-1.30)	1.25 (0.96-1.63)	0.99 (0.7-1.25)	
	Q3 9.65	1.06 (0.89-1.25)	0.98 (0.74-1.31)	1.13 (0.90-1.41)	
	Q4 12.27	1.07 (0.90-1.27)	1.11 (0.84-1.47)	1.01 (0.80-1.27)	
	Q5 17.59	0.95 (0.79-1.13)	1.11 (0.83-1.47)	0.82 (0.64-1.05)	
Kristal [20]	Q1 <3.999	1	1	1	Age, race/ethnicity, treatment arm and BMI.
	Q2 3.999-6.646	1.11 (0.96-1.27)	1.22 (0.73-2.04)	1.13 (0.97-1.32)	
	Q3 6.647-10.918	1.01 (0.87-1.16)	1.50 (0.90-2.51)	1.00 (0.85-1.18)	
	Q4>10.918	1.04 (0.90-1.20)	1.33 (0.76-2.34)	1.06 (0.89-1.26)	
Giovannucci [21]	Q1 3.415	1	NA	NA	Age, time period, ancestry BMI and intake of total energy, Ca, P, fructose, vitamin D, E, total fat and linolenic acid
	Q2 6.156	1.03 (0.91-1.17)	NA	NA	
	Q3 8.663	0.99 (0.87- 1.12)	NA	NA	
	Q4 12.198	0.97 (0.86- 1.11)	NA	NA	
	Q5 18.780	0.84 (0.73- 0.96)	NA	NA	
Schuurman [22]	Q1 0.1	1	1	NA	Age, FHPC, socioeconomic status and alcohol from white or fortified wine
	Q2 0.4	0.79 (0.57-1.09)	0.80 (0.49-1.31)	NA	
	Q3 0.7	1.08 (0.80-1.47)	1.09 (0.69-1.71)	NA	
	Q4 1.1	0.99 (0.72-1.36)	0.94 (0.59-1.50)	NA	
	Q5 2.0	0.98 (0.71-1.34)	0.92 (0.57-1.47)	NA	
Park [23]	Q1<0.748	1	NA	NA	Age, race, FHPC, nutrients, alcohol, PA, diabetes, Education, Smoking Status, height, BMI
	Q2 0.748-1.072	1.12(0.94-1.34)	NA	NA	
	Q3 1.073-1.434	1.10(0.92-1.31)	NA	NA	
	Q4 1.435-2.021	1.06(0.89-1.27)	NA	NA	
	Q5 ≥2.022	1.10(0.93-1.31)	NA	NA	
Zu [24]	Q1 0-3.687	1	1	NA	Age, height, BMI, race, FHPC, vigorous activity, smoking status, dietary intakes total calories
	Q2 3.688-5.301	1.00 (0.95-1.10)	0.90 (0.72-1.10)	NA	
	Q3 5.302-7.062	0.96 (0.89-1.00)	0.84 (0.66-1.10)	NA	
	Q4 7.063-10.130	0.96 (0.88-1.00)	0.99 (0.78-1.20)	NA	
	Q5 10.131-115.012	0.91 (0.84-1.00)	0.72 (0.56-0.94)	NA	

Graff [25]	Q1 0.3247	1	NA	NA	Age, height, BMI, race, FHPC, diabetes, physical activity, smoking status and multivitamin use
	Q2 5.085	1.05 (0.97, 1.14)	NA	NA	
	Q3 6.652	0.98 (0.90, 1.06)	NA	NA	
	Q4 8.711	0.95 (0.87, 1.03)	NA	NA	
	Q5 12.941	0.95 (0.87, 1.03)	NA	NA	
Stram [26]	Q1 <0.7525	1	1	NA	Age, BMI, Education, FHPC
	Q2 0.7525-1.0781	1.07(0.96-1.18)	0.98 (0.83-1.15)	NA	
	Q3 1.0781-1.4368	1.09(0.98-1.20)	1.01 (0.86-1.21)	NA	
	Q4 1.4368-20.179	1.10(0.99-1.21)	1.06 (0.89-1.04)	NA	
	Q5 >20.179	1.00(0.90-1.10)	0.87 (0.73-1.04)	NA	
Agalliu [34]	Q1 2.451	1	1	1	Age, race, BMI, Physical activity and Education
	Q2 4.868	0.71 (0.53-0.96)	0.96 (0.59-1.57)	0.66 (0.46-0.95)	
	Q3 6.769	0.77 (0.58-1.03)	0.67 (0.40-1.12)	0.86 (0.61-1.21)	
	Q4 9.614	0.77 (0.57-1.03)	0.74 (0.44-1.24)	0.82 (0.58-1.17)	
	Q5 15.871	0.82 (0.61-1.10)	0.71 (0.42-1.20)	0.86 (0.61-1.23)	
Jian [37]	Q1 <1.609	1	NA	NA	Age, locality, Education, income, marital status, FHPC, BMI, fat intake, calories, social class
	Q2 1.609-3.081	0.47 (0.25-0.86)	NA	NA	
	Q3 3.081-4.917	0.40 (0.21-0.77)	NA	NA	
	Q4 >4.917	0.17 (0.08-0.39)	NA	NA	
Goodman [38]	Q1 <0.732	1	NA	NA	Age, race, BMI, energy intake, fat intake, lycopene intake, plasma alpha-tocopherol, beta-carotene
	Q2 0.732-1.529	0.87(0.46-1.65)	NA	NA	
	Q3 >1.529	0.49(0.24-0.99)	NA	NA	
Norrish [39]	Q1 < 0.662	1	1	NA	Age, height, total NSAID drugs and socioeconomic status
	Q2 0.662-1.212	0.77 (0.50-1.19)	NA	NA	
	Q3 1.213-1.994	0.86 (0.56-1.32)	NA	NA	
	Q4 > 1.994	0.76 (0.50-1.17)	NA	NA	
Lu [40]	Q1 <1.458	1	NA	NA	Age, race, education, alcohol drinking, pack-years of smoking, FHPC and total caloric intake
	Q2 1.458-2.370	1.14 (0.36-3.62)	NA	NA	
	Q3 2.371-3.450	0.91 (0.27-3.11)	NA	NA	
	Q4 >3.450	0.69 (0.23-2.08)	NA	NA	
Hodge [41]	Q1 4.092-5.848	0.9 (0.6-1.2)	NA	NA	Age group, state, year, country of birth, socioeconomic group and FHPC
	Q2 5.849-8.224	0.8 (0.6-1.0)	NA	NA	
	Q3 8.225-11.088	0.9 (0.6-1.2)	NA	NA	
	Q4>11.088 0.8	(0.6-1.2)	NA	NA	

