Original Contribution

High-Dose Supplements of Vitamins C and E, Low-Dose Multivitamins, and the Risk of Age-related Cataract: A Population-based Prospective Cohort Study of Men

Jinjin Zheng Selin, Susanne Rautiainen, Birgitta Ejdervik Lindblad, Ralf Morgenstern, and Alicja Wolk*

* Correspondence to Dr. Alicja Wolk, Institute of Environmental Medicine, Karolinska Institutet, Box 210, 171 77 Stockholm, Sweden (e-mail: Alicja.Wolk@ki.se).

Initially submitted March 14, 2012; accepted for publication May 22, 2012.

We examined the associations of high-dose supplements of vitamins C and E and low-dose multivitamins with the risk of age-related cataract among 31,120 Swedish men, aged 45–79 years, in a population-based prospective cohort. Dietary supplement use was assessed from a questionnaire at baseline in 1998. During follow-up (January 1998–December 2006), 2,963 incident age-related cataract cases were identified. The multivariable-adjusted hazard ratio for men using vitamin C supplements only was 1.21 (95% confidence interval (CI): 1.04, 1.41) in a comparison with that of non–supplement users. The hazard ratio for long-term vitamin C users (≥10 years before baseline) was 1.36 (95% CI: 1.02, 1.81). The risk of cataract with vitamin C use was stronger among older men (>65 years) (hazard ratio = 1.92, 95% CI: 1.41, 2.60) and corticosteroid users (hazard ratio = 2.11, 95% CI: 1.48, 3.02). The hazard ratio for vitamin E use only was 1.59 (95% CI: 1.12, 2.26). Use of multivitamins only or multiple supplements in addition to vitamin C or E was not associated with cataract risk. These results suggest that the use of high-dose (but not low-dose) single vitamin C or E supplements may increase the risk of age-related cataract. The risk may be even higher among older men, corticosteroid users, and long-term users.

ascorbic acid; cataract; dietary supplements; oxidative stress; vitamin E

Abbreviations: CI, confidence interval; HR, hazard ratio.

Vitamin C and E supplement use has not shown protective effects in prevention of chronic diseases in large long-term randomized controlled trials (1, 2). On the contrary, studies have reported potential harmful effects of high-dose antioxidant supplements, such as increased risk of mortality (3, 4), heart failure (5), and some cancer types (6–8).

The etiology of age-related cataract is multifactorial, including oxidative damage of the lens (9). Antioxidants may protect the lens against oxidative stress (10). However, the effects of antioxidant supplements on cataract risk in randomized controlled trials (11–18) and results from observational studies (19–26) have been inconsistent. Interestingly, in vitro and animal studies show that high doses of vitamins C and E have prooxidative properties and increase oxidative stress in the lens (27–31). Indeed, we have recently observed in a prospective study of women that the use of high-dose vitamin C supplements (but not multivitamins with low-dose vitamin C) was associated with increased risk of age-related cataract extraction (19).

The use of dietary supplements is widespread in many countries. It is therefore of public health importance to investigate the association of antioxidant supplements with risk of cataract, especially if single, high-dose supplements are associated with cataract risk differently from low-dose (Recommended Daily Intake) supplements. We examined if high-dose vitamin C and E supplements and low-dose multivitamins are associated with the risk of age-related cataract in men, as well as whether the associations varied by
reactive oxygen species–generating factors, such as age, smoking, abdominal obesity, hypertension, and corticosteroid use.

MATERIALS AND METHODS

Study population

The Cohort of Swedish Men was established in the late fall of 1997 to study major chronic diseases including age-related cataract. A questionnaire regarding diet and lifestyle factors, including questions on dietary supplement use, diet, age, smoking status, waist circumference, educational level, medical history (including diagnoses of diabetes and hypertension), corticosteroid use, and alcohol intake, was sent out to all men, aged 45–79 years, living in central Sweden (Örebro and Västmanlands counties), and 48,850 (49%) men answered.

