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The effect of lycopene supplement from different sources on prostate specific antigen (PSA): A systematic review and meta-analysis of randomized controlled trials☆☆

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ABSTRACT

Background: Prostate cancer is a major malignancy, affecting men, worldwide. The protective effect of dietary or supplemental lycopene on prostate cancer has been reported in several studies; however, the findings are equivocal.
Objective: The aim of this study was to evaluate the effects of supplemental lycopene on PSA level, by conducting a systematic review and meta-analysis of randomized controlled trials.
Methods: We searched online databases, including PubMed, Scopus, and Web of Science, up to 9 Jun 2020, to obtain relevant publications. The publication search was not limited by language or date.
Results: A total of 1036 records were identified in the systematic search; from these, 9 were included in the systematic review and 6 in meta-analysis. The pooled analysis of the 6 studies showed no significant differences in PSA levels in subjects treated with lycopene or tomato extract containing lycopene (WMD= −0.12 ng/ml; 95% CI: −0.62, 0.38 ng/ml; P = 0.64) compared to the control.
Conclusion: Overall, tomato extracts or lycopene treatment yielded no significant effect on PSA level compared to the control. However, more consistent clinical trials, with larger sample sizes, are required to better discern the actual effect of tomato extract or lycopene on PSA level.

1. Introduction

Prostate cancer (PCa) is considered as a major cause of early mortality among men, with a globally increasing prevalence and wide geographical variation.[1–3] Prostate cancer is still recognized as a major malignancy influencing the male population. Its prevalence rates vary more than 25-fold across the world, with the highest prevalence in North America, Western and Northern Europe, Australia, and New Zealand and lower prevalence in Asian and Eastern Europe countries. [3]

Depending on the clinical stage, type of the cancer, serum levels of prostate specific antigen (PSA), and possible side effects, common treatments include active surveillance, surgery, chemotherapy and radiation therapy.[4,5] Although such intervention options aim to decrease the risk of PCa mortality and treatment-related complications, they are, unequivocally, most effective in early stages of the cancer, and especially if the cancer cells are still localized to the prostate gland. Once the tumor has spread outside of the prostate gland, or metastasized to other part of the body, it becomes more difficult to prevent its progression.[5–7] With an increasing awareness and accessibility to healthcare information, the prevention and treatment of PCa risk factors is of considerable importance due to the high health and economic burden it causes.[8] The role of lifestyle and dietary factors in the occurrence and progression of

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the PCa has been reported in several epidemiological studies.[9–12] Generally, a western dietary pattern, with excess amounts of red meat, processed meat, eggs, and sweets, is associated with high risk of PCa.[13] Conversely adherence to a healthy dietary pattern, characterized by high amount of fruit, vegetable, poultry, fish, whole grains, and antioxidants, is associated with a reduced risk of PCa.[14] As a part of a healthy dietary pattern, consumption of tomato and tomato derived products have attracted a particular attention due to their high content of carotenoid lycopene. [15] Indeed, lycopene is regarded as a potent antioxidant, with radical scavenging and anti-cancer activity,[16,17] and the potential protective effect of lycopene against prostate cancer has been reported in some studies.[18–22] However,the World Cancer Research Fund (WCRF) Continuous Update team categorized the finding regarding prostate cancer and the protective role of lycopene containing food as inconclusive due to limited evidence.[23] Prostate specific antigen (PSA) is a common biomarker used for screening of PCa, and is also used for assessing clinical risk, follow ups, and risk classification of patients with PCa.[24,25] The effect of dietary or supplemental lycopene on serum PSA levels in subjects, with or without PCa, has been evaluated in several studies[26–28]; however, the reported findings are equivocal. Therefore, the aim of this study was to systematically evaluate the effect of dietary or supplemental lycopene on serum levels of PSA.

2. Methods

2.1. Search strategy

A comprehensive literature search was done using online databases, including PubMed, Scopus, and Web of Science, up to 9 Jun 2020, to identify publications. Relevant MeSH (Medical Subject Headings) terms related to tomato and lycopene were searched in combination with key words related to PSA (Prostate specific antigen) (Supplementary table 1). In addition, the first 4 pages of Google Scholar and the references list of included studies and recent reviews were checked to determine other, potentially relevant, articles. The publication search was not limited by language or date. This review was conducted in accordance with the Preferred Reporting Items In Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] The study protocol was registered in the PROSPERO international prospective register of systematic review (CRD42020192960).

2.2. Eligibility criteria

One researcher (SS) searched the mentioned online databases to retrieve potentially related articles. Titles, abstracts, and full texts of the retrieved studies were screened independently by two authors (ESZ and MM), according to the following inclusion criteria: (1) all RCTs that involved men aged $>$ 18 years old, (2) studies that considered dietary (whole tomato, tomato sauce, or tomato juice) and/or supplemental lycopene (tablet/capsule) as an intervention (3) studies in which the comparator was no treatment, a placebo or standard treatment, (4) those that considered the serum level of PSA as an outcome, and (3) publications in which mean $\pm$ standard deviation (SD), mean $\pm$ standard error (SE), or mean (95% CI) were used to report effect sizes. In studies that assessed the effect of multiple doses of lycopene on PSA, the highest does was selected for evaluation in the meta-analysis. As well as for trials that evaluated changes in PSA at multiple time points, only the most recent measurement was included for assessment. In this review we excluded publications with any design other than RCT, studies in languages other than English, studies that included additional intervention combined with tomato or lycopene, in a way that the effects of lycopene or tomato was not separable (e.g. soy isoflavon + lycopene in comparison to lycopene), reviews, meta-analyses, and publications with no available full-text.

