Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

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See also pp 52 and 102.

Context Secondary analyses of 2 randomized controlled trials and supportive epidemiologic and preclinical data indicated the potential of selenium and vitamin E for preventing prostate cancer.

Objective To determine whether selenium, vitamin E, or both could prevent prostate cancer and other diseases with little or no toxicity in relatively healthy men.

Design, Setting, and Participants A randomized, placebo-controlled trial (Selenium and Vitamin E Cancer Prevention Trial [SELECT]) of 35 533 men from 427 participating sites in the United States, Canada, and Puerto Rico randomly assigned to 4 groups (selenium, vitamin E, selenium + vitamin E, and placebo) in a double-blind fashion between August 22, 2001, and June 24, 2004. Baseline eligibility included age 50 years or older (African American men) or 55 years or older (all other men), a serum prostate-specific antigen level of 4 ng/mL or less, and a digital rectal examination not suspicious for prostate cancer.

Interventions Oral selenium (200 μg/d from *L*-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/d of *all rac*-α-tocopheryl acetate) and matched selenium placebo, selenium + vitamin E, or placebo + placebo for a planned follow-up of minimum of 7 years and a maximum of 12 years.

Main Outcome Measures Prostate cancer and prespecified secondary outcomes, including lung, colorectal, and overall primary cancer.

Results As of October 23, 2008, median overall follow-up was 5.46 years (range, 4.17-7.33 years). Hazard ratios (99% confidence intervals [CIs]) for prostate cancer were 1.13 (99% CI, 0.95-1.35; n=473) for vitamin E, 1.04 (99% CI, 0.87-1.24; n=432) for selenium, and 1.05 (99% CI, 0.88-1.25; n=437) for selenium + vitamin E vs 1.00 (n=416) for placebo. There were no significant differences (all $P>.15$) in any other prespecified cancer end points. There were statistically nonsignificant increased risks of prostate cancer in the vitamin E group ($P=.06$) and type 2 diabetes mellitus in the selenium group (relative risk, 1.07; 99% CI, 0.94-1.22; $P=.16$) but not in the selenium + vitamin E group.

Conclusion Selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men.

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PROSTATE CANCER MORTALITY IN the United States has declined in recent years, but this cancer remains the most common nonskin epithelial malignancy in US men, with 186 320 new cases and 28 660 deaths (the second leading cause

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of cancer death) estimated for 2008.[1] An effective prevention strategy for prostate cancer would have substantial public health benefits, including the potential to reduce the incidence of biologically indolent prostate cancer, which is significantly overdetected by widespread screening with prostate-specific antigen (PSA) and for which most newly diagnosed men still undergo curative-intent therapy involving substantial morbidity despite surgical and other advances.[2-6]

Important secondary results of 2 randomized controlled trials, the Nutritional Prevention of Cancer (NPC) study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, showed prostate cancer risk reductions of 63% for selenized yeast and 32% for α-tocopherol (or vitamin E).[7-10] In addition, a large-scale randomized controlled trial[11] involving several different regimens found that a combination of selenium, vitamin E, and beta carotene reduced overall cancer mortality. These clinical data, supported by epidemiologic and preclinical data,[12-19] led to the design of the Selenium and Vitamin E Cancer Prevention Trial (SELECT).[20]

Investigators in the United States and Canada from major cooperative groups of the National Cancer Institute and Department of Veterans Affairs used the Prostate Cancer Prevention Trial (PCPT) accrual infrastructure (200 clinical sites, with 18 882 randomized men) in designing and activating SELECT. We report herein the effects of selenium and vitamin E, alone or in combination, on the risk of prostate cancer and secondary end points in SELECT.

METHODS

Study Design

SELECT is a phase 3 randomized, placebo-controlled trial of selenium (200 µg/d from *L*-selenomethionine), vitamin E (400 IU/d of *all rac*-α-tocopheryl acetate), or both (planned follow-up of minimum of 7 years and maximum of 12 years) for prostate cancer prevention. The major eligibility requirements included age 50 years or older for African American men and 55 years or older for all other men, no prior prostate cancer diagnosis, 4 ng/mL or less of PSA in serum, and a digital rectal examination (DRE) not suspicious for cancer. No current use of anticoagulant therapy other than 175 mg/d or less of acetylsalicylic acid or 81 mg/d or less of acetylsalicylic acid with clopidogrel bisulfate, no history of hemorrhagic stroke, and normal blood pressure were also required because of antiplatelet effects of vitamin E and related findings of the ATBC study.

Participant characteristics were based on self-report, including self-identification of race and ethnicity which were defined by the US Census Bureau. Race and ethnicity data were collected mainly for the generalizability of trial results. All potentially eligible men were required to provide written informed consent before being allowed to participate in the trial. The local institutional review board of each study site approved the study for activation and reviewed its progress annually. The trial was activated in July 2001 and follow-up blinded to the trial results ended on October 23, 2008.

Baseline blood and toenail specimens and a 5-year blood sample were collected for future biological studies. Prostate tissue samples collected during the trial were submitted for confirmation by central pathology review (no samples were collected at baseline). Participants without prostate cancer had clinic visits once every 6 months throughout the trial; with prostate cancer, annually. Adherence and adverse events were monitored every 6 months and a limited physical examination including assessments of blood pressure, weight, and smoking status was conducted annually. Prespecified adverse events known to be associated with vitamin E or selenium were graded according to the National Cancer Institute Common Toxicity Criteria.

Although eligible PSA and DRE results were required at study entry, annual prostate cancer screening with PSA and DRE was not mandatory because the benefits of this screening were under debate when the trial opened and community screening standards were expected to change during the trial. Participants were recommended during annual clinic visits to undergo a PSA test and DRE according to the standard of care at their study sites and the participant's preferences. A formal prerandomization period (28-90 days; no placebo run-in capsules) gave potential participants time to decide if they would agree to stop disallowed over-the-counter supplements of selenium or vitamin E throughout the study and to demonstrate, by returning for randomization, their willingness to adhere to the trial. Other adherence methods included offering each participant a free multivitamin containing no selenium or vitamin E and assessing serum levels of vitamin E and selenium in all participants at a subset of study sites (22 sites representing 7.8% of the trial population). These sites were chosen a priori to be representative of the broad range of sites in the trial.

End Point Assessment

Participants reported prostate cancers to the study site staff. Study staff obtained medical records supporting the diagnosis and abstracted the diagnostic method and clinical stage. Tissue and the corresponding pathology report were sent to the central pathology laboratory for confirmation. Gleason Score was based on central pathology review.

Men were asked at their first 6-month clinic visit to report new events since entering the trial and thereafter to report new events since their last visit. Cardiac-event data were collected in detail from the trial beginning (2001); data on diabetes were added through self-reported glitazone medication use (beginning in 2003) and self-report of diabetes (beginning in 2005) via the following question at each clinic visit: "Does the participant report having diabetes (either his doctor told him he has diabetes or he is taking medication for diabetes)?"

