

*Review*

# The Role of Tomato Products and Lycopene in the Prevention of Prostate Cancer: A Meta-Analysis of Observational Studies

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## Abstract

**Purpose:** To determine whether intake of tomato products reduces the risk of prostate cancer using a meta-analysis. **Methods:** We systematically searched MEDLINE and EMBASE and contacted authors to identify potential studies. Log relative risks (RRs) were weighed by the inverse of their variances to obtain a pooled estimate with its 95% confidence interval (CI). Logistic regression and Poisson regression analyses were used to determine the effect produced by a daily intake of one serving of tomato product. **Results:** Eleven case-control studies and 10 cohort studies or nested case-control studies presented data on the use of tomato, tomato products, or lycopene and met our inclusion criteria. Compared with nonfrequent users of tomato products (1st quartile of intake), the RR of

prostate cancer among consumers of high amounts of raw tomato (5th quintile of intake) was 0.89 (95% CI 0.80–1.00). For high intake of cooked tomato products, this RR was 0.81 (95% CI 0.71–0.92). The RR of prostate cancer related to an intake of one serving/day of raw tomato (200 g) was 0.97 (95% CI 0.85–1.10) for the case-control studies and 0.78 (95% CI 0.66–0.92) for cohort studies. **Conclusion:** Our results show that tomato products may play a role in the prevention of prostate cancer. However, this effect is modest and restricted to high amounts of tomato intake. Further research is needed to determine the type and quantity of tomato products with respect to their role in preventing prostate cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(3):340–345)

## Introduction

Prostate cancer is the most common cancer among men in North America. A growing body of evidence has shown that tomato products may decrease the risk of prostate cancer. This is thought to be due to a high concentration of lycopene, a potent antioxidant (1). As a result, intake of lycopene supplements has become popular among men who are concerned about their risk of prostate cancer. Although some observational studies have shown a protective effect (2, 3) with the use of tomato products, others have failed to show this benefit (4, 5). In addition, some unanswered questions remain. For example, it is uncertain whether the benefit with tomato products is consistent with all tomato products or whether this benefit varies with different preparations of tomatoes (cooked *versus* raw). To answer some of these

questions, we sought to explore this association by conducting a meta-analysis.

## Materials and Methods

**Study Selection.** We systematically searched MEDLINE from 1966 to March 2003 and EMBASE for all relevant articles entering terms including “carotenoids,” “tomatoes,” “lycopene,” and “prostatic neoplasms” as both subject heading and text word. Because some studies that may have presented data on the use of tomato products or lycopene may not have included these specific terms in their abstracts or keywords, we also carried out a broader search for all studies that looked at “diet” and “prostatic neoplasms.” In the case where only an abstract was available, we contacted the authors to obtain pertinent information. We also searched for potentially missed articles from the reference lists of retrieved articles and from previous narrative reviews on this topic.

**Data Extraction.** Studies were included if they met the following criteria: (a) presented original data from case-control studies or cohort studies, (b) the primary outcome was clearly defined as prostate cancer, (c) the

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exposure of interest was tomato or lycopene intake, and (d) provided relative risk (RR) estimates and their confidence intervals (CIs) or provided enough data to calculate them. If data were duplicated in more than one study, the most recent study was included in the analysis. We developed a questionnaire and recorded study name, year of publication, study design, sample size (cases and controls or cohort size), and variables used for adjustment in the studies. We carried out separate analyses for intakes of raw or unspecified tomato products, cooked tomato products, and lycopene with respect to risk of prostate cancer. An additional analysis focused on serum lycopene. We studied the effect of moderate intake (defined as the intake ranging from the 2nd to the 4th quintile of the distribution or from the 2nd to the 3rd quartile, depending on the presentation of the original studies). In a subsequent analysis, we focused on the data corresponding to high intakes (5th quintile or 4th quartile of intake).

**Statistical Analysis.** Log RRs (for cohort studies) or odds ratios (for case-control studies) were weighed by the inverse of their variances to obtain a pooled measure of RR. Nested case-control studies carried out within

well-defined cohorts were included among cohort studies. Odds ratios were considered an approximation of RRs. When results from fixed effects and random effects models were different, we presented the latter as it represents a more conservative approach. Differences between results yielded by the fixed effects and random effects models were assessed by the *P* value of the DerSimonian and Laird's  $Q^*$  test.

