

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

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Scott M. Lippman, MD

Eric A. Klein, MD

Phyllis J. Goodman, MS

M. Scott Lucia, MD

Ian M. Thompson, MD

Leslie G. Ford, MD

Howard L. Parnes, MD

Lori M. Minasian, MD

J. Michael Gaziano, MD, MPH

Jo Ann Hartline, MPH

J. Kellogg Parsons, MD, MHS

James D. Bearden III, MD

E. David Crawford, MD

Gary E. Goodman, MD

Jaime Claudio, MD

Eric Winquist, MD, MSc

Elise D. Cook, MD

Daniel D. Karp, MD

Philip Walther, MD

Michael M. Lieber, MD

Alan R. Kristal, DrPH

Amy K. Darke, MS

Kathryn B. Arnold, MS

Patricia A. Ganz, MD

Regina M. Santella, PhD

Demetrius Albanes, MD

Philip R. Taylor, MD, ScD

Jeffrey L. Probstfield, MD

T. J. Jagpal, CCRP

John J. Crowley, PhD

Frank L. Meyskens Jr, MD

Laurence H. Baker, DO

Charles A. Coltman Jr, MD

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.

Trial Registration clinicaltrials.gov identifier: NCT00006392

JAMA. 2009;301(1):39-51

www.jama.com

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

Author Affiliations are listed at the end of this article.

Corresponding Author: Scott M. Lippman, MD, Department of Thoracic and Head and Neck Medical Oncology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 432, Houston, TX 77030-4009 (slippman@mdanderson.org), or Eric A. Klein, MD, Cleveland Clinic Lerner College of Medicine, Desk A100, 9500 Euclid Ave, Cleveland, OH 44195 (kleine@ccf.org).

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 trial¹¹ 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 μ g/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 re-

quirements 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 un-

der 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 $\alpha=.005$ level (equivalent to a 2-sided $\alpha=.01$ level), there was 96% power to detect a 25% re-

duction 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).

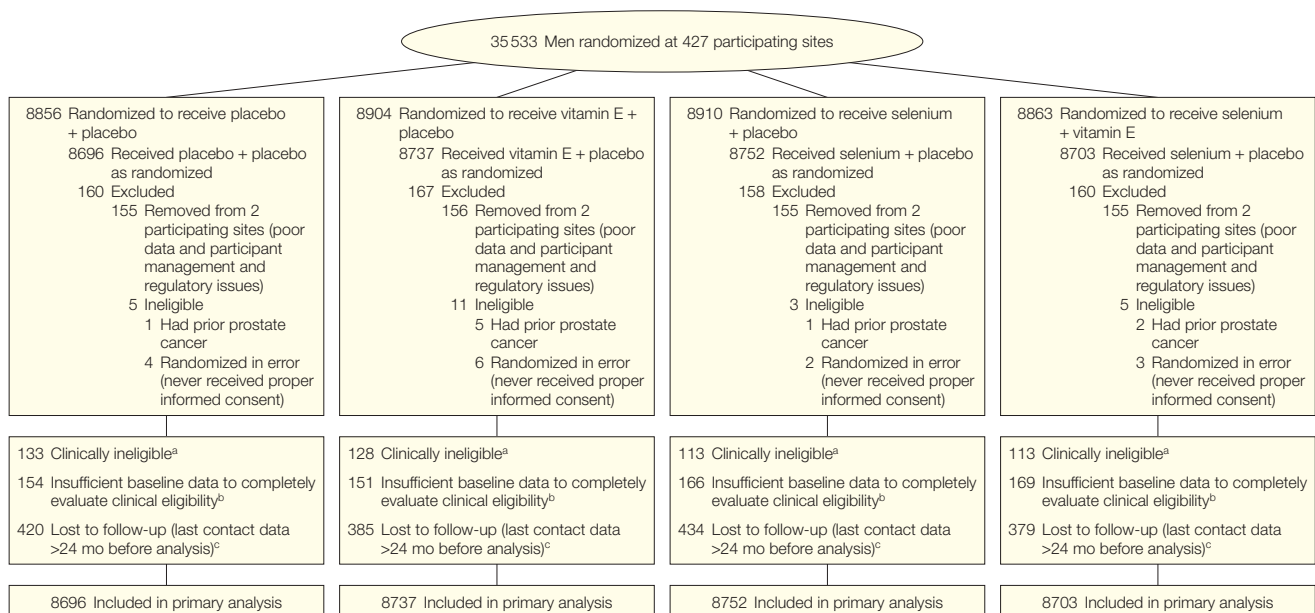
Design assumptions were based on the PCPT, ATBC, and NPC trials. The details of the statistical design have been described elsewhere.²⁰ Important elements included (1) constant accrual over 5 years; (2) prostate cancer incidence in the placebo group based on PCPT for the first 3 years and the 1995 Puget 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 $\alpha=.005$ level (equivalent to a 2-sided $\alpha=.01$ level) using a Bonferroni factor of 5 to preserve an overall 1-sided $\alpha=.0025$ level (equivalent to a 2-sided $\alpha=.05$ 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



