Chapter

Dietary Antioxidants in the Chemoprevention of Prostate Cancer

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Abstract

Prostate cancer is the second most common cancer and the fifth leading cause of cancer death. The incidence of prostate cancer is rising due to increased screening and awareness, and there is epidemiological evidence suggesting an interaction among biological and environmental risk factors in the development and progression of prostate cancer. Vegetables and fruits provide a wide range of antioxidants and phytochemicals that have been demonstrated to have a negative, positive, or no association with prostate cancer risk. Therefore, it is evident that the effect of dietary antioxidants on risk of prostate cancer remains undecided and inconclusive. The main focus of this review was to examine recent and past literature of the chemoprotective properties of five major groups of phytochemicals against prostate cancer development including both *in vivo* and *in vitro* findings.

Keywords: antioxidants, prostate, cancer, risk, association

1. Introduction

Among men worldwide, prostate cancer is the second most common cancer and the fifth leading cause of cancer death, with an estimated recorded amount of 1.3 million cases and 359,000 deaths in 2018 [1]. The incidence of prostate cancer is rising due to increased awareness and screening, and it is estimated that 42% of prostate cancer cases occur in men over 50 years old [2]. There is epidemiological proof that suggests an interaction among several known biological and environmental risk factors in the development and progression of prostate cancer [3]. These include age, race, family history, genetic risk, socioeconomic status, and modifiable risk factors such as physical activity, obesity, and possibly dietary factors [4].

Oxidative stress defined as an imbalance between prooxidant and antioxidant processes, and interference of the oxidation-reduction circuitry is one of the many proposed underlying mechanisms of prostate carcinogenesis [5, 6]. There is increasing epidemiological data that diet plays a key role in the biology and tumorigenesis of prostate cancer, and higher intake of the main phytochemical-containing diets lowers the risk of the disease [7]. Vegetables and fruits provide a wide range of phytochemicals and antioxidants that have been demonstrated to have a positive effect on decreasing the incidence or averting the occurrence of prostate cancer [8]. 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 instability prior to prostate cancer [9].

This paper will review information in the literature on the relationship between nutrients with antioxidant properties from the diet, and the risk of prostate cancer.

2. Method of article selection

A literature search was conducted for all English language literature published before December 2018. The search was conducted using the electronic databases, including PubMed, Embase, Web of Science, and Cochrane Library. The search strategy included keywords such as prostate cancer, epidemiology, incidence, mortality, risk factor, selenium, vitamin E, vitamin C, carotenoids, and polyphenols.

The authors include many interventional and observational studies that have reported findings of dietary antioxidants, prostate cancer incidence, and progression. The majority of these studies focused on vitamins E and C, carotenoids, specifically beta- and alpha-carotene and lycopene, phenols including tea and coffee, and the flavonoids, as well as selenium.

3. Vitamin E and prostate cancer

Vitamin E is a potent lipid-soluble antioxidant, which is well recognized for safeguarding the body against free radical-mediated peroxidative damage. It is a naturally occurring essential vitamin mainly found in foods such as nuts, oils, fruits, and vegetables and is available as a dietary supplement. Vitamin E scavenges highly reactive free radical species such as hydroxyls, superoxides, lipid peroxyls, hydroperoxyls, and nitrogen radicals; and prevents lipid peroxidation related to carcinogen-induced DNA damage [10].

It is known that a deficient antioxidant defense system can result in oxidative stress. As such, increased levels of reactive oxygen species over time may have an etiological role in the development of malignancies such as prostate cancer [11]. Vitamin E may therefore be considered as adjuvant therapy for the prevention of prostate cancer [12]. However, despite emerging evidence supporting vitamin E as a powerful antioxidant, its effect on prostate cancer risk remains poorly understood.

Two categories of vitamin E compounds exist: tocopherols (α, β, γ, and δ-Toc) and tocotrienols (α, β, γ, and δ-T3) [12]. Despite structural differences between both categories, tocopherols and tocotrienols each have sufficient antioxidant properties [12].

3.1 Alpha-, gamma-, and delta-tocopherols

Alpha-tocopherol accounts for the most abundant and active isoform of vitamin E in human tissues and is the most widely used in dietary supplements [10]. Alpha-tocopherol terminates free radical chain reactions by transferring hydrogen protons to free radicals yielding nonradical products [13]. Fairly stable alpha-tocopheroxyl radicals are generated, which do not react with polyunsaturated fatty acids but with each other or couples with other free radicals to form nonradical products [13]. The generation of nonradical products by vitamin E may therefore provide a protective effect against free radical-mediated cell membrane damage and consequently reduces mutagenesis and carcinogenesis.

A number of studies have reported findings on vitamin E supplementation (alpha-, gamma-, and delta-tocopherols) and risk of prostate cancer [14–18].

Notably, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), daily supplementation of alpha-tocopherol (50 mg) reduced the risk of prostate cancer [17] and moderate dose decreased posttrial mortality [15]. However, a follow-up of the Physicians Health Study II, a large-scale randomized trial, suggested that vitamin E supplementation had no immediate or long-term effect on the incidence of prostate cancer (HR 0.99; 95% CI: 0.89–1.10) [14]. Conversely, findings from the large-scale selenium and vitamin E cancer prevention trial (SELECT) demonstrated that the risk of prostate cancer was significantly increased with dietary vitamin E supplementation containing alpha-tocopherol [16]. However, it was found that the incidence of prostate cancer did not increase in men who received combination therapy of vitamin E and selenium [19]. As such, it can be speculated that there may be a synergistic effect between both antioxidants which attenuates prostate cancer risk [19]. The increased risk of the disease associated with vitamin E therapy could be attributed to the disturbance of the normal physiological balance of vitamin E isomers by the high dosage of alpha-tocopherol, which may result in depletion of other important isomers such as gamma-tocopherol [20].

