Vitamin E and the Risk of Prostate Cancer

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Eric A. Klein, MD
Ian M. Thompson Jr, MD
Catherine M. Tangen, DrPH
John J. Crowley, PhD
M. Scott Lucia, MD
Phyllis J. Goodman, MS
Lori M. Minasian, MD
Leslie G. Ford, MD
Howard L. Parnes, MD
J. Michael Gaziano, MD, MPH
Daniel D. Karp, MD
Michael M. Lieber, MD
Philip J. Walther, MD, PhD
Laurence Klotz, MD
J. Kellogg Parsons, MD, MHS
Joseph L. Chin, MD
Amy K. Darke, MS
Scott M. Lippman, MD
Gary E. Goodman, MD
Frank L. Meyskens Jr, MD
Laurence H. Baker, DO

Context The initial report of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found no reduction in risk of prostate cancer with either selenium or vitamin E supplements but a statistically nonsignificant increase in prostate cancer risk with vitamin E. Longer follow-up and more prostate cancer events provide further insight into the relationship of vitamin E and prostate cancer.

Objective To determine the long-term effect of vitamin E and selenium on risk of prostate cancer in relatively healthy men.

Design, Setting, and Participants A total of 35 533 men from 427 study sites in the United States, Canada, and Puerto Rico were randomized between August 22, 2001, and June 24, 2004. Eligibility criteria included a prostate-specific antigen (PSA) of 4.0 ng/mL or less, a digital rectal examination not suspicious for prostate cancer, and age 50 years or older for black men and 55 years or older for all others. The primary analysis included 34 887 men who were randomly assigned to 1 of 4 treatment groups: 8752 to receive selenium; 8737, vitamin E; 8702, both agents, and 8696, placebo. Analysis reflect the final data collected by the study sites on their participants through July 5, 2011.

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

Main Outcome Measures Prostate cancer incidence.

Results This report includes 54 464 additional person-years of follow-up and 521 additional cases of prostate cancer since the primary report. Compared with the placebo (referent group) in which 529 men developed prostate cancer, 620 men in the vitamin E group developed prostate cancer (hazard ratio [HR], 1.17; 99% CI, 1.004-1.36, $P=.008$); as did 575 in the selenium group (HR, 1.09; 99% CI, 0.93-1.27; $P=.18$), and 555 in the selenium plus vitamin E group (HR, 1.05; 99% CI, 0.89-1.22, $P=.46$). Compared with placebo, the absolute increase in risk of prostate cancer per 1000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination.

Conclusion Dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.

Trial Registration Clinicaltrials.gov Identifier: NCT00006392

JAMA. 2011;306(14):1549-1556 www.jama.com

LIFETIME RISK OF PROSTATE CANcer in the United States is currently estimated to be 16%.[1] Although most cases are found at an early, curable stage, treatment is costly and urinary, sexual, and bowel-related adverse effects are common.[2] Even men who choose active surveillance as an initial management strategy face anxiety, uncertain prognosis, and a measurable risk of sepsis with follow-up biopsies,[3] and more than one-third of those who initially defer therapy are ultimately treated.[4,5] With such a high prevalence, risk of morbidity from treatment, and treatment-related costs, primary prevention of prostate cancer is an attractive option.

With considerable preclinical and epidemiological evidence that selenium and vitamin E may reduce prostate cancer risk, we conducted and reported the results of a prospective randomized trial examining the effect of these 2 agents for prostate cancer prevention.[6] Coordinated by SWOG, a federally funded cancer research cooperative group, the Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Author Video Interview available at www.jama.com.

Author Affiliations are listed at the end of this article.
Corresponding Author: Eric A. Klein, MD, Glickman Urological and Kidney Institute, Cleveland Clinic, Desk Q10-1, 9500 Euclid Ave, Cleveland, OH 44195 (kleine@ccf.org).

began accrual on August 22, 2001, and randomized 35 533 men into 4 groups: selenium with matching placebo, vitamin E with matching placebo, both agents, or placebo.

Based on a preplanned interim analysis, the independent data and safety monitoring committee met on September 15, 2008, and recommended the early discontinuation of study supplements because of lack of efficacy for risk reduction and because futility analysis demonstrated no possibility of benefit to the planned degree with additional follow-up.[6]

As reported in the initial article,[6] with a median follow-up of 5.5 years, the numbers of prostate cancers detected were 473 (hazard ratio [HR], 1.13; 99% CI, 0.95-1.35) for vitamin E; 432 (HR, 1.04; 99% CI, 0.87-1.24) for selenium; 437 (HR, 1.05; 99% CI, 0.88-1.25) for selenium plus vitamin E; and 416 (HR, 1.0) for placebo. Although these results were not statistically significant, the data and safety monitoring committee expressed concern about the increased risk of prostate cancer observed in the vitamin E plus placebo group, which approached statistical significance ($P=.06$) and a statistically nonsignificant increased risk of type 2 diabetes mellitus in the selenium plus placebo group ($P=.16$).

Since that time, participant follow-up has continued, allowing observation of additional events. On May 20, 2011, the data and safety monitoring committee reviewed trial data and recommended reporting the finding regarding increased risk of prostate cancer with vitamin E. This recommendation was based on final data collection from the study sites and coincided with the preplanned final analysis at 7 years after the last participant was randomized.

