Research Article

Cancer Prevention Research

Oral Selenium Supplementation Has No Effect on Prostate-Specific Antigen Velocity in Men Undergoing Active Surveillance for Localized Prostate Cancer

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Abstract

The Nutritional Prevention of Cancer trial showed a 52% lower incidence of prostate cancer in men supplemented with selenium. As a result, our study was designed to assess whether selenium supplementation attenuates the progression of prostate cancer. A phase 2 randomized, double-blind, placebo-controlled clinical trial was conducted in men with localized nonmetastatic prostate cancer who had elected to forgo active treatment and be followed by active surveillance. A total of 140 men were randomized to placebo (n = 46), 200 μg/d (n = 47), or 800 μg/d (n = 47) selenium p.o. (as selenized yeast) and followed every 3 months for up to 5 years. Prostate-specific antigen (PSA) velocity was used as a marker of prostate cancer progression and was estimated using mixed-effects regression. Adjusting for age, body mass index, baseline selenium, smoking, baseline PSA, race, PSA method, and Gleason score, PSA velocities for the 200 μg/d and 800 μg/d treatment groups were not statistically significantly different from placebo (P = 0.32 and P = 0.61, respectively). In the highest quartile of baseline selenium, men supplemented with 800 μg selenium showed statistically significantly higher PSA velocity as compared with placebo (P = 0.018). Selenium supplementation did not show a protective effect on PSA velocity in subjects with localized prostate cancer. On the contrary, supplementation with high-dose selenium was observed to be a risk factor for increased PSA velocity in men with high baseline plasma selenium concentrations. *Cancer Prev Res; 3(8); 1035–43. ©2010 AACR.*

Introduction

With the exception of nonmelanoma skin cancer, prostate cancer is the most commonly diagnosed cancer in U.S. men. In 2009, approximately 192,280 men have been diagnosed with prostate cancer, resulting in almost 27,360 deaths (1). Radical prostatectomy and radiotherapy can be curative but these therapies carry a significant risk of morbidities including incontinence (up to 47%; ref. 2), erectile dysfunction (up to 89%; ref. 2), urinary strictures (up to 17%; ref. 3), and radiation proctitis (up to18.7%; ref. 3). Furthermore, the natural history of prostate cancer is extremely variable. Some men will live 20 or more years untreated and die from other causes while other men succumb to the illness rapidly (4). The significant incidence and mortality rates coupled with marked variability in biological behavior make the management of localized prostate cancer a challenge.

Over the past several decades, significant efforts have been made to identify sensitive and specific markers for diagnosing prostate cancer and predicting aggressiveness of the disease. Tumor volume, histologic grade, serum prostate-specific antigen (PSA) levels at diagnosis, rate of change of PSA before diagnosis, evidence for local tumor invasion, and overall patient health are established criteria associated with disease aggressiveness in localized prostate cancer. However, no standardized criteria have been established for selecting a specific management approach (5–7).

Because of this high degree of variability in the clinical behavior of prostate cancer, observation (commonly termed "active surveillance," "watchful waiting," or "delayed therapy") is a justifiable management approach (8–10). Surveillance can be entirely palliative with no consideration of a potentially curative intervention, or the objective could be to ultimately consider potentially curative interventions when the tumor displays characteristics indicative of progression (10). In the latter approach, there are no defined standards for initiating therapy. Men also frequently elect to receive therapy even in the absence of progression. All of these factors contribute to the inherent challenges in a controlled study of this population.

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The precise number of prostate cancer patients electing to initially forgo front-line therapy and elect active surveillance is not certain, but it is not an uncommon approach. Because of this, these men are potential study candidates for dietary or lifestyle interventions, such as selenium supplementation, which carry a relatively low risk of morbidity (10–12).

Selenium has shown promise as a chemopreventive agent for prostate cancer in ecological studies and clinical trials (13). The exact mechanism by which selenium may inhibit prostate cancer is not known, but it may support an antioxidant redox status as an essential cofactor for glutathione peroxidase (14). Other potential mechanisms of action include regulation of selenoprotein production, increased activity of proteins involved in apoptosis, and control of cell cycle regulatory proteins. Selenium has also been shown to inhibit transcription factors that play a role in carcinogenesis, such as NF-κB and activator protein-1 (13).

The Nutritional Prevention of Cancer (NPC) trial was a phase 3 randomized, double-blind, placebo-controlled clinical trial carried out to investigate the effect of selenium supplementation on the recurrence of nonmelanoma skin cancer (15). Although selenium supplementation did not lower the incidence of nonmelanoma skin cancer, secondary analysis indicated that men in the selenium arm had 52% lower incidence of prostate cancer as compared with the placebo arm after 13 years of follow-up (16). Consequently, our study was initiated to test the effects of selenium supplementation on men with organ-confined, non–high-grade prostate cancer who had elected to be followed by active surveillance as their principal management approach. The primary objective of this study was to investigate whether selenium would prevent the progression of clinical prostate cancer as measured by its ability to effectively modulate a prostate cancer biomarker, specifically the rate of change of serum PSA measurements over time (i.e., PSA velocity).

