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Overview of Dietary Supplements in Prostate Cancer

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Abstract Prostate cancer is a key health concern for men with its etiology still under investigation. Recently, the role of dietary supplements has been noted to have a major inhibitory effect on prostate cancer and numerous studies have been conducted in this regard. This review provides a summary on numerous recent studies conducted in this field. Some of the studies reviewed revealed a protective role for supplements, and others showed no correlation while some even had an adverse effect. The mechanism of how these supplements act on the prostate is still not clear. Further studies are warranted especially for supplements that have been shown to have a potential inhibitory role in prostate cancer.

Keywords Prostate cancer · Men's health · Dietary supplements

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Introduction

Prostate cancer is the most common cancer in American men other than skin cancer. It is also the second leading cause of death from cancer in American men after lung cancer. The American Cancer Society estimates that there were about 220,800 new cases and 27,540 deaths from prostate cancer in the USA in 2015. About one in seven men will be diagnosed with prostate cancer during their lifetime, and about one in 38 will die from prostate cancer complications [1]. Numerous clinical trials have been conducted with respect to vitamins, other dietary elements, and their potential role in prostate cancer prevention and control. Furthermore, many epidemiologic studies have shown that vitamin and supplement use is common among patients diagnosed with prostate cancer [2–4]. With the knowledge that many prostate cancers follow an extended indolent course, and the emergence of active surveillance as an attractive treatment option for many patients, prostate cancer represents a good scenario to investigate the effects of vitamins and other elements on tumor progression. Nevertheless, despite the available data, epidemiologic evidence on nutrition and its effects on prostate cancer remain controversial.

Vitamin D

Vitamin D is a fat-soluble vitamin. In addition to dietary sources, the human body produces it through sun exposure. Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemia. It modulates cell growth, neuromuscular and immune function as well as playing a role in reducing inflammation. It also modulates gene encoding proteins needed for cell proliferation, differentiation, and apoptosis. The Recommended Dietary Allowances (RDAs) for vitamin D is 15 mcg for both males and females aged 19–50 years [5].

Prostate cells express the vitamin D receptor, and a number of studies have suggested that vitamin D may exert its effect on prostate cancer cells via several different pathways [6••]. With current treatment standards shifting to managing patients with prostate cancer with a surveillance protocol, the association between prostate cancer aggressiveness and vitamin D merits further investigation [7].

Several studies have been conducted on vitamin D and its potential role in prostate cancer management. A clinical trial was undertaken to determine if vitamin D supplementation at 4000 IU/day for a year was safe in 52 patients and whether it would result in a decline in serum levels of prostate-specific antigen (PSA) or in the rate of progression. PSA serum levels were measured at start and every 2 months until 1 year. Biopsies were performed prior to entry for eligibility purposes and after 1 year of supplementation. There were no significant changes in PSA levels, but 55 % of patients showed a decrease in the number of positive cores or in Gleason score; 11 % showed no change; and 34 % showed an increase in the number of positive cores or in Gleason score on repeat biopsy. The study showed that such a treatment might reduce the chances of overtreatment for patients with low-risk prostate cancer [8]. However, it must be said that the randomness of prostate biopsies certainly makes these results difficult to interpret.

Another prospective case–control study nested within the Health Professionals Follow-up Study was conducted on 1260 men diagnosed with prostate cancer excluding T1a tumors and 1331 controls. There were 114 lethal cases with distant metastases at diagnosis or progression to bone and/or organ metastases or prostate cancer-specific death during follow-up. Although higher vitamin D levels were associated with a 57 % reduction in the risk of developing lethal prostate cancer, there was no statistically significant association between plasma vitamin D levels and the overall risk of prostate cancer [9].

A cross-sectional study nested within another epidemiological study including 1760 controls and men undergoing screening for prostate cancer examined the relationship between pathology at the time of radical prostatectomy and serum vitamin D levels. Among 190 men who underwent radical prostatectomy in the cohort, 45.8 % (87/190) had adverse pathology at radical prostatectomy. The univariate analysis showed that men with adverse pathology at radical prostatectomy had lower median serum vitamin D compared with their counterparts. The multivariate analysis also showed that serum vitamin D less than 30 ng/mL was associated with increased odds of adverse pathology while controlling for other factors such as age, serum PSA, and abnormal digital rectal examination [7].

