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Risk Factors and Prevention of Prostate Cancer

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Ⅰ. RISK FACTORS FOR PROSTATE CANCER

1. Epidemiology of Prostate Cancer Risk

Epidemiologic studies have provided the greatest amount of information to date regarding risk of prostate cancer. However, epidemiology is a relatively crude tool for examining what may prove to be an unusually complex etiology. Most of these studies have significant problems with exposure and disease characterization. The incidence of prostate cancer has increased in the past 50 years, with recent dramatic increases most likely due to early detection methods, such as the measurement of serum PSA, rather than true differences in underlying risk; a slight decline in the past few years most likely resulted from depletion of the pool of detectable cases. There is considerable international variation in the incidence of clinically detected prostate cancer, but comparisons are distorted by lead-time, case identification, detection, and reporting biases. Unlike clinical incidence, the age-specific prevalence of prostate cancer found at autopsy is relatively uniform across countries and ethnic groups, with contemporary studies indicating a rate as high as 80% by age 80 years.

Risk factors can be classified as endogenous or exogenous, although some factors are not exclusively one or the other (e.g., race, aging, oxidative stress). Recognizing that, some factors may reflect both endogenous and exogenous influences, and this is noted for those instances.

2. Endogenous Risk Factors

Endogenous risk factors for prostate cancer, include the following.

1) Family history

Family history is associated significantly with prostate cancer risk in epidemiologic studies but may be influenced by detection bias. The clinical and pathologic features of familial cancer are similar to nonfamilial cancer.

2) Hormones

Androgens significantly alter prostate cancer growth rates, and progression of prostate cancer from preclinical to clinically significant forms may result in part from altered androgen metabolism. Elevated concentrations of testosterone and its metabolite, dihydrotestosterone, over many decades may increase prostate cancer risk, but results have been inconsistent. Hormone levels may be affected both by endogenous factors (e.g., genetics) and by exogenous factors (e.g., exposure to environmental chemicals that affect hormone activity).

3) Race

Differences in prostate cancer risk by race may reflect three factors: differences in exposure, such as dietary differences (exogenous factors); differences in detection (reflecting exogenous factors); and genetic differences (endogenous factors). The highest incidence rates for prostate cancer in the world are among African-American men, who have a higher risk of prostate cancer than white American men. However, racial differences may reflect differences in access to care (exogenous factors), differences in the decision-making process of whether to seek medical attention and follow-up, and differences in allelic frequencies of microsatellites at the androgen receptor (AR) locus or polymorphic variation.

3. Exogenous Risk Factors

Exogenous risk factors for prostate cancer include the following.

1) Diet

A wide variety of dietary factors have been implicated in the development of prostate cancer

according to descriptive epidemiologic studies of migrants, geographic variations, and temporal studies. Fat consumption, especially polyunsaturated fat, shows a strong, positive correlation with prostate cancer incidence and mortality, perhaps resulting from fat-induced alterations in hormonal profiles, the effect of fat metabolites as protein or DNA-reactive intermediates, or fat-induced elevation of oxidative stress. Retinoids, including vitamin A, help regulate epithelial cell differentiation and proliferation, with a positive association with prostate cancer risk. Vitamin C is a scavenger of reactive oxygen species (ROS) and free radicals, but there is no consistent association of intake and prostate cancer risk. Vitamin D deficiency may be a risk factor for prostate cancer; the hormonal form, 1-25-dihydroxyvitamin D, inhibits invasiveness and has antiproliferative and antidifferentiative effects on prostate cancer. Vitamin E (-tocopherol) is an antioxidant that inhibits prostate cancer cell growth through apoptosis, and daily intake decreased the risk of prostate cancer by 32% in a large, controlled, clinical trial from Finland. Zinc (Zn) concentration is higher in the prostate than in any other organ in the body; although it is reduced > 90% in prostates with cancer; the relation of dietary zinc and prostate cancer risk is uncertain. Selenium is an essential trace element that inhibits viral and chemical, carcinogen-induced tumors in animals; a chemopreventative role for selenium is plausible, but the evidence in humans is limited. Alcohol intake has no significant association with prostate cancer risk. Consumption of cruciferous vegetables is associated with a decreased risk of many cancers, but there is no evidence of a protective effect for prostate cancer. Lycopene, an abundant constituent of tomato-based products and the most efficient carotenoid antioxidant, has a significant protective effect.