2.3. Data extraction

After reviewing the full text of identified studies, all required data were independently extracted, by two investigators (ESZ and MM), based on a predefined screening form that was checked by a third researcher (SS). Extracted information for each included article was as follows: first author's last name, year of publication, country, study design, study population characteristic, mean age of participants, study duration, sample size, dose and type of intervention (tomato/ lycopene), placebo type and outcome (mean of PSA). Any disagreement regarding data extraction was resolved by discussion.

2.4. Risk of bias assessment

Quality and risk of bias for included studies were assessed independently by (MM and ESZ) using the Cochrane Risk of bias assessment tool.[30] Assessment was performed based on the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and researcher), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and any other bias (Considering baseline age, BMI, PSA, serum lycopene or dietary lycopene intake). The quality of studies was identified as poor (low risk for less than four domains), fair (low risk for four domain), and good (low risk for more than four domain), respectively. Any disagreements regarding risk of bias were discussed and resolved by consultation with principal author (FS).

2.5. Assessment of the quality of meta-evidence

The quality of meta-evidence for this review was evaluated by using the NutriGrade (Grading of Recommendations Assessment, Development, and Evaluation) scoring system.[31] This system, for a systematic review of RCTs, has a maximum of 10 points and includes: (1) risk of bias, study quality and study limitations, (2) precision, (3) heterogeneity, (4) directness, (5) publication bias, (6) funding bias, (7) study design. The overall quality of meta-evidence for the outcome was classified as: high ($\geq$8 points), moderate (6–7.99 points), low (4–5.99), or very low (0–3.99).

2.6. Data synthesis and analysis

The differences in mean change (MD) for PSA and their corresponding standard deviations (SDs) between intervention (lycopene) and control groups in each study were utilized to calculate the effect size for PSA. Only one study reported the mean change value for PSA in intervention and control group,[26] therefore we calculated mean changes and their estimated SDs for PSA based on reported baseline and post intervention values in each study and by using the correlation r ($r = 0.5$). All reported units of PSA were converted to the ng/ml to standardize units of measurements before inclusion in the meta-analysis. The weighted mean difference (WMD) and its corresponding SD was calculated for PSA and pooled using the DerSimonian and Laird method,[32] taking between-study heterogeneity into account. Between-study heterogeneity was assessed using Cochrane's Q statistic and *I*-squared statistic.[33] Subgroup analyses, according to participant's disease status (diagnosed PCa and increased risk but free of PCa), study duration ($<$ 4 week and $\geq$4 week), and amount of supplemented lycopene ($\leq$15 mg/day and $>$ 15 mg/day), were conducted to determine heterogeneity between studies. Sensitivity analysis to evaluate the impact of a single study on the results was carried out by removing studies from the analysis, one by one; however, publication bias was not evaluated because the number of included studies were $<$ 10. Stata software (version 11.0; Stata Corporation) was used to conduct the meta-analysis; whilst statistical significance was accepted at $P < 0.05$.

3. Result

3.1. Study characteristics

Fig. 1 presents the detailed processes of study selection, where a total of 1036 publications were initially identified from the online databases search, of which, 450 duplicate and 539 irrelevant articles were excluded based on title and abstract screening. Of the remaining 47 articles, an additional 38 studies were removed due to the reasons mentioned in Fig. 1. Finally, 9 clinical trials remained for inclusion in the present systematic review, and 3 of these studies were excluded from the quantitative assessment because of insufficient data.[27,34,35] Thus, meta-analysis was done on the remaining 6 RCTs.[26,28,36–39] Table 1 details the main characteristics of the eligible studies for this systematic review. Of the nine included studies, eight had a parallel design and one had a cross over design, in which red tomato paste (equivalent to 16 mg lycopene) and supplemental purified lycopene were used as the interventions in the first and second phase, respectively.[35] The duration of intervention varied from 1 weeks to 24 weeks, and lycopene doses ranged from 8 mg/d to 45 mg/d. Three studies were conducted on men with diagnosed PCa,[26,28,38] 4 on men without PCa, but with increased risk of PCa,[27,34,36,37] 1 enrolled men with BPH free of PCa,[39] and 1 was carried out on healthy men.[35] Geographically, three studies were carried out in USA,[27,28,38] one in India[34] and single studies originated from Tobago,[37] Germany,[39] France,[35] Norway,[26] and the UK,[36] respectively.

3.2. Assessment risk of bias

Five studies included in the systematic review and meta-analysis had a good quality based on Cochrane Collaboration's tool,[26,27,36,37,39] and four studies were classified as poor.[28,34,35,38] Five studies for the method of random sequence generation[26,28,36–38] and five studies for the process to conceal the allocation of participants[26,27,36,37,39] had low risk of bias, whilst others were unclear or high risk. One study did not report blinding of researchers and outcome assessment.[28] No studies reported selective reporting and incomplete outcome bias, although four studies[26,34,35,38] had other bias as following; three studies did not consider the baseline BMI[38] and serum lycopene or dietary lycopene intake[26,35,38] and one study did not consider baseline age, BMI, serum PSA, and serum lycopene or dietary lycopene intake[34] (Fig. 2).

