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Dietary Carotenoids, Vitamins C and E, and Risk of Cataract in Women

A Prospective Study

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Objective: To examine in prospective data the relation between dietary intake of carotenoids and vitamins C and E and the risk of cataract in women.

Design: Dietary intake was assessed at baseline in 39 876 female health professionals by using a detailed food frequency questionnaire. A total of 35 551 women provided detailed information on antioxidant nutrient intake from food and supplements and were free of a diagnosis of cataract. The main outcome measure was cataract, defined as an incident, age-related lens opacity responsible for a reduction in best-corrected visual acuity in the worse eye to 20/30 or worse based on self-report confirmed by medical record review.

Results: A total of 2031 cases of incident cataract were confirmed during a mean of 10 years of follow-up. Comparing women in the extreme quintiles, the multivariate relative risk of cataract was 0.82 (95% confidence interval, 0.71-0.95; test for trend, $P = .04$) for lutein/zeaxanthin and 0.86 (95% confidence interval, 0.74-1.00; test for trend, $P = .03$) for vitamin E from food and supplements.

Conclusion: In these prospective observational data from a large cohort of female health professionals, higher dietary intakes of lutein/zeaxanthin and vitamin E from food and supplements were associated with significantly decreased risks of cataract.

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THE OXIDATIVE HYPOTHESIS OF cataract formation posits that reactive oxygen species can damage lens proteins and fiber cell membranes and that nutrients with antioxidant capabilities can protect against these changes.[1-3] Results of laboratory studies and studies in animals generally support the antioxidant hypothesis, but results of observational epidemiologic studies in humans have been inconsistent.[4-6] Moreover, results of completed randomized trials[7-14] indicate that supplemental use of vitamin E, ascorbic acid (vitamin C), or beta carotene for as long as 6.5 years (12 years for beta carotene[7]) has no marked effect on cataract incidence or progression. Whether a longer duration of treatment with these antioxidants can materially reduce the risk of cataract, which develops slowly across many years, remains to be determined in recently completed and ongoing trials.[15-17]

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In addition to those nutrients tested in completed and ongoing trials, evidence has also accumulated to suggest a possible role for lutein, a xanthophyll carotenoid, in lowering the risk of cataract. Lutein is concentrated in tissues of the eye, including the lens,[18-20] and may protect against cataract by filtering harmful short-wave blue light and possibly through antioxidant activity.[21-23] Findings from observational epidemiologic studies[24-32] generally support a possible beneficial effect of lutein. However, as encouraging data have accumulated, enthusiasm for its potential benefits has also led to the advocation of lutein-containing supplements to prevent eye disease, although there are no randomized trial data that assess its effectiveness in the eye, and prospective observational data for cataract are limited to 3 studies.[27-29,32] For this reason, the National Eye Institute[33] has cautioned that the possible benefit of lutein on the eye remains uncertain and warrants closer examination before conclusions can be drawn. In this article we examine in prospective data the relation of dietary intake of several carotenoids, including lutein (and its stereoisomer zeaxanthin), and vitamins C and E with the risk of cataract dur-

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ing 10 years of follow-up in a large cohort of female health professionals.

METHODS

Study participants were women enrolled in the Women's Health Study (WHS), a recently completed randomized, double-masked, placebo-controlled trial of low-dose aspirin, vitamin E, and beta carotene in the primary prevention of cardiovascular disease and cancer in 39 876 apparently healthy female health professionals 45 years and older.[15,34-36] Participants were willing to forego use of individual supplements of beta carotene, vitamin A, and vitamin E but could continue using multivitamins for the duration of the trial. Detailed information on antioxidant intake from food and supplements was provided by 39 310 of the randomized participants (98.58%), who completed a 131-item validated semiquantitative food frequency questionnaire (SFFQ) at baseline in 1993.[37] For this analysis we excluded participants who reported total energy intake less than 600 kcal/d or greater than 3500 kcal/d or who had more than 70 blanks on the SFFQ. Of the remaining participants, 35 551 were without a diagnosis of cataract at baseline and are included. This study was conducted according to the ethical guidelines of Brigham and Women's Hospital.

