Vitamin E and Cardiovascular Health
Does Sex Matter?

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The critical importance of preventive medicine for all people has long been recognized, as documented in the writings of Hippocrates and Osler. Moreover, in preventive health, it is clear that sex matters, as the 2001 Institute of Medicine report concluded after reviewing the basis for biological differences in health.

The goal of preventing cardiovascular disease is similar in men and women. However, the strategies and recommendations to achieve this goal differ, as exemplified in the 2004 American Heart Association Guidelines for Cardiovascular Disease Prevention in Women. Although it is increasingly well known and appreciated that heart disease is the leading cause of death in both women and men, it is also true that researchers are increasingly discovering sex differences in how cardiovascular disease may be prevented and treated.

All prevention, as well as treatment, involves some degree of balancing benefit and risk. The attractiveness of a particular strategy depends on the magnitude of the risk/benefit ratio. Put simply, it is difficult to improve the health of individuals who largely (apparently) have nothing wrong with them. Yet from a societal viewpoint, it is still reasonable to recommend a preventive therapy to individuals at very low risk; even though individual patient benefits are very small, the population benefits are huge.

This principle is applied in legislation mandating use of childhood vaccines. However, this strategy only works if the possible risks are trivial—even a low risk of harm (eg, Guillain-Barré syndrome from swine flu shots) cannot be justified.

Sex-specific benefits and risks can differ for many reasons, such as that the incidence and prevalence of coronary heart disease are lower in women than in men until after the sixth decade. For example, according to recent data from the Women’s Health Study (WHS), aspirin provides no benefit in healthy women (except in the subgroup of those aged 65 years or older), even though previous studies have shown a benefit in healthy men. Similarly, like studies in men, numerous statin trials in the last decade have not shown a benefit on total or coronary heart disease mortality in women.

In this issue of JAMA, Lee et al report on another promising prevention strategy, vitamin E, which earlier epidemiologic and observational studies suggest provides cardiovascular benefits in men and women. Vitamin E is a powerful biological antioxidant that can protect cells against the ravages of free radicals. Thus, there has been great interest in the value of vitamin E for preventing heart disease and cancer. Vitamin E is found in vegetable oils, nuts, green leafy vegetables, and fortified cereals, among other foods.

So how does vitamin E supplementation compare with other primary prevention strategies for women? Until publication of the Heart and Estrogen/progestin Replacement Study (HERS) in 1998, followed by the Women’s Health Initiative (WHI) a few years later, postmenopausal hormone therapy was the most popular primary prevention strategy for women. Hormone therapy has plausible pathophysiological mechanisms for cardiovascular risk reduction, such as lipid lowering and favorable vascular effects. In addition, epidemiologic and observational studies have suggested a benefit of hormone therapy on cardiovascular disease. However, after randomized controlled trials showed no benefit on total or cardiovascular mortality and in fact found increased cardiovascular events in the first year of use, hormone therapy has plummeted from 90 million US prescriptions annually between 1999 and 2002 to a drug with a black box warning on its label.

Like hormone therapy, vitamin E has plausible mechanisms and data from observational studies to support a meaningful role in prevention of cardiac disease. Data from approximately 90 000 women in the Nurses’ Health Study showed a 30% to 40% decrease in heart disease for women taking vitamin E supplements, after adjustment for risk factors for coronary disease and use of other antioxidant nutrients.

In this issue of JAMA, Lee et al report their findings from the WHS on the effects of 600 IU of vitamin E vs placebo every other day in 39 876 healthy women followed up for an average of 10 years. The investigators found no benefit...
of vitamin E on the primary outcome measure: a composite end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The participants in WHS were at very low risk; only 1100 of 28,000 women screened had a greater than 10% 10-year risk of coronary heart disease by Framingham scoring. It was not stated if any of the WHS participants had a more than 20% 10-year risk, a level considered high risk.

In an analysis of 13 different subgroups (Table 3 in the article by Lee et al), the only analysis to show a significant interaction with the end point of major cardiovascular events was stratification by age. Similar to the aspirin results in the WHS, only women older than 65 years randomized to vitamin E showed a benefit, with a relative risk of 0.74 for major cardiovascular events. Notably, this older subgroup accounted for 31% of major cardiovascular events, although the subgroup comprised only 10% of the WHS population. During 10 years of follow-up, the total event rate was 1.3% in the 45- to 54-year-old population compared with 7.5% in those older than 65 years. Clearly, even older women were still in a low-risk group and the middle-aged women were at extremely low risk.

