

BRIEF COMMUNICATION

Importance of α -Carotene, β -Carotene, and Other Phytochemicals in the Etiology of Lung Cancer

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Of all proposed cancer chemopreventive agents, β -carotene seemed the most promising (1)—until recently. Numerous retrospective and prospective studies have demonstrated that a reduced risk of lung and other cancers is associated with an increased intake of provitamin A carotenoids, the vitamin A precursors in vegetables and fruits (2-7). In prospective studies, elevated prediagnostic blood β -carotene levels have been consistently predictive of a reduced incidence of lung and other cancers (2-5,7,8). However, in a large, randomized, placebo-controlled trial in Finland (9), male smokers took β -carotene daily for 5-8 years at a dose substantially higher than that linked to reduced risk in observational studies, and lung cancer incidence was increased 18% (95% confidence interval [CI] = 3%-36%), contributing substantially to an 8% excess in total mortality. Interim results from a second large, randomized trial conducted in the United States with male and female smokers and men exposed to asbestos have corroborated that lung cancer incidence and total mortality are increased in subjects taking β -carotene supplements.¹

The observational studies of diet and cancer relied on food composition tables to estimate consumption of total pro-

vitamin A carotenoids, which include β -carotene, α -carotene, and chemically similar carotenoids. Recently, a database detailing the levels of the major individual carotenoids in U.S. foods was published (10,11). Consequently, we reanalyzed data from the first case-control study to evaluate the hypothesis that β -carotene could protect against cancer—a population-based study of diet and lung cancer conducted in New Jersey during 1980-1981 (12,13).

Eligible case subjects were white men² from six areas of New Jersey who were 25-89 years of age and diagnosed with primary, histologically confirmed cancer of the trachea, bronchus, or lung during a 14-month interval. Control subjects were randomly selected from licensed New Jersey drivers and were frequency matched to case subjects on the bases of age and geographic area. Of the 1084 case and 894 control subjects identified, 763 (70%) and 564 (63%), respectively, were successfully interviewed. Surrogate interviews were required for 43% of the case subjects because they had died or had become incapacitated. Analyses including only directly interviewed lung cancer patients and analyses including all case subjects gave similar results.

Diet was assessed by asking about the usual frequency of consumption, in season and out of season, approximately 4 years earlier, of 44 food items (13). These foods included the major sources of carotenoids and retinol (preformed vitamin A). Of the potential confounders [cigarette smoking, education, employment in high-risk occupations (14), age, and geographic area], only smoking confounded the relationships between diet and risk.

Increased lung cancer risk was associated with low vegetable and fruit intake in current and recent cigarette smokers and in pipe and/or cigar users. Risk was not elevated in cigarette smokers who had quit more than 5 years earlier or in never smokers. The effects of β -carotene intake and of α -carotene intake on lung cancer risk were similarly modified by smoking history. Thus, as before (13), the importance of diet was explored in current (464 case patients and 177 control subjects) and

recent (59 case patients and 31 control subjects) smokers.

Current and recent smokers in the lowest quartile of α -carotene intake had a smoking-adjusted risk more than twice that of smokers in the highest quartile of intake, whereas the corresponding risks associated with intakes of β -carotene and of lutein/zeaxanthin were increased only about 60% (Table 1). Statistically significant trends in risk were noted for intakes of both carotenoids, with the trend for α -carotene being more pronounced. Low intake of vegetables and fruits combined was more predictive of increased risk than low intake of either vegetables or fruits alone. Smokers in the lowest quartile of vegetable and fruit intake (\leq ~2 servings/day) had a risk 70% higher than those in the highest quartile (\geq ~4 servings/day). Dark-green vegetables and yellow-orange vegetables seemed especially important, with trends in risk intermediate between those for α -carotene and β -carotene.

When dietary exposures were stratified into octiles, trends with α -carotene and β -carotene were especially strong. The smoking-adjusted relative risks (RRs) of lung cancer by decreasing α -carotene intake were 1.0, 1.27, 1.74, 1.32, 1.46, 1.56, 2.11, and 2.72 (95% CI = 1.37-5.43),³ with the *P* for trend = .004. Corresponding risks for β -carotene were 1.0, 1.28, 1.02, 1.21, 1.37, 1.47, 1.55, and 1.98 (95% CI = 1.01-3.87),³ with the *P* for trend = .03.

Levels of intake of α -carotene and β -carotene were highly correlated, with 77% of the control subjects in the same tertile for both (Table 2). Smokers in the lowest tertile for both carotenoids had a risk almost twice that of smokers in the highest tertile for both (RR = 1.85; 95%

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See "Notes" section following "References."