ASSESSMENT OF ANTIOXIDANT NUTRIENT INTAKE

For each food item, a standard unit or portion size was specified and participants were asked how often, on average, during the previous year they had consumed that amount. Nine responses were possible, ranging from "never" to "6 or more times per day." Responses to the individual food items were converted to average daily intake of each nutrient based on food tables maintained by the Harvard School of Public Health. The carotenoid content of food items was determined by using the US Department of Agriculture–National Cancer Institute carotenoid food composition databases.[38,39] Participants also provided information about their current use of multivitamins and supplements of ascorbic acid, vitamin E, and beta carotene. The total intake of antioxidants was calculated by adding the contributions from vitamin supplements and foods. For beta carotene, ascorbic acid, and vitamin E, we also calculated intake from food sources alone. In the databases, the data for lutein and zeaxanthin have been combined.

The reproducibility and validity of SFFQ estimates of vitamin and carotenoid intake have been examined in a similar population of female nurses. The Pearson correlation coefficient between estimates from the SFFQ and the average of two 1-week diet records was 0.76 for energy-adjusted total ascorbic acid.[40] For vitamin E, the correlation between estimates of intake from the SFFQ and plasma concentrations of alpha tocopherol was 0.41.[41] For carotenoids, correlations between plasma concentrations and the SFFQ assessments in nonsmoking women were 0.27 for beta carotene, 0.27 for lutein, 0.32 for beta cryptoxanthin, 0.48 for alpha carotene, and 0.21 for lycopene.[42] These estimates were similar to those found between plasma levels of these nutrients and estimates from food records.[43]

OTHER COVARIATES

Information on possible risk factors for cataract was collected on the WHS baseline questionnaire and included age, height and weight, smoking status, alcohol use, frequency of exercise, parental history of myocardial infarction at younger than 60 years, history of hypertension, history of diabetes mellitus, history of hypercholesterolemia, postmenopausal hormone use, and history of an eye examination in the past 2 years.

ASCERTAINMENT AND DEFINITION OF END POINTS

Following the report of a cataract diagnosis, written consent identifying the diagnosing ophthalmologist or optometrist was obtained. The ophthalmologist or optometrist was asked to complete a cataract questionnaire supplying information about the presence of lens opacities, date of diagnosis, visual acuity loss, cataract extraction, other ocular abnormalities that could explain visual acuity loss, cataract type, and etiology. Medical record information was obtained for 95% of participants reporting cataract. The study end point was incident cataract, defined as a self-report confirmed by medical record review to be initially diagnosed after randomization, age-related in origin, with best-corrected visual acuity of 20/30 or worse and with no alternative ocular pathologic abnormalities to explain the visual acuity loss.

DATA ANALYSIS

The unit of analysis was individuals, rather than eyes, because eyes were not examined independently, and participants were classified according to the status of the worse eye based on disease severity. Participants were followed up until the time of diagnosis of cataract or until death or February 1, 2004, whichever came first. Nutrient intake was considered as a categorical variable (in quintiles), with adjustment for total energy using the residual method.[40] Estimates of relative risks (RRs) were computed as the rate of cataract in a specific quintile of intake divided by the corresponding rate in the lowest quintile (reference). Age- and treatment-adjusted RR estimates were obtained by adjusting for age (in years) and randomized treatment assignment in Cox proportional hazards regression models.[44] Multivariate RRs were obtained by further adjusting for smoking, alcohol use, history of diabetes, history of hypertension, history of hypercholesterolemia, body mass index, physical activity, parental history of myocardial infarction, postmenopausal hormone use, and history of an eye examination in the past 2 years. For each RR, 2-sided *P* values and 95% confidence intervals (CIs) were calculated.[45] Tests of linear trend across increasing quintiles of nutrient intake used the medians of intakes within quintiles as scores. We used an interaction term between ordinal scores for each nutrient and length of follow-up to evaluate the adequacy of the proportional hazards assumption across time. For each nutrient, $P > .05$, indicating that the proportionality assumption was not violated. We also performed tests of interaction to evaluate the statistical significance of any modifying effect of age and baseline smoking status (current vs not current) on the association of nutrient intake with cataract.

We examined the independent contribution of each nutrient to cataract risk by simultaneously entering all nutrients into a Cox regression model using the median scores from quintiles and adjusting for other cataract risk factors. Using a backward selection procedure, nutrients were removed according to level of significance until only those nutrients that were significantly associated with cataract at the $P < .05$ level remained. We also fit a model that retained only those nutrients that were significantly associated with cataract at the $P < .20$ level.

