Vitamin C supplements and the risk of age-related cataract: a population-based prospective cohort study in women[1–3]

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ABSTRACT

Background: Experimental animal studies have shown adverse effects of high-dose vitamin C supplements on age-related cataract.

Objective: We examined whether vitamin C supplements (≈1000 mg) and multivitamins containing vitamin C (≈60 mg) are associated with the incidence of age-related cataract extraction in a population-based, prospective cohort of women.

Design: Our study included 24,593 women aged 49–83 y from the Swedish Mammography Cohort (follow-up from September 1997 to October 2005). We collected information on dietary supplement use and lifestyle factors with the use of a self-administrated questionnaire. Cataract extraction cases were identified by linkage to the cataract extraction registers in the geographical study area.

Results: During the 8.2 y of follow-up (184,698 person-years), we identified 2497 cataract extraction cases. The multivariable hazard ratio (HR) for vitamin C supplement users compared with that for nonusers was 1.25 (95% CI: 1.05, 1.50). The HR for the duration of >10 y of use before baseline was 1.46 (95% CI: 0.93, 2.31). The HR for the use of multivitamins containing vitamin C was 1.09 (95% CI: 0.94, 1.25). Among women aged ≥65 y, vitamin C supplement use increased the risk of cataract by 38% (95% CI: 12%, 69%). Vitamin C use among hormone replacement therapy users compared with that among nonusers of supplements or of hormone replacement therapy was associated with a 56% increased risk of cataract (95% CI: 20%, 102%). Vitamin C use among corticosteroid users compared with that among nonusers of supplements and corticosteroids was associated with an HR of 1.97 (95% CI: 1.35, 2.88).

Conclusion: Our results indicate that the use of vitamin C supplements may be associated with higher risk of age-related cataract among women. *Am J Clin Nutr* doi: 10.3945/ajcn.2009.28528.

INTRODUCTION

Although vitamin C has been hypothesized to decrease the risk of age-related cataracts related to oxidative damage of the lens (1, 2), the opposite effect has been observed in animal and experimental cell studies. In vitro studies (3–5) have shown that vitamin C mediates glycation of lens proteins and generation of superoxide anions (6). Moreover, increased uptake of vitamin C by the lens in a humanized mouse model has been shown to modify lenticular proteins that then contribute to cataractogenesis (7).

To our knowledge, there are no randomized controlled trials (RCTs) that have investigated the effect of vitamin C specifically. Published RCTs have investigated a joint effect of vitamin C with other antioxidants and have yielded conflicting results; vitamin C supplements were not associated with the risk of cataract in 3 studies (8–10) and were associated with decreased risk in one (11). The majority of prospective cohort studies showed no association (12–16), and 2 studies showed decreased risk (17, 18) of age-related cataract. However, some studies suggest that long-term vitamin C supplement use may be associated with increased risk of some cataract subtypes among older women (15, 16) and decreased risk among younger women (15, 16). The majority of the epidemiologic studies only adjusted for limited numbers of confounders.

To our knowledge, no previous study has investigated whether an effect from supplement use may be modified by factors associated with higher reactive oxygen species (ROS) production such as obesity (19), alcohol consumption (20), hormone replacement therapy (HRT) (21), and corticosteroid use (22).

We designed our study to investigate the associations between use of high-dose vitamin C supplements and multivitamins (containing a low dose of vitamin C) and age-related cataract extractions in a large population–based, prospective cohort of women. We also examined whether the association varied by ROS-generating factors such as age, smoking, obesity, alcohol consumption, HRT, and corticosteroid use.

SUBJECTS AND METHODS

The Swedish Mammography Cohort was established between 1987 and 1990 among women residing in the Uppsala and Västmanland counties in central Sweden. All women born in the region between 1914 and 1948 (n = 90,303) received a mailed questionnaire concerning diet and other factors, and 74% of these women completed the questionnaire. A more detailed description of the cohort has been described elsewhere (23). In 1997, to update and expand exposure data, a second questionnaire was sent to all 56,030 cohort members who were alive. The

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1997 questionnaire included questions on diet, vitamin supplement use, cigarette smoking, alcohol consumption, waist circumference, educational level, use of some medications (including HRT and corticosteroids), and medical history (including diagnoses of hypertension, diabetes, or cardiovascular diseases). In the present study, the 1997 questionnaire [which was completed by 38,984 women (70%)] was used as the baseline questionnaire, because it provided information on potential confounders and modifiers of the studied association.