A general question regarding any events considered severe or life-threatening (grade 3 or 4), regardless

of attribution to the study supplements, was also asked. A Social Security Death Index search was conducted in July 2008 for participants who had a last contact date of more than 18 months before the search. Other specifically queried events (known at study inception to be related to either of the study supplements) included alopecia, dermatitis, fatigue, halitosis, nail changes, and nausea.

Statistical Analysis

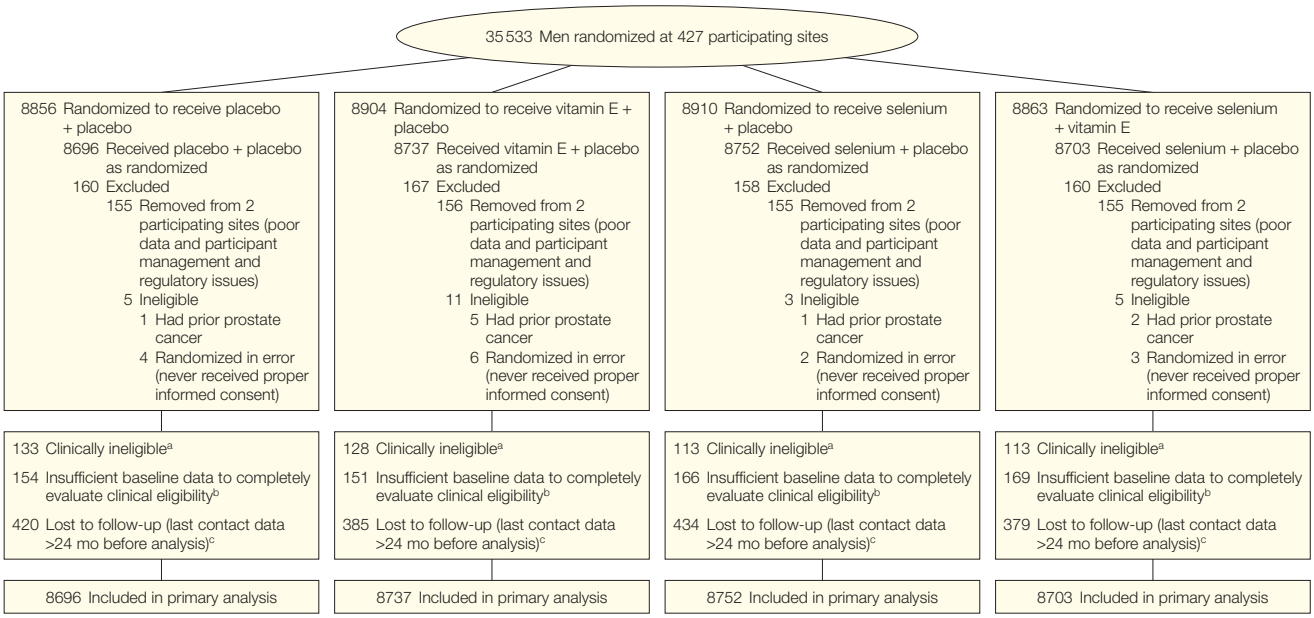
The primary end point was prostate cancer incidence as determined by routine clinical management. Cancers that were not confirmed centrally were included in the analysis. SELECT was designed as a 4 group trial with 5 prespecified comparisons (selenium vs placebo, vitamin E vs placebo, selenium + vitamin E vs placebo, selenium vs selenium + vitamin E, and vitamin E vs selenium + vitamin E). With a sample size of 32 400 men, using a 1-sided α=.005 level (equivalent to a 2-sided α=.01 level), there was 96% power to detect a 25% reduction in prostate cancer for either of the single agents (vs placebo), 89% power to detect a 25% reduction for selenium + vitamin E (vs an active single agent) and more than 99% power to detect a 44% reduction of selenium + vitamin E (vs placebo).

Design assumptions were based on the PCPT, ATBC, and NPC trials. The details of the statistical design have been described elsewhere.[20] Important elements included (1) constant accrual over 5 years; (2) prostate cancer incidence in the placebo group based on PCPT for the first 3 years and the 1995 Puget Sound SEER registry afterward; (3) adherence to the study supplements, which was assumed to decrease over the course of the trial with a 5-year rate of 68% and 12-year rate of 51%; (4) a constant 10% drop-in rate, defined as participants receiving placebo who are taking active supplementation off-study; (5) loss to follow-up of 0.5% per year; and (6) deaths estimated from PCPT for years 1 to 3 and from the 1995 US standard rates of men aged 63 years and all races for year 4 onward. The sample size was calculated to be 32 400 men and the number of prostate cancers expected in the placebo group was 533 over 12 years. Under the assumed conditions, the required median time under observation was estimated to be 8.8 years.

The primary analysis consisted of the 5 prespecified comparisons detailed above. These comparisons allowed for a meaningful analysis of the study results whether an interaction between vitamin E and selenium occurred. Each individual test was conducted at a 1-sided α=.005 level (equivalent to a 2-sided α=.01 level) using a Bonferroni factor of 5 to preserve an overall 1-sided α=.0025 level (equivalent to a 2-sided α=.05 level).

An independent data and safety monitoring committee met yearly and reviewed data on safety, adherence, and diagnosis of prostate cancer. In addition to the final analysis, interim analy-

Figure 1. Flow of Participants Included in Analysis by Intervention Group



[a] Due to increased blood pressure, high-grade prostatic intraepithelial neoplasia, suspicious digital rectal examination (DRE) or increased prostate-specific antigen (PSA), aspirin dosage, prior cancer less than 5 years before randomization, participation in another clinical trial, or other clinical reason.
[b] Blood pressure, PSA, and/or DRE not performed within required time frame (but normal) or other data-related reason.
[c] All data up until the last contact are included; these men also could have been either clinically ineligible or had insufficient baseline data. For time-to-event analyses, these men were censored at their last follow-up.

ses were planned for years 5, 7, 9, 10, and 11 after the first participant was randomized; the percentages of the expected total number of prostate cancer events in the placebo group at each interval were 14%, 35%, 61%, 74%, and 88%, respectively. Each interim analysis resulted in recommendations that could have included modifications to the study, including termination of accrual, modifications to data collection, or early reporting of results. Recommendations were made to the steering committee, which made the final decisions.

The interim analyses tested the null hypothesis at a 1-sided α=.0005 level (equivalent to a 2-sided α=.001 level) using the Cox proportional hazards regression model. In addition, the alternative hypothesis of a 25% reduction in prostate cancer incidence was tested at a 1-sided level of α=.0005 (equivalent to a 2-sided α=.001 level) using an extension of the Cox proportional hazards regression model that allows for testing a relative risk (RR) not equal to 1. The purpose of the second analysis was to allow for the study to stop if it was determined that the expected reduction in prostate cancer would not be observed. The frequencies of the number of cardiovascular events and cases of diabetes were tested with a χ^2 test. For cardiovascular event and diabetes analyses, we did not capture the report of the date of the event, which thus was not incorporated into the analysis.

