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ARTICLE

Baseline Selenium Status and Effects of Selenium and Vitamin E Supplementation on Prostate Cancer Risk

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Background The Selenium and Vitamin E Cancer Prevention Trial found no effect of selenium supplementation on prostate cancer (PCa) risk but a 17% increased risk from vitamin E supplementation. This case–cohort study investigates effects of selenium and vitamin E supplementation conditional upon baseline selenium status.

Methods There were 1739 total and 489 high-grade (Gleason 7–10) PCa cases and 3117 men in the randomly selected cohort. Proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for effects of supplementation within quintiles of baseline toenail selenium. Cox proportional hazards models were used to estimate hazard ratios, and all statistical tests are two-sided.

Results Toenail selenium, in the absence of supplementation, was not associated with PCa risk. Selenium supplementation (combined selenium only and selenium + vitamin E arms) had no effect among men with low selenium status (<60th percentile of toenail selenium) but increased the risk of high-grade PCa among men with higher selenium status by 91% ($P = .007$). Vitamin E supplementation (alone) had no effect among men with high selenium status (≥40th percentile of toenail selenium) but increased the risks of total, low-grade, and high-grade PCa among men with lower selenium status (63%, $P = .02$; 46%, $P = .09$; 111%, $P = .008$, respectively).

Conclusions Selenium supplementation did not benefit men with low selenium status but increased the risk of high-grade PCa among men with high selenium status. Vitamin E increased the risk of PCa among men with low selenium status. Men should avoid selenium or vitamin E supplementation at doses that exceed recommended dietary intakes.

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In 2001, the US National Cancer Institute initiated the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which tested whether selenium (Se; 200 μg/d from L-selenomethionine), vitamin E (400 IU/d of *all rac*-α-tocopheryl acetate) or both could reduce prostate cancer (PCa) risk (1). Study supplementation stopped 3 years before the expected trial end date because interim analyses showed very low likelihood of benefit with continued intervention (2). At that time, vitamin E alone modestly increased PCa risk (hazard ratio [HR] = 1.13; $P < .06$); with additional follow-up, this became statistically significant (HR = 1.17; $P < .008$) (3).

Here we examine two prespecified hypotheses related to baseline Se status and SELECT outcomes (4). First, we tested whether high Se status at baseline was associated with reduced cancer risk among men receiving placebo supplements, which addresses whether Se exposure within ranges common among US men was associated with risk. Second, we tested whether Se supplementation reduced cancer risk among men with low Se status at baseline. This was motivated by the Nutritional Prevention of Cancer Trial (NPC), which found that supplementation of men with moderate and low plasma Se decreased PCa risk by more than 75% but had no effect among men with high plasma Se (5). We also tested the a posteriori hypothesis that vitamin E supplementation increased PCa risk among men with low Se status at baseline, which was motivated by the finding that vitamin E alone, but not combined vitamin E and Se, increased cancer risk.

Methods

Participants and Data Source

Data and toenail samples are from SELECT, a randomized, placebo-controlled trial that tested whether Se and vitamin E, either alone or combined, reduced PCa risk (2). Briefly, in 427 participating sites across the United States, Canada, and Puerto Rico, black men aged 50 years or older or all other men aged 55 years or older, who had no history of PCa, and who had a serum prostate-specific antigen (PSA) of 4 ng/mL or less and nonsuspicious digital rectal exam were eligible to participate. Between July 2001 and May 2004, 35 533 men were block-randomized by study site to one of four groups: Se plus vitamin E; vitamin E plus placebo; Se plus placebo; or placebo plus placebo. On September 15, 2008, the Data

and Safety Monitoring Committee recommended the discontinuation of the trial supplements, although active follow-up continued through each participant's final clinic visit (between October 28, 2009, and August 12, 2011). All men provided written informed consent, and study procedures were approved by the local institutional review boards.

In this case–cohort study, case patients (n = 1739; high grade = 489) were men with baseline toenail samples available for analysis who were diagnosed with PCa before July 31, 2009. Most case patients (n = 1611, 92.7%) were diagnosed before the use of study supplements was discontinued, and most (n = 1459, 83.9%) were reviewed centrally for pathological confirmation and grading. High- and low-grade tumors were defined as Gleason scores 7 to 10 and 2 to 6, respectively (6). Grade was abstracted from local pathology reports for 43 case patients and was unknown for 237 case patients.

A subcohort (N = 3117) was created as the comparison group as follows. Men randomized into the study were separated into nine age/race strata: 1) black men aged less than 55 years, 2) black men aged 55 to 59 years, 3) black men aged 60 to 64 years, 4) black men aged 65 to 69 years, 5) black men aged 70 years or more and 6) men of all other races aged 55 to 59 years, 7) men of all other races aged 60 to 64 years, 8) men of all other races aged 65 to 69 years, and 9) men of all other races aged 70 years or more. For each case, men were selected randomly from within the same age/race strata, using a case:subcohort ratio of 1:3 for black men and 1:1.5 for men of all other races.

