

Selenium- or Vitamin E-Related Gene Variants, Interaction with Supplementation, and Risk of High-Grade Prostate Cancer in SELECT

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Abstract

Background: Epidemiologic studies and secondary analyses of randomized trials supported the hypothesis that selenium and vitamin E lower prostate cancer risk. However, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed no benefit of either supplement. Genetic variants involved in selenium or vitamin E metabolism or transport may underlie the complex associations of selenium and vitamin E.

Methods: We undertook a case-cohort study of SELECT participants randomized to placebo, selenium, or vitamin E. The subcohort included 1,434 men; our primary outcome was high-grade prostate cancer ($N = 278$ cases, Gleason 7 or higher cancer). We used weighted Cox regression to examine the association between SNPs and high-grade prostate cancer risk. To assess effect modification, we created interaction terms between randomization arm and genotype and calculated log likelihood statistics.

Results: We noted statistically significant ($P < 0.05$) interactions between selenium assignment, SNPs in *CAT*, *SOD2*, *PRDX6*, *SOD3*, and *TXNRD2*, and high-grade prostate cancer risk. Statistically significant SNPs that modified the association of vitamin E assignment and high-grade prostate cancer included *SEC14L2*, *SOD1*, and *TTPA*. In the placebo arm, several SNPs, hypothesized to interact with supplement assignment and risk of high-grade prostate cancer, were also directly associated with outcome.

Conclusion: Variants in selenium and vitamin E metabolism/transport genes may influence risk of overall and high-grade prostate cancer, and may modify an individual man's response to vitamin E or selenium supplementation with regards to these risks.

Impact: The effect of selenium or vitamin E supplementation on high-grade prostate cancer risk may vary by genotype. *Cancer Epidemiol Biomarkers Prev*; 25(7); 1050–8. ©2016 AACR.

Introduction

Primary prevention of prostate cancer holds promise to reduce the burden of this disease, yet specific preventive factors remain

elusive. In the 1990s, secondary analyses of two randomized clinical trials, the Alpha-Tocopherol & Beta Carotene Cancer Prevention Trial (ATBC) and the Nutritional Prevention of Cancer Trial, yielded provocative results suggesting that supplementation with selenium or vitamin E might markedly reduce the risk of clinically significant prostate cancer (1–3). Moreover, there was corroborating epidemiologic evidence suggesting that higher endogenous levels of vitamin E or selenium might be associated with lower risk of prostate cancer (4–9).

These data supported the development and implementation of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in which 35,533 men were randomized to supplementation with 200 $\mu\text{g}/\text{day}$ selenium (L-selenomethionine) alone, 400 IU/day vitamin E (α -tocopheryl acetate) alone, both, or placebo. The men were cancer-free at baseline and were followed prospectively for prostate cancer incidence. The trial was stopped early due to lack of efficacy of either supplement, and subsequent reports have indicated that men assigned to the vitamin E arm had a 17% greater risk of overall prostate cancer [HR 1.17; 99% confidence interval (CI), 1.004–1.36; $P = 0.008$; ref. 10]. Furthermore, men with higher baseline selenium or α -tocopherol levels assigned to selenium supplementation had greater risk of high-grade prostate cancer, while men assigned to vitamin E supplements who had low baseline selenium levels were at increased risk of prostate cancer (11, 12).

The SELECT results clearly do not support the use of supplemental selenium or vitamin E in adult life for primary prevention of prostate cancer. However, there is intriguing data that variation