Participants were randomized in a randomized block scheme, in which the block was the study site. This ensured a balance of the 4 intervention groups within each study site. All analyses were performed by using an intention-to-treat analysis in which men were classified according to the group to which they were randomized. All men were followed up until death or loss to follow-up. For cancer end points, men were censored at the time of their last follow-up or death. The analysis did not incorporate adjustments for baseline covariates. Data were analyzed by using SAS ver-

Table 1. Baseline Characteristics of Study Participants

Characteristics	No. (%) of Participants			
	Placebo (n = 8696)	Vitamin E (n = 8737)	Selenium (n = 8752)	Selenium + Vitamin E (n = 8703)
Age, y				
Median (interquartile range)	62.6 (58.1-67.8)	62.3 (58.0-67.8)	62.6 (58.2-68.0)	62.4 (58.1-67.8)
50-54	355 (4)	402 (5)	337 (4)	385 (4)
55-64	5078 (58)	5143 (59)	5076 (58)	5052 (58)
65-74	2702 (31)	2641 (30)	2733 (31)	2731 (31)
≥75	561 (6)	551 (6)	606 (7)	535 (6)
Race/ethnicity				
White	6863 (79)	6890 (79)	6942 (79)	6874 (79)
African American	1078 (12)	1107 (13)	1053 (12)	1076 (12)
Hispanic (non-African American)	492 (6)	477 (5)	481 (5)	484 (6)
Hispanic (African American)	76 (1)	103 (1)	86 (1)	95 (1)
Other[a]	187 (2)	160 (2)	190 (2)	174 (2)
Education (highest level)				
≤High school graduate or GED	1993 (23)	1875 (22)	1917 (22)	1898 (22)
Some college/vocational school	2291 (26)	2387 (27)	2327 (27)	2348 (27)
≥College graduate	4317 (50)	4394 (51)	4430 (51)	4372 (50)
Unknown/missing	95 (1)	81 (1)	78 (1)	85 (1)
PSA, ng/mL				
0.1-1.0	4122 (47)	4208 (48)	4218 (48)	4213 (48)
1.1-2.0	2728 (31)	2653 (30)	2661 (30)	2666 (31)
2.1-3.0	1168 (13)	1228 (14)	1211 (14)	1149 (13)
3.1-4.0	666 (8)	634 (7)	652 (7)	659 (8)
>4.0	5 (<1)	3 (<1)	2 (<1)	1 (<1)
Unknown/missing	7 (<1)	11 (<1)	8 (<1)	15 (<1)
Smoking status				
Never	3682 (42)	3752 (43)	3780 (43)	3666 (42)
Current	655 (8)	659 (8)	631 (7)	670 (8)
Former	4208 (48)	4194 (48)	4214 (48)	4242 (49)
Ever (unknown status)	63 (1)	55 (1)	61 (1)	56 (1)
Unknown	88 (1)	77 (1)	66 (1)	69 (1)

Abbreviations: GED, general equivalency diploma; PSA, prostate-specific antigen.
SI conversion: To convert PSA to μg/L, multiply by 1.0.
[a]Other race/ethnicity include Asian (n=420), Native American (n=99), Pacific Islander (n=39), multiple races (n=34), and unknown (n=119).

sion 9.1 (SAS Institute Inc, Cary, North Carolina).

Supplement Quality Control and Quality Assurance

The Pharmacy Coordinating Center received the study supplements for bottling as finished capsules in shipments containing lots of active capsules along with the appropriate matching placebo. As required by current good manufacturing practice,[21] each lot of capsules was quarantined upon receipt until testing was performed to ensure that capsules labeled "active" by the manufacturer contained the appropriate active agent and that capsules labeled as "placebo" did not contain an active agent. In addition, each time the capsules were bottled, production-run-verification testing was performed to ensure that bottles labeled as an active agent or placebo contained the appropriate material. To ensure that the quality of the blind was maintained, capsules received in each subsequent lot were compared with the previous lot and with matching capsules in the current shipment for their characteristics of weight, shape and size, color and external marking, odor, and comparability of contents of opened capsules. Whether the participant guessed or had an external validation of whether he was getting the active agent or placebo was not assessed.

RESULTS

On September 15, 2008, the independent data and safety monitoring committee met, reviewed data as of August 1, 2008, for the second formal interim analysis, and recommended the discontinuation of study supplements because the alternative hypothesis of no evi-

Table 2. Adherence to Study Supplements by Pill Counts and Bioadherence

	% (Range)[b]			
Pill Counts[a]	Placebo	Vitamin E	Selenium	Selenium + Vitamin E
Selenium/matching placebo				
Year 1 (n=34 708)	85 (76-85)	85 (77-85)	84 (76-84)	85 (77-84)
Year 2 (n=34 163)	81 (72-81)	80 (72-81)	79 (71-80)	80 (72-80)
Year 3 (n=33 616)	76 (68-77)	77 (69-77)	75 (68-76)	76 (69-77)
Year 4 (n=32 976)	69 (65-73)	73 (66-74)	71 (64-72)	72 (65-74)
Year 5 (n=23 419)	69 (63-71)	71 (64-73)	69 (62-70)	70 (64-71)
Vitamin E/matching placebo				
Year 1 (n=34 708)	85 (76-85)	85 (77-85)	85 (76-85)	85 (77-85)
Year 2 (n=34 163)	80 (71-80)	80 (71-80)	79 (70-79)	79 (71-80)
Year 3 (n=33 616)	75 (67-75)	75 (67-76)	74 (67-75)	76 (69-77)
Year 4 (n=32 976)	70 (63-72)	70 (63-72)	69 (62-71)	70 (63-72)
Year 5 (n=23 419)	67 (61-69)	69 (62-71)	67 (61-69)	68 (61-70)
	Median (Interquartile Range)			
Bioadherence	Placebo (n = 285)	Vitamin E (n = 290)	Selenium (n = 277)	Selenium + Vitamin E (n = 257)
Serum selenium, µg/L				
Baseline	137.6 (124.7-151.8)	135.9 (122.4-148.4)	135.0 (123.4-145.9)	136.4 (122.9-150.0)
6-mo visit	137.4 (123.3-152.0)	138.4 (124.1-154.0)	223.4 (198.6-251.8)	227.0 (199.4-251.2)
1st annual visit	138.1 (125.2-152.2)	137.7 (124.1-150.4)	232.4 (204.2-261.4)	228.5 (205.5-258.1)
2nd annual visit	132.0 (120.8-143.1)	129.8 (120.1-139.9)	228.0 (206.3-256.9)	220.7 (194.0-249.5)
4th annual visit[c]	140.1 (124.3-150.8)	143.8 (126.2-158.6)	251.6 (218.7-275.0)	253.1 (210.5-283.0)
Cholesterol-adjusted α-tocopherol, µg/mL				
Baseline	12.45 (10.70-14.95)	12.79 (10.69-15.37)	12.58 (10.43-14.75)	12.20 (10.12-15.35)
6-mo visit	11.68 (10.09-13.61)	18.14 (15.21-22.45)	11.62 (10.10-13.44)	17.90 (15.11-20.84)
1st annual visit	11.68 (10.24-13.44)	18.50 (15.08-22.46)	11.69 (10.10-13.03)	18.04 (14.77-22.35)
2nd annual visit	12.13 (10.80-13.72)	18.35 (15.13-22.85)	11.80 (10.57-13.58)	18.44 (15.32-22.89)
4th annual visit[c]	12.09 (9.95-14.41)	16.57 (13.86-22.61)	12.03 (9.57-13.53)	17.87 (14.68-22.31)
Cholesterol-adjusted γ-tocopherol, µg/mL				
Baseline	1.31 (0.83-2.01)	1.43 (0.89-2.21)	1.50 (0.96-2.21)	1.44 (0.96-2.02)
6-mo visit	1.50 (1.07-1.97)	0.78 (0.51-1.12)	1.64 (1.22-2.29)	0.74 (0.48-1.11)
1st annual visit	1.53 (1.09-2.05)	0.75 (0.52-1.16)	1.69 (1.27-2.33)	0.70 (0.48-1.04)
2nd annual visit	1.57 (1.13-2.13)	0.74 (0.49-1.08)	1.76 (1.26-2.43)	0.66 (0.50-1.03)
4th annual visit[c]	1.69 (1.14-2.29)	0.80 (0.50-1.23)	1.90 (1.48-2.70)	0.69 (0.47-1.07)