Demographic and health-related characteristics were collected at baseline by self-administered questionnaire. All men were requested to provide toenail samples at baseline, and 89% complied. Samples were collected from all toes, shipped to the specimen repository, and stored at room temperature and low humidity to prevent fungal growth.

Measuring Toenail Se Concentrations

Toenail Se concentration was measured by neutron activation analysis at the University of Missouri Research Reactor Center using previously described methods (7–12). Each daily analysis batch consisted of SELECT toenail samples (approximately 100), replicates (approximately 50), quality control samples (n = 3–5), cross-calibration check samples (n = 10), and Se standards (n = 3–5). All samples were well above the threshold for neutron activation analysis sensitivity. The coefficient of variability for duplicate pairs was 2.77%, the average cross-batch coefficient of variability was 3.03% (range = 2.30%–4.27%), and the mean value of quality control standards (1.112 ± 0.022 μg/g) was in good agreement with their certified value (1.1 ± 0.1 μg/g).

Statistical Analysis

Differences in distributions of demographic and health-related characteristics between case patients and noncase subjects were tested using general χ^2 statistics. Linear regression models were used to generate least squared means of toenail Se concentrations adjusted for covariables (baseline age, body mass index, PSA, diabetes, and use of Se supplements, as well as family history of PCa and race/ethnicity). Within these regression models, tests for differences in mean toenail Se across categorical covariables were based on *F* tests for the covariate overall and *t* tests for pairwise contrasts between specific categories; tests for trend across ordinal covariables were based on a linear variable coded 1 to n, where n is the number of categories. Cox proportional hazards models were used to estimate the hazard ratios and 95% confidence intervals (CIs) for the associations of baseline toenail Se with PCa risk (placebo arm only), and tests for trend were based on a linear variable for quintile of baseline toenail Se. Stratified Cox proportional hazards models were also used to estimate the effects of supplementation on PCa risk within quintiles of baseline toenail Se, defined by its distribution in the subcohort. Please see the Supplementary Statistical Appendix (available online) for details on how the assumption of proportionality was verified for the Cox proportional hazard models. Tests for differences across toenail Se quintiles were modeled as the cross-product of treatment with a linear variable for quintile of toenail Se concentration. Results are also given for effects for any Se (the combined Se-treated arms) and for contrasts of low vs high toenail Se, in which cutpoints were chosen a posteriori based on initial findings. Separate models were fit for total, low-grade, and high-grade PCa. The Supplementary Statistical Appendix (available online) gives a detailed description of statistical methods, as well as the numbers of case patients and subcohort men by grade and quintile of toenail Se.

Covariables in all Cox models were body mass index, history of diabetes, family history of PCa, and baseline PSA concentration. Results are also age- and race-adjusted because all models were stratified by race/age groups before being combined to generate summary statistics. Statistical analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC); all tests were two-sided, and *P* less than .05 was used as the criterion for statistical significance.

Results

Table 1 gives demographic characteristics and other study-related variables. Of case patients, 41.8% were aged 65 years or older and 13.7% were black. Because of matching, the age distribution of the subcohort was similar to that of case patients, and because of the sampling scheme, the ratio of case patients to subcohort members was 1.0:3:1 for blacks and 1.0:1.6 for other races. Risk factors for cancer were consistent with those in the epidemiological literature: compared with men without cancer, those with cancer were more likely to have a family history of PCa (15.7% vs 32.0%; $P < .001$) and baseline PSA greater than 2 μg/mL (21.2% vs 66.3%; $P < .001$) and less likely to have diabetes (12.0% vs 6.8%; $P < .001$); men with low-grade cancer were less likely to be obese than those without cancer (body mass index ≥30 kg/m^2: 27.4% vs 33.3%; $P < .001$). During the year before randomization, 30.6% of men used less than 50 μg/day of supplemental Se, which is a level common in multivitamins, and only 55 men (1.2%) reported using 150 μg/day or more. Prestudy Se supplement use was similar among men who were or were not subsequently diagnosed with cancer.