RESULTS

Baseline characteristics of the study population are given in **Table 1**. Women who were newly diagnosed as hav-

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Table 1. Baseline Characteristics of 35 551 Study Participants by Incident Cataract

	No Cataract (n=33 520)	Cataract (n=2031)	P Value
Age, mean, y	53.5	61.0	<.001
Cigarette smoking, %			<.001
Never	51.2	49.1	
Past	35.8	35.0	
Current	13.0	16.0	
Alcohol use, %			.06
≥1 drink per day	10.2	10.3	
1-6 drinks per week	32.2	28.3	
1-3 drinks per month	13.3	12.9	
Rarely/never	44.3	48.5	
Physical exercise, %			.02
≥4 times per week	10.7	10.1	
1-3 times per week	31.7	28.0	
<1 time per week	20.1	20.8	
Rarely/never	37.6	41.1	
Body mass index[a]	25.4	25.7	.03
Postmenopausal hormone use, %			.17
Never	48.7	41.3	
Past only	9.4	10.1	
Current	41.9	48.5	
History of hypertension, %[b]	24.4	30.8	<.001
History of diabetes mellitus, %	2.1	4.5	<.001
History of high cholesterol, %[c]	28.4	32.5	<.001
Parental history of myocardial infarction, %[d]	13.1	13.2	.99
Eye examination in the past 2 y, %	81.9	85.0	.13

[a] Body mass index was calculated as weight in kilograms divided by height in meters squared.
[b] Hypertension was defined as a reported systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or history of treatment for high blood pressure.
[c] High cholesterol was defined as a reported blood cholesterol level of 240 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0259) or a history of treatment with a cholesterol-lowering medication.
[d] Myocardial infarction in either parent before age 60 years.

ing cataract during follow-up were older and, after adjusting for age, were more likely to smoke than women without a diagnosis of cataract. Women with diagnosed cataract also had a higher body mass index, exercised less, and were more likely to report a history of hypertension, diabetes, and high cholesterol.

Mean intakes of lutein/zeaxanthin and several other nutrients were highly correlated with one another ($P < .001$ for all correlation coefficients; data not shown). The correlation coefficients between lutein/zeaxanthin and the other carotenoids ranged from 0.22 for lutein/zeaxanthin and beta cryptoxanthin to 0.72 for lutein/zeaxanthin and beta carotene from food sources (0.67 for beta carotene from food and supplements). The correlation coefficients between lutein/zeaxanthin and vitamins C and E ranged from 0.17 for total vitamin E to 0.45 for vitamin C from food sources only.

During an average of 10 years of follow-up, 2031 cases of incident cataract were confirmed. Significant inverse trends with cataract were observed for dietary intakes of lutein/zeaxanthin and vitamin E. Comparing women in the highest quintile of intake of lutein/zeaxanthin with those in the lowest quintile, the multivariate RR of cataract was 0.82 (95% CI, 0.71-0.95; test for trend, $P = .04$) (**Table 2**). The RR for vitamin E from food and supplements, comparing women in the extreme quintiles, was 0.86 (95% CI, 0.74-1.00; test for trend, $P = .03$) (Table 2). Vitamin E from food sources alone was not significantly associated with risk of cataract. For beta cryptoxanthin, there was a significant inverse trend with cataract in age- and treatment-adjusted analyses (test for trend, $P = .04$) but not in analyses that also adjusted for other cataract risk factors (test for trend, $P = .19$). Multivariate RRs for the other nutrients (alpha carotene, beta carotene, lycopene, and ascorbic acid) were generally less than 1.0, but none of the tests for trend across quintiles attained statistical significance.

We examined the independent contribution of each nutrient in Cox regression models using backward selection procedures. Values for beta carotene, vitamin E, and ascorbic acid in this analysis included intake from both food and supplements. After stepwise removal of nonsignificant nutrients, only vitamin E remained significantly associated with the risk of cataract (test for trend, $P = .03$). When the significance level for retention was set at 0.20, vitamin E (test for trend, $P = .04$) and lutein/zeaxanthin (test for trend, $P = .06$) were retained in the final model.

We also examined whether the associations between nutrient intake and cataract differed by age and smoking status at baseline. We found no evidence that associations between nutrient status and cataract differed by age. For smoking, inverse associations tended to be stronger in women who were nonsmokers at baseline, but formal tests for interaction were not statistically significant for any nutrient.