In this study, we excluded men with missing or erroneous personal identity number (n = 205), who sent a blank questionnaire (n = 92), who died before January 1, 1998 (n = 55), and with a previous cancer diagnosis other than nonmelanoma skin cancer (n = 2,592). We also excluded men with cataract diagnosis or extraction before baseline (n = 923), men with cardiovascular disease or diabetes before baseline to avoid potential changes in dietary habits and use of dietary supplements (n = 7,929), men with missing information on supplement use (n = 1,506), and those using supplements not including vitamin C, vitamin E, or multivitamins (n = 4,428).

Cancer diagnosis was identified through the Swedish National Cancer Register. History of cardiovascular disease (myocardial infarction, angina pectoris, heart failure, and stroke) was obtained through linkage with the National Inpatient and Outpatient Registers at the Swedish National Board of Health and Welfare. Diabetes history was identified through the Swedish Outpatient Register, National Diabetes Register, and self-reported data.

A total of 31,120 men were included in the analysis.

Assessment of dietary supplement use and diet

The questionnaire from 1997 inquired about dietary supplement use starting with a general question: “Do you use vitamin, mineral, or other supplements?” with 3 prespecified responses (no, regular use, and occasional use). This question was followed by more specific questions with pre-specified types of supplements and open answers about frequency and duration of use. Men that reported regular or occasional use were considered as supplement users. Duration of vitamin C, vitamin E, and multivitamin use was inquired by open-ended questions. Long-term and short-term users were defined as men that reported use ≥10 and <10 years before baseline, respectively. The most commonly used dose of vitamin C and vitamin E as single supplements was estimated to be ≈1,000 mg and ≈100 mg, respectively (32, 33), and multivitamins were estimated to contain ≈60 mg of vitamin C and ≈9 mg of vitamin E (doses close to the Recommended Daily Intake) (32).

Intakes of vitamin C and vitamin E from diet were assessed by a 96-item food frequency questionnaire at baseline with questions on how often, on average, during the past year the men had consumed different food items. Intakes of vitamins C and E were estimated by multiplying the frequency of consumption of different food items by the nutrient composition of those items obtained from the Swedish National Food Agency (34) and adjusted for energy intake by using the residual method (35).

Ascertainment of cases and follow-up

Between January 1, 1998, and December 31, 2006, we identified 2,963 incident cataract cases (defined as men with cataract diagnosis and/or cataract extraction). Cataract diagnoses and extractions were ascertained by linkage to the National Outpatient and Inpatient Registers at the National Board of Health and Welfare and to the “Swedish National Day-Surgery Register” (International Classification of Diseases, Tenth Revision, code H25 and operation codes designated CJC, CJD, CJE, and CJG). To complement the preceding data, we also matched against local cataract extraction registers at both public and private clinics in the study area. Among the men with both cataract diagnosis and extraction in this study, 83% got the extraction within 1 year after diagnosis. Cataracts that were considered to be congenital or secondary to ocular trauma, intraocular inflammation, or previous intraocular surgery were excluded. On the basis of the Swedish National Cataract Register, most men had a preoperative visual acuity in the cataract-containing eye of less than 20/40 Snellen equivalents, which corresponds to difficulties in driving. The mean preoperative visual acuity in the cataract-containing eye was 20/70 Snellen equivalents during the study period, which corresponds to difficulties in reading the newspaper. Approximately one-fourth of the men were legally blind (visual acuity of 20/200 Snellen equivalents) (36).

The Regional Ethical Board at Karolinska Institutet (Stockholm, Sweden) approved this study, and completion of the questionnaire was considered to imply informed consent to participate in this study.

Statistical analysis

All men were followed from January 1, 1998, until the date of cataract diagnosis, cataract extraction, date of death (through linkage to the Swedish Death Register), or the end of follow-up (December 31, 2006), whichever came first.