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

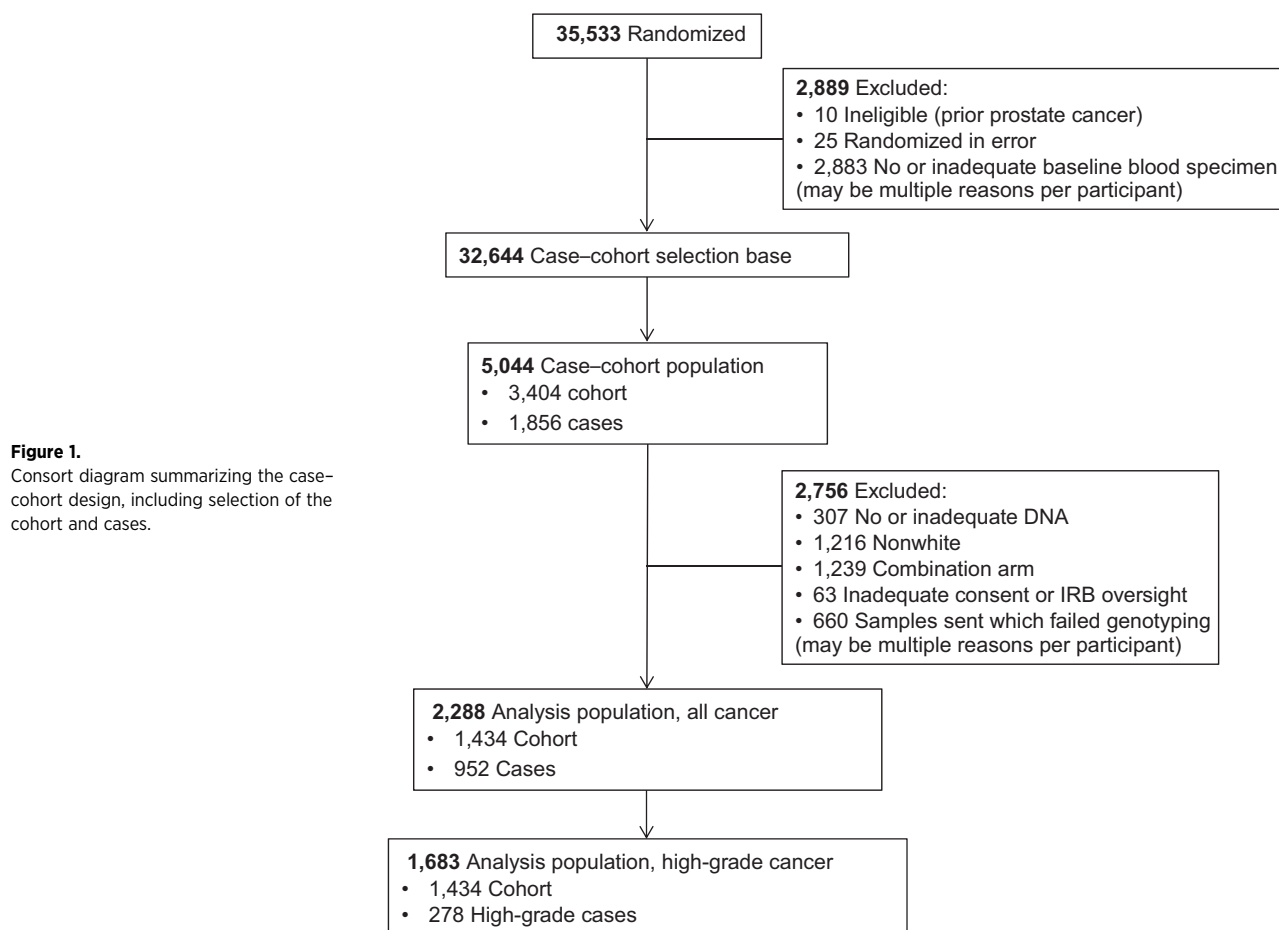
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Clinical Trial registration ID (for SELECT): NCT00006392.

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in genes associated with selenium or vitamin E metabolism or transport may underlie the complex associations and unexpected results among the clinical trials (13–17). We leveraged the unique study design of SELECT and evaluated variation across 21 genes that were hypothesized *a priori* to be related to selenium or vitamin E metabolism or transport (Supplementary Table S1) and the risk of overall and high-grade prostate cancer. We specifically hypothesized that variation in these genes may influence prostate cancer risk as a function of randomization to vitamin E or selenium supplementation (compared with placebo), particularly for risk of high-grade prostate cancer.

Materials and Methods

Study population

SELECT recruited 35,533 men from sites in the United States, Canada, and Puerto Rico. Details on the eligibility and enrollment methods can be found in Lippman and colleagues, 2009 (10). To control for population stratification, we limited the study to Caucasian men with available germline DNA samples, who consented to use the sample, and who were randomized to placebo, selenium alone, or vitamin E alone. We did not include the combination arm of vitamin E and selenium given the apparent interaction between the two supplements and prostate cancer risk (10). We used a case-cohort design and sampled the subcohort stratified by age group (55–59, 60–64,

65–69, ≥ 70 years). Figure 1 presents an overview of the case-cohort sampling for this study. The subcohort included 1,434 men, of whom 98 had been diagnosed with prostate cancer, including 29 with high-grade disease (defined as Gleason 7 or higher). We further included all remaining 854 prostate cancer cases, for a total of 952 cases of whom 278 had high-grade disease.

Genotyping

We selected 21 genes that had previously been reported to interact either with selenium or vitamin E levels, metabolism, or transport, in relation to prostate cancer risk (Supplementary Table S1). These included 18 genes with putative selenium-related antioxidant properties (*CAT*, *GPX1*, *GPX3*, *GPX4*, *PRDX1-6*; *SELENBP1*, *SEP15*, *SEPP1*, *SOD1*, *SOD2*, *SOD3*, *TXNRD1*, *TXNRD2* Fig. 2; ref. 14, 16, 18–23); 2 genes involved in vitamin E transport (*SEC14L2*, *TTPA*) (17); and a DNA repair gene that interacted with vitamin E and prostate cancer in multiple reports (*XRCC1*; refs. 24–28). We focused on SNPs to capture variation across these genes. The inclusion of the peroxiredoxin genes (*PRDX 1-6*) was more exploratory, based on limited data suggesting their (potentially selenium-dependent (29)) antioxidant properties, and corroborative studies indicating that somatic expression of *PRDX* influences androgen pathways in prostate cancer (29–39). While chosen primarily for their putative interaction with selenium, for completeness,

