

Review

Diet strategies for prostate cancer control

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Prostate cancer has become a major public health problem worldwide and prevention strategies would attenuate its economic, emotional, physical and social impact. Until recently, however, we have had only modest information about risk factors for this disease, apart from the well-established characteristics of age, family history and place of birth. The current body of literature supports the role of nutritional products in reduction of prostate cancer. Thus, dietary agents have gained considerable attention as chemopreventive agents against prostate cancer. This review critically addresses the natural products with the greatest potential to reduce the risk of prostate cancer, including, honey, vitamin E, selenium, soy, tomatoes, cruciferous vegetables and green tea. Many products have been linked with the development and aggressiveness of prostate cancer, through a range of molecular mechanisms. The toxicity of certain dietary products (fat, red and processed meat) is addressed. The direction of future clinical trials lies in clarifying the effects of these agents and exploring the biological mechanisms responsible for the prevention of prostate cancer. Until large randomized trials confirm the benefit of chemopreventive and dietary modifications, patients are advised to pursue a diet and lifestyle that enhances overall health.

Key words: Cancer, prostate, green tea, selenium, soy, vitamin D, vitamin E.

INTRODUCTION

Prostate cancer is a common frequent cause of cancer death. In the United States, prostate cancer is the most commonly diagnosed visceral cancer; in 2010, there were expected to be 218,000 new prostate cancer diagnoses and about 32,000 prostate cancer deaths. The current lifetime risk of prostate cancer for men living in the United States is estimated at approximately one in six (Jemal et al., 2010). The current survival from the time of diagnosis in patients with metastatic disease and those with locally advanced prostate cancer, if not-treated, is 3.5 and 4.5 years (Mazhar and Waxman, 2008), respectively. Despite a substantial morbidity and mortality, the etiology of prostate cancer remains largely unknown.

There are three well-known and indisputable risk

factors for development of prostate cancer, namely heredity, ethnic origin, and increasing age. Although several genetic factors that predispose to prostate cancer have been discovered, an environmental trigger is probably necessary for manifestation of the disease. Geographic variations in incidence rates are considerable; therefore, it has been suggested that environmental factors may also play an important role. Data from migration studies clearly show that men with similar genetic background (unless identical twins) raised in different environments present the risk of the disease associated with their country of residency (Schmid et al., 2011). Prostate cancer prevalence varies widely among different countries; this variation may be related to

environmental factor. Chemopreventive agents are subdivided into two main categories: blocking agents and suppressing agents (Wattenberg, 1985). Blocking agents prevent carcinogens from reaching the target sites, from undergoing metabolic activation, or from subsequently interacting with crucial cellular macromolecules (for example, DNA, RNA and proteins). Suppressing agents, on the other hand, inhibit the malignant transformation of initiated cells, in either the promotion or the progression stage (Surh, 2003). Preventing cancer by blocking development of these precancerous cells is extremely important, because even healthy people have a certain number of latent tumors in their tissues (Thompson, 2010).

There has been growing interest in the use of naturally occurring compounds with chemopreventive and chemotherapeutic properties in the treatment of cancer (Samarghandian et al., 2010; Samarghandian et al., 2011b; Mutee et al., 2012; Samarghandian and Shabestri, 2013). Plant foods are a source of biologically active compounds certain phytochemicals possess substantial anti-carcinogenic and anti-mutagenic properties (Surh, 2003, Wong et al., 2011). They may incite the immune system, reduce the toxicity of adverse chemical products, influence hormonal levels, and control cellular growth (Divisi et al., 2006; Maurice et al., 2009). Dietary factors are major elements accounting for the international and interethnic differences in the rate of prostate cancer (Folkman, 2006; Hahn-Obercyger et al., 2005; Karunagaran et al., 2005; Talalay and Fahey, 2001). Many agents have been evaluated for their primary and secondary chemopreventive capacities, including soy proteins, tomatoes and lycopene, vitamin E, selenium, fish and marine fats, ω -3 fatty acids, polyphenols, isoflavones, cruciforms and green tea (Hahn-Obercyger et al., 2005). These agents potentially interact with a range of carcinogenic pathways in the prostate, including androgen metabolism, cell cycle processes and apoptosis. Identifying molecular mechanisms involved in carcinogenesis provides the rationale for developing strategies for disease prevention. Dietary intervention targeting multiple pathways might be a particularly effective therapeutic approach, either alone, or in conjunction with targeted pharmaceutical agents.

We provide an evidence-based review of dietary recommendations for the prevention and treatment of prostate cancer. This review addresses clinical studies that focus on dietary factors that may reduce risk for the development for prostate cancer.

DIETARY RISK FACTORS

Many studies focus on the relationship between the intake of different types of foods and nutrients and the development of prostate cancer. Among individual food groups/nutrients, a high consumption of total fat, saturated fats, meat, dairy, and calcium are related to an

increased risk (Theobald, 2006).

