13. Mitchinson MJ, Stephens NG, Parsons A, Bligh E, Schofield PM, Brown MJ. Mortality in the CHAOS trial [Letter]. Lancet. 1999;353:381-2. [PMID: 9950454]

TO THE EDITOR: There are several flaws in the meta-analysis by Miller and colleagues (1), including erroneous interpretation of the pooled trials of α-tocopherol and lack of clarity in vitamin E nomenclature. The analysis includes trials from many time periods, with different trial designs, doses and combinations, and end points that make comparisons difficult and fallacious. Participants in several of the trials had significant medical conditions, such as coronary artery disease, end-stage renal disease, diabetes mellitus, Parkinson disease, and Alzheimer disease. Given this heterogeneity in the participant pool, we would consider it presumptuous to draw solid conclusions of the magnitude of Miller and colleagues', even with complex statistical tools such as meta-analysis, and to extend the observations to normal, healthy people. In addition to clinical heterogeneity, this analysis also suffered from heterogeneity in test nutrients. In many of the trials, vitamin E was used alone and in combination with another nutrient, such as β-carotene. In these cases, the authors combined the data for vitamin E alone with the data for vitamin E plus another nutrient even when the data for the other nutrient indicated that it was statistically significantly associated with increased mortality. Moreover, those studies in which fewer than 10 deaths occurred were excluded from the meta-analyses, giving an artificial weight to studies in which more patients died—that is, those in which patients had serious illness compared with studies of healthy individuals. A close look at the odds ratios in Miller and colleagues' Figure 2 does not suggest harmful effects at a dose of 400 IU of α-tocopherol, and yet the authors concluded that harmful effects begin at a dose of 150 IU.

Vitamin E is not a single compound and exists in 8 different isoforms in nature (4 tocopherols and 4 tocotrienols) that have distinct biopotencies, biokinetics, and cancer-preventive properties. Food sources vary in their content of the vitamin E isoforms. γ-Tocopherol, the primary source of dietary vitamin E, is abundant in plant seeds (corn, soybean, and sesame), vegetable oils, and nuts (walnuts, pecans, and peanuts). It is not appropriate to "lump" all the different forms of vitamin E into a single basket and call them "vitamin E." Natural vitamin E forms have different properties than synthetic vitamin E does. Most of the trials cited in Miller and colleagues' analysis used synthetic α-tocopherol. This should have been emphasized. Dietary and supplemental sources of vitamin E isoforms have unique properties that can influence critical pathways involved in cancer, inflammation, cardiovascular disease (CVD), and neurodegenerative disease. For example, mechanistic differences between the α- and γ-tocopherols and their metabolites provide a molecular basis for the superiority of γ-tocopherol (2–5). Although α-tocopherol has a high concentration in supplements, the primary form of vitamin E in the diet is γ-tocopherol, which is present at a concentration 2 to 4 times higher than that in α-tocopherol. A high intake of synthetic α-tocopherol can lower plasma and tissue levels of γ-tocopherol. We believe that carefully conducted randomized studies with long follow-up periods and well-defined end points are required to address the potential clinical efficacy of the different isoforms of vitamin E. We also have to be clear on the terminology that is used when we discuss the properties and effects of the different forms of vitamin E.

Koyamangalath Krishnan, MD
The University of Texas M.D. Anderson Cancer Center
Houston, TX 77030

Sharon Campbell, PhD
William L. Stone, PhD
East Tennessee State University
Johnson City, TN 37614

Potential Financial Conflicts of Interest: None disclosed.

