



HARVARD SCHOOL OF PUBLIC HEALTH

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April 26, 2000

Dr. Jane E. Henney
Commissioner
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, MD 20852

Re: Food additive petition to amend 21 C.F.R. & 172.867(e) and the "interim" label requirement for Olestra.

Dear Dr. Henney:

Thank you for this opportunity to comment on the proposed petition submitted by Procter & Gamble to amend the label requirement for Olestra. I would like to focus in particular on the evidence relating to the effect of Olestra on blood carotenoid levels and the evidence regarding the possible health effects of substantially reducing blood carotenoid levels.

First, it is important to reiterate that evidence is conclusive that regular consumption of Olestra can greatly reduce circulating levels of blood carotenoids, by as much as 50%, under realistic and plausible scenarios of savory snack consumption. This evidence is based on the pre-approval randomized trials conducted by Procter & Gamble and a similar study of another sucrose polyester product developed by Unilever. This conclusion is beyond dispute and the magnitude of carotenoid reduction is well beyond effects that might be the result of other realistic differences in diet. In their current petition, Procter & Gamble presents data from their post-marketing surveillance study and concludes that under actual levels of consumption the effects of Olestra on blood carotenoids are minor. However, it is clear that consumption of Olestra products in the population studied was rather trivial which has more to do with the popularity of the products with the effects of Olestra on blood carotenoids. I would note that representatives of Procter & Gamble met with Dr. Meir Stampfer and me before they began their study and we recommended that they not waste their resources in conducting such a study as it would not be scientifically informative and it was a highly inefficient way of evaluating the effects of Olestra on blood carotenoid levels (for purposes of disclosure, Dr. Stampfer and I asked Procter & Gamble to contribute a donation the American Cancer Society in lieu of a consulting fee, which they did). A more rigorous and efficient design would be to conduct randomized trials of Olestra consumption under different plausible scenarios. Any assumption about effects of Olestra on blood carotenoid levels should be based on the strong likelihood that at least some individuals will consume one to four ounces of Olestra-containing potato chips or similar snacks on a daily basis. The effects of this intake on blood carotenoids are quite clear from the pre-approval studies.

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The second major issue is whether we can be reasonably certain that the reductions in blood carotenoid levels caused by Olestra will not increase the risk of chronic disease. Dr. Graham Colditz reviewed existing evidence at his June 1998 presentation to the FDA's advisory committee and pointed out that low intakes of carotenoids or blood carotenoid levels have been associated with higher risks of various cancers, coronary heart disease, macular degeneration, and stroke. Since that time a substantial number of publications have continued to accrue associating low levels of carotenoids with high risks of various chronic diseases. For example, low levels of dietary lycopene and low plasma lycopene levels have been associated with higher risk of prostate cancer in prospective studies. Dr. Giovannucci has published a review of lycopene and tomato product consumption in relation to risks of various cancers and has noted potentially important inverse associations in the large majority of studies ¹. As another example, we have recently reported in separate publications that low intakes of the carotenoid lutein is associated with significantly greater risks of cataracts in both men and women ^{2, 3}.

In reviewing the literature on carotenoids and chronic disease, I believe that the logic of Procter & Gamble, unfortunately accepted by the FDA in the previous review, is fundamentally flawed. Procter & Gamble argue that we cannot be certain whether it is the carotenoids in fruits and vegetables or other substances that actually are protective against cancers, cardiovascular disease and ophthalmologic conditions. However, this logic violates the precautionary principle and the FDA guideline of reasonable certainty of no harm because the burden of proof should be upon Procter & Gamble to show evidence that the various carotenoids in these foods are not the protective factors.

Procter & Gamble has invoked the several beta-carotene trials in which a slightly higher risk of lung cancer was observed in smokers who took a beta-carotene supplement. However, this finding has little relevance to the issue at hand as these trials involve the high-dose administration of a purified specific carotenoid, beta-carotene. Those trials did not address the effects of other carotenoids or the impact of reductions, rather than large increases, in blood carotenoid levels. In fact, in most recent studies, carotenoids other than beta-carotene have been found to be most closely related to risks of chronic diseases. Moreover, the fact that there was a biological effect of beta-carotene illustrates how poorly we understand the related biological effects; one possible explanation is that beta-carotene in high doses interferes with the function of related carotenoids. The clear conclusion is that we understand these relations poorly and we cannot be reasonably confident that reductions in blood carotenoid levels will cause no harm.

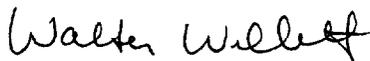
I would like to mention an incident that points out a fundamental flaw in the approval and labeling of Olestra. Several months ago a free package of WOW potato chips containing Olestra was distributed as a promotion with the Sunday morning issue of *The Boston Globe*. My close colleague's four year old daughter asked her yet-sleepy parents whether she could have the chips and they, without realizing it was an Olestra product, said yes. After several hours and for the rest of the day the daughter experienced severe and unprecedented abdominal distress and cramping. This anecdote (I recognize that it was not a double-blind trial) illustrates the point that young children are likely to consume Olestra and, on a body

weight basis, even a one-ounce bag can be a high dose. Further, this incident highlights the fact that Olestra has not been tested or evaluated in young children. I fundamentally believe that Olestra should not be allowed in the US food market at all because we cannot be reasonably certain that it will be without harm for humans of any age. However, if it is to remain, it should either be marketed in child-proof containers or the food label should include in large letters "Keep out of reach of children".

Finally, I would like to point out that the FDA approval process for Olestra has been seriously flawed from the beginning. In the first review, the committee did not include cancer or nutritional epidemiologists or other individuals qualified to review the evidence on carotenoid intake in relation to chronic disease risk. In the second review, the review committee was told explicitly to ignore data that was available to the first committee and only consider new evidence. As noted above, the review process has violated the precautionary principle and instead has focused on whether there was sufficient evidence to support the addition of specific carotenoids to Olestra, which is an entirely different question. Thus, I would strongly urge the FDA to have the issue of Olestra, carotenoids, and chronic disease risk reviewed by an impartial body such as the National Academy of Sciences to determine whether there is reasonable certainty that reducing carotenoid levels will not increase risks of various diseases. As we noted in a previous letter to the FDA, a survey of members of the National Academy of Sciences Committee on Diet, Nutrition and Cancer were asked whether they could be reasonably certain that the reductions in blood carotenoids caused by Olestra would not increase cancer risk. Not a single one replied in the affirmative (see attached survey).

I hope this will be helpful in your deliberations.

Sincerely,



Walter C. Willett, M.D., Dr.P.H.

Enclosure: NAS survey, reprints
WCW/es

References

1. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. *J Natl Cancer Inst* 1999; 91:317-331.
2. 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.
3. 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.

Expert Survey on Carotenoid Lowering and Cancer Risk

In controlled metabolic studies, consumption of olestra in realistic amounts causes major reductions in blood levels of most carotenoids. At the press conference announcing the approval of olestra, Dr. Kessler used a letter from one person at the National Cancer Institute as a basis for concluding that these reductions in blood carotenoid levels would, with "reasonable certainty", not increase the risk of various cancers. To determine whether this conclusion represented the view of scientists familiar with the area of nutrition and cancer, we conducted a survey in February and March, 1996 of a group of recognized experts in nutrient and cancer, asking:

1. "Are you reasonably certain that carotenoids contained in fruits and vegetables are not related to the apparent benefits of these foods in reducing cancer risk?"
2. "Are you reasonably certain that reductions in blood levels of carotenoids will not increase the risk of cancer?"

To avoid bias in the selection of experts for this survey, we used the list of 13 members of the Committee on Diet and Cancer of the National Academy of Sciences who authored the 1982 review of Diet, Nutrition, and Cancer (see attached list). The results were as follows:

- Two members did not respond to the survey
- Three members responded but did not want to, or felt they could not, answer the questions (one said he was too far removed from the issues at present)
- None answered yes to either question
- Seven answered no to both questions
- One did not specifically check answers, but said he was not reasonably certain that no harm would ensue from significantly lowering blood carotenoids over a long period of time.

Conclusion: The experts surveyed were not reasonably certain that reductions in blood carotenoid levels will not increase the risk of cancer. Thus, the conclusion by the FDA that there is "reasonable certainty of no harm" from the use of olestra does not appear to be supported by expert scientific opinion.

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May, 1996

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Tomatoes, Tomato-Based Products, Lycopene, and Cancer: Review of the Epidemiologic Literature

Edward Giovannucci

The epidemiologic literature in the English language regarding intake of tomatoes and tomato-based products and blood lycopene (a compound derived predominantly from tomatoes) level in relation to the risk of various cancers was reviewed. Among 72 studies identified, 57 reported inverse associations between tomato intake or blood lycopene level and the risk of cancer at a defined anatomic site; 35 of these inverse associations were statistically significant. No study indicated that higher tomato consumption or blood lycopene level statistically significantly increased the risk of cancer at any of the investigated sites. About half of the relative risks for comparisons of high with low intakes or levels for tomatoes or lycopene were approximately 0.6 or lower. The evidence for a benefit was strongest for cancers of the prostate, lung, and stomach. Data were also suggestive of a benefit for cancers of the pancreas, colon and rectum, esophagus, oral cavity, breast, and cervix. Because the data are from observational studies, a cause-effect relationship cannot be established definitively. However, the consistency of the results across numerous studies in diverse populations, for case-control and prospective studies, and for dietary-based and blood-based investigations argues against bias or confounding as the explanation for these findings. Lycopene may account for or contribute to these benefits, but this possibility is not yet proven and requires further study. Numerous other potentially beneficial compounds are present in tomatoes, and, conceivably, complex interactions among multiple components may contribute to the anticancer properties of tomatoes. The consistently lower risk of cancer for a variety of anatomic sites that is associated with higher consumption of tomatoes and tomato-based products adds further support for current dietary recommendations to increase fruit and vegetable consumption. [J Natl Cancer Inst 1999;91:317-31]

Nutritional factors are widely believed to be critical in carcinogenesis (1,2). Overwhelming evidence from epidemiologic studies indicates that diets high in fruits and vegetables are associated with a lower risk of numerous cancers (3-5). Dietary recommendations to increase intake of citrus fruits, cruciferous vegetables, green and yellow vegetables, and fruits and vegetables high in vitamins A and C to lower cancer risk have been made by several organizations, including the National Research Council of the National Academy of Sciences (1), the National Cancer Institute (6), the American Cancer Society (2,7), and the World Cancer Research Fund and the American Institute for Cancer Research (5). However, uncertainty exists concerning which components account for this benefit.

Until recently, the health aspects of tomatoes had received relatively little attention. The antioxidant properties of lycopene,

a carotenoid consumed largely from tomatoes, have raised interest in the tomato as a food with potential anticancer properties (8). Higher consumption of tomatoes is in fact compatible with current general recommendations aimed at increasing intake of fruits and vegetables. Nonetheless, whether unique benefits derive from tomatoes is important to establish because tomatoes are used in many processed items that are not necessarily identified with fruit or vegetable consumption. These items include tomato and spaghetti sauce, tomato soup, salsa, ketchup, and tomato paste. Moreover, many of these processed foods are better sources of bioavailable lycopene than are fresh tomatoes (9-11).

This review examines the epidemiologic evidence regarding consumption of tomato and related products with the risk of cancer at various body sites. The main purposes of this review are to assess the evidence for benefits by specific cancer site and to consider the strengths and limitations of the studies that help indicate whether observed associations are causal. Criteria considered include the strength of any associations, consistency of results by study design (case-control or cohort), method of exposure assessment (questionnaire or biomarker), the factors controlled for by matching or through data analysis, and the potential for residual or uncontrolled confounding. The potentially beneficial constituents of tomatoes and the implications for current dietary recommendations are then discussed.

REVIEW OF EPIDEMIOLOGIC STUDIES

All human studies reported in the English language of tomatoes or lycopene in relation to the risk of any cancer were considered. These studies were found in the MEDLINE® or CANCERLIT® databases and in several extensive reviews (3-5), or they were referenced in the identified studies. Because tomato intake or blood lycopene level was frequently one of numerous dietary factors examined, epidemiologic reports that had fruits, vegetables, or carotenoids as key words were scrutinized for results regarding tomato or lycopene. Two general types of study designs have been used to examine lycopene and tomato products in relation to risk of cancer. One study design has been based on a dietary questionnaire, used either to assess tomato products directly or to infer lycopene consumption; the other study design has been based on measuring levels of carotenoids in stored blood samples. Studies were summarized by type of

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See "Notes" following "References."

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design, years conducted, country, number of cases, main exposure assessment, relative risk (RR) with *P* values (two-sided) or confidence intervals (CIs), and covariates controlled for by matching or in analyses. The summarized RR is that for the cancer rate in the highest intake of tomatoes or level of lycopene divided by the rate in the lowest intake or plasma level. In case-control studies, the odds ratio was used to estimate the RR.