2) Environmental agents

One class of environmental agents that has received a lot of attention is the endocrine disrupting chemicals (EDCs). An EDC can be defined as an environmental agent that positively or negatively alters hormone activity (these are endocrine-active EDCs) and ultimately leads to effects on reproduction, development, and/or carcinogenesis, particularly of reproductive organs. EDCs have been identified that elicit effects on estrogen, androgen, and/or thyroid activities. Although it has been shown that the majority of the well studied EDCs are estrogen agonists, which bind the to

estrogen receptor (ER), thereby increasing estrogen activity, it has been shown that a number of EDCs affect other hormone activities. For example, it has been shown that the active metabolite of the pesticide vinclozolin is an androgen antagonist, binding to the AR and decreasing the expression of androgen-regulated genes, and an androgen agonist was identified in water downstream of pulp mills. Studies have shown that certain pesticide residues on foods, chemicals used in plastics production, and phytoestrogens in dietary plant products (e.g., soy) behave as EDCs. Exposure to EDCs can occur through ingestion of food or water or through inhalation. High-level exposure to estrogen agonists is unusual, but men may have chronic exposure to low doses of a mixture of EDCs. Individuals or groups with relatively high endogenous estrogen or androgen concentrations (serum or prostate tissue levels) may have a greater susceptibility to EDC exposure, because exposure to an EDC could add effectively to the endogenous activity. Cadmium is a significant environmental contaminant that has been linked to prostatic cancer in some, but not all, epidemiological studies. It is worth noting that the carcinogenic potential of cadmium may be modified by zinc.

3) Occupation and other factors

Many industrial and occupational exposures have been studied in relation to prostate cancer risk, but the findings are inconclusive; of greatest concern is farming and, to a lesser extent, working in the rubber industry. Numerous other factors have shown inconsistent results, negative associations, or have very limited data with prostate cancer risk, including smoking, energy intake, sexual activity, marital status, vasectomy, social factors (lifestyle, socioeconomic factors, and education), physical activity, and anthropometry.

Ⅱ. CHEMOPREVENTION OF PROSTATE CANCER

Prostate cancer has long been recognized as an appropriate target for chemoprevention. The incidence of the disease is high, it is prevalent and it has significant morbidity and mortality. Putative premalignant lesions and, therefore, targets exist in the form of prostatic intraepithelial

neoplasia (PIN) and possibly, proliferative inflammatory atrophy (PIA). It should be noted that true primary prevention of prostate cancer would have to take place among adolescents as autopsy data suggest that up to one-third of men in their thirties possess early prostate cancer. It is then more relevant to consider prevention from the aspect of a 'clinical' diagnosis of prostate cancer. Effective agents could work by slowing the growth and grade progression among existing prostate-cancer cells and could, therefore, be given to men in later adulthood.

1. Hormonal agents

Current agents that work primarily by a hormonal action include 5-[alpha]-reductase inhibitors and selective estrogen receptor modulators (SERMs).

1) 5-〔alpha〕 reductase inhibitors

The observation that men deficient in type 2,5-[alpha]-reductase fail to develop either benign prostatic hypertrophy (BPH) or prostate cancer contributed to the premise for the Prostate Cancer Prevention Trial (PCPT). The principle findings of this landmark trial bear reiteration. The point prevalence of prostate cancer was reduced for those on finasteride, relative to those on placebo, by 24.8% [95% confidence interval (CI) 18.6-30.6%] [hazard ratio (HR) = 0.75]. Differences were observed in both 'for-cause' biopsies [clinically indicated for elevated PSA or abnormal digital rectal examination (DRE)] and end-of-study biopsies. Prostate volume for men on finasteride was reduced 25% compared with placebo. Urinary symptoms improved, while breast and sexual side effects worsened, in the treatment group.

The most unexpected and controversial finding of the study was the small increase in the number of high-grade (Gleason grade 7-10) tumours detected at biopsy in the finasteride group (6.4 compared with 5.1%) (HR 1.27, 95% CI 1.07-1.50). Several hypotheses have been put forward to explain the differential grade distribution:

True drug induction of high-grade disease It is theoretically possible that by changing the androgen milieu, finasteride could induce genetic instability and hence grade progression. Interestingly the greatest ratio of high-grade cancers between the groups occurred in the first 2

years, then decreased after that. This observation goes against the concept of a true 'dose-response' seen in other iatrogenically induced tumors, such as endometrial cancers among Tamoxifen users.

