Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers
The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

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See also pp 52 and 102.

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

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

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

Interventions Oral selenium (200 µg/d from L-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/d of all rac-α-tocopheryl acetate) and matched selenium placebo, selenium + vitamin E, or placebo 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

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PROSTATE CANCER MORTALITY IN the United States has declined in recent years, but this cancer remains the most common nonskin epithelial malignancy in US men, with 186,320 new cases and 28,660 deaths (the second leading cause of cancer death) in 2008.
SELENIUM AND VITAMIN E FOR CANCER PREVENTION

of cancer death) estimated for 2008. 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.

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). In addition, a large-scale randomized controlled trial 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, led to the design of the Selenium and Vitamin E Cancer Prevention Trial (SELECT).

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

METHODS

Study Design

SELECT is a phase 3 randomized, placebo-controlled trial of selenium (200 μg/d from L-selenomethionine), vitamin E (400 IU/d of all rac-α-tocopherol acetate), or both (planned follow-up of minimum of 7 years and maximum of 12 years) for prostate cancer prevention. The major eligibility requirements included age 50 years or older for African American men and 55 years or older for all other men, no prior prostate cancer diagnosis, 4 ng/mL or less of PSA in serum, and a digital rectal examination (DRE) not suspicious for cancer. No current use of anticoagulant therapy other than 175 mg/d or less of acetylsalicylic acid or 81 mg/d or less of acetylsalicylic acid with clopidogrel bisulfate, no history of hemorrhagic stroke, and normal blood pressure were also required because of antplatelet 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 every 6 months throughout the trial; with prostate cancer, annually. Adherence and adverse events were monitored every 6 months and a limited physical examination including assessments of blood pressure, weight, and smoking status was conducted annually. Prespecified adverse events known to be associated with vitamin E or selenium were graded according to the National Cancer Institute Common Toxicity Criteria.

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

End Point Assessment

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

Men were asked at their first 6-month clinic visit to report new events since entering the trial and thereafter to report new events since their last visit. Cardiac-event data were collected in detail from the trial beginning (2001); data on diabetes were added through self-reported glitazone medication use (beginning in 2003) and self-report of diabetes (beginning in 2005) via the following question at each clinic visit: “Does the participant report having diabetes (either his doctor told him he has diabetes or he is taking medication for diabetes)?” A general question regarding any events considered severe or life-threatening (grade 3 or 4), regardless
of attribution to the study supplements, was also asked. A Social Security Death Index search was conducted in July 2008 for participants who had a last contact date of more than 18 months before the search. Other specifically queried events (known at study inception to be related to either of the study supplements) included alopecia, dermatitis, fatigue, halitosis, nail changes, and nausea.

**Statistical Analysis**

The primary end point was prostate cancer incidence as determined by routine clinical management. Cancers that were not confirmed centrally were included in the analysis. SELECT was designed as a 4-group trial with 5 prespecified comparisons (selenium vs placebo, vitamin E vs placebo, selenium + vitamin E vs placebo, selenium vs selenium + vitamin E, and vitamin E vs selenium + vitamin E). With a sample size of 32,400 men, using a 1-sided \( \alpha = 0.05 \) level (equivalent to a 2-sided \( \alpha = 0.01 \) level), there was 96% power to detect a 25% reduction in prostate cancer for either of the single agents (vs placebo), 89% power to detect a 25% reduction for selenium + vitamin E (vs an active single agent) and more than 99% power to detect a 44% reduction of selenium + vitamin E (vs placebo).

Design assumptions were based on the PCPT, ATBC, and NPC trials. The details of the statistical design have been described elsewhere. 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 \( \alpha = 0.005 \) level (equivalent to a 2-sided \( \alpha = 0.01 \) level) using a Bonferroni factor of 5 to preserve an overall 1-sided \( \alpha = 0.0025 \) level (equivalent to a 2-sided \( \alpha = 0.05 \) 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-

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

35,533 Men randomized at 427 participating sites

- 8856 Randomized to receive placebo + placebo
- 9856 Received placebo + placebo as randomized
- 160 Excluded
  - 155 Removed from 2 participating sites (poor data and participant management and regulatory issues)
  - 5 Ineligible
    - 1 Had prior prostate cancer
    - 4 Randomized in error (never received proper informed consent)

