

# Intake of Specific Carotenoids and Lung Cancer Risk<sup>1</sup>

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## Abstract

Using newly available food composition data for carotenoids, the authors reanalyzed a population-based case-control study of diet and lung cancer conducted in Hawaii in 1983–1985 (L. Le Marchand *et al.*, *J. Natl. Cancer Inst.*, 81: 1158–1164, 1989). The analysis included interviews with 230 men and 102 women with lung cancer and 597 men and 268 women as controls, frequency-matched to the patients by age and sex. A previously validated quantitative diet history assessed the usual intake of foods rich in carotenoids. After adjusting for smoking and other covariates, no association was found with lung cancer risk for dietary lycopene or  $\beta$ -cryptoxanthin intake, whereas dose-dependent inverse associations of comparable magnitude were found for dietary  $\beta$ -carotene,  $\alpha$ -carotene, and lutein. When subjects were cross-classified by their joint intakes of the latter three carotenoids, those who had a high intake (> median) for all three had the lowest risk for lung cancer. In a similar two-way interaction analysis, the previously reported inverse association of lung cancer with vegetable consumption in these data was found to be stronger than that with intake of these three carotenoids. Consistent with our previous findings, this analysis provides further evidence for a protective effect of certain carotenoids against lung cancer and for the greater protection afforded by consuming a variety of vegetables compared to only foods rich in a particular carotenoid.

## Introduction

Experimental studies have suggested that many fruit and vegetable constituents are capable of inhibiting carcinogenesis (1, 2). However, the epidemiological confirmation of these protective effects has been hindered by a paucity of food composition data on these constituents.

Attention has been particularly focused on the carotenoids because of their strong antioxidant activity (3). Until recently, only  $\beta$ -carotene had been examined in dietary epidemiological studies, most often using an index based on "vitamin A" intake from plant sources. These studies have been very consistent in suggesting a protective effect for  $\beta$ -carotene intake, especially against epithelial cancers of the respiratory tract (2, 4). Studies measuring serum  $\beta$ -carotene levels have also been supportive (2, 4). Although other carotenoids are found in the diet and serum of western populations at levels similar to those of  $\beta$ -carotene (5), they have rarely been studied in relation to cancer risk.

Recently, in a case-control study of lung cancer in Hawaii, we observed a negative association with risk for several vegetables rich in specific carotenoids (some of which contain little  $\beta$ -carotene) similar to that found for an index of  $\beta$ -carotene intake (6). Thus, the data were suggestive of a protective effect against lung cancer for carotenoids other than  $\beta$ -carotene. We also found an inverse association with total intake of vegetables which was stronger than that for  $\beta$ -carotene or particular carotenoid-rich food groups, suggesting that different constituents of vegetables may interact additively (or synergistically) to protect against lung cancer (6). In these data, we also found no association with vitamin C, fiber, or fruits.

Since the publication of this report, food composition values have become available for the main carotenoids. We have now reexamined our data using these new carotenoid values to more directly assess the associations of dietary  $\beta$ -carotene,  $\alpha$ -carotene, lutein, lycopene, and  $\beta$ -cryptoxanthin with lung cancer.

## Materials and Methods

The methodology of the study has been described previously (6). Briefly, the cases were identified through the rapid reporting system of the Hawaii Tumor Registry, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. All histologically confirmed primary lung cancers diagnosed between March 1, 1983 and September 30, 1985 among Oahu residents of the five main ethnic groups in Hawaii were eligible for the study. Two population-based controls were frequency-matched to each case by sex and 5-year age group. For patients over the age of 65, controls were randomly selected from a 10% sample of all Oahu residents registered with the Health Care Financing Administration. For younger cases, a random-digit dialing technique was used to select controls in the first 17 months of the study. After July 1984, we used a more cost-efficient approach by which controls were selected among the participants in an ongoing health survey conducted by the Hawaii State Department of Health on a 2% annual random sample of the state's households.