Studies have supported that gamma-tocopherol may have more superior chemopreventive effects than alpha-tocopherol, considering its stronger anti-inflammatory and antinitrative effects [12]. However, it is important to note that analysis of 15 prospective studies involving data for prostate cancer cases and controls and using risk estimation by multivariable-adjusted conditional logistic regression found that gamma-tocopherol was not associated with risk of aggressive prostate cancer, and the latter was inversely associated with alpha-tocopherol [21]. As such, it was suggested that the protective effect against prostate cancer may be lost with impaired balance of vitamin E isomers [20]. Findings from the SELECT trial were later recapitulated, as alpha-tocopherol was found to upregulate prostate cancer cell proliferation in the early stages of the disease [22]. It was found that premalignant rather than benign or malignant prostate cells had increased proliferation in response to vitamin E [22]. These data indicate that the effect of vitamin E antioxidant activity may be dependent on the stage of the prostate cells in the tumor development process [22]. Conversely, it was later found that combination therapy of delta-tocotrienol and gamma-tocopherol was efficacious in inhibiting the proliferation of prostate cancer cells by apoptosis and cell cycle arrest in the G1 and G2/M phases of the cell cycle [12].

A recent study conducted on mice revealed that delta-tocopherol and not alpha-tocopherol blocks the activation of the Akt pathway which drives tumorigenesis, inhibiting the survival of prostate cancer cells [23]. Another study which supports the chemopreventative activity of delta-tocopherol is that of Wang et al. which reported a novel mechanism by which this antioxidant inhibits prostate cancer cell growth by the attenuation of EGF/IGF-induced activation of Akt on T308 [24]. In examining the efficacy of other tocopherol, gamma-tocopherol (0.3% in diet) supplementation was found to significantly reduce the development of mouse prostatic intraepithelial neoplasia lesions and 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine-induced elevation of nitrotyrosine, 8-oxo-deoxyguanosine, p-Akt, Ki-67 and COX-2, and the loss of Nrf2 and PTEN [25].

There is supporting evidence that gamma-tocopherol significantly inhibits the growth of human prostate PC-3 tumor cell line by decreasing progression into the S-phase, upregulation of transglutaminase 2 and downregulation of (TG2), and downregulation of cyclin D1 and cyclin E levels [26]. These findings suggest that different isoforms of vitamin E may differ in their influence on prostate cancer risk and that alpha-tocopherol supplementation alone may increase the risk of the disease.

It was reported that the association between vitamin E and prostate cancer risk may be linked to genetic variation in genes that regulate antioxidant and vitamin E

metabolism [18, 27]. Furthermore, it was found that genetic variation in SOD genes responsible for detoxifying superoxide free radicals and protecting cells from oxidative stress may be associated with an increased risk of high-grade prostate cancer and disease recurrence [18]. Similarly, it was shown that single nucleotide polymorphisms (SNPS) in genes associated with vitamin E metabolism such as SEC14L2, SOD1, and TTPA may influence an individual's response to vitamin E supplementation and associated prostate cancer risk [28]. As such, inherited genotypes may confer prostate cancer risk.

It is therefore anticipated that clinical trials will be undertaken with vitamin E isomers combination therapy for further assessment of prostate cancer risk. It may be useful to conduct more studies including isomers other than alpha-tocopherol. Men with a strong family history of prostate cancer should undergo genetic testing, to identify antioxidant gene mutations that may be implicated in prostate cancer.

4. Carotenoids and prostate cancer

Fruits and vegetables supply dietary carotenoids, which are potent antioxidants as they modify cell growth and induce apoptosis [8]. Epidemiological studies indicate that consuming more fruits and vegetables containing plant carotenoids such as beta-carotene and lycopene may decrease the risk of prostate cancer as indicated by an inverse association [21, 29–31]. In addition to these two carotenoids, alpha-carotene, beta-cryptoxanthin, zeaxanthin, and lutein are commonly studied because of their potential protective benefit, although lycopene and, to some extent, beta-carotene have demonstrated so far the strongest evidence while that of the others have proven inconclusive [32, 33].

Carotenoids possess distinctive antioxidative properties including the protection of important biomolecules such as DNA from free radicals [34]. Peto et al. in 1981 hypothesized that β-carotene from vegetables and fruits could possibly decrease incidence rates of human cancers [35], and subsequently, there have been a number of epidemiological studies addressing this topic [7, 36, 37]. For many years, carotenes such as alpha-carotene and beta-carotene have been investigated relating to prostate cancer risk, but the results have proved mostly inconclusive.

