

FOR IMMEDIATE RELEASE:
Monday, October 27, 2008

CONTACT:
NCI Office of Media Relations
(301) 496-6641
ncipressofficers@mail.nih.gov

University of Michigan
Nicole Fawcett
(734) 764-2220
nfawcett@med.umich.edu

Selenium and Vitamin E Cancer Prevention Trial (SELECT): Questions and Answers

Key Points

- SELECT stands for the Selenium and Vitamin E Cancer Prevention Trial, a prevention clinical trial to see if one or both of these dietary supplements prevent prostate cancer.
- SELECT is continuing to evaluate the effects of the supplements but participants are no longer taking study supplements. The independent Data and Safety Monitoring Committee for the trial found that selenium and vitamin E, taken alone or together for an average of five years, did not prevent prostate cancer.
- The SELECT data showed two concerning, but not statistically significant, trends: there were slightly more cases of prostate cancer in men taking only vitamin E and slightly more cases of diabetes in men taking only selenium. Neither of these findings proves an increased risk from the supplements and may be due to chance.

1. What is SELECT?

SELECT stands for the Selenium and Vitamin E Cancer Prevention Trial, a clinical trial to see if one or both of these substances can help prevent prostate cancer when taken as dietary supplements. The trial is funded primarily by the National Cancer Institute (NCI) and is being coordinated by the Southwest Oncology Group (SWOG), an international network of research institutions that receives NCI funding. Enrollment for the trial began

in 2001 and ended in 2004. More than 400 sites in the United States, Puerto Rico, and Canada are taking part in the study. Over 35,000 men are participating in SELECT.

2. What is the status of SELECT?

SELECT participants are being told to stop taking their study supplements but will continue to have their health monitored by study staff for about three more years. The independent Data and Safety Monitoring Committee (DSMC) for the trial met on September 15, 2008, to review SELECT study data and found that selenium and vitamin E, taken alone or together for an average of five years, did not prevent prostate cancer. They also calculated that it was unlikely selenium and vitamin E supplementation would ever produce a 25 percent reduction in prostate cancer, as the study was designed to show.

The data also showed two concerning, but not statistically significant, trends: there were slightly more cases of prostate cancer in men taking only vitamin E and slightly more cases of diabetes in men taking only selenium. Neither of these findings proves an increased risk from the supplements and may be due to chance. But combined with the lack of benefit of selenium and vitamin E, the DSMC recommended that the men in SELECT stop taking study supplements but continue to be monitored. The DSMC also said that the data could not exclude a small chance that the study supplements might have effects later in the men's lives. SELECT investigators are preparing a report of these findings for a peer-reviewed scientific journal.

3. What is happening to the men on SELECT?

Men on the study are being informed about the initial findings and told to stop taking their study supplements. Participants will continue to have their health monitored by study staff, continue to respond to the study questionnaires, and will provide a blood sample at their five-year anniversary of joining the trial (if they have not already done so). The information from the questionnaires and the blood samples will allow a complete analysis of the study, including important molecular-level research on the role of antioxidants in cancer prevention and the natural history of prostate cancer, other cancers, and diseases of male aging.

4. What if a participant has moved or otherwise lost contact with their SELECT study team?

Any participant in SELECT who has lost contact with their study team can contact the NCI's Cancer Information Service for more information and to be referred to SELECT study staff. Participants in the United States and Puerto Rico can call the CIS toll-free at 1-800-4-CANCER (1-800-422-6237), Monday-Friday, 9 a.m. – 4:30 p.m. local time or use our LiveHelp® online chat service at <http://www.cancer.gov/livehelp>, Monday-Friday, 9 a.m. – 11 p.m. Eastern time. E-mails can also be sent to cancer.govstaff@mail.nih.gov.

5. Who got which supplement?

Men who participated in this study took two capsules a day. Participants were randomly assigned (that is, assigned by chance) to receive:

- selenium and vitamin E
- selenium and a placebo
- vitamin E and a placebo
- two placebos

Two placebos were used in the trial: one looked like a selenium capsule; the other looked like a vitamin E capsule. Each placebo contained only inactive ingredients. Neither the participants nor the researchers know who received the selenium and vitamin E, or the placebos, a process known as 'blinding.'

6. Have the men been 'unblinded'?

Study investigators have carefully considered how to follow (monitor) participants and feel it would be most proper and useful to continue to follow SELECT participants in a blinded fashion. Men in SELECT are followed with state-of-the art care including regular prostate cancer screening tests and questions about diabetes and other health issues. Data from men who remain blinded will provide the most reliable information on which to assess prostate cancer, adult onset diabetes, or other diseases of male aging.

If a participant asks to know which supplements they were receiving, he will be told. Men who request to be unblinded will continue to be followed by study staff in the manner originally outlined in the study.