High fat intake

Epidemiological studies have examined an array of dietary and nutritional factors in relation to prostate cancer incidence. In particular, epidemiological studies indicate that high intake of animal fat and of polyunsaturated oils may increase prostate cancer risk (Ma and Chapman, 2009; Lophatananon et al., 2010). Also, some studies in animal models have shown increased tumor growth with high fat intake and inhibition with low fat intake (Ngo et al., 2003a; Pollard and Luckert, 1986). However, other preclinical studies have found no relationship between the growth of transplanted prostate carcinoma and variations in dietary fat (Clinton et al., 1988; Pour et al., 1991). The three blood serum based studies that sought to link total fat and prostate cancer risk show no association (Harvei et al., 1997; Severson et al., 1989; Thune and Lund, 1994). Likewise, the Netherlands cohort study, a large prospective cohort study, found no association between prostate cancer and total fat intake (Rohan et al., 1995; Schuurman et al., 1999a).

Investigators have also searched for a potential association between specific kinds of fat and prostate cancer. Results have been mixed (Bostwick et al., 2004). Essential fatty acids found in fish inhibit the growth of prostate cancer cells *in vitro* and *in vivo* (Terry et al., 2001). In a study during 30 years of follow-up, men who ate no fish had a 2 to 3 fold higher frequency of prostate cancer than those who ate moderate or high amounts of fish (Terry et al., 2001). One epidemiological study found a negligible reduction in risk of prostate cancer (7%) in men who consumed fish three times a week versus two times a week (Augustsson et al., 2003). The two fatty acids whose potential association with prostate cancer risk is most frequently investigated are alpha-linolenic and linoleic acid. A study that has shown low plasma levels of alpha-linolenic acid might be associated with reduced risk of prostate cancer (Gann et al., 1994). For linoleic acid, with the predominate omega-6 fatty acid in the Western diet, three out of four studies showed no effect (Dagnelie et al., 2004).

Researchers have proposed several mechanisms to explain a possible association between dietary fat and prostate cancer development and progression. First, it has been demonstrated that dietary fat increases the levels of serum testosterone, thereby increasing the growth of prostate cancer cells (Hill et al., 1979). Second, others have shown that dietary fat also increases oxidative stress and levels of reactive oxygen species that interfere with cellular processes (Rao et al., 1999). In addition, dietary fat reduction may impact serum insulin-like growth factor levels in the serum (Table 1) (Ngo et al., 2003b). Therefore, there was a positive statistically significant association between prostate cancer risk and energy-adjusted intake of total fat and fat subtypes.

Table 1. Epidemiological studies considering association diet and prostate cancer.

Dietary agent	Effect	Epidemiologic study
Fat	Increase risk	Ma and Chapman (2009), Harvei et al. (1997), Severson et al. (1989), Thune and Lund (1994)
Dairy	Increase risk	Allen et al. (2008), Chan et al. (2001), Michaud et al. (2001), Gao et al. (2005), Mitrou et al. (2007), Neuhouser et al. (2007), Qin et al. (2007)
Meat	Increase risk	Kolonel (2001), John et al. (2011)
Soy	Decrease risk	Jacobsen et al. (1998), Nomura et al. (2004), Yan and Spitznagel (2009), Hebert et al. (1998), Hamilton-Reeves et al. (2007), Cheung et al. (2008), Khan et al. (2010), Theil et al. (2010)
Green Tea	Decrease risk	Jian et al. (2004), Kikuchi et al. (2006), Kurahashi et al. (2008), Severson et al. (1989)
Carotenoids	Decrease risk	Giovannucci et al. (1995), Giovannucci et al. (1995), Kavanaugh et al. (2007), Matos et al. (2001), Caraballoso et al. (2003), Tzonou et al. (1999), Etminan et al. (2004)
Vitamin E	Decrease risk	Ni and Yeh (2007), Wang et al. (2006), Zhao et al. (2006), Hartman et al. (1999), Wright et al. (2007), Jiang et al. (2004)
Vitamin D	Decrease risk	Gupta et al. (2009), Mucci and Spiegelman (2008)
Vitamin C	Decrease risk	Bidoli et al. (2009), Gaziano et al. (2009b), Lewis et al. (2009)
Selenium	Decrease risk	Helzlsouer et al. (2000), Yoshizawa et al. (1998), Li et al. (2004a), Yoshizawa et al. (1998), Li et al. (2004b)
Cruciferous	Decrease risk	Cohen et al. (2000b), Jain et al. (1999), Joseph et al. (2004), Kolonel et al. (2000)

These results potentially identify a modifiable risk factor for early-onset prostate cancer and also the high intake of total fat and certain saturated fatty acids may worsen prostate cancer survival.