The following exclusions were made: 1738 women with diagnosis of cancer (except nonmelanoma skin cancer) before baseline in 1997, 89 women with cataract extraction before 1997, 1788 women who moved away from the geographical study area between 1987 and 15 September 1997, and 1751 women with missing information on supplement use status. To avoid influence from changes in dietary habits and in use of dietary supplements due to prevalent chronic disease, we excluded women who, before baseline, reported or were hospitalized with (identified through inpatient registers) diabetes (n = 1040), high blood pressure (n = 5538), and cardiovascular disorders (n = 2447). After these exclusions, the study cohort included 24,593 women at the start of follow-up (September 1997).

Ascertainment of dietary supplement use and diet

Women were asked whether they were regular, occasional, or nonusers of dietary supplements. For regular and occasional users there were predefined questions on the duration of use of the following supplements: vitamin C, multivitamins/minerals, vitamin E, calcium, and fish oil. There were also questions on the use of β-carotene, selenium, zinc, coenzyme-Q10, ginseng, B vitamins, and magnesium. In 2 Swedish populations, the most frequently used dose of single nutrient vitamin C supplements has previously been observed to contain 1000 mg (24, 25). Multivitamins have been estimated to contain recommended daily allowances of vitamin C (60 mg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 μg), and folic acid (400 μg) (26). The sensitivity and specificity of the supplement use data obtained from the questionnaire have been estimated to be 78% and 93% for any dietary supplement use, 69% and 98% for multivitamin use, and 67% and 93% for vitamin C use, respectively (24). Women also completed a 96-item food-frequency questionnaire in which they answered how often, on average, they had consumed each type of food or beverage during the last year by using 8 predefined response categories. Open-ended questions were used for foods and beverages consumed daily (eg, bread, coffee, and tea).

Case definition

Women with age-related cataract extraction (*International Classification of Diseases, version 10*, code H25) were identified in the 2 counties between September 1997 and October 2005 by linking national registration numbers of the cohort members to registers of surgical cataract extraction in the study area. 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, the majority of women have a preoperative visual acuity (VA) in the cataract-containing eye of <0.6, which corresponds to difficulties in driving. During the study period, the mean preoperative VA in the cataract-containing eye was 0.3, which corresponds to difficulties in reading the newspaper, and approximately one-fourth of all women were legally blind (VA $<$ 0.1) (27).

Information on date of death and date of moving out of the study area was obtained from the Swedish Death Register and the Swedish Population Register, which are nearly 100% complete (28). Information on cancer, myocardial infarction, stroke, angina pectoris, diabetes, and hypertension from hospitalized women was obtained from the National Inpatient Register at the National Board of Health and Welfare. The Regional Ethical Board at Karolinska Institutet (Stockholm, Sweden) approved this investigation, and the self-administrated questionnaire was considered to imply informed consent to participate in the study.

Statistical analyses

All cohort members were followed until the date of surgical cataract extraction, death, migration out of the study area, or the end of follow-up (31 October 2005), whichever came first. The women were divided into dietary supplement users and nonsupplement users. Supplement users were further divided into use of vitamin C not in combination with other supplements or use of multivitamins/minerals not in combination with other supplements. Differences in characteristics were analyzed with analysis of variance. Bonferroni correction was used to adjust for multiple comparisons. We further investigated the duration of vitamin C supplements in relation to cataract extraction. A Cox proportional hazards model was used to estimate relative risks as hazard ratios (HRs) with 95% CIs (29) by using the PHREG procedure in SAS (version 9.1; SAS Institute Inc, Cary, NC). In the multivariable analysis, the HRs were adjusted for age, smoking, alcohol consumption, waist circumference, HRT use, corticosteroid use (tablets or inhaled corticosteroids), and educational level. Missing values for any potential confounder were treated as a separate "missing" category in the model. The proportional hazard assumption was tested; we did not find evidence of violation of this assumption. To evaluate the potential bias of the observed HRs due to exposure misclassification, we performed probabilistic sensitivity analyses (30, 31) by using the sensitivity and specificity estimates for the dietary supplement use data from a previous validation study (24). With the use of 2000 iterations, we assumed nondifferential misclassification to a triangular distribution with a minimum of 0.60 and a maximum of 0.90 for sensitivity and a minimum of 0.92 and a maximum of 0.99 for specificity. The sensitivity analysis was performed by using STATA (version 10; StataCorp, College Station, TX).

