A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women[1–4]

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ABSTRACT

Background: Oxidation of lens proteins plays a central role in the formation of age-related cataracts, suggesting that dietary antioxidants may play a role in prevention. However, the relation between specific antioxidants and risk of cataract remains uncertain.

Objective: Our objective was to examine prospectively the association between carotenoid and vitamin A intakes and cataract extraction in women.

Methods: A prospective cohort of registered female nurses aged 45–71 y and free of diagnosed cancer was followed; in 1980, 50 461 were included and others were added as they became 45 y of age for a total of 77 466. Information on nutrient intake was assessed by repeated administration of a food-frequency questionnaire during 12 y of follow-up.

Results: During 761 762 person-years of follow-up, 1471 cataracts were extracted. After age, smoking, and other potential cataract risk factors were controlled for, those with the highest intake of lutein and zeaxanthin had a 22% decreased risk of cataract extraction compared with those in the lowest quintile (relative risk: 0.78; 95% CI: 0.63, 0.95; *P* for trend = 0.04). Other carotenoids (α-carotene, β-carotene, lycopene, and β-cryptoxanthin), vitamin A, and retinol were not associated with cataract in multivariate analysis. Increasing frequency of intakes of spinach and kale, foods rich in lutein, was associated with a moderate decrease in risk of cataract.

Conclusions: Lutein and zeaxanthin and foods rich in these carotenoids may decrease the risk of cataracts severe enough to require extraction. *Am J Clin Nutr* 1999;70:509–16.

KEY WORDS Cataract, cataract extraction, diet, women, prospective studies, vitamin A, carotene, lutein, zeaxanthin, carotenoids, Nurses' Health Study, food-frequency questionnaire

INTRODUCTION

Oxidation of lens proteins plays a central role in the formation of age-related cataracts (1), suggesting that dietary antioxidants may play an important role in prevention. However, the relation between specific antioxidants and risk of cataract remains uncertain. Elevated plasma concentrations or dietary intakes of carotenoids were associated with decreased risk of cataract in some studies (2–8), but not others (9–11). Persons consuming low amounts of fruit and vegetables have been observed to be at increased risk of cataract (2, 3, 6).

Persons vary widely in the extent to which blood carotenoid concentrations change with dietary manipulation (12, 13). Furthermore, carotenoids such as β-carotene, lycopene, and β-cryptoxanthin have not been found in the human lens, whereas lutein and zeaxanthin have been measured, albeit in small amounts, and found to vary widely between individuals (14–16). Dietary intake of lutein and zeaxanthin in the form of supplements or foods high in lutein and zeaxanthin has been shown to increase the amount of macular pigment (17–19), which consists principally of the carotenoids lutein and zeaxanthin. In a recent study, Hammond et al (20) observed a significant inverse relation ($P < 0.0001$) between macular pigment density and lens density in 23 women aged 55–78 y, suggesting that macular lutein and zeaxanthin concentrations may be a marker for lutein and zeaxanthin in the lens, which, in turn, may retard age-related increases in lens density.

In a previous analysis of the Nurses' Health Study cohort after 8 y of follow-up, dietary carotene and vitamin A were inversely associated with cataract (3). Among specific food items, spinach was most consistently associated with a lower relative risk (RR). Specific dietary carotenoid values, however, were not available for analysis at that time. We therefore examined prospectively the associations between dietary intakes of vitamin A, specific carotenoids, and food items and the incidence of cataract extraction in the Nurses' Health Study during 12 y of follow-up.

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SUBJECTS AND METHODS

The Nurses' Health Study began in 1976 when 121 701 female registered nurses aged 30–55 y who resided in any of 11 states returned a mailed questionnaire on medical history, use of oral contraceptives, and risk factors for cancer and cardiovascular disease (21). Information on lifestyle factors and disease has been collected through biennial, mailed questionnaires since 1976. The study protocol was approved by the Brigham and Women's Hospital Human Subjects Review Committee.

Antioxidant intake

A semiquantitative food-frequency questionnaire described previously that assessed usual dietary intake was sent to cohort members at baseline in 1980. In 1982, an abbreviated version of the food-frequency questionnaire collected detailed information on intake of foods rich in carotenoids. In 1984, we sent an expanded version of the 1980 food-frequency questionnaire (22), and in 1986 we included questions that assessed usual dietary intake during high school (ages 13–18 y).