Intake of tomatoes and lycopene was reported as categorical data with a range in the studies included in this meta-analysis. We assigned the mean of upper and lower bounds in each quintile of intake as the average intake of this quintile. When the upper bound of the last quintile was not presented, we assumed the amplitude to be the same as the fourth quintile.

To determine the change in prostate cancer risk per serving of average size, we carried out a logistic regression model for case-control studies and a Poisson regression model for cohort studies, assuming linearity over the range of intake reported by each study. For the logistic regression model, the dependent variable was the case/control status and the independent variable was the mean intake value of each quintile calculated as

**Table 1. RRs and 95% CIs of prostate cancer by tomato intake**

Author	Raw tomatoes (moderate intake)	Raw tomatoes (high intake)	Cooked tomatoes (moderate intake)	Cooked tomatoes (high intake)	Cases/controls or cohort size	Variables of adjustment
<b>Case-control studies</b>						
Key <i>et al.</i> (5)	1.18 (0.87–1.60)	1.06 (0.55–1.62)	0.89 (0.66–1.20)	0.92 (0.59–1.42)	328/328	Age, energy intake, ethnicity
Tzonou <i>et al.</i> (2)	0.85 (0.40–1.81)	0.53 (0.08–2.9)	0.64 (0.27–1.53)	0.46 (0.04–3.60)	320/246	Age, height, BMI, energy intake
Jain <i>et al.</i> (3)	0.77 (0.64–0.94)	0.64 (0.45–0.91)	–	–	617/636	Age, calories, vasectomy, smoking, marital status, study location, BMI, vitamin use, diet
Cohen <i>et al.</i> (4)	1.20 (0.89–1.62)	1.22 (0.83–1.80)	0.97 (0.73–1.30)	0.90 (0.57–1.42)	682/602	Age, race, fat, energy, family history, BMI, antigen tests, education
Villeneuve <i>et al.</i> (14)	0.98 (0.84–1.14)	1.0 (0.7–1.3)	–	–	1623/1623	Age, location, race, smoking, BMI, diet, alcohol, income, diet, family history
Kolonel <i>et al.</i> (15)	1.00 (0.87–1.15)	1.07 (0.83–1.38)	1.07 (1.06–1.08)	0.94 (0.58–1.52)	1619/1618	Age, education, race
Norrish <i>et al.</i> (16)	0.89 (0.67–1.19)	1.01 (0.66–1.53)	0.90 (0.66–1.22)	0.82 (0.53–1.26)	317/480	Age, site, calories, height, NSAIDs, socioeconomic status
<b>Cohort studies</b>						
Mills <i>et al.</i> (21)	0.62 (0.40–0.96)	0.57 (0.35–0.93)	–	–	180/1400	Age
Giovanucci <i>et al.</i> (23)	0.91 (0.78–1.05)	0.74 (0.58–0.93)	–	–	773/47,894	Age, calories, family history, vasectomy, fat, retinol
Giovanucci <i>et al.</i> (22)	–	–	0.88 (0.74–1.05)	0.77 (0.66–0.90)	2481/47,365	Time, ancestry, BMI, calories, vitamins

Note: Moderate intake corresponds to the 2nd, 3rd, and 4th quintiles of the distribution, while high intake corresponds to the 5th quintile. *BMI*, body mass index; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

