An update of research evidence on nutrition and prostate cancer

Pao-Hwa Lin, Ph.D. a,*, William Aronson, M.D. b,c,1, Stephen J. Freedland, M.D. d,e

a Department of Medicine, Duke University Medical Center, Durham, NC
b Urology Section, Department of Surgery, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA
c Department of Urology, UCLA School of Medicine, Los Angeles, CA
d Department of Surgery, Center for Integrated Research on Cancer and Lifestyle, Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA
e Section of Urology, Department of Surgery, Durham Veterans Affairs Medical Center, Durham, NC

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Abstract

Background: Prostate cancer (PCa) remains a leading cause of mortality in US and other countries. Preclinical and clinical studies have examined the role of nutrition and dietary intake on the incidence and progression of PCa with mixed results.

Objective: The objective of this chapter is to provide an update of recent published literature and highlight progress in the field.

Main findings: Low carbohydrate intake, soy protein, ω3 fat, green teas, tomatoes and tomato products and the herbal mixture-zyflamend showed promise in reducing PCa risk or progression. On the contrary, a higher animal fat intake and a higher β-carotene status may increase risk. A “U” shape relationship may exist between folate, vitamin C, vitamin D and calcium with PCa risk. Conclusion Despite the inconclusive findings, the potential for a role of dietary intake for the prevention and treatment of PCa remains promising. Maintaining a healthy body weight and following a healthy dietary pattern including antioxidant rich fruits and vegetables, reduced animal fat and refined carbohydrates, should be encouraged.

Conclusion: Despite the inconclusive findings, the potential for a role of dietary intake for the prevention and treatment of PCa remains promising. Maintaining a healthy body weight and following a healthy dietary pattern including antioxidant rich fruits and vegetables, reduced animal fat and refined carbohydrates, should be encouraged. © 2017 Elsevier Inc. All rights reserved.

Keywords: Diet; Prostate; Cancer; Nutrients; Dietary pattern; Lifestyle; Prevention; Treatment

1. Introduction

Prostate cancer (PCa) is the most common cancer among US men, aside from nonmelanoma skin cancer, and a leading cause of cancer death [1]. Preclinical studies have shown a potential benefit of many nutrients, dietary factors, foods or dietary patterns, on PCa development or progression, however, findings remain inconclusive. The purpose of this review is to build upon our previous review and to provide an update on the role of nutrition and dietary intervention on PCa [2].

2. Nutrients

2.1. Carbohydrates

Various studies have examined the hypothesis that reducing carbohydrates may slow PCa growth by lowering serum insulin or altering the insulin-like growth factor (IGF) that has shown mitogenic and antiapoptotic effects on prostate epithelial cells [3,4]. Animal studies showed a no-carbohydrate ketogenic [5,6] or a low-carbohydrate (20% kcal) diet may slow prostate tumor growth [7,8]. Castrated mice, representing a more advanced castration...
resistant PCa, fed a low-carbohydrate high-protein diet instead of a Western diet, also showed a significant reduction in tumor growth [9].

In humans, one study found high intake of refined carbohydrates was associated with increased PCa risk [8]. Likewise, another study found a low-carbohydrate high-protein diet was associated with a lower PCa incidence [10]. Conversely, a cross-sectional analysis showed a higher-carbohydrate intake was associated with reduced PCa risk while glycemic index was unrelated but showed a trend among white men [11].

Metformin, known to reduce liver gluconeogenesis and possibly increase insulin sensitivity, has been shown to reduce PCa cell proliferation and delay progression in vitro and vivo, respectively [12–16], with some studies showed an association with reduced incident risk and mortality [17–19]. However, other retrospective cohort studies have not supported an effect of metformin on PCa recurrence or incident risk [20–26].

Designing dietary research in humans, supplementation studies aside, is often challenged by other dietary factors that may confound the main intervention. Comparing a low-carbohydrate diet to a control diet may involve differences in not only carbohydrate but also protein, fat and other nutrients. More well-defined research with comparable interventions is needed to clarify the role of carbohydrates on PCa.

2.2. Fiber

Dietary fiber has been suggested to benefit PCa by reducing circulating estrogen and androgen through increasing sex hormone—binding globulin or increasing fecal excretion of these hormones [27,28]. Fiber may also reduce PCa risk by improving insulin sensitivity and reducing the prostate-carcinogenic IGF [29]. However, results from epidemiologic studies are inconsistent and mostly negative. An inverse association between dietary fiber and PCa risk was observed in the Supplementation en Vitamines et Minéraux Antioxydants cohort [30] but not in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort [31]. A 11.6 year population-based prospective study showed that total fiber was unassociated with total or advanced PCa [32]. However, total fiber and insoluble fiber intake were associated with a decreased risk of advanced cancers detected by subjective symptoms in this study. Interpreting result from this study should consider the facts that this study was conducted among men in Japan where PCa prevalence was substantially lower than in the United States. Further, differences in PCa screening protocols and dietary intakes between Japan and the Western countries may limit its applicability. Two meta-analyses also showed no association between dietary fiber and PCa risk [33,34]. The role of fiber in PCa risk may be small or fiber may be a marker for other factors related to PCa.