7. What are a man's chances of developing prostate cancer?

Except for skin cancer, prostate cancer is the most common type of cancer in men in the United States. In the U.S. in 2008, there will be an estimated 186,320 new cases of prostate cancer and 28,660 deaths from this disease (1). All men are at risk for prostate cancer, but those at highest risk fall into one or more of the following categories: age 55 years or older; African-American; or have a father or brother with prostate cancer.

8. What is selenium? Why study it for prostate cancer prevention?

Our bodies need selenium, a nonmetallic trace element that we get from food -- especially plant foods such as rice and wheat, seafood, meat, and Brazil nuts. Selenium is an antioxidant that may help control cell damage that can lead to cancer.

The Nutritional Prevention of Cancer Trial, first reported in 1996, included 1,312 men and women who had skin cancer. Results of the trial showed that men who took selenium to prevent nonmelanoma skin cancer received no benefit from selenium in preventing skin cancer. However, approximately 60 percent fewer new cases of prostate cancer were

observed among men who had taken selenium for 6½ years than among men who took the placebo (2). In a 2002 follow-up report, the data showed that men who took selenium for more than 7½ years had about 52 percent fewer new cases of prostate cancer than men who took the placebo (3). This trial is one of the reasons for studying selenium in SELECT.

9. What is vitamin E? Why study it for prostate cancer prevention?

We get vitamin E in a wide range of foods, especially vegetables, vegetable oils, nuts, and egg yolks. Vitamin E, like selenium, is an antioxidant, which may help control cell damage that can lead to cancer.

In a 1998 study of 29,133 male smokers in Finland, 32 percent fewer new cases of prostate cancer and 40 percent fewer deaths from prostate cancer were observed among men who took vitamin E to prevent lung cancer than among men who took a placebo. Some men also took beta carotene, but neither substance helped prevent lung cancer and beta carotene did not affect prostate cancer (4).

10. What do researchers hope to learn from SELECT?

A large trial of selenium and vitamin E was needed to substantiate earlier, separate findings from studies in which prostate cancer was not the primary outcome investigated. The primary goal of SELECT was to assess the effect of these substances on the number of new cases of prostate cancer diagnosed during routine clinical practice. Initial analyses of SELECT data showed that selenium and vitamin E supplements do not help prevent prostate cancer.

Other objectives of SELECT include assessments of the impact of selenium and vitamin E on the incidence of lung cancer and colon cancer, as well as on total cancer incidence and survival. SELECT will provide the basis for studying the molecular genetics of cancer risk and associations between diet and cancer. A biorepository of blood samples obtained from SELECT participants at their entry into the trial and again after five years was created for use in molecular and mechanistic studies of prostate and other cancers, and other diseases of male aging. Additionally, SELECT has been examining the impact of selenium and vitamin E supplementation on participant quality of life.

11. Who was eligible to participate in SELECT? Were there restrictions on eligibility?

Many diseases, including prostate cancer, occur more frequently in older persons. The risk of developing prostate cancer increases with age. More than 90 percent of prostate cancer cases occur in men age 55 or older (5).

African American men had to be age 50 or older to participate, and men of other races and ethnicities had to be 55 or older. The age for eligibility was lower for African American men because, on average, they get the disease at an earlier age.

12. Could men with benign prostatic hyperplasia (BPH) join SELECT?

Men with BPH, a benign enlargement of the prostate gland, could join SELECT because BPH is not a cancerous or a precancerous condition. In BPH, the prostate grows larger and presses against the urethra and bladder, interfering with the normal flow of urine. More than half of the men in the United States between the ages of 60 and 70, and as many as 90 percent of men between the ages of 70 and 90, have symptoms of BPH.

BPH can be treated with four different U.S. Food and Drug Administration (FDA)-approved drugs: finasteride (Proscar®), terazosin (Hytrin®), doxazosin (Cardura®), and tamsulosin (Flomax®). Men were not excluded from SELECT on the basis of taking these drugs. Instead, use of these medications was recorded by SELECT investigators.

In 2003, the SWOG-coordinated Prostate Cancer Prevention Trial, in which more than 18,000 men took either finasteride or a placebo to see if the drug reduced the risk of developing prostate cancer, showed a 25 percent reduction in prostate cancer in men taking finasteride (6). Finasteride is not currently approved by the U.S. FDA for reducing the risk of developing prostate cancer. Men in SELECT were made aware of these findings and were allowed to take the drug.

13. What tests were used to determine eligibility for SELECT? What tests are being done during the study?

The tests included a digital rectal examination (DRE) and a prostate-specific antigen (PSA) test. During a DRE, a doctor inserts a gloved finger into the rectum and feels the prostate gland through the rectal wall to check for bumps or abnormal areas. The PSA test measures the level of PSA, a protein produced by cells of the prostate gland, in the blood. A person's PSA level can rise due to cancer or benign (not cancerous) conditions. Doctors often use the PSA test and DRE as prostate cancer screening tests in men who have no symptoms of the disease..

