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## Lycopene for the prevention of prostate cancer (Review)

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Lycopene for the prevention of prostate cancer (Review)

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[Intervention Review]

# Lycopene for the prevention of prostate cancer

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## ABSTRACT

### Background

Prostate cancer is a common cause of death in developed countries, yet the benefits of screening for prostate cancer still remain controversial. A prostate-specific antigen (PSA) test result greater than 4 ng/mL (nanograms/millilitre) has commonly been used as the cut-off level for seeking further tests to diagnose the presence (or absence) of prostate cancer. An increase in PSA levels may not necessarily be associated with an increased risk of prostate cancer, as PSA levels may also be increased in men with benign prostatic hyperplasia and prostatitis. Despite the uncertainty of the net benefit of early detection and treatment, safe and effective methods to prevent prostate cancer are of value. Consumers, seeking greater involvement in their healthcare, are increasingly turning to lifestyle modification and complementary and alternative medicines (CAMs) to maintain their health and prevent disease. Lycopene is a member of the carotenoid family, which is found abundantly in tomatoes, tomato-based products, strawberries, and watermelon. It has been hypothesised that lycopene is a strong antioxidant, which may lower the risk of cancer (including prostate cancer) in people who have diets rich in lycopene.

### Objectives

To determine whether lycopene reduces the incidence of prostate cancer and prostate cancer-specific mortality. Secondary objectives include changes in PSA levels, prostate symptoms and the nature of adverse events associated with lycopene use.

### Search methods

Electronic searches were conducted across MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. No language or other limitations were imposed.

### Selection criteria

Randomised controlled trials (RCTs) that investigated the use of lycopene for the prevention of prostate cancer were eligible for inclusion in this review.

### Data collection and analysis

A search of electronic databases, performed in August 2011, identified 64 citations. All articles were selected for full-text review. From these citations, three studies were identified as meeting the inclusion criteria. Handsearching did not provide any additional studies.

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## Main results

Three RCTs, with a total of 154 participants were included in this review. None of the studies reported data on prostate cancer mortality. All of the included studies differed with respect to design, participants included and allocation of lycopene. This clinical heterogeneity limits the value on the pooled estimated of the meta-analyses. The methodological quality of two of the three included studies was assessed as posing a 'high' risk of bias. Meta-analysis indicated no statistical difference in PSA levels between men randomised to receive lycopene and the comparison group (MD (mean difference) -0.34, 95% CI (confidence interval) -2.01 to 1.32). Only one study reported incidence of prostate cancer (10% in the lycopene group versus 30% in control group). The level of lycopene was also not statistically different in men randomised to receive lycopene and the comparison group (MD 0.39 µg/mL (micrograms/millilitre), 95% CI -0.19 to 0.98). No other meta-analyses were possible since other outcomes assessed only had one study contributing data.

## Authors' conclusions

Given that only three RCTs were included in this systematic review, and the high risk of bias in two of the three studies, there is insufficient evidence to either support, or refute, the use of lycopene for the prevention of prostate cancer. Similarly, there is no robust evidence from RCTs to identify the impact of lycopene consumption upon the incidence of prostate cancer, prostate symptoms, PSA levels or adverse events.

## PLAIN LANGUAGE SUMMARY

### Lycopene for the prevention of prostate cancer

Prostate cancer is a common form of cancer affecting men worldwide. Pharmaceutical interventions, such as 5-alpha reductase inhibitors, have been identified as potentially preventing prostate cancer incidence in men. Many men modify lifestyle and consume complementary and alternative medicines to maintain better health and prevent disease. Lycopene is a supplement that has been suggested may assist in the prevention of prostate cancer due to its antioxidant effects. The objective of this systematic review was to identify the effectiveness of lycopene in the prevention of prostate cancer. This review identified 3 relevant studies, comprising 154 participants in total. Two of the studies were assessed to be of 'high' risk of bias. Meta-analysis of two studies indicated no statistical difference in prostate specific antigen (PSA) levels between men randomised to receive lycopene and the comparison group (MD -0.34, 95% CI -2.01 to 1.32). None of the studies assessed prostate cancer mortality. No other meta-analyses were possible since other outcomes assessed only had one study contributing data.

## BACKGROUND

### Description of the condition

Prostate cancer is a common cause of death in developed countries with age standardised mortality rates ranging from 28 per 100,000 males in Norway and Sweden to 16 per 100,000 males in the US (AIHW 2007). A recent Cochrane systematic review concluded that screening for prostate cancer does not significantly decrease prostate cancer-specific mortality (Ilic 2006; Ilic 2011). A variety of factors may contribute to the effectiveness of screening at the individual and population levels including; the accuracy of screening and diagnostic tests (Andriole 2009), uncertainty and variability in prostate cancer disease progression (Cordon-Cordo

2007), and the impact of morbidities such as erectile dysfunction and incontinence that can occur as a consequence of common treatment methods (Stanford 2000). A prostate-specific antigen (PSA) test result greater than 4 ng/mL has commonly been used as the cut-off level for seeking further tests to diagnose the presence (or absence) of prostate cancer. An increase in PSA levels may not necessarily be associated with an increased risk of prostate cancer, as PSA levels may also be increased in men with benign prostatic hyperplasia and prostatitis (Hasui 1994). Despite the uncertainty of the net benefit of early detection and treatment, safe and effective methods to prevent prostate cancer are valued. Recent studies indicate that 5-alpha reductase inhibitors, commonly used to treat uncomfortable lower urinary tract symptoms related to benign prostatic obstruction, may be beneficial in reducing prostate cancer incidence among men who undergo regular screening (Wilt

2008).

Consumers, seeking greater involvement in their healthcare, are increasingly turning to lifestyle-based interventions and complementary and alternative medicines to maintain health and prevent disease, as evidenced through growth in the dietary supplements industry (Beebe-Dimmer 2004). Motives range from an improvement in general health and well-being, cures for cancer, improvement in quality of life and boosting of the immune system (Wilkinson 2008; Patterson 2002). CAMs are increasing being used by patients diagnosed with cancer. A 2005 study identified that up to 33% participants diagnosed with prostate cancer used some form of complementary and alternative medicine product or practice (Chan 2005). An overall rate of 25% was reported for ingested therapies, such as lycopene (Chan 2005).