Meat

Consumption of red meat, particularly well-done meat, has been associated with increased prostate cancer risk. High-temperature cooking methods such as grilling and barbecuing may produce heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), which are known carcinogens (John et al., 2011). Red meat is also a major contributor of zinc, which is essential for testosterone synthesis in addition to having anticancer effects in the prostate (Kolonel, 2001). Studies on meat consumption point to a possible increased risk of prostate cancer with high meat consumption, especially of processed or burned meats (Ma and Chapman, 2009; Koutros et al., 2008). One case-control study have shown the consumption of processed meat and red meat cooked at high temperature to be associated with increased risk of advanced, but not localized, prostate cancer (John et al., 2011).

Among epidemiological studies, 17 out of the 23 case control and cohort studies summarized in the review by Kolonel (2001) showed a positive relation between high consumption of meat and increased risk of prostate cancer. All these studies but one have shown at least a 30% increased risk related to high meat consumption (Kolonel, 2001). By contrast, a CARET (CARotene and RETinol) study has shown that red meat was not associated with prostate cancer (Table 1) (Neuhouser et al., 2007).

Dairy products

Despite the prevalence of prostate cancer worldwide, only a few risk factors have been well-established. The role of dairy products, in the etiology of prostate cancer is still controversial. Some large cohort studies (with 4500 cases) have reported significant positive associations between dairy products and/or calcium intake and risk (Allen et al., 2008; Chan et al., 2001; Michaud et al., 2001; Raimondi et al., 2010), while the results from some studies do not support this hypothesis (Park et al., 2007; Schuurman et al., 1999b), and the possible association between dairy products and prostate cancer risk also remains unclear. In a meta-analysis of 16 prospective trials, dairy products were found to slightly increase the risk of prostate cancer (relative risk (RR) = 1.09; 95% confidence interval (CI) = 1.00 to 1.2) (Gao et al., 2005; Severi et al., 2006). In another analysis of 18 cohort studies, it was found out that consumption of milk and dairy products increases the risk of prostate cancer (RR = 1.13; 95% CI = 1.02 1.24) (Qin et al., 2007). The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study reported that high versus low intake of dairy products may be associated with an increased risk of prostate cancer (Mitrou et al., 2007). However, CARET study has shown that higher dairy intake had a statistically significant reduced risk of aggressive prostate cancer than lower dairy intake (HR = 0.59, 95% CI = 0.40 to 0.85) (Neuhouser et al., 2007). A US cohort study (CLUE II) have shown that higher intake of dairy foods but not calcium was positively associated with increased risk of prostate cancer (HR = 1.65, 98% CI = 1.02 to 2.66) (Rohrmann et al., 2007). By contrast, a meta-analysis of 26,769 cases from 45 observational studies found that no evidence of an association between dairy

(RR = 1.06; 95% CI = 0.92 to 1.22) or milk intake (RR = 1.06; 95% CI = 0.91 to 1.23) and risk of prostate cancer (Huncharek et al., 2008). In a prospective study of 10,011 men with 815 prostate cancer cases, neither increasing intake levels of dairy products nor calcium from dairy products (P trend; 0.23 and 0.64, respectively, or calcium supplements was associated with prostate cancer risk (relative risk, 1.05; 95% CI = 0.84 to 1.31) (Table 1) (Koh et al., 2006).

DIETARY FACTORS POSSIBLY ASSOCIATED WITH DECREASED RISK

Plant food including tomato products, lycopene, soy and micronutrients (selenium, vitamin E) have been shown to possess certain anti-carcinogenic properties (Theobald, 2006). This section focuses on the epidemiological evidence for individual groups of dietary items postulated to specifically reduce the risk of prostate cancer.

Honey

Honey has been used as a traditional food source since ancient times. It consists of carbohydrates, proteins, amino acids, vitamins, water, minerals, and enzymes (all traces, except glucose and fructose). Honey is thought to exhibit a broad spectrum of therapeutic properties including antibacterial, antifungal, cytostatic and anti-inflammatory activity, proapoptotic, antiproliferative activity (Jeddar et al., 1985; Samarghandian et al., 2011a). Honey contained many biologically active compounds including caffeic acid, caffeic acid phenethyl ester, flavonoid glycones and Chrysin (Chen et al., 2003; El-Refaei and El-Naa, 2010; Samarghandian et al., 2011c). These compounds demonstrated to have an inhibitory effect on tumor cell proliferation and transformation by the down regulation of many cellular enzymatic pathways including protein tyrosine kinase, cyclooxygenase and ornithine decarboxylase pathways (O'Prey et al., 2003). Honey affected the growth patterns of prostate cancer cells. Higher concentrations of honey are safe for non-malignant cells, but exert antitumor cytotoxicity and anti-proliferative effects in a prostate cancer-derived cell line (Table 1) (Samarghandian et al., 2010).