On the food-frequency questionnaire, we asked about the usual frequency of consumption of specified foods over the past year, with 9 options ranging from <1 time/mo to >6 times/d. Intake scores were calculated by summing the nutrient contribution of each food multiplied by its frequency of use by using food-composition data from the US Department of Agriculture (USDA), food manufacturers, and other published sources (23). Vitamin A intake was assessed as preformed vitamin A (retinol from animal sources, supplements, and fortified foods) and carotene (provitamin A, primarily from fruit and vegetables). The derived values for carotene correspond to most of the β-carotene intake, about one-half of the α-carotene intake, and a small fraction of the intake of other carotenoids. Scores for the specific carotenoids were assessed in foods that are the major contributors to their intake, as described by the USDA (24, 25). The lutein score represents both lutein and zeaxanthin from foods only and not from supplements because these supplements were not routinely available in the United States during our follow-up period. Lycopene intake was assessed in 1984 only.

We assessed the validity of the dietary questionnaire extensively (22, 26). Both the original and revised questionnaire (1984) provided a reasonable measure of vitamin A intake when compared with multiple 1-wk dietary records. Correlation coefficients were 0.41 for total vitamin A without supplements and 0.55 for vitamin A with supplements for the 1980 questionnaire, and 0.37 for vitamin A without supplements and 0.44 for vitamin A with supplements for the 1984 questionnaire (26). When compared with a blood specimen collected after the 1986 questionnaire, the adjusted diet-plasma carotenoid associations in nonsmokers were 0.48 for α-carotene, 0.27 for β-carotene and lutein, 0.32 for β-cryptoxanthin, and 0.21 for lycopene (27). Recall of diet from high school was reproducible. The correlation coefficient between 2 recalls of high school diet was 0.57 (range: 0.38–0.74) (28).

Other exposures

We included as covariates several known or suspected risk factors for cataract extraction that may distort associations with carotenoid and vitamin A intakes. Age, cigarette smoking, and diabetes are established risk factors for cataract. Smoking status, diagnosis of diabetes, height, and weight were ascertained in 1976 and, except for height, have been updated biennially. Pack-years of smoking were calculated by multiplying the number of packs smoked per day (1 pack = 20 cigarettes) by the number of years over which that number was smoked. We chose pack-years as a measure of smoking status because cataract development is more strongly related to cumulative dose of cigarette smoking than to recency of smoking (29).

In 1978, participants were asked how often they had visited a physician or outpatient clinic in the previous 2 y. Aspirin has been hypothesized to decrease risk of cataract. Current use of aspirin (yes or no) was ascertained in 1980 and updated in each cycle except for 1986. Residence was included as a proxy for exposure to sunlight. Finally, alcohol consumption has been implicated in the pathogenesis of cataract in some but not all analytic studies. Total alcohol intake was assessed at baseline in 1980 and again in 1984, 1986, and 1990. Covariate categories are given in **Table 1**.

Study population

The 1980 food-frequency questionnaire was completed by 98 462 cohort members. Women who left ≥10 items blank or who had an implausible total energy intake [<2092 kJ (<500 kcal) or >14 644 kJ (>3500 kcal/d)] were excluded, leaving 92 468 women. The 1984 food-frequency questionnaire was completed by 81 757 cohort members.

We excluded women who reported a diagnosis of cancer (except nonmelanoma skin cancer; n = 3623) before 1980, the start of the follow-up period. At the beginning of each subsequent 2-y time period, we excluded women who reported a new diagnosis of cancer because these women may have altered their diet because of their illness. Women <45 y of age (n = 38 059) in 1980 were excluded because they were not considered eligible to have senile cataract; these women were added to the analysis as they became 45 y of age. These exclusions (and 325 baseline cataract case exclusions described below) left 50 461 women in the baseline population; by 1990, 77 466 women were included in the analysis cohort. Women contributed time in each 2-y follow-up interval until a report of cataract extraction (censored at the time of first cataract diagnosis), cancer, death, or June 1, 1992, for a total of 761 762 person-years.

Case definition

Participants were asked whether they had had a cataract extraction in 1984, 1986, 1988, 1990, or 1992, and if so, for permission to review their medical records. We then contacted their ophthalmologists to confirm the occurrence and dates of extraction and to determine any known cause of the cataract, the date of initial diagnosis, and the participant's best corrected visual acuity in both eyes before surgery. In addition, we asked about the location of the lens opacity in each eye with location defined as nuclear, cortical, posterior subcapsular, or any combination of the 3. A total of 2505 women reported a first cataract extraction since the return of their 1980 questionnaire. Of these women, 2212 confirmed their extraction and the remaining 293 were considered noncases. Of the 2212 confirmed cases, 1965 gave us permission to contact their ophthalmologist. Because the confirmation rate was 100% among the 1929 ophthalmologists who responded and because 91.6% of the confirmed dates of extraction were within 6 mo of the nurses' reports, we included the 283 cases that were confirmed by the nurse but for whom we had no information from the ophthalmologists.

