ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 387–401

UROLOGIC ONCOLOGY

Review article

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*

Received 18 April 2017; received in revised form 15 September 2017; accepted 6 October 2017

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.

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

Funding sources: 1K24CA160653 (Freedland), NIH P50CA92131 (W. Aronson). This article is the result of work supported with resources and the use of facilities at the Veterans.

*Corresponding author. Tel.: +1-919-660-6685; fax: +1-919-660-8802.
E-mail address: pao.hwa.lin@dm.duke.edu (P.-H. Lin).
[1]Administration Medical Center, West Los Angeles (W. Aronson).

https://doi.org/10.1016/j.urolonc.2017.10.006
1078-1439/

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 Mineraux 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 (20:5w3) 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/m^2 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 PCa [104], which may partially explain inconsistent findings.

A study even suggested a "U" shaped relationship between vitamin D and PCa 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 PCa and substantially reduced risk for Gleason 8 to 10 PCa [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 PCa [106]. Thus, the role of vitamin D in PCa 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 PCa 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 PCa 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 PCa cells from radical prostatectomy samples and metastatic biopsies as compared to benign tissues [122]. Very little is understood about how vitamin K affects PCa 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 PCa. 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 PCa [38]. Another study suggests a "U-shaped" association, where very low calcium levels or supplementation were both associated with PCa [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 inhihit 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 punicic acid, significantly inhibits PCa tumor growth and metastasis of highly invasive prostate tumors [151]. Additionally, pomegranate extracts reduced production of testosterone, dihydrotestesterone 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 NFkB [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 PCa 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 cohort study also found no association between tomato products 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 effect PCa. Epidemiological studies found either an inverse or no association between coffee consumption and PCa risk [2]. A case-control study found high coffee intake ($\geq$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-Louisana 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 postcomparison 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 on-going 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

Table
Summary of nutrients and food factors with prostate cancer (PCa)

Nutrient or food factor and references	Preclinical study	Epidemiological study	Clinical study	Summary
Carbohydrate [3–11]	Low-carbohydrate slowed tumor growth.	High refined carbohydrate increased risk.	On-going	Potential. Manipulation of carbohydrate intake likely change intakes in other nutrients and dietary factors also.
Protein [2,35–49]	Both high protein and protein restriction may reduce PCa growth. Both soy protein and genistein may inhibit PCa cell progression.	Dairy may increase PCa risk.	Mixed results. Soy-based supplement and geneistein may reduce PCa progression.	Soy products and isoflavone showed potential benefit.
Fat [2,50–63]	Low-fat reduced PCa risk and tumor growth, high-fat (animal fat) increased risk and progression.	Mixed results. Saturated fat may increase risk while plant fat and omega-3 PUFA may decrease risk.	Low-fat plus omega-3 PUFA reduced PCa proliferation and CCP.	Low-fat plus omega-3 PUFA promising for PCa risk reduction.
Vitamin A [2,64–70]	Retinol decreased proliferation of human refractory and PCa cells dose-depentently.	Higher serum retinol associated with higher PCa risk.	β-carotene supplement increased PCa risk.	Forms of Vitamin A may affect PCa differently. Supplement not advised, may increase risk.
Folate [2,71–77]	Folate depletion may slow tumor growth. Supplement had no effect.	Higher circulation folate associated with higher or lower PCa risk.	Supplement folate had no effect on PCa risk.	Potential dual role of folate in prostate carcinogenesis.
Fiber [27–34]	NA	Mixed results, mostly negative.	NA	May be small or act as marker for other factors.
Vitamin C [76,78–79]	May slow tumor growth in vitro and in vivo.	No effect of diet or supplement on incident PCa or total cancer.	Rare. One study showed no effect.	May act both as pro-oxidant and antioxidant.
Vitamin D [80–106]	May slow PCa progression.	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.	No effect of vitamin D supplement on PSA or PCa risk.	Association between vitamin D and PCa may depend on factors including Ca intake, disease stages and racial background.
Vitamin E [68,78,107–120]	May slow PCa tumor growth.	Diet and plasma vitamin E inversely associated with PCa risk, but not supplement.	400 IU supplement had no effect or increased high-grade PCa risk, 75 IU supplement lowered risk in smokers.	Dosage and selenium status may modulate association.
Vitamin K [121–123]	Antitumor, chemo and potential radiosensitizers.	Inverse relationship between vit K intake and PCa incidence.	NA	Inadequate evidence.
Calcium [38,124–127]	Rare	Calcium intake increased or decreased PCa risk. An “U” shaped relationship may exist.	NA	Inadequate evidence.
Selenium [118,120,128–131]	Inhibited angiogenesis, proliferation, and induced apoptosis.	Toenail Selenium associated with reduced advanced PCa risk.	Selenium supplement had no effect for PCa chemoprevention, or increased high-grade PCa risk among men with high Selenium status.	Effect of selenium may depend on selenium status and genotype.
Silibinin [135–141]	Inhibited PCa growth.	NA	NA	Potential as chemo-preventive agent. No human clinical trials.
Curcumin [2,142–149]	Inhibited proinflammatory NF-B, induced apoptosis, slowed PCa growth.	NA	3 g/day curcumin supplement for 3 months increased plasma antioxidant activity but did not affect PSA among patients treated with radiotherapy.	Potential to slow PCa growth, awaits further human research.
Pomegranate [143,150–154,179]	Inhibited PCa proliferation, tumor growth, angiogenesis and metastasis.	NA	Blend of pomegranate, green tea, broccoli and turmeric decreased rise in PSA.	Weak evidence of benefit in limited human trials.

(*continued on next page*)

Table (***Continued***)

Nutrient or food factor and references	Preclinical study	Epidemiological study	Clinical study	Summary
			Pomegranate extract may affect PSA doubling time in certain genotype only.	
Green tea [128,143,155−164,179]	Inhibited PCa growth, induced apoptosis, decreased inflammation.	Habitual and total tea consumption associated with decreased PCa risk.	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.
Resveratrol [143,165−172]	Inhibited PCa growth in some but not all studies.	NA	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.
Zyflamend [173−177]	Reduced PCa progression.	NA	Reduced risk among those with high-grade PCa.	Potential to slow PCa growth but very few human trials.
Fruits and vegetables [179−184]	NA	Allium vegetable reduced PCa risk. Inverse relationship between total fruit and vegetable intake and PCa risk.	NA	Limited evidence, but consistent with evidence of other nutrients and dietary factors.
Tomatoes and products [2,68,181,185−187]	Lycopene slowed PCa initiation, growth, and progression.	Higher lycopene intake or serum level associated with decreased PSA and lower PCa risk.	Lycopene or tomato sauce supplement lowered PSA, PCa symptoms or no effect on markers of PCa proliferation or even increased PCa incidence.	Potential but conflicting human trials results.
Coffee [2,188]	NA	Inverse or no association between coffee consumption and PCa risk.	NA	Weak evidence.
Dietary pattern [154,188−201]	NA	High HEI associated with lower PCa risk. Mediterranean, Asian and Vegan diets associated with lower risk but Western diet associated with higher PCa risk.	NA	Promising. Future RCTs needed.
Body weight [202−206]	Reduced PCa tumor growth and progression.	Obesity associated with increased risk for aggressive PCa incidence, biochemical failure, PCa-specific mortality, progression and increased treatment complication.	NA	Promising. Future RCT needed.

