Vitamin Supplement Use in a Low-Risk Population of US Male Physicians and Subsequent Cardiovascular Mortality

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Background: Although basic research suggests that vitamins may have an important role in the prevention of cardiovascular diseases (CVD), the data from cohort studies and clinical trials are inconclusive.

Methods: This prospective cohort study was conducted among 83,639 male physicians residing in the United States who had no history of CVD or cancer. At baseline, data on use of vitamin E, ascorbic acid (vitamin C), and multivitamin supplements were provided by a self-administered questionnaire. Mortality from CVD and coronary heart disease (CHD) was assessed by death certificate review.

Results: Use of supplements was reported by 29% of the participants. During a mean follow-up of 5.5 years, 1037 CVD deaths occurred, including 608 CHD deaths. After adjustment for several cardiovascular risk factors, supplement use was not significantly associated with total CVD or CHD mortality. For vitamin E use, the relative risks (RRs) were 0.92 (95% confidence interval [CI], 0.70-1.21) for total CVD mortality and 0.88 (95% CI, 0.61-1.27) for CHD mortality; for use of vitamin C, the RRs were 0.88 (95% CI, 0.70-1.12) for total CVD mortality and 0.86 (95% CI, 0.63-1.18) for CHD mortality; and for use of multivitamin supplements, the RRs were 1.07 (95% CI, 0.91-1.25) for total CVD mortality and 1.02 (95% CI, 0.83-1.25) for CHD mortality.

Conclusions: In this large cohort of apparently healthy US male physicians, self-selected supplementation with vitamin E, vitamin C, or multivitamins was not associated with a significant decrease in total CVD or CHD mortality. Data from ongoing large randomized trials will be necessary to definitely establish small potential benefits of vitamin supplements on subsequent cardiovascular risk.

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Oxidative processes may play an important role in the pathogenesis of atherosclerosis. In vitro and in vivo studies suggest that oxidized low-density lipoprotein may promote several steps in atherogenesis, including endothelial cell damage, foam cell accumulation, and growth, and induction of autoantibody formation. Vitamin E and ascorbic acid (vitamin C) might prevent or retard various steps in atherogenesis by inhibiting oxidation of low-density lipoprotein and other free radical reactions. In many animal models, vitamin E has been shown to prevent early steps of atherogenesis. Folic acid and B vitamins are ingredients of most multivitamin formulations. Low plasma levels of these vitamins are associated with increased homocysteine levels. During oxidation of homocysteine, potent reactive oxygen products are formed, including superoxide and hydrogen peroxide. Elevated homocysteine levels are implicated in many untoward effects on vessel walls, including endothelial cell damage and dysfunction, stimulation of smooth muscle cell proliferation, and increased adherence of platelets and coagulation products to the endothelium.

Human observational studies have raised the possibility of an inverse relationship between vitamin supplementation and the risk of cardiovascular disease (CVD). Vitamin E supplements have been associated with a decrease in risk of CVD events in most but not all studies. Vitamin C supplementation has been associated with a reduced risk in few studies, and had no apparent effect in others. Although there is evidence that higher serum levels of folic acid and some B vitamins are associated with decreased homocysteine levels, the role of supplementation with multivitamins in prevention of CVD has not been thoroughly studied. Intake of multivitamins was associated with a modest risk reduction in 1 large cohort among women, but another observational study found no association.
SUBJECTS AND METHODS

STUDY POPULATION

The Physicians’ Health Study was a randomized, double-blind, placebo-controlled trial that tested 2 primary-prevention hypotheses: (1) whether 325 mg of aspirin taken every other day reduces risk of CVD, and (2) whether 50 mg of beta carotene (vitamin A) taken on alternate days decreases the incidence of cancer. Potentially eligible participants in the Physicians’ Health Study were male physicians aged 40 to 84 years in 1982 who resided in the United States and were without a history of myocardial infarction, stroke, or cancer. Letters of invitation, informed consent forms, and baseline questionnaires were mailed to the 261,248 physicians who were listed on an American Medical Association mailing tape by December 31, 1983. 10,333 physicians had answered the enrollment questionnaire. We excluded 17,224 participants (16.5%) with a history of CVD (myocardial infarction or angina pectoris, stroke or transient ischemic attack, or use of digitalis, nitrates, or warfarin sodium) and/or cancer except nonmelanoma skin cancer. Participants with no information on vitamin supplementation (n = 3,490; 3.3%) were also excluded. This left 83,639 participants for the analyses.

