Vitamin E and Prostate Cancer: Research Focus Turns to Biologic Mechanisms

By Caroline McNeil

Not only do vitamin E supplements not prevent prostate cancer, but they may actually increase the risk, according to new data from the large clinical trial known as SELECT—the Selenium and Vitamin E Cancer Prevention Trial.

Up to now, a few studies have found hints that vitamin E may increase risk of prostate cancer. But the SELECT findings, which were published in October in *JAMA*, are the first data to show a statistically significant increase in risk in a large population. The headline-making news was one more blow to the general hypothesis that antioxidant supplements can reduce cancer risk, and it probably puts a damper on any new large intervention trials with vitamin E.

But according to leaders in the field, it could, and probably should, boost basic research on what is now recognized as the complex relationship between vitamin E and prostate cancer development.

The results raise many questions, said Laurence Baker, D.O., of the University of Michigan, Ann Arbor, one of the SELECT authors and chair of the Southwest Oncology Group (SWOG), which conducted the trial. “We don’t know why this study failed, why it got the opposite effect, or what the genetic dysregulation is that leads to prostate cancer,” he said.

Eric Klein, M.D., a physician at the Cleveland Clinic, and a SELECT author, said that the challenge now is to learn more about the biology. “We need to understand why vitamin E increased the risk and why selenium and vitamin E together did not,” he said.

Lori Minasian, M.D., another coauthor and acting director of the National Cancer Institute’s Division of Cancer Prevention, also stressed the need for biologic studies:
“The findings suggest that the next question under study would be, how does vitamin E interact with tissue that is becoming cancerous?” she said.

SWOG is now soliciting research proposals to use the SELECT biospecimens specifically to address why vitamin E supplements increased prostate cancer incidence rather than decreasing it, Baker said. The deadline for applications is November 14.

The SELECT investigators themselves are analyzing plasma and toenails in each arm of the study, looking at baseline and postintervention concentrations of selenium and tocopherols. (Vitamin E is actually a family of four tocopherols and four tocotrienols, organic compounds that function as antioxidants in the body.)

**ATBC and SELECT**

Much of the interest in antioxidants in general, and vitamin E in particular, began with lung cancer. The Alpha Tocopherol Beta Carotene (ATBC) trial, one of the first large intervention studies, tested vitamin E and beta carotene supplements to prevent lung cancer among male smokers. The findings, reported in 1994, showed that beta carotene supplements increased prostate cancer among the men taking vitamin E alone.

The newest data show that the risk grew with 18 months of additional follow-up. In the placebo-only group, 65 prostate cancer cases were diagnosed for every 1,000 men, compared with 76 cases for those who took vitamin E only. The difference—11 additional cases per 1,000 men over 7 years—was statistically significant. Given the number of prostate cancers in the United States each year, Baker said the outcome “was by no means a trivial observation.”

Analyses found no other factors that might account for the differences in SELECT’s large, nationally representative population. No group was screened more often than any other, nearly all the cancers were very early-stage disease, and the rate of advanced or aggressive cancers in the vitamin E group was no higher than in the placebo group. Biopsied tissue samples revealed no other differences in pathology between the cancers that developed in the four different arms of the trial.

**Vitamin E and Smoking**

Even before these findings, researchers had been trying to figure out why such conflicting results emerged for prostate cancer between the ATBC and SELECT trials. One area of interest was smoking. ATBC had enrolled only current or recent smokers, so vitamin E may have prevented prostate cancer only in smokers.

Several studies have supported that idea. For instance, in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, current or recent smokers who had taken high-dose vitamin E supplementation over a long period had a reduced risk of advanced prostate cancer compared with nonsmokers, according to a study led by Victoria Kirsh, Ph.D., at Cancer Care Ontario, in Toronto. Other studies have had similar results, including a subset analysis of the Health Professionals Follow-up Study, by Edward Giovannucci, M.D., Sc.D., at Harvard and colleagues, and a nested case-control study in the Carotene and Retinol Efficacy Trial (CARET), led by Marian Neuhouser, Ph.D., R.D., at the Fred Hutchinson Cancer Research Center, in Seattle.

