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A prospective study of dietary carotenoids, vitamins C and E, and risk of cataract in women

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Abstract

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

Design—Dietary intake was assessed at baseline in 1993 among 39,876 female health professionals by use of a detailed food-frequency questionnaire. A total of 35,551 of these women provided detailed information on antioxidant nutrient intake from food and supplements and were free of a diagnosis of cataract.

Main Outcome Measure—Cataract defined as an incident, age-related lens opacity, responsible for a reduction in best-corrected visual acuity to 20/30 or worse, based on self-report confirmed by medical record review.

Results—A total of 2,031 cases of incident cataract were confirmed during an average of 10 years of follow-up. Comparing women in extreme quintiles, the multivariate relative risk of cataract was 0.82 (95% confidence interval, 0.71-0.95; P, test for trend, 0.045) for lutein/zeaxanthin, and 0.86 (95% confidence interval, 0.74-1.00; P, test for trend, 0.03) for vitamin E from food and supplements.

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Conclusions—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.

Introduction

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 observational epidemiologic studies in humans have been inconsistent (4-6). Moreover, results of completed randomized trials indicate that supplemental use of vitamin E, 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 (7-14). Whether longer duration treatment with these antioxidants can materially reduce risks of cataract, which develop slowly over many years, remains to be determined in recently-completed and ongoing trials (15-17).

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 risks 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 of observational epidemiologic studies generally support a possible beneficial effect for lutein (24-32). 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 even though there are no randomized trial data to assess its effectiveness in the eye, and prospective observational data for cataract are limited to three studies (27-29,32). For this reason, the National Eye Institute has cautioned that the possible benefit of lutein for the eye remains uncertain and warrants closer examination before conclusions can be drawn (33). In this report, we examine in prospective data the relation of dietary intake of several carotenoids including lutein (and its stereoisomer zeaxanthin), as well as vitamins C and E, with the risk of cataract during 10 years of follow-up in a large cohort of female health professionals.

Materials and Methods

Study participants were women enrolled in the Women's Health Study (WHS), a recently completed randomized, double-blind, placebo-controlled trial of low-dose aspirin, vitamin E, and beta-carotene in the primary prevention of CVD and cancer among 39,876 apparently healthy female health professionals aged 45 years and older (34-37). 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 (99%) of the randomized participants, who completed a 131-item validated semiquantitative food-frequency questionnaire (SFFQ) at baseline in 1993 (38). 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 remainder, 35,551 participants 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 ”six or more times per day.“ Responses to the individual food items were converted to average daily intake of each nutrient based upon food tables maintained by the Harvard School of Public Health, Boston, MA. Carotenoid content of food items was determined with the use of US Department of Agriculture-National Cancer Institute carotenoid food composition databases (39,40). Participants also provided information about their current use of multivitamins and supplements of vitamin C, vitamin E, and beta-carotene. The total intakes of antioxidants was calculated by adding the contributions from vitamin supplements and foods. For beta-carotene, vitamin C, and vitamin E we also calculated intake from food sources alone. In our 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 vitamin C (41). For vitamin E, the correlation between estimates of intake from the SFFQ and plasma concentrations of alpha-tocopherol was 0.41 (42). For carotenoids, correlations between plasma concentrations and the SFFQ assessments among 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 (43). These estimates were similar to those found between plasma levels of these nutrients and estimates from food records (44).

Other covariates

Information on possible risk factors for cataract was collected on the WHS baseline questionnaire. Information included age, height and weight, smoking status, alcohol use, frequency of exercise, parental history of MI at age < 60 years, history of hypertension, history of diabetes, history of hypercholesterolemia, postmenopausal hormone use, and history of an eye exam in the last 2 years.

Ascertainment and definition of endpoints

Following the report of a cataract diagnosis, a written consent identifying the diagnosing ophthalmologist(s) or optometrist(s) was obtained. Ophthalmologist(s) and optometrist(s) were 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 endpoint 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 alternate ocular pathology 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 until the time of diagnosis of cataract, or until death or February 2004, whichever came first. Nutrient intake was considered as a categorical variable (in quintiles), with adjustment for total energy by the residual method (41). Estimates of relative risks (RR) 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 (45). Multivariate RRs were obtained by further adjusting for smoking, alcohol use, history of diabetes, history of hypertension, history of hypercholesterol, body mass index, physical activity, parental history of myocardial infarction, postmenopausal hormone use, and history of an eye exam in the last 2 years. For each relative risk, two-sided P values and 95 percent confidence intervals (CIs) were calculated (46). 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 over time. For each nutrient, P > 0.05 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 shown in Table 1. Women who were newly diagnosed with 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 higher body mass index, exercised less, and were more likely to report a history of hypertension, diabetes, and high cholesterol.