The men were categorized into non–supplement users and 1) users of vitamin C only, vitamin E only, or multivitamins only (including both regular and occasional users), not using other vitamin or mineral supplements, and 2) users of multiple supplements in addition to vitamin C or vitamin E. We estimated hazard ratios with 95% confidence intervals (37) using the Cox proportional hazards model and the PHREG procedure in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina). The first multivariable model was adjusted for age, smoking, abdominal obesity, educational level, history of hypertension, corticosteroid use, alcohol intake, and fruit and vegetable.
intake. The second model was further adjusted for physical activity and self-reported health. Missing values for any of the potential confounders were treated as a separate category in the model. The proportional hazard assumption was tested by including the product of vitamin C, vitamin E, and multivitamin use and the natural logarithm of time in the models, and we did not find evidence of violation of this assumption. The first 4 years of follow-up were excluded to evaluate potential risk of reversed causality. We used the Cox proportional hazards model to analyze the association between duration of vitamin C and multivitamin use and cataract risk. The difference between the observed risk estimates for long-term and short-term use and cataract was tested with the Wald test. Because of few cases, long-term estimates for long-term and short-term use and cataract was evaluated. To evaluate the effect of misclassification of self-reported supplement use on our risk estimates, we performed correction analyses, using the "episens" command in Stata, version 11, software (StataCorp LP, College Station, Texas) (38). Assumptions of sensitivity and specificity of 0.7 and 0.9 for vitamin C, 0.8 and 0.99 for vitamin E, and 0.7 and 0.98 for multivitamin use, respectively, were based on results from our previous validation study of men living in central Sweden (33).

We performed stratified analyses to examine if the risk between vitamin C use and cataract differed by reactive oxygen species–generating factors (age, smoking, abdominal obesity, history of hypertension, and corticosteroid use), as well as dietary intakes of vitamin C and vitamin E. The attributable proportion of risk due to interaction (in excess of the additive effects between the 2 exposures of interest) was calculated with 95% confidence interval (39, 40). Multiplicative interaction tests were also performed by the likelihood test. All P values shown are 2 sided, and we considered P < 0.05 as statistically significant.

### RESULTS

During an average follow-up of 8.4 years (259,949 person-years), we identified 2,963 cases of age-related cataract (among those 744 men with only diagnosis). The mean age in the cohort was 58.3 years (standard deviation: 9.2), the mean waist circumference was 95.4 cm (standard deviation: 10.1), and 24.5% were current smokers. Among the men, 5.3% reported vitamin C use only; 0.5%, vitamin E use only; and 11.3%, multivitamin use only.

Baseline characteristics of the study population by dietary supplement use are described in Table 1. The age- and multivariable-adjusted hazard ratios for dietary supplement use and age-related cataract are presented in Table 2. In the multivariable analysis, vitamin C supplement use only was associated with 21% (95% confidence interval (CI): 4, 41) increased risk of cataract compared with no-supplement use. Vitamin E use only was associated with 59% (95% CI: 12, 126) increased risk of cataract. Multivitamin use only was not statistically significantly associated with cataract risk. Additional adjustments for health status and healthy behavior as physical activity did not change the results. When the first 4 years of follow-up were excluded, similar results were obtained for users of vitamin C (hazard ratio (HR) = 1.28, 95% CI: 1.07, 1.53), vitamin E (HR = 1.62, 95% CI: 1.06, 2.48), and multivitamins (HR = 0.90, 95% CI: 0.78, 1.04). The hazard ratios corrected for measurement error in self-reported use of supplements were 3.0 for vitamin C, 3.2 for vitamin E, and 1.1 for multivitamins.

