Prospective Cohort Study of Antioxidant Vitamin Supplement Use and the Risk of Age-related Maculopathy

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In a prospective cohort study, the authors examined whether self-selection for antioxidant vitamin supplement use affects the incidence of age-related maculopathy. The study population consisted of 21,120 US male physician participants in the Physicians' Health Study I who did not have a diagnosis of age-related maculopathy at baseline (1982). During an average of 12.5 person-years of follow-up, a total of 279 incident cases of age-related maculopathy with vision loss to 20/30 or worse were confirmed by medical record review. In multivariate analysis, as compared with nonusers of supplements, persons who used vitamin E supplements had a possible but nonsignificant 13% reduced risk of age-related maculopathy (relative risk = 0.87, 95 percent confidence interval (CI) 0.53–1.43), while users of multivitamins had a possible but nonsignificant 10% reduced risk (relative risk = 0.90, 95% CI 0.68–1.19). Users of vitamin C supplements had a relative risk of 1.03 (95% CI 0.71–1.50). These observational data suggest that among persons who self-select for supplemental use of antioxidant vitamin C or E or multivitamins, large reductions in the risk of age-related maculopathy are unlikely. Randomized trial data are accumulating to enable reliable detection of the existence of more plausible small-to-moderate benefits of these agents alone and in combination on age-related maculopathy. Am J Epidemiol 1999;149:476–84.

antioxidants; maculopathy, age-related; prospective studies; vitamins

Basic research studies suggest that vitamins with antioxidant properties may help reduce the risk of age-related maculopathy, the leading cause of new cases of blindness in persons aged 65 years or older in the United States (1). A number of antioxidant vitamins, primarily the carotenoids lutein and zeaxanthin but also vitamin C (ascorbate) (2–4) and vitamin E (α-tocopherol) (5, 6), have been localized in the retina and are available to protect against the toxic effects of oxygen. Carotenoids and vitamin E are lipid-soluble oxidant scavengers that protect biomembranes, and vitamin C is a water-soluble antioxidant that also promotes regeneration of vitamin E and may spare carotenoids (7, 8). Results from several animal models show that dietary restriction of antioxidants can induce degenerative changes in the retina (4, 9–14), whereas dietary supplementation with antioxidants protects against the cumulative effects of oxidative stress (3, 9, 15–18).

To date, epidemiologic studies of humans are limited and inconclusive. Although results from most cross-sectional (19, 20) and case-control (21–26) studies generally suggest a possible protective role for high dietary or plasma levels of micronutrients, data regarding specific micronutrients and specific types of age-related maculopathy are inconsistent (27). The limited available data on vitamin supplement use also conflict (20, 21, 25, 26). This inconsistency may be due, at least in part, to uncontrolled confounding in all observational studies and/or inherent limitations of specific study designs. For example, in cross-sectional and case-control studies, the temporal relation between nutritional intake and age-related maculopathy can be difficult or impossible to determine. Additionally, in dietary studies, recall bias as an alternative explanation for any observed association can be difficult to
exclude. To our knowledge, there have been no prospective studies of the relation between antioxidant nutrients and age-related maculopathy.

We therefore examined prospectively the relation between self-selected use of vitamin supplements and the incidence of age-related maculopathy in the Physicians' Health Study I (PHS I), a randomized trial of aspirin and beta-carotene among US male physicians 40–84 years of age at entry in 1982. Because smokers may have higher levels of oxidative stress (28–32), we also examined whether the relation between vitamin supplement use and age-related maculopathy varied according to cigarette smoking.

MATERIALS AND METHODS

Study population

The study population consisted of participants in the US PHS I, a randomized, double-blind, placebo-controlled trial of aspirin (325 mg on alternate days, supplied as Bufferin (Bristol-Meyers Squibb Company, Princeton, New Jersey)) in preventing cardiovascular disease and beta-carotene (50 mg on alternate days, supplied as Lurotin (BASF Corporation, Ludwigshafen, Germany)) in preventing cancer and cardiovascular disease among 22,071 US male physicians aged 40–84 years in 1982. Follow-up information on compliance with the treatment regimen, adverse effects, and the occurrence of relevant endpoints was collected by mail via annual health questionnaires.

