**EDITORIAL**

**Vitamin E Supplements: Good in Theory, but Is the Theory Good?**

Much of the U.S. public has a deep, and seemingly unshakable, faith in the health benefits of nutritional supplements (1). Use of these products has increased so rapidly in recent years that a third of all adults, and half of those older than 55 years of age, report taking at least 1 supplement daily (2). The shelves of pharmacies, grocery stores, and “nutrition centers” are well stocked with a dazzling variety of nutritional supplements, and for sound business reasons; supplements accounted for an estimated $18.8 billion in sales in the United States in 2003 alone (3). Many of these supplements are promoted to the public as “antioxidants,” a fuzzily defined category that includes vitamins C and E, some carotenoids, and many other phytochemicals and plant extracts. Vitamin E is the most widely used of the individual products, and it is taken daily as a specific supplement (usually containing 400 IU of α-tocopherol) by 22% of U.S. adults older than 55 years of age (2).

The touted benefit of antioxidants is prevention of the major chronic diseases that affect modern adults. Belief in the preventive value of antioxidants rests largely on 2 bodies of evidence. The first is epidemiologic observation, which has been interpreted as showing a decreased risk for disease among persons who consume relatively greater amounts of antioxidants in their diets or as supplements (4). The second is laboratory experiment, which has implicated oxidative chemical processes in the pathogenesis of conditions such as atherosclerotic cardiovascular disease, cancer, neurodegenerative diseases, and chronic lung disease (5, 6). Clinical trials of antioxidant supplements have not shown a clear benefit from taking these agents. Nevertheless, they continue to be widely used, even by physicians (7, 8). Many doctors may share the view of a cardiology researcher who told me his reason for taking vitamin E: It won’t hurt and might help, so why not take it?

But could antioxidant supplements actually be harmful? Two large clinical trials reported in the 1990s showed a statistically significant increase in risk for death among participants (mostly men with a history of heavy smoking) who received β-carotene, an agent previously thought to be nearly free of serious toxicity (9, 10). More recently, the authors of a meta-analysis of clinical trials of antioxidant supplements and gastrointestinal cancer concluded that random assignment to supplements may have increased overall mortality (11). And now, in this issue, Miller and colleagues (12) report the results of a carefully conducted meta-analysis of clinical trials of vitamin E supplementation. They conclude that high doses of this agent increase the risk for death. Their meta-analysis involved 19 randomized trials, which recorded 12 504 deaths. Overall, being randomly assigned to receive vitamin E had no effect, either positive or negative. However, the data suggested a decreased risk for death associated with vitamin E in trials that used lower doses (<400 IU) and showed a statistically significant trend toward increased risk at doses of 400 IU and above.

The finding of possible harm with higher doses of vitamin E is surprising and has serious implications for the tens of millions of people who regularly use vitamin E supplements. Yet, how firm is the conclusion that the risk for death is increased? The wide range of vitamin E doses used in the various trials and the large number of study participants and deaths enabled detection of possible dose-related health effects that any single study could not identify and previous reports from meta-analyses have not addressed. Although Miller and colleagues excluded 17 trials from their meta-analysis, all were relatively small studies, and I doubt that inclusion of their data would have materially altered the principal conclusions of the report. However, I am not totally convinced that the authors have isolated the effects of vitamin E from those of other supplements, since 10 of the 19 trials included in the meta-analysis involved provision of vitamin E together with other nutritional supplements. Of particular concern, most of the evidence for an elevated mortality risk at high doses of vitamin E comes from 2 trials (13, 14) that administered vitamin E together with β-carotene, a supplement previously associated with an increased risk for death. Likewise, much of the data on low doses of vitamin E comes from trials (15, 16) of multiple vitamin and mineral supplements in Chinese populations whose nutritional status and causes of mortality differed profoundly from those of the North American and European participants in the other trials. Miller and colleagues controlled for the possible effect of other supplements (apparently considered together, not as separate agents), and they acknowledge the difficulty of drawing broad inferences based on results from poorly nourished populations. Nevertheless, one cannot fully discount the possibility that the effects of specific supplements, nutritional status, or the conjoint effects of these factors underlie at least part of the dose–response relationship observed between vitamin E and mortality. Thus, while Miller and colleagues’ report provides intriguing evidence suggesting that higher doses of vitamin E cause death, the case is not ironclad.

The lack of a benefit associated with vitamin E supplements in this meta-analysis accords with the published results of individual trials and previous meta-analyses. Despite my uncertainty about the finding of harm in this meta-analysis, I fully agree with the authors’ conclusion that high-dose vitamin E supplementation is unjustified. Ample evidence indicates that taking high-dose vitamin E in later adult life (when most use of vitamins currently occurs) has no favorable health effects, and Miller and colleagues’ meta-analysis raises the possibility of harm. Thus, our message to the public must be clear on this point:
Vitamin E supplements won’t help, and might harm, so save your money. However, many users of nutritional supplements report that they would continue to take the supplements even if they were shown to be ineffective in scientific clinical studies (1), so basing our advice simply on evidence of no benefit may not have much immediate effect.

The public’s faith in vitamin E, and in antioxidants generally, reflects the strong belief of scientists and health professionals in the theory that exogenous antioxidants prevent chronic diseases. Ten years have passed since publication of the first large trial showing that vitamin E supplementation had no effect in preventing cancer and cardiovascular disease (9), and subsequent trials have repeatedly confirmed this result. The story is similar for other presumed antioxidants, such as β-carotene and vitamin C. Yet the notion that consumption of antioxidants in diet and supplements can prevent disease appears to have drawn strength, rather than been weakened, by contrary results from clinical trials. Investigators have called attention to isolated findings of possible antioxidant benefits for subgroups of trial participants, or for secondary end points, when the overall results of a trial were clearly null. After β-carotene, initially viewed as an extremely potent antioxidant, was shown to be harmful in clinical trials (9, 10), some scientists opined that the result represented a provitamin property of the agent under certain conditions; thus, they made the seemingly perverse outcome fit the antioxidant theory. Meanwhile, research based on the antioxidant theory continues apace; a recent search of the 2004 National Institutes of Health funding database produced more than 700 hits for the term antioxidant. Most funded studies are basic research, but they include many clinical trials testing vitamin E supplements in tens of thousands of patients, with dosages ranging from 400 to 2000 IU/d, for prevention of a variety of conditions such as dementia, heart disease, and prostate cancer. These research projects have all passed a rigorous peer review, and I do not question the scientific merit of any one of them. But isn’t it past the time for the scientific and public health communities to loosen their ties to a theory that lacks predictive ability for human disease?

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Disclosure: The author led the research group that conducted one of the trials whose data are included in Miller and colleagues’ meta-analysis, and provided the unpublished data to the authors of that report.

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