The multivariable-adjusted hazard ratios for men who took multiple supplements (one or more other supplements) in addition to vitamin C (276 cases) or vitamin E (169 cases) were 1.06 (95% CI: 0.93, 1.20) and 1.02 (95% CI:

### Table 1. Baseline Characteristics of the Men in the Cohort of Swedish Men, 1998–2006

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Supplement Use (n = 22,015)</th>
<th>Vitamin C Only (n = 1,652)</th>
<th>Vitamin E Only (n = 144)</th>
<th>Multivitamins Only (n = 3,532)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.8 (9.0)</td>
<td>58.6 (9.4)</td>
<td>62.9 (9.4)</td>
<td>58.9 (9.7)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>25.8</td>
<td>21.1</td>
<td>19.0</td>
<td>21.5</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>46.4</td>
<td>45.8</td>
<td>43.0</td>
<td>43.6</td>
</tr>
<tr>
<td>Education &gt;12 years</td>
<td>16.9</td>
<td>19.1</td>
<td>13.2</td>
<td>25.7</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>17.6</td>
<td>18.6</td>
<td>21.4</td>
<td>16.8</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>8.2</td>
<td>9.2</td>
<td>12.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Alcohol intake, g/day</td>
<td>14.8 (20.7)</td>
<td>13.5 (15.1)</td>
<td>12.5 (12.0)</td>
<td>14.5 (28.8)</td>
</tr>
<tr>
<td>Fruits and vegetables, g/day</td>
<td>375.6 (235.8)</td>
<td>414.9 (246.7)</td>
<td>437.3 (246.3)</td>
<td>426.8 (245.5)</td>
</tr>
<tr>
<td>Vitamin C, mg/day</td>
<td>105.2 (52.8)</td>
<td>110.6 (54.6)</td>
<td>113.8 (56.4)</td>
<td>112.9 (55.1)</td>
</tr>
<tr>
<td>Vitamin E, mg/day</td>
<td>8.8 (1.5)</td>
<td>9.0 (1.5)</td>
<td>8.9 (1.6)</td>
<td>9.0 (1.5)</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

- All variables, except age, were directly standardized to the age distribution of the entire study cohort.
- No reported use of other vitamin or mineral supplements.
- Defined as waist circumference ≥94 cm.
0.87, 1.20), respectively, in a comparison with non–supplement users.

Long-term vitamin C use only (≥10 years before baseline) compared with non–supplement use was associated with 36% (95% CI: 2%, 81%) increased risk of cataract (Table 3). The difference between the observed risk estimates for long-term vitamin C users and short-term users was not statistically significant (P = 0.71). Multivitamin use only ≥10 or <10 years before baseline was not associated with cataract risk.

Furthermore, we examined if the association between vitamin C use and risk of cataract was modified by putative reactive oxygen species–generating factors (age, smoking, abdominal obesity, history of hypertension, and corticosteroid use). We observed a stronger positive association for vitamin C use among older men (>65 years) and corticosteroid users (Table 4). The attributable proportion due to interaction on the additive scale was borderline statistically significant for age and statistically significant for corticosteroid use. However, the multiplicative interaction was not statistically significant for age (P = 0.23) or corticosteroid use (P = 0.17). Interaction between the other reactive oxygen species–generating factors and vitamin C use was not statistically significant on either the additive (all 95% CI, confidence interval; HR, hazard ratio.

### Table 2. Age- and Multivariable-adjusted Hazard Ratios for Dietary Supplement Use and Risk of Age-related Cataract in the Cohort of Swedish Men, 1998–2006

<table>
<thead>
<tr>
<th>Dietary Supplement Use</th>
<th>Total No. of Subjects</th>
<th>No. of Cases</th>
<th>Person-Years</th>
<th>Age Adjusted HR 95% CI</th>
<th>Multivariable Adjusted 1a HR 95% CI</th>
<th>Multivariable Adjusted 2b HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplement use</td>
<td>22,015</td>
<td>1,937</td>
<td>184,911</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>Vitamin C onlyc</td>
<td>1,652</td>
<td>188</td>
<td>13,660</td>
<td>1.21 1.04, 1.40</td>
<td>1.21 1.04, 1.41</td>
<td>1.21 1.04, 1.41</td>
</tr>
<tr>
<td>Vitamin E onlyc</td>
<td>144</td>
<td>32</td>
<td>1,138</td>
<td>1.68 1.18, 2.39</td>
<td>1.59 1.12, 2.26</td>
<td>1.57 1.10, 2.22</td>
</tr>
<tr>
<td>Multivitamins onlyc</td>
<td>3,532</td>
<td>345</td>
<td>29,311</td>
<td>0.97 0.87, 1.09</td>
<td>0.96 0.86, 1.08</td>
<td>0.96 0.85, 1.07</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

