LIFETIME RISK OF PROSTATE CANCER in the United States is currently estimated to be 16%.1 Although most cases are found at an early, curable stage, treatment is costly and urinary, sexual, and bowel-related adverse effects are common.2 Even men who choose active surveillance as an initial management strategy face anxiety, uncertain prognosis, and a measurable risk of sepsis with follow-up biopsies.3 and more than one-third of those who initially defer therapy are ultimately treated.4 5 With such a high prevalence, risk of morbidity from treatment, and treatment-related costs, primary prevention of prostate cancer is an attractive option.7

With considerable preclinical and epidemiological evidence that selenium and vitamin E may reduce prostate cancer risk, we conducted and reported the results of a prospective randomized trial examining the effect of these 2 agents for prostate cancer prevention.6 Coordinated by SWOG, a federally funded cancer research cooperative group, the Selenium and Vitamin E Cancer Prevention Trial (SELECT)
began accrual on August 22, 2001, and randomized 35,533 men into 4 groups: selenium with matching placebo, vitamin E with matching placebo, both agents, or placebo.

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

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

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

**METHODS**

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

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

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

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

**Statistical Analysis**

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

A proportional hazards model was used to compare prostate cancer and other cancer incidence between placebo and each of the 3 study groups with active agents. Men without the end point of interest were censored at their last contact date. An additional analysis was performed on all the data using a variable for selenium supplementaion, a variable for vitamin E supplementation, and an interaction term. In all cases, the proportional hazards assumption was evaluated by assessing each study group × time interaction. The cumulative incidence curves for prostate cancer were generated accounting for the competing risk of death.8 A χ² test was used to test the difference in the relative risk of diabetes. Data were analyzed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).
Figure 1. Patient Flow Diagram

### RESULTS

The current report includes data as of July 5, 2011. There are 54,644 additional person-years of follow-up since the primary report, an increase of 23%. A summary of baseline characteristics is displayed in Table 1 and an updated flow diagram in Figure 1. The frequency of use of DRE and PSA is displayed in Table 2; there were no differences between groups in the intensity of PSA testing, absolute PSA levels, PSA change between groups in the intensity of PSA testing, and proportion of patients with prostate cancer detected.

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

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**Table 1. Baseline Participant Characteristics**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Median (IQR)</th>
<th>Placebo (n = 8896)</th>
<th>Vitamin E Alone (n = 8737)</th>
<th>Selenium Alone (n = 8752)</th>
<th>Vitamin E + Selenium (n = 8702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–54</td>
<td>355 (4)</td>
<td>403 (5)</td>
<td>337 (4)</td>
<td>385 (4)</td>
<td></td>
</tr>
<tr>
<td>55–64</td>
<td>5078 (58)</td>
<td>5142 (59)</td>
<td>5075 (58)</td>
<td>5051 (58)</td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>2702 (31)</td>
<td>2642 (30)</td>
<td>2734 (31)</td>
<td>2731 (31)</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>561 (6)</td>
<td>550 (6)</td>
<td>606 (7)</td>
<td>535 (6)</td>
<td></td>
</tr>
</tbody>
</table>

**Race/ethnicity**

- White: 6862 (79) Placebo, 6893 (79) Vitamin E, 6944 (79) Selenium, 6872 (79) Vitamin E + Selenium
- Black: 1083 (12) Placebo, 1106 (13) Vitamin E, 1054 (12) Selenium, 1075 (12) Vitamin E + Selenium
- Hispanic, nonblack: 406 (6) Placebo, 476 (5) Vitamin E, 484 (6) Selenium, 484 (6) Vitamin E + Selenium
- Hispanic, black: 76 (1) Placebo, 103 (1) Vitamin E, 86 (1) Selenium, 96 (1) Vitamin E + Selenium
- Aboriginal: 27 (<1) Placebo, 22 (<1) Vitamin E, 41 (<1) Selenium, 29 (<1) Vitamin E + Selenium
- Asian/Pacific Islander: 128 (1) Placebo, 110 (1) Vitamin E, 111 (1) Selenium, 123 (1) Vitamin E + Selenium
- Unknown: 24 (<1) Placebo, 27 (<1) Vitamin E, 32 (<1) Selenium, 23 (<1) Vitamin E + Selenium