Like the early findings from SELECT, the subset analyses of the PLCO and the Health Professionals Follow-up Study also found a suggestion, not statistically significant, that supplements increased the risk of nonadvanced cancer.

The SELECT investigators plan to look for an association between smoking and prostate cancer among the men taking vitamin E. However, the power of the trial to detect an association is limited because it enrolled relatively few smokers, Klein said. Only about 8% of participants were current smokers, and only about 40% had ever smoked.

One explanation for an increased risk in smokers could include hormone levels, according to researchers who analyzed data from the large national study of diet and lifestyle known as NHANES III, the National Health and Nutrition Examination Survey. Demetrius Albanes, M.D., at the National Cancer Institute, and colleagues found that smokers with higher alphatocopherol levels have lower levels of testosterone, estradiol, and SHBG (sex hormone–binding globulin), an association not found in nonsmokers.

The authors, in NCI’s Division of Epidemiology and Genetics, speculate that vitamin E may lower prostaglandin levels, particularly prostaglandin E2, and thus hormones that stimulate androgen production. Lower androgen levels are associated with lower prostate cancer risk. In their study, published in June in *Cancer Causes and Control*, they conclude that their findings “support vitamin E selectively influencing sex hormones in smokers and afford possible mechanisms through which vitamin E may impact prostate cancer risk.”
Albanes and colleagues are continuing their work with serum levels of tocopherols, using SELECT biospecimens. According to their statement on the SWOG website, they “propose to determine whether baseline circulating tocopherols are prospectively associated with prostate cancer risk.” They add that “interactions with smoking, trial interventions, and race will be specifically tested.”

**Genetic Factors**

Other research teams are already exploring genetic variants that might explain the increase in risk among SELECT participants taking vitamin E.

At Vanderbilt University, in Nashville, Tenn., Sarki Abdulkadir, M.D., Ph.D., and colleagues are studying a variant of the gene NKX3.1, a tumor suppressor that protects against oxidative damage. Cells with the variant, or risk allele, express lower levels of NKX3.1. The researchers originally hypothesized that their mouse model—an NKX3.1 risk allele mouse—would have an increased cancer risk that antioxidant treatment could counter. But they found the opposite was true: Antioxidant treatment increased prostatic epithelial proliferation in the mice, a finding that the latest data from SELECT now support.

Using SELECT biospecimens, the Vanderbilt researchers are now testing whether the risk allele is associated with a higher risk of prostate cancer among men in the study who took vitamin E.

NKX3.1 is of course only one of many genes that may be involved. The CARET subgroup analysis at Fred Hutchinson by Neuhouser and colleagues not only showed that tocopherol concentrations were associated with reduced risks of aggressive prostate cancer in current or recent smokers; it also found that two variants of the myeloperoxidase (MPO) gene made a difference in this association. Current smokers with high alpha-tocopherol levels had a lower risk of aggressive prostate cancer, but if they also had the MPO alleles, which help reduce oxidative stress, their risk was even lower. Men with low alpha-tocopherol levels had a higher risk, and if they had the
MPO alleles, their risk was twice as high. The differences were statistically significant.

Neuhouser said that a logical next step could be to study these MPO alleles in the general population, such as participants in SELECT. The alleles “were not uncommon among the CARET population,” she said, so if they are present in the general population, they might help in understanding the lack of consistency among studies of vitamin E and prostate cancer.

Studies already using the SELECT biospecimens are analyzing vitamin D levels, markers of methionine metabolism, and intraprostatic inflammation, in addition to the presence of the NKX3.1 risk allele and hormone levels. The next round of proposals to use the specimens, due November 14, will be evaluated according to two main criteria, Klein said. One is their relevance to the trial’s central hypothesis regarding antioxidants and prostate cancer. The other is to demonstrate that using the SELECT biorepository is essential to the proposed hypothesis and not answerable by studying a different cohort.

More studies exploring the basic biology of prostate cancer and how it reacts to antioxidants can be expected in the wake of the new findings from SELECT. “They do create a rethinking of our hypotheses,” said Minasian.

© Oxford University Press 2011. DOI: 10.1093/jnci/djr504