**Table 2. RRs and 95% CIs of prostate cancer by lycopene intake and serum lycopene**

Author	Diet lycopene (moderate intake)	Diet lycopene (high intake)	Serum lycopene (moderate value)	Serum lycopene (high value)	Cases/controls or cohort size	Variables of adjustment
Case-control studies						
Key <i>et al.</i> (5)	0.90 (0.63–1.29)	0.99 (0.68–1.45)	–	–	–	Age, energy intake, ethnicity
Meyer <i>et al.</i> (26)	1.28 (0.81–2.01)	1.73 (0.92–3.26)	–	–	215/593	Age, education, family history, energy intake
Jain <i>et al.</i> (3)	0.90 (0.74–1.10)	1.01 (0.76–1.35)	–	–	617/636	Age, total energy, vasectomy, smoking, marital status, study area, BMI, vitamin use, diet
Deneo-Pelligrini <i>et al.</i> (27)	1.13 (0.76–1.68)	1.2 (0.7–2.2)	–	–	175/233	Age, residence, education, family history, BMI, energy intake
Cohen <i>et al.</i> (4)	1.08 (0.83–1.39)	0.89 (0.60–1.31)	–	–	628/602	Age, race, fat, energy, family history, BMI, antigen tests, education
Norrish <i>et al.</i> (16)	0.81 (0.60–1.11)	0.76 (0.50–1.17)	–	–	317/480	Age, height, NSAIDs, socioeconomic status
Lu <i>et al.</i> (19)	1.03 (0.44–2.38)	0.69 (0.23–2.08)	0.45 (0.21–0.96)	0.17 (0.04–0.78)	65/132	Age, race, smoking, education, family history, alcohol, calories
Vogt <i>et al.</i> (10)	–	–	0.84 (0.57–1.23)	0.65 (0.36–1.15)	209/228	Age, race, study center, time of blood draw
Cohort or nested case-control studies						
Hsing <i>et al.</i> (18)	–	–	0.69 (0.39–1.23)	0.50 (0.20–1.29)	103/103	Age, race, smoking, education, time of last meal
Cerhan <i>et al.</i> (25)	–	0.5 (0.3–0.9)	–	–	101/1575	Age, energy, nondietary factors
Nomura <i>et al.</i> (20)	–	–	1.00 (0.64–1.57)	1.1 (0.5–2.2)	142/142	Age, smoking
Gann <i>et al.</i> (17)	–	–	0.89 (0.74–1.07)	0.75 (0.54–1.06)	578/1294	Age, smoking, exercise, follow-up time, BMI, plasma cholesterol, alcohol, vitamin use
Giovanucci <i>et al.</i> (22)	1.01 (0.92–1.10)	0.84 (0.73–0.96)	–	–	2481/47,365	Age, time, family history, BMI, energy intake, vitamins
Schuurman <i>et al.</i> (24)	0.95 (0.79–1.14)	0.98 (0.71–1.34)	–	–	642/58,279	Age, history, socioeconomic status, alcohol
Huang <i>et al.</i> (CLUE I; Ref. 28)	–	–	0.85 (0.62–1.18)	0.83 (0.46–1.48)	182/364	Age, race, date of blood donation, total lipid level, hours since last meal, education
Huang <i>et al.</i> (CLUE II; 28)	–	–	0.82 (0.56–1.21)	0.79 (0.41–1.54)	142/284	Age, race, date of blood donation, total lipid level, hours since last meal, education, BMI

Note: Moderate intake corresponds to the 2nd, 3rd, and 4th quintiles of the distribution, while high intake corresponds to the 5th quintile. Moderate value corresponds to the 2nd, 3rd, and 4th quintiles of the distribution, while high value corresponds to the 5th quintile.

**Table 3. Pooled RRs of prostate cancer and 95% CIs for intakes of tomato and lycopene and concentrations of serum lycopene**

	Moderate intake or concentration				High intake or concentration		
	No. studies	Pooled RR	$R_i$	Q test ( <i>P</i> value)	Pooled RR	$R_i$	Q test ( <i>P</i> value)
Raw tomato (all studies)	9	0.94 (0.88–1.01)	0.43	0.09	0.89 (0.80–1.00)	0.50	0.05
Raw tomato (case-control)	7	0.97 (0.89–1.05)	0.38	0.16	0.98 (0.86–1.12)	0.26	0.24
Raw tomato (cohort)	2	0.88 (0.77–1.00)	0.83	0.10	0.71 (0.57–0.87)	0.01	0.34
Cooked tomato (all studies)	6	1.07 (1.06–1.08)	0.98	0.10	0.81 (0.71–0.92)	0.00	0.90
Cooked tomato (case-control)	5	1.07 (1.06–1.08)	0.94	0.35	0.88 (0.71–1.11)	0.00	0.96
Lycopene intake (all studies)	10	0.99 (0.93–1.06) <sup>a</sup>	0.01	0.73	0.89 (0.81–0.98)	0.28	0.23
Lycopene intake (case-control)	7	0.97 (0.86–1.09)	0.01	0.58	0.98 (0.83–1.16)	0.00	0.48
Lycopene intake (cohort)	3	1.00 (0.92–1.08) <sup>b</sup>	0.01	0.55	0.84 (0.75–0.95)	0.67	0.14
Serum lycopene (all studies)	7	0.85 (0.75–0.97)	0.01	0.68	0.74 (0.59–0.92)	0.00	0.44
Serum lycopene (case-control)	2	0.74 (0.53–1.04)	0.63	0.15	0.55 (0.32–0.94)	0.79	0.11
Serum lycopene (cohort)	5	0.87 (0.76–1.00)	0.01	0.89	0.78 (0.61–1.00)	0.00	0.76

