Review

Chemoprevention of Prostate Cancer through Dietary Agents: Progress and Promise

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Abstract

Prostate cancer (CaP) is second only to lung cancer as the cause of cancer-related deaths in American men and is responsible for over 29,000 deaths per year. One promising approach to reduce the incidence of CaP is through chemoprevention, which has been recognized as a plausible and cost-effective approach to reduce cancer morbidity and mortality by inhibiting precancerous events before the occurrence of clinical disease. Indeed, CaP is an ideal candidate disease for chemoprevention because it is typically diagnosed in the elderly population with a relatively slower rate of growth and progression, and therefore, even a modest delay in the development of cancer, achieved through pharmacologic or nutritional intervention, could result in substantial reduction in the incidence of clinically detectable disease. In this review, we have summarized the recent investigations and mechanistic studies on CaP chemoprevention using dietary agents, such as selenium, vitamins D and E, lycopene, phytoestrogens, flavonoids, and green tea polyphenols. Well-designed trials are required to delineate the potential clinical usefulness of these agents through issues, such as determining the optimal period and route of administration, systemic bioavailability, optimal dosing and toxicity of the agent, and single or combinatorial approach. It is hoped that, combining the knowledge based on agents with targets, effective approaches for CaP chemoprevention can be established. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2193–203)

Introduction

Prostate cancer (CaP) remains one of the most frequently diagnosed cancers in men in Western countries for the past decade. According to the American Cancer Society, CaP has surpassed heart disease as the top killer of men over the age of 85 years in the United States. The number of new cases projected to be diagnosed in the United States alone in 2007 was estimated at 218,890, with 27,000 deaths expected from the disease (1). Most CaPs seem to be sporadic with <10% inherited, with multiple genetic and environmental factors, controlling the evolution of these sporadic tumors. Racial and ethnic differences in CaP incidence and mortality are well recognized, with African-American men being at the greatest risk for diagnosis (incidence rate, 271.3; death rate, 70.4), followed by Caucasian men (incidence rate, 167.4; death rate, 28.8) and Hispanic men (incidence rate, 140.0; death rate, 23.5). Asian Americans seem to be at the lowest risk for CaP (incidence rate, 100.7; death rate, 13.0; ref. 2). Furthermore, marked geographic variations have been observed in the incidence of clinical CaP, with higher rates in the North America and northern Europe, intermediate in Mediterranean region, and relatively low in many parts of Asia. Ecological studies have implicated a ''Western'' diet in CaP development. Asian immigrants, who adopt Western diet, show an increased incidence in CaP, which is thought to be related to environmental factors and variations in dietary pattern (3).

The process of CaP development is a consequence of genetic and epigenetic alterations that transform normal glandular epithelium to preneoplastic lesions and on to invasive carcinoma. The epigenetic phenomena and biochemical changes, such as elevated prostate specific antigen (PSA) and insulin-like growth factor I (IGF-I), however, occur much earlier than the development of CaP. Consistent chromosomal abnormalities in particular stages of CaP are well documented with losses of chromosomes 6q, 7q, 8p, 10q, 13q, 16q, 17q, and 18q seen in majority of cases (4). *NKX3.1*, a gene located nearly on 8p21.2 is involved in the initiation stage of prostatic tumorigenesis. There is considerable evidence that loss of *NKX3.1* expression, along with *PTEN* heterozygosity, a gene that codes for a lipid phosphatase and functions as a negative regulator of phosphoinositol-3-kinase (PI3K) signaling, is found at high frequency in CaP. In addition, DNA hypermethylation, DNA hypomethylation, and histone acetylation are thought to contribute to prostatic tumorigenesis. Hypermethylation of DNA damage repair genes *glutathione S-transferase 1* and *O^6-methylguanine DNA methyltransferase* has been reported in CaP, with methylation of *glutathione*

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S-transferase 1 gene promoter detected in greater that 70% of CaP specimens (4).

The pathologic process of carcinogenesis in the prostate involves the expansion of multiple clones of proliferating ductal/acinal epithelia being recognized as dysplasia. Well-recognized precursor lesions in the peripheral zones of the prostate, including low-grade or high-grade prostatic intraepithelial neoplasia (PIN), are associated with the development of invasive cancer. Recently, proliferative inflammatory atrophy has been proposed as a precursor to PIN with merging of proliferative inflammatory atrophy and high-grade PIN seen in ~34% of proliferative inflammatory atrophy lesions (4). Chronic inflammation may damage epithelial cells and result in proliferative lesions, likely precursors of PIN lesions and prostatic carcinomas; prostatitis has therefore been associated with a high risk of CaP (5).

Indeed, CaP is an ideal candidate disease for chemoprevention as it is typically diagnosed in men over 50 years of age, and thus, even a modest delay in disease progression could significantly affect the quality of life of these patients. The future role of dietary supplements in CaP is of much interest, and preliminary data are noteworthy. Regardless, unresolved issues still linger. For most cancer interventions, the expected time to achieve an effect is much longer, more variable, and far less well understood, and the progression of disease may be hard to follow. In addition, the optimal dose and duration needed to test nutritional agents for cancer prevention are largely unidentified, making null findings hard to interpret. Baseline nutritional status can be critical. In addition, particular nutrients may be effective only in subgroups defined by genotypes or by nutritional status of another nutrient. In this respect, a closer analysis of trials under way for selenium and vitamin E, probably two of the most popular dietary supplements against CaP, reveals that selenium supplements provided benefit only for those individuals who had lower levels of baseline plasma selenium, whereas subjects with normal or higher levels did not benefit and may have an increased risk for CaP (6). In addition, although vitamin E reduced the risk of CaP in smokers and those with low levels of this vitamin, vitamin E supplements in higher doses (≥100 IU) were associated with a higher risk of aggressive or fatal CaP in nonsmokers. A routine recommendation of any dietary or nutritional supplement for the prevention of CaP may therefore be premature, and serious analyses of findings obtained from *in vitro, in vivo* studies and clinical trials are essential. In this report, we review the literature regarding the role of dietary agents against CaP (Table 1).