In a case-cohort design nested within the Selenium and Vitamin E Cancer Prevention Trial (SELECT), neither unadjusted nor month-adjusted vitamin D concentrations were associated with total, Gleason 2–6, or Gleason 7–10 cancer. There was a 59 % ($P = 0.013$) reduction in risk for Gleason 8–10 cancer among men classified as "adequate" in vitamin D when plasma concentrations were not adjusted for month of blood sampling. When categorizing monthly adjusted vitamin D into quintiles based on the distribution in the sub-cohort, there were U-shaped associations of vitamin D with risks of total and Gleason 2–6, 7–10, and 8–10 cancers. This U-shaped association was strong for Gleason 7–10 and 8–10 cancers. Findings were similar among non-African Americans. There was a significant decrease in risk of Gleason 7–10 cancer at concentrations above 50 nmol/L [10, 11].

A nested case–control analysis of 1695 cases and 1682 controls from the Prostate Cancer Prevention Trial (PCPT) was done. There was no association between serum vitamin D levels and total prostate cancer risk. For Gleason 2–6 cancers, results were varying across treatment arms which suggest that the placebo group may have increased risk only but without any dose–response relationship between the placebo or treatment arms. For Gleason 8–10 prostate cancers, vitamin D concentrations were associated with a linear reduction in risk among joined treatment arms. These findings were somewhat stronger among men aged 65 years or older vs. those aged 55–64 years at baseline. There were no significant differences in associations of vitamin D with total or Gleason 8–10 cancer risk between normal weight, overweight, and obese men [12, 13].

Data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was obtained during 20 years of follow-up with 1000 cases and 1000 controls aged 50–69 years. Cases had non-significantly higher vitamin D levels. In this study, prostate cancer risk increased with higher vitamin D concentrations irrespective of the categorization and modeling approach used to adjust for date/season of blood collection. There was no modification of the serum vitamin D-prostate cancer association even when accounting for several elements like age, smoking intensity or duration, BMI, family history of prostate cancer, history of diabetes, serum HDL cholesterol or beta-carotene, the trial beta-carotene supplementation, alcohol consumption, or selenium intake [14•].

Vitamin A

Vitamin A is a group of fat-soluble retinoids that includes retinol, retinal, and retinyl esters. It is involved in immune function, vision, reproduction, cellular communication as well as cell growth and differentiation. The RDA for vitamin A for females is 700 mcg and for males 500 mcg [5].

Data analyzed from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study over a 20-year period showed that men in the highest quintile of baseline serum retinol were significantly more likely to develop prostate cancer during the follow-up period than were men in the lowest quintile. The relationship was found to be dose-dependent. Men in the highest quintile (fifth quintile) at both time points had the greatest increase in risk of prostate cancer vs. those in the first quintile [15, 16].

On the other hand, in a nested case–control study that included men who were randomized to the screening arm of the PLCO trial (692 cases and 844 controls), multivariate analyses comparing men in the highest vs. lowest quintiles revealed that serum retinol was associated with 20 % reduction in risk of prostate cancer with no significance and no indication of a linear trend. In cases of aggressive prostate cancers (Gleason score ≥7 or clinical stage III or IV), high concentrations of serum retinol were associated with a significant reduction in risk of prostate cancer [17].

Vitamin C

Vitamin C, also known as L-ascorbic acid, is involved in the biosynthesis of collagen, L-carnitine, in neurotransmitters, and protein metabolism. It is an antioxidant, which is able to regenerate other antioxidants within the body, including vitamin E. The RDA is 90 mg for males and 75 mg for females aged 19 years and above [5].

In a Danish prospective cohort study of 26,856 men aged 50–64 years followed up for 7 years, there were no associations between prostate cancer risk and dietary or supplemental vitamin C [18]. The Physicians' Health Study II is a randomized, double-blind, placebo-controlled factorial trial among 14,641 male physicians aged 50 years or older followed up for 10 years. There was no effect of vitamin C on prostate cancer (HR = 1.02; 95 % CI = 0.90–1.15; $P = 0.80$) [19]. A case–control study on prostate cancer was conducted between 1991 and 2002 in Italy with 1294 cases and 1451 controls. There was a non-significant but inverse relationship between prostate cancer risk and vitamin C [20].