Our *in vivo* recent results suggest that honey has anti-proliferative effects on prostate cancer cells and the effects are mainly due to chrysin (Samarghandian et al., 2011 c). Chrysin (5,7-dihydroxyflavone) is a natural flavone commonly found in honey and many of which cause biological activity in humans and animals. In test tubes, this substance inhibits the conversion of testosterone to estrogen. Chrysin is most well known for being a testosterone boosting compound.

Soy

Phytoestrogens (flavones, isoflavones and lignans) are

naturally occurring plant compounds that have estrogen-like activity. Phytoestrogens also are important regulators of proteins, such as 5 α -reductase, tyrosine kinase, topoisomerase, and P450 aromatase, and have inhibitory effect on vitamin D metabolism in the prostate (Qin et al., 2007). There is a lower incidence of prostate cancer and other common cancers in populations eating soy product. Soy isoflavones influence sex hormone metabolism and biological activity through intracellular enzymes, protein synthesis, growth factor actions, malignant cell proliferations, differentiation and angiogenesis (Choueiri et al., 2006; Messina, 2010). Genistein and daidzein, the predominant isoflavones in human nutrition, are derived mainly from soybeans and other legumes (Cheung et al., 2008). Some animal studies have suggested that isoflavones in soy may suppress the development of invasive prostate cancers (Khan et al., 2010; Theil et al., 2010). A study of soy protein isolate consumption in 58 men demonstrated an effect on androgen receptor expression, which suggests that soy consumption could be beneficial in preventing prostate cancer (Hamilton-Reeves et al., 2007). A large-scale epidemiological study of the effects of soy-derived products on prostate cancer development was a cross-national study conducted in 59 countries. In this study, soy products were shown to be significantly protective (Hebert et al., 1998). A 2009 meta-analysis of the research on the association between soy consumption and prostate cancer risk concluded that "consumption of soy foods is associated with a reduction in prostate cancer risk in men" (Yan and Spitznagel, 2009). A 16-year long prospective health study found that men who consumed more than one glass of soy milk per day had a 70% lower risk of prostate cancer (Jacobsen et al., 1998). Although, the majority of studies support a benefit of soy products; a few studies do not show a benefit, including a study of 5855 Japanese-American men who were followed for over 20 year (Nomura et al., 2004). Overall, the epidemiological data suggest that phytoestrogens may play a protective role against the development prostate cancer (Adlercreutz, 1995).

Green tea

Tea is the most consumed drink in the world after water. Green tea is a 'non-fermented' tea and it derived from the plant *Camellia sinensis* (Cabrera et al., 2006). Green tea has been considered a medicine and a healthful beverage since ancient times. The traditional Chinese medicine has recommended this plant for headaches, body aches and pains, digestion, depression, detoxification, as an energizer, and in general, to prolong life. Green tea leaves contain three main components which act upon human health: xanthic bases (caffeine and theophylline), essential oils and especially, polyphenolic compounds (Cabrera et al., 2006). Polyphenols constitute the most interesting group of green tea leaf components, and in consequence, green tea can be considered an

important dietary source of polyphenols, particularly flavonoids (Cabrera et al., 2006; Vinson et al., 1995). The main flavonoids present in green tea include catechins (flavan-3-ols). The four major catechins include epicatechin-3-gallate (ECG), epigallocatechin (EGC), epigallocatechin-3-gallate (EGCG), and epicatechin (EC) (McKay and Blumberg, 2002). Green tea also contains gallic acid (GA) and other phenolic acids such as chlorogenic acid and caffeic acid, and flavonols such as kaempferol, myricetin and quercetin (Wang et al., 2008). Many epidemiological, animal, and *in vitro* studies have demonstrated that green tea polyphenols may play a role in the risk and pathogenesis of several chronic diseases such as prostate cancer (Bemis et al., 2006; McKay and Blumberg, 2002). Over the last two decades a host of epidemiological studies that include cohort and case-control studies have suggested that green tea consumption correlates with a lower risk of certain cancers that include breast, colon, and prostate. A collection of six epidemiological studies that included two case-control, as well as four cohort studies, evaluated the role of green tea in reducing the risk of developing prostate cancer (Jian et al., 2004; Kikuchi et al., 2006; Kurahashi et al., 2008; Severson et al., 1989). In majority of these studies a significant decrease in the development of prostate cancer was observed with increasing intake of green tea. In another case control study performed in China of 130 cases of prostate cancer and 274 controls, tea drinking was strongly associated with decreased risk of prostate cancer. They reported reduced prostate cancer risk with increasing frequency, duration, and quantity of green tea consumption (Jian et al., 2004). Recently, a large cohort study of 49,920 subjects in Japan found a dose-dependent decrease in the risk of advanced prostate cancer for men drinking more than 5 cups a day (Kurahashi et al., 2008). Three other cohort studies have been performed and found green tea had a non-statistically significant effect in decreasing the risk of prostate cancer (Kikuchi et al., 2006; Kurahashi et al., 2008). A fourth cohort study of Japanese ancestry subjects [n=7,999] from Hawaii (USA) prospectively analyzed the demographics and diet for the risk of developing prostate cancer and found a non-significant relative risk of 1.47 (95% CI = 0.99 to 2.19) of developing prostate cancer with increased green tea consumption (Severson et al., 1989). The anti-carcinogenic potential of tea polyphenols has been shown by several *in vitro* and experimental studies, which have detailed the ability of these compounds to bind directly to carcinogens and induce phase II enzymes (Khan and Mukhtar, 2008). Several molecular anticancer mechanisms have been proposed, including cell cycle arrest in both androgen-sensitive and androgen-insensitive prostate cancer cells (Adhami et al., 2007), induction of apoptosis (Stuart et al., 2006), inhibition of transcription factors NF κ B (156) and AP-1, and reduction of protein tyrosine kinase activity and c-jun messenger RNA expres-