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a phase 3 randomized, double-blind, placebo-controlled clinical trial conducted to assess whether supplementation with 200 μg/d selenium and/or 400 IU/d vitamin E would prevent prostate cancer in average-risk men after a follow-up of 7 to 12 years (17, 18). Interim review indicated that selenium, with or without vitamin E, did not prevent prostate cancer in this population (18). The current study differs from the very definitive SELECT trial in three important aspects. The treatment agent used for SELECT was selenomethionine, whereas the current trial used selenized yeast, the same form of selenium that had shown negative association with prostate cancer incidence in the NPC study. Secondly, SELECT recruited men that had not been diagnosed with prostate cancer, whereas the current study was conducted in a population of men with biopsy-proven prostate cancer. Lastly, the main outcome measure for SELECT was diagnosis of prostate cancer, whereas for the current trial, it was change in PSA values over time (PSA velocity).

Materials and Methods

Study design

This is a randomized, double-blind, placebo-controlled, multicenter, phase 2 clinical trial designed to investigate the effects of two doses of selenized yeast versus placebo on the progression of clinically localized non–high-grade prostate cancer as determined by serum PSA changes over time. Subjects were removed from the study if, in the clinical judgment of the subject's urologist, the subject's PSA velocity or clinical course warranted initiation of therapy. Eligibility criteria for this trial required subjects to have biopsy-proven localized (nonmetastatic) prostate cancer documented within 48 months before enrolling in the trial, a Gleason score of <8, a serum PSA level of <50 ng/mL, age <85 years, and a life expectancy of ≥3 years. All subjects had elected to forgo front-line therapy and had elected to be followed by active surveillance. In addition, subjects had to limit daily selenium supplementation to no more than 50 μg from nonstudy sources. The protocol and informed consent forms were approved by the University of Arizona Institutional Review Board (IRB; IRB# 97-0395-01) and the IRB at each respective clinical site. Detailed methods of this trial have been described in an earlier publication (13).

Recruitment and randomization

Subjects were recruited from urology offices at nine sites in the United States (Annapolis, MD; Little Rock, AR; Shreveport, LA; Chicago, IL; Columbus, OH; Palo Alto, CA; Tucson, AZ; Chapel Hill, NC; and Fresno, CA). Recruitment began August 1, 1998 and ended on July 31, 2003. Subjects meeting the inclusion criteria who signed the IRB-approved informed consent form and successfully completed a 30-day run-in period with adequate adherence to the protocol were randomized to receive placebo, 200 μg/d selenium, or 800 μg/d selenium using a computer program. Treatment group assignment stratification was based on low (≤4) versus high (5-7) Gleason scores. At randomization, a 6-month supply of caplets was dispensed to each subject. Subjects were followed quarterly for up to 5 years.

Study agent and adherence

The study agent used in this trial was high-selenium yeast (IND #66,698), provided by Cypress Systems. It was identical to the agent used previously by Clarke et al. in the NPC study that showed 52% lower incidence of prostate cancer in the selenium arm versus placebo (16) and has also shown to have a low toxicity profile (19). The dietary reference intake for selenium for adults is 55 μg/d (20). All selenium and placebo caplets were identical in size and weight and were coated with titanium oxide to ensure identical appearance, taste, and smell. The drug supply was stored in a monitored, climate-controlled environment with controlled access.

Before randomization, placebo was dispensed and subjects were instructed to take one pill per day for

30 consecutive days to assess adherence to the administration schedule. Participants then returned to the clinic to be assessed and randomized to one of the three treatment groups. Participants with 80% or greater adherence measured by pill counts were considered eligible for randomization. During follow-up, returned caplets were counted and protocol adherence was ascertained at 3-month intervals. Mean percent adherence was calculated as [(number of pills dispensed – number of pills returned) / (daily prescribed dose)] / number of days in evaluation period × 100.

Biological sample collection and processing

Blood was drawn at baseline and at each subsequent visit to measure plasma selenium concentration, PSA, a comprehensive metabolic panel (including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatinine, and bilirubin), and a complete blood count. Additional serum samples were frozen at –80°C for future study. At the enrollment visit, questionnaires were administered to record demographic characteristics, medical history, selenium toxicity information, and urological symptoms to verify eligibility. Questionnaires were administered at each visit to capture changes in subject health status since the previous visit. Paraffin-embedded prostate tissue samples from the subject's qualifying biopsy were requested from the subject's physician and compiled in a biospecimen repository.