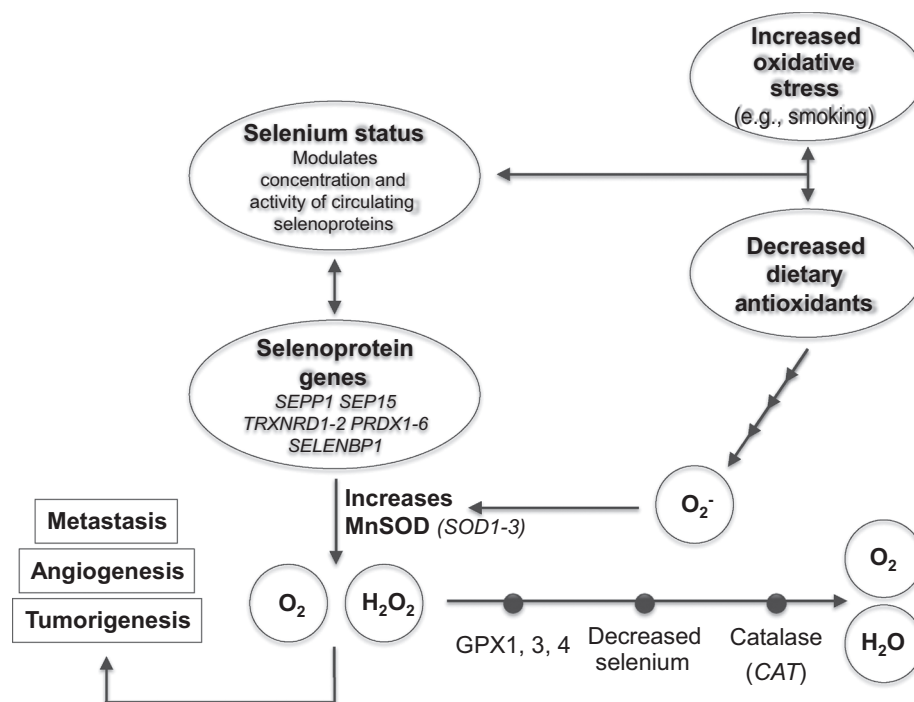


Figure 2. Schematic overview of the potential role of variants in genes in the antioxidant pathways to modify the effect of selenium on the risk of aggressive prostate cancer.

we also examined the interaction of *SOD1*, *SOD2*, and *SOD3* with vitamin E assignment, based on a prior report of an interaction for prostate cancer (40).

Using the HapMap3 R28 database, we undertook a haplotype tagging approach to capture genetic variation with an $R^2 > 0.80$ across each of the 21 genes, as well as 5 kb pairs up- and downstream using pairwise tagging. Selection was restricted to SNPs with a minor allele frequency $>5\%$ in the International HapMap CEPH samples. We tagged 135 SNPs. Genotyping was performed on DNA extracted from buffy coat using the Sequenom iPLEX platform assay at the Genotyping Core Facility at Children's Hospital, Boston. On each 96-well plate, we included 4% quality control specimens. A total of 130 SNPs had high genotyping success ($>90\%$) (Supplementary Table S1); the 5 SNPs that failed genotyping (rs1001179, rs35741824, rs1799895, rs548649, and rs5993853) were excluded from future analyses. We further excluded 6 SNPs with a minor allele frequency in our study population $<5\%$ (*GPX3* rs8177425, *PRDX2* rs35866106, *PRDX4* rs6653694, *SOD1* rs17885303, *TXNRD2* rs4485648, *XRCC1* rs25489). In addition, we excluded data from 318 participants because of low genotyping quality ($<85\%$). The sample size total varies by SNP, as genotyping a particular SNP may have failed for some participants.

Outcome and statistical analyses

Our primary outcome was time to diagnosis of high-grade prostate cancer, defined as a Gleason 7 or greater tumor. We additionally examined the risk of prostate cancer overall as a secondary outcome.

We used Cox proportional hazards models to examine the association between each SNP and risk of high-grade prostate cancer, as well as overall prostate cancer risk. Models were stratified by the four age groups to account for the case-cohort design, and weighted based on the fraction of men selected to

the cohort from each stratum compared with the total trial analysis population (Caucasian, 3 treatment arms). A second type of weight was used to construct the pseudolikelihood function, where all cohort members were weighted equally regardless of future prostate cancer diagnosis, and cases outside of the cohort were weighted only at the time of diagnosis as described by Prentice (41). The sampling and case-cohort weights were used to calculate HR and 95% confidence intervals (CI) of the association between each SNP and prostate cancer risk. For analyses of high-grade prostate cancer, participants in the subcohort diagnosed with low-grade prostate cancer were censored at time of diagnosis.

For the associations of the genotypes and prostate cancer risk, we calculated HRs and 95% CIs using a codominant genetic model, and estimated P values of linear trend across the genotypes using an additive model. For homozygous rare genotypes with a frequency less than 5%, we modeled SNPs using a dominant genetic model. To assess effect modification, we created interaction terms between randomization arm and each genotype assuming an additive model and calculated log likelihood statistics. Supplementary Table S1 presents the minor allele frequencies (MAF) of the investigated 130 SNPs in the 21 antioxidant-related genes of interest and also summarizes the specific evaluation of SNP-treatment interactions which were restricted depending on the gene function and its hypothesized role in either selenium or vitamin E. Five SNPs violated Hardy-Weinberg Equilibrium ($P < 0.001$) after sample filtering based on Pearson's goodness of fit, but these were retained in the analyses.

