

Serum carotenoids and tocopherols and incidence of age-related nuclear cataract¹⁻³

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ABSTRACT

Background: It is not known whether the protective effects of antioxidants on cataract observed in experimental animals are relevant to age-related opacities in humans.

Objective: The relations of serum carotenoids and tocopherols to the incidence of age-related nuclear cataract were investigated in a random sample of 400 adults, 50–86 y of age, in the Beaver Dam Eye Study.

Design: Nuclear opacity was assessed by using lens photographs taken at baseline (in 1988–1990) and follow-up (in 1993–1995). Nonfasting concentrations of individual carotenoids and α - and γ -tocopherol, were determined from serum obtained at baseline. A total of 252 persons were eligible for incident cataract, of whom 57 developed nuclear cataract in at least one eye. Results were adjusted for age, smoking, serum cholesterol, heavy drinking, adiposity, and, in the tocopherol models, dietary linoleic acid intake.

Results: Only serum tocopherol (the sum of α - and γ -tocopherol, in $\mu\text{mol}/\text{mmol}$ cholesterol) was associated with cataract. For total serum tocopherol, persons in tertile 3 had a lower risk of cataract than persons in tertile 1 [odds ratio (OR): 0.4; 95% CI: 0.2, 0.9; $P = 0.03$ for linear trend]. Although serum carotenoids were not significantly associated with nuclear cataract, marginal inverse associations with lutein (OR: 0.3; 95% CI: 0.1, 1.2; $P = 0.13$ for linear trend) and cryptoxanthin (OR: 0.3; 95% CI: 0.1, 1.3; $P = 0.11$ for linear trend) were suggested in people ≥ 65 y of age.

Conclusions: Findings were compatible with the possibility that nuclear cataract may be linked inversely to vitamin E status, but neither strongly supported nor negated the hypothesized inverse association of nuclear cataract with serum carotenoids. *Am J Clin Nutr* 1999;69:272–7.

KEY WORDS Serum carotenoids, serum tocopherols, humans, aging, nuclear cataract, vitamin E status, Beaver Dam Eye Study

INTRODUCTION

Opacification of the ocular lens, or cataractogenesis, is a multifactorial disease process that may be initiated or promoted by oxidative damage (1). Carotenoids and vitamin E may influence this process because of their ability to scavenge free radicals and thereby reduce oxidative damage to lens tissues. Although animal models have shown that β -carotene and vitamin E can help pro-

tect lenses from experimentally induced damage to the lens (2–6), their effect on age-related human lens opacities is not known.

Studies examining associations between self-reported antioxidant nutrient intakes and the presence of nuclear cataract have yielded inconsistent findings (7–9). This can be partly explained by an imprecise assessment of carotenoid and tocopherol status based on self-reported dietary intakes. For example, dietary intakes do not take into account differences in the utilization (including absorption) of carotenoids. Carughi and Hooper (10) reported large interindividual variability in plasma carotenoid concentrations after supplementation with a fruit and vegetable concentrate containing standardized doses of α -carotene, β -carotene, and lycopene. Also, vitamin E status is difficult to assess from reported food intakes because the type of oil used in prepared foods affects the vitamin E content, and this information is not easily obtained by dietary assessment. Serum concentrations of carotenoids and tocopherols provide a second measure of status that is independent of errors in dietary assessment and takes into account biological variation in the utilization of nutrients, including differences in absorption.

Several studies have assessed carotenoid or tocopherol status based on measured concentrations in serum. Plasma α -tocopherol was inversely associated with nuclear opacities in the Baltimore Longitudinal Study on Aging (11) and in the Lens Opacities Case-Control Study with both prevalent (12) and incident (13) nuclear opacities, but was not associated with nuclear opacities in the Italian American Cataract Study (9), the India-US case-control study (14), or the Kupio Atherosclerosis Prevention Study (15). Plasma β -carotene was not associated with nuclear opacities in the Baltimore Longitudinal Study on Aging (11).

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²Supported by National Institutes of Health grants EYO8012 (to JAM-P) and EYO6594 (to RK and BEKK) and by an unrestricted grant from the Research to Prevent Blindness.

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Received February 25, 1998.

Accepted for publication September 8, 1998.

Nuclear cataracts and individual serum carotenoids and tocopherols have been assessed previously only in cross-sectional analyses from the Beaver Dam Eye Study (16). In this cross-sectional study, nuclear opacities were inversely associated with serum concentrations of γ -tocopherol but not with α -tocopherol or 5 specific carotenoids (16).

