Dietary Carotenoids and Risk of Lung Cancer in a Pooled Analysis of Seven Cohort Studies

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Abstract

Intervention trials with supplemental β-carotene have observed either no effect or a harmful effect on lung cancer risk. Because food composition databases for specific carotenoids have only become available recently, epidemiological evidence relating usual dietary levels of these carotenoids with lung cancer risk is limited. We analyzed the association between lung cancer risk and intakes of specific carotenoids using the primary data from seven cohort studies in North America and Europe. Carotenoid intakes were estimated from dietary questionnaires administered at baseline in each study. We calculated study-specific multivariate relative risks (RRs) and combined these using a random-effects model. The multivariate models included smoking history and other potential risk factors. During follow-up of up to 7–16 years across studies, 3,155 incident lung cancer cases were diagnosed among 399,765 participants. β-Carotene intake was not associated with lung cancer risk (pooled multivariate RR = 0.98; 95% confidence interval, 0.87–1.11; highest *versus* lowest quintile). The RRs for α-carotene, lutein/zeaxanthin, and lycopene were also close to unity. β-Cryptoxanthin intake was inversely associated with lung cancer risk (RR = 0.76; 95% confidence interval, 0.67–0.86; highest *versus* lowest quintile). These results did not change after adjustment for intakes of vitamin C (with or without supplements), folate (with or without supplements), and other carotenoids and multivitamin use. The associations generally were similar among never, past, or current smokers and by histological type. Although smoking is the strongest risk factor for lung cancer, greater intake of foods high in β-cryptoxanthin, such as citrus fruit, may modestly lower the risk.

Introduction

Although cigarette smoking is the leading cause of lung cancer, only 15% of smokers are eventually diagnosed with lung cancer (1). This indicates that other factors, such as inherited differences (2), occupational or environmental exposures, or dietary habits (1, 3), may influence the outcome of exposure to chemical carcinogens in tobacco.

Carotenoids are red and yellow fat-soluble pigments found in many fruits and vegetables. The major carotenoids with vitamin A activity in human plasma are α-carotene, β-carotene, and β-cryptoxanthin, whereas the major carotenoids without vitamin A activity are lycopene, lutein, and zeaxanthin (4). Carrots contain high amounts of α-carotene and β-carotene. Broccoli and spinach provide lutein and its isomers whereas tomatoes contain high amounts of lycopene. β-Cryptoxanthin is mainly derived from orange juice, oranges, and tangerines (4–7).

In intervention trials, pharmacological doses of β-carotene supplements provided no protection against lung cancer compared with placebo (8–11). In fact, supplemental β-carotene modestly increased lung cancer risk in heavy smokers (8, 9) and asbestos workers (8). Although β-carotene at usual dietary levels has been inversely associated with lung cancer risk in some epidemiological studies, the current evidence is more consistent for showing a benefit of high consumption of fruits and vegetables (1, 12). Thus, β-carotene may not be among the nutrient(s) responsible for the inverse associations observed between fruit and vegetable consumption and lung cancer but rather may be an indicator of other bioactive components in these foods. As detailed food composition databases for specific carotenoids have become available only recently (5, 7), few studies have examined their associations with lung cancer risk, and their results have been inconsistent (13–22).

To gain a better understanding of how intakes of specific carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene) are related to lung cancer risk, we

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Table 1 Characteristics of the cohort studies included in the pooled analysis of dietary energy-adjusted carotenoids and lung cancer

Study	Follow-up period	Baseline cohort size	Number of cases	Mean (SD) μg/day				
				α-carotene	β-carotene	β-cryptoxanthin	Lutein/Zeaxanthin	Lycopene
α-Tocopherol, β-Carotene Cancer Prevention Study								
Men	1985–1996	6771[a]	298	527 (505)	1758 (1262)	25 (30)	1146 (328)	645 (597)
Canadian National Breast Screening Study								
Women	1980–1993	56837	149	986 (818)	4619 (2939)	79 (58)	3037 (3096)	8891 (8933)
Health Professionals Follow-up Study								
Men	1986–1996	44350	244	980 (1036)	5159 (3591)	88 (103)	3949 (3013)	10844 (7795)
Iowa Women's Health Study								
Women	1986–1996	33828	433	773 (820)	4527 (3147)	74 (71)	2795 (2832)	4180 (4267)
Netherlands Cohort Study								
Women		62412	131	685 (565)	2901 (1501)	206 (172)	2448 (1028)	1303 (1883)
Men	1986–1992	58279	843	687 (527)	2960 (1453)	155 (164)	2550 (1120)	1045 (1544)
New York State Cohort								
Women		21045	130	1144 (854)	6346 (3384)	247 (264)	5998 (3790)	5683 (4100)
Men	1980–1987	27936	392	1171 (865)	6382 (3458)	215 (273)	6025 (3489)	7274 (4764)
Nurses' Health Study (a)								
Women	1980–1986	88307	156	723 (838)	4424 (3629)	104 (92)	5086 (5289)	5255 (5305)
Nurses' Health Study (b)								
Women	1986–1996	68307[b]	379	764 (637)	4273 (2403)	62 (62)	3531 (2553)	9643 (6133)
Total number		399765	3155					

[a] Only the placebo group of the α-Tocopherol, β-Carotene Cancer Prevention Study is included in the lung cancer analyses.
[b] These participants were also included in the Nurses' Health Study (a).

analyzed the primary data from seven large cohort studies carried out in North America and Europe. These studies, taken together, provided a wide range of carotenoid intakes, a relatively large number of cases, and allowed for separate analyses by smoking status and by histological type of lung cancer.

