

Research Article

Phase III Trial of Selenium to Prevent Prostate Cancer in Men with High-grade Prostatic Intraepithelial Neoplasia: SWOG S9917

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Abstract

The threat of prostate cancer and the significant and often negative impact of its treatment underscore the importance of prevention. High-grade prostatic intraepithelial neoplasia (HGPIN) has been identified as a potential premalignant lesion marking an increased risk of prostate cancer and substantial evidence suggests that men with HGPIN are in need of prostate cancer prevention. *In vitro*, *in vivo*, epidemiologic, and clinical trial evidence that selenium supplementation protects against prostate cancer motivated the study we report here: a double-blind, randomized, placebo-controlled trial of selenium 200 (µg/d) as selenomethionine in men with HGPIN. The primary endpoint was progression of HGPIN to prostate cancer over a 3-year period. This National Cancer Institute Intergroup trial was coordinated by the Southwest Oncology Group (SWOG). Of 619 enrolled patients, 423 randomized men with HGPIN (212 selenium and 211 placebo) were eligible (by central pathology review) and included in the primary analysis. Three-year cancer rates were 36.6% (placebo) versus 35.6% (selenium; $P = 0.73$, adjusted). The majority of patients who developed cancer on trial (70.8%, selenium and 75.5%, placebo) had a Gleason score of 6 or less than 6; there were no differences in Gleason scores between the two arms. Subset analyses included the finding of a nonsignificantly reduced prostate cancer risk (relative risk = 0.82; 95% CI: 0.40–1.69) in selenium versus placebo patients in the lowest quartile of baseline plasma selenium level (<106 ng/mL). Overall, and in all other subsets defined by baseline blood selenium levels, selenium supplementation had no effect on prostate cancer risk. The 36% prostate cancer rate in men with HGPIN indicates the association of this lesion with an elevated prostate cancer risk. Future study in this setting should focus on selenium-deficient populations and selenium pharmacogenetics. *Cancer Prev Res*; 4(11); 1761–9. ©2011 AACR.

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Introduction

Prostate cancer continues to contribute significantly to cancer morbidity and mortality in the United States and other Western industrialized countries. It is estimated that in 2011, approximately 220,000 U.S. men will be diagnosed with prostate cancer and 32,050 will die from prostate cancer (1), reflecting the substantial burden of prostate cancer on patients, their families, and the public health. Prevention could be an important means of limiting this burden, and chemoprevention could be a viable component of this effort (2, 3).

Targeting chemoprevention to patients with premalignant lesions marking an increased risk of short-term progression to cancer could reduce the size, duration, and cost of a chemoprevention trial versus the one conducted in an average-risk population (4–6). According to biological, demographic, and clinical evidence, the intraepithelial neoplasia (IEN) high-grade prostatic IEN (HGPIN) is a

precursor lesion of prostate cancer (7–25). Men with this condition, thought to be at elevated risk for synchronous or subsequent diagnosis of prostate cancer, are suitable subjects for clinical chemoprevention (4–6). Finasteride and dutasteride decrease prostate cancer risk in moderate-risk men and have a similar effect on HGPIN (3, 26), but it is not known whether these agents prevent prostate cancer in men with HGPIN.

In vitro and animal experiment data, along with prospective observational studies, have suggested that selenium has anticancer properties (27–33). Although designed to study the recurrence of nonmelanoma skin cancer, the Nutritional Prevention of Cancer (NPC) study of supplemental selenium (200 µg/d) found an approximately 50% reduction in prostate cancer (a secondary endpoint) in the selenium versus the placebo arm (34, 35). Selenium in NPC was incorporated into baker's yeast; the major organoselenium component in the yeast is believed to have been selenomethionine, although not all the selenium components have been precisely characterized (36). Despite well-described limitations of the NPC study (35, 37, 38), its prostate cancer finding derived from a clinical prevention trial and thus provided a strong rationale for the trial we report here (39–41).

Also largely motivated by the NPC study, the Selenium and Vitamin E (prostate) Cancer Prevention Trial (SELECT) in selenium-replete men found no protective effect of selenium and left open the validity of the NPC results, which involved a number of selenium-deficient men (38); thus, SELECT provided strong evidence that selenium (200 µg/d) as selenomethionine is unlikely to prevent prostate or other cancers in U.S. males with average or greater blood concentrations of selenium and at an average prostate cancer risk. Results of selenium for prostate cancer prevention in men at an elevated risk because of HGPIN, however, have not been previously reported.