4.1 Beta-carotene

Several epidemiological studies have investigated the relationship between beta-carotene and prostate cancer risk [38–48]. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, subjects receiving beta-carotene supplementation had a 23% increase in prostate cancer incidence and 15% higher mortality from the disease [17]. However, during the postintervention follow-up, the effect of supplemental beta-carotene was no longer evident (RR 1.01, 95% CI: 0.96–1.05) [44]. In a case-control study involving men with primary histologically confirmed prostate cancer and population-based controls, beta-carotene (OR 0.60, 95% CI: 0.47–0.97) and alpha-carotene (OR 0.67, 95% CI: 0.47–0.97) were inversely associated with the risk of prostate cancer. Similarly, dietary beta-carotene intake had a protective effect for prostate cancer (RR 0.30, 95% CI: 0.13–0.66) among subjects younger than 68 years of age in a case control study conducted in the United States [47] (**Table 1**) and another in Japan [43]. In a recent study, circulating beta-carotene (RR 0.55, 95% CI: 0.28–1.08) and alpha-carotene (RR 0.31, 95% CI: 0.15–0.63) were inversely associated with risk of high-grade prostate cancer, especially among those with specific somatic variations [39] (**Table 1**).

Method	Name of author(s)	Year of study	Carotenoids	Risk	95% CI	P.R.E outcome
Case-control						
	Mettlin et al. [47]	1989	β-carotene (sup.)	RR = 0.60	0.47–0.97	40%
	Nordstrom et al. [43]	2016	β-carotene (diet) α-carotene (diet) Lycopene (diet)	RR = 0.31 RR = 0.34 RR = 0.55	0.15–0.63 0.18–0.66 0.28–1.08	69% 66% 45%
	Van Hoang et al. [45]	2018	Lycopene (diet)	OR = 0.46	0.27–0.77	54%
	McCann et al. [66]	2005	β-carotene (diet) α-carotene (diet) Lycopene (diet)	OR = 0.53 OR = 0.67 OR = 0.62	0.36–0.79 0.47–0.97 0.37–0.81	47% 33% 38%
Cohort						
	Umesawa et al. [46]	2014	α-carotene (diet)	OR = 0.50	0.26–0.98	50%
	Karppi et al. [50]	2012	β-carotene (serum)	RR = 2.29	1.12–4.66	129%
	Zu et al. [54]	2014	Lycopene (diet)	HR = 0.72	0.56–0.94	28%
	Giovanucci et al. [53]	2002	β-carotene (diet)	0.84	0.73–0.96	16%
Randomized control trial						
	Virtamo et al. [44]	2003	β-carotene (diet)	RR = 1.07	1.02–1.12	7%
Meta-analysis						
	Catano et al. [56]	2018	β-carotene (diet)	OR = 0.94	0.89–1.00	6%
	Rowles et al. [58]	2017	β-carotene (serum)	RR = 0.88	0.79–0.98	12%
	Key et al. [21]	2015	β-carotene	RR = 0.65	0.46–0.91	35%
	Wang et al. [33]	2015	α-carotene (diet) Lycopene (diet)	RR = 0.87 RR = 0.86	0.76–0.99 0.75–0.98	13% 14%

RR = relative risk, CI = confidence interval, P.R.E = percentage relative effect, Sel. Sup = selenium supplement.

Table 1.
Showing studies on the effect of carotenoids on prostate cancer.

There are epidemiological studies that have found no protective effect of carotenes on prostate cancer risk [7, 21, 44–50]. In a recent case-control study involving incident prostate cancer patients, no statistically significant was observed for dietary beta-carotene intake as well as for alpha-carotene and beta-cryptoxanthin [45]. In the Japan Collaborative Cohort study, beta-carotene had no protective effect

as there was no association with prostate cancer risk [46]. However, there are studies that have reported an adverse rather than a protective effect of beta-carotene on prostate cancer. In the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) cohort study conducted in Japan among middle-aged men, the highest levels of serum beta-carotene resulted in a 2.29-fold (RR 2.29, 95% CI: 1.12–4.6; P = 0.023) higher risk of prostate cancer compared to participants with lowest levels of the antioxidant [50]. In the 18-year postintervention follow-up of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, beta-carotene increased the posttrial prostate cancer mortality (RR 1.20, 95% CI: 1.01–1.42) [15] (**Table 1**). Thus, the effect of beta-carotene remains inconclusive and may involve an adverse effect where high serum concentrations may elevate prostate cancer risk and mortality.

4.2 Lycopene

Lycopene has been reported to possess more effective antioxidant properties compared to the carotenes and alpha-tocopherol [51]. Lycopene in the form of tomato-based products and to a lesser extent as a supplement is extensively studied with regards to risk of prostate cancer; however, the clinical evidence is inconclusive. In the prostate, lung, colorectal, and ovarian cancer screening trials, lycopene consumption decreased the risk of prostate cancer particularly in men with family history [52]. Similarly, in the Health Professionals Follow-Up Study, lycopene consumption was significantly associated with decreased prostate cancer risk (RR for high vs. low quintiles 0.84, 95% CI: 0.73–0.96; P = 0.003), and tomato sauce consumption had a greater reduction [53] (**Table 1**). Other prospective studies have reported that circulating levels of lycopene were inversely associated with high-grade prostate cancer (RR 0.55, 95% CI: 0.28–1.08) [39]; dietary intake of lycopene decreased the risk of lethal prostate cancer by lowering the degree of angiogenesis in the tumor [54], and lycopene consumption was associated with lower prostate cancer-specific mortality among men high-risk disease [55].