Materials and Methods

The Pooling Project of Prospective Studies of Diet and Cancer (the Pooling Project) has been described previously (23). For the carotenoid and lung cancer analyses, we identified seven cohort studies (Table 1; Refs. 17–20, 24, 25) that met the following predefined criteria: at least 50 incident lung cancer cases, assessment of long-term dietary intake including the specific carotenoids, a validation study of the dietary questionnaire or of a closely related instrument, and assessment of smoking status. The Adventist Health Study (26), the New York University Women's Health Study (27), and Sweden Mammography Cohort (28), all included in the Pooling Project, were thus excluded because they did not assess intakes of the specific carotenoids (26), nor did they assess smoking status at baseline (27, 28).

Outcome Ascertainment Lung cancer cases were ascertained using follow-up questionnaires with subsequent medical record review (17, 19) and/or linkage with a cancer registry (18–20, 24, 25). In addition, some studies used linkage with a death registry or death certificates (17, 19, 20, 29). We categorized lung cancers by histological type based on International Classification of Diseases for Oncology morphology codes (30) or the histological classification provided by the original study investigators.

Both the Netherlands Cohort Study and the New York State Cohort Study included women and men; each study was analyzed as two separate cohorts defined on the basis of sex. To take advantage of the more extensive diet assessment completed in 1986, the cases and person-time accumulated in the Nurses' Health Study were divided into two groups for analysis (1980–1986 and 1986–1996); these cohorts were referred to as the Nurses Health Study (a) and the Nurses Health Study (b), respectively.

Dietary Assessment Food consumption was assessed at baseline using a validated dietary questionnaire developed for each study population (31–37). The number of food items on the questionnaires ranged from 45 (New York State Cohort) to 276 (α-Tocopherol, β-Carotene Cancer Prevention Study). The food data were converted into daily nutrient intakes by the software and food composition database of each cohort study before they were sent to the Department of Nutrition at the Harvard School of Public Health. Nutrients were energy-adjusted according to the residual method (38) by using the predicted intake at 2100 kcal/day in men and at 1600 kcal/day in women. Mean energy intake ranged from 1988 kcal/day (Health Professionals Follow-up Study) to 2804 kcal/day (α-Tocopherol, β-Carotene Cancer Prevention Study) in men and from 1569 kcal/day [Nurses' Health Study (a)] to 2066 kcal/day (Canadian National Breast Screening Study) in women. Lutein intake was combined with zeaxanthin intake because of the difficulty in separating these two carotenoids in laboratory analyses (5, 7).

Few of the validation studies (31, 33–37, 39) for the dietary assessment methods used in these cohorts (or of closely related instruments) examined specific carotenoids. The correlation coefficients between dietary intakes and plasma concentrations varied between 0.21 for lycopene and 0.48 for α-carotene in a sample of women who were nonsmokers in the Nurses' Health Study, and between 0.35 for β-carotene and 0.47 for α-carotene among a sample of men who were nonsmokers in the Health Professionals Follow-up Study (40). The correlation coefficient between a food frequency questionnaire similar to the one used in the Canadian National Breast Screening Study and a seven-day dietary record was 0.60 for β-carotene (37). β-Cryptoxanthin is concentrated in fruits, particularly citrus fruits and fruit juices (4, 7). Because β-cryptoxanthin intake is highly correlated with dietary vitamin C intake (correlation coefficients ranged from 0.52 to 0.77 in

Table 2 Pooled relative risks (95% confidence intervals) of lung cancer for quintiles of dietary carotenoids

Carotenoid	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*		
						Test for trend	Test for between study heterogeneity for quintile 5	Test for between study heterogeneity due to sex for quintile 5
α-Carotene								
Age-adjusted	1.00	0.78 (0.70–0.88)	0.73 (0.65–0.82)	0.70 (0.61–0.80)	0.61 (0.53–0.71)	<0.001	0.15	0.06
Multivariate[a]	1.00	0.91 (0.80–1.05)	0.94 (0.84–1.06)	0.95 (0.84–1.07)	0.93 (0.82–1.06)	0.47	0.39	0.74
β-Carotene								
Age-adjusted	1.00	0.81 (0.70–0.94)	0.77 (0.67–0.90)	0.69 (0.59–0.80)	0.65 (0.58–0.73)	<0.001	0.68	0.73
Multivariate[a]	1.00	0.97 (0.82–1.16)	1.00 (0.84–1.20)	0.94 (0.82–1.08)	0.98 (0.87–1.11)	0.47	0.85	0.47
β-Cryptoxanthin								
Age-adjusted	1.00	0.71 (0.64–0.80)	0.59 (0.51–0.69)	0.56 (0.48–0.64)	0.50 (0.43–0.57)	<0.001	0.27	0.26
Multivariate[a]	1.00	0.90 (0.80–1.00)	0.83 (0.71–0.96)	0.86 (0.76–0.97)	0.76 (0.67–0.86)	<0.001	0.95	0.60
Lutein/Zeaxanthin								
Age-adjusted	1.00	0.86 (0.77–0.96)	0.76 (0.67–0.88)	0.78 (0.69–0.87)	0.74 (0.66–0.83)	0.001	0.57	0.16
Multivariate[a]	1.00	0.98 (0.87–1.10)	0.92 (0.79–1.06)	0.97 (0.86–1.10)	0.91 (0.81–1.03)	0.15	0.81	0.25
Lycopene								
Age-adjusted	1.00	0.78 (0.69–0.87)	0.74 (0.66–0.83)	0.74 (0.66–0.83)	0.77 (0.68–0.88)	0.03	0.25	0.55
Multivariate[a]	1.00	0.86 (0.75–0.97)	0.85 (0.74–0.99)	0.88 (0.77–1.01)	0.91 (0.78–1.07)	0.42	0.11	0.92