Materials and Methods

Patient selection and clinical methods

We opened this study (ClinicalTrials.gov identifier: NCT 00030901) on February 1, 2000, and closed it to new registration in November 2006. It was coordinated by the Southwest Oncology Group (SWOG), with participation by the Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and, under the Veterans Affairs (VA) Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) program, several VA hospitals that had also participated in the Prostate Cancer Prevention Trial (PCPT).

All patients gave oral and written informed consent in accordance with institutional and federal guidelines. The protocol was approved by the Institutional Review Boards at participating institutions and was monitored by the Data and Safety Monitoring Committee of SWOG. The following eligibility criteria were required: 40 years of age or older; digital rectal examination; biopsy-confirmed diagnosis of HGPIN with no evidence of cancer; upper limit of prostate-

specific antigen (PSA) of 10 ng/mL (as measured locally); American Urological Association symptom score of less than 20 (40), signifying no debilitating urinary problems; and ambulatory and able to carry out work of a light or sedentary nature. The following conditions were exclusion criteria: diagnosis of any cancer, other than nonmelanoma skin cancer, within 5 years prior to trial registration; taking selenium supplements containing more than 50 µg/d within 30 days prior to registration; and taking finasteride or other 5- α reductase inhibitors.

The diagnostic biopsy identifying HGPIN was to be confirmed by central pathology review. The biopsy could provide no evidence of cancer. This study was being developed in 1999, when cancer was commonly missed on the single sextant biopsy then in vogue (42, 43). Therefore, study registration required a first biopsy showing HGPIN and no cancer followed by a second sextant or greater, transrectal ultrasound (TRUS)-guided biopsy revealing no cancer; the second biopsy was not required to confirm HGPIN. Subjects could be randomized after no evidence of prostate cancer was found in the second biopsy (37). Between 1999 and 2002, the increasing use of an initial prostate biopsy of 10 or more core samples led us to amend the protocol in 2002, allowing men with an initial biopsy of 10 or more core samples that revealed HGPIN and no cancer and conducted 6 or fewer months prior to registration to be eligible for our trial without a second biopsy; these patients could be randomized after central pathology review, confirming the HGPIN diagnosis and absence of cancer.

After registration and central pathology review, subjects were randomized in a double-blind fashion to placebo or 200 µg/d of selenium, with daily treatment scheduled for 3 years or until a prostate cancer diagnosis (Supplementary Fig. S1). They were seen in clinic at baseline and every 6 months thereafter. Blood samples were collected for PSA testing and for future biological and nutritional studies. A digital rectal examination was conducted, and subjects were queried about symptoms, adverse events, and any cancer diagnoses. Adherence to treatment was evaluated by manual pill counts. Patients were also contacted by telephone 3 months after randomization and 3 months after each clinic visit, with queries about prostate cancer, symptoms, and adverse events. Tissue blocks and corresponding pathology reports for all prostate procedures were to be submitted to the central study pathologist for review. The central pathologist was blinded to study assignment. Patients were also asked to provide consent for ancillary tissue specimen studies, although this consent was not mandatory.

The protocol recommended TRUS-guided biopsy if a baseline PSA of less than 4 ng/mL increased by more than 1 ng/mL within a year, if a baseline PSA of 4 to 10 ng/mL increased by more than 25%, or if a digital rectal examination revealed any abnormality. Participating urologists were at liberty to recommend biopsy as they saw fit.

An end-of-study sextant-or-greater TRUS-guided prostate biopsy, within a window of ± 90 days, was planned for patients not diagnosed with prostate cancer during the

3-year course of the trial, for patients who received a negative interim biopsy, and for patients removed from study supplement early for any reason other than prostate cancer.

Subjects were stratified with dynamic balancing (44) for age (40–60 vs. 61 or older), race (African-American vs. other), prestudy PSA (<4 ng/mL vs. 4–10 ng/mL), and vitamin E supplementation (yes vs. no). In addition, after the protocol was changed in November 2002, subjects were stratified on the number of cores in the initial biopsy (<10 cores vs. ≥10 cores).

