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The Relationship Between Nutrition and Prostate Cancer: Is More Always Better?

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Abstract

Context—Prostate cancer (PCa) remains one of the most diagnosed malignancies in the world, correlating with regions where men consume more of a so-called Western-style diet. As such, there is much interest in understanding the role of lifestyle and diet on the incidence and progression of PCa.

Objective—To provide a summary of published literature with regard to dietary macro- and micronutrients and PCa incidence and progression.

Evidence acquisition—A literature search was completed using the PubMed database for all studies published on diet and PCa in June 2012 or earlier. Primary literature and meta-analyses were given preference over other review articles when possible.

Evidence synthesis—The literature was reviewed on seven dietary components: carbohydrates, protein, fat and cholesterol, vegetables, vitamins and minerals, and phytochemicals. Current literature linking these nutrients to PCa is limited at best, but trends in the published data suggest consumption of carbohydrates, saturated and ω-6 fats, and certain vitamin supplements may promote PCa risk and progression. Conversely, consumption of many plant phytochemicals and ω-3 fatty acids seem to slow the risk and progression of the disease. All other nutrients seem to have no effect or data are inconclusive. A brief summary about the clinical

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implications of dietary interventions with respect to PCa prevention, treatment, and survivorship is provided.

Conclusions—Due to the number and heterogeneity of published studies investigating diet and PCa, it is difficult to determine what nutrients make up the perfect diet for the primary and secondary prevention of PCa. Because diets are made of multiple macro- and micronutrients, further prospective studies are warranted, particularly those investigating the relationship between whole foods instead of a single nutritional component.

Keywords

Diet; Nutrition; Prostate cancer; Review

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men, with nearly a million new cases diagnosed worldwide [1]. Overall, Western countries have approximately a six-fold higher PCa incidence versus non-Western countries. Although increased screening likely accounts for some of this discrepancy, it has been hypothesized that differences in dietary intake may also contribute, although much of the research has resulted in no clear-cut conclusions [2,3]. A standard Western diet is typically high in calories, saturated fats, refined carbohydrates, animal protein, and low in fresh fruits, vegetables, and whole grains, resulting in a lower intake of essential minerals and phytochemicals and an excess intake of other factors. Not only has a Western diet been linked with the obesity epidemic, it can directly alter parameters known to promote PCa growth [4], and on a population level it is associated with an overall increased incidence of cancers including prostate [5]. However, because the Western diet is composed of many different parameters, as just outlined, it is difficult to discern which specific Western diet components may promote PCa. This creates a significant limitation to the current literature, and indeed the literature is conflicted on this point [6]; therefore more research is needed to elucidate the molecular pathways affected by specific nutrients and determine the precise effects of over- and underconsumption of particular nutrients and ultimately how this relates to PCa. In this review, we summarize the literature on PCa and nutrition, and we discuss how these data may provide insight into designing the optimal diet for primary and secondary PCa prevention. Although the end result of caloric excess (ie, obesity) and the opposite extreme (ie, caloric restriction) have been linked with aggressive PCa and delayed PCa growth, respectively, we do not discuss these here because they are the subject of our companion review.

2. Evidence acquisition

A literature search was performed on July 1, 2012, using PubMed to identify articles about diet and PCa. We searched using the following keywords (Table 1): *prostate cancer, carbohydrates, simple, complex, protein, animal meat, soy, phytoestrogens, dairy products, fat, saturated, unsaturated, omega-3, omega-6, statins, vitamin A, B, C, D, E,* and *K, folate, calcium, selenium, vegetables, cruciferous, allium, phytochemicals, curcumin, ellagitannins, pomegranate, EGCG, lycopene, resveratrol, active surveillance, dietary intervention, quality of life,* and *survivorship.* The search was limited to publications in English, and primary literature, meta-analyses, and systematic reviews were used where appropriate.

3. Evidence synthesis

3.1. Carbohydrates

Carbohydrates, or saccharides, are organic compounds that play critical roles in normal cellular functions including energy storage, coenzyme function, and structural composition

for plants, and they serve as the backbone of genetic material [7]. Carbohydrate-rich foods include fruits, breads, pastas, legumes, potatoes, and sugary treats. Although a common energy source, carbohydrates are nonessential macronutrients for humans; typically any molecular building block required for cellular function can be obtained through the metabolism of fat and proteins [8].

Carbohydrates are classified by their structure as monosaccharides, disaccharides, polysaccharides, or oligosaccharides. Nutritionally, mono- and disaccharides are simple carbohydrates, such as those found in fruits, dairy products, table sugar, and high-fructose corn syrup [7]. High consumption of simple carbohydrates (ie, simple sugars that are rapidly metabolized by the body) can lead to hyperinsulinemia and obesity accompanied by activation of inflammatory pathways and the insulinlike growth factor (IGF)-1 axis (see companion review).

