SYSTEMATIC REVIEW

Effect of Lycopene on Prostate Specific Antigen (PSA) and Stimulator Cell Growth Factor in Non-Metastatic Prostate Cancer Patients: A Systematic Review and Meta-Analysis

Akhmad Setyo Rahman[1,2], *Theresia Indah Budhy[3,4], Sakti Hoetama[5] and Nur Lailatul Fadhilah[6]

[1] Graduate Student of Immunology, Post Graduate School, Universitas Airlangga, Surabaya 60115 Indonesia
[2] General Practitioner, Ramelan Naval Central Hospital, Surabaya 60243, Indonesia
[3] Department of Immunology, Postgraduate School, Universitas Airlangga, Surabaya 60115, Indonesia
[4] Department of Oral and Maxillofacial Pathology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya 60115, Indonesia
[5] Urologist Staff, Ramelan Naval Central Hospital, Surabaya 60243, Indonesia
[6] Gynaecologic Obstetric Staff, Semen Gresik Hospital, Gresik 61122, Indonesia

ABSTRACT

Prostate cancer (PCa) is the third leading cause of death in the world. Dietary extract lycopene from tomato extract has been identified as one possible candidate for reducing risk of PCa. Some research findings are still equivocal. The aims of study to evaluate effects of dietary lycopene from tomato extract compare to the control on PSA level, IGF-1, and IGF BP-3 by conducting a systematic review and meta-analysis. Method for this research, we searched Cochrane Database, PUBMED, MEDLINE. All randomised controlled trials (RCTs) of lycopene from tomato extract for in prostate cancer patient were included, without language or date restrictions. Ten RCT's compared extract lycopene with control, total of 427 patients were analyzed. The mean number of PSA [MD] -0.35, 95% [CI] -0.64 to -0.07 (P 0.02), IGF-1 [MD] -2.01, 95% [CI] -3.33 to -0.69 (P 0.003), IGF BP-3 [MD] 2.70, 95% [CI] 0.96 to 4.44 (P 0.002). This result identified, extract lycopene had a significant difference in PSA level, IGF-1, and IGF BP-3 compared to control.

Keywords: Lycopene, PCa, PSA, IGF-1, IGF BP-3

Corresponding Author:
Prof. Dr. Theresia Indah Budhy, DDS, MDS
Email: theresia-i-b-s@fkg.unair.ac.id
Tel: +62315041536

INTRODUCTION

Prostate cancer (PCa) is the third most common cancer in men in the world with nearly 1.276.106 new cases diagnosed each year. PCa is the most frequently diagnosed cancer in 105 countries, followed by lung cancer in 37 countries, and liver cancer in 13 countries (1). The mortality of prostate cancer 361.800 patients each year (2). The epidemiological patterns suggest that lifestyle and dietary factors impact the occurrence of prostate cancer (3).

Complementary and alternative medicine (CAM) is defined by the National Centre for Complementary and Alternative Medicine as a group of diverse medical and healthcare systems, practices and products that are not normally considered to be conventional medicine (4). There is an increasing popularity and advocacy for the use of CAM amongst patients with cancer, especially prostate cancer and becoming more common in a wide circle. At least more than a quarter of prostate cancer patients use one CAM modality. Herbal product are the most commonly used CAM modalities although only as preclinical evidence of an underlying (5). The pattern towards the expanded utilization of CAM shows restraint driven and mirrors the adjustment of values apparent by patients toward customary clinical treatment. Besides, the requirement for individual control, the apparent wellbeing of a 'characteristic' item and a quest for potential remedial treatments when ordinary medicines are supposed to offer little advantage has driven the flood in the prevalence of CAM (4).

Lycopene have been identified as one possible candidate for reducing the risk of prostate cancer with lycopene as the major potential active component. Lycopene, a carotenoid consumed from tomatoes, is a promising nutritional component for the chemoprevention of PCa (6). Lycopene is a natural, prominent, and effective product which has a high value in diet. The anti-cancer effect, non-toxicity, safety and preventive or therapeutic roles of lycopene have been investigated in several studies (7). Lycopene intake and circulating lycopene

were associated with a reduced risk of prostate cancer in some meta-analyses, although not universally. A recent meta-analysis suggested that there was a 3% reduction in prostate cancer incidence per mg/day increase in dietary lycopene intake (8).