**PSA, ng/mL**

- Median (IQR)
  - 1.1 (0.6–1.9) Placebo: 4133 (48) Vitamin E: 4234 (48) Selenium: 4247 (49) Vitamin E + Selenium: 4235 (49)
  - 1.1 (0.6–1.9) Placebo: 2735 (31) Vitamin E: 2648 (30) Selenium: 2652 (30) Vitamin E + Selenium: 2667 (31)
  - 1.1 (0.6–1.9) Placebo: 1153 (13) Vitamin E: 1222 (14) Selenium: 1199 (14) Vitamin E + Selenium: 1147 (14)
  - 0.1–1.0: 668 (8) Placebo: 627 (7) Vitamin E: 649 (7) Selenium: 666 (7)
  - <4.0: 5 (<1) Placebo: 3 (<1) Vitamin E: 2 (<1) Selenium: 1 (<1)
  - Missing: 2 (<1) Placebo: 3 (<1) Vitamin E: 3 (<1) Selenium: 6 (<1)

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

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

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

In the initial SELECT report a statistically nonsignificant increased risk of type 2 diabetes mellitus (as defined by self-report or new use of glitazone medications) was observed in the selenium supplementation group (HR, 1.07). In the updated results the HR is 1.04 and is not statistically significant (P = .34; Table 5). Table 5 also displays updated data on the prespecified secondary end points of lung, colorectal, and total other cancers, deaths, and grade 4 cardiovascular events. There are no statistically significant differences in...
the HRs between groups, suggesting neither benefit nor harm from dietary supplementation with selenium or vitamin E for these end points.

**COMMENT**

Prevention of prostate cancer remains an important public health goal because of the relatively high incidence and the high likelihood of curative-intent treatment of this cancer even when indolent disease is present, and treatment related costs and morbidity. Although 2 large randomized trials have demonstrated that 5α-reductase inhibitors reduce prostate cancer risk by 20% to 25%, the use of these agents is controversial because of concerns related to an observed increased risk of high-grade disease. SELECT was designed to assess the effect of selenium and vitamin E alone and in combination as supplements to a normal diet on their ability to prevent prostate cancer in men at average risk. Other randomized studies have shown no benefit to dietary supplementation with selenium, lycopene, or soy in reducing the risk of invasive cancer in men with high-grade prostatic intraepithelial neoplasia on biopsy. In this article, we report an observation of important public health concern that has emerged with continued follow-up of SELECT participants. With primary end point ascertainment based on contemporary community practice across the United States, Canada, and Puerto Rico using PSA and DRE as indications for biopsy, the risk of prostate cancer at 7 years of median follow-up was increased by 17% in men randomized to supplementation with vitamin E alone, a difference that started to appear 3 years after randomization. Although there is debate about how to best handle accumulating results after the publication of primary findings and the appropriate threshold for statistical significance, the increased rate of prostate cancer in the vitamin E group was seen as early as 2006 and continued until the present analysis (HRs ranged from 1.12 to 1.17) suggesting that the current results are not an outlier observation due to multiple looks at the data. Extended follow-up with additional events has resulted in narrowed confidence intervals.

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

**Figure 2. Cumulative Incidence of Prostate Cancer**

![Graph of cumulative incidence of prostate cancer](image-url)
Table 4. Clinical and Pathological Characteristics of Incident Prostate Cancers

<table>
<thead>
<tr>
<th>No. (%) of Cancers</th>
<th>Placebo (n = 8696)</th>
<th>Vitamin E Alone (n = 8737)</th>
<th>Selenium Alone (n = 8752)</th>
<th>Vitamin E + Selenium (n = 8702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prostate cancers diagnosed, No.</td>
<td>529 (6)</td>
<td>629 (7)</td>
<td>575 (6)</td>
<td>555 (6)</td>
</tr>
<tr>
<td>After unbinding for primary article</td>
<td>416 (7)</td>
<td>473 (7)</td>
<td>453 (7)</td>
<td>437 (7)</td>
</tr>
<tr>
<td>Diagnosed prior to unbinding but data received afterwards</td>
<td>26 (5)</td>
<td>33 (5)</td>
<td>22 (4)</td>
<td>17 (3)</td>
</tr>
<tr>
<td>Diagnosed after unbinding</td>
<td>87 (16)</td>
<td>114 (18)</td>
<td>121 (21)</td>
<td>101 (18)</td>
</tr>
<tr>
<td>Confirmation status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not graded</td>
<td>110 (24)</td>
<td>155 (28)</td>
<td>133 (29)</td>
<td>110 (24)</td>
</tr>
<tr>
<td>4-6</td>
<td>286 (63)</td>
<td>310 (67)</td>
<td>281 (64)</td>
<td>281 (63)</td>
</tr>
<tr>
<td>7</td>
<td>102 (24)</td>
<td>118 (25)</td>
<td>135 (29)</td>
<td>124 (28)</td>
</tr>
<tr>
<td>Not graded</td>
<td>110 (24)</td>
<td>155 (28)</td>
<td>133 (29)</td>
<td>110 (24)</td>
</tr>
</tbody>
</table>