METHODS

Detailed descriptions of the rationale, design, conduct, and initial results of SELECT have been previously published.[6,7] The study enrolled healthy men at average risk of prostate cancer based on a baseline prostate-specific antigen (PSA) of ≤4 ng/mL and normal digital rectal examination (DRE) commencing at age 50 years for black men or at age 55 years for all others. Men were randomized into 1 of 4 groups: selenium (200 µg/d from L-selenomethionine) with matching vitamin E placebo, vitamin E (400 IU/d of all *rac*-α-tocopherol acetate) with matching selenium placebo, both agents, or matching placebo (FIGURE 1).

Participants without prostate cancer were monitored every 6 months with an annual limited physical examination including blood pressure, weight, and smoking status; participants who developed prostate cancer during the study were monitored annually thereafter. Participants were recommended to undergo PSA and DRE testing and prostate biopsy based on the standard of care in their community and in accordance with the participant's preference. To facilitate adherence, a multivitamin containing no selenium or vitamin E was offered. All participants were required to provide written informed consent and the local institutional review board of each study site approved the study.

At study visits, men were asked about new medical events in the previous 6 months. The primary end point of the study was prostate cancer incidence as determined by routine clinical management and confirmed by central pathology review. Blinded follow-up continued until October 23, 2008, at which time participants discontinued use of study supplements. Prostate cancer status was determined by self-report at each 6-month study visit. Medical records were obtained thereafter and clinical stage and diagnostic method were abstracted. The pathology report and tissue were forwarded to the SELECT central pathology laboratory for confirmation of diagnosis and for assignment of Gleason score. Median baseline and follow-up plasma vitamin E and selenium levels are included in the original report.[6]

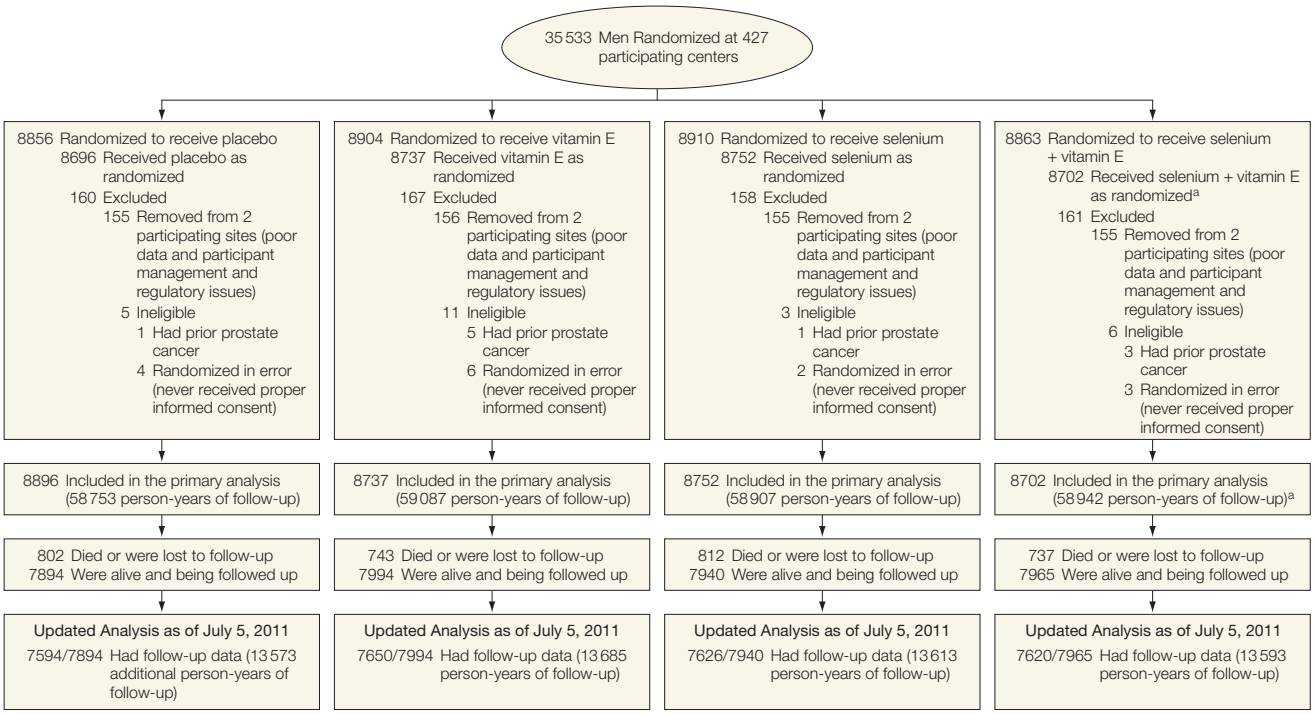
Follow-up continued in an unblinded fashion at study sites from October 2008 until July 2011. The final study site visits included follow-up for study end points and a blood sample from participants diagnosed with prostate cancer. An independent data and safety monitoring committee met yearly commencing with study inception, reviewing data on safety, adherence, and prostate and other cancer diagnoses. On September 15, 2008, the committee recommended reporting initial results related to the lack of efficacy of the agents on prevention of prostate cancer. Since that time the committee has continued to meet yearly via teleconference.

