Vitamin Supplement Use and Incident Cataracts in a Population-Based Study

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**Objective:** To determine the relationship between vitamin supplement use and the 5-year incidence of nuclear, cortical, and posterior subcapsular cataract in the Beaver Dam Eye Study cohort.

**Design:** The 5-year incidence of cataract, determined from slitlamp (nuclear cataract) and retroillumination (cortical and posterior subcapsular cataract) photographs, was assessed in a population-based cohort of persons participating in baseline (1988-1990) and follow-up (1993-1995) examinations. Detailed data regarding the type, dosage, and duration of supplement use were obtained by in-person interviews at follow-up.

**Participants:** Residents of Beaver Dam, Wis, aged 43 to 86 years, were identified by private census. Of the 3684 participants in both baseline and follow-up examinations, 3089 were eligible for incident cataract analysis in the present study.

**Results:** Compared with nonusers, the 5-year risk for any cataract was 60% lower among persons who, at follow-up, reported the use of multivitamins or any supplement containing vitamin C or E for more than 10 years. Taking multivitamins for this duration lowered the risk for nuclear and cortical cataracts but not for posterior subcapsular cataracts (odds ratios [95% confidence intervals]=0.6 [0.4-0.9], 0.4 [0.2-0.8], and 0.9 [0.5-1.9], respectively). Use of supplements for shorter periods was not associated with reduced risk for cataract. Measured differences in lifestyle between supplement users and nonusers did not influence these associations, nor did variations in diet as measured in a random subsample.

**Conclusions:** These data add to a body of evidence suggesting lower risk for cataract among users of vitamin supplements and stronger associations with long-term use. However, the specific nutrients that are responsible cannot be ascertained at this time, and unmeasured lifestyle differences between supplement users and nonusers may explain these results.

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CTARACTS ARE common among older Americans, and the incidence of age-related cataract is expected to increase sharply during the next 50 years, at which time it is estimated that the US population 75 years and older will have tripled. Cataract surgery accounts for a large volume of Medicare expenditures. Finding a means to delay cataract may curb the growing number of these operations. For example, it has been hypothesized that delaying cataract by 10 years could reduce the number of extractions by 50%. There is evidence that certain dietary components, such as vitamins and minerals involved in protection against oxidative stress, may have a role in slowing cataract development. Thus, it is possible that supplements that provide these nutrients may postpone the formation of cataracts. However, supplementation, while common, can be costly and may reduce attention to eating healthful foods. Furthermore, there is an increased finding of health risks with some types of supplements in certain segments of the population. For example, β-carotene supplements were linked with higher risk of cancer among smokers in 2 previous studies, and high levels of vitamin A were associated with higher rates of hip fracture in another study. Thus, before supplementation can be advocated as a possible means of reducing the risk of cataract, a strong body of evidence to support a protective role is needed.

Results of several cross-sectional studies indicate a lower prevalence of lens opacities among users of various types of supplements. Furthermore, 2 prospective studies in health professionals show lower rates of self-reported cataracts among those who took multivitamin supplements or who were long-term users of...
Subjects and Methods

Population

The Beaver Dam Eye Study is an ongoing study of middle- and older-aged adults in a primarily white community in south-central Wisconsin. This study was approved by the Human Subjects Review Board, University of Wisconsin, Madison, and informed consent was obtained from each participant. The entire population of persons aged 43 to 86 years in Beaver Dam was identified by private census, and 4926 (83.1%) participated in the study at the baseline examination (1988-1990). Nearly 73% (n=3684) of those completed the follow-up examination 5 years later. Of the subjects lost from the study between baseline and follow-up, 96 could not be located or had moved, 536 had died, and 950 declined reevaluation. Characteristics of nonparticipants in the follow-up examination have been previously described. Briefly, they were older and, after controlling for age, were more likely to have less education, poorer visual acuity, and a history of cardiovascular disease. Baseline levels of central cataract were similar among participants and nonparticipants. However, supplement use at baseline was more common in participants compared with nonparticipants (34% vs 30%; P=.04).