DATA COLLECTION

On the enrollment questionnaire, respondents reported their age, history of a number of diseases, medications, and risk factors. Study participants also gave information on current use of vitamins E, C, and A and multivitamin supplements. The number of years of vitamin supplementation was reported, as was the brand and the number of vitamin pills taken per week. From this information, we estimated the average daily dose of single vitamins E and C supplements.

RESULTS

Randomized trial data on the effect of vitamins E and C and multivitamin supplements in prevention of CVDs are limited and inconsistent. There are no completed large-scale randomized trials that have tested the benefits or risks of vitamin C or multivitamin supplementation in primary or secondary prevention of CVD. Results from randomized trials of vitamin E supplementation in primary prevention are limited, and secondary prevention results are inconsistent. To provide further information on the role of antioxidant vitamins, including multivitamins, in prevention of CVDs, we studied this issue in a large cohort of US male physicians.

Of the 83,639 participants, 24,270 (29.0%) were current users of 1 or more supplements of vitamin E, vitamin C, or multivitamins. Among those, 6,466 (7.7%) used vitamin E, and 10,512 (12.6%) used vitamin C supplements. The preparations most often used were multivitamins (20,549; 24.6%). Most users of specific vitamin E and C supplements took high daily average doses of these vitamins. For example, 64% of users of vitamin E supplements took 400 IU or more per day from supplements, while only 1.0% reported intake of less than 100 IU per day. Similarly, 73% of users of vitamin C supplements took an average of 500 mg or more per day. A large proportion of participants taking vitamin supplements were long-term users: 49% of vitamin E users, 52% of vitamin C users, and 54% of multivitamin users reported taking supplements for 4 years or longer at baseline. Table 1 summarizes the baseline characteristics of participants taking vitamin E, vitamin C, and multivitamin supplements compared with those who did not report supplement use. Users of vitamin supplements were more likely to be diabetic and/or hypertensive. Participants using vitamin supplements were more likely than nonusers to report exercising regularly and were leaner; users of vitamins E and C were less likely to be current smokers. Self-reported blood pressure and cholesterol levels were similar among users and nonusers of vitamin supplements.

During a mean follow-up period of 5.5 years, there were 1,037 total CVD deaths and 608 CHD deaths. The RRs of CVD and CHD mortality according to supplement use are summarized in Table 2. Age-adjusted and multivariate-adjusted models were not materially different. Compared with nonusers, among those taking vita-
We performed secondary analyses to explore whether subgroups of this cohort potentially benefited from vitamin supplements (Table 3). Among physicians who took 500 mg of vitamin C or more per day, the risk of CVD mortality tended to be reduced (RR, 0.81; 95% CI, 0.57-1.13). Conversely, among those taking high daily doses of vitamin E and at least daily multivitamin supplements, the risk of total CVD mortality was slightly elevated (RR, 1.09; 95% CI, 0.74-1.59 for vitamin E; RR, 1.11; 95% CI, 0.89-1.37 for multivitamins), but these results were far from statistical significance. Long-term intake of vitamin E was associated with a tendency toward reduced risk (RR, 0.82; 95% CI, 0.54-1.24), but there was no relationship between duration of supplement intake and cardiovascular risk for vitamin C and multivitamins. Among the subgroup of users of vitamins E and C supplements without major cardiovascular risk factors at baseline, there was an indication toward a decrease in risk of total CVD mortality (RR, 0.72; 95% CI, 0.44-1.18) and CHD mortality (RR, 0.68; 95% CI, 0.46-1.02).