At baseline, physicians provided information on dietary supplement use, including whether they had ever regularly taken capsules containing only vitamin A, only vitamin C, only vitamin E, or multivitamins (never, past only, current). For each vitamin used currently, physicians reported the number of years they had taken it. Only those physicians who reported current use of vitamin supplements were classified as supplement users in these analyses. (Physicians who reported using individual supplements of vitamin A were ineligible for enrollment in the PHS I study since beta-carotene was an assigned treatment.) Because a complete dietary questionnaire was not administered, food sources of antioxidant nutrients were not considered in this analysis. Information was provided on a number of baseline characteristics including cigarette smoking, alcohol consumption, history of diabetes mellitus, history of hypertension, height, weight, physical activity, and parental history of myocardial infarction.

Information about a previous diagnosis of age-related maculopathy was requested initially on the 84-month questionnaire. Physicians were asked, "Have you ever had macular degeneration diagnosed in your right (left) eye?" If they answered yes, they were requested to provide the month and year of diagnosis. Subsequent annual questionnaires asked about a new diagnosis of age-related maculopathy since the previous questionnaire. Signed permission to examine medical and hospital records pertaining to the diagnosis was also requested on the questionnaire and in separate follow-up mailings when necessary. This report includes information on the 21,120 participants who provided complete information about vitamin supplement use, did not report a diagnosis of age-related maculopathy that was made before they entered the study, and were followed for at least 7 years (i.e., physicians who died during the first 7 years of follow-up and therefore did not respond to the 84-month questionnaire were excluded). The average follow-up time for age-related maculopathy was 12.5 person-years.

Ascertainment and definition of endpoints

Medical record information was sought for all participant reports of age-related maculopathy. Following the report of a diagnosis of age-related maculopathy and the receipt of written consent, ophthalmologists and optometrists were contacted by mail and were requested to complete a questionnaire supplying information about the date of initial diagnosis of age-related maculopathy, the best-corrected visual acuity at the time of diagnosis, and the date on which visual acuity reached 20/30 or worse (if different from the date of initial diagnosis). Information was also requested about the pathologic findings observed (drusen, retinal pigment epithelium (RPE) hypopigmentation/hyperpigmentation, geographic atrophy, RPE detachment, subretinal neovascular membrane, or disciform scar) when visual acuity was first noted to be 20/30 or worse and the date on which exudative macular degeneration was first noted (defined by the presence of RPE detachment, subretinal neovascular membrane, or disciform scar). In addition, we asked whether there were other ocular abnormalities that would explain or contribute to visual loss and, if so, whether the age-related maculopathy by itself was significant enough to cause vision to deteriorate to 20/30 or worse.

This analysis considers cases of age-related maculopathy that impair visual acuity and thus are more likely to be clinically meaningful. Two categories of the diagnosis of age-related maculopathy were defined:

1. Age-related maculopathy with vision loss: a self-report confirmed by medical record evidence of an initial diagnosis of age-related maculopathy subsequent to randomization and vision loss to
20/30 or worse attributable to age-related maculopathy
2. Exudative macular degeneration: as in category 1 but including a diagnosis of exudative macular degeneration

As of October 1995, 773 of the 809 (95.6 percent) physicians who reported age-related maculopathy had consented to a review of medical records. Medical record data were obtained and were reviewed for 752 (93.0 percent) reports. For 556 reports, medical record review confirmed a diagnosis of age-related maculopathy with or without vision loss (reports not confirmed as age-related maculopathy were generally confirmed as other retinal pathologies such as macular hole, epiretinal membrane, and central serous chorioretinopathy), and 451 were confirmed as incident cases, initially diagnosed after study randomization. Of these, 279 cases were responsible for vision loss to 20/30 or worse, and 68 were confirmed as exudative macular degeneration.