Diagnostic bias Recent data from Kulkarni et al. have shown that a previously unrecognized bias exists in grading errors between biopsy and actual grade at radical prostatectomy. This study showed that men with larger prostates are more likely to have biopsies with low-grade cancer but are no less likely to have high-grade disease at radical prostatectomy. By shrinking the prostate, therefore, finasteride places men at greater risk of detecting high-grade disease than would otherwise occur, as the tumor would be harder to find at needle biopsy if the patient's prostate had not been reduced in size.

Pathological artifact It has long been hypothesized that finasteride may alter prostatic tissue, rendering it susceptible towards a higher grade ascertainment. Men in the PCPT who had high-grade cancers actually had less adverse features such as volume and seminal vesicle involvement. A recent consensus conference among expert uropathologists has concluded that the weight of evidence is for an artifactual effect on Gleason grade results in this trial. Awaited results from evaluation of PCPT radical prostatectomy specimens will probably resolve the issue.

2) Selective estrogen receptor modulators (SERMs)

Consideration of SERMs as prostatic chemopreventatives has originated from the identification of estrogen receptors in prostatic stromal, epithelial cells and prostatic cancer cell lines. These agents both agonize and antagonize estrogen receptors and inhibit prostate-cancer cell lines in animal models. A small phase IIA clinical trial shows the potential for toremifene to reduce high-grade PIN detection at biopsy and has led to an ongoing larger phase IIB/III trial to explore these promising results further.

2. Antioxidants

Reactive oxygen species (ROS) may interact with DNA bases to form putatively carcinogenic DNA adducts. ROS may also impact carcinogenesis via epigenetic mechanisms. Although an

important part of the host immune system, ROS are usually constrained by a combination of antioxidant enzymes and molecules. Imbalance between these forces results in oxidative stress causing intracellular damage, findings seen in both PIN and prostate-cancer cells. Selenium, vitamin E and lycopene are antioxidant molecules of impending significance in prostate-cancer chemoprevention.

1) Vitamin E ([alpha]-tocopherol)

Vitamin E is the major lipid-soluble antioxidant in cell membranes and dietary sources include plant oils and nuts. Basic scientific studies have demonstrated cell cycle arrest at the G1 phase, apoptotic and antiandrogen effects. The [alpha]-tocopherol, [beta]-carotene (ATBC) trial was designed to assess their effects on lung cancer prophylaxis, however a 32% reduction in incidence and a 41% reduction in disease specific mortality at 6 years for prostate cancer were coincident secondary outcomes. The relative risk estimate for prostate cancer, with low dose (50 IU/day) vitamin E supplementation, following the trial was 0.88. Recently data question the safety of vitamin E with reports that high doses (more than 400 IU/day) are associated with elevated heart failure and all-cause mortality rates. Doses are therefore recommended not to exceed 150 IU/day currently.

2) Selenium

Selenium is an essential trace element whose concentration is dependent on the soil content of the region from whence the produce has originated. Following digestion, it is metabolized to the physiologically active methylselenol or incorporated into antioxidative enzyme systems. Down-regulation of selenoprotein-P is seen in various prostate-cancer cell lines and appears to develop during the progression from HGPIN to invasive prostate cancer. Currently, the 200 [mu]g/day dose used in the nutritional prevention of cancer study would seem to be the closest to an adequately evaluated regimen that exists. In a similar fashion to vitamin E, the current interest in selenium stems largely from a trial designed to look at its effect on an alternative disease, in this case nonmelanoma skin cancer. The nutritional prevention of cancer trial randomized 1312

participants to 200 [mu]g of selenized yeast or placebo. Although the primary endpoint was not reached, a reduction in the incidence of prostate cancer at 4.5 years (HR = 0.35) and at 7.4 years (HR = 0.51) was noted. The association was most pronounced among those with initially low serum selenium levels and for men younger than 65 years of age or with a PSA below 4 ng/ml.