Prospective studies, in which nutritional status is assessed before changes in lens opacity occur, are needed to more carefully investigate relations between diet and the development of cataracts. The purpose of this study was to determine whether serum carotenoid or tocopherol concentrations were associated with the 5-y incidence of age-related nuclear cataracts in a population-based study of middle- to older-aged adults residing in Beaver Dam, WI.

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 University of Wisconsin Human Subjects Review Board and informed consent was obtained from each participant. The entire population of persons 43–86 y of age residing in Beaver Dam was identified by private census and recruited to participate in the study. Of the 5925 persons eligible, 4926 (83.1%) participated in the study at the baseline examination conducted in 1988–1990.

A 50% random sample of the noninstitutionalized participants from the baseline group was invited to participate in the nutrition portion of the study ($n = 2429$). Of persons invited, 90% ($n = 2152$) participated in the nutrition study by completing in-person interviews about their dietary habits. A subsample of 400 nutrition study participants, who were ≥ 50 y of age and whose lens photographs were gradeable, were selected at random to have serum carotenoid and tocopherol concentrations analyzed at baseline. Eighty-one percent ($n = 325$) of these persons participated in the follow-up eye examinations 5 y later. Of the 75 persons not examined at follow-up, 6 could not be located or had moved, 35 were deceased, and 34 refused to participate.

Data collection

Physical examinations and lens photography were conducted in 1988–1990 for baseline and in 1993–1995 for follow-up. Lens photographs were taken with a Topcon SL5 Slit Lamp camera (Paramus, NJ) with specially designed fixation targets for photographing the nuclear (central) region of the lens. Procedures for photographing lenses in this study have been reported previously (17). Medical histories and demographic and behavioral characteristics were obtained at baseline by using a standardized questionnaire administered in conjunction with the physical examinations.

Incidence of nuclear opacities

Opacification in the nuclear region of each ocular lens was graded from photographs on a 5-step ordinal scale. The procedures used to grade lenses and determine nuclear cataract were described previously (18). Briefly, slit lamp photographs were assessed by 2 graders who were unaware of the subjects' characteristics. The scale of severity is based on comparison with 4 standard photographs. Grades 4 and 5 were defined as nuclear

cataract. This level of severity of opalescence of the lens nucleus was chosen because it is similar to the severity a clinician would apply in evaluating the lens. This criteria is the same as was used in the prevalence publications from the Beaver Dam Studies and is the basis for excluding extant cases from consideration for incidence. Of the 325 participants examined at both time points, 252 were free of nuclear cataract at baseline and were at risk of developing nuclear cataract. Participants were ineligible if they had no lens to grade because of prior cataract surgery or lens photographs that were ungradeable ($n = 14$), had a preexisting severe nuclear opacity at baseline ($n = 52$), had an age-related cataract removed before baseline ($n = 6$), or the participant had a gradeable lens but reported experiencing trauma to the lens in the past, which could affect lens opacity ($n = 1$).

Serum analyses

Blood specimens were collected at the baseline examination from nonfasting participants. Total serum cholesterol concentrations were determined immediately (19) and the remaining serum was stored at -80°C in cryogenic vials with O-rings. Serum α -carotene, β -carotene, lutein/zeaxanthin, lycopene, β -cryptoxanthin, α -tocopherol, and γ -tocopherol were measured by using HPLC 2.5 y after baseline examinations had been completed in their entirety (20). Plasma carotenoids and tocopherols have been shown to be stable when frozen at -80°C (21, 22). Coefficients of variability over time using control serums were 6.4% for β -carotene, 5.6% for α -carotene, 6.6% for lutein, 5.8% for lycopene, 5.7% for cryptoxanthin, 3.2% for α -tocopherol, and 4.1% for γ -tocopherol. The sum of α - and γ -tocopherol was used as the estimate of total serum tocopherol concentrations.

Statistics

Participants were assigned to tertiles based on their serum carotenoid and tocopherol concentrations. Risk of incident nuclear cataract was estimated for tertiles 2 and 3 relative to tertile 1 using odds ratios (ORs) and 95% CIs calculated from logistic regression using SAS (SAS Institute, Inc, Cary, NC). Linear trends were assessed by examining P values from logistic regressions based on median serum concentrations for the tertiles.