Statistical Analysis

The primary end point was prostate cancer incidence resulting from routine community care. Cancers not centrally confirmed (17% of the total) are included in the analysis. Five prespecified comparisons of the 4 study groups were conducted: selenium vs placebo, vitamin E vs placebo, selenium plus vitamin E vs placebo, selenium vs selenium plus vitamin E, and vitamin E vs selenium plus vitamin E. Although a 1-sided significance level of .005 was specified to test for the preventive effect for each supplement comparison and thus 99% confidence intervals are reported, we have reported 2-sided *P* values throughout because the comparison of prevention vs increased risk of cancer is a 2-sided question.[6]

A proportional hazards model was used to compare prostate cancer and other cancer incidence between placebo and each of the 3 study groups with active agents. Men without the end point of interest were censored at their last contact date. An additional analysis was performed on all the data using a variable for selenium supplementation, a variable for vitamin E supplementation, and an interaction term. In all cases, the proportional hazards assumption was evaluated by assessing each study group × time interaction. The cumulative incidence curves for prostate cancer were generated accounting for the competing risk of death.[8] A χ^2 test was used to test the difference in the relative risk of diabetes. Data were analyzed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

Figure 1. Patient Flow Diagram



[a] Since the primary publication, there was additional review and 1 additional participant was found to have had prior prostate cancer.

RESULTS

The current report includes data as of July 5, 2011. There are 54 464 additional person-years of follow-up since the primary report, an increase of 23%. A summary of baseline characteristics is displayed in TABLE 1 and an updated flow diagram in Figure 1. The frequency of use of DRE and PSA is displayed in TABLE 2; there were no differences between groups in the intensity of PSA testing, absolute PSA levels, PSA change from study entry to year 1, nor rates of testing following study unblinding.

A total of 521 additional prostate cancers have been diagnosed since the initial report: 113 in the placebo group, 147 in the vitamin E group, 143 in the selenium group, and 118 in the combination group (TABLE 3). The rate of prostate cancer detection was greater in all treatment groups when compared with placebo but was statistically significant only in the vitamin E alone group (HR, 1.17; 99% CI, 1.004-1.36; P=.008; Table 3). After adjustment for the marginal effects of vita-

Table 1. Baseline Participant Characteristics

	No. (%) of Participants			
	Placebo (n = 8696)	Vitamin E Alone (n = 8737)	Selenium Alone (n = 8752)	Vitamin E + Selenium (n = 8702)
Age, y				
Median (IQR)	63 (58-67)	62 (58-67)	63 (58-68)	62 (58-67)
50-54	355 (4)	403 (5)	337 (4)	385 (4)
55-64	5078 (58)	5142 (59)	5075 (58)	5051 (58)
65-74	2702 (31)	2642 (30)	2734 (31)	2731 (31)
≥75	561 (6)	550 (6)	606 (7)	535 (6)
Race/ethnicity				
White	6862 (79)	6893 (79)	6944 (79)	6872 (79)
Black	1083 (12)	1106 (13)	1054 (12)	1075 (12)
Hispanic, nonblack	496 (6)	476 (5)	484 (6)	484 (6)
Hispanic, black	76 (1)	103 (1)	86 (1)	96 (1)
Aboriginal	27 (<1)	22 (<1)	41 (<1)	29 (<1)
Asian/Pacific Islander	128 (1)	110 (1)	111 (1)	123 (1)
Unknown	24 (<1)	27 (<1)	32 (<1)	23 (<1)
PSA, ng/mL				
Median (IQR)	1.1 (0.6-1.9)	1.1 (0.6-1.9)	1.1 (0.6-1.9)	1.1 (0.6-1.8)
0.1-1.0	4133 (48)	4234 (48)	4247 (49)	4235 (49)
1.1-2.0	2735 (31)	2648 (30)	2652 (30)	2657 (31)
2.1-3.0	1153 (13)	1222 (14)	1199 (14)	1147 (14)
3.1-4.0	668 (8)	627 (7)	649 (7)	656 (7)
>4.0	5 (<1)	3 (<1)	2 (<1)	1 (<1)
Missing	2 (<1)	3 (<1)	3 (<1)	6 (<1)

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

Table 2. Diagnostic Testing

	Placebo (n = 8696)	Vitamin E Alone (n = 8737)	Selenium Alone (n = 8752)	Vitamin E + Selenium (n = 8702)
Prostate biopsy, men ever having biopsy, No.				
Before unblinding[a]	1041	1046	1003	1014
After unblinding	256	268	267	254
DREs per participant, No.				
Before unblinding	3.20	3.20	3.20	3.21
After unblinding	0.64	0.63	0.64	0.64
No. of PSA tests/participant				
Before unblinding	3.87	3.88	3.87	3.90
After unblinding	0.84	0.85	0.86	0.86
Geometric mean PSA (95% CI), ng/mL				
Year 0	1.13 (0.24 to 4.41)	1.12 (0.23 to 4.37)	1.12 (0.23 to 4.41)	1.13 (0.23 to 4.42)
Year 1	1.16 (0.22 to 4.82)	1.14 (0.21 to 4.75)	1.14 (0.21 to 4.89)	1.15 (0.21 to 4.91)
Year 2	1.18 (0.21 to 5.08)	1.15 (0.21 to 4.95)	1.17 (0.21 to 5.12)	1.16 (0.21 to 5.08)
Year 3	1.19 (0.21 to 5.25)	1.17 (0.20 to 5.26)	1.20 (0.21 to 5.31)	1.19 (0.20 to 5.39)
Year 4	1.23 (0.21 to 5.62)	1.19 (0.20 to 5.40)	1.23 (0.21 to 5.61)	1.23 (0.21 to 5.66)
Year 5	1.25 (0.21 to 5.81)	1.23 (0.21 to 5.62)	1.26 (0.21 to 5.89)	1.23 (0.21 to 5.66)
Year 6	1.28 (0.21 to 6.03)	1.23 (0.20 to 5.83)	1.26 (0.20 to 5.98)	1.25 (0.20 to 6.00)
Year 7	1.30 (0.21 to 6.27)	1.26 (0.21 to 5.91)	1.30 (0.21 to 6.22)	1.28 (0.20 to 6.22)
Year 8	1.31 (0.20 to 6.52)	1.29 (0.20 to 6.30)	1.39 (0.23 to 6.59)	1.35 (0.22 to 6.58)
PSA velocity, year 0-year 1 median (Q1-Q3)	0 (–0.20 to 0.30)	0 (–0.20 to 0.22)	0 (–0.20 to 0.28)	0 (–0.20 to 0.30)