* Adjusted for age (5-year age groups: <50, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75), smoking (never, past, current smokers ≤10 and >10 cigarettes/day), abdominal obesity (waist circumference <94 or ≥94 cm), educational level (<9, 9–12, or >12 years), history of hypertension (yes or no), corticosteroid use (yes or no), alcohol intake (g/day in quartiles), and fruit and vegetable intake (g/day, continuous).

* No reported use of other vitamin or mineral supplements.

### Table 3. Age- and Multivariable-adjusted Hazard Ratios for Duration of Dietary Supplement Use and Risk of Age-related Cataract in the Cohort of Swedish Men, 1998–2006

<table>
<thead>
<tr>
<th>Duration of Dietary Supplement Use</th>
<th>Total No. of Subjects</th>
<th>No. of Cases</th>
<th>Person-Years</th>
<th>Age Adjusted HR 95% CI</th>
<th>Multivariable Adjusted 1a HR 95% CI</th>
<th>Multivariable Adjusted 2b HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplement use</td>
<td>22,015</td>
<td>1,937</td>
<td>184,911</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
<td>1.00 Referent</td>
</tr>
<tr>
<td>Vitamin C onlyb</td>
<td>521</td>
<td>56</td>
<td>4,355</td>
<td>1.28 0.98, 1.66</td>
<td>1.26 0.97, 1.65</td>
<td></td>
</tr>
<tr>
<td>≥10 years before baseline</td>
<td>420</td>
<td>48</td>
<td>3,458</td>
<td>1.34 1.01, 1.79</td>
<td>1.36 1.02, 1.81</td>
<td></td>
</tr>
<tr>
<td>Vitamin E onlyb</td>
<td>71</td>
<td>16</td>
<td>559</td>
<td>N/Ac</td>
<td>N/Ac</td>
<td></td>
</tr>
<tr>
<td>≥10 years before baseline</td>
<td>14</td>
<td>4</td>
<td>114</td>
<td>N/Ac</td>
<td>N/Ac</td>
<td></td>
</tr>
<tr>
<td>Multivitamins onlyb</td>
<td>1,212</td>
<td>102</td>
<td>10,185</td>
<td>0.99 0.81, 1.21</td>
<td>0.97 0.80, 1.19</td>
<td></td>
</tr>
<tr>
<td>≥10 years before baseline</td>
<td>657</td>
<td>65</td>
<td>5,418</td>
<td>0.94 0.73, 1.20</td>
<td>0.94 0.73, 1.21</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; N/A, not available.

* Adjusted for age (5-year age groups: <50, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75), smoking (never, past, current smokers ≤10 and >10 cigarettes/day), abdominal obesity (waist circumference <94 or ≥94 cm), educational level (<9, 9–12, or >12 years), history of hypertension (yes or no), corticosteroid use (yes or no), alcohol intake (g/day in quartiles), fruit and vegetable intake (g/day, continuous), physical activity (metabolic equivalent × hours/day, quartiles), and self-reported health (scale of 1–5, from good (i.e., 1) to bad (i.e., 5)).

* No reported use of other vitamin or mineral supplements.

* Not available because of too few cases.

was 1.12 (95% CI: 0.90, 1.40) (with reactive oxygen species risk was stronger with long-term use or among men to examine if the association between vitamin E use and cataract. The positive association between vitamin C use and among long-term users. The limited number of vitamin E users only did not allow us to evaluate the associations for long-term vitamin E use and associations between vitamin E use and factors associated with increased reactive oxygen species levels.