Notes: Moderate intake corresponds to the 2nd, 3rd, and 4th quintiles of the distribution, while high intake corresponds to the 5th quintile. Moderate value corresponds to the 2nd, 3rd, and 4th quintiles of the distribution, while high value corresponds to the 5th quintile.  $R_i$  is the proportion of the total variance due to between-study variance. Large values (>0.75) indicate high power of the corresponding significance test, while small values (<0.4) indicate that the test for heterogeneity is underpowered and may be deceptive if the number of studies is small (7).

<sup>a</sup>Results based on nine studies.

<sup>b</sup>Results based on two studies.

explained above. The weight was given by the number of subjects (either cases or controls) within each category. For cohort studies, the dependent variable of the Poisson regression was the case number within each category, the independent variable was the mean intake value of each quintile, and the offset term was the total person-time of each category. We repeated this analysis for the average content of lycopene found in one serving of a tomato (6). We explored publication bias using a funnel plot.

We tested for heterogeneity using the DerSimonian and Laird's *Q* statistic and its parametric bootstrap version (with 1000 replications; 7). We also quantified heterogeneity by calculating the proportion of total variance due to between-study variance ( $R_i$  statistic; 7). All analyses were done using HEpiMA version 2.13 (8).

## Results

Our search resulted in 23 potential articles (2–5, 9–27). Four studies were excluded, as they did not provide CIs of the RRs or any other information that allowed for their calculations (9, 11–13). We contacted the authors with the purpose of obtaining those missing figures, but up to the time of completion of this article, we had not received this information. One study, upon request to the first author, provided information that was missing in the original publication (10). Results of one cohort study were published in two separate publications (22, 23), while results of two separate nested case-control studies were published in the same article (28).

Eleven case-control studies (2–5, 10, 14–16, 19, 26, 27), five cohort studies (21–25), and five nested case-control studies met our inclusion criteria. Seven case-control studies (with 5506 cases and 5533 controls; 2–5, 14–16) and two cohort studies (21, 22) presented data on raw or unspecified tomato intake (Table 1). Five case-control studies (2, 4, 5, 15, 16) and one cohort study (22) presented data for cooked tomatoes. As for lycopene, seven case-control studies (3–5, 16, 19, 26, 27) and three

cohort studies (22, 24, 25) presented data on intake of this micronutrient, while two case-control studies (10, 19) and five nested case-control studies (17, 18, 20, 28) presented results referring to serum concentrations (Table 2).

Compared with people having a low consumption of raw tomato products, the RR of prostate cancer of those having a moderate intake was 0.94 (95% CI 0.88–1.01; Table 3). The RR of prostate cancer per additional serving of raw tomato daily (200 g) was 0.97 (95% CI 0.85–1.10) for case-control studies and 0.78 (95% CI 0.66–0.92) for cohort studies. The pooled RR for moderate intake of cooked tomato products was 1.07 (95% CI 1.06–1.08). As no universally accepted average size for cooked tomato products is available, we could not calculate the risk associated with one serving of cooked tomato. The pooled RR of moderate lycopene intake was 0.99 (95% CI 0.93–1.06; Table 3), while that corresponding to an increase of 12.7 mg/day of lycopene [the average content of one raw tomato serving of 200 g (29)] was 0.95 (95% CI 0.89–1.26) for case-control studies and 0.38 (95% CI 0.34–0.42) for cohort studies. The effect shown by increasing concentrations of serum lycopene was higher than that of lycopene intake: for high serum concentrations, the pooled RR was 0.74 (95% CI 0.59–0.92). In general, when we restricted our analysis to high intakes (5th quintile of intake) of tomato or tomato products, the preventive effect increased (Table 3; Fig. 1). The RRs were 0.89 (95% CI 0.80–1.00) for raw tomato and 0.81 (95% CI 0.71–0.92) for cooked tomato.