Table Abbreviations: Q: Quantile, OR: Odds Ratio, NA: Not Applicable, CI: Confident Interval, PCA: prostate cancer, BMI: Body Mass Index, FHPC: Family History of Prostate Cancer, NASIDS: Non-Steroidal Anti-Inflammatory Drugs

Table 3: Detailed Outcomes on Serum Lycopene and Odds Ratio of Prostate Cancer.

Authors (Year)	Serum lycopene (ug/dl)	OR (95%CI)	OR (95%CI) Advanced Pca	OR (95%CI) Non-Advanced Pca	Adjusted for Confounders
Karppe [27]	Q1 <4.29	1	NA	NA	Age, alcohol intake, FHPC, physical activity, waist-to-hip ration, education, year of smoking and serum folate
	Q2 4.29-10.20	1.10 (0.58-2.08)	NA	NA	
	Q3 >10.20	0.78 (0.37-1.66)	NA	NA	
Chadid [28]	Q1 0.38-2.94	1	NA	NA	Age, cholesterol, race, FHPC
	Q2 2.94-4.20	0.54 (0.21-1.38)	NA	NA	
	Q3 4.22- 10.20	1.51 (0.56-4.08)	NA	NA	

Gann [29]	Q1 <26.17	1	1	NA	Exercise frequency, BMI, plasma total cholesterol, alcohol
	Q2 26.17-35.36	0.89 (0.64-1.23)	0.64 (0.40-1.03)	NA	
	Q3 35.36-44.29	0.90 (0.65-1.24)	0.71 (0.44- 1.15)	NA	
	Q4 44.29-58.01	0.87 (0.63-1.19)	0.70 (0.44- 1.10)	NA	
	Q5 > 58.01	0.75 (0.54-1.06)	0.56 (0.34- 0.92)	NA	
Wu [30]	Q1	1	NA	NA	Age, cholesterol level, BMI, selenium and vitamin E supplement FHPC, exercise, history of vasectomy and smoking status
	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	
Key [31]	Q5	0.48 (0.26-0.89)	NA	NA	BMI, smoking status, alcohol intake, physical activity, marital status, and education
	Q1 < 15.04	1	1	1	
	Q2 15.04 -24.32	1.36 (1.02- 1.83)	1.35 (0.67- 2.74)	1.31 (0.87-1.97)	
	Q3 24.32-34.75	1.25 (0.93-1.68)	1.19 (0.62-2.29)	1.36 (0.90-2.05)	
	Q4 34.75-49.37	1.11 (0.83-1.49)	0.93 (0.47-1.85)	1.05 (0.69-1.59)	
Peters [32]	Q5 > 49.37	0.97 (0.70- 1.34)	0.40 (0.19-0.88)	1.40 (0.89-2.21)	Age, time since initial screening and year of blood draw and study center
	Q1 30.5	1	1	NA	
	Q2 46.8	1.00 (0.72-1.40)	0.74 (0.45-1.20)	NA	
	Q3 62.2	0.93 (0.66-1.31)	0.95 (0.59- 1.52)	NA	
	Q4 78.5	1.16 (0.84-1.61)	1.22 (0.78-1.91)	NA	
Nomura [33]	Q5 108.4	1.14 (0.82-1.58)	0.99 (0.62-1.57)	NA	None
	Q1	1	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	
Beilby [35]	Q1 0-0.19	1	NA	NA	Age and vitamin A supplement
	Q2 0.20-0.30	0.55 (0.30-0.99)	NA	NA	
	Q3 0.31-1.30	0.77 (0.40-1.47)	NA	NA	
Huang [36] (CLUE I)	Q1 < 21.7	1	NA	NA	Age, gender, race, date of blood donation, total lipid levels in the blood, hours since last meal, education and BMI at age 21years
	Q2 21.7-31.1	0.86 (0.51-1.47)	NA	NA	
	Q3 31.1-41.1	0.74 0.41-1.33	NA	NA	
	Q4 41.1-54.9	0.96 (0.55- 1.67)	NA	NA	
	Q5 > 54.9	0.83 (0.46- 1.48)	NA	NA	
Huang [36] (CLUE II)	Q1 < 24.3	1	NA	NA	Age, gender, race, and date of donation, total lipid levels in the blood, hours since last meal, education and BMI at age 21 years
	Q2 24.3-35.2	0.88 (0.45-1.70)	NA	NA	
	Q3 35.2-48.8	0.77 (0.40-1.47)	NA	NA	
	Q4 48.89-62.8	0.83 (0.42-1.62)	NA	NA	
	Q5>62.8	0.79 (0.41-1.54)	NA	NA	
Lu [40]	Q1<1.458	1	NA	NA	Age, race, education, alcohol drinking, pack-years of smoking, FHPC, and total caloric intake
	Q2 1.458-2.370	1.14 (0.36-3.62)	NA	NA	
	Q3 2.371-3.450	0.91 (0.27-3.11)	NA	NA	
	Q4 > 3.450	0.69 (0.23-2.08)	NA	NA	

