EXPERT REVIEWS

Diet and prostate cancer risk reduction

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Prostate cancer is the most commonly diagnosed malignancy in males. The current body of literature supports the role of nutritional products in the reduction of prostate cancer. This review critically addresses the natural products with the greatest potential to reduce the risk of prostate cancer, including lycopene, vitamin E, selenium, vitamin D, soy and green tea. The toxicities of the dietary products are addressed. The direction of future studies lies in clarifying the effects of these products and exploring the biological mechanisms responsible for the prevention of prostate cancer.

KEYWORDS: cancer • diet • green tea • lycopene • prostate • risk • selenium • soy • vitamin D • vitamin E

Prostate cancer is the most prevalent malignancy in men of industrialized countries and the second most common cause of cancer-related death. In 2007, an estimated 218,890 new cases will be diagnosed in the USA and 27,050 deaths will occur [1]. Prostate cancer prevalence varies widely among different countries and this variation may be related to environmental factors such as diet. A compelling argument for the relationship between diet and prostate cancer risk is the observation that the incidence of prostate cancer substantially increases when migrants move from countries with a low incidence of prostate cancer to North America and other industrialized countries. This review addresses clinical studies that focus on dietary factors that may reduce a male's risk for the development of prostate cancer.

Lycopene

Carotenoids are synthesized in a variety of fruits and vegetables and function as natural pigments and antioxidants. The major carotenoids in the human diet include lycopene, α-carotene, β-carotene, β-cryptoxanthin, lutein and zeaxanthin. Lycopene is a free radical scavenger found mainly in tomatoes.

Studies that are supportive of a relationship between prostate cancer reduction and lycopene or tomato product intake cite a risk reduction of 25–80%. Multiple studies have focused on information obtained from questionnaires. Mills *et al.* followed a cohort of approximately 14,000 men, 180 of whom developed prostate cancer after a follow-up period of 6 years [2]. Increased intake of a variety of fruits and vegetables, including tomatoes, was associated with significantly decreased prostate cancer risk (response rate [RR]: 0.60). Tzonou *et al.* conducted a case-control study in Greece that involved 320 prostate cancer cases and 246 controls and found that consumption of cooked tomatoes more so than raw tomatoes reduced prostate cancer risk by close to 15% [3]. Norrish *et al.* performed a population-based case-control study of 317 prostate cancer cases and 480 controls and found a weak association between lycopene and tomato-based foods and reduced risk of prostate cancer [4]. Giovannucci *et al.* performed two reviews of the Health Professionals Follow-Up Study (HPFS), the most recent of which was published in 2002 [5]. Lycopene had a RR for high versus low quintiles of 0.84. Intake of tomato sauce was associated with an even greater reduction in prostate cancer risk (RR: 0.77).

Several studies have attempted to identify an association between serum levels of lycopene and prostate cancer risk. Gann *et al.* conducted a nested case-control study from healthy men in the Physician's Health Study [6]. 578 men developed prostate cancer and were matched to 1294 controls. Lycopene was found at a significantly lower mean level in prostate cancer cases than in matched controls ($p = 0.04$) and prostate cancer risk likewise declined (odds ratio [OR] for fifth quintile: 0.75; p trend = 0.12). In a study by Lu *et al.*, a significant inverse association with prostate

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cancer was observed with plasma lycopene concentrations (OR: 0.17; p for trend = 0.0052) [7]. In another study, the serum levels of individual carotenoids in white and black males at a US center were examined [8]. Lycopene was inversely associated with prostate cancer risk (OR: 0.65; p = 0.09). In a case-control study by Wu *et al.* nested within the prospective HPFS, a statistically significant inverse association between higher plasma lycopene concentrations and lower risk of prostate cancer was discovered in patients older than 65 years (OR: 0.47) and without a family history of prostate cancer (OR: 0.48) [9].

Despite the positive results, several studies failed to show an association, including a case-control study by Key *et al.* of 328 men with prostate cancer and 328 matched controls [10], a detailed analysis of a case-control study of 452 prostate cancer cases and 899 controls performed in Hawaii [11], a population-based control study performed by Hayes *et al.* in the USA involving 932 black and white males with prostate cancer and 1201 controls [12], a multicenter, multiethnic study by Kolonel involving 1619 African–American, white, Japanese and Chinese men and 1618 controls [13], and a study performed by Schuurman *et al.* in the Netherlands involving over 1200 men [14].

