Title
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Journal
J Clin Oncol, 30(5_suppl)

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Publication Date
2012-02-10

Published in final edited form as:
JAMA. 2011 October 12; 306(14): 1549–1556. doi:10.1001/jama.2011.1437.

Vitamin E and the Risk of Prostate Cancer: Updated Results of The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

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Financial Disclosures: The following had no disclosures to report: Dr. Crowley, Ms. Darke, Dr. Ford, Dr. G. Goodman, Ms. P. Goodman, Dr. Klein, Dr. Klotz, Dr. Lieber, Lippman, Dr. Lucia, Dr. Minasian, Dr. Parnes, Dr. Parsons, Dr. Tangen, Dr. Thompson, Dr. Walther

Data Access and Responsibility: Catherine Tangen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract

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 non-statistically significant 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—SELECT randomized 35,533 men from 427 study sites in the United States, Canada and Puerto Rico in a double-blind manner between August 22, 2001 and June 24, 2004. Eligible men were 50 years or older (African Americans) or 55 years or older (all others) with a PSA ≤4.0 ng/mL and a digital rectal examination not suspicious for prostate cancer. Included in the analysis are 34,887 men randomly assigned to one of four treatment groups: selenium (n=8752), vitamin E (n=8737), both agents (n=8702), or placebo (n=8696). Data reflect the final data collected by the study sites on their participants through July 5, 2011.

Interventions—Oral selenium (200 μg/day 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 since the primary report. Hazard ratios (99% confidence intervals [CI]) and numbers of prostate cancers were 1.17(99% CI 1.004-1.36, p=.008, n=620) for vitamin E, 1.09 (99% CI 0.93-1.27, p=.18, n=575) for selenium, 1.05 (99%CI 0.89-1.22, p=.46, n=555) for selenium + vitamin E vs. 1.00 (n=529) for placebo.The absolute increase in risk compared with placebo for vitamin E, selenium and the combination were 1.6, 0.9 and 0.4 cases of prostate cancer per 1,000 person-years.

Conclusions—Dietary supplementation with Vitamin E significantly increases the risk of prostate cancer among healthy men.

Trial registration—clinicaltrials.gov identifier: NCT00006392

Lifetime risk of prostate cancer in the United Sates is currently estimated to be 16%.[1] While most cases are found at an early, curable stage, treatment is costly and urinary, sexual, and bowel-related side 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 epidemiologic 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 two 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) began accrual on August 22, 2001 and randomized 35,533 men into four groups: (1) selenium with matching placebo, (2) vitamin E with matching placebo, (3) both agents, or (4) placebo.

Based on a preplanned interim analysis, the independent data and safety monitoring committee (DSMC) 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] With a median follow-up of 5.5 years, the number of prostate cancers detected, hazard ratios [HR] and 99% confidence intervals [CI] were n=473, HR=1.13, 99% CI 0.95-1.35 for vitamin E; n=432, HR=1.04,99% CI 0.87-1.24for selenium; n=437, HR=1.05, 99% CI 0.88-1.25for selenium + vitamin E; and n=416, HR=1.0 for placebo. While these results were not statistically significant, the DSMC expressed concern about the increased risk of prostate cancer observed in the vitamin E + placebo group which approached statistical significance (p=0.06) and a statistically non-significant increased risk of type 2 diabetes mellitus in the selenium + placebo group (p=0.16). Since that time participant follow-up has continued, allowing observation of additional events. On May 20, 2011, the DSMC 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 PSA of ≤ 4 ng/mL and normal digital rectal exam (DRE) commencing at age 50 for African Americans or age 55 for all others. Subjects were randomized into one of four groups: (1) selenium (200 μg/day from *L*-selenomethionine) with matching vitamin E placebo, (2) vitamin E (400 IU/day of all *rac*-α-tocopherol acetate) with matching selenium placebo, (3) both agents, or (4) placebo + placebo. 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 while on 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 endpoint 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 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 our original report.

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 endpoints, and a blood sample for participants diagnosed with prostate cancer. An independent DSMC met yearly commencing with study inception, reviewing data on safety, adherence, and prostate and other cancer diagnoses. On September 15, 2008 the DSMC recommended reporting initial results related to the lack of efficacy of the agents on prevention of prostate cancer. Since that time the DSMC has continued to meet yearly via teleconference.