### Description of the intervention

Lycopene is a red pigment member of the carotenoid family found abundantly in tomatoes, tomato-based products, strawberries, and watermelon (Najm 2008). Humans and other animals are unable to synthesise carotenoids and rely on an adequate consumption for their intake (Magri 2008). Consumption of lycopene through diet (including the 'Mediterranean diet') and supplements can contribute towards half of the carotenoids in the human serum (Ansari 2003).

In 2007 the World Cancer Research Fund reported that a high fruit and vegetable intake may be beneficial in reducing the risk of cancer, including lycopene for prostate cancer (WCRF 2007). Similarly, a study of women with a history of breast cancer concluded that a diet with increased vegetable and fruit intake was linked with a significantly reduced risk of cancer recurrence (Rock 2005).

### How the intervention might work

Lycopene is an antioxidant whose actions prevent lipid oxidation in cells (Hwang 2005). It has been suggested that these antioxidant properties prevent carcinogenesis by protecting DNA, proteins, lipids and low density lipoproteins (Basu 2007). Molecular experiments have illustrated that the growth of human prostate cancer cells, which have been xenografted to immunosuppressed mice, is significantly suppressed when the diets of mice are supplemented with lycopene (Tang 2005).

### Why it is important to do this review

Lycopene has been identified an antioxidant compound that potentially has a range of anti-cancer properties, is abundant availability, is relatively low cost and has a lack of obvious side effects (Rackley 2006). A meta-analysis of observational studies (including cohort, case-control and nested-case control) identified a 6%

relative risk reduction in prostate cancer diagnosis in men consuming raw tomatoes and a 1% relative risk reduction in prostate cancer diagnosis in men consuming lycopene (Etminan 2004). The study authors concluded that tomato products may play a role in preventing the risk of prostate cancer (Etminan 2004). A recent Cochrane systematic review investigating selenium (which also has antioxidant properties) for preventing cancer identified a significant reduction in prostate cancer risk in men consuming selenium (OR (odds ratio) 0.78, 95% CI 0.66 to 0.92) (Dennert 2011). With increased consumer awareness of prostate cancer, many men may be attracted to consuming dietary supplements, such as lycopene, without the evidence to inform about its effectiveness about its cancer prevention properties and effectiveness.

## OBJECTIVES

The primary objective of this systematic review is to determine whether lycopene reduces prostate cancer-specific incidence and mortality. Secondary objectives included change in prostate specific antigen (PSA) levels, prostate symptoms and adverse events associated with lycopene use.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All forms of randomised controlled trials (RCTs) were eligible for inclusion in this review. No language restrictions were placed on studies.

#### Types of participants

Adult (> 18 years) men of any ethnicity who had not previously been diagnosed with prostate cancer were eligible for inclusion in this review. Those with an increased risk of prostate cancer due to a family history of the disease or an elevated PSA level were included.

#### Types of interventions

Intervention included: dietary interventions aimed at increasing lycopene intake; lycopene supplements; and lycopene-containing products used to prevent the development of prostate cancer. Studies employing any quantity of lycopene, taken over any duration of time and in combination with any other ingested supplements were included.

## Types of outcome measures

### Primary outcomes

The primary outcomes of this review were prostate cancer-specific mortality and incidence of prostate cancer.

### Secondary outcomes

Secondary outcomes measured included:

- changes in PSA levels (doubling of PSA level from baseline for outcomes relating to increase in PSA levels, and halving of PSA levels compared to baseline for outcomes relating to decrease in PSA levels);
- changes to prostate symptoms;
- incidence of benign prostatic hyperplasia;
- levels of lycopene; and
- adverse events.

## Search methods for identification of studies

### Electronic searches

Electronic searches were conducted across MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. No language or other limitations were imposed. The search strategy used for MEDLINE (and adopted for other databases) was:

1. exp Carotenoids/ or lycopene.mp. or exp Antioxidants/ or exp Lycopersicon esculentum/ or tomato\*.mp.
2. prostat\$ cancer.mp. or exp prostatic neoplasms/
3. exp Tertiary Prevention/ or exp Secondary Prevention/ or exp Primary Prevention/ or prevention.mp. or prevent\*.mp.
4. 1 and 2 and 3
5. limit 4 to humans
6. limit 5 to controlled trials

### Searching other resources

Bibliographies of identified studies were searched for additional studies.

## Data collection and analysis

Two reviewers (KF and DI) 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.

## Selection of studies

Two reviewers (KF and DI) independently screened the titles and abstracts of all articles identified through the search strategy. Full papers of those that could not be excluded based on the title and abstract were retrieved and again screened based on the selection criteria. Articles that met the selection criteria were included.

## Data extraction and management

Data extraction was conducted independently by two authors (KF and DI) using a data extraction form. The data extraction included information on the sample population (number of participants, demographic characteristics), method (intervention, setting, method of delivery, differences between intervention and control groups) and results.

## Assessment of risk of bias in included studies

A risk of bias assessment was conducted independently by two authors (KF and DI) on all included trials, to appraise sequence generation, allocation concealment, blinding of participants and outcome assessors, outcome data, and selective-outcome reporting. Each criterion was graded as 'met', 'unmet', 'unclear' or 'not appropriate'. A summary of the risk of bias assessment is presented in this review.

## Measures of treatment effect

Statistical analysis was performed according to the statistical guidelines referenced in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Risk ratios (RR), with 95% confidence intervals (CI), were used to express dichotomous outcomes whilst continuous outcomes scores were expressed as mean differences with 95% confidence intervals.

## Unit of analysis issues

No cluster RCTs were included in this systematic review.

## Dealing with missing data

Missing data was dealt with by contacting the original study investigators to request the missing data, or provide further clarification on data. Analysis was performed on the available data in cases where the missing data was not available.

## Assessment of heterogeneity

Heterogeneity was analysed by graphical interpretation of the forest plot and with the  $I^2$  statistic. An  $I^2$  value above 75% was considered to be an indicator of considerable heterogeneity (Higgins 2011).

### Assessment of reporting biases

Funnel plots were not graphed due to the small number of included studies.

### Data synthesis

Pooled results of dichotomous outcomes were analysed using relative risk, utilising a fixed-effects model. Continuous outcome measures were analysed using mean difference, utilising a fixed-effects model. A random effects model was used where significant heterogeneity was indicated ('[Analysis 1.7](#)').

### 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. Significant heterogeneity was identified in the analysis assessing lycopene levels ('[Analysis 1.7](#)'). This heterogeneity may be attributed to the differing doses used between the two studies (15 mg (milligrams) versus 30 mg).