A 50% random subsample of the population who were free-living (n=2429) was asked to provide in-depth information about diet and vitamin supplementation at baseline. This subgroup was used to investigate the influence of diet on relationships of supplement use to cataract. Of those invited, 2152 (88.6%) participated in the nutrition study, and 1709 (79.4%) of these were reexamined 5 years later.

Data Collection

Physical examinations and lens photography were conducted at the 1988-1990 baseline studies and the 1993-1995 follow-up visits. Procedures for photographing the lenses have been reported previously. Photographs were taken using a slitlamp camera (model SL5; Topcon America Corporation, Paramus, NJ) with specially designed fixation targets for visualizing the nuclear region of the lens. Cortical and posterior subcapsular cataracts were assessed from Neitz retroillumination photographs. Medical histories and information about demographic and behavioral characteristics were ascertained at baseline, using a standardized questionnaire administered in conjunction with the examinations.

For the primary analysis, a vitamin supplementation history was obtained at the follow-up examination from all participants in the Beaver Dam cohort. They were asked about vitamins they were taking on a regular basis (at least weekly) or had taken anytime in the past 5 years. They were queried as to the duration of use, brand, frequency, and dosage.

Secondary analyses were conducted in the subpopulation that provided detailed nutritional information at baseline. Information on diet and supplement use was collected as part of an in-home interview. Dietary content over the last year and in the distant past (10 years before baseline) was assessed using a 100-item modified form of the food frequency questionnaire developed by Block. Vitamin supplementation during each period was collected, as well as the brand, frequency of use, and amount of nutrient per pill.

Incidence of Opacities

Grading of the lenses was based on procedural rules that have been described in detail elsewhere. Graders were masked as to subject identity and to the presence or severity of lens opacities at the first examination. Scores for nuclear sclerosis were based on a 5-level photographic scale corresponding to increasing opacities of the nucleus. Cortical and posterior subcapsular cataracts were scored by weighted estimates of degree of opacity of the lens area as defined by a circular grid, divided into 8 “pie-wedged” peripheral areas, and a central area overlaid on the photograph.

For the present analyses, 3089 subjects were eligible for having 1 or more types of incident cataract. Of these, 2711 (2686 with complete information on supplement use and covariates) were at risk for an incident nuclear cataract based on their being free of nuclear cataracts at baseline. Those with complete data who were at risk for developing cortical opacities and posterior subcapsular cataracts were 2699 and 2771, respectively. There were 2436 who were free of any type of cataract at baseline, of whom 2434 had complete records. Participants were considered not at risk for incident cataract if: (1) their lens was absent or if photographs could not be graded at baseline or follow-up (275 for nuclear opacities and 374 for cortical or posterior subcapsular cataract); (2) they had preexisting cataract of the same type at baseline (493 for nuclear cataract, 473 for cortical cataract, and 151 for posterior subcapsular cataract); (3) they had cataract surgery.
before baseline (n = 157); or (4) they had experienced trauma to the lens in the past that could have resulted in lens opacity (n = 4). Eyes that had undergone cataract surgery subsequent to baseline examinations were excluded except where explicitly stated.

DEFINITIONS

Incidence refers to the classification of lens opacity of sufficient severity to meet the criteria that a clinical ophthalmologist would be comfortable in labeling as a cataract. The specific definitions used to classify such opacities are described in detail elsewhere. Briefly, nuclear cataracts were indicated by a level of 4 or 5 in the grading scheme that specifies 5 levels of increasing severity; cortical cataracts were indicated when opacities in the region involved 5% or more of the lens graded by involvement of 9 segments defined by a grid; and posterior subcapsular cataracts involved 5% or more of any of 9 segments in this lens region defined by the same circular grid.