Because of the inverse association between cataract and lutein/zeaxanthin, we also examined the association of cataract with specific food sources of lutein/zeaxanthin and other carotenoids (**Table 3**). Women with high overall intake of fruits and vegetables had an approximately 10% lower risk of cataract that was not statistically significant. There was, however, a borderline significant inverse trend between higher intake of green leafy vegetables and risk of cataract (test for trend, $P = .06$). When we considered specific foods that are important contributors to lutein/zeaxanthin intake, raw spinach showed a borderline significant inverse relation with risk of cataract in age- and treatment-adjusted analyses (test for trend, $P = .06$), but not after adjustment for other cataract risk factors.

COMMENT

In this large population of female health professionals, significant inverse trends with risk of cataract were observed for dietary intake of lutein/zeaxanthin and vitamin E. Comparing women in the extreme quintiles, women with high intake of lutein/zeaxanthin had an 18% lower risk of cataract in multivariate analysis. High intake of vitamin E from food and supplements was associated with a 14% lower risk of cataract. The inverse associations for lutein/zeaxanthin and vitamin E from food and supplements persisted in models that mutually adjusted for intake of several other carotenoids and ascorbic acid.

The prospective design of this study precluded the possibility that participant reports of nutrient intake at

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Table 2. Relative Risk of Cataract According to Quintiles of Dietary Intake of Nutrients in the Women's Health Study

	Quintile of Dietary Intake					*P* Value for Trend
	1	2	3	4	5	
Alpha carotene						
Intake, median, μg	197	427	638	953	1708	
Cases of cataract, No.	374	384	404	377	492	
Participants, No.	7111	7110	7110	7110	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.88 (0.76-1.01)	0.90 (0.78-1.04)	0.79 (0.68-0.91)	0.94 (0.82-1.07)	.74
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.90 (0.78-1.04)	0.92 (0.80-1.06)	0.82 (0.70-0.94)	0.96 (0.84-1.11)	.98
Beta carotene						
With supplements						
Intake, median, μg	1894	3039	4052	5415	8256	
Cases of cataract, No.	369	388	364	444	466	
Participants, No.	7111	7110	7110	7110	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.95 (0.82-1.09)	0.80 (0.69-0.92)	0.93 (0.81-1.07)	0.85 (0.74-0.98)	.07
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.97 (0.84-1.12)	0.82 (0.71-0.95)	0.97 (0.84-1.12)	0.87 (0.75-1.00)	.11
No supplements						
Intake, median, μg	1790	2857	3793	5007	7550	
Cases of cataract, No.	379	365	384	417	486	
Participants, No.	7111	7110	7110	7110	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.87 (0.75-1.01)	0.84 (0.73-0.97)	0.83 (0.72-0.96)	0.88 (0.77-1.01)	.21