Furthermore, we investigated whether the risk from vitamin C supplement use on surgical cataract extraction differed by age ($<$65 y or $\geq$65 y), smoking status (never or ever), alcohol consumption (never or ever), waist circumference ($<$80 cm or $\geq$80 cm), HRT use (never or ever), corticosteroid use (never or ever), and vitamin C derived from foods ($<$median or $\geq$median). We calculated the attributable proportion (AP) of risk due to interaction and the corresponding 95% CI (32, 33). The AP measures the excess over additivity of effects and is interpreted as the proportion of risk of a given outcome among cases with both exposures of interest (vitamin C supplement use, together with ROS-generating factors) that is due to the

TABLE 1
Baseline characteristics of women in the Swedish Mammography Cohort (n = 24,593)[1]

Variables	Dietary supplement use			
	No supplement use (n = 9974)	Only vitamin C (n = 1225)[2]	Only multivitamins (n = 2259)[3]	Any supplement (n = 14,619)
Age (y)	59.6 ± 8.5[4]	60.4 ± 8.7[5]	60.9 ± 9.2	60.6 ± 8.9[5]
Education >12 y (%)	18.1	19.6	25.5[5]	22.6[5]
Alcohol consumption (%)	82.5	85.9[5]	84.4[5]	86.6[5]
Current smoking (%)	25.9	25.2	23.1	23.5[5]
Waist circumference (cm)	83.0 ± 10.5	82.3 ± 10.4	81.3 ± 10.0[5]	81.8 ± 10.2[5]
Hormone replacement therapy use (%)	40.2	47.2[5]	51.5[5]	51.5[5]
Corticosteroid use (%)	10.9	11.3	13.0	14.3[5]
Vitamin C from diet (g/d)	111 ± 54	113 ± 55	113 ± 54	116 ± 56[5]

[1] Age-standardized to the entire study cohort.
[2] Vitamin C use not in combination with other supplements.
[3] Multivitamin use not in combination with other supplements.
[4] Mean ± SD (all such values).
[5] Significantly different from nonsupplement users, $P < 0.05$ (ANOVA).

interaction between the 2 exposures. A value close to zero means no interaction, a value above zero suggests synergistic interaction between the 2 exposures, and a value below zero suggests antagonistic interaction (34). We also performed multiplicative interaction tests on all categories with the likelihood tests. All P values shown are 2-sided. P values <0.05 were considered statistically significant.

RESULTS

During the 8.2 y of follow-up of the cohort (184,698 person-years), we identified 2497 cases of age-related cataract extraction in the cohort. At baseline, 59% of the women reported taking any kind of supplements, 9% taking only multivitamins, and 5% taking only vitamin C supplements. Women taking any dietary supplements were more likely to have >12 y of education, to consume alcohol, to smoke less, have a smaller waist circumference, to use HRT or corticosteroids, and to have a higher intake of vitamin C obtained from diet than those not taking supplements (**Table 1**).

The association between dietary supplement use and the incidence of age-related cataract extraction is presented in **Table 2**. In the multivariable analysis of cataract extraction, vitamin C users (incidence rate: 476/1000 person-years; 95% CI: 404/1000, 561/1000 person-years), compared with nonusers (incidence rate: 353.44 person-years; 95% CI: 331/1000, 378/1000 person-years), showed a 25% increased risk (95% CI: 5%, 50%) of cataract. In the multivariable analysis, users of any dietary supplements (incidence rate: 451 person-years; 95% CI: 430/1000, 474/1000 person-years) had a 10% increased risk (95% CI: 1%, 20%). The association between vitamin C use and cataract extraction was similar among regular and occasional users. The multivariable HR for a long duration (≥10 y) of vitamin C use (number of cases = 18) was 1.46 (95% CI: 0.93,

TABLE 2
Association between dietary supplement use and surgical cataract extraction in Swedish women (n = 24,593)[1]