[a] Adjusted for education (<high school graduate, high school graduate, and >high school graduate), body mass index (<23, 23 to <25, 25 to <30, and ≥30 kg/m^2), alcohol consumption (0, >0 to <5, 5 to <15, 15 to <30, and ≥30 g/day), energy (continuous), smoking status (current, past, and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), and amount smoked for current smokers (continuous). Because the α-Tocopherol, β-Carotene Cancer Prevention Study only includes current smokers, in this study we adjusted for smoking as smoking duration (continuous) and amount smoked (continuous).

these cohort studies), the validity correlation coefficients for vitamin C may approximate those for β-cryptoxanthin. In the validation studies (31, 33–37, 39), the correlation coefficients comparing the food frequency questionnaires or closely related instruments and multiple days of dietary records or 24 h recalls were between 0.52 and 0.77 for vitamin C. Analyses of fruits and citrus fruits were only included in the validation studies of the α-Tocopherol, β-Carotene Cancer Prevention Study (32), the Netherlands Cohort Study (36), and Health Professionals Follow-up Study (41). The correlation coefficients in these three studies exceeded 0.60 for fruits, citrus fruits, and/or fruit juices.

Statistical Methods After applying the exclusion criteria used by each study, we further excluded participants if they reported energy intakes greater or less than 3 standard deviations from the study specific $\log_e$-transformed mean energy intake, reported a history of cancer (except non-melanoma skin cancer) at baseline, or had unknown information on smoking habits.

Each study was analyzed using the Cox proportional hazards model (42). Person-years of follow-up were calculated from the date the baseline questionnaire was returned to the date of lung cancer diagnosis, date of death, or end of follow-up, whichever came first. Age at baseline in years and the year of the baseline questionnaire were included as stratification variables. The Canadian National Breast Screening Study and the Netherlands Cohort Study were analyzed as case-cohort studies (43) using Epicure software (44). In the other studies, incidence rate ratios were estimated using SAS PROC PHREG (45).

We analyzed associations with specific carotenoids by quintiles of intake. Study-specific quintiles were assigned based on the distributions in the subcohort in the Canadian National Breast Screening Study and the Netherlands Cohort Study and based on the distributions in the baseline cohort for the remaining studies. In further analyses, we defined categories using cutpoints based on identical absolute intakes across studies. Two-sided 95% confidence intervals (CIs) (95% CIs) and *P*s were calculated. To calculate the *P* for the test for trend across categories of intake, participants were assigned the median value of their category, and this variable was entered as a continuous term in the regression model.

RRs were adjusted for education, body mass index, alcohol consumption, smoking habits, and energy intake (see Table 2 for the categories used). We examined several parameterizations of smoking habits including controlling for smoking history as smoking status only, smoking pack-years, a 10-level categorical variable or as smoking status, years smoked as a continuous variable for past and current smokers, and amount smoked among current smokers. Of these, the last model explained more of the variation in risk and is the one reported here. Additional models were also adjusted for intakes of vitamin C, folate, and other carotenoids, and multivitamin use. An indicator variable for missing responses for measured covariates within a study was created, when needed. We had no missing data for any nutrients, and for each covariate, data were missing from <7% of the participants in each study. Because most of the cohorts included in this pooled analysis did not calculate carotenoid intakes in their validation studies, we could not correct our results for measurement error.

We used the random effects model (46) to combine the study-specific $\log_e$ RRs that were weighted by the inverse of their variance. We tested for heterogeneity among studies using the Q statistic (46, 47). We tested for variation in RRs by sex and by smoking status using the meta-regression model of Stram (48). For the analyses stratified by smoking status, identical quartile cutpoints were used for current, past, and never smokers within a cohort. We also tested whether associations differed among adenocarcinomas, small cell carcinomas, and squamous cell carcinomas using a two degree of freedom squared Wald test (49). Collectively, these three histological types represented at least 60% of the cases in each study.

Results

The final pooled data included 3,155 incident lung cancer cases (1,777 male and 1,378 female) diagnosed among 399,765 par-

ticipants who were followed for up to 7–16 years across studies (Table 1). The follow-up rate for these studies generally exceeded 90%. Carotenoid intakes varied across the cohorts (Table 1). The α-Tocopherol, β-Carotene Cancer Prevention Study reported the lowest intakes of each carotenoid, and the New York State Cohort reported the highest intakes with the one exception being that lycopene intake was the highest in the Health Professionals Follow-up Study. Among current smokers, the median Spearman correlation coefficients across studies between intake of each carotenoid and the number of cigarettes smoked per day was −0.09 for α-carotene, −0.09 for β-carotene, −0.14 for β-cryptoxanthin, −0.07 for lutein, and −0.03 for lycopene.