Analyses were performed with SAS statistical software versions 9.3 and 9.4 (SAS Institute) and P values are two-sided. As we undertook a pathway-based approach to test specific *a priori* hypotheses, we did not control for multiple comparisons; $P < 0.05$ was considered statistically significant.

Results

Table 1 compares baseline demographic, lifestyle, and clinical factors among men in the subcohort as well as with high-grade prostate cancer, separately in the placebo arm, selenium arm, and vitamin E arm. The median age of men in the subcohort was 63 years; among the men with high-grade disease, the median age was 64–65 years.

Table 2 presents statistically significant ($P < 0.05$) results for effect modification between antioxidant SNPs, selenium assignment, and risk of high-grade prostate cancer. This analysis included 1,109 participants randomized to selenium alone or placebo, including 934 in the subcohort and 175 high-grade cases. The identified SNPs included several in *CAT* (rs10836233, rs533425, rs7944397), 1 in *SOD2* (rs7855), 1 in *PRDX6* (rs11580117), and multiple SNPs in *SOD3* (rs699473, rs8192287) and *TXNRD2* (rs3804047, rs8141691). Full results for all analyzed SNPs and interactions with selenium assignment, for both high-grade prostate cancer and overall disease, can be found in Supplementary Table S2.

Table 3 provides statistically significant SNPs that appeared to modify the association of vitamin E assignment and risk of high-grade prostate cancer. This analysis included 1,124 participants (943 controls and 181 high-grade prostate cancer cases) in the vitamin E alone and placebo arms. The significant SNPs included *SEC14L2* (rs5753106) and *TTPA* (rs12679996, rs4606052). Full results for all analyzed SNPs and interactions with vitamin E assignment, for both high-grade prostate cancer and overall disease, can be found in Supplementary Table S3.

We also identified several SNPs that were nominally statistically significant ($P < 0.05$) for overall prostate cancer risk in the placebo arm only (Table 4), several of which were also associated with high-grade prostate cancer. Of note, SNPs in *CAT* (rs10836233, rs533425, rs7944397), *SEC14L2* (rs5753106), *SOD2* (rs2070424), *TTPA* (rs12679996, rs4606052), and *TXNRD2* (rs8141691) that were significantly associated with high-grade risk overall were also identified as modifiers of randomized supplement assignment. Full results for the association between each of the individual SNPs and risk of overall and high-grade prostate cancer are in Supplementary Table S4.

Discussion

In this large case-cohort study nested within SELECT, we found that genetic variants in several key antioxidant genes were nominally associated with risk of high-grade prostate cancer, including SNPs in *CAT*, *GPX1*, *SOD1*, *SOD2*, *SOD3*, *TXNRD2*, *SEC14L2*, and *TTPA*. Moreover, the associations of several of these genetic variants and high-grade prostate cancer differed as a function of selenium or vitamin E supplementation. For example, we observed significant effect modification of three SNPs in *CAT* by selenium supplementation. For rs7944397, we found an inverse association of the rare variant allele with high-grade disease among men in the placebo arm, whereas there was no association among men in the selenium arm. Similarly, for rs533425, we observed a significantly increased risk with the rare variant allele in the placebo arm, and no association in the supplementation arm. Given the high compliance of men in SELECT, these data suggest that the effect of these genetic variants on high-grade prostate cancer depends on endogenous levels of selenium.

It is noteworthy that none of the SNPs examined in *SEP15*, *GPX3*, *GPX4*, *SEPP1*, or *XRCC1* were associated with high-grade prostate cancer in SELECT, either individually or through an interaction with selenium or vitamin E supplement assignment, whereas at least one prior report had indicated a potential direct association or interaction between these genes and vitamin E or selenium intake or levels, and risk of prostate cancer (13–16, 19, 20, 27, 28, 42, 43).

SOD2, *GPX1*, and *CAT* have been researched most commonly in relation to various human diseases, including asthma, cardiovascular disease, diabetes, and cancer, including prostate cancer (44). Of these, *SOD2* has been investigated the most with regards to prostate cancer, and several (45–47), but not all (48) meta-analyses have reported significant associations between genetic variants in *SOD2* and risk of prostate cancer, particularly for more aggressive disease. We and others have previously reported on potential interaction effects between SNPs in *SOD1*, *SOD2*, selenoprotein, or seleno-binding proteins, and selenium status, and risk of aggressive prostate cancer (14, 16, 18, 19, 22, 43, 49–51). SNPs in *TXNRD1* and *TXNRD2* have been reported to modify the association of circulating selenium and risk of aggressive prostate cancer (52); and variants in *TXNRD1* and *GPX4* have been associated with prostate cancer-specific mortality, although results for the latter were not statistically significant after consideration for multiple comparisons (20). Lower *CAT* activity measured in blood has been associated with higher Gleason grade in one small study (53). The exact function of all the SNPs noted to interact potentially with selenium assignment for risk of high-grade prostate cancer, is not known. However, rs7855 is in the 3' UTR of *SOD2* and could be influencing splicing or acting as an enhancer. Also, rs10836233 in *CAT* is in linkage disequilibrium (LD; $r^2 = 0.93$) with rs11032717 in *ELF5*, which is an ETS transcription factor gene that has been implicated in androgen sensitivity and aggressiveness of prostate cancer cell lines (54–56); and rs533425 in *CAT* is in moderate LD ($R^2 = 0.42$) with the functional 262 C/T SNP (rs1001179) that has been associated with advanced stage prostate cancer risk (57).