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

P.-H. Lin and S. Freedland conducted the review, P.-H. Lin drafted the article and S. Freedland and W. Aronson edited and provided critical input. All authors provided final approval.

References

[1] Group USCSW. United States Cancer Statistics: 1999–2013 Incidence and Mortality Web-based Report. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2016.
[2] Lin PH, Aronson W, Freedland SJ. Nutrition, dietary interventions and prostate cancer: the latest evidence. BMC Med 2015;13:3.
[3] Mavropoulos JC, Isaacs WB, Pizzo SV, Freedland SJ. Is there a role for a low-carbohydrate ketogenic diet in the management of prostate cancer? Urology 2006;68:15–8.
[4] Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279:563–6.
[5] Freedland SJ, Mavropoulos J, Wang A, et al. Carbohydrate restriction, prostate cancer growth, and the insulin-like growth factor axis. Prostate 2008;68:11–9.
[6] Mavropoulos JC, Buschemeyer WC 3rd, Tewari AK, et al. The effects of varying dietary carbohydrate and fat content on survival in a murine LNCaP prostate cancer xenograft model. Cancer Prev Res (Phila) 2009;2:557–65. http://dx.doi.org/10.1158/1940-6207.CAPR-08-0188. Epub 2009 May 26.
[7] Masko EM, Thomas JA 2nd, Antonelli JA, et al. Low-carbohydrate diets and prostate cancer: how low is low enough? Cancer Prev Res (Phila) 2010;3:1124–31.
[8] Drake I, Sonestedt E, Gullberg B, et al. Dietary intakes of carbohydrates in relation to prostate cancer risk: a prospective study in the Malmo Diet and Cancer cohort. Am J Clin Nutr 2012;96:1409–18.
[9] Fokidis HB, Yieng Chin M, Ho VW, et al. A low carbohydrate, high protein diet suppresses intratumoral androgen synthesis and slows castration-resistant prostate tumor growth in mice. J Steroid Biochem Mol Biol 2015;150:35–45.
[10] Ax E, Garmo H, Grundmark B, et al. Dietary patterns and prostate cancer risk: report from the population based ULSAM cohort study of Swedish men. Nutr Cancer 2014;66:77–87.
[11] Vidal AC, Williams CD, Allott EH, et al. Carbohydrate intake, glycemic index and prostate cancer risk. Prostate 2015;75:430–9.
[12] Zhang J, Shen C, Wang L, et al. Metformin inhibits epithelial-mesenchymal transition in prostate cancer cells: Involvement of the tumor suppressor miR30a and its target gene SOX4. Biochem Biophys Res Commun 2014;26;452:746–52. http://dx.doi.org/10.1016/j.bbrc.2014.08.154. Epub 2014 Sep 6.
[13] Lee SY, Song CH, Xie YB, Jung C, Choi HS, Lee K. SMILE upregulated by metformin inhibits the function of androgen receptor in prostate cancer cells. Cancer Lett 2014;28;354:390–7. http://dx.doi.org/10.1016/j.canlet.2014.09.001. Epub 2014 Sep 6.
[14] Demir U, Koehler A, Schneider R, Schweiger S, Klocker H. Metformin anti-tumor effect via disruption of the MID1 translational regulator complex and AR downregulation in prostate cancer cells. BMC Cancer 2014;14:52.
[15] Joshua AM, Zannella VE, Downes MR, et al. A pilot "window of opportunity" neoadjuvant study of metformin in localised prostate cancer. Prostate Cancer Prostatic Dis 2014;17:252–8.
[16] Rothermundt C, Hayoz S, Templeton AJ, et al. Metformin in chemotherapy-naive castration-resistant prostate cancer: a multicenter phase 2 trial (SAKK 08/09). Eur Urol 2014;66:468–74. http://dx.doi.org10.1016/j.eururo.2013.12.057. Epub 2014 Jan 4.
[17] Margel D. Metformin to prevent prostate cancer: a call to unite. Eur Urol 2014;66:1021–2. http://dx.doi.org/10.1016/j.eururo.2014.05.012. Epub 2014 Jun 5.
[18] Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol 2013;31:3069–75.
[19] Tseng CH. Metformin significantly reduces incident prostate cancer risk in Taiwanese men with type 2 diabetes mellitus. Eur J Cancer 2014;50:2831–7. http://dx.doi.org/10.1016/j.ejca.2014.08.007. Epub 2014 Sep 5.
[20] Allott EH, Abern MR, Gerber L, et al. Metformin does not affect risk of biochemical recurrence following radical prostatectomy: results from the SEARCH database. Prostate Cancer Prostatic Dis 2013;16:391–7.
[21] Rieken M, Kluth LA, Xylinas E, et al. Association of diabetes mellitus and metformin use with biochemical recurrence in patients treated with radical prostatectomy for prostate cancer. World J Urol 2014;32:999–1005.
[22] Margel D, Urbach D, Lipscombe LL, et al. Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst 2013;105:1123–31.
[23] Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One 2013;8:e71583.
[24] Kaushik D, Karnes RJ, Eisenberg MS, Rangel LJ, Carlson RE, Bergstralh EJ. Effect of metformin on prostate cancer outcomes after radical prostatectomy. Urol Oncol 2014;32:43.e41–43.
[25] Bensimon L, Yin H, Suissa S, Pollak MN, Azoulay L. The use of metformin in patients with prostate cancer and the risk of death. Cancer Epidemiol Biomarkers Prev 2014;23:2111–8. http://dx.doi.org/10.1158/1055-9965.EPI-14-0056. Epub 2014 Jul 13.
[26] Tsilidis KK, Capothanassi D, Allen NE, et al. Metformin does not affect cancer risk: a cohort study in the U.K. Clinical practice research datalink analyzed like an intention-to-treat trial. Diabetes Care 2014;37:2522–32.
[27] Ross JK, Pusateri DJ, Shultz TD. Dietary and hormonal evaluation of men at different risks for prostate cancer: fiber intake, excretion, and composition, with in vitro evidence for an association between steroid hormones and specific fiber components. Am J Clin Nutr 1990;51:365–70.
[28] Longcope C, Feldman HA, McKinlay JB, Araujo AB. Diet and sex hormone-binding globulin. J Clin Endocrinol Metab 2000;85:293–6.
[29] Barnard RJ, Aronson WJ, Tymchuk CN, Ngo TH. Prostate cancer: another aspect of the insulin-resistance syndrome? Obes Rev 2002;3:303–8.
[30] Deschasaux M, Pouchieu C, His M, Hercberg S, Latino-Martel P, Touvier M. Dietary total and insoluble fiber intakes are inversely associated with prostate cancer risk. J Nutr 2014;144:504–10.
[31] Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 2014;100(Suppl. 1):394S–8S.
[32] Sawada N, Iwasaki M, Yamaji T, et al. Fiber intake and risk of subsequent prostate cancer in Japanese men. Am J Clin Nutr 2015;101:118–25.