In the age-adjusted analyses, intakes of all five carotenoids were inversely associated with lung cancer risk (*P*, test for trend ≤0.03; Table 2). The pooled RR for the highest compared with the lowest quintile of intake ranged between 0.50 for β-cryptoxanthin and 0.77 for lycopene. The associations were similar after adjustment for education, body mass index, alcohol consumption, and energy intake (data not shown) but were attenuated after additional adjustment for smoking status (as never *versus* past *versus* current smokers) and duration of smoking and amount smoked as continuous variables. Only the inverse association between β-cryptoxanthin intake and lung cancer risk remained monotonic and statistically significant (pooled RR = 0.76; 95% CI, 0.67–0.86; for comparison of the highest *versus* lowest quintile). Study-specific RRs for the highest *versus* lowest quintile of β-cryptoxanthin intake were statistically significantly inverse in the Nurses' Health Study (b) and among men in the New York State Cohort. The RR for the highest quintile was greater than unity only in the Nurses' Health Study (a) (RR = 1.09; 95% CI, 0.68–1.75). None of the associations was significantly modified by sex in the multivariate analyses (Table 2). In further analyses, lycopene intake also was not associated with lung cancer risk when the studies [α-Tocopherol, β-Carotene Cancer Prevention Study, Canadian National Breast Screening Study, Netherlands Cohort Study, and Nurses' Health Study (a)] not including tomato sauce consumption in their food frequency questionnaires were excluded (data not shown). When cases diagnosed during the first two or four years of follow-up were excluded from the analyses, the result for each carotenoid was unchanged (data not shown). The pooled RR for the highest *versus* lowest quintile of β-cryptoxanthin intake was 0.79 (95% CI, 0.66–0.95) among cases younger than 65 years (n = 1411), and 0.75 (95% CI, 0.63–0.90) among cases 65 years and older (n = 1743); the Nurses' Health Study (a) was excluded from the latter stratum because only one case was at least 65 years of age at diagnosis.

Because certain foods (*e.g.,* carrots, kale, spinach) are good sources of several carotenoids (5, 7), intakes of some carotenoids were highly correlated. For example, Spearman correlation coefficients between α-carotene and β-carotene intakes ranged from 0.66 to 0.98 across studies. However, correlation coefficients between β-cryptoxanthin and the other carotenoids were <0.4. To determine the independent association of each carotenoid with lung cancer risk, all five carotenoids were simultaneously entered in the analyses. Again, the intake of β-cryptoxanthin was inversely associated with lung cancer risk (pooled RR = 0.77; 95% CI, 0.68–0.88; for comparison of the highest *versus* lowest quintile), whereas intakes of α-carotene, β-carotene, lutein/zeaxanthin, and lycopene were not.

Additional adjustment for vitamin C intake (with or without supplemental intakes), folate intake (with or without supplemental intakes), or multivitamin use did not change appreciably the estimates observed in the multivariate analyses for any of the carotenoids. For example, the pooled RRs of lung cancer for participants in the highest compared with the lowest quintile of β-cryptoxanthin intake were 0.80 (95% CI, 0.69–0.93) after adjustment for dietary vitamin C, 0.75 (95% CI, 0.65–0.86) after adjustment for dietary and supplemental vitamin C intake, 0.77 (95% CI, 0.67–0.88) after adjustment for dietary and supplemental folate intake, and 0.76 (95% CI, 0.67–0.86) after adjustment for multivitamin use.

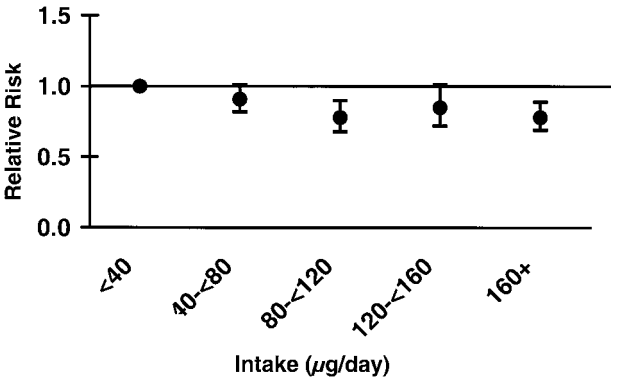

Fig. 1. Pooled multivariate relative risks and 95% confidence intervals for lung cancer by categories of β-cryptoxanthin intake. Relative risks were adjusted for the same covarietes listed in Table 2. For context, an orange contains about 160 μg of β-cryptoxanthin (Ref. 7).

We further analyzed the association between β-cryptoxanthin intake and lung cancer risk using identical categories defined by absolute intake cutpoints across studies. Compared with β-cryptoxanthin intakes <40 μg/day (the amount of β-cryptoxanthin in approximately one-fourth of an orange; Ref. 7), the pooled multivariate RRs of lung cancer were 0.91, 0.78, 0.85, and 0.78 (95% CI, 0.69–0.89; *P*, test for trend <0.001) for β-cryptoxanthin intakes of 40 to <80 μg, 80 to <120 μg, 120 to <160 μg, and ≥160 μg a day, respectively (Fig. 1). Study-specific RRs for β-cryptoxanthin were statistically significant among men in the Netherlands Cohort Study (Fig. 2). The RR for the ≥160 μg/day category was greater than unity only in the Nurses' Health Study (a) (RR = 1.02; 95% CI, 0.65–1.61).

