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Original Contribution

Long-term Use of β-Carotene, Retinol, Lycopene, and Lutein Supplements and Lung Cancer Risk: Results From the VITamins And Lifestyle (VITAL) Study

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High-dose β-carotene supplementation in high-risk persons has been linked to increased lung cancer risk in clinical trials; whether effects are similar in the general population is unclear. The authors examined associations of supplemental β-carotene, retinol, vitamin A, lutein, and lycopene with lung cancer risk among participants, aged 50–76 years, in the VITamins And Lifestyle (VITAL) cohort Study in Washington State. In 2000–2002, eligible persons ($n = 77{,}126$) completed a 24-page baseline questionnaire, including detailed questions about supplement use (duration, frequency, dose) during the previous 10 years from multivitamins and individual supplements/mixtures. Incident lung cancers ($n = 521$) through December 2005 were identified by linkage to the Surveillance, Epidemiology, and End Results cancer registry. Longer duration of use of individual β-carotene, retinol, and lutein supplements (but not total 10-year average dose) was associated with statistically significantly elevated risk of total lung cancer and histologic cell types; for example, hazard ratio = 2.02, 95% confidence interval: 1.28, 3.17 for individual supplemental lutein with total lung cancer and hazard ratio = 3.22, 95% confidence interval: 1.29, 8.07 for individual β-carotene with small-cell lung cancer for >4 years versus no use. There was little evidence for effect modification by gender or smoking status. Long-term use of individual β-carotene, retinol, and lutein supplements should not be recommended for lung cancer prevention, particularly among smokers.

beta carotene; carotenoids; cohort studies; dietary supplements; lung neoplasms; randomized controlled trials as topic; vitamins

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; CARET, Beta-Carotene and Retinol Efficacy Trial; COPD, chronic obstructive pulmonary disease; SEER, Surveillance, Epidemiology, and End Results; VITAL, VITamins And Lifestyle.

Lung cancer is the second most common cancer in the United States and the leading cause of cancer deaths (1, 2). It was estimated that 215,020 new cases of lung cancer would be diagnosed in the United States in 2008, constituting 15% of all cancer diagnoses (1, 2). Cigarette smoking is the most significant contributor to lung cancer development, accounting for as many as 90% of all lung cancers (1–3). Nonetheless, there are other, less prominent risk factors, including environmental exposure to secondhand smoke; occupational exposure to certain metals, radon, and asbestos; genetic susceptibility; and diet (1–8).

Vegetables and fruits have been repeatedly shown to be associated with reduced risk of lung cancer (1, 3–8). Carotenoids, red and yellow pigments found in many fruits and vegetables, are among the components of fruits and vegetables believed to confer protection, largely because of their antioxidant properties (9, 10). In principle, antioxidants should be associated with reduced lung cancer risk because they may protect against oxidative damage (9–11).

The observation that fruits and vegetables may reduce lung cancer risk led to implementation of 2 large, randomized clinical trials in which high doses of β-carotene were used: the Beta-Carotene And Retinol Efficacy Trial (CARET) in the United States and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial in Finland. The CARET intervention tested the efficacy of 30 mg of

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β-carotene plus 25,000 IU of retinyl palmitate daily in male and female heavy smokers and in men exposed to asbestos (12). The ATBC trial tested 20 mg of β-carotene plus 50 IU of vitamin E daily in male heavy smokers (13). Both trials found that β-carotene, alone or in combination with vitamin E or retinyl palmitate, increased the incidence of lung cancers by 36% (in CARET) and 16% (in the ATBC trial) compared with placebo.

The paradoxical findings between the observational studies and clinical trials may be attributable to several factors, including the fact that fruits and vegetables contain numerous substances (other than β-carotene) that may affect lung cancer risk, the interactions of nutrients within foods, and possible differential metabolism of nutrients from foods compared with those that are manufactured (12–16). Given the low likelihood of new randomized trials evaluating these associations, carefully designed observational studies are critical to untangling the potential associations of dietary supplement use with lung cancer risk.

These results also led to concern about the millions of Americans using supplements, because the doses of β-carotene and other carotenoids in dietary supplements are much higher than would typically be acquired from diet (17, 18). Most Americans' supplemental intakes of retinol and major carotenoids are from multivitamins; some people also ingest these nutrients by using individual supplements or other nonmultivitamin mixtures (17, 18). However, there are very few published studies on associations between supplement use of retinol and carotenoids and risk of lung cancer.

We used data from the VITamins And Lifestyle (VITAL) Study, the only known large cohort investigation focused on dietary supplement use and cancer risk, to rigorously examine associations of supplemental intakes of β-carotene, retinol, total vitamin A, lutein, and lycopene with lung cancer risk. We have previously shown that multivitamins do not increase lung cancer risk (19). Therefore, this study focused on use of the individual supplements and at higher doses than would be obtained from most common formulations of multivitamins.

MATERIALS AND METHODS

VITAL Study recruitment and response rates

The objectives of the VITAL Study were to investigate associations of supplemental vitamin C, vitamin E, and calcium; multivitamins; and other supplements with cancer risk. Details of the study design and methods have been published previously (20). Cohort members were men and women aged 50–76 years at entry living in a 13-county area in western Washington State, the catchment area of the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry, who were willing to complete a 24-page baseline questionnaire. To encourage supplement users to enroll, the approach letter described the study as one on supplement use and cancer risk, but the study was not restricted to supplement users. Recruitment was conducted from October 2000 to December 2002.

Names were purchased from a commercial mailing list, and 364,418 baseline questionnaires were mailed, followed by a postcard reminder 2 weeks later. A total of 79,300 questionnaires were returned (21.8% overall; 19.5% response proportion among men, 24.4% among women), of which 1,580 were ineligible and 241 failed quality control checks, leaving 77,719 eligible cohort members at baseline (20). The study protocol was approved by the institutional review board of the Fred Hutchinson Cancer Research Center (Seattle, Washington).

For the present analyses, we excluded 588 participants with a self-reported history of lung cancer at baseline (or who did not complete the baseline medical history section), 2 whose lung cancer was classified as lymphoma, and 3 whose diagnosis was based on a death certificate only. Therefore, 521 cases and 76,605 non–lung cancer cases remained for analysis ($n = 77,126$ total).

Data collection

Data were collected at baseline. A 24-page, self-administered, sex-specific, optically scanned questionnaire was used that covered 3 content areas: supplement use, diet, and health history and risk factors.