Table 1. Smoking-adjusted relative risks (RRs)* of lung cancer in white male current and recent cigarette smokers by intake of individual carotenoids, vegetables and fruits, and vitamin A sources†

Dietary factor	Level of consumption				P for linear trend	Interquartile range	
	Quartile 4 (highest)	Quartile 3	Quartile 2	Quartile 1 (lowest)		Low	High
<i>µg/day</i>							
Individual carotenoids							
α-Carotene	1.0	1.36	1.32	2.21 (1.34-3.64)‡	.004	363	1468
β-Carotene	1.0	0.97	1.28	1.59 (0.98-2.60)	.04	2541	5902
β-Cryptoxanthin	1.0	0.74	0.54	0.82 (0.52-1.31)	.13	3	13
Lutein/zeaxanthin§	1.0	1.50	1.14	1.62 (1.03-2.56)	.07	1727	4196
Lycopene	1.0	1.30	0.83	1.07 (0.67-1.72)	.87	3464	9055
α-Carotene + β-carotene + lutein/zeaxanthin	1.0	1.37	1.34	1.72 (1.07-2.76)	.03	5137	11 297
Total individual carotenoids	1.0	1.06	1.22	1.27 (0.80-2.03)	.27	9951	20 570
<i>Servings/day</i>							
Food groups							
Vegetables and fruits	1.0	1.16	1.46	1.70 (1.04-2.77)	.02	2.1	4.1
Fruits	1.0	1.49	1.67	1.07 (0.67-1.71)	.62	0.6	1.6
Vegetables	1.0	1.03	1.10	1.60 (0.99-2.60)	.06	1.1	2.4
<i>Servings/week</i>							
Dark-green vegetables¶	1.0	1.01	1.54	1.74 (1.08-2.79)	.009	2.5	6.4
Yellow-orange vegetables#	1.0	1.78	1.39	2.01 (1.23-3.29)	.014	1.1	3.3
<i>RE/day**</i>							
Vitamin A							
Provitamin A carotenoids‡‡	1.0	0.95	1.30	1.27 (0.78-2.07)	.21	347	762
Retinol‡‡	1.0	1.01	1.11	0.94 (0.58-1.51)	.98	469	1718
Total vitamin A‡‡	1.0	1.44	1.19	1.15 (0.72-1.84)	.51	958	2413

*RRs are adjusted for smoking intensity (<25 and ≥25 cigarettes/day) and duration (≤40 and >40 years) of cigarette smoking. No remarkable changes in RRs were noted with finer stratifications or with addition of years since stopping smoking.

† Current cigarette smokers include men who were smoking at diagnosis or quit within the year preceding diagnosis. Recent cigarette smokers are men who quit 2-5 years prior to diagnosis. Included for analysis are 523 case patients and 208 control subjects.

‡ Values in parentheses = 95% confidence intervals of the smoking-adjusted RRs for the lowest quartile of intake.

§ Lutein and zeaxanthin are not separated by the liquid chromatography method used to measure individual carotenoids in foods (10). Only the lutein/zeaxanthin content of vegetables and fruits is included. Addition of the lutein/zeaxanthin available in eggs and corn products did not substantially change the RRs.

|| Total individual carotenoids include α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene.

¶ Dark-green vegetables include broccoli; green beans; green peas; greens such as spinach, turnip greens, and collards; and leaf lettuce.

Yellow-orange vegetables include carrots, sweet potatoes or pumpkin, and winter squash.

** RE = retinol equivalents.

‡‡ Nutrient content was derived from U.S. Department of Agriculture food composition data (15).

CI = 1.16-2.95). Only seven smokers reported a low intake of α-carotene and a high intake of β-carotene; all had lung cancer. Smoking-adjusted RRs by decreasing tertile of intake were similar for the two carotenoids: 1.0, 0.98, and 1.65 (95% CI = 1.08-2.53) for α-carotene and 1.0, 1.21, and 1.57 (95% CI = 1.03-2.40) for β-carotene.⁴ Adjusting each for intake of the other attenuated the RRs, with the protective effect of β-carotene reduced more than that of α-carotene (Table 2).

Levels of intake of yellow-orange and dark-green vegetables were less correlated than intake of the two carotenoids; only 47% of the controls fell in the same tertile for both (Table 2). Smokers in the lowest tertile of consumption for both vegetable groups had 2.5 times the risk of smokers in the highest tertile for both (RR = 2.47; 95% CI = 1.35-4.50). Increases in risk associated with decreasing tertiles of each

vegetable group (smoking-adjusted RRs for yellow-orange vegetables and dark-green vegetables = 1.0, 1.34, and 1.89 [95% CI = 1.22-2.92] and 1.0, 1.66 [95% CI = 1.10-2.52], and 1.82 [95% CI = 1.21-2.76], respectively⁴) were partially, and similarly, reduced by adjusting for the other vegetable group (Table 2).

Our reanalysis suggests that β-carotene is not the dominant protective factor in vegetables and fruit. Intakes of α-carotene, yellow-orange vegetables, and dark-green vegetables were each more predictive of reduced lung cancer risk. Our results concur with the only other lung cancer study to evaluate individual carotenoids—a case-control study conducted in Hawaii (16). In that study, intakes of α-carotene, β-carotene, and lutein/zeaxanthin were each significantly associated with reduced risk in both men and women.