Our results are in agreement with our previous prospective observations in 24,593 women (2,497 cataracts), where the use of high-dose vitamin C supplements (but not low-dose multivitamins) was associated with increased risk of cataract extraction (HR = 1.25, 95% CI: 1.05, 1.50), especially among older women (HR = 1.74, 95% CI: 1.24, 2.46) and corticosteroid users (HR = 1.97, 95% CI: 1.35, 2.88) (19). The present results are partly in line with a recently published randomized controlled trial (8 years’ duration) that reported for high-dose vitamin C supplements (500 mg) a nonsignificant increased risk of cataract among obese (body mass index: ≥30) and smoking men (11). However, no effect was reported for high-dose vitamin E supplements (268 mg) in that study (11). Vitamin C and/or vitamin E use was associated with nonsignificant increased risk of cataract in men (26). Other prospective studies of vitamin C use observed statistically significant increased risk of cortical opacities among older women using vitamin C for >10 years (21) and a nonsignificant increased risk of cataract extraction among women aged ≥60 years (20). No association of cataract risk was reported in some randomized controlled trials testing vitamin E use only (50–402 mg daily or alternate days) (11–13, 15) or high-dose vitamin C and vitamin E use combined with other constituents (14–16), as well as in some observational studies of vitamin C and vitamin E use (20, 21, 23). In contrast, one randomized controlled trial testing daily high-dose vitamin C (750 mg), vitamin E (268 mg), and β-carotene (15 mg) supplements combined for 3 years reported a small deceleration of cataract progression (17), and another randomized controlled trial examining multivitamin/mineral supplements with

### DISCUSSION

In this large, prospective, population-based cohort of men, we observed that those who used high-dose vitamin C or vitamin E supplements (but not low-dose multivitamins) had a statistically significant increased risk of age-related cataract. The positive association between vitamin C use and risk of cataract was even stronger among those with higher oxidative stress because of older age and corticosteroid use and among long-term users. The limited number of vitamin E users only did not allow us to evaluate the associations for long-term vitamin E use and associations

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Total No. of Subjects</th>
<th>No. of Cases</th>
<th>HRd</th>
<th>95% CI</th>
<th>No. of Cases</th>
<th>HRd</th>
<th>95% CI</th>
<th>Attributable Proportion due to Interactionc</th>
<th>95% CId</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>18,311</td>
<td>804</td>
<td>1.00</td>
<td>Referent</td>
<td>63</td>
<td>1.07</td>
<td>0.83, 1.38</td>
<td>0.19</td>
<td>−0.01, 0.40</td>
</tr>
<tr>
<td>&gt;65</td>
<td>5,356</td>
<td>1,133</td>
<td>1.48</td>
<td>1.14, 1.91</td>
<td>125</td>
<td>1.92</td>
<td>1.41, 2.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never users</td>
<td>16,270</td>
<td>1,283</td>
<td>1.00</td>
<td>Referent</td>
<td>123</td>
<td>1.18</td>
<td>0.98, 1.42</td>
<td>0.29</td>
<td>0.01, 0.56</td>
</tr>
<tr>
<td>Ever users</td>
<td>1,942</td>
<td>239</td>
<td>1.33</td>
<td>1.16, 1.53</td>
<td>31</td>
<td>2.11</td>
<td>1.48, 3.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

a A total of 7,453 men (out of 31,120 men) using other supplements than vitamin C only were excluded.

b No reported use of other vitamin or mineral supplements.

c The attributable proportion of risk due to interaction (in excess of the additive effects between the 2 exposures) and the corresponding 95% confidence interval.

d Adjusted for age (5-year age groups: <50, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75), smoking (never, past, current smokers ≤10 and >10 cigarettes/day), abdominal obesity (waist circumference <94 or ≥94 cm), educational level (<9, 9–12, or ≥12 years), history of hypertension (yes or no), corticosteroid use (yes or no), alcohol intake (g/day in quartiles), fruit and vegetable intakes (g/day, continuous), physical activity (metabolic equivalent × hours/day, quartiles), and self-reported health (scale of 1 from good (i.e., 1) to bad (i.e., 5)).