When we stratified the lycopene intake case-control studies by control selection [hospital-based studies (26, 27) and population-based studies (3–5, 16, 19)], no major changes were noticed in the pooled estimates (Fig. 2). The pooled RR for moderate lycopene intake was 0.9 (95% CI 0.8–1.1) for population-based case-control studies and 1.1 (95% CI 0.9–1.6) for hospital-based studies.

We explored publication bias using a funnel plot taking into account that this graphical method may not be ideal in detecting publication bias when the number of studies is small as in our meta-analysis. In spite of the

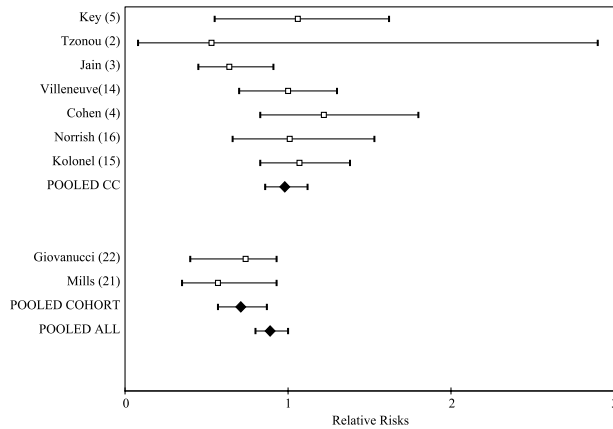


Fig. 1. RRs and 95% CIs for studies of high intake of raw tomatoes and prostate cancer.

absence of symmetry in Fig. 3, the funnel plot, which relates the magnitude of the RR of each study to the inverse of its variance, did not show strong evidence for publication bias for tomato intake. Figure 4 (lycopene intake) was consistent with a symmetrical funnel with a large base and a sharp upper part, showing that there is no evidence for publication bias.

**Discussion**

The anticarcinogenic effects of lycopene are thought to be through several mechanisms. Lycopene is thought to inhibit proliferation of cancerous cells at the G<sub>0</sub>-G<sub>1</sub> cell cycle phase (30). Lycopene has also been shown to prevent carcinogenesis by protecting important cellular biomolecules including lipoproteins and DNA (31). In healthy human subjects, lycopene or tomato free diets resulted in loss of lycopene and an increase in lipid oxidation (32). One study has shown that lycopene may have antioxidant properties similar to that of statins (33).

The results of our study are consistent with a modest inverse association between tomato intake and the risk of prostate cancer. However, unlike cooked tomatoes, the decrease in the risk for high consumption of raw (or

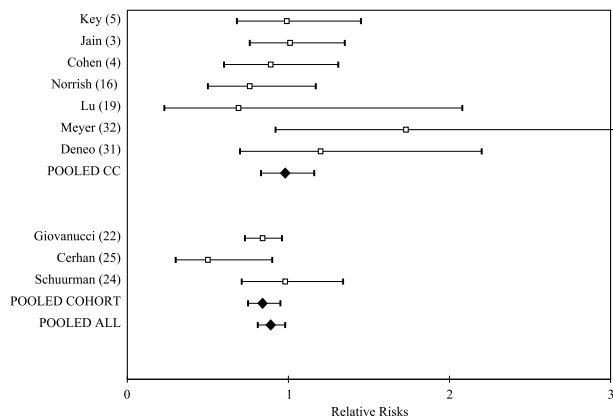


Fig. 2. RRs and 95% CIs for studies of high intake of lycopene and prostate cancer.