Experimental data on the potential role of α-carotene in carcinogenesis are

limited. Exposure to α-carotene has been reported to inhibit chemically induced malignant transformation (17) and cancer cell growth (18,19) in vitro. In animal models of spontaneous liver cancer and chemically induced lung and skin cancer, α-carotene was more protective than β-carotene (20). Similar to β-carotene, α-carotene can prevent lipid oxidation, scavenge free radicals, and enhance gap junction communication, all of which may play a role in cancer etiology (21,22).

It is premature to conclude that α-carotene is protective in humans. Levels of intake of α-carotene and β-carotene are highly correlated in unsupplemented diets. The database for individual carotenoids, though notable for its rational approach, is based on sparse analytic data for many foods, cooking procedures, and agricultural practices (10,11). Moreover, assessing dietary patterns by interview is a challenge.

Table 2. Smoking-adjusted relative risks (RRs)* of lung cancer by α - and β -carotene intake and by dark-green and yellow-orange vegetable intake in white male current and recent cigarette smokers†

β -Carotene intake	α -Carotene intake			β -Carotene intake adjusted for α -carotene intake
	Upper tertile	Middle tertile	Lower tertile	
Upper tertile	1.0 93/51‡	1.20 21/10	∞ 7/0	1.0
Middle tertile	1.92 28/8	1.08 96/50	1.74 41/13	1.19
Lower tertile	— 0/0	1.10 36/16	1.85§ 201/60	1.13
α -Carotene intake adjusted for β -carotene intake	1.0	0.88	1.50	

Dark-green vegetable intake	Yellow-orange vegetable intake			Dark-green vegetable intake adjusted for yellow-orange vegetable intake
	Upper tertile	Middle tertile	Lower tertile	
Upper tertile	1.0 53/33‡	1.13 45/29	1.36 36/17	1.0
Middle tertile	1.68 44/15	1.67 71/30	2.32§ 73/20§	1.56§
Lower tertile	0.81 14/10	1.94§ 55/19	2.47§ 132/35	1.54§
Yellow-orange vegetable intake adjusted for dark-green vegetable intake	1.0	1.22	1.63§	

*RRs are adjusted for smoking intensity (<25 and \geq 25 cigarettes/day) and duration (\leq 40 and >40 years) of cigarette smoking. No remarkable changes in RRs were noted with finer stratifications or with addition of years since stopping smoking.

†Current cigarette smokers include men who were smoking at diagnosis or quit within the year preceding diagnosis. Recent cigarette smokers are men who quit 2-5 years prior to diagnosis.

‡Number of case patients/number of control subjects.

§95% confidence intervals (CIs) for these RRs exclude or marginally exclude 1.0. Specifically, RR (95% CI) for low α -carotene, low β -carotene intake = 1.85 (1.16-2.95). RR (95% CI) for moderate dark-green vegetable, low yellow-orange vegetable intake = 2.32 (1.16-4.64); RR (95% CI) for low dark-green, moderate yellow-orange vegetable intake = 1.94 (0.95-3.94); RR (95% CI) for low dark-green, low yellow-orange vegetable intake = 2.47 (1.35-4.50). RRs (95% CIs) for moderate and low dark-green vegetable intakes adjusted for yellow-orange vegetable intake = 1.56 (1.02-2.38) and 1.54 (0.99-2.40), respectively. RR (95% CI) for low yellow-orange vegetable intake adjusted for dark-green vegetable intake = 1.63 (1.02-2.59).

The significant increase in lung cancer incidence among men taking β -carotene in the Finnish chemoprevention trial remains unexplained (9,23). At base line, the median β -carotene intake in these smokers was 1.7 mg/day (23), suggesting a diet relatively low in vegetables and fruits. Twenty mg/day of all-*trans*- β -carotene in a water-soluble beadlet raised serum β -carotene levels 15-fold in practically all participants (9). It is conceivable that the supplemental β -carotene interfered with the utilization of other β -carotene isomers, carotenoids, or phytochemicals. In our study, few smokers reported both high β -carotene and low α -carotene intakes; yet all seven of these developed lung cancer. Furthermore, several recent investigations have identified biological interactions between carotenoids (24-27).

Finally, low intake of both yellow-orange and dark-green vegetables was

more predictive of elevated lung cancer risk (RR = 2.47) than low intake of both α -carotene and β -carotene (RR = 1.85) in our study. Vegetables and fruits contain a wide variety of phytochemicals with the potential to modulate carcinogenesis (28). Our understanding of their biological functions and interactions is still rudimentary. Therefore, the most rational way to reduce lung cancer risk is to eat a variety of vegetables and fruits (29) and, most important, not to smoke.

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Notes

¹Press conference on Clinical Intervention Trials of β -Carotene Supplements, National Institutes of Health, January 18, 1996.

²Although the first phase of this study focused on white men only, subsequent phases, with somewhat different study designs and dietary assessment instruments, included women and blacks.

³As in Table 1, only the 95% CI for the RR of the lowest octile of intake is shown.

⁴95% CIs are not given when they include 1.0.

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Presented at the Gordon Conference on Carotenoids, Ventura, CA, February 5-9, 1995.

Manuscript received May 9, 1995; revised December 4, 1995; accepted February 14, 1996.

REFERENCE

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