Average intake of lutein/zeaxanthin and several other nutrients were highly correlated with one another (p < 0.001 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, 2,031 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 to those in the lowest, the multivariate relative risk (RR) of cataract was 0.82 (95% confidence interval [CI], 0.71-0.95; P, test for trend = 0.045) (Table 2). The RR for vitamin E from food and supplements, comparing women in extreme quintiles, was 0.86 (95% CI, 0.74-1.00; P, test for trend = 0.03). (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 (P, test for trend = 0.04), but not in analyses that also adjusted for other cataract risk factors (P, test for trend = 0.19). Multivariate RRs for the other nutrients (alpha-carotene, beta-carotene, lycopene, and vitamin C), were generally below 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 vitamin C in this analysis included intake from both food and supplements. After stepwise removal of nonsignificant nutrients, only vitamin E (P, test for trend = 0.03) remained significantly associated with the risk of cataract. When the significance level for retention was set at 0.20, vitamin E (P, test for trend = 0.04) and lutein/zeaxanthin (P, test for trend = 0.06) 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 among 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 approximate 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 (P, test for trend=0.06). 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 (P, test for trend=0.06), but not after adjustment for other cataract risk factors.

Discussion

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 extreme quintiles, women with high intake of lutein/zeaxanthin had an 18% lower risk of cataract in multivariate analysis (P, test for trend = 0.045). High intake of vitamin E from food and supplements was associated with a 14% lower risk of cataract (P, test for trend = 0.03). 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 vitamin C.

The prospective design of this study precluded the possibility that participant reports of nutrient intake at 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 endpoint, and thus would also attenuate the true associations. Random misclassification of the cataract endpoint 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 exam in the last two years in multivariate analyses. Finally, we controlled for a number of measured confounders (Table 1), but other potential confounders which were either unmeasured or unknown may have contributed to the findings.

There have been three other prospective studies that examined the relationship of 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 to those in the bottom quintile, had a 22% lower risk of cataract extraction (RR, 0.78; 95% CI, 0.63-0.95; P, test for trend = 0.04) during 12 years of follow-up (28). In another report 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 (32). In a second study, data from the Health Professionals Study of 36,644 male health professionals showed that men in the highest quintile of lutein/zeaxanthin intake, compared to those in the lowest, had a 19% lower risk of cataract extraction (RR, 0.81; 95% CI, 0.65-1.01; P, test for trend = 0.03) during 8 years of follow-up (27). A third study, based on data from 1,354 men and women participating in a nutrition substudy in 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 to those in the lowest quintile, had a 50% decreased risk of incident nuclear opacity (OR, 0.5; 95% CI, 0.3-0.8; P, test for trend = 0.002) at 5 years of follow-up (29). Our data from a large cohort of female health professionals indicate an approximate 20% decreased risk of cataract for those with high dietary intake of lutein/zeaxanthin, and thus appear most consistent with the findings for cataract extraction reported in the Nurses' Health Study and Health Professionals Study (27,28). Of note, lutein/zeaxanthin intake in the reference group in the WHS and the two other cohorts of health professionals (27,28) appear markedly higher than the reference intake for lutein/zeaxanthin in the population-based sample from Beaver Dam (29), which may at least partially explain the smaller risk reductions observed in the former.

Among the other carotenoids examined in our study, only beta-carotene from food and supplements showed a possible inverse relation with risk of cataract. Women in the highest, compared to the lowest, quintile of intake had a borderline significant (p=0.051) 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 appear consistent with most earlier prospective studies which report a weak and statistically nonsignificant inverse trend between beta-carotene level in the diet or blood and risk of cataract (27-29,32,47,48). More importantly, results of five randomized trials clearly indicate that supplemental use of beta-carotene (with or without other antioxidant supplements) for as long as 12 years has little impact on risks of cataract (7,8,10,11,14).

We observed a significant inverse trend between vitamin E intake from food and supplements and risk of cataract in our population of women. This inverse trend persisted after adjustment for other nutrients and appeared 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/day, a level of intake difficult to attain from food sources only. The reduction in risk appeared 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 extreme quintiles of vitamin E intake, 0.86; 95% CI, 0.73-1.00; p-trend = 0.048). Results of other prospective studies have been mixed with some supporting an inverse association between dietary or serum vitamin E and cataract (32,47-51) while others report no association (29,52,53). Data from five randomized trials completed to date provide little evidence that use of vitamin E supplements, alone or in combination with other vitamin supplements, for treatment periods as long as 6.5 years has any material impact on cataract development and progression (8,10-13). The final results for cataract during the 10 year treatment period for vitamin E in the WHS will be reported elsewhere.

