PROSTATE CANCER: ROLE OF NUTRITION

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INTRODUCTION

Prostate cancer is a major public health problem in the developed world. It is the most common human cancer and the second leading cause of cancer deaths among North American males. Current estimates suggest that approximately 180,000 North American men will be diagnosed with the disease in 1998 and that almost 40,000 will die from it.

There are currently only 2 well accepted risk factors for prostate cancer: family history and race (African-Americans). There is increasing evidence, however - epidemiological, experimental, and metabolic – suggesting that environmental factors, such as diet, may play an important role in the development and/or progression of prostate cancer.

The purpose of this paper is to review the descriptive epidemiology of prostate cancer and to review some of the promising agents that may play a role in managing prostate cancer in the 21st century.

EPIDEMIOLOGY OF PROSTATE CANCER

Descriptive epidemiological evidence suggests that environmental exposures, such as diet, play an important causative role in the development/progression of prostate cancer . A marked global discrepancy exists in age-adjusted mortality rates from prostate cancer . Despite this large global variation, autopsy studies have confirmed that small foci of prostate cancer exist ubiquitously in 42-80% of males in their 8th decade . In nations with a high incidence and death rate from prostatic carcinoma (CAP) (e.g. North America), these foci of cancer appear to be more voluminous, higher grade and multifocal compared to patients from nations with low rates of CAP (e.g. Japan, China).

Studies of migrating populations reveal that men from countries with a low incidence of CAP tend to acquire an increased incidence rate, approaching that of the host country .

Recent data also suggest that the origins of microfocal cancer occur in the fourth decade of life. Sakr et al performed a detailed autopsy study in American trauma victims and found that 30% of men between 30-39 had microfocal cancer . These observations have led to the concept of a late stage environmental promoter that converts latent prostatic

cancer into clinical CAP. Whether this late stage promoter relates to an error of commission or an error of omission in high-risk nation remains unclear. However increasing evidence suggests that both may be occurring. The interesting feature of the conversion of latent to clinical prostate cancer is the speed at which is transpires. Latent disease begins in the 4th decade of life whereas clinical disease manifests in the 6th or 7th. Therefore, if we can somehow, delay this process, we may be able to convert CAP into a chronic disease of little public health importance- as it is in Asia. In addition, it is important to realize that, in the context of CAP, primary prevention refers to the progression of established microscopic disease into clinically relevant disease. Interventions on a true primary level, which is on disease initiation and promotion, would require intervention prior to age 30. It is also important to stress that these interventions may also be beneficial to patients with established disease as progression from early detected disease until death ranges between 10-20 years. Thus any intervention, which may slow progression, may be of benefit.

AGENTS/INTERVENTIONS

a)DIETARY FAT REDUCTION:

The associated between dietary fat consumption and prostate cancer development is now well accepted. The association was first hypothesized as a result of correlation studies, which examined dietary fat consumption and prostate cancer mortality on a global scale . Hypothesis testing epidemiologic studies have subsequently been performed. Eleven of 14 case-control studies and 4 of 5 cohort studies (stronger methodology for determining causation as diet habits were collected prior to development of prostate cancer) revealed an association between either dietary fat consumption or high-fat food consumption and prostate cancer (Table 1). The consistency of these data is impressive given the nature of observational epidemiology.

In addition, recent data from University of Laval, have shown that cancer progression among men with CAP was more rapid among men who consumed a high-fat diet, even after adjusting for disease stage and grade.

Aside from observational data, there are also important laboratory studies

that confirm some of these observations. Wang et al found that a high fat (40% of total caloric intake) diet enhanced the growth of transplanted human LNCaP prostate cancers in male nude mice . This study also indicated that changing dietary fat consumption from high (40.9%) to low (21.3%) once LNCaP xenografts are established can slow tumor progression . These findings suggest that dietary fat reduction disease may play a beneficial role among men with established prostate cancer. At least 2 clinical trials are now evaluating this hypothesis.

There are a host of biologically plausible links between dietary fat consumption and prostate carcinogenesis including: increased androgen levels, oxidative stress, fat soluble pesticides and specific fatty acids contained within the fat.

i) Androgen Levels

Androgens are felt to play an important role in prostatic carcinogenesis . Individuals with chronically inhibited androgen function (eunuchs, 5-alpha-reductase deficiency) do not develop prostate cancer . There is some evidence that diets low in fat are associated with lower levels of androgens including 2 low fat intervention studies that have noted a drop in androgen levels. Other studies however are inconsistent on this point.