We excluded cataracts considered by the physicians to be either congenital or secondary to chronic steroid use, chronic intraocular

TABLE 1

Carotenoid intakes and relative risk (RR) of cataract extraction according to quintile of energy-adjusted nutrient intake as assessed in 1980: Nurses' Health Study, 1980–1992

Nutrient and RR	Quintile of intake[1]					*P* for trend[2]	Top 10% compared with bottom 20%
	1	2	3	4	5		
Carotene, with supplements (IU)	2944	4720	6625	9466	14583	—	18145
Cases (*n*)	278	285	284	300	324	—	161
Age-adjusted RR[3]	1.0	0.90	0.83	0.81	0.84	0.07	0.84
Multivariate RR[4]	1.0	0.90	0.84	0.82	0.85	0.09	0.85
95% CI	Referent	(0.76, 1.06)	(0.71, 0.99)	(0.69, 0.96)	(0.72, 1.00)	—	(0.70, 1.03)
α-Carotene (μg)	192	313	441	649	1563	—	2203
Cases (*n*)	267	270	295	317	322	—	156
Age-adjusted RR	1.0	0.94	0.99	0.98	0.98	0.89	0.96
Multivariate RR[4]	1.0	0.97	1.02	1.01	1.03	0.57	1.01
95% CI	—	(0.82, 1.15)	(0.87, 1.21)	(0.86, 1.19)	(0.88, 1.22)	—	(0.83, 1.24)
β-Carotene (μg)	1358	2235	3349	5281	8546	—	10863
Cases (*n*)	273	291	298	299	310	—	159
Age-adjusted RR	1.0	0.97	0.95	0.87	0.87	0.06	0.89
Multivariate RR[4]	1.0	0.98	0.96	0.89	0.89	0.09	0.92
95% CI	—	(0.83, 1.16)	(0.81, 1.13)	(0.76, 1.05)	(0.76, 1.05)	—	(0.76, 1.12)
Lycopene (μg)	3592	5693	7816	10543	15839	—	19132
Cases (*n*)	182	167	183	165	198	—	95
Age-adjusted RR	1.0	0.96	1.01	0.89	1.03	0.80	1.10
Multivariate RR[4]	1.0	0.97	1.02	0.89	1.01	0.98	0.93
95% CI	—	(0.79, 1.20)	(0.83, 1.25)	(0.72, 1.10)	(0.83, 1.24)	—	(0.73, 1.20)
β-Cryptoxanthin (μg)	19	49	80	125	220	—	272
Cases (*n*)	253	273	276	331	338	—	163
Age-adjusted RR	1.0	0.96	0.89	1.00	0.91	0.38	0.84
Multivariate RR[4]	1.0	1.01	0.93	1.05	0.94	0.53	0.87
95% CI	—	(0.85, 1.20)	(0.78, 1.11)	(0.89, 1.24)	(0.79, 1.11)	—	(0.72, 1.07)
Lutein and zeaxanthin (μg)	1172	2064	2817	6047	11685	—	13701
Cases (*n*)	295	306	296	265	309	—	138
Age-adjusted RR	1.0	0.99	0.93	0.81	0.86	0.03	0.75
Multivariate RR[4]	1.0	1.01	0.95	0.81	0.88	0.04	0.78
95% CI	—	(0.86, 1.19)	(0.80, 1.11)	(0.69, 0.96)	(0.75, 1.03)	—	(0.63, 0.95)
Retinol (IU)							
With supplements	855	1864	2710	5823	10441	—	14140
Cases (*n*)	247	282	278	310	354	—	176
Age-adjusted RR	1.0	0.96	0.91	1.01	1.08	0.12	1.07
Multivariate RR[5]	1.0	0.96	0.90	1.00	1.06	0.16	1.04
95% CI	—	(0.81, 1.15)	(0.76, 1.08)	(0.84, 1.18)	(0.90, 1.25)	—	(0.86, 1.27)
No supplements	719	1572	2060	2708	5466	—	6844
Cases (*n*)	139	152	149	152	183	—	94
Age-adjusted RR	1.0	1.01	0.89	0.90	1.04	0.57	1.01
Multivariate RR[5]	1.0	0.99	0.89	0.89	1.00	0.76	0.98
95% CI	—	(0.78, 1.24)	(0.70, 1.12)	(0.70, 1.12)	(0.80, 1.26)	—	(0.75, 1.27)
Total vitamin A (IU)							
With supplements	5133	8045	11111	14824	22461	—	27886
Cases (*n*)	245	281	294	323	328	—	164
Age-adjusted RR	1.0	0.97	0.95	0.98	0.92	0.44	0.93
Multivariate RR[4]	1.0	0.97	0.95	0.96	0.92	0.37	0.93
95% CI	—	(0.81, 1.15)	(0.80, 1.12)	(0.81, 1.13)	(0.78, 1.09)	—	(0.76, 1.14)
No supplements	4727	6965	9321	12391	17954	—	21648
Cases (*n*)	146	153	170	165	141	—	74
Age-adjusted RR	1.0	0.95	1.01	0.97	0.81	0.05	0.87
Multivariate RR[4]	1.0	0.94	0.99	0.93	0.79	0.04	0.84
95% CI	—	(0.75, 1.19)	(0.79, 1.24)	(0.74, 1.16)	(0.62, 1.00)	—	(0.63, 1.13)

[1] Values are the median intakes for each quintile and the top decile.