sion (Khan et al., 2010; Khan and Mukhtar, 2008; Mukhtar and Ahmad, 2000). An inhibition of angiogenesis, down regulates Cyclin D, Cyclin E, CDK 4, CDK 1, and induction of clusterin with cleavage of both pro-caspase 8 and pro-caspase 3 (Thangapazham et al., 2007; Yang et al., 2011; Yang and Wang, 2010) have also been observed. In addition, several studies have shown that EGCG is instrumental in inhibiting the IGF-I pathway (Adhami et al., 2004). EGCG effectively inhibits 5 α -reductase in cell-free assays, indicating that it can regulate androgen action in target organs. Replacement of the gallate ester in EGCG with long-chain fatty acids produces potent 5 α -reductase inhibitors that are active in both cell-free and whole-cell assay systems (Liao and Hiipakka, 1995).

Lycopene

Lycopene is a red carotenoid pigment found in tomatoes and a few red fruits and vegetables, such as, watermelons and papayas. However, the 11 conjugated and two non-conjugated double bonds in lycopene make it highly reactive towards oxygen and free radicals, and this anti-oxidant activity probably contributes to its efficacy as a chemoprevention agent (van Breemen and Pajkovic, 2008). Some early epidemiologic studies suggested that increasing consumption of tomatoes or tomato products was significantly associated with decreased prostate cancer risk (Giovannucci et al., 1995; Kavanaugh et al., 2007; Matos et al., 2001). Studies have shown that lycopene rich tomato sauce consumption could reduce oxidative DNA damage in human prostate and prostate cancer (Stacewicz-Sapuntzakis and Bowen, 2005). Lycopene in tomato was suggested to be the main factor for reducing prostate cancer risk (Zhang et al., 2007). In addition, a phase II study showed that whole-tomato lycopene supplementation had significant results and maintained its effect on prostate specific antigen (PSA) over one year (Caraballoso et al., 2003). A study in Greece, that involved 320 prostate cancer case and 246 controls, found that consumption of cooked tomatoes rather than raw tomatoes reduced prostate cancer risk by close to 15% (Tzonou et al., 1999). A meta-analysis of 11 case-control and ten cohort studies found an association between lycopene intake and a decreased risk of prostate cancer (Table 1) (Etminan et al., 2004).

However, several studies failed to show an association between lycopene and prostate cancer. A recently concluded phase II trial showed that lycopene-rich supplement was not effective in patients with androgen-independent prostate cancer (Jatoi et al., 2007).

Vitamin E

Vitamin E refers to a group of naturally occurring

compounds: the tocopherols, tocotrienols, and their natural and synthetic derivatives. Out of the eight different tocopherols included in the term, vitamin E, α -tocopherol exerts specific functions and is the predominant form of vitamin E found in plasma and tissues (Syed et al., 2007). While γ -tocopherol is the most prevalent form of vitamin E found in a typical diet, α -tocopherol is the most biologically available form and it is usually found in dietary supplements (Cheung et al., 2008; Phutthaphadoong et al., 2012). Vitamin E is a potent intracellular antioxidant, known to inhibit lipid peroxidation and DNA damage and recognized to have a wide range of anticancer properties (Venkateswaran and Klotz, 2010). Comprehensive studies from human epidemiological studies, animal tumor models, and molecular levels suggested that alpha-vitamin E and its derivatives possess remarkable chemopreventive and chemotherapeutic against prostate cancer (Ni and Yeh, 2007; Wang et al., 2006; Zhao et al., 2006). Vitamin E and its analogues have several mechanisms of action. Vitamin E protects polyunsaturated fatty acids against auto-oxidation and protects cell membranes from oxidative damage (Jansen et al., 2001). It can modulate transforming growth factor-h and AR/PSA signaling pathway and regulate cell cycle through DNA synthesis arrest prostate cancer cells (Israel et al., 1995).