Data analysis

Persons rather than eyes were the unit of analysis because eyes were not examined independently, and participants were classified according to the status of the worse eye based on disease severity. Participants contributed person-years of experience until they developed confirmed age-related maculopathy or until October 1995.

We computed incidence rates of age-related maculopathy by dividing the numbers of incident cases by person-years of follow-up in each category of supplement use. In initial analyses, we compared rates in four mutually exclusive categories of vitamin supplement use: vitamins C and/or E only, multivitamins only, multivitamins plus vitamins C and/or E, and no supplement use. Relative risks were computed as the rate of age-related maculopathy in a specific category of supplement use divided by the corresponding rate among nonusers. We also computed relative risks for each supplement by comparing rates of age-related maculopathy among users of a particular supplement (with or without other supplements) with rates among nonusers of supplements in separate models for each supplement.

Crude estimates of relative risks were obtained by controlling for age (in years) and randomized aspirin and beta-carotene assignment in Cox proportional hazards regression models. To control for multiple potential confounders, we added indicator terms for smoking (never, past, current), alcohol consumption (daily, weekly, monthly, rarely), history of diabetes, history of hypertension (systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 95 mmHg or higher, or history of treatment for high blood pressure), obesity (body mass index of 27.8 kg/m² or more), physical activity (reported vigorous exercise once or more per week), and parental history of myocardial infarction. Models were also fit in which we controlled for pack-years of smoking (33). Because relative risks obtained by using these models were virtually identical to those from models that controlled for categories of smoking (never, past, current), only the latter are presented here.

As cigarette smokers versus nonsmokers may have higher overall levels of oxidative stress (28-32), we also conducted stratified analyses to evaluate any possible modification of the association between vitamin supplement use and age-related maculopathy by category of smoking (ever vs. never). Those persons not using supplements were the referent in each category of smoking. We examined the validity of the proportional hazards assumption throughout the follow-up period by considering interactions between time and the effects of vitamin supplementation. We found no significant interactions suggesting that the proportional hazards assumption was reasonable. For each relative risk, two-sided p values and 95 percent confidence intervals were calculated (34).

RESULTS

The distribution of baseline characteristics according to mutually exclusive categories of vitamin supplement use is shown in table 1. At baseline, 4.0 percent of the physicians reported vitamin C and/or E supplementation only, 12.2 percent reported multivitamin use only, and 7.2 percent reported multivitamin plus vitamin C and/or E use. Vitamin supplement users were older and, after adjustment for age, tended to report more hypertension, more physical activity, and less obesity than nonusers.

During an average of 12.5 person-years of follow-up, 279 incident cases of age-related maculopathy responsible for a reduction in visual acuity to 20/30 or worse were confirmed by medical record review. Sixty-eight of these cases were confirmed as exudative macular degeneration.

The retinal signs of age-related maculopathy observed when visual acuity was first noted to be 20/30 or worse are presented in table 2. The most common manifestation of age-related maculopathy was a combination of drusen and RPE changes, noted in 34.8 percent of cases. RPE changes alone and drusen alone were observed in 23.7 percent and 10.0 percent of cases, respectively. In 21.9 percent of cases, one or more signs of exudative disease (RPE detachment, subretinal neovascular membrane, disci-
TABLE 1. Age-adjusted prevalences* of baseline characteristics that are possible risk factors for age-related maculopathy among study participants, by baseline vitamin supplement use, Physicians' Health Study I, 1982-1995