Our data for vitamin C indicate a weak, and statistically nonsignificant, inverse association with risk of cataract. This finding appears to conflict with cross-sectional data presented in two recent reports from the Nurses' Health Study (30,31), but is consistent with the results of several other prospective studies (29,50-53) including 5-year follow-up data in the Nurses' Health Study subsample (32). Furthermore, findings in three randomized trials indicate no major benefit for combined treatment with vitamin C and other antioxidants for treatment durations as long as 6.5 years (8,11,12).

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, vitamin C, 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 to suggest a possible beneficial effect for 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 (54) 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 risks of cataract. While 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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References

1. Bhuyan KC, Bhuyan DK, Podos SM. Lipid peroxidation in cataract of the human. Life Sci 1986;38:1463–1471. [PubMed: 3702587]
2. Spector A. Oxidative stress-induced cataract: mechanism of action. FASEB J 1995;9:1173–1182. [PubMed: 7672510]
3. Jacques, PF.; Taylor, A. Micronutrients and age-related cataracts. In: Bendich, A.; Butterworth, CE., Jr, editors. Micronutrients in health and disease prevention. Marcel Dekker; New York: 1991. p. 359-379.
4. Wu SY, Leske MC. Antioxidants and cataract formation: a summary review. Int Ophthalmol Clin 2000;40:71–81. [PubMed: 11064858]
5. Jacques PF. The potential preventive effects of vitamins for cataract and age-related macular degeneration. Int J Vitam Nutr. Res 1999;69:198–205. [PubMed: 10389028]
6. Christen WG. Antioxidant vitamins and age-related eye disease. Proc Assoc Am Physicians 1999;111:16–21. [PubMed: 9893153]
7. Christen WG, Manson JE, Glynn RJ, et al. A randomized trial of beta carotene and age-related cataract in US physicians. Arch Ophthalmol 2003;121:372–378. [PubMed: 12617708]
8. Sperduto RD, Hu TS, Milton RC, et al. The Linxian cataract studies. Two nutrition intervention trials. Arch Ophthalmol 1993;111:1246–1253. [PubMed: 8363468]
9. Teikari JM, Virtamo J, Rautalahti M, Palmgren J, Liesto K, Heinonen OP. Long-term supplementation with alpha-tocopherol and beta-carotene and age-related cataract. Acta Ophthalmol Scand 1997;75:634–640. [PubMed: 9527321]
10. Teikari JM, Rautalahti M, Haukka J, et al. Incidence of cataract operations in Finnish male smokers unaffected by alpha tocopherol or beta carotene supplements. J Epidemiol Community Health 1998;52:468–472. [PubMed: 9799882]
11. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 2001;119:1439–1452. [PubMed: 11594943]
12. Chylack LT Jr, Brown NP, Bron A, et al. The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. Ophthalmic Epidemiol 2002;9:49–80. [PubMed: 11815895]
13. McNeil JJ, Robman L, Tikellis G, Sinclair MI, McCarty CA, Taylor HR. Vitamin E supplementation and cataract: randomized controlled trial. Ophthalmology 2004;111:75–84. [PubMed: 14711717]
14. Christen W, Glynn R, Sperduto R, Chew E, Buring J. Age-related cataract in a randomized trial of beta-carotene in women. Ophthalmic Epidemiol 2004;11:401–412. [PubMed: 15590586]

15. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer. The Women's Health Study: a randomized controlled trial. JAMA 2005;294:56–65. [PubMed: 15998891]
16. Manson JE, Gaziano JM, Spelsberg A, et al. for the WACS Research Group: A secondary prevention trial of antioxidant vitamins and cardiovascular disease in women: rationale, design, and methods. Ann Epidemiol 1995;5:261–269. [PubMed: 8520707]
17. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II--a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. Ann Epidemiol 2000;10:125–134. [PubMed: 10691066]
18. Yeum KJ, Taylor A, Tang G, Russell RM. Measurement of carotenoids, retinoids, and tocopherols in human lenses. Invest Ophthalmol Vis Sci 1995;36:2756–2761. [PubMed: 7499098]
19. Bates CJ, Chen SJ, Macdonald A, Holden R. Quantitation of vitamin E and a carotenoid pigment in cataractous human lenses, and the effect of a dietary supplement. Int J Vitam Nutr Res 1996;66:316–321. [PubMed: 8979159]
20. Yeum KJ, Shang FM, Schalch WM, Russell RM, Taylor A. Fat-soluble nutrient concentrations in different layers of human cataractous lens. Curr Eye Res 1999;19:502–505. [PubMed: 10550792]
21. Sies H, Stahl W, Sundquist AR. Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. Ann N Y Acad Sci 1992;669:7–20. [PubMed: 1444060]
22. Sujak A, Gabrielska J, Grudzinski W, Borc R, Mazurek P, Gruszecki WI. Lutein and zeaxanthin as protectors of lipid membranes against oxidative damage: the structural aspects. Arch Biochem Biophys 1999;371:301–307. [PubMed: 10545218]
23. Krinsky NI, Landrum JT, Bone RA. Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annu Rev Nutr 2003;23:171–201. [PubMed: 12626691]
24. Hankinson SE, Stampfer MJ, Seddon JM, et al. Nutrient intake and cataract extraction in women: a prospective study. BMJ 1992;305:335–339. [PubMed: 1392884]
25. Mares-Perlman JA, Brady WE, Klein BE, et al. Diet and nuclear lens opacities. Am J Epidemiol 1995;141:322–334. [PubMed: 7840110]
26. Tavani A, Negri E, La Vecchia C. Food and nutrient intake and risk of cataract. Ann Epidemiol 1996;6:41–46. [PubMed: 8680624]
27. Brown L, Rimm EB, Seddon JM, et al. A prospective study of carotenoid intake and risk of cataract extraction in US men. Am J Clin Nutr 1999;70:517–524. [PubMed: 10500021]
28. Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women. Am J Clin Nutr 1999;70:509–516. [PubMed: 10500020]
29. Lyle BJ, Mares-Perlman JA, Klein BE, Klein R, Greger JL. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. Am J Epidemiol 1999;149:801–809. [PubMed: 10221316]
30. Jacques PF, Chylack LT Jr, Hankinson SE, et al. Long-term nutrient intake and early age-related nuclear lens opacities. Arch Ophthalmol 2001;119:1009–1019. [PubMed: 11448323]
31. Taylor A, Jacques PF, Chylack LT Jr, et al. Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities. Am J Clin Nutr 2002;75:540–549. [PubMed: 11864861]
32. Jacques PF, Taylor A, Moeller S, et al. Long-term nutrient intake and 5-year change in nuclear lens opacities. Arch Ophthalmol 2005;123:517–526. [PubMed: 15824226]
33. NEI Statement. Lutein and its Role in Eye Disease Prevention. National Eye Institute; National Institutes of Health; http://www.nei.nih.gov/news/statements/lutein.asp. Accessed February 6, 2005.
34. Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. J Myocardial Ischemia 1992;4:27–29.
35. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–1304. [PubMed: 15753114]
36. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer. The Women's Health Study: a randomized controlled trial. JAMA 2005;294:47–55. [PubMed: 15998890]

37. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:56–65. [PubMed: 15998891]
38. Liu S, Manson JE, Lee IM, et al. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. Am J Clin Nut 2000;72:922–928.
39. Mangels AR, Holden JM, Beecher GR, et al. Carotenoid content of fruits and vegetables: an evaluation of analytic data. J Am Diet Assoc 1993;93:284–296. [PubMed: 8440826]
40. Chug-Ahuja JK, Holden JM, Forman MR, et al. The development and application of a carotenoid database for fruits, vegetables, and selected multicomponent foods. J Am Diet Assoc 1993;93:318–323. [PubMed: 8440830]
41. Willett, WC. Nutritional epidemiology. 2nd. ed.. Oxford University Press; New York: 1998.
42. Ascherio A, Stampfer MJ, Colditz GA, Rimm EB, Litin L, Willett WC. Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. J Nutr 1992;122:1792–1801. [PubMed: 1512628]
43. Michaud DS, Giovannucci EL, Ascherio A, et al. Associations of plasma carotenoid concentrations and dietary intake of specific carotenoids in samples of two prospective cohort studies using a new carotenoid database. Cancer Epidemiol Biomarkers Prev 1998;7:283–290. [PubMed: 9568782]
44. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–1126. [PubMed: 1632423]
45. Cox DR. Regression models and life-tables (with discussion). J R Stat Soc B 1972;34:187–220.
46. Kleinbaum, D.; Kupper, L.; Morgenstern, H. Epidemiologic Research: Principles and Quantitative Methods. Lifetime Learning Publications; Belmont, Calif: 1982.
47. Knekt P, Heliovaara M, Rissanen A, Aromaa A, Aaran RK. Serum antioxidant vitamins and risk of cataract. BMJ 1992;305:1392–1394. [PubMed: 1486302]
48. Lyle BJ, Mares-Perlman JA, Klein BE, et al. Serum carotenoids and tocopherols and incidence of age-related nuclear cataract. Am J Clin Nutr 1999;69:272–277. [PubMed: 9989692]
49. Rouhiainen P, Rouhiainen H, Salonen JT. Association between low plasma vitamin E concentration and progression of early cortical lens opacities. Am J Epidemiol 1996;144:496–500. [PubMed: 8781465]
50. Leske MC, Chylack LT, He Q, et al. Antioxidant vitamins and nuclear opacities: the Longitudinal Study of Cataract. Ophthalmology 1998;105:831–836. [PubMed: 9593382]
51. Mares-Perlman JA, Lyle BJ, Klein R, et al. Vitamin supplement use and incident cataracts in a population-based study. Arch Ophthalmol 2000;118:1556–1563. [PubMed: 11074813]
52. Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of vitamin supplement intake and cataract extraction among U.S. women. Epidemiology 1999;10:679–684. [PubMed: 10535780]
53. Seddon JM, Christen WG, Manson JE, et al. The use of vitamin supplements and the risk of cataract among US male physicians. Am J Public Health 1994;84:788–792. [PubMed: 8179050]
54. Bernstein PS, Khachik F, Carvalho LS, Muir GJ, Zhao DY, Katz NB. Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye. Exp Eye Res 2001;72:215–223. [PubMed: 11180970]

