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Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: A pooled analysis of 8 prospective studies

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Intakes of vitamins A, C and E and folate have been hypothesized to reduce lung cancer risk. We examined these associations in a pooled analysis of the primary data from 8 prospective studies from North America and Europe. Baseline vitamin intake was assessed using a validated food-frequency questionnaire, in each study. We calculated study-specific associations and pooled them using a random-effects model. During follow-up of 430,281 persons over a maximum of 6–16 years in the studies, 3,206 incident lung cancer cases were documented. Vitamin intakes were inversely associated with lung cancer risk in age-adjusted analyses; the associations were greatly attenuated after adjusting for smoking and other risk factors for lung cancer. The pooled multivariate relative risks, comparing the highest *vs.* lowest quintile of intake from food-only, were 0.96 (95% confidence interval (CI) 0.83–1.11) for vitamin A, 0.80 (95% CI 0.71–0.91) for vitamin C, 0.86 (95% CI 0.76–0.99) for vitamin E and 0.88 (95% CI 0.74–1.04) for folate. The association with vitamin C was not independent of our previously reported inverse association with β-cryptoxanthin. Further, vitamin intakes from foods plus supplements were not associated with a reduced risk of lung cancer in multivariate analyses, and use of multivitamins and specific vitamin supplements was not significantly associated with lung cancer risk. The results generally did not differ across studies or by sex, smoking habits and lung cancer cell type. In conclusion, these data do not support the hypothesis that intakes of vitamins A, C and E and folate reduce lung cancer risk.

Key words: vitamin A; vitamin C; vitamin E; folic acid; lung neoplasms

Lung cancer is the most common incident cancer and cause of cancer death worldwide.[1] Intakes of vitamins A, C and E and folate have been hypothesized to reduce lung cancer risk because of their roles as regulators of cell differentiation (vitamin A),[2] antioxidants (vitamins C and E)[3] and modulators of DNA synthesis, methylation and repair (folate).[4,5] Some case–control studies have found inverse associations between intakes of these vitamins and lung cancer risk.[6–12] However, most of the prospective studies evaluating these nutrients have not found clear inverse associations.[1,13–18] Because many of these prospective studies have included less than 200 lung cancer cases, they lacked statistical power to detect modest inverse associations. In these studies, it was also difficult to examine associations among never-smokers, a group in which confounding by smoking (a strong risk factor for lung cancer)[19] is theoretically avoided to the extent that there is no misclassification of smoking status. We therefore examined the associations between vitamin intake and lung cancer risk in a pooled analysis of 8 cohort studies from Canada, Finland, the Netherlands, and the United States. Some of the studies[16–18,20] included in the pooled analysis have published results on intake of vitamins A, C and E or folate and multivitamin use and lung cancer risk, mostly with shorter duration of follow-up than that in the current analysis.

Methods

Population

The Pooling Project of Prospective Studies of Diet and Cancer has been described elsewhere.[21] For the lung cancer analyses, we identified 8 prospective studies[16,18,20,22–25] that met the following predefined criteria: (*i*) at least 50 incident lung cancer cases, (*ii*) assessment of usual dietary intake, (*iii*) completed validation study of either the dietary assessment method itself or a closely related instrument and (*iv*) assessment of smoking habits (Table I). Because most studies included only 1 sex, studies that included women and men were analyzed as 2 separate cohorts. Because the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was a clinical trial on association of vitamin E and β-carotene and lung cancer,[22] we included only the participants in the placebo group, in this analysis. To keep the study population consistent for the analyses of different vitamins, the Adventist Health Study was excluded from the specific vitamin analyses because this study lacked dietary vitamin intake data except for vitamin E. The person-time experienced during follow-up of the Nurses' Health Study (NHS) was divided into 2 segments (NHSa and NHSb) to

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TABLE I – CHARACTERISTICS OF THE COHORT STUDIES INCLUDED IN THE POOLED ANALYSIS OF VITAMINS A, C, E, AND FOLATE INTAKE AND LUNG CANCER