Measurement of vitamin supplement use. In a 6-page instrument, respondents were asked about use of various dietary supplements during the 10 years prior to baseline. For current multivitamin use, participants either selected one of 16 common brand names or provided dose information on each vitamin and mineral of their brand. Those who had used more than one brand over the 10 years or had used multivitamins only in the past selected from another list of brand names (reflecting past market availability). For analysis, the nutrient content of multivitamins was based on information from the *PDR* for nonprescription drugs (21) and from direct inquiry to manufacturers to determine composition of multivitamins in the past 10 years.

Respondents then reported their intake of vitamins including β-carotene, vitamin A/retinol, lycopene, and lutein from individual (single) supplements and all other mixtures not classified as multivitamins (e.g., ''stress''/B complex or antioxidant mixtures). We used a closed-ended format to inquire about current versus past use, frequency (days per week), duration (years) of use over the previous 10 years, and usual dose per day. Individual vitamin A supplements were assumed to be retinol. International Units of retinol were converted to micrograms of retinol by multiplying by 0.3, and International Units of β-carotene were converted to micrograms of β-carotene by multiplying by 0.6.

Average daily intakes (i.e., dose) over the previous 10 years of supplemental β-carotene and retinol were estimated by summing across intakes from the 3 sources (current multivitamin use, past multivitamin use, and individual supplements plus other mixtures) over the 10-year period prior to baseline, where intake from each nutrient was computed as years/10 × days per week/7 × dose per day. Ten-year average daily intake of total (multivitamins plus individual) supplemental vitamin A was computed in retinol activity equivalents as 10-year average retinol + 10-year average β-carotene × 0.5.

Supplemental lycopene and lutein intakes were computed based on duration (years) and frequency (days per week) of

use from 2 sources: current use of multivitamins (i.e., whether the multivitamin contained lutein or lycopene) and individual supplements plus other (nonmultivitamin) mixtures. For analytic purposes and because of limited distributions among users, supplemental lutein and lycopene use are defined in this paper as "no use," "multivitamin use only," and "individual supplement use."

In a study of 220 participants, the VITAL supplement questionnaire showed excellent reliability when compared with a repeat administration of the questionnaire 3 months after baseline and excellent validity when compared with a detailed home interview and supplement inventory and with nutrient biomarkers (22). Pearson correlation coefficients comparing current supplemental intakes according to the questionnaire versus the interview/supplement inventory were high: retinol, 0.72 (95% confidence interval: 0.63, 0.79); β-carotene, 0.58 (95% confidence interval: 0.46, 0.68). β-carotene showed a clear linear trend of increasing serum concentrations with higher self-reported supplemental intakes (Pearson's r partialed for potential confounding factors and diet, 0.31; 95% confidence interval: 0.19, 0.43).

Diet. Usual dietary intake was assessed by a 120-item food frequency questionnaire that included highly supplemented foods and adjustment questions on types of foods and preparation techniques (20, 23). The measurement properties of an earlier version of this questionnaire have been published; Pearson correlation coefficients between nutrient intakes estimated by the food frequency questionnaire and 8 days of dietary intake (4 dietary recalls and 4 food records) were 0.43 for β-carotene and 0.24 for retinol (23). The food frequency questionnaire analytic program, based on nutrient values from the Nutrition Data System (NDS) (version 5.0.35; University of Minnesota, Minneapolis, Minnesota), yields estimated intakes of over 50 nutrients.

Covariates. The 24-page questionnaire captured several covariates, including demographic characteristics, health history, physical activity over the 10 years prior to baseline, cancer screening practices, and other potential confounders of supplement-cancer associations. Covariates considered in these analyses include sociodemographic characteristics (self-reported age, gender, race, marital status, and education), anthropometric characteristics (weight, height, and body mass index (weight (kg)/height $(m)^2$)), first-degree family history of lung cancer, previous history of cancer, and self-report of physician-diagnosed chronic obstructive pulmonary disease (COPD) or emphysema as well as asthma (20).

Tobacco use. Smokers were defined as individuals who smoked at least one cigarette per day for at least a year. We classified smokers as never, current, quit 10 years ago or longer, or quit less than 10 years ago as of the date of questionnaire completion. Duration of smoking was estimated by the reported number of years of smoking and intensity by the usual number of cigarettes smoked per day. Pack-years were computed as duration × cigarettes per day/20.

Outcome ascertainment

Participants were followed for lung cancer occurring from baseline through December 31, 2005, by linking the cohort to the Seattle-Puget Sound SEER registry. SEER cases are ascertained through all hospitals in the area; through offices of pathologists, oncologists, and radiotherapists; and from state death certificates. After exclusion of the 5 cases noted above, 521 cases were identified in the cohort by using matching algorithms on personal identifiers and human review (20).

For each participant, the censored date was the earliest date of withdrawal from the study (0.03%), death (3.02%), move out of the SEER catchment area (4.57%), or last date of linkage to the SEER registry for remaining participants (December 31, 2005). Deaths were ascertained by linkage to Washington State death files, and moves out of the area were identified through the National Change of Address System and by follow-up letters and telephone calls. If a participant had multiple diagnoses of lung cancer, we used the time to first primary diagnosis.

Statistical analysis

Statistical analyses were performed by using SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina, 2002–2003). Cox proportional hazards regression was used to estimate the hazard ratios for associations of supplemental β-carotene, retinol, vitamin A, lutein, and lycopene with lung cancer risk. Robust standard errors were used to eliminate traditional proportional hazards assumptions.

A priori and using a stepwise procedure, we analyzed variables that measured smoking status, duration, and intensity (pack-years, pack-years squared, years of smoking, years of smoking squared, smoking status (4 categories as above), and age at which smoking started) at a $P = 0.05$ level. Our final model included years of smoking, pack-years, and a squared pack-years term. We also decided a priori to include age and gender in the model. Finally, we evaluated whether COPD/emphysema/asthma, previous history of cancer, first-degree family history of lung cancer, physical activity, education, body mass index, supplemental vitamin E, and daily fruit and vegetable servings were confounders of the supplement–lung cancer associations in models already adjusted for age, gender, and the smoking variables. In analyses of β-carotene, we further adjusted for fruit and vegetable intake, physical activity, supplemental vitamin E, and body mass index. These factors did not appear to confound associations of the other supplemental vitamins, so the more parsimonious models were used. Note that adjustment for the corresponding dietary variables (e.g., controlling supplemental β-carotene for dietary β-carotene) did not change the results appreciably, so our results were not adjusted for the diet-derived nutrients. Likelihood ratio tests were conducted to evaluate for effect modification by gender and smoking status in the supplement–lung cancer associations; P values for interaction were obtained to compare the fit of the models with the interaction terms and without them.