Total selenium content was measured by automated electrothermal atomic absorption spectrophotometry using a Perkin-Elmer Zeeman 3030 instrument. Serum PSA levels were measured using the Abbott tumor markers assay module on an IMX analyzer (Abbott Diagnostics). In March 2005, Abbott Diagnostics replaced the AxSYM-PSA assay with the Total AxSYM-PSA assay, a combined assay for free and bound PSA. A variable adjusting for this change in the PSA assay was used in all statistical models to account for any effects this change might have on PSA velocity. Both assays are approved by the Food and Drug Administration for use in the United States.

Study end point

The primary objective of this study was to assess whether selenium can prevent the progression of clinical prostate cancer as measured by effective modulation of a prostate cancer biomarker. Rate of change of serum PSA measurements over time (PSA velocity) was the primary biomarker of interest, estimated using mixed-effects models (21) that used data from serial measurements taken at baseline and during each quarterly follow-up visit.

Evaluation of adverse events

Expected adverse events included brittle nails, brittle hair, garlic breath, and liver/kidney function test abnormalities (17–19). Based on prior observations (19), additional potential expected adverse events included cataracts, glaucoma, and nonmelanoma skin cancers. Collection of adverse event reporting data occurred at each study visit. All data were entered on Case Report Forms for subsequent entry into the database.

Data and safety monitoring

An external Data and Safety Monitoring Committee (composed of unassociated, non–University of Arizona faculty with expertise in the areas of basic science, medicine, and biostatistics) was established before implementation of the study. This committee was responsible for reviewing protocol amendments, informed consent forms, subject accrual and retention rates, adverse events, and data analysis reports. Data and Safety Monitoring Committee meetings were held twice yearly.

Statistical analysis

Analysis was based on an intent-to-treat paradigm. A mixed-effects model with patient-level random effects was used to assess the effect of selenium on PSA velocity in the three treatment groups. This model allows random intercept and slope for individual subjects in the trial and accounts for correlated data due to repeated measures over time. PSA values were transformed using ln(PSA + 1) to correct for nonlinearity over time and to stabilize their variance. Subjects were treated as random effects, whereas treatment and time were treated as fixed effects. An interaction term between treatment group and the time variable was created to assess differences in PSA velocity between groups. Various correlation structures were tried while modeling these data. Power estimate for this study was derived from a linear mixed-effect model via Monte Carlo simulation. For a sample size of 140, with α of 0.05, using a two-sided test, the study was anticipated to have 90% power to detect a 31% reduction in PSA velocity, resulting in a false-negative rate of 10%.

Mixed-effects models were adjusted for duration of subject on study, race, baseline plasma selenium, age, body mass index (BMI), pack-years of smoking at baseline, type of assay used to estimate PSA, and Gleason score. BMI was calculated as weight in kilograms divided by square of height in meters (kg/m^2). Pack-years of smoking were calculated as packs of cigarettes smoked per day multiplied by the number of years the subject had been smoking at baseline. Because the majority of subjects were Caucasian (88%), race was dichotomized as "Caucasian" or "non-Caucasian." Analyses stratified by quartiles of baseline selenium were also done to assess if the effect of selenium supplementation differs by baseline selenium level. A significance level of 0.05 was used for main effects as well as interaction terms. Comparisons of adverse events across groups used Fisher's exact test. Kaplan-Meier survival estimates were generated to determine if time to treatment (surgery or radiation) was significantly different between the three treatment groups. Analyses were conducted using Stata10 (StataCorp IC) and verified using SAS 9.1 (SAS Institute, Inc.).

Results

Patient characteristics

Selected baseline characteristics of subjects, by treatment groups, are displayed in Table 1. The mean age of subjects was 72.8 years and the mean BMI was 26.9 kg/m^2. The majority of subjects were Caucasian (88%). Most participants (90%) had a Gleason score of >4. Mean PSA, plasma selenium, and pack-years of smoking at baseline were 7.9 ng/mL, 134 ng/mL, and 23 pack-years, respectively. Gleason score for one subject and pack-years of smoking data for two subjects were unavailable.

Treatment groups were balanced for all baseline characteristics except for BMI. Although BMI differed significantly between the 200 μg/d and the 800 μg/d selenium treatment groups, this difference might not be clinically significant, as the mean BMI for both groups (25.7 and 27.8 kg/m^2) falls in the overweight category as defined by WHO and NIH (22). However, models were adjusted for baseline BMI to account for this difference.