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Vitamins C and/or E only (n = 849)</th>
<th>Multivitamins only (n = 2,582)</th>
<th>Multivitamins, vitamins C and/or E (n = 1,531)</th>
<th>No vitamins (n = 16,158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>37.0</td>
<td>32.9</td>
<td>34.9</td>
<td>44.7</td>
</tr>
<tr>
<td>50-59</td>
<td>35.9</td>
<td>33.4</td>
<td>35.5</td>
<td>34.1</td>
</tr>
<tr>
<td>60-69</td>
<td>20.0</td>
<td>24.4</td>
<td>21.3</td>
<td>16.5</td>
</tr>
<tr>
<td>70-84</td>
<td>7.1</td>
<td>9.3</td>
<td>8.3</td>
<td>4.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9</td>
<td>2.9</td>
<td>2.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>15.6</td>
<td>15.6</td>
<td>13.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Obesity‡</td>
<td>9.9</td>
<td>12.3</td>
<td>10.9</td>
<td>14.2</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>23.8</td>
<td>26.9</td>
<td>26.5</td>
<td>24.0</td>
</tr>
<tr>
<td>Weekly</td>
<td>50.9</td>
<td>46.0</td>
<td>45.7</td>
<td>50.5</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>53.7</td>
<td>46.0</td>
<td>49.4</td>
<td>50.5</td>
</tr>
<tr>
<td>Past</td>
<td>39.7</td>
<td>41.1</td>
<td>40.6</td>
<td>38.8</td>
</tr>
<tr>
<td>Current</td>
<td>6.6</td>
<td>12.9</td>
<td>10.0</td>
<td>10.7</td>
</tr>
<tr>
<td>Physical activity§</td>
<td>77.2</td>
<td>74.8</td>
<td>78.7</td>
<td>71.4</td>
</tr>
<tr>
<td>Parental history of myocardial infarction¶</td>
<td>10.5</td>
<td>12.8</td>
<td>13.6</td>
<td>13.2</td>
</tr>
</tbody>
</table>

* All values are expressed as percentages.
† Systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 95 mmHg or higher, or history of treatment for high blood pressure.
‡ Body mass index of 27.8 kg/m² or more.
§ Reported vigorous exercise once or more per week.
¶ In either parent before age 60 years.

For exudative macular degeneration (data not shown), users of vitamins C and/or E only had a significantly elevated risk for disease (RR = 2.60, 95 percent CI 1.17–5.78) compared with nonusers of supplements according to analyses adjusted for age and treatment assignment. However, there were only seven cases of exudative macular degeneration in this supplement group. Relative risks for users of multivitamins plus vitamins C and/or E (RR = 1.06, 95 percent CI 0.45–2.50) were slightly lower than for users of vitamins C and/or E only (RR = 2.60, 95 percent CI 1.17–5.78).
TABLE 3. Relative risks and 95% confidence intervals for a diagnosis of age-related maculopathy, by vitamin supplement status, Physicians' Health Study I, 1982-1995

<table>
<thead>
<tr>
<th>Supplement use at baseline</th>
<th>Analysis A‡</th>
<th>Analysis B§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Cases</td>
</tr>
<tr>
<td>None</td>
<td>16,158</td>
<td>195</td>
</tr>
<tr>
<td>Vitamins C and/or E only</td>
<td>2,582</td>
<td>45</td>
</tr>
<tr>
<td>Multivitamins only</td>
<td>2,582</td>
<td>45</td>
</tr>
<tr>
<td>Multivitamins and vitamins C and/or E</td>
<td>1,531</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>21,120</td>
<td>279</td>
</tr>
</tbody>
</table>

* Adjusted for age, aspirin and beta-carotene treatment assignment, diabetes, hypertension, obesity, alcohol consumption, cigarette smoking, physical activity, and parental history of myocardial infarction.
† CI, confidence interval; RR, relative risk.
‡ Relative risks for mutually exclusive categories of vitamin supplement use.
§ Relative risks from separate proportional hazards models for each supplement compared with nonusers of supplements.

above 1.00. Results were essentially unchanged after controlling for other possible risk factors for age-related maculopathy.