The target sample size of 466 randomized patients, 233 per arm, was designed to provide 90% power, based on the following assumptions:

1. A 3-year period prevalence of prostate cancer among men with HGPIN of 50% in the placebo group;
2. A 33% reduction in 3-year period prevalence of prostate cancer in the selenium arm (vs. placebo);
3. One-sided α level of 0.025 (to address the 1-sided hypothesis that selenium would reduce the risk of prostate cancer); this α was halved from 0.05 to be comparable with the more acceptable convention of a 2-sided α of 0.05; and
4. Eighty percent of randomized patients with biopsy-confirmed 3-year prostate cancer status.

Statistical methods

The primary treatment comparison was to compare the proportion of men diagnosed with prostate cancer within 3

years \pm 90 days of randomization in the selenium arm versus this proportion in the placebo arm. The denominator was men with a known 3-year endpoint status; men with missing/unknown status were excluded. The χ^2 test was used to evaluate the statistical significance of the difference between the proportions. Cumulative incidence plots for time to prostate cancer were derived for the placebo arm and the selenium arm; patients not developing prostate cancer were censored at the earliest of the following dates: last contact, 3 years plus 90 days post-randomization, or at death if it occurred prior to a diagnosis of prostate cancer.

Results

We registered 619 men, of whom 167 were ineligible and 452 were randomly assigned to selenium (227 men) or placebo (225 men; Fig. 1). Twenty-nine randomized patients (15 selenium and 14 placebo) were later found to have been ineligible (11 by central pathology review and 18 for other reasons; Fig. 1), in all cases because of prerandomization status. Therefore, the final cohorts of randomly assigned men were 212 to selenium and 211 to placebo. No patients were declared ineligible on the basis of a condition that developed or emerged after randomization.

Table 1 summarizes the baseline status of patients with regard to stratification and other factors. Selenium and placebo patients were well balanced with respect to age,

Figure 1. CONSORT diagram. a, 5 had a major treatment violation (3 refused and 2 received wrong treatment) but were included in the analyses; b, 4 had a major treatment violation (2 refused and 2 received wrong treatment) but were included in the analyses. AUA, American Urological Association.

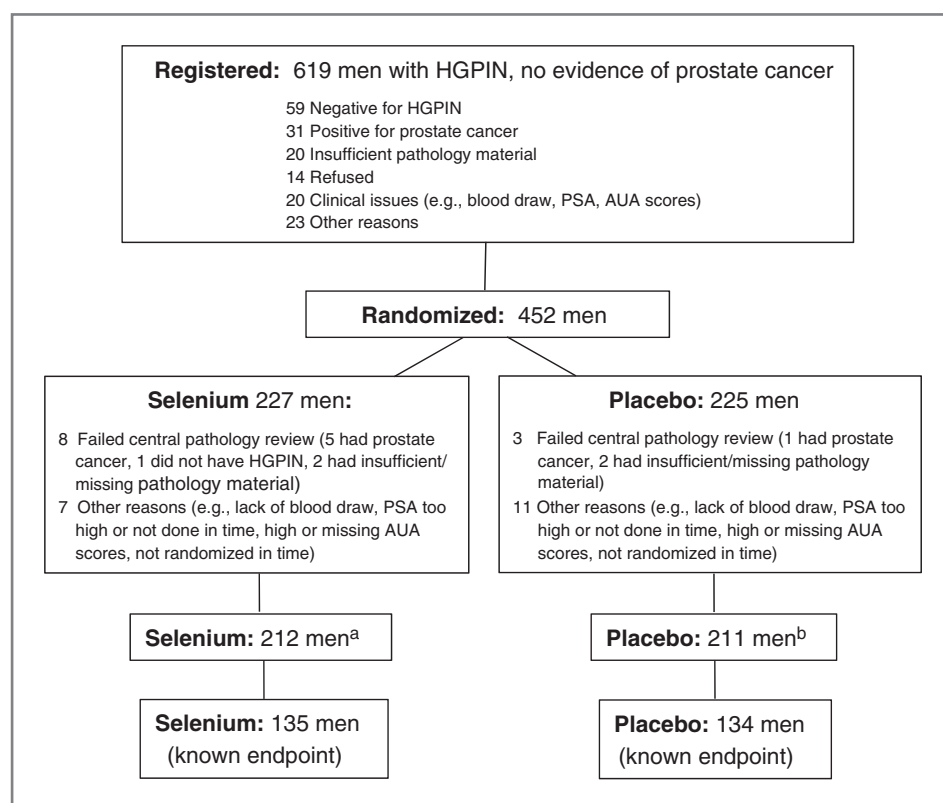


Table 1. Patient characteristics (eligible, randomized patients)