Study	Follow-up period	Baseline cohort size	No. of cases	Current smoker (%)	Past smoker (%)	Multivita min user (%)	Median intake/day[1]							
							Vitamin A from food (μg RE)	Total[2] vitamin A (μg RE)	Vitamin C from food (mg)	Total[2] vitamin C (mg)	Vitamin E from food (mg)	Total[2] vitamin E (mg)	Folate from food (μg)	Total[2] Folate (μg)
Adventist Health Study (W)	1976–1982	17,990	20	2	14	49	–	–	–	–	–	–	–	–
Adventist Health Study (M)		12,526	31	6	32	39	–	–	–	–	–	–	–	–
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (M)	1985–1996	6,771[3]	298	100	0	8	1,236	1,312	73	76	8	8	256	259
Canadian National Breast Screening Study (W)	1980–1993	56,837	149	20	28	–	1,013	–	131	–	16	–	243	–
Health Professionals Follow-up Study (M)	1986–1996	44,350	244	9	43	43	1,555	2,055	160	235	8	10	353	404
Iowa Women's Health Study (W)	1986–1996	33,828	433	15	19	33	1,480	1,883	132	177	8	10	248	281
Netherlands Cohort Study (W)	1986–1992	62,412	131	20	20	6	812	832	101	107	11	11	184	184
Netherlands Cohort Study (M)		58,279	843	33	53	3	936	947	91	94	13	14	210	210
New York State Cohort (W)	1980–1987	21,045	130	23	26	49	1,579	2,266	182	237	7	11	378	500
New York State Cohort (M)		27,936	392	21	49	38	1,642	2,162	196	240	7	10	408	496
Nurses' Health Study (a) (W)	1980–1986	88,307	156	29	28	34	1,375	1,766	120	155	4	5	240	277
Nurses' Health Study (b) (W)	1986–1996	68,307[4]	379	21	35	43	1,331	1,736	141	198	6	8	274	322
Total		430,281	3,206											

[1] Energy-adjusted values.–[2]Total values included contribution from food and supplements.–[3]Only the placebo group of the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was included.–[4]These women are a subset of the women included in the Nurses' Health Study (a) and are not included in the total.

take advantage of the more detailed dietary assessment completed in 1986. Following standard survival data analysis theory, blocks of person-time in different time periods are asymptotically uncorrelated, regardless of the extent to which they are derived from the same people.[26,27] Thus, pooling estimates from these 2 time periods, and the cases that arise within them, produces estimates and estimated standard errors, which are as valid as those from a single time period.

Exclusion criteria

After applying the exclusion criteria used by each study, we further excluded participants, if they had $\log_e$-transformed energy intakes beyond 3 standard deviations from the study-specific $\log_e$-transformed mean energy intake of the baseline population, reported a history of cancer other than nonmelanoma skin cancer at baseline or were missing information on smoking habits.

Case definition

Each study ascertained incident lung cancer cases by self-report with subsequent medical record review[23] or linkage with a cancer registry[16,18,20,25] or both[22,24]; in some studies, additional linkage with a death registry was used.[16,20,22–24] We categorized lung cancers on the basis of the International Classification of Diseases for Oncology morphology codes[28] or the histological classification provided by the original study investigators.

Dietary assessment

The baseline food-frequency questionnaire (FFQ) for each study inquired about usual consumption of food items, generally over the past year. Each study provided intake data for vitamins from food-only and from foods and supplements (total intake), if available. The New York State Cohort and the Netherlands Cohort Study each had entered their supplement data only as user *vs.* nonuser. To include these studies in the analyses of intakes from foods and supplements, we derived a total intake for each vitamin by assuming a frequency of once per day and a usual dose. For the Netherlands Cohort Study, we used the most common dose of each specific vitamin in multivitamins and supplements reported in their FFQ validation study. For the New York State Cohort, we used the dose for generic multivitamins and specific supplements used in the NHS. We used the regression-residual method[29] to adjust nutrient intakes for total energy intake of 1,600 kcal/day for women and 2,100 kcal/day for men.

The validity of intakes of these specific nutrients, as measured by the FFQ, was assessed in most of the cohorts.[30–37] The correlations between dietary intakes estimated by the FFQ and multiple diet records (or 24-hr recalls) ranged 0.14–0.76 for vitamin A, 0.53–0.77 for vitamin C, 0.42–0.79 for vitamin E and 0.26–0.92 for folate. The correlations for total vitamin intakes were generally higher than those for dietary intake, among those studies that measured both values. In the NHS and the Health Professionals Follow-up Study, additional validation studies were conducted using biochemical markers. Vitamin E intake was positively correlated with plasma concentrations of α-tocopherol ($r = 0.41$ for the NHS and 0.51 for the Health Professionals Follow-up Study)[38] and folate intake was positively related to erythrocyte folate levels ($r = 0.55$ for the NHS and 0.56 for the Health Professionals Follow-up Study).[39]

Nondietary covariates

Each study collected information on nondietary covariates by self-administered questionnaires at baseline. For smoking history, each study assessed whether individuals were never, past or current smokers. Among those who had ever smoked, the number of cigarettes smoked per day and the years smoked were assessed.