Data from the ATBC trial indicated there is potential effect modification between a variant in *SEC14L2* (rs2299829), vitamin E assignment, and risk of prostate cancer; and between variants in *SEC14L2* (rs2299825, rs2299826), dietary intake of α -tocopherol, and risk of advanced prostate cancer (17). This is noteworthy given the strong LD ($r^2 = 0.86$) between rs2299825 with rs5753106 that we identified in the current study. We previously reported on potential interaction effects between *GPX4*, γ -tocopherol, and risk of lethal prostate cancer (58). Our observation of potential interaction between a variant in *SEC14L2* (rs5753106), vitamin E assignment, and high-grade prostate cancer was somewhat consistent with the prior report from the ATBC trial, as rs2299825 is in strong LD with rs5753106. In addition, rs5753106 in *SEC14L2* is strong LD with the 3'- and 5'-UTR regions for several other genes, including: *SF3A1*, *CCDC157*, and *RNF215*. Furthermore, we identified a potential interaction between vitamin E assignment and rs4606052 in *TTPA* and risk of high-grade prostate cancer. While rs4606052 is intronic, it is in strong LD ($r^2 = 0.99$) with rs4587328 in the 3'-UTR of *TTPA*, which encodes instructions for making α -tocopherol transport protein that controls the delivery and distribution of vitamin E from food throughout the body.

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Table 1. Distribution of baseline demographic and health-related characteristics by treatment arm, analysis population (n = 1,683)^a