Table Abbreviations: Q: Quantile, OR: Odds Ratio, NA: Not Applicable, CI: Confident Interval, PCA: Prostate Cancer, BMI: Body Mass Index, FHPC: Family History of Prostate Cancer, NASIDS: Non-Steroidal Anti-Inflammatory Drugs.

Quality assessment of included studies

The quality of 23 studies included comprising 9 cohort, 9 nested case-control and 5 case-control studies-was evaluated using the Newcastle-Ottawa Scale (NOS), a standardized tool for assessing non-randomized studies. Most studies demonstrated good methodological quality.

Cohort studies: All 9 cohort studies included, 7 achieved a full NOS score of 9, indicating high quality. Kirsh [19] scored 7 due to a short follow-up period and unclear reporting. Cohort designs offer strong causal inference by establishing temporal relationships between exposure and outcome. These studies demonstrated rigorous population selection and control for confounders, supporting their reliability for quantitative synthesis.

Nested case-control studies: All 9 nested case-control studies scored between 7 and 9 on the NOS. Most scored 8 or 9, indicating high quality. The studies that scored 8 points were those by Wu

[30], Agalliu [34] and Chadid [28], primarily due to missing data on non-response rates or loss to follow-up. Nomura [33] and Key [31] scored 7 due to insufficient confounder adjustment and unclear non-response reporting. Overall, these studies showed robust design and valid exposure assessment, justifying inclusion in meta-analysis.

Case-control studies: The 5 case-control studies scored between 7 and 9, reflecting generally good quality. Goodman and Lu [40] scored 7 due to concerns about sample representativeness and response rate imbalance. Nonetheless, all case-control studies met minimum quality standards for inclusion in the analysis. Overall Assessment: most studies were of good quality (NOS $\geq$ 7). Cohort and nested case-control studies had slightly higher average scores than case-control studies, consistent with their stronger design features in reducing bias. The quality of included studies supports the credibility of the meta-analysis findings in Tables 4 & 5.

Table 4: Quality assessment of studies included in meta-analyses, using the Newcastle Ottawa scale for cohort studies

Author(year)	Section			Comparability			Outcome			Score
	1	2	3	4	5	6	7	8	9	
Kirsh [19]	√	√	√	√	√	√	√	-	-	7
Kristal [20]	√	√	√	√	√	√	√	√	√	9
Giovannucci [21]	√	√	√	√	√	√	√	√	√	9
Schuurman [22]	√	√	√	√	√	√	√	√	-	8
Park [23]	√	√	√	√	√	√	√	√	√	9
Zu [24]	√	√	√	√	√	√	√	√	√	9
Graff [25]	√	√	√	√	√	√	√	√	√	9
Stram [26]	√	√	√	√	√	√	√	√	√	9
Karppi [27]	√	√	√	√	√	√	√	√	√	9

Remarks:

- 1.The lycopene-consuming group should be representative of the general population.
- 2.The comparison group (non-lycopene consumers) should be selected from the same source population. 3: Lycopene intake should be measured using reliable methods, such as a validated food frequency questionnaire (FFQ) or serum lycopene levels.
- 3.Participants must be confirmed to be free of prostate cancer at the start of the study.
- 4.Age, as a key confounding factor, must be adequately controlled.
- 5.Other potential confounders such as body mass index (BMI), smoking status and family history should also be controlled.
- 6.The diagnosis of prostate cancer must be reliable, preferably confirmed through biopsy or cancer registry data.
- 7.A minimum follow-up duration of five years is recommended to allow sufficient time for disease development.
- 8.Follow-up data should be adequate, with minimal loss to follow-up.

Table 5: Quality assessment of studies included in meta-analyses, using the Newcastle Ottawa scale for nested case-control and case-control studies.

Author(year)	Section			Comparability			Exposure			Score
	1	2	3	4	5	6	7	8	9	
Nested Case-Control										
Gann [29]	√	√	√	√	-	√	√	√	√	8

Wu [30]	✓	✓	✓	✓	✓	✓	✓	✓	-	8
Key [31]	✓	✓	✓	✓	✓	-	✓	✓	-	7
Peters [32]	✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Nomura [33]	✓	✓	✓	✓	-	-	✓	✓	✓	7
Agalliu [34]	✓	✓	✓	✓	✓	✓	✓	✓	-	8
Beilby [35]	✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Chadid [28]	✓	✓	✓	✓	✓	✓	✓	✓	-	8
Huang [36]	✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Case-Control										
Jian [37]	✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Goodman [38]	-	✓	✓	✓	✓	✓	✓	✓	-	7
Norrish [39]	✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Lu [40]	-	✓	✓	✓	✓	✓	✓	✓	-	7
Hodge [41]	✓	✓	✓	✓	✓	✓	✓	✓	-	8

Remarks:

- 1.The lycopene-consuming group should be representative of the general population.
- 2The case group should adequately represent the at-risk population.
- 3.The control group should be selected from the same population and must be free of prostate cancer.
- 4.Controls must be confirmed to be free of prostate cancer at the time of selection.
- 5.Age, as a key confounding factor, must be appropriately controlled.
- 6.Other potential confounders, such as body mass index (BMI), smoking and family history, should also be adjusted for.
- 7.Lycopene intake should be assessed using reliable methods, such as a validated food frequency questionnaire (FFQ) or serum lycopene concentration.
- 8.The same measurement methods should be applied to both cases and controls.
- 9.The non-response rates between cases and controls should be comparable.