A number of meta-analysis sought to examine the efficacy of lycopene intake in primary prevention of prostate cancer. In a recent meta-analysis of 27 studies (22 were case studies), a statistically significant, though weak inverse association, was found between prostate cancer and lycopene [56]. In another systemic review and meta-analysis, circulating lycopene levels between 2.17 and 85 μg/dL were inversely associated with risk of prostate cancer; however, there was no linear association with levels greater than 85 μg/dL [57]. Further supporting evidence of the protective effect of lycopene intake was demonstrated in a recent meta-analysis of 42 studies where higher circulating and dietary lycopene levels were inversely associated with a 12% risk of prostate cancer but not with the advanced disease [58]. Other supporting evidence involves meta-analysis by Key et al. where lycopene though not associated with overall prostate cancer risk results in a 36% significantly lower risk with aggressive disease [21]; and a meta-analysis of 34 studies showed an association between reduced prostate cancer risk and dietary and blood lycopene levels [33]. Furthermore, Mariani et al. reported no overall benefit of decreasing the rate of high-grade prostatic intraepithelial neoplasia (HGPIN) progression from a 6-month lycopene supplementation [59].

Possible pathways involving multiple mechanisms exist through which lycopene intake may reduce prostate cancer risk. Lycopene attenuates prostate cancer risk by modulating the expression of genes such as EGFR, CDK7, BCL2, and IGF-1R which are related to growth and survival [60]. Another study showed that lycopene increases the expression of BCO2, a tumor suppressor which mediates the inhibition of NF-κB signaling [61]. There is also evidence that lycopene can inhibit the proliferation of prostate cancer cell via PPARγLXRα-ABCA1 pathway [62]. Additionally,

lycopene decreases prostate cancer cell proliferation partly by normal inhibition of cell cycle progression [63] and promotes cell cycle arrest in the G0/G1 phase [64]. The chemoprevention mechanism of lycopene could be the regulation of proteins involved in apoptosis, cytoprotection, growth inhibition, antioxidant responses, the Akt/mTOR cascade, and androgen receptor signaling [65].

4.3 Alpha-carotene and beta-cryptoxanthin

Other carotenoids such as alpha-carotene and that beta-cryptoxanthin have been investigated for possible association with prostate cancer risk. In a case control study, there was reduced risk of prostate cancer with lutein (OR 0.55, 95% CI: 0.37–0.81) and alpha-carotene (OR 0.67, 95% CI: 0.47–0.97) [66]. Nordström et al. found that circulating levels of alpha-carotene (RR 0.31, 95% CI: 0.15–0.63) were associated with decreased risk of prostate cancer [39]. Similarly, alpha-carotene intake was associated with decreased risk of prostate cancer (RR 0.87, 95% CI: 0.76–0.99) [33]. Further, a meta-analysis of 34 studies suggests that dietary alpha-carotene intake was associated with reduced risk of prostate cancer [14], and a study by Schuurman et al. showed similar findings for beta-cryptoxanthin [7].

However, in a case-control study conducted in Vietnam, there was no statistically significant association between prostate cancer risk and intake of alpha-carotene, beta-cryptoxanthin, zeaxanthin, and lutein [44]. Similarly, in the Japan Collaborative Cohort study, dietary alpha-carotene intake was not associated with risk of prostate cancer [46]. The absence of the association of dietary intakes of lutein, beta-cryptoxanthin, and zeaxanthin with prostate cancer risk requires confirmation in future studies.

5. Polyphenols and prostate cancer

Dietary polyphenols (PPs) have gained much traction over the last years for their potential as reliable chemopreventive and antitumor agents. This was partly due to their presence in a range of foods and beverages commonly consumed by humans including fruits, vegetables, coffee, tea, and wine [67, 68]. In terms of chemical structure, polyphenols are compounds with at least one aromatic ring with one or more hydroxyl group attached [68]. They are grouped into four different classes based on their chemical structure and orientation of the number of phenolic rings bound to each other. These four classes are as follows: phenolic acids, flavonoids, stilbenes, and curcuminoids [67]. Phenolic acids are found in all plant materials and account for 30% of all polyphenols consumed. They are found mainly in acidic-tasting fruits, coffee, and green tea. As the most abundant group of polyphenols, flavonoids account for 60% of all polyphenols consumed by humans. Good sources of flavonoids include berries, black tea, all citrus fruits, and wine. Together, phenolic acids and flavonoids are the most abundant dietary polyphenols consumed by humans and, consequently, are the most studied with regard to their health benefits to conditions including cancer.

5.1 Coffee

There are studies that have investigated the relationship between coffee consumption and risk of prostate cancer [55, 69–75]. There are those which have found an inverse relationship between coffee consumption and risk of prostate cancer [73–75]. The "Coffee Consumption and Prostate Cancer Risk Progression in Health Professionals Follow Up" report shows that there is a lower risk for prostate cancer

and significant association for reduced lethal and advanced cancer diagnosis in participants who consumed six or more cups of coffee per day. There was an inverse association for regular (each one cup per day increment: RR 0.94, P = 0.08) and decaffeinated coffee (RR 0.91, P = 0.05) [71].