Statistical analysis

Vitamin intake was examined as quintiles in the primary analysis and as quartiles in the stratified analyses. Study-specific quin-

tiles and quartiles were assigned on the basis of the distributions of the subcohorts in the Canadian National Breast Screening Study and the Netherlands Cohort Study, which each used a case–cohort design,[40] and on the distributions of the whole cohort in the remaining studies. The Netherlands Cohort Study and the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study were not included in the quantile analyses for total vitamins A, C and E and folate intakes, because fewer than 10% of the participants in these studies reported of using multivitamins, a main source of supplemental intake; thus, their total intakes in the higher quantiles were not comparable to those in other studies in which more than 30% of the participants used multivitamins. We also examined total vitamin intakes as categorical variables with uniform absolute intake cutpoints across the studies; both the Netherlands Cohort Study and the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study were included in these categorical analyses so that the contribution from supplemental intake to total intake in these studies could be taken into account. To calculate the *p*-value for the test for trend, participants were assigned the median value of their category of intake, and this variable was used as a continuous variable in the study-specific regression models. Each study was analyzed using the Cox proportional hazards model. Incidence rate ratios were estimated using SAS PROC PHREG[41] for all studies except the Canadian National Breast Screening Study and the Netherlands Cohort Study. These 2 studies were analyzed using Epicure software.[42] For the analyses of each study, we stratified participants by age at baseline and the year in which the baseline questionnaire was returned. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of lung cancer diagnosis, death or end of follow-up, whichever came first. Multivariate models were adjusted for education (less than high school graduate, high school graduate and more than high school graduate), body-mass index (<23, $23–<25$, $25–<30$ and ≥ 30 kg/m^2), alcohol consumption (0, $>0–<5$, $5–<15$, $15–<30$ and ≥ 30 gal/day), smoking status (current, past and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), amount smoked for current smokers (continuous) and energy intake (continuous). The proportion of missing values for each covariate was <7% in each study; in the multivariate analyses, an indicator variable for missing responses was created for covariates, if applicable. Two-sided 95% confidence intervals (CIs) and *p*-values were calculated.

To obtain a single pooled estimate, a random-effects model was used to combine the $\log_e$ relative risks (RRs) from the multiple studies[43]; the study-specific RRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. Tests of heterogeneity were conducted using the Q statistic.[43,44]

Evaluation of heterogeneity

We tested for variation in RRs by sex, smoking status and alcohol consumption, using a meta-regression model.[45] We also tested whether associations differed between adenocarcinomas, small cell carcinomas and squamous cell carcinomas, using a 2 degree of freedom squared Wald test statistic.[46] Collectively, these 3 histological types represented at least 60% of the cases in each study.

Results

During follow-up for 6–16 years in the 8 cohort studies, 3,206 incident cases of lung cancer (1,398 females and 1,808 males) were documented (Table I). The percentage of multivitamin users was higher for the studies from the United States (range: 33–49%) compared with those from other countries (range: 3–8%).

In the age-adjusted analyses, intakes of vitamins A, C and E and folate from food-only were statistically significantly associated with at least 28% reduction in the risk of lung cancer for comparison of the highest *vs.* lowest quintiles (Table II). Each of the associations was greatly attenuated in the multivariate analyses, when adjusted for smoking and other potential risk factors for lung cancer, but the associations for intakes of vitamins C and E from food-only remained statistically significant, although the test for trend for vitamin E was not statistically significant. The results were similar when we limited the analyses to those studies with intake data from both food and supplemental sources (data not shown). Among those studies, we also analyzed vitamin intakes from food-only in individuals who did not receive any contribution of that specific nutrient from supplemental sources, to avoid obscuring an effect by supplemental sources of the nutrient; the results were minimally changed (data not shown). Results for total intakes for each vitamin (including the contribution from multivitamins and specific supplements plus foods; 1,734 lung cancer cases) were weaker than those for intakes from food-only in the age-adjusted and multivariate analyses; indeed, no association was suggested for any of the vitamins in the multivariate analyses for the entire study population (Table II).

