Dietary Agents in the Chemoprevention of Prostate Cancer

Sanjeev Shukla and Sanjay Gupta

Abstract: Nutritional factors have been estimated to contribute 20–60% of cancers around the globe, and almost one-third of deaths are being reported in Western countries. According to estimates by the American Cancer Society, during the year 2005 about 232,090 new cases of prostate cancer will be diagnosed alone in the United States and 30,350 men will die of this disease. The high incidence and long latency period of prostate cancer offer plenty of time to pursue strategies toward prevention and/or treatment to suppress or revert this disease. Epidemiological evidence suggests that plant-based dietary agents decrease the risk of some types of human cancer, including prostate cancer. Intake of 400–600 g/day of fruits and vegetables is associated with reduced risk of several cancers. The use of micronutrients and/or other phenolic agents in the diet or synthetic exogenous supplements to prevent neoplastic transformation of normal cells or to slow the progression of established malignant changes in cancer cells is termed “chemoprevention.” Considerable attention has been devoted to identify plant-based dietary agents that may serve as natural inhibitors of prostate carcinogenesis. Much progress has been made in the last decade in this area of investigation through identification of pathways that play important roles in prostate tumorigenesis. This article summarizes epidemiological, clinical, and mechanistic studies and the significance of plant-derived dietary agents such as flavonoids, indoles, isothiocyanates, phenolics, monoterpenes, and complementary and alternative agents in the management of prostate cancer with recommendations for future studies to advance this area of research.

Introduction

Prostate cancer is the most common non-skin malignancy and the second leading cause of cancer death (after lung) in U.S. males. According to estimates by the American Cancer Society, 232,090 new cases of prostate cancer will be diagnosed, and 30,350 deaths are estimated from this disease, in the year 2005 (1). Although the death rate of prostate cancer is on the decline, in the past few years the number of new cases has been on the rise due to an increase in the aging population. In fact, by 2015 there will be >300,000 new prostate cancer cases each year, with a 50% increase (1). Epidemiological studies have suggested that diet and nutrition are critical determinants of prostate cancer risk, with dramatic variations in prostate cancer incidence and mortality between different geographic regions (2–4). Prostate cancer rates are high in North America and northern Europe, intermediate in Mediterranean nations, and relatively low in many parts of Asia (2–4). The low incidence of prostate cancer in Asian countries has been attributed to diets (the substances a person eats and drinks) that are low in animal fat and rich in plant-based agents. On the other hand, the incidence of prostate cancer is significantly higher in industrialized Western countries where the diet is typically high in animal fat (30–40% of calories from fat) (4,5). It is emphasized that, with a diet composed according to the guidelines by the American Institute for Cancer Research, it is likely that there would be at least a 60–70% decrease in breast, colorectal, and prostate cancers and even a 40–50% decrease in lung cancer along with similar reductions in cancers at other sites (Ref. 5 and references therein). It is also notable that Asian men who immigrate to the United States and adopt Western diets have a risk of developing prostate cancer that approaches the average U.S. incidence within one generation (6,7). This information suggests that environmental factors and lifestyle play significant roles in the initiation of prostate cancer; however, more importantly, these factors may also influence the rate of progression of established prostate cancers. Men above the age of 50 have about a 40% chance of having cancer in the prostate, regardless of nationality, race, and/or ethnicity. Autopsy studies have shown that malignant changes begin in the prostate as early as the 3rd decade of life, yet most men are not diagnosed with clinically evident prostate cancer until they are in their sixties (7,8). Therefore, the initiation of prostate cancer probably occurs somewhat similarly throughout the various nations of the world, but progression of prostate cancer to a clinically detectable stage differs between countries (7,8). The discrepancy between the frequency of “latent” and “clinically evident” cancer has been attributed to variations in environmental and lifestyle factors that control progression of previously initiated cancers. The addition of vegetables and fruits to meals to prevent prostate cancer has gained considerable attention as research...
demonstrates that various plant-based dietary agents (flavonoids, indoles, isothiocyanates, phenolics, carotenoids, and monoterpenes) and/or supplements (vitamins and minerals) may help to reduce the risk of developing clinically evident prostate cancer (9,10).

Cancer Chemoprevention

Chemoprevention is defined as pharmacological intervention with naturally occurring and/or synthetic compounds that may prevent, inhibit, or reverse carcinogenesis or suppress the development of invasive cancer (9,10). The expanded definition of cancer chemoprevention is to inhibit or delay the onset of neoplasia by blocking neoplastic inception as well as reversing the progression of transformed cells before the appearance of malignant lesions (10–12). Chemoprevention of cancer thus differs from cancer treatment in that the goal of this approach is to lower the rate of cancer incidence (13). Micronutrients (antioxidant vitamins and trace minerals) as well as certain phenolic compounds present in vegetables and fruits are regarded as the most desirable class of chemopreventive agents (14). This information is supported by the fact that populations consuming low amounts of vegetables and fruits have higher incidence and mortality from cancers of several organ sites as well as epidemiological studies suggesting that consumption of fresh fruits and yellow-green vegetables reduces cancer incidence and mortality (15,16). Extended studies have suggested that micronutrients present in vegetables are more effective than fruits in possessing potential anticarcinogenic properties (14–16). Some chemopreventive agents, in addition to preventing or delaying the onset of carcinogenesis, have also exhibited potential therapeutic effects (17–19). According to a bulletin from the National Cancer Institute, at present, approximately 400 compounds are being studied as potential chemopreventive agents, primarily in laboratory research (20). Over 40 of these compounds and agent combinations exist or are undergoing clinical evaluation (20). The protective effect of fruits and vegetables against carcinogenesis may be derived from many different plant components that include vitamins, minerals, fiber, and micronutrients, each acting via a variety of distinct and potentially interactive mechanisms (21,22). Some of these potentially beneficial components have been incorporated into herbal medicines, which have grown in popularity in recent years (23). Approximately 40% of Americans use alternative remedies, including herbal medicine, for disease prevention and therapy (24). The increasing cost, side effects of drugs, and therapeutic limitations of conventional medications are key factors that enhance interest in herbal medicines. Herbal medicines and/or botanical supplements are available without a prescription and, despite the fact that their safety and efficacy are generally not established by rigorous scientific testing, they are widely used (25–28). Given the wide range of botanical species and plant parts from which these herbal elements are derived, they may potentially contribute overlapping anti-neoplastic effects, including antioxidant effects, modulation of detoxification enzymes, stimulation of the immune system, reduction of inflammation, modulation of steroid metabolism, and antibacterial and antiviral effects.