[33] Sheng T, Shen RL, Shao H, Ma TH. No association between fiber intake and prostate cancer risk: a meta-analysis of epidemiological studies. World J Surg Oncol 2015;13:264.
[34] Wang RJ, Tang JE, Chen Y, Gao JG. Dietary fiber, whole grains, carbohydrate, glycemic index, and glycemic load in relation to risk of prostate cancer. Onco Targets Ther 2015;8:2415–26.
[35] Fontana L, Adelaiye RM, Rastelli AL, et al. Dietary protein restriction inhibits tumor growth in human xenograft models. Oncotarget 2013;4:2451–61.
[36] Young NJ, Metcalfe C, Gunnell D, et al. A cross-sectional analysis of the association between diet and insulin-like growth factor (IGF)-I, IGF-II, IGF-binding protein (IGFBP)-2, and IGFBP-3 in men in the United Kingdom. Cancer Causes Control 2012;23:907–17.
[37] Yang M, Kenfield SA, Van Blarigan EL, et al. Dairy intake after prostate cancer diagnosis in relation to disease-specific and total mortality. Int J Cancer 2015;137:2462–9.
[38] Aune D, Navarro Rosenblatt DA, Chan DS, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr 2015;101:87–117.
[39] Christensen MJ, Quiner TE, Nakken HL, Lephart ED, Eggett DL, Urie PM. Combination effects of dietary soy and methylselenocysteine in a mouse model of prostate cancer. Prostate 2013;73:986–95.
[40] van Die MD, Bone KM, Williams SG, Pirotta MV. Soy and soy isoflavones in prostate cancer: a systematic review and meta-analysis of randomized controlled trials. BJU Int 2014;113(5b):E119–30.
[41] Hamilton-Reeves JM, Banerjee S, Banerjee SK, et al. Short-term soy isoflavone intervention in patients with localized prostate cancer: a randomized, double-blind, placebo-controlled trial. PloS One 2013;8:e68331.
[42] Bosland MC, Kato I, Zeleniuch-Jacquotte A, et al. Effect of soy protein isolate supplementation on biochemical recurrence of prostate cancer after radical prostatectomy: a randomized trial. J Am Med Assoc 2013;310:170–8.
[43] Travis RC, Allen NE, Appleby PN, et al. Prediagnostic concentrations of plasma genistein and prostate cancer risk in 1,605 men with prostate cancer and 1,697 matched control participants in EPIC. Cancer Causes Control 2012;23:1163–71. https://doi.org/10.1007/s10552-012-9985-y. Epub May 22, 2012.
[44] Jackson MD, McFarlane-Anderson ND, Simon GA, Bennett FI, Walker SP. Urinary phytoestrogens and risk of prostate cancer in Jamaican men. Cancer Causes Control 2010;21:2249–57. https://doi.org/10.1007/s10552-010-9648-9. Epub October 6, 2010.
[45] Lazarevic B, Hammarström C, Yang J, et al. The effects of short-term genistein intervention on prostate biomarker expression in patients with localised prostate cancer before radical prostatectomy. Br J Nutr 2012;108(12):2138–47. https://doi.org/10.1017/S0007114512000384. Epub March 8, 2012.
[46] Lesinski GB, Reville PK, Mace TA, et al. Consumption of soy isoflavone enriched bread in men with prostate cancer is associated with reduced proinflammatory cytokines and immunosuppressive cells. Cancer Prev Res (Phila) 2015;8:1036–44.
[47] Schroder FH, Roobol MJ, Boeve ER, et al. Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement. Eur Urol 2005;48:922–30:. [discussion 930–921].
[48] Ables G, Johnson J. Pleiotropic responses to methionine restriction. Exp Gerontol 2017;94:83–8. http://dx.doi.org/10.1016/j.exger.2017.01.012. Epub 2017 Jan 17.
[49] Sinha R, Cooper TK, Rogers CJ, et al. Dietary methionine restriction inhibits prostatic intraepithelial neoplasia in TRAMP mice. Prostate 2014;74:1663–73.
[50] Kobayashi N, Barnard RJ, Said J, et al. Effect of low-fat diet on development of prostate cancer and Akt phosphorylation in the Hi-Myc transgenic mouse model. Cancer Res 2008;68(8):3066–73.
[51] Ngo TH, Barnard RJ, Cohen P, et al. Effect of isocaloric low-fat diet on human LAPC-4 prostate cancer xenografts in severe combined immunodeficient mice and the insulin-like growth factor axis. Clin Cancer Res 2003;9:2734–43.
[52] Huang M, Narita S, Numakura K, et al. A high-fat diet enhances proliferation of prostate cancer cells and activates MCP-1/CCR2 signaling. Prostate 2012;72:1779–88.
[53] Chang SN, Han J, Abdelkader TS, et al. High animal fat intake enhances prostate cancer progression and reduces glutathione peroxidase 3 expression in early stages of TRAMP mice. Prostate 2014;74:1266–77.
[54] Liang P, Henning SM, Schokrpur S, et al. Effect of dietary omega-3 fatty acids on tumor-associated macrophages and prostate cancer progression. Prostate 2016;76:1293–302.
[55] Huang M, Koizumi A, Narita S, et al. Diet-induced alteration of fatty acid synthase in prostate cancer progression. Oncogenesis 2016;5:e195.
[56] Xu H, Hu MB, Bai PD, et al. Proinflammatory cytokines in prostate cancer development and progression promoted by high-fat diet. BioMed Res Int 2015;2015:249741.
[57] Xu H, Jiang HW, Ding Q. Insulin-Like growth factor 1 related pathways and high-fat diet promotion of transgenic adenocarcinoma mouse prostate (TRAMP) cancer progression. Actas Urol Esp 2015;39:161–8.
[58] Kwon OJ, Zhang B, Zhang L, Xin L. High fat diet promotes prostatic basal-to-luminal differentiation and accelerates initiation of prostate epithelial hyperplasia originated from basal cells. Stem Cell Res 2016;16:682–91.
[59] Xu C, Han FF, Zeng XT, Liu TZ, Li S, Gao ZY. Fat Intake Is Not Linked to Prostate Cancer: A Systematic Review and Dose-Response Meta-Analysis. PLoS ONE 2015;10(7):e0131747.
[60] Galet C, Gollapudi K, Stepanian S, et al. Effect of a low-fat fish oil diet on proinflammatory eicosanoids and cell-cycle progression score in men undergoing radical prostatectomy. Cancer Prev Res (Phila) 2014;7:97–104.
[61] Brasky TM, Darke AK, Song X, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. J Natl Cancer Inst 2013;105:1132–41.
[62] Crowe FL, Appleby PN, Travis RC, et al. Circulating fatty acids and prostate cancer risk: individual participant meta-analysis of prospective studies. J Natl Cancer Inst 2014;106:pii: dju240. http//dx.doi.org/10.1093/jnci/dju240. Print 2014 Sep.
[63] Aucoin M, Cooley K, Knee C, et al. Fish-derived omega-3 fatty acids and prostate cancer: a systematic review. Integr Cancer Ther 2017;16:32–62. http://dx.doi.org/10.1177/1534735416656052. Epub 2016 Jun 29.
[64] Slawin K, Kadmon D, Park SH, et al. Dietary fenretinide, a synthetic retinoid, decreases the tumor incidence and the tumor mass of ras +myc-induced carcinomas in the mouse prostate reconstitution model system. Cancer Res 1993;53:4461–5.
[65] Lotan Y, Xu XC, Shalev M, et al. Differential expression of nuclear retinoid receptors in normal and malignant prostates. J Clin Oncol 2000;18:116–21.
[66] Thaller C, Shalev M, Frolov A, et al. Fenretinide therapy in prostate cancer: effects on tissue and serum retinoid concentration. J Clin Oncol 2000;18:3804–8.
[67] Cheung E, Pinski J, Dorff T, et al. Oral fenretinide in biochemically recurrent prostate cancer: a California cancer consortium phase II trial. Clin Genitourin Cancer 2009;7:43–50.
[68] Key TJ, Appleby PN, Travis RC, et al. Carotenoids, retinol, tocopherols, and prostate cancer risk: pooled analysis of 15 studies. Am J Clin Nutr 2015;102:1142–57.
[69] Nash SH, Till C, Song X, et al. Serum retinol and carotenoid concentrations and prostate cancer risk: results from the Prostate Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev 2015;24:1507–15.