## RESULTS

### Description of studies

A total of three RCTs (n=154) ([Bunker 2007](#); [Mohanty 2005](#); [Schwarz 2008](#)) assessing the effectiveness of lycopene for the prevention of prostate cancer were identified as meeting the inclusion criteria for this systematic review. All of the included studies differed with respect to design, participants included and allocation of lycopene. Participants across the studies ranged from a total of

37 to 82 men. The studies included men from Germany, India and Trinidad and Tobago. Mean age was not provided for any of the studies; however ages ranged between 40 and 79 years. Length of follow up varied from 4 months, 6 months and 24 months in duration. Outcomes reported in the three studies included incidence of prostate cancer, change in PSA levels, change in prostate symptom score, incidence of benign prostatic hyperplasia and lycopene levels. For further detailed descriptive information about the studies refer to '[Characteristics of included studies](#)' table.

### Results of the search

A search of electronic databases was performed in August 2011. This search produced 64 citations, of which all were selected for full-text review. Handsearching did not provide any additional studies. Of the 64 citations, three were eligible for inclusion in the review. The remaining 61 studies did not meet the eligibility criteria.

### Included studies

Three RCTs were included in this review. See '[Characteristics of included studies](#)' table for further details on the included studies.

### Excluded studies

Studies were primarily excluded because they were not randomised controlled trials. Studies were also excluded because they did not meet other aspects of the eligibility criteria including not limiting participants to only men diagnosed with prostate cancer, and not having lycopene as the intervention. See table of '[Excluded studies](#)' for further information.

### Risk of bias in included studies

Assessment for risk of bias for each included study is described in the '[Characteristics of included studies](#)' section. Risk of bias is also represented graphically in '[Figure 1](#)' and '[Figure 2](#)'. The risk of bias as determined for each included study is as follows.

**Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**

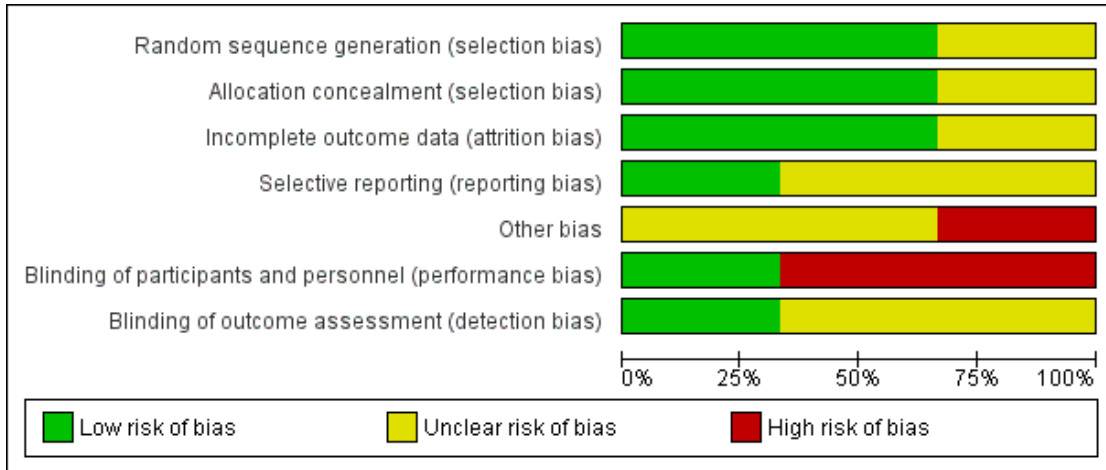




Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
Bunker 2007	+	+	+	+	?	-	+
Mohanty 2005	?	?	?	?	-	-	?
Schwarz 2008	+	+	+	?	?	+	?

- [Bunker 2007](#) - 'high' risk of bias (no blinding of participants)
- [Mohanty 2005](#) - 'high' risk of bias (no blinding of participants and lack of baseline demographic information)
- [Schwarz 2008](#) - 'low' risk of bias (an 'unclear' risk of bias was given to blinding of outcome assessors and selective reporting of data)

In addition, none of the studies were sufficiently powered with respect to sample size to explore effects on primary and secondary outcomes. Both the [Mohanty 2005](#) and [Schwarz 2008](#) studies had less than 40 participants, whereas the [Bunker 2007](#) study contained 82 participants. All studies also employed a highly specific eligibility criteria for recruiting participants, which affects the generalisability of results. The dose of lycopene across the three studies also differed significantly, ranging from 4 mg, 15 mg and 30 mg in dose. The composition of the lycopene intervention also differed across the studies, with some using a solely lycopene supplement, whilst other studies embedding the lycopene with other components within the pill. Participants also differed in terms of ingesting the pill - with some studies requesting that participants take the pill twice a day (morning and night). The duration of ingesting the lycopene pills also differed significantly between the studies, ranging from 4 months, 6 months and 2 years.

### Allocation

Sequence generation was clearly identified in the [Bunker 2007](#) and [Schwarz 2008](#) studies, whilst the [Mohanty 2005](#) study did not provide any information on sequence generation. Only the [Schwarz 2008](#) study described the method used for allocation concealment, whilst the study by other two studies did not provide sufficient information about methods used to account for allocation concealment. The authors of the [Bunker 2007](#) study replied to correspondence about the trial and provided further information about the process used for randomisation and allocation concealment.

### Blinding

Blinding of participants was only achieved in the [Schwarz 2008](#) study, which was achieved by making the supplements identical in terms of taste, form, smell and appearance between the intervention and control groups. There was insufficient detail to determine whether blinding of outcome assessor was present. The [Bunker 2007](#) study was an open trial, but did blind outcome assessors. The [Mohanty 2005](#) study did not provide sufficient detail regarding blinding of participants or study personnel.

### Incomplete outcome data

The [Bunker 2007](#) and [Schwarz 2008](#) studies provided complete data, with any withdrawal cited and explained. The [Mohanty 2005](#) study did not address the issue of attrition bias.

### Selective reporting

It was not possible to assess selective reporting for the three studies due to insufficient information. The authors of the [Bunker 2007](#) trial reported no selective reporting of data.

### Other potential sources of bias

No other potential sources of bias were identified.

### Effects of interventions

#### Prostate cancer-specific mortality

The impact of lycopene on prostate cancer-specific mortality was not assessed by any of the three studies included in this systematic review.