TOTAL CANCER

Only one study has reported on tomato intake in relation to total cancer risk. In this prospective study by Colditz et al. (12), based on 42 cancer deaths among 1271 elderly persons, individuals who were in the top half of tomato consumption had a lower risk of all cancers combined compared with those in the bottom half (RR = 0.5; 95% CI = 0.3–0.8). Other items, including green and yellow vegetables and strawberries, were also associated with a decreased risk of total cancer. Carrots and squash were unrelated to risk. There were too few cancers to allow examination of specific cancer sites.

LUNG AND PLEURAL CANCERS

One of the cancer sites for which a benefit of fruits and vegetables has been most apparent is for cancers of the lung (3), the leading cause of cancer death worldwide. Initial findings led investigators to focus on β -carotene and provided the impetus to examine supplemental β -carotene in relation to the risk of lung cancer in intervention trials. Unfortunately, the results from several trials either have been inconclusive (13) or have even indicated that smokers randomly assigned to receive β -carotene are at higher risk for lung cancer (14,15).

Although the focus has been on β -carotene, the literature shows that several fruit and vegetable groups, including leafy green and yellow/orange vegetables, are associated with a lower risk of lung cancer (3). Fourteen studies (16–29) have reported specifically on tomato or lycopene consumption in relation to lung cancer risk; of these, 10 (17,18,20–24,26–28) suggest either a statistically significant or a suggestive inverse association (Table 1). These studies, mostly case-control in design, generally adjusted for smoking history, the most important potential confounder for lung cancer. An additional study (30) indicated that higher prediagnostic dietary intake of tomatoes (recalled after diagnosis) among lung cancer case subjects was associated with better survival from lung cancer (Table 1). One study (22) found an inverse association between tomato intake and squamous cell and small-cell lung cancer but not with other histologic types. Statistically significant associations were observed in multiple U.S. populations, China, and Spain, and non-statistically significant inverse associations were noted in the U.K., Norway, and Finland.

A case-control study in Hawaii by Le Marchand et al. (17) found tomato intake related to a substantially reduced risk of lung cancer; however, the same case-control dataset analyzed several years later for lycopene intake (16) indicated only a modest inverse association between lycopene intake and lung cancer risk that was not statistically significant. In this population, tomatoes accounted for only 29% of the reported lycopene intake. The conflicting results for tomato and lycopene intakes suggest that the benefit of tomatoes is related to compounds other than lycopene or that lycopene from non-tomato sources is not readily bioavailable.

Only one study that reported on mesothelioma (cancer of the

pleura or peritoneum) was identified (31). Overall, a 40% reduction in risk was noted for those consuming tomato or tomato juice 16 or more times a month versus nonconsumers. Only 1.7% of control subjects reported not consuming tomatoes or tomato juice as opposed to 9% of case subjects, suggesting nonconsumers of tomato products to be at relatively high risk for mesothelioma.

STOMACH CANCER

Although becoming relatively uncommon in most economically developed countries, stomach or gastric cancer remains one of the major causes of cancer death in the world. Twelve case-control studies from a variety of populations, including the United States [New York (32), Louisiana (33), and Hawaiian Japanese (34)], Japan (35), Israel (36), Italy (37–39), Spain (40,41), Poland (42), Belgium (43), and Sweden (44) have reported data on tomato or lycopene intake and stomach cancer risk (Table 2). Inverse associations between tomato consumption and risk of gastric cancer were observed in all these diverse populations except for Spain (40,41) and Japan (35). A suggestive, but not statistically significant, inverse association was observed in a study conducted in Belgium (43), but this study population had a very low consumption of tomatoes. An ecologic study in Japan (45) that examined plasma levels of various nutrients in samples of populations in various regions found that regions high in plasma lycopene had the lowest gastric cancer rates and regions low in lycopene had the highest rates. While other fruits and vegetables have frequently been inversely associated with gastric cancer, inverse associations with tomatoes have been among the most consistent and strongest (36–39,44). Although no prospective studies of tomato intake and gastric cancer were identified, the consistent inverse association observed in diverse populations strongly suggests a protective effect of tomato or lycopene consumption on gastric cancer.

COLORECTAL CANCER

Cancers of the colorectum are common in economically developed areas. Five studies (37,46–50) have reported on tomato intake in relation to colorectal cancer risk (Table 3). One study in the United States (46) reported statistically significant inverse associations between tomato consumption and colon cancer risk for men and women. A study in Belgium (48) found no overall association but did find a suggestion of an inverse association between consumption of tomato puree and colon cancer risk. The consumption of tomato products was low in this population, and the contrast was ever versus never consumption; the impact of higher intakes could not be assessed. Case-control studies in Italy (37,50) and China (49) reported about a 60% reduction in risk of both colon and rectal cancers associated with higher tomato consumption. In a rodent model of *N*-methylnitrosourea-induced colonic aberrant crypt foci, lycopene and lutein, but not β -carotene, in relatively small doses demonstrated efficacy against this premalignant lesion (51).

ORAL/LARYNGEAL/PHARYNGEAL CANCER

Only three case-control studies (52–54) have reported on tomato intake in relation to oral cancers (Table 3). One study in China (52) reported that high consumption of tomatoes was related to approximately half the risk of oral cancer. A similar finding was observed between tomato consumption and cancers

Table 1. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of the lung and pleura

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
Kvåle, 1983 (22)	Norway, United States	1964-1978	Cohort	168	Tomato intake, 6-13 vs. <1/mo	0.87, <i>P</i> = .48 (total) 0.54, <i>P</i> = .07 (squamous cell and small-cell)	Age, smoking status, region, urban/rural
Fraser, 1991 (19)	California, Seventh-day Adventists	1977-1982	Cohort	61	Tomato intake, ≥7 vs. <3/wk	1.24 (0.51-2.99) <i>P</i> = .79	Age, sex, smoking status
Bond, 1987 (23)	Texas	1940-1980	Case-control	308	Tomato intake, 1/day vs. <1/mo	0.42 (0.14-1.33) <i>P</i> for trend = .05	Age, race, smoking status, educational level, vitamin supplement
Le Marchand, 1989 (17), 1993 (16)	Hawaii	1983-1985	Case-control	230 ♂ 102 ♀	Tomatoes† Quintile 5 vs. 1 Lycopene intake Quintile 5 vs. 1	0.43, <i>P</i> = .002 ♂ 0.27, <i>P</i> < .001 ♀ 0.67, <i>P</i> = .07 ♂ 0.77, <i>P</i> = .83 ♀	Age, ethnicity, smoking status, pack-years, cholesterol intake
Harris, 1991 (18)	U.K.	1979-1981	Case-control	96 ♂	Tomato intake, >29.1 vs. <1 g/day	0.69, <i>P</i> = .11	Age, smoking status
Knekt, 1991 (21)	Finland	1966-1986	Cohort	117	Lycopene intake, μg, mean	684 ± 850 (mean ± standard deviation) case subjects 718 ± 895 (mean ± standard deviation) control subjects	Age
Candelora, 1992 (27)	Florida	1987-?	Case-control (nonsmokers)	124 ♀	Lycopene Quartile 4 vs. 1 Tomatoes Quartile 4 vs. 1	0.6 (0.3-1.2) <i>P</i> = .13 0.7 (0.4-1.0)	Age, educational level, total calories, limited to nonsmokers
Forman, 1992 (24)	China	1985-1986	Case-control	183 ♂	Tomatoes Quartile 4 vs. 1	0.42 (0.19-0.96) <i>P</i> = .04	Age, educational level, body mass index, smoking status, income
Goodman, 1992 (30)	Hawaii	1979-1985	Prognosis (death)	463 ♂ 212 ♀	Tomatoes‡ Quartile 4 vs. 1 Prediagnostic diet	0.77, <i>P</i> < .01 ♂ 0.5, <i>P</i> = .14 ♀	Age at diagnosis, stage, histology, body mass index, smoking status
Steinmetz, 1993 (25)	Iowa	1986-1990	Cohort	138 ♀	Lycopene-rich food intake, ≥5 vs. ≤1/wk	1.21 (0.69-2.10) <i>P</i> = .53	Age, energy, smoking status
Mayne, 1994 (20)	New York State	1982-1985	Case-control	413	Tomato and tomato products Quartile 4 vs. 1	0.80, NS ♂ 0.76, NS ♀ 0.79, <i>P</i> < .10 ♂ and ♀	Age, cigarette smoking status, religion, educational level, body mass index, income
Muscat, 1996 (31)	New York	1985-1993	Case-control (mesothelioma)	94	Tomato/tomato juice intake, ≥16 vs. 0/mo	0.6 (0.2-1.9)	Age, educational level, religion, occupation
Agudo, 1997 (28)	Spain	1989-1992	Case-control	103 ♀	Tomatoes High vs. low tertile	0.45 (0.22-0.91) <i>P</i> = .026	Age, smoking status, total pack-years
Comstock, 1997 (29)	Maryland	1989-1991	Cohort	258	Serum lycopene Quintile 5 vs. 1	1.01, <i>P</i> for trend = .97	Age, race, sex, date of blood donation, smoking status
Li, 1997 (26)	United States		Case-control (non-small cell)	93	Plasma lycopene Tertile 3 vs. 1	0.37, <i>P</i> = .01 African-Americans: 0.12, <i>P</i> = .001	Age, sex, race

*Relative risk and 95% confidence interval or *P* value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

†Tomatoes accounted for only 29% of total lycopene.

‡For squamous cell cancer only.

Table 2. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancer of the stomach

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
Haenszel, 1972 (34)	Hawaiian Japanese	1963–1969	Case–control	223	Tomato intake, ≥ 11 vs. <4 /mo	0.39, $P < .05$, all 0.31, $P < .08$, Issei 0.49, NS, Nisei	Age, sex
Modan, 1981 (36)	Israel	1967–1969	Case–control	406	Tomato intake, daily vs. never	0.55, P for trend $< .0001$	Age, sex, ethnic origin
Correa, 1985 (33)	Louisiana	1979–1983	Case–control	391	Tomatoes, “high vs. low” intake	0.82 (0.53–1.28), whites 0.56 (0.34–0.90), blacks	Age, sex, race, educational level, income, tobacco smoking status, alcohol intake
Tajima, 1985 (35)	Japan	1981–1983	Case–control	93	Tomatoes Tertile 3 vs. 1	1.24, NS	Age, sex
Franceschi, 1994 (37) La Vecchia, 1987 (38)	Italy (Milan)	1985–1991	Case–control	723	Tomatoes Quartile 4 vs. 1	0.43 (0.33–0.55)	Age, sex, study center, educational level, alcohol intake, tobacco smoking status, calories
Buiatti, 1989 (39)	Northern Italy	1985–1987	Case–control	1016	Tomatoes Tertile 3 vs. 1	0.70, P for trend $< .001$	Age, sex
Graham, 1990 (32)	New York	1975–1985	Case–control	293 (181 ♂)	Tomatoes	Decreasing risk Statistically significant for ♂ only	Age, sex, neighborhood
Boeing, 1991 (42)	Poland	1986–1990	Case–control	741	Tomatoes Tertile 3 vs. 1	0.77, P for trend = .03	Age, sex, occupation, educational level, residence
Gonzalez, 1991 (41)	Spain	1987–1989	Case–control	354	Tomatoes Quartile 4 vs. 1	0.9 (0.5–1.5)	Age, total calories, other food items
Ramón, 1993 (40)	Spain	1986–1989	Case–control	177	Tomatoes Tertile 3 vs. 1	1.03, NS	Age, sex
Tsugane, 1992 (45)	Japan	1985–1989	Ecologic		Plasma lycopene	Regions high in lycopene have lowest gastric cancer rates; low lycopene areas have highest cancer rates	Age
Tuyns, 1992 (43)	Belgium	1979–1982	Case–control	449	Cooked tomato intake, >0 vs. 0 Raw tomato intake, >10 vs. 0 g/wk	0.12, $P = .50$ 0.74, $P = .08$	Age, sex, province, other vegetables
Hansson, 1993 (44)	Sweden	1989–1992	Case–control	456	Adolescence, >3 vs. 0/mo 20 y prior >15 vs. <2 /mo	0.36 (0.23–0.58) $P < .0001$ 0.72 (0.47–1.11) $P = .015$	Age, sex, socioeconomic status

*Relative risk and 95% confidence interval or P value (two-sided) for exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

of the oral cavity and pharynx in Italy (54). A study of tomato consumption and laryngeal cancer in China (53) did not find an association.

