**DIET AND PROSTATE CANCER - A HOLISTIC APPROACH TO MANAGEMENT**

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**Summary.** There is now increasing evidence from epidemiologic surveys and from laboratory, intervention, and case-control studies that diet and lifestyle plays a crucial role in prostate cancer biology and tumorigenesis. This applies to both the development and progression of prostate cancer, although in many cases the specific initiating factors in the diet are poorly understood. Conversely, many nutrients and herbs also show significant promise in helping to treat prostate cancer by slowing progression and reducing recurrence, ultimately reducing the risk of morbidity and mortality from the disease. Furthermore for all grades of prostate cancer, nutritional interventions complement conventional treatment to improve response and quality of life.

Slowing or even reversing the progression of high-grade prostate intraepithelial neoplasia [HGPIN]), with chemo-preventative agents could be the best primary defense against prostate cancer, preventing it from occurring in the first place.

The information given in this review about prostate cancer chemoprevention summarizes the key evidence for the role of different dietary components and their effect on prostate cancer prevention and progression. Most nutritional chemoprevention agents also have the added benefit of being beneficial for the cardiovascular system, bone health and for the prevention of other cancers.

**Keywords:** Diet. Dietary supplements. Prostatic neoplasms. Prevention. Recurrence. Prostate cancer.

**Resumen.** Existen cada vez más pruebas de las encuestas epidemiológicas y de los estudios de laboratorio, la intervención y de control de casos, de que la dieta y el estilo de vida juegan un papel fundamental en la biología del cáncer de próstata y la génesis tumoral. Esto se aplica a ambos: desarrollo y progresión del cáncer de próstata, aunque en muchos casos los factores iniciales específicos en la dieta son poco conocidos. Por el contrario, muchos nutrientes y hierbas también muestran una promesa significativa para ayudar a tratar el cáncer de próstata al disminuir la progresión y reducir la recurrencia, en última instancia, reduciendo el riesgo de morbilidad y mortalidad de la enfermedad. Además en todos los grados del cáncer de próstata, los controles nutricionales complementan el tratamiento convencional para mejorar la respuesta y la calidad de vida.

Frenar o incluso revertir la progresión de la neoplasia intraepitelial prostática de alto grado [HGPIN]), con agentes de quimioterapia preventiva podría ser la mejor defensa primaria contra el cáncer de próstata, evitando que se produzca en primer lugar.

La información contenida en esta revisión sobre la quimio-prevención del cáncer de próstata resume la evi-
Prostate cancer foci are believed to exist in 30% of men >50 years and in 75% of men >80 years (1). Most of these foci remain latent and do not grow or spread to any significant extent, and the occurrence of such foci is fairly consistent worldwide.

There is now increasing evidence from epidemiologic surveys and from laboratory, intervention, and case-control studies that diet and lifestyle plays a crucial role in prostate cancer biology and tumorigenesis. This applies to both the development and progression of prostate cancer, although in many cases the specific initiating factors in the diet are poorly understood. Conversely, many nutrients and herbs also show significant promise in helping to treat prostate cancer by slowing progression and reducing recurrence, ultimately reducing the risk of morbidity and mortality from the disease. Furthermore for all grades of prostate cancer, nutritional interventions complement conventional treatment to improve response and quality of life.

With high incidence (currently affecting one in six men in the United States), a long latency period, and strong environmental influences, prostate cancer is an ideal target for chemo-preventative approaches. In this context, the term chemoprevention is used to describe nutritional interventions (i.e. changes in diet, the use of specific nutritional supplements) to slow or reverse the progression of premalignant lesions (i.e. high-grade prostate intraepithelial neoplasia [PIN]). Reversing PIN with chemo-preventative agents could be the best primary defense against prostate cancer, preventing it from occurring in the first place.

The information given in this review about prostate cancer chemoprevention will benefit the health of every man, whether he has prostate cancer or not. Most nutritional chemoprevention agents also have the added benefit of being beneficial for the cardiovascular system, bone health and for the prevention of other cancers.

EPIDEMIOLOGY

African American men in the United States have the highest risk of prostate cancer on the planet, with a much greater risk of advanced, invasive prostate cancer and prostate cancer death. Caucasian and African-American men have a prostate cancer incidence that is 5-50 times greater than that of Japanese men residing in Japan (2,3).

Furthermore migration studies reveal that risk shifts in men who move from low-risk to high-risk countries. When a man adopts the lifestyle and diet of a high-risk country, his risk rises correspondingly. Risk of prostate cancer thus increases substantially within a single generation in lower risk men who relocate to the United States. The incidence of prostate cancer in Japanese immigrants to the United States is four times that of their native Japanese counterparts. The risk of prostate cancer in Indian men in the United States is comparable to that of native-born American men. These changes in risk are linked to changes in diet and lifestyle that most immigrants adopt when they make the United States their home. These men exercise less and eat a diet heavier in fats, alcohol, and meat and lower in fiber. As more of the planet eats like Americans, the incidence of prostate cancer is rising even in relatively low-risk countries. This, along with marked racial and cultural disparity indicates that diet plays a strong role in prostate cancer risk.

EVIDENCE FOR DIETARY INTERVENTION

In research conducted at the Preventive Medicine Research Institute at the University of California, San Francisco, Ornish et al. (4) demonstrated the power of diet and lifestyle changes in 87 men with prostate cancer (prostate-specific antigen [PSA] 4 to 10 ng/mL; Gleason score <7) who chose not to undergo conventional treatments during a 1-year period. Subjects were enrolled either in a program of extensive, comprehensive life-style changes, including a low-fat, vegetarian, soy-rich diet and nutritional supplements; exercise; psychosocial support; and stress reduction; or in a usual case-control group. Not one of the men in the experimental group required conventional treatment during the study period, but six control subjects required such treatment. This study and other research studies strongly suggest that if men who would otherwise be told to watch and wait were offered the information and motivation they need to enter into a focused chemoprevention program, we could have a significant impact on disease progression, as well as on other important aspects of men’s overall health. Following a nutritional plan also gives men the...
power to do much more than watch and wait; Active holistic surveillance that incorporates diet and lifestyle changes along with some of the herbs, supplements and other holistic interventions to promote the body’s natural defenses against cancer growth and spread gives men the tools they can use to heal themselves proactively.