For analytic purposes, supplemental use of the vitamins was defined as follows: 1) Duration (years) of individual/nonmultivitamin supplement use of β-carotene and retinol was categorized as "no use," "1–3 years," and " ≥4 years." 2) Ten-year average daily dose of β-carotene, retinol, and

Table 1. Selected Characteristics of Lung Cancer Cases and Non–Lung Cancer Cases, the VITAL Study, Washington State, 2000–2002 ($n = 77,126$)[a]

Characteristic	Non–Lung Cancer Cases ($n = 76,605$)		Lung Cancer Cases ($n = 521$)	
	No.	%	No.	%
Age at baseline, years				
50–59	35,291	46	94	18
60–69	26,544	35	211	41
≥70	14,770	19	216	41
Mean (SD)	61.9 (7.4)		67.0 (6.8)	
Gender				
Female	39,849	52	224	47
Male	36,756	48	297	53
Race				
White	70,146	93	473	94
Non-White	5,144	7	31	6
Education[b]				
≤High school education	15,072	20	188	37
Some college	28,835	38	200	39
College graduate/advanced degree	31,402	42	119	23
Smoking status				
Never smoker	36,399	48	42	8
Former smoker, quit ≥10 years ago	28,140	37	226	44
Former smoker, quit <10 years ago	4,941	7	93	18
Current smoker	6,269	8	155	30
Pack-years of cigarette smoking, mean (SD)	13.4 (21.1)		43.2 (27.9)	
No. of years as a smoker				
0 (nonsmokers)	36,399	48	42	8
2.5–24.5 (bottom half of smokers)	17,832	24	45	9
25–59 (top half of smokers)	21,610	28	429	83
Mean (SD)	11.9 (15.0)		33.3 (14.2)	
Physical activity (MET-hours per week)				
No exercise	11,285	15	118	23
1st quartile (0.01–3.03)	16,060	21	119	23
2nd quartile (3.04–8.06)	16,026	21	120	23
3rd quartile (8.07–17.81)	16,081	21	84	16
4th quartile (>17.81)	16,095	21	70	14
BMI category (kg/m^2)				
Underweight (<18.5)	654	1	14	2
Normal (18.5–24.9)	24,383	33	182	37
Overweight (25–29.9)	29,852	41	206	42
Obese (>30)	17,930	25	92	19
Supplemental vitamin E (mg/day)[c]				
No use	19,963	26.3	146	28.4
1st tertile (<42)	18,676	24.6	115	22.3
2nd tertile (42–215)	18,604	24.5	93	18.1
3rd tertile (>215)	18,778	24.7	161	31.3
Vegetables (servings/day)				
1st quartile (0–1.33)	17,288	25	126	28
2nd quartile (1.34–1.97)	17,261	25	121	27
3rd quartile (1.98–2.88)	17,340	25	114	25
4th quartile (>2.88)	17,319	25	87	19

Table continues

Table 1. Continued

Characteristic	Non–Lung Cancer Cases (n = 76,605)		Lung Cancer Cases (n = 521)	
	No.	%	No.	%
Fruit (servings/day)				
1st quartile (0–0.75)	17,256	25	151	34
2nd quartile (0.76–1.34)	17,297	25	109	24
3rd quartile (1.35–2.31)	17,314	25	100	22
4th quartile (>2.31)	17,331	25	86	19
Dietary β-carotene from the FFQ (mcg)				
1st quartile (14–2,134)	17,382	25	132	29
2nd quartile (2,135–3,502)	17,400	25	114	25
3rd quartile (3,503–5,650)	17,406	25	108	24
4th quartile (5,651–59,238)	17,420	25	94	21
Dietary retinol from the FFQ (mcg)				
1st quartile (1–276)	17,4.08	25	106	24
2nd quartile (277–420)	17,410	25	104	23
3rd quartile (421–635)	17,399	25	115	26
4th quartile (636–11,996)	17,391	25	123	27
Dietary total vitamin A from the FFQ (mcg)				
1st quartile (29–570)	17,397	25	117	26
2nd quartile (571–818)	17,408	25	106	24
3rd quartile (819–1,173)	17,392	25	122	27
4th quartile (1,174–13,864)	17,411	25	103	23
Dietary lutein + zeaxanthin from the FFQ (mcg)				
1st quartile (13–1,455)	17,390	25	124	28
2nd quartile (1,456–2,313)	17,399	25	115	26
3rd quartile (2,314–3,371)	17,404	25	110	25
4th quartile (3,372–100,884)	17,415	25	99	22
Dietary lycopene from the FFQ (mcg)				
1st quartile (0–3,120)	17,405	25	109	24
2nd quartile (3,121–5,216)	17,401	25	113	25
3rd quartile (5,217–8,664)	17,403	25	111	25
4th quartile (8,665–218,765)	17,399	25	115	26
Medical history				
Prior cancer				
Yes	15,320	20	154	30
No	61,285	80	365	70
COPD or emphysema				
Yes	2,667	3	80	15
No	73,920	97	439	85
Asthma				
Yes	7,482	10	59	11
No	69,105	90	460	89
Family history of lung cancer[d]				
Yes	9,522	13	104	20
No	66,080	87	409	80

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FFQ, food frequency questionnaire; MET, metabolic equivalent task; SD, standard deviation; VITAL, VITamins And Lifestyle.

[a] For all characteristics, <5% of the data were missing; percentages are of the total. Numbers may not sum to the total and percentages may not add to 100% because of missing data and/or rounding.

[b] Adjusted for age and gender.

[c] 10-year average dose from multivitamins and individual supplements.

[d] One or more first-degree relatives with lung cancer.

Table 2. Lung Cancer Risk by Duration of Use[a] and Daily Dose[b] During the Previous 10 Years of β-Carotene, Retinol, Total Vitamin A, Lutein, and Lycopene Supplements, the VITAL Study, Washington State, 2000–2002 ($n = 77{,}126$)[c]