Overall, differences in the results by sex were not statistically significant except for total vitamin C intake (Table II); total vitamin C intake was associated with a statistically significant reduced risk of lung cancer only in men, in the multivariate analysis (*p*-value, test for heterogeneity due to gender is 0.001). There also was a suggestion that the results differed between men and women for intakes of total vitamin A and vitamin E from food-only. In women, total vitamin A intake was associated with an elevated risk of lung cancer (*p*-value, test for heterogeneity due to gender is 0.14) and vitamin E intake from food-only was associated with a reduced risk of lung cancer (*p*-value, test for heterogeneity due to gender is 0.08).

Because vitamin C intake from food-only, but not total vitamin C intake, was associated with a reduced risk of lung cancer (Table II), the inverse association may not have been due to vitamin C itself but to other components that coexist with vitamin C in foods. We have reported previously in the Pooling Project that intake of fruits, particularly citrus fruits, was associated with a reduced risk of lung cancer.[47] We also found that β-cryptoxanthin intake was inversely related to lung cancer risk (the pooled multivariate RR for the highest *vs.* lowest quintile of intake was 0.76, 95% CI 0.67–0.86).[48] Because some of the food sources of β-cryptoxanthin and vitamin C are similar (*e.g.*, citrus fruits),[49] we included both nutrients (Spearman correlation coefficient = 0.5–0.8 across studies) in the multivariate model to examine the independent effect of these 2 nutrients. In this model, for comparisons of the highest *vs.* lowest quintiles of intake, the pooled multivariate RR for vitamin C intake from food-only was no longer statistically significant (RR = 0.91, 95% CI 0.76–1.08) while β-cryptoxanthin intake remained inversely related to lung cancer risk (RR = 0.80, 95% CI 0.69–0.93). When we simultaneously adjusted for intake of vitamin C from food-only and β-cryptoxanthin as continuous variables, we found a similar attenuation in the association between vitamin C intake from food-only and lung cancer risk. Higher vitamin E intake from food-only, but not total vitamin E intake, was inversely associated with lung cancer risk, although there was no statistically significant trend. Because β-cryptoxanthin intake may also confound these results (Spearman correlation coefficients between intakes of β-cryptoxanthin and vitamin E from food-only were <0.3 across studies), we also adjusted vitamin E intake from food-only, for β-cryptoxanthin intake. There was only a slight change in the pooled multivariate RR for the highest *vs.* lowest quintile of vitamin E intake from food-only (RR = 0.89, 95% CI 0.78–1.01) and of β-cryptoxanthin intake (RR = 0.78, 95% CI 0.69–0.89).

The pooled multivariate results for each vitamin were similar after excluding lung cancer cases that were diagnosed during the first 4 years of follow-up ($n = 1{,}750$ cases for analyses of vitamin intakes from food-only and 1,033 cases for analyses of total vitamin intake; data not shown).

We also examined total intakes of folate and vitamins A, C and E using uniform absolute intake cutpoints across studies to take

TABLE II – POOLED RRs (95% CIs) OF LUNG CANCER FOR QUINTILES OF VITAMIN INTAKES[1]

