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The principal purpose of this trial is to assess the potential for the essential nutrient selenium (Se) to modulate biomarkers of prostate cancer between initial diagnostic biopsy and radical prostatectomy. The scope of work is to randomize at lest 110 participants to either a placebo or Se dosages of 200ug, or 400ug/day. Recruitment is continuing as a result of a no-cost extension. A total of 90 subjects have been randomized. Of these, 82 have completed the study, 7 dropped before completing the study, and 1 is in the process of completing the study.

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INTRODUCTION

The principal purpose of this trial was to assess the potential for the essential nutrient selenium (Se) to modulate biomarkers of prostate cancer. The rationale for this trial was based on the results of the Nutritional Prevention of Cancer (NPC) Trial. In that study, a double-blind, randomized clinical trial, a 63% reduction in prostate cancer incidence was observed during the initial 10 years of follow-up in participants receiving 200 μg of Se compared to those receiving a placebo (JAMA 276:1957-63 (1996)). Objective: The primary endpoint for this trial consisted of changes in biomarkers between tissues obtained at the initial diagnostic biopsy and radical prostatectomy. Relevance: This study has the potential to provide direct evidence for the activity of selenium in prostate tissue. Methods: A study population of prostate cancer subjects scheduled for prostatecomy was selected so that prostate tissue can be examined for biomarker changes before and after supplementation with selenium. This trial randomized participants to either a placebo or one of two Se dosages: 200 μg, or 400 μg/day. The goal of this trial was to randomize at least 110 patients, in order to have 80% power to detect an effect size of 0.66 standard deviations. Progress: A total of 90 subjects were randomized. Of these, 82 completed the study, 7 dropped before completing the study, and 1 is in the process of completing the study (surgery scheduled for 2/16/04).

PROGRESS

Task 1: Training and Preparation for Trial (Months 1-36 - Ongoing)

- A database was created for this study and staff at the Tucson Coordinating Center (TCC) were trained in its use. Routine reports are available to assist staff in tracking subjects from initial referral through randomization.
- Staff at TCC and study sites were trained to explain the study requirements to subjects and to inquire about adverse effects. TCC laboratory staff established routines to ensure that the proper blood kits for the various tests performed after each visit were used.
- Randomization codes were prepared and appropriate staff were blinded to blood tests results that might reveal the subject's treatment.
- Pills were dispensed according to randomization codes by staff blinded to treatment status.
- An "Initial Questionnaire", "Follow-up Study Visit" questionnaire, and "Urological Symptoms Questionnaire" were developed. A food frequency questionnaire developed by the Fred Hutchinson Cancer Center in 1992 was also administered to study subjects.
- All appropriate laboratory materials to obtain, handle, store, and prepare blood and tissue samples for analyses were obtained.
- Training was ongoing as new sites were added to the study.

Task 2: Subject Recruitment, Enrollment (Months 3-34- Ongoing***)***

Recruitment for this study was slow despite frequent contact with physician offices. It appears that participating physicians overestimated the original number of eligible patients they could provide. In addition, we initially imposed a recruitment requirement for frozen tissue that led many urologists to withdraw from the study. Since we eliminated this requirement, we were able to reestablish participation from many of the urologists who originally agreed to refer patients. Still, actual referrals were far lower than original estimates. Factors which contributed to the slow pace of recruitment include:

- *Time for Patient Recruitment*. The window of opportunity for enrolling subjects to this study – the three to six week period between diagnosis and surgery – limits the type of

recruitment methods available. These subjects were identified as soon as possible after diagnosis during a time when they were struggling with the emotional impact of their diagnosis. Advertisements and health fairs, which have yielded some subjects for our other selenium and prostate cancer studies, were ineffective for this study.

- *Inadequate Number of Referring Physicians.* During the early stages of the study, the primary focus was on Tucson urologists. Dr. Bruce Dalkin has been the greatest source of subjects for this study. Urologists at remote sites (Dr. Martha Terris at the Palo Alto VA in Palo Alto, CA, and Dr. Christopher Julian at the Urological Associates of Central California in Fresno, CA) also enrolled patients on this study.
- *Protocol Changes.* Protocol changes were made in March and July 2000. The first change eliminated the requirement for frozen tissue samples and had a positive effect on recruitment. The protocol changes made in July 2000 significantly slowed the rate of physician referrals due to delays in securing IRB approval for these complex changes. These changes eliminated the follow-up portion of this study and made the changes in tissue biomarkers the primary endpoint. These changes were approved by HSRRB.
- *Documentation requested by HSRRB.* Due to the various IRB submissions and delays including events related to September 11, we were not allowed to open new sites which would have accelerated recruitment. Approvals were eventually granted by HSRRB for all participating sites.