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The participation rate in this study was 67% for cases and 70% for controls. Most interviews were conducted at home. In addition to information on smoking and use of vitamin supplements, the questionnaire included a diet history assessing frequencies and amounts consumed for over 130 food items or categories during the year before symptoms for cases and a corresponding time period for controls. The foods were chosen to include all of the major contributors to the intake of carotenoids, retinol, vitamin C, cholesterol, and total fat in our population. Colored photographs of foods showing three common portion sizes were used to help the subjects quantify their intake. We have recently demonstrated that this diet history method provides reasonably accurate estimates of the usual dietary intake of  $\beta$ -carotene, and presumably of other carotenoids, in our population (7). In this validation study, a correlation of 0.6 was found between  $\beta$ -carotene intake computed from four 1-week food records collected over a year and intake from the diet history.

Intake of specific carotenoids from fruits and vegetables was computed using food composition data from the Nutrient Composition Laboratory of the U.S. Department of Agriculture (8). Mangels *et al.* (8) systematically reviewed analytical data for levels of five carotenoids in fruits and vegetables ( $\beta$ -carotene,  $\alpha$ -carotene, lutein plus zeaxanthin, lycopene, and  $\beta$ -cryptoxanthin) in over 100 published papers (1971–1990) where a chromatographic analytical procedure was used. Data for each carotenoid were evaluated with regard to five general methodological areas: analytical method; analytical quality control; number of samples; sample handling; and sampling plan. Specific criteria were developed for each area, and data were included in the compilation when they met the minimum criteria for the analytical method and for two other areas.

In compiling carotenoid data for fruits and vegetables, similar foods were grouped into preliminary aggregates. For example, the aggregate "squash, winter, cooked, canned, frozen" included microwaved fresh acorn squash, frozen cooked butternut squash, and unspecified canned winter squash. For similar forms of a single food, all acceptable data were grouped together under the general food description. If the carotenoid data were widely divergent and clearly stratified by distinct forms of the food, then the food items were separated into two or more new aggregates. For example, pink grapefruit appeared to contain higher levels of lycopene and  $\beta$ -carotene than white grapefruit. Therefore, pink grapefruit and white grapefruit were listed separately. However, if the acceptable data for a single food were highly variable with no logical pattern of variance, the data were retained under a single description. For example, cooked and raw forms of a food were often aggregated together since insufficient data existed to support their separation. Similarly, data were not available to evaluate such factors as season, geographic location, and harvest condition.

The median content of each carotenoid was calculated for each aggregate of fruits or vegetables and utilized in the calculation of intake of specific carotenoids. We also utilized nutrient composition data for cereals and animal products from other sources (9–13). An index of total carotenoid intake was computed as the sum of

intakes of the five specific carotenoids listed above, since these carotenoids are the predominant ones in foods.

As in our previous report (6), this analysis excluded 61 subjects because of missing smoking variables, as well as 28 patients and 86 controls who smoked pipes or cigars (in order to simplify the statistical adjustment for smoking). Thus, 332 lung cancer cases and 865 controls were used in the analysis. Unconditional logistic regression models (14) were used to compute odds ratios and 95% confidence intervals for quartiles of intake of carotenoids. Adjustment for smoking was best accomplished in these data by including an indicator variable for smoking status (never-, ever-smoked) and a continuous term for pack-years. Other methods of smoking adjustment (e.g., treating pack-years as a categorical variable, replacing pack-years by duration and intensity, adding age started or calendar year started as a covariate) did not provide a better fit (6). All odds ratios were also adjusted for age (as a continuous variable) and ethnicity (using indicator variables). Cholesterol intake was an additional covariate in models that included males since cholesterol intake was associated with lung cancer risk in this sex (15).

The risk estimates presented here are directly comparable to those published in our previous report (6), since the same covariates were used in the regression analyses. Terms for interaction between specific carotenoids or between carotenoids and vegetable intake were successively added to a model with the covariate and relevant main effect terms. The log-likelihood ratio test was used to test the statistical significance of modeled interaction effects. Linear trends in the logit of risk were tested by fitting a term taking the median values of each quartile of intake. Spearman correlation coefficients ( $r_s$ ) were used to investigate collinearity among covariates.

## Results

A correlation of 0.9 was found between  $\beta$ -carotene intake computed with the new food composition values and the index of  $\beta$ -carotene intake based on vitamin A activity used in our previous analysis of these data (6). Hence, this supports the validity of the findings that we published for lung cancer and  $\beta$ -carotene, either as exposure variable or confounder (6).