113 Clinically ineligible
154 Insufficient baseline data to completely evaluate clinical eligibility
420 Lost to follow-up (last contact data >24 mo before analysis)
8696 Included in primary analysis

- 8904 Randomized to receive vitamin E + placebo
- 8737 Received vitamin E + placebo as randomized
- 167 Excluded
  - 156 Removed from 2 participating sites (poor data and participant management and regulatory issues)
  - 11 Ineligible
    - 5 Had prior prostate cancer
    - 6 Randomized in error (never received proper informed consent)

128 Clinically ineligible
151 Insufficient baseline data to completely evaluate clinical eligibility
385 Lost to follow-up (last contact data >24 mo before analysis)
8737 Included in primary analysis

- 8910 Randomized to receive selenium + placebo
- 8752 Received selenium + placebo as randomized
- 158 Excluded
  - 155 Removed from 2 participating sites (poor data and participant management and regulatory issues)
  - 3 Ineligible
    - 1 Had prior prostate cancer
    - 2 Randomized in error (never received proper informed consent)

113 Clinically ineligible
166 Insufficient baseline data to completely evaluate clinical eligibility
434 Lost to follow-up (last contact data >24 mo before analysis)
8752 Included in primary analysis

- 8863 Randomized to receive selenium + vitamin E
- 8703 Received selenium + placebo as randomized
- 160 Excluded
  - 156 Removed from 2 participating sites (poor data and participant management and regulatory issues)
  - 5 Ineligible
    - 2 Had prior prostate cancer
    - 3 Randomized in error (never received proper informed consent)

113 Clinically ineligible
169 Insufficient baseline data to completely evaluate clinical eligibility
379 Lost to follow-up (last contact data >24 mo before analysis)
8703 Included in primary analysis

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*Due to increased blood pressure, high-grade prostatic intraepithelial neoplasia, suspicious digital rectal examination (DRE) or increased prostate-specific antigen (PSA), aspirin dosage, prior cancer less than 5 years before randomization, participation in another clinical trial, or other clinical reason.*

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

*All data up until the last contact are included; these men also could have been either clinically ineligible or had insufficient baseline data. For time-to-event analyses, these men were censored at their last follow-up.*

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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 \( \chi^2 \) test. For cardiovascular event and diabetes analyses, we did not capture the report of the date, 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-

