Potential Agents for Prostate Cancer Chemoprevention

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INTRODUCTION

Studies of the incidence and mortality of prostate cancer in various countries suggest that changeable environmental elements are important in its etiology (1). Several studies have demonstrated that migration from areas of low risk to areas of high risk is associated with an increased risk of prostate cancer in the migrants compared with men remaining in the low-risk country of origin (1). In migration studies done before the prostate-specific antigen screening era, Japanese migrants to the United States were shown to have a marked increase in prostate cancer, although the rates of Japanese-Americans remain less than those of whites (2). Prostate cancer incidence rates are very low in eastern Europe and Russia, but Polish migrants to the United States acquire higher rates upon migration.

While population studies do suggest that there may be a genetic component to some prostate cancers, there are likely to be numerous environmental components to prostate carcinogenesis and prostate cancer prevention (3). Nutritional factors in defined populations, especially in those with high animal fat and high dairy intake, have been correlated with a greater risk of disease (4). It has been suggested that populations with higher circulating levels of androgens and insulin-like growth factors tend to have higher risk of prostate cancer (5, 6). Both circulating androgens and insulin-like growth factor levels are associated with diet (7, 8). In at least one case-control study with age-adjusted analyses, there were positive associations of prostate cancer (all stages combined) risk with total energy intake as well as intake of total fat (saturated and monounsaturated) (9). There are also correlations between populations with higher consumption of selenium and vitamin E, fructose/fruits, and tomatoes and lower risk of prostate cancer (10). These observations combined with an improved understanding of the biology of prostate cancer provide numerous leads in the effort to find workable prostate cancer chemoprevention (11).

CONCEPT OF CHEMOPREVENTION

Chemoprevention is the administration of agents to prevent induction and inhibit or delay progression of cancers. Important to chemoprevention is the fact that carcinogenesis is a process over time involving cellular growth and division. Inhibition of or slowing this process can potentially prevent cancers from becoming clinically significant (12). While chemoprevention of cancer is a relatively new concept, the chemoprevention of other diseases is common although often not called chemoprevention. The prevention of heart disease with lipid lowering drugs is widely accepted, as is the prevention of tooth decay with flouride or prevention of osteoporosis in postmenopausal women with estrogen (13). These are all examples of chemoprevention of disease.

Chemoprevention involves the treatment of healthy subjects. As such, chemopreventive agents must have low toxicity in order to be clinically useful (14–16). Because their purpose is to keep something from occurring, definitive clinical studies to demonstrate their efficacy are necessarily randomized, blinded, long-term, and large in size.

It has been suggested that androgen is an important promoter of prostate cancer. It has long been appreciated that prostate cancer is an androgen-driven illness. Removal of androgenic stimulation has been used to treat metastatic disease for some time (17). Populations with impaired androgen metabolism, such as congenital 5α-reductase deficiency, do not develop prostate cancer. There is also the suggestion that populations with higher circulating levels of androgen or higher sensitivity to androgens are at greater risk of prostate cancer (18, 19).

Oxidative stress has been proposed as a promoter of the process of carcinogenesis. Oxidation can lead to genetic mutations which can, in turn, lead to malignancy. Antioxidants have been suggested as potential preventative agents for a number of cancers (4).

DIET AND PROSTATE CANCER

Dietary intervention is not classically considered chemoprevention, but it could be very important in the prevention of prostate cancer. Some dietary elements may cause prostate cancer, whereas elements in other diets may
prevent prostate cancer. The latter elements, if identified, are excellent candidates for chemopreventive drugs.

**DIETARY FAT**

Several studies support a positive correlation between some aspect or component of animal fat and prostate cancer risk (1, 2). Armstrong and Doll (20) compared the prostate cancer death rate and average fat consumption in 32 countries. Populations with diets high in fat have increased prostate cancer relative risks by a factor of 1.6–1.9 (21–25). These studies may be limited by the inability to control adequately for potential confounders. As discussed above, fat consumption may inversely correlate with increased consumption of some chemopreventive agents, and increased fat consumption may be a marker for some other etiologic factor.