3.3. NutriGrade

The quality of meta-evidence for the effect of lycopene supplementation on the serum level of PCa was rated as "moderate" (Table 2).

3.4. Meta-analysis

In total, 6 RCTs (298 participants) reported the effects of lycopene or tomato extract containing lycopene on PSA level[26,28,36–39]. The overall analysis indicated no significant changes in PSA levels in subjects treated with tomato extract or lycopene (WMD= −0.12 ng/ml; 95% CI: −0.62, 0.38 ng/ml; P = 0.64), and the heterogeneity was low (Cochrane Q test=3.99, P = 0.551, I^2=0.0%) (Fig. 3). This result was also observed across all subgroups (Table3).

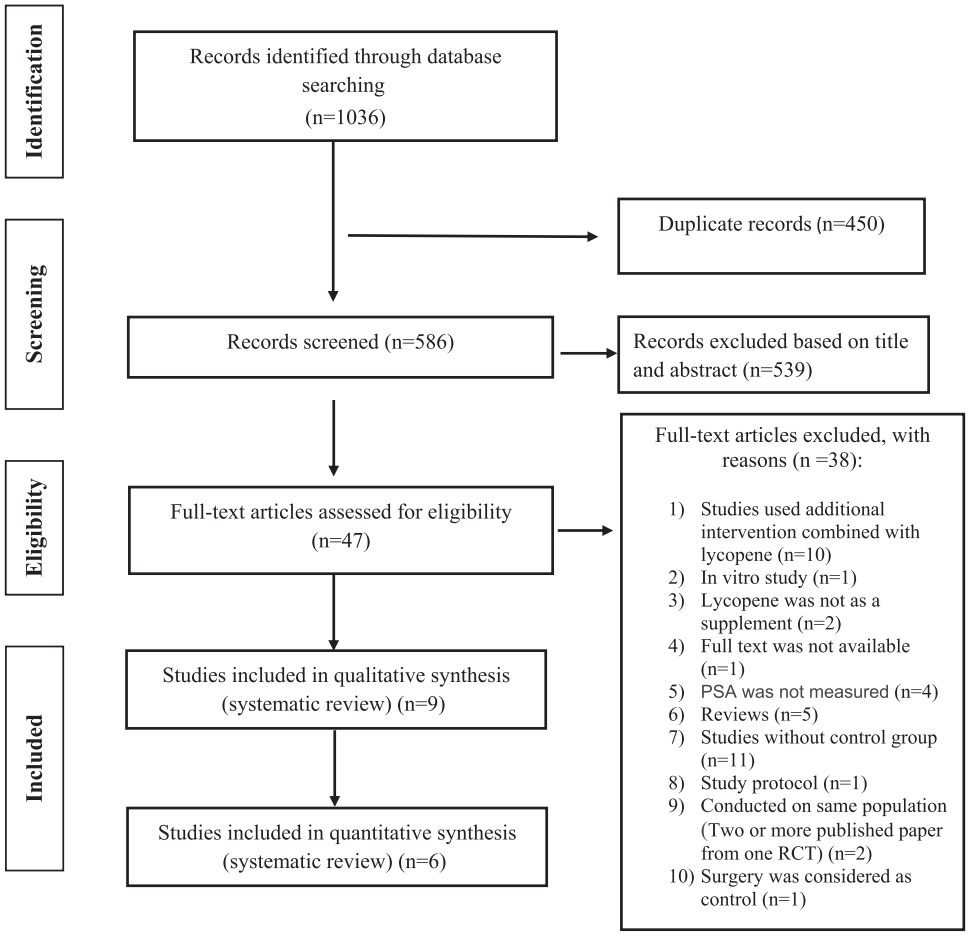

Fig. 1. Flowchart of the study selection process.

Table 1
Main characteristics of studies examining the effect of lycopene on PSA level.