Vitamins	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p*-value, test for trend	*p*-value, test for between study heterogeneity in quintile 5	*p*-value, test for between study heterogeneity due to sex in quintile 5
Vitamin A from food only								
Age-adjusted	1.00	0.80	0.76	0.80	0.72 (0.61–0.85)	0.002	0.04	0.02
Multivariate[2]	1.00	0.94	0.98	1.06	0.96 (0.83–1.11)	0.90	0.25	0.54
Multivariate[2] for women	1.00	0.89	1.03	1.09	0.93 (0.74–1.17)	0.78	0.18	
Multivariate[2] for men	1.00	1.01	0.94	1.04	1.00 (0.83–1.20)	0.97	0.33	
Total vitamin A								
Age-adjusted	1.00	0.89	0.73	0.88	0.85 (0.74–0.99)	0.18	0.52	0.42
Multivariate[2]	1.00	1.09	0.92	1.13	1.13 (0.90–1.43)	0.21	0.04	0.14
Multivariate[2] for women	1.00	1.07	0.94	1.15	1.28 (1.06–1.53)	0.006	0.42	
Multivariate[2] for men	1.00	1.06	0.91	1.08	0.99 (0.55–1.79)	0.99	0.02	
Vitamin C from food only								
Age-adjusted	1.00	0.74	0.62	0.56	0.52 (0.45–0.61)	<0.001	0.18	0.64
Multivariate[2]	1.00	0.93	0.88	0.86	0.80 (0.71–0.91)	0.002	0.47	0.89
Multivariate[2] for women	1.00	0.94	0.98	0.89	0.81 (0.68–0.97)	0.01	0.39	
Multivariate[2] for men	1.00	0.93	0.78	0.84	0.80 (0.66–0.96)	0.08	0.33	
Total vitamin C								
Age-adjusted	1.00	0.70	0.72	0.65	0.70 (0.56–0.89)	0.17	0.04	0.001
Multivariate[2]	1.00	0.93	1.06	0.96	1.00 (0.80–1.25)	0.94	0.05	0.001
Multivariate[2] for women	1.00	1.00	1.06	1.04	1.19 (0.99–1.41)	0.05	0.96	
Multivariate[2] for men	1.00	0.86	1.02	0.82	0.71 (0.55–0.92)	0.01	0.56	
Vitamin E from food only								
Age-adjusted	1.00	0.74	0.70	0.67	0.61 (0.51–0.73)	<0.001	0.02	0.14
Multivariate[2]	1.00	0.87	0.91	0.93	0.86 (0.76–0.99)	0.36	0.34	0.08
Multivariate[2] for women	1.00	0.80	0.92	0.97	0.78 (0.64–0.94)	0.23	0.33	
Multivariate[2] for men	1.00	0.94	0.89	0.88	0.96 (0.81–1.14)	0.81	0.72	
Total vitamin E								
Age-adjusted	1.00	0.70	0.61	0.85	0.71 (0.62–0.82)	0.06	0.87	0.57
Multivariate[2]	1.00	0.88	0.79	1.05	0.96 (0.83–1.12)	0.85	0.75	0.56
Multivariate[2] for women	1.00	0.88	0.77	1.05	1.00 (0.83–1.19)	0.60	0.52	
Multivariate[2] for men	1.00	0.89	0.83	1.06	0.91 (0.71–1.16)	0.68	0.78	
Folate from food only								
Age-adjusted	1.00	0.76	0.71	0.63	0.61 (0.51–0.72)	<0.001	0.03	0.61
Multivariate[2]	1.00	0.96	0.96	0.94	0.88 (0.74–1.04)	0.08	0.09	0.20
Multivariate[2] for women	1.00	1.09	1.13	1.10	0.95 (0.79–1.13)	0.31	0.56	
Multivariate[2] for men	1.00	0.82	0.81	0.78	0.80 (0.58–1.08)	0.18	0.03	
Total folate								
Age-adjusted	1.00	0.70	0.62	0.66	0.73 (0.60–0.89)	0.04	0.11	0.10
Multivariate[2]	1.00	0.89	0.88	0.91	1.02 (0.83–1.26)	0.51	0.07	0.10
Multivariate[2] for women	1.00	0.93	0.89	0.90	1.12 (0.93–1.34)	0.09	0.36	
Multivariate[2] for men	1.00	0.83	0.86	0.97	0.86 (0.54–1.38)	0.78	0.06	

[1]Number of lung cancer cases: 3,155 total, 1,378 women and 1777 men for vitamins A, C, E and folate from food only; 1,734 total, 1098 women and 636 men for total vitamins A, C, E and folate. The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, the Netherlands Cohort Study, and the Canadian National Breast Screening Study were not included in total vitamins A, C, E and folate analyses.–[2]Adjusted for education (less than high school graduate, high school graduate and more than high school graduate), body-mass index (<23, 23–<25, 25–<30 and ≥30 kg/m^2), alcohol consumption (0, >0–<5, 5–<15, 15–<30 and ≥30 gal/day), smoking status (current, past and never smokers), smoking duration for current smokers (continuous), smoking duration for past smokers (continuous), amount smoked for current smokers (continuous) and energy (continuous).

advantage of the different ranges of intakes among the studies included in this analysis and to limit the highest intake category to those who received contributions from multivitamins or individual supplements. The results were similar to those using quintiles (Table III).

We conducted a stratified analysis by smoking status, to examine the association among nonsmokers (to minimize residual confounding by smoking) and to consider the possibility that associations differed by smoking status (Table IV). The associations between vitamin intake and lung cancer risk did not differ significantly by smoking status except for vitamin A intake from food-only (*p*-value, test for heterogeneity due to smoking is 0.03); however, vitamin A intake from food-only was not significantly associated with lung cancer risk among never, past or current smokers.