References

1. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37-46. [PMID: 15537682]

2. Wagner KH, Kamal-Eldin A, Elmadfa I. Gamma-tocopherol—an underestimated vitamin? Ann Nutr Metab. 2004;48:169-88. [PMID: 15256801]

3. Hensley K, Benaksas EJ, Bolli R, Comp P, Grammas P, Hamdheydari L, et al. New perspectives on vitamin E: gamma-tocopherol and carboxyelthylhydroxychroman metabolites in biology and medicine. Free Radic Biol Med. 2004;36:1-15. [PMID: 14732286]

4. Stone WL, Krishnan K, Campbell SE, Qui M, Whaley SG, Yang H. Tocopherols and the treatment of colon cancer. Ann N Y Acad Sci. 2004;1031:223-33. [PMID: 15753148]

5. Campbell S, Stone W, Whaley S, Krishnan K. Development of gamma (gamma)-tocopherol as a colorectal cancer chemopreventive agent. Crit Rev Oncol Hematol. 2003;47:249-59. [PMID: 12962899]

TO THE EDITOR: In their important meta-analysis focusing on the potentially harmful effects of vitamin E supplementation, Miller and colleagues (1) assumed that there may be a precise threshold level and that larger intakes of the vitamin would progressively increase the risk for harm. However, there may be biological heterogeneity between population groups, meaning that persons' characteristics would determine whether vitamin E supplementation causes net benefit or harm.

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, the effect of vitamin E on the risk for pneumonia was significantly modified by the age of smoking initiation ($P < 0.001$) (2). Vitamin E increased pneumonia risk in those who began smoking at age 20 years or earlier (relative risk, 1.14 [95% CI, 0.98 to 1.32]), but decreased pneumonia risk in participants who began smoking at later ages (relative risk, 0.65 [CI, 0.49 to 0.86]). Furthermore, in the latter subgroup, the benefit was greater among those who smoked less or quit smoking during the trial. Thus, less exposure to cigarette smoking was associated with greater benefit of vitamin E.

In the ATBC Study, the vitamin E dosage was 50 IU/d (50 mg/d of dl-α-tocopheryl acetate), which is substantially less than the threshold of 150 IU/d estimated by Miller and colleagues (1). However, from the subgroup differences described in the ATBC Study, it seems probable that some population groups experience ill effects at this low dosage while other persons benefit. Assuming that there is biological heterogeneity between population groups, further studies should characterize people who benefit from or are harmed by vitamin E rather than just estimating a uniform threshold for harm and presuming it is valid for everyone.

Harri Hemilä, PhD, MD
University of Helsinki
FIN-00014 Helsinki, Finland

Potential Financial Conflicts of Interest: None disclosed.

References

1. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37-46. [PMID: 15537682]
2. Hemilä H, Virtamo J, Albanes D, Kaprio J. Vitamin E and beta-carotene supplementation and hospital-treated pneumonia incidence in male smokers. Chest. 2004; 125:557-65. [PMID: 14769738]

TO THE EDITOR: Miller and colleagues (1) highlighted the danger of assuming the safety of high-dose vitamin E in the absence of definitive long-term safety data. The impact of their study, however, may be mitigated by methodologic concerns.

The first issue is the restrictive inclusion criteria stipulating that a trial have at least 10 deaths, apparently because the authors "anticipated that many small trials did not collect mortality data." This exclusion contradicts the raison d'être of meta-analysis, which involves the statistical pooling of multiple trials that individually have inadequate statistical power. The exclusion of at least 3 reasonably large, well-conducted trials (2–4) of high-dose vitamin E in which fewer than 10 deaths occurred and the inclusion only of trials meeting this arbitrary cutoff would spuriously increase the power of the meta-analysis. We would also be interested in the funnel plot analysis to determine whether publication bias affected the study results.

Although the authors attempted to adjust for average follow-up in their analysis, a more robust statistical treatment of the variance in follow-up periods across included trials would be to express the summary statistic of pooled death risk as the number of deaths per 10 000 person-years (as opposed to per 10 000 persons).