^aDue 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.

^bBlood pressure, PSA, and/or DRE not performed within required time frame (but normal) or other data-related reason.

^cAll 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 $\alpha=0.0005$ level (equivalent to a 2-sided $\alpha=0.001$ 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 $\alpha=0.0005$ (equivalent to a 2-sided $\alpha=0.001$ 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 $\mu\text{g/L}$, multiply by 1.0.

^aOther 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

Pill Counts ^a	% (Range) ^b			
	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)
Bioadherence	Median (Interquartile Range)			
	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.

^aPercentage of men adherent, defined as taking at least 80% of their study supplements. Denominators decrease over time reflecting the varying amounts of follow-up.

^bThese ranges are estimates including those with missing data and assumes those missing were either all not adherent (low estimate) or all adherent (high estimate).

^cNumbers 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 $\mu\text{g/L}$, multiply by 1.0.

^aPercentages are based on alive participants who are prostate cancer-free and for whom the form was submitted.

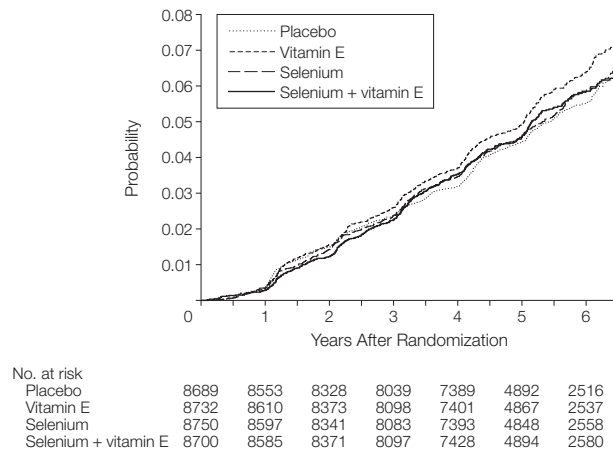
^bGleason score was based on central pathology review. The Gleason grade ranges from 1 to 5, with 5 having the worst prognosis. The Gleason score ranges from 2 to 10, with 10 having the worst prognosis.