Principles of Chemoprevention

The multistage process of cancer development leading to clinically visible and metastasized cancers in humans is a long process, generally taking many years through well-defined stages, known as initiation, promotion, and progression. Chemoprevention is defined as the use of specific agents to block or delay the process of carcinogenesis, thereby preventing the development of invasive cancer. The basic difference between cancer chemoprevention and cancer treatment lies in that the goal of the former approach is to lower the rate of cancer incidence by delaying or suppressing the process of cancer development. It is now recognized that cancer chemoprevention can be achieved by targeting various cell processes. Blocking the formation of the ultimate carcinogen by inhibiting its uptake by the body and/or inhibiting the formation of carcinogenic compounds or preventing metabolic activation of procarcinogens might well be one of the mechanisms to accomplish this goal. Secondarily, deactivation and detoxification through phase I and phase II metabolic enzymes, prevention of carcinogen binding to DNA with inhibition of DNA-carcinogen adduct formation, enhanced DNA repair, and modulation of enzymes like poly(ADP-ribosyl)transferase are other target processes of chemoprevention (7).

Compounds may exert their chemopreventive effect by scavenging oxygen radicals or inhibiting polyamine metabolism, thereby preventing mutagenesis and uncontrolled cell proliferation (7). Others may exert their antiproliferative effect through regulation of signal transduction pathways or modulation of hormones, growth factors, or target receptors present in the cells (7). Induction of apoptosis, inhibition of angiogenesis, preventing basement membrane degradation, and activation of antimetastasis genes are other mechanisms through which chemopreventive agents may act to retard the growth of tumor cells. The importance and usefulness of antibodies to oncogene products or oncoproteins cannot be ignored. Restoration of immune response with compounds acting as immunostimulants may result in augmentation of cell-mediated and natural killer cell cytotoxicity (7).

Selenium

Selenium an essential micronutrient, and part of the body's antioxidant defense system has been shown to inhibit tumorigenesis in a variety of experimental models. Methylated selenium sensitizes CaP cells to TRAIL-mediated apoptosis, effectively down-regulates the expression of androgen receptor (AR) and PSA in the androgen-responsive LNCaP cells, and inhibits the growth of LNCaP xenografts in nude mice (8, 9). Dong et al. have identified various selenium targets, including GADD153, cyclin A, cyclin-dependent kinase-1 (CDK-1), CDK-2, CDK-4, CDC25, E2Fs, and the mitogen-activated protein kinase/c-Jun-NH_2-kinase and PI3K pathways in PC-3 CaP cells (10). A body of evidence indicates that the chemopreventive efficacy of selenium depends on the chemical form in which it is given (11). The benefits of selenium are mediated, at least in part, by selenoproteins, in which selenium is specifically incorporated as selenocysteine. In addition, selenium can replace sulfur in methionine, forming selenomethionine. Hydrogen selenide acts as a precursor for selenoprotein synthesis and is also the form of excreted selenium. In majority of animal chemoprevention studies, either sodium selenite or selenomethionine has been used as the test agent. Hydrogen selenide seems to play a central role in selenium anticarcinogenesis by way of further metabolism. Its oxidative metabolism produces superoxide anion and hydrogen peroxide, which seems to induce apoptosis. Alternatively, its methylation produces a series of excreted metabolites, including methylselenol,

