

Potential Stages for Prostate Cancer Prevention with Selenium: Implications for Cancer Survivors

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Abstract

The lack of treatment for “worried well” patients with high-grade prostatic intraepithelial neoplasia combined with issues of recurrence and hormone resistance in prostate cancer survivors remains a major public health obstacle. The long latency of prostate cancer development provides an ample opportunity to intervene with mechanistically based chemopreventive agents at various stages of disease progression. Our rationale for selenium intervention is based on current mechanistic knowledge derived solely from preclinical investigations. Clearly, there is sufficient scientific support for its entry into current clinical trials, the outcome of which will be highly valuable in assessing whether selenium can be recommended for cancer survivors. [Cancer Res 2009;69(7):2699–703]

Introduction

Prostate cancer is a major public health problem in the United States. Males have a one in six lifetime probability of being diagnosed with prostate cancer, making it the most commonly diagnosed malignancy in men. The American Cancer Society estimates that >186,000 men will have been diagnosed with prostate cancer and >28,000 men will have died from this disease in 2008 alone (1). Prostate cancer development is a multistep process, which is thought to progress from premalignant lesions or prostatic intraepithelial neoplasia (PIN) through several stages of locally invasive, metastatic, and hormone refractory disease (2). Current treatments for localized prostate cancer remain imperfect, and the cancer eventually relapses into a hormone-resistant state called androgen-independent or androgen refractory disease (Fig. 1A; ref. 3). Moreover, subjects diagnosed with high-grade PIN can be considered “worried well” because there is currently no treatment offered for this stage of disease. The lack of treatment options for the worried well and the issues of cancer recurrence and hormone-resistant disease in cancer survivors remain enormous obstacles. However, the long latency of prostate cancer presents an ample opportunity to intervene before the disease can progress to an invasive state. Thus, there is a strong need for mechanism-based naturally occurring or synthetic agents that can inhibit prostate cancer development and/or progression and for agents that can improve cancer survivorship.

Cancer survivors are people who are living with a diagnosis of cancer, including those who have recovered (4). In the United States, estimates of the number of cancer survivors have increased from ~3 million (1.5% of the population) in 1970 to over 10 million (~4% of the population) in 2002. The corresponding value for the world in 2002 was estimated to be close to 25 million and, by 2050, may approach 70 million. Evidence supports that some aspects of food, nutrition, or physical activity may modify the condition of cancer survivors; however, specific recommendations to cancer survivors cannot be made at this time (4). The purpose of this review is to evaluate the potential of different forms of selenium, an agent currently being tested in multiple clinical trials, to intervene at various stages of prostate cancer progression, and to assess whether selenium supplements can be recommended for cancer survivors (Fig. 1A).

Although the etiology of prostate cancer remains poorly understood, epidemiologic studies have revealed a number of potential risk factors for prostate cancer. Risk factors that cannot be modified include age, race, and family history (5). However, risk factors that can be modified include life-style in general, and specifically, nutritional, environmental, and hormonal factors (5). Thus, diet-derived compounds have the potential to be safe, natural inhibitors of prostate cancer. Several of these agents have been shown to have chemopreventive potential against prostate cancer including retinoids, carotenoids (e.g., lycopene), vitamin E, indole-3 carbinol, isoflavone, polyphenols, and selenium (2).

Selenium and Prostate Cancer Prevention: The Evidence

Several case-control studies have shown that selenium levels (in blood, prostate tissue, or toenail) can be inversely correlated with prostate cancer risk, although a few reports have shown no association (reviewed in ref. 6). Based on this epidemiologic evidence as well as preclinical studies and clinical intervention trials, selenium has emerged as a strong contender in the arena of cancer chemoprevention. Perhaps the most notable and exciting evidence for the protective role of selenium came from Larry Clark's Nutritional Prevention of Cancer study, which showed a 63% reduction in prostate cancer incidence, as a secondary end point, in individuals that received a daily supplement of selenized yeast (200 µg daily for a mean of 4.6 years; ref. 7). This result prompted the initiation of a number of clinical intervention trials aimed at ascertaining the effects of selenium supplementation on prostate cancer development and progression.