[70] Li C, Imai M, Matsuura T, Hasegawa S, Yamasaki M, Takahashi N. Inhibitory effects of retinol are greater than retinoic acid on the growth and adhesion of human refractory cancer cells. Biol Pharm Bull 2016;39:636–40.
[71] Bistulfi G, Foster BA, Karasik E, et al. Dietary folate deficiency blocks prostate cancer progression in the TRAMP model. Cancer Prev Res (Phila) 2011;4:1825–34.
[72] Collin SM. Folate and B12 in prostate cancer. Adv Clin Chem 2013;60:1–63.
[73] Tio M, Andrici J, Cox MR, Eslick GD. Folate intake and the risk of prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2014;17:213–9.
[74] Wang R, Zheng Y, Huang JY, Zhang AQ, Zhou YH, Wang JN. Folate intake, serum folate levels, and prostate cancer risk: a meta-analysis of prospective studies. BMC Public Health 2014;14:1326.
[75] Tomaszewski JJ, Richman EL, Sadetsky N, et al. Impact of folate intake on prostate cancer recurrence following definitive therapy: data from CaPSURE. J Urol 2014;191:971–6.
[76] Roswall N, Larsen SB, Friis S, et al. Micronutrient intake and risk of prostate cancer in a cohort of middle-aged, Danish men. Cancer Causes Control 2013;24:1129–35.
[77] Rycyna KJ, Bacich DJ, O'Keefe DS. Opposing roles of folate in prostate cancer. Urology 2013;82:1197–203.
[78] Wang L, Sesso HD, Glynn RJ, et al. Vitamin E and C supplementation and risk of cancer in men: posttrial follow-up in the Physicians' Health Study II randomized trial. Am J Clin Nutr 2014;100:915–23.
[79] Bai XY, Qu X, Jiang X, et al. Association between dietary vitamin C intake and risk of prostate cancer: a meta-analysis involving 103,658 subjects. J Cancer 2015;6:913–21.
[80] Nelson SM, Batai K, Ahaghotu C, Agurs-Collins T, Kittles RA. Association between serum 25-hydroxy-vitamin D and aggressive prostate cancer in African American men. Nutrients 2016;9:pii: E12. http//dx.doi.org/10.3390/nu9010012.
[81] Nyame YA, Murphy AB, Bowen DK, et al. Associations between serum vitamin D and adverse pathology in men undergoing radical prostatectomy. J Clin Oncol 2016;34:1345–9.
[82] Deschasaux M, Souberbielle JC, Latino-Martel P, et al. A prospective study of plasma 25-hydroxyvitamin D concentration and prostate cancer risk. Br J Nutr 2016;115:305–14.
[83] Galunska B, Gerova D, Kosev P, Anakievski D, Hinev A. Serum 25-hydroxy vitamin D levels in Bulgarian patients with prostate cancer: a pilot study. Clin Lab 2015;61:329–35.
[84] Schenk JM, Till CA, Tangen CM, et al. Serum 25-hydroxyvitamin D concentrations and risk of prostate cancer: results from the Prostate Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev 2014;23:1484–93.
[85] Schwartz GG. Vitamin D in blood and risk of prostate cancer: lessons from the Selenium and Vitamin E Cancer Prevention Trial and the Prostate Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev 2014;23:1447–9.
[86] Brandstedt J, Almquist M, Manjer J, Malm J. Vitamin D, PTH, and calcium in relation to survival following prostate cancer. Cancer Causes Control 2016;27:669–77.
[87] Bernichtein S, Pigat N, Barry Delongchamps N, et al. Vitamin D3 prevents calcium-induced progression of early-stage prostate tumors by counteracting TRPC6 and calcium sensing receptor upregulation. Cancer Res 2017;77:355–65.
[88] Giangreco AA, Vaishnav A, Wagner D, et al. Tumor suppressor microRNAs, miR-100 and -125b, are regulated by 1,25-dihydroxyvitamin D in primary prostate cells and in patient tissue. Cancer Prev Res (Phila) 2013;6(5):483–94.
[89] Hollis BW, Marshall DT, Savage SJ, Garrett-Mayer E, Kindy MS, Gattoni-Celli S. Vitamin D3 supplementation, low-risk prostate cancer, and health disparities. J Steroid Biochem Mol Biol 2013;136:233–7.