To be eligible for the SELECT trial, participants had to have a DRE that found no signs of prostate cancer and a total PSA level less than or equal to 4.0 nanograms per milliliter (ng/ml). During the trial, DREs and PSA tests are suggested, but not required, on an annual basis throughout the course of the study. Even though supplement use is being stopped in SELECT, the participants will continue to have their health monitored by study staff, including PSA testing and DREs.

14. Who pays for these tests?

Physician, medical examination, and general clinic costs, including DREs, are charged to the participant in the same way as if he were not part of the trial. These costs may be covered by a participant's health insurance. Financial assistance may be available for some men. SELECT, however, pays for follow-up PSA tests. Men with questions about insurance coverage or reimbursement should check with their local SELECT site.

15. How much selenium was being used in SELECT? What risks were involved with taking selenium?

The amount of selenium (provided as l-selenomethionine) was 200 micrograms (μg) daily. Although the initial results of the Nutritional Prevention of Cancer Trial showed an overall decrease in cancer incidence from selenium, a 2003 update reported 17 percent more new nonmelanoma skin cancers in the selenium group compared with the placebo group (7). It is not clear how these results would apply to men who did not already have skin cancer when they enrolled in SELECT, or to men who are not at increased risk for skin cancer.

Since the start of SELECT, four studies have been published looking at the effect of selenium on blood glucose and risk of diabetes: two studies suggested that higher levels of selenium taken as supplements or received naturally were associated with an increased risk of diabetes. One study showed no association between the two, and one showed that people with higher levels of selenium in their blood had a reduced risk of diabetes (8-11). Starting in early 2007, the SELECT DSMC was specifically asked to review the study data for cases of diabetes because of these findings.

16. How much vitamin E was being used in SELECT? What risks were involved?

The amount of vitamin E (provided as dl-alpha-tocopherol acetate) was 400 milligrams (mg), which is equivalent to 400 International Units (IU) per day. This dose of vitamin E can thin the blood somewhat. Men with uncontrolled high blood pressure were not eligible to take part in SELECT because taking this much vitamin E might have increased their risk of stroke.

Vitamin E has been shown to increase the risk of some cardiovascular conditions. In a 2005 study, men and women with vascular disease or diabetes who took 400 IU of vitamin E daily for seven years had a 13 percent increased risk of heart failure compared with participants taking a placebo (12). Heart failure is a condition in which the heart's ability to pump blood is weakened. A 2005 analysis of several studies in which people with various medical problems took vitamin E suggested a link between high doses of vitamin E (400 IU or more) and increased mortality (13). The continued follow up of SELECT participants will provide more information about this possible risk.

17. What other requirements were there for SELECT participants?

Upon enrollment, men were asked to have toenail clippings collected to assess selenium levels in the body because selenium concentrates in fingernails and toenails. Toenails were chosen over fingernails because they take longer to grow and thus contain more history of someone's selenium intake. Blood samples were collected upon enrollment to assess levels of vitamin E, and again at five years after a man joined the study. These blood samples are placed in the SELECT biorepository for future studies.

Also upon enrolling, men filled out a questionnaire about their diet and past supplement use. There is also an annual questionnaire that asks for updates of some of this information. Men did not have to change their diets during this study. Each man is offered a supply of a special daily multivitamin, manufactured by The Perrigo Company, Allegan, Michigan, that contains no selenium or vitamin E. Vitamin E, selenium, placebo capsules, and multivitamins were provided free of charge to enrollees. SELECT men will still be able to receive and take the multivitamin now that supplement use has been stopped.

18. What happens if a participant develops prostate cancer while involved in SELECT?

Participants diagnosed with prostate cancer during the study will be referred for treatment and will continue to be followed by the SELECT study staff, although less frequently.

Costs for diagnosis and treatment of prostate problems, prostate cancer, or other medical conditions during the study are charged to the participant in the same way as if he were not part of the trial. A participant's insurance will pay for diagnosis and treatment according to the plan's policies. If the participant has no insurance, social services may be available at the local level to cover costs for diagnosis and treatment.