Alternatively, consumption of complex poly- and oligosaccharides (ie, sugars that are less rapidly metabolized by the body) including those found in whole grains, potatoes, and legumes are broken down more slowly by the enzyme amylase, leading to less dramatic insulin spikes and possible protection against obesity [9].

Given the potential role of insulin in promoting tumor growth (see companion review), it stands to reason that lowering insulin by limiting carbohydrate intake may slow tumor growth. Indeed, several studies investigated carbohydrate restriction for PCa prevention or treatment in animal models with promising results. Two studies showed a no-carbohydrate ketogenic diet (NCKD) slowed tumor growth similar to or better than a low-fat diet in PCa xenograft models [10,11]. In a follow-up study, consumption of a low-carbohydrate diet resembling the maintenance phase of an Atkins diet (ie, 20% carbohydrate) showed similar tumor growth rates and overall survival as a NCKD [12]. Known to be safe for humans [13], low-carbohydrate diets are extremely effective for losing weight and managing insulin resistance [14]. Given that weight loss may slow tumor growth (see companion review), there is reason to hypothesize that low-carbohydrate diets may slow PCa growth [15]. Aside from one feasibility study investigating prostate tissue genetic changes of men on a low-glycemic diet [16], there are currently no published human studies of carbohydrate restriction for PCa. Of note, there is one ongoing study testing whether a low-carbohydrate diet can prevent the metabolic side effects of hormonal therapy for men with PCa (Clinicaltrials.gov; NCT00932672). Taken together, these data suggest a potential role of low-carbohydrate diets for PCa management, although formal testing in future clinical trials is required.

3.2. Protein

Proteins are macromolecules constructed from amino acids and have essential functions in all known biologic processes. Among the 22 known amino acids are 9 essential acids that cannot be synthesized de novo. Therefore, humans and animals must consume a certain level of protein-rich foods to maintain the amino acid supply required for new protein synthesis. Human consumption of protein typically comes from one of three forms: animal meats, protein-rich plants (eg, soy), and dairy products. Although contradictory, much research exists concerning animal meat, soy, dairy products, and PCa; however, almost no study specifically examines overall protein intake and PCa. Given that proteins are vital to normal physiology, and tumors have an elevated need for nutrients to grow, divide, and move, it stands to reason that proteins themselves may be involved in either tumor development or progression. However, this association has yet to be tested.

Inconclusive data exist on the role of animal meats in PCa initiation and progression. Animal meat is composed not only of protein but also of fat and cholesterol. Adding to this

complexity is the variability of fat and cholesterol content between animal meats. For example, data suggest grass-fed beef may be more nutrient rich than grain-fed beef and associated with a lower incidence of cardiovascular disease and cancer [17]. It is believed this difference may be due to lower levels of saturated fat and cholesterol and increased levels of ω-3 polyunsaturated fatty acids (ω-3 PUFAs), vitamins A and E, and antioxidants in grass-fed beef. What is known about these nutrients and their role in PCa is discussed in more detail later in this review. Interestingly, consumption of skinless poultry, which is lower in cholesterol and saturated fat than many red meats, does not seem to have any association with PCa, especially in terms of recurrence or progression [18]. Overall consumption of oily fish, such as salmon, trout, and tuna, seems to have no association with overall PCa risk, but it may significantly reduce the rate of cancer-specific mortality [19,20]. This may be due to the large concentrations of ω-3 PUFAs present in these fish, discussed in greater detail later in this review. Processing, cooking, or smoking can alter the nature of these nutrients. Most published data discussing animal meats pertain to well-done meats (particularly red meat) and the formation of heterocyclic amines (HCAs). HCAs are mutagenic compounds formed during high-temperature cooking of creatine, amino acids, and sugar, all components in meat [21]. It is believed that consumption of HCAs causes genomic instability primarily through DNA damage, leading to excessive genetic mutations [6]. The primary carcinogenic HCA, 2-amino-1-methyl-6-phenylimidazo [4,5-β] pyridine, can induce PCa in rat models [22]. Studies investigating HCAs and men with PCa appear to show a dose response between intake of well-cooked meat and cancer incidence [23,24], but very little data exists on HCAs and PCa progression.

Soy and soy-based products are a staple of vegetarian diets, and they are consumed in high quantities in East Asian countries [6]. Besides being a great source of protein, soy contains high levels of phytoestrogens. The family of phytoestrogens is composed of four classes of compounds: isoflavones, flavonoids, coumestans, and lignans. In soy, the primary isoflavone and the most studied with regard to PCa is genistein [25]. Studies using tumor cells and animal models suggest phytoestrogens like genistein may compete with and block endogenous estrogens from binding to the estrogen receptor, thereby inhibiting cellular proliferation and inducing differentiation [26]. Several clinical studies suggest high soy consumption may facilitate PCa prevention, but its role as therapy for an established tumor is conflicting [27,28].