ESOPHAGEAL CANCER

Esophageal cancers have received little study regarding tomatoes and lycopene (Table 3). One study in Iran (55), which has extremely high rates of esophageal cancer particularly in men, found a 39% statistically significant reduction in risk for men who consumed tomatoes frequently, but no relationship was apparent for women. The only other diet-based study reported for this cancer, conducted in the United States (56), reported a 30% nonstatistically significant reduction in esophageal cancer

risk associated with high tomato consumption in men. A serum bank-based study by Nomura et al. (57) reported that case patients with oral, laryngeal, or esophageal cancers had a 5% lower mean prediagnostic serum lycopene level than control subjects that was not statistically significant; however, on the basis of only 28 case patients with esophageal cancer, case patients had a 16.4% lower lycopene level ($P = .08$).

PANCREATIC CANCER

Four studies (58–61) have examined tomato or lycopene status in relation to risk of pancreatic cancer; all of these studies support an inverse association (Table 3). Two studies (58,61) reported an inverse association but did not provide estimates of

Table 3. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of the digestive tract (excluding stomach)*

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk† (95% confidence interval)	Adjusted factors
Colorectal cancer							
Tuyns, 1988 (48)	Belgium	1978–1982	Case-control (colon, rectal)	453 C 365 R	Tomato intake, >0 vs. 0 g/wk Tomato puree intake, >0 vs. 0 g/wk	1.15, <i>P</i> = .31 C 1.03, <i>P</i> = .84 R 0.78, <i>P</i> = .12 C 0.93, <i>P</i> = .93 R	Age, sex, province
Freudenheim, 1990 (46)	New York State	1978–1986	Case-control (rectal)	277 ♂ 145 ♀	Tomatoes	SS decreased risk SS decreased risk	Age
Hu, 1991 (49)	China	1985–1988	Case-control (colon, rectal)	111 C 225 R	1966 diet (>15 kg/y) 1985 diet (>15 kg/y) ♂ rectal 1966 >20 kg/y	0.40 (0.17–0.94) C ♂ 0.26 (0.12–0.55) C ♀ 0.40 (0.17–0.94) R ♂ NS R ♀	Univariate
Centonze, 1994 (47)	Southern Italy	1987–1989	Case-control (colorectal)	132	Pizza, high vs. low intake	0.89 (0.51–1.53) <i>P</i> = .66	Age, sex, educational level, smoking status, modification of diet in past
Franceschi, 1994 (37) Franceschi, 1997 (50)	Northern Italy	1985–1991	Case-control (colon, rectal)	955 C 629 R	Tomatoes Quartile 4 vs. 1	0.39 (0.31–0.49) C 0.42 (0.32–0.55) R	Age, sex, study center, educational level, calories, alcohol intake, smoking status
Oral cancers							
Franceschi, 1991 (54)	Northern Italy	1985–?	Case-control (oral and pharynx)	266 ♂ 36 ♀	Fresh tomatoes Tertile 3 vs. 1	0.5, <i>P</i> < .01	Age, sex, occupation, smoking status, alcohol intake, other significant foods
Zheng, 1992 (53)	China	1988–1990	Case-control (larynx)	177 ♂ 24 ♀	Tomatoes Tertile 3 vs. 1	1.2, <i>P</i> = .45 ♂ 1.1 (0.4–3.1) ♀	Age, educational level, smoking status
Zheng, 1993 (52)	China	1989	Case-control (oral)	404	Tomato intake, ≥1/day vs. ≤3/wk	0.49 (0.26–0.94)	Age, tobacco smoking status, alcohol intake, dentition, body mass index, energy, educational level, sex
Esophageal and laryngeal cancers							
Cook-Mozaffari, 1979 (55)	Iran	1975–1976	Case-control (esophagus)	217 ♂ 127 ♀	Raw tomato intake, ≥1/wk vs. <1/mo	0.61 (0.43–0.86) ♂ 1.08 (0.69–1.67) ♀	Age, region
Brown, 1988 (56)	South Carolina	1982–1984	Case-control (esophagus)	207 ♂	Tomatoes, high vs. low intake	0.70 (0.4–1.4)	Age, cigarette smoking status, alcohol intake
Nomura, 1997 (57)	Hawaii	1971–1991	Cohort (esophagus and larynx)	69	Serum lycopene (mean)	Case subjects 19.1 ± 1.4 (mean ± standard error) Control subjects 21.1 ± 1.0 (mean ± standard error) <i>P</i> = .27	Age, smoking history (detailed), alcohol intake
Pancreatic cancer							
Mills, 1988 (58)	Seventh-day Adventists	1976–1983	Cohort (fatal)	50	Tomatoes	Inverse association (na)	Age
Burney, 1989 (59)	Maryland	1975–1986	Cohort	22	Serum lycopene High vs. lowest 2 tertiles	0.16 (0.04–0.57) <i>P</i> for trend < .02	Age, sex, race, hours since last meal, smoking status, educational level
Baghurst, 1991 (61)	Australia	1984–1987	Case-control	104	Tomatoes	Inverse trend, <i>P</i> < .05, ♂ only	Age
Bueno de Mesquita, 1991 (60)	The Netherlands	1984–1988	Case-control	164	Tomatoes Quintile 5 vs. 1	0.23, <i>P</i> < .05	Age, sex, smoking status, energy

*C = colon; R = rectum.

†Relative risk and 95% confidence interval or *P* value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. SS = statistically significant; NS = not significant; na = *P* value not available.

RR. The two that reported the magnitude of the RR found about a fourfold to fivefold risk elevation among low consumers of tomatoes (60) or among those with low levels of serum lycopene collected prospectively in a case-control study nested within a cohort (59). Although the serum-based study (59) involved only 22 case patients, the results were statistically significant ($P < .02$), and no association was seen with total carotenoids or β -carotene. It is unlikely that low lycopene levels were the result of the cancer because the relationship was apparent in cancers diagnosed 9–12 years after collection of the blood and pancreatic cancers are rapidly progressive and thus have a short latent period. Also suggestive of a specific effect of lycopene among carotenoids, the dietary-based study by Bueno de Mesquita et al. (60) did not find a benefit of carrots, a major source of β -carotene and α -carotene.

PROSTATE CANCER

Four cohort studies (62–65) report data on the relationship between tomato or lycopene consumption and prostate cancer risk (Table 4). In a cohort of 14 000 Seventh-day Adventist men (62), only tomato intake and intake of beans, lentils, and peas were statistically significantly related to lower prostate cancer risk in a multivariate analysis. β -Carotene-rich foods were unrelated to risk. In a larger, more comprehensive dietary study (64), intake of the carotenoids β -carotene, α -carotene, lutein, and β -cryptoxanthin was not associated with risk of prostate cancer, but high lycopene intake was related to a statistically significant 21% reduction in risk. High intake of tomatoes and tomato products, which accounted for 82% of lycopene, reduced risk of total prostate cancer by 35% and aggressive prostate cancer by 53%. Tomato sauce had the strongest inverse association with prostate cancer risk (RR = 0.66; 95% CI = 0.49–0.90; P for trend = .001), and weaker inverse associations were observed with tomatoes and pizza, but none with tomato juice. Preliminary results from two other cohort studies (63,65) also support this finding.

One case-control study conducted in Minnesota (66) found an inverse association between tomato intake and risk of prostate cancer that was not statistically significant. In another case-control study conducted in a multiethnic population in Hawaii (67), no association was found with consumption of “tomatoes.” However, the intake levels were not indicated, and it did not appear that tomato-based products such as tomato sauce were specifically addressed. A case-control study conducted in the U.K. (68) found no association between raw or cooked tomatoes and risk of prostate cancer. Of note, the strongest dietary association found in that study was for baked beans (RR = 0.52; 95% CI = 0.31–0.88); the authors suggest that tinned baked beans may provide highly bioavailable lycopene from the tomato sauce.

Three studies (69–71) have examined serum carotenoids using prediagnostic samples in relation to prostate cancer risk. The first study (69), which was based on serum obtained in 1974 from 25 802 persons in Washington County, MD, found a 6.2% lower median lycopene level in prostate cancer case subjects diagnosed during 13 years compared with age- and race-matched control subjects. The estimated RR was 0.50 (95% CI = 0.20–1.29) between high and low quartiles of lycopene. No other carotenoid was associated with prostate cancer risk. Preliminary results from the Physicians' Health Study (70), which was based on 581 case subjects, found a statistically significant

RR of 0.56 (95% CI = 0.34–0.91) when comparing high quintile with low quintile of plasma lycopene.

A serum-based study conducted during the period from 1971 through 1993 in a Japanese-American population in Hawaii (71) did not detect any association between serum lycopene levels and risk of prostate cancer. However, several characteristics of the study may have contributed to the lack of an association, including use of a single assessment of serum lycopene to characterize follow-up for up to a 22-year period (only 14 cases occurred within the first 5 years of follow-up), inclusion of “low virulence” disease (28% were diagnosed incidentally during surgery for benign prostatic hyperplasia), and very low serum lycopene levels [the median serum concentration among control subjects was only 134 ng/mL, compared with 320 ng/mL in the study by Hsing et al. (69) and 424 ng/mL in the sample of 121 health professionals (64)]. Ethnic differences in prostate cancer etiology may also be important, inasmuch as men of Asian descent may have an inherently low susceptibility to prostate cancer.

BLADDER CANCER

Four reports of tomato or lycopene consumption (72–74) or serum lycopene (75) and risk of bladder cancer were identified (Table 4). None of these studies found statistically significant associations with risk of bladder cancer, although tendencies for inverse associations were noted. Results from the sole serum-based study (75) were suggestive of an inverse trend (RR = 0.5; P for trend = .06). However, that study was based on only 35 case subjects. Unpublished data from a prospective cohort study of male health professionals do not indicate any association between consumption of tomato-based products or lycopene and bladder cancer (251 cases). A strong inverse association between tomato-based product intake and risk of prostate cancer was found in the same cohort (64). In a rat model of urinary superficial bladder cancer induced by nitrosamines, lycopene demonstrated modest anticancer properties (76).

BREAST CANCER

For breast cancer, a common cause of cancer in Western countries, an overall benefit of fruits and vegetables is suggested but is not as clearly apparent as for several other cancer sites (3,4). Considering the importance of this disease, relatively few studies have examined its relationship to tomato or lycopene intake (Table 5). Dietary-based studies (77–80) do not support an association between tomato intake and risk of breast cancer, although relatively few studies have reported on this. However, of four studies (81–84) based on biomarkers (blood level or breast adipose level) of lycopene, three (81,82,84) support a benefit, two of which were statistically significant (81,82). The small study (81) based on adipose levels of carotenoids in breast tissue from case and control subjects did find statistically significantly lower concentrations of lycopene among case subjects, although an impact of the cancer on tissue lycopene levels cannot be excluded. Of note, breast adipose tissue lycopene was weakly correlated with lycopene intake estimated by a food-frequency questionnaire in that study ($r = .17$). It is possible that a low correlation between reported intake and tissue level, whether due to measurement or biologic reasons, could account for the generally null results from dietary studies for breast cancer. Lycopene also has been shown to have antiproliferative effects against breast cancer cells in culture (85), and tomato oleoresin-treated rats developed fewer 7,12-dimethyl-

Table 4. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancer of the genitourinary tract

