

# Vitamin E Supplements May Raise the Risk for Prostate Cancer

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Authors and Disclosures

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October 11, 2011 — Vitamin E supplementation in men does not protect against prostate cancer; instead, it might increase risk.

The [initial report](#) of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found that neither selenium nor vitamin E supplements reduced the risk for prostate cancer. However, an [updated analysis](#), which appears in the October 12 issue of *JAMA*, shows that vitamin E supplementation can significantly increase the risk for prostate cancer.

Men who received a common dose and formulation of vitamin E (400 IU/d) had a significant 17% increased risk for prostate cancer than men who received placebo.

This observed increase in risk demonstrates "the potential for seemingly innocuous yet biologically active substances such as vitamins to cause harm," write the authors.

"This was a surprising finding and, at present, there is no biological explanation for why those who took vitamin E are at higher risk of developing prostate cancer," first author Eric Klein, MD, told *Medscape Medical News*. Dr. Klein is chair of the Glickman Urological and Kidney Institute, Cleveland Clinic, Ohio.

"We have made the SELECT biorepository available to the wider scientific community to test hypotheses that might explain the findings," he added.

Should vitamin supplementation be avoided until more is known about this possible link to prostate cancer?

### **There is no reason for otherwise healthy men to take vitamin E.**

"As we point out in the paper, there are few if any studies that show any health benefits for taking vitamin E, and the SELECT findings suggest it could be harmful," said Dr. Klein. "It seems there is no reason for otherwise healthy men to take vitamin E as a dietary supplement."

Senior author Laurence H. Baker, DO, professor of internal medicine and pharmacology at the University of Michigan, Ann Arbor, agrees that the findings were unexpected.

"Vitamin E doesn't prevent prostate cancer; it doesn't prevent any cancer, despite the claims of some, and it doesn't promote cardiovascular health, despite the claims of many." he said in an interview.

"There is no evidence to support any of these claims, yet thousands or even millions of men include vitamin E in their supplementation," Dr. Baker continued. "What this tells us is that even though we assume something to be good, it may not be. In fact, it may be harmful. The assumption is that because vitamin E is an antioxidant, it's good for us. But that isn't the case."

On the basis of these results, Dr. Baker noted that there is "good reason to avoid the dose of vitamin E...that was used in the study."

"The onus of proof should always be on the people" who advocate the use of a product, he explained.

Despite the negative results, the study offers a unique opportunity to learn more about prostate cancer. In the biorepository, there are blood samples and tissue samples from the 3500 men who participated in the trial. "Even though we don't know why these men had a higher incidence of prostate cancer, I am optimistic that these results may teach us why men get prostate cancer," Dr. Baker noted. "That would be a very important benefit."

### **No Evidence to Support Benefit**

The SELECT trial was conducted on the premise that selenium and vitamin E supplementation might reduce the risk for prostate cancer. This hypothesis stemmed from preclinical and epidemiologic studies that suggested that there might be a benefit. However, the use of the 2 supplements was halted in October 2008 because of an apparent lack of benefit and a possibility of harm.

After a median overall follow-up of 5.46 years, supplementation with selenium, vitamin E, or both did not prevent prostate cancer in a population of relatively healthy men. There was a statistically nonsignificant increased risk for prostate cancer among men who received vitamin E only ( $P = .06$ ) and a statistically nonsignificant increased risk for type 2 diabetes mellitus in the men who received selenium only ( $P = .16$ ) (*JAMA*. 2009;301:39-51).

Only the use of supplements was stopped by the Data and Safety Monitoring Committee, not the trial. The authors planned on following the study participants for 3 additional years to determine if there was any benefit or harm.

### **Contradicts Early Data**

Much of the evidence that vitamin E is protective came from epidemiologic studies, explained James R. Marshall, PhD, who was approached by *Medscape Medical News* for independent comment. "In spite of the publicity these studies received, it is very difficult — virtually impossible — to evaluate causality, and to disentangle causes from confounding factors, such as tobacco and alcohol use, physical activity, obesity, and other nutritional factors, in observational epidemiologic studies," he said.