**DIET AND PROSTATE CANCER RISK**

Fat content of the diet, overall caloric intake, the ratio of omega-6 to omega-3 fatty acids in the diet, and consumption (or lack thereof) of meat, antioxidants, and soy foods are the major factors that appear to correlate most closely with risk of prostate cancer and risk of death from this disease. These dietary factors may act as late-stage promoters, rather than initiators, transforming a relatively harmless, latent prostatic neoplasia into a more aggressive form.

**Dietary Fat**

Fat intake, especially from animal sources, has been linked to an increased risk of developing prostate cancer in several studies. In a 31-country study, investigators also found a close correlation between fat intake and prostate cancer mortality (5,6). Within populations with a low risk of prostate cancer, such as Chinese men, the percentage of fat in the diet is strongly predictive of whether they will ultimately develop the disease (7). Another case-control study, which was performed in Utah, found that men with high-fat intake had the highest risk of developing aggressive prostate tumors (8).

The exact mechanism by which dietary fat induces prostate carcinogenesis is unclear. Possible explanations include the effects of dietary fat on serum testosterone levels, oxi-dative stress, or increases in the hormone insulin-like growth factor-1 (IGF-1) with those on a high fat diet having higher IGF-1 levels.

Obesity

Men who are obese have an increased risk of developing prostate cancer. Obesity has also been strongly implicated as an independent risk factor for high-grade prostate cancer and prostate cancer mortality (9-11). Obesity is not only a risk factor for prostate cancer, it can also increase the risk of recurrence. In some cases, obesity may be correlated to high-fat intake, although the more likely culprit is high-caloric intake.

**Physical activity**

The increased risk of prostate cancer in obese men is related to changes in hormone balance. Excess body fat alters estrogen and testosterone activity, and lower testosterone is associated with lower PSA at diagnosis. Tymchuk (12) found that when obese men were put on a very-low-fat (<10% of calories from fat), high-fiber diet, and exercise programs, all of those men who had high PSA levels (>2.5 ng/mL) saw those values fall. Sex hormone-binding globulin (SHBG) rose and free testosterone levels dropped, possibly decreasing growth-promoting effects on the prostate. Another hazard of obesity—one that increases risks of all cancers, as well as heart disease—is that it exacerbates both inflammation and oxidative stress. Obese men are also more likely to have high insulin levels and high blood sugar levels.

Refined carbohydrates also fan the flames of chronic inflammation. Food sources rich in refined carbohydrates (or saccharides) include table sugar, corn syrup, fruit, white bread, white pasta, fizzy drinks and cakes. Carbohydrates, particularly those with a high glycemic load, consumed in excessive amounts, result in a state of relative hyperinsulinemia and obesity. This has been postulated to increase the risk of developing prostate cancer through higher bioavailability of circulating estrogen and IGF-1 (13). None of this bodes well for a man’s prostate; it exacerbates both inflammation and oxidative stress. Further studies and randomized controlled trials are thus urgently required to investigate the potential role of carbohydrate consumption and prostate cancer in humans.

**Saturated and Trans Fat**

Before the advent of highly processed diets, the ratio of omega-6 to omega-3 fats in typical diets was about two or three to one. Today’s standard processed-food American diets, however, yield a ratio as high as 40:1. An American high-fat diet is high in omega-6 poly-unsaturated fatty acids (PUFAs) and trans-fats.

A high intake of saturated fatty acids (SFA) (from red meats, processed meats, egg yolks, whole fat dairy foods), trans fatty acids (from processed, hydrogenated vegetable oils), and omega-6 PUFAs, particularly arachidonic acid (AA) and linoleic acid
(LA), have been associated with both an increase in the incidence of prostate cancer and of mortality. All authorities agree that trans fatty acids should be avoided completely. Saturated fats are probably not intrinsically carcinogenic. However there are chemical toxins found in most sources of saturated fat, as a result of modern factory farming methods. Toxins that can raise cancer risk concentrate in the fat of animals who eat a diet laced with pesticides and herbicides. Even higher concentrations of these toxins accumulate in dairy products and eggs.

Conversely, higher intake of the omega-3 fatty acids docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA) is associated with a reduced risk of prostate cancer. The protective effects of omega-3s (found in oily fish such as salmon and mackerel) may be prostate cancer protective by reducing inflammation. In a Swedish study, those subjects who ate oily fish more than three times a week had almost half the risk of metastatic prostate cancer compared with those who ate fish less than twice a month. Each additional daily intake of 0.5 g of marine fatty acid from food was associated with a 24% decreased risk of metastatic cancer (14).

Unrefined vegetable oils rich in phytosterols, including beta-sitosterol and campesterol, are also believed to reduce the risk of prostate cancer; Asian and Mediterranean diets, both rich in phytosterols, thus confer reduced risk compared with the standard American diet, with its abundance of cholesterol, refined oils, and saturated fats.

Olive oil in the diet, a source of neutral omega-9 fatty acids, has been found to be protective against many cancers, including prostate cancer.

**Dairy Products**

Clinical studies assessing dairy intake and risk of prostate cancer have shown conflicting results. A large meta-analysis of 45 observational studies showed no evidence of increased risk (15). Other large meta-analyses have shown that men who consume more dairy products have an 11-39% higher risk of prostate cancer (16,17). The most likely explanation for this increased risk is a high dairy diet resulting in increased levels of plasma calcium, which in turn cause suppression of 1,25 dihydroxyvitamin D3 (18). Other researchers have suggested the increased risk is attributable to the high amount of saturated fat present in dairy, as well as increased circulating IGF-1 levels which have also been implicated in an increased risk of prostate cancer (19,20,21). There is very limited data assessing the effect of dairy intake and prostate cancer progression, although some studies have suggested a low dairy diet may prolong PSA doubling time (22).