2.3. Protein

Preclinical studies showed that both a high-protein, in the context of low-carbohydrate, and a protein-restriction diet may reduce PCa growth [35]. Human studies strictly examining the effect of the amount or type of protein alone on PCa are difficult to design and may ideally be examined under the umbrella of overall dietary pattern.

2.4. Animal-based proteins

Various studies have indicated a potential benefit of consuming poultry and fish on PCa as compared to red meats [2]. However, consumption of these foods may represent a pattern beyond protein and may include influences from other dietary factors. Among animal protein studies, dairy has received relatively inconsistent results. Components like fat, calcium, protein, and specific amino acids in dairy may potentially effect PCa. A cross-sectional study showed that dairy protein was positively associated with serum IGF-1 which may stimulate PCa initiation or progression [36]. Further, an analysis from the Physicians’ Health Study showed a higher dairy intake after PCa diagnosis may be associated with increased PCa specific and all-cause mortality [37]. A higher total dairy intake was also shown to increase total PCa risk in a meta-analysis of 32 prospective studies [38].

2.5. Plant-based proteins

Many preclinical studies have shown the potential benefit of a plant protein component—total or primary isoflavone—genistein on PCa [2]. Potential mechanisms include reduction in hepatic aromatase, 5α-reductase, expression of androgen receptor and its regulated genes, FOXA1, urogenital tract weight, and PCa tumor progression [39]. However, human studies have been few, small and inconsistent. A meta-analysis showed no significant effect of soy intake on PSA levels, sex hormone-binding globulin, testosterone, free testosterone, estradiol or dihydrotestosterone [40]. Another randomized controlled trial (RCT) in preprostatectomy patients also found no effect of soy-isoflavone supplement on PSA, serum total testosterone, free testosterone, total estrogen, estradiol, or total cholesterol [41]. A RCT of men with high-risk disease postradical prostatectomy found soy protein supplementation for 2 years had no effect on risk of PCa recurrence [42]. Further, neither plasma nor urinary genistein levels were associated with PCa risk in case-control studies [43,44].

Contrarily, in a 3- to 6-week phase 2 placebo-controlled RCT, 30 mg genistein supplementation significantly reduced androgen-related markers of PCa progression [45]. A small RCT also showed isoflavone-enriched soy bread significantly reduced proinflammatory cytokines and immunosuppressive cells in PCa patients [46]. Another RCT showed that 10 weeks supplementation of a soy-based
supplement including isoflavone, lycopene, silymarin, and other antioxidants delayed PSA progression [47]. Future research should also examine amino acids like methionine, which was suggested in preclinical studies to play a role in PCa [48,49].

2.6. Fat

Preclinical studies generally show reducing dietary fat slows tumor growth [50–52] and high-fat diets, especially animal fat and corn oil, increase PCa progression [53]. However, a high-fat fish oil (ω-3) diet significantly reduced PCa tumor volume along with reductions in gene expression of markers for M1 and M2 macrophages, associated cytokines and chemokine CCL-2 [54]. Accordingly, fat type, especially animal and ω-6 fat, rather than simply fat amount may be important when examining the association with PCa.

The potential mechanisms that a high-fat diet may affect PCa progression include modulating fatty acid synthase expression [55] through elevated proinflammatory cytokines [56], IGF-1 [57], and by suppressing GPx3 expression and increasing proliferation of prostate intraepithelial neoplasia epithelial cells [53]. A high-fat diet also may promote immune cell infiltration into prostate tissues and basal to luminal differentiation [58].

Human studies are inconclusive [2]. Although a recent meta-analysis of 14 cohort studies showed no link between various fats (total, PUFA, MUFA, and SAT) with either total PCa or advanced PCa [59], previous studies support that diets rich in plant-based fat or ω-3 fat may be associated with a lower PCa risk. A low-fat fish oil diet resulted in decreased proinflammatory eicosanoids and cell-cycle progression score in men undergoing radical prostatectomy [60]. However, the evidence of fish oil in PCa has not been consistent. Analysis of SELECT trial data showed that men in the highest quartile of total long-chain ω-3 polyunsaturated fatty acids intake (20:5ω3; 22:5ω3; 22:6ω3) had increased risks for low grade, high grade, and total PCa [61]. This finding was consistent only for the individual fatty acids for low grade and total PCa, but not for high-grade PCa. Another meta-analysis of 5,078 case patients and 6,649 control patients from 7 studies also showed that PCa risk was 14% and 16% greater in the highest fifth of eicosapentaenoic acid (20:5ω3) and docosapentaenoic acid (22:5ω3), respectively (both P < 0.01) [62]. Further, stearic acid (18:0) was inversely associated with total PCa risk. The association between docosapentaenoic acid and PCa risk was significant for low-grade disease only and not for high-grade disease. Hence, definitive evidence relating fatty acids to PCa risk awaits further investigation [63].