Table 2 gives the geometric mean toenail Se concentrations in cancer case patients and noncase subjects, cross-classified by factors related to PCa risk. The mean toenail Se concentration was 0.89 μg/g (range = 0.48–8.97) and did not differ between case patients and noncase subjects. Mean toenail Se did not differ by

Table 1. Distribution of baseline demographic and health-related characteristics in subcohort and prostate cancer case (PCa) patients

			Cancer			
	All men (n = 4661)	Subcohort (n = 3117)	No cancer (n = 2922)	All PCa case patients (n = 1739)	Low-grade case patients (n = 1013)	High-grade case patients (n = 489)
Characteristic	**No. (%)**	**%**	**%**	**%**	**%**	**%**
Age, y						
<60	1412 (30.3)	30.8	31.0	29.1	30.8	23.5
60–64	1379 (29.6)	29.4	29.3	30.1	31.0	28.2
65–69	1087 (23.3)	23.4	23.0	23.8	23.1	25.8
≥70	783 (16.8)	16.4	16.7	17.0	15.1	22.5
Race/ethnicity						
Black	938 (20.1)	24.0	24.0	13.7	12.3	14.5
Hispanic	185 (4.0)	4.2	4.3	3.3	2.9	2.0
White	3458 (74.2)	70.1	70.0	81.2	83.0	81.4
Other	80 (1.7)	1.7	1.7	1.8	1.8	2.0
Family history of prostate cancer						
Yes	1016 (21.8)	16.5	15.7	32.0	33.1	29.4
No	3643 (78.2)	83.5	84.3	68.0	66.9	70.6
$P_{(vs. No Cancer)}$ *				<.001	<.001	<.001
Body mass index, kg/m^2						
<25	899 (19.3)	19.1	19.3	19.3	19.2	18.0
25–<30	2269 (48.7)	47.6	47.4	50.8	53.4	46.2
≥30	1493 (32.0)	33.3	33.3	30.0	27.4	35.8
$P_{(vs no cancer)}$ *				<.03	<.001	.67
Diabetes						
Yes	470 (10.1)	11.6	12.0	6.8	5.5	8.4
No	4191 (89.9)	88.4	88.0	93.2	94.5	91.6
$P_{(vs no cancer)}$ *				<.001	<.001	.14
Prostate-specific antigen, µg/mL						
<1.00	1438 (30.9)	42.5	44.8	7.5	6.8	7.0
1.00–1.99	1452 (31.2)	34.0	34.1	26.2	25.1	26.2
2.00–2.99	990 (21.2)	14.9	13.9	33.6	33.3	35.4
≥3.00	780 (16.7)	8.6	7.3	32.7	34.8	31.5
$P_{(vs no cancer)}$ *				<.001	<.001	<.001
Supplemental selenium, µg/d						
0	2841 (61.0)	61.5	61.4	60.1	61.1	57.9
<50	1426 (30.6)	30.3	30.4	30.9	30.6	32.9
50-<100	210 (4.5)	4.3	4.4	4.7	4.3	5.1
100-<150	129 (2.8)	2.7	2.7	2.9	2.7	2.7
≥150	55 (1.2)	1.2	1.1	1.3	1.3	1.4
$P_{(vs. No Cancer)}$ *				.90	.98	.60

* Two-sided χ^2 tests.

age, family history of PCa, body mass index, history of diabetes, or baseline PSA concentration. Among noncase subjects, toenail Se concentration was 8% ($P < .001$) lower in blacks and 7% (p=0.005) lower in Hispanics compared white whites; among case patients, toenail Se was 10% ($P < .001$) lower in blacks compared with whites. Mean toenail concentrations increased with higher prerandomization supplemental Se use, from 0.87 µg/g among nonsupplement users to 1.06 µg/g among noncase subjects and 1.09 µg/g among case patients using 150 µg Se/day or more ($P_{trend} < .001$).

Table 3 gives associations of baseline toenail Se concentrations with risks of total, low-grade, and high-grade cancer in the placebo arm. There were no statistically significant differences in risk contrasting the lowest quintile with higher quintiles of toenail Se concentration, nor was there a statistically significant trend across quintiles ($P \geq .30$ for all tests). When defining the lowest category as less than 0.70 µg/g (case patients = 37) to better match other US studies (11,13), there was no difference in risk compared with men with toenail Se of 0.9 µg/g or greater (HR = 1.27; 95% CI = 0.72 to 2.22).

Table 4 gives the effects of Se supplementation. Among men receiving Se alone, there were no statistically significant differences in the effects of supplementation on total, low-grade, or high-grade cancer across quintiles of toenail Se (all $P \geq .27$). Risks for high-grade cancer were non-statistically significantly increased by 52% ($P = .28$) and 74% ($P = .15$) among men in quintiles 4 and 5 of toenail Se; in the a posteriori test among men with toenail Se greater than or equal to the 60th percentile, it increased risk by 62% ($P = .08$). Among men receiving Se plus vitamin E, there were no differences in supplementation effects on risks of total or low-grade cancer across quintiles of toenail Se (all $P \geq .53$); however effects differed for high-grade cancer ($P_{interaction} = .05$). Supplementation increased the risks of high-grade cancer by 121% ($P = .03$) and 124% ($P = .04$) in quintiles 4 and 5 of toenail Se; in the a posteriori test among men with toenail Se greater