Moreover, studies involving measured serum levels of lycopene do not always correlate with a reduced risk of prostate cancer. Hsing *et al.* measured serum levels of lycopene in 25,802 men from Maryland, 103 of whom subsequently developed prostate cancer, and did not find a significant association between lycopene and prostate cancer risk [15]. A similar lack of correlation was reported by Nomura *et al.* who conducted a nested case-control study in 6860 Japanese–American men, 142 of whom developed prostate cancer [16], and Peters *et al.* who reported on 792 prostate cancer cases and 844 matched controls from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial [17].

Lycopene is a carotenoid readily found in a variety of vegetables, including tomatoes. No toxicities of lycopene intake have been identified. The conflicting data from epidemiologic and prospective trials may reflect the heterogeneity in the manner in which these studies were conducted. The food frequency questionnaires differed in their measurement of lycopene intake. The studies involving serum lycopene levels differed in their techniques of measurement. The conflicting data may reflect ethnic differences or other unidentified factors present in the various tomato products. Still, given the relative lack of reported toxicities of lycopene and in light of the studies affirming the association between lycopene and prostate cancer risk reduction, physicians may wish to consider providing a balanced discussion of the potential benefits of lycopene supplementation in patients interested in maximizing their prevention of prostate cancer.

Selenium

Selenium is an essential trace element found in the soil that enters the food chain through plants. Humans consume selenium in plant and animal products as well as supplements. Selenium plays a role in detoxification and antioxidant defense mechanisms.

Selenium nail levels are considered a long-term measurement of body selenium levels. Several studies have attempted to determine whether nail selenium levels correlate with decreased risk of prostate cancer. Yoshizawa *et al.* examined over 50,000 men previously enrolled in the HPFS and found that higher prediagnostic selenium levels were associated with lower risk of advanced prostate cancer (OR for highest to lowest quintile: 0.49) [18]. Helzlsouer *et al.* investigated over 10,000 men from Maryland, 117 of whom developed prostate cancer and found that higher levels of selenium were associated with a lower risk for developing prostate cancer when the levels of two types of vitamin E, α- (OR 0.65) and γ-tocopherol (fivefold reduction) were also high [19].

These results have been challenged by several other nail studies. Specifically, a study by Lipsky *et al.* comparing the toenail selenium levels of 70 newly diagnosed prostate cancer patients with those of 80 controls [20], a case-control study by Ghadirian *et al.*, which interestingly found that nonsmoker case and control subjects had higher selenium toenail levels [21], and a case-control study by Allen *et al.* of over 600 British men [22].

Plasma serum selenium levels have also been explored. In a study by Li *et al.* of men enrolled in the Physician's Health Study, 586 men with prostate cancer were compared with 577 control patients over a 13-year follow-up period [23]. The investigators found that prediagnostic plasma serum selenium levels were inversely related with risk of advanced prostate cancer (fifth vs first quintile; OR: 0.52). Vogt *et al.* conducted a study exploring the differences in serum selenium between black and white males who participated in the Third National Health and Nutrition Examination in order to determine whether such a difference may contribute to the racial disparity in prostate cancer incidence. The concentrations were 3% lower in blacks than whites ($p < 0.0001$) [24]. A nested case-control study within the PLCO Cancer Screening trial showed serum selenium was associated with prostate cancer risk only when subjects had high vitamin E intake (>28 international units [IU]/day; OR: 0.58), multivitamin use (OR: 0.61) or a smoking history (OR: 0.65) [25]. Nomura *et al.* conducted a nested case-control study in Japanese–American men and found an OR of 0.5 with a stronger association noted in cases of advanced disease, cases diagnosed 5–15 years after phlebotomy, and in current or past smokers rather than nonsmokers [26].