Prostate Cancer Development and Progression

Accumulated evidence indicates that prostate cancer results from the accumulation of multiple sequential genetic alterations and mutations in nuclear and cytoplasmic molecules (29,30). These events occur in three phases: initiation, promotion, and progression. Prostate cancer most likely develops initially as high-grade intraepithelial neoplasia (HGPIN). HGPIN is an androgen-dependent proliferation of neoplastic cells, occurring in the peripheral and transition zones and giving rise to small, latent low-grade carcinomas that may subsequently progress to large, high-grade potentially metastatic tumors (31). Promotion and progression of prostate cancer are controlled by cascades of signal transduction molecules (32–34). Generally, these cascades are triggered by hormones or growth factors, and in carcinogenesis they are either faultily expressed or activated by tumor-promoting stimuli (32–34).

Recent population-based perspective studies and clinical observations have provided evidence in support of the hypothesis that longstanding chronic prostatic inflammation leads to cumulative oxidative damage in prostatic epithelium (35,36). Chronic inflammation may influence the pathogenesis of prostate cancer by inflicting cell and/or genome damage, triggering restorative cell proliferation to replace damaged cells, and/or elaborating a portfolio of cytokines that promote cell replication, angiogenesis, and tissue repair (37). Oxidative damage to DNA and other cellular components accompanying chronic or recurrent inflammation may connect prostate inflammation with prostate cancer (38,39). In response to infections, inflammatory cells produce a variety of toxic compounds designed to eradicate microorganisms. These include superoxide ion, hydrogen peroxide, singlet oxygen, and nitric oxide that can react further to form the highly reactive peroxynitrite anion. Some of these highly reactive oxygen and nitrogen species can directly interact with DNA in the host bystander cells or react with other cellular components such as lipid, initiating a free-radical chain reaction (40). If the damage is severe, these compounds can kill host bystander cells as well as pathogens and can produce DNA damage and mutations among host cell survivors. We and others have shown that, within the prostate, chronic inflammation is commonly associated with postatrophic hyperplasia (PAH) and proliferative inflammatory atrophy, with significant up-regulation of cell survival signaling molecules in the prostatic epithelial cells close to inflammatory regions (41,42). It has been suggested that these morphological transitions occur frequently within the same acinar/duct between HGPIN and PAH that could lead to prostate carcinogenesis (43). This carcinogenic process may be accelerated
under altered physiological conditions, such as inappropriate diet, exposure to environmental pollutants, high circulating testosterone levels, viral infection, or preexisting genetic switch. The inflammation-carcinoma sequence has been believed to be a potential mechanism in the initiation and development of prostate cancer (44). This hypothesis has been supported by the evidence that age-related increase in the proportion of hydroxyl radical induces mutagenic base lesions, which is likely a significant factor in prostate cancer development and in characterizing cancer-like phenotypes (45). Other support for the concept that prostate cancer can result from oxidative damage through excess oxidants and electrophiles comes from epidemiological studies suggesting that decreased prostate cancer risk is associated with intake of various antioxidants and nonsteroidal anti-inflammatory drugs (39).

Prostate Cancer Chemoprevention

There is considerable interest in ascertaining whether diets rich in fruits and vegetables offer protection against prostate cancer (14–16,46). A number of macronutrients, micronutrients, and other dietary constituents have been or are currently being evaluated as potential prostate cancer chemopreventive agents (5,14–16,47). Dietary agents have gained considerable attention as chemopreventive agents against many forms of cancer including prostate cancer (46–48). This approach has practical implication in reducing prostate cancer risk. Although several carcinogenic environmental factors that are beyond anyone’s control also play a role, individuals are free to modify their dietary habits and lifestyles. Several studies have focused on the antioxidant and nonantioxidant effects of various dietary substances in the prevention of prostate cancer (49–54). In last 2 decades, there has been substantial progress in identifying the cellular events that play a major role in the process of carcinogenesis, and now we know how the dietary phytochemicals are able to modulate these events. Identification of numerous oncoproteins; tumor suppressor genes; specific genes encoding for carcinogen-metabolizing enzymes, DNA repair enzymes, and proteins; and regulators of apoptosis and cell cycle, some of the events related to cell-signaling pathways that regulate cell proliferation and differentiation, has provided us with accurate in-depth knowledge of molecular neoplastic transformation events. Some of the dietary phytochemicals, which are present in fruit and vegetables, have been shown to possess potential anticarcinogenic effects. These include numerous agents such as carotenoids, vitamins, dietary fiber, selenium, glucosinolates, indoles, isothiocyanates, flavonoids, phenols, protease inhibitors, plant sterols, and other complementary agents (55–63). These agents display complementary and overlapping mechanisms of action, including induction of detoxification enzymes, antioxidant effects, and inhibition of the formation of nitrosamines; binding/dilution of carcinogens in the digestive tract; alteration of hormone metabolism; and modulation of carcinogenic cellular events.

