Design and Progress of a Trial of Selenium to Prevent Prostate Cancer among Men with High-Grade Prostatic Intraepithelial Neoplasia

James R. Marshall,1 Wael Sakti,2 David Wood,3 Donna Berry,4 Catherine Tangen,5 Felicia Parker,1 Ian Thompson,6 Scott M. Lippman,7 Ronald Lieberman,8 David Alberts,9 David Jarrard,10 Charles Colman,11 Peter Greenwald,8 Lori Minasian,8 and E. David Crawford12

1Roswell Park Cancer Institute, Buffalo, New York; 2Wayne State University, Detroit; 3University of Michigan, Ann Arbor, Michigan; 4University of Washington; 5Fred Hutchinson Cancer Research Center, Seattle, Washington; 6University of Texas Health Science Center, San Antonio; 7M.D. Anderson Cancer Center, Houston, Texas; 8National Cancer Institute, Bethesda, Maryland; 9Arizona Cancer Center, Tucson, Arizona; 10University of Wisconsin, Madison, Wisconsin; 11Cancer Therapy and Research Center, San Antonio, Texas; and 12University of Colorado Health Sciences Center, Aurora, Colorado

Abstract

High-grade prostatic intraepithelial neoplasia (HGPIN) is generally regarded as a premalignant lesion that progresses toward prostate cancer. In light of the significant sequelae of prostate cancer treatment, prevention is desirable, and men with HGPIN would be suitable, high-risk subjects. There is in vitro, in vivo, epidemiologic, and human experimental evidence that selenium supplementation may protect against prostate cancer. This article introduces the rationale for, and progress to date, of a double-blind, randomized, placebo-controlled trial of selenium supplementation (200 μg/d in the form of selenomethionine), to prevent the development of prostate cancer among men with HGPIN. The trial, Southwest Oncology Group Protocol 9917, funded by a National Cancer Institute program supporting pivotal prevention trials has registered 537 patients and has randomized >380 to date. Subject accrual is expected to be completed by the fall of 2006, with trial completion in 2009. (Cancer Epidemiol Biomarkers Prev 2006;15(8):1479–84)

Introduction

Prostate cancer continues to contribute significantly to cancer morbidity and mortality in the U.S. and western industrialized countries. Diagnosed in ~200,000 Americans and causing ~30,000 deaths each year, it will affect the lives of approximately one in six men in the U.S. (1).

Prevention is clearly a rational component of our effort to limit prostate cancer’s human costs. Nonetheless, for all its importance, screening, including prostate-specific antigen (PSA) analysis and digital rectal examination, does not prevent prostate cancer. Screening aids in prostate cancer control, as it leads to earlier diagnosis and may prevent aggressive or metastatic disease; preventing prostate cancer may be more ambitious but remains an important goal.

The strategy of focusing on chemoprevention—the use of agents that block carcinogenesis—for high-risk individuals with premalignant lesions has received increased attention in recent years (2-4). Targeting those with premalignant lesions, whose risk of short-term progression to cancer is substantial, allows chemoprevention trials to be smaller and completed in a shorter time than if conducted among average risk individuals.

It is generally thought that high-grade prostatic intraepithelial neoplasia (HGPIN) is the key premalignant lesion for prostate cancer (5-7). Men with this premalignant lesion, at elevated risk for subsequent diagnosis of prostate cancer, may be ideal subjects for chemopreventive agent testing. Given the observational evidence that men with elevated selenium stores are at lower risk of prostate cancer, and the experimental evidence that selenium supplementation decreases the risk of prostate cancer and can be safely taken for an extended span of time, selenium represents a plausible first agent for prostate cancer chemoprevention focused on men with HGPIN.

The Significance of HGPIN

Research in the late 1980s and early 1990s focused on HGPIN as a premalignant lesion. Those with HGPIN have an increased risk of prostate cancer occurrence, and HGPIN cells bear a number of morphologic and phenotypic similarities to prostate cancer (5, 6). In total, the evidence suggests that HGPIN is a key intermediate in the development of prostate cancer (7-11).

An understanding of the predictive significance of HGPIN with respect to prostate cancer continues to evolve. Davidson showed that those with HGPIN are several times as likely as those without HGPIN to have cancer subsequently diagnosed; those with HGPIN have an ~50% chance of having prostate cancer diagnosed within 3 years (12, 13). Demographic data confirm that HGPIN appears earlier in high risk than in low risk populations (14).

Changes in urologic practice in the past 10 years have made it more difficult to understand the predictive significance of HGPIN. There is some debate over the extent to which HGPIN would indicate that a man is at an elevated probability of subsequent prostate cancer diagnosis (15-19). In all likelihood, HGPIN indicates a condition that is likely to progress to prostate cancer within 1 to 3 years (6, 7). Data recently collected by Steiner and colleagues confirm that those with HGPIN are at an elevated risk of metachronous cancer (20). With the risk approaching 30% after 1 year of observation, risk after 3 years may be close to or even greater than the 50% suggested by Davidson et al. (12, 13).