**Exercise and weight management**

Studies demonstrated that physical activity is important in preventing prostate cancer. In one large prospective study men over 65 who exercised the most had the lowest risk of prostate cancer (23). Exercise will also help maintain normal body weight as obesity is a risk factor. In one study involving men who previously had prostate cancer, those with the highest BMI had the highest risk of developing the disease. Physical activity, improving physical and psychological health, has also shown promising results in prostate cancer survivors. Physical activity for at least 30 minutes a day and lifting weights or performing resistance exercises several times a week has a positive effect on reducing the side effects of androgen deprivation therapy (ADT). Exercise reduces the risk of weight gain, reduces insulin resistance and minimizes bone loss, all of which are so prevalent in men on ADT.

**Meat**

There is considerable evidence across populations that the more red meat a man eats, the higher his risk of developing prostate cancer. Meat contains high amounts of arachadonic acid. Some byproducts of arachadonic acid have promoted prostate cancer in animals (24). Preliminary reports have suggested that frequently eating well-done steak or cured meats is a risk factor. Meat contains high concentrations of heterocyclic amines (HCAs) (in particular meat that has been cooked at high temperatures and is thus well done or charred, creating poly-aromatic hydrocarbons). Cured meats contain nitrosamines because meats contain amines, and sodium nitrite, a source of nitrosating agents, is added to cured meats as a preservative. These chemicals, concentrate preferentially in the prostate gland, where they enhance free radical production and trigger carcinogenesis. Colli and Colli found strong correlations between prostate cancer mortality and intake of meat, reported in two retrospective population studies assessing prostate cancer mortality in 71 countries (25,26). Marinating meats in a mixture of olive oil, vinegar, and protective spices like garlic, rosemary, or turmeric, reduces the production of carcinogenic substances during cooking. Eating plenty of crucifer vegetables – (broccoli, cauliflower, and cabbage) further helps by neutralizing the effects
of heterocyclic amines in the body.

**THE IDEAL PROSTATE CANCER CHEMOPREVENTION DIET**

Slowing the growth of latent foci of prostate cancer is best achieved with a combination of dietary and nutritional supplements. Current evidence supports the most effective prostate cancer protective diet to be low in red meat and dairy and high in fruits, vegetables, whole grains, herbs (especially Asian herbs like turmeric and ginger) and green tea.

Overall, the best diet for prostate cancer chemoprevention most closely resembles the traditional diets of the southern Mediterranean and Japan. Fish and soy foods take the place of red meats, and dairy products are kept to a minimum. When oils and fats are called for, they’re included in the form of oils that help reduce the omega-6 to omega-3 balance. Whole grains are favored over refined grains and foods made with flour and sugar. Both diets contain abundant fiber. These two diets do differ in many important ways: The Mediterranean diet is rich in tomatoes, which are the best source of cancer-fighting lycopene. Its main source of fat is olive oil, which (in its extra-virgin form) is high in important antioxidants. Olive oil is high in omega-9 fatty acids, which do not promote inflammation, and contains a compound called oleocanthal that has anti-inflammatory properties. The Japanese diet includes a variety of medicinal mushrooms that have great value when it comes to cancer prevention. Japanese diets also incorporate sea vegetables. Soy foods and ginger are important parts of Japanese cuisine; Mediterranean cuisine is often flavored with rosemary and oregano. All of these foods have cancer-fighting properties.

Fruit and vegetables have high concentrations of various phytochemicals, antioxidants, and fiber, and are therefore promoted not only in healthy populations for the prevention of cancer, but also in cancer survivors. Red meat should be a small part of the diet, if consumed at all, and grass-fed, organic beef, free-range poultry, game, eggs, and wild-caught ocean fish are the best options for flesh foods. Encourage patients to try tempeh, tofu, and miso as alternative protein sources.

Whole grains in the diet have an inverse relationship with prostate cancer risk. They are rich in fiber that helps remove carcinogens from the body. Grains should be chosen in a form as close as possible to the ones in which they occur in nature: brown rice instead of white and whole-grain or sprouted-grain crackers and breads, for example. Nuts and seeds are good additions to the chemo-preventive diet; unrefined extra-virgin olive oil should be the oil of choice; and ground flaxseeds can be added to the diet, stirred into organic, low-fat, and live-culture yogurt (the best choice of dairy product) or oatmeal. Patients should minimize refined flour and sugar intake, as well as the consumption of trans fats and other highly refined vegetable oils, which promote the proinflammatory eicosanoid cascade.

Research suggests that the following natural substances may be of some benefit in prostate cancer prevention:

**Fruit and Vegetables**

An antioxidant-dense diet made up primarily of whole plant foods (vegetables, fruit, whole grains, nuts, and seeds) provides a good antioxidant foundation. Certain foods like pomegranates, tomatoes, dark leafy greens, deeply colored fruits, and cruciferous vegetables (broccoli, cauliflower, and the like) are especially dense with protective antioxidants.

**Phytoestrogens**

Phyto-oestrogens are a group of biologically active plant compounds with a chemical structure similar to estrodial, of which isoflavones are the most important. Foods rich in isoflavones include soy bean, tofu, kidney beans, lentils, chick peas and peanuts.

There is conflicting information on soy and soy isoflavones and prostate cancer risk. Current evidence indicates a possible protective effect of dietary soy in prostate cancer prevention (27). The effects of concentrated soy extracts and other phyto-oestrogens are less clear.

Differences in the level of consumption of traditionally prepared dietary soy foods (ie, miso, tofu, tempeh, natto) is believed to contribute to the significant difference in prostate cancer incidence and mortality between Asian and American men. A large-scale epidemiologic study by Hebert et al. (28) of 59 countries found that soy-derived products offered highly significant protection against prostate cancer. Animal studies reveal that soy isoflavones, particularly genistein, inhibit prostate cancer growth in cell cultures (29). In rat models, genistein has been found to offer significant chemo-preventive activity against advanced prostate cancer. Possible mechanisms of action include estrogenic properties (binding to estrogen receptors thus suppressing cellular proliferation and promoting differentiation in
vitro and in vivo) and inhibition of 5α-reductase (5AR). Soy foods contain protease inhibitors, saponins, and phytates, which have putative anti-carcinogenic effects.