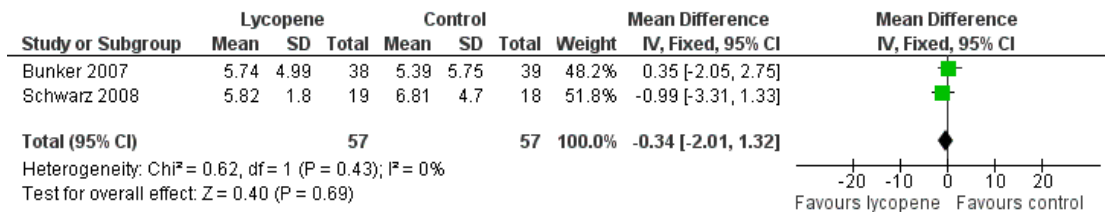
#### Incidence of prostate cancer

Incidence of prostate cancer was only reported as an outcome in the [Mohanty 2005](#) study. There was no significant difference between men randomised to the lycopene group and the comparison group (RR 0.33, 95% CI 0.08 to 1.46). The reported incidence of prostate cancer was 10% in the lycopene group versus 30% in control group.

#### PSA levels

PSA levels were reported in two of the included studies ([Bunker 2007](#) and [Schwarz 2008](#)). Whilst there was a decrease in PSA levels between groups, the difference was not statistically significant (MD -0.34, 95% CI -2.01 to 1.32) ('[Figure 3](#)'). The [Bunker 2007](#) study also reported decreases in PSA levels as an outcome. This study indicated no difference in the amount of men experiencing a decrease in PSA following their intervention, be it at one month post-intervention or four months post-intervention (RR 1.03, 95% CI 0.32 to 3.26). The [Mohanty 2005](#) study reported increases in PSA levels as an outcome. This study indicated no difference in the amount of men experiencing an increase in PSA following their intervention (RR 0.67, 95% CI 0.29 to 1.52).

**Figure 3. Forest plot of comparison: I Lycopene versus control, outcome: I.2 PSA levels (ng/mL).**



### Adverse events

The study by [Bunker 2007](#) reported no significant difference in adverse events experienced by participants in their study. One participant in the intervention group reported a heart attack. Nine men across both groups experienced indigestion/nausea throughout the trial, and seven men across both groups experienced diarrhoea. It was unknown whether these symptoms were attributable to the lycopene or multivitamin supplements in this study.

### Lycopene levels

Lycopene levels were reported by two studies ([Bunker 2007](#) and [Schwarz 2008](#)). Lycopene levels were significantly higher in the intervention groups (MD 0.39, 95% CI -0.19 to 0.98).

### Prostate symptom score

The [Schwarz 2008](#) study reported no difference between participants in prostate symptom score (as measured by the International Prostate Symptom Score Questionnaire) (MD 0.20, 95% CI -2.66 to 3.06).

### Incidence of Benign Prostatic Hyperplasia

Incidence of benign prostatic hyperplasia (BPH) was recorded by the [Mohanty 2005](#) study. It reported no significant difference in the incidence of BPH between study participants (RR 1.33, 95% CI 0.34 to 5.31).

## DISCUSSION

### Summary of main results

Three RCTs, with a total of 154 participants were included in this review. None of the studies reported data on prostate cancer mortality. All of the included studies differed with respect to design, participants included and allocation of lycopene. This clinical heterogeneity limits the value on the pooled estimated of the meta-

analyses. The methodological quality of two of the three studies was assessed as posing a 'high' risk of bias. Meta-analysis of two studies indicated no statistical difference in PSA levels between men randomised to receive lycopene and the comparison group (MD -0.34, 95% CI -2.01 to 1.32). The level of lycopene was also not statistically different in men randomised to receive lycopene and the comparison group (MD 0.39, 95% CI -0.19 to 0.98). No other meta-analyses were possible since other outcomes assessed only had one study contributing data.

### Overall completeness and applicability of evidence

There were several gaps in the reporting of criteria required for assessing the risk of bias of studies. All authors associated with studies that had an information gap were identified and contacted. Additional information about study information was only obtained from the authors of the [Bunker 2007](#) study.

### Quality of the evidence

The quality of the evidence was assessed using the approach outlined in 'Characteristics of included studies'. The body of evidence was classified as 'high', 'low', 'unclear' or 'not appropriate' risk of bias for each outcome. Risk of bias was assessed as 'high' for the majority of outcomes, as only the [Schwarz 2008](#) study was classified to have a 'low' risk of bias. It is also noteworthy that the [Schwarz 2008](#) study reported a positive effect of lycopene on selected outcomes.

### Potential biases in the review process

This review primarily consisted of published data. The authors of the [Mohanty 2005](#) study were contacted in order to obtain information regarding standard deviations for PSA and lycopene outcomes, but no reply was obtained. Future updated versions of the review will include more detailed analysis on primary and secondary outcomes as they become available.

## Agreements and disagreements with other studies or reviews

A meta-analysis of observational studies in 2004 identified 11 case-control studies, five nested case-control studies and five cohort studies, which examined the effectiveness of lycopene for the prevention of prostate cancer (Etmninan 2004). The pooled relative risk for prostate cancer diagnosis across all studies was 0.99 (95% CI 0.93 to 1.06). The American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention suggest that eating five or more servings of vegetables and fruits each day (which may include lycopene) may protect against prostate cancer - however, the effectiveness of which is still under investigation (Byers 2002). A systematic review of RCTs investigating lycopene supplementation in men with prostate cancer identified an inverse relationship between lycopene intake and PSA levels (Haseen 2009). The systematic review established that patients receiving lycopene reported lower cancer related symptoms, whilst also reporting no significant adverse events due to lycopene intake.

## AUTHORS' CONCLUSIONS

### Implications for practice

The findings of this systematic review conclude that there is insufficient evidence to either support, or refute, the use of lycopene for the prevention of prostate cancer. Similarly, there is no robust evidence from RCTs to identify the impact of lycopene consumption upon the incidence of prostate cancer, prostate symptoms, PSA levels or adverse events. Given the lack of RCTs on this topic, clinicians and consumers may refer to the 2004 meta-analysis of

observational studies that identified a 1% relative risk reduction in the risk of prostate cancer diagnosis in men consuming lycopene (Etmninan 2004).