Supplement	Total Lung Cancer Cases ($n = 521$)		Non–Lung Cancer Cases ($n = 76{,}605$)		Total Lung Cancer Cases ($n = 521$)		Non-Small-Cell Lung Cancer ($n = 391$)		Small Cell Lung Cancer ($n = 74$)		Other Lung Cancers ($n = 56$)	
	No.	%	No.	%	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI
β-Carotene (no. of years[a] used over 10 years)[e]												
No use	454	89	68,117	90	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
1–3 years	26	5	3,471	5	1.10	0.70, 1.72	0.86	0.49, 1.51	1.64	0.50, 5.40	2.42	1.92, 6.32
≥4 years	32	6	3,860	5	1.18	0.78, 1.78	1.10	0.69, 1.76	3.22	1.29, 8.07	0	
Overall *P*					0.69		0.78		0.01		0.20	
P for trend					0.40		0.62		0.04		0.41	
β-Carotene (10-year average daily dose)[e]											1.00 (Ref)	
No use	178	35	26,229	35	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
>0–1,200 mcg	286	56	43,276	57	1.07	0.89, 1.30	1.05	0.85, 1.31	1.24	0.68, 2.24	1.39	0.69, 2.78
>1,200 mcg	49	10	6,171	8	1.25	0.91, 1.71	1.22	0.85, 1.76	2.58	0.99, 6.72	1.95	0.63, 6.02
Overall *P*					0.39		0.55		0.15		0.47	
P for trend					0.19		0.32		0.11		0.22	
Retinol (no. of years[a] used over 10 years)												
No use	438	87	65,898	89	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
1–3 years	22	4	3,178	4	1.23	0.80, 1.88	0.97	0.55, 1.68	1.19	0.37, 3.79	3.15	1.34, 7.40
≥4 years	44	9	4,650	6	1.53	1.12, 2.08	1.80	1.29, 2.52	1.01	0.37, 2.79	0	
Overall *P*					0.02		0.002		0.96		0.01	
P for trend					0.004		0.0003		0.89		0.47	
Retinol (10-year average daily dose)												
No use	176	35	24,855	33	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
>0–1,200 mcg	274	54	42,913	57	1.00	0.83, 1.22	1.00	0.80, 1.25	0.98	0.59, 1.63	1.03	0.57, 1.86
>1,200 mcg	60	12	7,582	10	1.25	0.93, 1.69	1.29	0.92, 1.81	1.29	0.58, 2.87	0.96	0.36, 2.61
Overall *P*					0.27		0.27		0.77		0.99	
P for trend					0.27		0.28		0.68		0.99	
Total vitamin A (10-year average daily dose)												
No use	173	34	24,275	32	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
>0–1,500 mcg	269	53	41,464	55	1.00	0.83, 1.22	0.97	0.77, 1.21	1.00	0.61, 1.67	1.26	0.68, 2.30
>1,500 mcg	64	13	9,216	12	1.10	0.83, 1.47	1.24	0.90, 1.70	0.77	0.31, 1.87	0.53	0.15, 1.81
Overall *P*					0.78		0.28		0.82		0.31	
P for trend					0.60		0.36		0.67		0.68	

Lutein (over 10 years)														
No use	318	61	46,879	61	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)			
Multivitamin use only	181	35	27,945	37	0.94	0.78, 1.13	1.01	0.82, 1.25	0.76	0.46, 1.28	0.72	0.41, 1.28		
Individual supplement use	20	4	1,606	2	2.02	1.28, 3.17	2.48	1.53, 4.02	1.51	0.36, 6.24	0			
Overall *P*					0.006		0.01		0.46		0.53			
P for trend					0.44		0.08		0.51		0.14			
Lycopene (over 10 years)														
No use	399	77	60,528	79	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)			
Multivitamin use only	120	23	15,542	20	1.06	0.86, 1.30	1.14	0.90, 1.44	0.97	0.55, 1.71	0.67	0.33, 1.37		
Individual supplement use	2	0.4	429	1	0.98	0.25, 3.96	1.32	0.33, 5.30	0		0			
Overall *P*					0.86		0.52		0.99		0.55			
P for trend					0.61		0.25		0.81		0.24			

Abbreviations: CI, confidence interval; Ref, referent; VITAL, VITamins And Lifestyle.
[a] Based on duration (years) of use of the individual (single) supplement.
[b] Daily dose includes combined intakes from multivitamins and individual (single) supplements.
[c] For all supplements, <5% of the data were missing; percentages are of the total. Numbers may not sum to the total and percentages may not add to 100% because of missing data and/or rounding.
[d] Adjusted for age, gender, years of smoking, pack-years, and pack-years squared.
[e] Also adjusted for fruit and vegetable intake, physical activity, supplemental vitamin E use, and body mass index.

vitamin A from multivitamins plus individual/nonmultivitamin supplements was classified into categories of no use; use that could be obtained from 10 years of daily intake of a standard multivitamin (e.g., Centrum Silver; Wyeth Consumer Healthcare, Madison, New Jersey); and higher average daily dose (i.e., from individual or other nonmultivitamin supplements). 3) There is only one variable each for supplemental lutein and lycopene: "no use," "multivitamin use only," and "individual/nonmultivitamin supplement use."

Participants missing data on supplemental vitamin use or other covariates in the model were excluded from analysis. We treated 10-year average supplement use as a continuous variable to assess for trends in lung cancer risk.

RESULTS

After a mean of 4.05 years (standard deviation, 0.78) of follow-up, 521 participants developed lung cancer, and 391 cases of the disease (75%) were non-small-cell lung cancer; the breakdown was as follows: adenocarcinoma ($n = 174$ (33%)); squamous cell ($n = 93$ (18%)); large cell ($n = 10$ (2%)); and non-small-cell carcinoma, not otherwise specified ($n = 114$, 22%)). Small-cell lung cancer accounted for 14% ($n = 74$) of the total lung cancers. Other lung cancers, mostly comprising carcinomas not otherwise specified and carcinoid/neuroendocrine tumors, accounted for 11% of the total.

Table 1 gives the demographic and other selected characteristics of study participants, classified as cases and non–lung cancer cases. Lung cancer cases were somewhat older than individuals who did not develop lung cancer (mean ages = 67.0 years and 61.9 years, respectively) and were more often male and noncollege graduates. Not unexpectedly, only 8% of lung cancer cases were never smokers and, compared with noncases, were more likely to be current smokers (30% vs. 8%), to have smoked for a longer period of time (83% vs. 28% for 20–59 years of smoking), and to have smoked more cigarettes (43.2 pack-years vs. 13.4 pack-years). At baseline, lung cancer cases were also significantly more likely than noncases to be sedentary, consume fewer fruits and vegetables, and have a history of COPD or emphysema and a family history of lung cancer.