Another common protein source is dairy products like milk, butter, cheese, and yogurt. Several studies suggest an association with increased overall PCa risk and dairy intake but no association with aggressive or lethal disease [29,30]. However, the story is likely more complex. For example, one recent study found whole-milk consumption may promote PCa progression, whereas low-fat milk delays progression [29]; a different study found the exact opposite effects [31]. Although the precise component of dairy products driving these associations is unknown, it is believed the high concentrations of saturated fat and calcium may be involved.

3.3. Fat and cholesterol

Fatty acids, the primary building blocks of fat, are hydrophobic hydrocarbon chains attached to a hydrophilic carboxylic acid group. Found in many foods including animal meats, dairy products, and plant oils, the breakdown of fat molecules produces more than twice the usable energy per gram relative to glucose. Cells require fat for membrane synthesis, cellular growth, and energy production. Fatty acids are classified as “saturated” or “unsaturated,” depending on the presence of hydrocarbon double bonds in the tail [8].

The data linking total fat consumption with PCa risk or progression are quite controversial. Although animal studies repeatedly show reducing dietary fat intake slows tumor growth

[32,33], multiple case-control studies and cohort studies found no association between total fat consumption and PCa risk [34–37]. Therefore, newer studies are trying to elucidate the role of dietary fat types on PCa, not just total fat consumption.

High consumption of saturated fats such as those found in butter, lard, and animal meats do not seem to be associated with overall PCa risk, but they may be associated with a slight increase in biochemical recurrence after treatment [38,39]. It is hypothesized that saturated fats may lead to increased circulating IGF-1, which in turn leads to PCa progression [40], although this remains speculative.

Based on the number and position of double bonds in the tail, unsaturated fats can be divided into ω-3 and ω-6 PUFAs. Humans cannot synthesize these essential fats and must receive them via dietary consumption. Evolutionarily, the human diet had a 1:1 ratio of ω-6-to-ω-3 PUFAs. Over the past two centuries, this ratio has increased to about 10:1, due primarily to the increased use of vegetable oils in Western diets [41]. Studies have linked high consumption of ω-6 PUFAs and an increased risk of overall and high-grade PCa [42]. It is presumed this relates to the conversion of arachidonic acid (a ω-6 PUFA) to hydroxyeicosatetraenoic acids and epoxyeicosatrienoic acids by cytochrome P450 oxygenases, both of which lead to inflammation and cellular growth [41].

Conversely, emerging data suggest ω-3 PUFAs, which are found primarily in cold water oily fish like tuna, salmon, herring, and swordfish, as well as flaxseed, may slow growth of many tumors, including prostate [41,43]. In vitro and animal studies suggest these fats induce anti-inflammatory, proapoptotic, antiproliferative, and antiangiogenic pathways [44], making them a perfect antitumor molecule. A phase 2 trial showed ω-3 supplementation 4–6 wk prior to radical prostatectomy decreased PCa proliferation [43]. Current research in this area is driven toward investigating whether increased ω-3 intake may prevent PCa incidence because current data are inconclusive [45,46].

Cholesterol is an organic compound found in animal proteins, cheese, and egg yolks. Believed to be a so-called bad molecule according to the health conscious, cholesterol composes approximately a third of cellular membranes and is required to maintain normal membrane permeability and fluidity. Cholesterol is also a key component of membrane signaling microdomains known as lipid rafts [8]. Moreover, cholesterol is the precursor to all steroid hormones including androgens. In humans, cholesterol can be obtained via diet or synthesized de novo in the liver through the mevalonate pathway, where the rate-limiting conversion of acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl CoA (HMGCoA) occurs via HMGCoA reductase. Recent data suggest high cholesterol may be a risk factor for solid tumors, primarily through the upregulation of cholesterol synthesis, inflammatory pathways [47], and intratumoral steroidogenesis [48]. In terms of PCa, epidemiologic data suggest low-density lipoproteins may aid in cancer initiation and progression [49], whereas high-density lipoproteins may not affect PCa risk and progression, or they may even be protective [50,51]. Preclinical and epidemiologic studies suggest HMGCoA reductase inhibitors (statins) may prevent PCa progression but not initiation [52,53]. Animal studies using the cholesterol-uptake inhibitor ezetimibe as PCa chemoprevention showed lowering serum cholesterol resulted in slower tumor growth, decreased angiogenesis, and decreased intratumoral androgens [48,54]. One study of patients with advanced cancer showed that treatment with lovastatin resulted in no tumor responses, although the criteria used to assess tumor response were not well described [55]. Although these data suggest a role for cholesterol in PCa progression, to date no large studies exist examining the role of cholesterol-lowering drugs for PCa prevention or therapy.

3.4. Vegetables

A vegetable is characterized as the edible root, stem, or leaf of a plant. Vegetables are a good source of vitamins, minerals, and phytochemicals, and they are low in fat and protein. Although several families of vegetables exist, most PCa research has investigated two in particular: cruciferous and allium vegetables.