[2] Test for trend over nutrient quintiles.

[3] Adjusted for age in 5-y categories for each nutrient.

[4] Adjusted for age (5-y categories), time period (2-y intervals), diagnosis of diabetes (yes or no), cigarette smoking (never or 1–44, 45–64, or ≥65 pack-years), BMI (quintile), area of residence (Northeast United States, north central United States, Texas, California, or Florida), number of physician visits (0, 1, 2–3, or ≥4), aspirin use (yes or no), total energy intake (quintile), and alcohol intake (5 categories).

[5] Adjusted for the variables given above and energy-adjusted carotene intake (by quintile). Lycopene was assessed in 1984; follow-up for the variable began in 1984. Cases and person-years for "no supplement" use exclude supplement users and thus do not add up to the total.

inflammation, ocular trauma, previous intraocular surgery, or glaucoma (n = 189). Both the participant and her ophthalmologist indicated when a cataract had first been diagnosed. We used the earlier of the 2 dates to exclude cases diagnosed before completion of the 1980 questionnaire (n = 45) and cases reported with extraction after June 1, 1992, the end of the follow-up period (n = 79). Because women may have altered their diets in light of a diagnosis of cataract but before extraction, we considered the date of diagnosis as the time of event for women with a cataract extraction to avoid further updating of their exposure status. After all exclusions (including 428 cases with study population exclusions described above), 1471 cases remained for analysis.

Opacities in different areas of the lens (posterior subcapsular, cortical, or nuclear) may have different etiologies (9, 30). Therefore, in addition to our analysis in the entire case group of extractions, we performed an additional analysis using each subtype as the outcome variable and examined the association with nutrient intake. For these analyses, we used the information provided by the ophthalmologist indicating where the cataract was located in the lens. Three additional case groups were considered: *1*) those with only nuclear cataract in either 1 eye (if only 1 cataract) or both eyes (if bilateral cataract) and, similarly, *2*) those with only posterior subcapsular cataract, and *3*) those with only cortical type cataracts. Those with more than one types of cataract were omitted from these subanalyses to minimize misclassification of opacity type. Although this method results in smaller numbers of each type, any observed differences between type are more likely to reflect true differences.

Statistical analysis

For each participant, follow-up time, equal to the number of months between the return of the 1980 questionnaire and return of the 1982 questionnaire, was assigned to each covariate according to its status in 1980. Similarly, for each subsequent 2-y interval, additional months of follow-up were assigned according to the updated exposures at the beginning of the interval. For exposures that were not updated in this analysis (such as area of residence), the initial value was carried throughout the follow-up period.

To obtain a stable estimate of diet, we used nutrient intakes reported on the 1980 dietary questionnaire for the follow-up period 1980–1984 and, subsequently, an average of intakes from the 1980 and 1984 food-frequency questionnaires for the follow-up period from 1984 to 1992. Use of the average of the 2 questionnaires incorporated more recent dietary data while decreasing measurement error (31). Because age-related cataract generally takes many years to develop, changes in diet after 1984 were not incorporated. Nutrients were adjusted for total energy intake and standardized to 1600 kcal/d (6.7 MJ/d) as described elsewhere (32). We categorized the nutrients into quintiles and deciles on the basis of the distribution of intake derived from the 1980 dietary questionnaire. The adjusted nutrient intakes represent the nutrient composition of the diet with total energy held constant, as would be done in an experimental setting. We calculated vitamin A and retinol intakes, including and excluding the contribution from vitamin supplements.

We assessed the relation with individual foods as reported on the 1980, 1982, and 1984 questionnaires. In addition, we hypothesized that frequent consumption of carotenoid-rich foods early in life may be associated with lower risk of age-related cataract. We therefore examined the risk of cataract extraction according to reported food intake patterns during high school.

Cigarette smoking has been consistently associated with cataract (29, 33), and diabetes may also be a risk factor for cataract formation (7, 34). Therefore, we examined differences in risk of cataract within categories of these variables.