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



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

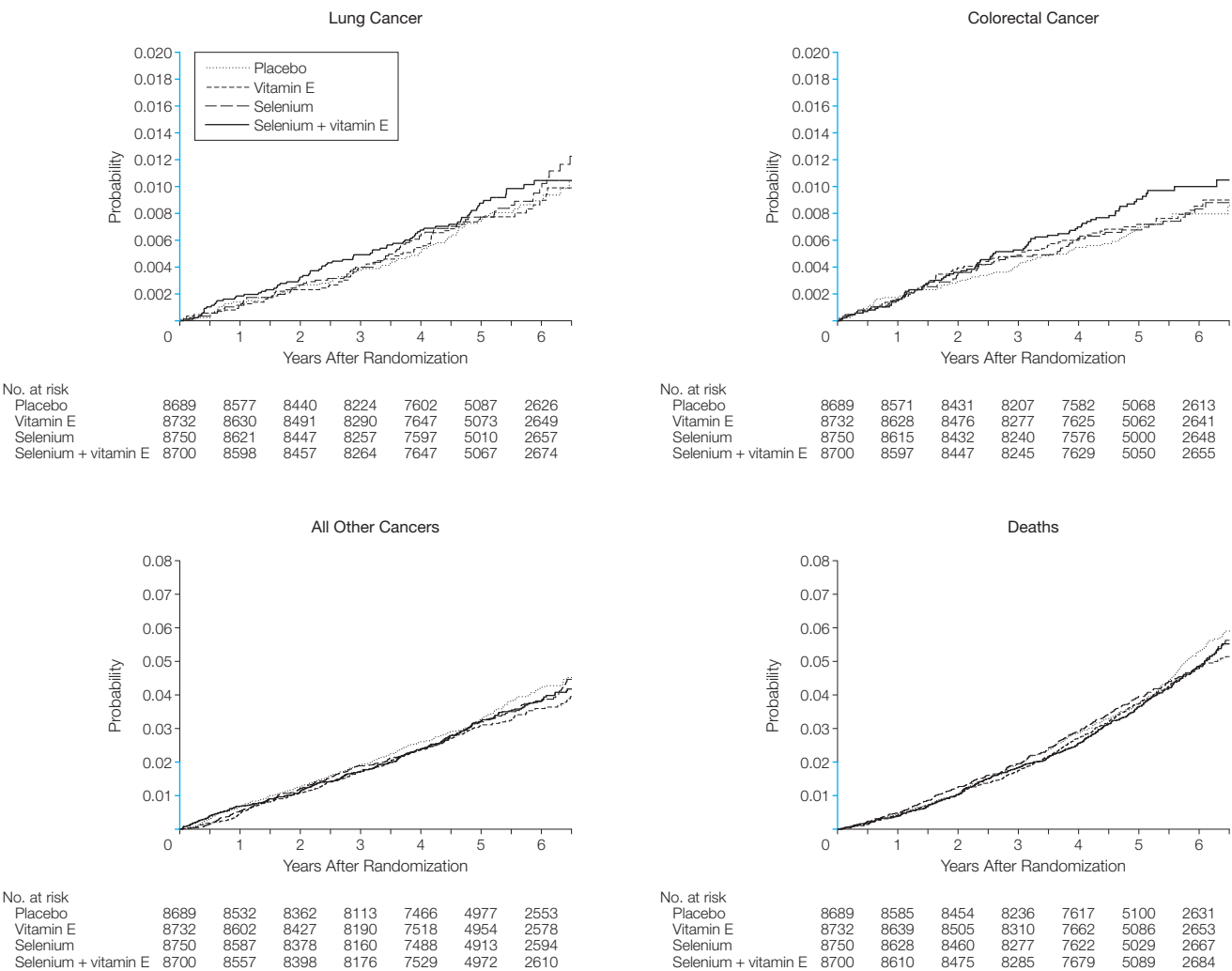
There were no significant differences (all $P > .15$) in any prespecified secondary cancer end points (FIGURE 3 and TABLE 4). At 5 years, the cumulative

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 ran-

domization) 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 dis-

continued 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.

^aThe HRs and RRs given for vitamin E, selenium, and selenium + vitamin E groups are compared with the placebo group.

^bNo. 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).

^cExcluding basal cell and squamous cell skin cancers.

^dBased on self-report or reported use of diabetes medications of the glitazone class; excludes prevalent cases at randomization.

^eNot specified as to whether an ischemic or hemorrhagic stroke.

^fAccording 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 availabil-

ity, 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 levels⁹; 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 trial²³ 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 mechanisms²⁵ 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

Adverse Event	Placebo (n = 8696)		Vitamin E (n = 8737)		Selenium (n = 8752)		Selenium + Vitamin E (n = 8703)	
	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.

^aThe 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-analysis³¹ found that vitamin E at doses of at least 400 IU/d increased all-cause mortality, and another study³² 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 ac-

tive 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.

Published Online: December 9, 2008 (doi:10.1001/jama.2008.864).