Associations of lung cancer risk (total cases and by histologic type) with duration of use of individual/nonmultivitamin mixtures of β-carotene and retinol supplements and 10-year average daily dose of β-carotene, retinol, vitamin A, lutein, and lycopene from multivitamins and individual/nonmultivitamin supplements during the previous 10 years are given in Table 2. Use of individual β-carotene supplements for ≥4 years was associated with a small, nonsignificant 18% elevated risk of total lung cancer; the association was considerably stronger for small-cell lung cancer: hazard ratio = 3.22 (95% confidence interval: 1.29, 8.07). Longer duration of use of individual retinol supplements was associated with hazard ratios of 1.53 (95% confidence interval: 1.12, 2.08) and 1.80 (95% confidence interval: 1.29, 2.52) for all lung cancers and non-small-cell lung cancer, respectively. Ten-year average daily intakes of supplemental β-carotene of >600 mcg and of retinol of >1,200 mcg, representing more than can be obtained from 10-year daily

Table 3. Associations of Lung Cancer Risk With Duration of Use[a] and Daily Dose[b] During the Previous 10 Years of β-Carotene, Retinol, Total Vitamin A, Lutein, and Lycopene Supplements, Stratified by Gender, the VITAL Study, Washington State, 2000–2002 ($n = 77,126$)[c]

Supplement	Lung Cancer Cases		Males ($n = 36,551$)		Females ($n = 39,309$)	
	No.	%	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI
β-Carotene (no. of years[a] used over 10 years)[e]						
No use	454	89	1.00 (Ref)		1.00 (Ref)	
1–3 years	26	5	0.90	0.46, 1.78	1.32	0.73, 2.40
≥4 years	32	6	1.06	0.60, 1.87	1.34	0.74, 2.42
Overall *P*			0.93		0.45	
P for trend			0.93		0.18	
			P for interaction = 0.65			
β-Carotene (10-year average daily dose)[e]						
No use	178	35	1.00 (Ref)		1.00 (Ref)	
>0–1,200 mcg	286	56	1.03	0.81, 1.32	1.02	0.71, 1.45
>1,200 mcg	49	10	1.10	0.71, 1.70	1.49	0.86, 2.58
Overall *P*			0.91		0.28	
P for trend			0.67		0.28	
			P for interaction = 0.50			
Retinol (no. of years[a] used over 10 years)						
No use	438	87	1.00 (Ref)		1.00 (Ref)	
1–3 years	22	4	1.09	0.56, 2.12	1.34	0.76, 2.35
≥4 years	44	9	1.58	1.04, 2.40	1.46	0.92, 2.32
Overall *P*			0.10		0.19	
P for trend			0.02		0.08	
			P for interaction = 0.85			
Retinol (10-year average daily dose)						
No use	176	35	1.00 (Ref)		1.00 (Ref)	
>0–1,200 mcg	274	54	0.96	0.75, 1.23	1.34	0.76, 2.35
>1,200 mcg	60	12	1.24	0.84, 1.85	1.46	0.92, 2.32
Overall *P*			0.42		0.19	
P for trend			0.56		0.08	
			P for interaction = 0.80			

Table continues

use of common multivitamin formulations, were each associated with a nonsignificant 25% elevated risk of total lung cancer. Although not statistically significant, the association for 10-year average daily dose was considerably stronger for β-carotene with small-cell lung cancer (hazard ratio = 2.58, 95% confidence interval: 0.99, 6.72) and "other lung cancers" (hazard ratio = 1.95, 95% confidence interval: 0.63, 6.02). Use of individual lutein supplements during the previous 10 years was associated with 102% and 148% increased risks of total lung cancers and non-small-cell lung cancer compared with nonuse of these supplements: hazard ratio = 2.02 (95% confidence interval: 1.28, 3.17) and hazard ratio = 2.48 (95% confidence interval: 1.53, 4.02), respectively. Lycopene supplement use was not associated with lung cancer risk. We also found no noticeable differences in these associations when histologic cell types were stratified as adenocarcinoma, squamous cell, and all other lung cancers) (data not shown).

Table 3 gives associations of duration of individual supplement use of β-carotene and retinol and 10-year average daily dose from multivitamins and individual/nonmultivitamin supplements of β-carotene, retinol, vitamin A, lutein, and lycopene with lung cancer risk, stratified by gender. Use of individual retinol supplements for ≥4 years was associated with a statistically significant 58% (95% confidence interval: 1.04, 2.40) increased risk of lung cancer for men

Table 3. Continued

Supplement	Lung Cancer Cases		Males (n = 36,551)		Females (n = 39,309)	
	No.	%	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI
Total vitamin A (10-year average daily dose)						
No use	173	34	1.00 (Ref)		1.00 (Ref)	
>0–1,500 mcg	269	53	0.96	0.75, 1.23	1.09	0.79, 1.49
>1,500 mcg	64	13	1.02	0.69, 1.51	1.23	0.80, 1.91
Overall P			0.92		0.64	
P for trend			0.94		0.35	
			P for interaction = 0.75			
Lutein (over 10 years)						
No use	318	61	1.00 (Ref)		1.00 (Ref)	
Multivitamin use only	181	35	1.10	0.86, 1.39	0.77	0.58, 1.03
Individual supplement use	20	4	1.64	0.73, 3.70	2.19	1.26, 3.81
Overall P			0.41		0.01	
P for trend			0.27		0.91	
			P for interaction = 0.12			
Lycopene (over 10 years)						
No use	399	77	1.00 (Ref)		1.00 (Ref)	
Multivitamin use only	120	23	1.17	0.89, 1.54	0.94	0.69, 1.29
Individual supplement use	2	0.4	0.71	0.10, 5.04	1.74	0.24, 12.41
Overall P			0.48		0.79	
P for trend			0.32		0.80	
			P for interaction = 0.42			

Abbreviations: CI, confidence interval; Ref, referent; VITAL, VITamins And Lifestyle.
[a] Based on duration (years) of use of the individual (single) supplement.
[b] Daily dose includes combined intakes from multivitamins and individual (single) supplements.
[c] For all supplements, <5% of the data were missing; percentages are of the total. Numbers may not sum to the total and percentages may not add to 100% because of missing data and/or rounding.
[d] Adjusted for age, gender, years of smoking, pack-years, and pack-years squared.
[e] Also adjusted for fruit and vegetable intake, physical activity, supplemental vitamin E use, and body mass index.

and a nonstatistically significant 46% (95% confidence interval: 0.92, 2.32) elevated risk for women (P for interaction = 0.85). Use of individual lutein supplements was associated with a statistically significant increased risk for women (hazard ratio = 2.19, 95% confidence interval: 1.26, 3.81) but not for men (hazard ratio = 1.64, 95% confidence interval: 0.73, 3.70) (P for interaction = 0.12). Use of individual lycopene supplements was associated with a 71% reduced risk for men but a 74% higher risk for women; however, these associations were not statistically significant. There was no appreciable effect modification by smoking status (defined as current; former smokers, quit <10 years ago; and former smokers, quit ≥10 years ago) based on either P values for interaction or stratification (Table 4).

DISCUSSION

In this study that examined associations of long-term use of β-carotene, retinol, vitamin A, lutein, and lycopene supplements with lung cancer risk, longer duration of use of individual supplemental retinol was associated with significantly elevated risk of non-small-cell lung cancer and total lung cancer, long-term use of individual β-carotene supplements was associated with elevated small-cell lung cancer risk, and use of individual lutein supplements was associated with elevated risk of non-small-cell lung cancer and total lung cancer. Results were generally similar for men and women, and there was no appreciable effect modification by smoking status. Lung cancer risk was not significantly associated with total average 10-year daily dose of any of these supplements or with lycopene supplement use.