Abbreviations: DRE, digital rectal examination; PSA, prostate-specific antigen.
[a]Trial was unblinded on October 23, 2008. Data in the primary article are as of this date.

Table 3. Number and Risk of Prostate Cancers

	Placebo (n = 8696)	Vitamin E Alone (n = 8737)	Selenium Alone (n = 8752)	Vitamin E + Selenium (n = 8702)
No. of prostate cancers				
October 2008	416	473	432	437
July 2011	529	620	575	555
Hazard ratio, (99% CI)				
October 2008		1.13 (0.95-1.35)	1.04 (0.87-1.24)	1.05 (0.88-1.25)
P value		.06	.62	.52
July 2011		1.17 (1.004-1.36)	1.09 (0.93-1.27)	1.05 (0.89-1.22)
P value		.008	.18	.46
Absolute risk[a]	9.3	10.9	10.1	9.7
Gleason ≥7, No.	133	155	161	164
Hazard ratio (99% CI)		1.16 (0.86-1.58)	1.21 (0.90-1.63)	1.23 (0.91-1.66)
P value		.20	.11	.08

[a]Prostate cancers per 1000 person-years.

min E and selenium, the interaction between vitamin E and selenium was statistically significant ($P=.02$), indicating no increased risk of prostate cancer when vitamin E and selenium were taken together. The risk of Gleason 7 or greater disease was higher for all 3 interventions (vitamin E: HR, 1.16 [99% CI, 0.86-1.58]; selenium: HR, 1.21 [99% CI, 0.90-1.63]; combination: HR, 1.23 [99% CI, 0.91-1.66]) but did not reach statistical significance for any group (Table 3). The elevated risk estimate for vitamin E was consistent across both low- and high-grade disease.

The cumulative incidence curves of prostate cancer by supplement group compared with placebo are presented in FIGURE 2. The difference in rates of prostate cancer between vitamin E and placebo became apparent during the participants' third year in the trial, at which point the HR was 1.10, and increased slightly each year thereafter. The proportional hazards assumption was reasonable for each study group (all $P \geq .17$). The unadjusted absolute increase in risk of cases of prostate cancer per 1000 person-years compared with placebo was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination.

Virtually all men with prostate cancer were without metastases at diagnosis (TABLE 4). Gleason 6 was the most common grade over all. For those with more aggressive disease, Gleason 7 was the most common score. Stage and grade distributions were similar among groups.

In the initial SELECT report a statistically nonsignificant increased risk of type 2 diabetes mellitus (as defined by self-report or new use of glitazone medications) was observed in the selenium supplementation group (HR, 1.07). In the updated results the HR is 1.04 and is not statistically significant ($P=.34$; TABLE 5). Table 5 also displays updated data on the prespecified secondary end points of lung, colorectal, and total other cancers, deaths, and grade 4 cardiovascular events. There are no statistically significant differences in

the HRs between groups, suggesting neither benefit nor harm from dietary supplementation with selenium or vitamin E for these end points.

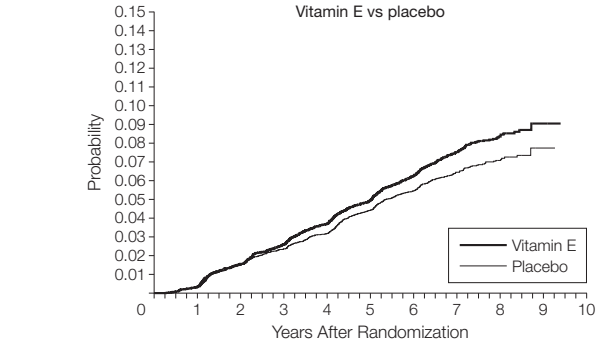
COMMENT

Prevention of prostate cancer remains an important public health goal because of the relatively high incidence and the high likelihood of curative-intent treatment of this cancer even when indolent disease is present,[9] and treatment related costs and morbidity. Although 2 large randomized trials have demonstrated that 5α-reductase inhibitors reduce prostate cancer risk by 20% to 25%,[10,11] the use of these agents is controversial because of concerns related to an observed increased risk of high-grade disease.[12] SELECT was designed to assess the effect of selenium and vitamin E alone and in combination as supplements to a normal diet on their ability to prevent prostate cancer in men at average risk. Other randomized studies have shown no benefit to dietary supplementation with selenium, lycopene, or soy in reducing the risk of invasive cancer in men with high-grade prostatic intraepithelial neoplasia on biopsy.[13,14]