SI conversions: To convert serum selenium to µmol/L, multiply by 0.0127; α-tocopherol and γ-tocopherol to µmol/L, multiply by 23.22.
[a] Percentage of men adherent, defined as taking at least 80% of their study supplements. Denominators decrease over time reflecting the varying amounts of follow-up.
[b] These ranges are estimates including those with missing data and assumes those missing were either all not adherent (low estimate) or all adherent (high estimate).
[c] Numbers of participants for 4th annual visit are placebo (n=79), vitamin E (n=78), selenium (n=72), and selenium + vitamin E (n=71).

dence of benefit from either study agent was convincingly demonstrated ($P<.0001$) and there was no possibility of a benefit to the planned degree with additional follow-up. Study sites were notified to discontinue supplements on October 23, 2008, and the data presented in this article are current as of this date.

Participants

A total of 35 533 men were accrued and randomly assigned at 427 participating sites in the United States, Canada,

Table 3. Clinically Diagnosed Prostate Cancers

	No. (%) of Participants			
	Placebo (n = 8696)	Vitamin E (n = 8737)	Selenium (n = 8752)	Selenium + Vitamin E (n = 8703)
Total No. of prostate cancers diagnosed by study site	416	473	432	437
Method of diagnoses				
Prostate biopsy	404 (97)	458 (97)	419 (97)	420 (96)
Other/unknown	12 (3)	15 (3)	13 (3)	17 (4)
No. of total prostate biopsies	1020	1011	982	997
PSA tests[a]				
Year 1	6708 (83)	6876 (84)	6807 (84)	6838 (84)
Year 2	6641 (86)	6652 (85)	6635 (85)	6673 (86)
Year 3	6284 (85)	6334 (85)	6376 (85)	6349 (85)
Year 4	6043 (85)	6087 (84)	6065 (85)	6045 (84)
Year 5	4265 (84)	4246 (84)	4271 (84)	4257 (84)
DRE tests[a]				
Year 1	5766 (72)	5936 (73)	5870 (72)	5833 (72)
Year 2	5567 (72)	5563 (72)	5561 (72)	5591 (72)
Year 3	5180 (70)	5188 (70)	5198 (70)	5190 (70)
Year 4	4862 (69)	4823 (67)	4878 (69)	4878 (68)
Year 5	3420 (68)	3418 (68)	3397 (68)	3425 (68)
Reason for biopsy (positive biopsies)				
Increased PSA	259 (64)	324 (71)	296 (71)	263 (63)
PSA prompting biopsy, median (IQR), ng/mL	4.60 (4.00-5.50)	4.60 (3.99-5.60)	4.83 (4.05-5.70)	4.70 (4.00-5.60)
PSA velocity	12 (3)	10 (2)	13 (3)	16 (4)
Abnormal DRE	66 (16)	58 (13)	46 (11)	56 (13)
Increased PSA/PSA velocity + abnormal DRE	55 (14)	49 (11)	56 (13)	72 (17)
Other	8 (2)	13 (3)	12 (3)	17 (4)
T stage				
T1a-c	278 (70)	343 (75)	301 (73)	286 (69)
T2a-b	122 (30)	114 (25)	108 (26)	128 (31)
T3a-b	0 (0)	2 (0)	5 (1)	3 (1)
TX/not staged	16	14	18	20
N stage				
N0	109 (100)	127 (100)	125 (99)	117 (100)
N1	0 (0)	0 (0)	1 (1)	0 (0)
NX/not staged	307	346	306	320
M stage				
M0	124 (100)	134 (99)	122 (96)	119 (98)
M1a-b	0 (0)	2 (1)	5 (4)	2 (2)
MX/not staged	292	337	305	316
Gleason score[b]				
No. graded by central laboratory	365	396	361	365
2-6	240 (66)	249 (63)	217 (60)	220 (60)
7 (grade 3 + grade 4)	80 (22)	97 (24)	105 (29)	91 (25)
7 (grade 4 + grade 3)	21 (6)	27 (7)	19 (5)	24 (7)
8-10	24 (7)	23 (6)	20 (6)	30 (8)

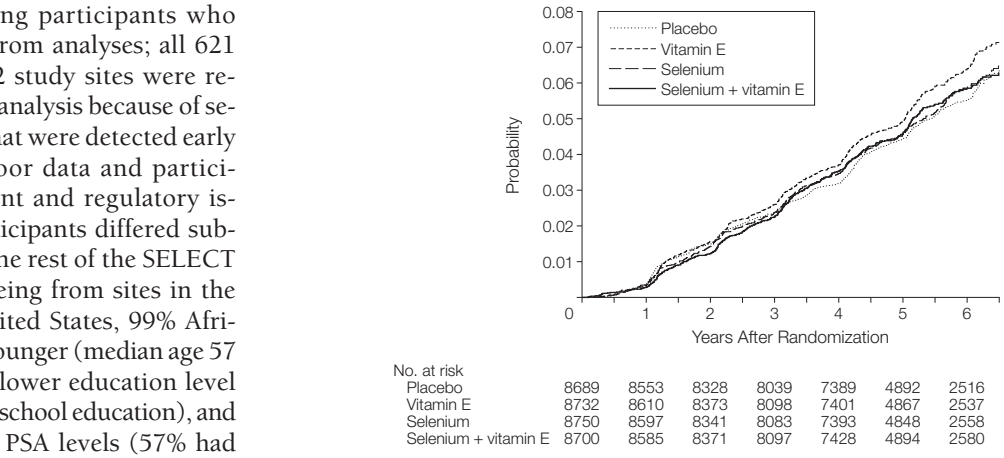
Abbreviations: DRE, digital rectal examination; IQR, interquartile range; PSA, prostate-specific antigen.
SI conversion: To convert PSA to µg/L, multiply by 1.0.
[a] Percentages are based on alive participants who are prostate cancer–free and for whom the form was submitted.
[b] Gleason score was based on central pathology review. The Gleason grade ranges from 1 to 5, with 5 having the worst prognosis. The Gleason score ranges from 2 to 10, with 10 having the worst prognosis.