Lycopene from tomato extract intake and its relation with prostate cancer illustrates this fact and is still a matter of debate (9). Several large-scale prospective studies have shown an association that lycopene have a protective function against prostate cancer, but not a few case-control studies have shown that there is no no significant relationship between lycopene extract on prostate cancer (10). In epidemiological studies, regular intake of fruit or vegetable especially lycopene with high antioxidant has been repeatedly associated with a reduced and prevent risk of developing PCa. In experimental studies have shown that lycopene can selectively inhibit the growth of cancer cells and induce apoptosis without affecting the surrounding normal cells (11).

Prostate specific antigen (PSA) is an important biomarker used in clinical risk assessments, follow-ups and as part of risk stratification of prostate cancers patients. Screening for prostate cancer with PSA)aims to detect prostate cancer at an early, intervenable stage amenable to curative treatment, and reduction in overall and disease-specific mortality (12). PSA is a glycoprotein that is secreted by both normal prostate epithelium and prostate cancer cells. PSA secretion may be increased in the presence of benign prostatic hyperplasia, prostate cancer, and prostatic inflammation (13).

A decrease in PSA could reflect a decrease in the number of cancerous prostate. Alternatively, the decrease could reflect a change in physiological factors regulating PSA secretion, e.g., androgen receptor pathway or IGF-1 activity (14). Lycopene was observed via proteomic analysis to downregulate the androgen receptor signaling pathway in primary prostatic epithelial cells and thus could reduce expression of PSA, a classical androgen response protein (15)

Insulin like growth factor-1 (IGF-1) is a potent stimulator of normal and neoplastic cell growth and has antiapoptotic actions on prostate epithelial cells. The IGF family of growth factors (IGF-1 and IGF-2) are mitogens that play important roles in the regulation of proliferation, differentiation, and apoptosis (16)

In vitro and in vivo experiments demonstrate that IGF-I increases proliferation of both androgen-dependent and androgen-independent prostate cancer cell lines, and Insulin Growth Factor Binding Protein 3 (IGF-BP-3) can decrease the growth-stimulating effects of IGF-I (17). Prostate cancer growth and invasion are thus controlled by a fine-tuned network between IGF-1 driven integrin-FAK signaling and the Akt-mTOR pathway (18). The insulin-like growth factor binding protein (IGF BP-3) is a proapoptotic and antiangiogenic protein in prostate cancer. IGF BP-3 is a potent inhibitor of prostatic IGF action and also mediates prostate apoptosis via an IGF-independent mechanism (19).

Lycopene found in high quantities in tomatoes and tomato-rich products (19). A number of epidemiological studies have suggested an inverse relationship between dietary lycopene intake and the risk of developing Pca (20).

The effects lycopene on PSA, IGF-1, and IGF BP-3 in patients with prostate cancer have not been well documented. It is known that lycopene is a powerful antioxidant that can accumulate in prostate tissue and then exert a protective effect against DNA damage due to oxidative stress which is the starting point for cancer development (21). Experimental studies have shown that short-term intake of lycopene can induce changes in serum lycopene concentrations, thereby modulating the expression of genes associated with prostate cancer cells. This is evidenced by the high expression of IGFBP-3 and reduced expression of IGF-1 in prostate cancer cells after being measured using a sandwich immunoassay. The role of IGFBP-3 is not only as a binding protein but also independently regulates cell growth, proliferation, and apoptosis (22).

Lycopene can act as a chemopreventive agent in preventing or delaying the development of malignancy (23). Lycopene is very safe for prolonged use (24).
Recently, there were several meta-analysis studies examining the effect of lycopene on psa levels alone, without assessing prostate tumor cell growth stimulator factors, like IGF-1 and IGFBP-3, It is important in assessing the efficacy of lycopene and the risk of prostate cancer. Given the previous studies with some experimental evidence of lycopene, the aim of this meta-analysis was to evaluate the efficacy of lycopene therapy compared with control in prostate cancer patients on total PSA levels and stimulator factor cell growth prostate cancer cells.

METHODS

Eligibility Criteria

We include all published or unpublished randomised controlled trials (RCTs). We would also have included cluster randomised controlled trials and cross over trials, but we found none. There were no language restrictions. Adult (> 18 years) men of any ethnicity who had not previously been diagnosed with histologically localized prostate cancer were eligible for inclusion in this review and patient scheduled for radical prostatectomy. Patients with normal blood biochemical profile and no previous or current therapy for prostate cancer. Those with an increased risk of prostate cancer due to a family history of the disease or an elevated PSA level were included.