Because previous studies of other cancers have found inverse associations with folate intake that were largely limited to regular alcohol consumers,[50–52] we hypothesized that there might be a similar pattern for lung cancer. However, no inverse association for folate intake with lung cancer risk was found among persons with alcohol intakes of ≥15 gal/day (data not shown).

We also examined the associations by lung cancer cell type (Table V). The associations between vitamin intake and lung cancer risk were not statistically significantly different by lung cancer cell type.

When multivitamin use was evaluated separately, the pooled multivariate RR for multivitamin users compared with nonusers was 1.08 (95% CI 0.98–1.20) for women and men combined, 1.17 (95% CI 1.04–1.32) for women and 0.97 (95% CI 0.84–1.12) for men (*p*-value, test for heterogeneity due to sex is 0.06). The age-adjusted results were similar to the multivariate results (data not shown). RRs did not differ by smoking status, lung cancer cell type and after excluding lung cancer cases that were diagnosed during the first 4 years of follow-up (data not shown).

TABLE III – POOLED RRs (95% CIs) OF LUNG CANCER FOR INTAKES OF TOTAL VITAMINS A, C, E AND FOLATE USING ABSOLUTE CUTPOINTS

Vitamins	Intake category						*p*-value, test for trend	*p*-value, test for between-study heterogeneity for top category	*p*-value, test for between-study heterogeneity due to sex for top category
Total vitamin A									
Category (mcg RE/d)	<1000	1000–<1500	1500–<2000	2000–<2500	2500–<4000	>4000			
Number of cases	944	716	396	252	449	249			
Age-adjusted	1.00	0.89	0.87	0.77	0.84	0.81 (0.68–0.97)	0.16	0.46	0.26
Multivariate[1]	1.00	1.02	1.06	0.99	1.12	1.14 (0.88–1.47)	0.12	0.08	0.07
Total vitamin C									
Category (mg/d)	<100	100–<140	140–<180	180–<240	240–<600	>600			
Number of cases	1088	541	349	318	379	331			
Age-adjusted	1.00	0.74	0.64	0.65	0.60	0.67 (0.52–0.86)	0.10	0.04	0.008
Multivariate[1]	1.00	0.93	0.92	0.92	0.94	0.97 (0.78–1.22)	0.82	0.12	0.01
Multivariate[1] for women	1.00	0.92	1.00	0.92	1.03	1.13 (0.93–1.38)	0.11	0.45	
Multivariate[1] for men	1.00	1.03	0.87	0.93	0.73	0.73 (0.55–0.96)	0.02	0.55	
Total vitamin E									
Category (mg/d)	<6	6–<9	9–<15	15–<25	25–<200	>200			
Number of cases	469	715	763	572	230	257			
Age-adjusted	1.00	0.63	0.63	0.78	0.86	0.61 (0.47–0.80)	0.06	0.05	0.75
Multivariate[1]	1.00	0.80	0.83	1.03	1.14	0.86 (0.72–1.03)	0.96	0.41	0.77
Total folate									
Category (mcg/d)	<200	200–<250	250–<300	300–<400	400–<600	>600			
Number of cases	708	638	433	418	352	457			
Age-adjusted	1.26	1.00	0.85	0.72	0.76	0.88 (0.63–1.24)	0.09	0.006	0.14
Multivariate[1]	1.06	1.00	0.94	0.86	0.94	1.12 (0.85–1.46)	0.45	0.09	0.38

[1]Adjusted for the same covariates as multivariate model in Table II.

TABLE IV – POOLED MULTIVARIATE RRs (95% CIs) OF LUNG CANCER FOR QUARTILES OF VITAMINS BY SMOKING STATUS[1]