Vitamin E

Vitamin E occurs in eight different forms: four tocopherols (alpha-, beta-, gamma-, and sigma-) and four tocotrienols (alpha-, beta-, gamma-, and sigma-). The alpha-tocopherol is the form of vitamin E that is commonly found in dietary supplements. It is the most abundant in the body and the most biologically active. Many studies have shown that alpha-tocopherol has been shown to possess an anticancer effect [21]. The RDA for vitamin E for both males and females above the age of 14 is 15 mg daily [5].

The NIH-AARP Diet and Health Study was conducted among 295,344 men for a year. There was no association between vitamin E supplements and prostate cancer risk. Higher intake of alpha-tocopherol was associated with significant reduction in the risk of advanced prostate cancer in a dose-dependent manner, especially among men with low selenium consumption. There was a reduction in the risk of advanced prostate cancer observed with high intakes of gamma-tocopherol, but this reduction did not reach statistical significance [22].

A case–control study on prostate cancer was conducted in Italy with 1294 cases and 1451 controls. Vitamin E intake was inversely related to prostate cancer [20]. In the same Danish prospective cohort study of 26,856 men aged 50–64 years followed up for 7 years mentioned before, no associations were found between prostate cancer risk and dietary or supplemental vitamin E [18]. The ATBC study showed that alpha-tocopherol decreased prostate cancer incidence by 32 % and mortality by 41 % during the 8-year study period. Among men receiving alpha-tocopherol, the cumulative incidence of prostate cancer decreased gradually from the second year in relation to those who did not receive alpha-tocopherol with a 32 % difference [23].

The Vitamins and Lifestyle (VITAL) prospective study of 35,342 men showed a trend toward statistical significance of vitamin E supplementation of ≥400 IU/day in decreasing risk of advanced prostate cancer [24]. The Cancer Prevention Study II Nutrition Cohort was conducted among 72,704 men. There was no association between prostate cancer and vitamin E [25].

Lycopene

Lycopene is a naturally occurring chemical of carotenoids that gives fruits and vegetables a red color. It is found in tomatoes and tomato products and is a powerful antioxidant that can protect cells from damage. Lycopene has the ability to stop androgen receptor expression in prostate cancer cells, decrease prostate cancer cell proliferation, and modify cell-cycle progression [6••].

A nested case–control study was done among 1683 cases and 1751 controls in the Prostate Cancer Prevention Trial (PCPT). Diagnosis of prostate cancer and pre-diagnostic serum lycopene concentration were not associated with the risk of total, low-grade, or high-grade cancer or within strata defined by age, race, BMI, or family history of prostate cancer [26]. A nested case–control from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial among 29,361 men was conducted for 4.2 years. There was no association between lycopene and prostate cancer [27]. The Health Professionals Follow-up Study (HPFS) was conducted among 49,898 male health professionals. Higher lycopene intake was inversely associated with total prostate cancer and more strongly with lethal prostate cancer (top vs. bottom quintile: HR = 0.72; 95 % CI = 0.56–0.94; $P = 0.04$) [28].

Pomegranate

The pomegranate (*Punica granatum* L.) is native to Asia and cultivated widely throughout the world. Pomegranate possesses numerous active chemical compounds like flavonoids, tannins, and anthocyanidins [29].

An 18-month, multi-center, randomized, double-blinded, two-dose trial among 80 patients was conducted. Median PSA doubling time in the intent-to-treat population extended from 11.9 months at baseline to 18.5 months after treatment ($P < 0.001$). PSA doubling time prolonged in the low-dose group from 11.9 to 18.8 months and 12.2 to 17.5 months in the high-dose group, but without any significance between the two groups ($P = 0.554$) [30]. Another phase II study evaluated two different doses of pomegranate extract (1 and 3 g) in 104 men with rising PSA values after therapy for localized prostate cancer. The extract was associated with an increase in PSA doubling time of at least 6 months in both treatment arms, without any adverse effects [31].

Selenium

Selenium is an essential trace mineral involved in different biological processes, including kinase regulation, gene expression, and immune function [6••].

A case–control study involved 248 incident cases and 492 controls nested within the EPIC-Heidelberg cohort followed for 10 years. Prostate cancer risk decreased significantly for those with higher blood selenium concentrations, especially high-grade prostate cancer, in the third quartile of serum selenium [32].

