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Disclosure: Veena Kulchaiyawat, DO, has disclosed no relevant financial relationships.

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Trash the Vitamins: Convince Your Patients

A Best Evidence Review

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Posted: 01/05/2012

Best Evidence Review of Dietary Supplements and Mortality Rates in Older Women

Mursu J, Robien K, Harnack LJ, Park K, Jacobs Jr DR. Dietary supplements and mortality rate in older women. *Arch Intern Med.* 2011;171:1625-1633.

Dietary supplements are widely used by older adults, even though the effectiveness of these supplements in preventing illness is questionable. But can dietary supplements actually promote a higher risk for death? A new study suggests that the answer is yes for some of the most common supplements. This Best Evidence Review describes the findings of this study and puts these results in context.

Background

Vitamins and dietary supplements play an important role in the health and healthcare of many adults, and the business of supplements constitutes a multibillion-dollar industry worldwide. Based on the Third National Health and Nutrition Examination Survey, 40% of men and 50% of women older than 60 years of age consume at least 1 vitamin or mineral supplement.[1] A national survey by the US Food and Drug Administration found that 73% of US adults were found to use dietary supplements in 2002, providing annual sale costs in 2005 of over $20 billion.[2,3]

The widespread use of dietary supplements is not supported by practice guidelines. The US Preventive Services Task Force (USPSTF) states that there is insufficient evidence to recommend for

or against the use of vitamins A, C, E, or multivitamins with folic acid or antioxidants.[4] Specifically, the USPSTF cites concerns regarding the balance of benefits vs harms of these supplements. The American Medical Association recommends supplements specifically for seniors who have generalized decreased food intake, while the American Dietetic Association advises low-dose multivitamin and mineral supplements depending on individualized dietary assessment.[5] The American Heart Association emphasizes healthy eating patterns rather than supplementation with specific nutrients.[6]

These recommendations against the routine use of supplements are grounded in good evidence. A Cochrane intervention review of 77 randomized controlled trials with 232,550 participants found no evidence to recommend antioxidant supplementation for primary or secondary prevention of mortality.[7] Moreover, there is the possibility of harm related to the use of some supplements. For example, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial demonstrated that beta-carotene supplements increased the risk for lung cancer among male smokers.[8]

The Study

The study under discussion by Mursu and colleagues raises even more concerns regarding the safety of dietary supplements. The study enrolled 41,836 women between the ages of 55 and 69 years in 1986. Women completed validated food frequency questionnaires at baseline and in 2004, and the use of any of 15 different dietary supplements was queried in 1986, 1997, and 2004.

The main study outcome was the relationship between supplement use and all-cause mortality, which was assessed from state and national registries. Researchers adjusted this result to account for the following factors: age, energy intake, educational level, place of residence, smoking status, body mass index (BMI), waist-to-hip ratio, physical activity, diet composition, alcohol consumption, the use of estrogen therapy, and the presence of diabetes mellitus and hypertension. Serum lipids or blood pressure were not measured as part of the study.

A total of 38,772 women provided study data. The mean age of participants at enrollment was 61.6 years, and over 99% of women were white. The average BMI was 27 kg/m^2 at baseline and follow-up in 2004, and the majority of women were physically active. The average consumption of fruits and vegetables exceeded 6 servings per day during the study period. Out of this population, 36.8% of women reported hypertension, and 6.8% had diabetes.

The use of dietary supplements increased with time; 62.7% of women reported use of at least 1 supplement in 1986, and this figure rose to 85.1% by 2004. The most commonly used supplements were calcium, multivitamins, vitamin C, and vitamin E.

Women who used supplements generally had better health characteristics compared with nonusers. They had higher educational status, lower BMI and waist-to-hip ratio, and lower rates of diabetes and hypertension compared with nonusers, and they were also less likely to smoke and had a healthier dietary profile. Supplement users were also more likely to use estrogen therapy compared with nonusers.