	Selenium arm (N = 212)	Placebo arm (N = 211)
Age, ^a n (%)		
<50 y	9 (4.3)	7 (3.3)
50–54 y	20 (9.4)	20 (9.5)
55–60 y	28 (13.2)	35 (16.6)
61–70 y	96 (45.3)	98 (46.5)
>70 y	59 (27.8)	51 (24.2)
Race, ^a n (%)		
White	177 (83.5)	162 (76.8)
Black	26 (12.3)	26 (12.3)
Nonblack Hispanic	4 (1.9)	13 (6.2)
Other	5 (2.4)	6 (2.8)
Unknown	–	4 (1.9)
Performance status 0 (at randomization), n (%)	201 (94.8)	194 (91.9)
Vitamin E supplementation, ^a n (%)	56 (26.4)	59 (28.0)
Baseline PSA, ^a n (%)—reported by site		
<4 ng/mL	81 (38.2)	90 (42.6)
4–10 ng/mL	131 (61.8)	121 (57.4)
Total	212 (100)	211 (100)
Baseline biopsy requirement, n (%)		
2 Biopsies required (< December 15, 2002)	70 (33.0)	70 (33.2)
2 Biopsies required (≥ December 15, 2002)	27 (12.7)	28 (13.3)
1 Biopsy (≥ December 15, 2002)	115 (54.3)	113 (53.5)
Body mass index, n (%)		
< 25	46 (21.7)	55 (26.1)
25–28	64 (30.2)	60 (28.4)
29–30	46 (21.7)	38 (18.0)
>30	56 (26.4)	58 (27.5)
Average cores biopsied (min–max); unknown %		
First biopsy ^{a,b}	10.5 (2–32); 12.7	10.7 (2–27); 10.9
Second biopsy	9.7 (4–18); 30.2	10.6 (4–25); 21.5
Average of HGPIN-positive cores (min–max); unknown %		
First biopsy	1.6 (1–12); 0.5	1.5 (1–10); 1.0
Second biopsy	0.8 (0–6); 12.4	0.9 (0–8); 9.8

^aStratification factors.^bStratification factor implemented in November 2002, after the trial had begun.

race, ethnicity, prestudy PSA category, vitamin E supplements, and number of cores in the initial biopsy. They also were well balanced in body mass index, baseline blood selenium, performance status, and number of cores revealing HGPIN.

Adherence to treatment was strong. More than 90% of selenium and placebo subjects who had not yet died or been diagnosed with prostate cancer were on study treatment for at least 1 year and nearly 80% were on for 3 years (Table 2, part A). Adherence was very similar in the selenium and placebo arms. Plasma selenium levels (ascertained in random subsets of patients randomized to each arm) are summarized in Table 2, part B. The impact of selenium supplementation on plasma selenium levels is evident across all time points in the selenium arm. The data

also suggest a slight increase in plasma selenium levels in the placebo arm, possibly due to some placebo subjects taking nonstudy supplements containing selenium.

Of the eligible randomized patients, 36.3% (77 of 212) of selenium and 36.5% (77 of 211) of placebo patients did not have their 3-year prostate cancer status confirmed (i.e., no interim cancer or end-of-study biopsy; Table 3). Small numbers of participants—similar numbers in each arm—died, had a primary cancer other than prostate cancer, or had an intercurrent illness. In a small, similar number of cases in each arm, a subject's physician recommended against the end-of-study biopsy and 21 selenium and 18 placebo patients declined the end-of-study biopsy.

