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Dietary Antioxidants and Prostate Cancer: A Review

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Abstract

Prostate cancer is the most common non-cutaneous cancer in men in the United States. Several studies have examined the relationship between prostate cancer and antioxidants; however, the results of these studies are inconsistent. This article provides a systematic review of studies on prostate cancer and antioxidant intake from diet and supplements. Tea and coffee appear to offer protection against advanced prostate cancer. Different forms of vitamin E appear to exert different effects on prostate cancer, with alpha-tocopherol potentially increasing and gamma-tocopherol potentially decreasing risk of the disease. There is no strong evidence for a beneficial effect of selenium, vitamin C, or beta-carotene, while lycopene appears to be negatively associated with risk of the disease. The effect of dietary antioxidants on prostate cancer remains undefined and inconclusive, with different antioxidants affecting prostate cancer risk differentially. Further studies are needed to clarify the relationship between antioxidants and prostate cancer risk and to delineate the underlying mechanisms.

Introduction

Prostate cancer is the leading non-cutaneous cancer in men in the U.S. Based on data from 2005 – 2007, 1 in 6 men in the U.S. may develop prostate cancer in their lifetime [1]. In 2011 prostate cancer accounted for approximately 29% of all cancer diagnoses and 11% of all cancer deaths in men[1]. The incidence of prostate cancer is increasing, mostly due to increased awareness and screening [2]. Current epidemiological evidence suggests an interaction among several risk factors in the development and progression of prostate cancer [3]. Several biological and environmental risk factors have been associated with prostate cancer including family history and genetic risk, lifestyle, socioeconomic status, inflammation, and diet [2, 4].

Many dietary components may play a role in the development and progression of prostate cancer [5]. Additionally, prostate cancer incidence and mortality have been shown to differ between countries and between men of different race or ethnicity [6–8], trends that may partly be explained by differences in dietary patterns [9]. Plant foods, especially fruits and vegetables, provide a multitude of antioxidants and phytochemicals which have a

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demonstrable beneficial effect on prostate cancer [9]. Several of these antioxidants may attenuate prostate cancer development, given that oxidative stress from reactive oxygen species and loss of antioxidant enzymes may contribute to genomic damage preceding prostate cancer [4].

This paper will review the relationship between antioxidants from diet and supplements and risk of prostate cancer.

Criteria for Article Selection

A literature search was performed using Pubmed with the medical subheadings *diet*, *antioxidants*, and *prostaticneoplasms* to search for human studies of prostate cancer risk and antioxidants from diet or supplements published until April, 2013. Studies examining only plasma levels of dietary antioxidants were excluded. The references of selected studies were reviewed to identify additional articles. Selected studies are detailed in Tables 1 and 2.

Antioxidants and Prostate Cancer

Several observational and intervention studies have investigated the effect of specific dietary antioxidants on prostate cancer incidence and progression (Tables 1 and 2). Supplementation with some of these antioxidants has been shown to decrease overall cancer risk, but these effects likely depend on baseline nutritional status [10]. The majority of human studies have focused on the carotenoids, specifically beta-carotene and lycopene, vitamins E and C, dietary sources of various phenolic substances (namely coffee and tea), and flavonoids. Generally, studies have yielded inconsistent results, with individual antioxidants having been shown to have positive, negative, or no association with prostate cancer risk.

Vitamin E

Vitamin E is found in a variety of foods, mostly in fruits, vegetables, nuts, and oils. The most abundant form of vitamin E in the U.S. diet is gamma-tocopherol; yet, alpha-tocopherol has been most studied as it is the biologically predominant form in humans and the most common form used in supplements.

The effect of dietary and supplemental vitamin E on prostate cancer risk in humans is less well understood. To date, four intervention [11–14], seven prospective [15–21], and five case control studies [22–26] have reported findings on vitamin E and prostate cancer (Tables 1 and 2). The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), found that alpha-tocopherol supplementation decreased risk of and mortality from prostate cancer [14];however, this effect was later found to be attenuated [19]. A beneficial effect of vitamin E was also observed in one prospective study [20], in which the effect was limited togamma-tocopherol, and three case control studies [22–24], whereas fourintervention studies [12–13], six prospective studies [15–19, 21], and two case control studies [25–26]found no effect.