The exclusion criteria are non-localized Prostate cancer or metastases prostate cancer, refuse radical prostatectomy, refuse to be involved in research, patients with abnormal blood biochemical profile, and previous or current therapy for prostate cancer. We also exclude non-full text articles (article that only displays the abstract part and the reader cannot access to get the full article consisting of methods, results, control and intervention group data, conclusions, etc) and articles not RCT.

Dietary intervention to increase lycopene intake; lycopene supplements and products containing lycopene which are used to prevent of prostate cancer. Studies using amounts of lycopene, taken for a certain duration of time and/or in combination with other supplements were included in this review. The primary outcomes of this review determine prostate specific antigen (PSA) level. Secondary outcomes included determine in IGF-1 level and determine in IGF BP-3 level

Information source

We conducted electronic searches for eligible studies within each of the following databases PubMed, MEDLINE, EMBASE, Science Direct and the Cochrane Controlled Trial Register databases. This research proposal has been registered on the Prospero protocol with ID number CRD4202231825.

Search strategy

Searches were performed using the following key words: 'Prostate cancer', 'Adenocarsinoma prostate', 'Prostatic neoplasm', 'Lycopene', 'Carotenoids', 'Tomatoes', Prostate Spesific Antigen' and 'PSA'. The title and abstract of all retrieved articles were screened for exclusion. In addition, review articles were screened to find additional eligible studies. The search results were then limited according to the following inclusion and exclusion criteria: (1) Dietary lycopene or tomatoes were given to human (2) articles involved follow-up results at 1 until 48 weeks, (3) articles were reported in English, and (4) non-full-text articles (article that only displays the abstract part and the reader cannot access to get the full article consisting of methods, results, control and intervention group data, conclusions, etc) were excluded.

Selection process

"Four researchers (ASR, TIB, SH, NLF) independently reviewed titles and abstracts of the first 100 records and discussed inconsistencies until consensus was obtained. Then, in pairs, the researchers independently screened titles and abstracts of all articles retrieved. In case of disagreement, consensus on which articles to screen full-text was reached by discussion. If necessary, the third researcher was consulted to make the final decision. Next, Three researchers (ASR, SH, and NLF) independently screened full-text articles for inclusion. Again, in case of disagreement, consensus was reached on inclusion or exclusion by discussion and if necessary, the third researcher (SH) was consulted."

Data collection process

Three reviewers (ASR, TIB, SH, and NLF) independently searched the identified studies for eligibility against a pre-determined check list of inclusion criteria. A full text version of the article was obtained to assess if its title, or abstract, appears met the eligibility criteria. Studies were excluded if they failed to meet the inclusion criteria.

Risk of bias assessment

In assessing the risk of bias of the selected studies, we used the Cochrane risk of bias tool based on specific results. We assessed the risk of bias in studies using the Cochrane 'Risk of bias' tool (RoB 2.0). RoB 2.0 contains five specific domains: bias arising from the randomization process; bias due to deviations from the intended intervention; bias due to missing outcome data; bias in outcome measurement; and bias in the selection of reported outcomes. the three review authors independently applied the tool to each of the included studies, and recorded supporting and justification information for the risk assessment of bias for each domain (low; high; some concern). Any discrepancies in the assessment of risk of bias or justification for the assessment were resolved by discussion to reach consensus between the two review authors. Any disagreements will be mediated by a fourth team member.Following the guidance provided for RoB 2.0, we obtained a summary of the overall 'Risk of bias' assessment (low; some concern; high) for each specific outcome, where the overall RoB for each study was determined by the level of Highest RoB in any of the assessed domains (25).

Data Extraction

The information extracted from included studies was: (A) Published time; (B) The first author's name; (C) Country of study; (D) The type of design; (E) Patient's received therapy; (D) Number of participants in each group; (E) Treatment period; (F) Lycopene dose; (G) Data on total PSA level, IGF-1, and IGF BP-3. Because they have a measurable impact on patient, these results were considered as meaningful indicators. No ethical approval was required for the study. The primary outcome was total PSA level and secondary outcomes including IGF-1 and IGF BP-3, these were reported consistently enough among studies to allow for analysis of data.