Some of the conflicting information on soy may be due to the fact that men eating a Western diet (full of meat and low in vegetables) have a different population of bacteria inhabiting their gut. These bacteria may not effectively break down soy into its active metabolite, genistein. Men eating a traditional Japanese diet tend to experience greater benefit from soy in terms of preventing prostate cancer because they have been eating soy foods as a part of their daily diet for years. They are therefore more likely to have a population of gut bacteria that effectively metabolize soy isoflavones into genistein: men who incorporate soy foods in the diet abruptly may not receive the same benefit.

Tomatoes and other lycopene–rich foods

Lycopene is a bright red carotenoid pigment found in tomatoes, watermelons, pink grapefruit and papaya. A number of small studies indicate that regular consumption of lycopene (from eating raw tomato and cooked tomato products) may help prevent prostate cancer (30), as well as reducing the risk of progression in those who have the disease (18-31). Cooked tomatoes and tomato sauce are better than raw tomatoes because cooking them releases lycopene from their storage sites. In vitro, lycopene has been shown to exert its anti-proliferative effects on various cancer cell lines by causing cell cycle arrest and inducing apoptosis (32). It also increases IGF-1 binding proteins thus resulting in a reduction in serum IGF-1, which has previously been associated with increased risk of prostate cancer (33).

However, no studies have proven that taking lycopene in supplement form can decrease the risk of prostate cancer. Further well designed large scale studies are required to establish the role of lycopene in the prevention and treatment of prostate cancer (34,35).

Silymarin

This phytochemical, found in the herb milk thistle was shown in vitro to inhibit prostate cancer cell growth (36). Silymarin actually refers to several different flavonoid compounds with similar structures: silibinin, the most prevalent form, has been entered into phase 1 and phase II clinical trials with prostate cancer patients (37).

Delphinidin

Delphinidin from berries caused apoptosis of prostate cancer cells along with significant inhibition of tumor growth in an animal study (38).

Quercetin

A preliminary cellular study in the journal of Carcinogenesis demonstrated that the flavanoid quercetin has potential as both a preventive agent and a complementary treatment for prostate cancer (39,40).

Fiber and Lignan Intake

Lignans are found in seeds, whole grains, vegetables, fruit, and legumes, but the richest dietary source of lignans is flaxseed. Diets rich in this and other fibers have consistently been associated with reduced prostate cancer risk (41). Duke University investigators added 30 g of ground flaxseed/day for an average of 34 days (21 to 77 days) to the diets of 25 patients scheduled for prostatectomy. The men were also placed on a 20% fat diet for the study’s duration. During the study, testosterone and free androgen levels fell; proliferation rate fell; and cell apoptosis was enhanced (42). To enhance lignan intake, patients may be advised to supplement their diets with three tablespoons of flaxseed daily; the seed meal can be added to yogurt, hot cereals, soups, stews, or nut butters. The seeds also can be ground in a coffee grinder, or they can be purchased already ground.

Cruciferous Vegetables

Consumption of cruciferous vegetables from the Brassicaceae family, including broccoli, cauliflower, and cabbage, is inversely related to the incidence of prostate cancer. Broccoli in particular has been shown in clinical trials to specifically help prevent prostate cancer. Sulfur-containing glucosinolate breakdown products indole-3-carbinol (I3C) and sulforaphane are phytochemicals found in crucifers, and both have been demonstrated to reduce the proliferation of prostate cancer in vivo in a dose-dependent manner. I3C reduces the proliferation of cancer cells and increases cell apoptosis; some investigations have found that supplemental doses of this nutrient chemosensitize chemoresistant prostate cancer cells, aiding in the treatment of hormone-resistant cancers (43). Supplements of I3C and sulforaphane are available, such as Broccoprotect® however more research is needed to determine whether these supplements are
more useful chemo-preventives than the foods from which they are derived.

**Fish and Fish Oils**

The long-chain w-3 fats DHA and eicosapentaenoic acid (EPA) are abundant only in fish, crustaceans, and some forms of algae. They have been found to suppress cancer initiation, induce cell apoptosis and decrease proliferation of several cancers including prostate cancer, causing decreased PSA doubling time in a mouse model. This appears especially true when the overall diet is altered to reduce intake of red meat, dairy products, hydrogenated oil, and highly unsaturated vegetable and seed oils, which are staples of the standard American processed-food diet and sources of saturated fats, w-6 polyunsaturated fats, and trans fats (44,45). These three classes of fat have been linked with increasing incidence of cancer in the prostate and breast.

The short-chain w-3 fat found in plant foods such as flaxseeds, which contain ALA, has not matched DHA and EPA in its chemo-preventive effects; to act as a substrate for the production of anti-inflammatory eicosanoids, ALA must first be converted to long-chain w-3 PUFAs, an inefficient process. Flaxseeds, walnuts, and soybeans, the most important dietary sources of ALA, are still good foods to include in the chemoprevention diet, but they should not be relied upon as sole sources of w-3 fats.

Numerous investigations have found that the consumption of fish three to four times/week confers a significant reduction in prostate cancer occurrence (a two- to threefold reduction in one study and a 40% to 44% reduction in risk in two other studies) (14,46,47).

The evidence in favor of fish oil supplementation is adequate to make general recommendations for patients to consume one each day. to use a fish oil supplement that has been purified (pharmaceutical grade or molecularly distilled); contains an antioxidant, such as vitamin E or rosemary oil, to prevent rancidity; and that comes from small, oily cold-water fish, such as anchovies or sardines. Current guidelines indicate that patients may benefit from 1,000 to 3,000 mg/day of combined EPA and DHA, with higher EPA than DHA content.