Author Affiliations: Divisions of Cancer Medicine (Drs Lippman and Karp) and Cancer Prevention and Population Sciences (Drs Lippman and Cook), University of Texas M. D. Anderson Cancer Center, Houston; Glickman Urological and Kidney Institute and Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio (Dr Klein); Southwest Oncology Group Statistical Center, Seattle, Washington (Dr Crowley and Mss P. Goodman, Hartline, Darke, and Arnold); Department of Pathology (Dr Lucia) and Division of Urologic Oncology (Dr Crawford), University of Colorado Health Sciences Center, Denver; Departments of Urology (Dr Thompson) and Medicine/Hematology and Medical Oncology (Dr Coltman), University of Texas Health Sciences Center, San Antonio; Division of Cancer Prevention (Drs Ford, Parnes, and Minasian) and Division of Cancer Epidemiology and Genetics (Drs Albanes and Taylor), National Cancer Institute, Bethesda, Maryland; Veterans Affairs Cooperative Studies Program and Massachusetts Veterans Epidemiology Research and Information Center, Boston VA Healthcare Center, Boston, Massachusetts (Dr Gaziano); Moores Cancer Center, La Jolla, California (Dr Parsons); Upstate Carolina CCOP, Spartanburg, South Carolina (Dr Bearden); Division of Hematology and Oncology, Swedish Cancer Institute, Seattle, Washington (Dr G. Goodman); Altamira Family Medicine, Rio Piedras, Puerto Rico (Dr Claudio); London Regional Cancer Program, London Health Sciences Center, London, Ontario, Canada (Dr Winquist); Department of Urologic Surgery, Duke University Medical Center, Durham, North Carolina (Dr Walther); Department of Urology, Mayo Clinic, Rochester, Minnesota (Dr Lieber); Departments of Epidemiology (Dr Kristal) and Medicine and Cardiology (Dr Probstfield), University of Washington, Seattle; Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center, University of California, Los Angeles (Dr Ganz); Mailman School of Public Health, Columbia University, New York, New York (Dr Santella); Center for Clinical Epidemiology and Evaluation, University of British Columbia, Vancouver, Canada (Mr Jagpal); Chao Family Comprehensive Cancer Center, University of California at Irvine, Orange (Dr Meyskens); and Division of Hematology and Oncology, University of Michigan (Dr Baker), and Southwest Oncology Group (Drs Baker and Coltman), Ann Arbor, Michigan.

Author Contributions: Drs Lippman and Klein had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Both contributed equally to the study.

Study concept and design: Lippman, Klein, P. Goodman, Thompson, Ford, Parnes, Minasian, Gaziano, Crawford, G. Goodman, Cook, Karp, Walther, Lieber, Ganz, Santella, Albanes, Taylor, Probstfield, Crowley, Meyskens, Coltman.

Acquisition of data: Klein, P. Goodman, Lucia, Hartline, Parsons, Bearden, G. Goodman, Claudio, Winquist, Cook, Lieber, Arnold, Jagpal, Crowley.

Analysis and interpretation of data: Lippman, Klein, P. Goodman, Thompson, Ford, Parnes, Minasian, Gaziano, Kristal, Darke, Arnold, Crowley, Baker, Coltman.

Drafting of the manuscript: Lippman, Klein, P. Goodman, Thompson, Minasian, Darke.

Critical revision of the manuscript for important intellectual content: Lippman, Klein, P. Goodman, Lucia, Thompson, Ford, Parnes, Minasian, Gaziano, Hartline, Parsons, Bearden, Crawford, G. Goodman, Claudio, Winquist, Cook, Karp, Walther, Lieber, Kristal, Arnold, Ganz, Santella, Albanes, Taylor, Probstfield, Jagpal, Crowley, Meyskens, Baker, Coltman.

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

Obtained funding: Lippman, Coltman.

Administrative, technical, or material support: Lippman, Klein, P. Goodman, Lucia, Thompson, Ford,

Minasian, Hartline, Bearden, Crawford, G. Goodman, Claudio, Cook, Lieber, Ganz, Santella, Albanes, Taylor, Probstfield, Meyskens.

Study supervision: Lippman, Klein, Thompson, Ford, Minasian, Gaziano, Hartline, G. Goodman, Karp, Lieber, Probstfield, Crowley, Baker, Coltman.