Our primary analysis involved the 135 men (63.7%) of the selenium arm and 134 men (63.5%) of the placebo arm

Table 2. Compliance with study treatment

A. Number (%) of eligible, randomized, no-cancer subjects on treatment		
	Selenium	Placebo
At 6 mo	194 (93.7)	192 (94.1)
At 1 y	181 (90.5)	178 (90.8)
At 2 y	165 (88.2)	157 (87.2)
At 3 y	120 (78.9)	122 (81.3)
B. Plasma selenium concentrations by study arm in randomly selected subset samples		
	Selenium (N = 46)	Placebo (N = 51)
	Median (p25–p75) ^a	
At baseline	138.1 (104.7–166.4)	135.2 (113.3–166.8)
At 6 mo	220.9 (181.9–257.9) ^{b,c}	152.7 (119.7–169.4)
At 1 y	240.4 (203.6–275.9) ^{b,c}	145.7 (121.2–166.7)
At 2 y	259.3 (207.2–305.1) ^{b,c}	154.3 (125.8–177.9)
At 3 y	261.2 (233.0–290.4) ^{b,c}	152.1 (125.1–185.9)

Abbreviations: p25, 25th percentile; p75, 75th percentile.

^aThe median and p25 and p75 concentrations represented in nanogram per milliliter. Twenty-five percent of the concentrations fall below the p25 level; 75% of the concentrations fall below the p75 level.

^b $P < 0.05$, compared with baseline levels.

^c $P < 0.05$, compared with change among placebo patients.

with an endpoint status known through an interim biopsy or a biopsy taken at ± 90 days of the end of study (Table 3). Among these patients, prostate cancer was diagnosed in 48 subjects (35.6%) on selenium versus 49 (36.6%) on placebo ($P = 0.73$, adjusted for stratification factors; $P = 0.86$, unadjusted). The numbers of prostate cancer diagnoses after an interim biopsy were similar in the selenium and placebo arms, as were the numbers of prostate cancer diagnoses after an end-of-study biopsy. End-of-study biopsies were negative in 64.4% of selenium and 63.4% of placebo subjects with a known endpoint status. A previous negative interim biopsy occurred in 12 selenium patients and 23 placebo patients who were still alive, had no interim prostate cancer and therefore were expected to have, but did not have, an end-of-study biopsy. An analysis that widened the window of the end-of-study biopsy to ± 180 days and thus increased the proportion of biopsy-confirmed endpoints to 68% of selenium and 72% of placebo patients, also found highly similar prostate cancer rates in the 2 arms ($P = 0.90$, adjusted for stratification factors; $P = 0.96$, unadjusted).

We also analyzed the cumulative incidence of prostate cancer by treatment arm over the 3-year treatment period (Fig. 2), finding that the cumulative incidence curves of the 2 arms are extremely similar, with no evidence of diverging trends ($P = 0.98$). This analysis approximates an intent-to-treat analysis in that it includes all randomized men (and assuming that those not known to have prostate cancer and with no end-of-study biopsy to be negative for prostate

Table 3. Study endpoints (by treatment assignment)

	Selenium	Placebo
<i>Number randomized</i>	227	225
Ineligible	15	14
Eligible	212	211
<i>Endpoint status at 3 y, n (%)</i>	77 (36.3)	77 (36.5)
EOS > 90 d out	9	18
Died	4	6
Non-prostate cancer primary cancer	4	1
Intercurrent illness	5	3
MD recommended no EOS biopsy	6	5
Declined EOS biopsy	21	18
Lost to follow-up	13	12
Withdrew consent	4	5
Other	11	9
<i>Endpoint known, n (%)</i>	135 (63.7)	134 (63.5)
Prostate cancer, ^a n (%)	48 (35.6)	49 (36.6) ^a
Interim	24	22
EOS	24	27
Negative EOS biopsy, n (%)	87 (64.4)	85 (63.4)

Abbreviation: EOS, end of study.

^a P value comparing selenium versus placebo patients is 0.73 for 3-year biopsy-proven carcinoma, adjusted for the stratification factors age older than 60, African American, baseline PSA, and vitamin E supplementation.

cancer); it also evaluates whether the time to a prostate cancer diagnosis differed between the 2 treatment groups. The preponderance of patients diagnosed with prostate cancer—70.8% (selenium) and 75.5% (placebo)—were diagnosed with a Gleason sum score of 6 or less (Fig. 3). A Gleason score of 7 was diagnosed in 25% of selenium and 20.4% of placebo patients with prostate cancer. Among the 12 selenium patients with a Gleason score of 7, 10 had pattern 3 + 4 whereas 2 had pattern 4 + 3; among the 10