In the Collaborative Prospective Cohort study conducted in the United Kingdom between 1970 and 1973 and followed up after 34 years, there was an inverse association between coffee consumption and risk of high-grade prostate cancer, but not the overall risk of the disease [70]. Notably, adjusting for social class and age, higher coffee consumption (three or more cups of coffee) was associated with significantly reduced risk of high Gleason grade prostate cancer compared with noncoffee drinkers [70]. Similarly, in a population cohort study, men with highest coffee consumption (>3 cups per day) had a 53% lower risk of prostate cancer compared with those with lower consumption (<2 cups per day) [72]. Another study supporting the potential beneficial effect of coffee consumption is a population-based case-control study reported by Russnes et al. where high coffee consumption (>6 cups per day) was associated with reduced risk of high grade (OR 0.45, 95% CI: 0.22–0.90; P < 0.05) and fatal prostate cancer [76]. In a recent population-based case-control study in a single institution in Italy, multivariate logistic regression demonstrated that both ferulic acid (OR 0.30, P < 0.05) and caffeic acid (OR 0.32, P < 0.05) were associated with decreased risk of prostate cancer, and higher dietary intake of the latter may be associated with reduced risk of the disease [67].

However, population-based study reported by Arab et al. using data from the North Carolina-Louisiana Prostate Cancer Project showed no association between decaffeinated or caffeinated coffee (4 cups per day) and highly aggressive prostate cancer (OR 0.92, 95% CI 0.61–1.39) [69] (**Table 2**). Similarly, in a most recent European study, there was no evidence of association for risk of total prostate cancer or cancer by grade, grade or fatality, and consumption of total, decaffeinated, or caffeinated coffee [77]. The findings of these studies bring attention to potential anticancer effect of polyphenols in coffee in reducing progression and metastasis of prostate cancer. However, some studies show no association with reduced nonlethal or advanced prostate cancer.

5.2 Green tea

Green tea (GT) is one of the most widely studied source of phenolic acids such epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), and epicatechin (EC). There are a number of studies that have investigated the relationship between risk of prostate cancer and green tea [78–82], and preclinical, clinical, and epidemiological data suggest that green tea catechins may reduce prostate cancer risk [83]. In a recent case-control study of Chinese men, epigallocatechin 3-gallate and green tea reduced the risk of prostate cancer; however, the authors indicated that these results should be replicated in larger cohort or case-control studies [84]. In a systematic review conducted by Cui et al., green tea catechins significantly decreased prostate cancer in high-grade prostatic intraepithelial patients (7.60 vs. 23.1%, RR 0.39, P = 0.044) [82]. In another systematic review and meta-analysis study involving three randomized controlled trials and seven observational studies, there was a linear association between green tea catechins consumption (>7 cups per day) and risk of prostate cancer [78].

There is further evidence of the chemopreventative effect of green tea. In a recent case-control involving Vietnamese men, increasing tea consumption (>500 ml/day) was found to be associated with decreased risk of prostate cancer [84]. Similar findings were reported in a case-control study of Algerian men, although the results were borderline statistically [80]. In one of the first clinical

Method	Name of author(s)	Year of study	Sample	RR	95% CI	P.R.E outcome
Cohort						
	Shafique et al. [70]	2012	Tea (>7 cups/day)	HR = 1.50	1.06–2.12	50%
	Wilson et al. [71]	2011	Coffee (>6 cups/day)	RR = 0.82	0.68–0.98	18%
	Sen et al. [77]	2019	Coffee (375 ml/day) Green tea (106 ml/day)	HR = 1.02 HR = 0.98	0.93–1.27 0.90–1.07	2% 2%
Case-control						
	Russnes et al. [76]	2016	Coffee (6 cups/day)	OR = 0.45	0.22–0.90	55%
	Lee et al. [81]	2017	Green tea	OR = 0.60	0.37–0.98	40%
	Kikuchi et al. [88]	2006	Green tea (> 5 cups/day)	HR = 0.85	0.50–1.43	15%
Observational						
	Arab et al. [69]	2012	Coffee (>4 cups/day)	OR = 0.92	0.61–1.39	8%
Meta-analysis						
	Zong et al. [74]	2014	Coffee (moderate)	RR = 0.92	0.85–1.00	8%

RR = relative risk, CI = confidence interval, P.R.E = percentage relative effect, Sel. Sup = selenium supplement.

Table 2.
Showing studies on the effect of coffee and green tea on prostate cancer.

studies to examine the effect of polyphenols (from green tea) on prostate cancer, Betuzzi and colleagues showed that green tea consumption reduces the incidence of prostate cancer in men with high-grade prostate intraepithelial neoplasia (HGPIN). HGPIN is the most likely precursor to prostate cancer, and this study demonstrated that 30% of men with HGPIN would develop prostate cancer 1 year after biopsy [85]. In this double-blind placebo-control study, the green tea consumption group had a 3% incidence rate, while the placebo-treated group had 30% [85]. In a follow-up study by the same authors 2 years later, men in the green tea consumption group had lower incidence of prostate cancer compared with those in the nontreatment group [86].

There have being inconsistent results that do exist with regards to the chemopreventive capacity of green tea. For instance, one study showed a decreased risk of prostate cancer in a multisite case-control study in which participants consumed two cups or more of tea per day [87]. In another study, no association between tea consumption and prostate cancer risk was found [88]. In both studies, there was no association with prostate cancer and coffee consumption. In a large cohort European Study reported by Sen and colleagues, no association was observed for tea consumption and risk of prostate cancer by grade, stage, or fatality [77].