2.7. Vitamins and minerals

Retinoids, including natural and synthetic analogs of vitamin A, have been suggested to inhibit carcinogenesis in animal models of several cancers including prostate but the exact mechanism is unclear. Fenretinide, a synthetic retinoid, has been shown to decrease both prostate tumor incidence and mass in the mouse prostate reconstitution model [64]. However, supplementing fenretinide at 200 mg/d for 4 weeks did not increase retinoids in the prostate tissue to a level that may be effective or influence the expression of retinoid receptors in PCa patients [65,66]. Supplementing at a higher level of 900 mg/m² twice daily for 1 week, every 3 weeks, for a year, among 23 patients with biochemically recurrent PCa showed modest clinical activity [67]. In all, 7 (30%) of the 23 patients had prolonged PSA stable disease. Thus, further research is needed to investigate different formulation of fenretinide, and the safe and effective dose.

Large observational studies have shown inconsistent findings in the association between vitamin A and PCa [2], which may be contributed to the forms of vitamin A. Circulating retinol were positively associated with overall PCa risk in a large pooled analysis [68] and with total and high-grade PCa risk in the Prostate Cancer Prevention Trial [69]. However, retinol was shown to inhibit proliferation of human refractory and PCa cells dose-dependently while retinoic acid and retinyl palmitate showed little effect [70]. Preclinical evidence suggests folate depletion may slow tumor growth, while supplementation has no effect on growth or progression, but may lead to epigenetic changes via increasing DNA methylation [71]. Observational studies in humans, however, have shown no effect of dietary folate on PCa and conflicting relationship between circulating folate and PCa [2]. Three meta-analysis showed dietary folate was unassociated with PCa risk [72,73]. However, one of the meta-analyses showed serum folate was inversely associated with PCa risk whereas the other 2 showed a positive association [74]. A RCT also found dietary folate unassociated with risk of PCa recurrence [75]. In a Danish prospective cohort, supplemental, but not total dietary, folate intake was inversely associated with PCa risk [76]. The study suggested folate may play a dual role in prostate carcinogenesis [77].

Despite the potential role of vitamin C as an antioxidant in anticancer therapy, trials examining dietary or supplemental vitamin C are few. A RCT and a follow-up study to the Physicians’ Health study II both showed vitamin C intake or supplementation had no effects on incident PCa or total cancer [76,78]. However, in a meta-analysis of 18 studies, dietary vitamin C was inversely associated with PCa risk [79]. The fact that vitamin C at high doses may act more as a pro-oxidant than antioxidant may have complicated the research interpretation.

Numerous studies have examined the relationship between dietary or circulating vitamin D and PCa. Vitamin D deficiency not only increased risk for aggressive PCa in African-American men [80] but also increased odds of adverse pathology with localized patients with PCa [81]. Increased circulating vitamin D was associated with decreased PCa risk, PCa severity [82–85], and lower
prostate-specific mortality in the Malmo Diet and Cancer Study [86]. Vitamin D supplementation blocked the progression of early-stage prostate lesions induced by a calcium-rich diet [87], and slowed PCA progression or induced apoptosis in PCA cells [88–90]. Further, a higher prediagnostic serum 25(OH)D was associated with a longer PCA survival in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [91].

Other studies, however, have reported neither impact of vitamin D supplement on PSA [92] nor effect of vitamin D status on PCA risk [93,94]. Serum 25(OH)D pretreatment was not associated with PCA survival among 125 newly diagnosed stage IV patients with PCA [95]. In a large case-control study, neither circulating vitamin D nor vitamin D-related single nucleotide polymorphisms were associated with fatal PCA [96]. A meta-analysis also reported no relationship between vitamin D receptor polymorphisms (BsmI and FokI) and PCA risk [97].

Conversely, some studies have shown a positive association between vitamin D status and PCA risk [98,99,100]. In both a meta-analysis and a large cohort study, serum 25(OH)D was positively associated with PCA risk [99,101]. Plasma 25(OH)D3 was associated positively with PCA aggressiveness among African-American men with low calcium intake and inversely among those with high calcium intake [102]. Both serum 25(OH)D and calcium were associated with increased PCA risk in Caribbean men of African ancestry [103]. Thus, the relationship between vitamin D and PCA may be complicated by other factors. For example, vitamin D-binding protein modulated the association between vitamin D and PCs [104], which may partially explain inconsistent findings.