Not all of the serum selenium trials have shown an inverse relationship between selenium levels and prostate cancer risk, including a study by Hartman *et al.* involving a cohort of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [27], and a trial by Goodman *et al.* involving participants of the Carotene and Retinol Efficacy Trial (CARET) [28].

The data on trials involving selenium supplementation are limited. In a nutritional cancer prevention trial by Clark *et al.*, 974 men who were randomly assigned to receive 200 μg of selenium daily for 4.5 years or placebo were followed for a mean of 6.5 years [29]. The selenium-treated group had more than 50% fewer cases of prostate cancer (13 cases of prostate

cancer vs 35 cases in the placebo group). Duffield-Lillico *et al.* performed a secondary analysis on the Nutritional Prevention of Cancer (NPC) Trial, a study originally designed to determine if selenium supplementation could reduce the risk of recurrent nonmelanoma skin cancer in US subjects and found that selenium supplementation significantly reduced the overall incidence of prostate cancer (RR: 0.51), although the effect was limited to those with lower baseline prostate-specific antigen and plasma selenium concentrations [30].

Selenium is an important mineral. Deficiency of selenium has been reported to cause cardiomyopathy and to be related to asthma, cancer, atherosclerosis and cataracts [31–35]. The conflicting data on the effect of selenium on prostate cancer risk may again reflect differences in study methodology, measurement techniques and ethnic populations. Fortunately, a large trial is being conducted that will elucidate the benefits of selenium. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) as described by Lippman opened in July 2001 with an anticipated accrual of over 35,000 patients [36]. SELECT is a Phase III trial in which men are randomized to 200 μg/day of selenium and/or 400 IU/day of vitamin E versus placebo for a minimum of 7 years. This trial will provide much anticipated information regarding the benefits of selenium supplementation.

Vitamin E

Vitamin E is the collective term for eight tocopherols and tocotrienols. While γ-tocopherol is the most prevalent form of vitamin E found in a typical diet, α-tocopherol is the most biologically available form as well as the form found in dietary supplements. Vitamin E may affect prostate cancer risk by altering sex hormone concentrations.

Several studies based on questionnaires supported a risk reduction of prostate cancer by increased vitamin E intake, including case-control studies by Deneo-Pellegrini *et al.* performed in Uruguay that involved over 400 subjects [37], and Tzonou *et al.* performed in Greece involving 566 patients [3]. Hartman *et al.* performed a cross-sectional analysis to assess the relationship between baseline levels of serum α-tocopherol and serum sex hormones in men [38]. Serum α-tocopherol levels were inversely associated with serum androstenedione testosterone, sex hormone-binding globulin and estrone.

Studies also support an association between vitamin E serum levels and prostate cancer incidence, including a study of 2974 Swedish men by Eichholze *et al.* who found that low vitamin E levels in smokers were related to an increased risk for prostate cancer and prostate-cancer mortality [39], and a nested case-control study by Goodman *et al.* [40].

Some of the difficulty in interpreting vitamin E trials results from the different forms of vitamin E that are being studied. In a well-known Finnish lung cancer prevention trial published by Heinonen *et al.* known as the Alpha-Tocopherol, Beta-Carotene (ATBC) Study, over 29,000 male smokers were randomly assigned to 50 mg of α-tocopherol, 20 mg of β-carotene, both or placebo for 5–8 years [41]. There was a 32% decrease in the incidence of prostate cancer noted among men receiving vitamin E alone. In a recently released 19-year follow-up of the ATBC Study, Weinstein *et al.* found that higher serum α-tocopherol (RR: 0.80) was associated with reduced prostate cancer risk but not dietary vitamin E [42]. Several studies have examined γ-tocopherol. In an examination of two nested case-control studies (CLUE I and II) of more than 20,000 men in Maryland, Huang *et al.* noted that while serum α-tocopherol was weakly associated with prostate cancer, γ-tocopherol was strongly associated with a risk reduction for prostate cancer [43]. From the ATBC Study cohort, Weinstein *et al.* reported on 100 prostate cancer-case patients and 200 matched control subjects and found that subjects with higher concentrations of α- and γ-tocopherol had lower prostate cancer risk [44].