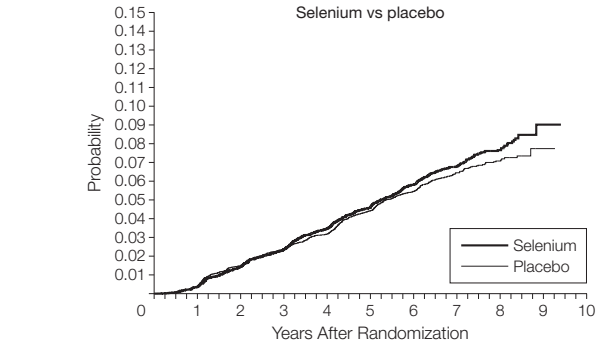
In this article, we report an observation of important public health concern that has emerged with continued follow-up of SELECT participants. With primary end point ascertainment based on contemporary community practice across the United States, Canada, and Puerto Rico using PSA and DRE as indications for biopsy, the risk of prostate cancer at 7 years of median follow-up was increased by 17% in men randomized to supplementation with vitamin E alone, a difference that started to appear about 3 years after randomization. Although there is debate about how to best handle accumulating results after the publication of primary findings and the appropriate threshold for statistical significance, the increased rate of prostate cancer in the vitamin E group was seen as early as 2006 and continued until the present analysis (HRs ranged from 1.12 to 1.17) suggesting that the current results are not an outlier observation due to multiple looks at the data. Extended follow-up with additional events has resulted in narrowed confidence intervals.

A biological explanation for the observed increased risk of prostate cancer in the vitamin E arm is not apparent from these data. The risk does not appear to be due to an increased bi-

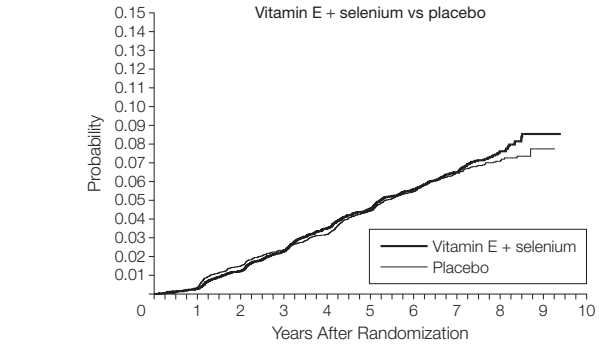
Figure 2. Cumulative Incidence of Prostate Cancer



No. at risk									
Placebo	8565	8344	8081	7831	7471	6399	4044	1833	70
Cumulative cases	32	127	201	268	367	446	503	524	529
Vitamin E	8620	8397	8150	7839	7442	6394	4010	1821	50
Cumulative cases	29	135	223	314	415	512	586	614	620



No. at risk									
Placebo	8565	8344	8081	7831	7471	6399	4044	1833	70
Selenium	8600	8360	8131	7826	7456	6425	4075	1829	66
Cumulative cases	31	123	202	293	384	474	532	563	575



No. at risk									
Placebo	8565	8344	8081	7831	7471	6399	4044	1833	70
Vitamin E + selenium	8592	8389	8136	7862	7486	6378	4035	1835	76
Cumulative cases	25	105	193	295	378	458	509	545	555

Table 4. Clinical and Pathological Characteristics of Incident Prostate Cancers

	No. (%) of Cancers			
	Placebo (n = 8696)	Vitamin E Alone (n = 8737)	Selenium Alone (n = 8752)	Vitamin E + Selenium (n = 8702)
Total prostate cancers diagnosed, No.	529	620	575	555
After unblinding for primary article	416 (79)	473 (76)	432 (75)	437 (79)
Diagnosed prior to unblinding but data received afterwards	26 (5)	33 (5)	22 (4)	17 (3)
Diagnosed after unblinding	87 (16)	114 (18)	121 (21)	101 (18)
Confirmation status				
Confirmed by central pathology[a]	444 (84)	506 (82)	474 (82)	475 (86)
T stage				
TX	5 (1)	9 (1)	7 (1)	8 (1)
T1a-c	375 (72)	460 (75)	425 (76)	391 (72)
T2a-b	143 (27)	138 (23)	127 (23)	144 (26)
T3a-b	1 (<1)	3 (<1)	3 (1)	2 (<1)
Not staged	5	10	13	10
N stage				
NX	378 (72)	441 (73)	397 (70)	393 (72)
N0	145 (28)	167 (27)	166 (29)	154 (28)
N1	0	0	2 (<1)	1 (<1)
Not staged	6	12	10	7
M stage				
MX	364 (70)	435 (72)	399 (71)	391 (72)
M0	159 (30)	170 (28)	159 (28)	153 (28)
M1a-c	0	3 (<1)	7 (1)	3 (1)
Not staged	6	12	10	8
Gleason score				
4-6	286 (69)	310 (67)	281 (64)	281 (63)
7	102 (24)	118 (25)	135 (31)	124 (28)
8-10	31 (7)	37 (8)	26 (6)	40 (9)
Not graded	110	155	133	110

[a] There were no disagreements. The cases not confirmed by central pathology review were either because no materials or inadequate materials were sent for review.

opsy rate prompted by changes in DRE, PSA, or unblinding. There was not a statistically significant increased risk of prostate cancer in the vitamin E and selenium combination group (HR, 1.05; $P = .46$), suggesting that selenium may have a protective effect by dampening the increased risk associated with vitamin E alone, a hypothesis reinforced by the P value (.02) of the interaction term in the marginal analysis. Tests of this hypothesis and other potential explanations for the results will be addressed by analysis of the effects of baseline plasma vitamin E levels and their interaction with baseline plasma and toenail selenium levels from samples collected from participants at study entry. Despite the lack of a mechanistic explanation, the findings show that vitamin E supplementation in the general population of healthy men significantly increases the risk of being diagnosed with prostate cancer.