Table 1 presents the covariate-adjusted odds ratios for lung cancer by decreasing intake of specific carotenoids. Interquartile ranges (25th–75th percentile) for daily intake of specific carotenoids are also given for comparison with other populations. Strong inverse associations with lung cancer risk were found for  $\beta$ -carotene,  $\alpha$ -carotene, and lutein in both sexes. Intake of lycopene and  $\beta$ -cryptoxanthin was not associated with lung cancer risk in either sex.

To examine the correlations among intakes of these carotenoids, we computed Spearman correlation coefficients based on all subjects (Table 2). Strong correlations were found among  $\beta$ -carotene,  $\alpha$ -carotene, and lutein intakes, reflecting important food sources in common for these carotenoids. More unexpected was the relatively high correlation between intakes of lycopene and  $\beta$ -carotene ( $r_s = 0.5$ ), since the main food sources for these nutrients differ. The high correlation found between  $\beta$ -cryptoxanthin and vitamin C was due to the high intake of papaya in our population, a food which is rich in both of these nutrients.

Table 1 Odds ratios<sup>a</sup> for lung cancer by decreasing quartile of carotenoid intake and sex, Hawaii, 1983–1985

Carotenoid <sup>b</sup>	Males (230 cases, 597 controls)					Females (102 cases, 268 controls)				
	Q <sub>4</sub> (high)	Q <sub>3</sub>	Q <sub>2</sub>	Q <sub>1</sub> (low)	P for trend <sup>c</sup>	Q <sub>4</sub> (high)	Q <sub>3</sub>	Q <sub>2</sub>	Q <sub>1</sub> (low)	P for trend <sup>c</sup>
	β-Carotene	1.0	1.8	2.5	2.1	0.001	1.0	2.1	2.2	3.8
α-Carotene	1.0	2.2	2.1	2.3	0.001	1.0	1.7	2.4	2.2	0.02
Lutein	1.0	1.5	1.5	1.8	0.04	1.0	0.9	2.3	3.6	0.002
Lycopene	1.0	1.4	1.6	1.5	0.07	1.0	0.6	0.7	1.3	0.83
β-Cryptoxanthin	1.0	1.3	0.9	1.1	0.81	1.0	1.1	0.9	1.1	0.99

<sup>a</sup> Adjusted for age, ethnicity, smoking status, pack-years of cigarette smoking, and cholesterol intake (for males only).

<sup>b</sup> The interquartile ranges (25th–75th percentile) for daily carotenoid intakes (in μg) were as follows: β-carotene, males, 1650–4000, females, 1700–4400; α-carotene, males, 110–600, females, 200–700; lutein, males, 1300–3300, females, 1300–3300; lycopene, males, 1000–4200, females, 900–3600; β-cryptoxanthin, males, 90–650, females, 130–570.

<sup>c</sup> Test of significance for trend variable assigned the median value of the quartile.

Next, we attempted to determine whether the associations observed with β-carotene, α-carotene, and lutein were independent of each other. Since the intakes of these carotenoids were highly correlated, we cross-classified the subjects on their joint intakes, based on the median values of these variables, and constructed a three-way interaction logistic model using indicator variables. In order to increase power, the analysis was conducted in the two sexes combined. This was appropriate since similar associations were found for each sex in Table 1. Table 3 displays the lung cancer odds ratio for each category of intake, relative to subjects who had intakes above the median for β-carotene, α-carotene, and lutein. The *P* value for three-way interaction was 0.004 compared with a main effects model. Subjects who had a high intake of all three carotenoids had the lowest risk of lung cancer. No clear pattern of interaction was discernible, with the exception of a stronger effect for β-carotene than for α-carotene or lutein. Two-way interactions were also explored among these three carotenoids, but none of the interactions tested approached statistical significance.

In our previous analysis of these data, total intake of vegetables showed a protective effect that was stronger than that of β-carotene or of any carotenoid-rich food (6). Hence, we examined the independent association of total carotenoid intake in relation to that with total vegetable intake. Since these two variables were highly correlated ( $r_s = 0.8$ ), we cross-classified the subjects in a 2 × 2 table, based on the median intake values for these variables. (Our sample size did not permit a categorization by tertile.) Table 4 shows that the inverse association

with lung cancer was indeed stronger for an index of total vegetable consumption than for a variable summarizing the intake of the three carotenoids (β-carotene, α-carotene, lutein) found associated with risk. However, there was no interaction between these two variables ( $P = 0.11$ ). Similar results were obtained with a summary variable which included intake of all five carotenoids.