Table 2. Mean toenail selenium concentration by baseline demographic and health-related characteristics

Characteristic	Toenail selenium (μg/g)	
	Noncase subjects (n = 2922) Mean*	Case patients (n = 1739) Mean*
Overall, mean (95% CI)	0.89 (0.55 to 1.43)	0.89 (0.58 to 1.38)
Age, y		
<60	0.88	0.90
60–64	0.89	0.89
65–69	0.89	0.88
≥70	0.89	0.89
P_{trend}†	0.43	0.23
Race/ethnicity		
Black	0.84‡	0.82‡
Hispanic	0.85§	0.88
White	0.91	0.91
Other	0.85	0.87
$P_{overall}$‖	<.001	<.001
Family history of prostate cancer		
Yes	0.88	0.90
No	0.89	0.89
P‖	.62	.60
Body mass index, kg/m²		
<25	0.90	0.90
25–<30	0.89	0.90
≥30	0.88	0.88
P_{trend}†	.14	.20
Diabetes		
Yes	0.90	0.89
No	0.89	0.89
P‖	.39	.77
Prostate-specific antigen, μg/mL		
<1.00	0.88	0.91
1.00–1.99	0.89	0.89
2.00–2.99	0.88	0.90
≥3.00	0.92	0.89
P_{trend}†	.13	.44
Supplemental selenium, μg/d		
0	0.87	0.87
<50	0.90	0.91
50–<100	0.94	0.92
100–<150	0.96	0.98
≥150	1.04	1.09
P_{trend}†	<.001	<.001

* Geometric means, back-transformed for ease of interpretation, adjusted for other variables in table using multiple regression. CI = confidence interval

† Two-sided *F* test for linear variable of ordered categories.

‡ Two-sided *t* test; vs white $P < .001$.

§ Two-sided *t* test; vs white $P < .005$

‖ Two-sided *F* test for categorical variable overall.

than or equal to the 60th percentile, supplementation increased risk by 124% ($P = .002$). When both Se-treated arms were combined, the interaction of supplementation with baseline toenail Se on high-grade disease was statistically significant only in the a posteriori test contrasting low with high toenail Se ($P_{interaction} = .02$), in which Se supplementation increased risk by 91% ($P = .007$). We also examined these data using lower cutpoints for baseline toenail Se categories (<0.7, 0.7–<0.8, 0.8–<0.9, and ≥0.9 μg/g), which yielded hazard ratios for any Se treatment of 0.79, 0.89, 1.05, and 1.22 ($P_{trend} = .30$) for total cancer, respectively, and 1.19, 0.82, 1.08, and 1.81 ($P_{trend} = .05$) for high-grade cancer, respectively.

Table 5 gives the effects of vitamin E supplementation. In quintile 1 of toenail Se, supplementation non-statistically significantly increased risks for total, low-grade, and high-grade cancer by 39%, 20%, and 63%, respectively (all $P \geq .23$). In quintile 2, risks for total, low-grade, and high-grade cancer were increased by 92% ($P = .02$), 77% ($P = .07$), and 179% ($P = .007$), respectively. Among men with higher toenail Se, there were no effects of vitamin E supplementation. In the a posteriori tests, supplementation of men with toenail Se less than the 40th percentile increased the risks of total, low-grade, and high-grade disease by 63% ($P = .02$), 46% ($P = .09$), and 111% ($P = .008$), respectively.

Discussion

In this large clinical trial, baseline Se status alone, in the absence of supplementation, was not associated with PCa risk. Nevertheless, the effects of supplementation with Se and vitamin E differed substantially between men with low and high Se status at baseline. Among men with high baseline toenail Se (≥60th percentile), Se supplementation increased the risk of high-grade cancer by 91% ($P = .007$). Among men with low baseline toenail Se (<40th percentile), vitamin E supplementation (alone) increased the risks of total PCa by 63% ($P = .02$), and this effect was somewhat stronger for high-grade (111%; $P = .01$) compared with low-grade (46%; $P = .09$) cancer. The results for Se supplementation were contrary to our hypothesis that supplementation might benefit men with low Se status at baseline and suggest instead that supplementation is harmful for men with already high Se stores. The results for vitamin E supplementation were also unexpected at the time of trial design, however they are consistent with primary trial findings that vitamin E alone, but not vitamin E plus Se, increased risk.