DIET ANALYSES

In the smaller nutrition study sample, food and nutrient intakes from food and supplement sources were calculated using version 3.4 of the computer software and nutrient database developed for the Block food frequency questionnaire. To evaluate the likelihood that associations between supplement use and cataract reflect better diets, we constructed an index of diet quality that divided the sample into 3 groups of approximately the same size but whose intake of a variety of micronutrients was classified as high, medium, or low. We assigned 1 point for energy-adjusted intake of each of the following types of food that was above (or below for saturated fat) the median for the subject’s sex and age (<65 and ≥65 years at baseline): (1) fruits and vegetables, (2) grains, cereals, or legumes, (3) dairy products, and (4) saturated fat. The “high” group (n = 388) was defined by scores of 3 or 4, indicating better than median intakes in at least 3 of the 4 categories. The “low” group had scores of 1 or less (n = 385), representing worse than median intakes in 3 of the 4 categories. All other scores resulted in placement in the “medium” category (n = 385). There were significantly (P < .05) higher average intakes in the high group compared with the low group for a variety of vitamins and minerals, including vitamins C and E, lutein, α-carotene, β-carotene, β-cryptoxanthin, lycopene, vitamin B₆, folate, calcium, and zinc (data not shown).

STATISTICAL METHODS

Duration of supplement use, which was assessed in the full cohort at follow-up, was divided into 3-year increments (no prior use, ≤5 years, 6-10 years, and >10 years). Odds ratios (ORs) and 95% confidence intervals for incident cataract were calculated for each period, with nonusers as the reference category, by logistic regression analysis. Linear trends were assessed using median durations for each period of supplement use. Variables examined as confounders or effect modifiers, as assessed at baseline were: age; sex; smoking (pack-years); total weekly alcohol intake (in grams); weekly intake of beer, wine, or hard liquor (in grams); history of ever drinking more than 4 drinks per day; hypertension (self-reported history and use of antihypertensive medications, mean systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥95 mm Hg, or both); body mass index (weight in kilograms divided by the square of height in meters); diabetes (self-report of physician’s diagnosis or glycosylated hemoglobin or non-fasting glucose levels above age and sex standards); sun-light exposure (average Wisconsin sun years); use of a hat in teen years; goat; steroid use; and uric acid, hemoglobin, and glycosylated hemoglobin concentrations. We also evaluated the influence of adjusting for education, which may be a marker for unmeasured factors associated with the development of cataracts. After adjusting for age, none of these factors individually affected ORs by 10% or more for the highest level or duration of any supplement use. Because some potential risk factors had small but relatively consistent effects on ORs, regression models include adjustments for 1 or more of the following: pack-years of smoking, alcohol intake, and body mass index.

We tested for interactions to determine whether the associations between supplement use and incident cataract differed according to the levels of other risk factors. Likelihood ratio tests were used to compare logistic regression models fit with and without the interactions of the risk factor and levels of supplement use. An α level of .10 was used to determine significance. Diet quality score and level of intake of specific nutrients from food sources that were potentially protective against cataract (vitamins C and E, riboflavin, and lutein plus zeaxanthin) were also evaluated as effect modifiers.

There have been no prospective studies in the general population of supplement use and the development of specific types of lens opacities. In this article, we describe relationships between the use of supplements for varying durations and the 5-year incidence of nuclear, cortical, posterior subcapsular, and overall cataract in a population-based cohort of the Beaver Dam Eye Study. This is an extension of research reported elsewhere of relationships in smaller subsamples of this population between nutrients in the diet and serum and incident nuclear opacities.