Incidence rates were calculated for each exposure category by dividing the number of cataract extractions by the person-time of follow-up for that category. RRs were used as the measure of association and were calculated as the ratio of incidence rates in exposed subjects to those in unexposed subjects. We used proportional hazards models to control simultaneously for other potential risk factors (35). We calculated 95% CIs for each RR. The P values for trend across categories of nutrient intake were calculated by treating the medians of each categorized level of intake as a continuous variable in the proportional hazards model. For categories of food intake, we calculated two-sided P values for the Mantel extension test for trend.

RESULTS

During 761 762 person-years of follow-up, we observed 1471 incident cases of cataract extraction. After cigarette smoking, body mass index, diagnosis of diabetes, energy intake, area of residence in 1976, aspirin use, number of visits to a physician in 1978, alcohol intake, and time period were controlled for; those in the highest quintile of carotene intake had a multivariate RR of 0.85 (95% CI: 0.72, 1.00) compared with those in the lowest quintile (Table 1). In addition, there were significant linear trends of decreasing risk with increasing intake of lutein and zeaxanthin and vitamin A without supplements (P for trend = 0.04), with modest but nonsignificant decreases in risk in the top (compared with the bottom) quintile (RR: 0.88; 95% CI: 0.75, 1.03; RR: 0.79; 95% CI: 0.62, 1.00, respectively). Intakes of other specific carotenoids were unrelated to risk of cataract extraction.

To examine a wider range of intake, we divided intake into deciles and compared the top decile with the lowest quintile. Intake in the top decile of lutein and zeaxanthin was associated with a significantly decreased risk (RR: 0.78; 95% CI: 0.63, 0.95) compared with intake in the bottom quintile. All other multivariate RRs in the top decile were similar to those presented in the top quintile. We obtained similar but slightly attenuated results when we defined intake by using either the 1980 diet alone, the most recently completed dietary questionnaire, or the cumulative average intake from all available dietary questionnaires up to and including the 1990 questionnaire.

We then placed 2 nutrients in a model simultaneously to assess their independent effects. In a model with lutein and zeaxanthin, multivariate RRs for vitamin A intake without supplements were slightly attenuated and high lutein and zeaxanthin intakes remained significant. A similar attenuation was observed for carotene when placed in a model with lutein and zeaxanthin, although high lutein and zeaxanthin intakes were also slightly attenuated and no longer significant.

Because the influence of carotenoids may differ between women according to cigarette smoking and diabetes (7, 29, 33), we analyzed the association between nutrient intake and cataract within categories of these variables. The RRs did not vary significantly between categories of smoking (never and 1–44, 45–64, or ≥65 pack-years), but tended to be more strongly inverse in nonsmokers for several nutrients. For example, in nonsmokers the multivariate RRs for the highest compared with the lowest quintiles of intakes were 0.78 (95% CI: 0.61, 1.01) for lutein and zeaxanthin and 0.58 (95% CI: 0.40, 0.86) for vitamin A without supplements. Removing diabetics from the analysis did not substantially alter any of the multivariate RRs.

We performed a similar analysis in cases with nuclear cataract only (n = 388) and posterior subcapsular cataract only (n = 314); too few cases (n = 56) of cortical cataract only were available (**Table 2**). RRs for nuclear-type cataract were slightly attenuated compared with those for total cataract, but those for posterior subcapsular cataract appeared to be more strongly inverse. Compared with intake in the lowest quintile, risks of posterior subcapsular cataract were 31–50% lower for those in the highest quintile of vitamin A intake without supplements, lutein and zeaxanthin, β-carotene, and carotene. Tests for trend of decreasing risk with increasing intake were significant for these nutrients.

Because of the inverse associations between several of the specific carotenoids and cataract noted above, we assessed the associations with individual foods high in carotenoids (**Table 3**). Of those foods assessed at baseline in 1980, only spinach and other greens were associated with a significant decreased risk of cataract extraction (P for trend = 0.03). When these items were assessed again in 1982 and 1984, increasing frequencies of consumption of broccoli, carrots, and winter squash were moderately, although not consistently, associated with significantly decreased risk. Frequent intake of spinach, particularly cooked spinach, appeared to be most strongly associated with a lower risk. Those who consumed cooked spinach ≥2 times/wk had a 30–38% lower risk than those who consumed it <1 time/mo. We combined the top 2 categories of intake for kale because few women in our group consumed kale ≥2 times/wk (17 cases and 12551 person-years). Those in the highest category of kale intake (≥1 time/wk) had a multivariate RR of 0.60 (95% CI: 0.37, 0.98). Placement of 2 foods in the model simultaneously did not materially affect the RRs for any food, except for spinach, which was consistently more protective.