There have been multiple high-quality reviews of Se and PCa risk (14–18), each generally agreeing that low Se status may increase risk. Previous observational studies based on toenail Se concentrations have all reported lower PCa risk among men with high toenail Se concentrations. Two small US studies reported reduced risks of approximately 60% when Se concentration was greater than 0.69 μg/g (13) and 40% when Se concentration was greater than 0.76 μg/g (19), with no trend above these cutpoints. When we defined low Se status similarly (<0.70 μg/g), we could not replicate these findings (data given in Results). A large study from the Netherlands reported a strong, inverse association with risk of advanced cancer, with a hazard ratio of 0.37 contrasting the lowest quintile with the highest quintile of toenail Se (≤0.469 vs >0.617 μg/g) (20). Because only 13 cancer case patients (0.9%) in SELECT had toenail Se concentrations less than 0.617, this study cannot address whether the very low Se status seen in Dutch men is associated with PCa risk. Our findings to do not support previous US studies and suggest that, at least within the ranges of toenail Se found in US men, Se status is not associated with PCa risk.

Two previous supplementation trials have examined high-dose Se and PCa prevention. The NPC supplemented 928 men from areas of the United States with low soil Se with 200 μg Se/d (from selenized yeast) and increased mean plasma Se to 190 μg/L (21). The Negative Biopsy Trial supplemented 699 men with 200 or 400 μg Se/d (from selenized yeast) and increased mean plasma Se to 190 and 250 μg/L, respectively (1). Mean post-treatment plasma

Table 3. Association of baseline toenail selenium concentration with risk of total, low-grade, and high-grade prostate cancer: placebo arm only

	Total	Low-grade	High-grade
Quintile	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***
No. (subcohort, case patients)†	(1567, 879)	(1567, 518)	(1567, 230)
Q1‡	1.00 (referent)	1.00 (referent)	1.00 (referent)
Q2	0.87 (0.49 to 1.54)	0.81 (0.43 to 1.52)	0.90 (0.38 to 2.11)
Q3	1.27 (0.76 to 2.13)	1.13 (0.63 to 2.03)	1.71 (0.80 to 3.62)
Q4	0.86 (0.50 to 1.48)	0.85 (0.46 to 1.56)	0.87 (0.38 to 2.01)
Q5	0.76 (0.44 to 1.31)	0.71 (0.38 to 1.32)	0.69 (0.29 to 1.62)

* Adjusted for age and race by matching. Adjusted for family history of prostate cancer, diabetes, body mass index, and prostate-specific antigen in statistical model. CI = confidence interval; HR = hazard ratio.

† Numbers in subcohort and of case patients within each table cell are given in Supplementary Appendix Table 1 (available online).

‡ Quintile cutpoints for toenail selenium (μg/g) are 0.758, 0.832, 0.901, and 1.003.

Se in SELECT was 225 μg/L. Based on 101 PCa case patients in the NPC, there was no effect of supplementation among men in the highest tertile of baseline plasma Se (>123.2 μg/L); supplementation decreased risk by 67% among men in the second tertile (106.8–123.2 μg/L) and by 86% in the first tertile (≤106.4 μg/L). Based on 73 case patients in the Negative Biopsy Trial, there were no differences in the risk of cancer between arms, either overall or stratified by tertile of baseline Se status. The analysis of our data using lower cutpoints for baseline toenail Se categories, in an attempt to replicate findings from the NPC, also showed no evidence of benefit from supplementation among men with low baseline Se status (data given in Results). Given these findings, we believe it reasonable to conclude that Se supplementation of men at the low range of Se intake common in US men will not reduce PCa risk.

Previous clinical and epidemiological studies provide little insight into the SELECT finding that Se supplementation of men with high Se status at baseline increased the risk of high-grade disease. This is because neither the NPC nor the Negative Biopsy Trial had enough high-grade case patients (both <40) to examine this relatively rare outcome, and in large cohort studies that have examined risk associated with supplemental Se use, the highest categories of exposure are far less than the 200 μg Se/d used in SELECT (14,22). One possible explanation is based on experimental studies in dogs, who develop spontaneous PCa similar to humans, among which both very low and high Se supplementation increased DNA damage in prostate tissue (23). Future analysis of biological specimens from SELECT may be useful to address questions about biological mechanisms.

SELECT findings on vitamin E supplementation suggest complex interactions between Se and vitamin E. The overall study finding, that supplementation with vitamin E alone increased cancer risk by 17%, was unexpected and remains unexplained (3). Here we add two additional complexities: 1) the overall small increased risk for total cancer attributed to vitamin E supplementation (13% during the period examined in the analyses given here) was actually a 63% increased risk among men in the lower 40th percentile of baseline toenail Se; and 2) this increase in risk was larger for high-grade compared with low-grade cancer (111% vs 46%). An interaction between vitamin E and Se has long been hypothesized because of their activities in preventing lipid peroxidation (24), and in some animal models they have synergistic effects on cancer prevention (25); however, this early research has not been replicated in more recent studies (26). It is possible that some of the inconsistency of findings on high-dose vitamin E supplementation and PCa risk (27–31) could be attributable to differences in the underlying Se status of study populations. None of the previously completed vitamin E supplementation trials have examined their results stratified by baseline Se status, which we judge would be worthwhile.