The current findings of SELECT differ from findings from other large randomized intervention trials that examined the effects of vitamin E supplementation on prostate cancer risk. The Alpha-Tocopherol, Beta Carotene (ATBC) trial reported a 35% risk reduction for prostate cancer in men taking 50 mg/d of vitamin E for a median of 6.1 years,[15] although there are important differences with SELECT: (1) the participants of ATBC were all long-term smokers (36 years on average) compared with 43% who had never smoked and 8% current smokers in SELECT; (2) prostate cancer was a secondary end point in ATBC; and (3) men in ATBC were not screened so that prostate cancer was diagnosed at more advanced stages than in SELECT. In the Physicians Health Study II (PHS II) conducted contemporaneously with SELECT, intervention with 400 IU of vitamin E every other day for a median of 8 years had no effect on the incidence of prostate cancer (HR,0.97; 95% CI, 0.85-1.09; $P = .58$), although like SELECT there was no effect on total cancer incidence (HR, 1.04; 95% CI, 0.95-1.13; $P = .41$) or overall mortality (HR, 1.08; 95% CI, 0.98-1.19).[16]

Furthermore, both ATBC and PHS II were designed and analyzed as factorial trials, so the reported effect of vitamin E is estimated across the secondary factor (beta carotene or vitamin C, respectively). In contrast, SELECT was designed as a 4-group trial because of concerns about the potential interaction of vitamin E and selenium, for which a statistically significant interaction between these agents was indeed observed.

Given that more than 50% of individuals 60 years or older are taking supplements containing vitamin E and that 23% of them are taking at least 400 IU/d[17] despite a recommended daily dietary allowance of only 22.4 IU for adult men,[18] the implications of our observations are substantial. Consistent with the original SELECT report, longer follow-up did not demonstrate a benefit for selenium or vitamin E supplementation on risk of colorectal or lung cancer or cardiovascular events.

Although modest benefits for vitamin E supplementation have been observed in a limited number of randomized clinical trials for Alzheimer disease[19] and (as 1 part of a combination of oral antioxidants) for age-related macular degeneration,[20] no benefits were demonstrated for prevention of cardiac events or mortality,[21-23] colorectal adenomas,[24] respiratory infections in elderly individuals,[25] preeclampsia in women with type 1 diabetes,[26] or prevention or progression of cataracts or macular degeneration.[27,28] Moreover, the increased incidence of prostate cancer seen in SELECT, the previously reported increased incidence of lung cancer with

high-dose beta carotene in both ATBC[15] and the Beta-Carotene and Retinol Efficacy Trial (CARET),[29] and the increased risk of colon polyps seen in a trial administering high-dose folate,[30] suggest that caution should be used when recommending or studying high doses of micronutrients. As opposed to synthetic pharmaceuticals, these naturally occurring dietary constituents are part of normal physiology, and a *U*-shaped-dose response curve may exist where either deficiency or supraphysiological doses are harmful.

The findings of SELECT, ATBC, and CARET emphasize the importance of large-scale, population-based, randomized trials in accurately assessing the benefits and harms of micronutrients as dietary supplements. Because a statistically significant interaction was observed between vitamin E and selenium, we believe that caution should be used when designing factorial prevention trials in the future. Although factorial designs are appealing because of their statistical efficiency, interactions can make it difficult to evaluate the underlying effects of each treatment component.[31]

Furthermore, the fact that the increased risk of prostate cancer in the vitamin E group of participants in SELECT was only apparent after extended follow-up (allowing for additional events) suggests that health effects from these agents may continue even after the intervention is stopped, emphasizing the need for long-term follow-up even in trials closed before the planned intervention period is completed. Consenting SELECT participants have the opportunity to transition to a centralized follow-up study where annual updates to general health and cancer status are obtained either via a mailed questionnaire or data entered by the participant on the SELECT participant Web site, which will allow additional follow-up to further address these issues.