It is also worth noting that the RCTs included in this systematic review relied on lycopene to be administered to men as supplements. Previous research has suggested that any beneficial effects from lycopene may be related to the antioxidants in the diet, rather than as supplements (Ahn 2005). Similarly, it may be the overall effect of a range of micronutrients rather than one which produces the benefit (Ahn 2005). Best estimates have suggested that the average daily intake ranges from 3.7 to 6.5 mg per day (Schweitzer 1999). It should be noted that the men who participated in the included studies received between 15 to 30 mg supplements of lycopene, without demonstrable improvement in primary and secondary outcomes.

### Implications for research

The increased number of men in the community consuming CAMs for the prevention of prostate cancer, and the current lack of high quality evidence, both support the call for a well designed, high methodological quality, randomised controlled trial to investigate the effectiveness lycopene for the prevention of prostate cancer. Such a trial should account for prostate cancer diagnosis, mortality, changes in PSA levels, adverse events, and cost-effectiveness.

## ACKNOWLEDGEMENTS

None.

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- \* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Bunker 2007

Methods	Randomised controlled trial in Tobago, Trinidad and Tobago. Individuals were randomised to receive either a multivitamin alone or the 30 mg/day lycopene plus multivitamin. This study reports on participants that were followed for a four month period from August to December 2003
Participants	Participants included men from the island of Tobago. The inclusion criteria for the trial were pathological evidence of HGPIN or atypical foci, or more than one non-cancerous biopsy, no history of prostate cancer. Men were assigned sequential intervention study ID numbers at enrolment before randomisation Numbers include: <ul style="list-style-type: none"> <li>• Intervention group - 41</li> <li>• Control group - 41</li> </ul>
Interventions	All participants underwent a three week course of oral ciprofloxacin, 250 mg/day, prior to randomisation, to reduce the likelihood that serum PSA decline after lycopene administration might reflect an anti-inflammatory response in men with subclinical prostatitis rather than cancer regression Participants in the intervention received 'Lyc-O-Mato', which was 15 mg lycopene. The supplement was provided in two capsules (total 30 mg lycopene/day) with instructions to take one with breakfast, and one with the evening meal A standard multivitamin with minerals was used daily in the multivitamin group (This multivitamin included vitamin A (vitamin A acetate and 40% as beta-carotene), 5000 IU, Vitamin E (dl-alpha tocopheryl acetate), 30 IU, vitamin C (as ascorbic acid), 60 milligrams (mg), and selenium (as sodium selenate), 20 micrograms (µg).)
Outcomes	PSA Serum samples were taken at baseline, 1 month and 4 months post-randomisation. Patients were also assessed via the American Urological Association Benign Prostatic Hyperplasia (BPH) Scale and National Institutes of Health Chronic Prostatitis Symptom Index was assessed during these time points as well
Notes	Adverse events were also reported within the text.

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a random number table and blocking by the trial statistician "The randomization assignment for each ID was prepared in Pittsburgh by the Data Safety and Monitoring Board biostatistician (not a study investigator) using a random number table and blocking in groups

		of six to assign intervention group at randomization”
Allocation concealment (selection bias)	Low risk	Randomisation assignments were kept by a third party, but detail about how concealment was achieved was not provided “the randomization assignments were sent to the study nurse in Tobago, who concealed the assignment until the randomization visit” Further contact with the authors of the study revealed that during the pre-randomisation phase, the randomisation sequence prepared by the external biostatistician and was kept in the proverbial sealed envelope until the randomisation visit
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups “Eighty-two participants were recruited to the study. One participant dropped out during the pre-trial antibiotic run-in. ...one participant with pre-randomization PSA of 64.8 ng/mL was excluded from the study...”
Selective reporting (reporting bias)	Low risk	Insufficient information to in paper to permit judgement of 'Yes' or 'No'. However, contact with made with the authors who stated that the study was free of selective reporting
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open label trial. “This study was a four-month, randomized, open-label, two-arm clinical trial...”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This was an open label trial, however scientists analysing PSA serum were blind to randomisation “The laboratory was blind to randomization group.” Further contact with the authors identified that the serum tubes were labelled only by study ID and date of blood draw. There was no indication of intervention group on

**Bunker 2007** (Continued)

		the serum tubes. The tubes were boxed in study ID numerical order and sent to the University of Pittsburgh Pathology lab for analysis of PSA by technicians with no connection to the study
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**Mohanty 2005**

Methods	Randomised controlled trial at the Department of Urology in New Delhi, India. Individuals were randomised to receive either 4 mg lycopene, to be consumed twice a day for a year, or nothing (for the control participants). Both groups were followed for a two year period
Participants	A total of 40 patients with high-grade prostatic intraepithelial neoplasia (HGPIN) were randomised into two groups. Both the intervention and control groups had equal number of participants with HGPIN, with grade II disease and HGPIN Number include: <ul style="list-style-type: none"> <li>• Intervention group - 20</li> <li>• Control group - 20</li> </ul>
Interventions	Participants randomised to the intervention group received 4 mg lycopene, twice a day for one year continuously. Participants in the control group were not given any interventions, but advised to reduce intake of tomato and melon
Outcomes	Outcomes assessed included changes in PSA levels, and incidence of BPH and prostate cancer
Notes	

***Risk of bias***

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	No description of random sequence generation is provided. "There were 40 patients with HGPIN who were randomized into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method was not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study did not address the issue of attrition in the study
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Yes' or 'No'

**Mohanty 2005** (Continued)

Other bias	High risk	Insufficient information to assess whether an important risk of bias exists, however no baseline characteristics are provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of patients was not sufficiently described. The intervention group were given lycopene, whilst the control group were not given any medication (including a placebo) "All 20 patients in group A (study group) received 4 mg lycopene... None of the 20 patients in group B (control group) received any medication"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding outcome assessment personnel was not described.