Initially, polyphenols were thought to eliminate cancer cells only through direct radical scavenging in a random manner. However, they were found to have moderate efficiency in this function, inferring that more complex action must be at work

in eliminating cancer cells. Further investigations proved that polyphenols employ biological methods in providing cancer prevention and even elimination, such as binding to multiple cellular proteins and regulating signal transduction. Alterations in signal pathways affect multiple processes that hinder cancer initiation, progression, and metastasis [89]. Among green tea catechins, epigallocatechin-3-gallate (EGCG) is widely investigated for its cancer preventive properties. In a recent study, the difluoro analog, called (-)-5,7-difluoro-epicatechin-3-O-gallate and (-)-epicatechin-3-O-gallate from green tea dose-dependently, inhibits tumorigenesis during initiation, promotion, and progression in low-metastatic LNCaP and high-metastatic PC-3 prostate cancer cells [90]. There is also recent evidence that green tea catechins contribute to the inhibition of prostate carcinogenesis by modifying miRNA expression and their target mRNAs, as well as acting as epigenetic modulators [91]. Epicatechin-3-O-gallate and theaflavins have been found to reduce the rate of cell growth in DU 145 human prostate cancer cells [92]. The inhibition of proliferation in the human prostate cancer DU145 cells by tea polyphenols may be associated with reduction in the expression of the surviving gene [93].

The extensive methylation of green tea polyphenols and low bioavailability limits their chemopreventive activity. A combination of green tea polyphenols and a methylation inhibitor quercetin inhibit growth and proliferation in androgen-sensitive LAPC-4 prostate cancer cells. There was also evidence of stimulation of apoptosis and inhibition of phosphatidylinositol 3-kinase/Akt signaling [14]. More in-depth studies have demonstrated that green tea polyphenols induced p53-dependent and p53-independent apoptosis in human prostate cancer LNCaP cells by two distinct pathways. One pathway involved the inhibition of the survival pathway where there is Akt deactivation and loss of BAD phosphorylation, while in the other, there is FAS upregulation via activation of c-jun-N-terminal kinase resulted in caspase-8 activation, FADD phosphorylation, and truncation of BID [94]. There is documentation of other molecular mechanisms by which green tea polyphenols trigger death and apoptosis of human prostate cancer cells via inhibition histone deacetylase, irrespective of their p53 status [6].

6. Selenium and prostate cancer

Selenium (Se) is a natural nutrient which can be found in different types of food. The human body utilizes a trace amount of this mineral in order to function optimally. It is reported to have powerful antioxidant properties which prevent and reduce oxidative stress. Selenium is an essential micronutrient that functions as a redox gatekeeper through its incorporation into proteins to alleviate oxidative stress in cells [95]. It also plays a crucial role in development and a wide variety of other physiological processes including effect immune responses, metabolism, and thyroid function [96, 97]. This has been attributed to selenium's ability to reduce DNA damage and oxidative stress, boost the immune system, and destroy cancer cells. The nutritional status of this metalloid has been difficult to assess via food intake data alone because many factors influence its presence in the food chain [98]. Regular adult intakes of at least 40 μg/day are required to support the maximal expression of the selenium enzymes, and perhaps as much as 300 μg/day to reduce risks of cancer is needed [99].

A number of randomized intervention trials and epidemiological studies suggest that prostate cancer risk may be decreased by selenium intake [100–105]. Studies from 2008 to 2014 (**Table 3**) have shown that selenium supplementation may have some level of a protective role against prostate cancer. In the Nutritional Prevention Cancer Study (a multicenter, double-blind, randomized, placebo-controlled cancer

Method	Name of author(s)	Year of study	Sample	RR	95% CI	P.R.E outcome
Random control trials						
	Lippman et al. [132]	2009	Sel. Sup	1.04	0.90–1.18	4%
	Dunn et al. [133]	2010	Sel. Sup	1.04	0.87–1.24	4%
	Marshall et al. [134]	2011	Sel. Sup	1.09	0.93–1.27	9%
	Klein et al. [16]	2011	Sel. Sup	0.90	0.93–1.27	10%
	Algatar et al. [135]	2013	Sel. Sup	0.90	0.48–1.70	10%
	Kristal et al. [42]	2014	Sel. Sup	1.25	0.79–1.98	25%
Cohort						
	Peters et al. [104]	2008	Sel. Sup	0.90	0.62–1.30	10%
	Chan et al. [105]	2009	Plasma	1.35	0.99–1.84	35%
	Geybels et al. [112]	2013	Nail	0.37	0.27–0.51	63%
Case-control						
	Allen et al. [136]	2008	Plasma	0.96	0.07–1.31	4%
	Pourmand et al. [137]	2008	Serum	0.16	0.06–0.49	84%
	Gill et al. [138]	2009	Serum	0.82	0.59–1.14	18%
	Zhang et al. [139]	2009	Diet	1.30	0.30–5.70	30%
	Outzen et al. [108]	2016	Plasma	1.01	0.94–1.08	1%

RR = relative risk, CI = confidence interval, P.R.E = percentage relative effect, Sel. Sup = selenium supplement.

Table 3.
Showing studies on the effect of selenium on prostate cancer.

prevention trial), oral selenium supplementation (200 μg of selenium per day) lowers the incidence of prostate cancer (RR 0.37, 95% CI: 0.18–0.71, P = 0.02) [106]. Follow-up from this study reported 2 years later found that selenium supplementation reduced the incidence of localized and also advanced prostate cancer disease [106].

