# Lycopene and prostate cancer

*MS Ansari*[†] *&*
*Sofia Ansari*

[†]*Author for correspondence*
*Sanjay Gandhi Postgraduate Institute of Medical Sciences, Department of Urology and Renal transplantation, Rae Breli Road, Lucknow-UP (226014), India*
*Fax: +91 522 266 8129;*
*ansarimsa@hotmail.com*

Despite being one of the most common malignancies, the prevenatble measures for prostate cancer remain poorly defined. Dietary intake of tomatoes and tomato products containing lycopene have been shown in cell culture, animal, epidemiologic and case–control studies to be inversely associated with the risk of prostate cancer. Its unique structural and biologic properties enable lycopene to prevent free-radical damage to cells caused by reactive oxygen species, thus acting as a potent antioxidant. Although some studies have provided contradictory results, these should not be considered incongruous to the many larger studies which have shown reliable results in favor of prostate cancer. Further research involving large randomized case–control trials would confirm the potential anticancer effect of this molecule, which might provide new dimensions not only to the prevention but also the treatment of prostate cancer.

Cancer of the prostate is the most commonly diagnosed solid malignancy and the second leading cause of cancer-related death in many developed countries [1]. Several epidemiological and clinical trials have suggested that a diet rich in certain carotenoids is associated with a reduced risk of prostate cancer [2–5]. Lycopene is one of the carotenoids that is emerging as a potential chemopreventive agent in the prevention and treatment of various types of cancers, owing to its unique properties of cancer prevention and regression, in addition to being a potent quencher of free radicals and an immunomodulator [6,7]. Many laboratory and clinical studies are now underway with the goal of assessing the ability of lycopene to act as a chemopreventive agent for prostate cancer. To date, thus authors have produced many epidemiological studies to support this theory but prospective randomized human trials investigating the potential effect of lycopene supplementation on the prevention and treatment of prostate cancer are still not enough [2–9]. The potential impact of lycopene on the risk of prostate is the focus of the present review.

## Chemistry

Lycopene, also known as ψ-carotene, is a lipophilic compound, an acyclic isomer of β-carotene, and is insoluble in water. It is a $C_{40}$, open-chain carotenoid ($C_{40}H_{56}$) with 11 conjugated double bonds. Lycopene lacks the β-ionone ring structure and is therefore devoid of provitamin A activity [10]. The linear all-*trans* configuration is the predominant form of lycopene, making up approximately 90% of its dietary sources. Stahl and colleagues reported that heating tomato juice resulted in *trans*-to-*cis* isomerization of lycopene, that the *cis* isomers of lycopene seem to be better absorbed [11,12]. The highly conjugated nature of lycopene makes it vulnerable to oxidative degeneration and isomerization. Other factors leading to degradation are exposure to light, elevated temperature and oxygen, extremes of pH and active surfaces [10]. Lycopene is a prominent carotenoid in the testes, adrenal glands, prostate and liver [13,14]. In prostate tissue, concentration (mainly *cis* isomer) ranges from 0–2.58 nmol/g. Serum concentration in men ranges from between 0.22 to 1.06 nmol/ml [15].

## Lycopene in food & its absorption

Foods rich in lycopene include tomatoes (richest source), watermelon, guava and papaya. The lycopene content can vary considerably with variety and ripening stage of tomatoes. Lycopene concentration in red strains approaches 50 mg/kg compared with only 5 mg/kg in yellow varieties [16]. Lycopene from plant sources exist primarily in the all-*trans* form which is the most thermodynamically stable. Exposure to thermal treatment during food processing causes changes in physiochemical stability of carotenoids and can result in a loss of all-*trans* lycopene content by up to 20% [17]. Carotenoids are strongly bound to intracellular macromolecules in many foods and absorption may therefore be limited unless released from the food matrix [18]. Chylomicrons are responsible for transporting carotenoids from the intestinal mucosa (small intestine) to the blood via lymphatics [19]. In blood, it is then

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carried by low-density lipoproteins (LDLs). Processed foods are the best sources of lycopene and it is interesting to note that the consumption of tomato paste leads to higher lycopene levels compared with fresh tomatoes. It is suggested that the release of lycopene from processed tomato products might be as a result of thermally induced rupture of the cell walls [18,19]. The plasma half-life of lycopene has been reported to be approximately 2 weeks (range 2–33 days) [10,20]. It is suggested that lycopene undergoes oxidation to an intermediate epoxide, which may undergo metabolic reduction to form metabolites such as 5,6-dihydroxy-5-6′-dihydroxylycopene and 2,6-cyclolycopene-1,5-diol [10].