19. How much did SELECT cost? Who else funded the study, and why?

NCI is the primary funding agency for SELECT, awarding about \$114 million to SWOG from 1999 through 2008, with an additional \$4.5 million contributed by the National Center for Complementary and Alternative Medicine (NCCAM), also an agency of the National Institutes of Health (NIH). NCI has been funding a substudy to see if the supplements affect colon polyp growth. In addition, ancillary studies are funded by three other NIH institutes:

- The National Institute on Aging (NIA) has provided almost \$7 million for the Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE) trial. This trial is NIA's add-on to SELECT. It is evaluating whether these supplements can help prevent memory loss and dementia, such as that found in Alzheimer's disease. Studies show that increased oxidative stress may damage brain cells and is linked with Alzheimer's disease. Animal and tissue culture studies of vitamin E and selenium suggest that they can protect brain cells from oxidative damage.
- The National Eye Institute (NEI) has provided almost \$2 million for the SELECT Eye Endpoints Study (SEE). Age-related macular degeneration (AMD) and cataracts are two leading causes of visual impairment in older Americans. AMD is a disease that affects the central vision, and is the leading cause of visual problems and blindness, with about 25 percent of people over 65 showing some AMD. Cataract is a clouding of the eye's lens that causes loss of vision. More than 50 percent of adults in the U.S. age 75 and older suffer from visually significant cataracts. Some evidence suggests that the dietary supplements (selenium and vitamin E) being studied in SELECT might prevent these eye problems. The SELECT Eye Endpoints (SEE) study is looking at this question in a large group of SELECT participants.

- The National Heart, Lung and Blood Institute (NHLBI) has provided more than \$3 million for the Respiratory Ancillary Study (RAS). The overall objective of RAS is to understand whether the supplements being studied in SELECT affect the loss of lung function experienced with aging, which is higher in persons who smoke cigarettes. This study closed to accrual in 2007. Specific SELECT study sites were invited to participate in RAS. All smokers at these study sites were invited to participate, as well as a random selection of former smokers.

20. What other research is being done for prostate cancer prevention?

In 2003, the Prostate Cancer Prevention Trial, in which more than 18,000 men took either finasteride or a placebo to see if the drug reduced the risk of developing prostate cancer, showed a 25 percent reduction in prostate cancer in men taking finasteride. Finasteride is not currently approved by the U.S. FDA for reducing the risk of developing prostate cancer. (See <http://cancer.gov/pcpt> for more information).

Currently, NCI has several different agents in early prevention clinical trials of men at risk for prostate cancer or who have been diagnosed with prostate cancer and have not yet received treatments. These agents include polyphenon E, a green tea extract; di-indolylmethane (DIM), a compound found in brassica vegetables such as broccoli, kale and cauliflower; lycopene, a carotenoid found in tomatoes and other red plants; and soy.

21. Where is more information about SELECT available?

In the United States and Puerto Rico, call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) for information in English or Spanish. People with TTY equipment can call 1-800-332-8615 for information in English. In Canada, call the Canadian Cancer Society's Cancer Information Service at 1-888-939-3333 for information in English or French.

The following Web sites provide additional information:

- <http://.swog.org>– choose the SELECT option
- <http://www.cancer.gov/clinicaltrials/digestpage/SELECT>– from the NCI
- <http://www.cancer.gov/newscenter/SELECT>– provides images of the prostate, the crystalline and chemical structures of vitamin E, and selenium and vitamin E capsules

###

Selected References

1. National Cancer Institute (2008). *SEER Cancer Statistics Review 1975-2005*. Bethesda, MD: Retrieved October 24, 2008 from http://seer.cancer.gov/csr/1975_2005/results_single/sect_01_table.01.pdf.

2. Clark LC, Combs GF Jr., Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *Journal of the American Medical Association* 1996; 276(24):1957–1963.
3. 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 Epidemiology, Biomarkers & Prevention* 2002; 11(7):630–639.
4. 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. *Journal of the National Cancer Institute* 1998; 90(6):440–446.
5. National Cancer Institute (2008). *SEER Cancer Statistics Review 1975-2005*. Bethesda, MD: Retrieved October 24, 2008 from http://seer.cancer.gov/csr/1975_2005/results_merged/topic_age_dist.pdf.
6. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *New England Journal of Medicine* 2003; 349:215-224.
7. Duffield-Lillico AJ, Slate EH, Reid ME, et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *Journal of the National Cancer Institute* 2003; 95(19):1477–1481.
8. Stranges et al, Effects of Long-Term Use of Selenium Supplements on the Incidence of Type 2 Diabetes. *Ann Intern Med.* 147:217-233, 2007.
9. Bley J et al: Serum Selenium and Diabetes in U.S. Adults. *Diabetes Care* 30:829-834, 2007.
10. Rajpathak et al: Toenail Selenium and Cardiovascular Disease in Men with Diabetes. *Journal of the American College of Nutrition*, 24: 250–256, 2005.
11. Czernichow et al: Antioxidant supplementation does not affect fasting plasma glucose in the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) study in France: association with dietary intake and plasma concentrations. *Am J Clin Nutr* 84:395–9, 2006.
12. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. *Journal of the American Medical Association* 2005; 293(11):1338–1347.
13. Miller ER III, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Annals of Internal Medicine* 2005; 142(1):37–46.