Characteristic	Placebo arm		Selenium arm		Vitamin E arm	
	Cohort ^b (n = 481) N (%)	High-grade ^c (n = 78) N (%)	Cohort ^b (n = 476) N (%)	High-grade ^c (n = 97) N (%)	Cohort ^b (n = 477) N (%)	High-grade ^c (n = 103) N (%)
Age, years						
Median (IQR)	63 (59,68)	65 (60,69)	63 (59,69)	64 (60,69)	63 (59,68)	65 (61,69)
<60	126 (26.2%)	19 (24.4%)	131 (27.5%)	22 (22.7%)	120 (25.2%)	14 (13.6%)
60–64	150 (31.2%)	20 (25.6%)	135 (28.4%)	29 (29.9%)	146 (30.6%)	33 (32.0%)
65–69	116 (24.1%)	22 (28.2%)	121 (25.4%)	26 (26.8%)	131 (27.5%)	33 (32.0%)
≥70	89 (18.5%)	17 (21.8%)	89 (18.7%)	20 (20.6%)	80 (16.8%)	23 (22.3%)
Family history of prostate cancer						
No	406 (84.4%)	56 (71.8%)	403 (84.7%)	71 (73.2%)	396 (83.0%)	78 (75.7%)
Yes	74 (15.4%)	22 (28.2%)	73 (15.3%)	26 (26.8%)	81 (17.0%)	25 (24.3%)
Unknown	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Body mass index, kg/m ²						
Median (IQR)	28.1 (25.6,31.4)	28.5 (26.1,30.5)	27.7 (25.6,30.8)	28 (25.5,31.1)	28.1 (25.8,31)	27.8 (25.2,31.7)
<25	93 (19.3%)	14 (17.9%)	89 (18.7%)	18 (18.6%)	83 (17.4%)	24 (23.3%)
25–<30	223 (46.4%)	40 (51.3%)	243 (51.1%)	47 (48.5%)	243 (50.9%)	46 (44.7%)
≥30	164 (34.1%)	24 (30.8%)	143 (30.0%)	31 (32.0%)	150 (31.4%)	33 (32.0%)
Unknown	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (1.0%)	1 (0.2%)	0 (0.0%)
Diabetes						
No	441 (91.7%)	73 (93.6%)	437 (91.8%)	88 (90.7%)	430 (90.1%)	95 (92.2%)
Yes	40 (8.3%)	5 (6.4%)	39 (8.2%)	9 (9.3%)	47 (9.9%)	8 (7.8%)
Prostate-specific antigen (ng/mL) ^d						
Median (IQR)	1.1 (0.7,1.8)	2.2 (1.5,3.1)	1.2 (0.7,2)	2.5 (1.8,3.2)	1.1 (0.6,1.9)	2.4 (1.7,3.1)
<1.0	211 (43.9%)	6 (7.7%)	184 (38.7%)	7 (7.2%)	200 (41.9%)	9 (8.7%)
1.01–1.99	165 (34.3%)	24 (30.8%)	166 (34.9%)	26 (26.8%)	161 (33.8%)	27 (26.2%)
2.00–2.99	61 (12.7%)	25 (32.1%)	77 (16.2%)	30 (30.9%)	75 (15.7%)	37 (35.9%)
3.00–3.99	44 (9.1%)	23 (29.5%)	49 (10.3%)	34 (35.1%)	40 (8.4%)	30 (29.1%)
≥4.00	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Smoking status						
Never	201 (41.8%)	34 (43.6%)	206 (43.3%)	48 (49.5%)	200 (41.9%)	50 (48.5%)
Former	252 (52.4%)	39 (50.0%)	241 (50.6%)	45 (46.4%)	256 (53.7%)	49 (47.6%)
Current	25 (5.2%)	3 (3.8%)	29 (6.1%)	4 (4.1%)	20 (4.2%)	4 (3.9%)
Unknown	3 (0.6%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Highest level of education completed						
High school or less	96 (20.0%)	10 (12.8%)	91 (19.1%)	22 (22.7%)	81 (17.0%)	23 (22.3%)
Some college or vocational school	113 (23.5%)	20 (25.6%)	135 (28.4%)	23 (23.7%)	129 (27.0%)	22 (21.4%)
College graduate or higher	268 (55.7%)	46 (59.0%)	249 (52.3%)	52 (53.6%)	266 (55.8%)	58 (56.3%)
Unknown	4 (0.8%)	2 (2.6%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Marital status						
Currently married/cohabitating	421 (87.5%)	66 (84.6%)	391 (82.1%)	82 (84.5%)	414 (86.8%)	86 (83.5%)
Previously married	45 (9.4%)	7 (9.0%)	62 (13.0%)	13 (13.4%)	46 (9.6%)	15 (14.6%)
Never married	12 (2.5%)	3 (3.8%)	21 (4.4%)	2 (2.1%)	15 (3.1%)	2 (1.9%)
Unknown	3 (0.6%)	2 (2.6%)	2 (0.4%)	0 (0.0%)	2 (0.4%)	0 (0.0%)
% of annual PSA tests done						
<25%	47 (9.8%)	2 (2.6%)	46 (9.7%)	3 (3.1%)	36 (7.5%)	2 (1.9%)
25–<50%	47 (9.8%)	7 (9.0%)	54 (11.3%)	5 (5.2%)	56 (11.7%)	5 (4.9%)
50–<75%	185 (38.5%)	30 (38.5%)	167 (35.1%)	35 (36.1%)	182 (38.2%)	38 (36.9%)
75–<100%	154 (32.0%)	28 (35.9%)	155 (32.6%)	23 (23.7%)	164 (34.4%)	25 (24.3%)
100%	48 (10.0%)	11 (14.1%)	54 (11.3%)	31 (32.0%)	39 (8.2%)	33 (32.0%)
Supplemental vitamin E (IU/day)						
Median (IQR)	15 (10,20)	15 (11,20)	15 (10,22)	16 (11,23)	15 (10,23)	15 (11,22)
<25	400 (83.2%)	64 (82.1%)	390 (81.9%)	77 (79.4%)	379 (79.5%)	85 (82.5%)
25–<50	68 (14.1%)	12 (15.4%)	74 (15.5%)	19 (19.6%)	89 (18.7%)	15 (14.6%)
50–<75	11 (2.3%)	2 (2.6%)	9 (1.9%)	1 (1.0%)	8 (1.7%)	3 (2.9%)
75–<100	0 (0.0%)	0 (0.0%)	3 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥100	2 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Supplemental selenium (µg/day)						
Median (IQR)	134 (101,172)	136 (97,183)	131 (94,174)	148 (113,189)	133 (98,170)	132 (96,175)
0	2 (0.4%)	2 (2.6%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
<50	14 (2.9%)	1 (1.3%)	17 (3.6%)	1 (1.0%)	9 (1.9%)	1 (1.0%)
50–<100	103 (21.4%)	18 (23.1%)	119 (25.0%)	16 (16.5%)	116 (24.3%)	28 (27.2%)
100–<150	170 (35.3%)	27 (34.6%)	159 (33.4%)	35 (36.1%)	175 (36.7%)	34 (33.0%)
≥150	192 (39.9%)	30 (38.5%)	180 (37.8%)	45 (46.4%)	176 (36.9%)	40 (38.8%)

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen.

^aAnalysis population was taken from the pre-existing SELECT case-cohort, restricted to Caucasian only, and to the Placebo, Selenium, and Vitamin E treatment arms only.^bThe cohort includes high-grade cases as follows: placebo arm, 9; selenium arm, 14; vitamin E arm, 6.^cHigh-grade cases are those with Gleason scores available for the diagnostic biopsy, with Gleason score 7 or higher.^dOne patient in the cohort had a baseline PSA of 10.6, although the study eligibility criteria required PSA ≤ 4.00. This participant was retained in analyses.