**Schwarz 2008**

Methods	Randomised controlled trial in Hohenheim, Stuttgart, Germany. Individuals were randomised to receive either a placebo or 15 mg/day lycopene. This study reports on participants that were followed for a 6-month period from October 2004 to July 2005
Participants	Participants included men from Hohenheim. The inclusion criteria for the trial included a serum prostate-specific antigen (PSA) concentration greater than 4.0 mg/L, histologically confirmed BPH, aged between 45 and 70 years and absence of acute illness. A total of 40 participants were initially recruited, with three participants dropping out during the course of the study. Two participants dropped out before commencing the supplement intake and one participant in the placebo group was excluded after 50 days due to an unexpected hospitalization due to factors not related to the trial (family member's death) Numbers include: <ul style="list-style-type: none"> <li>• Intervention group - 18</li> <li>• Control group - 19</li> </ul>
Interventions	Lycopene supplements were provided as hard gelatin capsules containing 15 mg synthetic lycopene. A commercially available powder formulation containing 10% lycopene embedded in a matrix of gelatin and sucrose was used to fill the capsules. The placebo was a powder formulation without lycopene
Outcomes	The primary endpoint was defined as inhibition of the delta increase or decreased PSA levels in blood. Secondary endpoints were increases in the lycopene concentrations in blood and tissue (buccal mucosa cells (BMC)), reduced circulating insulin-like growth factor (IGF-1), and increases in IGF-binding protein-3 (IGF-BP-3) concentrations in blood. Additional variables measured were circulating concentrations of testosterone (free and bound), LDL cholesterol and total cholesterol, and blood glucose concentrations and routine hemograms. Additional examinations were digital rectal examination (DRE), trans-rectal ultrasonography (TRUS) of the prostate and assessment of the International

Prostate Symptom Score (IPSS)		
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved via computer generated randomisation "Neither the study clinician nor any patients had access to the computer-generated randomization plan."
Allocation concealment (selection bias)	Low risk	Allocation was based on a randomisation schedule, with sealed envelopes "The study clinician was informed to allocate the supplements to the patients after inclusion into the study using increasing randomization numbers. In case of an emergency, the treatment information was available at the center in sealed envelopes. The envelopes were returned after study termination and none of them had been opened."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups "A total of 40 patients entered the study. Two participants quit before beginning supplement intake. One participant in the placebo group was excluded after 50d due to an unexpected hospitalization resulting from a family member's death."
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Yes' or 'No'
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants was achieved. "The supplements were identical in form, taste, smell and appearance for lycopene and placebo."

**Schwarz 2008** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is insufficient information regarding blinding of investigators
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**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
<a href="#">Albanes 1995</a>	Not a lycopene intervention
<a href="#">Alkhenizan 2007</a>	Not a lycopene intervention
<a href="#">Allen 2009</a>	Not a lycopene intervention
<a href="#">Brawley 2001</a>	Not a RCT
<a href="#">Burri 2009</a>	Not exclusively a lycopene intervention and outcomes are not specific
<a href="#">Canby-Hagino 2005</a>	Not a RCT
<a href="#">Chan 2000</a>	Not exclusively a lycopene intervention
<a href="#">Chlebowski 2010</a>	Not a RCT on lycopene use
<a href="#">Christen 2000</a>	Report of a study protocol
<a href="#">Cook 1999</a>	Not exclusively a lycopene intervention
<a href="#">Cook 2000</a>	Not exclusively a lycopene intervention
<a href="#">Costello 2001</a>	Not a RCT of a lycopene intervention
<a href="#">DeFrancesco 2001</a>	Descriptive report of prevention trial
<a href="#">Dennert 2011</a>	Systematic review on selenium
<a href="#">DePrimo 2001</a>	Not a RCT of a lycopene intervention
<a href="#">Druesne-Pecollo 2010</a>	Systematic review on beta-carotenes
<a href="#">Dunn 2010</a>	Relates to a selenium study
<a href="#">Ellinger 2006</a>	Descriptive report

(Continued)

Etminan 2005	Systematic review on selenium
Fitzpatrick 2009	Descriptive report
Frankel 2007	Not related to lycopene
Gaziano 2009	Not exclusively a lycopene intervention
Gey 1998	Review
Gronberg 2003	Descriptive report
Hatfield 2009	Study relating to selenium
Heinonen 1994	Does not include lycopene as an intervention
Heinonen 1998	Not exclusively a lycopene intervention
Jiang 2010	Meta-analysis relating to selenium
Klein 2001	RCT relating to selenium
Klein 2003	RCT relating to selenium
Klein 2003b	RCT relating to selenium
Klein 2004	Review article
Klein 2004b	Study relating to selenium
Lee 2006	Report relating to Vitamin E
Li 2005	Study not related to lycopene
Lin 2000	Study not related to lycopene
Lippman 2005	Study relating to selenium
Lippman 2009	Not a single RCT
Marshall 2001	RCT relating to selenium
Mayne 2005	Report not related to lycopene
Meyer 2005	Not exclusively a lycopene intervention
Nelson 2004	Report not related to lycopene

(Continued)

Neuhouser 2009	Does not include lycopene as an intervention
Pak 2002	Study relating to selenium and Vitamin E
Pathak 2003	Review article
Platz 2009	Study relating to selenium and Vitamin E
Pryor 2000	Study relating to Vitamin E
Rennert 2002	Review article
Schröder 2005	Does not meet inclusion criteria
Tan 2010	Does not meet inclusion criteria
Thompson 2003	Does not meet inclusion criteria
Trump 1994	Does not meet inclusion criteria
Vaishampayan 2007	Treatment group has existing prostate cancer
van Breemen 2005	Treatment group has existing prostate cancer
Van Patten 2008	Review article
Virtamo 2003	Does not meet inclusion criteria
Watters 2009	Does not meet inclusion criteria
Weinstein 2006	Does not meet inclusion criteria
Wilkinson 2003	Review article
Woodson 2002	Does not meet inclusion criteria
Woodson 2003	Does not meet inclusion criteria