Table 5. Secondary End Points

	Placebo (n = 8696)	Vitamin E Alone (n = 8737)	Selenium Alone (n = 8752)	Vitamin E + Selenium (n = 8702)
Colorectal cancer, No.	75	85	74	93
Hazard ratio (99% CI)		1.09 (0.72-1.64)	0.96 (0.63-1.46)	1.21 (0.81-1.81)
P value		.60	.79	.22
Lung cancer, No.	92	104	94	104
Hazard ratio (99% CI)		1.11 (0.76-1.61)	1.02 (0.70-1.50)	1.11 (0.76-1.62)
P value		.49	.89	.48
All other primary cancers, excludes prostate, includes colorectal and lung, No.	579	570	557	594
Hazard ratio (99% CI)		0.97 (0.83-1.14)	0.96 (0.83-1.13)	1.02 (0.88-1.19)
P value		.65	.54	.74
All cancers, including prostate	1108	1190	1132	1149
Hazard ratio (99% CI)		1.07 (0.96-1.19)	1.02 (0.92-1.14)	1.02 (0.92-1.14)
P value		.13	.59	.60
Deaths, all cause	564	571	551	542
Hazard ratio (99% CI)		1.01 (0.86-1.17)	0.98 (0.84-1.14)	0.96 (0.82-1.12)
P value		.91	.67	.47
October 23, 2008[a] Diabetes[b]	669	700	724	660
Relative risk (99% CI)		1.04 (0.91-1.18)	1.07 (0.94-1.22)	0.97 (0.85-1.11)
P value		.47	.16	.61
July 5, 2011 Diabetes[b]	869	918	913	875
Relative risk (99% CI)		1.05 (0.93-1.17)	1.04 (0.93-1.17)	0.99 (0.89-1.12)
P value		.29	.34	.91
Cardiovascular events, grade ≥4[c]	969	909	939	943
Hazard ratio (99% CI)		0.93 (0.83-1.05)	0.97 (0.86-1.09)	0.97 (0.86-1.09)
P value		.11	.45	.51

[a] Date of data freeze for initial publication
[b] Prevalent cases at baseline and men who never submitted a form with a diabetes assessment are excluded from the analysis.
[c] Time to first reported cardiovascular event, cardiovascular procedure (eg, coronary artery bypass graft surgery), or hemorrhagic stroke, all men. Cardiovascular end points were not centrally adjudicated.

CONCLUSION

Extended follow-up of SELECT participants shows that healthy men with average risk of prostate cancer subjected to contemporary community standards of screening and biopsy who took a common dose and formulation of vitamin E (400 IU/d) have a significantly increased risk of prostate cancer. The observed 17% increase in prostate cancer incidence demonstrates the potential for seemingly innocuous yet biologically active substances such as vitamins to cause harm. The lack of benefit from dietary supplementation with vitamin E or other agents with respect to preventing common health conditions and cancers or improving overall survival, and their potential harm, underscore the need for consumers to be skeptical of health claims for unregulated over-the-counter products in the absence of strong evidence of benefit demonstrated in clinical trials.

Author Affiliations: Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio (Dr Klein); Cancer Therapy and Research Center, University of Texas Health Science Center, San Antonio (Dr Thompson); SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, Washington (Drs Tangen and Crowley and Mss Goodman and Darke); Department of Pathology, University of Colorado Health Science Center, Aurora (Dr Lucia); Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland (Drs Minasian, Ford, and Parnes); Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, and the Brigham and Women's Hospital, Division of Aging, Boston, Massachusetts (Dr Gaziano); Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, MD Anderson Cancer Center/University of Texas, Houston (Drs Karp and Lippman); Department of Urology, Mayo Clinic, Rochester, Minnesota (Dr Lieber); Department of Urology, Duke University Medical Center, Durham, North Carolina (Dr Walther); Department of Urology, Sun-

nybrook Medical Center, North York, Ontario, Canada (Dr Klotz); Department of Surgery, Moores Cancer Center, University of California San Diego, La Jolla (Dr Parsons); London Health Sciences Center, London, Surgical Oncology, Ontario, Canada (Dr Chin); Swedish Medical Center Cancer Institute, Medical Oncology, Seattle, Washington (Dr Goodman); University of California at Irvine, Department of Medicine, Orange (Dr Meyskens); and University of Michigan, Division of Hematology/Oncology, Ann Arbor (Dr Baker). Dr Karp's previous affiliation was Beth Israel Deaconess Medical Center, Medical Oncology, Boston, Massachusetts.

Author Contributions: Dr Tangen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Klein, Thompson, Tangen, Crowley, P. Goodman, Minasian, Ford, Parnes, Lieber, Walther, Klotz, Lippman, G. Goodman, Baker.

Acquisition of data: Klein, Thompson, Tangen, Crowley, Lucia, P. Goodman, Parsons, Chin.

Analysis and interpretation of data: Klein, Thompson, Tangen, Crowley, P. Goodman, Minasian, Ford, Karp, Klotz, Darke, Lippman, G. Goodman, Meyskens.

Drafting of the manuscript: Klein, Thompson, Tangen, P. Goodman, Lieber, Klotz, G. Goodman, Baker.

Critical revision of the manuscript for important intellectual content: Klein, Thompson, Tangen, Crowley, Lucia, P. Goodman, Minasian, Ford, Parnes, Karp, Walther, Parsons, Chin, Darke, Lippman, Meyskens, Baker.

Statistical analysis: Tangen, Crowley, P. Goodman, Darke.

Obtained funding: Klein, Thompson, Lippman, Baker.

Administrative, technical, or material support: Klein, Thompson, Lucia, Minasian, Parnes, Lieber, Walther, Parsons, Chin, Lippman.