Table 1. Effect of dietary agents on CaP

Dietary agent	*In vitro* studies	*In vivo* studies	Epidemiologic studies/clinical trials
Selenium	Decrease in AR and PSA, increase in TRAIL-mediated apoptosis (8), p53 phosphorylation, induction of Bax, loss of mitochondrial membrane potential, cytochrome *c* release, activation of caspase-9 and caspase-3 (94), inhibition of mitogen-activated protein kinase, PI3K pathways (10)	Inhibition of CaP development, increase in p27, decrease in proliferating cell nuclear antigen, AR expression, serum PSA levels (9)	Decrease in CaP incidence (16, 17)
Vitamin E	Modulation of transforming growth factor-β, AR/PSA signaling (21), DNA synthesis arrest induction of apoptosis, decrease in vascular endothelial growth factor and inhibition of matrix metalloproteinases (22)	Disruption of PI3K/Akt pathway, regulation of phosphoinositide homeostasis, tumor growth inhibition (26, 27), decrease in CaP incidence, decrease in PSA, increase in median survival time, induction of apoptosis (95, 96)	Decrease in CaP incidence α-tocopherol β-carotene trial (29), SU. VIMAX trial (30) No significant association between vitamin E levels and CaP risk (31, 32)
Vitamin D	Promotes differentiation, inhibits proliferation, invasion and metastasis, decrease in cyclooxygenase-2, increase in PGDH (34, 35)	Decrease in CaP growth and tumors, reduction in PIN (44)	Decrease in CaP incidence, decrease in PSA (36-39, 44)
Lycopene	Induction of apoptosis, inhibits cell proliferation, metastatis and cell invasion, decrease in cyclin D1, cell cycle G_0-G_1 arrest (46, 47)	Prevents oxidative DNA damage (45), inhibits CaP growth and decrease in PSA, IGF-I, IL-6, and 5α-reductase (48), induction of phase II enzymes like GPx, glutathione *S*-transferase, GR and glutathione, 8-oxodGuo levels, prevention of lipid damage (49)	Decrease in CaP incidence and PSA levels (50-53) No significant association between lycopene levels and CaP risk (54-56)
Green tea	Inhibition of cell growth, induction of apoptosis, induction of p21, p53, and Bax (57), inhibition of HIF-1α degradation, inhibition of PSA-triggered basement membrane degradation, and matrix metalloproteinase-2 activation (97, 98), inhibition of 5α-reductase (60) and ODC activity (61)	Overexpression of clusterin (59), decrease in IGF-I and increase in IGF-binding protein-3 levels in TRAMP, inhibition of tumor growth and PSA secretion (62), decrease CaP progression with reduction of S100A4 and restoration of E-cadherin (63)	Decreased CaP risk (64, 67) Minimal activity against CaP (65, 66)
Pomegranate	Antiinvasive, antiproliferative, antimetastatic effects (69) Induction of apoptosis, increase in Bax, Bak, p21/p27, decrease in cyclins D1, D2, and E, cdk2, cdk4, cdk6, Bcl-xL, and Bcl2 (68)	Reduction in tumor growth and decrease in serum PSA levels (68)	Prolongation of PSA doubling time (70)
Silymarin	Induction of cell cycle arrest, Increases cdks, cyclins, p21, p27, modulates epidermal growth factor receptor, IGF-I, NF-κB pathways (72), inhibition of telomerase and decrease in PSA inhibition of AR, with down-regulation of prostate epithelium-derived Ets transcription factor, human glandular kallikrein, and FKBP51(73, 74)	Decrease in CaP growth, down-regulation of proliferating cell nuclear antigen, cyclin D1, vascular endothelial growth factor, and CD31 (72)	Delay in PSA progression (75)
Resveratrol	Induction of apoptosis and cell cycle arrest, increase in p53 (76) modulation of HSP27 and HSP70 (78), TRAIL-induced apoptosis with survivin depletion (79), modulates Src-Stat3 signaling, inhibits protein kinase C–mediated Erk1/Erk2 activation (80), inhibits NF-κB activation, down-regulates PSA, AR, ARA24 (76)		

(*Continued on the following page*)

Table 1. Effect of dietary agents on CaP (Cont'd)

Dietary agent	*In vitro* studies	*In vivo* studies	Epidemiologic studies/clinical trials
Indole-3-carbinol	Inhibition of cell growth, induction of apoptosis, down-regulation of Bcl-2, Bcl-xL, survivin, IAP, XIAP, c-FLIP, increase in Bax, release of cytochrome c and caspase activation, down-regulation of cyclins D1 and E, CDK2, CDK4, CDK6, up-regulation of p15, p21, p27, p53, modulation of PI3K/Akt, mitogen-activated protein kinase, NF-κB pathways, inhibition of SP1, ER, AR, Nrf2 (82), augments TRAIL-mediated apoptosis (83), induces BRCA1 and BRCA2 genes (84)	Decrease in CaP growth and metastases (85)	
Phytoestrogens	Induction of apoptosis, inhibition of angiogenesis (86), modulates 5α-reductase, tyrosine kinase, topoisomerase, P450 aromatase (87), inhibition of cell growth, decreases PSA levels (88) down-regulates PART-1 gene (92)	Reduction in tumor growth with decrease in serum PSA levels (88, 89)	Decreased CaP risk (90)

which seems to arrest cells in the G_1 or early S phase and induce apoptosis (12). Inorganic selenium serves as a precursor to the synthesis of selenoproteins, such as glutathione peroxidase (GPx), thioredoxin reductase, and selenoprotein P. Polymorphisms of selenoprotein P and Sep15, by altering their ability to incorporate selenium, may be important in protecting against the development of CaP (13). Although loss of heterozygosity at the *GPx-1* locus has been associated with the development of several cancer types, including those occurring in lung, breast, and head and neck, no significant association between *GPx-1* genotypes and CaP has been elucidated. Selenium, as a component of GPx, has been shown to play an important role in the manganese superoxide dismutase antioxidative pathway (14). A cohort study of Finnish male heavy smokers found that the manganese superoxide dismutase AA polymorphism was significantly associated with increased risk of CaP (15). Incidentally, the current recommended daily allowance for selenium in men is 70 μg/day, which reflects the selenium intake required to achieve maximal plasma GPx activity.

The double-blind, randomized Nutritional Prevention of Cancer trial, designed to test whether selenized yeast could prevent the recurrence of nonmelanoma skin cancer in 1,312 patients, showed a statistically significant increase in nonmelanoma skin cancer, although a secondary end point analysis revealed a striking reduction in CaP incidence in those with low-serum selenium levels. Furthermore, no evidence of selenium toxicity was seen at doses of 400 μg selenium daily in 424 persons for 1,220 person-years of observation (16). In another study, risk of CaP was found to be inversely related with long-term selenium intake measured by prediagnostic level of selenium in toenails (17). Interestingly, an apparent threshold effect was observed, with no additional cancer protective effect at toenail concentrations exceeding 0.82 ppm, suggesting that not all men will necessarily benefit from increasing their dietary intake of selenium.