	Dietary supplement use			
	No supplement use (n = 9974)	Only vitamin C (n = 1225)[2]	Only multivitamins (n = 2259)[3]	Any supplement (n = 14,619)
No. of cases	878	143	252	1,619
Person-years	75,524	9134	16,815	109,173
Age-adjusted HR	1.00 (ref)	1.27 (1.07, 1.52)	1.10 (0.95, 1.26)	1.13 (1.04, 1.23)
Multivariable HR[4]	1.00 (ref)	1.25 (1.05, 1.50)	1.09 (0.94, 1.25)	1.10 (1.01, 1.20)
Excluding first 5 y[5]				
No. of cases	464	76	131	822
Person-years	74,316	8938	16,448	106,793
Age-adjusted HR	1.00 (ref)	1.34 (1.05, 1.71)	1.12 (0.95, 1.36)	1.12 (0.99, 1.25)
Multivariable HR[4]	1.00 (ref)	1.32 (1.03, 1.68)	1.12 (0.92, 1.37)	1.08 (0.97, 1.22)

[1] HR, hazard ratio (obtained from Cox proportional hazards models); ref, reference.
[2] Vitamin C use not in combination with other supplements.
[3] Multivitamin use not in combination with other supplements.
[4] Adjusted for age (5-y age groups: ≤52, 53–57, 58–62, 63–67, 68–72, 73–77, or ≥78 y), waist circumference (<80 or >80 cm), smoking (never; mean lifetime: ≤10 or >10 cigarettes/d), alcohol consumption (g/d in quartiles), steroid medication use (yes or no), educational level (<10, 10–12, or >12 y), and hormone replacement therapy use (never, past, or current).
[5] Risk of reversed causality checked by excluding the first 5 y of follow-up.

2.31). Additional adjustment for physical activity did not change the results. In further analysis, we investigated whether the observed association could be due to reversed causality, as visual difficulties might lead to vitamin C supplement use. When we excluded individuals who had undergone the surgery during the first 5 y of follow-up, we observed a statistically significant 32% increased risk (95% CI: 3%, 68%). We also performed sensitivity analysis to quantify the likely effects of misclassification of vitamin C supplement use. The sensitivity analysis showed that by using sensitivity of 0.67 and specificity of 0.93 for vitamin C supplement use, the median HR for vitamin C supplement users, compared with that in nonusers, would be 2.

To evaluate whether the increased risk of cataract among vitamin C supplement users was modified by a potential high presence of ROS, we performed subgroup analyses of participants in the Swedish Mammography Cohort including age, smoking status, alcohol consumption, HRT, and corticosteroid use (**Table 3**). The AP due to interaction indicated no synergistic effects (AP $>$ 0) between vitamin C supplement use and age, HRT, and corticosteroid use. However, the interaction on the additive scale was only statistically significant for age and HRT use. The *P* value for interaction on the multiplicative scale was 0.12 for age and 0.15 for HRT use, whereas the *P* value for interaction was $>$0.2 for smoking, alcohol consumption, and corticosteroid use. The risk was higher among women aged $\geq$65 y (HR: 1.38; 95% CI: 1.12, 1.69), who never smoked (HR: 1.38; 95% CI: 1.11, 1.72), who consumed alcohol (HR: 1.25; 95% CI: 1.01, 1.53), who ever used HRT (HR: 1.42; 95% CI: 1.10, 1.84), and who ever

TABLE 3
Association (with 95% CIs) between vitamin C supplement use and cataract extraction by subgroups of age, smoking status, alcohol consumption, hormone replacement therapy (HRT) use, and corticosteroid use (n = 11,199)[1]