To our knowledge, very few studies (and only one cohort investigation) have reported on associations of vitamin A and carotenoids from supplements only with lung cancer risk because most previous studies focused exclusively on diet or on diet plus supplements together (6, 15, 24–37). In general, case-control studies have suggested reduced risk of

Table 4. Associations of Lung Cancer Risk With Duration of Use[a] and Daily Dose[b] During the Previous 10 Years of β-Carotene, Retinol, Total Vitamin A, Lutein, and Lycopene Supplements, Stratified by Smoking Status, the VITAL Study, Washington State, 2000–2002 ($n = 77,126$)[c]

	Lung Cancer Cases		Current Smokers ($n = 6,313$)		Former Smokers, Quit <10 Years Ago ($n = 4,933$)		Former Smokers, Quit ≥10 Years Ago ($n = 27,907$)	
	No.	%	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI
β-Carotene (no. of years[a] used over 10 years)[e]								
No use	454	89	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
1–3 years	26	5	1.56	0.74, 3.25	1.58	0.67, 3.73	0.76	0.33, 1.74
≥4 years	32	6	0.72	0.26, 2.02	1.17	0.41, 3.31	1.29	0.74, 2.27
Overall *P*			0.38		0.57		0.51	
P for trend			0.57		0.89		0.25	
					P for interaction = 0.57			
β-Carotene (10-year average daily dose)[e]								
No use	178	35	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
>0–1,200 mcg	286	56	0.84	0.56, 1.26	1.04	0.63, 1.71	0.94	0.68, 1.31
>1,200 mcg	49	10	0.96	0.45, 2.07	1.52	0.64, 3.60	1.06	0.61, 1.84
Overall *P*			0.73		0.60		0.85	
P for trend			0.59		0.49		0.98	
					P for interaction = 0.50			
Retinol (no. of years[a] used over 10 years)								
No use	438	87	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
1–3 years	22	4	0.97	0.69, 1.36	0.87	0.55, 1.36	0.99	0.74, 1.33
≥4 years	44	9	1.34	0.78, 2.29	1.43	0.72, 2.84	1.05	0.66, 1.65
Overall *P*			0.48		0.32		0.97	
P for trend			0.53		0.68		0.90	
					P for interaction = 0.98			
Retinol (10-year average daily dose)								
No use	176	35	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
>0–1,200 mcg	274	54	1.58	0.77, 3.24	1.60	0.65, 3.96	1.10	0.56, 2.15
>1,200 mcg	60	12	1.38	0.75, 2.56	1.97	0.95, 4.10	1.46	0.93, 2.29
Overall *P*			0.29		0.13		0.25	
P for trend			0.11		0.32		0.04	
					P for interaction = 0.18			

Table continues

lung cancer with higher carotenoid intakes (25–31); cohort study findings have typically been null (6, 29–35); and randomized trials have reported slightly elevated risk for β-carotene, particularly among high-risk groups, such as smokers (12, 13, 29, 30, 36, 37). Overall, our findings are more in agreement with the randomized clinical trials of supplements than with the prior observational studies of diet. The CARET trial reported a weighted 36% increase in lung cancer incidence (relative risk = 1.36, 95% confidence interval: 1.07, 1.73; $P = 0.01$) among male smokers who received a combination of β-carotene (30 mg daily) and retinyl palmitate (25,000 IU daily) compared with placebo after a mean 4.1 years of follow-up (12). In the ATBC trial, β-carotene supplementation (20 mg daily) increased lung cancer risk by 16% (relative risk = 1.16, 95% confidence interval: 1.02, 1.33) after a mean follow-up of 6.1 years (13). In the Physicians' Health Study, daily supplementation of 50 mg of β-carotene plus aspirin did not have any effect on lung cancer incidence (36). Similarly, the Women's Health Study (37), a randomized trial testing β-carotene, aspirin, and vitamin E in preventing cancer and cardiovascular disease among 39,876 healthy female health professionals, found no significant benefit or harm of β-carotene after 2 years of 50-mg β-carotene supplementation on alternate days compared with placebo (relative risk = 1.03, 95% confidence interval: 0.89, 1.18).

Table 4. Continued

	Lung Cancer Cases		Current Smokers (n = 6,313)		Former Smokers, Quit <10 Years Ago (n = 4,933)		Former Smokers, Quit ≥10 Years Ago (n = 27,907)	
	No.	%	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI	Adjusted Hazard Ratio[d]	95% CI
Total vitamin A (10-year average daily dose)								
No use	173	34	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
>0–1,500 mcg	269	53	0.99	0.70, 1.40	0.80	0.50, 1.26	0.99	0.73, 1.33
>1,500 mcg	64	13	1.13	0.66, 1.94	1.32	0.71, 2.47	1.05	0.68, 1.61
Overall P			0.89		0.23		0.96	
P for trend			0.76		0.78		0.89	
					P for interaction = 0.12			
Lutein (over 10 years)								
No use	318	61	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Multivitamin use only	181	35	0.92	0.65, 1.31	0.92	0.51, 1.41	0.90	0.68, 1.19
Individual supplement use	20	4	3.31	1.53, 7.16	1.16	0.28, 4.78	1.58	0.77, 3.23
Overall P			0.006		0.89		0.29	
P for trend			0.39		0.95		0.94	
					P for interaction = 0.22			
Lycopene (over 10 years)								
No use	399	77	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Multivitamin use only	120	23	1.22	0.75, 1.76	0.96	0.58, 1.59	1.02	0.75, 1.39
Individual supplement use	2	0.4					1.65	0.41, 6.65
Overall P			0.56		0.99		0.78	
P for trend			0.36		0.81		0.72	
					P for interaction = 0.99			

Abbreviations: CI, confidence interval; Ref, referent; VITAL, VITamins And Lifestyle.
[a] Based on duration (years) of use of the individual (single) supplement.
[b] Daily dose includes combined intakes from multivitamins and individual (single) supplements.
[c] For all supplements, <5% of the data were missing; percentages are of the total. Numbers may not sum to the total and percentages may not add to 100% because of missing data and/or rounding.
[d] Adjusted for age, gender, years of smoking, pack-years, and pack-years squared.
[e] Also adjusted for fruit and vegetable intake, physical activity, supplemental vitamin E use, and body mass index.