Financial Disclosures: Dr Lucia reported serving as a consultant for GlaxoSmithKline and Veridex, and being a member of the Advisory Board for GenProbe. Dr Thompson reported serving as a consultant for Veridex and Mission Pharmacal (with fees paid to University of Texas Health Sciences Center, San Antonio). Dr Gaziano reported receiving investigator-initiated research funding from Veroscience, Amgen, and BASF Corporation, and research support in the form of study agents and packaging from BASF Corporation, Wyeth Pharmaceuticals, and DSM Nutritional Products Inc (formerly Roche Vitamins); serving as a consultant or receiving honoraria from Bayer AG and Pfizer; and serving as an expert witness for Merck. Dr Meyskens reported being a co-founder of Cancer Prevention Pharmaceuticals. No other authors reported financial disclosures.

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 (Parsippany, New Jersey).

Role of the Sponsor: The National Cancer Institute was involved in the design and conduct of the study, in the analysis and interpretation of the data, and in the preparation, review, and approval of the manuscript.

Active SELECT Clinical Sites With ≥100 Participants as of October 23, 2008: San Diego, U of CA: J. Kellogg Parsons, principal investigator (PI) [1743 men]; Upstate Carolina CCOP: Jay Bearden III, PI (1201 men); London Regional Cancer Program, London Health Sciences Centre: Joseph L. Chin and Eric Winquist, PIs (981 men); University of Colorado: E. David Crawford, PI (964 men); Swedish Medical Ctr: Gary E. Goodman, PI (934 men); VAMC Jesse Brown: Thomas E. Lad, PI (749 men); Harbor-UCLA: Rowan T. Chlebowski, PI (629 men); Le Centre de Recherche: Yves Fradet, PI (628 men); Altamira Family Med: Jaime Claudio, PI (610 men); Mayo, Rochester: Michael M. Lieber, PI (606 men); Capital Region Prostate Centre: Gary Steinhoff, PI (543 men); Vancouver Hospital: Mark FitzGerald, PI (423 men); Rush University Medical Center: Steven K. Rothschild, PI (385 men); MD Anderson Cancer Center: Elise D. Cook, PI (381 men); VAMC San Juan: Luis Baez, PI (359 men); SUNY Stony Brook: Iris A. Granek, PI (358); Sherbrooke University Hospital: Abdenour Nabid, PI (348 men); George Washington University: Richard J. Katz, PI (342 men); William Beaumont Hospital: David A. Decker, PI (321 men); Wilford Hall Medical Center: Kyle J. Weld, PI (309 men); Cascadia Cancer Prevention at St. Joseph Hospital: Frank E. James, PI (299 men); Dayton CCOP: Lawrence J. Litscher, PI (296 men); Grand Rapids CCOP: Marianne K. Lange, PI (287 men); VAMC Minneapolis: Timothy J. Wilt, PI (270 men); Carle Cancer Center CCOP: David L. Graham, PI (253 men); LDS Hospital: Scott Chidester, PI (250 men); University of Mississippi: Charles R. Pound, PI (238 men); Greenville CCOP: Jeffrey K. Giguere, PI (230 men); Metro-Minnesota CCOP: Alice C. Shapiro, PI (229 men); VAMC Cleveland: Donald R. Bodner, PI (227 men); Wichita CCOP: Shaker R. Dakhlil, PI (219 men); Arizona Cancer Center: Frederick R. Ahmann, PI (219 men); Marshfield Clinic: Matthias Weiss, PI (215 men); University of Iowa Hospital: Richard D. Williams, PI (207 men); Baptist Hospital East: Kerry Short, PI (202 men); Downstate Medical Center: Richard J. Macchia, PI (197 men); Kalamazoo CCOP: Raymond S. Lord III, PI (181 men);