Of 23,667 men, there were 5,455 men with missing information on corticosteroid use.

CIs for interaction including 0) or the multiplicative (all P’s for interaction > 0.8) scale. There were too few cases to examine if the association between vitamin E use and cataract risk was stronger with long-term use or among men with reactive oxygen species–generating factors.

Compared with that for non–supplement users, the multivariable-adjusted hazard ratio for vitamin C only supplement users with low vitamin C intake from diet (< median, 96.9 mg/day) was 1.30 (95% CI: 1.06, 1.58), and for high vitamin C intake from diet (≥ median), the hazard ratio was 1.12 (95% CI: 0.90, 1.40) (P for interaction = 0.32). Among vitamin E only supplement users with low vitamin E intake from diet (< median, 8.8 mg/day), the hazard ratio for cataract was 1.70 (95% CI: 1.09, 2.65), and for high vitamin E intake (≥ median), the hazard ratio was 1.38 (95% CI: 0.78, 2.44) (P for interaction = 0.56). Vitamin C or vitamin E from diet (≥ median compared with < median) was not associated with cataract risk; the hazard ratios were 1.04 (95% CI: 0.95, 1.13) and 1.00 (95% CI: 0.92, 1.08), respectively.

relatively low doses of vitamin C (180 mg/day) and vitamin E (40 mg/day) reported decreased risk of nuclear cataracts only among participants aged ≥ 65 years (18). Prospective studies have also observed decreased risk for nuclear (22, 24) and cortical cataracts among women aged < 60 years (21) and for long-term users (25). Multivitamin use was not associated with cataract risk in some prospective studies (20, 21) and randomized controlled trials (14, 18), whereas others observed a decreased risk of cataract (23, 25, 26) and some cataract subtypes (18, 22, 24).

Several factors may contribute to the differences between our results and those of other studies. First, the outcomes differed, as some studies investigated the risk of cataract diagnosis or extraction (11–15, 18), while others examined the change in lens opacification (16, 17). Second, the dose of supplements used differed. Third, the randomized controlled trials were based on populations with different baseline nutritional status and were ongoing for shorter periods (3–6 years), except for 2 studies (8–9 years) (11, 12). However, the populations in these 2 studies were based on physicians and nurses, who are generally more health conscious and well nourished: Only 3%–4% among the physicians were current smokers (11), compared with 24% of the men in this study. In another randomized controlled trial, malnutrition was common at baseline (18).

Although vitamin C and vitamin E have been proposed, because of antioxidant properties, to decrease the risk of cataract (10, 41), in vitro and animal studies using large doses of vitamin C and vitamin E have shown their prooxidative effects, such as enhancing the toxic effect of hydrogen peroxide in glutathione-depleted lens epithelial cells (42). High vitamin C concentrations may disturb oxidation-reduction homeostasis of the lens and promote cataractogenesis (43), for example, by increasing glycation of lens proteins (28–30) and generating superoxide (31). The plasma vitamin C concentration is suggested to reach a plateau by intake of ≈ 200 mg of vitamin C/day (44). However, vitamin C concentrations in the lens are from 50- to 60-fold higher than in plasma, and a linear relation between dietary intake and lens concentrations has been reported (44). This suggests that oversupplementation may lead to an even higher vitamin C accumulation in the lens and result in a prooxidative state. High vitamin E concentrations may also disturb oxidation-reduction homeostasis of the lens, by inducing lipid peroxidation (45) and inhibiting glutathione S-transferase (27). Moreover, vitamin E supplements containing only α-tocopherol may also reduce other natural forms of vitamin E (46). Studies have shown 2-fold higher vitamin E concentrations in cataract lenses compared with noncataract lenses (47), and high plasma vitamin E concentrations have been associated with increased risk of all types of cataracts, but this was not observed for vitamin C (48).