RESULTS

The characteristics of participants using supplements at the 1993-1995 follow-up and reporting use of multivitamins for more than 10 years are given in Table 1. Compared with nonusers, multinutrient users were more likely to be female, have a physically active lifestyle, and have a low body mass index. Among men, supplement use was somewhat more common in older age groups. Those using supplements containing vitamin C or E supplementation (not exclusive of multinutrient use) followed similar patterns. The duration of using vitamins C and E and multinutrients was also highly correlated (Pearson correlation coefficient = 0.9 in all cases). Despite similar levels of energy intake among users and nonusers, vitamins C and E from foods and overall consumption of fruits and vegetables, which contribute a variety of potentially protective micronutrients, were higher among supplement takers.
The incidence of overall cataract was 27%. The rate was highest for nuclear cataract (17%), followed by cortical cataract (10%) and posterior subcapsular cataract (4%). A 60% reduction in risk for incident cataract was related to the use of supplements of any type, multivitamins, or vitamin C or E supplementation for 10 years before follow-up (Table 2). Use for shorter durations was not associated with reduced risk for cataract. The ORs by use of multivitamins are given for cataracts in each of 3 regions of the lens in Table 3. The reduction in risk was similar for opacities in the cortical and nuclear regions. The strongest trend for decreasing risk with increased duration was observed for cortical cataract. For nuclear cataract, no risk reduction was found among persons taking supplements for 10 or fewer years, and the trend with longer use was marginally significant (P=.08). There was no association with posterior subcapsular cataract opacities (adjusted OR [95% confidence interval] = 0.9 [0.5-1.9]). As expected, because of the high correlation in supplementation practices, relationships with the duration of using vitamins C and E were similar to those with multivitamin use (data not shown).

To evaluate the possibility that recall bias may have influenced our results, we performed separate analyses in the subsample (n=1709) who participated in the nutrition study and gave detailed data regarding supplement use at baseline before developing the cataract as-
We investigated subgroups within the Beaver Dam cohort indicating that supplement users have diets that are more dense compared with nonusers in a variety of nutrients that may protect against cataracts. This is also illustrated in Table 1, which demonstrates that subjects in the nutrition study who took supplements had higher average intakes of vitamins C and E and fruits and vegetables, despite energy intake levels that were similar to the others. It is not possible to effectively simultaneously adjust in regression models for the numerous dietary factors that are hypothesized to protect against cataract. For this reason, we evaluated the associations in people with diets that were high and low in a variety of vitamins and minerals. As reflected by the diet quality scores in Table 5, supplements use for more than 10 years was associated with a lower risk for cataract with nutrient-dense and with nutrient-sparse diets. Similarly, ORs for cataract in long-term users vs nonusers of supplements remained less than 1 regardless of the level of intake of specific nutrients from foods.

We have previously reported36 observations from this cohort indicating that supplement users have diets that are more dense compared with nonusers in a variety of nutrients that may protect against cataracts. Based on the 5-year incidence of nuclear, cortical, and posterior subcapsular cataract among nutrition subjects reporting the use of multivitamin supplements for more than 10 years, ORs (95% confidence intervals) were 0.5 (0.3-1.1), 0.4 (0.2-1.0), and 0.6 (0.1-2.0), respectively, after adjusting for the same variables in Table 3.

We investigated subgroups within the Beaver Dam cohort stratified by the presence or absence of other cataract risk factors (Table 4) to more completely determine whether association with long-term supplement use could be explained by other health and lifestyle factors. The inverse direction of relationships of multivitamin supplementation and cataract remained regardless of their status of glycosylated hemoglobin, smoking, alcohol use, diabetes, age, body mass index, or level of physical activity. There was also no strong evidence for effect modification. Although ORs appeared lower in some groups (eg, 0.1 for current smokers compared with 0.5 for past and nonsmokers), the interactions with these variables were not statistically significant.

We have previously reported36 observations from this cohort indicating that supplement users have diets that are more dense compared with nonusers in a variety of nutrients that may protect against cataracts.
Results of this study add to evidence from several earlier studies that supplement use is associated with lower occurrence of cataract. This is the first prospective study conducted in the general population to indicate lower incidence among multivitamin users of 2 types of cataract, nuclear and cortical, detected from lens photographs. Two previous studies found nuclear cataract to be less common in supplement users but observed similar or higher rates of cortical cataract among the same subjects. The present finding of lower incidence of both types of cataract suggests alternative explanations for higher rates of cortical opacities in these earlier studies. It is possible that the short period of vitamin use in one of these studies and the change in supplementation practices subsequent to new information about cortical cataracts in the other might explain the differing results in the 2 studies.