**Green Tea**

Green tea is derived from the plant *Camellia sinensis*. The tea leaves are very rich in polyphenols, known as catechins, of which epigallocatechin-3-gallate (EGCG) makes up 10-50% of the total catechin content. EGCG inhibits cellular proliferation primarily by acting as a very potent anti-oxidant scavenging free radicals along with 51 other compounds present in green tea that have anti-inflammatory activity. Other modes of anti-tumorigenic action include apoptosis and cell cycle arrest via alterations in the mitogen-activated protein kinase, phosphatidylinositol-3-kinase (PI3K)/Akt and protein kinase C pathways, inhibition of inflammatory pathways (nuclear factor kB and cyclooxygenase -2(COX-2) and modulation of the insulin-like growth factor and androgen receptor axes (48).

In oriental cultures in which green tea plays a major role in diet, the incidence of and mortality from prostate cancer is significantly lower. Several studies have confirmed green tea as a potent agent against many cancers, including prostate cancer (49). A recent small double-blind human trial demonstrated that green tea was effective at treating high grade prostatic intraepithelial neoplasia (HGPIN) with a significant reduction in the incidence of prostate cancer (50). Researchers at Louisiana State University conducted a study involving 26 cancer patients. Prior to their scheduled surgery the patients were given a green tea extract containing 800mg of EGCG (equivalent to 12 cups daily) for an average of 34.5 days. The patients had significant reductions in blood levels of PSA, VEGF and HGT, all of which are correlated with prostate cancer growth (51). Furthermore in a population study published in 2008, researchers looked at data on 49,920 men (ages 40 to 69) and found that consumption of green tea was linked to a dose-dependent reduced risk of advanced prostate cancer in men who drink more than 5 cups of green tea per day (52). Most men will not drink 6 cups/day of green tea; therefore, supplementation with a concentrated extract appears to be an important aspect of herbal chemoprevention (50-53).

Essiac Tea – a combination of four herbs (Rheum palmatum, Trifolium pretense, Arctium lappa, and Rumex acetosella) has also been found in vitro to inhibit prostate cancer cell growth.

**Pomegranate juice**

Pomegranate is a rich source of polyphenolic compounds, including anthocyanins and hydrolysable tannins. It has a reportedly higher antioxidant activity than green tea and red wine as well as anti-inflammatory properties. Recent studies show that anatomically discrete sections of the pomegranate fruit acting synergistically exert anti-proliferative and anti-metastatic effect against prostate cancer cells.
Furthermore, pomegranate fruit extract treatment of highly aggressive PC-3 cells resulted in a dose-dependent inhibition of cell growth/cell viability along with induction of apoptosis coupled with corresponding laboratory effects on prostate cancer in vitro cell proliferation and apoptosis, as well as oxidative stress (54).

Pomegranate juice has also been shown to increase mean PSA doubling time. A human clinical trial featuring men with rising PSA levels demonstrated that drinking just 8 ounces of pomegranate juice daily was effective at stabilizing PSA levels up to four times longer than normal, potentially delaying the growth of prostate cancer cells (55).

**Eicosanoids and Anti-Inflammatory Chemoprevention**

Inflammation is mediated by hormone like chemicals called eicosanoids. Some eicosanoids encourage chronic inflammation; others discourage it. They impact the action of the immune system as well as the constriction of blood vessels, blood clotting, stomach acid secretion, and the intensity and longevity of pain and fever. Eicosanoids are built from polyunsaturated fats in the foods we eat. The fats we consume dictate the action of enzymes that build eicosanoids. Certain enzymes make “good,” anti-inflammatory eicosanoids; others make “bad,” pro-inflammatory eicosanoids. “Good” eicosanoids are made from omega-3 fats, found in fish, walnuts, flaxseeds, and leafy green vegetables. “Bad” eicosanoids are made from omega-6 fats, found in many vegetable oils used to make processed foods, including oils made from corn, soybeans, sunflower, safflower, and cottonseed. Meats and dairy products, which come mostly from animals that are fed a grain-rich diet, also are high in omega-6s. The body’s production of eicosanoids depends in large part on the balance of these fats in the diet.

In prostate cancer, the eicosanoid-building enzymes that seem to have the greatest impact on progression are cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), and 12-lipoxygenase (12-LOX). These enzymes lead to the production of pro-inflammatory eicosanoids like prostaglandin E2 and leukotriene B4. COX-2 overexpression is a predictor of a worse prostate cancer outcome (45).

Other studies have suggested that angiogenesis is orchestrated in part by increased COX-2 activity and ensuing prostaglandin production, a hypothesis supported by the effects of some COX-2 inhibitor drugs (i.e. celecoxib) on the biochemical measures of apoptosis.

The anti-inflammatory aspect of chemoprevention appears to be a pivotal one, particularly in cases of PIN, which can appear up to 10 years before diagnosable cancer and which coexists with cancer in >85% of cases. PIN also offers investigators the opportunity to apply chemopreventive measures when dysplasia is present and the point at which prostate carcinogenesis may be at its earliest stage.

Manipulation of pro-inflammatory eicosanoids can be achieved in two ways:

1) with manipulation of fatty acid intake, providing the body with increased substrate for the production of anti-inflammatory eicosanoids, which then competitively inhibits formation of pro-inflammatory eicosanoids; and

2) with manipulation of COX and lipoxygenase (LO) enzyme isoforms, inhibiting those that promote the inflammation that encourages prostate carcinogenesis. So far, it appears that fatty acid intake is a safe and effective intervention in this regard. Manipulating COX and LO with pharmaceutical agents, however, has proven to be a less promising avenue for chemoprevention. Recent case-control studies have found significant risks regarding long-term COX-2 inhibitor therapy, with increases in mortality and risk of heart failure and gastrointestinal (GI) bleeding.