and Puerto Rico between August 22, 2001, and June 24, 2004. FIGURE 1 shows the SELECT randomization scheme including participants who were excluded from analyses; all 621 participants at 2 study sites were removed from the analysis because of severe problems that were detected early on including poor data and participant management and regulatory issues. These participants differed substantially from the rest of the SELECT population in being from sites in the south of the United States, 99% African American, younger (median age 57 years), and of a lower education level (67% had <high school education), and in having lower PSA levels (57% had <1.0 ng/mL) and a higher prevalence of current smokers (33%). An additional 9 participants were removed because they were found to have had prostate cancer at randomization and 15 were removed because their informed consent was never received. More men were accrued (35 533 in 3 years) than initially planned (32 400 in 5 years) mainly because of a faster-than-expected accrual rate and the administrative time it takes to close down accrual.

The baseline characteristics of SELECT participants by each of the 4 groups (placebo, vitamin E, selenium, and selenium + vitamin E) are shown in TABLE 1. All potentially important risk factors were well balanced among the groups. A total of 2.6% of SELECT men were former PCPT men randomized to finasteride; during the trial, 4.8% of the non-PCPT participants reported use of finasteride at 5 mg (n=1602) or 1 mg (n=86).

The median overall follow-up was 5.46 years (range, 4.17-7.33 years). The percentages of participants with a recent last-contact date were more than 88% within 7 months and 92% within 13 months of the SELECT data analysis. Loss to follow-up, defined as having a last contact date of more than 24 months before analysis, involved 5.1% of participants, which was higher than had been estimated for the trial design (3.5% at 7 years after trial activation).

Figure 2. Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group



No. at risk							
Placebo	8689	8553	8328	8039	7389	4892	2516
Vitamin E	8732	8610	8373	8098	7401	4867	2537
Selenium	8750	8597	8341	8083	7393	4848	2558
Selenium + vitamin E	8700	8585	8371	8097	7428	4894	2580

Compared with placebo, there was a statistically nonsignificant increase in prostate cancer in the vitamin E group (*P*=.06) and not in the selenium + vitamin E group (*P*=.52) or the selenium group (*P*=.62).

Adherence to both study agents as determined by pill count was similar across all study groups, and averaged 83% at year 1 and 65% at year 5. Adherence to at least 1 of the 2 agents was 87% at year 1 and 72% at year 5 (the design-estimated adherence rates were 90% at year 1 and 68% at year 5). Bioadherence was measured in a subset of participants by serum levels of selenium and cholesterol-adjusted α-tocopherol and γ-tocopherol (which is suppressed by α-tocopherol) and showed a good separation in agent serum levels between the groups (TABLE 2). The drop-in rate was assessed by a direct question to the participants about taking either of the supplements. Positive responses were 3.1% or less for vitamin E and 1.8% or less for selenium in each year (below the design drop-in estimate of 10%). Prostate tissue samples were sent to the central pathology laboratory for confirmation in 86% of cases. The central laboratory agreed with the clinical site's prostate cancer diagnosis in 99% of these cases.

Prostate Cancer

There were no statistically significant differences in the rates of prostate cancer between the 4 groups (placebo, 416 cases [5-year rate of 4.43%]; selenium, 432 cases [4.56%]; vitamin E, 473 cases [4.93%]; selenium + vitamin E, 437 cases [4.56%]) (TABLE 3 and FIGURE 2). Compared with placebo, the hazard ratios (HRs) for prostate cancer were 1.13 (99% confidence interval [CI], 0.95-1.35; 95% CI, 0.99-1.29; *P*=.06) in the vitamin E-alone group, 1.05 (99% CI, 0.88-1.25; 95% CI, 0.91-1.20; *P*=.52) in the selenium + vitamin E group, and 1.04 (99% CI, 0.87-1.24; 95% CI, 0.90-1.18; *P*=.62) in the selenium-alone group. The data and safety monitoring committee had some concern over the statistically nonsignificant increase in prostate cancer in the vitamin E-alone group (*P*=.09 per interim data of August 1, 2008) and over a nonsignificant increase in diabetes mellitus associated with selenium (*P*=.08 per interim data of August 1, 2008).

The majority of prostate cancers diagnosed during the trial were early-stage and low-grade, and cancer stage and grade were similar across all groups (Table 3). The percentage of patients who had an annual PSA examination and DRE was similarly high and the biopsy rate was similar across all groups, indicating that the prostate cancer findings were not due to screening-associated detection bias. More than 95% of prostate cancers were diag-