Selenomethionine has been selected for the SELECT trial, which tests the effectiveness of dietary supplements of selenium and tocopherol, individually or in combination, in the reduction of clinical incidence of CaP in a population-based cohort of men at risk (18). The enrollment for SELECT began in 2001, and the final results are anticipated by 2013. SELECT will be analyzed as a four-arm study, with primary analyses consisting of five pairwise comparisons of CaP incidence, in association with vitamin E versus placebo, selenium versus placebo, vitamin E plus selenium (combination) versus placebo, combination versus vitamin E, and combination versus selenium. The participants are required to take 200 μg/day L-selenomethionine and/or vitamin E (400 IU/day of α-tocopheryl acetate) supplementation for a minimum of 7 years (maximum of 12 years; ref. 18). In addition, there are several other trials, currently in progress, examining the effect of selenomethionine or high-selenium baker's yeast (200-800 μg) on specific populations of CaP patients. These include Negative Biopsy Trial, High-Grade PIN Trial, Preprostatectomy Trial, and Watchful Waiting Trial. In another preliminary trial, 24 men with biopsy-proved CaP were given either 1,600 or 3,200 μg selenized yeast for an average of 12 months. Although subjects on the higher dose reported side effects, they did not correspond to plasma selenium levels, and all subjects in the study had normal blood chemistries for the duration of the study. In addition, several other trials, including the Prevention of Cancer by Intervention with Selenium, and the Australian CaP Prevention Trial Using Selenium trial are under way to assess the efficacy of selenium as an anticarcinogenic agent (19). The optimal intake of selenium or other nutrients necessary to protect against CaP remains to be validated. The relationship between selenium dose and prostate carcinogenesis is complex, and overaccumulation of selenium is potentially dangerous, as indicated by the U-shaped dose-response curve of selenium in association with increased DNA damage in aging dogs (20). Moreover, there is increasing evidence that nutritionally adequate selenium intake may not be sufficient to reduce cancer risk. Indeed, selenium status sufficient to saturate the activity of plasma GPx (equivalent to 0.6 ppm selenium concentration in toenails) does not necessarily minimize prostatic DNA damage in the canine model or CaP risk in men. Aggressive pursuit of new functional markers of selenium status that can

accurately reflect the biologically effective concentration of selenium that optimizes human health are needed.

Vitamin E

Vitamin E refers to a group of naturally occurring compounds: the tocopherols, tocotrienols, and their natural and synthetic derivatives. Out of the eight different tocopherols included in the term vitamin E, α-tocopherol often exerts specific functions and is the predominant form of vitamin E found in plasma and tissues, whereas γ-tocopherol, and not α-tocopherol, is the major form present in the diet. Besides its antioxidant function, vitamin E and its analogues can modulate transforming growth factor-β and AR/PSA signaling pathway and regulate cell cycle through DNA synthesis arrest in LNCaP, PC-3, and DU-145 CaP cells (21). Induction of apoptosis, by causing depletion of cytosolic Fas with increase in the membrane levels of Fas, decreased production of vascular endothelial growth factor, and inhibition of matrix metalloproteinases are other mechanisms through which vitamin E inhibits prostate carcinogenesis (22). Interestingly, tocopherol metabolites have been reported to be as effective as their vitamin precursors in inhibiting PC-3 growth through down-regulation of cyclin expression, with stronger inhibition seen with the γ forms. However, the more subtle mechanistic effects of these compounds deserve further investigations on CaP cell proliferation (23). It has been suggested that a decrease in CaP risk with α-tocopherol occurs through a mechanism that is non-hormonal and independent of IGF-I (24). γ-Tocopherol exhibits antiinflammatory activities by inhibiting cyclo-xygenase and possibly lipoxygenase-catalyzed formation of prostaglandin E and leukotriene B, respectively. It is strongly nucleophilic and is more efficient than α-tocopherol in trapping reactive nitrogen species (25). Evidence suggests that men in the highest quintile of plasma concentration of γ-tocopherol had a 5-fold reduced risk of CaP. Significant protective effects of high concentrations of selenium and α-tocopherol were observed only when γ-tocopherol concentrations were high. The expression level of tocopherol-associated protein significantly governs CaP cell growth *in vitro* and *in vivo*, independent of its vitamin E–related action, with disruption of the PI3K/Akt pathway and regulation of phosphoinositide homeostasis. Decreased expression of tocopherol-associated protein in human CaP tissue points to its role in tumor suppression (26). An *in vivo* study showed growth inhibition of established prostate LNCaP tumors in nude mice on dietary supplementation of tocopheryl acetate (27). A more recent study showed a significant reduction in CaP incidence in male *Lady* transgenic mice fed with a diet supplemented with Vitamin E succinate, selenium, and lycopene (28). Both studies reported data emphasizing the fact that a high-fat diet promotes the incidence and growth of CaP and that vitamin E alone or in combination with other anti-oxidants ameliorates this high-fat–associated CaP effect.

The α-tocopherol β-carotene cancer prevention trial in 29,133 male smokers found a 32% reduction in CaP incidence and a 41% lower mortality in those receiving 50 mg α-tocopherol daily for 5 to 8 years. However, the 6-year posttrial follow-up assessment showed that the beneficial effects of α-tocopherol supplementation disappeared after the intervention, suggesting that benefit from vitamin E requires long-term supplement use (29). Three other serum-based case control studies showed similar protective effect against CaP. A recently concluded SU.VI.MAX trial studied the role of antioxidant vitamin and mineral supplementation in CaP prevention by assessing their effect on intermediary markers of CaP risk: PSA and IGF. The trial is composed of 5,141 men monitored for 8 years, taking either a placebo or supplementation with nutritional doses of vitamin C, vitamin E, β-carotene, selenium, and zinc daily. A significant reduction in CaP was seen in men receiving the supplements with normal PSA; however, in men with elevated PSA at baseline, the supplementation was associated with an increased incidence of CaP of borderline statistical significance (30). Moreover, one serum-based study refuted any association between vitamin E levels and CaP risk (31), and six of seven prospective cohort studies based on questionnaire data failed to show a significant association suggestive of a nonsignificant protective trend among smokers. Another study on vitamin E supplementation (400 IU/day) in patients over 55 years with vascular disease or diabetes found no significant difference in cancer incidence or cardiovascular events, but an increased risk of heart failure (32). In addition, vitamin E in doses >400 IU/day have been associated with an increased mortality rate (32). These data have raised doubts on the protective role of vitamin E against CaP, and more information will be generated by the on going SELECT trial designed to determine whether selenium and vitamin E can reduce CaP risk among healthy men.