Recruitment and randomization

Figure 1 describes patient recruitment and randomization. One hundred ninety-nine subjects were recruited. On review of subject records, 19 (9.5%) subjects were found to be ineligible. One subject (0.5%) elected to withhold consent, 7 (3.5%) did not complete the run-in period satisfactorily, and 32 (16%) dropped after signing the consent but before being randomized. The remaining 140 (70.35%) subjects were randomized to receive placebo (n = 46), 200 μg/d selenium (n = 47), or 800 μg/d selenium (n = 47). Twenty-nine subjects (20.7%) remained in follow-up for the full 5 years, 27 (19.3%) ended follow-up prematurely because of study discontinuation, and 45 (32%) were withdrawn because they met the criteria for study end point. Six subjects (4.3%) withdrew from the study due to concurrent illness not related to prostate cancer, 5 subjects (3.6%) died during the course of the study due to reasons not related to prostate cancer, 14 (10%) withdrew due to study-related reasons, and 14 (10%) withdrew for unrelated causes. None of the treatment groups were significantly different from placebo in terms of study completion or withdrawal. The mean, SD, and median months of follow-up were 36.3, 20.7, and 38.4 in the placebo group; 33.4, 20.3, and 33.3 in the 200 μg/d selenium group; and 33.3, 23.3, and 33.8 in the 800 μg/d selenium group, respectively. Duration of follow-up was not significantly different between the three treatment groups (P = 0.7411).

Effects of selenium on PSA

Mean adherence for the placebo, 200 μg/d selenium, and 800 μg/d selenium treatment groups was 90%, 90%, and 89% respectively, with no statistically significant difference between the groups (P = 0.695). Mean PSA velocities estimated by the mixed-effects model are shown in Table 2. The median PSA doubling times for the three treatment groups were 6.24, 6.98, and 8.45 years, respectively. Point estimates and 95% confidence intervals for differences in PSA trajectories of the 200 μg/d selenium and 800 μg/d selenium treatment groups as compared with placebo were −0.03 (−0.09-0.03) and −0.02 (−0.08-0.04), respectively. Thus, after adjusting for baseline plasma selenium concentration, age, race, BMI, pack-years of smoking at baseline, baseline PSA, type of assay used to estimate PSA, and Gleason score, the PSA velocities for the 200 μg/d selenium and 800 μg/d selenium treatment groups did not differ significantly from placebo or from each other (Fig. 2). Unstructured correlation structure was used to model these data.

Analyses stratified by quartiles of baseline selenium were done to assess if selenium supplementation had a differential effect on PSA velocity (Fig. 3). In the lower three quartiles, selenium supplementation was nonsignificantly associated with placebo. In the fourth quartile, the trajectory of PSA for the 200 μg/d selenium treatment group was not statistically significantly different than that shown by subjects on placebo (P = 0.243), whereas the trajectory of PSA for men in the 800 μg/d selenium treatment group was statistically significantly higher than that for men on placebo (P = 0.018). This suggests that supplementation with a relatively high dose of selenium may have deleterious effects on PSA

Table 1. Baseline descriptive statistics by treatment group

Variable	Total population (n = 140)	Placebo (n = 46)	Se 200 μg (n = 47)	Se 800 μg (n = 47)	P
Age (y), mean (SD)	72.8 (6.65)	72.9 (6.5)	73.6 (6)	72 (7.5)	0.50
BMI (kg/m^2), mean (SD)	26.9 (4.1)	27.0 (4.3)	25.7 (3)	27.8 (4.6)	0.03
PSA (ng/mL), mean (SD)	7.9 (6.2)	7.4 (5.6)	8.0 (7.0)	8.3 (6.2)	0.79
Baseline selenium (ng/mL), mean (SD)	134.5 (41.5)	127.9 (17.3)	129.8 (21.3)	145.7 (65.3)	0.07
Pack-years, mean (SD)	23.3 (29.8)	22.3 (27.6)	21.2 (27.6)	26.5 (34.1)	0.67
High Gleason score (>4), n (%)	125 (89.93)	41 (91.11)	41 (87.23)	43 (91.49)	0.75
Caucasian, n (%)	123 (87.86)	40 (86.96)	42 (89.36)	41 (87.23)	0.93

NOTE: To calculate the P value, ANOVA was used for continuous variables and χ^2 for categorical variables.