We examined associations between carotenoid intakes and lung cancer risk separately among current (number of lung cancer cases = 1915), past (cases = 981), and never smokers (cases = 259; Table 3). The α-Tocopherol, β-Carotene Cancer Prevention Study was excluded in the analyses of past and never smokers because this cohort included only current smokers. There were no statistically significant differences in the RRs for the highest quartile for any of the carotenoids. However, there was a significant difference among the three smoking strata for the test for trend for β-cryptoxanthin intake (*P*, test for between-study heterogeneity due to smoking status = 0.01). A significant trend for β-cryptoxanthin intake was observed only among current smokers. Among never smokers, there was significant between-study heterogeneity in the RRs for the highest quartile of β-cryptoxanthin intake (P = 0.02); study-specific RRs comparing the highest *versus* lowest quartile ranged from 0.24 (95% CI, 0.06–0.99) among men in the New York State Cohort to 3.74 (95% CI, 0.99–14.1) among women in the Netherlands Cohort Study. There was a suggestion that β-cryptoxanthin intake was inversely associated with the risk of lung cancer among male never smokers (RR = 0.46; 95% CI, 0.22–0.95 comparing the highest *versus* lowest quartile) but not female never smokers (RR = 1.05; 95% CI, 0.48–2.31; *P* for

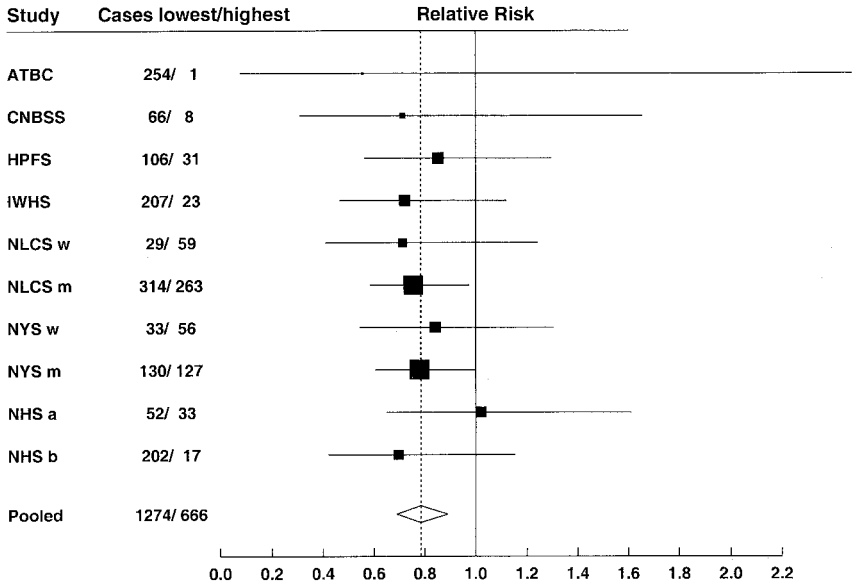

Fig. 2. Study-specific and pooled multivariate-adjusted relative risks (RRs) and (95% confidence intervals) of lung cancer between the highest (≥160 μg/day) and lowest (<40 μg/day) absolute intake cutpoint categories for β-cryptoxanthin intake. For context, an orange contains about 160 μg of β-cryptoxanthin; Reference 7. RRs were adjusted for the same covariates listed in Table 2. The *black squares* and *horizontal lines* correspond to the study-specific RRs and 95% confidence intervals, respectively, for the comparison of the highest to lowest categories of β-cryptoxanthin intake. The area of the *black squares* reflects the study-specific weight (inverse of the variance). The *diamond* represents the pooled RR and 95% confidence interval. The *vertical dash line* represents the pooled RR. *ATBC*, α-Tocopherol, β-Carotene Cancer Prevention study; *CNBSS*, Canadian National Breast Screening Study; *HPFS*, Health Professionals Follow-up Study; *IWHS*, Iowa Women's Health Study; *NLCS w*, Netherlands Cohort Study-women; *NLCS m*, Netherlands Cohort Study-men; *NYS w*, New York State Cohort-women; *NYS m*, New York State Cohort-men; *NHS a*, Nurses' Health Study (a); and *NHS b*, Nurses' Health Study (b).

between-study heterogeneity due to sex = 0.12). High lycopene intake was marginally associated with a lower risk of lung cancer in current smokers (*P*, test for trend = 0.06).

For each carotenoid, there were no statistically significant differences in the associations for adenocarcinomas (number of lung cancer cases = 956), small cell carcinomas (cases = 538), and squamous cell carcinomas (cases = 901; Table 4). The women in the New York State Cohort were excluded from the analyses of small cell carcinomas because there were only 14 such carcinomas in this study. The association between β-cryptoxanthin intake and lung cancer risk was significantly inverse for all histological types. No associations between intakes of the other carotenoids and lung cancer risk by histological types were found.