While it has been shown that a western diet increases serum androgen levels, the precise mechanism for increased production of sexual hormones is not well understood (26). However, it is established that a high fat diet can increase hormonal bioavailability. Plasma concentrations of fatty acids are increased with increasing consumption of fat, and these plasma fatty acids inhibit binding of gonadal steroids to sex hormone-binding globulin (23, 27). A fatty diet may increase prostate cancer risk by causing long-term androgenic stimulation.

A potential preventive strategy is to lower androgenic stimulation. This could be accomplished by drug therapy or by diet modification. Diets high in fiber and presumably lower in fat are associated with lower incidences of prostate cancer (28). A low-fat, high-fiber diet increases fecal excretion of gonadal hormones and possibly lowers serum androgen levels (29).

**SOY**

The diet in many Asian countries is especially high in plant products and phytoestrogens. Plant-based weak estrogens, such as isoflavonoids, may prevent prostate cancer by weakly binding androgen hormone receptors in the prostate thereby interfering with androgenic stimulation of prostate cells (30). There is a case-control study suggesting that populations consuming high amounts of soy milk have lower rates of prostate cancer (31). The most prominent isoflavonoid to be a candidate preventive agent is genistein (32).

**SELENIUM**

Selenium is found in many vegetables and grains grown in selenium-rich soil. It has antioxidant activity and may have other direct effects on tumor cells. Serum selenium levels in humans living in high selenium areas may be as high as 10^4 molar. This level inhibits the growth of tumor cells in vivo (33). It is unclear how this laboratory observation translates into human biology. In a nested case-control study of selenium levels in the toenails of men with prostate cancer compared with matched controls, higher selenium levels were associated with a 50 percent reduced risk of metastatic prostate cancer (34). Several prospective epidemiologic studies question the chemopreventive worth of selenium. They report inverse associations between prostate cancer risk and selenium content of prediagnostically collected toenail clippings (35) or serum (36).

In a randomized placebo-controlled trial to assess the ability of 200 μg per day of selenized yeast to decrease skin cancer, an analysis of secondary endpoints revealed a statistically significant reduction in prostate cancer incidence of 63 percent (37).

**VITAMIN E**

α-Tocopherol is the most prevalent chemical form of vitamin E found in vegetable oils, seeds, grains, nuts, and other foods. It is a potent antioxidant and has been suggested as a potential preventative of several cancers, particularly lung cancer (38). In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (39), a total of 29,133 men aged 50–69 years who smoked five or more cigarettes daily were randomized to receive α-tocopherol (50 mg), β-carotene (20 mg), α-tocopherol and β-carotene, or placebo daily for 5–8 years. At the conclusion of the trial there was a median of 6.1 years of therapy. In this lung cancer prevention trial there was a serendipitous finding of a 32 percent decrease in prostate cancer incidence among those males who received vitamin E alone (40). While the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study suggests that α-tocopherol administration reduces prostate cancer risk, there are inconsistent observational epidemiologic studies concerning serum levels of α-tocopherol. Some studies even suggest an inverse relation between blood α-tocopherol levels and prostate cancer risk (35, 37, 41, 42).

**CAROTENOIDs**

There are a number of carotenoids with antioxidative activity. While there is literature supporting a protective role in prostate cancer prevention, the literature is inconsistent. This is partially due to the inconsistent methods used to measure carotenoid content in foods (43). The intake of vitamin A from plant sources is associated with decreased prostate cancer risk while the intake of vitamin A from animal sources may be associated with increased prostate cancer risk (44). These findings, if true, may be due to the lower fat content in the diets of men with high plant vitamin A intake and a higher fat content in the diets of men with high animal vitamin A intake. Prospective epidemiologic studies also suggest that lycopene, a vitamin A analog, is associated with a decreased risk of prostate cancer (10, 45). Lycopene is commonly found in tomato products. Cooking with oils, such as in the preparation of tomato sauces and tomato paste, increases the bioavailability of lycopene (46–48).