Although selenium compounds show promise for the prevention of prostate cancer, the mechanisms by which these agents act have

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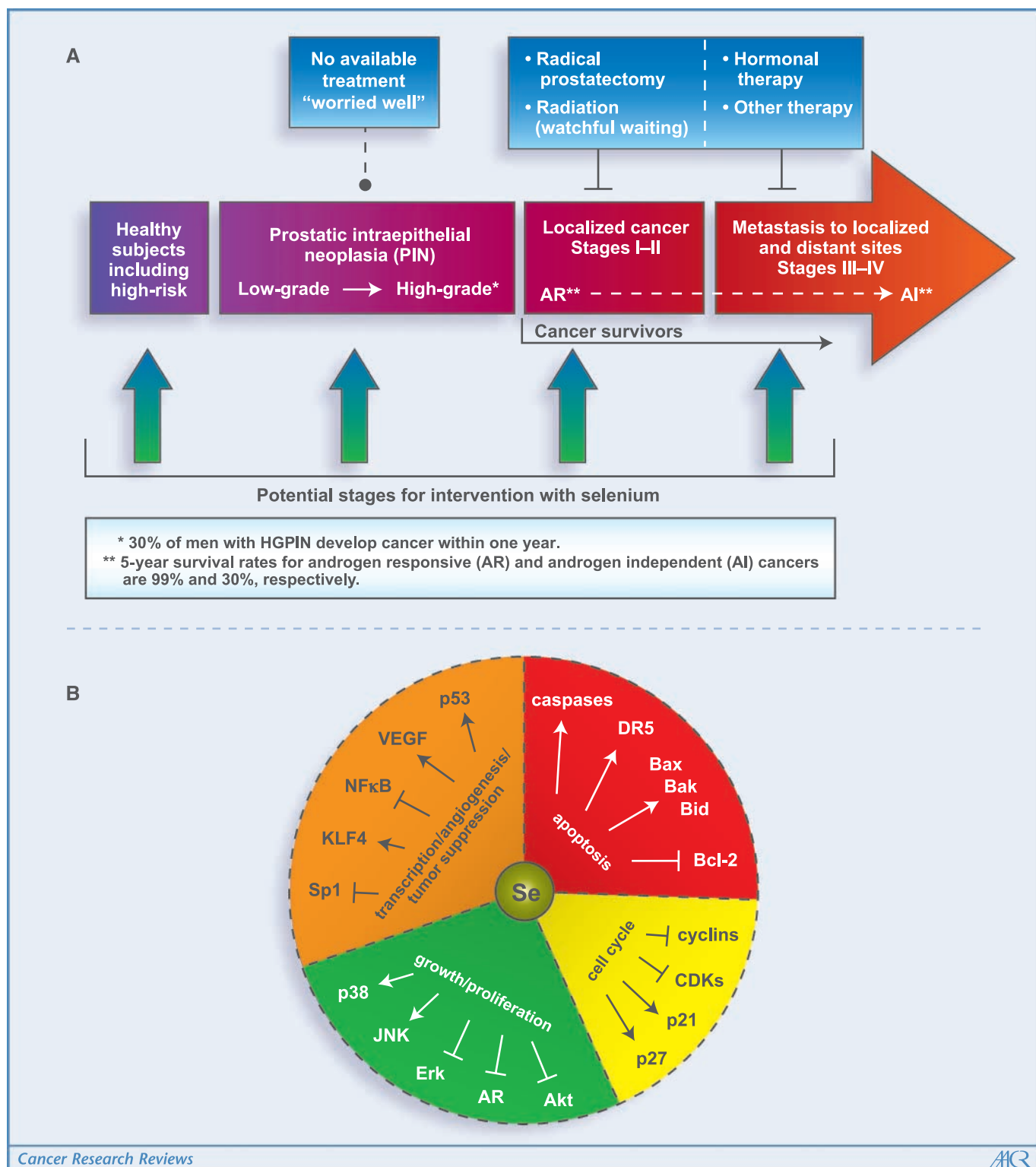


Figure 1. A, prostate cancer progression, treatment options, and opportunities for intervention with selenium. B, cellular and molecular targets of selenium (Se) *in vitro* and *in vivo* related to prostate cancer progression. HGPIIN, high-grade PIN.

yet to be fully elucidated. It is abundantly clear, however, that both dose and form are critical for the anticancer activity of selenium. Preclinical studies do, however, show that selenium compounds can modulate cellular process (cell proliferation, apoptosis, cell

cycle regulation, angiogenesis, immune response) and molecular targets [e.g., androgen receptor, Bcl2, Akt, nuclear factor-κB (NFκB), vascular endothelial growth factor (VEGF); reviewed in ref. 6] involved in prostate cancer development, progression,

recurrence, and metastasis (Fig. 1B). Therefore, it is reasonable to propose that selenium may also have a place in the arena of chemotherapy.