Meta-analysis

A total of twenty-three observational studies comprising 414,128 participants, were included in the meta-analysis.

Lycopene intake and prostate cancer risk: Fourteen studies evaluated the association between high vs. low lycopene intake and

prostate cancer risk. Using a random-effects model due to moderate heterogeneity ($I^2=60\%$), the pooled OR was 0.91 (95%CI (0.84-0.99); $p=0.03$). This indicates a statistically significant inverse association between high lycopene intake and prostate cancer risk (Figure 2).

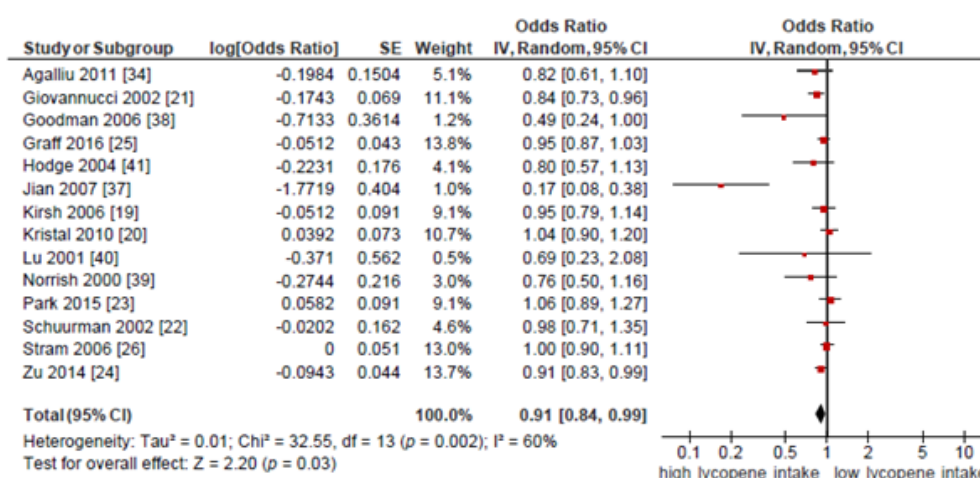


Figure 2: Forest plot for the association of the highest vs the lowest lycopene intake on prostate cancer risk.

A. Subgroup analysis based on lycopene dose and prostate cancer

A subgroup meta-analysis was conducted to assess the association between dietary lycopene intake and the risk of

prostate cancer, stratified by three intake levels: low dose (<5mg/day), medium dose (5-10mg/day) and high (>10mg/day). Only the high-dose group (>10mg/day) showed a statistically significant reduction in the risk of prostate cancer. OR=0.95 (95% CI (0.91-0.99); p=0.02), indicating a significant protective effect (Figure 3).