Our observation that the increased risk of cataract was attenuated and not statistically significant for users of multiple supplements in addition to vitamin C or vitamin E could be because the use of other supplements may lessen the increased risk associated with use of vitamin C or vitamin E only. These results resemble the results from a recently published large randomized controlled trial examining the effect of vitamin E and selenium supplements (taken separately or together) on the risk of prostate cancer (7). The risk was increased in the groups receiving only vitamin E (HR = 1.17, 95% CI: 1.004, 1.36) or selenium (HR = 1.09, 95% CI: 0.93, 1.27), but in the group receiving vitamin E and selenium together, the risk was attenuated (HR = 1.05, 95% CI: 0.89, 1.22) (7).

The biological mechanisms behind the observed statistically significant interaction between vitamin C use and corticosteroid use may involve an inflammatory mechanism (49). Corticosteroid use is a known risk factor for cataract (50) and has also been associated with increased reactive oxygen species production (51). Furthermore, use of corticosteroids may indicate an underlying illness associated with increased oxidative stress and inflammation. Oxidative stress associated with aging may also explain the higher risk estimates for cataract among men aged > 65 years using vitamin C.

There are several strengths of this study. First, the large, population-based, prospective design includes many cases of cataract. Second, we had information on both cataract diagnosis and extraction. Third, the validity of the self-reported supplement use data, as assessed by sensitivity and specificity, was relatively high, which allowed us to correct for misclassification bias of the exposure.

There are also some limitations of this study. The possibility of outcome misclassification exists because lens opacities can occur without symptoms. This may lead to underestimation of the association. Because of the lack of standardized eye examinations in the cohort, we did not have information on cataract subtypes or grade of lens opacity and could therefore not examine whether the association was restricted to a certain subtype. As we did not have information on the exact doses of supplements used in this study, we used an estimation of the most commonly used doses in Sweden (32, 33). One could speculate that our results may be affected inasmuch as men using supplements may be more health conscious and seek medical help earlier. However, multivitamin use was not associated with increased cataract risk. By excluding the first 4 years of follow-up, we found that the risk estimates remained similar, which contradicts the notion that the association is due to reversed causality. After adjustments for health status and health behavior–related factors, such as fruit and vegetable intakes, education, and physical activity, similar results were obtained. Moreover, everyone has the same access to cataract extractions (patient charge of <$50/surgery) in the Swedish health-care system.

In conclusion, the use of high-dose vitamin C or vitamin E supplements (but not low-dose multivitamins or vitamins C and E together with other supplements) may be associated with increased risk of age-related cataract among men. The risk for cataract with vitamin C use may be even higher among those with potentially higher oxidative stress and among long-term users. In the broader context of accumulating evidence from other recent studies also showing potentially harmful effects of high-dose antioxidant supplements, our results further underscore the need to consider use of unregulated supplements with caution.
ACKNOWLEDGMENTS

Author affiliations: Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Jinjin Zheng Selin, Susanne Rautiainen, Birgitta Ejdervik Lindblad, and Alicia Wolk); Division of Biochemical Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Ralf Morgenstern); Division of Preventive Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts (Susanne Rautiainen); Department of Ophthalmology, Örebro University Hospital, Örebro, Sweden (Birgitta Ejdervik Lindblad); and School of Health and Medical Sciences, Örebro University, Örebro, Sweden (Birgitta Ejdervik Lindblad).

This work was supported by research grants from the Swedish Council for Working Life and Social Research (Dnr. blad); and School of Health and Medical Sciences, Örebro University Hospital, Örebro, Sweden (Birgitta Ejdervik Lindblad and Susanne Rautiainen); Department of Ophthalmology, Örebro University Hospital, Örebro, Sweden (Birgitta Ejdervik Lindblad); and School of Health and Medical Sciences, Örebro University, Örebro, Sweden (Birgitta Ejdervik Lindblad).

Conflict of interest: none declared.

REFERENCES