Subgroups	No supplement use (n = 9974)	Only vitamin C (n = 1225)	Attributable proportion due to interaction[2]
Age			
$\leq$65 y (n = 8324)			
No. of cases	278	34	
Multivariable HR[3]	1.00 (ref)	0.99 (0.69, 1.41)	
$>$65 y (n = 2875)			
No. of cases	600	109	
Multivariable HR[3]	1.28 (0.94, 1.73)	1.74 (1.24, 2.46)	0.28 (0.06, 0.50)
Smoking status[4]			
Never smokers (n = 10,017)			
No. of cases	535	96	
Multivariable HR[3]	1.00 (ref)	1.39 (1.11, 1.71)	
Current and ex-smokers (n = 1002)			
No. of cases	326	45	
Multivariable HR[3]	1.09 (0.94, 1.27)	1.15 (0.85, 1.57)	−0.27 (−0.70, 0.15)
Alcohol consumption[4]			
Never drinkers (n = 1757)			
No. of cases	220	29	
Multivariable HR[3]	1.00 (ref)	1.24 (0.84, 1.83)	
Drinkers (n = 9087)			
No. of cases	612	106	
Multivariable HR[3]	1.12 (0.95, 1.33)	1.40 (1.10, 1.77)	−0.01 (−0.35, 0.32)
HRT[4]			
Never users (n = 6477)			
No. of cases	560	70	
Multivariable HR[3]	1.00 (ref)	1.10 (0.86, 1.42)	
Ever users (n = 4567)			
No. of cases	213	53	
Multivariable HR[3]	1.08 (0.92, 1.27)	1.56 (1.20, 2.02)	0.24 (0.01, 0.46)
Corticosteroid use			
Never users (n = 9972)			
No. of cases	761	115	
Multivariable HR[3]	1.00 (ref)	1.19 (0.98, 1.45)	
Ever users (n = 1227)			
No. of cases	117	28	
Multivariable HR[3]	1.25 (1.04, 1.54)	1.97 (1.35, 2.88)	0.27 (−0.03, 0.57)

[1] Of 24,593 women in the study, we excluded 13,394 women who reported taking supplements other than vitamin C only, which left 11,199 women in our analyses. HR, hazard ratio (obtained from Cox proportional hazards models); ref, reference.

[2] We calculated the attributable proportion of risk due to interaction and the corresponding 95% CI. There was no evidence of interaction when the attributable proportion was equal to zero.

[3] Adjusted for age (5-y age groups: $\leq$52, 53–57, 58–62, 63–67, 68–72, 73–77, or $\geq$78 y), waist circumference ($<$80 or $>$80 cm), smoking (never; mean lifetime: $\leq$10 or $>$10 cigarettes/d), alcohol consumption (g/d in quartiles), steroid medication use (yes or no), educational level ($<$10, 10–12, or $>$12 y), and HRT use (never, past, or current).

[4] Of 11,199 women, 180, 355, and 144 women had missing information on smoking status, alcohol consumption, and HRT use, respectively.

used corticosteroids (HR: 1.57; 95% CI: 1.03, 2.39). We also performed subgroup analysis by educational level. The HRs were 1.33 (95% CI: 0.76, 2.32) among women with ≥12 y of education and 1.28 (95% CI: 1.06, 1.55) among women with <9 y of education. Vitamin C supplement use and risk of cataract extraction did not differ in subgroups of waist-circumference measurement or vitamin C from diet (data not shown).

DISCUSSION

In this large prospective population-based cohort of Swedish women, we observed a statistically significant 25% increased risk of age-related cataract extraction among vitamin C supplement users but not among multivitamin users. A ≥10 y duration of vitamin C use was associated with 46% increased risk, although this association did not reach statistical significance. Furthermore, our data suggest that vitamin C use in combination with older age (≥65 y), HRT, or corticosteroid use is associated with even higher risks of cataract. We investigated the effect of relatively high-dose vitamin C supplements, and therefore our findings should not be translated to vitamin C obtained from diet such as fruit and vegetables.

The hypothesis that vitamin C supplement use may decrease the risk of age-related cataract has not received support in previous studies. In fact, a harmful effect from high-dose vitamin C supplements has been suggested in several in vitro and in vivo studies (3–7), although not in all (35–37). Oxidized vitamin C, dehydroascorbate, has been shown to contribute to glycation of lens proteins (3–5) and generation of superoxide anions (6). Moreover, increased lens uptake of vitamin C in a humanized mouse model led to modification of lenticular proteins, contributing to cataractogenesis (7).

RCTs have only investigated vitamin C together with other nutrients (8–11). Supplementation of 120 mg vitamin C and molybdenum showed a nonsignificant 25% increased risk of posterior subcapsular cataract but a decreased risk of cortical cataract (10). In a recent 5-y RCT with strict inclusion criteria, 500 mg vitamin C, vitamin E, and β-carotene was not associated with cataract (8). Another 6.3-y RCT with 250 mg vitamin C, vitamin E, and β-carotene showed no association (9). In a third 3-y RCT of American and English patients with early age-related cataract, 250 mg vitamin C together with vitamin E and β-carotene was associated with less cataract progression only among American patients (11). Our results are in line with some observational prospective studies showing that vitamin C supplements may increase the risk of cataract. A study in men observed a nonsignificant increased risk of cataract (13). Long-term use among women aged ≥60 y was also associated with a nonsignificant increased risk of cataract extraction (15) and with a statistically significant 2-fold increased risk of cortical opacities (16). However, among women aged <60 y, a nonsignificant inverse association was shown with cataract extraction (15), and statistically significant inverse associations were shown with cortical (16) and nuclear opacities (18). Women and men with >10 y of use had statistically significant decreased risk of any cataract (17).