Statistical Analysis and Meta-Analysis

Rev Man version 5.3.0 (Cochrane Collaboration, Oxford, UK) (AR, 1998) was used to the analysis of data. Fixed or random effects models were applied to assess the study. Mean difference (MD) was used to explain continuous data and odds ratio (OR) for dichotomous results with the corresponding 95% confidence interval (CI). The data were tested for heterogeneity. To assess heterogeneity in research, it is necessary to assess ToH (Test for Heterogeneity), the higher the value of I2, the

higher the heterogeneity between studies and the smaller the value of I2, the lower the heterogeneity between studies. If analysis showed p-value > 0.05 or small I2 value, the study was homogeneous, and fixed-effect model (FEM) was used in the study. But if p-value < 0.05 or big I2 value, the study was heterogenous, and random-effect model (REM) was used in the study. After that, the data were tested for the combined effect, to assess the combined effect between studies, an assessment was made on the test for overall effect with the results being meaningful or not. It is said to be meaningful if the P value is < 0.05, and it is said to be meaningless if the P value is > 0.05 (26).

RESULT

Study selection process, search results, and characteristics of the studies

The search found 304 articles in database. The researchers identifiy all articles with screening duplicate records by covidence software, exclude 98 articles. After that researcher identify all abstracts and titles, and excluded 140 articles. For remaining 66 articles, 56 articles were excluded because of lacking of available data (Fig. 1). Excluded articles are listed in Table III including reasons for exclusion. Finally, ten articles containing RCTs were used to evaluate lycopene from tomato extract theraphy compared with control in treating men with localized prostate cancer after 1 until 48 weeks treatment. The details of ten articles were listed in Table I and Table II.

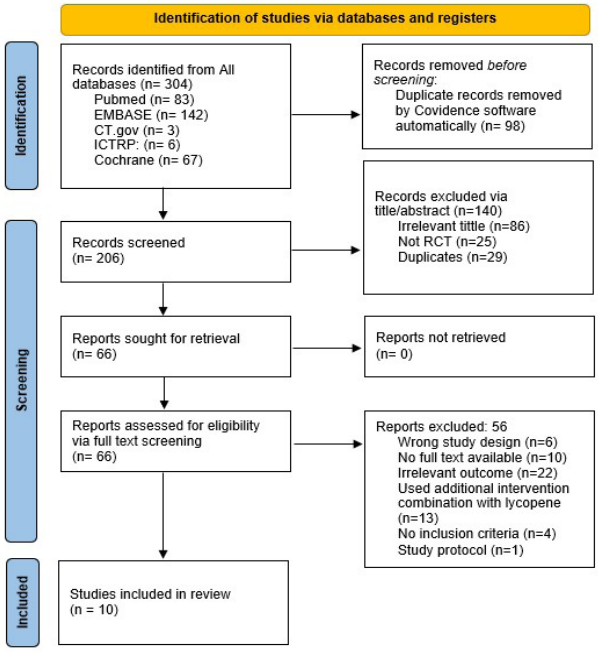
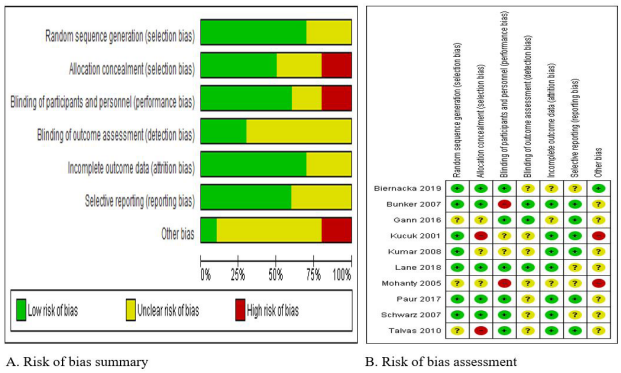


Fig. 1: Flowchart of the study selection process. RCT, Randomized controlled trials; PCa, Prostate cancer.

Risk of bias in studies

All studies included in the analysis were randomized control trial study and some of them were use random allocation concealment. Only one study was not described yet about the allocation concealment. The blinding of personal method was clearly described as double blinding. Two studies explained about open label study of blinding personal in his study. One study was no explained yet about the blinding's method. Risk of bias summary and graph has presented in Fig. 2A and 2B.



A. Risk of bias summary B. Risk of bias assessment

Fig. 2: Resume of bias studies. A. Risk of bias summary among the articles. the criteria are fully explained: low risk of bias; criteria were not described: unclear risk of bias; criteria hasn't sufficient information to assess whether an important risk of bias exists, however no baseline characteristics are provided: high risk of bias; B. Risk of bias assessment in individual article. Green colour; low risk of bias; yellow colour: unclear risk of bias; red colour: high risk of bias.