Analyses of selenium-induced changes in global genomic and proteomic profiles show that selenium alters several genes and proteins in a manner that can account for cancer prevention. Microarray analyses in human prostate cancer cell lines treated with various forms of selenium have identified target genes involved in a number of biological processes, including proliferation, cell cycle regulation, apoptosis, and cell adhesion (reviewed in ref. 8). These studies have also shown that androgen receptor status may influence the effect of selenium on gene expression profile in prostate cancer (8). Proteomic approaches, used to elucidate changes in prostate cancer cells associated with selenium supplementation, have also identified several novel targets (9, 10). Furthermore, a clinical study showed that short-term (3–6 weeks) supplementation of selenomethionine combined with vitamin E in men with organ-confined prostate cancer induced statistically significant proteomic pattern changes associated with prostate cancer-free status (11). As more information is compiled about the global changes that occur as prostate cancer develops and progresses, the potential merit for selenium to inhibit specific stages of the disease will likely become clearer.

Selenium Intervention in Healthy and High-Risk Men

The results of the Nutritional Prevention of Cancer trial have had a profound effect on the field of cancer chemoprevention. The trial, designed to determine the effect of selenium on the incidence of recurrent nonmelanoma skin cancer in high-risk individuals, showed an increase in incidence of basal or squamous cell carcinoma of the skin, but a 63% decrease in prostate cancer incidence, a secondary end point, in the selenium-supplemented arm of the study. This sparked the initiation of multiple trials worldwide to elucidate the role of selenium (in various forms and doses) in the prevention of prostate cancer.

Two large-scale double-blind, placebo-controlled clinical intervention trials are following the incidence of prostate cancer in healthy men supplemented with selenium: the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in the United States and the Prevention of Cancer by Intervention with Selenium Trial in Europe. The SELECT study used 200 μg daily selenomethionine, the major form of selenium in selenized yeast (SeY), alone or in combination with vitamin E, to track prostate cancer in healthy men above the age of 50 years with no history of cancer (12). Data analysis showed a nonsignificant increase in prostate cancer in men taking only vitamin E, but selenomethionine had no effect; selenomethionine, however, caused a nonsignificant increase in diabetes (12). Although the potential association of selenium with increased diabetes remains controversial, the mechanisms by which selenomethionine increased diabetes in the SELECT population deserve further exploration. The SELECT trial was halted in October 2008, but subjects will be monitored for the next 3 years. These results do not prove there is a risk from the supplement and may be “due to chance” as stressed by Dr. Scott Lippman, a cochair of the SELECT scientific steering committee [National Cancer Institute (NCI) Cancer Bulletin,

November 4, 2008]. Considering the potential limitations that the dose and form of selenium used in SELECT were wrong, it may be difficult to predict whether SeY would have been more effective than selenomethionine without credible information comparing the effects of both forms of selenium on intermediate biomarkers of prostate cancer risk. Nevertheless, based on extensive preclinical data, we believe that the protective effect of SeY in the Nutritional Prevention of Cancer trial could be due to the presence of several forms of selenium, some of which (e.g., Se-methylselenocysteine) are more effective than selenomethionine (8). Furthermore, as shown by our group, there is an ample opportunity to develop even more effective and less toxic synthetic organoselenium compounds than known naturally occurring selenium compounds such as selenomethionine. It is intriguing that the Prevention of Cancer by Intervention with Selenium Trial, which includes cohorts in three European countries (United Kingdom, Denmark, and Sweden) supplemented participants with a range of doses (100–300 μg) of SeY, the form shown to be effective in the Nutritional Prevention of Cancer trial (7, 13). A third large-scale trial, the Australian Prostate Cancer Prevention Trial Using Selenium, is being conducted in high-risk individuals. The Australian Prostate Cancer Prevention Trial Using Selenium will survey the incidence of prostate cancer in healthy males with a family history of the disease supplemented with 200 μg daily selenium (14). Although the results of these studies will not be known for several years, we conducted a pilot study in healthy adult males supplemented with 240 $\mu\text{g}/\text{day}$ SeY for 9 months to provide some insights on the role of selenium in cancer prevention. Our study showed increases in serum glutathione levels, an endogenous antioxidant, accompanied by decreases in protein-bound serum glutathione and prostate-specific antigen in individuals supplemented with SeY, suggesting that selenium may protect against oxidative stress, a risk factor for prostate cancer (15). It was intriguing to learn that in contrast to SeY, selenomethionine seems to lack an inhibitory effect on prostate-specific antigen levels (12). Furthermore, the effects of selenomethionine on levels of antioxidants in men in the SELECT trial need to be determined. In fact, a clinical pilot study is currently being conducted in our laboratory aimed at comparing the effect of selenomethionine and SeY on biomarkers of prostate cancer risk.