Table 3 Pooled multivariate relative risks (95% confidence intervals) of lung cancer for quartiles of dietary carotenoids by smoking status[a]

Carotenoid	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*		
					Test for trend	Test for between study heterogeneity for quartile 4	Test for between study heterogeneity due to smoking status for quartile 4
α-Carotene							
Current smokers[b,c]	1.00	0.99 (0.87–1.13)	1.08 (0.94–1.23)	0.99 (0.85–1.15)	0.97	0.45	
Past smokers[b,d,e]	1.00	0.90 (0.74–1.11)	0.96 (0.78–1.19)	0.94 (0.72–1.23)	0.44	0.15	
Never smokers[b,e]	1.00	0.77 (0.52–1.13)	0.95 (0.66–1.36)	0.92 (0.64–1.33)	0.82	0.47	0.88
β-Carotene							
Current smokers[b,c]	1.00	1.01 (0.85–1.20)	0.98 (0.85–1.13)	0.98 (0.84–1.14)	0.62	0.89	
Past smokers[b,d,e]	1.00	0.88 (0.71–1.07)	0.86 (0.70–1.05)	1.06 (0.86–1.32)	0.61	0.35	
Never smokers[b,e]	1.00	1.11 (0.76–1.62)	0.98 (0.67–1.44)	1.02 (0.70–1.47)	0.73	0.80	0.83
β-Cryptoxanthin							
Current smokers[b,c]	1.00	0.84 (0.74–0.96)	0.87 (0.75–1.01)	0.70 (0.60–0.81)	<0.001	0.47	
Past smokers[b,d,e]	1.00	0.80 (0.64–1.00)	0.93 (0.73–1.18)	0.84 (0.69–1.03)	0.43	0.45	
Never smokers[b,e]	1.00	0.74 (0.43–1.28)	0.79 (0.45–1.37)	0.77 (0.42–1.42)	0.80	0.02	0.30
Lutein/zeaxanthin							
Current smokers[b,c]	1.00	1.00 (0.87–1.15)	0.95 (0.83–1.09)	0.91 (0.79–1.05)	0.08	0.92	
Past smokers[b,d,e]	1.00	1.05 (0.80–1.38)	0.99 (0.78–1.27)	1.03 (0.84–1.26)	0.69	0.51	
Never smokers[b,e]	1.00	0.87 (0.60–1.28)	0.94 (0.66–1.35)	0.88 (0.61–1.26)	0.75	0.82	0.52
Lycopene							
Current smokers[b,c]	1.00	0.79 (0.68–0.93)	0.85 (0.74–0.98)	0.81 (0.70–0.94)	0.06	0.65	
Past smokers[b,d,e]	1.00	0.89 (0.68–1.15)	0.82 (0.65–1.05)	1.05 (0.86–1.27)	0.76	0.42	
Never smokers[b,e]	1.00	0.80 (0.55–1.17)	0.90 (0.63–1.29)	0.86 (0.60–1.23)	0.29	0.68	0.11

[a] Number of lung cancer cases were as follows: 1915 current smokers, 981 past smokers, and 259 never smokers.
[b] Adjusted for education (<high school graduate, high school graduate, and >high school graduate), body mass index (<23, 23 to <25, 25 to <30, and ≥30 kg/m^2), alcohol consumption (0, >0 to <5, 5 to <15, 15 to <30, and ≥30 g/day), energy (continuous).
[c] Also adjusted for smoking duration (continuous) and amount smoked (continuous).
[d] Also adjusted for smoking duration (continuous).
[e] The α-Tocopherol, β-Carotene Cancer Prevention Study was excluded because the cohort included only current smokers.

Table 4 Pooled multivariate relative risks[a] (95% confidence intervals) of lung cancer for quartiles of dietary carotenoids by cell type[b]

Carotenoid	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*		
					Test for trend	Test for between study heterogeneity for quartile 4	Test for common effects by cell type for quartile 4[c]
α-Carotene							
Adenocarcinomas	1.00	0.96 (0.82–1.12)	1.14 (0.93–1.38)	0.99 (0.84–1.17)	0.96	0.40	
Small cell carcinomas[c]	1.00	0.91 (0.76–1.10)	1.08 (0.86–1.35)	1.07 (0.88–1.29)	0.53	0.68	
Squamous cell carcinomas	1.00	0.83 (0.70–0.98)	0.97 (0.82–1.15)	0.97 (0.80–1.16)	0.86	0.40	0.73
β-Carotene							
Adenocarcinomas	1.00	0.98 (0.78–1.25)	1.03 (0.88–1.20)	1.04 (0.85–1.27)	0.84	0.19	
Small cell carcinomas[c]	1.00	1.13 (0.85–1.51)	1.03 (0.83–1.27)	1.18 (0.97–1.43)	0.21	0.85	
Squamous cell carcinomas	1.00	0.88 (0.73–1.07)	0.96 (0.81–1.14)	1.06 (0.89–1.27)	0.50	0.78	0.66
β-Cryptoxanthin							
Adenocarcinomas	1.00	0.79 (0.68–0.92)	0.86 (0.72–1.03)	0.80 (0.68–0.93)	0.01	0.77	
Small cell carcinomas[c]	1.00	0.84 (0.69–1.02)	0.74 (0.62–0.90)	0.66 (0.51–0.87)	0.02	0.19	
Squamous cell carcinomas	1.00	0.71 (0.60–0.84)	0.76 (0.64–0.90)	0.67 (0.56–0.80)	<0.001	0.94	0.24
Lutein/zeaxanthin							
Adenocarcinomas	1.00	0.97 (0.78–1.21)	0.99 (0.82–1.19)	0.86 (0.73–1.02)	0.10	0.39	
Small cell carcinomas[c]	1.00	0.96 (0.79–1.15)	1.00 (0.77–1.31)	1.02 (0.85–1.23)	0.71	0.51	
Squamous cell carcinomas	1.00	0.94 (0.77–1.15)	0.92 (0.78–1.10)	1.01 (0.85–1.19)	0.96	0.89	0.41
Lycopene							
Adenocarcinomas	1.00	0.86 (0.73–1.01)	0.98 (0.83–1.14)	0.93 (0.79–1.09)	0.64	0.96	
Small cell carcinomas[c]	1.00	0.78 (0.65–0.94)	0.89 (0.74–1.07)	0.95 (0.79–1.14)	0.98	0.96	
Squamous cell carcinomas	1.00	0.74 (0.62–0.87)	0.80 (0.67–0.95)	0.86 (0.72–1.02)	0.11	0.95	0.64