3) Lycopene

Lycopene has been regarded as the major phytochemical of interest found in tomatoes. It provides the red pigment of tomatoes as well as other red fruits such as watermelon and grapefruit. The predominant effect of lycopene is antioxidant, as it efficiently scavenges singlet oxygen and ROS. Additionally, however, lycopene may down-regulate certain androgen target genes and promote cellular apoptosis. Interest in lycopene has been driven by the report in 1995 from the health professionals' follow-up study that men with higher consumption of tomato products have a substantially lower risk of prostate cancer. A meta-analysis found that compared with nonfrequent users of tomato products, the relative risk of prostate cancer among consumers of high amounts of raw tomato was 0.89 (95% CI 0.8-1.0). For high intake of cooked tomato products, the relative risk was 0.81 (95% CI 0.71-0.92). They concluded that the effect of tomato consumption was modest and restricted to high-intake consumers.

3. Other candidates

The remaining agents work through alternative or multiple pathways or have mechanisms of action that are poorly understood.

1) Isoflavones

The consumption of soy products is widespread in Asian countries in which the incidence of prostate cancer is low. A recent meta-analysis has estimated the relative risk for prostate cancer in groups with large soy consumption to be 0.70 (95% CI 0.59-0.83). The isoflavones, of which the most active compounds appear to be daidzein and genistein, form a subgroup of phytoestrogens and bear a chemical resemblance to 17[beta]-oestradiol. The scientific evaluation of isoflavones is

perhaps less advanced than for other chemopreventatives. Specific dietary recommendations for these foods are not yet possible for prostate-cancer prevention.

2) Green tea

Like soy products, green tea has been proposed as a potential prostate-cancer preventative on the epidemiologic observation that prostate-cancer incidence is low in Asian countries where consumption is high. Polyphenols, particularly (-)-epigallocatechin-3-gallate (EGCG), are held to be the chief candidate for active prostate-cancer inhibition caused by green tea consumption. In established prostate cancer, green tea may interfere with matrix metalloprotease (MMP)-related cell migration and neoangiogenesis.

3) Nonsteroidal anti-inflammatory drugs

The role of inflammation has assumed increasing importance in carcinogenesis with recent findings of a preventative role for anti-inflammatory drugs in colorectal and breast cancer. Animal models have shown inhibition of prostate-cancer growth with both cyclooxygenase-2 (COX-2) inhibitors and other non-COX-inhibiting nonsteroidal anti-inflammatories (NSAIDs). NSAIDs also reduce the number of PIN lesions in mouse models. There has been recent interest in nitric oxide (NO)-donating NSAID forms such as NO-ibuprofen, NO-aspirin and nitrosulindac, resulting from the well documented side effects. These agents theoretically protect gastric mucosa by inducing mucosal blood flow and mucus secretion. Each of the compounds was more effective at inhibiting proliferation and promoting apoptosis in LNCaP and PC3 prostate-cancer cell lines than their non-nitric-oxide-donating counterparts. Nitric oxide-donating NSAIDs appear to present a promising option for development. A recent meta-analysis of the effects of aspirin on prostate-cancer risk found a modest inverse association odds ratio 0.9 (95% CI 0.82-0.99). Subsequent studies have confirmed similar findings. Information from the General Practice Research Database in the United Kingdom showed a somewhat stronger risk reduction with current aspirin use, odds ratio = 0.70 (95% CI 0.61-0.79) with no differences in dose or duration of treatment. Data from the American Cancer Society's Cancer Prevention Study II Nutrition Cohort suggested a modest benefit among

regular long-term users of aspirin and NSAIDs. It would seem that men on low-dose aspirin for cardiovascular preventative reasons might potentially derive a secondary urological benefit, but that long-term regular use is important to achieve it.

4) Statins

A recent systematic review of 33 case-control and cohort studies found consistent indirect evidence for the concept of dietary fat as a promoter of prostatic carcinogenesis but that this evidence was insufficient to demonstrate causation. Subsequently published studies have reiterated aspects of these results for untreated hyperlipidaemia (relative risk = 1.5, 95% CI 1.1-2.0) and metabolic syndrome (relative risk = 1.9, 95% CI 1.1-3.5) [62,63]. Statins or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors have a number of potential mechanisms of action in prostatic carcinogenesis prevention. Recently a small case-control study found significant risk reduction (odds ratio = 0.38, 95% CI 0.21-0.53) with statin use (predominantly Simvastatin and Lovastatin) after adjustment for potential risk factors and this was particularly strong for Gleason grade score at least 7 (odds ratio = 0.24, 95% CI 0.11-0.53). These compelling data require further study.