## DATA AND ANALYSES

### Comparison 1. Lycopene versus control

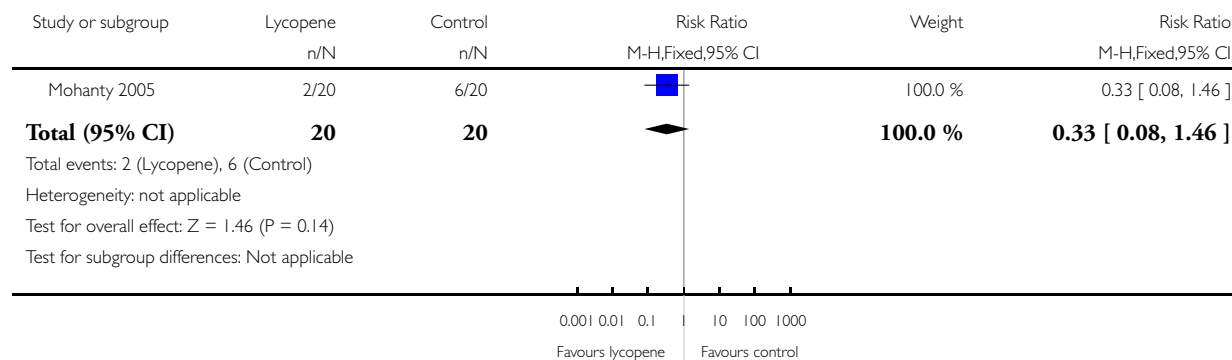
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of prostate cancer	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.08, 1.46]
2 PSA levels (ng/mL)	2	114	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-2.01, 1.32]
3 Decrease in PSA levels	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.32, 3.26]
4 Increase in PSA levels	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.29, 1.52]
5 Prostate symptom score (IPSS)	1	37	Mean Difference (IV, Fixed, 95% CI)	0.20 [-2.66, 3.06]
6 Incidence of Benign Prostatic Hyperplasia	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.21]
7 Lycopene levels (µg/mL)	2	114	Mean Difference (IV, Random, 95% CI)	0.39 [-0.19, 0.98]

#### Analysis 1.1. Comparison 1 Lycopene versus control, Outcome 1 Incidence of prostate cancer.

Review: Lycopene for the prevention of prostate cancer

Comparison: 1 Lycopene versus control

Outcome: 1 Incidence of prostate cancer

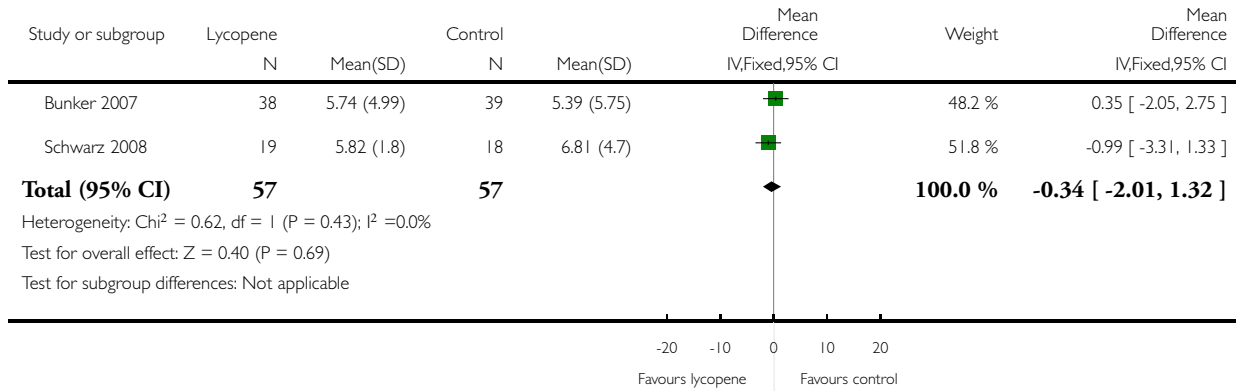


### Analysis 1.2. Comparison 1 Lycopene versus control, Outcome 2 PSA levels (ng/mL).

Review: Lycopene for the prevention of prostate cancer

Comparison: 1 Lycopene versus control

Outcome: 2 PSA levels (ng/mL)