Potential confounders examined were age; sex; smoking [never, past, current, and pack-years (number of packs of cigarettes smoked per year times the number of years smoked)]; weekly intake of beer, wine, hard liquor, and total alcohol; a history of ever drinking >4 drinks/d; body mass index (BMI; in kg/m^2); hemoglobin and glycosylated hemoglobin concentrations; and a history of hypertension (systolic blood pressure ≥ 160 mm Hg, diastolic ≥ 95 mm Hg, or reported history of hypertension with current use of antihypertensive medication). Variables were retained in fully adjusted logistic regression models if they altered the OR for tertile 3 by $\geq 10\%$ for ≥ 1 nutrient and included age, smoking (in pack-years), history of heavy drinking (never, ever), serum cholesterol concentration, and BMI. Dietary linoleic acid intake was included in models for the tocopherols because of its influence on the physiologic need for vitamin E and because it affected ORs by $>10\%$. Effect modification was tested by using interaction terms in logistic regression. These tests indicated that age, BMI, smoking, and hypertension were possible modifiers of the relation between nuclear cataract and at least one nutrient. Age-stratified results are shown where appropriate. Stratification by the other factors did not alter conclusions, so the data are not shown.



TABLE 1

Characteristics of persons with high and low concentrations of selected serum carotenoids and tocopherol at baseline examinations in the Beaver Dam Eye Study, 1980–1990¹

	β-Carotene (μmol/L)		Lutein (μmol/L)		Total tocopherol (μmol/mmol serum cholesterol)	
	Tertile 1 (0.14, 0.02–0.19) ²	Tertile 3 (0.50, 0.35–1.20)	Tertile 1 (0.18, 0.04–0.22)	Tertile 3 (0.38, 0.31–0.80)	Tertile 1 (4.5, 2.5–4.8)	Tertile 3 (7.0, 5.9–20.9)
Mean age (y)	60.5	62.5	60.7	61.0	60.5	61.7 ³
Sex (% women)	41	53 ⁴	55	51	47	57
Smokers with ≥25 pack-years (%) ⁵	37	18 [*]	30	27	30	29
Alcohol intake ≥91 g/wk (%) ⁶	31	8 ⁴	21	17	21	15
Hypertension (%) ⁷	41	35	36	40	41	42
Body mass index ≥30 (%) ⁸	40	21 ⁴	39	22 ⁴	33	35
Serum cholesterol ≥6.2 mmol/L (%) ⁹	33	56 ⁴	28	59 ⁴	47	41

¹Except for average age, data were standardized to the age distribution of the study cohort.

²Medians and ranges.

^{3,4}Significantly different across tertiles 1 through 3, $P < 0.05$; ³by ANOVA, ⁴by Cochran-Mantel-Haenszel chi-square test for linear trend.

⁵≥25 pack-years was the median among smokers in the full nutrition cohort.

⁶≥91 g alcohol/wk is ≈1 drink/d.

⁷Defined as use of antihypertension medication at baseline, mean systolic blood pressure ≥160 mm Hg, or mean diastolic blood pressure ≥95 mm Hg.

⁸Weight (kg)/height² (m). ≥30 is the cutoff point for class II obesity (24).

⁹Serum cholesterol ≥6.2 mmol/L (240 mg/dL) was determined to be high by the National Cholesterol Education Program (25).

RESULTS

Medical, lifestyle, and dietary correlates of the 5 carotenoids measured in serum in this study population were published previously (23). A brief summary of associations between potential risk factors for nuclear cataract and serum concentrations of selected nutrients is provided in **Table 1**. Persons with high compared with low serum concentrations of β-carotene were more likely to be women (53% in tertile 3 and 41% in tertile 1) and have high serum cholesterol concentrations, but were less likely to be heavy smokers, ingest high amounts of alcoholic beverages, or be obese (Table 1). Similar relations for α-carotene and cryptoxanthin were found (data not shown). There were few differences in these characteristics among persons with high compared with low concentrations of serum lutein (Table 1), lycopene (data not shown), or tocopherols (Table 1). Serum α- and γ-tocopherol concentrations were correlated with serum cholesterol [$r = 0.41$ ($P = 0.001$) and $r = 0.31$ ($P = 0.001$), respectively]. This was expected because tocopherols are transported in lipoproteins along with cholesterol (26). Because of this physiologic link, results for serum tocopherols are presented in micromoles tocopherol per millimoles serum cholesterol. Findings for tocopherol per liter of serum were not significantly different and are not shown.

Of the 252 persons at risk of developing incident cataract, 22% ($n = 57$) developed a cataract during the 5 y of follow-up. Older participants were more likely to have an incident cataract than were younger participants. Among persons ≥65 y of age, 38% ($n = 33$) had an incident cataract compared with 14% ($n = 24$) in those <65 y of age ($\chi^2 P < 0.001$).