Vitamin D

A normal vitamin D status seems to be an important precondition via the local and autocrine synthesis of calcitriol [1,25(OH)2D] in the target tissues for a lower risk of overall morality due to organ cancer (33). A plethora of evidence that vitamin D and its synthetic analogues promote differentiation and inhibit the proliferation, invasiveness, and metastasis of human prostatic cancer cells both in *in vitro* and *in vivo* models exists (34, 35). In addition, data from various studies support the concept that adequate exposure to UV radiation results in reduced risk of various diseases, including cancer through a vitamin D–mediated mechanism. A recent analysis of mortality data over a 45-year period (1950-1994) by Schwartz et al. confirmed their earlier findings that the geographic distribution of CaP mortality is the inverse of that of UV radiation (36). Another study conducted in patients with clinically localized CaP showed that the rise in PSA is slower during the spring-summer than during the rest of the year (37). On this basis, it was suggested that vitamin D supplementation in the range of 2,000 IU/day, a dose comparable with the effect of summer, can benefit men monitored for rising PSA (37). Analysis of CaP mortality rates in 71 countries showed that increased sunlight levels and consumption of oilseeds, soybeans, and onions increasingly correlated with reduced CaP risk (38). An earlier study in U.S. had shown that Southern diet characterized by foods, such as cornbread, grits, sweet potatoes, okra, beans, and rice pattern, with a history of living in the South served as an integrative marker of sunlight exposure and protection

through 1,25(OH)2D production (39). A recent report has linked CaP susceptibility to interactions between exposure to UV radiation and polymorphisms in the 5′ haplotype block of the vitamin D receptor gene; nonetheless, studies investigating the associations between specific vitamin D receptor polymorphisms and CaP risk have yielded inconsistent results. Although *TaqI* genotypes were shown to be at greater risk of developing CaP in a Portugese population (40), *BsmI, ApaI* and *TaqI* polymorphisms in the Japanese population showed no significant association with familial CaP risk (41). In addition, recent analysis of the available literature indicates a lack of evidence to support association between vitamin D receptor polymorphisms and risk of CaP (42). Currently, over 2,000 vitamin D analogues have been evaluated, and several have entered phase I or phase II trials in patients with advanced cancer. A variety of drug administration schedules have been tried, including daily or intermittent administration of p.o. calcitriol, s.c. injections, or combination with other chemotherapeutic agents (43), as the dose-limiting hypercalcemia associated with calcitriol has limited the use of natural vitamin D in cancer prevention. Clinical responses have been seen with the combination of high-dose calcitriol and dexamethasone, and in a large randomized trial in men with an androgen-independent CaP, calcitriol potentiated the antitumor effects of docetaxel (44). Randomized phase III clinical trials are necessary to determine the optimal dose and preferred vitamin D analogue along with the route and schedule of administration.

Lycopene

Tomato is the main dietary source of lycopene, a red-orange caretenoid, linked with decreased risk of CaP. Lycopene, an $O_2^{\cdot}$ quencher, has been shown to reduce the amount of oxidative DNA damage in cell culture and animal studies (45). There is evidence that lycopene effectively inhibits proliferation of various cancer cell lines with down-regulation of cyclin D1 and consequent cell cycle arrest at the G_0-G_1 phase of the cell cycle. This growth inhibition is extended to the three broadly used CaP cell lines PC-3, DU-145, and LNCaP cells. In addition normal prostate epithelial cells were observed to be even more sensitive to growth inhibition by lycopene than cancer cells. This is important because the pathologic hyperproliferation of prostate cells in men developing benign prostatic hyperplasia may be positively affected by lycopene (46). Acyclo retinoic acid, the oxidative metabolite of lycopene, has been reported to induce apoptosis in PC-3 and DU-145 cells (47). Lycopene supplementation to rats resulted in decreased IGF-I and IL-6 expression; also a reduction in the expression of 5α-reductase in prostate tumors with subsequent down-regulation of several androgen target genes was noted (48). Lycopene increased the activity of the phase II enzymes GPx, glutathione-*S*-transferase, and glutathione reductase, as well as glutathione levels in several animal models, presumably due to antioxidant-response element–mediated induction of genes (49).

A 3-week tomato intervention study in CaP patients showed an increase in the apoptotic index of hyperplastic and neoplastic cells in the resected prostate tissue along with lower plasma levels of PSA (50). Similar results were obtained when lycopene was given to patients undergoing orchidectomy with subsequent decrease in serum PSA level and reduction in the size of primary and secondary tumors (51). Supplementation of tomato products, containing lycopene, helped lower biomarkers of oxidative stress and carcinogenesis in healthy and type II diabetic patients and CaP patients, respectively (52). In addition, a phase II study showed that whole-tomato lycopene supplementation had significant results and maintained its effect on PSA over 1 year (53). However, a more recently concluded phase II trial shows that lycopene-rich tomato supplement was not effective in patients with androgen-independent CaP (54). In addition, lycopene supplementation in men with biochemically relapsed CaP did not result in any discernible response in serum PSA (55), and a lack of association between CaP risk and lycopene intake was observed in a multicenter study by Kirsh et al. (56). In view of these seemingly conflicting results, well-designed studies are necessary to establish the role of tomatoes and tomato products in the prevention and therapy of CaP.