Several studies have failed to show that vitamin E reduced the risk of prostate cancer development. Nomura *et al.* performed a nested case-control study of 6860 Japanese–American men and measured serum vitamin E levels [16]. Interestingly, several vitamin E supplementation studies have likewise failed to show a significant risk reduction of prostate cancer, including a US study by Chan *et al.* that involved health professionals who consumed at least 100 IU/day of supplemental vitamin E [45], and the Heart Outcomes Prevention Evaluation – The Ongoing Outcomes trial (HOPE-TOO), which gave men with or at risk for cardiovascular disease 400 IU/day of supplemental vitamin E [46]. In the Cancer Prevention Study II Nutrition Cohort by Rodriguez *et al.*, while the use of supplemental vitamin E was not associated with overall risk of prostate cancer or advanced prostate cancer, there was a suggestion of slightly reduced risk among smokers [47]. This observation was also noticed by Kirsch *et al.* in an analysis of the PLCO Cancer Screening Trial who likewise found a decreased risk of advanced prostate cancer among current and recent smokers who took higher doses of vitamin E (RR: 0.29 for >400 IU/day) [48].

Vitamin E toxicity may manifest as blurred vision, diarrhea, flu-like symptoms, dizziness, headache and nausea. The conflicting data on vitamin E and prostate cancer risk reduction may result from the varying forms of vitamin E being studied and confounding factors such as smoking. Selenium potentiates the antioxidant activity of vitamin E. The aforementioned SELECT trial, in which men are randomized to selenium and/or vitamin E versus placebo, will provide more information regarding the potential benefits of vitamin E supplementation.

Soy

Phytoestrogens (flavones, isoflavones and lignans) are naturally occurring plant compounds that have estrogen-like activity. Genistein and daidzein, the predominant isoflavones in human nutrition, are derived mainly from soybeans and other legumes.

Isoflavones have also been shown to influence the production, metabolism and excretion of testosterone and estrogens, hormones that can play important roles in the development and

spread of prostate cancer [49]. Soy intake may be associated with endogenous hormone levels in Japanese men [50]. According to one meta-analysis published in 2005, soy food intake is associated with a lower risk of prostate cancer (OR: 0.70) [51]. In a study of 59 countries, soy products were found to be significantly protective ($p = 0.0001$) with an effect size per kilocalorie at least four times greater than that of any other dietary factor [52].

More soy products are consumed in Asian countries than in Western countries and this dietary difference may contribute to the differences observed in prostate cancer incidence. Multiple studies have been performed in China and Japan that support an association between soy intake and prostate cancer risk reduction. In a case-control study performed in China, 133 cases and 265 matched controls found a reduced risk of prostate cancer with consumption of soy foods (OR: 0.51) and isoflavones (genistein; OR: 0.53) [52]. Ozasa *et al.* performed a nested case-control study of Japanese men in which serum concentrations of phytoestrogens and sex hormones were measured [53]. Serum genistein, daidzein and equol were associated with prostate cancer risk reduction (OR: 0.38, 0.41 and 0.34, respectively). Kurahashi *et al.* recently conducted a population-based prospective study of 43,509 Japanese men, 307 of whom subsequently developed prostate cancer [54]. According to initial questionnaires, intake of genistein, daidzein, miso soup and soy food were not associated with total prostate cancer, although they were associated with decreased risk of localized prostate cancer. Moreover, isoflavones were associated with decreased risk of advanced prostate cancer, especially in men aged over 60 years (RR: 0.52). These results were supported by another Japanese case-control study by Nagata *et al.* involving 200 Japanese men and 200 matched controls that found isoflavones and their aglycones, genistein and daidzein, were significantly associated with decreased risk of prostate cancer (OR for ≥ 89.9 mg/day: 0.42; $p < 0.01$) [55].

Heald *et al.* performed a population-based case-control study in Scottish men and found significant associations between serum concentrations of enterolactone (OR: .40) and soy foods (OR: 0.52) and prostate cancer risk, although no significant associations were found for isoflavone intake or serum genistein, daidzein and equol [56].

The majority of studies support a benefit of soy products; a few studies do not show a benefit, including a study of 5855 Japanese–American men who were followed for over 20 years [57].