In the selenium and vitamin E cancer prevention trial (SELECT), there was decrease in prostate cancer risk with either vitamin E or selenium supplements [107]. In a follow-up from this study, there was an absolute elevation of the risk of prostate cancer (per 1000 person-years) that was 0.8 for selenium, 1.6 for vitamin E, and 0.4 for the combination [16]. Chan and colleagues conducted a case-cohort study of participants in SELECT, randomized to placebo, vitamin E and selenium. They reported that selenium- or vitamin E variants may influence the overall and high-grade risk of prostate cancer and could possibly modify the patient's response to either selenium or vitamin E supplementation [28]. Furthermore, from the SELECT trial involving a stratified case-cohort sample of incident prostate cancer cases, elevated high-grade prostate cancer risk was observed in men supplemented with high-dose alpha-tocopherol and selenium, possibly due to interaction between selenium (or selenomethionine) and alpha-tocopherol [41]. The results of the SELECT study showed that it failed to demonstrate any significant decrease in prostate cancer ascribable vitamin E and selenium supplementations.

Researchers found it useful to investigate any possible association between plasma selenium levels and prostate cancer risk. In the case-control study by Brooks et al., low plasma selenium levels were associated with a four- to fivefold

elevated risk of prostate cancer [101]. In a retrospective cohort study, higher levels of selenium were associated with decreased risk of aggressive prostate cancer (RR 0.60, 95% CI: 0.32–1.12), and the relationship at diagnosis may be modified by the manganese superoxide dismutase (SOD2) gene [105]. Furthermore, in a study involving the Within the Danish "Diet, Cancer and Health" cohort, higher levels of plasma selenium were not associated with lower risk of high-grade prostate cancer disease or prostate cancer-specific mortality [108]. A systematic review and meta-analysis of case-control studies, randomized controlled trials, and prospective cohort studies showed decreased prostate cancer risk with increasing serum/plasma selenium levels (up to 170 ng/ml) when 12 studies were analyzed and also lower risk of disease with toenail selenium levels between 0.85 and 0.94 μg/g (estimated RR 0.29, 95% CI: 0.14–0.61) in three high-quality studies [109]. Therefore, although there is evidence of a potential protective effect of selenium in terms of its status and supplementation, further studies are required especially in low-selenium status populations.

In the last 10 years, a number of systematic and meta-analysis have been conducted to examine the relationship between selenium status and prostate cancer. In one study reported by Sayehmirj and colleagues, the relative risks for prostate cancer (based on case-control, cohort, and randomized control trials) on serum and nail samples were 0.85 (95% CI: 0.61–1.17) and 0.66 (95% CI: 0.41–1.05), respectively. They also reported a relative risk of 0.67 (95% CI: 0.52–0.87) between selenium levels and advanced prostate cancer [110]. The authors concluded that selenium supplementation could have a protective role against the initiation and progression to advanced stages [110]. A MOOSE-compliant meta-analysis of 17 studies showed a significant inverse association between prostate cancer risk and serum selenium levels (RR 0.76, 95% CI: 0.64–0.76) [82].

Even though these studies suggest that higher levels of selenium are associated with decreased risk of prostate cancer; there are others that have demonstrated otherwise. An analysis of 15 prospective studies by Allen et al. failed to show any association between blood selenium levels and risk of prostate cancer (OR, 1.01, 95% CI: 0.83–1.23). However, high blood selenium levels were not associated with nonaggressive disease, but with aggressive disease (OR 0.43, 95% CI: 0.21–0.87) [111]. Another key finding in this study was that nail selenium levels were significantly inversely associated with prostate cancer risk (OR 0.29, 95% CI: 0.22–0.40, $P < 0.001$) and also with both aggressive and nonaggressive disease [111]. Similarly, in the prospective Netherlands cohort study, toenail selenium levels were associated with a significant reduction in the risk of advanced prostate cancer (RR 0.37, 95% CI: 0.27–0.51; $P < 0.001$) [112]. However, in a case-control study, selenium levels in toenail were not associated with prostate cancer risk, and its supplementation while not having any effect among participants with low selenium status elevates the risk (by 91%, $P = 0.07$) among those with higher selenium status [42]. The authors suggest that men with low selenium status did not benefit from its supplementation which increased the risk of high-grade prostate cancer among those participants with high selenium status [42].

The effects of selenium on prostate cancer remain uncertain. In a prospective cohort study in the United States, reported by Peter et al., showed that long-term selenium supplementation did not lower the overall risk of prostate cancer (HR 0.90, 95% CI: 0.62–1.3) with participants having an average intake of >50 μg/day over a 10-year period [104]. In a Cochrane review including randomized controlled trials and longitudinal observational studies, there was no association between selenium supplementation and the risk of prostate cancer [113], nor in a Mendelian randomization analysis by Yarmolinsky et al. where the authors suggested that selenium supplementation could have unfavorable effects on risks of advanced disease

[114]. There is further supporting evidence in the follow-up of the Procomb trial where there was no association between selenium supplementation and prostate cancer risk [115]. Conversely, there are studies that suggest caution with selenium supplement usage among males with prostate cancer. In the Health Professionals Follow-Up Study (over a 22-year period) of men diagnosed with nonmetastatic prostate cancer, supplementation of 140 or more μg/day of selenium had a 2.6-fold risk of prostate cancer mortality (95% CI: 1.44–4.70, P = 0.001) compared with nonusers [116].