Common cruciferous vegetables include broccoli, brussels sprouts, cabbage, and cauliflower. Not only are these vegetables high in fiber and vitamins C, E, and folate, they also contain high levels of phytochemicals known as isothiocyanates. With respect to PCa, isothiocyanates can inhibit cell growth, in part by inhibiting androgen receptor transcription [56]. Several epidemiologic studies found inverse relationships between cruciferous vegetable intake and PCa risk [57,58]. To date, there are no prospective trials investigating these vegetables with regard to PCa.

Allium vegetables such as garlic, leeks, chives, and shallots contain multiple sulfurous phytochemicals believed to enhance the immune system, inhibit cell growth, modulate expression of androgen-responsive genes, and induce apoptosis [59]. Although the number of published studies is limited, both preclinical and epidemiologic data suggest allium vegetable intake may be protective against PCa, particularly localized disease [60]. Similar to cruciferous vegetables, no prospective trials have been performed investigating the role of these vegetables in PCa incidence or progression.

3.5. Vitamins and minerals

Vitamins are small organic compounds required for proper cellular metabolism, growth, and differentiation. Humans are unable to synthesize the required concentrations of most vitamins and therefore must obtain them via diet or supplementation. Some vitamins even possess antioxidant properties [8]. To date, 13 compounds are classified as vitamins; 6 of these have been researched with regard to PCa prevention: vitamins A, B complex, C, D, E, and K. Because an estimated one-third of adults take some form of vitamin or mineral supplement [61], it is critical to understand the relationships between vitamins, minerals, and cancer prevention. Similar to macronutrients, the body functions best within an optimal range of vitamin intake, which is currently unknown; thus both under- and oversupplementation may affect PCa risk. The concept that the body functions best in an optimal range of nutrient intake is best exemplified by calories: Low intake leads to malnutrition, and excess intake leads to obesity.

Vitamin A, also known as retinol or carotene, is found in foods such as cheese, eggs, oily fish, vegetables, and fruit. Vitamin A is a precursor for signaling molecules involved in early development and everyday processes like vision [7]. Related to PCa, vitamin A supplementation has been investigated in two large clinical trials: the Carotene and Retinol Efficacy Trial (PCa was a secondary outcome) and the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health study (a prospective cohort study). In both cases, excessive vitamin supplementation was associated with a *higher* risk of developing aggressive PCa but not overall disease [62,63]. Of note, both studies investigated multivitamin supplementation, not specifically vitamin A supplementation.

B vitamins are found in a wide range of foods including pork, chicken, salmon, potatoes, lentils, brewer's yeast, and dairy products. The family of B vitamins contains eight members: B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B6 (pyridoxine), B_7 (biotin), B_9 (folate), and B_{12} (cobalamins). B vitamins are required for proper metabolism, muscle tone, immune and nervous system functions, and cellular growth and division [7]. To date, most studies involving B vitamins primarily investigated folate in

PCa risk and progression. Emerging preclinical evidence suggests folate depletion may slow tumor growth. Supplementation has no effect on growth or progression but may lead directly to epigenetic changes via increases in DNA methylation [64]. This evidence conflicts with observational data and a randomized clinical trial of folate supplementation; both suggested that higher serum folate levels may increase PCa risk [65,66]. The truth may be more complicated because some data suggest the fully oxidized folate received via supplements is less bioavailable than the naturally occurring form [66]. Breads and cereals are supplemented with folate. Thus high folate intake may reflect high vegetable intake (ie, a "good" diet) or excess intake of refined carbohydrates (ie, a "bad" diet) and is yet another level of complexity to the story.

Vitamin C (ascorbic acid), which is found in various fruits and vegetables including peppers, broccoli, brussels sprouts, and citrus fruits, is an antioxidant required for proper immune cell function. Because increases in free radicals derived from oxygen known as tissue reactive oxygen species (ie, oxidative stress) are important for cancer initiation and progression, it is believed vitamin C supplementation may prevent many cancers including PCa. Similar to published data for folate, preclinical studies show vitamin C may slow tumor growth using in vitro and in vivo models [67], but multiple randomized controlled trials have shown no effect on PCa risk [68,69]. At high doses, vitamin C may act more as a pro-oxidant than antioxidant, further highlighting that more is not always better.