Recently, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found that prostate cancer incidence was increased in men receiving only the vitamin E supplement [11]. Interestingly, incidence was not increased in men receiving both vitamin E and selenium, suggesting that these two nutrients may interact in some way that affects prostate cancer risk. The effect of vitamin E may depend on baseline levels of oxidative stress, as a decreased risk of prostate cancer has been reported with increasing dose and duration of vitamin E supplementation in current and recent smokers [21]. Although some of the evidence regarding vitamin E and prostate cancer is inconsistent, the majority of studies suggest vitamin E does not reduce prostate cancer risk. Many studies on dietary vitamin E

may be limited by data on the vitamin E content of foods, underreporting of dietary fat, and difficulty in measuring specific types of fats or oils in the diet, since dietary fat is a major source of vitamin E [27].

Vitamin E may increase the risk of prostate cancer. However, most studies have focused specifically on vitamin E in the form of alpha-tocopherol; two studies measuring gamma-tocopherol [15, 20]showed an inverse association with prostate cancer risk. Gamma-tocopherol has been shown to inhibit the proliferation of LNCaP and PC-3 prostate cancer cells by interfering with de novo synthesis of sphingolipids, while having no effect on normal prostate epithelial cells [28]. Recently, gamma-tocopherol has been shown to prevent hypermethylation of CpG sequences in the Nrf2 promoter region in the transgenic adenocarcinoma of the mouse prostate model [29], potentially contributing to protection against oxidative stress and prevention of prostate tumorigenesis. Taken together, this evidence suggests that not all forms of vitamin E are equal with regard to prostate cancer, and that alpha-tocopherol may actually be harmful.

Selenium

Selenium is an essential trace element that is part of at least 25 different selenoproteins, such as glutathione peroxidase, an antioxidant enzyme that neutralizes free radicals. Selenium has been investigated as a potential anticarcinogenic agent since 1949 [30], and estimated intake of dietary selenium has been correlated with mortality from several cancers [31]. Selenium supplementation, in combination with other antioxidant nutrients, has been shown to reduce the risk of various types of cancer [10].

Regarding prostate cancer and selenium, there have been fourintervention studies [11, 32–34], one prospective study [15], and one case control study [35](Tables 1 and 2). In the Nutritional Prevention of Cancer (NPC) Study by Clark et al, men receiving supplemental selenium in the form of high-selenium yeast, had a reduced incidence of prostate cancer (RR 0.37, 95% CI, 0.18–0.71; p=0.002) [36]. Follow-up from this study showed that men receiving supplemental selenium had lower incidence of localized and advanced prostate cancer [37] with the association between selenium supplementation and incidence of prostate cancer persisting to the end of blinding (HR 0.48, 95% CI 0.28–0.80) [32]. However, the protective effect of selenium on prostate cancer was restricted to men with the lowest plasma selenium concentration at baseline, which indicates potential confounding due to selenium deficiency. Additionally, in the NPC study prostate cancer was not a primary endpoint, and men in the treatment and control arms of the study did not have an equal opportunity to be diagnosed with prostate cancer; this, considering the few cases of prostate cancer, means the findings might have been due to chance.

Other studies found no effect of selenium supplementation on prostate cancer incidence [11, 15, 33–35]. One could argue that the form of selenium used might account for these null results. Marshall et al and SELECT used L-selenomethionine whereas the NPC study used high-selenium brewer’s yeast, which might contain over twenty different forms of selenium in addition to L-selenomethionine [30]. However, this is unlikely given the contribution of baseline selenium status to the findings of the NPC study, and the absence of an effect observed byAlgotar et al. [34].