Kale and spinach are particularly rich in lutein compared with other fruit and vegetables (218.14 and 110.0 μg lutein/g, respectively) (25). To ascertain whether the relation with cataract was specific to spinach or kale, we examined the association between other leafy green vegetables and cataract extraction. Iceberg lettuce has about one-tenth and romaine lettuce about one-half the lutein content of spinach (25). Neither iceberg nor romaine lettuce was associated with a decreased risk of cataract, although the RR for romaine was borderline significant (RR: 0.87; 95% CI: 0.71, 1.03). Eggs, a nonvegetable source of carotene high in zeaxanthin, were not associated with risk of extraction (RR: 1.03; 95% CI: 0.74, 1.29). Corn, a vegetable high in zeaxanthin, was also not associated with decreased risk (RR: 0.95; 95% CI: 0.71, 1.19). To assess whether a high intake of spinach and kale simply reflected a healthy lifestyle, we examined the association with intakes of other fruit and vegetables such as apples, oranges, alfalfa, and cauliflower; none of these foods were associated with cataract extraction.

We also examined the risk of cataract extraction according to intake of carotenoid-rich foods during high school. Intakes of carrots, broccoli, and cooked spinach were not significantly associated with risk of cataract extraction. Those who reported consuming spinach ≥2 times/wk had an RR of 0.88 (95% CI: 0.71, 1.09) compared with those who consumed it <1 time/mo.

DISCUSSION

In this large prospective study, those with the highest intake of lutein and zeaxanthin had a 22% lower risk of cataract extraction than did those in the lowest quintile of intake (RR: 0.78; 95% CI: 0.63, 0.95; P for trend = 0.04) after age, smoking, and other potential cataract risk factors were controlled for. Other specific carotenoids (α-carotene, β-carotene, lycopene, and β-cryptoxanthin), vitamin A, and retinol were not associated with cataract in multivariate analysis. Increasing frequency of intake of spinach and kale, foods rich in lutein, was associated with a moderate decrease in risk. The observation that other fruit and vegetables were not associated with decreased risk suggests that the relation may be due to lutein, a specific carotenoid predominantly found in spinach and kale, and not to a healthy lifestyle per se.

Although cataract type was not assessed in a standardized manner and documentation of subtype in the medical record may be

TABLE 2
Multivariate relative risk of cataract extraction and 95% CIs by type of cataract among those in the fifth quintile compared with the first quintile of intake: Nurses' Health Study, 1980–1992[1]

	Type of cataract		
Nutrient	Total cataract (n = 1471)	Nuclear only (n = 388)	Posterior subcapsular only (n = 314)
Carotene	0.85 (0.72, 1.00)	0.79 (0.57, 1.09)	0.69 (0.49, 0.98)
α-Carotene	1.03 (0.88, 1.22)	1.01 (0.73, 1.41)	0.86 (0.61, 1.21)
β-Carotene	0.89 (0.76, 1.05)	0.88 (0.63, 1.22)	0.68 (0.48, 0.97)
Lycopene	1.01 (0.83, 1.24)	0.79 (0.54, 1.15)	0.92 (0.58, 1.46)
β-Cryptoxanthin	0.94 (0.79, 1.11)	0.92 (0.67, 1.28)	1.06 (0.74, 1.51)
Lutein and zeaxanthin	0.88 (0.75, 1.03)	0.93 (0.68, 1.28)	0.68 (0.48, 0.97)
Retinol with supplements[2]	1.06 (0.90, 1.25)	1.33 (0.95, 1.88)	1.07 (0.76, 1.50)
Retinol without supplements[2]	1.00 (0.80, 1.26)	1.13 (0.73, 1.74)	0.95 (0.55, 1.62)
Total vitamin A with supplements	0.92 (0.78, 1.09)	0.98 (0.70, 1.38)	0.77 (0.53, 1.10)
Total vitamin A without supplements	0.79 (0.62, 1.00)	0.99 (0.61, 1.61)	0.50 (0.29, 0.85)

[1] Multivariate model adjusted for age (5-y categories), time period (2-y intervals), diagnosis of diabetes (yes or no), cigarette smoking (never or 1–44, 45–64, or ≥65 pack-years), BMI (quintile), area of residence (Northeast United States, north central United States, Texas, California, or Florida), number of physician visits (0, 1, 2–3, or ≥4), aspirin use (yes or no), total energy intake (quintile), and alcohol intake (5 categories). P values for tests for trend for posterior subscapular cataract were ≤0.05 for carotene, β-carotene, lutein and zeaxanthin, and total vitamin A without supplements.

[2] Adjusted for the variables given above and energy-adjusted carotene intake (by quintile).