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.88 (0.76-1.02)	0.87 (0.75-1.01)	0.87 (0.75-1.00)	0.89 (0.77-1.02)	.27
Beta cryptoxanthin						
Intake, median, μg	10	30	50	80	146	
Cases of cataract, No.	355	374	408	445	449	
Participants, No.	7113	7112	7107	7109	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	1.00 (0.87-1.16)	0.97 (0.84-1.12)	1.00 (0.87-1.15)	0.88 (0.76-1.01)	.04
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	1.01 (0.87-1.17)	1.01 (0.87-1.16)	1.05 (0.91-1.21)	0.92 (0.80-1.06)	.19
Lycopene						
Intake, median, μg	3342	5439	7694	10 843	16 765	
Cases of cataract, No.	428	381	427	410	385	
Participants, No.	7111	7110	7110	7110	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.95 (0.83-1.09)	1.04 (0.91-1.18)	0.98 (0.85-1.12)	0.98 (0.85-1.12)	.84
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.94 (0.82-1.08)	1.04 (0.91-1.19)	0.98 (0.86-1.13)	0.96 (0.84-1.11)	.77
Lutein/zeaxanthin						
Intake, median, μg	1177	2162	3070	4245	6716	
Cases of cataract, No.	429	358	438	393	413	
Participants, No.	7111	7110	7110	7110	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.77 (0.67-0.89)	0.91 (0.79-1.04)	0.78 (0.68-0.89)	0.82 (0.72-0.94)	.03
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.77 (0.67-0.89)	0.92 (0.80-1.05)	0.79 (0.69-0.91)	0.82 (0.71-0.95)	.045
Vitamin E						
With supplements						
Intake, median, mg	4.4	5.6	7.3	23.0	262.4	
Cases of cataract, No.	374	376	463	439	379	
Participants, No.	7143	7118	7070	7110	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.90 (0.78-1.04)	0.98 (0.85-1.12)	0.96 (0.84-1.10)	0.84 (0.73-0.97)	.02
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.92 (0.80-1.07)	0.99 (0.86-1.14)	1.00 (0.87-1.15)	0.86 (0.74-1.00)	.03
No supplements						
Intake, median, mg	4.3	5.1	5.8	6.5	8.4	
Cases of cataract, No.	369	354	405	435	468	
Participants, No.	7171	7167	7002	7129	7082	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.88 (0.76-1.02)	0.94 (0.81-1.08)	0.91 (0.79-1.04)	0.89 (0.78-1.03)	.25
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.91 (0.78-1.05)	0.97 (0.84-1.12)	0.92 (0.80-1.06)	0.92 (0.80-1.06)	.39
Ascorbic acid (vitamin C)						
With supplements						
Intake, median, mg	83	127	166	220	439	
Cases of cataract, No.	337	364	409	473	448	
Participants, No.	7112	7110	7109	7110	7110	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.94 (0.81-1.08)	0.92 (0.80-1.07)	0.96 (0.84-1.11)	0.90 (0.78-1.04)	.24
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.97 (0.84-1.13)	0.97 (0.84-1.13)	1.01 (0.87-1.17)	0.94 (0.81-1.09)	.39
No supplements						
Intake, median, mg	76	109	137	169	225	
Cases of cataract, No.	328	396	380	432	495	
Participants, No.	7111	7111	7112	7110	7107	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	1.06 (0.91-1.23)	0.92 (0.79-1.07)	0.93 (0.80-1.07)	0.96 (0.83-1.11)	.28
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	1.09 (0.94-1.26)	0.96 (0.82-1.11)	0.98 (0.84-1.13)	1.00 (0.86-1.16)	.61