[90] Sha J, Pan J, Ping P, et al. Synergistic effect and mechanism of vitamin A and vitamin D on inducing apoptosis of prostate cancer cells. Mol Biol Rep 2013;40:2763–8.
[91] Mondul AM, Weinstein SJ, Moy KA, Mannisto S, Albanes D. Circulating 25-hydroxyvitamin D and prostate cancer survival. Cancer Epidemiol Biomarkers Prev 2016;25:665–9.
[92] Chandler PD, Giovannucci EL, Scott JB, et al. Null association between vitamin D and PSA levels among black men in a vitamin D supplementation trial. Cancer Epidemiol Biomarkers Prev 2014;23:1944–7.
[93] Skaaby T, Husemoen LL, Thuesen BH, et al. Prospective population-based study of the association between serum 25-hydroxyvitamin-D levels and the incidence of specific types of cancer. Cancer Epidemiol Biomarkers Prev 2014;23:1220–9.
[94] Holt SK, Kolb S, Fu R, Horst R, Feng Z, Stanford JL. Circulating levels of 25-hydroxyvitamin D and prostate cancer prognosis. Cancer Epidemiol 2013;37:666–70.
[95] Gupta D, Trukova K, Popiel B, Lammersfeld C, Vashi PG. The association between pre-treatment serum 25-hydroxyvitamin D and survival in newly diagnosed stage IV prostate cancer. PLoS One 2015;10:e0119690.
[96] Sawada N, Inoue M, Iwasaki M, et al. Plasma 25-hydroxy vitamin D and subsequent prostate cancer risk in a nested case-control study in Japan: The JPHC study. Eur J Clin Nutr 2017;71:132–6.
[97] Guo Z, Wen J, Kan Q, et al. Lack of association between vitamin D receptor gene FokI and BsmI polymorphisms and prostate cancer risk: an updated meta-analysis involving 21,756 subjects. Tumour Biol 2013;34:3189–200.
[98] Wong YY, Hyde Z, McCaul KA, et al. In older men, lower plasma 25-hydroxyvitamin D is associated with reduced incidence of prostate, but not colorectal or lung cancer. PLoS One 2014;9:e99954.
[99] Xu Y, Shao X, Yao Y, et al. Positive association between circulating 25-hydroxyvitamin D levels and prostate cancer risk: new findings from an updated meta-analysis. J Cancer Res Clin Oncol 2014;140:1465–77.
[100] Meyer HE, Robsahm TE, Bjorge T, Brustad M, Blomhoff R. Vitamin D, season, and risk of prostate cancer: a nested case-control study within Norwegian health studies. Am J Clin Nutr 2013;97:147–54.
[101] Meyer HE, Stoer NC, Samuelsen SO, et al. Long-term association between serum 25-hydroxyvitamin D and mortality in a cohort of 4,379 men. PLoS One 2016;11:e0151441.
[102] Steck SE, Arab L, Zhang H, et al. Association between plasma 25-hydroxyvitamin D, ancestry and aggressive prostate cancer among African Americans and European Americans in PCaP. PLoS One 2015;10:e0125151.
[103] Jackson MD, Tulloch-Reid MK, Lindsay CM, et al. Both serum 25-hydroxyvitamin D and calcium levels may increase the risk of incident prostate cancer in Caribbean men of African ancestry. Cancer Med 2015;4:925–35.
[104] Weinstein SJ, Mondul AM, Kopp W, Rager H, Virtamo J, Albanes D. Circulating 25-hydroxyvitamin D, vitamin D-binding protein and risk of prostate cancer. Int J Cancer 2013;132:2940–7.
[105] Kristal AR, Till C, Song X, et al. Plasma vitamin D and prostate cancer risk: results from the Selenium and Vitamin E Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev 2014;23:1494–504.
[106] Anic GM, Albanes D, Rohrmann S, et al. Association between serum 25-hydroxyvitamin D and serum sex steroid hormones among men in NHANES. Clin Endocrinol (Oxf) 2016;85:258–66.
[107] Wang H, Hong J, Yang CS. delta-Tocopherol inhibits receptor tyrosine kinase-induced AKT activation in prostate cancer cells. Mol Carcinog 2016;55:1728–38.
[108] Chen JX, Li G, Wang H, et al. Dietary tocopherols inhibit PhIP-induced prostate carcinogenesis in CYP1A-humanized mice. Cancer Lett 2016;371:71–8.