Results of syntheses

Ten randomized controlled trials (RCTs) directly compared PSA level in non-metastatic prostate cancer patient incidence between lycopene and control groups. These RCTs enrolled 427 patients (214 patients in the lycopene therapy group and 213 patients in the control grup). Four of the trials were low risk of bias and five had moderate risk of bias, owing information of blinding and allocation concealment to lack of blinding and allocation concealment.

Prostatic spesific antigen (PSA)

Ten RCT's that compared lycopene from tomato extract therapy with control, including a total of 427 patients (214 patients in the lycopene from tomato extract group and 213 patients in the control grup), were analyzed the change of total PSA level. The mean number of Prostatic Spesific Antigen (PSA) Score (mean difference [MD] -0.35, 95% [CI] -0.64 to -0.07 (p= 0.02) (Fig. 3). On average, the intervention or lycopene therapy reduced PSA by 0.35 points on the PSA level. This result suggested that lycopene therapy had a significant improvement to decrease total PSA level compared with control group.

Insulin growth factor 1 (IGF-1)

Five RCT's that compare lycopene from tomato extract group theraphy with control, including a total of 220 patients (108 patients in lycopene from tomato extract group and 112 patients in control group), were analyzed the change of IGF-1. The mean difference [MD] -2.01, 95% [CI] -3.33 to -0.69 (p= 0.003) (Fig. 3). On average,

Table I: Quality assessment of individual study

Study	Allocation sequence generation	Allocation conceal-ment	Blinding	Loss to fol-low-up	Calculation of sample size	Statistical analysis	Level of quality
Kucuk et al (2001)	A	C	B	6	Yes	X^2, Fisher's exact, Paired t test	B
Mohanty et al (2005)	B	B	B	0	Yes	ANOVA, Paired t test, Spear-man, Pearson	B
Gann et al (2016)	A	A	A	0	Yes	X2, Fisher's exact, Paired t test	A
Bunker et al (2007)	B	B	A	0	Yes	Paired t test, X^2	B
Schwarz et al (2016)	A	A	A	1	Yes	Paired t test, wilcoxon	A
Kumar et al (2008)	A	B	B	3	Yes	ANOVA, Paired t test, Spear-man, Pearson	B
Talvas et al (2010)	B	C	A	0	Yes	Unpaired t test	B
Paur et al (2017)	A	A	A	1	Yes	Kruskal wallis, Mann whitney, Fisher Freeman Halton, Spearman	A
Lane et al (2018)	A	A	A	6	Yes	ANOVA, Mann whitney,	A
Biernacka (2019)	B	B	B	0	Yes	ANOVA, Paired t test, Spear-man, Pearson	B

Noted: A. Almost all quality criteria met: low risk of bias; B. One or more quality criteria met: moderate risk of bias; C. One or more criteria not met: high risk of bias.

the intervention or lycopene therapy reduced IGF-1 by 2.01 points on the IGF-1 level. This result showed that lycopene from tomato extract group therapy had a significant improvement to decrease IGF-1 compare with control group.

Insulin growth factor binding protein 3 (IGF BP-3)

Total patient in Five RCT's that compared lycopene from tomato extract group therapy and control were 223 patients (111 patients in lycopene from tomato extract group and 112 patients in control group), were analyzed the change of IGF BP-3. The mean difference [MD] 2.70, 95% [CI] 0.96 to 4.44 (p= 0.002) (Fig. 3). On average, the intervention or lycopene from tomato extract group therapy increase IGF BP-3 by 2.70 points on the IGF BP-3 level. This result interpreted that lycopene from tomato extract group therapy had a significant improvement to increase IGF BP-3 compared with control group.