Table 1

Baseline characteristics of study participants by incident cataract.

	No Cataract (n=33,520)	Cataract (n=2,031)	P-value
Mean age (y)	53.5	61.0	<0.001
Cigarette smoking (%)			
Never	51.2	49.1	<0.001
Past	35.8	35.0	
Current	13.0	16.0	
Alcohol use (%)			
1+ drinks/day	10.2	10.3	0.06
1-6 drinks/wk	32.2	28.3	
1-3 drinks/month	13.3	12.9	
Rarely/never	44.3	48.5	
Physical exercise (%)			
4+ times/wk	10.7	10.1	0.02
1-3 times/wk	31.7	28.0	
<1 time/wk	20.1	20.8	
Rarely/never	37.6	41.1	
Body mass index (kg/m^2)	25.4	25.7	0.03
Postmenopausal hormone use (%)			
Never	48.7	41.3	0.17
Past only	9.4	10.1	
Current	41.9	48.5	
History of hypertension* (%)	24.4	30.8	<0.001
History of diabetes (%)	2.1	4.5	<0.001
History of high cholesterol† (%)	28.4	32.5	<0.001
Parental history of MI‡ (%)	13.1	13.2	0.99
Eye exam in past 2 years (%)	81.9	85.0	0.13

Footnotes

*Hypertension was defined as 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.

†High cholesterol was defined as reported high cholesterol, reported blood cholesterol of 240 mg/dl or greater, or history of treatment with cholesterol-lowering medication.

‡Myocardial infarction in either parent before age 60 years.

Table 2

Relative risk (95% CI) of cataract according to quintiles of dietary intake of nutrients in the Women's Health Study.