Concentrations of each of the 5 serum carotenoids measured were not associated with 5-y incidence of severe nuclear cataract (**Table 2**). Even when combined, total carotenoid concentration was not associated with nuclear cataract (tertile 3 adjusted OR: 0.7; 95% CI: 0.3, 1.7, $P = 0.48$ for linear trend). There were possible interactions by age for lutein ($P = 0.09$) and cryptoxanthin ($P = 0.06$). Adjusted ORs for incidence of cataract for the highest serum cryptoxanthin concentrations (tertile 3) were 1.5 (95% CI: 0.5, 4.8; $P = 0.48$ for linear trend) for persons aged <65 y

and 0.3 (95% CI: 0.1, 1.3; $P = 0.11$ for linear trend) for persons aged <65 y. For lutein, the adjusted OR for cataract among younger persons in tertile 3 was 1.4 (95% CI: 0.3, 6.0; $P = 0.73$ for linear trend), but was 0.3 (95% CI: 0.1, 1.2; $P = 0.15$ for linear trend) among older participants.

ORs for the incidence of nuclear cataracts and serum α- and γ-tocopherol concentrations are shown in **Table 3**. The odds of developing nuclear cataracts were consistently, albeit nonsignificantly, lower for the persons with the highest serum concentrations of α- and γ-tocopherols at baseline. Incidence of nuclear cataract was significantly and inversely related to total serum tocopherol at baseline (**Figure 1**). Compared with persons with the lowest concentrations of serum tocopherol at baseline (tertile 1), persons with concentrations in the middle tertile (tertile 2) had half the risk, and persons with serum concentrations in the top tertile (tertile 3) had less than half the risk [adjusted OR: 0.4 (95% CI: 0.2, 0.9), $P = 0.03$ for linear trend] of developing a severe nuclear cataract over the 5-y follow-up period.

In other analyses using the Beaver Dam Eye Study cohort, high intake of vitamin E from food and supplements appeared to be somewhat more strongly related to nuclear cataract in older persons than in younger persons ($P = 0.01$ for age interaction). To examine the consistency of this pattern using other measures of vitamin E status, results for serum tocopherol were stratified by age. Adjusted ORs for the highest serum concentrations of total tocopherol (μmol/mmol serum cholesterol) were 0.8 (95% CI: 0.3, 2.7; $P = 0.81$) for persons <65 y of age and 0.3 (95% CI: 0.1, 0.9; $P = 0.04$) for persons ≥65 y of age. Despite the appearance of stronger inverse relations among older persons for serum α-, γ-, and total tocopherols (data not shown for α- and γ-tocopherols), regression coefficients for age interaction were not significant ($P = 0.48, 0.36, \text{ and } 0.74$, respectively).

DISCUSSION

This is the first prospective, population-based study of relations between severe nuclear cataract and serum concentrations of individual carotenoids. Because this was a prospective study,

TABLE 2Associations between serum carotenoid concentrations and incidence of nuclear cataract 5 y after baseline examinations in the Beaver Dam Eye Study¹

	Tertiles of serum concentration			<i>P</i> value for trend ²
	1	2	3	
α-Carotene				
Median (μmol/L)	0.04	0.07	0.14	
Range (μmol/L)	0.01–0.05	0.05–0.10	0.10–0.33	
Age-adjusted OR	1.0	0.8 (0.4, 1.8)	0.8 (0.4, 1.8)	0.66
Fully-adjusted OR	1.0	0.8 (0.4, 1.9)	0.9 (0.4, 2.2)	0.96
β-Carotene				
Median (μmol/L)	0.14	0.26	0.50	
Range (μmol/L)	0.02–0.19	0.19–0.35	0.36–1.20	
Age-adjusted OR	1.0	1.3 (0.6, 2.8)	0.8 (0.4, 1.9)	0.54
Fully-adjusted OR	1.0	1.3 (0.6, 2.8)	0.9 (0.4, 2.2)	0.71
Lutein				
Median (μmol/L)	0.18	0.27	0.38	
Range (μmol/L)	0.04–0.22	0.23–0.31	0.31–0.80	
Age-adjusted OR	1.0	1.0 (0.5, 2.1)	0.6 (0.3, 1.4)	0.23
Fully-adjusted OR	1.0	1.1 (0.5, 2.3)	0.7 (0.3, 1.6)	0.35
Lycopene				
Median (μmol/L)	0.29	0.47	0.73	
Range (μmol/L)	0.06–0.38	0.39–0.59	0.59–1.39	
Age-adjusted OR	1.0	0.8 (0.4, 1.7)	1.0 (0.5, 2.3)	0.92
Fully-adjusted OR	1.0	0.8 (0.4, 1.7)	1.1 (0.5, 2.6)	0.79
Cryptoxanthin				
Median (μmol/L)	0.08	0.14	0.29	
Range (μmol/L)	0.01–0.11	0.11–0.20	0.20–0.78	
Age-adjusted OR	1.0	0.7 (0.3, 1.6)	0.6 (0.3, 1.4)	0.27
Fully-adjusted OR	1.0	0.8 (0.3, 1.7)	0.7 (0.3, 1.6)	0.42