Heterogeneity in the study samples may not have been fully accounted for despite the use of the random-effects model and dosage differentiation. In particular, people with CVD may be a select group at distinct risk from the effects of high-dose vitamin E. Seven of the 8 high-dosage trials showing harmful effects of vitamin E involve participants with vascular risk factors or those who had established CVD. In contrast, the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study and the Alzheimer's Disease Cooperative Study (ADCS) used megadoses of vitamin E (2000 IU/d) in individuals with neurodegenerative disorders rather than in those with CVD but did not reveal safety concerns. A separate meta-analysis looking solely at neurodegenerative diseases (including a recent study using 5000 mg of vitamin E per day [5]) may be warranted.

Although Miller and colleagues' study may have focused on safety, the data ultimately challenge the advocates of high-dose vitamin E to reexamine the evidence for benefit. Efficacy in controlled trials ranges from minimal to modest, in contrast to the more positive results of observational studies. It is time for clinicians to return to the drawing board and review both the safety and efficacy data for vitamin E supplementation.

Wee-Shiong Lim, MBBS
Rajka M. Liscic, MD, PhD
Chengjie Xiong, PhD
John C. Morris, MD
Washington University School of Medicine
St. Louis, MO 63108

Potential Financial Conflicts of Interest: None disclosed.

References

1. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37-46. [PMID: 15537682]
2. Berson EL, Rosner B, Sandberg MA, Hayes KC, Nicholson BW, Weigel-DiFranco C, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. Arch Ophthalmol. 1993;111:761-72. [PMID: 8512476]
3. de Waart FG, Kok FJ, Smilde TJ, Hijmans A, Wollersheim H, Stalenhoef AF. Effect of glutathione S-transferase M1 genotype on progression of atherosclerosis in lifelong male smokers. Atherosclerosis. 2001;158:227-31. [PMID: 11500195]
4. Wluka AE, Stuckey S, Brand C, Cicuttini FM. Supplementary vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind randomized placebo controlled study. J Rheumatol. 2002;29:2585-91. [PMID: 12465157]
5. Graf M, Ecker D, Horowski R, Kramer B, Riederer P, Gerlach M, et al. High dose vitamin E therapy in amyotrophic lateral sclerosis as add-on therapy to riluzole: results of a placebo-controlled double-blind study. J Neural Transm. 2005;112:649-660. [PMID: 15517433]

TO THE EDITOR: In a meta-analysis of selected randomized trials, Miller and colleagues (1) found an increase in all-cause mortality associated with high-dosage vitamin E supplementation for at least 1 year (1). Their analysis included the DATATOP study, a randomized, placebo-controlled trial of selegiline and vitamin E in 800 patients with early Parkinson disease (2). In the DATATOP trial, 399 of 800 participants were randomly assigned to receive 2000 IU of vitamin E per day, the highest dosage studied in Miller and colleagues' meta-analysis. Median duration of vitamin E exposure during the randomized phase was 2.6 years. We have now accrued 13 years of follow-up and have documented 296 deaths compared with the 137 DATATOP deaths incorporated into Miller and colleagues' meta-analysis (3).

A slightly but not significantly higher proportion of patients randomly assigned to vitamin E had died by 13 years after enrollment (154 of 399 in the vitamin E group [39%] vs. 142 of 401 in the placebo group [35%]; $P = 0.35$). However, after adjustment for age and sex in a logistic regression, there was no excess mortality in the group assigned to vitamin E (odds ratio, 0.996 [95% CI, 0.72 to 1.38]; $P = 0.98$).

We also constructed a Cox model to make full use of survival information, incorporating duration of blinded exposure to vitamin E as a time-dependent covariate. We did not observe increased mortality for each additional year of exposure to vitamin E (hazard ratio, 1.05 [CI, 0.95 to 1.16]; $P = 0.31$). Similar results were obtained when both blinded and subsequent open-label tocopherol supplementation were considered.

We found no evidence of increased mortality in DATATOP related to 2.6 years of high-dosage vitamin E exposure through 13 years of observation. The DATATOP cohort was selected for absence of serious comorbid illness and was more highly educated than the general population. These and other differences in selection may