[109] Huang Y, Wu R, Su ZY, et al. A naturally occurring mixture of tocotrienols inhibits the growth of human prostate tumor, associated with epigenetic modifications of cyclin-dependent kinase inhibitors p21 and p27. J Nutr Biochem 2017;40:155–63.
[110] Antwi SO, Steck SE, Zhang H, et al. Plasma carotenoids and tocopherols in relation to prostate-specific antigen (PSA) levels among men with biochemical recurrence of prostate cancer. Cancer Epidemiol 2015;39:752–62.
[111] Weinstein SJ, Peters U, Ahn J, et al. Serum alpha-tocopherol and gamma-tocopherol concentrations and prostate cancer risk in the PLCO Screening Trial: a nested case-control study. PloS One 2012;7:e40204.
[112] Cui R, Liu ZQ, Xu Q. Blood alpha-tocopherol, gamma-tocopherol levels and risk of prostate cancer: a meta-analysis of prospective studies. PloS One 2014;9:e93044.
[113] Major JM, Yu K, Weinstein SJ, et al. Genetic variants reflecting higher vitamin e status in men are associated with reduced risk of prostate cancer. J Nutr 2014;144:729–33.
[114] Antwi SO, Steck SE, Su LJ, et al. Dietary, supplement, and adipose tissue tocopherol levels in relation to prostate cancer aggressiveness among African and European Americans: the North Carolina-Louisiana Prostate Cancer Project (PCaP). Prostate 2015;75:1419–35.
[115] Lawson KA, Wright ME, Subar A, et al. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. J Natl Cancer Inst 2007;99:754–64.
[116] Calle EE, Rodriguez C, Jacobs EJ, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. Cancer 2002;94:2490–501.
[117] Virtamo J, Taylor PR, Kontto J, et al. Effects of alpha-tocopherol and beta-carotene supplementation on cancer incidence and mortality: 18-year postintervention follow-up of the alpha-tocopherol, beta-carotene Cancer Prevention Study. Int J Cancer 2014;135:178–85.
[118] Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). J Am Med Assoc 2011;306:1549–56.
[119] Albanes D, Till C, Klein EA, et al. Plasma tocopherols and risk of prostate cancer in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Cancer Prev Res (Phila) 2014;7:886–95.
[120] Kristal AR, Darke AK, Morris JS, et al. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. J Natl Cancer Inst 2014;106:djt456.
[121] Tomasetti M, Nocchi L, Neuzil J, et al. Alpha-tocopheryl succinate inhibits autophagic survival of prostate cancer cells induced by vitamin K3 and ascorbate to trigger cell death. PloS One 2012;7:e52263.
[122] Tew BY, Pal SK, He M, et al. Vitamin K epoxide reductase expression and prostate cancer risk. Urol Oncol 2017;35:112.e13–18. http://dx.doi.org/10.1016/j.urolonc.2016.10.020. Epub 2016 Nov 23.
[123] Nimptsch K, Rohrmann S, Kaaks R, Linseisen J. Dietary vitamin K intake in relation to cancer incidence and mortality: results from the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg). Am J Clin Nutr 2010;91(5):1348–58.
[124] Ma RW, Chapman K. A systematic review of the effect of diet in prostate cancer prevention and treatment. J Hum Nutr Diet 2009;22:187–99:[quiz 200–182].
[125] Bristow SM, Bolland MJ, MacLennan GS, et al. Calcium supplements and cancer risk: a meta-analysis of randomised controlled trials. Br J Nutr 2013;110:1384–93.
[126] Williams CD, Whitley BM, Hoyo C, et al. Dietary calcium and risk for prostate cancer: a case-control study among US veterans. Prev Chronic Dis 2012;9:E39.
[127] Wilson KM, Shui IM, Mucci LA, Giovannucci E. Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study. Am J Clin Nutr 2015;101:173–83.
[128] Hori S, Butler E, McLoughlin J. Prostate cancer and diet: food for thought? BJU Int 2011;107:1348–59.
[129] Chan JM, Darke AK, Penney KL, et al. Selenium- or vitamin E-related gene variants, interaction with supplementation, and risk of high-grade prostate cancer in SELECT. Cancer Epidemiol Biomarkers Prev 2016;25:1050–8.
[130] Geybels MS, Verhage BA, van Schooten FJ, Goldbohm RA, van den Brandt PA. Advanced prostate cancer risk in relation to toenail selenium levels. J Natl Cancer Inst 2013;105:1394–401.
[131] Lu J, Zhang J, Jiang C, Deng Y, Ozten N, Bosland MC. Cancer chemoprevention research with selenium in the post-SELECT era: promises and challenges. Nutr Cancer 2016;68:1–17.
[132] Masko EM, Allott EH, Freedland SJ. The relationship between nutrition and prostate cancer: is more always better? Eur Urol 2013;63:810–20.
[133] Kallifatidis G, Hoy JJ, Lokeshwar BL. Bioactive natural products for chemoprevention and treatment of castration-resistant prostate cancer. Semin Cancer Biol 2016;40–41:160–9.
[134] Farzaei MH, Bahramsoltani R, Rahimi R. Phytochemicals as adjunctive with conventional anticancer therapies. Curr Pharm Des 2016;22:4201–18.
[135] Nambiar DK, Rajamani P, Singh RP. Silibinin attenuates ionizing radiation-induced pro-angiogenic response and EMT in prostate cancer cells. Biochem Biophys Res Commun 2015;456:262–8.
[136] Schlaepfer IR, Nambiar DK, Ramteke A, et al. Hypoxia induces triglycerides accumulation in prostate cancer cells and extracellular vesicles supporting growth and invasiveness following reoxygenation. Oncotarget 2015;6:22836–56.
[137] Nambiar DK, Deep G, Singh RP, Agarwal C, Agarwal R. Silibinin inhibits aberrant lipid metabolism, proliferation and emergence of androgen-independence in prostate cancer cells via primarily targeting the sterol response element binding protein 1. Oncotarget 2014;5:10017–33.
[138] Ting HJ, Deep G, Jain AK, et al. Silibinin prevents prostate cancer cell-mediated differentiation of naive fibroblasts into cancer-associated fibroblast phenotype by targeting TGF beta2. Mol Carcinog 2015;54:730–41.
[139] Kim S, Han J, Jeon M, et al. Silibinin inhibits triple negative breast cancer cell motility by suppressing TGF-beta2 expression. Tumour Biol 2016;37:11397–407.
[140] Ting H, Deep G, Kumar S, Jain AK, Agarwal C, Agarwal R. Beneficial effects of the naturally occurring flavonoid silibinin on the prostate cancer microenvironment: role of monocyte chemotactic protein-1 and immune cell recruitment. Carcinogenesis 2016;37:589–99.
[141] Deep G, Kumar R, Jain AK, Agarwal C, Agarwal R. Silibinin inhibits fibronectin induced motility, invasiveness and survival in human prostate carcinoma PC3 cells via targeting integrin signaling. Mutat Res 2014;768:35–46.
[142] Yang J, Ning J, Peng L, He D. Effect of curcumin on Bcl-2 and Bax expression in nude mice prostate cancer. Int J Clin Exp Pathol 2015;8:9272–8.
[143] Khan N, Adhami VM, Mukhtar H. Apoptosis by dietary agents for prevention and treatment of prostate cancer. Endocr Relat Cancer 2010;17:R39–52.
[144] Guo H, Xu Y, Fu Q. Curcumin inhibits growth of prostate carcinoma via miR-208-mediated CDKN1A activation. Tumour Biol 2015;36:8511–7.
[145] Klippstein R, Bansal SS, Al-Jamal KT. Doxorubicin enhances curcumin's cytotoxicity in human prostate cancer cells in vitro by enhancing its cellular uptake. Int J Pharm 2016;514:169–75.
[146] Sha J, Li J, Wang W, et al. Curcumin induces G0/G1 arrest and apoptosis in hormone independent prostate cancer DU-145 cells by down regulating Notch signaling. Biomed Pharmacother 2016;84:177–84.