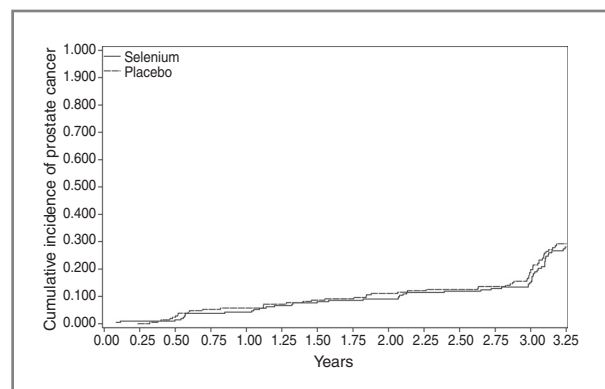


Figure 2. Cumulative incidence of prostate cancer by study arm.

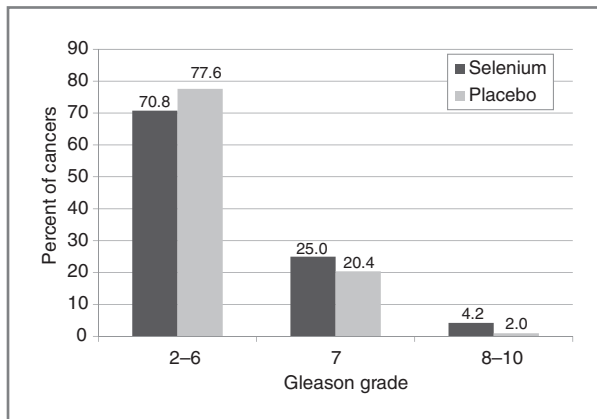


Figure 3. Gleason score of diagnosed prostate cancers (by study arm).

placebo patients with a Gleason score of 7, 7 had pattern 3 + 4 and 3 had pattern 4 + 3. Only 3 patients overall had a Gleason score of 8 or higher. None of these differences between the selenium and placebo arms is statistically significant.

We assessed the association between baseline serum selenium concentration and prostate cancer risk for randomized patients with a known endpoint in each treatment arm (Table 4). The probability of a prostate cancer diagnosis [relative risk (RR)], stratified by baseline selenium concentration, is reflected in column 5 of Table 4. Although the CIs are wide because of the modest sample sizes, there is no clear dose-response trend between the baseline selenium strata and the impact of selenium supplementation on a prostate cancer diagnosis. With adjustment for stratification factors and baseline selenium quartiles, there is no appreciable or statistically significant association between selenium treatment and a prostate cancer diagnosis ($P = 0.73$). Subset analyses

did show, however, a nonsignificantly reduced prostate cancer risk (RR = 0.82; 95% CI: 0.40–1.69) in selenium versus placebo patients in the lowest quartile of baseline selenium level (<106 ng/mL).

Adverse events were graded by clinicians using the National Cancer Institute Common Toxicity Criteria (CTC) version 2.X. There were 21 grade 2 events in the selenium arm and 13 in the placebo arm (detailed data not shown). There was only one grade 3 event, which was dermatologic, in the selenium arm, and there were three grade 3 events—1 cardiovascular, 1 gastrointestinal, and 1 renal/bladder—in the placebo arm.

Discussion

This trial focused on men potentially at an elevated risk of prostate cancer on the basis of biopsy-identified HGPIN. The study extends SELECT, which randomized average-risk subjects to selenomethionine and/or vitamin E (α -tocopherol; ref. 38) and showed that neither agent had any effect in preventing prostate cancer. Fleshner and colleagues (45) also found no effect on the progression of HGPIN to prostate cancer in a trial of a putative prevention cocktail containing vitamin E, selenium, and soy in HGPIN patients.

These results differ strikingly from those of the NPC, in which selenium supplementation was associated with a 50% decrease in prostate cancer incidence (34, 35). The effect of selenium supplementation on prostate cancer risk appeared early enough in the NPC trial to suggest that a 3-year treatment period in the present trial would be adequate to reveal a protective effect. The benefit of selenium supplementation in the NPC trial was confined to subjects in the lowest 2 tertiles of baseline plasma selenium. In general, the NPC participants had much lower baseline blood selenium levels (mean: 114 ng/mL; refs. 34, 35) than did the HGPIN patients in the present trial (>135 ng/mL).