Southern Nevada CCOP: John A. Ellerton, PI (173 men); Sunnybrook Health Science Center: Laurence Klotz, MD, PI (171 men); Missouri Baptist Medical Center: Paul K. Schultz, PI (170 men); Geisinger Clinic: Albert M. Bernath, PI (165 men); VAMC Kansas City: Peter J. Van Veldhuizen Jr., PI (163 men); Orocovis Med Ctr: Jose S. Aponte, PI (163 men); Sutter Health Cancer Research Group-Eastern Division: Vincent Caggiano, PI (160 men); VAMC Washington, DC: Steven H. Krasnow, PI (154 men); Bay Area CCOP: Norman R. Cohen, PI (153 men); Sentara Cancer Institute: Robert W. Given, PI (152 men); VAMC Fargo: William K. Becker, PI (151 men); Medical College of Wisconsin: Robert F. Donnell, PI (149 men); VAMC Houston: Teresa G. Hayes, PI (146 men); Baptist Regional Cancer Institute: Neil Abramson, PI (136 men); Mount Sinai CCOP: Rogerio C. Lilienbaum, PI (134 men); Methodist Hospitals of Dallas: John V. Cox, PI (133 men); Miguel Sosa Padilla: Miguel Sosa-Padilla, PI (133 men); Kaiser Permanente: Nagendra R. Tirumali, PI (132 men); Duluth CCOP: Steven A. Kuross, PI (131 men); Stormont-Vail Health Care: Stanley J. Vogel, PI (130 men); Decatur Memorial Hospital: James L. Wade III, PI (126 men); VAMC Puget Sound: Daniel W. Lin, PI (124 men); VAMC Boston: Mary T. Brophy, PI (122 men); Scott & White CCOP: Scott Coffield, PI (119 men); Schiffler Cancer Center: Gregory S. Merrick, PI (116 men); Merit-Care Hospital CCOP: Preston D. Steen, PI (115 men); Gaston Memorial Hospital: Steven W. Yates, PI (114 men); VAMC Phoenix: James V. Felicetti, PI (113 men); Lehigh Valley Hospital: Gregory R. Harper, PI (113 men); Cancer Resource Ctr: Sushil S. Lacy, PI (112 men); Holy Cross Hospital: Leonard J. Seigel, PI (112 men); Cleveland Clinic: Eric A. Klein, PI (111 men); Walter Reed AMC: Rob Dean, PI (111 men); Kaiser Permanente-GA: Joshua I. Barzilay, PI (110 men); Columbia River CCOP: Keith S. Lanier, PI (110 men); Oregon Health & Science University: Mark G. Garzotto, PI (110 men); H Lee Moffitt Cancer Center: Julio M. Pow-Sang, PI (110 men); McGill University Health Center: Simon Tanguay, PI (110 men); Vanderbilt University: Michael S. Cookson, PI (109 men); St Luke's Mountain State Tumor Institute: Thomas M. Beck, PI (107 men); Washington University: Robert L. Grubb III, PI (107 men); VAMC Southern Arizona: Maria C. Bishop, PI (106 men); Andres Grillasca: Luis Baez, PI (106 men); VAMC Hines: Nirmala Bhoopalani, PI (102 men); University of Oklahoma: Daniel J. Cullin, PI (102 men); Kaiser Permanente-Oakland: Louis Fehrenbacher, PI (100 men); St Vincent Hospital: Thomas J. Saphner, PI (100 men).

Intergroup Participants: Eastern Cooperative Oncology Group: D. Karp (chief liaison); Cancer and Leukemia Group B: P. Walther (chief liaison); North Central Cancer Treatment Group: M. Lieber (chief liaison); Radiation Therapy Oncology Group: P. Khuri (chief liaison); and Veterans Affairs Cooperative Studies Program: M. Gaziano (chief liaison).