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
Prostate cancer							
Schuman, 1982 (66)	Minnesota	1976–1979	Case-control	223	Tomatoes, high vs. low intake	0.70, NS	Age
Mills, 1989 (62)	California Seventh-day Adventists	1974–1982	Cohort	180	Tomato intake, ≥ 5 vs. < 1 /wk	0.60 (0.37–0.97) $P = .02$	Age, educational level, consumption of meat, poultry, fish, beans, legumes, peas, citrus fruit, nuts, or fruits
Hsing, 1990 (69)	Maryland	1974–1985	Cohort	103	Serum lycopene Quartile 4 vs. 1	0.50 (0.20–1.29) $P = .26$	Age, smoking status, race, educational level, hours since last meal
Le Marchand, 1991 (67)	Hawaii	1970–1983	Case-control	452	Lycopene Quartile 4 vs. 1	0.9 $P = .35$, < 70 y 1.1, $P = .57$, ≥ 70 y	Age, ethnicity
Giovannucci, 1995 (64)	United States	1986–1992	Cohort	773	Dietary tomato-based products, > 10 vs. < 1.5 servings/wk	0.65 (0.44–0.95) $P = .01$	Age, total energy, ancestry, vasectomy, animal fat, retinol
					Tomato sauce intake, 2–4 vs. 0/wk	0.66 (0.49–0.90) $P = .001$	
Baldwin, 1997 (abstract) (65)	California	1995	Cohort retrospective		“Consistently high tomato consumption”	0.59, $P = .03$	—
Key, 1997 (68)	U.K.	1989–1992	Case-control	328	Dietary lycopene intake, ≥ 718 μg vs. < 402 μg	0.99 (0.68–1.45) $P = .88$	Age, social class
					Raw tomato intake, ≥ 5 /wk vs. ≤ 3 /mo	1.06 (0.55–1.62) $P = .88$	
					Cooked tomato intake, ≥ 2 /wk vs. < 1 /mo	0.92 (0.57–1.42) $P = .64$	
Nomura, 1997 (71)	Hawaii	1971–1993	Cohort	142	Serum lycopene Quartile 4 vs. 1	1.1 (0.5–2.2) $P = 0.86$	Age
Cerhan, 1998 (abstract) (63)	United States	1987–1990	Cohort	101	Dietary tomatoes Quintile 5 vs. 1	0.50 (0.3–0.9) $P = .03$	Age, total energy, other dietary and nondietary factors
Gann, 1998 (abstract) (70)	United States	1982–1995	Cohort	581	Plasma lycopene Quintile 5 vs. 1	0.56 (0.34–0.91) $P = .05$	Age, smoking status, body mass index, alcohol consumption, exercise, multivitamin use, plasma cholesterol level
Bladder cancer							
Helzlsouer, 1989 (75)	Maryland	1974–1986	Cohort	35	Serum lycopene Tertile 3 vs. 1	0.5, P for trend = .06	Age, sex, race, interval since last meal
Nomura, 1991 (74)	Hawaii	1977–1986	Case-control	195 δ 66 η	Lycopene Quintile 5 vs. 1	0.7, P for trend = .27 δ 0.9, P for trend = .41 η	Age, cigarette pack-years
Riboli, 1991 (73)	Spain	1985–1986	Case-control	432 δ	Tomatoes	No association	Age
Bruemmer, 1996 (72)	Washington State	1987–1990	Case-control	262	Tomato intake, > 0.29 vs. ≤ 0.07 /day	0.71 (0.39–1.29) P for trend = .13	Age, sex, county, smoking status, calories

*Relative risk and 95% confidence interval or P value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

benz[a]anthracene-induced mammary tumors, whereas β -carotene had no effect (86).

CERVICAL CANCER AND PRECURSORS

Two studies have reported on tomato consumption and risk of cervical cancer (87,88), and three have examined serum lycopene in relation to cervical cancer (89,90) or precursor lesions (91) (Table 5). Monthly tomato consumption was higher in control subjects than in case subjects in one case-control study (87), although this finding did not attain statistical significance. A study in The Netherlands (88) found women who consumed tomatoes three or more times a week to have a 40% reduction in

precursor lesions (91) (Table 5). Monthly tomato consumption was higher in control subjects than in case subjects in one case-control study (87), although this finding did not attain statistical significance. A study in The Netherlands (88) found women who consumed tomatoes three or more times a week to have a 40% reduction in

Table 5. Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of female reproductive organs

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
Breast cancer							
Ewertz, 1990 (79)	Denmark	1983–1984	Case–control	1486	Tomatoes Quartile 4 vs. 1	1.04 (0.79–1.31)	Age, residence
Potischman, 1990 (84)	New York State	1985–1986	Case–control	83	Plasma lycopene Quartile 4 vs. 1	0.62 (0.19–2.0) <i>P</i> = .43	Age, age at first birth, family history of cancer, age at menarche, body mass index, age at menopause, income, marital status, plasma cholesterol level, triglyceride level
London, 1992 (83)	Massachusetts	1986–1988	Case–control	377	Serum lycopene Quintile 5 vs. 1	1.0 (0.7–1.7)	Age, alcohol consumption, age at first birth, parity, family history of cancer, age at menopause, age at menarche, body weight, benign breast disease
Levi, 1993 (78)	Switzerland	1990–1992	Case–control	107	Tomatoes Tertile 3 vs. 1	0.9, NS	Age
Freudenheim, 1996 (80)	New York State	1986–1991	Case–control	297	Lycopene intake, ≥ 7123 $\mu\text{g}/\text{day}$ vs. ≤ 3775 $\mu\text{g}/\text{day}$	0.87 (0.55–1.39) <i>P</i> = .24	Age, educational level, age at first birth, age at menarche, family history of cancer, benign breast disease, body mass index, energy
Järvinen, 1997 (77)	Finland	1967–1992	Cohort	88	Lycopene Tertile 3 vs. 1	~1.0	Age, body mass index, parity, region, smoking status, occupation
Zhang, 1997 (81)	Massachusetts	1989–1992	Case–control (breast adipose)	46	Breast adipose lycopene levels, \geq vs. $<$ median	0.32 (0.11–0.94)	Age, smoking status, menopausal status
Dorgan, 1998 (82)	Missouri	1977–1987	Cohort	105	Serum lycopene levels, >0.51 $\mu\text{mol}/\text{L}$ vs. ≤ 0.22 $\mu\text{mol}/\text{L}$	0.5 (0.2–1.2) <i>P</i> = .02	Age, benign breast disease, serum cholesterol level, cigarette smoking status, body mass index
Cervical cancer							
Marshall, 1983 (87)	New York State	1957–1965	Case–control	513	Tomato intake, mean monthly servings	8.02, case subject 8.49, control subject <i>P</i> = .2	Age
de Vet, 1991 (88)	The Netherlands	1984–1987	Case–control (cervical dysplasia)	257	Tomato intake, ≥ 3 vs. 0/wk	0.58 (0.33–1.02) <i>P</i> = .01	Age, demographics, marital status, educational level, smoking status, children, contraception, age at first intercourse, frequency of intercourse, sexual partners, frequency of pap smear, other food group consumption
Potischman, 1991 (89)	Latin America	1986–1987	Case–control	387	Serum lycopene level, >21.4 $\mu\text{g}/\text{dL}$ vs. <6.4 $\mu\text{g}/\text{dL}$	1.14 (0.8–2.1) <i>P</i> = .69	Age, study site, age at first intercourse, No. of sex partners, No. of pregnancies, Pap smear, papillomavirus 16/18, No. of household facilities, cholesterol level, level of triglycerides

Table 5 (continued). Summary of epidemiologic studies examining tomato intake or lycopene intake or level and cancers of female reproductive organs

First author, year of publication (reference No.)	Place of study	Years of study	Type of study	No. of case subjects	Exposure	Relative risk* (95% confidence interval)	Adjusted factors
VanEenwyk, 1991 (91)	Illinois	1987–1989	Case-control (cervical intraepithelial neoplasm I, II, or III)	102	Serum lycopene level, >41.3 µg/dL vs. <21.3 µg/dL Diet lycopene Quartile 4 vs. 1	0.26 (0.08–0.9) <i>P</i> = .004 0.19 (0.04–0.77) <i>P</i> = .02	Age, smoking status, income, vitamin C, Pap smear frequency, spermicidal contraception, genital warts, body mass index
Baticha, 1993 (90)	Maryland	1975–1990	Case control	50† 18 (invasive) 32 (carcinoma <i>in situ</i>) Ovarian cancer	Serum lycopene level, >41.8 µg/dL vs. <24.9 µg/dL	0.40 (0.15–1.04) <i>P</i> = .08	Age, race, time since last meal
Helzlsouer, 1996 (92)	Maryland	1974–1989	Cohort	35	Serum lycopene level, >35.2 µg/dL vs. <21.9 µg/dL	1.36 (0.4–4.3) <i>P</i> = .59	Age, menstrual status, hours since last meal prior to collection

*Relative risk and 95% confidence interval or *P* value (two-sided) for the exposure comparison indicated; in some cases, measures other than the relative risk were given. NS = not significant.

†The relative risk is only for all 50 cases; the 50 cases comprise 18 invasive carcinomas and 32 carcinomas *in situ*; results are not presented for the 18 and 32 cases individually.

risk of cervical dysplasia relative to nonconsumers. One study (89) found no association between serum lycopene and risk of cervical cancer, but another study (90) found a borderline statistically significant inverse association between serum lycopene and risk of invasive (*n* = 18) or preinvasive (*n* = 32) cervical cancer. A study of cervical cancer precursor lesions (cervical intraepithelial neoplasm [CIN] I, II, III) (91) found a fourfold higher risk in women with low serum lycopene levels and a fivefold excess risk among those with low dietary lycopene levels. Thus, three of three studies of preinvasive lesions reported an inverse association with tomato intake (88) or serum lycopene (90,91). In one study (90), levels of serum carotenoids were also related to lower risk, whereas the study by VanEenwyk et al. (91) found benefits only for lycopene.

OVARIAN CANCER

Only one study that reported data regarding tomato or lycopene and ovarian cancer was found. This was a prospective serum-based study of 35 case subjects (Table 5) (92). This small study indicated no association, although the mean level of serum lycopene in the case subjects was 7.4% lower than in the control subjects. More study of this cancer is clearly required before firmer conclusions can be reached.

SUMMARY OF EPIDEMIOLOGIC EVIDENCE

Consistency of Results

Including studies that have reported results but did not specify RRs, 72 studies have reported on intake of tomatoes, tomato-based products, and lycopene or blood or tissue level of lycopene and risk of a cancer site. These were based on 66 reports, some of which separately analyzed various cancer sites (e.g., colon and rectum). Of these 72 studies, 57 found inverse associations between tomato or lycopene consumption or blood

lycopene level and risk of cancer; 35 of these inverse associations were statistically significant. The remaining 15 studies were inconclusive or indicated a slight direct association, with RRs mostly within the range between 1.0 and 1.2. No statistically significant direct association between tomato or lycopene consumption and risk for any cancer site was noted.

Table 6 shows the RRs from 61 studies that provide data; there are 74 RRs because some studies present results stratified by sex, racial or ethnic group, colon and rectum cancers separately, and results both for blood lycopene level and for dietary tomato or lycopene intakes. Almost half the studies found RRs around 0.6 or less, about two thirds with RRs less than 0.8. The results did not vary appreciably whether they were based

Table 6. Summary of the relative risks for high versus low intakes (levels) of tomatoes (lycopene) across the study characteristics

Study type	Total No. (%)	No. (%) by relative risk			
		≤0.6	0.61–0.8	0.81–1.0	>1.0
Cohort	16 (100)	10 (63)	0 (0)	1 (6)	5 (31)
Case-control	58 (100)	26 (45)	13 (22)	10 (17)	9 (16)
Diet based	59 (100)	27 (46)	12 (20)	11 (19)	9 (15)
Biomarker* based	15 (100)	9 (60)	1 (7)	0 (0)	5 (33)
Both sexes	33 (100)	18 (55)	5 (15)	6 (18)	4 (12)
Male	20 (100)	10 (50)	6 (30)	2 (10)	2 (10)
Female	21 (100)	8 (38)	2 (10)	3 (14)	8 (38)
Total†	74 (100)	36 (49)	13 (18)	11 (15)	14 (19)

*14 blood-based and one study based on lycopene level in breast adipose tissue.

†From 61 studies that provided data (17–20,22–29,31,33–37,39–44,47–49,52–56,59,60,62–72,74,75,77–84,86,88–92); there are 74 relative risks because some studies present results stratified by sex, racial or ethnic group, colon and rectum cancers separately, and results both for blood lycopene level and for dietary tomato or lycopene intakes.

on prospective or retrospective data or whether they were based on dietary intakes or blood lycopene levels. The RRs (two-sided P values) for biomarker-based studies are 0.16 ($P < .02$), 0.26 ($P = .004$), 0.32 ($P < .05$), 0.37 ($P = .01$), 0.4 ($P = .08$), 0.5 ($P = .02$), 0.5 ($P = .06$), 0.50 ($P = .26$), 0.56 ($P = .05$), 0.62 (not significant), 1.01 ($P = .97$), 1.0 (not significant), 1.1 ($P = .86$), 1.14 ($P = .69$), and 1.36 ($P = .59$). Of these 15 studies, 10 had RRs less than or equal to 0.62, and eight were statistically significant or of borderline statistical significance ($P \leq .08$), and in five of the studies (59,69,70,75,91), an inverse relationship was limited to lycopene among carotenoids.

Comparisons by sex tended to show more studies with inverse associations for males, but most studies also supported a benefit for women (Table 6). Cancers, such as those of the lung or stomach, for which both sexes are at risk, do not indicate strong differences in findings by sex. Evidence for a benefit was strong for prostate cancer. For several female-associated cancers, particularly cancers of the ovary and endometrium, data are very sparse.

RR estimates for the various cancers are shown in Fig. 1. The tendency for an inverse association between consumption of tomatoes or tomato products or lycopene levels is observed for a variety of cancer sites. The data are most compelling for cancers of the prostate gland, lung, and stomach. Data are also suggestive for several other cancers, including pancreatic, colorectal, esophageal, oral, breast, and cervical cancers. Data regarding the relationship between tomato consumption or lycopene level and cancer risk for other cancer sites are too limited at present to support firm conclusions.