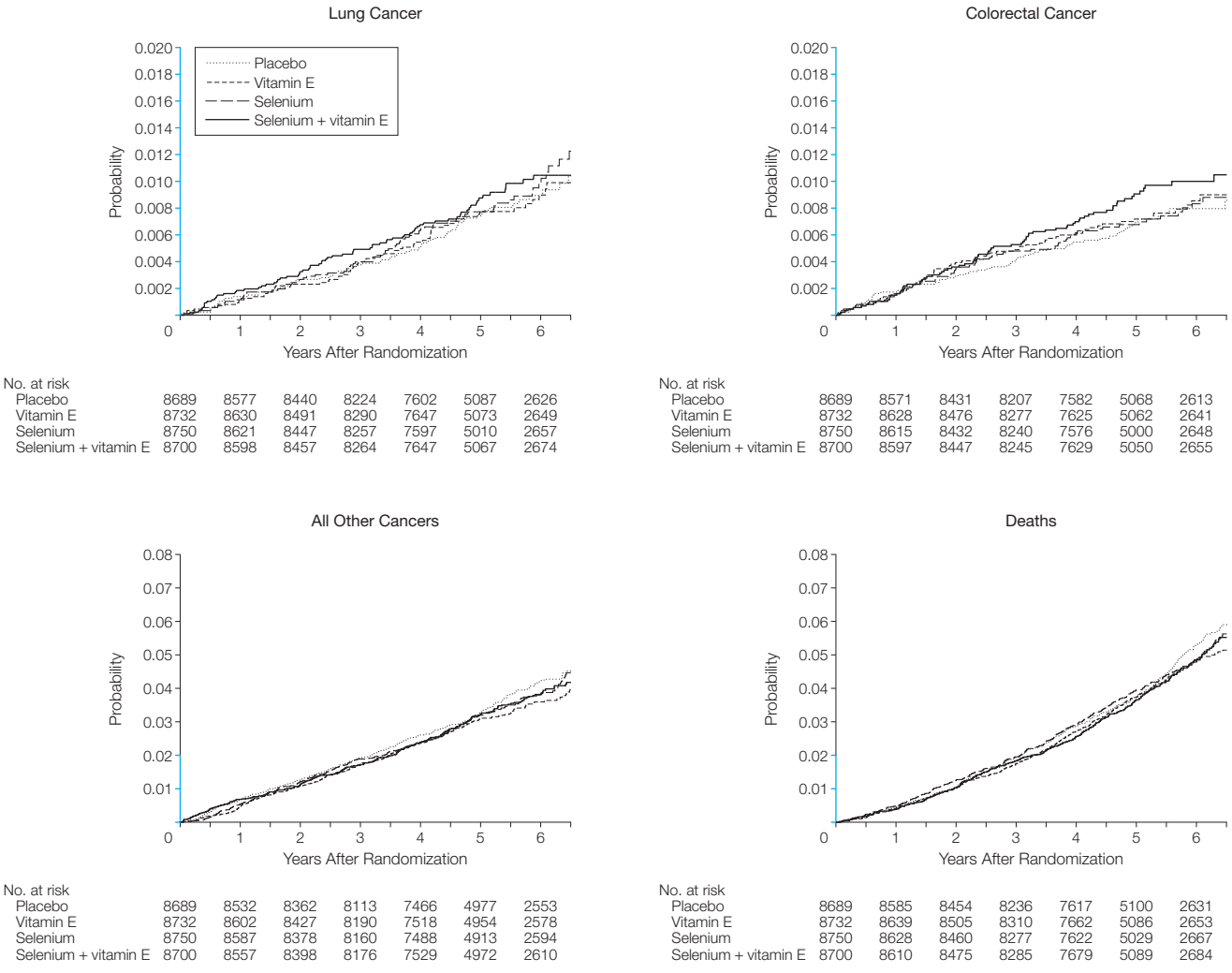
nosed by biopsy, the triggers for which (based on PSA and other factors) are shown in Table 3 and were similar across all groups. The number of prostate cancers in the placebo cohort was higher than what was estimated at study inception. This was due to the faster than expected accrual, the larger than expected sample size, and higher baseline PSA levels than anticipated.

Secondary Outcomes

There were no significant differences (all $P>.15$) in any prespecified secondary cancer end points (FIGURE 3 and TABLE 4). At 5 years, the cumulative death rate in the placebo group was 38 deaths per 1000 participants (95% CI, 34 deaths per 1000 participants to 42 deaths per 1000 participants); the estimated rate at trial inception was 48 deaths per 1000 participants. The numbers of deaths from any cause were similar across the 4 groups (382 in placebo group, 358 in vitamin E group, 378 in selenium group, and 359 in selenium + vitamin E group).

The study agents had no significant effects on the overall incidence of cardiovascular events (Table 4). A statistically nonsignificant increase in type 2 diabetes mellitus (diagnosed after randomization) occurred in the selenium-alone group vs placebo group (n = 724; 10.0%; 99% CI, 9.1%-11.0%; vs n = 669; 9.3%; 99% CI, 8.5%-10.2%, respectively; RR, 1.07; 99% CI, 0.94-1.22; $P=.16$). The number (percentage) of cases of diabetes mellitus was 700 (9.7%; 99% CI, 8.8%-10.6%) in the vitamin E group and 660 (9.1%; 99% CI, 8.2%-10.0%) in the selenium + vitamin E group (P values of these data compared with placebo were 0.47 for vitamin E and 0.61 for selenium + vitamin E). Data on known, clinically less significant adverse effects of the study agents (alopecia, dermatitis, halitosis,

Figure 3. Cumulative Incidence of Lung Cancer, Colorectal Cancer, All Other Primary Cancers, and Deaths by Intervention Group



There were no significant differences in any prespecified secondary cancer or death end points (all $P>.15$). The blue portions of the y-axes indicate 0 to 0.02 cancer probability.

nail changes, fatigue, and nausea) are shown in TABLE 5. The only statistically significant differences ($P<.01$) were for selenium vs placebo for alopecia and grades 1 to 2 dermatitis.

COMMENT

In SELECT, neither 200 µg of selenomethionine or 400 IU of synthetic DL α-tocopherol, given orally alone or combined for a median of 5.5 years had significant effects on the primary or secondary end points. A statistically nonsignificant increased incidence of prostate cancer ($P=.06$) was observed in the vitamin E group but not in the selenium + vitamin E group. The trial supplements were discontinued early (in year 7 of the overall 12-year study) in accordance with a unanimous recommendation of the data and safety monitoring committee stating that, based on the evidence to date from the 7-year planned interim analyses, there was no evidence of a benefit from either study agent and no possibility of a benefit to the planned degree with additional follow-up. Sensitivity analyses suggested that the prespecified 25% risk reduction was extremely unlikely to be reached for either agent even with additional exposure.

The statistical assumptions made in SELECT involving accrual rate, study supplement adherence and drop-in rates, prostate cancer incidence, death rate, and loss to follow-up were largely met and gave the trial significant power to detect the estimated preventive effects. Furthermore, the large sample size, inclusion of a substantial proportion of non-white men, and equal distribution of known risk factors across all trial groups make the conclusions drawn from SELECT especially robust and generalizable.

Why were selenium and vitamin E ineffective in preventing prostate cancer in SELECT despite strong secondary evidence suggesting efficacy?[7,8] Considering selenium first, the secondary reduction in prostate cancer incidence in the NPC study could have been subject to

Table 4. Secondary Outcomes Including Diagnosis of Other Primary Cancers, Diabetes, Cardiovascular Events, and Deaths[a]