Long latency of disease to develop the malignant form of prostate cancer affords opportunities for intervention with chemopreventive agents to delay disease initiation or progression. This article focuses on epidemiological, clinical, and mechanistic studies that have evaluated the antioxidant and/or anticarcinogenic activity of chemopreventive agents in prostate cancer. Some of the agents that are being investigated for prostate cancer chemoprevention are discussed subsequently.

Carotenoids and Prostate Cancer Chemoprevention

Among the carotenoids, β-carotene and lycopene have been most extensively studied with respect to their possible roles in preventing prostate cancer (64). The results of a number of epidemiological studies investigating the relationship between β-carotene intake and the risk of prostate cancer have been inconsistent (65,66). Prospective cohort studies on intake of α- and β-carotene, vitamins A, C, and E, and lycopene have shown inverse associations for vitamin A and α- and β-carotene in prostate cancer risk (67). Another case-control study evaluating an association between retinol and various carotenoids has shown a weak protective effect of carotene, particularly β-carotene, on the risk of prostate cancer (68). Although the results are encouraging, it is difficult to analyze the complex network and the protective role of dietary antioxidants in such clinical settings. Due to the complexity of results little preclinical research has been conducted with β-carotene and prostate cancer.

Compelling epidemiological studies have suggested that a diet rich in tomato products is associated with a reduction in prostate cancer risk (69). Prospective case-control studies and meta-analysis of observational studies have shown that tomato products may play a role in the prevention of prostate cancer (70,71). It is hypothesized that lycopene may be one of the components of tomato that contributes to this association. Lycopene has been shown to be present in the human prostate at significant concentrations, a finding that supports the plausibility of a direct effect on prostate biology (72). Studies of the cell culture system have shown that lycopene inhibits growth of prostate cancer cells through the pathways that influence expression of gap junction proteins and growth factor signaling (73,74). A recent study on a preclinical model of prostate cancer suggests that consumption of tomato powder but not lycopene inhibited prostate carcinogenesis, suggesting that tomato products contain compounds in addition to lycopene that modify the prostate carcinogenic process (75). These studies are very encouraging and strongly support further mechanistic studies with lycopene in preclinical models of prostate cancer.

Recent studies on men with prostate cancer supplemented with lycopene-enriched enhancement or tomato products for several weeks prior to radical prostatectomy demonstrated that lycopene concentrations in the prostate could change rapidly in response to dietary intake and induce apoptotic cell death along with modulations in oxidative stress and tumor.
biology markers (76,77). A phase II randomized clinical trial of 15 mg of lycopene supplementation twice daily for 3 wk before radical prostatectomy exhibited a decrease in the plasma insulin-like growth factor-1 (IGF-1) levels with no significant changes in Bax and Bcl-2 (78). Another study by this group using tomato oleoresin extract containing the equivalent of 30 mg/day of lycopene extract for 3 wk before radical prostatectomy substantially reduced prostate volume in prostate cancer patients (79). In another study, the efficacy of 10 mg/day supplementation of lycopene to hormone-refractory prostate cancer patients was shown to be effective in reducing serum prostate-specific antigen (PSA) levels, bone pain, and lower urinary tract symptoms (LUTS) (80). A randomized trial for the lycopene is still on going to test the efficacy of this compound.

**Vitamins and Prostate Cancer Chemoprevention**

A major portion of prostate cancer research on dietary influence has been focused on the antioxidant functions of vitamins. In this regard, vitamins A, C, D, and E have been most extensively studied for their effects on prostate cancer.

Vitamin A (retinol) and its active metabolites are essential for cell differentiation, visual function, and physiological growth (81). Vitamin A and its analogs modulate the growth of cancer cells, presumably by activating gene transcription via the nuclear retinoic acid receptors α, β, and γ (82). The chemopreventive effects of retinoids are exerted at the tumor promotion phase through inhibition of cell proliferation, induction of apoptosis, cell cycle arrest, and/or a combination of these actions (83,84). All-trans-retinoic acids reduce urokinase-type plasminogen-mediated degradation of fibronectin and laminin (85). Despite numerous studies, no consistent association between vitamin A intake and prostate cancer risk has been established (67,68,86). Some studies have shown an inverse relationship between serum retinol and the risk of prostate cancer, whereas others indicate a positive association, particularly in men more than 70 yr old (86,87).

Vitamin C is a potent antioxidant that scavenges reactive oxygen species and other free radicals capable of causing damage to lipids and DNA (88). Vitamin C has been shown to inhibit malignant transformation by diminishing cellular chromosomal damage (89). Diets that include substantial amounts of fruits and vegetables rich in vitamin C are associated with a low incidence of many forms of cancer (90). In animal studies, vitamin C has been shown to inhibit prostate tumor growth and viability in athymic nude mice transplanted with both androgen-sensitive and -insensitive human prostate cancer cells (91,92). Studies have shown that combinations of vitamins C and E inhibit surviving protein, a promoter of prostate cancer cell growth (93).