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### Table 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 8696)</th>
<th>Vitamin E (n = 8737)</th>
<th>Selenium (n = 8752)</th>
<th>Selenium + Vitamin E (n = 8703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Median (interquartile range)</td>
<td>62.6 (58.1-67.8)</td>
<td>62.3 (58.0-67.8)</td>
<td>62.6 (58.2-68.0)</td>
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<td>50-54</td>
<td>355 (4)</td>
<td>402 (5)</td>
<td>337 (4)</td>
<td>385 (4)</td>
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<tr>
<td>55-64</td>
<td>5078 (58)</td>
<td>5143 (59)</td>
<td>5076 (58)</td>
<td>5052 (58)</td>
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<tr>
<td>65-74</td>
<td>2702 (31)</td>
<td>2641 (30)</td>
<td>2733 (31)</td>
<td>2731 (31)</td>
</tr>
<tr>
<td>≥75</td>
<td>561 (6)</td>
<td>551 (6)</td>
<td>606 (7)</td>
<td>535 (6)</td>
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<tr>
<td>Race/ethnicity</td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>6863 (79)</td>
<td>6890 (79)</td>
<td>6942 (79)</td>
<td>6874 (79)</td>
</tr>
<tr>
<td>African American</td>
<td>1078 (12)</td>
<td>1107 (13)</td>
<td>1053 (12)</td>
<td>1076 (12)</td>
</tr>
<tr>
<td>Hispanic (non-African American)</td>
<td>492 (6)</td>
<td>477 (5)</td>
<td>481 (5)</td>
<td>484 (6)</td>
</tr>
<tr>
<td>Hispanic (African American)</td>
<td>76 (1)</td>
<td>103 (1)</td>
<td>86 (1)</td>
<td>95 (1)</td>
</tr>
<tr>
<td>Othera</td>
<td>187 (2)</td>
<td>160 (2)</td>
<td>190 (2)</td>
<td>174 (2)</td>
</tr>
<tr>
<td>Education (highest level)</td>
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<td></td>
<td></td>
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<tr>
<td>≥High school graduate or GED</td>
<td>1903 (23)</td>
<td>1875 (22)</td>
<td>1917 (22)</td>
<td>1898 (22)</td>
</tr>
<tr>
<td>Some college/vocational school</td>
<td>2291 (26)</td>
<td>2387 (27)</td>
<td>2327 (27)</td>
<td>2348 (27)</td>
</tr>
<tr>
<td>College graduate</td>
<td>4317 (50)</td>
<td>4394 (51)</td>
<td>4430 (51)</td>
<td>4372 (50)</td>
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<tr>
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<td>95 (1)</td>
<td>81 (1)</td>
<td>78 (1)</td>
<td>85 (1)</td>
</tr>
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<td>PSA, ng/mL</td>
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<td></td>
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<tr>
<td>0.1-1.0</td>
<td>4122 (47)</td>
<td>4208 (48)</td>
<td>4218 (48)</td>
<td>4213 (48)</td>
</tr>
<tr>
<td>1.1-2.0</td>
<td>2728 (31)</td>
<td>2653 (30)</td>
<td>2661 (30)</td>
<td>2666 (31)</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>1168 (13)</td>
<td>1228 (14)</td>
<td>1211 (14)</td>
<td>1149 (13)</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>666 (8)</td>
<td>634 (7)</td>
<td>652 (7)</td>
<td>659 (8)</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>5 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
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<td>11 (&lt;1)</td>
<td>8 (&lt;1)</td>
<td>15 (&lt;1)</td>
</tr>
<tr>
<td>Smoking status</td>
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</tr>
<tr>
<td>Never</td>
<td>3682 (42)</td>
<td>3752 (43)</td>
<td>3780 (43)</td>
<td>3666 (42)</td>
</tr>
<tr>
<td>Current</td>
<td>655 (8)</td>
<td>659 (8)</td>
<td>631 (7)</td>
<td>670 (8)</td>
</tr>
<tr>
<td>Former</td>
<td>4208 (48)</td>
<td>4194 (48)</td>
<td>4214 (48)</td>
<td>4242 (49)</td>
</tr>
<tr>
<td>Ever (unknown status)</td>
<td>63 (1)</td>
<td>55 (1)</td>
<td>61 (1)</td>
<td>56 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>88 (1)</td>
<td>77 (1)</td>
<td>66 (1)</td>
<td>69 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: GED, general equivalency diploma; PSA, prostate-specific antigen.

SI conversion: To convert PSA to µg/L, multiply by 1.0.

a Other race/ethnicity include Asian (n=420), Native American (n=99), Pacific Islander (n=39), multiple races (n=34), and unknown (n=119).

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, each lot of capsules was quarantined upon receipt until 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 |
|-----------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
|                            | Placebo                  | Vitamin E                | Selenium                  | Selenium + Vitamin E      |
| Pill Counts\(^a\)           |                          |                          |                           |                           |
| 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 (67-77)               | 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 (67-75)               | 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                | Placebo                  | Vitamin E                | Selenium                  | Selenium + Vitamin E      |
|                            | (n=285)                  | (n=290)                  | (n=277)                   | (n=257)                   |
| Serum selenium, µg/L        | 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 (198.6-251.9)       | 227.0 (199.4-251.2)       |
| 1st annual visit            | 138.1 (125.2-152.2)      | 137.7 (124.1-154.0)      | 232.4 (204.2-261.4)       | 226.5 (205.5-258.1)       |
| 2nd annual visit            | 132.0 (120.8-143.1)      | 129.8 (120.1-133.9)      | 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)       |

| 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)        |

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

\(^b\) These ranges are estimates including those with missing data and assumes those missing were either all nonadherent (low estimate) or all adherent (high estimate).

\(^c\) Numbers of participants for 4th annual visit are placebo (n=79), vitamin E (n=78), selenium (n=72), and selenium + vitamin E (n=71).