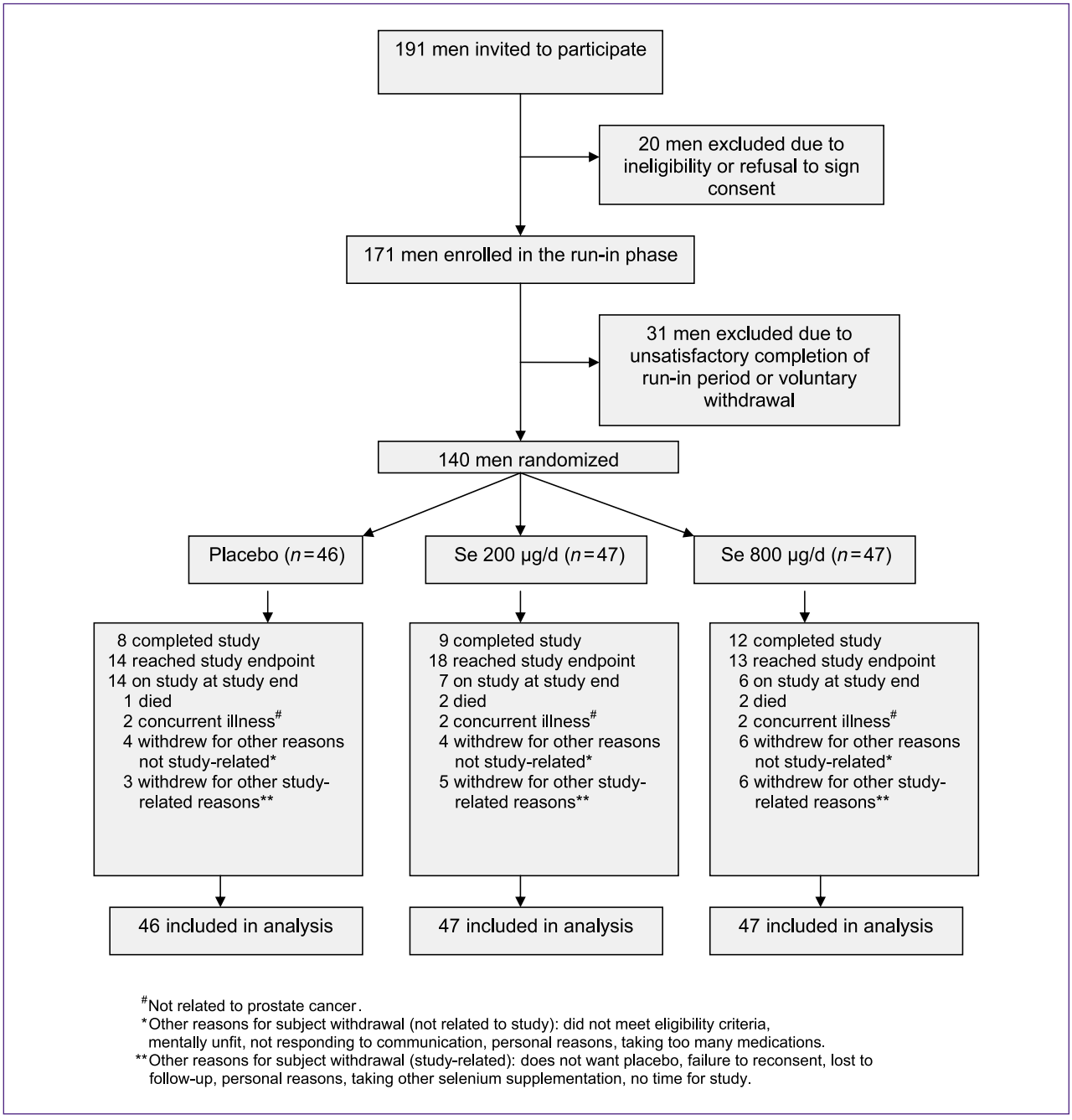

Fig. 1. Participant cohort distribution.

velocity in men already at modestly high levels of plasma selenium. Kaplan-Meier survival estimates indicate that time to treatment was not significantly different for the two selenium-supplemented groups as compared with placebo (Fig. 4).

Adverse events

Of the 140 randomized participants, there was 1 death (2.2%) in the placebo group, 2 deaths (4.3%) in the 200 μg/d selenium treatment group, and 2 deaths (4.3%) in the 800 μg/d selenium treatment group (P = 0.99; Table 3). With respect to serious adverse events, there were 14 (30.4%) in the placebo group, 17 (36.2%) in the 200 μg/d selenium treatment group, and 13 (27.7%) in the 800 μg/d selenium treatment group (P = 0.69). None of the serious adverse events were study related. Time to onset of the first serious adverse event for each participant was the same in all treatment groups (P = 0.73). There