The active form of vitamin D is calcitrol (1α,25-D3), produced in the skin through exposure of 7-dehydrocholesterol to ultraviolet light and proximal renal tubules in the kidneys through 1,25-dihydroxyvitamin D3 hydroxylase (94). Studies have shown that 25-hydroxyvitamin D1α-hydroxylase, the enzyme that synthesizes 1α,25 dihydroxyD3, is also expressed in cultured prostate cells (95). Recent studies have provided evidence that residential sunlight exposure is associated with a decreased risk of prostate cancer that may be linked with vitamin D synthesis (96). Epidemiological studies have further suggested that an increased prostate cancer risk is associated with decreased production of vitamin D (97,98). Studies in cell culture systems and preclinical models of prostate cancer have shown that the biologically active form of vitamin D (1α,25-D3) inhibits proliferation of human prostate cancer cells through mechanisms that include cell cycle arrest, induction of apoptosis, and altered activation of growth factor signaling (99,100). Consistent with tumor suppressor activity, vitamin D compounds and retinoids have been shown to act synergistically with genistein in inhibiting the growth of human prostate epithelial cells (101). Genistein is the component in soy that has been employed in chemoprevention strategies with other putative chemopreventive agents. The combination of vitamin D compounds and retinoids has emerged as an attractive tool for use in controlling prostate cancer progression (98). However, hypercalcemia induced by 1α,25-D3 in vivo limits its use clinically as a therapeutic agent. Population-based studies with vitamin D as well as plasma 1,25-dihydroxyvitamin and 25-hydroxyvitamin D levels have not provided any significant data on protective effects in prostate carcinogenesis (102–104).

Vitamin E is a family of naturally occurring, essential, fat-soluble vitamin compounds that constitutes at least eight structurally related molecules as four tocopherols and four tocotrienols (105). Vitamin E functions as the major lipid-soluble antioxidant in cell membranes; it is a chain-breaking free-radical scavenger and specifically inhibits lipid peroxidation, a biological activity relevant to carcinogen-induced DNA damage (106). The most active form of vitamin E is α-tocopherol, a compound that is abundant and widely distributed in nature and present in most types of human tissue and plasma (107,108). Epidemiological studies have shown that supplementation of vitamin E in the diet lowers the incidence of prostate carcinoma (109). However, some epidemiological studies did not support the role of vitamin E in prostate cancer (110,111). Further studies have observed that men with lower plasma levels of vitamin E had an increased risk of developing prostate cancer (112). Tocopherols have inherent antioxidant affinity for highly reactive and genotoxic electrophiles, such as hydroxyl, superoxide, lipid peroxyl, lipid hydroperoxyl, and nitrogen radicals (113). Consequently, tocopherols prevent free-radical damage in biological membranes and decrease mutagenesis and carcinogenesis (113). Animal studies have shown that dietary supplementation of vitamin E slows prostate cancer growth due to its ability to inhibit androgen signaling (114). The mechanisms through which tocopherols inhibit cell proliferation include inhibition of protein kinase C activity, induction of NADPH detoxification enzyme, and reduction of arachidonic acid and prostaglandin metabolism (115). Vita-
min E has been shown to inhibit the growth of chemically and hormonally induced prostate cancer cells via modulation of cell cycle regulatory machinery and induction of apoptosis (116). Other putative mechanisms through which vitamin E may inhibit proliferation of human prostate cancer cells include inhibition of androgen receptor (AR) function, inhibition of PSA production, and inhibition of the production of vascular endothelial growth factor (117). The Alpha Tocopherol Beta Carotene (ATBC) cancer prevention trial, in which 29,133 male smokers were studied for prevention of lung cancer using vitamin E (50 mg/day) and/or β-carotene (20 mg/day), demonstrated that, although there was an increase in lung cancer risk, the incidence of prostate cancer was reduced by 32% in men receiving α-tocopherol compared with the control group, which did not receive it. Additionally, 41% lower mortality rates were observed in men receiving α-tocopherol. Among subjects receiving β-carotene, the incidence of prostate cancer was 23% higher and mortality rate was up by 15% compared with subjects who did not receive β-carotene supplementation (118). More recent studies have shown that α-tocopherol has a stronger association with the lower risk of prostate cancer, and higher circulating concentration of major vitamin E fractions α- and γ-tocopherol was similarly associated with lower prostate cancer risk (119). These studies suggest that vitamin E may perhaps be used in prevention of prostate cancer.

Although much progress has been made with studies of the effects of vitamins on prostate cancer, additional studies are required to determine their potential use as chemopreventive agents for prostate cancer. The Selenium and Vitamin E Cancer Prevention Trial (SELECT), an intergroup phase III, randomized, double-blind, placebo-controlled, population-based clinical trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer, is an example of the ongoing interest in this area of research (120).

Minerals and Prostate Cancer Chemoprevention

Minerals that appear to play important roles in the chemoprevention of prostate cancer are selenium and zinc. Selenium is an essential dietary trace element; its concentration in various foods, such as fruits and vegetables, is dependent on the soil content of selenium in the region where these foodstuffs are grown (121). As a constituent of selenoproteins, selenium has several structural and enzymatic roles (122). A number of natural and synthetic organoselenium compounds have been examined as chemopreventive agents in several animal tumor bioassay systems. Selenium in the form of sodium selenite or selenomethionine functions as an essential micronutrient at levels of about 0.1 ppm in the animal diet and acts as a chemopreventive agent at 3–5 ppm and is toxic at levels higher than 5 ppm (123). Most of the selenium chemoprevention studies have used either sodium selenite, selenomethionine, or methylseleninic acid as a test agent. Epidemiological studies, preclinical investigations, and clinical intervention trials support the role of selenium compounds as potent chemopreventive agents for prostate cancer (123). A randomized trial on selenium supplementation from the National Prevention of Cancer Study in 974 men with 200-µg/day doses of selenium in 0.5 g high-selenium yeast demonstrated 63% reduction in incidence of prostate cancer (124). However, no significant associations were observed between baseline serum α-tocopherol, dietary vitamin E, or selenium and prostate cancer in the ATBC trial, a randomized, double-blind, placebo-controlled, primary prevention study of lung cancer, upon secondary analysis (125). The compelling findings in the ATBC trial prompted the establishment of a large prospective study, the SELECT trial for prostate cancer chemoprevention (120).