Author/date	Country	Study design	Participants, n, T/C	Subject characteristic	Dose and Type intervention	Duration (week)	Results	Reported PSA values	Total score
Kucuk 2001 [38]	USA	Parallel RCT	15/11	Men with newly diagnosed Pca	30 mg/d lycopene (Lyc-O-Mato)	3	Reduction in PSA	Lycopene, B: 6.89 ± 0.81, A: 5.64 ± 0.87, C: NR Control, B: 6.74 ± 0.88, A:7.65 ± 1.78, C:NR	3
Mohanty2005 [34]	India	Parallel RCT	20/20	Men with HGPIN	8 mg/d lycopene (Lyc-O-Mato)	48	Reduction in PSA	Lycopene, B: 6.07, A: 3.5, C:NR Control, B: 6.55, A: 8.06, C: NR	2
Gann 2016[27]	USA	Parallel RCT	25/30	Men with HGPIN	30 mg/d lycopene (Lyc-O-Mato)	24	Increase in PSA	Lycopene, B: NR, A: NR, C: 0.08 Control, B: NR, A: NR, C: 0.08	6
Bunker 2007[37]	Tobago	Parallel RCT	38/39	Men with HGPIN	30 mg/d lycopene (Lyc-O-Mato)+Multivitamin	16	Increase in PSA	Lycopene +MV, B:5.31 ± 5.37, A: 5.74 ± 4.99, C: NR MV, B: 5.31 ± 5.4, A: 5.39 ± 5.75, C: NR	5
Schwarz 2007[39]	Germany	Parallel RCT	19/18	Men with BPH free of Pca	15 mg/d synthetic lycopene	24	Reduction in PSA	Lycopene, B; 6.56 ± 2.3, A: 5.82 ± 1.8. C:NR Control, B: 6.85 ± 2.3, A: 6.81 ± 4.7 C:NR	6
Kumar 2008[28]	USA	Parallel RCT	14/11	Men with localized Pca	45 mg/d lycopene (Lyc-O-Mato)	4–6	Increase in PSA level	Lycopene, B: 5.97 ± 4.0, A: 6.39 ± 3.46, C: NR, Control, B: 5.48 ± 3.38 A: 5.12 ± 1.86, C: NR	3
Talvas 2010[35]	France	Cross over RCT	15/15	Healthy men	200 g/d red tomato paste in the first phase and purified lycopene (16 mg/d) in the second phase	1	After treatment data were not reported	Lycopene, B:1.55 ± 0.41, A: NR, C:NR Control, B:2.42 ± 0.83, A: NR, C: NR	2
Paur 2017[26]	Norway	Parallel RCT	26/24	Men with non-metastatic Pca	Tomato product, provided 30 mg/d lycopene	3	No differences in change of PSA	Lycopene Med (Range), B: 8.54 (1.52, 25.90), A: NR, C: 0.00 (−3.30, 2.40) Control Med (Range), B: 9.34 (4.42, 55.0), A: NR, C: 0.41 (−8.53, 4.0)	5
Lane 2018[36]	UK	Parallel RCT	41/42	Men at increased risk of Pca	15 mg/d tomato-derived extract of lycopene (Solanum lycopersicon L. Solanaceae, Lyc-O-Mato, Lycored Ltd)	24	Increase in PSA	Lycopene Med (IQR), B: 3.2 (2.6–4.5), A: 3.2 (2.7–4.5), C:NR Control Med (IQR), B: 3.0 (2.3–3.8) A: 3.2 (2.4–4.3), C: NR	7

RCT, randomized controlled trial; T, treatment; C, control; PCa, prostate cancer; HGPIN, high grade prostatic intraepithelial neoplasia; BPH, benign prostate hyperplasia; PSA, prostate specific antigen. B, before intervention; A, after intervention; C, change.

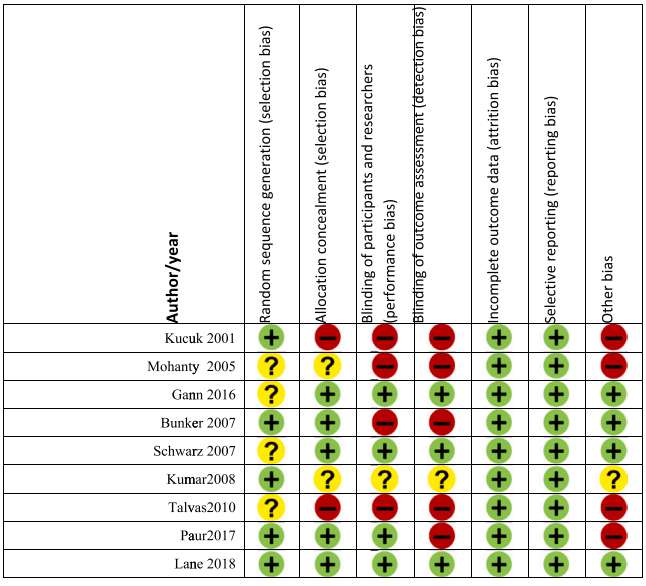

Fig. 2. Risk of bias of the included studies. + shows a low risk, - shows a high risk and ? shows unclear risk of bias.

3.5. Sensitivity analysis

We sequentially removed each trial from the analysis in order to perform sensitivity analysis, and found no significant effect of a single study on the overall results ($P > 0.05$). In addition, as the study by Lane et al.[36] accounted for the larger percent of the total weight of the included studies, we assessed the effect of removing of Lane's study on the overall result and observed no significant effect (WMD= 0.152 ng/ml: 95% CI: −0.768, 1.072 ng/ml; $P = 0.746$).

4. Discussion

The results of the current meta-analysis indicated that supplementation with lycopene or tomato extract containing lycopene had no significant effect on PSA level compared to the control group. This result was also observed across all subgroups. In addition, our sensitivity analysis showed no significant effect of a single study on the overall results. Findings from previous systematic reviews regarding the effect of lycopene on prostate cancer risk are inconclusive. Ilic et al. indicated a significant reduction in PSA level after lycopene supplementation, based on the pooled effect size of two studies.[5] Most recently in a systematic review and meta-analysis, Sadeghian et al. reported no beneficial effect of lycopene on PSA level in men with non-metastatic prostate cancer.[40] However, their subgroup analysis revealed a significant reduction effect of lycopene on PSA level in patients with higher levels of baseline PSA. Although consisting with our overall results, the

Table 2
Meta-evidence judgment based on the NutriGrade[a].