SELECT Steering Committee: Gary E. Goodman, MD, Philip R. Taylor, MD, ScD, Powell H. Brown, MD, PhD, Paul Godley, MD, PhD, Charles Bennett, MD, PhD, Michael M. Lieber, MD, Lewis Musgrave, Ellen Richmond, MS, RN, Alan R. Kristal, DrPH, Julia E. Verrees, PharmD, Regina M. Santella, PhD, M. Scott Lucia, MD, Demetrius Albanes, MD, Patricia A. Ganz, MD, Jeffrey L. Probstfield, MD, Neil E. Fleshner, MD, MPH, Isaac J. Powell, MD, T. J. Jagpal, CCRP, William R. Markesbery, MD, William Christen, ScD, Patricia A. Cassano, PhD, M. Peter Lance, MD, Carolyn J. Hoban, DSc, Marjorie A. Godfrey, Abbie L. Brown, Dana B. Sparks, MAT, Elaine Armstrong, MS, Frank L. Meyskens Jr, MD, Cathy Tangen, DrPH, Garnet L. Anderson, PhD, Amy Darke, MS, Katie Arnold, MS, Karen Anderson, Monica Yee, Scott M. Lippman, MD, Eric A. Klein, MD, Phyllis J. Goodman, MS, Ian M. Thompson, MD, Leslie G. Ford, MD, Howard L. Parnes, MD, J. Michael Gaziano, MD, MPH, Lori Minasian, MD, Jo Ann L. Hartline, MPH, J. Kellogg Parsons, MD, MHS, James D. Bearden, III, MD, Jaime

Claudio, MD, Elise D. Cook, MD, Laurence H. Baker, DO, John J. Crowley, PhD, Charles A. Coltman Jr, MD. **SELECT Committees and Subcommittees:** Recruitment and Adherence Committee: J. L. Probstfield (chair); Minority and Medically Underserved Sub-committee: E. D. Cook (chair); Health-related Quality of Life Committee: C. M. Moinpour and P. A. Ganz (co-chairs); Pathology and Biomarkers Committee: M. S. Lucia (chair); Molecular Epidemiology Committee: R. M. Santella (chair); Diet and Nutrition Committee: A. R. Kristal (chair); Site Coordinators Committee: T. J. Jagpal (chair).

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

Additional Contributions: We thank the 35 533 men and many principal investigators and clinical research associates at our 427 clinical sites, whose participation in SELECT has written an important chapter in the history of cancer prevention. We also thank the many personnel of the Southwest Oncology Group (the coordinating group of this Intergroup trial), whose tireless efforts allowed SELECT to successfully complete the test of its primary hypotheses. No compensation was received.