Statistical Analysis

The primary endpoint of SELECT was prostate cancer incidence resulting from routine community care. Cancers not centrally confirmed (17% of the total) are included in the analysis. Five pre-specified comparisons of the four study groups were conducted: (1) selenium vs placebo, (2) vitamin E vs placebo, (3) selenium + vitamin E vs placebo, (4) selenium vs selenium + vitamin E, and (5) vitamin E vs selenium + vitamin E. Although a one-sided significance level of 0.005 was specified to test for the preventive effect for each supplement comparison and thus 99% confidence intervals are reported, we have reported two-sided p-values throughout because the comparison of prevention vs. increased risk of cancer is a two-sided question.[6] A proportional hazards model was used to compare prostate cancer and other cancer incidence between placebo and each of the three arms with active agents. Those without the endpoint 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 arm by time interaction. The cumulative incidence curves for prostate cancer were generated accounting for the competing risk of death.[8] A chi-square 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).

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 are displayed in Table 1 and an updated CONSORT diagram in Figure 1. The frequency of use of DRE and PSA is displayed in Table 2; no differences between arms are apparent 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=0.008) (Table 3). After adjustment for the marginal effects of vitamin E and selenium, the interaction between vitamin E and selenium was statistically significant (p=0.021), 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 three interventions (vitamin E, HR = 1.16, 99% CI 0.86 – 1.58; selenium, HR = 1.21, 99% CI 0.90 – 1.63; combination, HR = 1.06, 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. There was no difference in overall survival between any of the treatment groups (all p≥ 0.47, Table 5).

The cumulative incidence curves of prostate cancer by supplement arm compared to placebo are presented in Figures 2a-c. The difference in rates of prostate cancer between vitamin E and placebo became apparent during participants' third year on 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 arm (all p≥ 0.17). The unadjusted absolute increase in risk compared with placebo for vitamin E, selenium, and the combination were 1.6, 0.9, and 0.4 cases of prostate cancer per 1,000 person-years.

Virtually all men with prostate cancer were without metastases at diagnosis (Table 4). Gleason 6 was the most common grade with the most common form of more aggressive disease being Gleason score 7. Stage and grade distributions were similar among groups.

In the initial SELECT report a non-statistically significant 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 hazard ratio has moved closer to 1(HR=1.04) and is not statistically significant (p=0.34) (Table 5). Table 5 also displays updated data on the pre-specified secondary endpoints of lung, colorectal, and total other cancers, deaths, and grade 4 cardiovascular events. There are no statistically significant differences in the hazard ratios between groups, suggesting neither benefit nor harm for dietary supplementation with selenium or vitamin E for these endpoints.

Comment

Prostate cancer prevention remains an important public health goal because of its incidence, high likelihood of curative-intent treatment even when indolent disease is present,[9] and treatment related costs and morbidity. Although two large randomized trials have demonstrated that 5α-reductase inhibitors reduce risk by 20 – 25%,[10,11] their use 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 risk of invasive cancer in men with high- grade prostatic intraepithelial neoplasia (HGPIN) on biopsy.[13,14]

In this report we detail an observation of serious public health concern that has emerged with continued follow-up of SELECT participants. With primary endpoint ascertainment based on contemporary community practice across the US, 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 which started to appear about two years post randomization. While there is debate over how to best handle accumulating results after the publication of the primary findings and the appropriate threshold for statistical significance, the increased rate of prostate cancer in the vitamin E arm was seen as early as 2006 and continued until the present analysis (HR 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; it does not appear to be due to an increased biopsy 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=0.46), suggesting that selenium has a protective effect by dampening the increased risk associated with vitamin E alone, a hypothesis reinforced by the p-value (0.021) 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 are at odds with 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 50mg/day 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 to 43% never smokers and 8% current smokers in SELECT; 2) prostate cancer was a secondary endpoint 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 400IU 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 four-arm trial because of concerns about the potential interaction of vitamin E and selenium, and a statistically significant interaction between these agents was indeed observed.

Given that more than 50% of individuals 60 or older are taking supplements containing vitamin E and that 23% of them are taking ≥400 IU per day[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 to selenium or vitamin E supplementation on risk of colorectal or lung

cancer or cardiovascular events. While modest benefits for vitamin E supplementation have been observed in a limited number of randomized clinical trials for Alzheimer's disease[19] and (as one part of a cocktail of oral antioxidants) for age-related macular degeneration,[20] no benefits were demonstrated for prevention of cardiac events or mortality,[21,22,23] colorectal adenomas,[24] respiratory infections in elderly individuals,[25] pre-eclampsia in women with type 1 diabetes,[26] or prevention or progression of cataracts or macular degeneration.[27,28] Furthermore, 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 supraphysiologic doses are harmful.