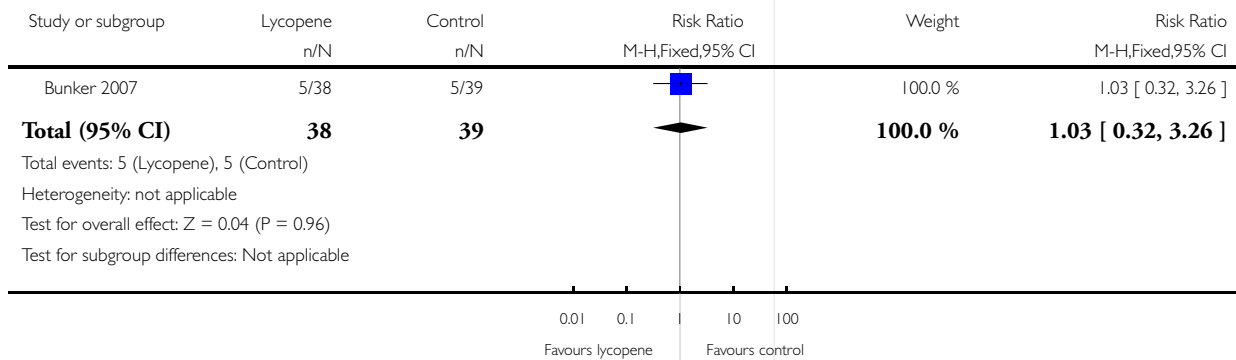


### Analysis 1.3. Comparison 1 Lycopene versus control, Outcome 3 Decrease in PSA levels.

Review: Lycopene for the prevention of prostate cancer

Comparison: 1 Lycopene versus control

Outcome: 3 Decrease in PSA levels

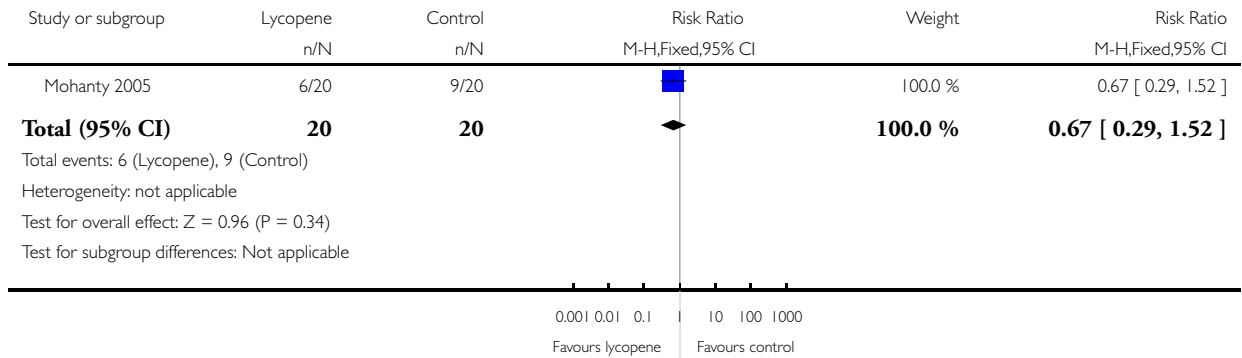


### Analysis 1.4. Comparison 1 Lycopene versus control, Outcome 4 Increase in PSA levels.

Review: Lycopene for the prevention of prostate cancer

Comparison: 1 Lycopene versus control

Outcome: 4 Increase in PSA levels

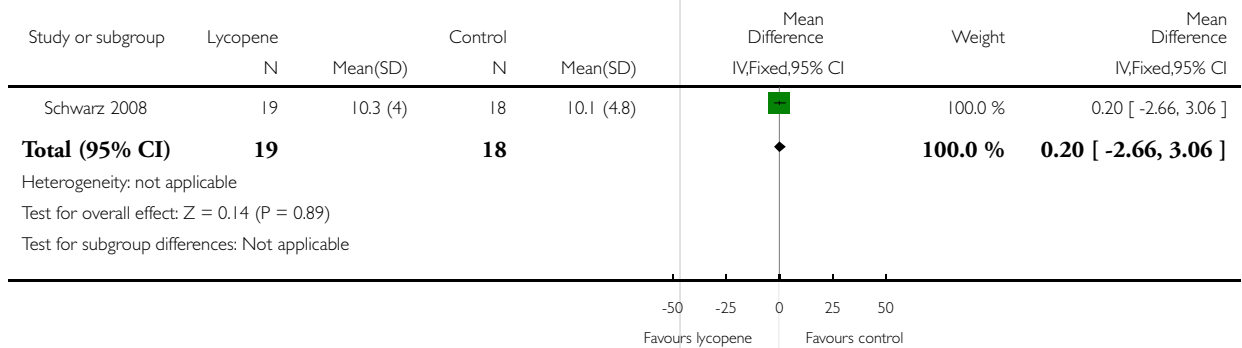


### Analysis 1.5. Comparison 1 Lycopene versus control, Outcome 5 Prostate symptom score (IPSS).

Review: Lycopene for the prevention of prostate cancer

Comparison: 1 Lycopene versus control

Outcome: 5 Prostate symptom score (IPSS)

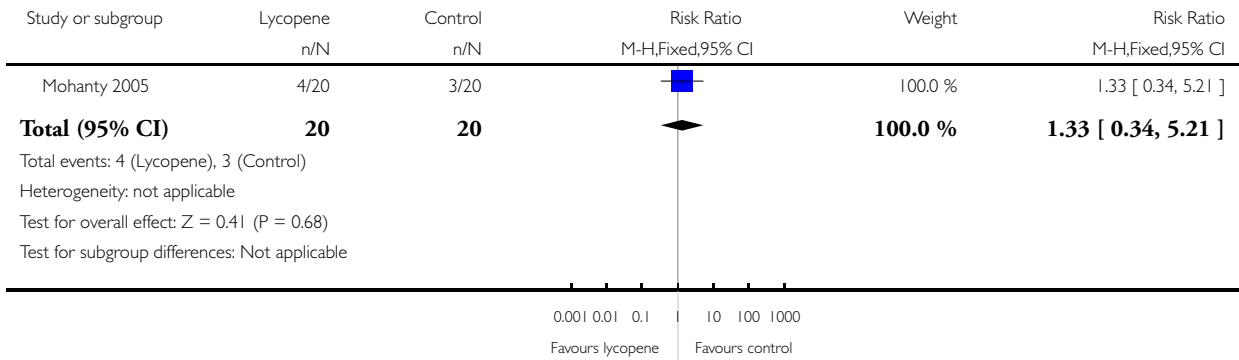


**Analysis 1.6. Comparison 1 Lycopene versus control, Outcome 6 Incidence of Benign Prostatic Hyperplasia.**

Review: Lycopene for the prevention of prostate cancer

Comparison: 1 Lycopene versus control

Outcome: 6 Incidence of Benign Prostatic Hyperplasia

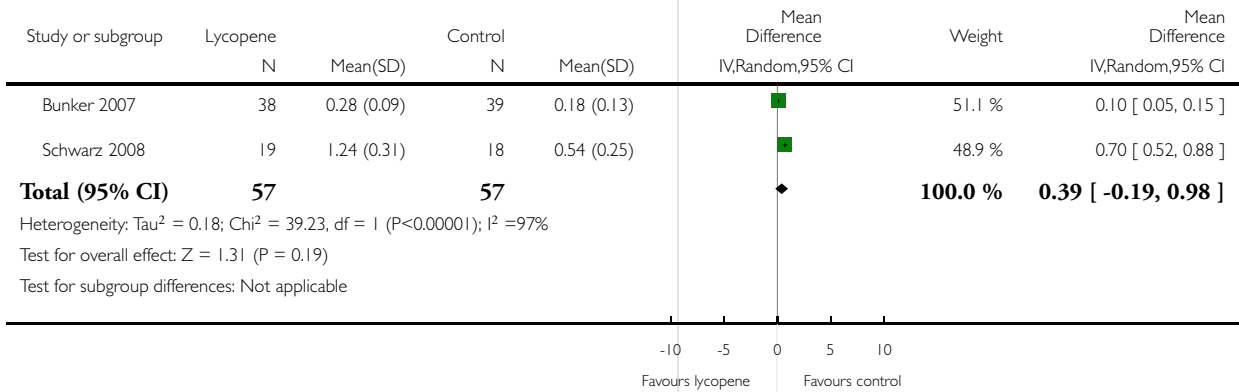


**Analysis 1.7. Comparison 1 Lycopene versus control, Outcome 7 Lycopene levels (µg/mL).**

Review: Lycopene for the prevention of prostate cancer

Comparison: 1 Lycopene versus control

Outcome: 7 Lycopene levels ( µg/mL)



## WHAT'S NEW

Date	Event	Description
25 October 2011	Amended	A few slight edits.

## CONTRIBUTIONS OF AUTHORS

Dragan Ilic (DI), Kristian Forbes (KF) and Craig Hased (CH) all initiated the review and wrote the protocol. DI and KF conducted the literature search, reviewed abstracts and full text studies for inclusion, performed quality assessment, data extraction, analysis and writing of the review. CH assisted with the inclusion of studies, quality assessment and contributed to the writing of the review.

## DECLARATIONS OF INTEREST

None known.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Change of contact author.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Anticarcinogenic Agents [\*therapeutic use]; Carotenoids [\*therapeutic use]; Prostate-Specific Antigen [blood]; Prostatic Neoplasms [blood; \*prevention & control]; Randomized Controlled Trials as Topic

### MeSH check words

Humans; Male