In summary, the epidemiologic data indicate that high consumers of tomatoes and tomato products are at substantially decreased risk of numerous cancers, although probably not all cancers. The results are consistent for a variety of cancers across numerous diverse populations and with the use of different types of study designs. These include ecologic, case-control dietary studies, prospective dietary studies, and blood specimen-based investigations. Because the evidence available is based on observational studies, and thus causality cannot be directly inferred, the possibility for biases and confounding is considered next.

Potential for Bias and Confounding as Explaining the Results

Biases occur when, through faulty data-collection techniques, the associations in the study population are distorted. For example, in some case-control studies, for which the disease status is known at the time of interview, case subjects may recall past diet differently from control subjects. Biases possibly may have occurred in specific settings, but that a single, strong methodologic bias accounts for all these findings is not plausible. Recall biases, for instance, cannot account for associations observed in prospective studies, particularly those based on blood levels of lycopene rather than on dietary recall.

Publication bias (e.g., results reported in the literature only from studies that found a relationship) is unlikely to be of major importance for our overall findings because, if no underlying association existed, one would expect as many direct associations as inverse associations to be reported. Here, 35 statistically significant inverse associations were identified, but none with direct associations were found. However, for specific cancer sites for which only a small number of reports have been published, selective publication may be a potential factor.

Although systematic errors or bias in reporting tomato or lycopene intake cannot account for all the findings, it is possible that the association between high tomato consumption and lower risk for numerous cancers is not causal but rather is secondary to some confounding factor(s) associated with tomato intake. This possibility cannot be ruled out entirely, but it is unlikely for several reasons. For confounding to occur, the confounding factor has to be simultaneously an important risk or protective factor for that cancer and correlated substantially with tomato intake. As shown in the tables, known or suspected risk factors were controlled for in many of the studies. In general, confounding from the considered factors did not account for the observed relationships.

It is possible that some unidentified confounding factor accounted for these associations. However, given the variety of cancers studied, the different etiologies for cancers, and the diversity of populations studies, uncontrolled confounding is unlikely to account for most of the inverse associations with tomatoes or lycopene. The pattern of potentially confounding factors for tomato products will likely vary among cancers, which have different risk factors. Moreover, dietary patterns differ among countries, and at least one statistically significant inverse association for tomato products was observed in 10 countries (United States, Italy, Holland, Spain, Sweden, Poland, Australia, Iran, China, and Japan). The pattern of covariates will also likely vary by type of tomato product. For example, in the Health Professionals Follow-up Study (64), fresh tomatoes tended to be associated with "healthy" lifestyle practices, tomato sauce displayed no discernible pattern, and pizza was associated slightly with "unhealthy" practices, yet all three items were inversely associated with risk of prostate cancer.

The inverse association between plasma lycopene level and cancers of the prostate, lung, cervix, breast, and pancreas is particularly interesting because plasma and tissue lycopene levels are poorly correlated with overall vegetable and fruit intake because of the diverse nature of tomato products [$r = .11$ (93); $r = .11$ in women and $.16$ in men (94)]. Unlike lycopene levels, most other carotenoid levels correlate reasonably well with vegetable and fruit intake (93,94). Furthermore, in a study of a

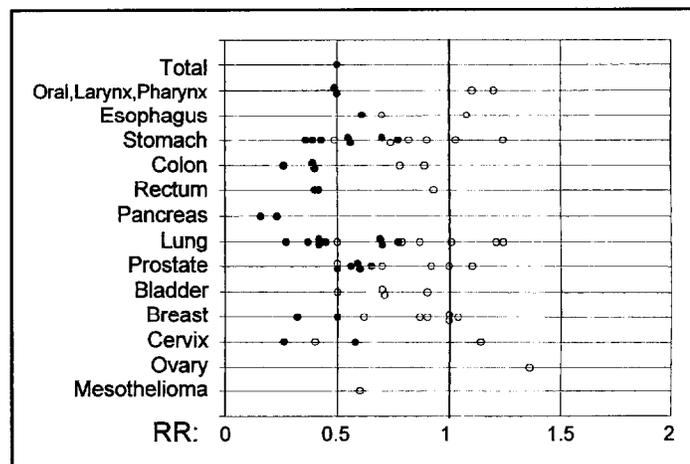


Fig. 1. Summary relative risks (RR) for high versus low consumption of tomatoes or level of lycopene from epidemiologic studies. • = statistically significant; ○ = not statistically significant.

general U.S. population, lower serum concentrations of β -carotene, α -carotene, lutein, and β -cryptoxanthin were generally associated with male sex, higher alcohol intake, increased smoking, and higher body mass index; dietary and serum lycopene levels were not associated with these factors (95). Thus, it is unlikely that the inverse association between plasma lycopene level and risk of various cancers is a result of lycopene's being a nonspecific marker of fruit and vegetable intake or related "healthy" behaviors.

Dose-Response Relationship

Although most studies indicate an anticancer benefit of tomato consumption, it is difficult to draw firm conclusions regarding the dose-response relationship. For the most part, RRs appeared to decrease proportionally to increasing intake of tomatoes or related products. Within the observable range, there was no firm evidence of an intake level where the trend toward decreasing risk begins to reverse, although few data are available regarding intakes of tomatoes or tomato-based products exceeding one serving per day. Caution is advisable regarding pharmacologic doses of lycopene because all of the epidemiologic data are based on typical dietary intakes. Moreover, one animal study of lung cancer (96) suggests a benefit of lycopene intake at lower levels but possibly an adverse effect of lycopene intake at very high levels. Benefits may also vary by the specific type of tomato products because processing and cooking may influence the level or bioavailability of the bioactive compounds (e.g., lycopene).

POTENTIALLY BENEFICIAL ASPECTS OF TOMATOES AND TOMATO-BASED PRODUCTS

Tomato and tomato-based products are important sources of many established nutrients and are predominant sources of some phytochemicals that may have health benefits. Tomatoes are relatively rich sources of folate, vitamin C, vitamin A, and potassium. Because other good sources of these nutrients are available, the relative importance of tomatoes as contributors of these nutrients varies across populations. In the United States, consumption of tomatoes and tomato products ranks number two to potatoes among vegetables (97). Because they are highly consumed, tomatoes and related products rank as the number three contributor of vitamin C and the number four contributor of provitamin A and are the ninth highest contributor of potassium to the U.S. diet. In Italy, tomatoes have been estimated as the second most important source of vitamin C after oranges (98). In contrast, tomato consumption in some populations appears to be too low for them to be a good source of these nutrients [e.g., the study by Tuyns et al. (43) in Belgium]. Anticancer properties for several of these nutrients have been hypothesized.

In addition to being a substantial source of some traditional nutrients, tomatoes are rich in several phytochemicals believed to have anticancer properties. Among the most prominent phytochemicals in tomatoes are the carotenoids, important pigments found in plants, and photosynthetic bacteria, fungi, and algae. These organisms synthesize phytoene, a 40-carbon molecule with 9 double bonds (in the *trans* configuration), which serves as a precursor for more than 600 carotenoids. A series of desaturation steps leads sequentially to phytofluene, ζ -carotene, neurosporene, and lycopene, a symmetrical, acyclic 40-carbon molecule with 13 double bonds (11 conjugated). Enzymatic cyclization of the end groups of lycopene results in γ -carotene

(one β -ionone ring) and β -carotene (two β -ionone rings). The β -ionone rings are critical for vitamin A activity; other ring structures formed are devoid of vitamin A activity. Thus, cleavage of γ -carotene forms one vitamin A molecule, while cleavage of β -carotene leads to two vitamin A molecules. Oxygenation of the β -ionone rings leads to the more polar oxycarotenoids or xanthophylls, such as β -cryptoxanthin (one oxygenated ring, half the provitamin A activity of β -carotene) and lutein (two oxygenated rings and hence no provitamin A activity).

Plants vary substantially in their overall production of carotenoids and in the activities of various enzymes involved in desaturation, cyclization, and oxygenation to produce a wide range of carotenoids. For example, the red color of tomatoes results from lycopene, suggesting that red tomatoes have insufficient cyclase activity to convert lycopene to γ -carotene and β -carotene efficiently. Variation in different strains of tomatoes exists, as evidenced by yellow tomatoes, which are relatively low in lycopene. Among foods typically consumed by humans, tomatoes are a particularly rich source of several carotenoids. Of 14 carotenoids found in human serum, tomato and tomato-based products contribute to nine and are the predominant source of about half of the carotenoids (99). Tomatoes are low in β -carotene (most of the provitamin A activity from tomatoes is from γ -carotene) and low in the polar xanthophylls, but they are by far the major source of the remaining nonpolar carotenoids.

Overall, tomatoes are an important source of several nutrients and a predominant source of several carotenoids, particularly lycopene. Very few items other than tomato products contribute to dietary lycopene; these include watermelon, pink grapefruit, and apricots. Tomatoes are also a source of other potentially beneficial phytochemicals, including phenylpropanoids (phenolic acids), phytosterols, and flavonoids (97). However, the biologic relevance of these latter compounds, plus the relative importance of tomatoes as a dietary source of these, is unknown.

BIOLOGIC PLAUSIBILITY OF AN ANTICANCER EFFECT OF LYCOPENE

Lycopene has received the most attention, but whether apparent anticancer properties of tomatoes result from lycopene remains unproven. Nonetheless, lycopene has several notable characteristics that may confer potentially beneficial properties. Because lycopene is not converted to vitamin A, it may be entirely available for other properties (e.g., antioxidation). The lack of the β -ionone ring structure for lycopene may increase its antioxidant activity (100). The stereochemical properties of lycopene are quite different from those of other commonly consumed carotenoids (101), making it uniquely present in specific subcellular environments. Lycopene appears to be the most efficient quencher of singlet oxygen and free radicals among the common carotenoids *in vitro* (8,102-104). In some populations, lycopene is the predominant carotenoid in plasma (105-107) and in various tissues (108,109).

The unique biochemical properties of lycopene may render it able to protect cellular components against specific types of damage from highly reactive oxygen species. The source of the reactive compounds differs by tissue type and includes smoking, sunlight, chronic inflammation, and normal metabolic processes (110-112). For example, smokers' lungs are exposed to high levels of nitric oxide (NO), which can react with oxygen to produce the $\text{NO}_2\cdot$ radical. NO_2 radicals survive for long enough in fresh smoke to reach lung tissue (113). Lycopene is one of the

major carotenoids found in lung tissue, and concentrations vary widely among individuals (114). Using an *in vitro* assay, Böhm et al. (115) showed that carotenoids are effective in protecting lymphocytes from NO₂ radical damage and that lycopene was at least twice as effective as β-carotene. Lycopene was shown to possess anticancer properties in a mouse lung carcinogenesis model (96).

Chronic infection by *Helicobacter pylori* is a major established risk factor for gastric cancer. Chronic infections may increase cancer risk by increasing the oxidative load (116). Elevated DNA oxidation occurs early during *H. pylori* infection (117). Dietary antioxidants, including lycopene, may potentially reduce the impact of oxidative load from *H. pylori* infections in the stomach. Another potential contributing factor to stomach cancer is the endogenous formation of *N*-nitrosamines. Vitamin C has been considered to be an inhibitor of the nitrosation that generates *N*-nitrosamines. It is interesting that an ecologic study in Japan (45), an area with a high incidence of stomach cancer, showed no association between average plasma vitamin C level and stomach cancer, and, in fact, the area with the lowest gastric cancer incidence had the lowest vitamin C level. In contrast, plasma lycopene level was associated with stomach cancer rate more so than the levels of other "antioxidant" nutrients assessed (vitamins A, C, and E and β-carotene) (45). A study of determinants of endogenous generation of *N*-nitrosamine in rats (118) suggested that various aspects of food products may explain their inhibitory effect, including pH, and ascorbic acid, lycopene, and β-carotene contents. Tomato and tomato-based products are the predominant sources of lycopene and one of the major sources of ascorbic acid in some populations.

Reactive oxygen compounds may contribute to prostate carcinogenesis (119,120). Prostate epithelial cells in many men at the age of risk for prostate cancer are likely to be exposed to inflammatory-related reactive oxygen species because of the high prevalence of prostatitis. However, whether an antioxidant property accounts for the apparent benefit of tomato product consumption on prostate cancer risk remains unproven.

If oxidation proves critical to carcinogenesis, the dietary contribution to antioxidation is likely to be immensely complex. Synergy among antioxidants exists in experimental systems (121), and synergistic effects are likely to be more complex *in vivo*. For example, synergy between α-tocopherol and ascorbic acid is well established (121), resulting from the ability of ascorbic acid to reduce α-tocopheroxyl radicals, thereby recycling α-tocopherol. Complex synergistic effects may occur as a result of such direct interactions (e.g., recycling), different abilities of antioxidants to scavenge the various reactive oxygen species thus enhancing overall protection (103), and the localization of different antioxidants in diverse subcellular compartments. Possibly, the benefits of tomatoes may result from the complex interaction of various carotenoids, ascorbic acid, and other antioxidant polyphenolic compounds.