Do further questions on vitamin E remain after this large study with long-term follow up? Was the population of the WHS just too low-risk of a cohort to be able to demonstrate a benefit of vitamin E? At what point do clinical researchers stop adjusting doses, follow-up periods, and types of preparations of vitamin E and conclude no benefit? Vitamin E, in doses greater than 400 IU/d, has also been associated with harm—specifically, an increased mortality risk. A dose-response analysis reported in a meta-analysis by Miller et al showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk at dosages greater than 150 IU/d. The study by Lee et al also noted increased mortality (4%) for women taking 600 IU vitamin E every other day. Although the increase was not statistically significant, in a healthy low-risk population it is difficult to justify an intervention with no proven benefit and a suggestion of harm.

Perhaps it is time to consider devoting some of the limited resources necessary to perform randomized controlled trials to other pressing, unanswered questions in the field of cardiovascular disease prevention in women. With the publication of the WHS vitamin E results, it is time to redirect attention to interventions that have been shown to or could provide significant benefit. For example, lifestyle changes—such as heart-healthy diets, daily walking or other exercise, and smoking cessation—are underused but proven prevention strategies for heart disease. Interestingly, these positive lifestyle changes are also associated with the prevention of cancer and Alzheimer disease. Data from epidemiologic studies and a single trial had suggested that vitamin E would slow progression of Alzheimer disease, but in a recent double-blind study, vitamin E showed no benefit in patients with mild cognitive impairment. However, lifestyle changes, such as increasing physical activity, have been shown to slow decline of cognitive function in women.

A Mediterranean diet that includes more fruits and vegetables and less fats has been shown to reduce the risk of coronary heart disease. In the United States, physical inactivity is rampant and is more prevalent among women than men. Data from the Centers for Disease Control and Prevention show that more than one third of white women are physically inactive, as are more than one half of black and Hispanic women. The relative risk of coronary heart disease associated with physical inactivity ranges from 1.5 to 2.4, comparable to that for smoking, high blood pressure, or high cholesterol. Data from the WHI Observational Study show that increasing physical activity had a strong, graded, inverse association with the risk of both coronary events and total cardiovascular events among white and black women, with a risk reduction of greater than 50% for women in the highest quintile of physical activity. Walking and vigorous exercise were associated with similar risk reductions, and the results applied to women of all categories of race, age, and body mass index. Fewer hours spent sitting daily also predicted lower risk. Diet and physical activity are also effective preventive measures for obesity, now increasing in epidemic proportions. More than half of white women are overweight or obese, compared with about three fourths of black and Mexican American women. In addition, psychosocial interventions to relieve isolation, decrease depression, and promote laughter are largely unstudied but promising therapies. In fact, there are some data suggesting that humor and laughter can decrease cardiac risk.

Thus, vitamin E enters the category of therapies that were promising in epidemiologic and observational studies but failed to deliver in adequately powered randomized controlled trials. As in other studies, the “healthy user” bias must be considered, ie, the healthy lifestyle behaviors that characterize individuals who care enough about their health to take various supplements are actually responsible for the better health, but this is minimized with the rigorous trial design.

It is estimated that almost 1 million preventable deaths per year are due to smoking, poor diet, and physical inactivity. Perhaps the most important outcome of the WHS reports will be greater recognition that it is time to concentrate on teaching nutrition, promoting regular physical activity, and strongly encouraging smoking cessation and particularly increasing outreach to women of racial and ethnic minorities. Clearly, no adverse effects can come of such recommendations, even in an already low-risk population.

The Physicians’ Health Study results on vitamin E in healthy men are not expected until late 2008. Although vitamin E is not a successful primary prevention strategy for women,
one should not make the mistake of concluding that it will not turn out to be beneficial for men. The WHS highlights the importance of recognizing biological differences between the sexes in cardiovascular research by providing valuable sex-specific data on primary prevention.

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REFERENCES