[147] Huang H, Chen X, Li D, et al. Combination of alpha-tomatine and curcumin inhibits growth and induces apoptosis in human prostate cancer cells. PloS One 2015;10:e0144293.
[148] Hejazi J, Rastmanesh R, Taleban FA, et al. Effect of curcumin supplementation during radiotherapy on oxidative status of patients with prostate cancer: a double blinded, randomized, placebo-controlled study. Nutr Cancer 2016;68:77–85.
[149] Antony B, Merina B, Iyer VS, Judy N, Lennertz K, Joyal S. A pilot cross-over study to evaluate human oral bioavailability of BCM-95CG (Biocurcumax), a novel bioenhanced preparation of curcumin. Indian J Pharm Sci 2008;70:445–9.
[150] Heber D. Pomegranate ellagitannins. In: Benzie IFF, Wachtel-Galor S, eds. Herbal Medicine: Biomolecular and Clinical Aspects, 2nd ed., Boca Raton, FL: CRC Press; 2011.
[151] Wang L, Li W, Lin M, et al. Luteolin, ellagic acid and punicic acid are natural products that inhibit prostate cancer metastasis. Carcinogenesis 2014;35:2321–30.
[152] Ming DS, Pham S, Deb S, et al. Pomegranate extracts impact the androgen biosynthesis pathways in prostate cancer models in vitro and in vivo. J Steroid Biochem Mol Biol 2014;143:19–28.
[153] Pantuck AJ, Pettaway CA, Dreicer R, et al. A randomized, double-blind, placebo-controlled study of the effects of pomegranate extract on rising PSA levels in men following primary therapy for prostate cancer. Prostate Cancer Prostatic Dis 2015;18(3):242–8.
[154] Thomas R, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer—the UK NCRN Pomi-T study. Prostate Cancer Prostatic Dis 2014;17:180–6.
[155] Tsai YJ, Chen BH. Preparation of catechin extracts and nanoemulsions from green tea leaf waste and their inhibition effect on prostate cancer cell PC-3. Int J Nanomedicine 2016;11:1907–26.
[156] Thakur VS, Gupta K, Gupta S. Green tea polyphenols causes cell cycle arrest and apoptosis in prostate cancer cells by suppressing class I histone deacetylases. Carcinogenesis 2012;33:377–84.
[157] Wang P, Aronson WJ, Huang M, et al. Green tea polyphenols and metabolites in prostatectomy tissue: implications for cancer prevention. Cancer Prev Res (Phila) 2010;3:985–93.
[158] Henning SM, Wang P, Said JW, et al. Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy. Prostate 2015;75:550–9.
[159] McLarty J, Bigelow RL, Smith M, Elmajian D, Ankem M, Cardelli JA. Tea polyphenols decrease serum levels of prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients and inhibit production of hepatocyte growth factor and vascular endothelial growth factor in vitro. Cancer Prev Res (Phila) 2009;2:673–82.
[160] Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. Cancer Res 2006;66:1234–40.
[161] Kumar NB, Pow-Sang J, Egan KM, et al. Randomized, placebo-controlled trial of green tea catechins for prostate cancer prevention. Cancer Prev Res (Phila) 2015;8:879–87.
[162] Hoang VD, Lee AH, Pham NM, Xu D, Binns CW. Habitual tea consumption reduces prostate cancer risk in vietnamese men: a case-control study. Asian Pacific J Cancer Prev 2016;17:4939–44.
[163] Fei X, Shen Y, Li X, Guo H. The association of tea consumption and the risk and progression of prostate cancer: a meta-analysis. Int J Clin Exp Med 2014;7:3881–91.
[164] Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S. Green tea consumption and prostate cancer risk in Japanese men: a prospective study. Am J Epidemiol 2008;167:71–7.
[165] Fraser SP, Peters A, Fleming-Jones S, Mukhey D, Djamgoz MB. Resveratrol: inhibitory effects on metastatic cell behaviors and voltage-gated na(+) channel activity in rat prostate cancer in vitro. Nutr Cancer 2014;66:1047–58.
[166] Oskarsson A, Spatafora C, Tringali C, Andersson AO. Inhibition of CYP17A1 activity by resveratrol, piceatannol, and synthetic resveratrol analogs. Prostate 2014;74:839–51.
[167] Ferruelo A, Romero I, Cabrera PM, Arance I, Andres G, Angulo JC. Effects of resveratrol and other wine polyphenols on the proliferation, apoptosis and androgen receptor expression in LNCaP cells. Actas Urol Esp 2014;38:397–404.
[168] Osmond GW, Masko EM, Tyler DS, Freedland SJ, Pizzo S. In vitro and in vivo evaluation of resveratrol and 3,5-dihydroxy-4'-acetoxy-trans-stilbene in the treatment of human prostate carcinoma and melanoma. J Surg Res 2013;179:e141–8.
[169] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov 2006;5:493–506.
[170] Klink JC, Tewari AK, Masko EM, et al. Resveratrol worsens survival in SCID mice with prostate cancer xenografts in a cell-line specific manner, through paradoxical effects on oncogenic pathways. Prostate 2013;73:754–62.
[171] Paller CJ, Rudek MA, Zhou XC, et al. A phase I study of muscadine grape skin extract in men with biochemically recurrent prostate cancer: safety, tolerability, and dose determination. Prostate 2015;75:1518–25.
[172] 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.
[173] Huang EC, Zhao Y, Chen G, et al. Zyflamend, a polyherbal mixture, down regulates class I and class II histone deacetylases and increases p21 levels in castrate-resistant prostate cancer cells. BMC Complement Altern Med 2014;14:68.
[174] Huang EC, McEntee MF, Whelan J. Zyflamend, a combination of herbal extracts, attenuates tumor growth in murine xenograft models of prostate cancer. Nutr Cancer 2012;64:749–60.
[175] Yan J, Xie B, Capodice JL, Katz AE. Zyflamend inhibits the expression and function of androgen receptor and acts synergistically with bicalutimide to inhibit prostate cancer cell growth. Prostate 2012;72:244–52.
[176] Kunnumakkara AB, Sung B, Ravindran J, et al. Zyflamend suppresses growth and sensitizes human pancreatic tumors to gemcitabine in an orthotopic mouse model through modulation of multiple targets. Int J Cancer 2012;131:E292–303.
[177] Capodice JL, Gorroochurn P, Cammack AS, et al. Zyflamend in men with high-grade prostatic intraepithelial neoplasia: results of a phase I clinical trial. J Soc Integr Oncol 2009;7:43–51.
[178] Rafailov S, Cammack S, Stone BA, Katz AE. The role of Zyflamend, an herbal anti-inflammatory, as a potential chemopreventive agent against prostate cancer: a case report. Integr Cancer Ther 2007;6:74–6.
[179] Thomas R, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer-the UK NCRN Pomi-T study. Prostate Cancer Prostatic Dis 2014 Jun;17:180–6. http://dx.doi.org/10.1038/pcan.2014.6. Epub 2014 Mar 11.
[180] Turati F, Rossi M, Pelucchi C, Levi F, La Vecchia C. Fruit and vegetables and cancer risk: a review of southern European studies. Br J Nutr 2015;113(Suppl. 2):S102–10.
[181] Diallo A, Deschasaux M, Galan P, et al. Associations between fruit, vegetable and legume intakes and prostate cancer risk: results from the prospective Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) cohort. Br J Nutr 2016;115:1579–85.
[182] Umesawa M, Iso H, Mikami K, et al. Relationship between vegetable and carotene intake and risk of prostate cancer: the JACC study. Br J Cancer 2014;110:792–6.