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.
idence 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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 8696)</th>
<th>Vitamin E (n = 8737)</th>
<th>Selenium (n = 8752)</th>
<th>Selenium + Vitamin E (n = 8703)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% of Participants)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of prostate cancers diagnosed by study site</td>
<td>416</td>
<td>473</td>
<td>432</td>
<td>437</td>
</tr>
<tr>
<td>Method of diagnoses Prostate biopsy</td>
<td>404 (97)</td>
<td>458 (97)</td>
<td>419 (97)</td>
<td>420 (96)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>12 (3)</td>
<td>15 (3)</td>
<td>13 (3)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>No. of total prostate biopsies</td>
<td>1020</td>
<td>1011</td>
<td>982</td>
<td>997</td>
</tr>
<tr>
<td>PSA tests(^a) Year 1</td>
<td>6708 (83)</td>
<td>6876 (84)</td>
<td>6807 (84)</td>
<td>6838 (84)</td>
</tr>
<tr>
<td>Year 2</td>
<td>6641 (86)</td>
<td>6652 (85)</td>
<td>6635 (85)</td>
<td>6673 (86)</td>
</tr>
<tr>
<td>Year 3</td>
<td>6284 (85)</td>
<td>6334 (85)</td>
<td>6376 (85)</td>
<td>6349 (85)</td>
</tr>
<tr>
<td>Year 4</td>
<td>6043 (85)</td>
<td>6087 (84)</td>
<td>6065 (85)</td>
<td>6045 (84)</td>
</tr>
<tr>
<td>Year 5</td>
<td>4265 (84)</td>
<td>4246 (84)</td>
<td>4271 (84)</td>
<td>4257 (84)</td>
</tr>
<tr>
<td>DRE tests(^a) Year 1</td>
<td>5766 (72)</td>
<td>5936 (73)</td>
<td>5870 (72)</td>
<td>5833 (72)</td>
</tr>
<tr>
<td>Year 2</td>
<td>5567 (72)</td>
<td>5563 (72)</td>
<td>5561 (72)</td>
<td>5591 (72)</td>
</tr>
<tr>
<td>Year 3</td>
<td>5180 (70)</td>
<td>5188 (70)</td>
<td>5196 (70)</td>
<td>5190 (70)</td>
</tr>
<tr>
<td>Year 4</td>
<td>4862 (69)</td>
<td>4823 (67)</td>
<td>4878 (69)</td>
<td>4878 (68)</td>
</tr>
<tr>
<td>Year 5</td>
<td>3420 (68)</td>
<td>3418 (68)</td>
<td>3397 (68)</td>
<td>3425 (68)</td>
</tr>
<tr>
<td>Reason for biopsy (positive biopsies) Increased PSA</td>
<td>259 (64)</td>
<td>324 (71)</td>
<td>296 (71)</td>
<td>263 (63)</td>
</tr>
<tr>
<td>PSA prompting biopsy, median (IQR), ng/mL Year 1</td>
<td>4.60 (4.00-5.50)</td>
<td>4.60 (3.99-5.60)</td>
<td>4.83 (4.05-5.70)</td>
<td>4.70 (4.00-5.60)</td>
</tr>
<tr>
<td>Year 2</td>
<td>4.60 (4.00-5.50)</td>
<td>4.60 (3.99-5.60)</td>
<td>4.83 (4.05-5.70)</td>
<td>4.70 (4.00-5.60)</td>
</tr>
<tr>
<td>Year 3</td>
<td>4.60 (4.00-5.50)</td>
<td>4.60 (3.99-5.60)</td>
<td>4.83 (4.05-5.70)</td>
<td>4.70 (4.00-5.60)</td>
</tr>
<tr>
<td>Year 4</td>
<td>4.60 (4.00-5.50)</td>
<td>4.60 (3.99-5.60)</td>
<td>4.83 (4.05-5.70)</td>
<td>4.70 (4.00-5.60)</td>
</tr>
<tr>
<td>Year 5</td>
<td>4.60 (4.00-5.50)</td>
<td>4.60 (3.99-5.60)</td>
<td>4.83 (4.05-5.70)</td>
<td>4.70 (4.00-5.60)</td>
</tr>
<tr>
<td>PSA velocity</td>
<td>12 (3)</td>
<td>10 (2)</td>
<td>13 (3)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Abnormal DRE</td>
<td>66 (16)</td>
<td>58 (13)</td>
<td>46 (11)</td>
<td>56 (13)</td>
</tr>
<tr>
<td>Increased PSA/PSA velocity + abnormal DRE</td>
<td>55 (14)</td>
<td>49 (11)</td>
<td>56 (13)</td>
<td>72 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (2)</td>
<td>13 (3)</td>
<td>12 (3)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>T stage T1a-c</td>
<td>278 (70)</td>
<td>343 (75)</td>
<td>301 (73)</td>
<td>296 (69)</td>
</tr>
<tr>
<td>T2a-b</td>
<td>122 (30)</td>
<td>114 (25)</td>
<td>108 (26)</td>
<td>128 (31)</td>
</tr>
<tr>
<td>T3a-b</td>
<td>0 (0)</td>
<td>2 (0)</td>
<td>5 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>TX/not staged</td>
<td>16</td>
<td>14</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>N stage N0</td>
<td>109 (100)</td>
<td>127 (100)</td>
<td>125 (99)</td>
<td>117 (100)</td>
</tr>
<tr>
<td>N1</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NX/not staged</td>
<td>307</td>
<td>346</td>
<td>306</td>
<td>320</td>
</tr>
<tr>
<td>M stage M0</td>
<td>124 (100)</td>
<td>134 (99)</td>
<td>122 (96)</td>
<td>119 (98)</td>
</tr>
<tr>
<td>M1a-b</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>5 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>MX/not staged</td>
<td>292</td>
<td>337</td>
<td>305</td>
<td>316</td>
</tr>
<tr>
<td>Gleason score(^b) No. graded by central laboratory</td>
<td>365</td>
<td>396</td>
<td>361</td>
<td>365</td>
</tr>
<tr>
<td>Grade 2-6</td>
<td>240 (66)</td>
<td>249 (63)</td>
<td>217 (60)</td>
<td>220 (60)</td>
</tr>
<tr>
<td>Grade 7 (grade 3 + grade 4)</td>
<td>80 (22)</td>
<td>97 (24)</td>
<td>105 (29)</td>
<td>91 (25)</td>
</tr>
<tr>
<td>Grade 7 (grade 4 + grade 3)</td>
<td>21 (6)</td>
<td>27 (7)</td>
<td>19 (5)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Grade 8-10</td>
<td>24 (7)</td>
<td>23 (6)</td>
<td>20 (6)</td>
<td>30 (8)</td>
</tr>
</tbody>
</table>