A study even suggested a “U” shaped relationship between vitamin D and PCs and a narrow optimal range of circulating vitamin D for PCA prevention [105]. Indeed, a greater intake of a favorable nutrient may not always be better. A nested case-control study from the Prostate Cancer Prevention Trial showed serum 25(OH)D modestly increased risk of Gleason 2 to 6 PCs and substantially reduced risk for Gleason 8 to 10 PCs [84]. Another case-control analysis from the Selenium and Vitamin E Cancer Prevention Trial also showed both low and high plasma vitamin D were associated with increased PCA risk and more strongly for high-grade disease [105]. Serum 25(OH)D was positively associated with testosterone and sex hormone-binding globulin, suggesting a potential mechanism through which vitamin D effects PCs [106]. Thus, the role of vitamin D in PCs may depend on factors including disease stages, calcium intake and racial background.

Preclinical studies continue to show vitamin E, as γ-tocopherol and δ-tocopherol, may inhibit PCA cell growth by inducing cell-cycle arrest and apoptosis via receptor tyrosine kinase-induced AKT activation [107,108]. A tocotrienols mixture inhibited human prostate tumor xenograft growth, associated with up-regulation of CDK inhibitors p21 and p27 [109]. Unfortunately, human studies have been less supportive [110]. A pooled analysis of 15 prospective studies also showed plasma α-tocopherol was inversely associated with PCA risk [68]. Further, a higher serum α-tocopherol but not γ-tocopherol was associated with decreased risk of PCA [111,112] and the association may be modified by genetic variations in vitamin E related genes [113]. Dietary α- and γ-tocopherols were also inversely related to PCA aggressiveness among European Americans [114]. Conversely, 2 observational studies (Cancer Prevention Study II Nutrition Cohort and NIH-AARP Diet and Health Study) both showed no association between vitamin E supplementation and PCA risk [115,116].

When vitamin E supplementation was examined in RCTs, results have been similarly inconsistent. In a large RCT of males aged ≥50 year, 400 IU of vitamin E supplementation every other day for a mean of 10.3 year had no immediate or long-term effects on total cancers or PCA risk [78]. A follow-up study to Physicians’ Health study II showed neither vitamin E nor C supplementation had effects on incident PCs or total cancer [78].

However, a moderate dose of vitamin E supplement (50 mg or ~75 IU) resulted in lower PCA risk among 29,133 male smokers [117]. Conversely, a prospective randomized trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), showed vitamin E supplementation significantly increased PCA risk [118] and higher plasma α-tocopherol may interact with selenium supplements to increase high-grade PCA risk [119]. This finding is consistent with a case-cohort study that showed vitamin E increased PCs risk among those with low selenium status but not those with high selenium status [120]. Future research should consider dose effect, different forms of vitamin E, and interaction with other nutrients.

Preclinical studies have shown antitumor potential of vitamin K. A combination of vitamin K3, ascorbic acid and a vitamin E analog α-tocopheryl succinate efficiently suppressed tumor growth in mice [121]. Vitamin K epoxide reductase was not expressed or expressed at very low levels in PCs cells from radical prostatectomy samples and metastatic biopsies as compared to benign tissues [122]. Very little is understood about how vitamin K affects PCs in humans. An inverse relationship between vitamin K (as menaquinones) intake and PCA incidence was observed in the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort [123].

Few preclinical studies have examined the role of calcium with PCs. Some, retrospective, studies and meta-analyses suggest a positive association between calcium intake and PCA risk, whereas others suggest no association [124,125]. In a meta-analysis of 32 prospective studies, total and dairy calcium intakes, but not nondairy calcium or supplemental calcium intakes, were positively associated with total PCA risk. Supplemental calcium also increased risk of fatal PCs [38]. Another study suggests a “U-shaped” association, where very low calcium levels or supplementation were both associated with PCs [126]. In the Health
Professionals Follow-Up Study, calcium intake > 2,000 mg/d was associated with greater risk of total, lethal and high-grade PCa [127]. However, these associations were attenuated and became statistically insignificant when phosphorus intake was adjusted for. In this study, phosphorus intake was associated with greater risk of total, lethal, and high-grade PCa, independent of calcium and intakes of red meat, white meat, dairy, and fish. Thus, phosphorus may independently associate with risk of lethal and high-grade PCa.