## Anticancer mechanism of lycopene

Oxidative stress is recognized as one of the major contributors to an increased risk of cancer. One major mechanism by which the environment can influence carcinogenesis is oxidative damage. This refers to the generation of reactive oxygen species (ROS) that act as free radicals and damage important biomolecules, including DNA, protein and lipids. A free radical is an atom or molecule that has one or more unpaired electrons; its consequent tendency to acquire an electron makes it highly reactive. Antioxidant is defined as any compound that breaks the free radical reaction chain. Lycopene is the most potent antioxidant among various common carotenoids and acts by preventing damage to DNA by protecting 2′-deoxyguanosine against singlet oxygen damage [6]. Epidemiologic data suggest that the environment is responsible for most prostate cancers. Experimental studies provide valuable insights into the mechanisms by which carotenoids, such as lycopene, exert their cellular and intracellular effects [21–25]. Cell-culture studies have shown that lycopene inhibits neoplastic cell growth in the prostate gland [21]. Various mechanisms have been proposed to explain the biologic effects of lycopene including: inhibition of autocrine growth factor effects [22], enhanced gap-junction communication [23], and intervention in cell-cycle progression [22] but none have been proven very precisely.

## Epidemiologic studies

In recent years, the authors have seen an accumulated body of evidence from several epidemiological studies strongly supporting a diet rich in fruits and vegetables specially laced with lycopene are associated with a lower risk of prostate cancer [2–5]. The study by Gann and Giovannucci, which is a nested case–control study of aspirin and β-carotene included 578 men who developed prostate cancer within 13 years of follow up and 1294 age- and smoking-status-matched controls. The five major plasma carotenoid peaks (α- and β-carotene, β-cryptoxanthin, lutein and lycopene) plus α- and γ-tocopherol and retinol, were quantitated using high-performance liquid chromatography. Lycopene was the only antioxidant found at significantly lower mean levels in all cases than in matched controls ($p = 0.04$ for all cases). The odd ratios (ORs) for all prostate cancers declined slightly with an increasing quintile of plasma lycopene; there was a stronger inverse association for aggressive prostate cancers. In the placebo group, plasma lycopene was very strongly related to lower prostate-cancer risk, whereas there was no evidence for a trend among those assigned to β-carotene supplements [2]. In another prospective study published by the department of epidemiology at Harvard School of Public Health, MA, USA, concluded that both tomato-product consumption and blood lycopene levels correlated well with prostate-cancer risk [3]. In the Health Professional Follow-up Study (HPFS), which is the largest study to date, Giovannucci and colleagues found that a frequent intake of tomato products or lycopene, a carotenoid from tomatoes, is associated with a reduced risk of prostate cancer. This prospective study evaluated data from the HPFS to determine whether the association would persist. Results confirmed previous findings that frequent tomato or lycopene intake was associated with a reduced risk of prostate cancer. The intake of tomato sauce, the primary source of bioavailable lycopene, was associated with an even greater reduction in prostate cancer risk [4]. A case–control study of prostate cancer conducted in Minnesota, MA, USA, reported that high tomato consumers (> 14 times/month) had an approximately 30% lower risk of total prostate cancer than low consumers (< 3 times/month) [26].

### *Studies based on serum lycopene levels*

One of the initial studies published by Hsing and colleagues involving serum was obtained acquisition from 25,802 individuals in Washington (MD, USA). Lower median lycopene levels were found in men with prostate cancer diagnosed during a 13-year period, compared with age- and race-matched controls. The relative risk (RR) was 0.50 (95% confidence interval [CI], 0.20–1.29) between high and low quartiles of lycopene [27].