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

Vitamin E and Prostate Cancer

In the Physicians Health Study II (PHS II) conducted contemporaneously with SELECT, intervention with 400 IU of vitamin E every other day for a median of 8 years had no effect on the incidence of prostate cancer (HR, 0.97; 95% CI, 0.85-1.09; P = .58), although like SELECT there was no effect on total cancer incidence (HR, 1.04; 95% CI, 0.95-1.13; P = .41) or overall mortality (HR, 1.08; 95% CI, 0.98-1.19).16

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

Given that more than 50% of individuals 60 years or older are taking supplements containing vitamin E and that 23% of them are taking at least 400 IU/d17 despite a recommended daily dietary allowance of only 22.4 IU for adult men,18 the implications of our observations are substantial. Consistent with the original SELECT report, longer follow-up did not demonstrate a benefit for selenium or vitamin E supplementation on risk of colorectal or lung cancer or cardiovascular events.

Although modest benefits for vitamin E supplementation have been observed in a limited number of randomized clinical trials for Alzheimer disease19 and (as 1 part of a combination of oral antioxidants) for age-related macular degeneration,20 no benefits were demonstrated for prevention of cardiac events or mortality.21-23 Moreover, the increased incidence of prostate cancer in SELECT, the previously reported increased incidence of lung cancer with

**Diagnosis after unblinding**

87 (16) 114 (18) 121 (21) 101 (18)

**Diagnosed prior to unblinding but data received afterwards**

26 (5) 33 (5) 22 (4) 17 (3)

**Diagnosed after unblinding**

87 (16) 114 (18) 121 (21) 101 (18)

**Confirmation status**

- **Not graded**: 110 (24) 155 (28) 133 (29) 110 (24)
- **4-6**: 286 (63) 310 (67) 281 (64) 281 (63)
- **7**: 102 (24) 118 (25) 135 (29) 124 (28)
- **Not graded**: 110 (24) 155 (28) 133 (29) 110 (24)

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

In the general population of healthy men significantly increases the risk of being diagnosed with prostate cancer.

The current findings of SELECT differ from findings from other large randomized intervention trials that examined the effects of vitamin E supplementation on prostate cancer risk. The Alpha-Tocopherol, Beta Carotene (ATBC) trial reported a 35% risk reduction for prostate cancer in men taking 50 mg/d of vitamin E for a median of 6.1 years,19 although there are important differences with SELECT: (1) the participants of ATBC were all long-term smokers (36 years on average) compared with 43% who had never smoked and 8% current smokers in SELECT; (2) prostate cancer was a secondary end point in ATBC; and (3) men in ATBC were not screened so that prostate cancer was diagnosed at more advanced stages than in SELECT.

In the Physicians Health Study II (PHS II) conducted contemporaneously with SELECT, intervention with 400 IU of vitamin E every other day for a median of 8 years had no effect on the incidence of prostate cancer (HR, 0.97; 95% CI, 0.85-1.09; P = .58), although like SELECT there was no effect on total cancer incidence (HR, 1.04; 95% CI, 0.95-1.13; P = .41) or overall mortality (HR, 1.08; 95% CI, 0.98-1.19).16
high-dose beta carotene in both ATBC29 and the Beta-Carotene and Retinol Efficacy Trial (CARET),29 and the increased risk of colon polyps seen in a trial administering high-dose folate,30 suggest that caution should be used when recommending or studying high doses of micronutrients. As opposed to synthetic pharmaceuticals, these naturally occurring dietary constituents are part of normal physiology, and a U-shaped-dose response curve may exist where either deficiency or supra-physiological doses are harmful.