Even though in vitro studies suggested selenium may inhibit angiogenesis and proliferation while inducing apoptosis [128], the SELECT study showed no benefit of selenium alone or in combination with vitamin E for PCa chemoprevention [118]. A follow-up study showed the effect of selenium or vitamin E supplementation on high-grade PCa risk may vary by genotype [129]. Further, selenium supplementation did not benefit men with low selenium status but increased risk of high-grade PCa among men with high selenium status [120]. A prospective Netherlands Cohort Study also showed toenail selenium was associated with a reduced risk of advanced PCa [130]. Further research should consider different forms of selenium such as methylselenol precursors that was proposed to be biologically appropriate for cancer chemoprevention [131].

3. Phytochemicals

Plants contain phytochemicals with antioxidant and anti-inflammatory properties, and may be used for chemoprevention and cancer treatment with low toxicity [132,133]. However, most supporting evidence comes from animal studies [134].

Silibinin is a polyphenolic flavonoid that has shown a diverse effect on PCa. Recent in vitro and in vivo studies showed silibinin may inhibit PCa growth by targeting epidermal growth factor receptor [135-137], TGFb2 expression [138], mitochondrial reactive oxygen species-dependent apoptosis [139], cancer-associated fibroblasts [140], and PCa cells’ interaction with fibronectin and inhibits their motility and invasiveness [141]. Further, silibinin, combined with ionizing radiation, strongly down-regulated endothelial cell proliferation and attenuates ionizing radiation-induced proangiogenic response in PCa cells [135]. The growing body of preclinical evidence awaits confirmation with human RCTs.

Many studies have examined the effect of curcumin on PCa. Potential mechanisms [2] include decreasing tumor weight/volume, inducing cell apoptosis under the skin of nude mice by up-regulating Bax and down-regulating Bcl-2 [142], and inhibiting the proinflammatory protein NF-B while inducing apoptosis through increased expression of proapoptotic genes [143]. The inhibiting effect of curcumin on PCa growth was shown to be dose-dependent via miR-208-mediated CDKN1A activation [144]. Curcumin also increased PCa cell apoptosis when combined with cancer drug doxorubicin [145] and by down-regulating Notch signaling in DU-145 cells [146]. Curcumin combined with α-tomatine, a glycoalkaloid in tomatoes, showed a synergistic inhibition of growth and induced apoptosis in PCa cells [147]. However, very few human clinical trials have been conducted. Supplementation of 3 g/d curcumin for 3 months increased total plasma antioxidant activity but did not affect PSA among 40 patients treated with radiotherapy [148]. Further, a randomized phase II trial is currently underway to compare the effect of oral curcumin supplementation 500 mg twice a day for 6 months as compared to placebo in treating PCa patients postradical prostatectomy (ClinicalTrials.gov identifier: NCT02064673). The hypothesis of this trial was that curcumin may stop the growth of tumor cells by blocking some enzymes needed for cell growth and may help to decrease or prevent PCa from returning after surgery. It should be noted that the bioavailability of curcumin is poor in human and formulations with noncurcuminoid components of turmeric have been shown to increase bioavailability substantially [149].

3.1. Pomegranate

Pomegranates are rich in phytochemicals such as ellagitannins (punicalagins) that in animal studies have inhibited PCa proliferation and angiogenesis under hypoxic conditions and induced apoptosis [143,150]. Animal studies also showed components of pomegranate juice, luteolin, ellagic acid, and punical acid, significantly inhibits PCa tumor growth and metastasis of highly invasive prostate tumors [151]. Additionally, pomegranate extracts reduced production of testosterone, dihydrotestosterone in PCa cell lines and decreased PSA in PTEN knockout mouse model [152]. A RCT showed no effect of pomegranate extract on PSA doubling time as compared to placebo but those with manganese superoxide dismutase AA genotype was shown to be more sensitive to its antiproliferative effects [153]. Further, a blend of pomegranate, green tea, broccoli, and turmeric supplement for 6 months significantly reduced the rise in PSA among men with localized PCa [154].

3.2. Green tea

Green tea contains a number of antioxidant polyphenols including catechins like epigallocatechin gallate (EGCG), EGC, (−)-epicatechin-3-gallate, and (−)-epicatechin. Preclinical studies suggest EGCG, a potent antioxidant [128], inhibits PCa growth, induces intrinsic and extrinsic apoptotic pathways, and decreases inflammation by inhibiting NFκB [143]. Green tea polyphenols may cause cell-cycle arrest and apoptosis in PCa cells [155] by suppressing class I histone deacetylases [156].