Most vitamin D is synthesized by the body from skin exposure to sunlight, but this vitamin is also found in eggs, butter, oily fish, and whole-milk products. Although it is a fat-soluble vitamin and often supplemented into dairy products, the amount of vitamin D absorbed from consuming fat-free dairy products is likely small. The primary active form of vitamin D, 1,25 dihydroxyvitamin D3 (calcitriol), is required to maintain proper calcium and phosphorus homeostasis [7]. Calcitriol aids in proper bone formation, induces differentiation of some immune cells, and inhibits pro-tumor pathways like proliferation and angiogenesis [6]. Despite a strong rationale for the benefits of vitamin D, most epidemiologic literature suggests no association between vitamin D and PCa risk [70]. When only aggressive cancers are examined, one study found low vitamin D was associated with *increased* fatal PCa risk [71]; another found a link with a *decreased* risk of aggressive PCa [72]. Thus the role of vitamin D in PCa remains unclear. Interestingly, calcium can bind vitamin D, rendering it inactive. This inhibition of vitamin D may, in part, explain the proposed associations between increased calcium and dairy intake and PCa risk [6]. One clinical trial tested whether a calcitriol derivative, DN-101, slowed the growth of metastatic castrate-resistant PCa [73]. Unfortunately, this study was stopped early due to excessive deaths in the DN-101 arm.

Vitamin E is a group of eight compounds, with α- and γ-tocopherol the most abundant in the Western diet. Found primarily in plant oils like corn, soybean, sunflower, and palm, these compounds act as antioxidants similar to vitamin C. Multiple preclinical studies suggest vitamin E slows tumor growth, partly due to inhibiting DNA synthesis and inducing apoptotic pathways [74]. Unfortunately, human studies have been less than supportive. Specifically, two observational studies (the Cancer Prevention Study II Nutrition Cohort and the NIH-AARP Diet and Health Study) both showed no association between vitamin E supplementation and PCa risk [62,75]. A prospective randomized trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), showed vitamin E supplementation significantly *increased* PCa risk [76]. Found in green leafy vegetables like spinach and broccoli, vitamin K is required for normal clotting functions through the conversion of glutamate to a modified form of glutamic acid, creating a stronger calcium chelator [7]. Thus one could hypothesize that vitamin K may help prevent PCa by reducing bioavailable calcium. Preclinical studies show that the combination of vitamins C and K has potent

antitumor activity in vitro and acts as a chemo- and radiosensitizer in vivo [67]. To date, few studies have investigated this, although one study using the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort found an inverse relationship between vitamin K intake and PCa incidence [77].

Calcium is an alkaline earth metal critical for normal physiology. Cells maintain an extremely tight regulation of calcium gradients, allowing calcium to be a ubiquitous well-regulated intracellular messenger in processes like embryonic development, muscle contraction, neuronal secretion, and bone development [8]. As described earlier, calcium can inhibit vitamin D, which may have anticancer properties. In terms of PCa risk and calcium intake, data are conflicting. Retrospective and meta-analyses suggest increased PCa risk with increased calcium intake; others suggest no association [78]. Another study suggests a U-shaped association, where very low calcium levels *or* supplementation are associated with PCa [79]. Little to no preclinical evidence currently exists supporting one or the other.

The trace mineral selenium, found in Brazil nuts, mushrooms, fish, and eggs, biologically serves as an antioxidant in a similar manner to several of the vitamins previously discussed. Thus it was hypothesized that selenium may prevent PCa. Whereas in vitro studies suggested selenium inhibited angiogenesis and proliferation while inducing apoptosis [6], results from SELECT showed no benefit of selenium alone or in combination with vitamin E [76].

3.6. Phytochemicals

Along with vitamins and minerals, plants contain phytochemicals implicated in many diseases including cancer. Typically not considered essential compounds, phytochemicals have antioxidant and anti-inflammatory properties. We briefly discuss a few phytochemicals not mentioned earlier and their associations with PCa.

The phytochemical curcumin occurs naturally in the plant *Curcuma longa Linn* (turmeric). With its bright yellow color, curcumin is used in Asian cultures as an additive in foods and cosmetics, and in herbal medicines [80]. In vitro, curcumin inhibits the proinflammatory protein nuclear factor κB (NFκB) while inducing apoptosis through increased expression of proapoptotic genes [25]. In vivo, curcumin slows PCa growth in mice while sensitizing tumors to chemo- and radiotherapies [80]. To date, no epidemiologic studies or clinical trials have been published looking at associations between curcumin consumption and PCa.

The peel and fruit of pomegranates and walnuts are rich in ellagitannins (punicalagins). These phytochemicals are readily metabolized to the active form ellagic acid by gut flora [81]. Preclinical experiments show ellagitannins inhibit PCa proliferation and angiogenesis under hypoxic conditions and induce apoptosis [25,81]. Although more prospective clinical trials are warranted, two studies showed men with a rising prostate-specific antigen (PSA) after primary treatment who consumed pomegranate juice or POMx, a commercially available pomegranate extract, increased their PSA doubling time relative to values prior to consumption [82,83]. Epigallocatechin gallate (EGCG) is the most abundant phytochemical in green teas. Similar to curcumin, preclinical studies suggest EGCG inhibits PCa growth, induces intrinsic and extrinsic apoptotic pathways, and decreases inflammation by inhibiting NFκB [25]. The antioxidant properties of EGCG are 25–100 times more potent than vitamins C and E [6]. Clinically, EGCG was studied both in a small proof-of-principle trial and a larger observational study. These studies suggest EGCG consumption may be associated with lower PCa incidence and potentially prevent the progression of precancerous lesions in a dose-dependent manner, but it has no effect on more established advanced disease [25,84,85].