In Table 4, the odds ratio (1.5) and its 95% confidence interval (0.9–2.7) associated with low carotenoid intake in the high vegetable intake category did not quite reach statistical significance. However, this result should probably not be interpreted as supporting a lack of association with carotenoids since the number of cases was small ( $n = 27$ ) and since it was obtained with only a limited contrast between risk categories ( $\leq$  median versus  $>$  median of intake).

## Discussion

In this population-based case-control study, we used newly available food composition data to investigate associations between the five main dietary carotenoids and lung cancer risk, after adjustment for smoking and other confounders. We found a protective effect against lung cancer for β-carotene, α-carotene, and lutein. Intakes of these carotenoids were highly correlated, making it difficult to assess their independent effects. However, lung cancer risk was lowest among subjects who consumed high quantities of all three carotenoids, and the effect of β-carotene appeared somewhat stronger than that of α-carotene and lutein. No association was found with β-cryptoxanthin or lycopene.

Experimental and epidemiological studies have strongly suggested a cancer protective effect for β-carotene (2, 4, 6, 16). One proposed mechanism involves its provitamin A activity. Retinoids have been shown to inhibit carcinogenesis in many experimental systems (17) and, in humans, to prevent neoplasia or to revert pre-neoplastic lesions at several anatomical sites (18, 19). In support of this hypothesis, Stich *et al.* (20) showed that vitamin A and β-carotene reversed oral leukoplakia in betel nut/tobacco chewers, but that canthaxanthin, a carotenoid with no known vitamin A activity, had no effect.

However, a growing number of experimental studies have demonstrated cancer-inhibiting effects for various carotenoids, not just those with provitamin A activity. Mathews-Roth (21) has shown that both β-carotene and canthaxanthin inhibit UV-induced skin tumors. In cell cultures, not only β-carotene and α-carotene, but also canthaxanthin, lutein, and lycopene, carotenoids with no known provitamin A activity, have been shown to inhibit chemically induced neoplastic transformation (22). One common property shared by all these carotenoids is their

Table 2 Spearman correlation coefficients<sup>a</sup> for carotenoid and vitamin C intakes, Hawaii, 1983–1985

	β-Carotene	α-Carotene	Lutein	Lycopene	β-Cryptoxanthin	Vitamin C
β-Carotene	—	0.78	0.73	0.48	0.20	0.50
α-Carotene	0.72	—	0.46	0.32	0.17	0.39
Lutein	0.73	0.44	—	0.37	0.20	0.46
Lycopene	0.54	0.38	0.41	—	0.05	0.42
β-Cryptoxanthin	0.29	0.22	0.22	0.16	—	0.75
Vitamin C	0.52	0.38	0.43	0.45	0.81	—

<sup>a</sup> Coefficients to the left of the dashes refer to males; those to the right refer to females.

Table 3 Odds ratios for three-way interaction among carotenoids

Lutein intake ( $\mu\text{g}/\text{day}$ )	$\leq 2620 \mu\text{g } \beta\text{-carotene}/\text{day}$						$> 2620 \mu\text{g } \beta\text{-carotene}/\text{day}$					
	$\leq 350 \mu\text{g } \alpha\text{-carotene}/\text{day}$			$> 350 \mu\text{g } \alpha\text{-carotene}/\text{day}$			$\leq 350 \mu\text{g } \alpha\text{-carotene}/\text{day}$			$> 350 \mu\text{g } \alpha\text{-carotene}/\text{day}$		
	<i>n</i> <sup>a</sup>	OR <sup>b</sup>	(95% CI) <sup>c</sup>	<i>n</i>	OR	(95% CI)	<i>n</i>	OR	(95% CI)	<i>n</i>	OR	(95% CI)
$\leq 2150$	118/236	2.5	(1.7–3.8)	35/75	2.6	(1.5–4.5)	12/24	3.5	(1.5–8.1)	23/76	1.8	(1.0–3.2)
$> 2150$	34/68	2.2	(1.3–4.0)	15/18	5.5	(2.3–13.2)	32/79	1.6	(0.9–2.9)	63/289	1.0 <sup>d</sup>	

<sup>a</sup> Number of cases/number of controls.