When we analyzed supplement use by comparing users of specific supplements (with or without other supplements) with nonusers of supplements in separate regression models, we noted no significant increase or decrease in risk for either age-related maculopathy or exudative macular degeneration. At baseline, 9.8 percent of physicians reported use of vitamin C supplements, 5.1 percent reported vitamin E supplementation, and 19.5 percent reported multivitamin use. Compared with nonusers of supplements, users of vitamin C supplements had a relative risk of 1.03 (95 percent CI 0.71–1.50) for age-related maculopathy after adjustment for age, treatment assignment, and other possible risk factors (table 3, analysis B). Persons taking vitamin E supplements had a nonsignificant 13 percent reduced risk of age-related maculopathy (RR = 0.87, 95 percent CI 0.53–1.40) and users of multivitamins had a nonsignificant 10 percent reduced risk of disease (RR = 0.90, 95 percent CI 0.68–1.19) in models controlling for other possible risk factors for age-related maculopathy. There were no statistically significant trends of decreased risk with increasing duration of supplemental use (<5 years, 5–10 years, >10 years) of vitamin C, vitamin E, or multivitamins (data not shown).

For exudative macular degeneration, there was a modest but statistically nonsignificant increased risk of disease for users of vitamin C supplements (RR = 1.41, 95 percent CI 0.70–2.83) after adjustment for other possible risk factors for age-related maculopathy. Relative risks for users of vitamin E (RR = 1.10, 95 percent CI 0.43–2.80) and users of multivitamins (RR = 1.07, 95 percent CI 0.61–1.88) were near the null value of 1.0.

When we stratified on smoking history, we noted generally lower relative risks for supplement users in the group of past and current smokers as compared with never smokers (table 4). The data for specific supplements indicated that relative risks for users of vitamin C supplements and multivitamins, but not vitamin E supplements, were lower for smokers (table 4). However, none of these risk reductions in the various subgroups attained statistical significance. An interaction term for any supplement use (yes/no) and smoking (ever/never), when added to a multivariate model, was also not statistically significant (p = 0.18). (Similarly, an interaction term for any supplement use (yes/no) and smoking (current/not current) was not statistically significant (p = 0.93.)

We also examined whether the association between supplement use and age-related maculopathy differed according to beta-carotene treatment. We found no interaction between any of the vitamin supplement groups shown in table 3 and beta-carotene randomized treatment assignment.

DISCUSSION

These prospective data from a large population of physicians suggest that for men who self-select to use antioxidant vitamins, a major reduction in the risk of age-related maculopathy is unlikely. Compared with nonusers, physicians who used vitamin E supplements had a possible but nonsignificant approximate 13 per-
cent reduced risk of age-related maculopathy, and multivitamin users had a 10 percent reduced risk. There was no associated reduction for vitamin C use. Although we had limited dietary data and therefore did not consider food sources of antioxidant vitamins in these analyses, results in other populations suggest that users of vitamin supplements, particularly users of individual supplements of vitamin E or C, can be expected to generally exceed the highest quintile for total intake of these nutrients in the cohort (25, 35, 36).

The prospective study design eliminated the potential for biased recall of vitamin supplement use, and random misclassification of supplement use was unlikely since this information is usually recalled accurately (37). The use of medical records to confirm the self-reports reduced random misclassification of reported age-related maculopathy. Nonrandom misclassification of age-related maculopathy was unlikely since medical records were reviewed without knowledge of participants' supplement status, and treating ophthalmologists and optometrists are unlikely to diagnose age-related maculopathy differentially depending on vitamin supplement use.

However, since participants were not examined, it is possible that some cases of age-related maculopathy were not identified (underascertainment of disease). As expected, the rates of age-related maculopathy in the PHS I study are lower than the rates reported in examined populations. For example, 68 incident cases of exudative macular degeneration were confirmed in the PHS I study, whereas approximately 200 cases of exudative macular degeneration were confirmed in the Beaver Dam Eye Study (38). Underascertainment of disease may partially explain this difference in rates, although most participants with exudative disease, the most severe form of the disease, would be expected to seek ophthalmologic attention. However, another possibility is that the comparatively lower rates of disease in the PHS I study may simply reflect the general good health of our study population.