Lycopene is a bright red phytochemical in the carotenoid family. Found abundantly in tomatoes, watermelon, and grapefruit, lycopene has strong antioxidant properties and is often used in food coloring due to its deep red color. In vitro, lycopene halts the cell cycle in several PCa cell lines and decreases IGF-1 signaling by inducing IGF-1 binding proteins [6]. Although some studies found lycopene specifically slows PCa growth [86], another study found tomato paste but not lycopene significantly inhibited PCa growth [87]. Earlier studies found that higher lycopene consumption [88] or higher serum levels were both associated with lower PCa risk [89], but these findings have not been replicated in recent studies [90,91]. Several small clinical trials suggested an inverse relationship between lycopene supplementation, PSA levels, and decreases in cancer-related symptoms [90,92]; no large-scale randomized trials have tested the role of lycopene on PCa prevention or therapy.

Coffee contains caffeine and several unidentified phenolic compounds that may serve as antioxidants, among other roles currently unknown. Epidemiologic studies suggest an inverse relationship between coffee consumption and PCa risk, independent of caffeine content [93,94]. Because no preclinical studies exist investigating this relationship, the precise mechanisms and pathways involved are unknown. No prospective trials have been performed, leaving much room for research in this area.

The stilbenoid resveratrol, found in the skins of red grapes, among other fruits, is found in abundance in red wines. Previous studies showed resveratrol activates the deacetylase SIRT1, mimicking the effects of caloric restriction and leading to longer life spans [95]. Knowing the proposed associations between caloric restriction and cancer prevention (see companion review), recent studies investigated resveratrol supplementation and cancer prevention in many tumor types including prostate. Results in other tumors were promising, but the data for PCa are conflicting. Although most in vitro studies suggest resveratrol inhibits PCa growth, it suppresses tumor growth in some [25] but not all animal models [96], possibly due to limited bioavailability [97]. To date, there are no clinical trials investigating the PCa preventive or therapeutic effects of resveratrol.

3.7. Clinical implications

Dietary intervention for the prevention and treatment of cancer is an exciting area of research. Early humans consumed diets rich in fat and protein, and low, but not completely void, of unrefined carbohydrates [98]. As societies became industrialized, diets became more processed and carbohydrate based, correlating with increased obesity, cardiovascular disease, and cancer incidence. One study examined the effect of a paleolithic caveman-type diet, high in meat, vegetables, and nuts, in nonobese healthy subjects versus the consumption of a typical Western diet [99]. Researchers found significant reductions in blood pressure, plasma insulin, glucose, total cholesterol, and triglycerides while consuming the paleolithic-type diet. This does not suggest we should all consume a caveman diet but rather that dietary changes away from a Western diet may have benefits. Because these Western diet–associated metabolic abnormalities may be associated with PCa risk, it is easy to see why understanding how nutrients affect PCa prevention and management is critical.

Aside from the paleolithic diet, the Mediterranean and Asian diets may provide insight into the relationship between nutrition and PCa. The Mediterranean diet, which is high in vegetables, complex carbohydrates, lean meats, and antioxidants, is consistently recommended to patients for the prevention of cardiovascular disease and obesity [100], and it may show promise in PCa prevention [101]. People in Asian countries with their high consumption of ω-3 PUFAs and phytochemicals from soy and green tea have lower incidences of PCa versus countries consuming a Western-style diet [5].

Active surveillance (AS) has recently emerged as a viable PCa treatment, due in part to concerns surrounding PCa overdiagnosis and overtreatment. Unfortunately, many men halt AS due to their anxiety associated with “doing nothing.” Studies show men on AS will adhere to strict lifestyle changes for 6–12 mo [102], making this subset a good target for dietary intervention that may aid in curbing the psychological effects of AS.

Importantly, most men with PCa will become survivors. Over time these men are at risk for developing comorbidities and long-term side effects from cancer treatments. Thus this population should be considered for dietary intervention to optimize quality of life. Some small studies suggested survivors who are more active and report healthy eating habits (ie, consuming low-fat, low refined-carbohydrate diets rich in fruits and vegetables) have better overall quality of life versus their inactive unhealthy counterparts [103]. Thus more prospective studies are warranted to determine the overall long-term effects in this population.