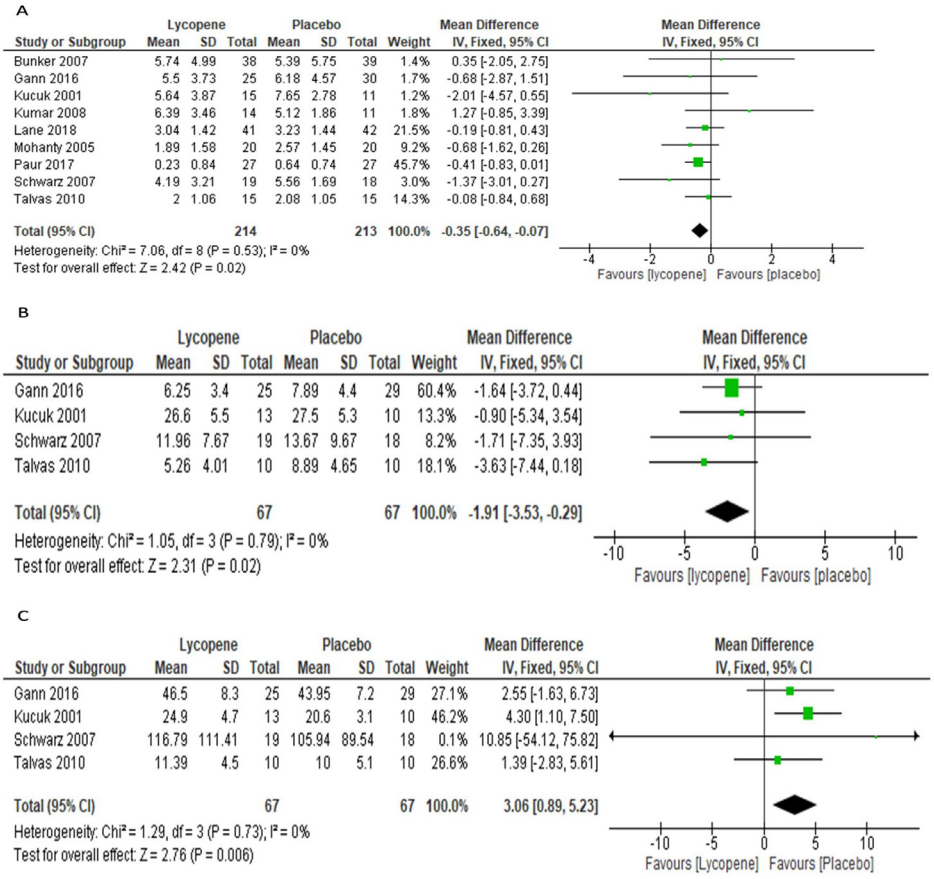


Fig. 3: Forest plots. The plots showing changes in (A) PSA; (B) IGF-1; (C) IGF-BP-3.

Subgroup analysis and investigation of heterogeneity
None of the planned subgroup analyses were performed as detailed in our protocol due to a lack of studies and data.

Sensitivity analysis
Sensitivity analysis was not performed to identify the robustness of results to trial quality since there were a small number of studies included in this review.

Reporting biases
To examine small study and publication bias we created a contour-enhanced funnel plot and egger"s test of the 11 effect sizes plotted against their standard errors (Fig. 4A). Visual inspection of the funnel plot reveals an absence of adverse intervention effects. Given the absence of negative effects in the regions of statistical significance and non-significance, the results from this contourenhanced funnel plot indicate a potential risk of publication bias.

Then supported by egger's test and (Fig. 4B), if you are still unsure in determining the symmetry of the funnel plot, an egger's test is assessed, if the P value > 0.05 then the potential risk of bias is low.

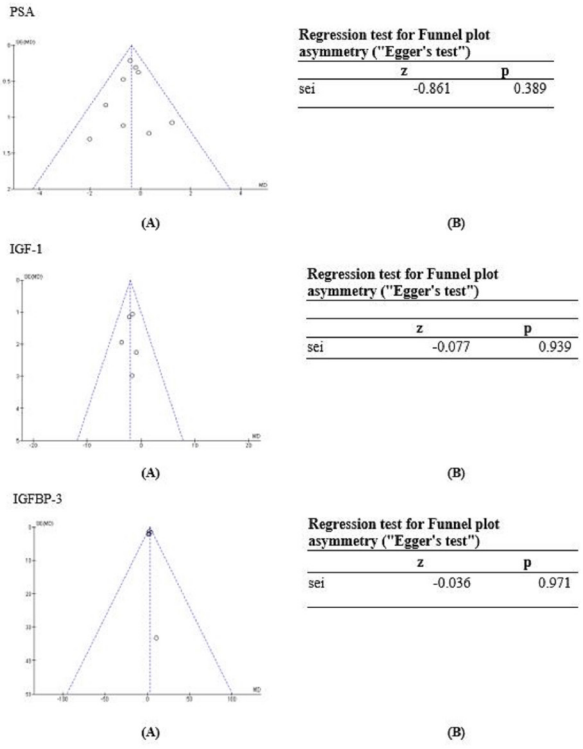


Fig. 4: Reporting publication bias. A. Funnel plot of the studies included in the meta-analysis. OR, odds ratio; SE, standard error; B. Egger's test of regressiom test of studies in the meta-analysis.