**VITAMIN D**

Geographic differences in sun exposure lead to varying amounts of vitamin D in populations and variances in calcium level. There are epidemiologic correlations between lack of sun exposure in colder latitudes and increased prostate cancer risk. In a case-control study, men with high levels of serum calcium (both from dairy products and supplements) had a
four- to fivefold elevated risk of metastatic prostate cancer (48, 49). This has led to interest in vitamin D and vitamin D analogs as chemopreventive agents (50). The active metabolite of vitamin D, 1,25-dihydroxyvitamin D3 (calcitriol) inhibits growth of both primary cultures of human prostate cancer cells and cancer cell lines, but the mechanism by which the cells are growth-inhibited has not been clearly defined. Initial studies suggest that calcitriol alters cell cycle progression and may also initiate apoptosis. One of the disadvantages of vitamin D are the side-effects, such as hypercalcemia at doses above physiologic levels. Analogs of calcitriol have been developed that have comparable or more potent antiproliferative effects but are less calcemic (51).

NON-Steroidal anti-INFLAMMATORY drugs

The non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and sulindac, may have prostate cancer chemopreventive activity (52, 53). In a case-control study of 417 prostate cancer patients and 420 group-matched control subjects, regular daily use of over-the-counter NSAIDs, ibuprofen or aspirin, was associated with a 66 percent reduction in prostate cancer risk (odds ratio = 0.34; 95 percent confidence interval: 0.23, 0.58; \( p < 0.01 \)). The risk of prostate cancer was also significantly reduced in men who reported taking prescription NSAIDs (odds ratio = 0.35; 95 percent confidence interval: 0.15, 0.84; \( p < 0.05 \)) (54). The cyclooxygenase-2 inhibitors provide great promise in the prevention of prostate and colon cancer.

5α-REDUCTASE INHIBITORS

If long-term androgenic stimulation is important to prostate carcinogenesis, decreasing this stimulation through drug therapy may impede carcinogenesis. Androgenic blockers, such as flutamide, bicalutamide, and nilutamide, have too many side effects to be of practical use in an asymptomatic healthy population. Dihydrotestosterone is the principal androgen responsible for normal and hyperplastic growth of the prostate gland. Dihydrotestosterone is 10 times more potent an androgen than testosterone. Inhibition of 5α-reductase decreases the amount of dihydrotestosterone in prostate cancer tissue thereby lowering androgenic stimulation to the prostate. Systemic androgenic stimulation is only mildly effected (55). In vitro studies suggest that 5α-reductase inhibition slows the growth of previously established prostate cancer cell lines (56, 57). In studies of prostate cancer tumors grafted into animals, the 5α-reductase inhibition impedes tumor implantation and growth (58–60).

In studies in which rats are given a cancer initiator and high-dose testosterone, 5α-reductase inhibition can prevent actual prostate carcinogenesis (61, 62). In these studies half the rats are treated with a 5α-reductase inhibitor and their rate of prostate cancer development is compared with the half that was not treated with the 5α-reductase inhibitor. The fact that these studies require long-term androgenic stimulation (administration of testosterone) in itself suggests that decreasing this stimulation will prevent prostate cancer.

Finasteride was the first 5α-reductase inhibitor to enter human trials. It lowers intraprostatic dihydrotestosterone levels while causing intraprostatic testosterone levels to increase slightly (13, 63, 64). Because dihydrotestosterone is more potent than testosterone, there is a net decrease in androgenic stimulation. In clinical trials and in common usage, finasteride has been shown to have few side effects. In a randomized, double-blind study, a very small but statistically significant proportion of men reported impotence and/or loss of libido on therapy when compared with men treated with placebo (64). Finasteride is effective in the treatment of moderate benign prostatic hyperplasia (59, 62, 65). It was approved by the US Food and Drug Administration for the treatment of benign prostatic hyperplasia in 1992 and for treatment of male pattern baldness in 1997.

