

An Editorial Update: *Annus horribilis* for Vitamin E

In January 2005, we published a dose–response meta-analysis showing that high-dosage (≥ 400 IU/d) vitamin E supplementation was associated with a small but statistically significant increased risk for mortality (relative risk, 1.04 [95% CI, 1.01 to 1.07]) (1). The precise dosage of vitamin E at which the relative risk for mortality exceeded 1 and the magnitude of the risk increase were uncertain. However, the analysis showed that high-dosage vitamin E supplementation was likely to be harmful. Even in the best case, it offered no benefit in prolonging life. These findings were highly controversial: Together with our response, this issue of *Annals* includes 11 of more than 40 electronic rapid responses to the *Annals* Web site. Rather than summarizing this exchange of views, this editorial reports further developments in the vitamin E story.

VITAMIN E AND THE PREVENTION OF CANCER, CARDIOVASCULAR DISEASE, AND MORTALITY

Recently, vitamin E has suffered several setbacks. The Women's Health Study (WHS), a 10-year, primary prevention trial that randomly assigned 39 876 healthy women to either 600 IU of vitamin E or placebo on alternate days, found that vitamin E did not reduce cardiovascular disease or cancer (2). Indeed, total mortality was slightly—although nonsignificantly—increased with vitamin E (relative risk, 1.04 [CI, 0.93 to 1.16]). The WHS was particularly important since its target population, healthy women, was underrepresented in the trials included in our meta-analysis.

The Heart Outcomes Prevention Evaluation—The Ongoing Outcomes (HOPE-TOO) study recently reported its findings (3). This report extended the follow-up of the original HOPE trial (4), in which 9541 patients with vascular disease or diabetes mellitus were randomly assigned to natural vitamin E (400 IU/d) or placebo. After 7 years of follow-up, the incidence of cancer, major cardiovascular events, and mortality was similar in both treatment groups (3). However, patients in the vitamin E group had a significantly increased risk for heart failure (relative risk, 1.13 [CI, 1.01 to 1.26]) and hospitalization for heart failure (relative risk, 1.21 [CI, 1.00 to 1.47]). In addition to these large trials, several articles have reported evidence of new biological mechanisms that could explain some of the adverse effects of vitamin E (3, 5, 6).

VITAMIN E AND NEUROPROTECTION

While studies showed that high-dosage vitamin E supplementation did not prevent cardiovascular disease or cancer, many still hoped that it could reduce the risk for neurodegenerative conditions, such as Alzheimer disease (7) or amyotrophic lateral sclerosis (ALS) (8). The case for Alzheimer disease was particularly compelling. Oxidative dam-

age was considered a key pathophysiologic process in disease progression (7, 9). Observational studies showed that a high intake of vitamin E was associated with a lower risk for Alzheimer disease (7, 9, 10), and a randomized, double-blind, controlled trial conducted by the Alzheimer's Disease Cooperative Study Group (ADCSG) in patients with moderately severe Alzheimer disease found that 2000 IU of vitamin E per day could delay disease progression (11).

Many observers have eagerly awaited the outcome of a new ADCSG study—a randomized, double-blind, controlled trial that evaluated the potential of vitamin E and donepezil, a cholinesterase inhibitor, to prevent progression to Alzheimer disease in high-risk patients (12). Participants in the trial had the amnesic subtype of mild cognitive impairment, a condition associated with a high risk for progression to Alzheimer disease (16% per year). In the study, 769 participants with mild cognitive impairment were randomly assigned to 3 groups: vitamin E (2000 IU/d), donepezil (10 mg/d), or placebo. All groups also received a daily multivitamin containing 15 IU of vitamin E.

At the end of 3 years of follow-up, the 3 treatment groups had similar risk for progression to Alzheimer disease. Compared with placebo, the hazard ratios for developing Alzheimer disease were 1.02 (CI, 0.74 to 1.41) for vitamin E and 0.80 (CI, 0.57 to 1.13) for donepezil. However, donepezil reduced progression to Alzheimer disease during the first 24 months of follow-up, with a strong protective effect during the first year (hazard ratio, 0.42 [CI, 0.24 to 0.76]). It also improved performance on several cognitive function tests, including an overall cognitive function score, but the benefits were largely limited to the first 18 months of follow-up. The moderate but transient effects of donepezil in high-risk patients were consistent with the modest benefits of donepezil and other cholinesterase inhibitors in patients with established Alzheimer disease (13, 14).

The ADCSG trial was designed specifically to test interventions to prevent progression to Alzheimer disease in a group of high-risk participants (12). Vitamin E had no effect. Because of wide confidence intervals around the estimates of effect, the study could not completely rule out modest beneficial or harmful effects. Clearly, the results did not support a neuroprotective effect of vitamin E.

The German Vitamin E/ALS Study Group has also reported the results of a randomized, double-blind, controlled trial of a megadose of vitamin E (5000 IU/d) versus placebo in 160 patients with ALS (15). Patients in both groups were also treated with riluzole. After 18 months of follow-up, 32 patients in each group reached the primary end point: a combination of death, need for permanent assisted ventilation, or tracheotomy. There were also no statistically significant differences in results of functional

assessment tests between vitamin E and placebo. Vitamin E was not effective in slowing the progression of ALS.

WHAT SHOULD THE PUBLIC DO?

We think that high-dosage vitamin E supplementation may increase all-cause mortality. Therefore, we believe that high-risk and healthy people should avoid this vitamin at high dosages (1). While it is possible that ongoing trials may show some benefit of high-dosage vitamin E supplementation in specific conditions, current evidence does not justify using it to reduce the risk for cancer, cardiovascular disease, or Alzheimer disease.

Patients with established Alzheimer disease have limited therapeutic options. Although the effects are modest and transitory, patients with Alzheimer disease should consider anticholinesterase drugs. The glutamate antagonist memantine remains an option for patients with advanced disease (16). Physicians should focus on controlling hypertension, hyperlipidemia, and diabetes because of the high frequency of mixed dementia where vascular dementia coexists with Alzheimer disease (17). In addition, they should encourage these patients to participate in ongoing clinical trials (information on ongoing trials for patients with Alzheimer disease can be found at www.alz.org/Resources/ClinicalTrialsIndex.asp). Vitamin E has been considered an optional treatment to slow the progression of established Alzheimer disease (18). Since this recommendation rests on the results of only 1 trial (11), we should require additional studies before deciding on the role of vitamin E in Alzheimer disease (19).

Vitamin E has enjoyed superstar status among dietary supplements. Because of perceived health benefits, vitamin E supplements are consumed by many people. As this editorial shows, recent trials have further weakened the evidence for benefit, while the evidence for harm has accumulated. We did not fully appreciate just how many people may be putting themselves at risk by using high-dosage vitamin E supplementation until this issue of *Annals*, in which Ford and colleagues use data from the 1999–2000 National Health and Nutrition Examination Survey to estimate that about 12% of U.S. adults (24 million people) consumed 400 IU or more of vitamin E daily from supplements (20). Furthermore, older adults were more likely to use high-dosage vitamin E supplementation. We are disturbed that a presumption of benefit by so many may increase risk for mortality. We call on health professionals to warn the public against the use of ineffective or even harmful interventions, such as vitamin E, that may compete with well-established preventive measures. High-dosage vitamin E is a prime example of misplaced priorities.

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