Rao and colleagues conducted a case–control study to investigate the serum and prostate tissue lycopene and other major carotenoid concentrations in cancer patients and their controls. A total of 12 prostate-cancer patients and 12 age-matched subjects were involved in the study. Significantly lower serum and tissue lycopene levels were observed in the cancer patients than in their controls [28]. In the Physicians' Health Study, 578 prostate cancer cases were detected over the 13 years of follow up. Of the 578 cases, 259 were classified as aggressive based on high grade or advanced stage. A low risk was found, particularly for aggressive (high-grade or -stage) prostate cancer when comparing high with low quintile of plasma lycopene [2]. However, a study performed between 1971 and 1993 in Japanese–American population in Hawaii did not show any association between serum lycopene levels and prostate cancer risk [29].

### *Human intervention studies*

Kucuk and colleagues published interesting clinical observations in their study involving 26 men with newly diagnosed, clinically localized, (14 $T_1$ and 12 $T_2$) prostate cancer. Patients were randomly assigned to receive 15 mg of lycopene (n = 15) twice daily or no supplementation (n = 11) for 3 weeks before radical prostatectomy. A total of 11 (73%) in the intervention group and two (18%) subjects in the control group had no involvement of surgical margins and/or extraprostatic tissues with cancer (p = 0.02). A total of 12 (84%) subjects in the lycopene group and five (45%) in the control group had tumors below 4 ml in size (p = 0.22). Diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia was present in ten (67%) subjects in the intervention group and 11 (100%) in the control group (p = 0.05). Prostate-specific antigen (PSA) levels decreased by 18% in the intervention group, and increased by 14% in the control group (p = 0.25) [6]. In a prospective study, from the authors' center, the efficacy of lycopene plus orchiectomy versus orchiectomy alone was assessed in the management of advanced prostate cancer. A total of 54 patients with histologically proven, metastatic prostatic cancer ($M_{1b}$ or $D_2$) and performance status of 0 to 2 World Health Organization (WHO) were entered into the trial between March 2000 and June 2002. At month 6, initial observations demonstrated significant reduction in PSA level in both the treatment arms, but with a more marked reduction in the combination treatment with a mean of 9.1 versus 26.44 ng/ml (p = 0.9). Analysis of data at the end of 24 months showed that these changes were more consistent in the combination treatment (mean 3.01 vs 9.02) group (p < 0.001). A total of 11 (59.25%) patients in orchiectomy group as compared with 21 (77.78%) patients in the combination treatment arm had complete response (p < 0.05). Partial response was observed in seven (25.93%) and four (14.81%) patients, respectively. Four patients (14.81%) showed progression in the orchiectomy arm compared with only two (7.40%) in the combination treatment (p < 0.05). Bone scans showed that in the orchiectomy arm, only four (14.81%) patients achieved complete response compared with eight (29.62%) in the combination treatment arm (p < 0.02). The partial response was seen in 19 (70.37%) and 17 (62.96%) of the patients. Four (14.81%) patients demonstrated progression in the orchiectomy group compared with only two (7.40%) in the combination treatment group (p < 0.02). It was concluded that addition of lycopene to orchiectomy produces a more reliable and consistent decrease in serum PSA levels, it not only shrinks the primary tumor, but also takes care of secondary growth more effectively [7]. Matlaga and colleagues described a case of hormone-resistant prostate cancer (HRPC), which failed to respond to multiple treatment regimens and finally responded to lycopene (10 mg/day) and saw palmetto (300 mg three times a day) [8]. More recently, in another trial from the authors' center, in which lycopene was administered for the treatment of patients with metastatic hormone-refractory prostate cancer (HRPC). Between January 2001 and December 2002, 20 consecutive patients (median age 72; range 56–90) with metastatic HRPC were enrolled in the study. Lycopene in a dose of 10 mg/day was administered for a period of 3 months. One patient (5%) had complete response, partial response was achieved in six (30%) and disease remained stable in ten (50%) and progressed in three (15%) patients. Eastern Cooperative Oncology Group Performance Status (ECOG PS) was Grade 0 in five, Grade I in ten and Grade II in 5 of the 20 patients. It improved from Grade I to 0 in seven and Grade II to I in three patients. It deteriorated in three and remained unchanged in the remaining seven patients. Bone pain was present in 16 (Grade I in six and Grade II in ten) of the 20 patients. Grade I changed to Grade 0 in five, and Grade II to I in five patients. Bone pain remained unchanged in five patients (31%) and worsened in one (6%).