Comparison outcome reference	Risk of bias[b]	Precision	Heterogeneity	Directness	Publication bias	Funding bias	Study design	NutriGrade	Meta-evidence judgment
PCa	2	0	0.5	1	0	1	2	6.5	Moderate

[a] GRADE, Grading of Recommendations Assessment, Development and Evaluation.
[b] Including study quality, and study limitations.Table 2

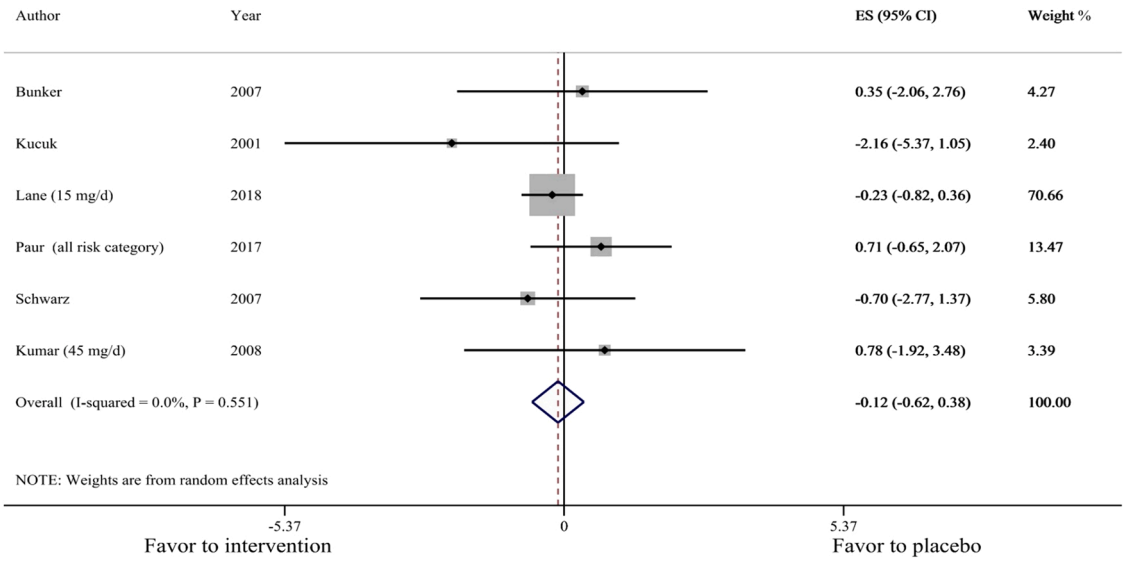

Fig. 3. Forest plot of studies that examined the effect of lycopene or tomato extract containing lycopene on PSA level.

Table 3
Meta-analysis showing the effect of lycopene supplementation on PSA level.

Meta-analysis				Heterogeneity			
Study group	Number of studies	WMD[1] (95%CI)	P effect	Q statistic	P within group	I^2 (%)	P between group
Overall	6	-0.12 (−0.62, 0.38)	0.643	3.99	0.551	0.0%	
PCa							
Diagnosed PCa	3	0.210 (−1.278, 1.698)	0.782	2.71	0.258	26.2%	0.354
Without PCa	3	-0.233 (−0.787, 0.321)	0.410	0.42	0.810	0.0%	
Duration							
< 4 wk	2	-0.340 (−3.049, 2.369)	0.806	2.60	0.107	61.5%	0.501
≥ 4 wk	4	-0.192 (−0.735, 0.351)	0.488	0.94	0.816	0.0%	
Lycopene dose							
≤ 15 mg/d	3	-0.226 (−0.782, 0.331)	0.427	0.59	0.439	0.0%	0.324
> 15 mg/d	5	0.362 (−0.665, 1.389)	0.490	2.71	0.743	0.0%	

Sadeghian's study has several limitations that affect the validity and interpretation of the study findings. Theses includes the use of studies with overlapping population[38,41] both in overall and subgroup analysis, subgrouping based on mean value of serum PSA of participants at the beginning of the study, but not based on the inclusion criteria (which may lead to misclassification of subgroups) and comparison of the three intervention arms versus one placebo group which can lead to overestimation of the effect size and misleading results, according to the Cochrane handbook.[42] In the present study although we adapted a comprehensive and robust methodology to determine the effect of lycopene on PSA levels in men with and without PCa, we failed to detect a favorable effect of this supplement compared to control group. This may be related to the small number of eligible studies, with relatively small number of total participants (totally 298 participants) that limits our ability to detect significant results. In addition, other contributing factors including baseline dietary intake, circulating lycopene, body weight, and changes in dietary habits or body weight during interventions were not taken into account in most of the studies reviewed. However, the role of diet and BMI on PCa progression and PSA level has been well indicated.[43] In fact, an inverse association between obesity and PSA level, due to the increased blood plasma volume and hemodilution of serum PSA has been previously reported.[44–46]