The discordance between the intervention studies [11, 32–33] could be in part due to differences in geographic regions, as the major sources of selenium in the diet are seafood, cereals, and meat, of which the selenium content of cereals and meat varies geographically [31]. Observational studies using other markers of selenium status, such as blood levels, suggest a beneficial effect of selenium on risk of prostate cancer [38].

Available evidence from intervention and observational studies is limited and conflicting with regards to selenium and prostate cancer. While observational studies have not found any association between selenium and prostate cancer risk, this may be in part due to the difficulty in assessing dietary selenium [38].

Vitamin C

Vitamin C is an antioxidant abundant in fruits and vegetables. Vitamin C prevents oxidative damage to cells by scavenging free radicals, recycles vitamin E (alpha-tocopherol), and inhibits the growth and viability of prostate cancer cells [9]. Epidemiological research has shown vitamin C to protect against many types cancer [39]. However, only one intervention [13], two prospective [18, 21], and three case control [23–24, 26] studies of dietary or supplemental vitamin C and prostate cancer have been reported (Tables 1 and 2). Of these, two case control studies [23, 26] reported reduced prostate cancer risk associated with vitamin C intake, while other studies reported no association. The study by McCann et al [26] found that the effect of vitamin C was attenuated after adjusting for total vegetable intake, while the other study made no such adjustments. Thus it seems likely that vitamin C does not influence prostate cancer risk, but rather mayindicate vegetable intake.

Carotenoids

Dietary carotenoids are supplied almost exclusively from fruits and vegetables. Carotenoids function as potent antioxidants and have also been shown to influence cell growth and induce apoptosis; some carotenoids serve as vitamin A precursors [9]. The carotenoids most studied in relation to prostate cancer are beta-carotene and lycopene.

There have been several studies on beta-carotene on prostate cancer (Table 1 and 2). Of these, two were intervention studies, one found no effect of beta-carotene on prostate cancer [40], while the other, the ATBC study, found that beta-carotene supplementation resulted in a 23% increase in incidence of and 15% increase in mortality from prostate cancer [14]. However, no effect of beta-carotene was observed in the post-intervention follow-up [19]. Considering that prostate cancer incidence and mortality were not the primary endpoints of the ATBC, and that other studies do not report a detrimental effect due to beta-carotene, these findings may be due to chance. One prospective study [21] and three case control studies [26, 41–42] found a protectiveeffect of beta-carotene, while six other case control studies and one prospective study found no effect [18–19, 23, 25, 35, 43–45].

Two prospective studies of lycopene and risk of prostate cancer have been reported [46–47]. In a study of men from the Health Professionals' Follow Up Study, Giovannucci et al found lycopene intake to be significantly associated with a decreased risk of prostate cancer (RR 0.84; 95% CI, 0.73–0.96; p(trend)=0.003) [47]. Similarly, Kirsh et al found that increased intake of lycopene was associated with a decreased risk of prostate cancer, but only in men with a family history of the disease [46]. Five case control studies of lycopene and prostate cancer have been conducted; of these, one reported a beneficial effect of lycopene [26] and four reported no effect [18, 23, 25, 44]. In the case-control study by McCann et al, high intakes of lycopene were associated with a decreased risk of prostate cancer (OR 0.62; 95% CI, 0.42–0.92) [26].

In a few studies, other carotenoids have been associated with prostate cancer risk. McCann et al found that high intakes of alpha-carotene (OR 0.67; 95% CI, 0.47–0.97) and lutein (OR 0.55; 95% CI, 0.37–0.81)was associated with a decreased risk of prostate cancer [26]. However, associations between prostate cancer risk and individual carotenoids were attenuated after controlling for vegetable intake. Schuurman et al showed that beta-

cryptoxanthinwas positively associated with prostate cancer risk, while other carotenoids were not associated with risk [18].