The strengths of this research include its experimental design, large number of cancer case patients, and the use of toenail Se concentration, a biomarker of long-term Se exposure (32).

There are several important limitations. As a measure of Se exposure, toenail Se will have error because of factors that affect Se absorption and metabolism, and it does not measure the functional activity of Se-dependent proteins in prostate or other tissues. There were too few black case patients (n = 243) to yield stable race-specific results, however, overall results in blacks were similar to those from other races. The modest number of high-grade (Gleason 7–10) cancers precluded a separate analysis of highly-aggressive Gleason 8–10 cancers (n = 101). It also motivated the use of a posteriori statistical contrasts that 1) combined quintiles of toenail Se to characterize effects of low and high Se status and 2) combined the Se only with the Se plus vitamin E study arms to characterize effects of Se supplementation. The *P* values of these a posteriori statistical tests are not adjusted for multiple contrasts and may be further inflated because cutpoints to define high and low Se exposure were determined after examining initial results. Lastly, SELECT tested the most commonly available forms of supplemental Se and vitamin E, and it is possible, although in our opinion unlikely, that results would differ if alternative supplement formulations were used.

The findings from SELECT add to an already complex set of findings on the use of high-dose micronutrient supplementation for the primary prevention of cancer. A comprehensive review of this literature suggests that effects of supplementation are dependent upon the nutrient status of the target population, such that supplementation of populations with adequate nutrient status, leading to supraphysiological exposure, has either no effect or increases cancer risk (33). In SELECT, supplementation with Se increased the risk of high-grade PCa among men with high Se stores at baseline, whereas supplementation with vitamin E

Table 4. Effect of selenium supplementation on risk of total, low-grade, and high-grade prostate cancer within quintiles of baseline toenail selenium concentration

	Supplementation effect				Supplementation effect		
	Total	Low-grade	High-grade		Total	Low-grade	High-grade
Quintile	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	Quintiles	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*
Selenium only vs placebo							
No. (subcohort, case patients)†							
	(1554, 838)	(1554, 501)	(1554, 231)				
Q1‡	0.83 (0.46 to 1.48)	0.73 (0.37 to 1.44)	1.17 (0.52 to 2.63)	Q1–Q3	0.91 (0.68 to 1.24)	0.89 (0.63 to 1.25)	0.98 (0.65 to 1.49)
Q2	1.09 (0.64 to 1.85)	1.14 (0.63 to 2.05)	0.96 (0.42 to 2.17)	Q4–Q5	1.24 (0.85 to 1.81)	1.10 (0.72 to 1.68)	1.62 (0.95 to 2.77)
Q3	0.86 (0.53 to 1.37)	0.82 (0.47 to 1.42)	0.89 (0.48 to 1.65)				
Q4	1.19 (0.70 to 2.04)	1.07 (0.58 to 1.96)	1.52 (0.71 to 3.25)				
Q5	1.29 (0.76 to 2.19)	1.13 (0.62 to 2.06)	1.74 (0.81 to 3.72)				
$P_{interaction}$§	.27	.45	.29		.21	.45	.15
Selenium + vitamin E vs placebo							
No. (subcohort, case patients)†							
	(1548, 830)	(1548, 296)	(1548, 230)				
Q1‡	1.00 (0.57 to 1.77)	0.89 (0.47 to 1.70)	1.04 (0.45 to 2.41)	Q1–Q3	1.03 (0.76,1.40)	1.03 (0.73,1.45)	0.94 (0.61,1.44)
Q2	1.18 (0.68 to 2.05)	1.23 (0.67 to 2.28)	1.13 (0.51 to 2.48)	Q4–Q5	1.29 (0.90,1.86)	1.08 (0.71,1.64)	2.24 (1.34,3.75)
Q3	0.96 (0.59 to 1.55)	0.98 (0.57 to 1.70)	0.81 (0.42 to 1.57)				
Q4	1.37 (0.84 to 2.22)	1.14 (0.66 to 1.98)	2.21 (1.10 to 4.45)				
Q5	1.21 (0.70 to 2.07)	1.01 (0.54 to 1.88)	2.24 (1.05 to 4.77)				
$P_{interaction}$§	.53	.87	.05		.36	.87	.01
Any selenium vs placebo							
No. (subcohort, case patients)†							
	(2325, 1264)	(2325, 596)	(2325, 360)				
Q1‡	0.91 (0.55 to 1.50)	0.81 (0.46 to 1.42)	1.11 (0.54 to 2.30)	Q1–Q3	0.97 (0.75 to 1.27)	0.96 (0.71 to 1.29)	0.96 (0.67 to 1.39)
Q2	1.14 (0.71 to 1.83)	1.19 (0.70 to 2.02)	1.04 (0.52 to 2.09)	Q4–Q5	1.27 (0.92 to 1.74)	1.09 (0.76 to 1.56)	1.91 (1.20 to 3.05)
Q3	0.90 (0.60 to 1.36)	0.89 (0.56 to 1.43)	0.85 (0.50 to 1.47)				
Q4	1.28 (0.82 to 1.99)	1.10 (0.67 to 1.82)	1.86 (0.98 to 3.54)				
Q5	1.25 (0.79,1.98)	1.07 (0.64,1.81)	1.96 (1.00,3.86)				
$P_{interaction}$§	.32	.59	.09		.21	.59	.02