[a] Adjusted for education (<high school graduate, high school graduate, and >high school graduate), body mass index (<23, 23 to <25, 25 to <30, and ≥30 kg/m^2), alcohol consumption (0, >0 to <5, 5 to <15, 15 to <30, and ≥30 g/day), energy (continuous), smoking status (current, past and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), and amount smoked for current smokers (continuous). Because the α-Tocopherol, β-Carotene Cancer Prevention Study only includes current smokers, in this study we adjusted for smoking as smoking duration (continuous) and amount smoked (continuous).
[b] Number of lung cancer cases were as follows: 956 adenocarcinomas, 538 small cell carcinomas, and 901 squamous cell carcinomas.
[c] The women in the New York State Cohort were excluded because of too few cases with small cell carcinoma.

Discussion

In this pooled analysis of seven cohort studies with a total of 3,155 cases, intakes of α-carotene, β-carotene, lutein/zeaxanthin, and lycopene were not associated with lung cancer risk. These results do not support some previous suggestions that high carotenoid intakes are more effective for men than women, for current smokers compared with past or never smokers, or for a specific histological type of lung cancer. Intake of β-cryptoxanthin, however, was inversely associated with lung cancer risk in categorical analyses using either study-specific quintiles or identical absolute intake cutpoints. Although there are potentially different sources of misclassification for these two types of analyses, the pooled multivariate risk of lung cancer was 22–24% lower in the highest compared with the lowest category of β-cryptoxanthin intake in each analysis. Because lung cancer is often diagnosed at a late stage (3), dietary behavior may be altered in individuals with undiagnosed lung cancer. Our results, however, did not change when cases diagnosed during the first 2 or 4 years of follow-up were excluded from the analyses. Results were also similar after excluding cases who died within a year of their diagnosis. Furthermore, the results did not change when only the cases ≥65 years of age were examined separately.

A comprehensive review by the IARC concluded that the evidence suggests a lack of cancer preventive activity for supplemental β-carotene at high doses (50). However, the evidence relating usual dietary levels of β-carotene or other carotenoids to the risk of lung cancer was judged to be too limited to be conclusive. Eleven studies (13–22) have examined the association between the intakes of specific carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, and lycopene) and lung cancer risk. An analysis from one cohort study included in this pooled analysis concluded that folate, vitamin C, and β-cryptoxanthin intakes might be better protective factors against lung cancer than α-carotene, β-carotene, lutein/zeaxanthin, and lycopene intake (18). Two large United States cohorts also included in this pooled analysis reported a significantly lower risk of lung cancer with higher intakes of α-carotene and lycopene but not with the other carotenoids (17). The α-Tocopherol, β-Carotene Cancer Prevention Study from Finland (the placebo group was included in this pooled analyses) showed an inverse association between β-cryptoxanthin, lycopene, and lutein/zeaxanthin intakes and lung cancer risk (19). Another cohort study of Finnish men suggested that dietary α-carotene may be more protective against lung cancer than the other four carotenoids (16). Three case-control studies in the United States (13, 14, 22) found inverse associations with lung cancer for dietary α-carotene and β-carotene; an inverse association was observed for lutein in two of the studies (13, 14) and cryptoxanthin in the other study (22). The Canadian National Breast Screening Study (included in this analysis; Ref. 20) and a small case-control study (15) found no associations between intakes of any of the specific carotenoids and lung cancer risk. A recent case-control study in the United States showed a significantly lower risk of lung cancer for dietary β-carotene, β-cryptoxanthin, lutein and zeaxanthin, and total carotenoids; however, after adjustment for total vegetable consumption, the risks for the specific carotenoids were attenuated and no longer statistically significant (21).

In addition to the studies examining intakes of specific carotenoids, two nested case-control studies have shown that plasma α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin were each inversely associated with lung cancer risk in analyses that did not control for smoking (51, 52). One of these studies also presented findings after adjustment for smoking, after which only β-cryptoxanthin continued to be inversely

associated with lung cancer risk (51). In a nested case-control study of Chinese tin miners, serum β-cryptoxanthin and β-carotene were each positively associated with lung cancer risk after adjustment for tobacco use and radon exposure (53).

There is some evidence, albeit limited, relating β-cryptoxanthin intake and the risk of cancers other than lung cancer. Borderline or statistically significant inverse associations have been found more often for cancer sites related to smoking (aerodigestive, esophageal, or cervical cancer; Refs. 54–57) than for bladder cancer (58) or hormonally related cancers (breast or prostate cancer; Refs. 59–61).