We did not detect a relationship of supplement use to the incidence of posterior subcapsular cataract. However, the power to detect an association with this less frequently observed cataract was low (power \(1−\beta\) of 26% to detect a relative risk of 0.5) in persons using multivitamin sources for more than 10 years. Larger and longer-term studies are needed in which a greater number of subjects who develop these types of cataract are included.

The stronger association of cataracts to long-term, compared with short-term, use of supplements has been observed previously in this and other populations. However, use of vitamin C supplements for 10 or more years was not associated with reduced risk for cataract extraction in 1 cohort. Results of another recent short-term clinical trial, conducted for a median of 5.7 years, also indicated no benefit of \(\alpha\)-tocopherol or \(\beta\)-carotene supplements in lowering rates of cataract extraction in Finnish male smokers. A relationship with long-term use, that is consistently observed across most studies, could reflect a latency period for the influence of multivitamins on cataract development. Vitamin supplementation may buffer the cumulative minor insults from a variety of causal factors that occur over a long period. However, the finding of fewer nuclear opacities among the Chinese Linxian population who took multivitamins vs placebo for approximately 5 years does suggest that there may be short-term effects under some circumstances. Also, it is possible that we failed to detect an association with short-term use because the influence over a few years is too modest in a generally well-nourished population to be detected with the available statistical power. However, ORs for short-term supplement use that were near unity argue against this possibility.

In addition, long-term users of supplements may differ from short-term users in lifestyles that protect against cataract development. The observations in this study, however, do not suggest other aspects of a healthy lifestyle that could explain these associations with supplement use. Furthermore, consistency of the inverse association among subjects with or without other risk factors for cataract (Table 4) indicates that residual confounding by some of these lifestyle variables is not a likely explanation. Moreover, our data from the smaller subset in the nutrition study (Table 5) indicate that more-nutrient dense diets among supplement users are not likely to explain the association. However, it is possible that there are differences in unidentified and unmeasured risk factors for cataract in long-term users that would explain these findings.

One might expect that nutritional supplements would have greater benefit among people who consume low levels of nutrients from food sources. Indeed, the one study to date in which vitamin supplementation resulted in a lower prevalence of nuclear opacities was conducted in an area of China in which malnutrition is known to exist. In the present study, we did not observe that the inverse relationship of supplement use was limited to participants in the Beaver Dam Eye Study with relatively poorer quality diets. This suggests either that nutrients may have benefits beyond prevention of marginal deficiencies or that nonnutritive factors are responsible for the findings in this study. Alternatively, even the poorest diets in this Wisconsin community may not be low enough in nutrients to observe a substantial greater benefit of supplementation among people with the poorest diets.

Assuming that the nutrients that supplements provide are responsible for a lower incidence of cataract among long-term users, it is still not yet possible to determine which may be responsible for the associations found. There is evidence that oxidative stress is a contributor to lens opacification and that the dietary antioxidants vitamin C, vitamin E, and \(\beta\)-carotene protect against it in experimental animals and in cultured lenses. These data are supported by associations between levels of vitamins C or E in the diet or serum and lower prevalence or risk of some types of cataract. While previous studies have reported links

### Table 5. Incident Cataract in 249 Long-Term Multivitamin Supplement Users vs 984 Nonusers by Diet Characteristics in a Subsample of Beaver Dam Eye Study Participants in the Nutrition Study