The experiences 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 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 website, which will allow additional follow up to further address these issues.

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 per day) 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 from clinical trials.

Acknowledgments

Dr. Gaziano reported receiving grant support (to his institution) from Wyeth (now Pfizer) in the form of vitamin and placebo pills and packaging. 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 Astra Zeneca, Novartis and Firmagon. Dr. Meyskens reported being a co-founder of Cancer Prevention Pharmaceuticals. Dr. Baker reported Board Membership for Merck (no compensation). Dr. Karp reported receiving grants (to his institution) from Pfizer.

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 Company (Allegan, Michigan), Sabinsa Corporation (Piscataway, New Jersey), Tishcon Corporation (Westbury, New York), and DSM Nutritional Products Inc. (Parsipanny, New Jersey).

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 Complimentary and Alternative Medicine. Representatives from the NIH (NCI) participated in design, oversight, and reporting of this study.

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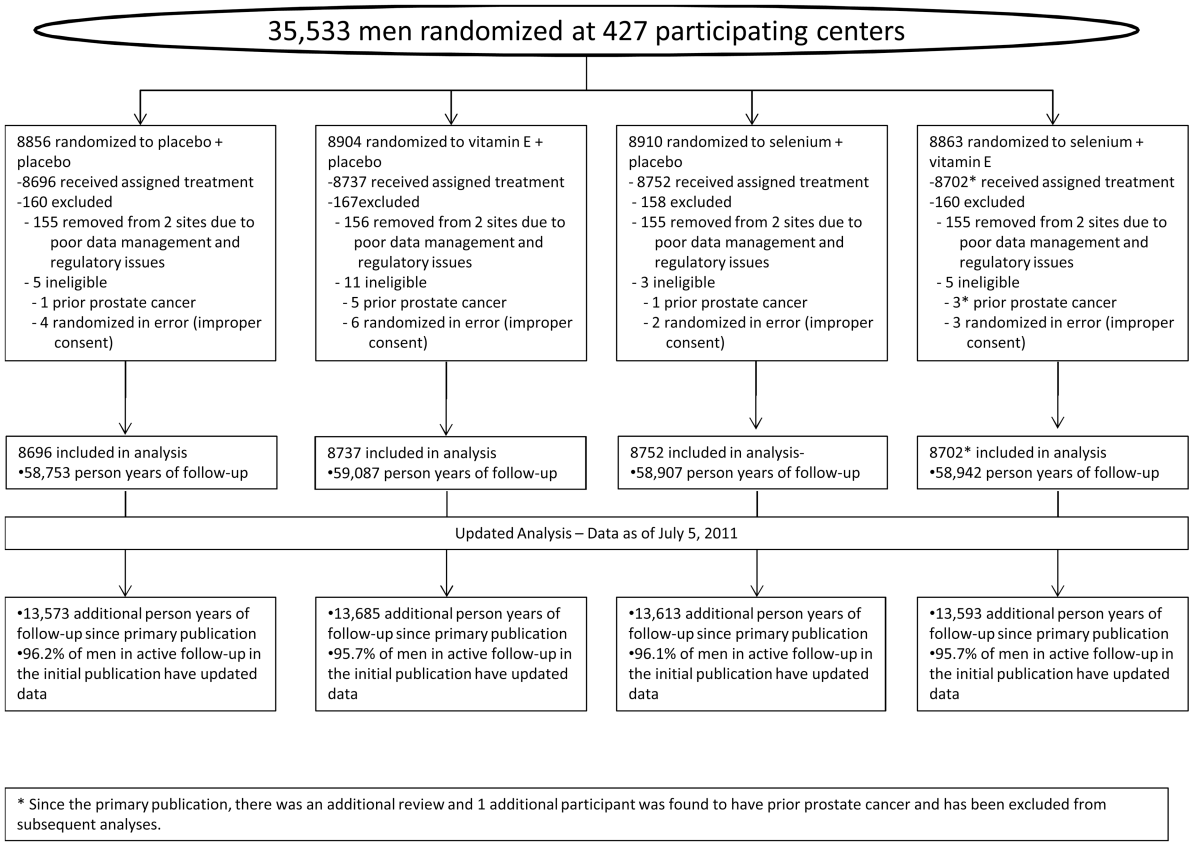