In this large prospective cohort study among apparently healthy US male physicians, use of vitamin E, vitamin C, and multivitamin supplements was not significantly associated with a decrease or increase in risk of total CVD mortality or CHD mortality. There were nonsignificant trends toward lower risk associated with use of vitamin C and vitamin E supplementation among those without cardiovascular risk factors.

In observational primary prevention studies, vitamin E supplementation has been associated with a reduction in cardiovascular risk of 20% to 40% in most, but not all, studies. Several randomized trials of vitamin E supplements among high-risk populations have been published. In the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study, in which current smok-
ers—including those with a history of myocardial infarction—were randomized to vitamin E (50 mg/d) or placebo regimens. CVD mortality was similar between the 2 groups (RR, 0.98 for the vitamin E group compared with placebo). The dose of vitamin E used in this trial was lower than that associated with decreased risk in observational studies, and it has been suggested that this dose might have been too low to exhibit a protective effect. In the Cambridge Heart Antioxidant Study (CHAOS), conducted among patients with established CHD, the primary end point of combined fatal and nonfatal cardiovascular events was significantly reduced among those randomized to vitamin E. While CVD mortality was nonsignificantly increased by 18%, the number of deaths was very small. In the Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) trial, vitamin E reduced the risk of CVD events. However, in 3 other trials, the Primary Prevention Project (PPP), and the Heart Outcomes Prevention Evaluation (HOPE) study, all conducted among high-risk patients or those with CHD, vitamin E supplementation did not reduce CVD event rates. In the GISSI trial there was a nonsignificant trend toward lower CVD rates among those assigned to vitamin E. The RR of CHD mortality among those randomized to vitamin E were 0.94 for CVD mortality and 0.91 for CHD mortality. In our observational primary prevention study, the RRs for total CVD (0.92) and CHD (0.88) mortality were very close to the latter results. Among participants who took supplements of 400 IU of vitamin E or more per day, there was no evidence for a larger benefit. In subgroups of participants without major cardiovascular risk factors at baseline and among long-term users, intake of vitamin E supplements was compatible with a small benefit, but the CIs were wide.

Compared with data on vitamin E use, observational evidence that intake of vitamin C supplements decreases CVD risk is weaker. and clinical trial results are not yet available. As was the case for vitamin E, in this cohort the RR of CHD mortality among users of vitamin C was slightly lower than among nonusers. Among participants who used higher daily supplement doses and in those without major cardiovascular risk factors at baseline, the apparent risk reduction was more pronounced. These subgroup findings may be due to chance or uncontrolled subgroup confounding, or they may represent a true small benefit of vitamin C supplementation.

While most multivitamins contain lower amounts of antioxidants than single-vitamin supplements, they contain other potentially beneficial ingredients. In particular, folic acid and B vitamins may be beneficial by lowering serum homocysteine levels. In a cohort of US nurses, multivitamin use was associated with a small but statistically significant 24% reduction in cardiovascular risk, and a 29% reduction among long-term users but there was no apparent benefit found in another observational study. In our cohort, we found neither an increase nor a decrease in risk among users of multivitamins. This lack of association was stable across subgroups. Specifically, long-term users of multivitamins had an RR for CVD mortality of 1.02. Further studies are necessary to determine whether use of multivitamins can decrease cardiovascular risk in adequately nourished populations, or whether population segments with low intake of fruits and vegetables benefit from multivitamin use.

Our study has several potential limitations. We were able to adjust our models for traditional cardiovascular risk factors, and the similarity of age-adjusted and multivariate-adjusted models suggests that residual confounding by these known variables is unlikely. However, this does not exclude residual confounding because self-selection for vitamin intake may be associated with uncontrolled or uncontrollable confounders. For example, if a larger proportion of participants with unreported diseases used vitamin supplements than truly healthy participants, the risk estimates would tend to be biased toward no benefit or an increase in risk. Conversely, in observational studies there is a possible bias toward an overestimation of the benefits of vitamin supplementation. In addition to healthier lifestyle practices and a more favorable cardiovascular risk profile among supplement users, other factors might account for a distortion of the risk estimates toward an apparent benefit, including improved access to health care or better knowledge of medical conditions requiring urgent treatment. Because our cohort consists of physicians, these potential sources of confounding should be smaller than in most other observational studies.