These results are in marked contrast to those from prospective cohort studies. Using pooled data from 8 cohort studies, Cho et al. (24) found that neither dietary nor supplemental vitamin A was associated with lung cancer risk. Männistö et al. (6), using data from 7 cohort studies in the United States and Europe, reported that none of the carotenoids evaluated in the current study were associated with lung cancer risk. In the Health Professionals Follow-up Study and the Nurses' Health Study, lycopene and total carotenoids (from diet) were associated with reduced lung cancer risk (32). Even in the ATBC cohort (34), lower risks of lung cancer were reported for the highest versus the lowest quintiles of self-reported dietary intakes of total carotenoids (16%) and lycopene (28%), as well as serum β-carotene (19%) and serum retinol (27%).

It is interesting that duration of use of individual β-carotene, retinol, and lutein supplements, but not high average 10-year daily dose from multivitamins plus individual supplements, was positively associated with elevated lung cancer risk. It has been suggested that 1) these nutrients from supplements may be more bioavailable than those from dietary sources; 2) large intakes may interfere with absorption, transport, and distribution and/or metabolism of other carotenoids or micronutrients that could have offered significant protection; and 3) too high a dose of an antioxidant vitamin may interfere with generation of reactive oxygen species needed for beneficial processes, such as normal immune response and apoptosis (15, 16, 38, 39). Therefore, one might have expected that higher doses of these supplements would be associated with higher risk (similar to randomized trials), whereas long-term use may or may not be associated with higher risk (analogous to studies of diet). However, it is possible that duration of individual supplement use was more predictive of risk because individual supplements contain the highest dosages of the nutrients. Nonetheless, note that β-carotene supplement doses in the

intervention arms of the ATBC trial (20 mg/day) and CARET (30 mg/day) are appreciably higher than in the VITAL Study, where the median 10-year daily dose and years of use of individual supplemental β-carotene were 4,500 μg/day and 5 years, respectively. Thus, it is possible that the cumulative effect of relatively high doses of β-carotene and other carotenoids taken over a longer period of time (in the VITAL Study) may have a stronger effect on risk than supranutritional doses of shorter or similar duration (in the randomized trials). Additional studies examining the potential effect of long-term supplement use on lung cancer risk would be valuable in explaining these discrepancies.

Because lutein supplement use was relatively infrequent in our study population, we decided to classify lutein supplement use as nonusers, (lutein-containing) multivitamin users, and individual supplement users rather than presenting information on average dose and years of use. Although there were only 2 lung cancer cases in the individual lutein supplement use category, the respective mean and median daily doses among users were 1.5 mcg (standard deviation, 0.7) and 1.0 mcg, and only 0.22% of participants had used the individual supplement for 6 years or longer, the results are strongly suggestive of elevated risk associated with lutein use. Given that lutein supplements have been used only in the past 15 years and only recently at high doses, this potential risk factor for lung cancer may be more important than suggested by the present study.

We found no significant associations of supplemental lycopene with lung cancer risk in the present study. As noted above, observational studies have generally reported that dietary lycopene is associated with reduced lung cancer risk (25–30), which is not surprising given that lycopene is a potent antioxidant (9, 11). The lack of an association may be due to the fact that 77% of VITAL participants did not consume lycopene from either multivitamins or individual supplements, and only 2 participants (0.4%) used the individual supplement.

There is inconsistency in the associations of carotenoids with lung cancer risk when examined separately in men and women. In the present study, we found few differences in the results between men and women. In a report by Wright et al. (31) that included 587 female lung cancer cases and in the Canadian National Breast Screening Study (35), dietary intakes of carotenoids were not associated with lung cancer risk. In contrast, in the Nurses' Health Study and the Health Professionals Follow-up Study, inverse associations of carotenoids with lung cancer risk were stronger for women than for men (32). In a New York State cohort, inverse associations of carotenoids with lung cancer risk were observed for men, but there were no associations for women (33). Reasons why associations may differ by gender are not clear, although it has been suggested that, compared with men, women may be more susceptible to the carcinogenic effects of cigarette smoke (40).

There was no appreciable effect modification by smoking versus nonsmoking status in our study, which is not surprising because there were few nonsmokers among our lung cancer cases: 30% and 62% were current or former smokers, respectively. Results also did not differ significantly when we compared current with former smokers. Some observational studies of diet have reported more pronounced "protective" effects of vitamin A and carotenoids on lung cancer risk for current and former smokers compared with nonsmokers (8, 15, 33, 41), whereas others have not reported these differences (6, 34).

Our study has several strengths. We used a comprehensive and validated instrument that captured long-term use of multivitamins and of individual and multinutrient supplements. Assessment of (long-term) intake during the 10 years prior to baseline allowed us to more closely investigate supplement exposure over the relevant period of lung cancer development. Exposure and risk factor ascertainment were obtained prior to the diagnosis of cancer, and this prospective approach reduced any possibility of selection bias. We controlled for several factors that affect or modify lung cancer risk, particularly the strong effects of tobacco smoking. Finally, lung cancer cases were ascertained by using a comprehensive linkage system with the SEER registry, which we have estimated to be almost 100% complete for the year 2005, suggesting that the number of nonidentified cases should be minimal.

The study also has some potential limitations. Response bias is a potential concern; however, in general, response bias is unlikely in a prospective study because potential participants cannot choose to take part in the study based on both supplement use and future (unknown) lung cancer diagnosis. However, participants could have volunteered to enroll based jointly on a risk factor for lung cancer (smoking or COPD) and supplement use (e.g., a greater proportion of supplement users who were current or former smokers may have joined the study than supplement users who did not smoke). Nonetheless, our careful control for smoking history and our evaluation of other potential confounding factors such as COPD should have appreciably minimized this bias. As with other observational studies, residual confounding is possible. Generalizability is limited by the fact that the VITAL cohort is predominantly white and generally healthy, which is reflected in the fact that there were fewer current smokers than in the US population as a whole. Also, we were unable to stratify cases by smoking versus nonsmoking status because of the small number of never smokers who developed lung cancer (8%).

This observational epidemiologic study is one of the first to report that long-term use of individual β-carotene, retinol, and lutein supplements is associated with elevated lung cancer risk, results generally in agreement with randomized clinical trials. Although the results do not universally suggest that retinol, β-carotene, and other carotenoid supplements increase lung cancer risk, there is clearly no evidence of a protective effect. These findings are particularly relevant to those who use the individual supplements; they suggest that long-term use of these supplements, at doses higher than in a typical multivitamin, may be harmful with regard to lung cancer risk. Clearly, prevention of lung cancer will continue to be based largely on tobacco smoking prevention efforts. Nonetheless, in light of these findings, long-term use of individual β-carotene, retinol, and lutein supplements should not be recommended for lung cancer prevention, particularly among smokers. Furthermore, additional

studies examining the effects of supplement use on risk of lung and other cancers are warranted.