Vitamins	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value, test for trend	*p*-value, test for between-study heterogeneity in quartile 4	*p*-value, test for between-study heterogeneity due to sex in quartile 4	*p*-value, test for between-study heterogeneity due to smoking status in quartile 4
Vitamin A from food-only								
Never smokers[2,3]	1.00	1.10	0.94	0.71 (0.48–1.06)	0.06	0.48	0.85	
Past smokers[2,4]	1.00	0.88	1.01	1.19 (0.97–1.45)	0.07	0.66	0.75	
Current smokers[5]	1.00	0.96	1.08	0.93 (0.80–1.08)	0.54	0.49	0.40	0.03
Total vitamin A								
Never smokers[2,3]	1.00	0.95	1.14	1.11 (0.56–2.17)	0.60	0.07	0.94	
Past smokers[2,4]	1.00	0.94	1.16	1.22 (0.97–1.54)	0.04	0.63	0.56	
Current smokers[5]	1.00	1.07	0.96	1.09 (0.84–1.42)	0.59	0.07	0.05	0.50
Vitamin C from food-only								
Never smokers[2,3]	1.00	0.73	0.65	0.68 (0.41–1.12)	0.41	0.11	0.27	
Past smokers[2,4]	1.00	1.01	0.86	0.89 (0.73–1.10)	0.17	0.58	0.52	
Current smokers[5]	1.00	0.94	0.90	0.85 (0.70–1.02)	0.08	0.15	0.53	0.35
Total vitamin C								
Never smokers[2,3]	1.00	0.74	0.77	0.84 (0.42–1.66)	0.95	0.07	0.10	
Past smokers[2,4]	1.00	1.04	0.96	0.92 (0.73–1.16)	0.53	0.74	0.37	
Current smokers[5]	1.00	0.91	0.92	1.04 (0.84–1.29)	0.40	0.19	0.02	0.89
Vitamin E from food-only								
Never smokers[2,3]	1.00	1.04	1.08	0.99 (0.67–1.46)	0.89	0.62	0.61	
Past smokers[2,4]	1.00	0.99	0.85	0.83 (0.67–1.01)	0.22	0.60	0.13	
Current smokers[5]	1.00	0.87	0.92	0.94 (0.82–1.09)	0.95	0.49	0.09	0.38
Total vitamin E								
Never smokers[2,3]	1.00	1.22	1.19	1.42 (0.85–2.38)	0.37	0.29	0.72	
Past smokers[2,4]	1.00	0.88	0.97	0.97 (0.77–1.22)	0.94	0.86	0.26	
Current smokers[5]	1.00	0.88	0.87	1.01 (0.85–1.19)	0.47	0.85	0.49	0.34
Folate from food-only								
Never smokers[2,3]	1.00	0.87	0.78	0.69 (0.38–1.26)	0.23	0.03	0.12	
Past smokers[2,4]	1.00	1.01	0.94	0.96 (0.78–1.17)	0.69	0.89	0.71	
Current smokers[5]	1.00	0.94	0.92	0.86 (0.75–1.00)	0.06	0.56	0.30	0.37
Total folate								
Never smokers[2,3]	1.00	0.82	1.04	1.21 (0.59–2.45)	0.41	0.04	0.74	
Past smokers[2,4]	1.00	0.76	0.98	1.00 (0.80–1.25)	0.38	0.66	0.93	
Current smokers[5]	1.00	0.98	0.78	1.03 (0.83–1.27)	0.77	0.20	0.04	0.83

[1]Number of lung cancer cases: 259 never smokers, 981 past smokers and 1,915 current smokers for vitamins A, C, E and folate from food-only; 181 never smokers, 598 past smokers and 955 current smokers for total vitamins A, C, E and folate. The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, the Netherlands Cohort Study and the Canadian National Breast Screening Study were not included in total vitamins A, C, E and folate analyses.–[2,]The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was excluded because the cohort had only current smokers.–[3]Adjusted for education (less than high school graduate, high school graduate and more than high school graduate), body-mass index (<23, 23–<25, 25–<30 and ≥30 kg/m^2), alcohol consumption (0, >0–<5, 5–<15, 15–<30 and ≥30 gal/day), and energy (continuous).–[4]Covariates as in footnote 3 as well as smoking duration (continuous).–[5]Covariates as in footnote 3 as well as smoking duration (continuous) and amount smoked (continuous).

We further examined the association between vitamins A, C and E and folate from supplemental sources. For each vitamin, participants who used multivitamins or a supplement containing that vitamin or both were compared with those who did not use supplemental sources of that vitamin. No inverse association was observed for each nutrient (data not shown). In addition, there was no inverse association for each nutrient, when supplemental intake was categorized into 2 groups on the basis of dose (data not shown).

Discussion

In this pooled analysis of prospective studies, we found that intakes of vitamins A, C, E and folate were not associated with a lower risk of lung cancer after adjusting for multiple risk factors, including smoking habits and β-cryptoxanthin intake. The results were similar with different analytic approaches (study-specific quantiles *vs.* uniform absolute intake cutpoints across studies). The results generally were consistent across studies, sex, smoking status and lung cancer cell type.