The ideal diet for PCa prevention or treatment is unknown because the data are often inconsistent (Table 2). However, there are guidelines that can be used when counseling patients with or at risk for PCa. Avoid refined carbohydrates and overcooked meats. Consume more whole fruits and vegetables, not just the fiberless juices from these foods, because fiber slows the absorption of the sugar when consuming the whole food. Finally, minimize the need for excessive supplementation of vitamins and minerals by maintaining the healthy dietary practices mentioned here. Although many data are conflicting and no current dietary regimen appears to hold all the answers, one theme emerges every time: everything in moderation.

4. Conclusions

Our understanding of how diet affects PCa incidence and progression continues to grow, but it is safe to say we are a long way from finding the “miracle diet molecule” that cures or prevents cancer. It is likely such a molecule does not exist. Although emerging data suggest certain nutrients may provide some benefit, the heterogeneity of studies makes it difficult to develop a fundamental conclusion regarding which nutrients are “good” or “bad” For counseling patients on diet for primary and secondary PCa prevention, many believe “heart healthy equals prostate healthy.” Specifically, diets low in simple refined carbohydrates and saturated fats, high in lean protein, ω-3 PUFAs, and colorful fruits and vegetables along with moderate consumption of calories seems to be the best advice given the current inconclusive results. There is likely much truth in the old adage that “genes load the gun, but lifestyle pulls the trigger,” but the exact definition of which lifestyle pulls the trigger remains unclear.

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Take-home message

Our understanding of how nutrition affects prostate cancer (PCa) is growing but still is conflicting. By knowing how consumption of certain nutrients can affect a person, we can learn how these nutrients can fundamentally affect PCa incidence and progression.

Table 1

Summary of the current literature linking macro- and micronutrients with prostate cancer risk and progression

Macronutrient	No. of current publications	Dates of publication
Component/Micronutrient		
Carbohydrates	52	1964–2012
Simple carbohydrates	1	2001
Complex carbohydrates	4	1999–2007
Protein	486	1979–2012
Animal meats	125	1981–2012
Soy	364	1991–2012
Dairy products	159	1970–2012
Fat	191	1976–2012
Saturated fat	81	1983–2012
ω-6 PUFAs	146	1985–2012
ω-3 PUFAs	123	1985–2012
Cholesterol	594	1968–2012
Vegetables	43	1981–2012
Cruciferous vegetables	82	1991–2011
Allium vegetables	31	1997–2012
Vitamins and minerals	365	1981–2012
Vitamin A	115	1979–2012
B vitamins	109	1992–2012
Vitamin C	70	1979–2012
Vitamin D	676	1988–2012
Vitamin E	361	1988–2012
Vitamin K	14	2001–2011
Calcium	834	1978–2012
Selenium	463	1985–2012
Phytochemicals	92	1991–2011
Curcumin	121	1999–2012
Ellagitannins	8	2007–2011
Epigallocatechin gallate	83	1998–2012
Lycopene	295	1990–2012
Phenolic compounds	32	1964–2012
Resveratrol	100	1999–2012

PUFA = polyunsaturated fatty acid.

Studies in components/micronutrients are not included in the number of studies in the corresponding macronutrient.

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Table 2

A summary of nutrients and evidence for their association with prostate cancer risk and progression

Nutrient	Source examples	Preclinical data	Clinical data	References
Carbohydrates				
Simple carbohydrates	Fruit, dairy products, table sugar, high-fructose corn syrup	Low- and no-carbohydrate diets slow tumor growth in mouse xenograft models	Low-carbohydrate diets are effective for weight loss and cause genetic changes in prostate epithelium	[10–12,15,16]
Complex carbohydrates	Whole grains, potatoes, legumes			
Protein	Animal meat, soy, dairy products	Animal meat: N/A	Animal meat: data inconclusive	[17–24]
		Soy phytoestrogens inhibit cell proliferation and induce differentiation by blocking estrogens from binding to the receptors	Soy consumption may prevent cancer; conflicting results exist on soy consumption and established tumors	[26–28]
		Dairy products: N/A	Although contradictory, data suggest increased milk consumption may increase risk, but no effect on aggressive or lethal disease	[29–31]
Fat		Reduced fat intake slows tumor growth in mouse models	No association between overall fat intake and cancer risk	[32–37]
Saturated fat	Butter, lard, animal meats	N/A	May be associated with biochemical recurrence but not overall risk	[38,39]
ω-6 PUFAs	Vegetable oils such as corn, olive, and sunflower	Increased concentrations lead to increased inflammation and cellular growth through the conversion of molecules by cytochrome P450 oxygenases	High consumption may lead to increased risk of overall and high-grade cancer	[41,42]
ω-3 PUFAs	Oils found in tuna, salmon, and herring; flaxseed oil	Increased concentrations lead to the induction of antitumor pathways both in vitro and in vivo	Although inclusive, data suggest supplementation decreases tumor proliferation; it is unknown whether it prevents the disease	[43,45,46]
Cholesterol	Animal meat, cheese, egg yolks	Increased serum concentrations may lead to increased tumor cholesterol synthesis, activation of inflammatory pathways, and intratumoral steroidogenesis in vitro and in vivo; statin and ezetimibe treatments inhibit tumor growth in vitro and in vivo	Data suggest statins may prevent cancer progression but not overall incidence of the disease	[48,49,52–54]
Vegetables	Broccoli, cabbage, cauliflower, garlic, leeks, chives	Isothiocyanates within cruciferous vegetables inhibit cell growth by inhibiting androgen receptor transcription in vitro; sulfurous chemicals in allium vegetables boost immune response, inhibit tumor growth, and induce apoptosis in vitro and in vivo	Increased cruciferous and allium vegetable intake is associated with a decreased risk in overall PCa risk	[56–60]
Vitamins and minerals				
Vitamin A	Cheese, eggs, oily fish, vegetables, fruit	N/A	Excessive vitamin supplementation (not vitamin A per se) was associated with higher PCa risk	[62,63]