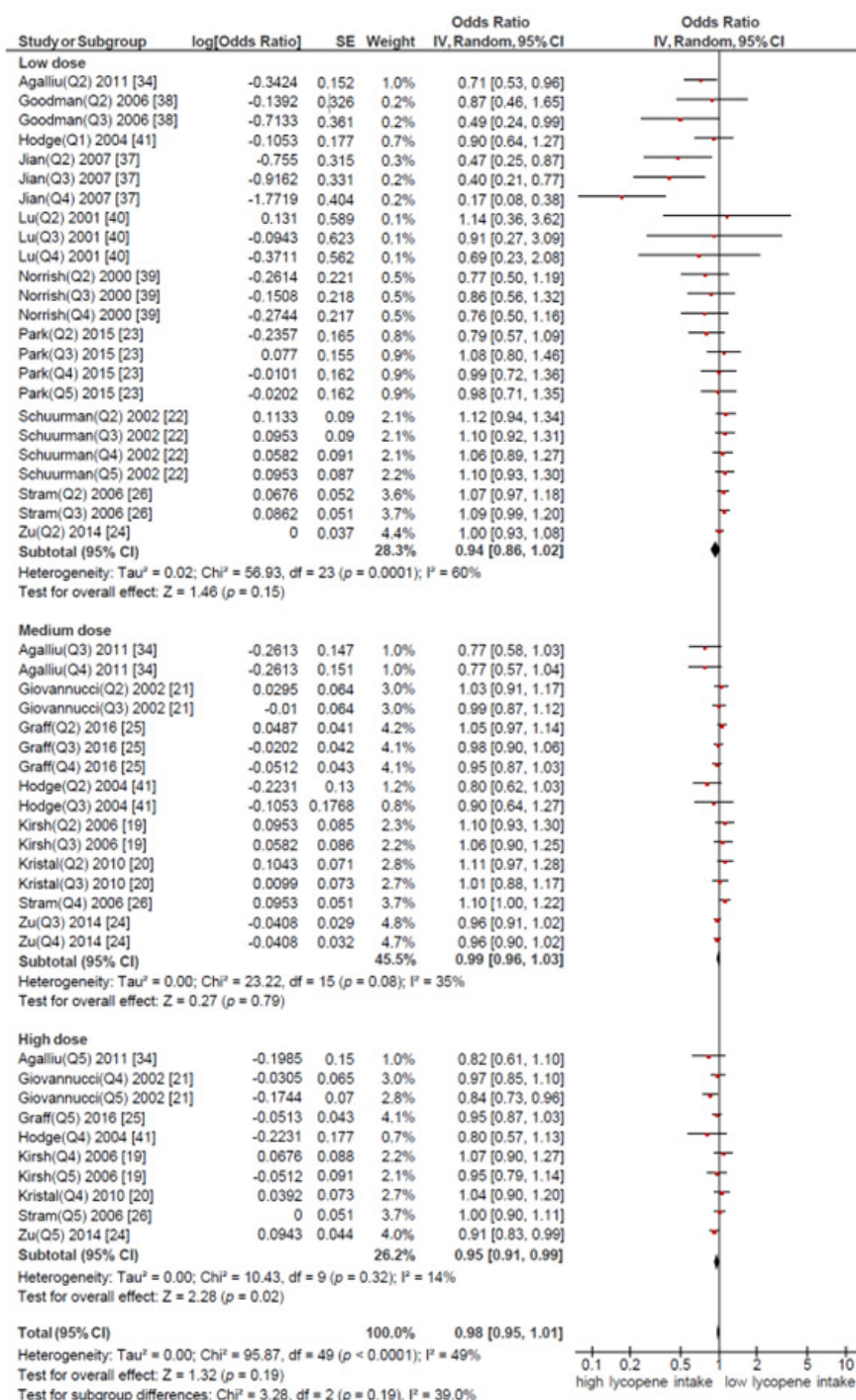


Figure 3: Forest plot of subgroup meta-analysis by lycopene dose and prostate cancer risk.

B. Subgroup analysis based on advanced prostate cancer

A subset of studies focused on advanced prostate cancer outcomes. Using a fixed-effects model ($I^2=34\%$), the pooled OR

was 0.88 (95% CI: 0.78-0.99, $p=0.04$), indicating that high dietary lycopene intake was significantly associated with reduced risk of advanced prostate cancer (Figure 4).

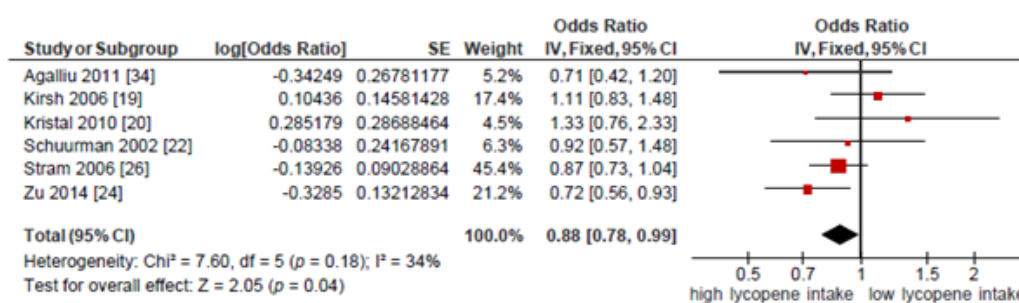


Figure 4: Forest plot for the association of the highest vs the lowest lycopene intake on advanced prostate cancer risk.

C. Subgroup analysis based on lycopene dose and advanced prostate cancer

A subgroup meta-analysis was conducted to assess the association between dietary lycopene intake and the risk of advanced prostate cancer, stratified by four intake levels: low dose (<5mg/day), medium dose (5-10 mg/day), high (10-15mg/day)

and very high dose (>15mg/day). Only the very high dose group (>15 mg/day) demonstrated a statistically significant inverse association with advanced prostate cancer risk. Odds ratio (OR) for this group was 0.86 (95% CI: 0.76-0.98, $p=0.02$), indicating a significant protective effect. In contrast, no statistically significant associations were observed for the lower intake categories (Figure 5).

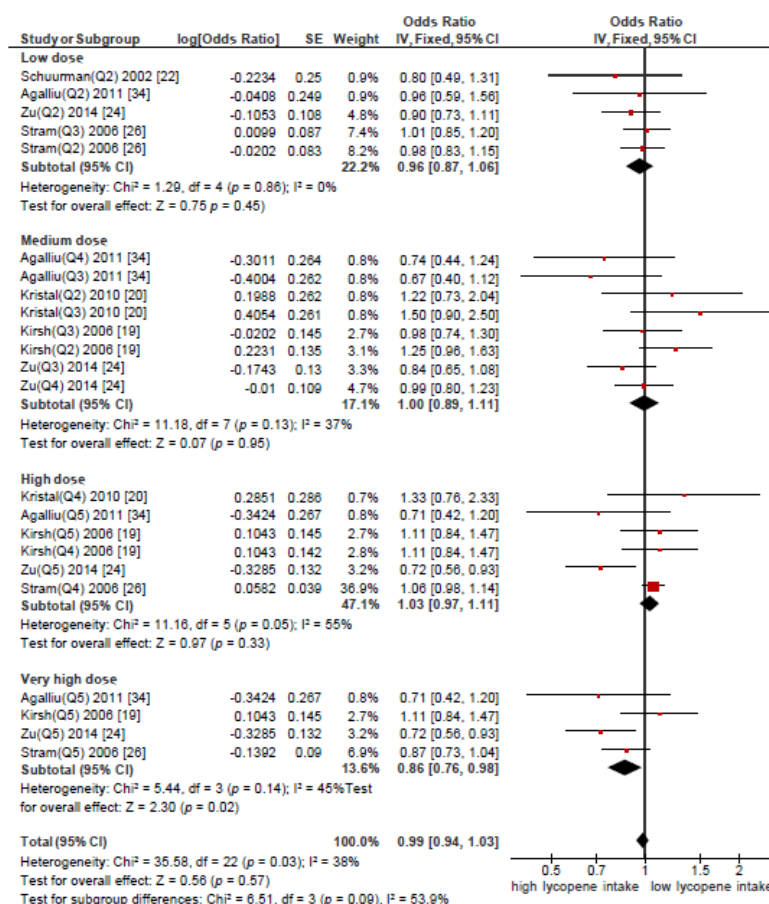


Figure 5: Forest plot for the association of the highest vs the lowest lycopene intake on advanced prostate cancer risk.