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

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

**CONCLUSION**

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

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**Table 5. Secondary End Points**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 8696)</th>
<th>Vitamin E Alone (n = 8737)</th>
<th>Selenium Alone (n = 8752)</th>
<th>Vitamin E + Selenium (n = 8702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer, No.</td>
<td>75</td>
<td>85</td>
<td>74</td>
<td>93</td>
</tr>
<tr>
<td>Hazard ratio (99% CI)</td>
<td>1.09 (0.72-1.64)</td>
<td>0.96 (0.63-1.46)</td>
<td>1.21 (0.81-1.81)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.60</td>
<td>.79</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>Lung cancer, No.</td>
<td>92</td>
<td>104</td>
<td>94</td>
<td>104</td>
</tr>
<tr>
<td>Hazard ratio (99% CI)</td>
<td>1.11 (0.76-1.61)</td>
<td>1.02 (0.70-1.50)</td>
<td>1.11 (0.76-1.62)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.49</td>
<td>.89</td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>All other primary cancers</td>
<td>579</td>
<td>570</td>
<td>557</td>
<td>594</td>
</tr>
<tr>
<td>Hazard ratio (99% CI)</td>
<td>0.97 (0.83-1.14)</td>
<td>0.96 (0.83-1.13)</td>
<td>1.02 (0.88-1.19)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.65</td>
<td>.54</td>
<td>.74</td>
<td></td>
</tr>
<tr>
<td>All cancers, including prostate</td>
<td>1108</td>
<td>1190</td>
<td>1132</td>
<td>1149</td>
</tr>
<tr>
<td>Hazard ratio (99% CI)</td>
<td>1.07 (0.96-1.19)</td>
<td>1.02 (0.92-1.14)</td>
<td>1.02 (0.92-1.14)</td>
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</tr>
<tr>
<td>P value</td>
<td>.13</td>
<td>.59</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Deaths, all cause</td>
<td>564</td>
<td>571</td>
<td>551</td>
<td>542</td>
</tr>
<tr>
<td>Hazard ratio (99% CI)</td>
<td>1.01 (0.86-1.17)</td>
<td>0.98 (0.84-1.14)</td>
<td>0.96 (0.82-1.12)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.91</td>
<td>.67</td>
<td>.47</td>
<td></td>
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</tbody>
</table>

**October 23, 2008a
Diabetes b**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 8696)</th>
<th>Vitamin E Alone (n = 8737)</th>
<th>Selenium Alone (n = 8752)</th>
<th>Vitamin E + Selenium (n = 8702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk (99% CI)</td>
<td>1.04 (0.91-1.18)</td>
<td>1.07 (0.94-1.22)</td>
<td>0.97 (0.85-1.11)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.47</td>
<td>.16</td>
<td>.61</td>
<td></td>
</tr>
</tbody>
</table>

**July 5, 2011
Diabetes b**

<table>
<thead>
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<th>Placebo (n = 8696)</th>
<th>Vitamin E Alone (n = 8737)</th>
<th>Selenium Alone (n = 8752)</th>
<th>Vitamin E + Selenium (n = 8702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk (99% CI)</td>
<td>1.05 (0.93-1.17)</td>
<td>1.04 (0.93-1.17)</td>
<td>0.99 (0.89-1.12)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.29</td>
<td>.34</td>
<td>.91</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiovascular events, grade ≥4c**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 8696)</th>
<th>Vitamin E Alone (n = 8737)</th>
<th>Selenium Alone (n = 8752)</th>
<th>Vitamin E + Selenium (n = 8702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio (99% CI)</td>
<td>0.93 (0.83-1.05)</td>
<td>0.97 (0.86-1.09)</td>
<td>0.97 (0.86-1.09)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.11</td>
<td>.45</td>
<td>.51</td>
<td></td>
</tr>
</tbody>
</table>

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aDate of data freeze for initial publication
bPrevalent cases at baseline and men who never submitted a form with a diabetes assessment are excluded from the analysis.

cTime to first reported cardiovascular event, cardiovascular procedure (eg, coronary artery bypass graft surgery), or hemorrhagic stroke, all men. Cardiovascular end points were not centrally adjudicated.
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