Ten (62%) patients managed to reduce the dose of analgesics on a daily basis. Modest results could potentially have been obtained however, the study had certain limitations such as the fact that a nonrandomized trial with small patient population and serum lycopene levels were obtained in a few patients due to financial constraints [9]. It cannot be denied that the randomized controlled studies based on serum lycopene levels recruiting larger number of patients would be more enlightening prior to reaching definitive conclusion.

### *Nonsupportive literature on the association of lycopene & prostate cancer*

Although many previous analyses have shown a positive association between intake of β-carotene, a nutrient presently being tested for chemoprevention, several authors re-examined the data for consistency among the main food sources of β-carotene. In a study by Le Marchand and colleagues, they presented the analysis of a case–control study of 452 prostate cancer cases and 899 population controls that was conducted from 1970 to 1983 among the multi-ethnic population of Hawaii. The results suggest that intake of β-carotene, lycopene, lutein, indoles, phenols, or other phytochemicals was not associated with a risk of prostate cancer [19]. In another study by Key and colleagues, in which total of 328 men diagnosed with prostate cancer before the age of 75 years and 328 age-matched population controls were interviewed. The principal hypotheses were that risk would increase with a high intake of total or saturated fat and would decrease with a high intake of carotene (β-carotene equivalents) or lycopene. Risk was lower in subjects with higher carotene intake. Lycopene was not associated with risk [29]. Similarly, a study by Hayes and colleagues did not support the lycopene–prostate cancer hypothesis in both white and black men. They did not find a statistically significant association between prostate cancer and various components of tomato products. The interesting findings were that raw, not cooked, tomatoes had a suggestive inverse association with advanced prostate cancer, but that tomato juice was related to a higher risk of prostate cancer for white men [30]. In a more recent study by Cohen and colleagues, a similar negative association was found. Neither cooked nor raw tomatoes were appreciably correlated with a risk of prostate cancer; although a negative association was found for cooked tomatoes [31].

Whilst some of these studies provide contradictory results, these should not be considered incongruous to the many larger studies conducted, particularly the HPFS, which was much larger and involved some 2481 cases of prostate cancer with a different study design [2]. The failure of the above, smaller studies, to identify an association may be on account of the sample size being inadequate or flaws in on study being design itself, rather than the study designed on a case–control basis.

## Dosage requirement

It is pertinent to discuss the dosage requirement for lycopene therapy, as the optimal dose of lycopene has not been established thus far. Bohm and colleagues demonstrated that the intake of 5 mg of lycopene comprised in tomato oleoresin/day resulted in a 2.5-fold increase in plasma lycopene levels [32]. Giovannuci and colleagues demonstrated that the highest quintile for lycopene intake was above 6.5 mg/day with a mean level of 10 mg/day [5]. It is interesting to note that a plateau is achieved once a dose above 10 mg/day is administered. A dose of 6 mg for chemoprevention or maintenance and 10 mg for the therapeutic purpose should be adequate.

## Conclusion

Intake of lycopene, a carotenoid found prdominantly in tomatoes, has been consistently associated with a lower risk of a variety of cancers. These findings are still speculative but more plausible for prostate cancer. Appropriate, large, randomized trials are needed to further confirm the anticancer effect of this molecule, which might provide new dimensions not only to the prevention but also the treatment of prostate cancer.

## Future perspective

Thus far, various dietary case–control studies suggest that the intake of lycopene lowers the risk of prostate cancer. Inclusion of blood samples in dietary-based studies would; however, cancer more precisely prove the potential benefits. Moreover, most of the data available have dealt with lycopene intake before the diagnosis of prostate cancer to investigate the causal relationship and not much work has been carried out regarding its influence on the disease process once cancer has been diagnosed [6,7,9]. Ideally, long-term randomized, controlled, intervention studies would provide an ultimate test of this theory.