The studies cited above on carotenoids and prostate cancer provide inconclusive evidence. Randomized trials of beta-carotene do not clearly demonstrate any beneficial effect on prostate cancer. Prospective studies indicate a potentially beneficial effect of carotenoids, particularly lycopene, on prostate cancer risk. Several clinical trials have shown interesting results, particularly with lycopene [48–50], but these studies are of small sample size and relatively brief in duration.

Polyphenols from Tea and Coffee

A multitude of phytochemicals and phenolic substances are found in fruits, vegetables, and plant-derived beverages, such as tea and coffee. Several of these substances remain unidentified, but numerous polyphenols, such as (−)-epigallocatechin-3-gallate (EGCG), have been shown to have antitumor effects. While these chemicals exert antioxidant effects, they may also affect cancer by influencing cell signaling pathways [9]. Studies of dietary polyphenols and prostate cancer are limited to studies of green tea, coffee, and flavonoids. (Tables 1 and 2).

There have been three studies which have examined the relationship between green tea and prostate cancer: one intervention [51], one prospective [52], and one case control study [53]. Bettuzzi et al found that after one year of supplementation with green tea catechins, prostate cancer was significantly less prevalent compared to controls (3.3% vs 30%, $p<0.01$) [51]. In a follow-up to this study, men in the treatment group were found to have a significantly lower incidence of prostate cancer compared to those in the control group [54]. Similarly, both the prospective study [52] and the case control study [53]found a beneficial effect of drinking green tea on prostate cancer risk, with the prospective study finding a reduced risk of advanced prostate cancer [52].

In a multisite case-control study, Jain et al found that a decreased risk of prostate cancer was associated with tea consumption greater than 2 cups per day (OR 0.70, 95% CI, 0.50 – 0.99), while no association was observed between prostate cancer risk and coffee consumption [55]. In two other case control studies [56–57] and three prospective studies [58–60], no association was found between coffee or tea consumption and risk of prostate cancer.

In a case-control study by Bosetti et al [61], dietary flavonoids were not associated with prostate cancer risk. In one case-control study, quercetin was found to be significantly associated with a decreased risk of prostate cancer (OR 0.64; 95% CI, 0.42–0.92), although this association did not remain after controlling for total vegetable intake [26]. Currently, evidence regarding prostate cancer and non-nutrient polyphenols is limited, with only a few studies showing a potential benefit.

Some recent observational studies have examined the relationship between coffee consumption and risk of prostate cancer [62–64]. In an analysis of the Health Professionals Follow-up Study, coffee consumption was found to be inversely associated with lethal, but not non-advanced or low grade prostate cancer, and men who drank six or more cups of coffee per day had a lower risk of overall prostate cancer (RR 0.40, 95% CI 0.22 to 0.75) [62]. Similarly, in a prospective cohort study from the UK [63], coffee drinking was found to be inversely associated with risk of high grade prostate cancer (HR 0.45, 95% CI, 0.23–0.90; p(trend)=0.01), but not overall risk of the disease. However, a population-based case study showed no association between coffee consumption and aggressive prostate cancer [64]. The above prospective studies are limited given that dietary data was based on self report, while the population-based case study captured a relatively shorter time frame of

dietary habits. As with other dietary antioxidants, the studies on sources of polyphenolshave shown inconsistent results; whereas only a few studies have shown a reduced risk of prostate cancer associated with consumption of green tea or coffee, others have not shown such a relationship. One reason for this inconsistency is that many studies did not have an adequate sample size to determine the effect of tea or coffee consumption on advanced prostate cancer. Thus it seems that while tea and coffee consumption may not have an effect on risk of localized prostate cancer, they may confer protection from advanced disease.