Table 2. Estimated PSA velocities (ng/mL/y) at 1-y intervals

	Total	Placebo	200 μg/d	800 μg/d
End of year 1	0.25	0.24	0.19	0.19
End of year 2	0.27	0.26	0.20	0.21
End of year 3	0.29	0.28	0.22	0.23
End of year 4	0.31	0.31	0.23	0.25
End of year 5	0.34	0.33	0.24	0.27
P value for difference in PSA trajectory as compared with placebo		Reference	0.328	0.613

were 4 (8.7%) new cancers diagnosed (excluding prostate and skin cancers) in the placebo group, 3 (6.4%) in the 200 μg/d selenium treatment group, and 2 (4.3%) in the 800 μg/d selenium treatment group ($P = 0.64$). Seven incidences (15.2%) of cataract/glaucoma in the placebo group were diagnosed, 6 (12.8%) in the 200 μg/d selenium treatment group, and 9 (19.2%) in the 800 μg/d selenium treatment group ($P = 0.71$). There were 10 (21.7%) nonmelanoma skin cancers in the placebo group, 13 (27.7%) in the 200 μg/d selenium treatment group, and 7 (14. 9%) in the 800 μg/d selenium treatment group ($P = 0.32$). The incidences of brittle hair and brittle nail (grade 1 or 2 and possibly, probably, or definitely related to the intervention) were 10 (21.7%), 6 (12.8%), and 8 (17.0%; $P = 0.51$) and the incidences of garlic breath and liver/kidney function test abnormalities (grade 1 and possibly, probably, or definitely related to the intervention) were 5 (10.9%), 0 (0.0%), and 4 (8.5%; $P = 0.05$) in the placebo, 200 μg/d selenium, and 800 μg/d selenium treatment groups, respectively.

Discussion

The NPC study showed an inverse relationship between selenium supplementation and prostate cancer risk (11). Our study suggests that selenium supplementation does not elicit a protective effect on prostate cancer progression with respect to PSA velocity in men with non–high-grade, organ-confined disease. Conversely, it is of interest that our analyses suggest that supplementation with high-dose selenium may be a risk factor for prostate cancer progression as measured by PSA velocity in men with relatively high baseline selenium plasma concentrations. Although these results were similar to those from the SELECT trial, direct comparison may not be appropriate because the study agent, the study population, and the outcome measures for these two studies were different.

There are several factors that may contribute to these seemingly contradictory results. Selenium may not elicit a chemopreventive effect in this cohort. Alternatively, the

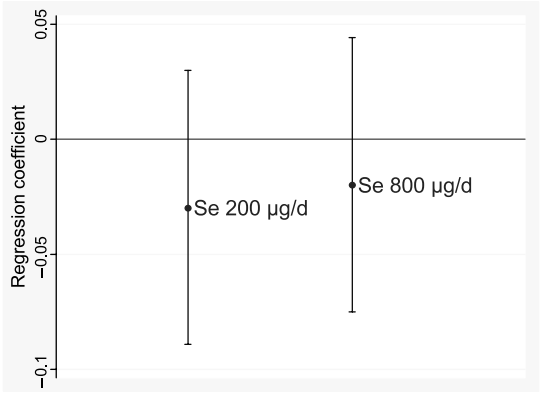

Fig. 2. Point estimates and 95% confidence intervals for differences in PSA trajectories of the 200 μg/d selenium and 800 μg/d selenium treatment groups as compared with placebo (reference). Models were adjusted for age, BMI, race, Gleason score, pack-years of smoking, baseline PSA, baseline selenium, and type of assay used to estimate PSA. Confidence intervals crossing zero indicate no statistically significant difference at $P = 0.05$. Regression coefficient is for the interaction term between years on study and treatment group.

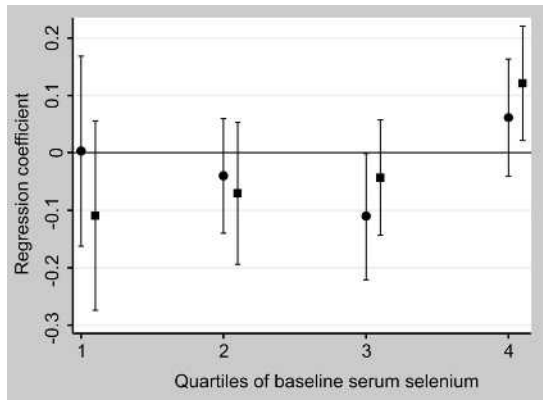

Fig. 3. Point estimates and 95% confidence intervals for differences in PSA trajectories of the 200 μg/d selenium (circle) and 800 μg/d (square) selenium treatment groups as compared with placebo (reference) stratified by quartiles of baseline selenium. Models were adjusted for age, BMI, race, Gleason score, pack-years of smoking at enrollment, baseline PSA, and type of assay used to estimate PSA. Confidence intervals crossing zero indicate no statistically significant difference at $P = 0.05$. Regression coefficient is for the interaction term between years on study and treatment group.