Table 2. Statistically significant ($P < 0.05$)^a interactions between antioxidant SNPs and selenium supplementation for risk of high-grade prostate cancer ($N = 1,109$)

Gene	Genotype	Genotype frequency		HR (95% CI) high-grade cancer		P^b
		N (%) cases	N (%) controls	Placebo arm	Selenium arm	
CAT	rs10836233					
	GG	145 (83.3%)	750 (80.6%)	1.0	1.02 (0.71-1.46)	0.005
	Any A	29 (16.7%)	180 (19.4%)	0.38 (0.18-0.83)	1.56 (0.90-2.71)	
	rs533425					
	GG	58 (33.3%)	351 (37.7%)	1.0	2.58 (1.42-4.68)	0.003
	AG	91 (52.3%)	443 (47.6%)	2.31 (1.29-4.13)	2.28 (1.28-4.07)	
AA	25 (14.4%)	136 (14.6%)	2.35 (1.13-4.87)	1.51 (0.67-3.37)		
rs7944397						
AA	143 (82.7%)	676 (72.8%)	1.0	1.02 (0.71-1.46)	0.02	
Any G	30 (17.3%)	253 (27.2%)	0.30 (0.14-0.62)	0.93 (0.55-1.60)		
PRDX6	rs11580117					
	AA	157 (89.7%)	843 (90.3%)	1.0	1.08 (0.75-1.54)	0.05
any G	18 (10.3%)	91 (9.7%)	0.72 (0.36-1.42)	1.84 (1.09-3.13)		
SOD2	rs7855					
	AA	157 (89.7%)	843 (90.3%)	1.0	1.46 (1.04-2.06)	0.02
Any G	18 (10.3%)	91 (9.7%)	2.14 (1.06-4.31)	0.77 (0.31-1.88)		
SOD3	rs699473					
	TT	73 (46.2%)	379 (44.1%)	1.0	2.18 (1.29-3.69)	0.04
	CT	37 (23.4%)	248 (28.8%)	1.40 (0.75-2.63)	1.11 (0.57-2.17)	
	CC	48 (30.4%)	233 (27.1%)	1.68 (0.92-3.07)	1.66 (0.88-3.11)	
	rs8192287					
	GG	153 (87.4%)	826 (88.5%)	1.0	1.44 (1.02-2.03)	0.04
any T	22 (12.6%)	107 (11.5%)	1.69 (0.89-3.23)	0.85 (0.39-1.87)		
TXNRD2	rs3804047					
	AA	87 (50.9%)	483 (52.8%)	1.0	1.78 (1.12-2.84)	0.03
	AG	72 (42.1%)	355 (38.8%)	1.48 (0.89-2.48)	1.51 (0.91-2.50)	
	GG	12 (7.0%)	77 (8.4%)	1.63 (0.67-3.94)	0.91 (0.33-2.50)	
	rs8141691					
	GG	65 (37.8%)	398 (43.1%)	1.0	1.64 (0.97-2.77)	0.05
AG	77 (44.8%)	388 (42.0%)	1.34 (0.78-2.31)	1.76 (1.06-2.94)		
AA	30 (17.4%)	138 (14.9%)	2.18 (1.11-4.25)	1.29 (0.65-2.56)		

^aFull results for all analyzed SNP × selenium assignment interactions are presented in Supplementary Table S2.

^b P for test for interaction between SNP and selenium assignment for the outcome of risk of high-grade prostate cancer.

While our data are consistent with prior reports indicating potential interactions between *SOD2*, *SOD3*, and *TXNRD2*, and selenium status and prostate cancer risk (43, 49–52), the specific SNPs previously implicated in each of these genes were not statistically significantly related to the outcomes of interest in the current study and not the same as the SNPs we identified (59). The differences across studies may in part be due to these genes having multiple roles at different time points in prostate cancer progression, and each study addressed a slightly different question based on their study populations and outcome definitions. Moreover,

the SNPs studied to date may be tagging to varying degree the true causal SNP within each of these genes. Further research is warranted to understand the downstream functional effects of these individual SNPs to confirm and elucidate the role of these genes on selenium metabolism and prostate cancer.

There are strengths and limitations to consider in assessing the impact of these findings. This is the first study to examine potential interactions between selenium-related genes and selenium supplementation and risk of aggressive prostate cancer using a randomized design. Leveraging the randomized

Table 3. Statistically significant ($P < 0.05$) interactions^a between antioxidant and vitamin E transport SNPs and vitamin E supplementation interactions ($P < 0.05$) for the risk of high-grade prostate cancer ($N = 1,124$)

Gene	Genotype	Genotype frequency		HR (95% CI) high-grade cancer		P^b
		N (%) cases	N (%) controls	Placebo arm	Vitamin E arm	
SECI4L2	rs5753106					
	AA	106 (59.2%)	543 (57.6%)	1.0	0.98 (0.64-1.49)	0.008
	AG	65 (36.3%)	347 (36.8%)	0.74 (0.44-1.24)	1.25 (0.80-1.97)	
GG	8 (4.5%)	52 (5.5%)	0.14 (0.02-0.99)	1.57 (0.63-3.91)		
TTPA	rs12679996					
	CC	69 (38.5%)	361 (38.9%)	1.0	2.29 (1.32-3.97)	0.001
	CT	77 (43.0%)	426 (46.0%)	1.34 (0.74-2.40)	1.70 (0.98-2.94)	
	TT	33 (18.4%)	140 (15.1%)	2.76 (1.44-5.29)	1.33 (0.60-2.97)	
	rs4606052					
	CC	62 (35.4%)	271 (29.9%)	1.0	2.25 (1.26-4.03)	0.007
CT	68 (38.9%)	434 (48.0%)	0.97 (0.53-1.79)	1.27 (0.71-2.25)		
TT	45 (25.7%)	200 (22.1%)	2.02 (1.06-3.82)	1.38 (0.69-2.75)		

^aFull results for all analyzed SNP × vitamin E assignment interactions are presented in Supplementary Table S3.