Dr. Marshall, who is chair of the Department of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute, Buffalo, New York, explained that he was on the Institute of Medicine committee that developed the 2000 guidelines for antioxidants, including vitamin E and selenium. "Some members of the committee proposed that the daily recommended intake of vitamin E be raised to 400 IU per day, which was the dose tested in the SELECT trial," he said. "That recommendation did not become a part of the guidelines."

One of the major pieces of evidence that justified the SELECT study was the Alpha-Tocopherol, Beta-Carotene trial that was conducted in Finland. In that study, beta-carotene was expected to decrease lung cancer risk but did not, and

vitamin E was expected to decrease heart disease risk but did not, although it was associated with a largely unanticipated 40% decrease in prostate cancer incidence, Dr. Marshall explained.

"We don't to this day understand how that decrease in prostate cancer risk appeared, other than to attribute it to chance — a statistical fluke," he said. "Often, there are unanticipated outcomes from observational epidemiologic studies — generally, most of the outcomes of these studies are unanticipated — and from clinical trials."

"We probably need to be more careful than we have been of the common practice of paying attention to these unanticipated outcomes," Dr. Marshall continued. "This new result, from the analysis of SELECT by Klein and colleagues, should be seen as definitive. It is drawn from a huge, well-designed, -managed, and -analyzed trial."

"The likelihood that vitamin E in the dose studied in SELECT confers health benefits has to be, at this point, seen as 0," he added.

### **Elevated Risk Observed**

The SELECT trial involved 35,533 healthy men from 427 study sites in the United States, Canada, and Puerto Rico who were randomized from 2001 and 2004. All participants had a prostate-specific antigen level of 4.0 ng/mL or less, a digital rectal examination not suspicious for prostate cancer, and were 50 years or older (black men) or 55 years or older (all others).

The men were randomized to 1 of 4 treatment groups: 8752 received selenium (200 µg/d from L-selenomethionine), 8737 received vitamin E (400 IU/d of all-rac-alpha-tocopheryl acetate), 8702 received both agents, and 8696 received placebo.

After 5.56 years of follow-up, there were 473 cases of prostate cancer in the vitamin E group (hazard ratio [HR], 1.13); 432 in the selenium group (HR, 1.04); 437 in the selenium plus vitamin E group (HR, 1.05); and 416 in the placebo group (HR, 1.0).

The current analysis reflects the final data collected by the study sites up to July 5, 2011, and includes 54,464 additional person-years of follow-up and 521 additional cases of prostate cancer — 113 in the placebo group, 147 in the vitamin E group, 143 in the selenium group, and 118 in the combination group.

Findings showed that the rate of prostate cancer detection was higher in all groups that received active treatment than in the placebo group, but only the vitamin E group reached statistical significance (HR, 1.17;  $P = .008$ ).

### **Secondary End Points**

The initial findings of the SELECT study showed a nonsignificant increased risk for type 2 diabetes mellitus in the selenium group; in the updated results, this finding was still not statistically significant ( $P = .34$ ).

The authors also updated findings on prespecified secondary end points, including lung, colorectal, and total other cancers, deaths, and grade 4 cardiovascular events. They found no statistically significant differences in the hazard ratios of any group, which suggests that for these end points, there is neither benefit nor harm related to the use of these supplements.

### **Proceed With Caution**

Matthew R. Smith, MD, PhD, associate professor of medicine at Harvard University Medical School in Boston, Massachusetts, reiterated that this study highlights the need to be skeptical of claims attributed to over-the-counter products, although he noted that vitamin E, per se, is not specifically marketed to prevent cancer.

"The cautionary part is that if you look at the background information, it is a compelling narrative," said Dr. Smith. "Unfortunately, the definitive trial has now been done, and shows it is not true."

He agrees that there is no basis for recommending these products to prevent prostate cancer. "On a larger scale, we should be careful about claims. They may not be harmful; they may just be neutral," he said in an interview. Dr. Smith was not involved in the study.

Dr. Smith also pointed out that although the reason for the increased risk for prostate cancer observed with vitamin E supplementation is unclear, the dose given was much higher than would normally be found in food. "These are nonphysiologic doses and methods of delivery," he said. "With food, you don't get a 400 IU slug of vitamin E. The biology of these vitamins is very complex, and this is not how they are normally taken in the diet."

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