Nutrient	Source examples	Preclinical data	Clinical data	References
B vitamins	Pork, chicken, salmon, potatoes, lentils, dairy products	In vivo, folate depletion slows tumor growth; supplementation has no effect on PCa growth but directly increases DNA methylation	Folate supplementation (specifically oxidized folate) may increase PCa risk	[64–66]
Vitamin C	Peppers, broccoli, brussels sprouts, citrus fruits	Supplementation slows tumor growth in both in vitro and in vivo models by acting as an antioxidant	Supplementation has no effect on PCa risk	[67–69]
Vitamin D	Eggs, butter, oily fish, whole-milk products	Increased concentrations inhibit proliferation and angiogenic pathways in both in vitro and in vivo models	Data suggest no association between supplementation and overall PCa risk; data investigating only aggressive PCa are contradictory	[6,70–73]
Vitamin E	Corn, soybean, sunflower, and palm oils	Data from in vitro and in vivo studies suggest treatment may inhibit DNA synthesis and induce apoptotic pathway signaling	Supplementation has no effect or may in fact increase PCa risk	[62,74–76]
Vitamin K	Spinach, kale, broccoli	In vitro, treatment dramatically slows tumor growth, in part by acting as a calcium chelator; in vivo, supplementation radiosensitizes tumors	One study to date showed an inverse relationship between supplementation and PCa incidence	[67,77]
Calcium	Milk, cheese, yogurt	N/A	Existing data are conflicting, with some studies suggesting increased PCa risk with increased consumption, no association between risk and calcium consumption, and others suggesting both calcium depletion and supplementation increase PCa risk (U shaped)	[78,79]
Selenium	Brazil nuts, mushrooms, fish, eggs	In vitro studies suggest increased concentrations inhibit angiogenesis and proliferation while inducing apoptotic pathways	Supplementation alone or in combination with vitamin E shows no association with PCa incidence	[6,76]
Phytochemicals				
Curcumin	Turmeric	In vitro data suggest treatment inhibits NFκB signaling and induces apoptosis; in vivo, supplementation slows and radiosensitizes PCa tumors in mouse models	N/A	[25,80]
Ellagitannins	Pomegranates, walnuts	Data suggest treatment slows proliferation and inhibits angiogenesis while inducing apoptosis, particularly under hypoxic conditions	Increased consumption of pomegranate juice or supplementation with POMx increased PSA doubling time relative to the values prior to consumption or supplementation	[25,81–83]
Epigallocatechin gallate	Green teas	As an antioxidant, treatment induces both intrinsic and extrinsic apoptotic pathways and inhibits NFκB signaling, thereby inhibiting PCa growth	Consumption may be associated with decreased PCa incidence and possibly prevent the progression of HGPIN lesions; the effect of consumption on advanced disease is unknown	[25, 84,85]
Lycopene	Tomatoes, watermelon, grapefruit	In vitro, increased concentrations inhibit cell cycle progression, induce expression of IGF-1 binding proteins, and activate the PPARγ pathway; in vivo, tomato paste inhibits PCa growth in rats	Some studies suggest increased consumption is associated with lower PCa risk; others suggest an association between decreased PSA levels with increased consumption but no association with PCa incidence	[86–92]
Phenolic Compounds	Coffee	N/A	Increased coffee consumption may be associated with a decreased risk of PCa, independent of caffeine intake	[93,94]

Nutrient	Source examples	Preclinical data	Clinical data	References
Resveratrol	Fruit, in particular red grapes	In vitro data suggest treatment inhibits PCa growth, in part by activating SIRT1 and mimicking caloric restriction; data from in vivo studies are conflicting, with consumption slowing tumor growth in some mouse models but not in others	N/A	[25,96,97]

HGPIN = high-grade prostatic intraepithelial neoplasia; IGF = insulinlike growth factor; N/A = not applicable; NFκB = nuclear factor κB; PCa = prostate cancer; PPAR= peroxisome proliferator activated receptor.