It may seem paradoxical that vitamin C contributes to cataract development. However, antioxidants in a free radical–rich environment may function as prooxidants (38). Reactive oxygen and nitrogen species also function as signaling molecules in various physiologic processes (38), which suggests that high doses of vitamin C may contribute to a disturbance in redox homeostasis and thereby promote cataractogenesis. Glutathione is thought to play a vital role in the lens as the primary defense against free radicals (2). Absence of glutathione may mediate the reactive properties of vitamin C due to impaired redox cycling of oxidized vitamin C, ie, dehydroascorbate (39).

Our study is the first to investigate whether the association between vitamin C use and cataract risk is modified by ROS-generating factors such as smoking, obesity, alcohol consumption, HRT, and corticosteroids. We have previously shown in this cohort that smoking (23), alcohol consumption (40), and HRT use (41) are associated with higher cataract risk. The increased risk from vitamin C supplement use was higher among older, HRT, and corticosteroid users. The interaction tests on the additive scale were statistically significant for age and HRT use and close to significant for corticosteroid use. However, the multiplicative interaction tests were nonsignificant. The underlying mechanisms for an interaction between high doses of vitamin C and age, HRT, and corticosteroids are unclear; however, they may involve an enhanced inflammatory burden. High blood concentrations of C-reactive protein, a proposed inflammatory biomarker, have been associated with higher risk of cataract (42). Age (2) and HRT (21) have been associated with higher amounts of proinflammatory components that in turn generate ROS. Although corticosteroids, a known risk factor for cataract (43), are anti-inflammatory drugs, they are also associated with enhanced ROS production (22). Corticosteroid use may also be an indicator of an underlying illness contributing to inflammation. Thus, a potential mechanism may involve prooxidative properties of vitamin C and/or involve the enhanced production of dehydroascorbate in the presence of proinflammatory or other ROS-generating factors.

Human studies suggest that plasma vitamin C reaches a plateau at ≈200 mg/d (44, 45) due to lower bioavailability and higher urinary excretion with higher intake. One could therefore question whether high doses of vitamin C lead to increased tissue concentrations. However, at the plateau, plasma vitamin C is still increasing, albeit slowly (44, 45). Moreover, a linear relation between vitamin C intake and concentrations in the lens (50-fold higher than in plasma) has been observed (45). The slow increase in plasma vitamin C with higher intake may suggest that blood concentrations are regulated—implying that higher plasma vitamin C can be detrimental.

This study has several strengths, including the large population-based cohort design as well as a complete follow-up of a relatively homogenous population. We had almost-complete computerized registers of surgical cataract extractions from eye clinics in the study area. Validity of self-reported supplement use, as measured by sensitivity and specificity, was relatively high and allowed us to correct for misclassification bias of the exposure.

There are, however, some limitations with this study. Our outcome was cataract extraction instead of cataract diagnosis because of the lack of standardized eye examinations in the entire cohort and incomplete information on cataract status from medical records. We cannot, therefore, exclude the possibility of misclassification of outcome as lens opacities can exist without symptoms; this would draw the risk estimates toward no association. However, cataract is clinically relevant only if VA is dramatically impaired; women defined as cases had cataracts severe enough to cause visual impairment affecting daily life (VA < 0.6). In the Swedish health care system, everyone has the

same access to cataract surgery, with a patient charge of <$50/surgery. Furthermore, we had no information on cataract subtype and cannot exclude the possibility that the increased risk was restricted to a specific subtype. It may seem a contradiction that we only observed an increased risk of cataract extraction for vitamin C use and not for multivitamin use. Swedish multivitamins include 60 mg ascorbic acid (26), which is a much lower dose than vitamin C–only supplements that contain 1000 mg (24, 25). However, the exact dose of ascorbic acid in supplements was unknown. The effect of vitamin C may vary by duration of corticosteroid use, which can be used for a wide range of clinical illnesses varying in severity and duration of treatment. Women who use corticosteroids may also take vitamin C supplements due to an illness associated with cataract. However, the prevalence of corticosteroid users was the same among nonsupplement (11%) and vitamin C supplement users (11%). Women taking vitamin C supplements could be more health conscious and therefore more likely to seek medical help, which could also explain the interaction between vitamin C and HRT use. However, we did not observe the same association for multivitamin use, and we found no evidence of interaction when performing subgroup analysis of educational level that contradicts the above statement. The observed association could also be due to reversed causality, although; when excluding the first 5 y of follow-up, we observed the same increased risk. Additionally, due to the lack of data we could not take into account the effect of sunlight exposure, which may confound our results.