Combination Studies

Three large intervention studies have been conducted using combinations of antioxidants [65–67]. The design of these studies does not permit ascribing the observed effects to any one particular antioxidant and as such these studies are presented separately from intervention studies on the effects of single antioxidants. The largest of these studies, the SU.VI.MAX trial, found that a daily antioxidant and micronutrient supplement had a differential effect on prostate cancer rates; a reduced rate of prostate cancer was found in men with normal PSA (<3.0ng/ml) at baseline, while an increased rate of prostate cancer was found in men with an elevated PSA (≥3.0 ng/ml) at baseline [65]. The increased rates observed in men with elevated PSA at baseline may have been due to the presence of undiagnosed malignancies. The other two studies did not find any effect of antioxidant supplementation on prostate cancer risk [66–67]. However, a limitation of these studies is that they administered supplements composed of multiple antioxidants and nutrients, for this reason there is no way to determine the effects or possible interactions of individual components.

Conclusions

From the studies discussed, it is clear that the effect of dietary antioxidants on prostate cancer remains undefined and inconclusive. However, although studies on antioxidants and prostate cancer have been inconsistent, there is evidencethat some dietary antioxidants may influence prostate cancer risk. Different forms of vitamin E appear to exert different effects on prostate cancer, with alpha-tocopherol potentially increasing and gamma-tocopherol potentially decreasing risk. There is no strong evidence for any beneficial effect of selenium, vitamin C, or beta-carotene, regarding prostate cancer, while lycopene appears to be beneficial.

Studies on diet and disease are problematic due to:1) error in measuring nutrient intake, 2) the associations between many nutrients in foods, and 3)the possibility that the population being studied may have little variation in intake of certain nutrients [39]. Measuring the association between diet and prostate cancer is further complicated, as the relevant exposure time for which dietary factors affect prostate cancer development is unknown. Additionally, the definition of a case of prostate cancer has changed over recent decades as screening practices have changed, which means that the results of some older studies may not be comparable to results of more recent ones, as the populations in question are likely different. These factors may account for some of the conflicting results between observational studies.

Few studies have been conducted on individual antioxidants and only a small fraction of dietary antioxidants have been studied. A recent meta-analysis of a few randomized trials failed to show any effect of antioxidant vitamins and beta-carotene on prostate cancer incidence or mortality [68].

It has been shown that prostate cancer patients have low levels of antioxidants in blood [69] and increased markers of lipid peroxidation [70–71]. This may reflect either increased oxidative stress in patients with prostate cancer leading to depletion of antioxidants or low

levels of antioxidants leading to increased oxidative stress and lipid peroxidation. Dietary antioxidants in plasma may influence prostate cancer risk by interacting with inflammatory genes [72] and influencing repair of oxidative DNA damage [73]. The effects of dietary antioxidants on prostate cancer risk and mortality may in part depend on the genotype of antioxidant enzymes, such as superoxide dismutase [74]. In addition to interactions between dietary antioxidants and genes, there may be interactions between different dietary antioxidants which could modify prostate cancer risk [75]. There is also evidence that antioxidants, particularly polyphenols, may influence prostate cancer through both antioxidant and non-antioxidant mechanisms [9, 76].

The effect of dietary antioxidants on prostate cancer remains undefined and inconclusive, with different antioxidants affecting prostate cancer risk differentially. Of the intervention studies reviewed, 7 studies reported no effect, 1 study reported an increased risk, 2 found a decreased risk, and 2 studies reported both an increased and decreased risk of prostate cancer with antioxidant supplementation (Table 1); of the observation studies reviewed, 15 studies reported a decreased risk and 1 an increased risk of prostate cancer, while 16 studies reported no effect (Table 2). Further studies are needed to better understand prostate cancer biology and how antioxidants influence prostate cancer risk.