<sup>b</sup> Odds ratio adjusted for age, ethnicity, smoking status, pack-years of cigarette smoking, and cholesterol intake.

<sup>c</sup> Ninety-five % confidence interval.

<sup>d</sup> Reference category.

antioxidant activity (3). Active oxygen and free radicals can induce lipid peroxidation in membranes and damage DNA (23). Antioxidants, therefore, may exert an inhibitive effect on carcinogenesis, as has been demonstrated in experimental models for vitamins E and C (24). Recently, carotenoids have also been shown to increase gap junctional intercellular communication, effectively suppressing cell transformation by enhancing cell growth control (25).

The present study provides further support for a protective effect of  $\beta$ -carotene against lung cancer, as well as new evidence for beneficial effects of dietary  $\alpha$ -carotene and lutein intakes against this disease. However, these data failed to corroborate the cancer-inhibiting property suggested for lycopene and  $\beta$ -cryptoxanthin in experimental studies. Although reasons for these discrepancies are unclear, studies of uptake of diverse carotenoids by cells in tissue culture have suggested a lower uptake for lycopene (22). Consequently, for this particular carotenoid, tissue concentrations may be more informative with regard to a possible association with cancer risk than dietary intake (26). The present findings suggest that the inverse association with tomatoes, which we previously reported (6), may reflect a protective effect of other constituents of tomatoes since this food contributed only 29% of the lycopene intake of our subjects. We also found no association between papaya consumption and lung cancer in our previous examination of these data (6). This finding is consistent with the lack of an association with  $\beta$ -cryptoxanthin in the present analysis, since papaya contributed 80% of the  $\beta$ -cryptoxanthin intake of our subjects.

Part of the protective effect observed in this study for carotenoids was due to that of vegetable intake. Indeed, the apparent protection afforded by vegetable

consumption was greater than that from carotenoids per se. This is consistent with a growing number of laboratory studies suggesting cancer-inhibiting properties for phytochemicals other than carotenoids, such as indoles, isothiocyanates, flavonoids, phenols, dithiolthiones, etc. (1, 2).

Certain limitations of the data need to be considered. Although we used the best and most comprehensive available estimates of individual carotenoids in foods, there is still much variation in the quality of these data (8). Also, these values cannot reflect the heterogeneity in carotenoid levels in foods due to varietal differences, growth and harvesting conditions, and handling and processing (8). However, such imprecision in the food composition values does not appear to differ between vegetables, fruits, or other sources. Thus, it is unlikely to explain the greater effect observed for vegetables than for other food sources of carotenoids in this study. Although our dietary instrument included all the important sources of carotenoids in our population, there is a certain amount of measurement error in assessing dietary intake (7). The resulting misclassification is likely to have attenuated the odds ratios presented here.

In summary, this new analysis largely confirms our previous results based on consumption of specific vegetables and fruits and provides further evidence for a protective effect of various carotenoids against lung cancer, although this effect may not extend to all carotenoids. It also confirms our earlier report that the protection against lung cancer achieved by increased intakes of several carotenoids, and probably of other protective phytochemicals present in a diet that includes a variety of vegetables, may be greater than that achieved with foods rich in a single carotenoid.

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Table 4 Odds ratios for two-way interaction between vegetable consumption and combined intake of  $\beta$ -carotene,  $\alpha$ -carotene, and lutein

Total vegetable intake ( $\text{g}/\text{day}$ )	<i>n</i> <sup>b</sup>	OR <sup>c</sup>	$\leq 5365^a$			
			(95% CI) <sup>d</sup>	<i>n</i>	OR	(95% CI)
$\leq 115$	167/330	2.1	(1.5–2.9)	35/73	1.7	(1.0–2.8)
$> 115$	27/71	1.5	(0.9–2.7)	102/389	1.0 <sup>e</sup>	

<sup>a</sup> Combined  $\beta$ -carotene,  $\alpha$ -carotene, and lutein intake ( $\mu\text{g}/\text{day}$ ).

<sup>b</sup> No. of cases/no. of controls.

<sup>c</sup> Odds ratio adjusted for age, ethnicity, smoking status, pack-years of cigarette smoking, and cholesterol intake.

<sup>d</sup> Ninety-five % confidence interval.

<sup>e</sup> Reference category.

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