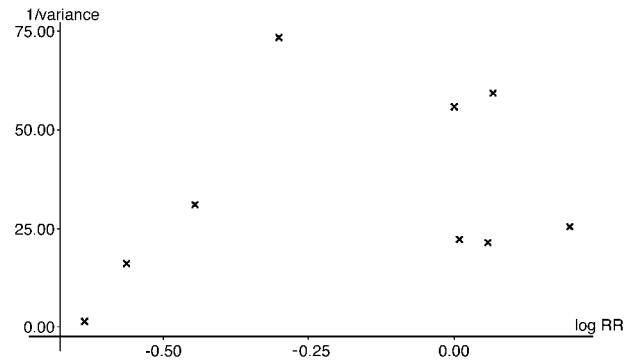


Fig. 3. Funnel plot of studies of high intake of raw tomatoes and prostate cancer.

uncooked) tomatoes presents only borderline statistical significance. In general, the lack of precision in the magnitude of the pooled measures is due to the relatively small number of studies.

Globally, the pooled results between groups of studies were homogeneous. Except for the studies of high intake of raw tomato, which show a borderline heterogeneity ( $P$ -value  $Q^* = 0.05$  for  $R_i = 0.5$ ), the rest does not provide any evidence of heterogeneity. It is remarkable that this borderline heterogeneity disappears when we stratify the studies by design. However, only two cohort studies are included in this analysis.

Further stratification of the case-control studies by control selection did not find any meaningful difference in the effect. However, the small number of studies (five for population-based studies and two for hospital-based studies) may limit any meaningful comparison.

The preventive effect was slightly stronger for high intakes of cooked tomato products than for high intakes of raw tomatoes. Several explanations may exist for this possible greater benefit. The effect may be due to the higher concentration of lycopene in tomato products, as in tomato sauce, but it may also be due partially to the bioavailability of lycopene, which is a lipophilic molecule. Studies have shown that absorption of lycopene is increased with processing, heat, and presence of fat (34-36). These results are corroborated by our results regarding a protective effect of lycopene, essentially when measured in serum. It is already known that the correlation between dietary lycopene intake and serum

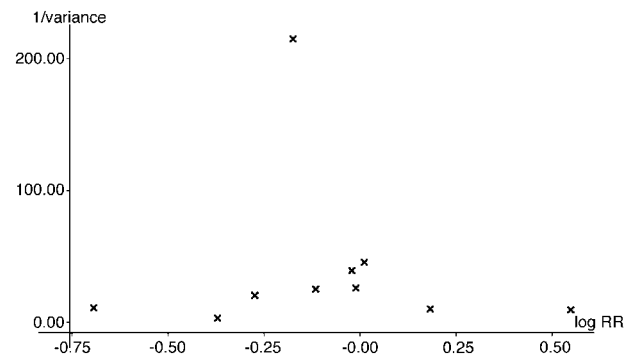


Fig. 4. Funnel plot of studies of high intake of lycopene and prostate cancer.

lycopene is low (37). This is probably due to saturation of absorption at higher intakes. This saturation may occur at lower doses for subjects at risk for prostate cancer than for the rest of subjects. This differential saturation could partially explain the stronger protective effect observed in studies of plasma lycopene compared with that found in studies of lycopene intake.

Our meta-analysis may be subject to several limitations. Although there was little evidence of publication bias from our funnel plot, results from the studies that were not accepted for publication apparently may have changed the results of our meta-analysis. Recall bias may be present in case-control studies of tomato and lycopene intake included in our meta-analysis. The preventive effect is weaker than that found in cohort studies, especially for high intakes. This difference between the effects across study designs is not found for studies of serum lycopene, in which exposure is measured in an objective fashion and where recall bias is not a concern. Finally, residual confounding (confounding from unknown variables that is not eliminated by adjustment), as in any meta-analysis of observational studies, may introduce considerable bias. The direction of this bias is unpredictable.

In summary, our results show that tomato products may play a role in the prevention of prostate cancer. However, this effect is modest. Despite the preventive benefits of lycopene found in this study, the existing evidence is not overwhelming enough to recommend the use of lycopene supplements in the prevention of prostate cancer. The lack of clinical evidence as well as the suboptimal quality of nutritional supplements in general (38) further strengthens the argument that more research in this area is needed to determine the type and quantity of products involved in this prevention.

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