¹Fully-adjusted models included age, smoking (pack-years), history of heavy alcohol consumption (never, ever), serum cholesterol concentration, and body mass index (in kg/m²). One person was excluded because information was missing on pack-years. OR, odds ratio. 95% CIs in parentheses.

²Tertile medians used.

serum carotenoid concentrations were determined before severe changes in lens opacities occurred; therefore, only changes in carotenoid status occurring between baseline and follow-up would have directly confounded relations between nutrient status and cataract. The results did not support an association between nuclear cataract and serum concentrations for the 5 carotenoids measured, although these results were inconclusive for lutein and cryptoxanthin. These findings were in contrast with the more severe nuclear cataracts in women in the Beaver Dam Eye Study

with high serum concentrations of the same 5 carotenoids when associations were examined cross-sectionally at the baseline exam (16). Results reported here for the prospective study support previous speculation that temporal confounding may explain the direct associations between serum carotenoids and cataract previously reported in the cross-sectional study.

Inverse associations between important food sources of lutein and nuclear cataract have been reported previously (8, 27, 28), and were also observed in prospective analyses of the Beaver

TABLE 3Associations between concentrations of serum α- and γ-tocopherol and incidence of nuclear cataracts 5 y after baseline examinations in the Beaver Dam Eye Study¹

	Tertiles of serum concentration			<i>P</i> value for trend ²
	1	2	3	
α-Tocopherol				
Median (μmol/mmol cholesterol)	3.2	4.2	5.6	
Range (μmol/mmol cholesterol)	1.3–3.7	3.7–4.7	4.7–20.5	
Age-adjusted OR	1.0	1.0 (0.5, 2.1)	0.6 (0.3, 1.3)	0.18
Fully-adjusted OR	1.0	0.9 (0.4, 2.0)	0.5 (0.2, 1.1)	0.07
γ-Tocopherol				
Median (μmol/mmol cholesterol)	0.6	1.1	1.6	
Range (μmol/mmol cholesterol)	0.1–0.9	0.9–1.3	1.3–4.4	
Age-adjusted OR	1.0	1.4 (0.7, 2.9)	0.5 (0.2, 1.3)	0.16
Fully-adjusted OR	1.0	1.2 (0.6, 2.6)	0.4 (0.2, 1.1)	0.09

¹Fully-adjusted models included age, smoking (pack-years), history of heavy alcohol consumption (never, ever), serum cholesterol concentration, body mass index (in kg/m²), and dietary linoleic acid intake. One person was excluded because information was missing on pack-years. OR, odds ratio. 95% CIs in parentheses.

²Tertile medians used.

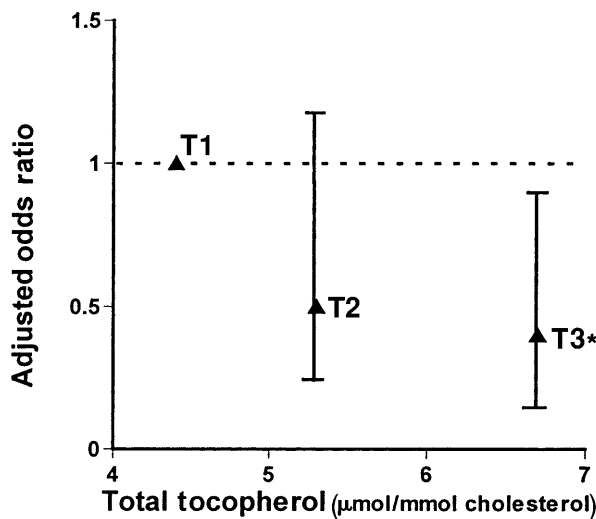



FIGURE 1. Odds ratios (ORs) and 95% CIs for the association between total serum tocopherols and incidence of nuclear cataract 5 y after baseline in the Beaver Dam Eye Study. ORs were adjusted for age, pack-years, history of heavy alcohol consumption (never, ever), serum cholesterol concentration, body mass index (in kg/m²), and dietary linoleic acid intake. Total tocopherol is the sum of α - and γ -tocopherols. $P = 0.03$ for linear trend based on tertile medians. T1, tertile 1; T2, tertile 2; T3, tertile 3. *OR: 0.4; 95% CI: 0.2, 0.9.