REFERENCES

- Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58(2):71-96.
- Harlan SR, Cooperberg MR, Elkin EP, et al. Time trends and characteristics of men choosing watchful waiting for initial treatment of localized prostate cancer: results from CaPSURE. *J Urol*. 2003;170(5):1804-1807.
- Potosky AL, Legler J, Albertsen PC, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. *J Natl Cancer Inst*. 2000;92(19):1582-1592.
- Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. *JAMA*. 2000;283(3):354-360.
- Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. *J Urol*. 2007;178(3 pt 2):S14-S19.
- Hoffman RM, Gilliland FD, Penson DF, Stone SN, Hunt WC, Potosky AL. Cross-sectional and longitudinal comparisons of health-related quality of life between patients with prostate carcinoma and matched controls. *Cancer*. 2004;101(9):2011-2019.
- 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.
- Clark LC, Combs GF Jr, Turnbull BW, et al; Nutritional Prevention of Cancer Study Group. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA*. 1996;276(24):1957-1963.
- Duffield-Lillico AJ, Dalkin BL, Reid ME, et al; Nutritional Prevention of Cancer Study Group. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int*. 2003;91(7):608-612.
- Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst*. 1998;90(6):440-446.
- Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst*. 1993;85(18):1483-1492.
- Fleshner N, Fair WR, Huryk R, Heston WD. Vitamin E inhibits the high-fat diet promoted growth of established human prostate LNCaP tumors in nude mice. *J Urol*. 1999;161(5):1651-1654.
- Ip C, Thompson HJ, Zhu Z, Ganther HE. In vitro and in vivo studies of methylseleninic acid: evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention. *Cancer Res*. 2000;60(11):2882-2886.
- Jiang C, Wang Z, Ganther H, Lu J. Caspases as key executors of methyl selenium-induced apoptosis (anoikis) of DU-145 prostate cancer cells. *Cancer Res*. 2001;61(7):3062-3070.
- Menter DG, Sabichi AL, Lippman SM. Selenium effects on prostate cell growth. *Cancer Epidemiol Biomarkers Prev*. 2000;9(11):1171-1182.
- Redman C, Scott JA, Baines AT, et al. Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. *Cancer Lett*. 1998;125(1-2):103-110.
- Taylor PR, Albanes D. Selenium, vitamin E, and prostate cancer—ready for prime time? *J Natl Cancer Inst*. 1998;90(16):1184-1185.
- Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst*. 1998;90(16):1219-1224.
- Zhong W, Oberley TD. Redox-mediated effects of selenium on apoptosis and cell cycle in the LNCaP human prostate cancer cell line. *Cancer Res*. 2001;61(19):7071-7078.
- 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.
- Current good manufacturing practice regulations, 21 CFR §210, 211.
- Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev*. 2002;11(7):630-639.
- Lonn E, Bosch J, Yusuf S, et al; HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*. 2005;293(11):1338-1347.
- Venkateswaran V, Fleshner NE, Klotz LH. Modulation of cell proliferation and cell cycle regulators by vitamin E in human prostate carcinoma cell lines. *J Urol*. 2002;168(4 pt 1):1578-1582.
- Traber MG. How much vitamin E? just enough! *Am J Clin Nutr*. 2006;84(5):959-960.
- Weinstein SJ, Wright ME, Pietinen P, et al. Serum alpha-tocopherol and gamma-tocopherol in relation to prostate cancer risk in a prospective study. *J Natl Cancer Inst*. 2005;97(5):396-399.
- Kirsh VA, Hayes RB, Mayne ST, et al; PLCO Trial. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst*. 2006;98(4):245-254.
- Bleys J, Navas-Acien A, Guallar E. Serum selenium and diabetes in U.S. adults. *Diabetes Care*. 2007;30(4):829-834.
- Rajpathak S, Rimm E, Morris JS, Hu F. Toenail selenium and cardiovascular disease in men with diabetes. *J Am Coll Nutr*. 2005;24(4):250-256.
- Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(4):217-223.
- Miller ER III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142(1):37-46.
- Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA*. 2007;297(8):842-857.
- 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.
- Lee IM, Gaziano JM, Buring JE. Vitamin E in the prevention of prostate cancer: where are we today? *J Natl Cancer Inst*. 2006;98(4):225-227.
- Li H, Stampfer MJ, Giovannucci EL, et al. A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst*. 2004;96(9):696-703.
- Taylor PR, Parnes HL, Lippman SM. Science peels the onion of selenium effects on prostate carcinogenesis. *J Natl Cancer Inst*. 2004;96(9):645-647.
- Lippman SM, Lee JJ, Sabichi AL. Cancer chemoprevention: progress and promise. *J Natl Cancer Inst*. 1998;90(20):1514-1528.
- Bertagnoli MM, Eagle CJ, Zauber AG, et al; APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med*. 2006;355(9):873-884.
- Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 1998;90(18):1371-1388.
- Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet*. 2007;369(9573):1603-1613.
- Fukase K, Kato M, Kikuchi S, et al; Japan Gast Study Group. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet*. 2008;372(9636):392-397.
- Meyskens FL, McLaren CE, Pelot D, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. *Cancer Prev Res*. 2008;1:9-11.
- 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.
- Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295(23):2727-2741.
- Scardino PT. The prevention of prostate cancer: the dilemma continues. *N Engl J Med*. 2003;349(3):297-299.
- Logothetis CJ, Schellhammer PF. High-grade prostate cancer and the Prostate Cancer Prevention Trial. *Cancer Prev Res*. 2008;1(3):151-152.
- Lucia MS, Darke AK, Goodman PJ, et al. Pathologic characteristics of cancers detected in the Prostate Cancer Prevention Trial: implications for prostate cancer detection and chemoprevention. *Cancer Prev Res*. 2008;1(3):167-173.
- Lucia MS, Epstein JI, Goodman PJ, et al. Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst*. 2007;99(18):1375-1383.
- Redman MW, Tangen CM, Goodman PJ, Lucia MS, Coltman CA Jr, Thompson IM. Finasteride does not increase the risk of high-grade prostate cancer: a bias-adjusted modeling approach. *Cancer Prev Res*. 2008;1(3):174-181.