* Adjusted for age and race by matching. Adjusted for family history of prostate cancer, diabetes, body mass index, and prostate-specific antigen in statistical model. CI, confidence interval; HR, hazard ratio.

† Numbers in subcohort and of case patients within each table cell are given in Supplementary Appendix Table 1 (available online).

‡ Quintile cutpoints for toenail selenium (μg/g) are 0.758, 0.832, 0.901, and 1.003.

§ Two-Sided *P* value for Cox regression coefficients for the cross-product of treatment with a linear term for quintile of toenail selenium. In a posteriori contrasts for low vs high categories of baseline toenail selenium, two-sided *P* value for Cox regression coefficients for the cross-product of treatment with categorized toenail selenium.

Table 5. Effect of vitamin E supplementation on risk of total, low-grade, and high-grade prostate cancer within quintiles of baseline toenail selenium concentration

	Supplementation effect				Supplementation effect		
	Total	Low-grade	High-grade		Total	Low-grade	High-grade
Quintile	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	Quintiles	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*
Vitamin E vs placebo							
No. (subcohort, case patients)†	(1569, 879)	(1569, 518)	(1569, 230)				
Q1‡	1.39 (0.81 to 2.38)	1.20 (0.65 to 2.20)	1.63 (0.74 to 3.61)	Q1–Q2	1.63 (1.11 to 2.40)	1.46 (0.95 to 2.25)	2.11 (1.22 to 3.65)
Q2	1.92 (1.13 to 3.26)	1.77 (0.97 to 3.22)	2.79 (1.33 to 5.88)	Q3–Q5	0.96 (0.71 to 1.28)	0.90 (0.64 to 1.25)	0.90 (0.60 to 1.36)
Q3	0.93 (0.57 to 1.53)	0.94 (0.54 to 1.64)	0.74 (0.38 to 1.43)				
Q4	0.97 (0.59 to 1.59)	0.76 (0.43 to 1.34)	1.19 (0.57 to 2.47)				
Q5	0.98 (0.58 to 1.66)	1.00 (0.55 to 1.81)	0.85 (0.38 to 1.94)				
$P_{interaction}$§	.13	.24	.12		.03	.08	.02

* Adjusted for age and race by matching. Adjusted for family history of prostate cancer, diabetes, body mass index, and prostate-specific antigen in statistical model.

† Numbers in subcohort and of case patients within each table cell are given in Supplementary Appendix Table 1 (available online).

‡ Quintile cutpoints for toenail selenium (μg/g) are 0.758, 0.832, 0.901, and 1.003.

§ Two-Sided *P* value for Cox regression coefficients for the cross-product of treatment with a linear term for quintile of toenail selenium. In a posteriori contrasts for low vs high categories of baseline toenail Se, two-sided *P* value for Cox regression coefficients for the cross-product of treatment with categorized toenail selenium.

increased the risk (primarily of high-grade cancer) among men with low Se stores at baseline. It is unlikely that there will be another trial of high-dose Se or vitamin E supplementation for the primary prevention of PCa, and thus public health recommendations must be made without replication of these unexpected findings. Given the risks and lacking evidence of benefit for other diseases of equal or greater public health importance than PCa, men aged greater than 55 should avoid supplementation with either vitamin E or Se at doses that exceed recommended dietary intakes.