[183] Hsing AW, Chokkalingam AP, Gao YT, et al. Allium vegetables and risk of prostate cancer: a population-based study. J Natl Cancer Inst 2002;94:1648–51.
[184] Chan R, Lok K, Woo J. Prostate cancer and vegetable consumption. Mol Nutr Food Res 2009;53:201–16.
[185] Smith JW, Rowles JL III, Miller RJ, Clinton SK, O'Brien WDJ, Erdman JW Jr. Dietary tomato reduces castration-resistant prostate cancer burden in the TRAMP model. FASEB J 2016;30:147.141.
[186] Gann PH, Deaton RJ, Rueter EE, et al. A phase II randomized trial of lycopene-rich tomato extract among men with high-grade prostatic intraepithelial neoplasia. Nutr Cancer 2015;67:1104–12.
[187] Gontero P, Marra G, Soria F, et al. A randomized double-blind placebo controlled phase I-II study on clinical and molecular effects of dietary supplements in men with precancerous prostatic lesions. Chemoprevention or "chemopromotion"? Prostate 2015;75:1177–86.
[188] Russnes KM, Moller E, Wilson KM, et al. Total antioxidant intake and prostate cancer in the Cancer of the Prostate in Sweden (CAPS) study. A case control study. BMC Cancer 2016;16:438.
[189] Linnewiel-Hermoni K, Khanin M, Danilenko M, et al. The anti-cancer effects of carotenoids and other phytonutrients resides in their combined activity. Arch Biochem Biophys 2015;572:28–35.
[190] Bosire C, Stampfer MJ, Subar AF, et al. Index-based dietary patterns and the risk of prostate cancer in the NIH-AARP diet and health study. Am J Epidemiol 2013;177:504–13.
[191] Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. Cancer Med 2015;4:1933–47.
[192] Kenfield SA, Dupre N, Richman EL, Stampfer MJ, Chan JM, Giovannucci EL. Mediterranean diet and prostate cancer risk and mortality in the health professionals follow-up study. Eur Urol 2014;65:887–94.
[193] Ostan R, Bene MC, Spazzafumo L, et al. Impact of diet and nutraceutical supplementation on inflammation in elderly people. Results from the RISTOMED study, an open-label randomized control trial. Clin Nutr 2016;35:812–8.
[194] Baade PD, Youlden DR, Krnjacki LJ. International epidemiology of prostate cancer: geographical distribution and secular trends. Mol Nutr Food Res 2009;53:171–84.
[195] Yang M, Kenfield SA, Van Blarigan EL, et al. Dietary patterns after prostate cancer diagnosis in relation to disease-specific and total mortality. Cancer Prev Res (Phila) 2015;8:545–51.
[196] Tantamango-Bartley Y, Knutsen SF, Knutsen R, et al. Are strict vegetarians protected against prostate cancer? Am J Clin Nutr 2016;103:153–60.
[197] Lall RK, Syed DN, Adhami VM, Khan MI, Mukhtar H. Dietary polyphenols in prevention and treatment of prostate cancer. Int J Mol Sci 2015;16:3350–76.
[198] Vance TM, Wang Y, Su LJ, et al. Dietary total antioxidant capacity is inversely associated with prostate cancer aggressiveness in a population-based study. Nutr Cancer 2016;68:214–24.
[199] Muller DC, Severi G, Baglietto L, et al. Dietary patterns and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2009;18:3126–9.
[200] Tseng M, Breslow RA, DeVellis RF, Ziegler RG. Dietary patterns and prostate cancer risk in the National Health and Nutrition Examination Survey Epidemiological Follow-up Study cohort. Cancer Epidemiol Biomarkers Prev 2004;13:71–7.
[201] Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. Cancer Epidemiol Biomarkers Prev 2006;15:167–71.
[202] Bhindi B, Kulkarni GS, Finelli A, et al. Obesity is associated with risk of progression for low-risk prostate cancers managed expectantly. Eur Urol 2014;66:841–8.
[203] Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol 2013;63:800–9.
[204] Wright JL, Plymate S, D'Oria-Cameron A, et al. A study of caloric restriction versus standard diet in overweight men with newly diagnosed prostate cancer: a randomized controlled trial. Prostate 2013;73:1345–51.
[205] Barrington WE, Schenk JM, Etzioni R, et al. Difference in association of obesity with prostate cancer risk between US African American and non-hispanic white men in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA Oncol 2015;1:342–9.
[206] Vidal AC, Freedland SJ. Obesity and prostate cancer: a focused update on active surveillance, race, and molecular subtyping. Eur Urol 2017;72:78–83. http://dx.doi.org/10.1016/j.eururo.2016.10.011. Epub 2016 Oct 19.
[207] Klement RJ, Sweeney RA. Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. BMC Res Notes 2016;9:143.
[208] Gilbert SE, Tew GA, Fairhurst C, et al. Effects of a lifestyle intervention on endothelial function in men on long-term androgen deprivation therapy for prostate cancer. Br J Cancer 2016;114:401–8.
[209] Freedland S, Aronson W, Howard L, et al. MP04-06 a prospective randomized trial of dietary carbohydrate restriction for men initiating androgen deprivation therapy: carbohydrate and prostate study I (CAPS1). J Urol 2016;195:e29–30.
[210] Parsons JK, Pierce JP, Mohler J, et al. A randomized trial of diet in men with early stage prostate cancer on active surveillance: rationale and design of the Men's Eating and Living (MEAL) Study (CALGB 70807 [Alliance]). Contemp Clin Trials 2014;38:198–203.
[211] Parsons JK, Pierce JP, Mohler J, et al. Men's Eating and Living (MEAL) study (CALGB 70807 [Alliance]): recruitment feasibility and baseline demographics of a randomized trial of diet in men on active surveillance for prostate cancer. BJU Int. 2017. http://dx.doi.org/10.1111/bju.13890. [Epub ahead of print].
[212] Schleper A, Sullivan DK, Thrasher JB, et al. Weight management to reduce prostate cancer risk: a survey of men's needs and interests. Cancer Clin Oncol 2016;5:43–52.
[213] Bhindi B, Locke J, Alibhai SM, et al. Dissecting the association between metabolic syndrome and prostate cancer risk: analysis of a large clinical cohort. Eur Urol. 2015;67:64–70. http://dx.doi.org/10.1016/j.eururo.2014.01.040. Epub 2014 Feb 14.
[214] Esposito K, Chiodini P, Capuano A, et al. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. J Endocrinol Invest 2013;36:132–9.