Induction of apoptosis, by causing depletion of cytosolic Fas with increase in the membrane levels of Fas, decreased production of vascular endothelial growth factor, and inhibition of matrix metalloproteinases are other mechanisms through which vitamin E inhibits prostate carcinogenesis (Basu and Imrhan, 2005). α -Tocopherol, Beta-Carotene Cancer Prevention study (ATBC trial, 1994) indicated that daily supplementation of vitamin E could reduce the incidence of prostate cancer among men who smoked (1994). This study of 29,133 male smokers found a 32% reduction in prostate cancer incidence and a 41% lower mortality in those receiving 50 mg of α -tocopherol daily for 5 to 8 years. Hartman et al. (1999) performed a cross-sectional analysis to assess the relationship between baseline levels of serum α -tocopherol and serum sex hormones in men. Serum α -tocopherol levels were inversely associated with serum androstendione, testosterone, sex hormone-binding globulin and estrone. Some studies suggested that γ -tocopherol may be more relevant than α -tocopherol to the protection by vitamin E against prostate cancer (Helzlsouer et al., 2000; Ju et al., 2010). A recent large prospective study examined 295,344 American men for the association of prostate risk with supplemental vitamin E consumption and dietary intakes of α -, β -, γ -, and δ -tocopherols. The study showed that supplemental vitamin E did not reduce prostate cancer risk. However, an increase in γ -tocopherol uptake was significantly inversely associated with the risk of advanced prostate cancer (Wright et al., 2007). Men in the highest quintile of plasma concentration of γ -tocopherol had a 5-fold reduc-

ed risk of prostate cancer (Jiang et al., 2004). Several studies have failed to show that vitamin E reduces the risk of prostate cancer development (Chan et al., 1999; Gaziano et al., 2009; Kirsh et al., 2006). Vitamin E was tested prospectively in a large, well-designed clinical trial in 31,000 men with incident prostate cancer as the end point Selenium and Vitamin E Cancer Prevention Trial (SELECT). This study documented no apparent benefit of administering vitamin E (Table 1) (Lippman et al., 2009).

Vitamin D

Vitamin D is a group of fat-soluble prohormones which synthesis in the skin is induced by ultraviolet radiation. It is also contained in various types of food, including fish and eggs. The two major physiologically relevant forms of which are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) (Vieth, 2004). The active metabolite of vitamin D, apart from a crucial role in maintaining mineral homeostasis and skeletal functions, has anti-proliferative, apoptosis and differentiation inducing, as well as immunomodulatory effects in cancer (Speer, 2010).

Epidemiological, molecular, and cellular studies have implicated vitamin D deficiency as a risk factor for the development and/or progression of prostate cancer (Gupta et al., 2009; Mucci and Spiegelman, 2008). Studies using cell culture systems and animal models suggest that vitamin D acts to reduce the growth of prostate cancer through regulation of cellular proliferation and differentiation. However, although preclinical studies provide a strong indication for anti-cancer activity, proof of therapeutic benefits in men is still lacking. The anti-proliferative and pro-differentiating properties of vitamin D have been attributed to calcitriol [1, 25(OH)₂ D₃], the hormonally active form of vitamin D, acting through the vitamin D receptor (VDR).

Calcitriol exhibits several anti-inflammatory effects including suppression of prostaglandin (PG) action, inhibition of p38 stress kinase signaling, and the subsequent production of pro-inflammatory cytokines and inhibition of NF- κ B signaling. Calcitriol also decreases the expression of aromatase, the enzyme that catalyzes estrogen synthesis in breast cancer, both by a direct transcriptional repression and indirectly by reducing PGs, which are major stimulators of aromatase transcription. Other important effects include the suppression of tumor angiogenesis, invasion, and metastasis. These calcitriol actions provide a basis for its potential use in cancer therapy and chemoprevention (Krishnan and Feldman, 2011). In study by Tuohimaa et al. (2004), the serum 25 (OH) - vitamin D levels of 622 prostate cancer cases and 1451 matched controls found that low (<19 nmol/L) and high (>80 nmol/l) levels are associated with higher prostate cancer risk. Several studies suggest that vitamin D does not decrease prostate cancer risk (Table 1) (Ahn et al., 2008; Travis et al., 2009).

Vitamin C

Vitamin C or ascorbic acid is an essential nutrient for humans in collagen, carnitine and neurotransmitter biosynthesis. The following foods are excellent sources: citrus fruits, strawberries, currants, cabbages, and potatoes. Vitamin C is a cofactor in at least eight enzymatic reactions, including several collagen synthesis reactions that cause the most severe symptoms of scurvy when they are dysfunctional. It also influences cell metabolism and has anti-oxidative qualities (Mandl et al., 2009).