DISCUSSION

We need to be careful in interpreting these findings because the small number of studies appears to be in line with a recent systematic review of the role of lycopene from tomato extract as adjunctive therapy in prostate cancer. A meta-analysis of 10 RCTs showed that there was a statistically and clinically significant difference in PSA levels between men with non-metastatic PCa randomized to receive lycopene from tomato extract and the control group (MD -0.34, 95%CI -2.01 to 1 ,32). Levels of IGF-1 and IGFBP-3 were also significantly different in men randomized to receive lycopene from tomato extract and the control group (MD 0.39, 95%CI -0.19 to 0.98) and (MD 0.39, 95%CI -0.19 to 0.98).

This finding is in line with Chen, et al (2013), they found that the intake of lycopene extract in patients with prostate cancer as an adjunct therapy had an inverse relationship to the risk of prostate cancer compared to the control group. Patients with high consumption of lycopene reduced the likelihood of prostate cancer by up to 93% compared to the control group. This suggests that lycopene extract may play an important role in prostate cancer prevention and disease prevention (27). This is consistent with our findings that the administration of lycopene extract as adjunctive therapy in patients with non-metastatic prostate cancer can reduce serum PSA and IGF-1 protein levels in the blood and increase IGFBP-3 levels, which play a role in reducing the risk and progression of prostate cancer to men. advanced stage.

In line with our study, Chen, et al (2015) found clinical evidence that consumption of lycopene with higher blood concentrations of lycopene was associated with a 91% reduced risk of prostate cancer compared with low daily consumption of lycopene less than 5mg/day. This explains that lycopene supplementation and circulating concentrations of lycopene in the blood show a preventive effect on prostate cancer as well as aggravating effects. In the study of Chen et al, further research is needed to determine the mechanism of lycopene in reducing the risk of prostate cancer and other factors in lycopene extract that have the potential to reduce the risk and worsen prostate cancer (28).

These results are in line with the results of our meta-analysis which showed that Lycopene from tomato extract was effective in reducing the risk of and worsening of advanced stage prostate cancer, both clinically and statistically there was a significant difference between the intervention and control groups.

However, neither study Chen, et al. (2013) and Chen, et al. (2015) had significant similarities in clinical interpretation but statistically there was no significant difference (P > 0.05) and high heterogeneity between studies. This might be due to the small number of studies and subjects included in this study and the high variation in data in both studies. The review of the two previous meta-analyses contains 5 studies (4 cohort studies and 1 case control) (Chen, et al 2013), and 6 cohort studies (Chen, et al 2015) which have similarities, namely

Table II: The detail of individual study

Study	Country	Design	Therapy in experimental group	Therapy in control group	Experimental	Control	Method	Time (weeks)	Dossage (mg)	Outcome	Inclusion Criteria
Kucuk et al (2001)	USA	RCT	Lycopene or tomato extract	Placebo	15	11	Oral	4	2x15	PSA IGF-1 IGFBP-3	Localized PCa, scheduled for radical prostatectomy, histologically prostate localized PCa, men aged 50-70 y.o.
Mohanty et al (2005)	India	RCT	Lycopene or tomato extract	Placebo	20	20	Oral	48	2x4	PSA	HGPIN, scheduled for radical prostatectomy,
Bunker et al (2007)	Tobago	RCT	Lycopene or tomato extract	Multivitamin	38	39	Oral	16	1x30	PSA	HGPIN, scheduled for radical prostatectomy, pathological evidence of HGPIN or atypical foci, and men aged 40–79 y.o,
Kumar et al (2008)	USA	RCT	Lycopene or tomato extract	Placebo	14	11	Oral	4	1x45	PSA	Localized PCa, scheduled for radical prostatectomy, men aged of 45 and 80, histologically prostate localized PCa, no prior or current therapy for PCa.
Talvas et al (2010)	France	RCT	Lycopene or tomato extract	Placebo	15	15	Oral	2	1x16	PSA IGF-1 IGFBP-3	Localized PCa, scheduled for radical prostatectomy, normal blood biochemical profile, men aged 50–70 y.o.
Gann et al (2016)	USA	RCT	Lycopene or tomato extract	Placebo	25	30	Oral	24	2x15	PSA IGF-1 IGFBP-3	diagnosis of isolated HGPIN or Localized PCa, scheduled for radical prostatectomy.
Schwarz et al (2016)	Germany	RCT	Lycopene or tomato extract	Placebo	19	18	Oral	24	1x15	PSA IGF-1 IGFBP-3	HGPIN or Localized PCa, scheduled for radical prostatectomy, serum PSA concentration < 4.0 mg/L, men aged between 45 and 70 y.o.
Paur et al (2017)	Norway	RCT	Lycopene or tomato extract	Placebo	27	27	Oral	3	1x30	PSA	Localized PCa, scheduled for radical prostatectomy,
Lane et al (2018)	UK	RCT	Lycopene or tomato extract	Placebo	40	41	Oral	24	1x15	PSA	Localized PCa, scheduled for radical prostatectomy, PSA result was below 3.0 ng/mL or negative biopsy results, men aged 50-69 y.o.
Biernacka (2019)	UK	RCT	Lycopene or tomato extract	Placebo	44	43	Oral	24	1x15	IGF-1 IGFBP-3	Localized PCa, scheduled for radical prostatectomy, men aged of 50 and 69, histologically prostate localized PCa, no prior or current therapy for PCa.