Herbal anti-inflammatory agents have a broader, less specific effect and the research community is beginning to recognize their therapeutic value. Many researchers have explored a variety of natural plant extracts and other natural products to elucidate their specific and nonspecific effects on COX and LO. Curcumin (turmeric), ginger, holy basil, resveratrol (concentrated in grape skins), and berberine (from barberry and Chinese goldthread) are among the most promising candidates in the burgeoning field of herbal anti-inflammatory agents. A novel compound under further study zyflamend (New Chapter, Brattleboro, VT), is composed of these and a few other herbs, most of which have a nonselective COX inhibitory effect. Each of the mixture’s components has been found to have anti-inflammatory, antioxidant, or anti-proliferative effects; some are even anti-angiogenic. In 2005, Bemis et al. (56) published the results of an analysis of zyflamend’s effects on LNCaP cells—significant decrease in both COX-1 and -2 activity; increased p21 expression; attenuated cell growth; and induced cell apoptosis. A phase 1 clinical trial is currently being conducted at Columbia University in men with PIN to determine whether zyflamend can influence the progression of biopsy-proven high-grade PIN to prostate cancer. Preliminary results are promising (57).
Curcumin

Curcumin, or turmeric, has been found to be a potent radiosensitizer that enhances radiation-induced clonogenic inhibition in tumor cells (58). A recent in vivo study showed that curcumin can help prevent prostate cancer. Dorai et al. (59) found that curcumin modulates proteins that suppress cell apoptosis and interferes with growth factors that promote cancer progression (60).

Ginger

Ginger flavors many cuisines, and has been a herbal medicine since antiquity, used to treat nausea, motion sickness, upper respiratory infections, and intestinal parasites. Modern investigators have discovered >20 phytochemicals in this rhizome that inhibit COX-2 and 5-LO. Ginger constituents have potent anti-oxidant and anti-inflammatory activities; some, particularly shogaols and vallinoids [6]-gingerol and [6]-paradol, exhibit cancer preventive activity in experimental carcinogenesis. The chemo-preventive effects of ginger have been illustrated in a variety of experimental models (61).

Prostabell, a herbal combination containing extract of Pao pereira (an Amazonian tree) and Rauwolfia vomitoria (from the bark of a subsaharan plant), was created by the late molecular biologist Mirko Beljanski. These plants have been used in indigenous medical traditions for centuries; Beljanski found that they had anticancer activities in various cancer cell lines, including prostate cancer. Research has revealed that both Rauwolfia and Pao extracts suppress prostate tumor cell growth in culture and in vivo. Patients with elevated PSA and negative biopsy results are now being enrolled in a phase 1 study of this herbal medicine. Results are awaited (62).

The herbs discussed in this review are relatively free of interactions with prescription drugs. However, turmeric may potentiate anti-platelet activity in patients on anti-platelet agents; ginger and turmeric may potentiate the effects of anticoagulants. Patients should be advised that herbs and drugs can interact in harmful ways, and that they should reveal the use of all medications and supplements to their physicians so that these adverse interactions can be avoided.

Individual Micronutrients as Chemopreventatives

Vitamins are a group of structurally and functionally unrelated organic compounds that are essential for the normal functioning of the body and are present in various different food sources.

According to a survey by the American Institute of Cancer Research (AICR), roughly half of adults >45 years take multi-vitamins specifically to lower the risk of developing cancer. In this same survey, 23% to 36% of subjects reported using other supplements for the same purpose (63). No single nutrient has been found to stand alone as a chemo-preventive agent. Current evidence in favor of individual nutrients from animal and in vitro models notwithstanding, the synergistic action and interaction of a wide spectrum of micro-nutrients is the most likely reason for the health benefits of disease-preventive foods, not the isolated action of any one or two nutrients in those foods.

The evidence does point strongly to the supplemental use of a handful of nutrients, in addition to a diet composed of beneficial and nutrient-dense foods in prostate cancer prevention. Vitamin E, selenium, vitamin D, and calcium all appear to play roles in prostate health. Supplementation of some vitamins and minerals may be appropriate as part of a chemo-preventive program.

Vitamin E

Vitamin E is a general term referring to a class of related compounds, including α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienols. δ-Tocopherol has the highest biologic activity of all these compounds. In foods, vitamin E exists as a mixture of these various compounds, each of which have unique and interactive effects. The inhibitory effect of vitamin E on prostate carcinogenesis is probably attributable to its potent antioxidant effect in membrane phospholipids. It is the major hydrophobic chain-breaking antioxidant that protects membrane lipids from oxidation. Animal and preclinical studies have found that vitamin E also has direct anti-proliferative effects unrelated to its antioxidant capacity (64), including inhibition of protein kinase C (PKC) activity, which plays an important role in proliferation, adhesion immune response, free radical production, and gene expression. Vitamin E also appears to interfere with hormone signaling, which is particularly relevant to prostate carcinogenesis.

Several RCTs have evaluated the role of Vitamin E either alone or in combination with other vitamins. In the large α-Tocopherol, β-Carotene (ATBC) RCT study, 29,133 male smokers received daily doses of 50 mg α-tocopherol (Vitamin E), 20 mg β-carotene (Vitamin A), both, or a placebo for 5 to 8 years. Although β-carotene had no effect on prostate cancer
risk, and it increased the risk of lung cancer and total mortality in this cohort, \( \alpha \)-tocopherol supplementation reduced the risk of prostate cancer by 32% \((65,66)\). Other research by the same Finnish investigators found that higher circulating concentrations of \( \alpha \)-tocopherol and \( \psi \)-tocopherol, the major vitamin E fractions, correlated with a reduced risk of prostate cancer \((67)\). A role for \( \alpha \) - and \( \psi \)-tocopherol in prostate cancer chemoprevention is further supported by the results of serum case-control studies. Follow-up analysis of the cohort involved in the ATBC studies found that the risk ratio for prostate cancer rose again to 0.94 in the 6 years following the end of the supplementation protocol, suggesting that continual supplementation with vitamin E is necessary to maintain its chemopreventive effects in the prostate. Men should take a minimum of 240 international units (IU) of vitamin E daily as mixed tocopherols (\( \alpha \) and \( \psi \) in particular).