Green Tea

Tea, next to water, is the most consumed beverage in the world. Green tea, obtained from the plant *Camellia sinensis*, with its high polypheniolic content has been shown to be an effective chemopreventive agent against various cancers (57). The polyphenols present in tea leaves as flavanols, or more commonly known as catechins, are epicatechin, epigallocatechin, epicatechin-3-gallate, and epigallocatechin-3-gallate (EGCG), of which the latter has gained the most attention with respect to its anticarcinogenic activity. EGCG makes up ~10% to 50% of the total catechin content and has a higher antioxidant activity than vitamins C and E. EGCG inhibits cellular proliferation primarily by acting as antioxidants and scavenging the free radicals, by inhibiting the enzymes involved in cell replication and DNA synthesis along with interfering with cell-to-cell contact adhesion, and inhibiting intracellular communication pathways required for cell division. Inhibition of proteasome by the ester bond–containing EGCG results in the accumulation of proteasome substrates p27/Kip1 and IκBα, followed by growth arrest in the G_1 phase of the cell cycle, contributing to the cancer-preventive effects of tea EGCG treatment, has been shown to result in the induction of apoptosis in LNCaP, DU145, and PC-3 cells. It is thought to impose an artificial cell cycle checkpoint status in these cells independent of p53. Furthermore, EGCG induces the cyclin kinase inhibitor WAF1/p21 in these cells, causing cell cycle arrest cells in the G_0-G_1 phase (57).

Evidence suggests that its cancer inhibitory effect may be mediated through the 67-kDa laminin receptor that allows it to bind to the cell surface of cancer cells. This receptor is expressed on a variety of tumor cells, and its expression level strongly correlates with the risk of tumor invasion and metastasis (58). The inhibitory effect of EGCG on cell growth is thought to result from its ability to reduce the phosphorylation of myosin regulatory light chain with consequent disruption of the contractile ring mediated by the cell surface target molecule 67LR (58). More recently, Bettuzzi et al. reported that EGCG treatment to CaP cells, but not

normal cells, resulted in the induction of clusterin with cleavage of both pro–caspase 8 and pro–caspase 3, resulting in apoptosis of cancer cells. Moreover, the chemopreventive action of catechins in the TRAMP mouse model was also accompanied by overexpression of clusterin (59).

EGCG effectively inhibits 5α-reductase in cell-free assays, indicating that it can regulate androgen action in target organs. Replacement of the gallate ester in EGCG with long-chain fatty acids produces potent 5α-reductase inhibitors that are active in both cell-free and whole-cell assay systems (60). Testosterone mediated induction of ornithine decarboxylase, and an important contributor of CaP development is inhibited by green tea polyphenols both under *in vitro* and *in vivo* situations (61). Significant inhibition of IGF-I and restoration of IGF-binding protein-3 levels in green tea polyphenol–fed mice with marked delay in the progression of CaP and concomitant apoptosis suggests that the autocrine/paracrine loop is a target for CaP chemoprevention by green tea (62). A more recent study showed that with progression of age and CaP growth, an increase in the expression of S100A4 at mRNA and protein level occurs in dorsolateral prostate of TRAMP, but not in non-transgenic mice. Green tea polyphenol feeding to TRAMP mice resulted in marked inhibition of CaP progression, with reduction of S100A4 and restoration of E-cadherin (63).

A case control study, conducted in southeast China during 2001 to 2002, reported a reduced CaP risk with increasing frequency, duration, and quantity of green tea consumption (64). In another study, patients with asymptomatic androgen-independent metastatic prostate carcinoma and progressive PSA elevation were evaluated after ingestion of 6 g of green tea per day (65). Only one patient manifested a decline in serum PSA, and no patient manifested a tumor response on radiographic assessment or physical examination. Thus, a limited antineoplastic effect with a maximum response rate of 2% was seen with green tea (65). Similar results were seen in another clinical trial involving patients with hormone refractory CaP. Green tea extract capsules, prescribed at a dose level of 250 mg twice daily, showed minimal clinical activity against the disease (66). Both these studies were conducted in end-stage disease, signifying that green tea may be more effective if used in the early stages of the disease or in patient at high risk. In this context, Bettuzzi et al. (67) have shown that after a year's p.o. administration of green tea catechins, only one man in a group of 32 with high-grade PIN developed CaP compared with 9 of 30 in the control group; a rate of only 3% in men developing the disease versus the expected rate of 30% in men treated with placebo. Hence, large-scale, prospective, randomized trials are necessary to test the efficacy of green tea for the prevention and treatment of CaP.

Pomegranate

Pomegranate, a rich source of polyphenolic compounds, including anthocyanins and hydrolyzable tannins, with a reportedly higher antioxidant activity than green tea and red wine (68). Recent studies show that anatomically discrete sections of the pomegranate fruit acting synergistically exert antiproliferative and antimetastatic effect against CaP cells (69). Invasion across matrigel by PC-3 cancer cells was found to be inhibited after treatment with combinations of fermented pomegranate juice polyphenols, pomegranate peel polyphenols, and pomegranate seed oil, with a decrease in the expression of phospholipase A2, associated with invasive potential of theses cells (69).