Study supervision: Thompson, Crowley, P. Goodman, Minasian, Ford, Klotz, Lippman, G. Goodman, Baker.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Thompson reported receiving research support from the National Cancer Institute for a randomized controlled trial testing finasteride against placebo, both of which are supplied by Merck. Dr Gaziano reported receiving grant support (to his institution) from Wyeth (now Pfizer) in the form of vitamin and placebo pills and packaging. Dr Karp reported receiving grants to his institution from Pfizer. Dr Klotz reported receiving travel support for meetings from sanofi-aventis, Merck, and AstraZeneca and research support for investigator-initiated trials from Abbott and GlaxoSmithKline, and institutional grants pending. Dr Chin reported receiving consultancy fees from Janssen, Amgen, Novartis, and Firmagon; receiving payment for lectures from Firmagon; and payment for development of educational presentations from AstraZeneca, Novartis, and Firmagon. Dr Meyskens reported being a co-founder of Cancer Prevention Pharmaceuticals. Dr Baker reported board membership for Merck for which he receives no compensation. Otherwise there were no other conflicts of interest disclosed.

Funding/Support: This work was supported in part by Public Health Service Cooperative Agreement grant CA37429 awarded by the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and in part by the National Center for Complementary and Alternative Medicine (National Institutes of Health). Study agents and packaging were provided by Perrigo Co, Allegan, Michigan; Sabinsa Corp, Piscataway, New Jersey; Tishcon Corp, Westbury, New York; and DSM Nutritional Products Inc, Parsipanny, New Jersey.

Disclaimer: Dr Gaziano, a contributing editor for *JAMA*, was not involved in the editorial review of or the decision to publish this article.

Role of the Sponsor: This work was supported by the National Institutes of Health, primarily the National Cancer Institute (NCI) and the National Center for Complementary and Alternative Medicine. Representatives from the National Institutes of Health (NCI) participated in design, oversight, and reporting of this study.

Online-Only Material: The Author Video Interview is available at http://www.jama.com.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277-300.

2. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008;358(12):1250-1261.

3. Zaytoun OM, Vargo EH, Rajan R, Berglund R, Gordon S, Jones JS. Emergence of fluoroquinolone-resistant Escherichia coli as cause of postprostate biopsy infection: implications for prophylaxis and treatment. *Urology*. 2011;77(5):1035-1041.

4. Latini DM, Hart SL, Knight SJ, et al; CaPSURE Investigators. The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol*. 2007;178(3 pt 1):826-831.

5. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol*. 2011;29(16):2185-2190.

6. 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.

7. 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.

8. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18(6):695-706.

9. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol*. 2010;28(7):1117-1123.

10. Andriole GL, Bostwick DG, Brawley OW, et al; REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010;362(13):1192-1202.

11. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349(3):215-224.

12. Theoret MR, Ning YM, Zhang JJ, Justice R, Keegan P, Pazdur R. The risks and benefits of 5α-reductase inhibitors for prostate-cancer prevention. *N Engl J Med*. 2011;365(2):97-99.

13. Fleshner NE, Kapusta L, Donnelly B, et al. Progression from high-grade prostatic intraepithelial neoplasia to cancer: a randomized trial of combination vitamin-E, soy, and selenium. *J Clin Oncol*. 2011;29(17):2386-2390.

14. Marshall JR, Tangen CM, Sakr WA, et al. Phase III Trial of Selenium to Prevent Prostate Cancer in Men with High-Grade Prostatic Intraepithelial Neoplasia: SWOG S9917 [published online September 6, 2011]. *Cancer Prev Res (Phila Pa)*. doi: 10.1158/1940-6207.CAPR-10-0343.

15. 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. *N Engl J Med*. 1994;330(15):1029-1035.

16. 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.

17. Ford ES, Ajani UA, Mokdad AH. Brief communication: The prevalence of high intake of vitamin E from the use of supplements among US adults. *Ann Intern Med*. 2005;143(2):116-120.

18. Office of Dietary Supplements. National Institutes of Health, Dietary Supplement Fact Sheet: Vitamin E. http://ods.od.nih.gov/factsheets/VitaminE-QuickFacts. Reviewed June 24, 2011. Accessed August 26, 2011.

19. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med*. 1997;336(17):1216-1222.

20. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119(10):1417-1436.

21. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P; The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(3):154-160.

22. Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2008;300(18):2123-2133.

23. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294(1):56-65.

24. Greenberg ER, Baron JA, Tosteson TD, et al; Polyp Prevention Study Group. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med*. 1994;331(3):141-147.

25. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin-mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA*. 2002;288(6):715-721.

26. McCance DR, Holmes VA, Maresh MJ, et al; Diabetes and Pre-eclampsia Intervention Trial (DAPIT) Study Group. Vitamins C and E for prevention of pre-eclampsia in women with type 1 diabetes (DAPIT): a randomised placebo-controlled trial. *Lancet*. 2010;376(9737):259-266.

27. McNeil JJ, Robman L, Tikellis G, Sinclair MI, McCarty CA, Taylor HR. Vitamin E supplementation and cataract: randomized controlled trial. *Ophthalmology*. 2004;111(1):75-84.

28. Taylor HR, Tikellis G, Robman LD, McCarty CA, McNeil JJ. Vitamin E supplementation and macular degeneration: randomised controlled trial. *BMJ*. 2002;325(7354):11.

29. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst*. 1996;88(21):1550-1559.

30. Cole BF, Baron JA, Sandler RS, et al; Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA*. 2007;297(21):2351-2359.

31. Green S, Liu PY, O'Sullivan J. Factorial design considerations. *J Clin Oncol*. 2002;20(16):3424-3430.