	Placebo (n = 8696)		Vitamin E (n = 8737)		Selenium (n = 8752)		Selenium + Vitamin E (n = 8703)	
	No. of Men	HR (99% CI)	No. of Men	HR (99% CI)	No. of Men	HR (99% CI)	No. of Men	HR (99% CI)
Any cancer (including prostate)[b]	824	1 [Reference]	856	1.03 (0.91-1.17)	837	1.01 (0.89-1.15)	846	1.02 (0.90-1.16)
Lung	67	1 [Reference]	67	1.00 (0.64-1.55)	75	1.12 (0.73-1.72)	78	1.16 (0.76-1.78)
Colorectal	60	1 [Reference]	66	1.09 (0.69-1.73)	63	1.05 (0.66-1.67)	77	1.28 (0.82-2.00)
Other primary cancer[c]	306	1 [Reference]	274	0.89 (0.72-1.10)	292	0.95 (0.77-1.17)	290	0.94 (0.76-1.16)
	No. of Men	RR (99% CI)	No. of Men	RR (99% CI)	No. of Men	RR (99% CI)	No. of Men	RR (99% CI)
Diabetes[d]	669	1 [Reference]	700	1.04 (0.91-1.18)	724	1.07 (0.94-1.22)	660	0.97 (0.85-1.11)
Cardiovascular events								
Any (including death)	1050	1 [Reference]	1034	0.98 (0.88-1.09)	1080	1.02 (0.92-1.13)	1041	0.99 (0.89-1.10)
Nonfatal strokes								
Hemorrhagic	11	1 [Reference]	7	0.63 (0.18-2.20)	11	0.99 (0.33-2.98)	12	1.09 (0.37-3.19)
Ischemic	56	1 [Reference]	49	0.87 (0.53-1.44)	51	0.90 (0.55-1.49)	67	1.20 (0.75-1.90)
Not specified[e]	25	1 [Reference]	14	0.56 (0.24-1.32)	11	0.44 (0.17-1.11)	20	0.80 (0.37-1.73)
Other nonfatal (worst grade)[f]								
Grade 3	626	1 [Reference]	642	1.02 (0.89-1.17)	685	1.09 (0.95-1.25)	624	1.00 (0.87-1.15)
Grade 4	190	1 [Reference]	203	1.06 (0.82-1.38)	193	1.01 (0.78-1.31)	201	1.06 (0.82-1.37)
	No. of Men	HR (99% CI)	No. of Men	HR (99% CI)	No. of Men	HR (99% CI)	No. of Men	HR (99% CI)
Deaths	382	1 [Reference]	358	0.93 (0.77-1.13)	378	0.99 (0.82-1.19)	359	0.94 (0.77-1.13)
Cancer	125	1 [Reference]	106	0.84 (0.60-1.18)	128	1.02 (0.74-1.41)	117	0.93 (0.67-1.30)
Prostate	0	1 [Reference]	0	NA	1	NA	0	NA
Lung	41	1 [Reference]	38	0.92 (0.52-1.65)	45	1.10 (0.63-1.91)	39	0.95 (0.53-1.69)
Colorectal	10	1 [Reference]	13	1.30 (0.44-3.83)	10	1.00 (0.32-3.16)	15	1.49 (0.52-4.28)
Other primary cancer[c]	74	1 [Reference]	55	0.74 (0.47-1.17)	72	0.97 (0.63-1.49)	63	0.85 (0.55-1.32)
Cardiovascular	142	1 [Reference]	119	0.84 (0.61-1.15)	129	0.91 (0.66-1.24)	117	0.82 (0.60-1.13)
Hemorrhagic stroke	8	1 [Reference]	9	1.12 (0.32-3.92)	9	1.12 (0.32-3.93)	12	1.49 (0.46-4.84)
Other cardiovascular	134	1 [Reference]	110	0.82 (0.59-1.14)	120	0.89 (0.65-1.24)	105	0.78 (0.56-1.09)
Other deaths	115	1 [Reference]	133	1.15 (0.83-1.60)	121	1.05 (0.75-1.47)	125	1.08 (0.78-1.51)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; RR, relative risk.
[a] The HRs and RRs given for vitamin E, selenium, and selenium + vitamin E groups are compared with the placebo group.
[b] No. of participants that had more than 1 cancer for each group are placebo (n=25), vitamin E (n=24), selenium (n=25), and selenium + vitamin E (n=36).
[c] Excluding basal cell and squamous cell skin cancers.
[d] Based on self-report or reported use of diabetes medications of the glitazone class; excludes prevalent cases at randomization.
[e] Not specified as to whether an ischemic or hemorrhagic stroke.
[f] According to National Cancer Institute Common Toxicity Criteria.

limitations inherent in secondary analyses, such as chance findings due to multiple testing, especially because the overall NPC sample size was relatively small (1312 men and women vs 29 133 men in the ATBC study). Second, the formulation (high-selenium yeast) given in the NPC trial may have been more active than the *l*-selenomethionine given in SELECT (both trials gave an equivalent selenium dose). In designing SELECT, we carefully evaluated the choice of *l*-selenomethionine vs high-selenium yeast (and other formulations),[20] and our rationale for selecting *l*-selenomethionine included the following considerations: selenomethionine was the major component of apparently active high-selenium yeast; evidence indicated substantial batch-to-batch variations in specific organoselenium compounds in samples of NPC yeast, making it unlikely that we could duplicate the selenium yeast formulation used in the NPC study; potential genotoxicity of highly active inorganic selenium compounds, such as selenite, made them potentially unsuitable for long-term prevention; lowering (vs selenomethionine) of overall body selenium stores with selenite, which is neither absorbed nor retained well; practical and safety concerns over newer selenium compounds, such as monomethylated forms (eg, lacking availability, investigational new drug certification, and clinical data); and in vitro data indicating that selenomethionine was effective in suppressing malignant and not normal prostate cells.[15]

Despite this careful rationale, it is impossible to know now whether selenized yeast would have been more active than *l*-selenomethionine was in SELECT. Finally, the NPC trial was conducted in men chosen for deficient levels of selenium, finding that selenium was most preventive in the men with the lowest baseline selenium levels[9]; SELECT men generally were replete in selenium at baseline, with median serum selenium levels of 135 ng/mL vs 113 ng/mL in NPC. The NPC cutpoint for the lowest 2 tertiles was 121.6 units; 78% of SELECT men were above this level. The NPC trial found a nonsignificant increase in overall cancer rate in its highest tertile (HR, 1.20; 95% CI, 0.77-1.86).[22]

There are potential reasons why vitamin E did not prevent prostate cancer in SELECT. First, the high dose (400 IU/d) of the α-tocopherol form of vitamin E in SELECT may have been less effective than a lower dose such as the 8-fold lower 50 mg/d (roughly equivalent to 50 IU/d) that produced the earlier positive secondary findings in the ATBC study.[7] (The vitamin E formulation, synthetic *all rac*-α-tocopheryl acetate, was the same in SELECT and the ATBC study.) A secondary analysis of the HOPE trial[23] found that a relatively high dose of natural vitamin E did not reduce prostate cancer incidence. Achieving higher plasma or tissue levels of α-tocopherol within the physiological range, such as through a 50-mg/d supplement, may have some prostate cancer (or other) preventive effect such as cell proliferation or tumor growth inhibition.[24] Furthermore, high pharmacological doses of α-tocopherol may have an adverse effect on cytochrome p450 enzyme and other regulatory mechanisms[25] that a lower dose would not have. It is also possible (but not certain) that the known effect of α-tocopherol in suppressing potentially beneficial plasma γ-tocopherol levels would have been less with the lower than higher dose of α-tocopherol.[20] Nevertheless, men taking vitamin E with the highest baseline (and thus total) serum vitamin E levels in the ATBC study had the highest reduction in prostate and lung cancer,[26] which supported our choice of the higher dose. A higher dose also was associated with potential benefits such as reductions in aging-related Alzheimer disease and macular degeneration.