Although consuming brewed green tea increased green tea polyphenols in prostate tissue [157,145], drinking 6
cups of either green tea, black tea, or water before prostatectomy did not affect markers of cancer proliferation, apoptosis, and oxidation, though it significantly reduced PSA [158]. Another small trial also showed that EGCG supplement resulted in a significant reduction in PSA, hepatocyte growth factor and vascular endothelial growth factor in men with PCa [159]. Further, in a RCT of patients with high-grade prostate intraepithelial neoplasia, supplementation of 600 mg/d green tea catechin extract for 1 year was associated with 1 cancer diagnosis out of 30 patients compared to 9 out of 30 in the placebo group [160]. However, daily catechin supplement containing 400 mg EGCG for 1 year did not reduce the likelihood of PCa in men with baseline high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation [161]. A case-control study showed habitual total tea consumption was associated with a reduced PCa risk [162]. A meta-analysis of 21 studies also showed that total tea consumption, but not green and black tea separately, reduced PCa risk [163]. Thus, green tea polyphenols and even total tea consumption holds promise in lowering PCa risk [143,160,164].

3.3. Resveratrol

While most in vitro studies suggest resveratrol inhibits PCa growth or slows progression [165–167], resveratrol suppresses tumor growth in some [143] but not all animal models [168], possibly due to limited bioavailability [169,170]. Very few clinical trials have investigated the preventive or therapeutic effects of resveratrol on PCa. A small single-arm phase I study in men with biochemically recurrent PCa showed that a resveratrol-rich muscadine-grape skin extract increased PSA doubling time by 5.3 months [171]. However, neither 150 mg nor 1,000 mg resveratrol supplement for 4 months affected prostate volume, PSA level, testosterone, or dihydrotestosterone [172].

3.4. Zyflamend

Zyflamend is an anti-inflammatory herbal mixture including Holy basil, turmeric, ginger, green tea, rosemary, Hu-Zhang, Chinese goldthread, barberry, oregano, and skullcap. It has been shown to reduce PCa progression by lowering expression of markers including pAKT, PSA, histone deacetylases, and androgen receptor in animal models and PCa cell lines [173–175]. Despite its anticancer potential [176], few human studies have been conducted [177,178]. In an open-label Phase I trial of 23 patients with high-grade prostatic intraepithelial neoplasia, Zyflamend alone or in conjunction with other dietary supplements for 18 months reduced the risk for developing PCa [177]. It is possible that singular phytochemical may not exert a detectable effect on PCas in clinical trials but a combination of multiple phytochemicals [179] may be a preferred approach.

4. Other whole foods

4.1. Fruits and vegetables

Fruits and vegetables such as cruciferous and allium vegetables are rich in vitamins, minerals, and phytochemicals and have been shown an inverse relationship with PCa risk in some epidemiologic studies [180], but not all [181,182]. Potential mechanisms for the phytochemical rich vegetables to benefit PCa include enhancing the immune system, inhibiting cell growth, modulating expression of androgen-responsive genes, and inducing apoptosis [183,184]. Although whole foods contain multiple nutrients and phytochemicals that may benefit PCa synergistically, differing study methodology may explain the inconsistent findings.

4.2. Tomatoes and tomato products

Some preclinical studies showed that the antioxidant lycopene in tomato may halt the cell cycle in several PCa cell lines and decrease IGF-1 signaling by inducing IGF-1 binding proteins, slow PCa growth or reduce PCa epithelial cells at stages of initiation, promotion, and progression [2]. Consumption of tomato products also inhibited progression of castrate resistant PCa in the TRAMP model [185]. In some human studies, higher lycopene consumption or higher serum levels were associated with lower PSA levels, PCa risk, and reduction in cancer-related symptoms. Short-term tomato sauce or lycopene supplementation also demonstrated lycopene uptake in prostate tissue and potential anticancer effects [2].

However, a pooled analysis of 15 prospective studies showed that plasma lycopene was only associated inversely with aggressive PCa [68]. Consuming a tomato extract containing 30 mg/d of lycopene had no effect on markers of PCa proliferation and cell cycle inhibition [186]. The Supplementation en Vitamines et Mineraux AntioXydants (SU.VI.MAX) cohort study also found no association between tomato product intake and PCa risk [181]. Further, supplementation of 35 mg lycopene, 55 µg selenium, and 600 mg green tea catechins for 6 months was even associated with a higher PCa incidence [187]. As the presence of tomato-based products in the United States dietary intakes is pervasive, designing a control arm with limited intake of tomato-based products in randomized trials is likely to be very difficult.

4.3. Coffee

Coffee contains caffeine and several unidentified phenolic compounds that may serve as antioxidants and affect PCa. Epidemiologic studies found either an inverse or no association between coffee consumption and PCa risk [2]. A case-control study found high coffee intake (≥6 cups/day) significantly reduced the risk for high-grade PCa [188]. This study also examined chocolate, which is rich in caffeine
but found chocolate intake was positively associated with risk of total, advanced, localized, and low-grade PCa. The potential mechanism(s) and pathway(s) involved may include antioxidant, anti-inflammatory effects, glucose and insulin metabolism, and effect on IGF-I and circulating sex hormones.