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age, randomized treatment assignment, smoking (current, past, or never), alcohol use (rarely/never, 1-3 drinks per month, 1-6 drinks per week, or ≥1 drink per day), body mass index (continuous), exercise (rarely/never, <1 time per week, 1-3 times per week, or ≥4 times per week), postmenopausal hormone use (never, past, or current), history of hypertension (ever diagnosis by a physician or self-reported blood pressure ≥140/90 mm Hg; yes or no), history of hypercholesterolemia (baseline history of cholesterol medication use or a physician diagnosis of high cholesterol or a self-reported cholesterol level of ≥240 mg/dL [to convert to millimoles per liter, multiply by 0.0259]; yes or no), history of diabetes mellitus (yes or no), family history of myocardial infarction before age 60 years (yes or no), and history of eye examination in the past 2 years.

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Table 3. Relative Risk of Cataract According to Quintiles of Total and Specific Subgroups of Fruits and Vegetables and Categories of Specific Foods in the Women's Health Study

Characteristic	Quintile of Intake 1	2	3	4	5	*P* Value for Trend
Total fruits and vegetables						
Servings, median, No./d	2.5	4.1	5.4	7.0	10.0	
Cases of cataract, No.	353	364	408	443	462	
Participants, No.	7108	7104	7108	7106	7103	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.93 (0.80-1.07)	0.91 (0.79-1.05)	0.91 (0.79-1.05)	0.89 (0.77-1.02)	.14
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.94 (0.81-1.09)	0.93 (0.81-1.08)	0.93 (0.81-1.08)	0.90 (0.78-1.05)	.23
All fruits						
Servings, median, No./d	0.6	1.3	1.9	2.6	3.8	
Cases of cataract, No.	334	353	411	451	481	
Participants, No.	7134	7077	7136	7069	7103	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.92 (0.79-1.07)	0.95 (0.82-1.10)	0.93 (0.80-1.07)	0.87 (0.76-1.00)	.08
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.95 (0.82-1.11)	0.99 (0.85-1.15)	1.00 (0.87-1.16)	0.93 (0.80-1.08)	.44
All vegetables						
Servings, median, No./d	1.5	2.5	3.4	4.5	6.8	
Cases of cataract, No.	378	366	418	424	444	
Participants, No.	7121	7089	7108	7103	7104	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.93 (0.81-1.08)	0.95 (0.82-1.09)	0.94 (0.82-1.08)	0.92 (0.80-1.06)	.35
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.94 (0.81-1.09)	0.96 (0.83-1.11)	0.96 (0.83-1.10)	0.92 (0.80-1.06)	.38
Green leafy vegetables						
Servings, median, No./d	0.1	0.4	0.6	0.9	1.4	
Cases of cataract, No.	461	377	389	399	402	
Participants, No.	7695	6624	6648	7584	6957	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.99 (0.86-1.13)	0.96 (0.84-1.10)	0.83 (0.73-0.95)	0.91 (0.80-1.04)	.03
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	1.00 (0.87-1.14)	0.98 (0.86-1.12)	0.84 (0.74-0.97)	0.93 (0.81-1.06)	.06
Cruciferous vegetables						
Servings, median, No./d	0.1	0.2	0.4	0.6	1.0	
Cases of cataract, No.	361	460	378	385	446	
Participants, No.	6437	8143	6964	7343	6636	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.92 (0.81-1.06)	0.84 (0.73-0.98)	0.82 (0.71-0.95)	0.98 (0.85-1.12)	.86
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.93 (0.81-1.07)	0.86 (0.74-0.99)	0.83 (0.72-0.96)	0.96 (0.84-1.11)	.93
Dark yellow vegetables						
Servings, median, No./d	0.1	0.2	0.3	0.6	1.0	
Cases of cataract, No.	394	333	425	427	449	
Participants, No.	7590	6359	7497	6981	7088	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.94 (0.81-1.08)	0.91 (0.79-1.04)	0.95 (0.83-1.09)	0.92 (0.81-1.06)	.47
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.95 (0.82-1.11)	0.94 (0.82-1.08)	0.99 (0.86-1.14)	0.96 (0.83-1.10)	.83
Citrus fruits						
Servings, median, No./d	0.1	0.3	0.6	1.0	1.6	
Cases of cataract, No.	363	358	333	513	462	
Participants, No.	7207	7073	6789	7586	6846	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.97 (0.84-1.12)	0.88 (0.76-1.02)	1.02 (0.89-1.17)	0.93 (0.81-1.06)	.60
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	1.01 (0.87-1.17)	0.93 (0.79-1.08)	1.08 (0.94-1.25)	1.00 (0.86-1.15)	.65

Characteristic	Category of Intake 1st	2nd	3rd	4th	*P* Value for Trend
Broccoli, servings	≤1-3/mo	1/wk	2-4/wk	≥5-6/wk	
Cases of cataract, No.	626	712	571	112	
Participants, No.	10 400	13 065	10 153	1745	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.92 (0.83-1.03)	0.95 (0.85-1.06)	1.06 (0.86-1.29)	.78
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.95 (0.85-1.06)	0.97 (0.86-1.09)	1.07 (0.87-1.32)	.69
Brussels sprouts, servings	None	1-3/mo	≥1/wk		
Cases of cataract, No.	1409	425	179		
Participants, No.	24 892	7766	2696		
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.92 (0.83-1.03)	1.03 (0.88-1.21)		.67
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.92 (0.82-1.02)	0.98 (0.83-1.15)		.34

(continued)

baseline were associated with subsequent cataract status. However, random or nondifferential misclassification of dietary intake was likely and would tend to underestimate any association of diet with risk of cataract. Changes in dietary behavior during follow-up seem unlikely to be differential with respect to the cataract end point and, thus, would also attenuate the true associations. Random misclassification of the cataract end point was reduced by the use of medical records to confirm the participant reports and by the use of strict diagnostic criteria. To control for possible surveillance bias, we included a term for the baseline report of an eye examination in the past 2 years in multivariate analyses. Finally, we controlled for a variety of measured confounders (Table 1), but other potential con-

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Table 3. Relative Risk of Cataract According to Quintiles of Total and Specific Subgroups of Fruits and Vegetables and Categories of Specific Foods in the Women's Health Study *(cont)*