In the PHS I study, men who had a history of myocardial infarction, stroke, transient cerebral ischemia, or cancer (except nonmelanoma skin cancer) were not eligible for inclusion in the trial. Several epidemiologic studies have suggested that cardiovascular disease (19, 39, 40) and cardiovascular risk factors such as elevated blood pressure (19, 39, 41–43) and elevated lipid levels (43, 44) are associated with increased risks of age-related maculopathy. By excluding men who had a history of cardiovascular disease (or cancer), the PHS I population may have been at a comparatively lower risk for developing age-related maculopathy.
and, in this important way, may have differed from study populations of other investigations. For example, in the Beaver Dam Eye Study (45), a history of cardiovascular disease was reported at baseline by 15.1 percent of the study population. In the PHS I study, the low prevalence of cigarette smoking (approximately 11 percent current smokers at baseline), an important risk factor for age-related maculopathy (33), further differentiates this population from others and may have contributed to the lower than expected rates of age-related maculopathy in these men.

To the extent that cases of age-related maculopathy were either undiagnosed or unreported, differential ascertainment of disease is a possibility. For example, if supplement users are generally more health conscious, they also may have more medical contacts, which could increase the probability of disease detection (we have no information on the number of medical contacts for study participants). The effect of such a diagnostic or surveillance bias would be to obscure any true protective effect of antioxidant vitamin use. Vitamin supplement users did report more physical activity and less obesity (but more hypertension), but these differences were not striking, and adjustment for a wide range of risk factors had only a modest effect on the relative risk estimates. Antioxidant level may also be associated with the risk of cataract (27), and cataract probably contributed to visual acuity changes in some cases of age-related maculopathy. However, in this analysis we considered only those cases of age-related maculopathy that, even in the presence of other ocular abnormalities such as cataract, were judged by the treating ophthalmologists to be of sufficient severity to reduce visual acuity to 20/30 or worse when considered alone. However, cataracts that were dense enough to preclude adequate visualization of the fundus may have further limited our ability to detect any true protective effect of antioxidant vitamin use. Morbidity follow-up was over 99 percent complete and medical records were obtained for 92.3 percent of supplement users, and for 93.3 percent of nonusers of supplements who reported age-related maculopathy, indicating that results cannot be materially biased by incomplete follow-up.

There have been few epidemiologic studies of antioxidant vitamins and age-related maculopathy, including both blood-based and dietary investigations, and the data conflict. Cross-sectional data from the first National Health and Nutrition Examination Survey indicated that a high intake of fruits and vegetables rich in vitamin A was associated with a reduced risk of age-related maculopathy, but no reduction in risk was observed for foods rich in vitamin C (19). Cross-sectional data from the Baltimore Longitudinal Study of Aging showed a significantly reduced risk of age-related maculopathy associated with high plasma values of vitamin E but not high levels of vitamin C or beta-carotene (20). In the Eye Disease Case-Control Study, there was a significantly reduced risk of neovascular macular degeneration among those with high serum levels of carotenoids but not among those with high serum levels of vitamin C or E (24). Similar results were obtained when dietary data in that population were analyzed (25). On the other hand, recent case-control data from the Beaver Dam Eye Study indicated no association of serum vitamin E or total carotenoids with the combined endpoint of atrophic and neovascular macular degeneration (26). Three other case-control studies have reported no association between serum levels of vitamin A (21), vitamin C (21), vitamin E (21–23), or total carotenoids (23) and the risk of age-related maculopathy, but these studies may have been limited by a small sample size.