Table 4. Baseline plasma selenium and the effect of treatment on prostate cancer diagnosis among those evaluable for study outcome

Quartile	Selenium concentration, ng/mL	Known endpoints		Cancer in patients with known endpoint		RR of prostate cancer in the selenium arm compared with placebo arm RR (95% CI)
		Selenium, N	Placebo, N	Selenium, N (%)	Placebo, N (%)	
1	<106	31	31	9 (29.0)	11 (35.48)	0.82 (0.40–1.69)
2	106–132	30	31	12 (40.0)	9 (29.3)	1.38 (0.68–2.78)
3	132–162	32	36	14 (43.8)	16 (44.4)	0.98 (0.58–1.68)
4	>162	32	32	10 (31.25)	11 (34.4)	0.91 (0.45–1.84)
Missing baseline selenium ^a		10	4	3	2	
Total		125	130	45 (36.0)	47 (36.2)	0.97 (0.68–1.39)

^aNot included in totals.

There was no protective effect of selenium among NPC participants with baseline selenium levels comparable with those of generally replete subjects in the present trial (35). The levels in our study, as in SELECT, were well above even the mean of 123 ng/mL estimated for the U.S. population (46). Selenium was not protective, however, even in HGPIN patients in the lowest baseline selenium quartile (an upper boundary of 106 ng/mL), although the risk was nonsignificantly reduced in this group. Although selenium had no effect in the second quartile, the levels in this quartile ranged from 106 to 132 ng/mL, which substantially overlaps the highest tertile of the NPC study. The NPC study tested selenized yeast whereas selenomethionine was tested in our present study and SELECT; nonetheless, if there was a protective organoselenium compound other than selenomethionine in this yeast, it remains to be identified (36).

A key limitation of the NPC results—a substantial number of patients with elevated PSA tests were not biopsied—has been reported (35). More critical, subjects on selenium were less likely than subjects on placebo to have a biopsy following an elevated PSA test (35). The NPC investigators attempted to adjust for this difference between the arms statistically, and the association between selenium supplementation and decreased risk persisted despite the adjustment (35). Nonetheless, the association between selenium supplementation and prostate cancer in NPC was a secondary trial endpoint that could have resulted from confounding because of an unmeasured or imperfectly measured factor or to statistical error inherent in secondary analyses; it could have been a chance occurrence.

Our present study focused strictly on prostate cancer and was not powered or otherwise designed to evaluate other chronic disease endpoints such as diabetes. The NPC study found that selenium was associated with a statistically significantly higher rate of diabetes than was placebo. In SELECT, a slight, statistically nonsignificant excess of diabetes was observed in patients who received selenium alone (vs. placebo), although the excess was much smaller than that in NPC. Additional analyses of the SELECT data are ongoing.

Although family history of prostate cancer is linked to prostate cancer risk, the present study was not powered to control for family history. We relied on randomization to balance a number of potential confounding factors between the selenium and placebo arms, and the congruence of our present results with those of SELECT (38) and Fleshner and colleagues (45) strongly suggests that they were not confounded by family history.

In the present study, 29 men proposed by the clinical sites to be eligible for enrollment and randomization were deemed ineligible by centralized pathology review of their biopsy samples or other reasons following their randomization. However, no subject was ruled ineligible on the basis of a condition that developed after randomization, and excluding these ineligible subjects likely did not lead to a study bias.

This study's 36% period prevalence of prostate cancer in 3 years suggests that its HGPIN patients were at a higher prostate cancer risk than were men recruited to other prostate cancer prevention trials. Men in the PCPT were believed to be at a low risk with no known HGPIN and a PSA level of 3.0 ng/mL or less at study entry (2) and 24% (placebo) were diagnosed with prostate cancer within the approximately 7-year study period. In the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial (PSA eligibility: 2.5–10.0 ng/mL), 25% of men were diagnosed with prostate cancer within the 4 years of the trial (3). Although secondary analyses of variables—including the number of biopsy cores positive for HGPIN, baseline micronutrient status, body mass index, and potential germ line and somatic molecular biomarkers (47)—that may have predicted progression of HGPIN to invasive disease are beyond the scope of this report, we plan to conduct such analyses within the present trial's population for a future report.