## Executive summary

***Chemistry***

- Lycopene, also known as ψ-carotene, is a lipophilic compound, an acyclic isomer of f-carotene, and is insoluble in water.
- Lycopene lacks the β-ionone ring structure and is therefore devoid of provitamin A activity.
- The linear all-trans configuration is the predominant form of lycopene, making up approximately 90% of its dietary sources.
- Heating tomato juice results in a *trans*-to-*cis* isomerization of lycopene, with the cis isomers of demonstrating better absorption.
- The highly conjugated nature of lycopene makes it vulnerable to oxidative degeneration and isomerization.

***Lycopene in food***

- Foods rich in lycopene include tomatoes (richest source), watermelon, guava and papaya; however, processed foods are the best sources of lycopene and it is interesting to note that the consumption of tomato paste leads to higher lycopene levels compared with fresh tomatoes.
- Lycopene from plant sources exist primarily in the all-trans form, which is the most thermodynamically stable.
- Carotenoids are strongly bound to intracellular macromolecules in many foods and absorption may therefore be limited unless released from the food matrix. Chylomicrons are responsible for carrying carotenoids from the intestinal mucosa (small intestine) to the blood via lymphatics.

***Distribution of lycopene in body tissues***

- Lycopene is a prominent carotenoid in the testes, adrenal glands, prostate and liver.
- In blood, it is carried by low-density lipoproteins (LDLs).
- In prostate tissue, concentration (mainly *cis* isomer) ranges from 0–2.58 nmol/g.

***Anticancer mechanism of lycopene***

- Reactive oxygen species act as a free radical and damage important biomolecules, including DNA, protein and lipids.
- Lycopene is the most potent antioxidant among various common carotenoids and acts by preventing damage to DNA by protecting 2´-deoxyguanosine against singlet-oxygen damage.

***Epidemiologic studies***

- Diets rich in fruits and vegetables high in lycopene are associated with a lower risk of prostate cancer.
- Both tomato-product consumption and blood-lycopene levels correlated well with the risk of prostate cancer.

***Studies based on serum-lycopene levels***

- Significantly lower serum- and tissue-lycopene levels were observed in cancer patients compared with their controls.

***Human-intervention studies***

- A significant reduction in prostate-specific antigen (PSA) levels occurred after lycopene administration. Lycopene not only shrinks the primary tumor, but also eradicates secondary potentials.
- Hormone-resistant prostate cancer, which failed to respond to multiple-treatment regimens, may respond to lycopene.

***Nonsupportive literature on the association of lycopene & prostate cancer***

- Although many previous analyses have shown a positive association with the intake of certain carotenoids, several authors re-examined the data for consistency among the main food sources of these carotenoids. The results suggest that intake of ψ-carotene, lycopene, lutein, indoles, phenols or other phytochemicals was not associated with the risk of prostate cancer. Neither cooked nor raw tomatoes were appreciably correlated with a risk of prostate cancer.

***Dosage requirement***

- Intake of 5 mg of lycopene comprised in tomato oleoresin/day resulted in a 2.5-fold increase in plasma–lycopene levels. The highest quintile for lycopene intake was above 6.5 mg/day with a mean level of 10 mg/day. A plateau is achieved once a dose above 10 mg/day is administered. A dose of 6 mg for chemoprevention or maintenance and 10 mg for the therapeutic purpose should be adequate.

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## Affiliations


- *MS Ansari*
  *Sanjay Gandhi Postgraduate Institute of Medical Sciences, Department of Urology and Renal transplantation,*
  *Rae Breli Road,*
  *Lucknow-UP (226014),*
  *India*
  *Fax: +91 522 266 8129;*
  *ansarimsa@hotmail.com*
- *Sofia Ansari*
  *Sanjay Gandhi Postgraduate Institute of Medical Sciences, Department of Urology and Renal transplantation,*
  *Rae Breli Road,*
  *Lucknow-UP (226014),*
  *India*
  *Fax: +91 522 266 8129*