	Quintile of Intake					
	1*	2	3	4	5	p-trend
alpha-carotene (:g)						
Median intake	197	427	638	953	1,708	
Cases of cataract	374	384	404	377	492	
N	7,111	7,110	7,110	7,110	7,110	
Age- and treatment-adjusted RR	1.00	0.88 (0.76-1.01)	0.90 (0.78-1.04)	0.79 (0.68-0.91)	0.94 (0.82-1.07)	0.74
Multivariate-adjusted risk RR †	1.00	0.90 (0.78-1.04)	0.92 (0.80-1.06)	0.82 (0.70-0.94)	0.96 (0.84-1.11)	0.98
beta-carotene (:g)						
With supplements						
Median intake	1,894	3,039	4,052	5,415	8,256	
Cases of cataract	369	388	364	444	466	
N	7,111	7,110	7,110	7,110	7,110	
Age- and treatment-adjusted RR	1.00	0.95 (0.82-1.09)	0.80 (0.69-0.92)	0.93 (0.81-1.07)	0.85 (0.74-0.98)	0.07
Multivariate-adjusted RR	1.00	0.97 (0.84-1.12)	0.82 (0.71-0.95)	0.97 (0.84-1.12)	0.87 (0.75-1.00)	0.11
No supplements						
Median intake	1,790	2,857	3,793	5,007	7,550	
Cases of cataract	379	365	384	417	486	
N	7,111	7,110	7,110	7,110	7,110	
Age- and treatment-adjusted RR	1.00	0.87 (0.75-1.01)	0.84 (0.73-0.97)	0.83 (0.72-0.96)	0.88 (0.77-1.01)	0.21
Multivariate-adjusted RR	1.00	0.88 (0.76-1.02)	0.87 (0.75-1.01)	0.87 (0.75-1.00)	0.89 (0.77-1.02)	0.27
beta-cryptoxanthin (:g)						
Median intake	10	30	50	80	146	
Cases of cataract	355	374	408	445	449	
N	7,113	7,112	7,107	7,109	7,110	
Age- and treatment-adjusted RR	1.00	1.00 (0.87-1.16)	0.97 (0.84-1.12)	1.00 (0.87-1.15)	0.88 (0.76-1.01)	0.04
Multivariate-adjusted risk RR	1.00	1.01 (0.87-1.17)	1.01 (0.87-1.16)	1.05 (0.91-1.21)	0.92 (0.80-1.06)	0.19
Lycopene (:g)						
Median intake	3,342	5,439	7,694	10,843	16,765	
Cases of cataract	428	381	427	410	385	
N	7,111	7,110	7,110	7,110	7,110	
Age- and treatment-adjusted RR	1.00	0.95 (0.83-1.09)	1.04 (0.91-1.18)	0.98 (0.85-1.12)	0.98 (0.85-1.12)	0.84
Multivariate-adjusted risk RR	1.00	0.94 (0.82-1.08)	1.04 (0.91-1.19)	0.98 (0.86-1.13)	0.96 (0.84-1.11)	0.77
Lutein/Zeaxanthin (:g)						
Median intake	1,177	2,162	3,070	4,245	6,716	
Cases of cataract	429	358	438	393	413	
N	7,111	7,110	7,110	7,110	7,110	
Age- and treatment-adjusted RR	1.00	0.77 (0.67-0.89)	0.91 (0.79-1.04)	0.78 (0.68-0.89)	0.82 (0.72-0.94)	0.03
Multivariate-adjusted risk RR	1.00	0.77 (0.67-0.89)	0.92 (0.80-1.05)	0.79 (0.69-0.91)	0.82 (0.71-0.95)	0.045
Vitamin E (mg)						
With supplements						
Median intake	4.4	5.6	7.3	23.0	262.4	
Cases of cataract	374	376	463	439	379	
N	7,143	7,118	7,070	7,110	7,110	
Age- and treatment-adjusted RR	1.00	0.90 (0.78-1.04)	0.98 (0.85-1.12)	0.96 (0.84-1.10)	0.84 (0.73-0.97)	0.02
Multivariate-adjusted risk RR	1.00	0.92 (0.80-1.07)	0.99 (0.86-1.14)	1.00 (0.87-1.15)	0.86 (0.74-1.00)	0.03
No supplements						
Median intake	4.3	5.1	5.8	6.5	8.4	
Cases of cataract	369	354	405	435	468	
N	7,171	7,167	7,002	7,129	7,082	
Age- and treatment-adjusted RR	1.00	0.88 (0.76-1.02)	0.94 (0.81-1.08)	0.91 (0.79-1.04)	0.89 (0.78-1.03)	0.25
Multivariate-adjusted risk RR	1.00	0.91 (0.78-1.05)	0.97 (0.84-1.12)	0.92 (0.80-1.06)	0.92 (0.80-1.06)	0.39
Vitamin C (mg)						
With supplements						

	Quintile of Intake					
	1*	2	3	4	5	p-trend
Median intake	83	127	166	220	439	
Cases of cataract	337	364	409	473	448	
N	7,112	7,110	7,109	7,110	7,110	
Age- and treatment-adjusted RR	1.00	0.94 (0.81-1.08)	0.92 (0.80-1.07)	0.96 (0.84-1.11)	0.90 (0.78-1.04)	0.24
Multivariate-adjusted risk RR	1.00	0.97 (0.84-1.13)	0.97 (0.84-1.13)	1.01 (0.87-1.17)	0.94 (0.81-1.09)	0.39
No supplements						
Median intake	76	109	137	169	225	
Cases of cataract	328	396	380	432	495	
N	7,111	7,111	7,112	7,110	7,107	
Age- and treatment-adjusted RR	1.00	1.06 (0.91-1.23)	0.92 (0.79-1.07)	0.93 (0.80-1.07)	0.96 (0.83-1.11)	0.28
Multivariate-adjusted risk RR	1.00	1.09 (0.94-1.26)	0.96 (0.82-1.11)	0.98 (0.84-1.13)	1.00 (0.86-1.16)	0.61

Footnotes

Abbreviations: RR, relative risk (95% confidence intervals in parentheses).

*Reference category

†Adjusted for age, randomized treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1-3 drinks/month, 1-6 drinks/week, and ∃1 drinks/day), BMI (continuous), exercise (rarely/never, <1 time/week, 1-3 times/week, and ∃4 times/week), postmenopausal hormone use (never, past, current), history of hypertension (ever diagnosis by physician or selfreported blood pressure ∃ 140/90; yes or no), history of hypercholesterolemia (baseline history of cholesterol-medication use or a physician diagnosis of high cholesterol or a self-reported cholesterol of at least 240 mg/dL; yes or no), history of diabetes (yes or no), family history of myocardial infarction before the age of 60 (yes or no), history of eye exam in the last 2 years.

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Table 3

Relative risk (95% CI) 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.