Although the notion that lycopene may exert its role in humans through limiting cellular macromolecule damage from reactive oxygen species is appealing, other mechanisms may be operative. In addition, preliminary *in vitro* evidence indicates that lycopene reduces cellular proliferation of various cancer cell lines induced by insulin-like growth factor-I (IGF-I) (85). This finding, which requires confirmation, is intriguing, given recent evidence that the circulating level of IGF-I is positively associated with higher risk of various cancers, including prostate can-

cer (122). Various other potential mechanisms have been postulated (100,108,123,124). Most of the mechanistic data have been based on *in vitro* studies, but a recent study (125) found that supplementation with tomato products, as well as carrot and spinach products, resulted in a marked decrease in endogenous levels of strand breaks in lymphocyte DNA. More human studies are clearly needed.

CONCLUSIONS

Intake of tomatoes and tomato-based products and plasma levels of lycopene, a carotenoid found predominantly in tomatoes, have been relatively consistently associated with a lower risk of a variety of cancers. Evidence is strongest for cancers of the lung, stomach, and prostate gland and is suggestive for cancers of the cervix, breast, oral cavity, pancreas, colorectum, and esophagus. A large body of evidence also indicates that other fruits and vegetables may have additional or complementary benefits (3–5). The likelihood that the associations between increased consumption of tomato and tomato-based products and lower risk for several cancer sites are causal is supported by the consistency of evidence by study design (ecologic, case-control, and prospective) and by exposure assessment (dietary-based and plasma-based) and by the unlikelihood that biases or uncontrolled confounding could plausibly account for all these associations in diverse populations. These findings add further support to current dietary recommendations to increase consumption of fruits and vegetables to reduce cancer risk.

The benefits of tomatoes and tomato products are often attributed to the carotenoid lycopene. However, a direct benefit of lycopene has not been proven, and other compounds in tomatoes alone or interacting with lycopene may be important. It is critical to recognize that the current evidence regarding dietary intake and lycopene blood concentrations reflects consumption of tomatoes and tomato products rather than purified lycopene supplements. The pharmacokinetic properties of lycopene remain poorly understood, and it is premature to recommend use of pharmacologic doses of lycopene for any health benefit. Further research on the bioavailability, pharmacology, and biology of this potentially important carotenoid is clearly warranted. Until more definitive data regarding specific benefits of purified forms of lycopene are available, current recommendations should emphasize the health benefits of diets rich in a variety of fruits and vegetables, including tomatoes and tomato-based products.

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NOTES

Supported by Public Health Service grants CA55075, CA72036, CA76622, and CA67883 (National Cancer Institute) and HL35464 (National Heart, Lung, and Blood Institute), National Institutes of Health, Department of Health and Human Services.

I thank Kathleen Markham for her outstanding technical support.

Manuscript received July 24, 1998; revised November 5, 1998; accepted December 30, 1998.

A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women¹⁻⁴

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See corresponding editorial on page 431.

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, 50461 were included and others were added as they became 45 y of age for a total of 77466. Information on nutrient intake was assessed by repeated administration of a food-frequency questionnaire during 12 y of follow-up.

Results: During 761762 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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Received January 13, 1999.

Accepted for publication April 26, 1999.

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 >14644 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 type 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, 1980–1992¹

Nutrient	Type of cataract		
	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)

¹Multivariate 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 subcapsular cataract were ≤ 0.05 for carotene, β -carotene, lutein and zeaxanthin, and total vitamin A without supplements.

²Adjusted 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, 1980-1992¹

Food	Frequency of consumption				P for trend
	<1 time/mo	1-3 times/mo	1 time/wk	≥2 times/wk	
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

¹Multivariate 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).

²Category 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 36 644 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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A prospective study of carotenoid intake and risk of cataract extraction in US men¹⁻³

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ABSTRACT

Background: Dietary antioxidants, including carotenoids, are hypothesized to decrease the risk of age-related cataracts by preventing oxidation of proteins or lipids within the lens. However, prospective epidemiologic data concerning this phenomenon are limited.

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

Design: US male health professionals ($n = 36644$) who were 45–75 y of age in 1986 were included in this prospective cohort study. Others were subsequently included as they became 45 y of age. A detailed dietary questionnaire was used to assess intake of carotenoids and other nutrients. During 8 y of follow-up, 840 cases of senile cataract extraction were documented.

Results: We observed a modestly lower risk of cataract extraction in men with higher intakes of lutein and zeaxanthin but not of other carotenoids (α -carotene, β -carotene, lycopene, and β -cryptoxanthin) or vitamin A after other potential risk factors, including age and smoking, were controlled for. Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (relative risk: 0.81; 95% CI: 0.65, 1.01; P for trend = 0.03). Among specific foods high in carotenoids, broccoli and spinach were most consistently associated with a lower risk of cataract.

Conclusions: Lutein and zeaxanthin may decrease the risk of cataracts severe enough to require extraction, although this relation appears modest in magnitude. The present findings add support for recommendations to consume vegetables and fruit high in carotenoids daily. *Am J Clin Nutr* 1999;70:517–24.

KEY WORDS Cataract, cataract extraction, diet, men, prospective studies, vitamin A, carotene, lutein, zeaxanthin, carotenoids, food-frequency questionnaire, Health Professionals Follow-up Study

INTRODUCTION

Cataract is an opacification of the lens that causes decreased visual acuity and can lead to blindness (1). Cataracts become more common with increasing age and are an important cause of disability among older adults; >1 million extractions are per-

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formed annually in the United States (2). Thus, identification of factors that could delay or prevent cataract development would be important both for increasing the well-being of older adults and for reducing medical care costs. Oxidative damage plays a major role in cataractogenesis and the intake of dietary antioxidants is hypothesized to help prevent cataract formation by blocking the oxidative modification of lens protein (3) or by preventing lipid peroxidation within the epithelium of the lens (4).

Much evidence suggests that elevated intakes or plasma concentrations of antioxidants are associated with decreased risk of cataract (5–16). However, the association between specific antioxidants and the risk of cataract is unclear. Also, in some studies, nutrient intakes of antioxidants were not associated with risk of cataract (16, 17). Frequent intake of fruit and vegetables has been associated with decreased risk of cataract in some, but not all, studies (6, 7, 14, 15). In an 8-y prospective study in women, Hankinson et al (6) reported that dietary carotene and total vitamin A intake were inversely associated with risk of cataract. Among specific foods, high intake of spinach, which is rich in lutein, was most consistently associated with a lower risk of cataract, whereas carrot intake (a major source of α - and β -carotene) showed no consistent relation with cataract.

Carotenoids can be effective antioxidants, especially at low partial pressures of oxygen such as in the lens (18, 19). Lutein and zeaxanthin may be particularly effective in protecting the eye because they are the only carotenoids accumulated by the retina and other ocular tissues (20–22). The extent to which blood

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²Supported by grants HL 35464, CA 55075, and EY09611 from the National Institutes of Health.

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Received January 13, 1999.

Accepted for publication May 14, 1999.

carotenoid concentrations change with dietary manipulation varies between individuals (23). However, dietary supplementation with lutein and zeaxanthin increases the amount of macular pigment, which consists mainly of lutein and zeaxanthin (22). Macular lutein and zeaxanthin concentrations are inversely associated with lens density and may be markers for lutein and zeaxanthin in the lens (24). To evaluate these relations further in men, we examined prospectively the associations between dietary intake of vitamin A and specific carotenoids and the incidence of cataract extraction in participants enrolled in the Health Professionals Follow-up Study.

SUBJECTS AND METHODS

The Health Professionals Follow-up Study is a prospective investigation of dietary etiologies of chronic disease in 51 529 US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians who were aged 40–75 y in 1986. The men responded to a mailed questionnaire sent in February 1986 that elicited information on age, marital status, height and weight, ancestry, medication use, disease history, physical activity, and diet (described below). The men are followed up with mailed questionnaires every 2 y. The study protocol was approved by the Harvard School of Public Health.

Dietary assessment

To assess dietary intake, we used a semiquantitative food-frequency questionnaire. A description of the questionnaire and of the procedures for calculation of nutrient intakes were published previously (25). The questionnaire included 131 food items plus questions on vitamin and mineral supplements. The participants were asked about the average frequency of consumption of a given unit or portion size for each food during the previous year (eg, 1 apple or 1 slice of bread). There were 9 possible responses ranging from “never” to “ ≥ 6 times/d.” Intake scores were calculated by summing the nutrient contribution of each food multiplied by its frequency of use, using food-composition data from the US Department of Agriculture (USDA), food manufacturers, and other published sources (26–28). The carotenoid food composition database contains values for the most commonly occurring carotenoids in fruit and vegetables, including α -carotene, β -carotene, lutein and zeaxanthin, β -cryptoxanthin, and lycopene. The carotenoid content of tomato-based food products was updated with values from the USDA (28). Although “lutein” intake represents both lutein and zeaxanthin intake, the main contributors to lutein intake (green leafy vegetables) contain essentially no zeaxanthin, and therefore lutein + zeaxanthin values for these foods represent primarily lutein (27). Peaches and corn contain both lutein and zeaxanthin in varying ratios (29). In addition to specific carotenoids, total vitamin A intake was assessed as preformed vitamin A (retinol from animal sources, supplements, and fortified foods) plus provitamin A carotenoids (provitamin A, primarily from fruit and vegetables). The derived values for provitamin A carotenoids accounted for most of the β -carotene intake, about half of the α -carotene intake, and a small fraction of the intake of other carotenoids. Energy-adjusted nutrients were calculated as the residuals after regression of each specific nutrient on total energy intake by using linear regression (30).

Data on the reproducibility and validity of the food-frequency questionnaire were published elsewhere (25). Correlation coefficients (adjusted for energy intake) between intake of antioxidant vitamins as assessed by the 1986 questionnaire and 2 wk of

dietary records provided by a subsample of 127 men were 0.64 for carotene and 0.48 for total vitamin A (25). Among nonsmokers, intakes of specific dietary carotenoids were significantly correlated with the corresponding plasma concentrations for β -carotene ($r = 0.30$), α -carotene ($r = 0.37$), and lutein ($r = 0.19$), but not for lycopene ($r = 0.01$) (31).

In addition to recent diet, we also examined the relation between diet during high school and cataract risk. Questions about intake of foods during high school (age ≈ 13 –18 y), including those high in carotenoids, were asked on the 1988 follow-up questionnaire. The abbreviated list of food items included apples, oranges or orange juice, broccoli or cauliflower, carrots, and spinach.

Other covariates

We included as covariates other known or suspected risk factors for cataract extraction that could distort associations with carotenoid and vitamin A intakes. Age, cigarette smoking, and diabetes are established risk factors for cataract (32–35). From the baseline questionnaire, we obtained information on age, body weight, height, diagnosis of diabetes, and past and present smoking habits. The number of cigarette pack-years of smoking was calculated by multiplying the number of packs (20 cigarettes) smoked per day by the number of years over which that amount was smoked. We chose pack-years as a measure of smoking status because cataract extraction has been more strongly related to cumulative dose of cigarette smoking than to recent exposure (32). Aspirin use, which was ascertained at baseline, has been hypothesized to decrease the risk of cataract (36). Alcohol consumption has been implicated in the pathogenesis of cataract in some studies (37, 38) and was assessed at baseline. Recreational physical activity influences insulin resistance and hyperglycemia and was assessed by using metabolic equivalents (METs), which represent multiples of the metabolic equivalent of sitting quietly for 1 h (39). We included area of residence to account for possible geographic variation in sun exposure, diet, and cataract extraction practices. To evaluate the influence of access to health care on cataract extraction, participants were asked how often they had visited an eye doctor in the previous 2 y.

Study population

We excluded from the analysis 2107 men who did not adequately complete the food-frequency questionnaire [≥ 70 items blank of 131 listed food items or reported intakes $> 17 600$ kJ (4200 kcal) or < 3350 kJ (800 kcal/d)]. In addition, we excluded men who reported on the 1986 questionnaire a diagnosis of cancer (except nonmelanoma skin cancer; $n = 1960$). These men might have recently altered their dietary pattern after diagnosis and, thus, the reported baseline diet might not have reflected long-term dietary intake. Men < 45 y of age ($n = 10 224$) at baseline were excluded because they were not considered eligible to have senile cataracts; follow-up for these men began as they became 45 y of age. These exclusions (total of 14 885 men, including 594 baseline case exclusions as described below) left 36 644 men eligible for inclusion in the baseline population.