The Selenium and Vitamin E Chemo-prevention Trial (SELECT), the largest prevention trial ever undertaken using a drug or nutrient involved over 35,000 men randomized to one of four arms (to receive either 200\( \mu \)g selenium, 400 IU of Vitamin E, both nutrients, or two placebo capsules alone). This large double-blind placebo controlled trial closed enrollment in 2004. The trial was terminated early as interim results failed to show any benefit with either of the components in reducing prostate cancer risk \((68)\). The evidence for vitamin E being a chemo-protective agent in prostate cancer thus remains controversial.

Selenium

Selenium is an essential trace mineral that gives reduction/oxidation (redox) potential to vitamin E. It is found in brazil nuts and fish such as tuna, swordfish and oysters. Furthermore the amount of selenium obtained in any diet can vary widely because of variations in the selenium con-tent of soil in different parts of the world where food is grown. Population studies consistently show that men with higher intake of selenium have a lower risk of prostate cancer, and that men with prostate cancer have lower selenium levels than men who do not have the disease.

In 1996, the Nutritional Prevention of Skin Cancer study found that although daily supplementation with 200\( \mu \)g selenium did not prevent recurrence of skin cancer in men with a previous history of skin cancer, it did result in a substantial reduction in the incidence of prostate cancer \((69)\). Supplementation for 6.5 years correlated with a 60% reduction in the number of new cases of prostate cancer compared with placebo, and 7.5 years of supplementation yielded 52% fewer cases compared with placebo. These investigators used a form of selenium that had been fermented with Saccharomyces cerevisiae yeast, a process that increases the nutrient's bio-availability \((69)\). These results, and the overall reduction in the risk of other cancers, were so promising that the control arm of the trial was stopped early.

Other studies demonstrate that selenium supplementation alone may slow prostate cancer growth or aid in the prevention of recurrence. In one study, 974 men with a history of prostate cancer received 200\( \mu \)g selenium/day or placebo. With about 4.5 years of treatment and a 6.5-year follow-up, the authors concluded that selenium treatment was associated with a 63% reduction in prostate cancer recurrence.

Laboratory studies have determined that selenium inhibits angiogenesis and cellular proliferation, \(70\) as well as inducing apoptosis in vitro \((71)\). Selenium also potentiates vitamin E-induced inhibition of prostate cancer cell growth \((72)\). Vitamin E combined with selenium has been found to induce cellular arrest in abnormal cells. Five of six biomarker-based studies found an association between selenium intake and either a reduced risk of prostate cancer or a non significant trend toward a lower risk of the disease \((73-77)\).

The studies above initially raised the prospect of using selenium supplementation for chemoprevention of prostate cancer. However, the interim results of the SELECT trial \((68)\) were disappointing, showing no benefit of selenium alone or when combined with vitamin E for prevention of prostate cancer, which led to the early closure of this trial. Recently, the results of another large multicentre phase III RCT using selenium vs placebo in men with HGPIN has proved equally disappointing with no benefit seen in the intervention group receiving selenium supplementation \((78)\). The role of selenium supplementation in men with an already established diagnosis of prostate cancer was recently studied by Chan et al. \((79)\). The authors concluded that selenium supplementation in certain patients may result in a more aggressive prostate cancer phenotype especially when patients have an altered genotype for the manganese superoxide dismutase (SOD2) enzyme. These results taken together now challenge the previous notion of a protective role of selenium supplementation with some studies even suggesting the converse. Further investigations into selenium for chemoprevention are ongoing \((80-82)\).

Calcium

Current guidelines for calcium intake for osteoporosis prevention recommend that men >50
years take 1,200 mg calcium daily. However, in epidemiologic studies of calcium intake from diet and supplements, men with the highest intake of calcium have a significantly elevated risk of prostate cancer.\textsuperscript{18,83} The calcium intake found to raise the risk of prostate cancer was >1,200 mg; however, calcium intake of >2,000 mg/day from food and supplements elevated men’s risk of the disease to varying extents, with risk ratios for prostate cancer ranging from 1.2 in the 86,404 men enrolled in the Cancer Prevention Study II (CPS-II) Nutrition Cohort to 1.71 in the Physicians’ Health Study. The risk ratio for metastatic disease was found to be 2.97 in the latter investigation. A small proportion of men (1% of study subjects) consumed enough calcium to raise their risk of prostate cancer, but the link does exist and it is consistent. Physicians should thus ensure that patients recognize the upper limit for calcium intake. If the patient consumes significant amount of dairy products along with a calcium supplement, it may be prudent to evaluate the patient’s diet to reduce calcium intake.

The interplay between vitamin D and calcium is probably the reason behind this association. High calcium intake reduces the production of 1,25(OH)\textsubscript{2} vitamin D, which has anti-proliferative, differentiating, and anti-metastatic effects (84).

**Vitamin D**

Several studies have demonstrated that vitamin D can inhibit prostate cancer growth, by promoting cellular differentiation and inhibiting proliferation, invasiveness and metastases (85). In areas of the world where sun exposure is low, and thus vitamin D deficiency is more prevalent prostate cancer rates increase (86) and geographical distribution of CaP mortality is the inverse of that of UV radiation (87).

An international placebo-controlled randomized trial is looking into whether vitamin D has benefits for those with prostate cancer. In a pilot study, PSA levels decreased or remained unchanged after patients were given 2000IU (50mcg) of cholecalciferol daily. This was sustained for as long as 21 months. Also, there was a statistically significant decrease in the rate of PSA rise after administration of vitamin D. The doubling time for PSA was increased by approximately 50% in the men taking vitamin D (88,89). A recent study of 3763 urology patients revealed that 68% were deficient in vitamin D (90). It thus seems appropriate to measure 25-hydroxy vitamin D in patients to check they have normal levels between 30-70ng/ml. Randomized phase III clinical trials are necessary to determine the optimal dose and most optimal vitamin D analogue along with route and schedule of administration.