References

1. Lippman SM, Goodman PJ, Klein EA, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *J Natl Cancer Inst*. 2005;97(2):94–102.
2. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers. The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2009;301(1):39–51.
3. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306(14):1549–1556.
4. Hoque A, Albanes D, Lippman SM, et al. Molecular epidemiologic studies within the selenium and vitamin E cancer prevention trial (SELECT). *Cancer Causes Control*. 2001;12(7):627–633.
5. Duffield-Lillico AJ, Dalkin BL, Reid ME, et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int*. 2003;91(7):608–612.
6. Gleason DF. Histologic grading of prostate cancer: a perspective. *Human Pathol*. 1992;23(3):273–279.
7. Morris JS, Stampfer MJ, Willett W. Dietary selenium in humans: toenails as an indicator. *Biol Trace Element Res*. 1983;5(6):529–537.
8. Hunter DJ, Morris JS, Chute CG, et al. Predictors of selenium concentration in human toenails. *Am J Epidemiol*. 1990;132(1):114–122.
9. Longnecker MP, Taylor PR, Levander OA, et al. Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. *Am J Clin Nutr*. 1991;53(5):1288–1294.
10. Longnecker MP, Stram DO, Taylor PR, et al. Use of selenium concentration in whole blood, serum, toenails, or urine as a surrogate measure of selenium intake. *Epidemiology*. 1996;7(4):384–390.
11. Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst*. 1998;90(16):1219–1224.
12. Morris JS, Ngwenyama RA, Guthrie JM, et al. Quality control in the neutron activation analysis of biological markers for selenium in epidemiological investigations. *J Radioanal Nucl Chem*. 2008;276(1):7–13.
13. Helzlsouer KJ, Huang H-Y, Alberg AJ, et al. Association between α-tocopherol, γ-tocopherol, selenium and subsequent prostate cancer. *J Natl Cancer Inst*. 2000;92(24):2018–2023.
14. Hurst R, Hooper L, Norat T, et al. Selenium and prostate cancer: systematic review and meta-analysis. *Am J Clin Nutr*. 2012;96(1):111–122.
15. World Cancer Research Fund/AICR. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR; 2007.
16. Etminan M, FitzGerald JM, Gleave M, et al. Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis. *Cancer Causes Control*. 2005;16(9):1125–1131.
17. Brinkman M, Reulen RC, Kellen E, et al. Are men with low selenium levels at increased risk of prostate cancer? *Eur J Cancer*. 2006;42(15):2463–2471.
18. Dennert G, Zwahlen M, Brinkman M, et al. Selenium for preventing cancer. *Cochrane Database Syst Rev*. 2011; Issue 5. Art. No: CD005195. doi:10.1002/14651858.CD005195.pub2.
19. Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst*. 1998;90(16):1219–1224.

20. Geybels MS, Verhage BAJ, van Schooten FJ, et al. advanced prostate cancer risk in relation to toenail selenium levels. *J Natl Cancer Inst*. 2013;105(18):1394–1401.
21. Clark LC, Combs GF, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*. 1996;276(24):1957–1963.
22. Richman EL, Chan JM. Selenium and prostate cancer: the puzzle isn't finished yet. *Am J Clin Nutr*. 2012;96(1):1–2.
23. Chiang EC, Shen S, Kengeri SS, et al. Defining the optimal selenium dose for prostate cancer risk reduction: insights from the U-shaped relationship between selenium status, dna damage, and apoptosis. *Dose Response*. 2010;8(3):285–300.
24. Combs GF, Scott ML. Nutritional interrelationships of vitamin E and selenium. *Bioscience*. 1977;27(7):467–473.
25. Horvath PM, Ip C. Synergistic effect of vitamin E and selenium in the chemoprevention of mammary carcinogenesis in rats. *Cancer Res*. 1983;43(11):5335–5341.
26. McCormick DL, Rao KVN, Steele VE, et al. Chemoprevention of rat prostate carcinogenesis by 9-*cis*-retinoic acid. *Cancer Res*. 1999;52(3):521–524.
27. Peters U, Littman AJ, Kristal AR, et al. Vitamin E and selenium supplementation and risk of prostate cancer in the VITamins And Lifestyle (VITAL) study cohort. *Cancer Causes Control*. 2008;19(1):75–87.
28. Kirsh VA, Hayes RB, Mayne ST et al. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst*. 2006;98(4):245–254.
29. Rodriguez C, Jacobs EJ, Mondul AM, et al. Vitamin E supplements and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev*. 2004;13(3):378–382.
30. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men. The Physicians' Health Study II Randomized Controlled Trial. *JAMA*. 2009;301(1):52–62.
31. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New Engl J Med*. 1994;330(15):1029–1035.
32. Garland M, Morris JS, Colditz GA, et al. Toenail trace element levels and breast cancer: a prospective study. *Am J Epidemiol*. 1996;144(7):653–660.
33. Mayne ST, Ferrucci LM, Cartmel B. Lessons learned from randomized clinical trials of micronutrient supplementation for cancer prevention. *Annu Rev Nutr*. 2012;32(1):369–390.

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