Selenium appears to exert its cancer chemopreventive effects through induction of cell cycle arrest and apoptosis and reduction of angiogenesis (126). Selenium compounds have been shown to alter the expression and/or activities of a number of cell cycle regulatory proteins, signaling molecules, proteases, mitochondrial associated factors, transcription factors, tumor suppressor genes, polyamines, and glutathione levels (123,127). Selenium compounds have also been shown to decrease PSA expression by inducing protein degradation and suppressing androgen-stimulated gene transcription (128). Combination studies with selenium and vitamin E have shown decreased prostate cancer cell proliferation via distinct mechanistic pathways (114,129). Although selenium appears to hold significant promise as a chemopreventive agent, more detailed in vivo studies elucidating the molecular mechanisms of selenium-mediated effects on prostate cancer are warranted. The ongoing SELECT clinical trial with selenium (200 µg/day from L-selenomethionine) and vitamin E (400 IU/day of all-rac-α-tocopheryl acetate) alone and in combination for a planned minimum of 7 yr (maximum of 12 yr) on 32,400 American men will determine the chemopreventive potential of selenium against prostate cancer (120).

Zinc is another essential trace element known to possess antioxidant properties (130). Zinc is present in high concentrations in the prostate (130). In cell culture systems, zinc has been shown to inhibit prostate cancer cell growth via inhibition of cell cycle and induction of apoptosis through disruption of mitochondrial function (131). More research is required to understand the essential role and mechanism of zinc in the prostate and chronic zinc oversupply in prostate cancer.

Flavonoids and Prostate Cancer Chemoprevention

Flavonoids are polyphenolic compounds that are ubiquitously present in foods of plant origin (132). The flavonoid family includes about 5,000 compounds that are defined chemically as substances composed of a common phenylchromanone structure (C6–C3–C6), with one or more hydroxyl substituents (132–134). These are mainly classified into flavones, flavanols (catechins), isoflavones, flavonols,
flavanones, and anthocyanins (133,134). The dietary flavonoids possess antioxidative, anti-inflammatory, and possibly anticarcinogenic properties and are receiving increasing attention (135). The plant flavonoids whose roles in prostate carcinogenesis have been studied are soy isoflavones, catechins from green and black tea, silymarin from milk thistle, resveratrol, apigenin, and proanthocyanidins from grape seed.

Soy isoflavones have been identified as dietary components that may play an important role in reducing the incidence of prostate cancer (136). The major soy isoflavones include genistein and daidzein. Genistein, the predominant isoflavone found in soy, has been shown to reduce proliferation of prostate cancer cells (137). The antiproliferative effects of genistein are attributed to the modulation of genes related to control of cell cycle and apoptosis (137,138). The pathways through which genistein exerts its antiproliferative effects include inhibition of tyrosine kinase, proteasome activity, angiogenesis, metastasis, P3K/Akt and NF-κB survival signaling pathways, and induction of glutathione peroxidase in human prostate cancer cells (139,140). Genistein is also recognized as a phytoestrogen, which targets estrogen- and androgen-mediated signaling pathways in prostate carcinogenesis (141). Administration of a genistein-enriched diet to mice has been shown to correlate positively with changes in prostate DNA methylation at CpG islands (142). This study demonstrates that epigenetic alterations may influence prostate cancer risk. Recent studies have shown that dietary genistein feeding improves survival and reduces expression of osteopontin, which may delay progression of prostate cancer from benign to malignant tumors in a transgenic adenocarcinoma of the mouse prostate (TRAMP) model (143). Further studies have shown that dietary genistein feeding inhibits bone metastasis in SCID mice by regulating metastasis-related genes (144). Epidemiological and case-control studies are supportive of a chemopreventive action for these compounds; however, clinical studies with soy isoflavones have not been encouraging (145). Various soy isoflavone supplementation regimens in prostate cancer patients have shown no statistically significant changes in serum PSA levels (146). A randomized controlled trial demonstrated that soy isoflavone did not modulate PSA concentrations in men between 50 and 80 yr of age (147). It is possible that soy isoflavones may be more beneficial in preventing prostate cancer when used in combination with other compounds. Additional studies are needed to ascertain this.

Tea, the most widely consumed beverage in the world, has been shown to possess strong antioxidant potential (148). The major catechins present in green tea are (−)-epicatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin, and (−)-epigallocatechin-3-gallate. Epigallocatechin-3-gallate accounts for approximately 40% of the total polyphenolic mixture in green tea (148). The major constituents of black tea are theaflavins and thearubigins (148,149). Epidemiological studies show that, in Asian countries, where tea is very popular, the incidence of all types of cancer, including prostate cancer, is low compared with that in the West (150). The Japanese and Chinese people, who regularly consume green tea, have the lowest prostate cancer incidence in the world (Ref. 151 and references therein). Consequently, researchers have developed considerable interest in tea, and especially in green tea polyphenols (GTPs), as a cancer chemopreventive agent. Tea catechins have been shown to modulate a number of cellular signaling pathways that have relevance to prostate cancer (152–156). These include proteins related to cell cycle progression, inflammation, angiogenesis, metastasis, tyrosine kinases, P3K/Akt and NF-κB survival signaling pathways, AR, 5α-reductase, protein kinase C, proteasome inhibition, and apoptosis (153–156). A recent study has shown that GTPs inhibit DNA methyltransferase and have potential to reactivate methylation-silenced genes in prostate cancer cells (157). Studies on the TRAMP model have shown that oral infusion of GTPs in drinking water for 24 wk resulted in approximately 44% reduction in tumor volume and 70% increase in overall survival compared with the control group, which did not receive GTP (158). More recent studies employing a similar protocol for GTP infusion to TRAMP mice have shown significant reduction in IGF-1 levels with concomitant increase in IGFBP-3 expression in dorsolateral prostate of these mice (159). Further, GTP infusion has been reported to inhibit protein expression of the S100A4 gene (Mts1) and restored the expression of E-cadherin in TRAMP mice (160). These studies indicate that GTPs may prove useful as chemopreventive agents for prostate cancer. Epidemiological and case-control studies have further supported the chemopreventive properties of green tea; however, clinical studies with green tea have not been encouraging (161,162). A phase II study, in which 6 g/day of tea was administered to 42 patients with asymptomatic, androgen-independent prostate cancer, demonstrated that a single patient achieved a PSA response of >50% that lasted for approximately 1 mo (162). These patients suffered with side effects that include diarrhea, nausea, and fatigue. Another recent clinical study used a 250-mg dose of GTPs twice daily. In this study, 6 of 19 patients had disease control for 3–5 mo and only 1 patient whose PSA rise was affected by green tea supplementation. The dose used in this study did not discernibly alter the course of hormone-refractory prostate cancer (163). These results suggest that green tea possesses minimal anti-neoplastic activity against advanced-stage prostate cancer. Well-designed clinical studies are further required to test the validity of GTPs in prevention-based trials.