**Active Hexose Correlated Compound (AHCC)**

Active hexose correlated compound (AHCC) is a mushroom mycelium extract derived from a liquid culture of basidiomycetous mycelia of lentinula edodes (shiitake mushroom). It was developed by Amino Up Chemical Co.Ltd (Sapporo, Japan) in 1989 and has been used throughout the world for its anti-tumor effects through the purported up-regulation of the innate and adaptive immune responses (91). Its main active component is a mixture of oligosaccharides with an average molecular weight of 5000kDa, with about 20% of them being of the α-1,4glucan type, which is likely to be the molecule responsible for the therapeutic effects of AHCC (92-94). In studies to date, AHCC has been shown to have some biological response modifier-like activity in certain cancer patients.

AHCC has a number of effects at the cellular level on immune function. AHCC has been shown to significantly increase the number of total dendritic cells (DCs) (94). AHCC has also been shown to have direct anticancer activity against certain tumor cell-lines (95) as well as increasing natural killer (NK) cell activity which is important in the elimination of tumor cells. AHCC was also found to increase production of IFN-γ, TNF-α and other cytokines important in the activation of effector cells, which translates into anti-tumor activity in the cancer microenvironment. These results may indicate that AHCC can improve immunological competence in cancer patients, many who are already on therapies that cause immunosuppression. Despite the relative lack of large scale randomized controlled trials, the existing literature has shown AHCC to be effective in the treatment of numerous cancers including breast (96), liver (97) and prostate (98).

The only studies in the existing literature utilize the reduction of prostate specific antigen (PSA) as the primary endpoint to indicate the effectiveness of AHCC in treating prostate cancer. Case reports, although not conclusive, have shown AHCC to be an effective treatment option for prostate cancer showing that PSA levels drop significantly as early as 1 to 2 months and reach normal levels by 4 months (95). However the relatively small number of patients in AHCC studies, as well as lack of controls and statistical analysis, greatly limit their power.

While based on the two small clinical studies, AHCC does not appear to lower PSA scores of the general population of prostate cancer patients.
patients, but it has potential to lower PSA levels in older patients and in patients with advanced disease, which should be confirmed in larger trials focusing on these population groups. Case studies also indicate that patients with certain characteristics may benefit from supplementation with AHCC. Besides looking at PSA values as a standard of efficacy, other clinical correlates should be analyzed, such as using imaging techniques to assess for resolution of cancer, as well as eliciting overall symptom response and assessment of patients’ physical and psychosocial improvement. Given the strong safety profile of this natural compound and its apparent lack of side-effects, supplementation with AHCC holds much potential to help certain prostate cancer patients, but further studies need to be conducted in order to support this.

As AHCC has not been shown to be harmful thus far and is not associated with any significant adverse effects, its clinical utility can still be assessed with little overall risk to the patient. While AHCC seems like a promising alternative treatment in patients with malignancy, there is a need to conduct randomized-controlled double blind trials on a larger scale to understand its true implications in prostate cancer patients. To date, PSA has been used as the primary outcome measure to quantify the effectiveness of AHCC, but the utility of this measure needs to be considered against other clinical outcomes. By performing studies with higher statistical power and including the measurement of other clinical endpoints while controlling for prostate cancer grade and stage, AHCC may be confirmed as a safe, natural, and effective alternative to standard medical therapy for prostate cancer.

CONCLUSION

The popularity of complementary and alternative medicine continues to grow in prostate cancer management. Nutritional and herbal interventions in early prostate cancer and high-grade PIN have strong support in the published research. Furthermore they show significant promise in helping to slow progression and reduce recurrence of prostate cancer. The interventions described in this review are beneficial for multiple body systems, including the endocrine, cardiovascular, immune, and central nervous systems. In all grades of prostate cancer, diet and supplements complement conventional treatment to improve response and quality of life and help empower the patient to be proactive and play their role in taking control of their disease.

In a series of studies, Demark-Wahnefried et al. (99) of the Duke University Program of Cancer Preventive, Detection, and Control Research have pointed out the growing role of oncologists as advisors and supporters of cancer patients who will greatly benefit from long-term diet and lifestyle changes. According to their review article on the subject, cancer survivors frequently initiate diet, exercise, and other lifestyle changes after the wakeup call of cancer diagnosis; but that older men and less well-educated men are less likely to do so. In reviewing relevant studies from 1966 to the present, Demark-Wahnefried and colleagues found that only 25% to 42% of cancer survivors consume adequate fruit and vegetables, and that approximately 70% of prostate and breast cancer survivors are obese or overweight. They conclude that ‘oncologists can play a pivotal role in health promotion, yet only 20% provide such guidance.’

With the number of cancer survivors continually rising as the result of early detection and improved treatments, and with our increasing understanding of the benefits of dietary changes and nutritional interventions in early-stage cancers, the time has come for urologists to disclose all pertinent information regarding their knowledge of specific foods and nutritional supplements to their patients. Accountability and responsibility are required of both doctor and patient.

At this writing, clinical research into the use of such therapies in early prostate cancer and high-grade PIN is relatively new. Much more of this kind of research is imperative for the creation of consistent and effective protocols for chemoprevention, not just of prostate cancer, but of other cancers as well. Recommendations for standardization and dosages of herbal medicines are often frustratingly difficult to determine because of the lack of this research. However, the benefits of herbal and nutritional chemoprevention appear to greatly outweigh any harm that could come to a patient, particularly in the earliest stages of detectable disease, in whom active surveillance would be the most likely first intervention.

REFERENCES AND RECOMMENDED READINGS

*(of special interest, **of outstanding interest)*


*3. Moradi T, Delfino RJ, Bergstrom SR, Yu ES, Ada-


17. Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K. Milk consumption is a risk factor for prostate cancer in Western countries: evidence from cohort studies.


32. Amir H, Karp M, Giat J, et al. Lycopene and...
58. Chendil D, Ranga RS, Meigooni D, Sathishkumar