Selenium as a Chemopreventive Agent

In vitro and animal experiment data indicate that selenium has anticancer properties (21). A number of prospective...
observational studies have shown that those with elevated body stores of selenium, as indicated by elevated blood or toenail concentrations, are at a decreased risk of a number of cancers (22-57). These associations seem stronger for prostate than for other cancers, and they seem stronger yet for advanced or metastatic cancer (22, 24, 38, 40, 41). These associations have been interpreted as indicating that selenium intake is protective. As the selenium content of a food is less dependent on the identity of the food than on the selenium content of the soil in which it is grown, observational dietary studies cannot be based on food intake–derived indices of selenium intake (58).

In the Nutritional Prevention of Cancer study, prostate cancer was a secondary end point of a trial designed to test selenium for preventing the recurrence of non–melanoma skin cancer. The dose of selenium in the Nutritional Prevention of Cancer trial, which seemed not to induce significant toxicity, was 200 μg/d. The incidence of prostate cancer among those who received selenium was approximately half that among those who received placebo (58-60). Cautious interpretation of this finding is warranted; it was secondary, rather than primary, not anticipated in advance, and derived from a relatively small study (61). That the Nutritional Prevention of Cancer finding was based on an experiment helped provide an impetus for selenium’s inclusion in the Selenium and Vitamin E Cancer Prevention Trial prostate cancer chemoprevention trial (62). Selenium in the Nutritional Prevention of Cancer trial was incorporated into selenized baker’s yeast. The major organic component in selenized yeast is believed to be selenomethionine (63). The pharmacokinetics and safety profile of selenomethionine are well understood (21).

Study Design

The first eligibility criterion is that HGPIN must be identified by biopsy; the tissue must then be confirmed by centralized pathology review to show HGPIN and no cancer. The PSA at study entry cannot exceed 10 ng/mL, the PSA cutoff of 10 ng/mL was selected in recognition of the widespread understanding among urologists that HGPIN is associated with increased prostate cancer risk; it is recognized that the combination of HGPIN and a PSA in excess of 10, probably signifies the presence of prostate cancer missed by biopsy. The subject cannot be taking finasteride, any other drug known to affect PSA, or selenium supplements in excess of 50 μg/d.

Excluding those taking any selenium supplements would have resulted in a clearer research design in terms of study validity. Because most multivitamin supplements contain selenium, however, we decided that we would lose an excess of patients by allowing no selenium supplementation. Thus, we allowed participants to take up to 50 μg of selenium per day; this is the dose in most multivitamins. The procedure for enrolling and randomizing potential participants is defined by the number of biopsy cores drawn. When this study was initiated in 1999, the standard biopsy consisted of six or fewer cores, this biopsy was to be followed by a six-core or greater biopsy showing no cancer. Cancer on the second biopsy required exclusion. Figure 1 displays this initial enrollment schema. As biopsy procedures have changed and the number of cores drawn has increased, it has become clear that immediate follow up of a 10-core or greater biopsy showing HGPIN and no cancer is unlikely to reveal cancer (15-18). Thus, in 2002, the protocol was changed, so that men whose initial biopsy revealing HGPIN and no cancer was based on 10 or more cores done within 6 months prior to registration can be randomized as soon as centralized review confirms HGPIN. Figure 2 displays the revised enrollment schema.

The patient is randomly assigned to 200 μg/d of selenium as L-selenomethionine, or to placebo, with treatment scheduled for 3 years. The patient is to be evaluated at baseline and every 6 months, including blood sample, PSA test, digital rectal examination, and queries about symptoms, adverse events, and cancer diagnoses. Adherence is evaluated by manual pill counts. The patient is also contacted by telephone 3 months after randomization and 3 months after each clinic visit for queries about symptoms and changes.

Paperwork is minimized; the only data requests are for patient symptoms, adherence to study drug, and vitamin and mineral supplement use. Community Clinical Oncology Programs receive 1.0 cancer-control credits for the registration of each new subject and 0.3 credits for each subsequent year on study. Informed consent, approved by the cooperative groups and by each study site, describes the study protocol, informs the subject that HGPIN is believed to signal increased prostate cancer risk, and that the use of selenium in men with HGPIN is investigational.