Serum lycopene and prostate cancer risk: Ten studies examined the association between serum lycopene levels and prostate cancer risk. A fixed-effects model was used due to the absence of heterogeneity ($I^2=0\%$), indicating a high degree of

consistency among the included studies. The pooled OR was 0.83 (95% CI: 0.73-0.96, $p=0.009$), suggesting a statistically significant inverse relationship between high serum lycopene levels and prostate cancer risk (Figure 6).

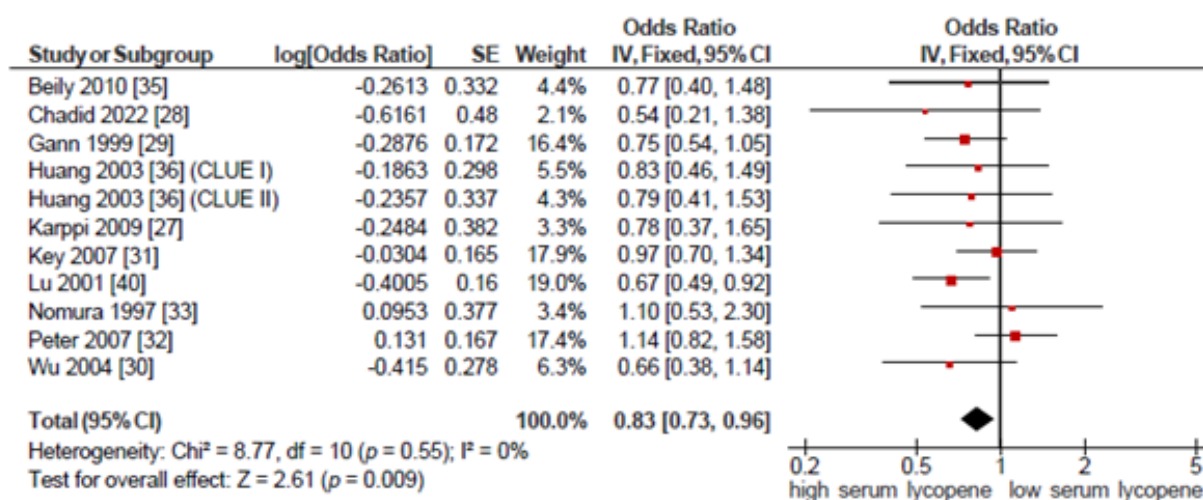


Figure 6: Forest plot for the association of the highest vs the lowest serum lycopene on prostate cancer risk.

A. Subgroup analysis based on advanced prostate cancer
 For advanced prostate cancer, the pooled OR from serum

lycopene studies was 0.64 (95% CI: 0.39-1.07, $p = 0.09$), using a random-effects model ($I^2 = 59\%$). This did not reach statistical significance but suggested a protective trend (Figure 7).

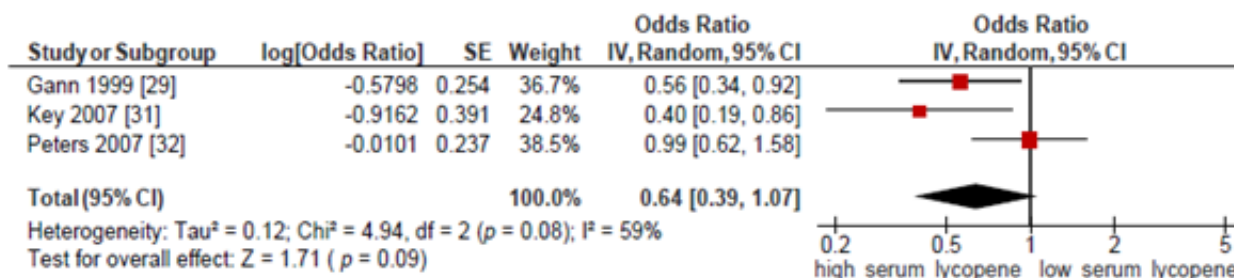


Figure 7: Forest plot for association of highest vs lowest serum lycopene on advanced prostate cancer risk.

Follow-up duration and prostate cancer risk: Subgroup analyses based on study follow-up duration revealed that subgroup with follow-up duration of 10 years or less, no statistically significant association was observed between lycopene intake and prostate cancer risk. The pooled OR was 0.99 (95% CI: 0.93-1.06, $p = 0.77$), with no observed heterogeneity ($I^2 = 0\%$), indicating a high degree of consistency among the included studies. Conversely, in the subgroup of studies with follow-up periods greater than 10

years, lycopene consumption was significantly associated with a reduced risk of prostate cancer. The pooled OR was 0.92 (95% CI: 0.88-0.97, $p = 0.003$) and the heterogeneity was low ($I^2 = 9\%$), reflecting substantial consistency across studies in this group. These findings suggest that the protective effect of lycopene may become more evident with longer-term exposure, emphasizing the potential importance of sustained dietary lycopene intake for prostate cancer prevention (Figure 8).