Case definition

Follow-up questionnaires were sent in 1988, 1990, 1992, and 1994 to all study participants to determine whether they had a variety of conditions including cataract extraction and, if so, we asked for permission to review their medical records. Dates of

extraction were confirmed by medical record review. Other information abstracted from the medical records included date of initial diagnosis, any known cause of cataract, the participant's best-corrected visual acuity in each eye before surgery, and the location of the lens opacity (nuclear, cortical, posterior subcapsular, or any combination of the 3) in each eye. A total of 1969 men reported a first cataract extraction after the return of the 1986 questionnaires. Of these men, 274 (14%) either subsequently denied the diagnosis or had undergone cataract extraction before 1986; 1530 (78%) gave us permission to contact their ophthalmologist. Most of the ophthalmologists responded to our request (1415; 92%) and all confirmed the extractions. Because the confirmation rate was 100% and because all of the confirmed dates of extraction were within 6 mo of the participants' reports, we included 280 (14%) cases confirmed by the participants but for whom we had no information from their ophthalmologists, for a total of 1695 cases.

We excluded cataracts considered by the physicians to be either congenital or secondary to chronic steroid use, chronic intraocular inflammation, ocular trauma, previous intraocular surgery, or glaucoma ($n = 66$). Both the participant and his ophthalmologist indicated when the cataract had been extracted. We used the ophthalmologists' reported dates of extraction, and, if missing, the participants' reported extraction dates. Because we began follow-up in 1986, we excluded cases diagnosed before the 1986 questionnaire ($n = 391$), those with an unknown date of diagnosis ($n = 131$), and reported cases of extraction after January 1994, the end of the follow-up period ($n = 6$). After further exclusion of 261 cases with any of the factors described in the section above (eg, previous diagnosis of cancer), 840 cases remained for analysis.

Opacities may form in different areas of the lens (posterior subcapsular, cortical, or nuclear) and these types may have different etiologies (12, 14, 17). We therefore performed an additional analysis using each subtype as the outcome variable and examining the association with carotenoid intake. Three different case groups were defined on the basis of cataract subtype: nuclear, posterior subcapsular, and cortical only cataract in either eye if unilateral, or both eyes if bilateral, as determined by the participant's ophthalmologist. Those with more than one type of cataract were omitted from these subgroup analyses to minimize misclassification of opacity type.

Data analysis

Each participant's follow-up time began with the date of return of the 1986 questionnaire or the date they turned 45 y of age, whichever occurred first. Follow-up continued until the report of cataract, death, cancer, or February 1, 1994, for a total of 307 259 person-years of follow-up.

In our primary analysis, age was updated at the beginning of each 2-y interval because we included individuals as they became 45 y old. Baseline values for nutrients and other exposures were carried forward throughout the follow-up period because cataracts develop over many years. To reduce the effect of measurement error associated with a single questionnaire (40), we also conducted analyses using the cumulative average of carotenoid intakes. In this analysis, we used the carotenoid intake from the 1986 questionnaires for the 1986–1990 follow-up and the average intakes from both the 1986 and 1990 dietary questionnaires for the 1990–1994 follow-up. Other covariates (including body mass index, age, alcohol intake, and smoking) were updated at the start of each 2-y interval. For exposures that were not updated in this analysis (number of physician visits,

physical activity, and area of residence), the initial value was carried forward throughout the follow-up period. The SAS computer analysis program (version 6; SAS Institute, Cary, NC) was used for the statistical analyses.

Relative risks (RRs) were first calculated by dividing the incidence rate of cataract extraction in men in each category of nutrient intake by the rate for the men in the lowest category. RRs adjusted for age (in 5-y categories) were derived by the Mantel-Haenszel method (41). The Mantel extension test was used to test for linear trends (42). To adjust for other risk factors, we used pooled logistic regression with 2-y time intervals to estimate rate ratios (43). In multivariate logistic models, we tested for significant monotonic trends by assigning each participant the median value for the category and modeling this value as a continuous variable. We assessed possible interactions between nutrient intake, smoking status, and diabetes using the likelihood ratio test. All *P* values were two sided.

RESULTS

Nutrient intake

Intakes of provitamin A carotenoids and lutein and zeaxanthin were associated with a moderately decreased risk of cataract extraction in analyses adjusted for age (Table 1). When these relations were examined after several additional potential risk factors were controlled for—including cigarette smoking, body mass index, history of diabetes, energy and alcohol intake, area of residence in 1986, aspirin use, whether participants had undergone an eye exam between 1988 and 1990, and time period—the RRs were all attenuated. In the multivariate analyses, the trend of decreased risk of first cataract extraction with increasing intake of antioxidants remained significant only for lutein and zeaxanthin. Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (RR: 0.81; 95% CI: 0.65, 1.01; *P* for trend = 0.03). This inverse association was not materially altered when we included terms for duration of vitamin supplement use (vitamins C or E, or multivitamins) in the multivariate model. We found similar results for the cumulatively updated nutrients. For example, the multivariate RR when comparing the lowest and highest quintiles of intake for lutein and zeaxanthin was 0.78 (95% CI: 0.62, 0.98; *P* for trend = 0.01). We also found similar results when we examined a wider range of intake by comparing the top decile (median: 8745 $\mu\text{g}/\text{d}$) with the lowest quintile (median: 1300 $\mu\text{g}/\text{d}$) of intake. Men in the top decile had a significantly lower risk than did those in the lowest quintile of intake (RR: 0.78; 95% CI: 0.59, 1.03; *P* for trend = 0.02).

We examined the influence of smoking and diabetes on the association between carotenoid intake and cataract risk. The inverse association between lutein and zeaxanthin intake and cataract appeared strongest among never smokers (Table 2), but a formal test of interaction with smoking was not significant. The relations with other carotenoids were essentially null in smokers and nonsmokers. The differences in RR by diabetes status were not significant; however, we had limited power to detect interactions because there were so few cases in diabetics. Exclusion of diabetics from the total group did not appreciably alter the RRs for other carotenoids.

Next, we evaluated the association with nutrient intakes separately for cataract subtypes. There were 207 nuclear, 136 posterior subcapsular, and 46 cortical cataracts. The remaining

TABLE 1
Relative risk (RR) of cataract extraction in men from 1986 to 1994 for energy-adjusted carotenoid intake as assessed in 1986¹

Nutrient	Quintile of intake					P for trend
	1	2	3	4	5	
Carotene with supplements (IU)						
Median intake	3777	5770	7782	11231	18499	
Cases (n)	142	164	181	178	175	
Age-adjusted RR	1.00	1.02	1.05	0.96	0.87	0.03
Multivariate RR	1.00	1.02	1.05	0.94	0.85	0.05
95% CI		0.81, 1.28	0.84, 1.31	0.75, 1.18	0.68, 1.07	
α-Carotene (μg)						
Median intake	292	473	634	1010	1886	
Cases (n)	156	164	162	181	177	
Age-adjusted RR	1.00	1.05	0.95	1.02	0.88	0.13
Multivariate RR	1.00	1.07	0.96	1.04	0.89	0.18
95% CI		0.86, 1.34	0.77, 1.20	0.84, 1.30	0.72, 1.11	
β-Carotene (μg)						
Median intake	2046	3136	4225	5806	9214	
Cases (n)	136	169	174	181	180	
Age-adjusted RR	1.00	1.11	1.06	1.01	0.93	0.11
Multivariate RR	1.00	1.13	1.07	0.99	0.92	0.14
95% CI		0.90, 1.42	0.85, 1.34	0.79, 1.24	0.73, 1.16	
Lycopene (μg)						
Median intake	3413	6159	8692	12212	18901	
Cases (n)	164	159	171	163	183	
Age-adjusted RR	1.00	1.05	1.10	1.02	1.10	0.49
Multivariate RR	1.00	1.05	1.11	1.01	1.10	0.54
95% CI		0.84, 1.31	0.89, 1.38	0.81, 1.26	0.88, 1.36	
β-Cryptoxanthin (μg)						
Median intake	10.8	33.2	56.2	92.5	175.1	
Cases (n)	142	157	161	193	187	
Age-adjusted RR	1.00	1.14	1.07	1.21	1.04	0.97
Multivariate RR	1.00	1.20	1.12	1.28	1.09	0.76
95% CI		0.95, 1.50	0.89, 1.41	1.03, 1.60	0.87, 1.37	
Lutein and zeaxanthin (μg)						
Median intake	1300	2279	3182	4342	6871	
Cases (n)	173	180	181	153	153	
Age-adjusted RR	1.00	1.01	0.97	0.82	0.80	0.01
Multivariate RR	1.00	1.00	0.98	0.83	0.81	0.03
95% CI		0.81, 1.23	0.79, 1.20	0.67, 1.04	0.65, 1.01	
Retinol (IU)						
With supplements						
Median intake	1056	1933	3078	6218	12598	
Cases (n)	148	148	194	160	190	
Age-adjusted RR	1.0	0.93	1.10	0.89	0.99	0.70
Multivariate RR	1.0	0.92	1.08	0.87	0.96	0.56
95% CI		0.73, 1.16	0.87, 1.34	0.69, 1.09	0.77, 1.19	
No supplements (IU)						
Median intake	873	1440	2028	2788	5079	
Cases (n)	132	161	171	198	178	
Age-adjusted RR	1.0	1.17	1.18	1.22	1.06	0.94
Multivariate RR	1.0	1.17	1.17	1.20	1.04	0.72
95% CI		0.93, 1.47	0.93, 1.47	0.96, 1.50	0.83, 1.31	
Vitamin A (IU)						
With supplements						
Median intake	6252	9249	12713	17335	27222	
Cases (n)	145	155	172	184	184	
Age-adjusted RR	1.0	0.86	0.89	0.88	0.82	0.09
Multivariate RR	1.0	0.87	0.87	0.86	0.80	0.10
95% CI		0.69, 1.09	0.70, 1.09	0.70, 1.07	0.64, 1.00	
No supplements (IU)						
Median intake	5683	8047	10388	13890	20694	
Cases (n)	144	157	183	175	181	
Age-adjusted RR	1.0	0.91	0.98	0.89	0.83	0.10
Multivariate RR	1.0	0.91	0.97	0.88	0.81	0.06
95% CI		0.73, 1.14	0.78, 1.21	0.70, 1.10	0.64, 1.01	

¹ Each logistic model included terms for age (5-y categories), time period (2-y intervals), diagnosis of diabetes (yes or no), cigarette smoking (never or 1-44 or >44 pack-years), BMI (quintile), area of US residence (east, central, west, or Texas, California, or Florida), aspirin use (yes or no), energy intake (quintile), physical activity (quintile of metabolic equivalents), alcohol intake (0, 1-4, 5-9, 10-14, 15-29, ≥30 g/d), routine eye exams (yes or no), and profession.

TABLE 2
Multivariate-adjusted relative risk and 95% CI of cataract extraction by lutein and zeaxanthin intake within smoking category¹

Smoking (pack-years) ²	Quintile of intake					P for trend
	1	2	3	4	5	
Never (n = 294)	1.00	1.02 (0.73, 1.46)	0.96 (0.67, 1.36)	0.71 (0.49, 1.04)	0.71 (0.49, 1.03)	0.02
1-44 (n = 359)	1.00	1.06 (0.76, 1.48)	0.94 (0.67, 1.33)	0.99 (0.73, 1.39)	0.87 (0.62, 1.23)	0.32
≥45 (n = 144)	1.00	0.97 (0.59, 1.60)	1.14 (0.70, 1.88)	0.77 (0.44, 1.35)	1.00 (0.59, 1.70)	0.83

¹Each logistic model included terms for age (5-y categories), time period (2-y intervals), diagnosis of diabetes (yes or no), BMI (quintile), area of US residence (east, central, west, or Texas, California, or Florida), aspirin use (yes or no), energy intake (quintile), physical activity (quintile of metabolic equivalents), alcohol intake (0, 1-4, 5-9, 10-14, 15-29, ≥30 g/d), routine eye exams (yes or no), and profession.

²Values add to less than total number of cases because of missing information.

451 cataracts were classified as having either a combination of the 3 types or were missing this information. Because of sparse data for cortical cataracts, we limited our analyses to nuclear and posterior subcapsular cataract types. In multivariate models, those in the highest quintile of intake of lycopene had a reduced risk of nuclear cataract (RR: 0.69; 95% CI: 0.44, 1.10; *P* for trend = 0.05) but not of posterior subcapsular cataract (RR: 1.36; 95% CI: 0.82, 2.25; *P* for trend = 0.13). No other substantial differences were noted between subtypes, and the relations given above were similar to those reported for all extractions combined.