<table>
<thead>
<tr>
<th>Diet quality index score</th>
<th>Adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>0.3 (0.1-0.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.6 (0.2-2.2)</td>
</tr>
<tr>
<td>Low</td>
<td>0.3 (0.1-1.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nutrient intake from foods</th>
<th>Adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td></td>
</tr>
<tr>
<td>&lt;Median</td>
<td>0.5 (0.2-1.3)</td>
</tr>
<tr>
<td>≥Median</td>
<td>0.3 (0.1-0.8)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
</tr>
<tr>
<td>&lt;Median</td>
<td>0.7 (0.3-1.6)</td>
</tr>
<tr>
<td>≥Median</td>
<td>0.2 (0.0-0.6)</td>
</tr>
<tr>
<td>Riboflavin</td>
<td></td>
</tr>
<tr>
<td>&lt;Median</td>
<td>0.2 (0.0-0.9)</td>
</tr>
<tr>
<td>≥Median</td>
<td>0.5 (0.2-1.2)</td>
</tr>
<tr>
<td>Lutein/zeaxanthin</td>
<td></td>
</tr>
<tr>
<td>&lt;Median</td>
<td>0.3 (0.1-0.9)</td>
</tr>
<tr>
<td>≥Median</td>
<td>0.5 (0.2-1.3)</td>
</tr>
</tbody>
</table>

†Data are given as adjusted odds ratio OR (95% confidence interval [CI]) adjusted for age, sex, pack-years of smoking, diabetes, hypertension, body mass index, UV-B exposure, and hat use in teen years. Age specific (<65 and ≥65 years at baseline) and sex-specific median intake levels were used.
with the use of vitamins C\textsuperscript{19} or E\textsuperscript{24} in supplements, it should be noted that these subjects are also likely to have taken other supplements.\textsuperscript{36,41} Moreover, some studies report no such links with the use of vitamin C\textsuperscript{21} or E\textsuperscript{26} supplements. Therefore, it is difficult to draw conclusions regarding the causal relationships of specific nutrients in the present or previous\textsuperscript{19,24} studies.

Clinical trials could be useful in this regard. Data from only 1 clinical trial are available to date, indicating no influence of vitamin E or \( \beta \)-carotene taken for a median of 5.7 years on the incidence of cataract extraction in Finnish male smokers.\textsuperscript{26} If long-term use is necessary to observe a beneficial effect, findings of potentially protective relationships in short-term clinical trials may be missed. Data from long-term prospective studies will be helpful in evaluating this possible explanation for the absence of effect seen in short-term clinical trials.

The overall health benefits and risks of consuming certain supplements, particularly at high doses, are unknown. For example, there is evidence of higher rates of cancer among smokers or asbestos-exposed subjects who take \( \beta \)-carotene.\textsuperscript{12,13} Potential biologic mechanisms for adverse effects of vitamin C include an oxidation product cross-linked to human lens proteins that increases with lens pigmentation\textsuperscript{15} and higher levels of certain DNA adducts in the blood or urine of users.\textsuperscript{43} For this reason, despite the growing evidence that supplement use may protect against cataracts, recommendations for taking high doses of antioxidant nutrients are not warranted at this time.

One limitation of the present study is that detailed information was collected from the study population at follow-up interviews. Therefore, it is possible that participants’ recall of supplement use could have been different in those with and without newly developed cataracts. However, this type of bias is unlikely to explain the inverse associations between cataract and supplementation because similar relationships were also observed between long-term use reported at baseline and 5-year incident cataract in the nutrition study participants.

A second limitation is the absence of data from persons lost to follow-up at the 5-year examinations. Because those who did not participate at follow-up were less likely to have used supplements at baseline, the relationship that we observed might have been biased toward the null if the cataract incidence were higher in the missing subjects. Alternatively, if the prevalence in this group were lower, the correlations found could be stronger than those in the overall population.

In conclusion, data from the present study add to an increasing body of evidence that suggests that vitamin supplement use may protect against the development of cataract. However, associations were limited to durations of use, and this may reflect the protective influences of other aspects of lifestyle among long-term users. Furthermore, the nutrient(s) responsible cannot yet be determined with certainty. Additional data from clinical trials and longer-term prospective studies are needed to confirm suspected causal relations, characterize the time course for the associations, and determine the specific nutrients involved.

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REFERENCES


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**A look at the past . . .**

**FIG. 1.—Principle of Method of Localization.**

**FIG. 2.—Indicating Apparatus and Plate-Holder.**