The majority of epidemiological studies of vegetable and fruit consumption and lung cancer risk have shown an inverse relation (1). However, the specific types of vegetables or fruits as well as the substances that may be responsible for these associations have remained unclear. We previously found in the Pooling Project a nonsignificant 12% reduction in lung cancer risk with high vegetable consumption and a statistically significant 23% reduction in lung cancer risk with high fruit consumption (62). Among the specific groups of fruits and vegetables examined, inverse associations were observed for apples and pears, for oranges and tangerines, and for orange juice and grapefruit juice. The inverse association we observed for β-cryptoxanthin complements the finding for fruits because β-cryptoxanthin is mainly derived from oranges, orange juice, and tangerines (4, 7).

Our study had several strengths. We specified *a priori* that we would only include prospective studies that used a validated food frequency questionnaire to estimate dietary intake. These inclusion criteria minimized sources of variation because of study design or study quality. Most of the results in our analyses were consistent across studies, and the test for between-study heterogeneity was not statistically significant ($P > 0.05$). We included only prospective studies because they are less vulnerable to selection and recall biases that may affect case-control studies of diet-disease associations. We analyzed the primary data from these studies rather than conducting a meta-analysis of the published literature. As a result, we were able to create identical categories for carotenoid intakes and covariates across studies, which removes potential sources of heterogeneity that may occur in a meta-analysis of the published literature.

Our study also had some limitations. Because the association between smoking and lung cancer is very strong and because dietary habits differ between smokers and non-smokers (1), it is difficult to ensure that all of the potential confounding by smoking habits has been removed in analyses of dietary factors in relation to lung cancer risk (63–65). We found in our study that controlling for smoking status, the number of years smoked, and the number of cigarettes smoked per day provided the strongest control of confounding compared with other parameterizations of smoking history. However, the most remarkable changes in risks occurred when smoking status was added to the models. Additional factors that influence lung cancer risk, such as passive smoking, inhalation patterns, time since quitting or intensity of smoking among former smokers, the type of cigarettes smoked, and pipe and cigar smoking habits, were not generally measured in these cohorts and thus could not be controlled for in our analysis.

Stram *et al.* (65) has suggested that differential bias in the assessment of smoking exposure (usually self-reported) between smokers with low β-carotene intake compared with high intake may explain much of the observed protective effects of high β-carotene intakes in observational studies. Because in our study the correlation coefficients between intakes of the specific carotenoids and the number of cigarettes smoked per day among current smokers ranged from −0.03 for lycopene to −0.14 for β-cryptoxanthin, we cannot exclude some degree of residual confounding by smoking. But we also observed an inverse association for β-cryptoxanthin among never smokers, which suggests that the association may not only be because of confounding by smoking.

Another limitation of our study concerns the assessment of the intake of the specific carotenoids. We only had a one-time measure of carotenoid intakes at baseline and were not able to investigate carotenoid intakes at younger ages or changes in carotenoid intakes during follow-up. Furthermore, correlation coefficients between estimated carotenoid intakes and blood carotenoid concentrations have usually ranged between 0.2 and 0.5, being the highest for β-cryptoxanthin ($r = 0.4–0.5$) and the lowest for lycopene ($r < 0.3$) and lutein ($r < 0.4$; Refs. 40, 66–70). These modest correlations may be explained by errors in intake estimates due to the dietary questionnaires and nutritional databases (51) or by variation among individuals in carotenoid bioavailability (40). Furthermore, a single blood carotenoid measure does not perfectly reflect long-term intake (71). A human experimental trial, however, found that plasma α-carotene, β-carotene, β-cryptoxanthin, lutein, and lycopene responded well to moderate alterations in diet within a short time, although the magnitude of the response may be related to the baseline carotenoid concentration (72).

The bioavailability of carotenoids can vary substantially depending on the cooking method or the presence of other nutrients (73, 74). It is especially difficult to assess the effect of lycopene because many food questionnaires do not include all relevant foods in this respect. Previous studies have shown that lycopene is more bioavailable in cooked than in raw products (73). In our data, four of the cohort studies did not ask about tomato sauce consumption in their food frequency questionnaires. However, no association was found between high intake of lycopene and lung cancer risk regardless of whether these four studies were included in the analysis. Furthermore, because fruits and vegetables contain many compounds that may decrease cancer risk (75), we also adjusted for vitamin C, folate, and other carotenoid intakes and for multivitamin use in the analyses of each carotenoid. Although the associations between specific carotenoids and lung cancer risk did not change substantially, it is possible that other substances in fruits and vegetables, particularly citrus fruit, are primarily responsible for the inverse associations observed for β-cryptoxanthin.

The findings from this combined analysis of several large prospective studies do not support any benefit of higher intake of β-carotene from dietary sources in the prevention of lung cancer, nor do they suggest that higher β-carotene intake in the context of normal diets increases lung cancer risk, as was observed in two of the trials of β-carotene supplements (8, 9). Our results also suggest that high β-cryptoxanthin intake may decrease the risk of lung cancer, but whether β-cryptoxanthin or other bioactive compounds present in fruits are responsible for this association is unclear and deserves further evaluation. In addition, because smoking is the main cause of lung cancer, we cannot rule out the possibility that our results are attributable to residual confounding by smoking. The most effective actions against lung cancer continue to be smoking prevention and cessation.

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