TABLE 3
Multivariate relative risk of cataract extraction and 95% CIs by frequency of consumption of foods rich in carotenoids as assessed in 1980, 1982, and 1984: Nurses' Health Study, 1980–1992[1]

	Frequency of consumption				
Food	<1 time/mo	1–3 times/mo	1 time/wk	≥2 times/wk	*P* for trend
Broccoli					
1980	1.0 (Referent)	0.85 (0.71, 1.02)	0.89 (0.75, 1.06)	0.83 (0.69, 1.01)	0.23
1982	1.0	0.84 (0.69, 1.02)	0.82 (0.67, 1.01)	0.75 (0.59, 0.95)	0.03
1984	1.0	0.97 (0.75, 1.26)	0.86 (0.67, 1.11)	0.83 (0.63, 1.08)	0.05
Carrots					
1980	1.0	1.07 (0.84, 1.36)	1.10 (0.87, 1.38)	1.07 (0.85, 1.36)	0.70
1982	1.0	0.97 (0.74, 1.27)	0.88 (0.67, 1.16)	0.80 (0.61, 1.05)	0.006
1984	1.0	0.87 (0.67, 1.14)	0.80 (0.61, 1.04)	0.87 (0.66, 1.14)	0.45
Spinach and other greens					
1980	1.0	0.90 (0.74, 1.09)	0.90 (0.75, 1.09)	0.82 (0.68, 0.98)	0.03
Spinach (raw)					
1982	1.0	0.94 (0.82, 1.06)	1.02 (0.83, 1.26)	0.74 (0.54, 1.02)	0.14
1984	1.0	1.07 (0.92, 1.24)	0.68 (0.52, 0.88)	0.97 (0.66, 1.41)	0.12
Spinach (cooked)					
1982	1.0	0.98 (0.86, 1.11)	0.87 (0.73, 1.03)	0.62 (0.45, 0.86)	0.005
1984	1.0	1.02 (0.88, 1.18)	0.96 (0.79, 1.16)	0.70 (0.46, 1.06)	0.24
Winter squash					
1980	1.0	0.95 (0.84, 1.07)	0.95 (0.81, 1.11)	0.95 (0.75, 1.20)	0.45
1982	1.0	1.00 (0.88, 1.13)	0.86 (0.70, 1.07)	0.97 (0.72, 1.30)	
1984	1.0	0.87 (0.75, 1.02)	0.82 (0.67, 1.01)	0.78 (0.51, 1.18)	0.02
Sweet potatoes					
1980	1.0	0.89 (0.79, 1.00)	0.94 (0.73, 1.21)	1.21 (0.77, 1.92)	0.30
1982	1.0	1.00 (0.88, 1.12)	0.99 (0.73, 1.34)	0.70 (0.33, 1.49)	0.66
1984	1.0	0.96 (0.83, 1.12)	0.98 (0.74, 1.30)	1.15 (0.61, 2.16)	0.86
Kale					
1984	1.0	0.94 (0.72, 1.23)	0.60 (0.37, 0.98)[2]	—	0.06

[1] Multivariate model adjusted for age (5-y categories), time period (2-y intervals), diagnosis of diabetes (yes or no), cigarette smoking (never or 1–44, 45–64, or ≥65 pack-years), BMI (quintile), area of residence (Northeast United States, north central United States, Texas, California, or Florida), number of physician visits (0, 1, 2–3, or ≥4), aspirin use (yes or no), total energy intake (quintile), and alcohol intake (5 categories).

[2] Category adjusted to ≥1 time/wk.

imperfect, our use of the definition "nuclear only" or "posterior subcapsular only" assured that for most cases the subtype made up a substantial component of the opacity. The effect of specific carotenoids was slightly more pronounced in those with posterior subcapsular cataracts only. Posterior subcapsular cataracts are relatively uncommon in the general population, yet, because they cause symptoms early in their development, they make up a disproportionate number of cataracts requiring surgical extraction.

Because repeated and standardized ophthalmologic exams in this large cohort were not possible, we could not assess incident cataracts. Thus, the procedure of cataract extraction was used to define disease; in this way, we were unlikely to include any false-positive cases. Underascertainment of cases, if not associated with exposure, does not bias the RR in a cohort study (36). The cataracts in this study were those sufficiently severe to affect vision and therefore of greatest clinical and public health importance. Results were not materially altered when we excluded the 5957 noncases that were reported in 1992 to have ever been diagnosed with a cataract not requiring extraction.