If at any point the patient’s baseline PSA of <4 ng/mL has increased by >1 ng/mL in a year, or if a patient’s baseline PSA of 4 to 10 ng/mL has increased by >25%, or if the digital rectal examination is abnormal, transrectal ultrasound–guided biopsy is recommended. The urologist is at liberty to recommend biopsy or other diagnostic or interventional procedures as he or she sees fit. Pathology materials are

### Schema I

**Men Ages 40-80 with Biopsy Proven HGPIN Diagnosed Within 2 Years Prior to Registration**

- **Step 1. Registration**
  - HGPIN
  - Normal
  - Cancer

- **Step 2. Randomization Within 3 Months After Repeat Biopsy (Sextant or Greater)**
  - Placebo for 3 years
  - L-Selenomethionine for 3 years

- **At 3 years from randomization**
  - Sextant Prostate Biopsy

**Figure 1.** Schema I. Men ages 40 to 80 with biopsy-proven HGPIN diagnosed within 2 years prior to registration.

### Schema II

**Men Ages 40-80 with Biopsy Proven HGPIN**

- **Step 1. Registration**
  - <10 cores on initial biopsy
  - Repeat Biopsy* (Sextant or Greater)
  - ≥10 cores on Initial biopsy*

- **Step 2. Randomization Within 3 Months After Repeat Biopsy (Sextant or Greater)**
  - Placebo for 3 years
  - L-Selenomethionine for 3 years

- **At 3 years from randomization**
  - Sextant Prostate Biopsy

**Figure 2.** Schema II. Men ages 40 to 80 with biopsy-proven HGPIN.
submitted to the study pathologist (W. Sakr) for evaluation. The biopsy triggers of a PSA increase of 1 ng/mL in a year for those with a baseline level of <4 ng/mL, or of a 25% increase in a baseline of 4 to 10 ng/mL are benchmark decision guides, chosen because they are widely accepted in clinical practice.

After 3 years in the study, patients not diagnosed with prostate cancer are scheduled for transrectal ultrasound–directed sextant or greater prostatic biopsy. Patients removed from treatment early for any reason other than cancer are also to have this biopsy.

**Statistical Considerations**

Treatment assignment is randomized, double-blinded, to placebo or to selenium, stratified with dynamic balancing for age (40-60 versus 61 or older), race (African-American versus other), pre-study PSA (<4 versus 4-10 ng/mL), vitamin E supplementation (yes versus no), and initial biopsy (<10 cores versus ≥10 cores).

The target sample size of 466 patients, 233 per arm, provides 90% power, based on the following assumptions:

(a) a 3-year incidence of prostate cancer among men with HGPIN of 50%,
(b) a 33% reduction in 3-year incidence of prostate cancer,
(c) one-sided α level of 0.025
(d) 80% of randomized patients provide valid end point data.

**Biomarkers**

The rationale for this trial was that, although there is empirical evidence that selenium is protective, there is a need for the experimental validation of its effects. In addition, there is only a limited understanding of the mechanisms of its apparent effects (64). As a first step in delineating these mechanisms, we are evaluating cellular proliferation by Ki67 (65, 66) and apoptosis by terminal nucleotidyl transferase–mediated nick end labeling (67). We are using machine vision histometry to quantitatively characterize nuclear characteristics: nuclear size, roundness, staining intensity, staining variance, and intracellular staining patterns.

We are examining the degree to which proliferation, apoptosis, and morphometry in tissue from patients who receive two biopsies prior to randomization are correlated; this will provide a basic description of the repeatability of our proliferation, apoptosis, and morphometric measures. We will also analyze these factors as they are changed by selenium treatment, and we will evaluate whether the factors mediate any of the effects of selenium. We will thus examine whether changes in the factors seem to statistically explain any of the effects of treatment. Double-blind clinical trials require that these intermediate biomarkers not be examined until the end of the trial, or until the study has been unblinded with respect to the primary end point.

**Accrual Progress**

The original study design called for 50 registrations and 20 randomizations per month, which would have completed recruitment within 24 months. However, registration and randomization initially progressed a good deal more slowly than was expected.

The cooperative oncologists have been effective at bringing cancer patients into therapeutic trials and normal patients into prevention trials. They have been less effective at identifying and enrolling patients with high-risk or premalignant conditions to prevention trials. The most active clinician members of the cooperative oncology groups are medical and surgical oncologists; unfortunately, these clinicians do not see people whose most significant affliction is a premalignant lesion like HGPIN. Urologists are more likely than urologic or medical oncologists to come in contact with HGPIN; thus, we have directed attention to urologists as well as to members of the cooperative oncology groups.

Several clinicians have indicated that the recruitment reimbursement offered by the cooperative groups is not adequate to cover the cost and effort of identifying patients. With drug company reimbursement an order of magnitude greater than that offered by the cooperative groups, drug company trials often take precedence over those of cooperative groups. However, it is not readily possible to attribute changes in accrual to any specific effort.