Characteristic	Category of Intake 1st	2nd	3rd	4th	*P* Value for Trend
Corn, servings	≤1-3/mo	1/wk	≥2-4/wk		
Cases of cataract, No.	1063	685	264		
Participants, No.	18 055	12 504	4789		
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.98 (0.89-1.07)	1.00 (0.87-1.14)		.97
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	1.00 (0.91-1.10)	0.99 (0.86-1.14)		.91
Lettuce, iceberg, servings	≤1-3/mo	1/wk	2-4/wk	≥5-6/wk	
Cases of cataract, No.	427	401	687	500	
Participants, No.	7358	7788	12 319	7855	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.96 (0.84-1.10)	1.01 (0.90-1.14)	0.99 (0.87-1.12)	.88
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.94 (0.82-1.08)	1.01 (0.89-1.14)	0.97 (0.85-1.11)	.93
Peas, servings	None	1-3/mo	1/wk	≥2-4/wk	
Cases of cataract, No.	382	729	638	268	
Participants, No.	7303	12 499	11 233	4318	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.97 (0.85-1.09)	0.96 (0.84-1.09)	1.00 (0.85-1.16)	.91
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.97 (0.86-1.10)	0.96 (0.85-1.09)	1.01 (0.86-1.18)	.81
Spinach, cooked, servings	None	1-3/mo	≥1/wk		
Cases of cataract, No.	992	663	362		
Participants, No.	17 455	11 800	6077		
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.93 (0.84-1.02)	1.02 (0.91-1.15)		.93
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.92 (0.83-1.02)	1.03 (0.91-1.16)		.93
Spinach, raw, servings	None	1-3/mo	≥1/wk		
Cases of cataract, No.	1157	645	212		
Participants, No.	18 914	11 856	4544		
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.96 (0.88-1.06)	0.86 (0.75-1.00)		.06
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.98 (0.89-1.08)	0.88 (0.76-1.02)		.13
Eggs, servings	≤1-3/mo	1/wk	2-4/wk	≥5-6/wk	
Cases of cataract, No.	959	502	496	57	
Participants, No.	16 632	8957	8752	1022	
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	1.01 (0.90-1.12)	1.01 (0.91-1.13)	1.03 (0.79-1.34)	.79
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	1.02 (0.91-1.14)	0.99 (0.88-1.10)	0.99 (0.75-1.30)	.75
Squash, servings	None	1-3/mo	≥1/wk		
Cases of cataract, No.	1119	631	257		
Participants, No.	20 632	10 668	3997		
Age- and treatment-adjusted RR (95% CI)	1 [Reference]	0.94 (0.85-1.04)	0.97 (0.84-1.11)		.38
Multivariate-adjusted RR (95% CI)[a]	1 [Reference]	0.96 (0.87-1.07)	0.97 (0.85-1.12)		.54

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age, randomized treatment assignment, smoking (current, past, or never), alcohol use (rarely/never, 1-3 drinks per month, 1-6 drinks per week, or ≥1 drink per day), body mass index (continuous), exercise (rarely/never, <1 time per week, 1-3 times per week, or ≥4 times per week), postmenopausal hormone use (never, past, or current), history of hypertension (ever diagnosis by a physician or self-reported blood pressure ≥140/90 mm Hg; yes or no), history of hypercholesterolemia (baseline history of cholesterol medication use or a physician diagnosis of high cholesterol or a self-reported cholesterol level of ≥240 mg/dL [to convert to millimoles per liter, multiply by 0.0259]; yes or no), history of diabetes mellitus (yes or no), family history of myocardial infarction before age 60 years (yes or no), and history of eye examination in the past 2 years.

founders that were either unmeasured or unknown may have contributed to the findings.

There have been 3 other prospective studies that have examined the relationship between dietary intake of lutein and risk of cataract. In the Nurses' Health Study of 77 466 female nurses, women in the top 10% of lutein/zeaxanthin intake, compared with those in the bottom quintile, had a 22% lower risk of cataract extraction (RR, 0.78; 95% CI, 0.63-0.95; test for trend, $P=.04$) during 12 years of follow-up.[28] In another study[32] from that cohort, based on a small subsample of 408 participants, there was no association between intake of lutein/zeaxanthin and 5-year change in nuclear density as measured by analysis of digital images. In a second study,[27] data from the Health Professionals Study of 36 644 male health professionals showed that men in the highest quintile of lutein/zeaxanthin intake, compared with those in the lowest quintile, had a 19% lower risk of cataract extraction (RR, 0.81; 95% CI, 0.65-1.01; test for trend, $P=.03$) during 8 years of follow-up. A third study,[29] based on data from 1354 men and women participating in a nutrition substudy of the Beaver Dam Eye Study, showed that those in the highest quintile of intake of lutein/zeaxanthin in the distant past (10 years before baseline), compared with those in the lowest quintile, had a 50% decreased risk of incident nuclear opacity (odds ratio, 0.5; 95% CI, 0.3-0.8; test for trend, $P=.002$) at 5 years of follow-up. The present data from a large cohort of female health professionals indicate an approximately 20% decreased risk of cataract for those with high dietary intake of lutein/zeaxanthin and, thus, seem most consistent with the findings for cataract extraction reported in the Nurses' Health Study and the Health Professionals Study.[27,28] Of note, lutein/zeaxanthin intake in the reference group in the WHS and the 2 other cohorts of health professionals[27,28] seem markedly higher than the reference intake for lutein/zeaxanthin in the population-based sample from Beaver Dam, Wiscon-