There were 15,594 deaths (40.2% of the study cohort) during a mean follow-up period of 19 years. In fully adjusted models, the use of multiple supplements was associated with a higher risk for mortality, including multivitamins (hazard ratio [HR], 1.06; 95% confidence interval [CI], 1.02-1.10), vitamin B6 (1.10; 1.01-1.21), folic acid (1.15; 1.00-1.32), iron (1.10; 1.03-1.17), magnesium (1.08; 1.01-1.15), zinc (1.08; 1.01-1.15), and copper (1.45; 1.20-1.75). The use of vitamin A, beta-carotene, and selenium

were associated with nonsignificant trends toward a higher risk for mortality, and the use of vitamins C, D, and E had nearly no effect on mortality. In contrast, taking calcium supplements significantly reduced the risk for mortality (HR, 0.91, 95% CI, 0.88-0.94).

Researchers performed a number of additional analyses of the data to evaluate the validity of their outcomes. The main study results were not significantly changed after excluding women with a known history of cardiovascular disease or diabetes at baseline. An analysis using shorter follow-up intervals also confirmed the findings of higher risks for mortality with the use of iron. Moreover, there was evidence of a positive dose-response relationship between iron supplements and the risk for mortality. However, no dose-response effect was found for vitamins A, C, D, and E as well as the minerals selenium and zinc.

Commentary

The principal limitation of the current study was its observational nature, which leaves open the possibility of confounding by indication. Specifically, there is the possibility that women with higher risks for mortality or who developed serious chronic illnesses as they grew older had a wider use of supplements.

Nonetheless, it is worth remembering that women who used supplements had superior health characteristics compared with nonusers. Therefore, supplement users should have experienced a lower risk for death overall. While it is plausible that some women started taking multiple supplements when confronted with news of a severe illness, such as cancer, it is hard to imagine that this practice alone was common enough to tip the scales toward a higher overall risk for mortality associated with the use of supplements.

One of the more fascinating findings in this very interesting study is the higher risk for mortality associated with the use of iron supplements. Higher levels of serum iron and transferrin saturation have been associated with a lower risk for mortality.[9,10] However, another study found that men with a serum ferritin level of 200 mcg/L or more experienced more than a twofold increased risk for myocardial infarction.[11] Finally, both increased serum iron levels and higher transferrin saturation have been associated with an increased risk for death due to cancer.[12] Of course, in this study, women with existing anemia due to any number of chronic serious medical conditions, such as cancer or chronic kidney disease, could have been told to take iron supplements by their physician, and these illnesses might account for their higher mortality. In any case, it appears that the role of iron among adults without iron deficiency is controversial, and there is little data from clinical trials to suggest a benefit to the routine use of iron supplementation among adults.

An additional interesting finding in the current study is the effect of calcium, but not vitamin D, supplements in reducing the risk for mortality. This is another controversial area because calcium supplements have been implicated in promoting a higher risk for myocardial infarction among women.[13] However, in the Women's Health Initiative trial, the use of calcium plus vitamin D reduced the risk for some types of cancer without an overall effect on the risk for mortality.[14]

The findings from the current study offer several lessons to physicians. First, physicians need to pay close attention to nonprescription therapies used by patients. These treatments are routinely omitted from the history of many patients, but the current study suggests that physicians make such errors at the peril of their patients.

Physicians should be a trusted resource for patients interested in dietary supplements. We can help balance self-treatment practices that might be effective against those that appear harmful or excessive. The findings of the current study should be sobering for the most ardent supporters of supplements, and patients need to understand the potential risks inherent in the treatment choices they make.

Clinical Pearls

- Nearly half of older adults routinely use dietary supplements, with higher rates of use among women compared with men.
- The routine use of many dietary supplements is discouraged in practice guidelines.
- The use of multivitamins, vitamin B6, folic acid, iron, magnesium, zinc, and copper was associated with a higher risk for mortality among older women in the current study.
- Conversely, calcium supplements were associated with a lower risk for mortality.
- Physicians need to analyze nonprescription therapies used by patients and warn them of potential harms associated with the use of supplements.

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