ii) Oxidative Stress- [this will be discussed in the Vitamin E section of this article]

iii) Fat- Soluble Pesticides

There are some who believe that fat of itself is not responsible for the observed associations but it is the pesticides contained within the fat that are to blame. Increased risk of prostate cancer among farmers/pesticide applicators also adds some credence to this hypothesis. Numerous pesticides are fat soluble and thus accumulate up the food chain. They also possess hormone-like properties. For example, ichlorodiphenyldichloroethylene (DDT) and its derivative p,p’-dichlorodiphenyldichloroethylene (p,p’-DDT) possess anti-androgen and anti-estrogenic properties.

iv) Fatty Acids

Certain fatty acids may stimulate or inhibit prostate cancer growth. For example, arachidonic acid, an omega-6-fatty acid has been shown to stimulate prostate cancer cell

proliferation. Other fatty acids such as omega-3, have been shown to induce apoptosis or
block 5-alpha-reductase. More work is needed in this area. Although the animal models suggest that reduction of dietary fat can slow disease
progression among men with established disease, more work needs to be done. We have
completed a study in which we lowered dietary fat consumption from 40% to 20% (of
total calories) among 20 men with elevated PSA and no cancer. A significant reduction in
PSA (less than 20% from baseline) was noted in 45% (9 of 20) of these men. The
significance of these reductions are unknown but the suggestion that even a marker of
prostate cancer can be reduced by lowering dietary fat is exciting. We are currently aware
of at least 2 randomized trials that are testing this hypothesis. Therefore answers should
become available within the next 10 years.

b) VITAMIN D

Although Vitamin D is called a vitamin –it is in fact, a steroidal hormone.
Vitamin D is naturally synthesized under the influence of ultraviolet light (U-V) with
conversion into biologically active compounds by hydroxylation in the liver and kidneys.
Although vitamin D is primarily involved in bone and calcium metabolism, there is
increasing evidence that vitamin D may be important in preventing certain cancers
including CAP.
The association between vitamin D deficiency and prostate cancer was first noted
via an intranational study that showed a correlation between U.S. U-V exposure and
local rates of prostate cancer deaths. This was further reinforced by an epidemiological
study that has shown that individuals with the highest calcium intake (which naturally
suppresses vitamin D) had a 3-fold highest risk of prostate cancer. Subsequent laboratory
research has since demonstrated that prostate cancer cells possess vitamin D receptors
and that stimulation of those receptors inhibits cell growth and can trigger apoptosis
(programmed cell death).
Numerous studies continue to examine the use of Vitamin D in the management
of prostate cancer. It remains unclear whether physiologic or pharmacologic doses are
necessary for therapeutic efficacy. Using a physiologic model, 400-800 IU of vitamin D3

should suffice. Significantly higher doses may cause hypercalcaemia. Vitamin D analogues, devoid of the hypercalcemic effects have now been developed and are in phase I-II testing. Vitamin D may also have a role in preventing disease progression.

Data from Stanford University suggests that the rate of rise of PSA levels among men who have failed radical prostatectomy. Moreover, preliminary data among men with metastatic disease suggest that treatment with vitamin D can improve quality-of life.

c) VITAMIN E

Vitamin E, the major intracellular antioxidant in cell membranes, inhibits lipid peroxidation and has been demonstrated to have a wide range of anti-cancer properties .

These properties include both protection against carcinogenesis and inhibition of tumour progression. The precise mechanistic pathways of vitamin E's beneficial benefits are largely unknown. Numerous in vitro and in vivo cell lines from a wide variety of human primary cancers have shown responsiveness to Vitamin E . Fleshner and colleagues have shown that supplemental vitamin E can inhibit tumor progression in nude mice bearing human prostate cancer xenografts [figure 1].

Data from a double-blinded randomized clinical trial suggest that Vitamin E is beneficial in reducing the prostate cancer burden. The Finnish α-Tocopherol, β-Carotene Study randomized 28 000 men to receive these agents in a two-factorial design . At 6 year follow-up, there was a 32% reduction in prostate cancer incidence and a 41% reduction in prostate cancer mortality, among the men who received supplementary Vitamin E . Critics of this study cite the fact that this finding may have been caused by multiple comparisons and that prostate cancer prevention was not an *a priori* hypothesis of the study.

Daily supplementation with vitamin E doses up to 800 IU per day have been safely used in clinical trials and has been reported to exert a protective effect on oxidative damage in the elderly .