OTHER POSSIBLE AGENTS

The relations between prostate cancer and consumption of vitamin C, vitamin B1, vitamin B2, niacin, calcium, zinc, protein, and carbohydrates has been investigated. No clear association exists between these common dietary factors and prostate cancer (10). Other drugs have been suggested as chemopreventive agents based on theory and limited in vitro data. These are nonclassic antioxidant agents, including the polyphenols, the isothiocyanates, difluoromethylornithine (eflornithine hydrochloride), oltipraz, and N-acetylcysteine (66, 67). These drugs have not been rigorously assessed in clinical trials.

CLINICAL PREVENTION TRIALS

The potential for selenium and α-tocopherol as prostate cancer preventives are intriguing. These drugs have minimal side effects. The leads from the above studies are being explored in a prospective randomized clinical trial titled the Selenium and Vitamin E Comparison Trial (SELECT). This is a 2 × 2 design in which one-fourth of all participants will be randomized to receive yeast-derived selenium daily, one-fourth will receive vitamin E, one-fourth will receive both drugs, and one-fourth will receive placebo. The trial will enroll more than 32,000 men and run for more than 12 years. It has a 90 percent power to detect a 25 percent difference in incidence. SELECT will begin in 2001.

The Prostate Cancer Prevention Trial began in 1993. More than 18,800 healthy men, aged 55 years and older, were randomized to finasteride (5 mg/day) or placebo from 1993 to 1997. All men are screened annually for prostate cancer with digital rectal examination and serum prostate-specific antigen. Serum prostate-specific antigen testing is performed in a central laboratory. The primary endpoint of the Prostate Cancer Prevention Trial is the reduction of biopsy-proven prostate cancer incidence over a 7-year period (a reduction of the period prevalence of the disease). The impact of finasteride on serum prostate-specific antigen does complicate the trial, as both groups of participants must have equal risk of prostate cancer diagnosis through screening. Doubling the prostate-specific antigen levels in finasteride-treated patients allows appropriate interpretation of prostate-specific antigen.
values and does not mask the detection of prostate cancer (68, 69). At 7 years all available participants will undergo a sextant biopsy to determine the period prevalence of prostate cancer. The trial has a 90 percent power to detect a 25 percent reduction in period prevalence of biopsy-proven disease using a two-sided test with \( \alpha = 0.05 \). The study will end in late 2004 (70). In addition to its primary objective, the Prostate Cancer Prevention Trial will provide opportunities to better understand prostate cancer biology and the prevention and treatment of benign prostatic hyperplasia (71, 72).

CONCLUSION

The prevention of prostate cancer is a relatively new concept. No intervention, through dietary modification or a drug, has been found to clearly decrease prostate cancer risk. No intervention can be definitively proven efficacious without a randomized clinical trial. Because these trials are trying to demonstrate that something does not happen, they are large, expensive, and long in duration. The size of the trials makes a mortality endpoint prohibitive so they are designed to assess the incidence of diagnosed disease. This is an unfortunate but necessary shortcoming.

Ultimately, phase II trials using validated surrogate markers of prostate incidence are critical for the efficient evaluation of a preventive strategy. Validation of these markers will themselves need large, long-term randomized trials. Suggested markers include the regression of prostatic intraepithelial neoplasia as measured in radical prostatectomy specimens, or the decline in prostate-specific antigen both in men with intact prostates and in men with prostate-specific antigen relapse after radical prostatectomy. Again, the utility of these methods will remain controversial until validated (73, 74).

Eventually one or several of the drugs discussed above in combination may be found to decrease an individual's risk of prostate cancer. Questions for research include who would benefit from such drugs. Those with a genetic predisposition to prostate cancer may not benefit from some successful interventions compared with men at risk for sporadic prostate cancer. Until an efficacious prostate cancer chemoprevention is found, scientists and physicians must be careful not to mislead the lay public. We must stress what is known, what is not known, and what is believed about chemoprevention.

REFERENCES

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