Prostate cancer: chemoprevention update 2005

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Introduction: *If an agent can slow the growth of existing prostate cancer cells, it remains plausible that it may be effective as an adjunct to surgery, radiation or chemotherapy.*

Discussion: *Level-1 evidence will be needed in order to definitively prove the efficacy of agents as chemoprevention strategies for prostate cancer. Currently, only finasteride fulfills this criterion. Two major trials are underway that will assess the role of soy, vitamin E and selenium in prostate cancer prevention.*

Conclusion: *Tantalizing prospects for effective of prostate cancer exist. Fortunately, well-conducted randomized trials will allow us to answer many of these questions within the next 2 to 8 years.*

Key Words: chemoprevention, prostate cancer, prevention

Introduction

Prostate cancer is the most common human visceral cancer and the 2nd most common cause of cancer related deaths among men (2.5% of Canadian men).[1] It is estimated that approximately 60% of men in the 6th decade of life harbor occult malignancy. The lifetime risk of developing prostate cancer approaches 1 in 7. Given the large discordance between histological incidence and death, there is great potential for over detection and over treatment of this disease. This is even more relevant as treatment-related morbidities associated with prostate cancer treatment can impact on urinary function, sexual function and quality of life.[2] Disease prevention thus offers an attractive paradigm for addressing this important public health problem.

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Descriptive epidemiology

The descriptive epidemiology of prostate cancer provides insights into the role of the environment in disease ontogeny. Prostate cancer has a wide global variation with high-risk nations, such as Canada displaying a 10-fold higher disease-specific mortality than low-risk nations such as China and Japan.[3] Despite these wide variations in disease incidence and mortality, autopsy studies of aging men suggest an equal rate of histological prostate cancer, regardless of country of residence. Volume, grade and number of malignant foci however tend to be less within the prostates among men from the Pacific rim.[3] The age-old question of genetics versus environment is raised by global variation data. Migrating populations from areas of low risk to areas of high risk help sort out this question. Data among both Japanese and Chinese Americans suggest that immigrants gain increased risk within 11 years after they migrate to America and that their offspring have virtually similar rates of

prostate cancer as Caucasian Americans. This suggests that it is primarily the environment, and not some innate genetic resistance among Asians, that is responsible for prostate carcinogenesis. Given that prostate cancers start histologically among men in their 30s, these data also suggest that early prostate cancer events such as the development of high grade prostatic intraepithelial neoplasia (HGPIN) are likely similar regardless of environmental factors and that intraprostatic progression to clinically detectable disease and metastases are likely driven by unfavorable environmental conditions such as diet or androgenic effects.[4] It must also be recognized that if an effective agent exists that can prevent prostate cancer, the same agent should be studied as a complementary therapeutic strategy among men with clinical prostate cancer. The rationale for this is that unless we intervene among men in their early 20s, prevention in the context of prostate cancer refers to a slowing of the growth of existing prostate cancer cells, so that they never harm the host. If an agent can slow the growth of existing prostate cancer cells, it remains plausible that it may be effective as an adjunct to surgery, radiation or chemotherapy.[3]

Agents studied for prostate cancer prevention

Five-alpha reductase inhibtors

The prostate is a hormonally regulated organ. Prostate development, benign prostatic hyperplasia and prostate cancer are all, in part, regulated by androgen activity.[5] The Prostate Cancer Prevention Trial (PCPT) randomized 18882 men to finasteride, a 5-alpha reductase inhibitor, or to placebo.[6] Five-alpha reductase is the enzyme that coverts testosterone into dihydrotestosterone, the major effector hormone on prostate tissue. At the end of 7 years, all men were to have a prostate biopsy although many had biopsies during trial surveillance for prostate cancer suspicions (so-called "for cause" biopsies). The trial was terminated early as the primary end point had been reached. Prostate cancers were less frequent among men randomized to finasteride (24.4% versus 18.4%, relative risk reduction 25%). These data represent the first level-1 evidence demonstrating that prostate cancer is preventable. There was a marginally higher incidence of breast and sexual adverse effects among men on finasteride; however, they were less likely to have urinary problems such as prostatism and prostatitis. Of concern from the PCPT data was that a higher proportion and absolute number of high-grade cancers (Gleason pattern 4 or higher) was noted among men randomized to finasteride. Three hypotheses have been put forward to explain this difference. One hypothesis is that the alteration in hormonal milieu can lead to true genetic instability and grade progression.[6] A second hypothesis is that the hormonal milieu leads to an artifactual change in grade.[7] A third hypothesis, recently demonstrated by Kulkarni and Fleshner[8] is that men with larger prostate are at higher risk for upgrading from Gleason 6 to 7. Therefore, simply shrinking the prostate, as finasteride does, will lead to an apparent increase in high-grade cancers, which in fact would not exist if the true grade were demonstrated such as at radical prostatectomy. These tantalizing data prove that prostate cancer is a preventable disease. Increasing evidence also suggests that the increased grade among finasteride-treated men is artifactual. Clinicians and patients must weigh the relative risks and benefits of using 5-alpha reductase inhibitors for prostate cancer prevention.