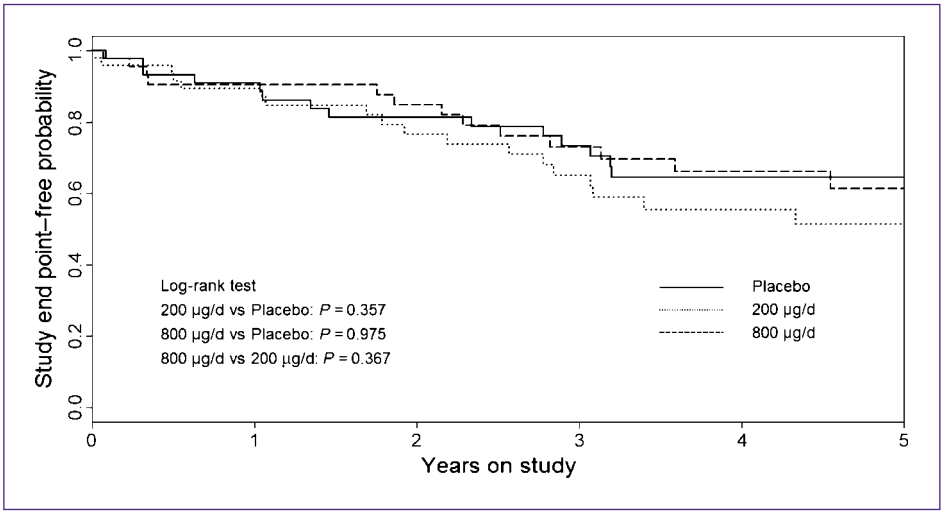

Fig. 4. Kaplan-Meier analysis illustrating differences between treatment groups in probability of receiving therapy for prostate cancer (study endpoint). No statistically significant differences were observed.

study design may not have sufficiently captured any putative chemopreventive effects. Although selenium may have chemopreventive properties for the earliest stage of carcinogenesis (before disease is detected), this may not be consistent with its efficacy in attenuating cancer progression at the stage of carcinogenesis represented by this population of men. The chemopreventive effect observed in the NPC study was primary and was not preventive of cancer progression in a cohort of men with biopsy-proven disease. Additionally, the number of prostate cancer cases in the NPC study was relatively small [22 of 457 (4.8%) in the selenium-supplemented group and 42 of 470 (8.9%) in the placebo group; ref. 16]. Therefore, the possibility of differential screening rates in the two groups and hence a false-positive result cannot be ruled out.

Dissimilarity between the subjects enrolled in the NPC study compared with the subjects enrolled in the present study may confound a direct comparison between the two. Nevertheless, the major differences between the two study populations may support the hypothesis that selenium is ineffective for prevention of progression in this cohort. In the NPC study, the chemopreventive effect was observed only in men with baseline plasma selenium levels that fell within the two lowest tertiles, and the chemopreventive effect was most pronounced in the group falling within the lowest tertile of baseline plasma selenium (16). Unfortunately, these analyses of the NPC study population had not been completed before initiation of the present study, where baseline plasma selenium levels were markedly higher than in the NPC study population (Table 4). In the NPC study, no chemopreventive effect was observed in men with baseline plasma selenium concentrations higher than 123 ng/mL. In the present study, two thirds of randomized subjects are in that category.

The results of this study show no statistically significant effect of selenium on PSA velocity in the lower three tertiles of baseline plasma selenium, whereas supplementation with high-dose selenium in men in the highest quartile of baseline selenium may be a risk factor for increased PSA velocity. Although the effect of small numbers in each category, created by dividing the population into quartiles of baseline selenium as well as three treatment

Table 3. Number of subjects experiencing adverse events (all randomized participants by treatment group)

Events, *n* (%)*	Placebo (*n* = 46)	200 (*n* = 47)	800 (*n* = 47)	*P*
Death	1 (2.17)	2 (4.26)	2 (4.26)	0.99
Serious adverse events	14 (30.43)	17 (36.17)	13 (27.66)	0.69
All cancers (except prostate and skin)	4 (8.70)	3 (6.38)	2 (4.26)	0.64
Cataract/glaucoma	7 (15.22)	6 (12.77)	9 (19.15)	0.71
Nonmelanoma skin cancer	10 (21.74)	13 (27.66)	7 (14.89)	0.32
Brittle hair, brittle nails†	10 (21.74)	6 (12.77)	8 (17.02)	0.51
Garlic breath, liver/kidney problems†	5 (10.87)	0 (0.00)	4 (8.51)	0.05

*Some subjects had more than one adverse event.
†Only events that are possibly, probably, or definitely associated with the intervention and grade 1 or 2 are listed.