As the PSA level is proportional to the prostate tumor volume, a reduction in PSA level may represent lower numbers of prostate cancer cells and tumor regression.[47] Although the reduction effects of lycopene on PSA level has been shown in several clinical trials,[48–50] findings from other studies are equivocal.[51,52] In a meta-analysis of observational studies each 1 mg/d increase in dietary lycopene was associated with a 3% reduction in PCa risk.[53] The exact mechanism by which lycopene might exert its protective effects on PCa is not fully understood. Beside its antioxidant activity, some evidence indicates that an accumulation of lycopene in the prostate gland may interfere with cell growth progression and block cell cycle at the G1/S phase transition.[17,54,55] Additional effects, including inhibition of interleukin-6 expression, insulin-like growth factor-1 (IGF-1) signaling, and androgen signaling, have also been reported as protective roles of lycopene in PCa.[55,56] As mentioned

previously population health status, including subjects baseline BMI, PSA level, and PCa stage are important factors influencing the response of PSA to lycopene.[27,37] Due to the pathophysiologic differences between individuals with increased risk of PCa and patients with PCa,[57] we performed a subgroup analysis based on PCa risk and failed to detect any significant effect of lycopene on PSA. Moreover, subgroup analysis according to the subject's baseline PSA level, BMI, and circulating lycopene was not possible due to limited number of studies. Although the appropriate dose of lycopene supplementation for men at high risk of developing PCa is not determined, daily intake of 6 mg was suggested to provide sufficient antioxidant activity.[58] Our subgroup analysis based on the lycopene dose revealed no significant results. The relatively narrow range of lycopene doses (15–45 mg/d) across the included studies and the small number of studies in the subgroups may contribute to our null results.

The current meta-analysis exhibits some strengths. The first of which is adopting a comprehensive and robust methodology to identify available studies that assessed the effect of lycopene on PSA. Also conducting sensitivity and subgroup analysis to determine the source of heterogeneity, and evaluating the effects of a single study on the overall result represent additional strengths. However, some limitations should be considered when interpreting our results. The overall quality of the available studies was moderate, whilst two of the six included studies in the meta-analysis had a poor quality, which may be considered as a contributing factor to heterogeneous finding in subgroup analyses. Additionally, the effect of lycopene on PSA may depend on baseline PSA, stage of PCa, duration of the intervention, dose of lycopene, BMI, and changes in serum lycopene compared to the baseline. As most of the included studies did not take these variables into account, it is difficult to draw a clear conclusion. Furthermore, our finding of no significant effect of tomato extract or lycopene on PSA response, despite significant effects on the prostate cancer risk reported in some observational studies,[22,59] might indicate that serum PSA does not serve well as a surrogate outcome for assessing the efficacy of nutritional supplements in PCa risk. Additionally, the sources of lycopene differed among included studies, thus the presence of other tomato component such as phytochemicals made it difficult to provide a definitive conclusion about the effect of lycopene alone on PSA. Hence the results of this study can be more attributed to the tomato extract containing lycopene rather than lycopene alone. However due to the small number of the included studies and also small sample size in each study conclusion regarding our results should be taken with caution.

5. Conclusion

The results of this review indicated that supplementation with lycopene or tomato extract containing lycopene had no significant effect on PSA level. However, due to the limited number of available studies, heterogeneity regarding source and dose of lycopene, participant's health status, baseline PSA, and circulating lycopene, caution should be taken when interpreting the current results. More consistent clinical trials, with larger sample size, and consideration for the aforementioned confounding variables, are required to better discern the actual effect of lycopene supplementation on PSA level.

Ethics approval and consent to participate

Not applicable.

Data availability

The dataset applied and analyzed for the present study is available from the corresponding author on a reasonable request.

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Consent for publication

All authors of this study declared their consent for publication.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

FS: Participated in the study conception, revising the paper critically and approving the version of the manuscript being submitted. ESZ, MM, LR and CTC: Contributed to the study design and data collection, and interpretation and drafting the manuscript. Statistical analysis was done by SS. All authors read the final content of the manuscript before submission.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2022.102801.