Of the 90 randomized subjects, there are 4 Hispanics, 2 African American, 1 Asian, 79 Caucasian, 1 other, 3 not given.

Task 3: Baseline Data Collection (Months 3-34- Ongoing)

At time of enrollment, all participants were presented with a standard set of questionnaires and forms. This set included an informed consent form and a baseline questionnaire that asked detailed information about previous and current illnesses, medications (including OTC and herbal supplements or vitamins), family history of cancer, and lifestyle. In addition, dietary information was gathered using a well validated Food Frequency Questionnaire. The TCC collected biopsy tissue, medical records, a registration form, and a blood sample.

The following table summarizes data collected to-date:

Data Type	
Baseline questionnaire	91
Follow-up Questionnaire	127
FFQ	85
Blood sample	200
Urological Symptoms Questionnaire	53*
Pathology Reports	168
Frozen tissue sample	59

*Discontinued under revised protocol

Task 4: Randomization (Months 4-34- Ongoing)

There was no run-in period for this study. Subjects were randomized at the time of enrollment. Due to the short time subjects were required to participate in the study, randomization of new patients continued throughout the study period.

Task 5: Follow-Up (Months 4-36- Ongoing)
Although the original statement of work called for selenium supplementation and follow-up through the end of the grant period, we limited supplementation and follow-up to the completion of prostate surgery in accordance with the revised study objectives. Under the revised study design, participants had their blood drawn and completed a follow-up questionnaire just prior to their prostate surgery. The follow-up questionnaire was designed to document pill compliance and possible adverse events.

Task 6: Laboratory Analyses (Months 3-30- Ongoing***)***
The following table describes the schedule for blood collection and analyses:

	Initial	Pre-Surgery
CMP	X	
Selenium	X	X
Lycopene	X	
Alpha Tocopherol (Vitamin E)	X	

Other analyses are ongoing as outlined below.

Task 7: Data Entry (Months 3-36- Ongoing***)***
All forms, questionnaires, and laboratory results were entered into the database by the trained coordinators and laboratory assistants as they were received. Data was audited semi-annually during Quality Control reviews.

Task 8: Data Analyses and Report Writing (Ongoing)
The last participant will complete the Preprostatectomy study on February 16th, 2004. Therefore, the study has not been unblinded and analyses have not been completed. Immunohistochemical analyses for tissue biomarkers including ki-67, p53, bcl-2, IL-6, P504S and E-cadherin are ongoing. Tissue and serum analyses will be completed by March 31st, 2004 at which time a manuscript will be prepared and submitted for publication. Data will be provided as they are completed.

- IL-6, a cytokine downstream of the transcription factor nuclear factor kappa B (NFκB), has been shown to be upregulated in prostate cancer [1]. Hobisch and colleagues demonstrated that IL-6 is expressed at a low level only by basal cells in normal prostate tissue BPH. However, in prostate cancer, expression is increased and is also seen in atypical intraluminal cells.
- Immunohistochemical analyses for α-methyl-Coa Racemase (P504S) willalso be performed. P504S is an enzyme involved with metabolism of branched chain fatty acids in the peroxisome. This enzyme is overexpressed in prostate cancer tissue and some studies have suggested that the increase in expression pattern appears to correlate with Gleason grade [2].
- Expression of the adhesion molecule, E-cadherin, will also be examined. E-cadherin is involved with cell-cell interaction and expression has been shown to be lost with progression of prostate cancer [3, 4].

KEY RESEARCH ACCOMPLISHMENTS

Analyses have not been completed.

REPORTABLE OUTCOMES

Analyses have not been completed.

CONCLUSIONS

This innovative Phase II clinical trial, the *Chemoprevention Trial of Selenium and Prostate Cancer*, will provide new information on biological endpoints in a population of ethnically diverse men with localized PCa prior to the initiation of other therapy. The effect of selenium supplementation on study participants who have undergone surgical resection of the prostate will provide insight into the possible effect of selenium supplementation on biomarkers for PCa and potential mechanisms of Se action. This research can provide direct evidence for the effects of selenium on prostate tissue by examining this tissue before and after selenium supplementation.

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