Table 4. Comparison of baseline selenium tertiles between the present study and the NPC study

Tertile	Present study (ng/mL), mean (SD)	NPC study, mean (SD)	*P*
1	109.6 (5.97)	92.4 (11.1)	<0.0001
2	127.1 (4.72)	114.6 (5.0)	<0.0001
3	165.8 (58.0)	138.4 (16.0)	<0.0001
Total population	134.5 (41.5)	115 (22.0)	<0.0001

groups, cannot be denied, combining the results of our study with those of NPC leads us to hypothesize that selenium supplementation could have a differential effect on prostate cancer incidence or progression based on plasma selenium concentrations. Supplementation, especially with a higher dose of selenium, may not always be beneficial. In pursuing assessment of selenium as an agent to prevent or inhibit prostate cancer, limiting baseline selenium concentrations to determine eligibility may enable future studies to focus only on those subjects most likely to benefit.

Several contributing factors may account for the difference in baseline selenium between the two studies. The NPC study enrolled subjects located in the Eastern United States, where low soil selenium levels historically correlated with lower selenium levels in plants and livestock ingested by humans. This leads to a lower plasma selenium concentration in populations inhabiting those areas who ingest local foods (23). Enrollment in the present study was more broad and included locations with higher indigenous soil selenium levels, including Arizona, California, and the Midwest. Furthermore, since the early 1980s, when the NPC study was enrolling subjects, supplementation of selenium has increased dramatically both in human diets (24) and in the diets of livestock (25). Therefore, there may be less variation in the food supply in different locations. Thus, there has been an overall nationwide increase in plasma selenium levels, which may preclude a chemopreventive effect elicited by supranutritional supplementation (26). Additionally, the observed rate of increase of PSA in all three treatment groups was unexpectedly low (Table 2), which precluded our ability to detect significant differences as clinically meaningful.

The total sample size achieved was also adversely affected by an underestimation of numbers of men with newly diagnosed prostate cancer who would choose to forgo front-line therapy and be followed by active surveillance. This could be due partially to reports being published during that time frame that reported higher disease-specific mortality for active surveillance as compared with radical prostatectomy (27). Only 140 of the proposed 199 subjects were able to be randomized during the 6-year accrual period. Furthermore, because selenium is readily available over the counter, some men elected to take selenium independently and not participate in the study to avoid the risk of being randomized to the placebo arm. Another factor that presented a challenge was the dropout rate, which had been predicted to be 5% per year. The actual dropout rates ranged from 1.94% to 11.43% per year (Table 5). Subjects were most likely to drop out within the first year.

Selection of the primary end point presented an additional difficulty in the study design. Although PSA velocity is a widely used biomarker of disease status following front-line therapy, the specificity and accuracy of PSA velocity as a reflection of disease progression in the active surveillance population are poorly characterized especially in the absence of a repeat biopsy. Yearly prostate biopsies were not part of the study protocol, and hence, we were restricted to using PSA velocity as a marker to track prostate cancer progression. Identification of suitable end points for prostate cancer chemopreventive studies (and other studies in the active surveillance population) is very challenging. Free-to-total PSA ratio may improve the accuracy of predicting progression, but this has not been elucidated; characterizing biomarkers in this population is particularly challenging in current medical practice where active surveillance is often not encouraged. An additional and unanticipated analytic challenge exists because many men in this population subsequently elect front-line therapy even in the absence of evident disease progression. Therefore, observation of a true surveillance outcome may be skewed.

In conclusion, our data do not show that selenium prevents prostate cancer progression, as measured by PSA

Table 5. Number of subject dropouts by year on study

Treatment group	Year 1	Year 2	Year 3	Year 4	Year 5	Total dropouts	Total subjects
Placebo	4	3	1	1	1	10	46
Se 200 μg	3	6	2	1	1	13	47
Se 800 μg	9	2	4	1	0	16	47
Total no. of dropouts	16	11	7	3	2	39	140
Total yearly dropout rate (%)	11.43	8.87	6.1	2.83	1.94		

velocity in men with organ-confined disease. However, we must consider that several factors adversely affected study power, including smaller-than-anticipated sample size and a secular trend toward increased baseline plasma selenium levels within the U.S. population. Thus, larger studies would have to be conducted to confirm these results or to show that selenium can indeed prevent prostate cancer progression in men with early-stage prostate cancer. Based on the results of this study and the NPC trial, future studies would most likely benefit from excluding men with relatively high baseline plasma selenium levels to maximize efficacy. This would potentially minimize adverse effects given that secondary analyses of the NPC trial showed a significant increase in recurrence of nonmelanoma skin cancer in individuals with medium and high levels of baseline plasma selenium (28). Additionally, any possible deleterious effect of selenium supplementation on PSA velocity could also be prevented. Our study experience suggests that this cohort is a challenge to recruit; there are no ideal end points to measure cancer progression; and studies are further compromised when men elect to have treatment even in the absence of true disease progression. It should also be considered that exclusion of subjects with higher baseline plasma selenium would further increase the difficulty in recruitment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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