Abbreviations: DRE, digital rectal examination; IQR, interquartile range; PSA, prostate-specific antigen.

\(^a\)Percentages are based on alive participants who are prostate cancer-free and for whom the form was submitted.

\(^b\)Gleason score was based on central pathology review. The Gleason grade ranges from 1 to 5, with 5 having the worst prognosis. The Gleason score ranges from 2 to 10, with 10 having the worst prognosis.
and Puerto Rico between August 22, 2001, and June 24, 2004. Figure 1 shows the SELECT randomization scheme including participants who were excluded from analyses; all 621 participants at 2 study sites were removed from the analysis because of severe problems that were detected early on including poor data and participant management and regulatory issues. These participants differed substantially from the rest of the SELECT population in being from sites in the south of the United States, 99% African American, younger (median age 57 years), and of a lower education level (67% had < high school education), and in having lower PSA levels (57% had <1.0 ng/mL) and a higher prevalence of current smokers (33%). An additional 9 participants were removed because they were found to have had prostate cancer at randomization and 15 were removed because their informed consent was never received. More men were accrued (35 533 in 3 years) than initially planned (32 400 in 5 years) mainly because of a faster-than-expected accrual rate and the administrative time it takes to close down accrual.

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

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

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). 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 group (P = .06) and not in the selenium + vitamin E group (P = .52) or the selenium group (P = .62).