Figure 1. CONSORT Diagram

2a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Placebo (at risk)	8565	8344	8081	7831	7471	6399	4044	1833	70
Cumulative Cases	32	127	201	268	367	446	503	524	529
Vitamin E (at risk)	8620	8397	8150	7839	7442	6394	4010	1821	50
Cumulative Cases	29	135	223	314	415	512	586	614	620

2b

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Placebo (at risk)	8565	8344	8081	7831	7471	6399	4044	1833	70
Selenium (at risk)	8600	8360	8131	7826	7456	6425	4075	1829	66
Cumulative Cases	31	123	202	293	384	474	532	563	575

2c

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Placebo (at risk)	8565	8344	8081	7831	7471	6399	4044	1833	70
Vitamin E + selenium (at risk)	8592	8389	8136	7862	7486	6378	4035	1835	76
Cumulative Cases	25	105	193	295	378	458	509	545	555

Figure 2.

a: Cumulative Incidence of Prostate Cancer, Vitamin E vs. Placebo

b: Cumulative Incidence of Prostate Cancer, Selenium vs. Placebo

c: Cumulative Incidence of Prostate Cancer, Combination vs. Placebo

Table 1

Baseline participant characteristics

	Placebo (n=8,696)		Vitamin E alone (n=8,737)		Selenium alone (n=8,752)		Vitamin E + selenium (n=8,702)	
AGE								
Median (interquartile range)	63	(58-67)	62	(58.0-67)	63	(58-68)	62	(58-67)
50 - 54 years	355	4%	403	5%	337	4%	385	4%
55 - 64 years	5,078	58%	5,142	59%	5,075	58%	5,051	58%
65 - 74 years	2,702	31%	2,642	30%	2,734	31%	2,731	31%
75+ years	561	6%	550	6%	606	7%	535	6%
RACE								
White	6,862	79%	6,893	79%	6,944	79%	6,872	79%
African American	1,083	12%	1,106	13%	1,054	12%	1,075	12%
Hispanic (Non-Afri. American)	496	6%	476	5%	484	6%	484	6%
Hispanic (Afri. American)	76	1%	103	1%	86	1%	96	1%
Aboriginal	27	0%	22	0%	41	0%	29	0%
Asian/Pacific Islander	128	1%	110	1%	111	1%	123	1%
Unknown	24	0%	27	0%	32	0%	23	0%
PSA (NG/ML)								
Median (interquartile range)	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	4,133	48%	4,234	48%	4,247	49%	4,235	49%
1.1 - 2.0	2,735	31%	2,648	30%	2,652	30%	2,657	31%
2.1 - 3.0	1,153	13%	1,222	14%	1,199	14%	1,147	14%
3.1 - 4.0	668	8%	627	7%	649	7%	656	7%
>4.0	5	0%	3	0%	2	0%	1	0%
Missing	2	0%	3	0%	3	0%	6	0%

Table 2

Diagnostic Testing

	Placebo (n=8,696)	Vitamin E alone (n=8,737)	Selenium alone (n=8,752)	Vitamin E + selenium (n=8,702)
Prostate biopsy (men ever having biopsy)				
Prior to unblinding[1]	1,041	1,046	1,003	1,014
Post unblinding	256	268	267	254
Number of DREs/participant				
Prior to unblinding	3.20	3.20	3.20	3.21
Post unblinding	0.64	0.63	0.64	0.64
Number of PSA tests/participant				
Prior to unblinding	3.87	3.88	3.87	3.90
Post unblinding	0.84	0.85	0.86	0.86
Geometric mean PSA (95% CI)				
Year 0	1.13 (0.24, 4.41)	1.12 (0.23, 4.37)	1.12 (0.23, 4.41)	1.13 (0.23, 4.42)
Year 1	1.16 (0.22, 4.82)	1.14(0.21, 4.75)	1.14 (0.21, 4.89)	1.15 (0.21, 4.91)
Year 2	1.18 (0.21, 5.08)	1.15 (0.21, 4.95)	1.17 (0.21, 5.12)	1.16 (0.21, 5.08)
Year 3	1.19 (0.21, 5.25)	1.17 (0.20, 5.26)	1.20 (0.21, 5.31)	1.19 (0.21, 5.25)
Year 4	1.23 (0.21,5.62)	1.19 (0.20, 5.40)	1.23 (0.21, 5.61)	1.23 (0.21, 5.62)
Year 5	1.25 (0.21, 5.81)	1.23 (0.21, 5.62)	1.26 (0.21, 5.89)	1.23 (0.21, 5.81)
Year 6	1.28 (0.21, 6.03)	1.23 (0.20, 5.83)	1.26 (0.20, 5.98)	1.25 (0.21, 6.03)
Year 7	1.30 (0.21, 6.27)	1.26 (0.21, 5.91)	1.30 (0.21, 6.22)	1.28 (0.21, 6.27)
Year 8	1.31 (0.20, 6.52)	1.29 (0.20, 6.30)	1.39 (0.23, 6.59)	1.35 (0.20, 6.52)
PSA velocity Year 0 – Year 1 median (Q1, Q3)	0 (-0.20, 0.30)	0 (-0.20, 0.22)	0 (-0.20, 0.28)	0 (-0.20, 0.30)