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Alphabetized footnote of all author-defined abbreviations

ATBC	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BPH	Benign prostatic hypertrophy
CARET	Beta-Carotene and Retinol Efficiency Trial
DRE	digital rectal examination
HOPE-TOO	The Heart Outcomes Prevention Evaluation – The Ongoing Outcomes
NPC	Nutritional Prevention of Cancer study
MRC/BHF	Medical Research Council/British Heart Foundation
PLCO	The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PSA	prostate specific antigen
SELECT	The Selenium and Vitamin E Cancer Prevention Trial
SU.VI.MAX	Supplementation en Vitamines et Mineraux Antioxydants

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Table 1

Selected Intervention Studies of Antioxidants and Prostate Cancer

Antioxidant(s)	Study	Sample size	Intervention	Effect	Risk
Vitamin E	Lonn et al. [12] (International)	6,996	400 IU per day all rac-α-tocopheryl acetate	None	
Vitamin E and Selenium	Klein et al. [11] (USA)	35,533	400IU per day all rac-α-tocopheryl acetate; 200mcg per day L-selenomethionine 2×2 factorial	increase (α-tocopherol)	HR 1.17 (99% CI, 1.00–1.36; p = 0.008)
Vitamin E and Selenium	Fleshner et al. [67] (Canada)	303	800 IU vitamin E, 200mcg Selenium, and 40g soy protein per day	None	
Vitamins E and C	Gaziano et al. [13] (USA)	14,641	400 IU vitamin E every other day, 500mg per day vitamin C 2×2 factorial	None	
Vitamins E and C, and β-carotene	Heart Protection Study Collaborative Group [66] (UK)	20,436	600mg vitamin E, 250mg vitamin C, and 20mg β-carotene per day	None	
Vitamin E, β-carotene	Heinonen et al. [14] (Finland)	29,133	50 mg per day α-tocopherol, 20 mg per day β-carotene 2x2 factorial	decrease (α-tocopherol)	α-tocopherol: 32% and 41% decrease in prostate cancer incidence and mortality
				increase (β-carotene)	β-carotene: 23% and 15% increase in prostate cancer incidence and mortality,
Vitamin C, Carotenoids and Selenium	Meyer et al. [65] (France)	5,141	120mg vitamin C, 30 mg α-tocopherol, 6 mg β-carotene, 100 mcg selenium, 20 mg zinc	decrease (PSA < 3.0 ng/mL)	HR 0.52 (95% CI: 0.29–0.92)
				increase (PSA ≥ 3.0 ng/mL)	HR 1.54 (95% CI: 0.87–2.72)
β-carotene	Omenn et al. [40] (USA)	12,025	30 mg per day β-carotene, 20,000 IU per day retinol	None	
Selenium	Duffield-Lillico et al. [32] (USA)	1,312	200 mcg per day selenium	Decrease	HR 0.48 (95% CI 0.28–0.80)
Selenium	Marshall et al. [33] (USA)	423	200 mcg per day selenomethionene	None	
Selenium	Algotar et al. [34] (USA)	699	200mcg or 400mcg per day selenium, in the form of selenized yeast	None	
Green Tea Catechins	Bettuzzi et al. [51] (Italy)	60	600 mg per day green tea catechins	Decrease	Reduced prevalence of prostate cancer (3.3% vs 30%, (p<0.01).