No toxicities of soy isoflavones have been identified. Instead, soy isoflavones have been shown to have various other beneficial effects, including an ability to lower serum lipid levels, reduce the risk of coronary heart disease and strengthen bones in persons with osteoporosis [58–60]. The US FDA has authorized claims that 25 g/day of soy protein, in addition to a diet low in saturated fat and cholesterol, may reduce the risk of coronary heart disease. The data on soy and prostate cancer is mostly supportive of an association with risk reduction. Further studies into the specific components of soy isoflavones and phytoestrogens, such as genistein, are being pursued. Given the current lack of any identified toxicities, physicians may wish to provide a balanced discussion of the potential benefits of increased soy intake with their patients.

Vitamin D

Vitamin D is a fat-soluble vitamin. The two major forms of vitamin D are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). The sun's ultraviolet rays convert 7-dehydroergosterol into vitamin D3 in the skin. Vitamin D3 is hydroxylated to 25-hydroxycholecalciferol in the liver and then undergoes hydroxylation to form 1,25-dihydroxycholecalciferol (calcitriol) in the kidney. Calcitriol is the most active form of vitamin D.

A couple of studies support that 25(OH)-vitamin D levels are associated with prostate cancer risk. In a nested case-control study by Ahonen of 19,000 men, 149 of whom developed prostate cancer, prostate cancer risk was inversely related to serum 25-hydroxyvitamin D levels [61]. In a longitudinal nested case-control study by Tuohimaa, the serum 25(OH)-vitamin D levels of 622 prostate cancer cases and 1451 matched controls found that low (<19 nmol/l) and high (>80 nmol/l) levels are associated with higher prostate cancer risk [62]. They conjectured that high vitamin D levels may lead to vitamin D resistance through increased inactivation by enhanced expression of 24-hydroxylase and thus recommended that vitamin D deficiency be supplemented but not to extreme vitamin D serum levels.

Several studies suggest that vitamin D does not decrease prostate cancer risk. Kristal *et al.* measured energy, fat, vitamin D and calcium intake via questionnaires that were obtained over a 3–5-year period and were not able to find an association between vitamin D and a lower prostate cancer risk [63]. Other studies fail to show a link between serum vitamin D levels and prostate cancer risk. Corder performed a study involving stored sera and measured 25-D levels in 90 black and 91 white men who were subsequently diagnosed with prostate cancer [64]. While the mean serum 1,25-D was 1.81 pg/ml lower in prostate cancer cases than in matched controls ($p = 0.002$), the risk of prostate cancer was not significantly different in prostate cancer cases and controls. Other studies included a nested case-control study by Gann *et al.* of the Physician's Health Study [65], a nested case-control study by Nomura *et al.* of Japanese–American men from Hawaii [66], a study by Platz *et al.* of men from the HPFS [67], and a recent small study from the National Prevention of Cancer Trial [68].

Vitamin D deficiency can lead to bone and tooth disorders, rickets and osteomalacia. Vitamin D toxicity can present with dehydration, nausea, vomiting, anorexia, headache, weakness, constipation, hypercalcemia, kidney stones and arterial calcium deposits. It is generally recommended to avoid doses greater than 1000 IU daily. The conflicting data regarding vitamin D and prostate cancer risk may be related to the form of vitamin D that is being studied and to calcium intake, which in multiple studies has been shown to increase a man's risk of prostate cancer. Physicians may wish to provide a balanced perspective of vitamin D to their patients.

Green tea

Green tea has been used as a beverage and medicine for hundreds of years. Green tea protects cells and tissues from oxidative damage. Its antioxidant activity comes from polyphenols (catechin). One component of green tea that has gained interest in the media and public is epigallocatechin gallate (EGCG).

Several studies have shown that green tea consumption is associated with a decreased risk of prostate cancer. In a case-control study performed in Canada, 617 cases of prostate cancer and 637 matched controls were interviewed for beverage intake history [69]. A decrease in risk was observed with tea intake exceeding 500 g/day (OR: 0.70). In another study performed in China of 130 cases of prostate cancer and 274 controls, tea drinking was strongly associated with decreased risk of prostate cancer (OR: 0.28) [70]. In a recent double-blind, placebo-controlled study by Bettuzzi *et al.* involving men with high-grade prostate intraepithelial neoplasia and thus at high risk for developing prostate cancer, 60 volunteers were randomized to green tea catechin (GTC) pills or placebo [71]. After 1 year, only one tumor was diagnosed in the GTC-arm while nine cancers were diagnosed in the placebo arm.