Dam Eye Study (29). An association between lutein and nuclear cataract is biologically plausible because lutein/zeaxanthin has been observed in human lens tissue (30, 31). The lack of corroborating evidence linking serum lutein with nuclear cataract in this study, except possibly in relatively older persons, could mean that apparent associations with dietary intakes may have been due to another component of diet or to unmeasured lifestyle factors. Alternatively, if lutein was associated with cataract, the relation may not have been detected in this study for 2 reasons. First, it is likely that serum lutein concentrations reflect relatively recent status compared with self-reported dietary intakes that describe usual dietary habits. Plasma carotenoid concentrations have been shown to decline rapidly in subjects fed a low-carotenoid diet (32). Second, our ability to detect relations was limited by the small number of persons in the overall study who had their serum analyzed for carotenoid and tocopherol concentrations. The statistical power to detect a 50% reduction in risk among persons in the highest versus lowest tertiles was only 52%; a power of 80% would have been necessary to conclude that this level of reduction was not missed by chance.

Incidence of nuclear cataract was inversely associated with serum tocopherol concentration in this study. This finding is consistent with the lower risk of increasing nuclear opacification in case-control study participants with high concentrations of serum vitamin E at baseline than in those with low concentrations and who were followed longitudinally for ≈ 5 y (13). The association in the present study was stronger in older participants. One possible explanation is that lenses in older persons are more susceptible to oxidative damage. Fecondo and Augusteyn (33) showed that glutathione peroxidase and superoxide dismutase activities are lower in the nuclei of human lenses compared with those without nuclear opacities, even at very early stages of opacity. Less protection in the cell cytosol

could result in greater insults to cellular membranes, in which tocopherols are thought to be effective antioxidants. Alternatively, the apparent difference between age groups could be related to differences in lifestyle factors that are unrelated to the proposed mechanisms.

The inverse association with serum tocopherols observed in this study and 3 other studies (11–13) contrast with cross-sectional observations from the Beaver Dam Eye Study (16). In the cross-sectional analyses, serum α -tocopherol was associated with increased risk of more severe nuclear opacities. The inverse associations between nuclear cataracts and serum concentrations of tocopherols reported in this study suggest that the direct association with serum α -tocopherol in cross-sectional analyses may be the result of temporal confounding, which could occur if older or less healthy people improved their diets to the extent that nutrient status at baseline examinations did not reflect the exposures that preceded the onset or progression of nuclear opacities. A similar pattern was observed in the Baltimore Longitudinal Study on Aging (11), in which plasma α -tocopherol concentrations were significantly associated with nuclear opacities in persons who had serum concentrations measured 2–4 y before assessment of lens status (highest quintile adjusted OR: 0.5; 95% CI: 0.3, 1.0), but associations were not as strong for persons whose blood samples were collected concurrent with their eye examinations (highest quintile adjusted OR: 0.8; 95% CI: 0.3, 1.9).

In conclusion, results from this study are compatible with the possibility that nuclear cataracts may be associated with vitamin E status. Nuclear cataracts were not significantly related to serum concentrations of α -carotene, β -carotene, lutein, lycopene, or cryptoxanthin in this small subsample of the Beaver Dam Eye Study. However, nonsignificant inverse associations of lutein and cryptoxanthin in older participants indicate that a protective influence of these carotenoids on the development of nuclear cataract cannot be ruled out. Additional prospective studies of longer duration and with larger sample sizes would add to the consistency of data supporting the link between these fat-soluble dietary antioxidants and the development of nuclear cataract. 

We thank William E Brady and Alicia Fisher for their technical assistance, Maria Stacewicz-Sapuntzakis from the University of Illinois at Chicago for conducting the carotenoid and tocopherol analyses, and members of the Scientific Advisory Committee for the Beaver Dam Eye Study, including Mary Frances Cotch, Mae Gordon, Lee Jampol, Daniel Seigel, and Robert Wallace, for their support and advice.

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