Noted: PSA, prostate specific antigen; IGF-1, insulin like growth factor 1; IGF BP-3, insulin like growth factor binding protein 3; HGPIN, high grade prostate intraepitel neoplasia; PCa, Prostate Cancer; RCT, randomized controlled trial.

the intervention in the form of giving tomato products (tomato juice, tomato sauce, raw tomatoes, etc).

This most recent review of studies was based on 10 study RCTs and had a total of 427 participants and consisted of more rigorous studies whose outcomes assessed PSA, IGF-1, and IGFBP-3 levels in patients as marker proteins in prostate cancer. The intervention was giving lycopene from tomato extract from relatively the same source, which was formed in daily capsule supplement and the same prostate cancer stage, namely non-metastatic prostate cancer, thus allowing to reduce the heterogeneity of the research outcome.
Despite using a comprehensive search strategy, almost all of the included studies were from European countries, reflecting the lack of resources for studies in Asia. This means that our findings cannot be generalized to Asian countries. In addition, the research sample is still small and the trade name of lycopene from tomato extract is different in each study, and the presence of other tomato components such as phytochemicals makes it difficult to give definite conclusions about the effect of lycopene alone on PSA, IGF-1 and IGFBP-3. Therefore, the results of this study can be attributed to lycopene from tomato extract rather than lycopene alone.

We acknowledge some limitations to our meta-analysis. Although it included all RCTs, we were unable to perform a subgroup analysis to identify specific patient groups due to the small sample size. In addition, we did not evaluate symptoms due to adverse events, survival after therapy, quality of life, and other important outcomes. Another limitation is the heterogeneity of the dose of lycopene given and the duration of administration varies from study to study. Such inconsistencies may have increased the heterogeneity of the meta-analyses and potentially reduced the magnitude of the observed associations.

The increasing number of men with prostate cancer each year in the community taking adjunctive therapy for prostate cancer prevention, and the lack of quality evidence, both support the call for a well-designed, high-quality randomized controlled trial to investigate the effectiveness of lycopene for prostate cancer prevention. Such trials must take into account prostate cancer diagnosis, mortality, changes in PSA levels, changes in IGF-1 levels, changes in IGFBP-3 levels, side effects, and cost-effectiveness.

Limitation

The limitations of this meta-analysis are mostly not a crossover design and the number of patients is too small to get a solid conclusion, and that the men enrolled in the trial may represent a highly motivated sample seeking medical advice rather than the overall male prostate cancer population. Also, a patient in combination regimen has the tendency to have greater psychogenic effect of improvement compared with control that may lead to greater perceived benefit in subjective parameters.

This analysis could not infer the long-term efficacy and tolerance of lycopene from tomato extract therapy, and selection bias, subjective factor, publication bias and non-fixed dose regimen may also affect the final results of the study. Our findings should be confirmed with RCTs with long-term follow-up, sufficient sample size, and fixed-dose data. More high quality RCTs with suitable study cohorts are needed to ascertain the efficacy and tolerance of lycopene in treating men with non-metastatic prostate cancer.

CONCLUSION

Although at this time there are limited data to support recommending the routine use of lycopene therapy for patients with non-metastatic prostate cancer, this meta-analysis suggests that lycopene had significant therapeutic effect in patient with prostate cancer.

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