Other studies have shown that tea consumption is not associated with a decreased risk of prostate cancer, including a Canadian retrospective cohort study [72], and a study of 362 prostate cancer cases and 685 matched controls performed in Utah [73].

While considered relatively nontoxic, green tea may affect platelet aggregation. The caffeine in green tea may cause gastric irritability, insomnia and tachycardia. Green tea has other beneficial effects. It may provide protection from cardiovascular disease by reducing LDL cholesterol and triglyceride levels while raising HDL cholesterol, and inhibiting thromboxane formation thereby blocking platelet aggregation. Green tea may also enhance immunity. Based on the aforementioned studies that show a positive correlation between green tea and prostate cancer risk reduction, physicians may wish to initiate a conversation with patients who do not have bleeding or hemostasis disorders regarding the potential benefits of green tea or products containing catechins such as EGCG.

Conclusion

Chemoprevention is the use of products to delay, reverse or prevent the development and/or progression of a malignancy. Prostate cancer represents an ideal malignancy for the use of chemoprevention owing to its high prevalence and relatively slow rate of progression. An ideal chemopreventative agent would be nontoxic, affordable and effective.

There are data to support the consideration of several natural products for the risk reduction of prostate cancer. Lycopene, a carotenoid found in tomatoes, is a product with relatively few reported side effects that physicians may wish to discuss with their patients. Selenium, an essential trace mineral, and vitamin E may work in conjunction to lower a person's risk for prostate cancer. Soy isoflavones such as genistein and EGCG found in green tea may account for the lower rate of prostate cancer in Asian countries. Vitamin D may also be considered as a potential chemopreventative agent.

Some of the data are conflicting. In general, this may be due to the manner in which some of the studies were conducted. Some studies involved dietary questionnaires that have obvious limitations in reliability and are subject to recall bias. Other studies involved serum and nail measurements, which may not accurately reflect a patient's chronic levels of a certain dietary product. Some of the discrepancies noted may reflect the confounding effects of other dietary products or differences in the ethnic populations being studied.

Further investigations into the potential mechanisms of action of these products are warranted. These agents may work to decrease prostate cancer risk by altering hormonal levels or by reducing inflammation, both of which have been identified as playing key roles in the development and promotion of prostate cancer. The next goal beyond simply identifying natural dietary products that reduce prostate cancer risk is to identify biologically plausible mechanisms that account for risk reduction. We anticipate the continued pursuit of high-quality prospective trials with tissue studies or molecular correlates so that future physicians can recommend preventative measures with more confidence.

Expert commentary

The data regarding natural products and their relationships to prostate cancer risk reduction are widely heterogeneous. Future studies should preferably seek to be prospective, randomized and to encompass a greater sample size and patient population.

Five-year view

We predict the discovery of other natural dietary products that affect the risk of prostate cancer development. We predict, via molecular and tissue studies, a greater understanding of how the aforementioned natural products work in delaying and abrogating prostate cancer development. With this understanding, new and more effective dietary compound supplements will be developed that may then be tested in prospective, placebo-controlled, double-blinded trials.

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Key issues

- Prostate cancer is the most commonly diagnosed malignancy in males and an ideal target for preventative measures.
- Lycopene is a carotenoid found in tomatoes that has been associated with prostate cancer risk reduction.
- Selenium, an essential trace mineral, and vitamin E may, jointly or separately, be able to reduce prostate cancer risk.
- Genistein and other isoflavones in soy, and epigallocatechin gallate in green tea may account for the lower incidence of prostate cancer in Asian countries.
- Vitamin D has the potential to reduce prostate cancer risk.
- The future lies in designing randomized controlled studies that not only identify natural products which may reduce prostate cancer risk but elucidate the molecular and biological mechanisms responsible for risk reduction.

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