The mechanism of action of selenium in the inhibition of cancer development could include reduction in DNA damage. Waters et al. reported that dietary supplementation of selenium increases epithelial cell apoptosis in prostate and DNA damage in prostate tissue [117].

7. Vitamin C and prostate cancer

Vitamin C is mainly obtained from vegetables and fruit sources and is considered to be a very important water-soluble antioxidant [118]. Foods and supplements are sources, which provide vitamin C intake while that from foods only is referred to as dietary vitamin C. There is evidence that the mechanisms by which vitamin C prevents the harmful effects of carcinogens include decreasing oxidative DNA damage [119, 120]. Vitamin C functions as a scavenger of free radicals and, therefore, has a potential role in the chemoprevention of prostate cancer [121]. Animal and *in vitro* studies have demonstrated that it could inhibit the cell growth and viability [8]. Menon and colleagues suggested that vitamin C may be a potent anticancer agent as it inhibits tumor growth by producing reactive oxygen species [122]. In another study, vitamin C inhibits cell growth and division via the generation of hydrogen peroxide, which eventually damages the cell [123].

A number of epidemiological studies have documented the relationship between risk of prostate cancer and vitamin C intake; however, the findings have been inconclusive [48, 66, 124, 125]. In a case-control study conducted in Italy involving men with incident, histologically confirmed prostate cancer, there was a significant inverse association (OR 0.78, 95% CI: 0.58–0.96; P = 0.02), especially among men with the highest vitamin C intake [125]. Similar findings were reported in another case-control study where vitamin C decreased prostate cancer risks among men in the highest quartile of intake of the antioxidant (OR 0.49, 95% CI: 0.33–0.74) [66]. There are two other case control studies that have reported reduced prostate cancer risk due to vitamin C intake [48, 126]. There is also evidence in prospective studies such as the North Carolina-Louisiana Prostate Cancer Project where >1500 mg (compared with <500 mg vitamin C equivalent/day) reduced prostate cancer risk (RR 0.31, 95% CI: 0.15–0.67; P < 0.01) [127] (**Table 4**). In meta-analysis conducted by Bai and colleagues involving 103,658 subjects, dietary vitamin C intake (150 mg/day) reduced risk among case-control studies (RR 0.79, 95% CI: 0.69–0.91, P = 0.001) and 0.95 (95% CI: 0.90–0.99, P = 0.039) in cohort studies [125].

However, a number of studies have reported no association between prostate cancer risk and vitamin C [14, 128]. In The Prostate Cancer and Environment Study (PROtEuS), a recent population-based case-control study conducted in Montreal, there was the absence of an association between overall or grade of prostate cancer incidence and either recent dietary or supplemented vitamin C uptake [129]. Key evidence also comes from the posttrial follow-up in the Physicians' Health Study II randomized trial where no effect was observed of vitamin C on incidence of prostate cancer (HR 0.99, 95% CI: 0.89–1.10) [14]. Earlier in the Physicians' Health Study II randomized controlled trial, vitamin C supplement (500 mg daily) had

Method	Name of author(s)	Year of study	Sample	Risk	95% CI	P.R.E outcome
Case-control						
	Bidoli et al. [124]	2009	Diet	OR = 0.86	0.65–1.08	14%
	McCann et al. [66]	2005	Diet	OR = 0.49	0.33–0.74	51%
	Deneo-Pellegrini et al. [126]	1999	Diet	OR = 0.40	0.0.20–0.80	60%
	Vance et al. [127]	2016	Sup.	OR = 0.31	0.15–0.67	69%
	Parent et al. [129]	2018	Diet	OR = 0.95	0.77–1.18	5%
Cohort						
	Gaziano et al. [128]	2009	Sup.	HR = 1.02	0.90–1.15	2%
	Wang et al. [14]	2014	Sup.	OR = 1.03	0.93–1.15	2%
Meta-analysis						
	Bai et al. [125]	2015	Sup.	RR = 0.91	0.84–0.98	9%
	Jiang et al. [130]	2010	Sup.	RR = 0.98	0.91–1.06	2%

RR = relative risk, OR = odds ratio, CI = confidence interval, P.R.E = percentage relative effect, Sup. = supplement.

Table 4.
Showing studies on the effect of vitamin C on prostate cancer.

no effect on prostate cancer (HR 1.02, 95% CI: 0.90–1.15; P = 0.80), a finding that remained even after stratification by various cancer risk factors [128]. Further, a systematic review of nine randomized controlled trials found no significant effects of vitamin C supplementation (RR 0.98, 95% CI: 0.91–1.06) on prostate cancer incidence [130] (**Table 4**).

Studies involving the use of supplements might favor results that are bias as the period of use may be relatively short term, associated health problems in persons who use vitamin C supplements, and the different biological activity or absorption contributing to the possibly different effects of dietary compared with supplemental use of vitamin C [121, 131].

The studies cited above on vitamin C and prostate cancer risk provide inconclusive evidence. While some case-control studies demonstrate a protective effect, randomized trials and meta-analysis fail to clearly demonstrate any beneficial effect of vitamin C on the risk of prostate cancer.

8. Conclusion

The effect of dietary and supplemental antioxidants on risk of prostate cancer remains undecided and inconclusive. More epidemiological and human clinical trials as well as animal studies are needed to give an improved understanding on the biology of prostate cancer and how antioxidants at supranutritional and nutritional levels influence the risk of prostate cancer.

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