In a more recent study, 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 (68). The antiproliferative effect of pomegranate fruit extract was shown to be mediated through the cyclin kinase inhibitor-cyclin-cdk network with a significant up-regulation of WAF1/p21 and KIP1/p27 during G_1-phase arrest, independent of p53, with a concomitant down-modulation of the cyclins D1, D2, and E and CDK2, CDK4, and CDK6, operative in the G_1 phase of the cell cycle. Furthermore, p.o. administration of pomegranate fruit extract (0.1% and 0.2%, wt/vol) to athymic nude mice implanted with androgen-sensitive CWR22Rν1 cells resulted in a significant inhibition in tumor growth concomitant with a significant decrease in serum PSA levels (68). A recently concluded 2-year, single center study showed that pomegranate juice increased the mean PSA doubling time coupled with corresponding laboratory effects on CaP *in vitro* cell proliferation and apoptosis, as well as oxidative stress (70). No serious adverse effects were reported, and the treatment was well tolerated. These results are being further tested in a randomized, double-blind, three-arm, placebo-controlled study, which began in April 2006, and addresses several limitations of the current study, with the inclusion of two treatment arms in a dose-response design, as well as the use of a placebo control (70).

Silymarin

Silymarin, a polyphenolic flavonoid isolated from the seeds of milk thistle has recently gained much attention due to its anticancer properties. Silibinin, isosilybinin, silychristin, and silydianin are various isomers present in the compound, of which silibinin is thought to be the most active (71). The underlying mechanism of silibinin/silymarin efficacy against CaP involves alteration in cell cycle progression with induction of CDKIs, Cip1/p21 and Kip1/p27, and a resultant G_1 arrest (72). Molecular modeling of silibinin shows that it is a highly lipophilic compound capable of interacting with lipid-rich plasma membrane, including binding with erbB1, and thus competing with the epidermal growth factor–erbB1 interaction (72). In addition to the impaired erbB1–Src homology and collagen–extracellular signal-regulated kinase 1/2–mediated mitogenic signaling, silibinin treatment to human CaP cells has been shown to interfere with other cell survival signaling pathways, such as inhibition of constitutive and tumor necrosis factor-α–induced activation of nuclear factor-κB (NF-κB; ref. 72). Silibinin has shown a strong potential to modulate IGF signaling in CaP cells toward cell growth inhibition with an increased IGF-binding protein-3 gene expression and inhibition of insulin receptor substrate-1 tyrosine phosphorylation (72). Silymarin can inhibit nuclear localization and transactivation activity of the AR (73) with down-regulation of the AR coactivator, the prostate

epithelium-derived Ets transcription factor, and several androgen-regulated genes, including PSA, human glandular kallikrein, and an immunophilin, FKBP51 (74). Interestingly, silibinin treatment is shown to have an inhibitory effect on DHT-dependent telomerase activity in LNCaP cells related to cell immortality and carcinogenesis (73). In addition, silibinin strongly synergizes the effects of chemotherapeutic agents, such as cisplatin, carboplatin, and doxorubicin in CaP cells, making it a strong candidate for combination chemotherapy (72). Dietary supplements of silibinin significantly inhibited advanced human prostate carcinoma growth and malignant progression in *in vivo* CaP models without any apparent signs of toxicity (72). In a randomized, double-blind, placebo-controlled crossover study, a significant delay in PSA progression was seen in patients with a history of CaP and rising PSA levels after radical prostatectomy supplemented with soy, isoflavones, lycopene, silymarin, and antioxidants in their diet (75). Recently, phase I clinical trials for silibinin have started in CaP patients due to its nontoxic and mechanism-based strong preventive/therapeutic efficacy observed in preclinical models (72).

Resveratrol

Resveratrol (3,4′,5-transtrihydroxystilbene), a plant-derived polyphenolic compound with chemopreventive properties, is found in grapes, red wine, peanuts, and other edible products (76). It exerts its diverse biological effects by interacting with specific targeting proteins, probably via its stilbenoid core and hydrophilic side groups, and has been proved to check carcinogenesis at each discrete stage. Cell culture studies show that resveratrol inhibits tumor growth by stimulating apoptosis and arresting cells at different locations in the cell cycle and is associated with modulation of phosphoglycerate mutase and accumulation of endogenous ceramide in CaP cell lines (76). The phenolic moiety is considered critical for the ceramide-associated growth inhibitory effect of resveratrol (77). An increase in cell cycle control through increase in p53 levels and modulation of HSP27 and HSP70 expression has also been suggested (78). Resveratrol is a potent sensitizer of tumor cells for TRAIL-induced apoptosis through p21-mediated cell cycle arrest with concomitant survivin depletion through transcriptional and posttranscriptional mechanisms (79). Its antitumor activity is consistent with repression of Src-Stat3 signaling, as well as protein kinase C–mediated Erk1/Erk2 activation (80). Gene expression studies have provided additional insights into the mechanisms of action of this compound in prostate cells. Resveratrol treatment resulted in decreased expression of genes involved in cell proliferation, apoptosis, and polyamine biosynthesis (80). Down-regulation of PSA, AR coactivator ARA24, and NF-κB/65 by resveratrol is associated with an activation of p53-responsive genes, such as *p53, PIG 7, p21, p300/CBP,* and *Apaf-1* in LNCaP cells (76). Overexpression of c-Jun induced by resveratrol with a direct protein-protein interaction between the DNA- and ligand-binding domains of the AR and the leucine zipper region of c-Jun has been implicated in inhibiting the expression and function of the AR in human CaP cells (81). Although considerable *in vitro* data exist, well-designed preclinical studies in animal models are required to evaluate the future of this compound as an effective agent against CaP.