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sin,[29] which may at least partially explain the smaller risk reductions observed in the former.

Of the other carotenoids examined in this study, only beta carotene from food and supplements showed a possible inverse relation with risk of cataract. Women in the highest, compared with the lowest, quintile of intake had a borderline significant 13% reduced risk of cataract in multivariate analysis. However, the test for trend across quintiles was not significant in the multivariate model or after adjustment for intake of other nutrients. These findings seem to be consistent with most earlier prospective studies[27-29,32,46,47] that report a weak and statistically nonsignificant inverse trend between beta carotene level in the diet or blood and risk of cataract. More important, the results of 5 randomized trials[7,8,10,11,14] indicate that supplemental use of beta carotene (with or without other antioxidant supplements) for as long as 12 years has little impact on risk of cataract.

We observed a significant inverse trend between vitamin E intake from food and supplements and risk of cataract in this population of women. This inverse trend persisted after adjustment for other nutrients and seemed to be due largely to a 14% reduced risk of cataract for women in the highest quintile of intake. Median intake of vitamin E for this group of women was 262.4 mg/d, a level of intake difficult to attain from food sources alone. The reduction in risk seemed to reflect supplemental use of vitamin E rather than multivitamins. Seventy-one percent of women in the highest quintile of vitamin E intake reported using supplements of vitamin E at baseline, and adjustment for use of multivitamins had little impact on the RR estimate (RR comparing the extreme quintiles of vitamin E intake, 0.86; 95% CI, 0.73-1.00; test for trend, $P=.048$). Results of other prospective studies have been mixed, with some supporting an inverse association between dietary or serum vitamin E and cataract[32,46-50] and others reporting no association.[29,51,52] Data from 5 randomized trials[8,10-13] completed to date provide little evidence that use of vitamin E supplements, alone or in combination with other vitamin supplements, for as long as 6.5 years has any material impact on cataract development and progression. The final results for cataract during the 10-year treatment period for vitamin E in the WHS will be reported elsewhere.

The present data for vitamin C indicate a weak, and statistically nonsignificant, inverse association with risk of cataract. This finding seems to conflict with cross-sectional data presented in 2 recent substudies of the Nurses' Health Study[30,31] but is consistent with the results of several other prospective studies,[29,49-52] including 5-year follow-up data in the Nurses' Health Study subsample.[32] Furthermore, findings from 3 randomized trials[8,11,12] indicate no major benefit of combined treatment with ascorbic acid and other antioxidants for as long as 6.5 years.

The hypothesis that antioxidant nutrients may protect against age-related damage to the human lens was derived from laboratory and animal studies and has been generally supported by findings of observational epidemiologic studies in humans. However, the results of completed randomized trials testing vitamin E, ascorbic acid, or beta carotene have been disappointing, and ongoing trials will determine whether observable benefits on cataract can emerge with longer-term treatment with these antioxidant vitamins. In the meantime, the results of the present study add to the growing body of observational evidence that suggests a possible beneficial effect of lutein/zeaxanthin in delaying cataract formation. Lutein and zeaxanthin are the only carotenoids detected in the human lens,[18-20] and the presence of oxidation products of lutein and zeaxanthin in the lens[53] further supports a functional role for xanthophylls in maintaining lens clarity.

In conclusion, these prospective data from a large cohort of female health professionals indicate that higher intakes of lutein/zeaxanthin and vitamin E are associated with decreased risk of cataract. Although reliable data from randomized trials are accumulating for vitamin E and other antioxidant vitamins, randomized trial data for lutein/zeaxanthin are lacking. Such information will help to clarify the benefits of supplemental use of lutein/zeaxanthin and provide the most reliable evidence on which to base public health recommendations for cataract prevention by vitamin supplementation.

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