^b P for test for interaction between SNP and selenium assignment for the outcome of risk of high-grade prostate cancer.

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Table 4. Statistically significant associations^a between antioxidant metabolism and transport SNPs and risk of high-grade prostate cancer, in the placebo group of SELECT (*N* = 550)

Gene	Genotype	Genotype frequency		High-grade prostate cancer	
		<i>N</i> (%) cases	<i>N</i> (%) controls	HR (95% CI)	<i>P</i>
CAT	rs10836233				
	GG	69 (89.6%)	363 (77.4%)	1.0	
	Any A	8 (10.4%)	102 (21.7%)	0.39 (0.18–0.84)	0.02
	rs533425				
	GG	18 (23.1%)	190 (40.3%)	1.0	0.005
	AG	45 (57.7%)	215 (45.6%)	2.29 (1.28–4.09)	
rs7944397	AA	15 (19.2%)	66 (14.0%)	2.31 (1.12–4.76)	
	AA	68 (88.3%)	325 (69.3%)	1.0	0.001
	Any G	9 (11.7%)	144 (30.7%)	0.30 (0.14–0.62)	
	rs17650792				
GPX1	AA	30 (39.0%)	139 (29.9%)	1.0	0.04
	AG	37 (48.1%)	231 (49.7%)	0.71 (0.42–1.18)	
	GG	10 (13.0%)	95 (20.4%)	0.48 (0.23–1.03)	
SECT4L2	rs5753106				
	AA	52 (67.5%)	263 (55.7%)	1.0	0.01
	AG	24 (31.2%)	178 (37.7%)	0.71 (0.43–1.19)	
SELENBP1	GG	1 (1.3%)	31 (6.6%)	0.14 (0.02–1.00)	
	rs2769264				
	TT	46 (59.0%)	334 (71.2%)	1.0	0.05
SOD1	any G	32 (41.0%)	121 (25.8%)	1.65 (1.01–2.69)	
	rs2070424				
	AA	74 (94.9%)	400 (85.8%)	1.0	0.04
SOD2	Any G	4 (5.1%)	62 (13.3%)	0.33 (0.12–0.95)	
	rs7855				
	AA	66 (84.6%)	433 (91.7%)	1.0	0.03
TTPA	any G	12 (15.4%)	39 (8.3%)	2.16 (1.08–4.33)	
	rs12679996				
	CC	22 (28.9%)	189 (41.1%)	1.0	0.004
	CT	31 (40.8%)	196 (42.6%)	1.29 (0.72–2.31)	
	TT	23 (30.3%)	75 (16.3%)	2.82 (1.48–5.38)	
	rs4606052				
TXNRD2	CC	20 (26.7%)	142 (31.5%)	1.0	0.04
	CT	28 (37.3%)	209 (46.3%)	0.96 (0.52–1.76)	
	TT	27 (36.0%)	100 (22.2%)	2.03 (1.07–3.85)	
	rs8141691				
GG	28 (36.4%)	217 (46.4%)	1.0	0.03	
AG	33 (42.9%)	194 (41.5%)	1.37 (0.80–2.37)		
AA	16 (20.8%)	57 (12.2%)	2.19 (1.12–4.28)		

^aFull results for all SNP-supplement interactions presented in Supplementary Table S3.

design of SELECT reduces potential confounding in the gene-antioxidant interactions. The study includes a large number of high-grade prostate cancers, and comprehensively assesses genetic variation across 21 unique selenium- or vitamin E-related genes. Nonetheless, the results must be interpreted with caution given the large number of potential effects evaluated. We focused on prespecified hypotheses and did not adjust for multiple testing in our analyses. It is noteworthy, however, that many of the SNPs that were nominally associated with high-grade prostate cancer were also the SNPs that were significant in the interaction analyses. We also did not have sufficient numbers to examine any minority populations individually, and results presented are for Caucasian participants only. In addition, SELECT assigned participants to higher doses of selenium and vitamin E than would usually be consumed by diet alone, and at least for selenium, data suggest that the biologic relationship may be U-shaped (i.e., highest and lowest levels confer adverse health effects, whereas a middle level is considered optimal; refs. 60–62). Thus, caution is warranted in generalizing these results to comment on the potential interaction effects

between these gene variants and dietary intakes of selenium and vitamin E, and prostate cancer risk.

In conclusion, this report on more than 130 SNPs in 21 genes provides support for the hypothesis that genetic variation in selenium and vitamin E metabolism/transport genes may influence risk of overall and high-grade prostate cancer, and may modify an individual man's response to vitamin E or selenium supplementation with regards to these risks.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Selenium- or Vitamin E–Related Gene Variants, Interaction with Supplementation, and Risk of High-Grade Prostate Cancer in SELECT

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