Besides its anti-oxidant activities, there was little information about other potential anticancer mechanisms for vitamin C, except that the expression and function of the androgen receptor was shown to be inhibited by vitamin C in a prostate cancer cell line (Wang et al., 2003). The epidemiologic evidence on dietary vitamin C and prostate cancer is controversial. In an overview of epidemiological and intervention trial studies for vitamin C out of nine reports (Berndt et al., 2005; Kirsh et al., 2006; Meyer et al., 2005) mentioned, only three (Bidoli et al., 2009; Gaziano et al., 2009; Lewis et al., 2009) showed that vitamin C had protection effects on prostate cancer risk. It has been shown that injection of mega doses of vitamin C can produce pharmacologic levels in circulation that cannot be achieved by oral administration (Frei and Lawson, 2008). Some studies show that the pharmacologic levels of vitamin C may selectively be toxic to cancer cells (Table 1) (Chen et al., 2008; Yeom et al., 2009).

Selenium

Selenium is an essential trace element found in the soil that enters the food chain through plants. Humans receive selenium in their diet through plant and animal products (Venkateswaran and Klotz, 2010). Selenium serves as a precursor to the synthesis of selenocysteine and selenoproteins, such as glutathione peroxidase (GPx), thioredoxin reductase, and selenoprotein P (Sabichi et al., 2006). Recent epidemiological studies have demonstrated that selenium may be an effective chemopreventive and anticancer agent with a broad spectrum against several human cancer cells (prostate, colon, bladder, lung, liver, ovarian, leukemia). A wide range of potential mechanisms have been proposed for the antitumorigenic effects of selenium and these include antiandrogen activity, growth inhibitory effects by regulation of p53 and antioxidant function, and through DNA damage (Sanmartin et al., 2008).

Several large prospective studies reported 50 to 65% reductions in risk of developing prostate cancer associated with high versus low selenium levels as measured in toenails (Helzlsouer et al., 2000; Yoshizawa et al., 1998) and plasma (Li et al., 2004a; Yoshizawa et al., 1998). In a study by Li et al. (2004a), 586 men with

prostate cancer were compared with 577 controls over a 13-year follow-up period. The investigators found that prediagnostic plasma serum selenium levels were inversely related with risk of advanced prostate cancer (Li et al., 2004b). In addition, an analysis of the Nutritional Prevention of Cancer Trial revealed that the men who took selenium supplements daily were half as likely to be diagnosed with prostate cancer (Beer and Myrthue, 2004). These findings have been confirmed *in vitro* together with animal models, and many observational studies (Brinkman et al., 2006; Jian et al., 2004; Muecke et al., 2010a; Penney et al., 2010; Ramoutar and Brumaghim, 2010; Valdiglesias et al., 2010).

Not all studies agree on the cancer-fighting effects of selenium. One study of naturally occurring levels of selenium in over 60,000 participants did not show a significant correlation between those levels and cancer (Garland et al., 1995). In 2009, the 5.5 year SELECT study reported selenium and vitamin E supplementation, both alone and together, did not significantly reduce the incidence of prostate cancer in 35,000 men who "generally were replete in selenium at baseline" (Lippman et al., 2009).

Selenium has several mechanisms of action, depending on its form (Duffield-Lillico et al., 2002). Selenomethionine inhibits proliferation and induces cell cycle arrest of human prostate cancer cells (Brinkman et al., 2006). Selenium in the form of selenomethionine or methyl seleninic acid induces apoptosis and inhibits angiogenesis, mediated in part by the androgen receptor (Dong et al., 2004; Morris et al., 2006; Venkateswaran et al., 2002).

Methylseleninic acid induces apoptosis through a caspase-mediated pathway, as well as through the release of cytochrome c, the exhibition of cleaved polymerase (PARP) and the end stage of DNA fragmentation (Hu et al., 2005). These events are associated with the phosphorylation of c-jun and p38 (Jiang et al., 2002). Some study have identified various selenium targets, including GADD153, cyclin A, cyclin-dependent kinase-1 (CDK-1), CDK-2, CDK-4, CDC25, E2Fs, and the mitogen-activated protein kinase/c-Jun-NH2-kinase and PI3K pathways in pc-3 prostate cancer cells (Muecke et al., 2010b). The relationship between selenium dose and prostate carcinogenesis is complex, and excessive accumulation of selenium is potentially dangerous, as indicated by the U-shaped dose-response curve of selenium in association with increased DNA damage in aging dogs (Table 1) (Waters et al., 2005).

Cruciferous vegetables

Cruciferous or brassica vegetables come from plants in the family known to botanists as Cruciferae or alternatively, Brassicaceae. Many commonly consumed cruciferous vegetables come from the Brassica genus,

including broccoli, Brussels sprouts, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard, rutabaga, turnips, bok choy and Chinese cabbage (Kristal and Lampe, 2002).