Resveratrol, a dietary stilbene, is another plant product derivative that has been proposed as a chemopreventive agent based on safety and efficacy studies in cell culture and animal models (164). Resveratrol has been shown to possess strong anti-inflammatory, antioxidant, and anticarcinogenic properties (165). Resveratrol has shown growth-inhibitory effects on both androgen-sensitive and -insensitive human prostate cancer cells; its effects are mediated through inhibition of the cell cycle and induction of apoptosis (166). Interactive gene expression patterns in prostate cancer LNCaP cells exposed to resveratrol have shown alterations in multiple signaling pathways that include p53-responsive genes, the PPAR fam-
ily, tyrosine kinase family members, Rel/NF-κB family members, heat-shock proteins, cell cycle regulatory genes, and apoptosis-related genes (167–170). Resveratrol has also been shown to modulate AR function and inhibits PSA expression in prostate cancer cells (171). Based on cell culture studies, evaluation of resveratrol as a chemopreventive agent in preclinical models of prostate cancer may be warranted.

Silymarin is a plant flavonoid that has been shown to possess exceptionally high anti-inflammatory, antioxidant, and anticarcinogenic properties (172). The major active constituent of silymarin is silibinin; other minor constituents include dehydrosilibinin, silychristin, and silydianin (173). Silymarin and silibinin have shown remarkable antiproliferative effects on both androgen-sensitive and -insensitive human prostate cancer cells (174,175). The underlying mechanisms of silibinin activity against prostate cancer involve alterations in cell cycle progression and inhibition of mitogenic and cell survival signaling, including modulation of epidermal growth factor receptor, IGF-1, and NF-κB signaling (176). Silibinin has been shown to modulate AR function and to inhibit telomerase activity and PSA expression in prostate cancer cells (176). Silibinin has also been shown to inhibit prostate cancer progression through reduced secretion of pro-angiogenic factors from prostate cancer cells (177). Silibinin has also been shown to synergize the therapeutic effects of doxorubicin in prostate cancer cells and to sensitize it to TNFα-induced apoptosis (178). Translational studies with silibinin on preclinical models of prostate cancer have demonstrated similar results with reduced tumor proliferation, induction of IGFBP-3 and apoptosis, and inhibition of angiogenesis (179). These findings suggest a rationale for clinical studies to be conducted in prostate cancer patients.

Proanthocyanidins and procyanidins are flavonoids that are found in high concentrations in grape seed extract, a popular dietary supplement (180). Grape seed extract has been shown to possess significant anti-inflammatory, antioxidant, antiviral, and anticarcinogenic properties (181). Grape seed extract has been shown to induce apoptosis in prostate cancer cells through activation of caspases and disruption of mitochondrial function (182). The pathways involved in the chemopreventive activity of grape seed extract on prostate cancer include inhibition of protein tyrosine kinase, matrix metalloproteinases, and Rel/NF-κB family members (183,184). Grape seed extract has recently been shown to inhibit prostate tumor growth and angiogenesis through up-regulation of IGFBP-3 in an athymic nude mouse model (185). More mechanistic studies on cell cultures and in vivo models of prostate cancer are required to assess the possible efficacy of grape seed extract as a chemopreventive agent for prostate cancer.

Apigenin, a widely distributed plant flavonoid abundantly present in fruits and vegetables, is a free-radical scavenger that has been shown to possess anti-inflammatory and anticarcinogenic effects (186). Studies have shown that apigenin possesses growth-inhibitory properties against many types of human cancer cells, including prostate cancer (187,188). We have shown that apigenin causes tumor cell growth inhibi-

tion, cell cycle deregulation, and apoptosis in both androgen-sensitive and -insensitive human prostate cancer cells without affecting normal cells (188,189). The molecular mechanisms underlying the activities of apigenin include inhibition of telomerase, inhibition of 17β-hydroxysteroid dehydrogenase, inhibition of AR function, modulation in cell cycle regulatory proteins, disruption of mitochondrial function, and NF-κB inhibition in prostate cancer cells (190–192). More recently we have shown that apigenin is capable of sensitizing human prostate cancer PC-3 cells to TNFα-induced apoptosis, which correlates with down-regulation of genes relevant for prostate cancer progression (193). Additional mechanistic cell culture studies with apigenin are required, targeting other signaling pathways that have relevance to prostate cancer development and progression. Further testing of apigenin in preclinical models of prostate cancer is warranted.