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

Secondary Outcomes

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

The study agents had no significant effects on the overall incidence of cardiovascular events (Table 4). A statistically nonsignificant increase in type 2 diabetes mellitus (diagnosed after randomization) occurred in the selenium-alone group vs placebo group (\( n = 724; \) 10.0%; 99% CI, 9.1%-11.0%; vs \( n = 669; \) 9.3%; 99% CI, 8.5%-10.2%, respectively; RR, 1.07; 99% CI, 0.94-1.22; \( P = .16 \)). The number (percentage) of cases of diabetes mellitus was 700 (9.7%; 99% CI, 8.8%-10.6%) in the vitamin E group and 660 (9.1%; 99% CI, 8.2%-10.0%) in the selenium + vitamin E group (\( P \) values of these data compared with placebo were 0.47 for vitamin E and 0.61 for selenium + vitamin E). Data on known, clinically less significant adverse effects of the study agents (alopecia, dermatitis, halitosis, ...
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 DLα-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 increase in incidence of prostate cancer (P = .06) was observed in the vitamin E group but not in the selenium + vitamin E group. The trial supplements were discontinued early (in year 7 of the overall 12-year study) in accordance with a unanimous recommendation of the data and safety monitoring committee stating that, based on the evidence to date from the 7-year planned interim analyses, there was no evidence of a benefit from either study agent and no possibility of a benefit to the planned degree with additional follow-up. Sensitivity analyses suggested that the prespecified 25% risk reduction was extremely unlikely to be reached for either agent even with additional exposure.

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

Why were selenium and vitamin E ineffective in preventing prostate cancer in SELECT despite strong secondary evidence suggesting efficacy?7,8 Considering selenium first, the secondary reduction in prostate cancer incidence in the NPC study could have been subject to...
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), and our rationale 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 (e.g., lacking availability, investigational new drug certification, and clinical data); and in vitro data indicating that selenomethionine was effective in suppressing malignant and not normal prostate cells.13

Despite this careful rationale, it is impossible to know now whether selenium yeast would have been more active than l-selenomethionine 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 levels5; 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 tertile 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,13 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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 8696)</th>
<th>Vitamin E (n = 8737)</th>
<th>Selenium (n = 8752)</th>
<th>Selenium + Vitamin E (n = 8703)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Men RR (99% CI)</td>
<td>No. of Men RR (99% CI)</td>
<td>No. of Men RR (99% CI)</td>
<td>No. of Men RR (99% CI)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>206 1.06 (0.83-1.36)</td>
<td>265 1.28 (1.01-1.62)</td>
<td>238 1.07 (0.92-1.25)</td>
<td>1.15 (0.91-1.47)</td>
</tr>
<tr>
<td>Dermatitis Grades 1-2</td>
<td>516 1.14 (0.98-1.32)</td>
<td>605 1.17 (1.00-1.35)</td>
<td>554 1.07 (0.92-1.25)</td>
<td>1.07 (0.92-1.25)</td>
</tr>
<tr>
<td>Grades 3-4</td>
<td>12 1.49 (0.46-4.83)</td>
<td>14 1.74 (0.56-5.44)</td>
<td>16 2.00 (0.66-6.09)</td>
<td>2.00 (0.66-6.09)</td>
</tr>
<tr>
<td>Halitosis</td>
<td>427 1.15 (0.97-1.36)</td>
<td>503 1.17 (0.99-1.38)</td>
<td>531 1.24 (1.06-1.46)</td>
<td>1.24 (1.06-1.46)</td>
</tr>
<tr>
<td>Nail changes</td>
<td>1035 1.00 (0.90-1.11)</td>
<td>1087 1.04 (0.94-1.16)</td>
<td>1075 1.04 (0.93-1.15)</td>
<td>1.04 (0.93-1.15)</td>
</tr>
<tr>
<td>Fatigue Grades 1-2</td>
<td>586 1.03 (0.89-1.19)</td>
<td>645 1.09 (0.95-1.26)</td>
<td>612 1.04 (0.90-1.20)</td>
<td>1.04 (0.90-1.20)</td>
</tr>
<tr>
<td>Grades 3-4</td>
<td>24 1.20 (0.59-2.45)</td>
<td>21 0.87 (0.40-1.88)</td>
<td>20 0.83 (0.38-1.81)</td>
<td>0.83 (0.38-1.81)</td>
</tr>
<tr>
<td>Nausea Grades 1-2</td>
<td>203 0.94 (0.72-1.21)</td>
<td>244 1.19 (0.94-1.52)</td>
<td>202 0.99 (0.77-1.28)</td>
<td>0.99 (0.77-1.28)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9 0.33 (0.08-1.85)</td>
<td>9 0.99 (0.30-3.34)</td>
<td>8 0.89 (0.25-3.10)</td>
<td>0.89 (0.25-3.10)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