In the VITAL prospective study among 35,342 men, there was no association between selenium supplementation and prostate cancer risk [24]. A study was conducted from the Health Professionals Follow-up Study among 4459 men. Selenium supplement users had an increased risk of mortality from prostate cancer. In the multivariate analysis, men who consumed 1–24 μg/day, 25–139 μg/day, and 140 or more μg/day of supplemental selenium after diagnosis had a 1.18 greater risk, 1.33 greater risk, and 2.60-fold greater risk of prostate cancer mortality vs. nonusers. There was no statistically significant association between selenium supplementation after diagnosis and risk of biochemical recurrence [33].

SELECT was a phase III, randomized, placebo-controlled human trial among 35,533 men and had a planned follow-up time of 12 years. However, the trial was ended in 2008 ahead of time after 18 months of the study. The selenium and vitamin E doses and formulations used in SELECT were not found to be effective and a statistically nonsignificant increased risk of prostate cancer was seen in the vitamin E group participants. The authors added that there were some deficits in understanding of the mechanisms of vitamin E and selenium, which may account for the failure of the investigation [21].

Discussion

This review showed that a definitive relationship between the aforementioned dietary supplements and prostate cancer cannot be established since the studies demonstrated conflicting results.

Although confounders were taken into account in some studies (such as body mass index, race, smoking, physical activity, height, diabetes status, total energy intake, coffee intake, family history of prostate cancer, vasectomy status, red meat, and fish intake), many studies have shown that the association between dietary elements and prostate cancer risk may not be linear and that higher doses may even have adverse effects [9, 18, 33•]. This discrepancy in results may be due to several reasons. For example, the design of some studies, such as cross-sectional studies, may contribute to different results. Another factor may be the different types of biases that arose in the studies like selection bias, observer bias, and analytical bias [7]. It is also well known that study results cannot be easily extrapolated and applied to different populations due to differences in genetic variation, dietary intake, and prostate cancer risk [7, 9]. The use of one measurement method for nutrient concentration may not be illustrative of an individual's long-term status [12]. Another reason for bias is because of the inclusion of smokers only in certain studies [14•, 16]. Moreover, some studies did not have any information on family history of prostate cancer or Gleason score [18, 22]. Short time for follow-up could lead to the likelihood of having undiagnosed prostate cancers at baseline because of the slow tumor growth rate [22]. There are considerable differences in populations across these studies, and even variations in assay techniques could account for some of the differences in findings across studies [12].

Assessment of dietary consumption may also be inaccurate because of the difference in micronutrient content of foods with climate and storage [18]. For instance, measuring the bioavailability of lycopene may be inexact because its bioavailability differs in food sources. When lycopene is consumed through raw tomatoes, its absorption may be lower, and different food processing methods can actually improve the bioavailability of lycopene [28]. Approximating selenium intake by a food questionnaire is hindered by the large difference of selenium content in the same food [32]. Furthermore, the anticancer effects of selenium may hinge on the status of other antioxidants such as vitamin E, vitamin C, or β-carotene and this synergistic effect of supplements further complicates our attempts at reaching definitive conclusions on their protective role [32].

Conclusion

Due to conflicting data, no specific vitamin or mineral demonstrated a role in prostate cancer pathogenesis. The relationship between nutrition and prostate cancer risk remains controversial and remains inconclusive. There is little evidence to support the routine consumption of vitamins or antioxidants for the protection against prostate cancer. Further studies are necessary to better outline the mechanisms of action involved in prostate cancer and supplementation. More prospective cohort studies, experiments, and randomized trials are needed to entirely understand and further assess the exact role of dietary components in controlling prostate cancer. It is crucial to include a wide range of representative samples as several studies reviewed included either healthy men only or patients with early onset of prostate cancer or at advanced stage. In addition, biological explanations are simply lacking with respect to some vitamins and their inhibitory role in prostate cancer. It is also important to take the heterogeneity of the discussed findings into account such as the background diet of the population, random bias, and the type of study carried out. Elements to take into account when reaching conclusions on the benefit of various supplements include the relatively small sample sizes of some studies, restricted statistical power, retrospective study design, as well as recall and selection biases [20, 27, 34].

Consequently, while we believe that there may be a beneficial role for some vitamins in prostate cancer, it remains difficult to give a final assessment about all the mentioned vitamins and minerals.

Compliance with Ethical Standards

Conflict of Interest Aline Yacoubian, Rana Abu Dargham, Raja B. Khauli, and Bassel G. Bachir each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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