[1] Trial was unblinded on October 23, 2008. Data in the primary paper are as of this date.

Table 3

Number and risk of prostate cancers

	Placebo (n=8,696)	Vitamin E alone (n=8,737)	Selenium alone (n=8,752)	Vitamin E + selenium (n=8,702)
Number of prostate cancers				
As of 10/2008	416	473	432	437
As of 07/2011	529	620	575	555
Hazard ratio, (99% CI), p-value				
As of 10/2008		1.13 (0.95 – 1.35), p=.06	1.05 (0.88 – 1.25), p=.52	1.04 (0.87 – 1.24), p=.62
As of 07/2011		1.17 (1.004 – 1.36), p=.008	1.09 (0.93 – 1.27), 0=.18	1.05 (0.89 – 1.22), p=.46
Absolute risk†	9.3	10.9	10.1	9.7
Gleason ≥ 7 (n)	133	155	161	164
Hazard ratio (99% CI), p-value		1.16 (0.86, 1.58), p=.20	1.21 (0.90, 1.63), p=.11	1.23 (0.91, 1.66), p=.08

†Prostate cancers per 1,000 person years

Table 4

Clinical and Pathological Characteristics of Incident Prostate Cancers

	Placebo (n=8,696)		Vitamin E alone (n=8,737)		Selenium alone (n=8,752)		Vitamin E + selenium (n=8,702)	
TOTAL PROSTATE CANCERS DIAGNOSED	529		620		575		555	
Number as of unblinding (primary paper)	416	79%	473	76%	432	75%	437	79%
Number diagnosed prior to unblinding but data received afterwards	26	5%	33	5%	22	4%	17	3%
Number diagnosed after unblinding	87	16%	114	18%	121	21%	101	18%
CONFIRMATION STATUS								
Confirmed by central pathology*	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	0%	3	0%	3	1%	2	0%
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%	0	0%	2	0%	1	0%
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	0%	3	0%	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		134		110	

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

Table 5

Secondary Endpoints

	Placebo (n=8,696)	Vitamin E alone (n=8,737)	Selenium alone (n=8,752)	Vitamin E + selenium (n=8,702)
Colorectal Cancer	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		p=0.60	p=0.79	p=0.22
Lung Cancer	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		p=0.49	p=0.89	p=0.48
All other primary cancers (excludes prostate, includes colorectal and lung)	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		p=0.65	p=0.54	p=0.74
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		p=0.13	p=0.59	p=0.60
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		p=.91	p=.67	p=.47
October 23, 2008†				
Diabetes*	669	700	724	660
Relative Risk (99% CI)		1.04 (0.90 – 1.18)	1.07 (0.94 – 1.22)	0.97 (0.86 – 1.11)
p-value		p = 0.47	p = 0.16	p = 0.61
July 5, 2011				
Diabetes*	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		p = 0.29	p = 0.34	p = 0.91
Cardiovascular events, grade 4 or higher**	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		p = 0.11	p = 0.45	p = 0.51

† Date of data freeze for initial publication

* Prevalent cases at baseline and men who never submitted a form with a diabetes assessment are excluded from the analysis.

** Time to first reported cardiovascular event, cardiovascular procedure (e.g., CABG), or hemorrhagic stroke, all men. Cardiovascular endpoints were not centrally adjudicated.