The RRs given for vitamin E, selenium, and selenium + vitamin E groups are compared with the placebo group. Maximum grade experienced by a participant are given. Alopecia, halitosis, and nail changes were only defined for grades 1 and 2. National Cancer Institute Common Toxicity Criteria were used for alopecia, nail changes, fatigue, and nausea. Halitosis and dermatitis were defined in the study protocol. Generally, grade 1=mild, grade 2=moderate, grade 3=severe, and grade 4=life-threatening. b p<.01.
less than 60% of SELECT men were cur-
rent 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, Co-
lorectal, and Ovarian Cancer Screening
Trial (PLCO),27 a trial of screening vs
standard health care routines, showed a
71% reduction in the incidence of ad-
vanced prostate cancer associated with
supplemental vitamin E use in current
and recent smokers. A subgroup analy-
sis of current and former smokers in
SELECT, however, did not show a smok-
ing-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 can-
cer incidence in the ATBC study could
have been due to chance findings in sec-
ondary analyses.

Selenium was not associated with sig-
nificant effects on cardiovascular events,
lung cancer, other cancers, or overall
mortality in SELECT. One safety con-
cern with selenium is a potential asso-
ciation with increased risk for type 2
diabetes mellitus, for which there are
mixed data from prior studies.28,29 A re-
cent analysis of the NPC study popu-
lation showed a significant increase in
type 2 diabetes mellitus (by self-
report and medical records), largely lim-
ited to the top tertile of plasma sele-
nium levels at baseline.30

In SELECT, a nonsignificant in-
crease in risk (RR, 1.07; P = .16) of dia-
abetes 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 evi-
dence that vitamin E supplementation,
alone or in combination with other an-
tioxidants, may increase mortality. Nei-
ther study is directly relevant to the doses
and population studied in SELECT; many
studies included in these meta-
analyses were in patients with serious dis-
ease, and the finding of increased mor-
tality was driven by studies using doses
far higher than 400 IU/d. In more rel-
vant, placebo-controlled trials com-
pleted in healthy men and women, there
were no associations of vitamin E supple-
mentation with increased risks of either
cardiovascular disease or overall mor-
tality.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 mor-
tality in the vitamin E groups.

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

The statistical rigor of the trial was
matched by the rigor of its implementa-
tion. Features of this implementation in-
cluded the SELECT Workbench, a se-
cure Web site administered by the
SELECT statistical center and used by
study-site staff and investigators. The
SELECT Workbench was used to ac-
cess participant and site-specific re-
ports, the study protocol, and a detailed
study manual and to submit data using
Web-based forms. Form submission in-
cluded detailed edit checks and a track-
ing system to identify all expected forms.
Training and monitoring consisted of
semi-annual workshops, quality assur-
ance audits at least once every 3 years,
and mentoring by trained statistical cen-
ter staff and experienced clinical re-
search associates. SELECT also main-
tained 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.30

Potential limitations of SELECT in-
clude that it did not test different for-
mulations or doses of selenium and vi-
tamin 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 vi-
tamin E and selenium.30,27,34-36 SELECT
also could not assess intervention ef-
fects in a population deficient in vita-
mmin E, selenium, or both since our trial
population was well-nourished at base-
line, or in current smokers since they rep-
resented only 7.5% of the SELECT popu-
lation, a substantial difference from the
ATBC study in predominantly heavy
smokers.

Cancer chemoprevention is an im-
portant approach for reducing cancer
burden.37 Several randomized con-
trolled trials have demonstrated sig-
nificant cancer or premalignancy risk
reductions in the breast, colon,
rectum, prostate, and stomach.38-44 Pro-
state cancer is a particularly attractive
target for chemoprevention because of
its clinical ubiquity, substantial treat-
ment-associated morbidity, and step-
wise molecular pathogenesis. In the
large-scale PCPT, which was reported
2 years after SELECT was activated, fi-
nasteride produced a 25% relative re-
duction in the 7-year period preva-
lence of prostate cancer (vs placebo),43
and recent data suggest that finaste-
rside reduces the risk of clinically sig-
nificant disease and may not induce
high-grade cancers despite initial con-
cerns 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 pre-
vent prostate cancer in the generally
healthy, heterogeneous population of
men in SELECT. These data under-
score the prudence that is needed in con-
sidering 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 con-
tinue the search for new, effective agents
for prostate cancer prevention.
SELENIUM AND VITAMIN E FOR CANCER PREVENTION

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