Another potential limitation of our study is that we had no measurements of adherence to vitamin use dur-

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Table 3. Subgroup Analysis for Relative Risks Among Participants Taking Vitamin Supplements

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E Supplementation</th>
<th>Ascorbic Acid (Vitamin C)</th>
<th>Vitamins E and C</th>
<th>Multivitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CVD mortality</td>
<td>1.09 (0.74-1.59)</td>
<td>0.81 (0.57-1.13)</td>
<td>0.91 (0.67-1.23)</td>
<td>1.11 (0.89-1.37)</td>
</tr>
<tr>
<td>High-dose supplementation†</td>
<td>0.82 (0.54-1.24)</td>
<td>0.87 (0.62-1.23)</td>
<td>0.88 (0.64-1.20)</td>
<td>1.02 (0.82-1.27)</td>
</tr>
<tr>
<td>Supplement intake for ≥4 y at baseline</td>
<td>0.72 (0.44-1.18)</td>
<td>0.68 (0.46-1.02)</td>
<td>0.66 (0.46-0.93)</td>
<td>1.13 (0.88-1.45)</td>
</tr>
<tr>
<td>CHD mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose supplementation†</td>
<td>0.80 (0.45-1.42)</td>
<td>0.81 (0.51-1.28)</td>
<td>0.84 (0.56-1.27)</td>
<td>0.97 (0.72-1.31)</td>
</tr>
<tr>
<td>Supplement intake for ≥4 y at baseline</td>
<td>0.41 (0.19-0.85)</td>
<td>0.91 (0.57-1.44)</td>
<td>0.75 (0.48-1.18)</td>
<td>0.91 (0.67-1.22)</td>
</tr>
<tr>
<td>Without major CVD risk factors‡</td>
<td>0.71 (0.36-1.38)</td>
<td>0.65 (0.37-1.13)</td>
<td>0.59 (0.36-0.96)</td>
<td>1.01 (0.37-1.42)</td>
</tr>
</tbody>
</table>

*All data are relative risks (95% confidence intervals) adjusted for history of hypertension, history of hypercholesterolemia, diabetes mellitus, current and past smoking, alcohol intake, body mass index, complementary vitamins, and randomization status. CVD indicates total cardiovascular disease.

†Models for mean daily vitamin E supplementation of 400 IU or more, vitamin C of 500 mg/d or more, and multivitamins of 1 or more pills per day, respectively.
‡Participants without hypertension, hypercholesterolemia, or diabetes mellitus, and not current smokers.
ing the follow-up period. It is likely, however, that among long-term users at baseline, supplement intake remained fairly stable during the follow-up period, and in this subgroup the associations were close to those for the whole cohort. Similarly, if many physicians had started using vitamin supplements during the observation period, the result could be biased toward no effect. However, during this period, large cohort studies suggesting a benefit of vitamin supplements had not yet been published, and vitamin supplement intake was stable in the US general population. 28 Misclassification of non-CVDs as CVDs on death certificates could potentially attenuate the estimate of a benefit of vitamin supplementation.

In the randomized part of the cohort, however, death certificate diagnoses of CVD agreed very well with confirmation from hospital records. As our study included a population of well-nourished men, the results cannot be extended to poorly nourished populations.

In conclusion, in this large cohort of apparently healthy US male physicians, there was no clear decrease or increase in mortality from total CVD or CHD among users of vitamin E, vitamin C, and multivitamin supplements. There was a suggestion of benefit among those at low risk. Because our study is observational, these data cannot be extended to poorly nourished populations.

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