Because all subjects are nurses, their access to medical care and their threshold for surgery are likely to be more uniform than that of the general population. In 1992, >80% of respondents reported having had an eye examination in the past 2 y. Nevertheless, if nurses who were more health conscious and likely to consume more carotenoid-rich foods also tended to have cataracts extracted at an earlier stage, RRs would be biased toward the null. We evaluated this possibility in detail. Correlations between each nutrient and the visual acuity before surgery in the eye being operated on (an index of disease severity) were very small (range: −0.06 to 0.06) as were the correlations with the visual acuity of the best eye (range: −0.06 to 0.07). Controlling for the number of physician visits did not alter the nutrient coefficients in a multivariate model. Finally, women in the highest quintile of intake for each nutrient were only 0.01–1.3% less likely to have foregone eye care for financial reasons and only 2.7–5.4% more likely to have had an eye examination from 1990 to 1992 than were women in the lowest quintile. Therefore, any bias from using cataract extraction is likely to have been small in this study and would have tended to obscure protective effects.

Censoring of cataract extraction according to the time of the initial diagnosis of cataract reduces bias due to change in diet as a consequence of diagnosis. However, the diagnosis date is less reliably remembered than is the extraction date. We used the earlier of the ophthalmologists' and the nurses' reported diagnosis dates because the ophthalmologists were often seeing the nurse as a referral. Data on exposure were collected before diagnosis, thus, any misclassification would be unrelated to risk of cataract and would bias our associations toward the null. The high follow-up rate in this cohort, 90.2% in 1992, minimizes this as a source of bias. Although we controlled for many cataract risk factors in the analysis, we did not have information on exposure to sunlight; however, because the cohort is not occupationally exposed, such variation is not likely to be as large as in a general population sample.

In our previous study with follow-up until 1988, intake of vitamin A was associated with a 39% decreased risk of cataract extraction (3) but no data on specific carotenoids were available. In this updated analysis with 978 additional cases, findings were similar but more modest for vitamin A. Similarly, RRs for carotene were no longer significant. With such modest inverse associations, it is difficult to distinguish the independent effects of specific nutrients. In addition, the nutrients are highly correlated; correlations between vitamin A without supplements, lutein and zeaxanthin, and carotene as assessed in 1980 ranged from 0.68 to 0.88. When we placed 2 nutrients in a model simultaneously, lutein and zeaxanthin appeared to be most strongly associated with lower risk of cataract.

Similar findings were observed in a recent large, prospective study conducted over 8 y of follow-up in 36644 male participants of the Health Professionals Follow-up Study (37). Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (95% CI: 0.65, 1.01; *P* for trend = 0.03). No other specific carotenoids were significantly associated with risk in multivariate models. Previous studies of specific antioxidants and cataract have been inconsistent. In the Lens Opacities case-control study, high dietary intake of vitamin A was significantly associated with decreased risk of nuclear and cortical cataracts (7); however, 4 other studies observed no association for vitamin A intake (4, 5, 9, 10). In a nested case-control study, Knekt et al (4) observed an increased risk of cataract in those in the lower one-third of both plasma α-tocopherol and β-carotene compared with the top two-thirds. No association was observed for retinol. In the Baltimore Longitudinal Study on Aging (10), neither plasma β-carotene nor retinol concentrations measured 2–4 y before lens assessment was associated with risk of nuclear cataract; however, only 318 cases were included. Mares-Perlman et al (6) examined the relation between diet (10 y previous) assessed retrospectively and early nuclear sclerosis in 1919 persons in the Beaver Dam Eye Study (6). Lutein was the only nutrient significantly related to decreased risk (*P* for trend = 0.02); women in the highest quintile of intake had an RR of 0.73 (95% CI: 0.50, 1.06) compared with those in the lowest.

Few studies have examined associations between specific foods and cataract risk. Brown et al (37) observed that foods high in carotenoids, such as broccoli, spinach, and tomato sauce, were consistently associated with a lower risk of cataract extraction. Jacques and Chylack (2) observed that the consumption of foods rich in carotenoids other than β-carotene was associated with a decreased risk of cataract. In the Beaver Dam Eye Study (6), only spinach was significantly related to decreased risk of more severe nuclear sclerosis in women. Women in the highest category of spinach intake (median frequency of 0.7 times/wk) had a multivariate RR of 0.69 (95% CI: 0.50, 0.95) compared with those in the lowest category. However, only one food was placed in a model at a time. Because foods are often highly correlated, these findings may be explained by another highly correlated food. We found a significantly decreased risk with high spinach intake, even in models controlling for other carotenoid-rich foods.

In summary, our prospective findings, and those of others, suggest that dietary carotenoids may contribute to protection against cataracts. Of the specific carotenoids, lutein and zeaxanthin may provide the greatest protection. Intake of spinach and kale, 2 lutein-rich vegetables, in particular, may be associated with a reduced risk. Continued assessment in this and other studies is needed to better elucidate the relation between carotenoid intake and specific opacity subtypes.

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