Specific information regarding vitamin supplement use has been reported in several prior studies. In the Baltimore Longitudinal Study of Aging, participants who reported recent supplement use, defined as any use of a vitamin or supplement of any type during the previous 2 years, had a nonsignificant 10 percent reduced risk of age-related maculopathy (odds ratio = 0.9, 95 percent CI 0.6–1.3) compared with nonusers of supplements (20). In the Beaver Dam Eye Study, age-related maculopathy cases were significantly less likely than controls (matched on age, sex, and current smoking status) to report the use of vitamin C supplements (25 percent vs. 38 percent, p = 0.01). Age-related maculopathy cases were also less likely to report the use of vitamin E supplements (23 percent vs. 32 percent), although this difference was not statistically significant (26). In two other case-control studies, there were too few supplement users to permit meaningful analysis (21, 22). The results of our study, which to our knowledge is the first prospective investigation of this research question, indicate only a slight and statistically nonsignificant reduction in the risk of age-related maculopathy among users of vitamin E supplements and among users of multivitamins. Together with the previous observational studies, these findings suggest no large beneficial effect on the risk for age-related maculopathy among persons who self-select for supplemental use of antioxidant vitamins.

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It has been suggested that the potential benefits of vitamin supplementation may be confined to people at high risk of oxidative stress, such as those with suboptimal dietary intake of antioxidant nutrients (7, 32). Although the lack of detailed dietary data in our study precluded examination according to dietary intake of nutrients, we did explore the possibility that the effects of vitamin supplements in this generally well-nourished population of physicians were different in smokers and nonsmokers. Previous studies have indicated that smokers may be under greater oxidative stress as a result of oxidants present in cigarette smoke (46–49) and a depressive effect of smoking on plasma antioxidant levels (28–32) and may therefore benefit more from vitamin supplementation than nonsmokers would. Although we observed that relative risks were generally lower in past and current smokers (table 4), the number of observed events in several of these subgroups was small, and none of the risk reductions attained statistical significance. Furthermore, an interaction term for any supplement use and a history of smoking, when added to a multivariate model, also was not statistically significant (p = 0.18). Nonetheless, the observation that among past and current smokers, the relative risks associated with use of vitamin C supplements and multivitamins, but not vitamin E supplements, were lower than the corresponding relative risks among never smokers is consistent with blood-based data indicating that smokers have lower plasma levels of vitamin C and carotenoids but not vitamin E (23, 30, 50, 51).

The retina is particularly vulnerable to oxidative stress because of the exceptional exposure of this tissue to both light and oxygen and because of the high level of polyunsaturated fatty acids in the photoreceptor outer segment membranes (52–54). Vitamin supplement use may increase the retinal stores of antioxidant nutrients and thereby decrease oxygen-mediated tissue damage. Although the available epidemiologic evidence suggests that a major effect of vitamin supplement use is unlikely, further study is warranted. Age-related maculopathy is a common cause of severe visual impairment, and even a modest benefit would have public health importance.

In summary, these prospective data suggest that for persons who elect to use supplemental antioxidant vitamins, a major reduction in the risk of age-related maculopathy is unlikely. Although additional descriptive and observational studies would add to the evidence regarding the association between antioxidants and age-related maculopathy, including valuable information on the most promising antioxidants and dosage, the magnitude of uncontrolled confounding in these studies could easily be as large as the most plausible small-to-moderate beneficial effects that may be expected. Randomized trials of sufficient size and duration will be required to enable reliable detection of the more plausible small-to-moderate benefits of antioxidant vitamins (55, 56). The Age Related Eye Disease Study (57), a 10-year, multicenter randomized trial conducted by the National Eye Institute testing a combination of antioxidant vitamins, should provide the most reliable evidence on this question. The PHS I study (58) of beta-carotene and the PHS II study of beta-carotene, vitamin E, vitamin C, and a multivitamin, both conducted in men, as well as the Women's Health Study (59) of vitamin E in women, also should contribute important relevant information to the totality of evidence on the question of whether antioxidant vitamin supplements reduce the risk of age-related maculopathy.

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