### Indoles and Prostate Cancer

#### Chemoprevention

A diet rich in fruits and vegetables provides a rich source of indoles, which may be responsible for prevention of many types of cancer (21,22). Indoles are naturally occurring constituents of Brassica vegetables. Cruciferous vegetables contain glucobrassicin, which during metabolism yields indole-3-carbinol (I3C) and its in vivo dimeric product 3,3’-diindolylmethane (DIM). These derivatives have been shown to inhibit cell proliferation and induce apoptosis in prostate cancer cells (194). The mechanisms through which indoles exert their anticarcinogenic effects include modulations in cell cycle regulatory proteins and inhibition of cell survival pathways (PI3K/Akt) and NF-κB transcription factor (195). Gene expression profiles have demonstrated that I3C and DIM affect the expression of a large number of genes that have relevance to cancer, cell survival, and physiological behavior (196). Further, it has been shown that indoles are strong androgen antagonists and that they inhibit PSA production in human prostate cancer cells (197). These findings suggest that dietary indoles may prove useful in the chemoprevention of prostate cancer. Therapeutic studies with plant indoles were performed on preclinical prostate cancer models. Intraperitoneal administration of DIM to C57BL/6 mice bearing TRAMP-C2 malignant cells has been shown to inhibit tumor growth (198). Systemic administration of I3C to Copenhagen rats injected with MAT-LyLu cells has been shown to inhibit prostate tumor growth and metastasis (199). More mechanistic in vivo studies are required to assess the potential of indoles in this capacity.

### Isothiocyanates and Prostate Cancer

#### Chemoprevention

There is evidence to suggest that thiol conjugates of isothiocyanates present in cruciferous vegetables are effective cancer chemopreventive agents (200). At least two population-based, case-controlled studies have documented re-
duced risk of prostate cancer in men consuming cruciferous vegetables (201,202). These salutary effects have been attributed to 2-phenylethyl isothiocyanate, allyl isothiocyanate, and sulforaphane (203). These agents exert their anti-carcinogenic activities in cell culture system through mechanisms that include cell cycle inhibition, induction of phase II enzymes, inhibition of extracellular signal-regulated kinases, suppression of NF-κB and its regulated genes, proteasome degradation, caspase activation, and induction of apoptosis (204–208). Phenylethyl isothiocyanate and allyl isothiocyanate have been shown to inhibit the growth of human prostate cancer PC-3 xenografts through cell cycle perturbation and induction of apoptosis (207). More detailed mechanistic studies are required to assess the potential of isothiocyanates in the chemoprevention of prostate cancer.

Phenolic Acids and Prostate Cancer

Chemoprevention

Phenolic acids are aromatic secondary plant metabolites, widely present throughout the plant kingdom (209). Phenolic acids are well recognized for their antioxidant potential (210). Curcumin, a phenolic acid and active component of turmeric, has received a great deal of attention as a possible chemopreventive agent against prostate cancer (210). Curcumin has been shown to inhibit proliferation of both androgen-sensitive and -insensitive human prostate carcinoma cells via inhibition of the cell cycle and induction of apoptosis (211). Diets containing 2% curcumin provided to LNCaP tumor xenograft in nude mice for 6 wk have been shown to induce apoptosis and inhibited proliferation and angiogenesis (212). The molecular pathways that contribute to its anticarcinogenic activity include tyrosine kinase and protein kinase C inhibition, down-regulation of AR gene expression, inhibition of PI3K/Akt and NF-κB, and modulation of the motility of prostate cancer cells through effects on their microfilament organization (211,213–215). Curcumin has been shown to enhance tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)–induced apoptosis; it also radiosensitizes prostate carcinoma cells (216). Curcumin in combination with radiation showed significant enhancement to radiation-induced clonogenic inhibition and apoptosis in PC-3 cells (217). These findings suggest that curcumin may have some potential as a chemopreventive agent for prostate cancer, which needs further evaluation.

Organosulfur Compounds and Prostate Cancer

Chemoprevention

Organosulfur compounds are the biologically active components of allium vegetables (218). The primary sulfur-containing constituents in garlic are the γ-glutamyl-S-alk(en)yl-L-cysteines and S-alk(en)yl-L-cysteine; the odor of garlic is attributable to allicin and other oil-soluble sulfur components (219,220). Once garlic undergoes cutting or crushing, hundreds of organosulfur compounds are released in a short period of time. The transiently formed compound, allicin, comprises 70–80% of the thiosulfimates and quickly decomposes to other compounds, such as diallyl sulfide, diallyl disulfide, diallyl trisulfide, dithiine, and ajoene (219). Many health benefits have been ascribed to organosulfur compounds including inhibition of carcinogenesis. Two studies have shown that S-allylmercaptocysteine inhibits prostate cancer cell proliferation (118,221). More studies of the potential of organosulfur compounds in prostate cancer chemoprevention appear to be warranted.

Monoterpenes and Prostate Cancer

Chemoprevention

Monoterpenes are oils found in many plants including members of the citrus family. Monoterpenes are commonly used as flavoring agents and food additives and in various fragrances (222). Monoterpenes, especially D-limonene and perillyl alcohol, are recognized as chemopreventive agents through their demonstrated ability to induce phase II carcinogen-metabolizing enzymes, inhibit posttranslational iso-prenylation of small G-proteins including Ras oncogene, and induce apoptosis in cancer cells (223,224). Only limited efficacy of perillyl alcohol has been observed in clinical studies of patients with advanced prostate cancer (225). Other studies have shown that monoterpenes are more effective when used in combination with chemotherapeutic agents (226). It has also been suggested that monoterpenes are capable of radiosensitizing prostate cancer cells (227). Additional studies of the potential usefulness of monoterpenes in the management of prostate cancer are needed.