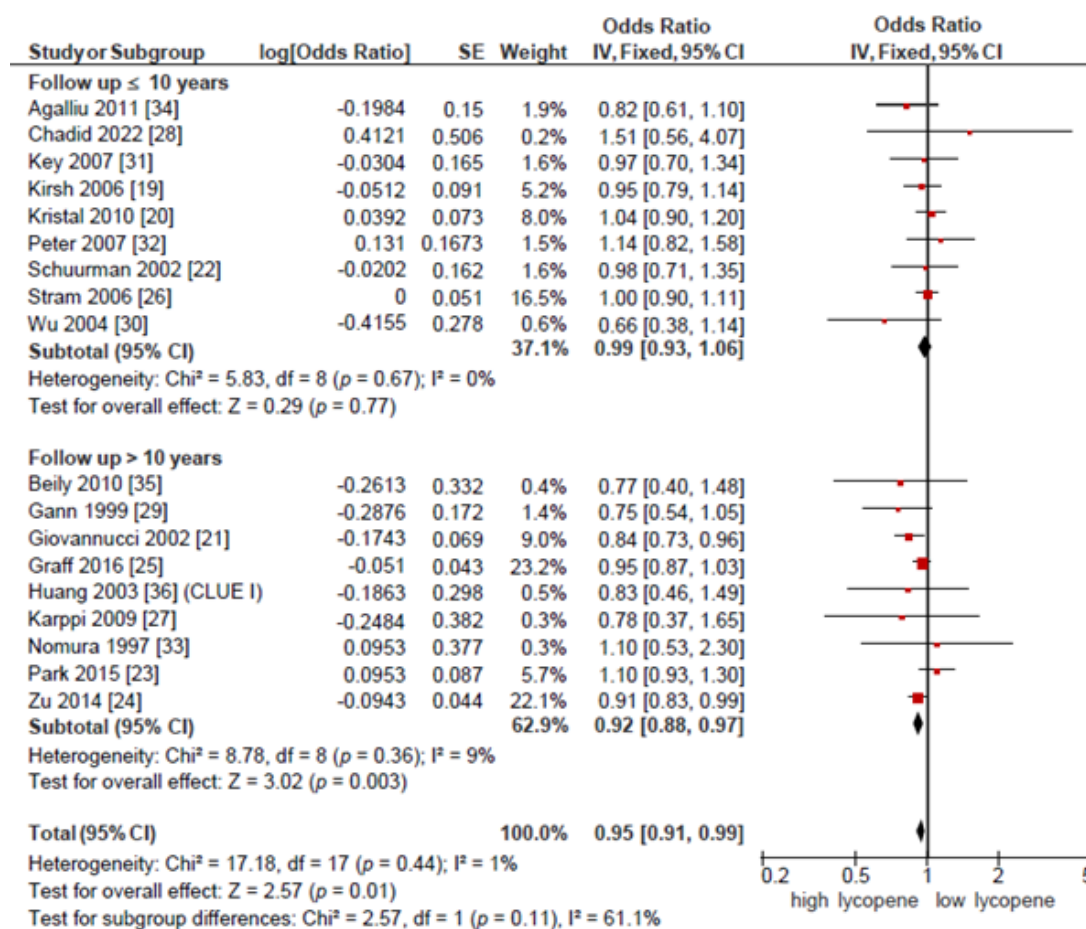


Figure 8: Forest plot of subgroup analysis stratified by follow-up duration (≤ 10 years vs. > 10 years) for the association between lycopene intake and prostate cancer risk.

Publication bias

Publication bias was assessed using funnel plots for both dietary and serum lycopene analyses, which showed approximate symmetry, suggesting no major publication bias. The results of Egger's tests supported these findings across all subgroups: lycopene intake and prostate cancer ($Z=0.08$, $p=0.62$), serum lycopene and prostate cancer ($Z=-0.01$, $p=0.94$), lycopene intake and advanced prostate cancer ($Z=-0.24$, $p=0.47$) and serum lycopene and advanced prostate cancer ($Z=0.84$, $p=0.52$). All p -values were greater than 0.05, indicating no statistically significant evidence of publication bias in any subgroup.

Discussion

Prostate cancer is a common and deadly malignancy among men. While early detection offers a high survival rate, advanced disease has a poor prognosis, highlighting the need for effective prevention. Current treatments improve outcomes but face challenges like side effects and recurrence [42]. As a result, attention has shifted toward preventive strategies, particularly dietary approaches. Lycopene, a carotenoid predominantly found in tomatoes, has demonstrated potential anticancer effects, including antioxidant activity [43], modulation of gene expression and induction of apoptosis in prostate cancer cells [44]. The anti-aging gene Sirtuin 1 has been

shown to be activated by lycopene. Sirtuin 1 has been linked with the development of prostate cancer. The role of lycopene levels may be linked to Sirtuin 1 levels to reduce the risk of prostate cancer [45-47]. Observational studies, including cohort, case-control and nested case-control designs, have produced mixed results regarding the association between lycopene and prostate cancer risk. These inconsistencies are attributable to variability in study designs, methods for measuring lycopene intake or blood levels, duration of follow-up and population characteristics. Consequently, this systematic review and meta-analysis aimed to synthesize the existing evidence and clarify the potential protective effect of lycopene against prostate cancer. A total of 23 eligible studies were included, encompassing diverse geographical settings and study populations. Most studies originated from high-income countries and focused on middle-aged to elderly men of predominantly Caucasian ethnicity. Notably, none of the included studies utilized mortality (i.e., prostate cancer-specific deaths) as an outcome, focusing instead on incidence as the primary endpoint. The quality of studies was assessed using the NOS and most studies scored between 7 and 9 points, indicating generally high methodological quality. Cohort studies tended to receive higher scores, reflecting their advantage in establishing temporal relationships and minimizing recall bias. The overall pooled analysis revealed a