Indole-3-carbinol

Indole-3-carbinol is a common phytochemical present in a wide variety of plant food substances, including cruciferous vegetables (cabbage, radishes, cauliflower, broccoli, brussels sprouts, and daikon). The glucosinolates contained in these on ingestion are rapidly converted into a range of polyaromatic indolic compounds (3-5) responsible for its biological effects *in vivo*, among which 3,3′-diindolylmethane is a major component (82). Its varied anticancer effects are mediated through the regulation of the cell cycle, cell proliferation, apoptosis, oncogenesis, transcription, and cell signal transduction. The molecular mechanisms by which indole-3-carbinol inhibits cell growth and induces apoptosis in CaP cells involve the inactivation of Akt, mitogen-activated protein kinase, and NF-κB signaling pathways, along with other transcription factors, including SP1, ER, AR, and Nrf2 (82). Apoptosis by indole-3-carbinol involves down-regulation of antiapoptotic gene products, including Bcl-2, Bcl-xL, survivin, XIAP, and c-FLIP, up-regulation of proapoptotic protein Bax, release of micochondrial cytochrome *c*, and activation of caspases. *In vitro*, indole-3-carbinol–induced cell cycle arrest involves down-regulation of cyclin D1, cyclin E, CDK2, CDK4, and CDK6 and up-regulation of p15, p21, and p27 (82). Furthermore, indole-3-carbinol has been shown to potentiate the effects of TRAIL through induction of death receptors and synergizes with chemotherapeutic agents through down-regulation of P-glycoprotein (83). Indole-3-carbinol, in conjunction with genistein, is able to induce the expression of both BRCA1 and BRCA2 in breast and CaP cell types, suggesting potential relevance to cancer prevention (84). Indole-3-carbinol injections given to rats, both i.p. and i.v., were equally effective in inhibiting the incidence, growth, and metastases of CaP cells (85). Although a number of studies have been conducted in humans to test the efficacy of indole-3-carbinol as a chemotherapeutic agent for breast and cervical cancers, clinical trial have yet to be carried out for the assessment of indole-3-carbinol against human CaP.

Phytoestrogens

Phytoestrogens are plant compounds with estrogen-like activity. Various phytoestrogens, like apigenin, silybinin, isosilybinin, silychristin, and silydianin are thought to be involved in the induction of apoptosis and inhibition of angiogenesis in various CaP cell lines (86). Phytoestrogens, such as genistein and daidzein, may influence sex hormone metabolism by increasing the concentration of sex hormone–binding globulin, thereby reducing the availability of active sex steroids. Their chemopreventive activity has been attributed to a direct inhibition of DNA methyltransferase activity, reversal of DNA hypermethylation, and reactivation of methylation-silenced genes. Phytoestrogens are important regulators of proteins, such as 5α-reductase, tyrosine kinase, topoisomerase, and P450 aromatase, besides exerting an inhibitory effect

on vitamin D metabolism in the prostate (87). Isoflavonoid phytoestrogens, such as genistein, daidzein, and glycitein, show structural similarities with mammalian estrogens and are present in large amounts in soybean and soy products, such as miso and tofu. There is evidence that genistein, equol, and enterolactone inhibit the growth of LNCaP cells and reduce both intracellular and extracellular PSA concentrations. In addition, genistein is an effective inhibitor of angiogenesis and has been reported to decrease PSA levels and prevent metastatic disease in male Lobund-Wistar rats (88). Studies in animal models showed that rats fed on soy or rye bran exhibited a significant delay in the growth of implanted prostate tumors. Osteopontin, an extracellular matrix protein, may be involved in the transition from clinically insignificant tumors to metastatic CaP. A recent study suggests that dietary genistein improved survival and inhibited progression to advanced CaP in TRAMP mice associated with reduced expression of osteopontin (89). A 16-year long prospective health study showed that men who consumed more than one glass of soy milk per day had a 70% lower risk of CaP (90). Soy containing genistein and dadzein in abundance is consumed in large quantities in China and Japan, with reportedly lower incidence of CaP. This may be related not only to the regular consumption of soy by the Asian population, but also due to their ability to convert daidzein to equol and to concentrate it within prostatic secretions. Genistein is being studied in ongoing clinical trials based on experimental data obtained from carcinogen-triggered rat models of CaP and a reduced incidence of advanced CaP in TRAMP mice. National Cancer Institute has set up phase II clinical trials, in which the effect of dietary soy in patients with elevated PSA (14.0 ng/mL) is being investigated. Another trial under way in The National Cancer Institute of Canada is studying the effect of soy protein when combined with selenium and vitamin E in patients with high-grade PIN.

The phytoestrogen daidzein found in soy is further metabolized by the intestinal microflora to equol and *O*-desmethylangolensin. Several lines of evidence suggest that equol has increased bioactivity compared with daidzein and has been found to be 10-fold more potent than daidzein at reducing the growth of normal and malignant prostatic epithelial cells *in vitro* (91). Daidzein, along with genistein, has been shown to significantly down-regulate androgen-induced *PART-1* gene expression in androgen-sensitive LNCaP cells (92). There is, however, limited data on the effect of p.o. phytoestrogen supplements in prostate tissue. In one of the three studies conducted thus far, daily p.o. supplementation of clover phytoestrogen induced a 23-fold and 7-fold increase in prostate tissue concentrations of genistein and daidzein, respectively, when compared with the placebo group (93). In addition, 90% of the supplemented patients had a detectable plasma equol concentration after the supplementation (93). However, a definite association with reduced CaP incidence has yet to be established in controlled human trials.

Conclusion

A promising strategy is the identification of cancer risk factors through epidemiologic and experimental research with life-style and medical approaches that allow translation of clinical trial results to clinical practice. Nutritional science can contribute substantially to this effort. Identification of biomarkers can play an important role in this effort through the use of new and emerging technologies. At the same time, gene expression profiling and proteomics are providing novel insights into cancer-related traits. Clinical trials remain the gold standard for testing hypotheses developed from epidemiologic and experimental animal studies on prevention agents to reduce cancer risk. Because early detection remains the desired strategy for reducing cancer morbidity and mortality, collaborative effort among academic and industry leaders can bring together expertise in many fields to address disease across the cancer spectrum.

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