References

1 Campbell JK, Canene-Adams K, Lindshield BL, Boileau TW-M, Clinton SK, Erdman Jr JW. Tomato phytochemicals and prostate cancer risk. *J Nutr*. 2004;134 (12):3486S–3492SS.
2 Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. *Cold Spring Harb Perspect Med*. 2018;8(12), a030361.
3 Hussein AA, Baban R, Hussein A. Prostate-specific antigen and free prostate-specific antigen/prostate-specific antigen ratio in patients with benign prostatic hyperplasia and prostate cancer. *Baghdad J Biochem Appl Biol Sci*. 2020;1(01):18–26.
4 Mokbel K, Wazir U, Mokbel K. Chemoprevention of prostate cancer by natural agents: evidence from molecular and epidemiological studies. *Anticancer Res*. 2019; 39(10):5231–5259.
5 Ilic D, Misso M. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. *Maturitas*. 2012;72(4): 269–276.
6 Ferraldeschi R, Pezaro C, Karavasilis V, De Bono J. Abiraterone and novel antiandrogens: overcoming castration resistance in prostate cancer. *Annu Rev Med*. 2013;64:1–13.
7 Roudier MP, True LD, Higano CS, et al. Phenotypic heterogeneity of end-stage prostate carcinoma metastatic to bone. *Hum Pathol*. 2003;34(7):646–653.
8 Stokes ME, Ishak J, Proskorovsky I, Black LK, Huang Y. Lifetime economic burden of prostate cancer. *BMC Health Serv Res*. 2011;11(1):349.
9 Polesel J, Gini A, Dal Maso L, et al. The impact of diabetes and other metabolic disorders on prostate cancer prognosis. *J Diabetes Complicat*. 2016;30(4):591–596.
10 Cicione A, De Nunzio C, Tubaro A, et al. Metabolic syndrome diagnosis and widespread high grade prostatic intraepithelial neoplasia significantly increase prostate cancer risk: results from a multicenter biopsy study. *BMC Cancer*. 2016;16 (1):1–6.
11 Bhindi B, Xie WY, Kulkarni GS, et al. Influence of metabolic syndrome on prostate cancer stage, grade, and overall recurrence risk in men undergoing radical prostatectomy. *Urology*. 2016;93:77–85.
12 Ilic D, Forbes KM, Hassed C. Lycopene for the prevention of prostate cancer. *Cochrane Database Syst Rev*. 2011;(11).
13 Fabiani R, Minelli L, Bertarelli G, Bacci S. A western dietary pattern increases prostate cancer risk: a systematic review and meta-analysis. *Nutrients*. 2016;8(10): 626.
14 Bahrami A, Movahed M, Teymoori F, et al. Dietary nutrient patterns and prostate cancer risk: a case-control study from Iran. *Asian Pac J Cancer Prev APJCP*. 2019;20 (5):1415–1420.
[15] Fraser GE, Jacobsen BK, Knutsen SF, Mashchak A, Lloren JI. Tomato consumption and intake of lycopene as predictors of the incidence of prostate cancer: the Adventist Health Study-2. *Cancer Causes Control*. 2020;31(4):341–351.
16 Tierney AC, Rumble CE, Billings LM, George ES. Effect of Dietary and supplemental lycopene on cardiovascular risk factors: a systematic review and meta-analysis. *Adv Nutr*. 2020;11:1453–1488.
17 Wertz K, Siler U, Goralczyk R. Lycopene: modes of action to promote prostate health. *Arch Biochem Biophys*. 2004;430(1):127–134.
18 Rackley JD, Clark PE, Hall MC. Complementary and alternative medicine for advanced prostate cancer. *Urol Clin*. 2006;33(2):237–246.

19 Chen J, Song Y, Zhang L. Lycopene/tomato consumption and the risk of prostate cancer: a systematic review and meta-analysis of prospective studies. *J Nutr Sci Vitaminol*. 2013;59(3):213–223.

20 Holzapfel NP, Holzapfel BM, Champ S, Feldthusen J, Clements J, Hutmacher DW. The potential role of lycopene for the prevention and therapy of prostate cancer: from molecular mechanisms to clinical evidence. *Int J Mol Sci*. 2013;14(7):14620–14646.

21 Lin P-H, Aronson W, Freedland SJ. Nutrition, dietary interventions and prostate cancer: the latest evidence. *BMC Med*. 2015;13(1):3.

22 Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. *J Natl Cancer Inst*. 2002;94(5):391–398.

[23] Research WCRFIAIfC. Continuous update project report: diet, nutrition, physical activity, and prostate cancer. World Cancer Research Fund International London, UK; 2014.

24 Abrahamsson P-A, Lilja H, Oesterling JE. Molecular forms of serum prostate-specific antigen: the clinical value of percent free prostate-specific antigen. *Urol Clin N Am*. 1997;24(2):353–365.

25 Catalona WJ. Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. *Jama*. 1995;274(15):1214–1220.

26 Paur I, Lilleby W, Bøhn SK, et al. Tomato-based randomized controlled trial in prostate cancer patients: effect on PSA. *Clin Nutr*. 2017;36(3):672–679.

27 Gann PH, Deaton RJ, Rueter EE, et al. A phase II randomized trial of lycopene-rich tomato extract among men with high-grade prostatic intraepithelial neoplasia. *Nutr Cancer*. 2015;67(7):1104–1112.

28 Kumar NB, Besterman-Dahan K, Kang L, et al. Results of a randomized clinical trial of the action of several doses of lycopene in localized prostate cancer: administration prior to radical prostatectomy. *Clin Med Urol*. 2008;1:S718.

29 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1–e34.

[30] Higgins J, Altman D, Stern J. Assessing risk of bias in included studies. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0. 0*. The Cochrane Collaboration; 2008.

31 Schwingshackl L, Knüppel S, Schwedhelm C, et al. Perspective: NutriGrade: a scoring system to assess and judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research. *Adv Nutr*. 2016;7(6):994–1004.

32 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.

33 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.

34 Mohanty NK, Saxena S, Singh UP, Goyal NK, Arora RP. Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. *Urol Oncol Semin Orig Investig*. 2005;23(6):383–385.

35 Talvas J, Caris-Veyrat C, Guy L, et al. Differential effects of lycopene consumed in tomato paste and lycopene in the form of a purified extract on target genes of cancer prostatic cells. *Am J Clin Nutr*. 2010;91(6):1716–1724.