Complementary Agents for Prostate Cancer

Chemoprevention

Complementary medical therapies often referred to as “complementary and alternative medicine” (CAM) are used alongside conventional medicine. The National Centre for Complementary and Alternative Medicine (NCCAM) has defined CAM as a group of diverse medical and health care systems, practices, and products that are not normally considered to be conventional medicine (228). In 1994, the Dietary Supplements Health and Education Act opened the market to many herbals, botanicals, and other food ingredients that would have otherwise needed safety testing before being sold; these agents are being used with increasing frequency in men with prostate cancer (229). Little is known about the efficacy of such agents in cancer. There are limited prospective data supporting the chemopreventive or therapeutic value of such nutritional agents in prostate cancer. To date, one of the most studied herbal agents for prostate cancer is PC-SPES (230). PC-SPES is a mixture composed of extracts from eight herbs: Scutellaria baicalensis, Glycyrrhiza glabra, Ganoderma lucidum, Isatis indigotica, Panax pseudo-ginseng, Serenoa repens, Dendranthera mori-folium, and Rabdosia rubescens (230,231). All of these are Chinese herbs except S. repens, an extract of the American dwarf palm or saw palmetto. A proprietary herbal blend,
PC-SPES has been used since 1996 by thousands of men for “prostate health” (232). PC-SPES contains flavonoids that have antioxidant, anti-inflammatory, and anticarcinogenic activity and also contains isoflavones that have some estrogen-like activity (233). PC-SPES has been shown to interfere with testosterone metabolism and prevent testosterone from binding to prostate cells (233). Because it is a mixture of many herbs, it is possible that individual components act synergistically to provide opposition to prostate cancer progression, in part by blocking androgen-supported prostate cell growth. In cell culture studies, PC-SPES has demonstrated significant dose-dependent decreases in cell viability in both androgen-sensitive and -insensitive human prostate cancer cells (234). The mechanisms that account for its anticarcinogenic effects include induction of apoptosis; cell cycle modulation; down-regulation of Bcl-2, proliferating cell nuclear antigen, and PSA proteins; down-regulation of AR; and up-regulation of p53 and Bax proteins (235). Gene expression profiling on LNCaP prostate cancer cells exposed to PC-SPES has shown alterations in the expression of transcripts encoding cell cycle regulatory proteins, α- and β-tubulins, and AR (236). Studies on animal models of prostate cancer have confirmed a dose-dependent suppressive effect of PC-SPES on tumor volumes and tumor progression (234). Clinical studies have suggested that PC-SPES may reduce PSA levels in patients with either androgen-dependent or -independent prostate cancer (237, 238). The clinical effects of PC-SPES appear to be more pronounced in advanced-stage prostate cancer. Additional testing became necessary to identify the active components of PC-SPES and to define its role in the management of patients with prostate cancer. However, these studies identified several synthetic compounds that were present in varying doses in different batches of PC-SPES, including DES, the synthetic estrogens; ethinyl estradiol; warfarin, an anticoagulant; and indomethacin, an anti-inflammatory agent. The presence of these drugs prompted the California Department of Health Services and, subsequently, the Food and Drug Administration to issue warnings describing the adulteration of PC-SPES. The product was recalled, production was subsequently stopped, and studies supported by NCCAM were halted. This incident raised important concern about clinical trials utilizing herbal therapies that must account for issues of purity and consistency (239).

Another CAM used in southern India prescribed by Siddha practitioners is rasangetti lehyam (RL). RL is composed of 38 different botanicals as well as 8 inorganic compounds, all prepared in a paste form in palm sugar and hen’s egg base. Preliminary studies with RL extract in different organic solvents have been shown to result in clonogenic inhibition and induction of apoptosis in human prostate cancer PC-3 cells (240).

Permixon® is another CAM that is an extract from American dwarf palm fruit. S. repens is an effective dual inhibitor of 5α-reductase isoenzyme activity in human prostate cancer cells without interfering with PSA expression (241). Clinical trials for symptomatic benign prostatic hyperplasia demonstrated significant improvement in peak flow rate and reduction in nocturia above placebo and five-point reduction in International Prostate Symptom Score (242).

Equiguard is a composite supplement consisting of standardized extracts from nine Chinese herbs, originally formulated to correct physiological decline in kidney functions associated with age, and was fortuitously found to display anti-prostate cancer properties. Ethanol extracts of Equiguard significantly inhibited prostate cancer LNCaP cell growth, induced apoptosis, lowered expression of the AR, decreased intracellular and secreted PSA levels, and completely abolished the colony-forming activities in these cells (243).

The number and brands of CAM are increasing in the market and, until definitive evidence of chemopreventive or antiproliferative effects of these agents is available, the safest, most affordable, and beneficial approach is to consume a complex mixture in the diet.

Conclusions and Future Directions

Increasing knowledge of prostate carcinogenesis has led to the widely held view that prostate cancer is a preventable disease. Because of its long latency period, prostate cancer is an important target for chemoprevention. 1) Continued efforts are needed to unravel the underlying molecular events through which chemopreventive agents may exert their anticarcinogenic effects. Identification of disease subtypes based on etiological mechanisms may also help to formulate better preventive approaches for individual patients with specific disease susceptibilities. 2) Novel chemopreventive strategies should be designed that could limit both exposure and adverse health effects from dietary carcinogens and attenuate the incidence of prostate tumorigenesis because the complete elimination of exposure to these agents is not possible. 3) Additional studies are required to identify agents from complex dietary mixtures, which could be developed for primary or advanced therapy in the prevention and treatment of the disease. 4) An important future aspect of chemoprevention research should be identification of additional surrogate endpoint biomarkers for clinical disease that will advance this area of investigation. 5) The development of “combination chemoprevention” to study the synergistic effects of interactions between agents will be helpful in explaining epidemiological observations investigating prostate cancer risk. This should be followed by clinical trials on pharmacokinetics and mechanism-based markers to evaluate the efficacy of promising agents. Overall, more emphasis is needed on preventing prostate cancer in its earliest stages rather than trying to treat it in its terminal stages.

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28 Nutrition and Cancer 2005


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