	Quintile of Intake					
	1*	2	3	4	5	p-trend
Total fruits and vegetables						
Sevings per day (median)	2.5	4.1	5.4	7.0	10.0	
Cases of cataract	353	364	408	443	462	
N	7,108	7,104	7,108	7,106	7,103	
Age- and treatment-adjusted RR	1.00	0.93 (0.80-1.07)	0.91 (0.79-1.05)	0.91 (0.79-1.05)	0.89 (0.77-1.02)	0.14
Multivariate-adjusted risk RR †	1.00	0.94 (0.81-1.09)	0.93 (0.81-1.08)	0.93 (0.81-1.08)	0.90 (0.78-1.05)	0.23
All fruits						
Sevings per day (median)	0.6	1.3	1.9	2.6	3.8	
Cases of cataract	334	353	411	451	481	
N	7,134	7,077	7,136	7,069	7,103	
Age- and treatment-adjusted RR	1.00	0.92 (0.79-1.07)	0.95 (0.82-1.10)	0.93 (0.80-1.07)	0.87 (0.76-1.00)	0.08
Multivariate-adjusted risk RR †	1.00	0.95 (0.82-1.11)	0.99 (0.85-1.15)	1.00 (0.87-1.16)	0.93 (0.80-1.08)	0.44
All vegetables						
Sevings per day (median)	1.5	2.5	3.4	4.5	6.8	
Cases of cataract	378	366	418	424	444	
N	7,121	7,089	7,108	7,103	7,104	
Age- and treatment-adjusted RR	1.00	0.93 (0.81-1.08)	0.95 (0.82-1.09)	0.94 (0.82-1.08)	0.92 (0.80-1.06)	0.35
Multivariate-adjusted risk RR †	1.00	0.94 (0.81-1.09)	0.96 (0.83-1.11)	0.96 (0.83-1.10)	0.92 (0.80-1.06)	0.38
Green leafy vegetables						
Sevings per day (median)	0.1	0.4	0.6	0.9	1.4	
Cases of cataract	461	377	389	399	402	
N	7,695	6,624	6,648	7,584	6,957	
Age- and treatment-adjusted RR	1.00	0.99 (0.86-1.13)	0.96 (0.84-1.10)	0.83 (0.73-0.95)	0.91 (0.80-1.04)	0.03
Multivariate-adjusted risk RR †	1.00	1.00 (0.87-1.14)	0.98 (0.86-1.12)	0.84 (0.74-0.97)	0.93 (0.81-1.06)	0.06
Cruciferous vegetables						
Sevings per day (median)	0.1	0.2	0.4	0.6	1.0	
Cases of cataract	361	460	378	385	446	
N	6,437	8,143	6,964	7,343	6,636	
Age- and treatment-adjusted RR	1.00	0.92 (0.81-1.06)	0.84 (0.73-0.98)	0.82 (0.71-0.95)	0.98 (0.85-1.12)	0.86
Multivariate-adjusted risk RR †	1.00	0.93 (0.81-1.07)	0.86 (0.74-0.99)	0.83 (0.72-0.96)	0.96 (0.84-1.11)	0.93
Dark yellow vegetables						
Sevings per day (median)	0.1	0.2	0.3	0.6	1.0	
Cases of cataract	394	333	425	427	449	
N	7,590	6,359	7,497	6,981	7,088	
Age- and treatment-adjusted RR	1.00	0.94 (0.81-1.08)	0.91 (0.79-1.04)	0.95 (0.83-1.09)	0.92 (0.81-1.06)	0.47
Multivariate-adjusted	1.00	0.95 (0.82-1.11)	0.94 (0.82-1.08)	0.99 (0.86-1.14)	0.96 (0.83-1.10)	0.83
Citrus fruits						
Sevings per day (median)	0.1	0.3	0.6	1.0	1.6	
Cases of cataract	363	358	333	513	462	
N	7,207	7,073	6,789	7,586	6,846	
Age- and treatment-adjusted RR	1.00	0.97 (0.84-1.12)	0.88 (0.76-1.02)	1.02 (0.89-1.17)	0.93 (0.81-1.06)	0.60
Multivariate-adjusted risk RR †	1.00	1.01 (0.87-1.17)	0.93 (0.79-1.08)	1.08 (0.94-1.25)	1.00 (0.86-1.15)	0.65

	Category of Intake				
	1st (Lowest)*	2nd	3rd	4th (Highest)	p-trend
Broccoli	#1-3 servings/mo	1 serving/wk	2-4 servings/wk	∃5-6 servings/wk	