36 Lane JA, Er V, Avery K, et al. ProDiet: a phase II randomized placebo-controlled trial of green tea Catechins and lycopene in men at increased risk of prostate cancer. *Cancer Prev Res*. 2018;11(11):687–696.

37 Bunker CH, McDonald AC, Evans RW, De La Rosa N, Boumosleh JM, Patrick AL. A randomized trial of lycopene supplementation in Tobago men with high prostate cancer risk. *Nutr Cancer*. 2007;57(2):130–137.

38 Kucuk O, Sarkar FH, Sakr W, et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol Biomark Prev*. 2001;10(8):861–868.

39 Schwarz S, Obermuller-Jevic UC, Hellmis E, Koch W, Jacobi G, Biesalski HK. Lycopene inhibits disease progression in patients with benign prostate hyperplasia. *J Nutr*. 2008;138(1):49–53.

40 Sadeghian M, Asadi M, Rahmani S, Sadeghi N, Hosseini SA, Zare Javid A. Lycopene does not affect prostate-specific antigen in men with non-metastatic prostate cancer: a systematic review and meta-analysis of randomized controlled trials. *Nutr Cancer*. 2020:1–12.

41 Kucuk O, Sarkar FH, Sakr W, et al. Lycopene in the treatment of prostate cancer. *Pure Appl Chem*. 2002;74(8):1443–1450.

[42] *Cochrane Handbook for Systematic Reviews of Interventions*; 2011. Available from: ⟨https://handbook-5–1.cochrane.org/chapter_16/16_5_4_how_to_include_multiple_groups_from_one_study.htm⟩.

43 Campi R, Brookman-May SD, Subiela Henríquez JD, et al. Impact of metabolic diseases, drugs, and dietary factors on prostate cancer risk, recurrence, and survival: a systematic review by the European Association of Urology Section of Oncological Urology. *Eur Urol Focus*. 2019;5(6):1029–1057.

44 Choi HC, Park JH, Cho BL, Son KY, Yoo YJ, Kwon HT. The illusion of prostate-specific antigen decline in patients with metabolic syndrome and insulin resistance. *Int Braz J Urol*. 2011;37(3):415–416.

45 Naito M, Asai Y, Mori A, et al. Association of obesity and diabetes with serum prostate-specific antigen levels in Japanese males. *Nagoya J Med Sci*. 2012;74(3–4):285–292.

46 Zhang J, Ma M, Nan X, Sheng B. Obesity inversely correlates with prostate-specific antigen levels in a population with normal screening results of prostate cancer in northwestern China. *Braz J Med Biol Res*. 2016;49:49.

47 Kim H-S, Bowen P, Chen L, et al. Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. *Nutr Cancer*. 2003;47(1):40–47.

48 Chen L, Stacewicz-Sapuntzakis M, Duncan C, et al. Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. *J Natl Cancer Inst*. 2001;93(24):1872–1879.

49 McDonald AC, Bunker CH, De La Rosa N, Matar J, Patrick AL. Serum PSA response to lycopene supplementation along with multivitamin does not differ from response to multivitamin alone in men with high grade intraepithelial neoplasia in a randomized trial. *Cancer Res*. 2006;66(8).

50 Bowen P, Chen L, Stacewicz-Sapuntzakis M, et al. Tomato sauce supplementation and prostate cancer: lycopene accumulation and modulation of biomarkers of carcinogenesis. *Exp Biol Med*. 2002;227(10):886–893.

51 Jatoi A, Burch P, Hillman D, et al. A Tomato-based, lycopene-containing intervention for androgen-independent prostate cancer: results of a phase II study from The North Central Cancer Treatment Group. *Urology*. 2007;69(2):289–294.

52 Clark PE, Hall MC, Borden LS Jr, et al. Phase I-II prospective dose-escalating trial of lycopene in patients with biochemical relapse of prostate cancer after definitive local therapy. *Urology*. 2006;67(6):1257–1261.

53 Wang Y, Cui R, Xiao Y, Fang J, Xu Q. Effect of carotene and lycopene on the risk of prostate cancer: a systematic review and dose-response meta-analysis of observational studies. *PLoS One*. 2015;10(9), e0137427.

54 Heber D, Lu Q-Y. Overview of mechanisms of action of lycopene. *Exp Biol Med*. 2002;227(10):920–923.

55 Trejo-Solís C, Pedraza-Chaverrí J, Torres-Ramos M, et al. Multiple molecular and cellular mechanisms of action of lycopene in cancer inhibition. *Evid Based Complement Altern Med*. 2013;2013:2013.

56 Goyal A, Delves GH, Chopra M, Lwaleed BA, Cooper AJ. Prostate cells exposed to lycopene in vitro liberate lycopene-enriched exosomes. *BJU Int*. 2006;98(4):907–911.

57 De Marzo AM, Coffey DS, Nelson WG. New concepts in tissue specificity for prostate cancer and benign prostatic hyperplasia. *Urology*. 1999;53(3):29–40.

58 Porrini M, Riso P. What are typical lycopene intakes? *J Nutr*. 2005;135(8):2042S–2045SS.

59 Graff RE, Pettersson A, Lis RT, et al. Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression. *Am J Clin Nutr*. 2016;103(3):851–860.