<table>
<thead>
<tr>
<th>6-Month period</th>
<th>Registrations</th>
<th>Randomizations</th>
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<tbody>
<tr>
<td>July 2000</td>
<td>December 2000</td>
<td>12</td>
</tr>
<tr>
<td>January 2001</td>
<td>June 2001</td>
<td>39</td>
</tr>
<tr>
<td>July 2001</td>
<td>December 2001</td>
<td>48</td>
</tr>
<tr>
<td>January 2002</td>
<td>June 2002</td>
<td>57</td>
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<tr>
<td>July 2002</td>
<td>December 2002</td>
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<tr>
<td>July 2003</td>
<td>December 2003</td>
<td>67</td>
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<td>January 2004</td>
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<tr>
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<td>34</td>
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<tr>
<td>July 2005</td>
<td>December 2005</td>
<td>44</td>
</tr>
</tbody>
</table>

**Figure 3.** Randomization and baseline study data.
As Table 1 illustrates, only 12 people were registered and 2 were randomized during the first 6 months. By the end of the first year, only 51 had been registered and 25 had been randomized.

Between 2000 and 2003, study leaders were repeatedly summoned to meetings of the Southwest Oncology Group Data Safety and Monitoring Board to defend continuation, rather than closure, of the study.

We have employed several strategies to increase enrollment. We directed e-mails and telephone reminders to Southwest Oncology Group principal investigators, urologists, clinical research associates, and nurses, and provided reminders at group meetings. We arranged for the Chair of the Southwest Oncology Group Genitourinary Committee (E.D. Crawford), for the Director of the Southwest Oncology Group (C. Coltman), and for an influential leader of the American Urological Association (I. Thompson) to send letters urging greater effort. We opened the study to other major cooperative oncology groups and several Veteran's Administration Medical Centers. We arranged for participants in the Prostate Cancer Prevention Trial, whose end-of-study biopsy revealed HGPIN, to be invited to join this trial. We placed paid advertisements in journals of the American Urological Association, and in trade periodicals The initial enrollment stipend was U.S.$500; study sites also receive U.S.$200 for each year a subject is on study. In 2002, we increased this initial enrollment stipend from U.S.$500 to U.S.$1,000. Gradually, these efforts and changes led to increased study accrual. As Fig. 3 shows, 370 of the study goal of 466 patients have been randomized after a recruitment period of 4 years. Given the present rate of recruitment, enrollment should be complete by the fall of 2006, with study completion anticipated in 2009.

Table 2, describing the first 280 subjects randomized, shows that the two study groups are well balanced in terms of age, race, pre-study PSA, the use of vitamin E supplements, and the biopsy procedure or sequence that brought the participant into the study. The differences observed in central tendency and in distribution are insignificant, both in statistical and substantive terms, which suggests that confounding of any effect of selenium treatment by the stratification variables is unlikely.

Table 3. Baseline plasma selenium levels for HGPIN patients randomized to treatment groups 1 or 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 142)</th>
<th>Group 2 (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>147.5</td>
<td>151.7</td>
</tr>
<tr>
<td>Median</td>
<td>145.4</td>
<td>149.3</td>
</tr>
<tr>
<td>SD</td>
<td>31.1</td>
<td>36.7</td>
</tr>
</tbody>
</table>

Table 3 shows that the baseline plasma selenium concentrations of both groups are similar, both in mean and dispersion. These levels are considerably higher than those observed in the Nutritional Prevention of Cancer trial: the mean baseline concentration in that study was 114 ng/mL (59). The levels are well above even the mean of 123 ng/mL estimated for the U.S. population (68). The distributions about the means are fairly symmetric, as can be seen by the proximity of each mean to the median.

Table 4, completed on a subset of patients, shows that temporal lags in enrollment—between the initial biopsy and registration, between the initial biopsy and randomization, and between the second biopsy and randomization—are similar for the two study groups.

A number of characteristics of trial progress, such as changes in blood selenium status of experimental subjects and controls, and the proportions of subjects with a valid end point, with cancer, or with prostate cancer would be of interest. Unfortunately, very strict blinding is maintained for cooperative group studies with extended recruitment and treatment, so that such information will not be available until the end of the trial.

Conclusion

HGPIN may offer an important opportunity for chemopreventive intervention. Men with HGPIN, which seems to be a significant premalignant lesion, are at substantially increased cancer risk; thus, chemical intervention can be more readily defended than if those individuals were at average risk. Among potential chemopreventive agents, selenium seems, given its safety and the confluence of epidemiologic, experimental, in vitro and in vivo data, to be a leading candidate. The trial is premised on the need for experimental validation of the accumulating evidence.

Accrual to this study has been difficult; a great deal of effort has been denoted to raising trial awareness and encouraging cooperative groups to enroll patients. These efforts seem to have borne fruit; at this point, >80% of the study participants have been randomized. It seems likely that enrollment will be completed in the fall of 2006. Randomization is working well, balancing experimental and placebo study groups in characteristics believed predictive of prostate cancer.


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