	Category of Intake				
	1st (Lowest)*	2nd	3rd	4th (Highest)	p-trend
Cases of cataract	626	712	571	112	
N	10,400	13,065	10,153	1,745	
Age- and treatment-adjusted RR	1.00	0.92 (0.83-1.03)	0.95 (0.85-1.06)	1.06 (0.86-1.29)	0.78
Multivariate-adjusted risk RR †	1.00	0.95 (0.85-1.06)	0.97 (0.86-1.09)	1.07 (0.87-1.32)	0.69
Brussels sprouts	None	1-3 servings/mo	∃1 serving/wk		
Cases of cataract	1,409	425	179		
N	24,892	7,766	2,696		
Age- and treatment-adjusted RR	1.00	0.92 (0.83-1.03)	1.03 (0.88-1.21)		0.67
Multivariate-adjusted risk RR †	1.00	0.92 (0.82-1.02)	0.98 (0.83-1.15)		0.34
Corn	#1-3 servings/mo	1 serving/wk	∃2-4 servings/wk		
Cases of cataract	1,063	685	264		
N	18,055	12,504	4,789		
Age- and treatment-adjusted RR	1.00	0.98 (0.89-1.07)	1.00 (0.87-1.14)		0.97
Multivariate-adjusted risk RR †	1.00	1.00 (0.91-1.10)	0.99 (0.86-1.14)		0.91
Lettuce, iceberg	#1-3 servings/mo	1 serving/wk	2-4 servings/wk	∃5-6 servings/wk	
Cases of cataract	427	401	687	500	
N	7,358	7,788	12,319	7,855	
Age- and treatment-adjusted RR	1.00	0.96 (0.84-1.10)	1.01 (0.90-1.14)	0.99 (0.87-1.12)	0.88
Multivariate-adjusted risk RR †	1.00	0.94 (0.82-1.08)	1.01 (0.89-1.14)	0.97 (0.85-1.11)	0.93
Peas	None	1-3 servings/mo	1 serving/wk	∃2-4 servings/wk	
Cases of cataract	382	729	638	268	
N	7,303	12,499	11,233	4,318	
Age- and treatment-adjusted RR	1.00	0.97 (0.85-1.09)	0.96 (0.84-1.09)	1.00 (0.85-1.16)	0.91
Multivariate-adjusted risk RR †	1.00	0.97 (0.86-1.10)	0.96 (0.85-1.09)	1.01 (0.86-1.18)	0.81
Spinach, cooked	None	1-3 servings/mo	∃1 serving/wk		
Cases of cataract	992	663	362		
N	17,455	11,800	6,077		
Age- and treatment-adjusted RR	1.00	0.93 (0.84-1.02)	1.02 (0.91-1.15)		0.93
Multivariate-adjusted risk RR †	1.00	0.92 (0.83-1.02)	1.03 (0.91-1.16)		0.93
Spinach, raw	None	1-3 servings/mo	∃1 serving/wk		
Cases of cataract	1,157	645	212		
N	18,914	11,856	4,544		
Age- and treatment-adjusted RR	1.00	0.96 (0.88-1.06)	0.86 (0.75-1.00)		0.06
Multivariate-adjusted risk RR †	1.00	0.98 (0.89-1.08)	0.88 (0.76-1.02)		0.13
Eggs	#1-3 servings/mo	1 serving/wk	2-4 servings/wk	∃5-6 servings/wk	
Cases of cataract	959	502	496	57	
N	16,632	8,957	8,752	1,022	
Age- and treatment-adjusted RR	1.00	1.01 (0.90-1.12)	1.01 (0.91-1.13)	1.03 (0.79-1.34)	0.79
Multivariate-adjusted risk RR †	1.00	1.02 (0.91-1.14)	0.99 (0.88-1.10)	0.99 (0.75-1.30)	0.75
Squash	None	1-3 servings/mo	∃1 serving/wk		
Cases of cataract	1,119	631	257		
N	20,632	10,668	3,997		
Age- and treatment-adjusted RR	1.00	0.94 (0.85-1.04)	0.97 (0.84-1.11)		0.38
Multivariate-adjusted risk RR †	1.00	0.96 (0.87-1.07)	0.97 (0.85-1.12)		0.54

Footnotes

Abbreviations: RR, relative risk (95% confidence intervals in parentheses).

* Reference category

† Adjusted for age, randomized treatment assignment, smoking (current, past, never), alcohol use (rarely/never, 1-3 drinks/month, 1-6 drinks/week, and ∃1 drinks/day), BMI (continuous), exercise (rarely/never, <1 time/week, 1-3 times/week, and ∃4 times/week), postmenopausal hormone use (never, past, current), history of hypertension (ever diagnosis by physician or selfreported blood pressure ∃

140/90; yes or no), history of hypercholesterolemia (baseline history of cholesterol-medication use or a physician diagnosis of high cholesterol or a self-reported cholesterol of at least 240 mg/dL; yes or no), history of diabetes (yes or no), family history of myocardial infarction before the age of 60 (yes or no), history of eye exam in the last 2 years.