Vitamin E (alpha tocopherol)

Vitamin E is a major antioxidant and has been touted to have many health benefits for a variety of chronic conditions.[9] The association of vitamin E intake and prostate cancer arose from a non-a priori-driven result from a large cancer-prevention trial. The alpha tocopherol beta carotene (ATBC) trial randomized 19000 Finish men in a 2-factorial fashion to either vitamin E, beta-carotene, both or placebo. The primary end point of the study was lung-cancer development. Quite surprisingly, at the end of 4 years, there was a one-third reduced chance of prostate cancer among men randomly allocated vitamin E. Furthermore, a 41% reduction in prostate cancer deaths was noted at 6 years. These results motivated many basic scientific studies demonstrating in-vivo and in-vitro effects of vitamin E on apoptosis, cell cycle arrest and proliferation arrest in prostate cancer tumor model systems.[9] Recent data has questioned the safety of vitamin E at high doses (> 400 IU/day). Heart failure and all cause mortality increases have been noted in recent publications.[10,11] Although these trials were largely conducted among men with multiple co-morbidities, some caution must be exercised in recommending these dosages to men at risk for prostate cancer.

Selenium

Selenium is a trace micronutrient important in cellular host defenses to oxidative stress.[3] Canada is considered a "low selenium" nation since most of the country has low levels of selenium in the soil where local produce is growth.[3] The association of selenium and prostate cancer was also serendipitous, in that it was derived from a non-a priori endpoint of a cancer-

prevention study. The selenium intervention trial by Clarke looked at 1312 men with non-melanoma skin cancer. This cohort was randomized to selenmethionine (200 micrograms per day) or placebo. Surprisingly, at 10 years, there was a two-thirds lower chance of having clinically diagnosed prostate cancer among the men randomized to the selenium. This trial led to additional studies suggesting that selenium possessed significant anticancer properties including induction of apoptosis and cell cycle arrest in human prostate cancer cell lines.[12]

Soy and lycopene

The low incidence of prostate cancer in Asia led to an interest in the study of soy, which is highly consumed in those nations.[3] Soy is rich in isoflavones, which have been shown to induce cell cycle arrest and inhibit cancer cell proliferation in a variety of prostate cancer tumor model systems. Soy is also rich in vitamin E.

Lycopene is an additional antioxidant found, in the North American diet, primarily in tomato and tomato–based products.[13] Men who consume tomato-rich diets are at lower risk of cancers in general, including prostate cancer. Giovanucci and colleagues demonstrated that men who consume more than 10 servings of tomato per week are at one-third lower risk of getting prostate cancer.[14] There was also a dissociative benefit favoring protection from advanced and metastatic disease. This suggests that this agent may inhibit progression. Numerous in-vivo and in-vitro studies have demonstrated anticancer properties of lycopene.

Clinical trials

Level-1 evidence will be needed in order to definitively prove the efficacy of agents as chemoprevention strategies for prostate cancer. Currently, only finasteride fulfills this criterion. Two major trials are underway to assess micronutrients and prostate cancer prevention. The NCIC PRP-1 trial has completed accrual. This study has randomized 310 men with HGPIN to placebo or to a soy-based powder containing supplemental vitamin E and selenium. Serial biopsies are performed at 6, 12, 24, and 36 months. This trial should be ready to report in late 2007. SELECT is a 2-factorial randomized trial of 32400 participants. The two tested agents are vitamin E and selenium. This study will be ready to report in 2012.[15]

Conclusions

Tantalizing prospects for effective chemoprevention of prostate cancer exist. Fortunately, well-conducted randomized trials will allow us to answer many of these questions within the next 2 to 8 years. □

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