5. Dietary patterns

Although many single nutrients or food factors have been examined for their association with PCa risk or progression, the results have largely been inconclusive. The inconsistency may relate to the fact that the effect of single nutrients or food factors may be too small to detect and combinations of nutrients or food factors may contribute to a larger effect synergistically [189]. For example, in a cohort of 293,464 men, a high dietary quality, as indicated by the Healthy Eating Index score capturing multiple dietary features, was associated with a lower risk of total PCa [190]. Adherence to the Mediterranean diet was associated with a greater reduction in PCa risk [191], and lower overall mortality but not with advanced PCa risk [192]. This finding is consistent with the fact that Mediterranean diet is rich in vegetables, olive oil, complex carbohydrates, lean meats, and antioxidants, components related to carcinogenesis, and inflammatory processes [193]. Fish and omega-3 fatty acid consumption in the Mediterranean pattern were also shown to significantly and inversely associate with fatal PCa risk.

Further, Asian countries with high consumption of omega-3 PUFAs, soy and green tea-based phytochemicals, have lower PCa incidences versus countries consuming a “Western-style” diet [194]. A western diet postdiagnosis was significantly related to higher PCa risk in the Physicians’ Health study [195], whereas a vegan diet was associated with lower PCa risk [196]. These studies suggest that total antioxidants or polyphenols content may be important contributors to the relationship between dietary patterns and PCa [154,197]. In the North Carolina-Louisiana Prostate Cancer Project, total antioxidant capacity from diet and supplements was associated with significantly reduced odds of high aggressive PCa [198]. In the Cancer of the Prostate in Sweden study, antioxidant intake from supplements, but not foods, was associated with total, advanced, localized, high-grade, and low-grade PCa risk [188]. Future studies may generate more consistent findings if methodology used in identifying dietary pattern, the length of observation or population included are more comparable [199–201].

5.1. Body weight

Obesity is a metabolic disorder associated with increased risk for aggressive PCa incidence, biochemical failure following major treatments, PCa-specific mortality, and progression and increased treatment complication [202,203]. Weight loss resulted in changes in serum proteins that may be related to prognosis among newly diagnosed patients with PCa in a 6-week RCT [204]. Further, obesity was more strongly associated with increased PCa risk among African-American than among non-Hispanic white men [205], supporting that obesity may affect subset of population such as those with TMPRSS2-ERG-positive tumors [206].

6. Future direction for clinical trials

Multiple epidemiologic, preclinical, and clinical trials support a potential role of dietary intervention as primary or secondary prevention of PCa, or to minimize side effect from PCa treatment [207–209]. Indeed, more than 40 intervention trials testing various aspects of diet including low fat, low carbohydrate, fish oil, tomato products, lycopene, tea, pomegranate juice, low calorie, and a high vegetable diet on PCa-related outcomes are currently underway (ClinicalTrials.gov). Combining beneficial dietary factors, with or without concurrent therapy, are clearly indicated from existing evidence and should be incorporated in future RCTs. Further, an ideal design for tertiary prevention is to incorporate dietary intervention in men with PCa on active surveillance receiving serial biopsies using advanced biopsy technology that allows for precomparasion and postcomparaison of same sight biopsies, and to track magnetic resonance imaging detected tumors. A large scale clinical trial, Men’s Eating and Living (MEAL study) is ongoing now and will provide valuable evidence regarding dietary prevention for PCa progression [210]. The MEAL study randomized 478 men on active surveillance for PCa from 91 study sites to either a vegetable-intense diet or a control diet [211]. Results from this study are expected in early 2018. Future dietary intervention trials should also define responders and nonresponders to interventions, thus allowing a “personalized medicine” approach.

The fact that PCa patients are often motivated for lifestyle intervention postdiagnosis [212] suggests a “teachable moment” to be grasped for the maximum benefit of dietary intervention. Dietary intervention that improves metabolic profile is a win-win option for PCa prevention and treatment, as increasing evidence shows that metabolic abnormalities increase risk for PCa. Dietary intervention uniquely holds the possibility to improve overall and prostate health and should be encouraged [213,214].