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58(2):71–96.
2. American Cancer Society. *Cancer Facts & Figures 2008*. Atlanta, GA: American Cancer Society; 2008. (http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf). (Accessed August 3, 2008).
3. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: looking to the future. *J Clin Oncol*. 2005;23(14):3175–3185.
4. World Cancer Research Fund; American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR; 2007.
5. Linseisen J, Rohrmann S, Miller AB, et al. Fruit and vegetable consumption and lung cancer risk: updated information from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*. 2007;121(5):1103–1114.
6. Männistö S, Smith-Warner SA, Spiegelman D, et al. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. *Cancer Epidemiol Biomarkers Prev*. 2004;13(1):40–48.
7. Dosil-Díaz O, Ruano-Ravina A, Gestal-Otero JJ, et al. Consumption of fruit and vegetables and risk of lung cancer: a case-control study in Galicia, Spain. *Nutrition*. 2008;24(5):407–413.
8. Voorrips LE, Goldbohm RA, Verhoeven DT, et al. Vegetable and fruit consumption and lung cancer risk in the Netherlands Cohort Study on diet and cancer. *Cancer Causes Control*. 2000;11(2):101–115.
9. Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. *Mol Aspects Med*. 2005;26(6):459–516.
10. Holden JM, Eldridge AL, Beecher GR, et al. Carotenoid content of U.S. foods: an update of the database. *J Food Compost Anal*. 1999;12:169–196.
11. Arab L, Steck-Scott S, Fleishauer AT. Lycopene and the lung. *Exp Biol Med (Maywood)*. 2002;227(10):894–899.
12. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst*. 1996;88(21):1550–1559.
13. Albanes D, Heinonen OP, Huttunen JK, et al. Effects of alpha-tocopherol and beta-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. *Am J Clin Nutr*. 1995;62(6 suppl):1427S–1430S.
14. Byers T. Nutrition and lung cancer: lessons from the differing effects of foods and supplements. *Am J Respir Crit Care Med*. 2008;177(5):470–471.
15. Ruano-Ravina A, Figueiras A, Freire-Garabal M, et al. Antioxidant vitamins and risk of lung cancer. *Curr Pharm Des*. 2006;12(5):599–613.
16. Greenwald P, Anderson D, Nelson SA, et al. Clinical trials of vitamin and mineral supplements for cancer prevention. *Am J Clin Nutr*. 2007;85(1):314S–317S.
17. Radimer K, Bindewald B, Hughes J, et al. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999–2000. *Am J Epidemiol*. 2004;160(4):339–349.
18. Murphy SP, White KK, Park SY, et al. Multivitamin-multimineral supplements' effect on total nutrient intake. *Am J Clin Nutr*. 2007;85(1):280S–284S.
19. Slatore CG, Littman AJ, Au DH, et al. Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer. *Am J Respir Crit Care Med*. 2008;177(5):524–530.
20. White E, Patterson RE, Kristal AR, et al. VITamins And Lifestyle cohort study: study design and characteristics of supplement users. *Am J Epidemiol*. 2004;159(1):83–93.
21. *PDR: Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements*. 23rd ed. Montvale, NJ: Medical Economics Company; 2002.
22. Satia-Abouta J, Patterson RE, King IB, et al. Reliability and validity of self-report of vitamin and mineral supplement use in the Vitamins and Lifestyle Study. *Am J Epidemiol*. 2003;157(10):944–954.
23. Patterson RE, Kristal AR, Tinker LF, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9(3):178–187.
24. Cho E, Hunter DJ, Spiegelman D, et al. Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: a pooled analysis of 8 prospective studies. *Int J Cancer*. 2006;118(4):970–978.
25. De Stefani E, Brennan P, Boffetta P, et al. Diet and adenocarcinoma of the lung: a case-control study in Uruguay. *Lung Cancer*. 2002;35(1):43–51.
26. Brennan P, Fortes C, Butler J, et al. A multicenter case-control study of diet and lung cancer among non-smokers. *Cancer Causes Control*. 2000;11(1):49–58.
27. Stefani ED, Boffetta P, Deneo-Pellegrini H, et al. Dietary antioxidants and lung cancer risk: a case-control study in Uruguay. *Nutr Cancer*. 1999;34(1):100–110.
28. Garcia-Closas R, Agudo A, Gonzalez CA, et al. Intake of specific carotenoids and flavonoids and the risk of lung cancer in women in Barcelona, Spain. *Nutr Cancer*. 1998;32(3):154–158.

29. Patterson RE, White E, Kristal AR, et al. Vitamin supplements and cancer risk: the epidemiologic evidence. *Cancer Causes Control*. 1997;8(5):786–802.
30. Cooper DA, Eldridge AL, Peters JC. Dietary carotenoids and lung cancer: a review of recent research. *Nutr Rev.* 1999; 57(5 pt 1):133–145.
31. Wright ME, Mayne ST, Swanson CA, et al. Dietary carotenoids, vegetables, and lung cancer risk in women: the Missouri women's health study (United States). *Cancer Causes Control*. 2003;14(1):85–96.
32. Michaud DS, Feskanich D, Rimm EB, et al. Intake of specific carotenoids and risk of lung cancer in 2 prospective U.S. cohorts. *Am J Clin Nutr.* 2000;72(4):990–997.
33. Bandera EV, Freudenheim JL, Marshall JR, et al. Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). *Cancer Causes Control*. 1997;8(6):828–840.
34. Holick CN, Michaud DS, Stolzenberg-Solomon R, et al. Dietary carotenoids, serum β-carotene, and retinol and risk of lung cancer in the Alpha-Tocopherol, Beta-Carotene cohort study. *Am J Epidemiol*. 2002;156(6):536–547.
35. Rohan TE, Jain M, Howe GR, et al. A cohort study of dietary carotenoids and lung cancer risk in women (Canada). *Cancer Causes Control*. 2002;13(3):231–237.
36. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334(18):1145–1149.
37. Lee IM, Cook NR, Manson JE, et al. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst*. 1999; 91(24):2102–2106.
38. Jakóbisiak M, Lasek W, Golab J. Natural mechanisms protecting against cancer. *Immunol Lett.* 2003;90(2-3):103–122.
39. Greenwald P. Beta-carotene and lung cancer: a lesson for future chemoprevention investigations [electronic article]? *J Natl Cancer Inst*. 2003;95(1):E1.
40. Osann KE. Epidemiology of lung cancer. *Curr Opin Pulm Med*. 1998;4(4):198–204.
41. Woodson K, Tangrea JA, Barrett MJ, et al. Serum alpha-tocopherol and subsequent risk of lung cancer among male smokers. *J Natl Cancer Inst*. 1999;91(20):1738–1743.