Table 2

Selected Observational Studies of Dietary Antioxidants and Prostate Cancer

Antioxidant(s)	Study	Sample size	Effect	Risk
Vitamins E and C	Bidoli et al. [24] (Italy)	1,294 cases 1,451 controls	decrease (vitamin E)	OR 0.78 (95% CI: 0.58–0.96, p(trend)=0.02)
Vitamins E and C, carotenoids, and phytochemicals	McCann et al. [26] (USA)	433 cases, 538 controls	decrease	OR 0.49 (95% CI, 0.33–0.74) vitamin C OR 0.53 (95% CI, 0.36–0.79) β-carotene OR 0.67 (95% CI, 0.47–0.97) α-carotene OR 0.55 (95% CI, 0.37–0.81) lutein OR 0.62 (95% CI, 0.42–0.92) lycopene OR 0.64 (95% CI, 0.42–0.92) quercetin
Vitamins E and C, and carotenoids	Hodge et al. [25] (Australia)	858 cases, 905 controls	None	
Vitamins E and C, and carotenoids	Deneo-Pellegrini et al. [23] (Uruguay)	175 cases, 233 controls	decrease	OR 0.4 (95% CI, 0.2–0.8; p(trend)=0.008)vitamin C OR 0.6 (95% CI, 0.3–1.1; p(trend)=0.03) vitamin E
Vitamin E, β-carotene	Virtamo et al. [19] (Finland)	29,133 men	None	
Vitamins E and C, and Carotenoids	Schuurman et al. [18] (The Netherlands)	58,279 men	increase (β-cryptoxanthin)	OR 1.41 (95% CI, 1.03–1.92; p(trend)<0.01)
Vitamin E	Wright et al. [20] (USA)	295,344 men	decrease(γ-tocopherol)	RR 0.68 (95% CI, 0.56–0.84; p(trend)=0.001)
Vitamin E	Rodriguez et al. [17] (USA)	72,704 men	None	
Vitamin E	Weinstein et al. [16] (Finland)	29,133 men	None	
Vitamin E	Vlajinac et al. [22] (Serbia)	101 cases, 202 controls	decrease (α-tocopherol)	OR 0.15 (95% CI, 0.05–0.53)
Vitamins E and C, and β-carotene	Kirsh et al. [21] (USA)	29,631 men	decrease (β-carotene)	RR 0.52 (95% CI = 0.33 to 0.81)
Selenium and Vitamin E	Hartman et al. [15] (Finland)	29,133 men	None	
Selenium, Vitamin C, β-carotene	West et al. [35] (USA)	358 cases, 679 controls	None	
β-carotene	Ohno et al. [41] (Japan)	100 cases, 100 controls	Decrease	Decreased risk of prostate cancer with increasing dietary β-carotene (p=0.007)
β-carotene	Mettlin et al. [42] (USA)	371 cases, 371 controls	Decrease	RR 0.60 (95% CI, 0.37–0.99)
β-carotene	Hsing et al. [43] (USA)	17,633 men	None	
Carotenoids	Ghadirian et al. [45] (Canada)	232 cases, 231 controls	None	
β-carotene and lycopene	Norrish et al. [44] (New Zealand)	317 cases, 480 controls	None	
Lycopene	Kirsh et al. [46] (USA)	29,631 men	decrease	RR 0.62 (95% CI, 0.37–1.06; p(trend)=0.04)

Antioxidant(s)	Study	Sample size	Effect	Risk
Lycopene	Giovannucci et al. [47] (USA)	47,365 men	Decrease	RR 0.84 (95% CI, 0.73–0.96; p(trend)=0.003)
Flavonoids	Bosetti et al. [61] (Italy)	1,294 cases 1,451 controls	None	
Green tea	Kurahashi et al. [52] (Japan)	49,920 men	decrease	RR 0.52 (95% CI, 0.28–0.96; p(trend)=0.01)
Green tea	Jian et al. [53] (China)	130 cases, 274 controls	decrease	OR 0.28 (95% CI, 0.17–0.47)
Coffee	Shafique et al. [63] (UK)	6,012 men	decrease	HR 0.45 for high Gleason grade (95% CI, 0.23–0.90; p(trend)=0.01)
Coffee	Wilson et al. [62] (USA)	5,035 men	decrease	RR 0.40 (95% CI 0.22 to 0.75) ≥6 cups per day
Coffee	Arab et al. [64] (USA)	2,132 men	None	
Tea and Coffee	Severson et al. [58] (USA)	7,999 men	None	
Tea and Coffee	Kikuchi et al. [59] (Japan)	19,561 men	None	
Tea and Coffee	Sonoda et al. [57] (Japan)	140 cases, 140 controls	None	
Tea and Coffee	Jain et al. [55] (Canada)	617 cases, 637 controls	decrease (tea)	OR 0.70 (95% CI, 0.50 – 0.99)
Tea and Coffee	Slattery and West [56] (USA)	362 cases, 685 controls	None	
Tea and Coffee	Allen et al. [60] (Japan)	18,115 men	None	