Second, several studies have suggested that vitamin E is more protective against prostate cancer in smokers, and

Table 5. Adverse Events Known to Be Associated With the Study Supplements[a]

	Placebo (n = 8696)		Vitamin E (n = 8737)		Selenium (n = 8752)		Selenium + Vitamin E (n = 8703)	
Adverse Event	No. of Men	RR (99% CI)	No. of Men	RR (99% CI)	No. of Men	RR (99% CI)	No. of Men	RR (99% CI)
Alopecia	206	1 [Reference]	220	1.06 (0.83-1.36)	265	1.28 (1.01-1.62)[b]	238	1.15 (0.91-1.47)
Dermatitis								
Grades 1-2	516	1 [Reference]	591	1.14 (0.98-1.32)	605	1.17 (1.00-1.35)[b]	554	1.07 (0.92-1.25)
Grades 3-4	8	1 [Reference]	12	1.49 (0.46-4.83)	14	1.74 (0.56-5.44)	16	2.00 (0.66-6.09)
Halitosis	427	1 [Reference]	493	1.15 (0.97-1.36)	503	1.17 (0.99-1.38)	531	1.24 (1.06-1.46)
Nail changes	1035	1 [Reference]	1041	1.00 (0.90-1.11)	1087	1.04 (0.94-1.16)	1075	1.04 (0.93-1.15)
Fatigue								
Grades 1-2	586	1 [Reference]	604	1.03 (0.89-1.19)	645	1.09 (0.95-1.26)	612	1.04 (0.90-1.20)
Grades 3-4	24	1 [Reference]	29	1.20 (0.59-2.45)	21	0.87 (0.40-1.88)	20	0.83 (0.38-1.81)
Nausea								
Grades 1-2	203	1 [Reference]	191	0.94 (0.72-1.21)	244	1.19 (0.94-1.52)	202	0.99 (0.77-1.28)
Grade 3	9	1 [Reference]	3	0.33 (0.06-1.85)	9	0.99 (0.30-3.34)	8	0.89 (0.25-3.10)

Abbreviations: CI, confidence interval; RR, relative risk.
[a] The RRs given for vitamin E, selenium, and selenium + vitamin E groups are compared with the placebo group. Maximum grade experienced by a participant are given. Alopecia, halitosis, and nail changes were only defined for grades 1 and 2. National Cancer Institute Common Toxicity Criteria were used for alopecia, nail changes, fatigue, and nausea. Halitosis and dermatitis were defined in the study protocol. Generally, grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = life-threatening.
[b] $P < .01$.

less than 60% of SELECT men were current or former smokers (whereas all men in the ATBC study were smokers). For example, observational analyses in a trial-based cohort of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO),[27] a trial of screening vs standard health care routines, showed a 71% reduction in the incidence of advanced prostate cancer associated with supplemental vitamin E use in current and recent smokers. A subgroup analysis of current and former smokers in SELECT, however, did not show a smoking-related benefit (placebo, 4.6% [223/4863] vs vitamin E alone, 4.8% [232/4853]). As with selenium in the NPC study, vitamin E effects on prostate cancer incidence in the ATBC study could have been due to chance findings in secondary analyses.

Selenium was not associated with significant effects on cardiovascular events, lung cancer, other cancers, or overall mortality in SELECT. One safety concern with selenium is a potential association with increased risk for type 2 diabetes mellitus, for which there are mixed data from prior studies.[28,29] A recent analysis of the NPC study population showed a significant increase in type 2 diabetes mellitus (by self-report and medical records), largely limited to the top tertile of plasma selenium levels at baseline.[30]

In SELECT, a nonsignificant increase in risk (RR, 1.07; P=.16) of diabetes mellitus compared with placebo was observed in the selenium group but not in the selenium + vitamin E group (RR, 0.97; P=.62). Concerns about the safety of vitamin E supplementation arose during SELECT. One meta-analysis[31] found that vitamin E at doses of at least 400 IU/d increased all-cause mortality, and another study[32] found evidence that vitamin E supplementation, alone or in combination with other antioxidants, may increase mortality. Neither study is directly relevant to the doses and population studied in SELECT; many studies included in these meta-analyses were in patients with serious disease, and the finding of increased mortality was driven by studies using doses far higher than 400 IU/d. In more relevant, placebo-controlled trials completed in healthy men and women, there were no associations of vitamin E supplementation with increased risks of either cardiovascular disease or overall mortality.[33] SELECT results support the safety of vitamin E at 400 IU/d in healthy men, because there were no increases in either cardiovascular disease or total mortality in the vitamin E groups.

The 35 533 randomized men of SELECT were needed because of the robust statistical design accommodating 4 study groups with 5 primary comparisons; this large trial population made SELECT the largest cancer chemoprevention trial ever conducted to our knowledge. African American men have among the highest prostate cancer risks in the world, and SELECT had the highest participation of African American men (13%) of any large-scale cancer chemoprevention trial to date.

The statistical rigor of the trial was matched by the rigor of its implementation. Features of this implementation included the SELECT Workbench, a secure Web site administered by the SELECT statistical center and used by study-site staff and investigators. The SELECT Workbench was used to access participant and site-specific reports, the study protocol, and a detailed study manual and to submit data using Web-based forms. Form submission included detailed edit checks and a tracking system to identify all expected forms. Training and monitoring consisted of semi-annual workshops, quality assurance audits at least once every 3 years, and mentoring by trained statistical center staff and experienced clinical research associates. SELECT also maintained a public Web site initially designed to recruit participants and later used to promote participant adherence and to keep SELECT in the public's eye.[20]

Potential limitations of SELECT include that it did not test different formulations or doses of selenium and vitamin E and that it did not definitively assess results in subgroups of men who may have responded differently than did the overall population. Because of active annual screening (eg, PSA in 85%; Table 3) and early detection (eg, 99.4% stage T1 or T2; Table 3), SELECT could not assess effects in reducing advanced or fatal prostate cancer, which recent data suggest may be a potential benefit of vitamin E and selenium.[18,27,34-36] SELECT also could not assess intervention effects in a population deficient in vitamin E, selenium, or both since our trial population was well-nourished at baseline, or in current smokers since they represented only 7.5% of the SELECT population, a substantial difference from the ATBC study in predominantly heavy smokers.

Cancer chemoprevention is an important approach for reducing cancer burden.[37] Several randomized controlled trials have demonstrated significant cancer or premalignancy risk reductions in the breast, colon-rectum, prostate, and stomach.[38-44] Prostate cancer is a particularly attractive target for chemoprevention because of its clinical ubiquity, substantial treatment-associated morbidity, and stepwise molecular pathogenesis. In the large-scale PCPT, which was reported 2 years after SELECT was activated, finasteride produced a 25% relative reduction in the 7-year period prevalence of prostate cancer (vs placebo),[43] and recent data suggest that finasteride reduces the risk of clinically significant disease and may not induce high-grade cancers despite initial concerns to the contrary.[45-49]

CONCLUSION

In conclusion, SELECT has definitively demonstrated that selenium, vitamin E, or selenium + vitamin E (at the tested doses and formulations) did not prevent prostate cancer in the generally healthy, heterogeneous population of men in SELECT. These data underscore the prudence that is needed in considering recommendations to use agents for the prevention or control of disease in the absence of convincing clinical trial results. These findings also compel the medical research community to continue the search for new, effective agents for prostate cancer prevention.

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