statistically significant inverse association between high lycopene intake and prostate cancer risk, (OR=0.91, 95% CI: 0.84-0.99, P=0.03). This finding supports the hypothesis that lycopene may exert a protective effect against prostate carcinogenesis [43,44] and aligns with previous research, the meta-analysis by Chen [48], which included 26 studies, reported an inverse association between lycopene consumption and prostate cancer risk. Similarly, Rowles [49] found a significant risk reduction associated with lycopene intake, particularly among individuals with higher levels of consumption. Subgroup analyses provided additional insight into potential dose-response effects. Specifically, only individuals consuming lycopene at levels exceeding 10mg/day showed a significant reduction in risk (OR=0.95, 95% CI: 0.91-0.99, P=0.02) and aligns with previous findings by Zu [24], who reported that each 2mg/day increase in lycopene intake was associated with a 3-5% reduction in prostate cancer risk, whereas lower levels of intake (<10mg/day) did not yield statistically significant results.

The subgroup meta-analysis for advanced prostate cancer revealed a statistically significant inverse association between overall lycopene consumption and disease risk (OR=0.88, 95% CI: 0.78-0.99, P=0.04). This finding highlights the potential of lycopene in delaying or preventing the progression of more aggressive forms of prostate cancer [50]. When stratified by cancer severity, lycopene intake >15mg/day was significantly associated with a decreased risk of advanced prostate cancer (OR=0.86, 95% CI: 0.76-0.98, P=0.02). This supports a biologically plausible dose-response relationship and aligns with previous findings by Zu [24], who reported that each 2mg/day increase in lycopene intake was associated with a 3-5% reduction in prostate cancer risk. However, heterogeneity across studies was moderate ($I^2=60\%$), reflecting differences in study methodology, participant characteristics and lycopene assessment methods. In addition to dietary intake, the analysis examined serum lycopene levels in relation to prostate cancer risk. A separate pooled analysis of 10 studies showed that individuals with the highest serum lycopene concentrations had a significantly lower risk of prostate cancer (OR=0.83, 95% CI: 0.73-0.96, P=0.009). The results of this study are consistent with the meta-analysis conducted by Chen [48]. Importantly, heterogeneity among these studies was minimal ($I^2=0\%$), increasing confidence in the reliability of this association. Since serum lycopene reflects both dietary intake and bioavailability, this biomarker may serve as a more accurate indicator of lycopene exposure than dietary assessment alone. Although the association between serum lycopene and advanced prostate cancer did not reach statistical significance (OR=0.64, 95% CI: 0.39-1.07, P=0.09), the effect estimate was suggestive of a protective trend. The lack of significance may be attributable to limited sample sizes, inconsistencies in defining advanced disease and variability in serum measurement techniques. Nevertheless, these findings warrant further exploration. Follow-up duration was also a significant modifier of observed associations. Studies with longer follow-up periods (>10 years) demonstrated a clear inverse relationship between lycopene intake and prostate cancer risk (OR=0.92, 95% CI: 0.88-0.97, P=0.003), whereas no association was found in studies with follow-up ≤ 10 years. This suggests that

lycopene's protective effect may require prolonged exposure and accumulation in tissue before manifesting a measurable benefit [51] and aligns with previous research, the meta-analysis by Rowles [49]. This study has several notable strengths. First, the use of systematic review and meta-analytic methodologies reduces selection bias and increases statistical power. Second, subgroup analyses enabled exploration of key moderators such as lycopene dosage, cancer stage and follow-up duration. Third, inclusion of both dietary and biomarker data provides a more comprehensive understanding of lycopene exposure. Finally, the robustness of the findings was reinforced by consistency across studies and minimal evidence of publication bias.

However, limitations must be acknowledged. Most studies assessed lycopene intake using FFQs, which are prone to recall and reporting biases, especially in older populations. Additionally, the observational nature of the included studies precludes definitive causal inference. Although RCTs of lycopene supplementation exist, they remain limited in number, sample size and short follow-up duration, emphasizing the need for further high-quality interventional research. It is recommended that future studies should include participants from developing countries and varied genetic and dietary backgrounds to enhance generalizability. Long-term prospective studies with extended follow-up are needed to capture cumulative effects, with careful adjustment for confounders such as diet, medication use and screening practices. Although observational data offers useful insights, high-quality Randomized Controlled Trials (RCTs) are essential to establish causality. These trials should focus on high-risk groups such as men with elevated PSA or a family history of prostate cancer. Combining FFQ-based dietary assessments with plasma or serum lycopene levels will reduce recall bias and improve exposure accuracy. Additionally, future research should emphasize dose-response analyses to identify intake thresholds necessary for protective effects, guiding both clinical and public health recommendations.

Conclusion

This systematic review and meta-analysis offer comprehensive evidence supporting a protective association between high lycopene intake and a reduced risk of prostate cancer. Protective effects were more pronounced among individuals with higher intake levels and in studies with extended follow-up durations, suggesting a dose and time dependent relationship. Additionally, serum lycopene levels showed an inverse correlation with prostate cancer risk, reinforcing the potential biological relevance of lycopene in inhibiting prostate carcinogenesis. These findings highlight lycopene as a promising, non-pharmacologic, diet-based preventive approach and provide a strong scientific basis for future interventional studies and public health guidelines.

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Conflict of Interest

The authors declare no conflicts of interest.

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