Like other vegetables, cruciferous vegetables contain a number of nutrients and phytochemicals with cancer chemopreventive properties, including folate, fiber, carotenoids and chlorophyll. However, cruciferous vegetables also have a high content of other phytochemicals, such as phenethyl isothiocyanate, sulfophorane and indole-3-carbinol, which have been shown to exhibit potential anti-cancer (Kristal and Lampe, 2002; Singh et al., 2005). Consumption of cruciferous vegetables has been reported to be associated with reduced incidence of prostate cancer cases. The results of epidemiological studies of cruciferous vegetable intake and prostate cancer risk are inconsistent. Four out of eight case control studies published since 1990 found that cruciferous vegetable intake was significantly lower in men diagnosed with prostate cancer than men in a cancer-free control group (Cohen et al., 2000; Jain et al., 1999; Joseph et al., 2004; Kolonel et al., 2000). Of the four prospective cohort studies that have examined associations between cruciferous vegetable intake and the risk of prostate cancer, none found statistically significant inverse associations overall (Giovannucci et al., 2003; Hsing et al., 1990; Key et al., 2004; Hardin et al. 2011). However, the prospective study that included the longest follow-up period and the most cases of prostate cancer found a significant inverse association between cruciferous vegetable intake and the risk of prostate cancer when the analysis was limited to men who had a PSA test (Giovannucci et al., 2003). Since men who have PSA screening are more likely to be diagnosed with prostate cancer, limiting the analysis in this way is one way to reduce detection bias (Kristal and Stanford, 2004). Presently, epidemiological studies provide only modest support for the hypothesis that high intakes of cruciferous vegetables reduce prostate cancer risk (Kristal and Lampe, 2002). Kirsh et al. (2007) similarly found that a high intake of cruciferous vegetables decreased the risk of disseminated prostate cancer compared to a low intake ($P = 0.02$) providing some evidence for the possible reduction of risk of advanced prostate cancer with dietary intervention (Kirsh et al., 2007). Large randomized controlled trials could provide more definitive evidence (Ma and Chapman, 2009).

DISCUSSION

Here, this study sought to provide an update on the latest studies investigating the role of dietary to reduce prostate cancer risk. Multiple molecular signaling pathways are involved in prostate carcinogenesis and cancer progression, many of which are affected by dietary and

lifestyle factors. In ancient times, man ate food that was available in nature: wild fruit, vegetables, seeds and roots. They drank animal milk, but did not eat lots of meat. In modern times, many countries have adopted the meat-and-fat diet with an excessive use of salt. Scientific research has indicated some guidelines for a healthy lifestyle aiming at the reduction of the risk of tumors. Several countries have detrimental food habits, because of the large use of fats, meat, and salted food associated to an insufficient use of fibers. On the other hand, several lines of evidence have emerged regarding the anticancer and therapeutic benefit of dietary agents. Substantial epidemiologic and preclinical evidence supports the view that dietary modification and ingestion of appropriate micronutrients will reduce the incidence and mortality of prostate cancer. Overall, a diet low in saturated fat, high in vegetables, fruits and whole grains can be recommended for disease prevention, in addition to avoiding excessive intake of red meat. Such a diet would target multiple pathogenic pathways in prostate cancer, and mimics traditional diets in geographical regions with low incidences of the disease. Better food habits should include soya, honey, vitamins, legumes, fruits and vegetables. However, despite the plethora of confounding factors present in clinical studies assessing the effect of diet on cancer risk, the sum total of data remains compelling in regards to the potential for a variety of nutrients to potentially prevent the development and progression of prostate cancer. Data from migration studies provide evidence that environmental factors are responsible for the transformation of latent prostate cancer to a clinically apparent form and that diet appears to influence this progression. Insufficient clinical evidence exists to warrant recommending wholesale dietary changes to patients to reduce their risk of prostate cancer. However, until more interventional studies are carried out, physicians should recognize the importance of dietary modification in a patient's overall health profile. Although prostate cancer is the most common non-skin cancer in American men and the second leading cause of cancer death, cardiovascular disease was the leading cause of patient mortality in each of the previously mentioned clinical trials. Dietary changes that reduce the risk of cardiovascular disease, such as reducing dietary fat should be recommended to all patients. Some mechanisms potentially involved in increasing a man's risk for heart disease may also increase his risk of prostate cancer. The most practical approach for physicians is to recommend changes that may favorably benefit the risk of both cardiovascular and prostate cancer. Fortunately, many of the lifestyle changes proven to reduce cardiovascular risk seem helpful in reducing prostate cancer risk as well. This fact should be reinforced with patients who inquire about ways to lessen their risk of prostate cancer.

The review of the literature led to the following conclusions: a diet rich in fruit and vegetables may reduce

the risk of prostate cancer; a diet rich in saturated fat, red meat probably increases the risk of prostate cancer slightly; supplementation with vitamins (E, D and C) offers the low risk of prostate cancer; natural products may reduce the risk of prostate cancer; prostate cancer and its effects can be ameliorated by a healthy diet.

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