Food intake

On the basis of our findings of an inverse association between lutein and zeaxanthin intake and cataract extraction, we assessed the associations with intakes of individual foods high in carotenoids (Table 3). When added to the basic multivariate model one at a time, increasing frequency of intakes of broccoli and cooked spinach were each associated with a significantly decreased risk of cataract extraction. Consumption of broccoli and spinach each showed a consistent inverse relation with cataract after these and other foods rich in carotenoids were added simultaneously into the multivariate model. Kale, a vegetable rich in lutein, was not associated with cataract extraction, although few men reported intakes ≥1 time/wk. There was no association between intake of other leafy green vegetables (iceberg lettuce and romaine lettuce) and cataract extraction. Intake of corn, a primary source of zeaxanthin, also appeared unrelated to risk of cataract extraction. No other associations with specific fruit or vegetables were observed.

Because cataract develops over many years, we hypothesized that frequent consumption of foods high in carotenoids early in life or for long periods of time may be associated with a lower risk of senile cataract extractions. We therefore examined the risk of cataract extraction according to food intake during high school and for those with consistent long-term intake of vegetables (including those rich in carotenoids). Among foods high in carotenoids that were included in the questionnaire about intake during high school, intakes of broccoli, spinach, and carrots were not significantly associated with decreased risk. We further examined the risk of cataract in the subjects classified jointly according to their intake in high school and intake reported in 1986. When subjects were classified jointly according to frequency of intake of specific foods, men consuming broccoli > 2 times/wk both early in life and in 1986 had the lowest risk of senile cataract compared with those in the opposite extreme, although the association was not significant (RR: 0.77; 95% CI: 0.49, 1.21). The comparable RR for intake of spinach both early

in life and in 1986 was similar (RR: 0.71; 95% CI: 0.46, 1.10). Joint classification of intake of carrots did not reveal an association with cataract risk.

When we examined the risk of cataract in participants who did not change their intake of vegetables in the 10 y before completing the dietary questionnaire (511 cases; 169 399 person-years), the multivariate RR for the comparison of the lowest with the highest quintile of lutein and zeaxanthin intake was 0.80 (95% CI: 0.60, 1.07; *P* for trend = 0.06). There were no other significant associations between cataract extraction and other carotenoids (α-carotene, β-carotene, lycopene, and β-cryptoxanthin). Intakes of spinach and broccoli were also each associated with a significantly decreased risk of cataract extraction among participants who did not change their intake of vegetables for 10 y.

DISCUSSION

In this large prospective study, we observed a modest inverse association between intake of lutein and zeaxanthin and extraction of cataracts. Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract extraction compared with those in the lowest fifth of intake. There was no significant association between intake of vitamin A or other carotenoids and risk of cataract in multivariate analyses. Increased consumption of some foods high in lutein, including broccoli and spinach, was associated with a lower risk of cataract extraction. The finding that increased intake of other fruit and vegetables was not associated with a decreased risk suggests that the relation may be specifically due to lutein and zeaxanthin and not simply to a healthy lifestyle.

Our finding of an apparently protective effect of lutein and zeaxanthin and lutein-rich foods on risk of cataract extraction agrees with other studies investigating the relation between dietary carotenoids and risk of cataract. In the largest study, Hankinson et al (6) observed in the Nurses' Health Study that among specific food items, spinach was most consistently associated with a lower risk. Mares-Perlman et al (13) found a higher concentration of carotenoids, including serum lutein, to be significantly related to a lower risk for nuclear sclerosis. Our findings are also consistent with those of other studies reporting a lower risk of cataract in people with high serum concentrations of carotenoids or high intakes of foods rich in carotenoids (7, 8, 12, 15).

Vitamin A intake was associated with a modest but nonsignificantly decreased risk of cataract extraction in this cohort of men. In an earlier report of a study in women, vitamin A was associated with a 39% decreased risk of cataract extraction (6). Updated analyses, which included a larger number of cases, showed a more modest RR of 0.87 (95% CI: 0.66, 1.15; *P* for

TABLE 3
Relative risk (RR) of cataract extraction from 1986 to 1994 by frequency of consumption of foods rich in carotenoids as assessed in 1986¹

Food ²	Frequency				<i>P</i> for trend
	<1 time/mo	1-3 times/mo	1 time/wk	>2 times/wk	
Broccoli					
Cases (<i>n</i>)	133	275	256	160	
Age-adjusted RR	1.00	0.86	0.79	0.71	0.003
Multivariate RR	1.00	0.89	0.83	0.77	0.02
95% CI		0.73, 1.09	0.67, 1.02	0.61, 0.97	
Carrots					
Cases (<i>n</i>)	76	288	216	247	
Age-adjusted RR	1.00	1.01	0.82	0.87	0.04
Multivariate RR	1.00	1.02	0.83	0.88	0.06
95% CI		0.80, 1.30	0.65, 1.07	0.68, 1.12	
Raw spinach					
Cases (<i>n</i>)	494	222	65	19	
Age-adjusted RR	1.00	0.88	0.88	0.70	0.03
Multivariate RR	1.00	0.90	0.89	0.73	0.04
95% CI		0.77, 1.05	0.68, 1.15	0.46, 1.16	
Cooked spinach					
Cases (<i>n</i>)	360	320	114	18	
Age-adjusted RR	1.00	1.02	0.97	0.52	0.09
Multivariate RR	1.00	1.02	0.97	0.51	0.08
95% CI		0.88, 1.19	0.78, 1.20	0.32, 0.82	
Kale					
Cases (<i>n</i>)	673	79	23	11	
Age-adjusted RR	1.00	1.03	0.93	0.83	0.66
Multivariate RR	1.00	1.06	0.98	0.85	0.86
95% CI		0.84, 1.34	0.65, 1.49	0.47, 1.56	
Corn					
Cases (<i>n</i>)	129	339	233	118	
Age-adjusted RR	1.00	0.96	0.90	0.95	0.46
Multivariate RR	1.00	0.97	0.92	0.99	0.72
95% CI		0.80, 1.17	0.74, 1.14	0.77, 1.27	
Yellow squash					
Cases (<i>n</i>)	411	281	95	27	
Age-adjusted RR	1.00	0.96	0.85	0.70	0.04
Multivariate RR	1.00	0.99	0.87	0.72	0.05
95% CI		0.85, 1.15	0.70, 1.09	0.49, 1.05	
Sweet potatoes					
Cases (<i>n</i>)	417	305	81	22	
Age-adjusted RR	1.00	1.02	1.03	0.73	0.54
Multivariate RR	1.00	1.05	1.08	0.76	0.74
95% CI		0.90, 1.22	0.84, 1.38	0.49, 1.18	
Tomatoes					
Cases (<i>n</i>)	39	103	178	507	
Age-adjusted RR	1.00	0.85	0.90	0.93	0.78
Multivariate RR	1.00	0.87	0.89	0.91	0.97
95% CI		0.62, 1.22	0.65, 1.22	0.68, 1.21	
Tomato sauce					
Cases (<i>n</i>)	197	364	173	78	
Age-adjusted RR	1.00	1.02	0.82	0.81	0.01
Multivariate RR	1.00	1.09	0.87	0.89	0.07
95% CI		0.92, 1.29	0.71, 1.06	0.68, 1.16	
Cantaloupe					
Cases (<i>n</i>)	246	307	164	84	
Age-adjusted RR	1.00	0.83	0.88	0.88	0.24
Multivariate RR	1.00	0.86	0.90	0.87	0.11
95% CI		0.73, 1.01	0.74, 1.09	0.68, 1.11	

¹ Each logistic model included terms for age (5-y categories), time period (2-y intervals), diagnosis of diabetes (yes or no), cigarette smoking (never or 1-44 or >44 pack-years), BMI (quintile), area of US residence (east, central, west, or Texas, California, or Florida), aspirin use (yes or no), energy intake (quintile), physical activity (quintile of metabolic equivalents), alcohol intake (0, 1-4, 5-9, 10-14, 15-29, ≥30 g/d), routine eye exams (yes or no), and profession.

² Values add to less than total number of cases because of missing responses for specific foods.

trend = 0.04) (44). Our RR estimate was similar and the lack of statistical significance may have been due to the smaller number of cases ($n = 840$ for men compared with 1471 for women).

Assessment of nutritional antioxidant status at the time of cataract diagnosis may not be valid unless it can be assumed that current nutritional status reflects past nutritional status. The assessment of diet in this study was made before diagnosis. We were also able to examine the possible relation between intake of foods rich in carotenoids earlier in life and risk of cataract. Recall of diet from high school is reasonably reproducible and may be sufficiently precise to assess the influence of remote diet in epidemiologic studies (45). Spearman correlations between reported vegetable intake in high school and that reported in 1986 ranged between 0.20 and 0.41. We did not find a significant association between intake of broccoli and spinach early in life and decreased risk of cataract. However, when subjects were classified jointly according to their dietary pattern in high school and that reported in 1986, those consuming broccoli and spinach most frequently both early in life and in 1986 tended to have the lowest risk of cataract extraction.

Cigarette smoking is associated with increased lipid peroxidation (46), low plasma antioxidant concentrations (47), and an increased risk of cataract (6, 32–34). Thus, we hypothesized that the association between cataract and carotenoid intake might vary by smoking status. The protective effect of lutein and zeaxanthin appeared somewhat stronger in never smokers, as expected, but interaction terms added to the multivariate models were not significant. We had limited power to test this interaction because only 10% of men were current smokers in 1986. The potential interaction between smoking and risk of cataract requires further evaluation with additional follow-up in this and other cohorts.

Each cataract type has unique biochemical properties and thus may be initiated by different factors (12, 14, 17). We examined the risk of cataract extraction by cataract subtype and found that most associations were similar across types, although those within the highest quintile of lycopene intake had a reduced risk of nuclear cataract ($P = 0.05$). However, Mares-Perlman et al (13, 14) reported an odds ratio of 1.10 (95% CI: 0.71, 1.72) for severe nuclear sclerosis in the highest compared with the lowest quintile for usual daily intake of lycopene. Thus, given the discrepant results from other reports and the small number of cases ($n = 208$) of nuclear-only cataract in our cohort, these findings must be interpreted with caution. Because cataract subtype was not assessed in a standard manner and documentation in medical records may be imperfect, some cases were likely misclassified by specific type. Although these errors are unlikely to be associated with dietary intake, their effect would tend to bias RRs toward the average effect seen with all cases combined, thus making type-specific associations more difficult to detect.

We were unable to assess "incident" cataracts because repeated ophthalmologic examination of this large cohort in a standardized manner would be impossible. Therefore, the procedure of cataract extraction was used to define the occurrence of disease. By restricting the analysis to these cases, we were unlikely to include false-positive cases. Although there were men with cataracts not requiring extraction in our noncase group, underascertainment of cases, if not related to exposure status, would not bias the RR in a cohort study (41). The use of cataract extraction rather than cataract diagnosis as an endpoint decreases the chance for variation in the threshold for diagnosis of disease. Because all participants are health professionals, access to med-

ical care is likely to be more uniform than in the general population. Our results could be biased if men who were more health conscious and likely to consume diets high in carotenoids also tended to have cataracts extracted at either an earlier or later stage. To examine this issue, we assessed the Spearman correlation between each nutrient and visual acuity before surgery in the eye being operated on as an index of disease severity. These correlations were all very small (range: from -0.17 to 0.11). Also, controlling for whether subjects had an eye exam between 1988 and 1990 did not alter the nutrient coefficients in the multivariate models. Men in the highest fifth of intake for each nutrient were just 2–6% more likely to be examined by a doctor in 1988–1990 than were those in the lowest fifth. Therefore, any bias from using cataract extraction as the endpoint is likely to be small and, if anything, it would understate the inverse relation with lutein and zeaxanthin intake.

Data on exposures were collected before diagnosis; thus, any misclassification would be unrelated to risk of cataract and would tend to bias our results toward the null. The high follow-up rate in this cohort (average: 94% biennially), minimizes this as a source of bias.

Our findings strengthen the evidence that dietary carotenoids, and specifically lutein and zeaxanthin, may lower the incidence of cataracts severe enough to require extraction. Although further study of carotenoid intake and cataract is warranted, including a more detailed evaluation by cataract subtype and important risk factors such as smoking, the present findings support recommendations to consume vegetables and fruit high in carotenoids daily (48). 

We are indebted to the participants of the Health Professionals Follow-up Study for their continued cooperation; to Al Wing, Mira Kaufman, Karen Corsano, and Steve Stewart for computer assistance; to Jill Arnold, Betsy Frost-Hawes, Kerry Demers, and Mitzi Wolff for their assistance in the compilation of the data for the manuscript; and to Laura Sampson and Helaine Rockett for maintaining our food-composition tables.

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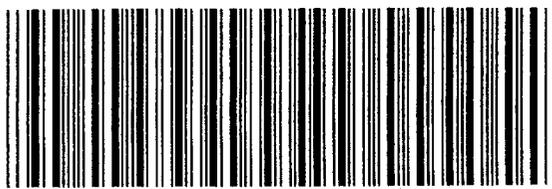
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