We minimized the enrollment of men with prostate cancer (accompanying HGPIN) that was missed at the baseline biopsy. At the beginning of the study, subjects whose initial biopsy showed HGPIN and no cancer were required to undergo a second, negative biopsy of 6 or more cores before they could be randomized. After November 2002, subjects whose initial biopsy of 10 or more cores showed HGPIN and no cancer were not required to be rebiopsied. The rationale for this change was that 10 or more core biopsies were coming into use in 2002 and substantially lowered the probability that prostate cancer would be missed on a single biopsy. It is likely that a few small cancers were missed at study entry, both before and after 2002, but it is unlikely that they hampered the trial's ability to assess selenium for prostate cancer prevention.

Prostate cancer that developed in the present trial was, in large part, low grade, with Gleason score 6 or lower in 70.8% of graded cancers in the selenium arm and in 75.5% in the placebo arm. In the placebo arm of the 7-year PCPT, 78% of graded cancers had Gleason score of 6 or lower. In the placebo arm of REDUCE, about 73% of prostate cancer had Gleason score of 6 or lower (3). In SELECT, 53% of diagnosed prostate cancer subjects were Gleason score 6 or lower, likely reflecting the fact that biopsies in SELECT were not mandated but were triggered by clinical criteria. These collective findings suggest that the presence of HGPIN does not signal an increased risk of high-grade or aggressive disease.

Although the endpoint for more than 60% of men in the present trial was definitively assessed per protocol (by biopsy within 90 days of ending the 3-year duration of study), this percentage was not as high as we had intended. The percentage of endpoint assessments, however, was virtually identical for selenium and placebo participants and is in line with the rates of endpoint assessment in the PCPT (60%, finasteride arm and 63%, placebo arm; ref. 2) and in the 4-year REDUCE (58% protocol-directed biopsy rate at 25–48 months, although 82% had at least 1 biopsy and 80% had a protocol-directed biopsy at 19–24 months;

ref. 3). Men who had a negative interim biopsy, but no end-of-study biopsy, were not counted as having complied with the end-of-study biopsy requirement. Counting these 35 interim biopsy patients and assuming that a 3-year biopsy also would have been negative increases the biopsy-defined endpoint rates to 69% for selenium and 74% for placebo patients. An alternate analysis expanded the end-of-study window to ± 180 days and provided further evidence that prostate cancer risk was similar in the selenium and placebo arms.

Recruitment to cancer therapy trials or to prevention trials in non-IEN people (such as PCPT and SELECT) is generally easier than is recruitment to trials designed for IEN patients, and our HGPIN trial was no exception to the rule. Major hindrances to IEN patient recruitment include the fact that IEN patients generally are not seen in cooperative cancer treatment (primarily) groups or tertiary academic referral centers and that IEN trials involve complexities (e.g., in sampling and monitoring) not common to prevention trials in generally healthy volunteers. Recruitment during our first 1 to 2 years was very slow. We successfully addressed this problem in several ways, including doubling the initial enrollment payment from 500 to 1,000 dollars and adding more recruitment sites. We have previously reported the obstacles to recruitment and our solutions to them in completing accrual to the present trial in reference 42, where we would refer readers interested in further information on this critical issue of clinical cancer prevention.

Despite advances in prostate cancer therapy, it still imposes significant human costs and complications for men diagnosed with prostate cancer (48). Ambiguities in the management of men with low-grade, low-volume prostate cancer and overscreening for prostate cancer persist (49, 50). Prostate cancer prevention would lessen the need for patients to undergo treatment and would bear on the debate over the value of aggressive screening and therapy for low-grade, low-volume prostate cancer (51). An increased preventive focus on HGPIN as a marker of an increased prostate cancer risk, as shown in the present trial, is warranted. Selenium (200 $\mu\text{g}/\text{d}$), in the form of selenomethionine, is clearly ineffective for reducing prostate

cancer risk in selenium-replete men with HGPIN. However, men with HGPIN might well be treated with agents, such as 5- α reductase inhibitors or other molecular-targeted agents, that would not be acceptable for those at average or low risk. The present trial's suggestion of a selenium benefit in selenium-deficient men, which is consistent with earlier NPC findings, and selenium pharmacogenetics (52) may identify men who would benefit from selenium, suggesting an approach for future study of selenium. As the largest randomized controlled trial of a preventive agent in HGPIN patients, the present study extends the findings of the massive SELECT in showing that selenium does not prevent prostate cancer in selenium-replete men, which is an important contribution to the public health.

Disclosure of Potential Conflicts of Interest

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