Although the precise mechanism of vitamin E activity is unknown-increasing evidence suggests that it may exert its effects by inhibiting oxidative damage within the

prostatic epithelium. Reactive oxygen species (ROS) and oxidative damage to biomolecules is a major focus of recent etiologic cancer research . There is strong evidence that ROS generated both endogenously and from external sources are associated with carcinogenesis and cancer progression. ROS are generated endogenously as byproducts of normal metabolic processes and cause oxidative damage to important biomolecules such as lipids, proteins, and DNA. Oxidative modification of DNA bases leads to mutation and altered gene function resulting in carcinogenesis . ROS can also induce the expression of a variety of transcriptional factors involved in neoplastic transformation such as c-fos and c-jun oncogenes . ROS have also been shown to alter the conformational structure of the p53 protein; mimicking a mutant phenotype . P53 mutations are associated with the progression of numerous human cancers including prostate cancer.

Increasing evidence suggests an association between oxidative damage and prostate cancer incidence/progression. Many factors associated with the development of prostate cancer increase oxidative damage including androgens, advancing age, and dietary fat (which is the substrate for ROS) consumption. Moreover, data from Nelson et al, have shown that abnormalities in the glutathione-s-tranferase (GST-pi) system are common to all forms of prostate cancer but not BPH. The GST-pi system is one of the endogenous pathways important in minimizing oxidative damage within cells. These data coupled with the compelling findings associated with vitamin e and selenium (see below)--both powerful antioxidants are intriguing.

D)SELENIUM

The biochemical function of selenium was elucidated by Rotruck and colleagues. They demonstrated that glutathione peroxidase, an enzyme that protects the cell from oxidative damage, is selenium dependent . A large number of epidemiological studies have since confirmed an inverse association between selenium intake or tissue levels and various human cancers including prostate cancer . The largest of these studies was a nested case-control study assessing toenail selenium levels and prostate cancer risk

within the context of the Health Professionals Follow-Up Study. The adjusted odds ratio for advanced prostate cancer among men with the highest quantile of toenail selenium was 0.35 (95%CI 0.16-0.78).

Data have been reported on the efficacy of 200 µg of selenomethionine in a placebo-controlled intervention study in 1312 patients with non-melanoma skin cancer . After 8269 years of patient follow-up, there was a 3-4 fold reduction in prostate cancer incidence (RR 0.29, p<.001). No selenium toxicity was observed. Although it could be argued that the reduction of prostate cancer incidence was not an *a priori* hypothesis of the study, these highly significant findings mandate further investigation.

e)LYCOPENE

Lycopene is a carotenoid naturally present in tomatoes and other fruits. Lycopene is also a potent antioxidant and the most significant free radical scavenger among the carotenoid family . A series of epidemiologic studies suggest that this antioxidant may be beneficial in preventing prostate cancer. In a large Seventh-day Adventist cohort study, Mills et al reported that tomato consumption was most strongly associated with reduced prostate cancer risk . In a nested case-control study, Hsing et al noted a 50% reduction in odds of prostate cancer among men with the highest quartile of prediagnostic serum lycopene . However that study included only 103 case-control pairs, and these associations were not statistically significant. A nested case-control study within the context of the Health Professional Follow –Up study showed that individuals consuming more than 10 servings per week of tomato-based products had an adjusted odds ratio of 0.65 (95% CI 0.44-0.95) for developing advanced/aggressive prostate cancers . This unique association with more advanced disease suggests that lycopene supplementation may be beneficial in preventing the progression of prostate cancer.

Although numerous nutritional supplements contain lycopene, most only contain trivial amounts (5-20 mg). Based on the epidemiologic data it would appear that 25-50 mg would be appropriate.

F)SOY

Soy is a dietary compound widely consumed in Japan; a nation with one of the

lowest incidences of prostate cancer in the world . Soy is thought to possess broad
anticancer properties . Genistein and Daidzein, two isoflavenoid components of soy are
known to have mild estrogenic effects . Estrogens are known to cause programmed cell
death in prostate cancer cells . These soy compounds have also been shown to inhibit
enzymes and processes associated with cellular growth, motility, and proliferation in
vivo. These observations make soy product an ideal candidate for trials in the
chemoprevention of prostate cancer. Studies of these compounds in mouse and human
(LNCaP & PC-3) prostate cancer cell lines have confirmed their anti-cancer properties .
Data have also shown that mouse xenografts bearing human LNCaP prostate cancer
tumors grow at a slower rate if fed a diet containing soy product .
Isolated soy protein in a powdered beverage form has historic and general
recognition of safety including general and specific recognitions from the FDA and
USDA. It is derived from soybeans, using processing aids approved by the FDA. These
products have been used in the Armed Forces canteens and in the federal school lunch
programs for over 10 years. No risks to humans have been reported with the use of soy
products at this level.
Many soy supplements are available on the market. Most have been developed for
menopausal women and thus contain a significant amount of calcium. In addition, the
isoflavone content varies from preparation to preparation. We recommend 50-100 mg of
isoflavone and 20-40 grams of soy protein per day