7. Conclusion

Determining the ideal diet for PCa prevention and treatment requires additional research. The effect of dietary intervention on PCa-related metabolic changes including glucose and lipids has been well acknowledged. Thus, the best dietary advice for PCa prevention or management as of
## Summary of nutrients and food factors with prostate cancer (PCa)

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<td>Fiber [27–34]</td>
<td>NA</td>
<td>Mixed results, mostly negative.</td>
<td>NA</td>
<td>May be small or act as marker for other factors.</td>
</tr>
<tr>
<td>Vitamin C [76,78–79]</td>
<td>May slow tumor growth in vitro and in vivo.</td>
<td>No effect of diet or supplement on incident PCs or total cancer.</td>
<td>Rare. One study showed no effect.</td>
<td>May act both as pro-oxidant and antioxidant.</td>
</tr>
<tr>
<td>Vitamin D [80–106]</td>
<td>May slow PCs progression.</td>
<td>Serum vitamin D associated with a higher or lower risk. An “U” shaped relationship may exist. Ca intake and vitamin D-binding protein may modulate the association.</td>
<td>No effect of vitamin D supplement on PSA or PCs risk.</td>
<td>Association between vitamin D and PCs may depend on factors including Ca intake, disease stages and racial background.</td>
</tr>
<tr>
<td>Vitamin E [68,78,107–120]</td>
<td>May slow PCs tumor growth.</td>
<td>Diet and plasma vitamin E inversely associated with PCs risk, but not supplement.</td>
<td>400 IU supplement had no effect or increased high-grade PCs risk, 75 IU supplement lowered risk in smokers.</td>
<td>Dosage and selenium status may modulate association.</td>
</tr>
<tr>
<td>Calcium [38,124–127]</td>
<td>Rare</td>
<td>Calcium intake increased or decreased PCs risk.</td>
<td>NA</td>
<td>Inadequate evidence.</td>
</tr>
<tr>
<td>Selenium [118,120, 128–131]</td>
<td>Inhibited angiogenesis, proliferation, and induced apoptosis.</td>
<td>Toenail Selenium associated with reduced advanced PCs risk.</td>
<td>Selenium supplement had no effect for PCs chemoprevention, or increased high-grade PCs risk among men with high Selenium status.</td>
<td>Effect of selenium may depend on selenium status and genotype.</td>
</tr>
<tr>
<td>Curcumin [2,142–149]</td>
<td>Inhibited proinflammatory NF-B, induced apoptosis, slowed PCs growth.</td>
<td>NA</td>
<td>3 g/day curcumin supplement for 3 months increased plasma antioxidant activity but did not affect PSA among patients treated with radiotherapy.</td>
<td>Potential to slow PCs growth, awaits further human research.</td>
</tr>
<tr>
<td>Pomegranate [143, 150–154,179]</td>
<td>Inhibited PCs proliferation, tumor growth, angiogenesis and metastasis.</td>
<td>NA</td>
<td>Blend of pomegranate, green tea, broccoli and turmeric decreased rise in PSA.</td>
<td>Weak evidence of benefit in limited human trials.</td>
</tr>
<tr>
<td>Supplement</td>
<td>Effect Description</td>
<td>Evidence and Clinical Implications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Green tea [128,143, 155–164,179]</td>
<td>Inhibited PCa growth, induced apoptosis, decreased inflammation.</td>
<td>Pomegranate extract may affect PSA doubling time in certain genotype only. Green tea catechin or EGCG supplement reduced PCa incidence or PSA. Drinking black or green tea had no effect on markers of proliferation, apoptosis or oxidation. Some evidence of benefit, more human RCTs needed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resveratrol [143,165–172]</td>
<td>Inhibited PCa growth in some but not all studies.</td>
<td>A resveratrol-rich muscadine-grape skin extract increased PSA doubling time, but neither 150 mg nor 1000 mg resveratrol supplement for 4 months affected prostate volume, PSA level, testosterone, or dihydrotestosterone. Potential benefit, very few RCTs, awaits further clarification.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zyflamend [173–177]</td>
<td>Reduced PCa progression.</td>
<td>Reduced risk among those with high-grade PCa.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits and vegetables [179–184]</td>
<td>NA</td>
<td>Inverse relationship between total fruit and vegetable intake and PCa risk.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomatoes and products [2,68,181,185–187]</td>
<td>Lycopene slowed PCa initiation, growth, and progression.</td>
<td>Higher lycopene intake or serum level associated with decreased PSA and lower PCa risk.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffee [2,188]</td>
<td>NA</td>
<td>Inverse or no association between coffee consumption and PCa risk.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary pattern [154, 188–201]</td>
<td>NA</td>
<td>High HEI associated with lower PCa risk. Mediterranean, Asian and Vegan diets associated with lower risk but Western diet associated with higher PCa risk. Promising. Future RCTs needed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
today include increasing antioxidants rich fruits and vegetables, replacing refined carbohydrates with fiber and nutrient-dense whole grains, replace total and saturated fat with ω-3 rich fat, replacing red meats with fish or plant-based protein, and maintaining a healthy body weight (Table).

Acknowledgments

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References


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Kjaer TN, Ornstrup MJ, Poulsen MM, et al. Resveratrol reduces the levels of circulating androgen precursors but has no effect on, testosterone, dihydrotestosterone, PSA levels or prostate volume. A 4-month randomised trial in middle-aged men. Prostate 2015;75:1255–63.