In conclusion, our results suggest that vitamin C supplement use, particularly in higher dose and for longer duration, may increase the risk of age-related cataract. Further studies are needed to confirm our observation that use of vitamin C supplements may be associated with higher risk of cataract, especially in subgroups of women of older age taking HRT or corticosteroids.

The authors' responsibilities were as follows—SR, BEL, RM, and AW: responsible for the study concept and design; AW: responsible for data collection; SR: performed data analysis; SR and AW: responsible for statistical analyses; AW, BEL, and RM: provided additional expertise; SR: wrote the first draft of the manuscript; AW: obtained funding; and SR, BEL, RM and AW: reviewed and revised the manuscript. None of the authors had any personal or financial conflict of interest.

REFERENCES

1. Chiu CJ, Taylor A. Nutritional antioxidants and age-related cataract and maculopathy. Exp Eye Res 2007;84:229–45.
2. Lou MF. Redox regulation in the lens. Prog Retin Eye Res 2003;22:657–82.
3. Linetsky M, Shipova E, Cheng R, Ortwerth BJ. Glycation by ascorbic acid oxidation products leads to the aggregation of lens proteins. Biochim Biophys Acta 2008;1782:22–34.
4. Cheng R, Lin B, Lee KW, Ortwerth BJ. Similarity of the yellow chromophores isolated from human cataracts with those from ascorbic acid-modified calf lens proteins: evidence for ascorbic acid glycation during cataract formation. Biochim Biophys Acta 2001;1537:14–26.
5. Cheng R, Feng Q, Ortwerth BJ. LC-MS display of the total modified amino acids in cataract lens proteins and in lens proteins glycated by ascorbic acid in vitro. Biochim Biophys Acta 2006;1762:533–43.
6. Linetsky M, James HL, Ortwerth BJ. Spontaneous generation of superoxide anion by human lens proteins and by calf lens proteins ascorbylated in vitro. Exp Eye Res 1999;69:239–48.
7. Fan X, Reneker LW, Obrenovich ME, et al. Vitamin C mediates chemical aging of lens crystallins by the Maillard reaction in a humanized mouse model. Proc Natl Acad Sci USA 2006;103:16912–7.
8. Gritz DC, Srinivasan M, Smith SD, et al. The Antioxidants in Prevention of Cataracts Study: effects of antioxidant supplements on cataract progression in South India. Br J Ophthalmol 2006;90:847–51.
9. AREDS Study. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 2001;119:1439–52.
10. Sperduto RD, Hu TS, Milton RC, et al. The Linxian cataract studies. Two nutrition intervention trials. Arch Ophthalmol 1993;111:1246–53.
11. Chylack LT Jr, Brown NP, Bron A, et al. The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. Ophthalmic Epidemiol 2002;9:49–80.
12. Klein BE, Knudtson MD, Lee KE, et al. Supplements and age-related eye conditions: The Beaver Dam Eye Study. Ophthalmology 2008;115:1203–8.
13. Seddon JM, Christen WG, Manson JE, et al. The use of vitamin supplements and the risk of cataract among US male physicians. Am J Public Health 1994;84:788–92.
14. Leske MC, Chylack LT Jr, He Q, et al. Antioxidant vitamins and nuclear opacities: the longitudinal study of cataract. Ophthalmology 1998;105:831–6.
15. Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of vitamin supplement intake and cataract extraction among U.S. women. Epidemiology 1999;10:679–84.
16. Taylor A, Jacques PF, Chylack LT Jr, et al. Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities. Am J Clin Nutr 2002;75:540–9.
17. Mares-Perlman JA, Lyle BJ, Klein R, et al. Vitamin supplement use and incident cataracts in a population-based study. Arch Ophthalmol 2000;118:1556–63.
18. Jacques PF, Chylack LT Jr, Hankinson SE, et al. Long-term nutrient intake and early age-related nuclear lens opacities. Arch Ophthalmol 2001;119:1009–19.
19. Pou KM, Massaro JM, Hoffmann U, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation 2007;116:1234–41.
20. Szabo G, Mandrekar P, Oak S, Mayerle J. Effect of ethanol on inflammatory responses. Implications for pancreatitis. Pancreatology 2007;7:115–23.
21. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab 2006;8:538–54.
22. Urban Jr RC, Cotlier E. Corticosteroid-induced cataracts. Surv Ophthalmol 1986;31:102–10.
23. Lindblad BE, Hakansson N, Svensson H, Philipson B, Wolk A. Intensity of smoking and smoking cessation in relation to risk of cataract extraction: a prospective study of women. Am J Epidemiol 2005;162:73–9.
24. Messerer M, Wolk A. Sensitivity and specificity of self-reported use of dietary supplements. Eur J Clin Nutr 2004;58:1669–71.
25. Holmquist C, Larsson S, Wolk A, de Faire U. Multivitamin supplements are inversely associated with risk of myocardial infarction in men and women–Stockholm Heart Epidemiology Program (SHEEP). J Nutr 2003;133:2650–4.
26. Messerer M, Johansson SE, Wolk A. The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men. J Nutr 2004;134:1800–5.
27. National Cataract Register 08/11/08, Nationella Kataraktregistret Eye-Net Sweden, Blekingesjukhuset, 371 85 Karlskrona, Sweden. Available from: http://www.cataractreg.com/Cataract_Sve/forstasida.htm (cited 8 November 2008).
28. Mattsson B, Wallgren A. Completeness of Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984;23:305–13.
29. Cox D. Regression models and life-tables. J Roy Stat Soc B 1972;34:187–220.
30. Orsini N, Bellocco R, Bottai M, Wolk A, Greenland S. A tool for deterministic and probabilistic sensitivity analysis of epidemiologic studies. Stata J 2008;8:29–48.
31. Fox MP, Lash TL, Greenland S. A method to automate probabilistic sensitivity analyses of misclassified binary variables. Int J Epidemiol 2005;34:1370–6.

32. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2008.
33. Assmann SF, Hosmer DW, Lemeshow S, Mundt KA. Confidence intervals for measures of interaction. Epidemiology 1996;7:286–90.
34. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005; 20:575–9.
35. Reddy VN, Giblin FJ, Lin LR, Chakrapani B. The effect of aqueous humor ascorbate on ultraviolet-B-induced DNA damage in lens epithelium. Invest Ophthalmol Vis Sci 1998;39:344–50.
36. Tung WH, Chylack LT Jr, Andley UP. Lens hexokinase deactivation by near-UV irradiation. Curr Eye Res 1988;7:257–63.
37. Reddy GB, Bhat KS. Protection against UVB inactivation (in vitro) of rat lens enzymes by natural antioxidants. Mol Cell Biochem 1999;194: 41–5.
38. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44–84.
39. Truscott RJ. Age-related nuclear cataract-oxidation is the key. Exp Eye Res 2005;80:709–25.
40. Lindblad BE, Hakansson N, Philipson B, Wolk A. Alcohol consumption and risk of cataract extraction: a prospective cohort study of women. Ophthalmology 2007;114:680–5.
41. Lindblad BE, Hakansson N, Philipson B, Wolk A. Hormone replacement therapy in relation to risk of cataract extraction—a prospective study of women. Ophthalmology (in press).
42. Schaumberg DA, Ridker PM, Glynn RJ, Christen WG, Dana MR, Hennekens CH. High levels of plasma C-reactive protein and future risk of age-related cataract. Ann Epidemiol 1999;9:166–71.
43. Cumming RG, Mitchell P. Inhaled corticosteroids and cataract: prevalence, prevention and management. Drug Saf 1999;20:77–84.
44. Levine M, Wang Y, Padayatty SJ, Morrow J. A new recommended dietary allowance of vitamin C for healthy young women. Proc Natl Acad Sci USA 2001;98:9842–6.
45. Taylor A, Jacques PF, Nowell T, et al. Vitamin C in human and guinea pig aqueous, lens and plasma in relation to intake. Curr Eye Res 1997;16:857–64.