Two more clinical trials are examining the role of selenium in other groups of high-risk individuals: men who have had negative prostate biopsies and men with high-grade PIN. The Negative Biopsy study, which includes men who have had at least one negative sextant prostate biopsy, will be using selenium supplementation in the form of SeY (200 or 400 μg ; reviewed in ref. 16). The high-grade PIN study will determine the incidence of prostate cancer in men with biopsy-proven high-grade intraepithelial neoplasia supplemented daily with 200 μg selenomethionine (reviewed in ref. 16). The results of these studies will be critical in defining a role for intervention with selenium in high-risk individuals, for whom there is no current treatment.

Selenium Intervention in Prostate Cancer Patients

Many of the cellular processes and molecular markers shown to be modified by selenium play key roles in prostate cancer

progression. For example, there is evidence that apoptosis is down-regulated in prostate cancer and targets such as antiapoptotic protein Bcl-2 and prosurvival Akt signaling are up-regulated (5). Thus, selenium may be useful for intervention at this stage of the disease.

One clinical trial is testing the effect of selenium in prostate cancer patients, the Watchful Waiting study. This trial will follow prostate cancer progression and prostate-specific antigen velocity in men with biopsy-proven prostate cancer supplemented with 800 μg SeY/day (reviewed in ref. 16). Information gained from this study will be crucial for evaluating the potential for selenium as a chemotherapeutic agent for prostate cancer. Clearly, there is an urgent need to define the role of selenium in cancer survivors, both as a therapeutic agent and to improve the quality of life.

Implications for Cancer Survivors

The current state of prostate cancer treatment leaves ample opportunity for the development of individual or combination therapeutic strategies. Emerging evidence suggests that common treatments, such as androgen deprivation therapy, may be ineffective as a primary treatment in certain populations and an effective adjuvant to other treatments only against specific disease stages (17, 18).

Preclinical studies conducted in several laboratories, including our own, support the use of selenium in treating prostate cancer at later stages; toward this end, synthetic organoselenium compounds developed in our laboratory were superior to selenomethionine. Several of the targets shown in preclinical studies to be altered by selenium (Fig. 1B) have been clinically linked to prostate cancer recurrence (androgen receptor, Akt, NF κ B), metastasis (angiogenesis, VEGF, NF κ B), and androgen-independent disease (androgen receptor, Akt; ref. 5). Selenium-mediated alteration of such targets presents a case for the use of selenium compounds for direct or adjuvant chemotherapeutic purposes. Furthermore, intervention at the above stages is crucial to improving prostate cancer survivorship.

Selenium compounds may also be useful as adjuvant agents to new or existing chemotherapeutic agents; however, research in this area is scarce. Yamaguchi and colleagues (19) showed that methylseleninic acid could sensitize prostate cancer cells to tumor necrosis factor-related apoptotic-inducing ligand, an agent that preferentially induces apoptosis in a variety of human cancer cells. Selenium supplementation also enhances the chemotherapeutic effects of Andriamycin or Taxol in human prostate cancer cells (20).

Commentary

In this review, we chose to focus our attention on the potential stages for prostate cancer intervention with selenium. We envisioned, based on the wealth of mechanistic knowledge derived solely from preclinical investigations, that selenium can act as a chemopreventive as well as a chemosuppressive agent. We also emphasize that form (structure) and not selenium *per se* is the critical determinant of success in future small-scale clinical intervention trials. Currently, in a clinical pilot study, we are comparing the effects of SeY and selenomethionine on biomarkers of prostate cancer risk. It is of paramount importance to assess the effect of selenomethionine in subgroups of men who may have responded differently than the overall population in the SELECT study.

Clinical investigations, such as the high-grade PIN, Negative Biopsy, and Watchful Waiting studies, will provide valuable information about the potential for selenium to inhibit the occurrence of cancer in high-risk individuals and slow the progression of the disease in individuals with prostate cancer. It will be beneficial to explore the effects of selenium at stages beyond localized prostate cancer as evidence supports a potential role for various selenium compounds in inhibiting metastasis and the disease transition to androgen independence, events critical to mortality. With the goal of increasing survivorship and improving quality of life, selenium compounds should be considered for further exploration as primary or supplemental treatment options for advanced prostate cancer.

Obviously, this is an exciting field of research; however, future clinical pilot studies are needed to answer the following questions: Do men at different ages require different levels of selenium? What is the most effective form (synthetic or naturally occurring, such as selenomethionine or SeY) of selenium? Do African Americans need more selenium than white Americans? Do we have sensitive biomarkers to monitor disease progression and the efficacy of selenium individually and in combination with chemotherapeutic agents?

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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