Several epidemiologic studies have examined vitamin intakes in relation to lung cancer risk. Few case–control studies have found an inverse association between vitamin A intake (either from food-only or from food and supplements) and lung cancer risk[13], and few case–control studies have examined vitamin E intake and lung cancer risk.[12] Most of the prospective studies not meeting the criteria for the current analysis have not supported an inverse association for vitamins A and E from food-only or from supplemental sources.[1,13–15] In clinical trials, use of vitamin A (or β-carotene) and vitamin E supplement did not protect individuals from lung cancer development, compared with placebo.[22,53] Our results confirmed no benefit, but also showed no harmful effect, of both dietary and supplemental vitamin A and E intakes on lung cancer risk.

For vitamin C intake either from food-only or from food and supplements, cohort studies not meeting the criteria for the current analysis and some case–control studies have reported inverse associations in relation to lung cancer risk,[8,9,11,14,15,54,55] but others have not found statistically significant associations.[6,7,10,12,56,57] Because several studies have found an inverse association between fruit intake and lung cancer risk,[1] the inverse association between vitamin C and lung cancer risk might represent the effect of fruit itself or other components in fruits. In fact, in some of the studies[8,15,55] that found an inverse association between dietary vitamin C intake and lung cancer, the association for dietary vitamin C

TABLE V – POOLED MULTIVARIATE RRs (95% CIs) OF LUNG CANCER FOR QUARTILES OF VITAMINS BY LUNG CANCER CELL TYPE[1]

Vitamins	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p*-value, test for trend	*p*-value, test for between-study heterogeneity in quartile 4	*p*-value, test for between-study heterogeneity due to sex in quartile 4	*p*-value, test for between-study heterogeneity due to cell type in quartile 4
Vitamin A from food only								
Adenocarcinomas	1.00	0.99	1.08	1.01 (0.85–1.20)	0.61	0.37	0.80	
Small cell carcinomas	1.00	1.10	1.12	1.08 (0.89–1.30)	0.60	0.85	0.15	
Squamous cell carcinomas	1.00	0.94	1.00	1.01 (0.77–1.33)	0.65	0.04	0.22	0.86
Total vitamin A								
Adenocarcinomas	1.00	1.04	1.33	1.29 (0.98–1.70)	0.06	0.23	0.87	
Small cell carcinomas	1.00	1.00	0.80	1.19 (0.86–1.66)	0.30	0.65	0.36	
Squamous cell carcinomas	1.00	0.94	0.89	0.96 (0.49–1.85)	>0.99	0.001	0.17	0.70
Vitamin C from food only								
Adenocarcinomas	1.00	1.02	0.85	0.90 (0.74–1.09)	0.22	0.20	0.98	
Small cell carcinomas	1.00	0.92	0.83	0.83 (0.68–1.00)	0.07	0.91	0.17	
Squamous cell carcinomas	1.00	0.94	0.83	0.84 (0.70–1.00)	0.02	0.61	0.24	0.26
Total vitamin C								
Adenocarcinomas	1.00	1.00	1.06	1.04 (0.78–1.37)	0.93	0.18	0.03	
Small cell carcinomas	1.00	0.88	1.01	1.18 (0.71–1.96)	0.31	0.09	0.19	
Squamous cell carcinomas	1.00	0.85	0.90	0.82 (0.62–1.10)	0.27	0.94	0.55	0.34
Vitamin E from food only								
Adenocarcinomas	1.00	0.98	1.08	0.89 (0.72–1.09)	0.58	0.20	0.25	
Small cell carcinomas	1.00	0.91	0.85	1.06 (0.86–1.32)	0.52	0.32	0.61	
Squamous cell carcinomas	1.00	0.94	1.01	0.99 (0.80–1.21)	0.74	0.28	0.29	0.40
Total vitamin E								
Adenocarcinomas	1.00	0.99	1.09	1.19 (0.96–1.48)	0.14	0.89	0.85	
Small cell carcinomas	1.00	0.71	0.99	1.00 (0.65–1.53)	0.61	0.24	0.43	
Squamous cell carcinomas	1.00	0.90	0.82	0.92 (0.69–1.22)	0.84	0.86	0.83	0.45
Folate from food only								
Adenocarcinomas	1.00	1.04	1.04	0.93 (0.71–1.20)	0.47	0.02	0.25	
Small cell carcinomas	1.00	1.13	0.97	1.02 (0.80–1.31)	0.79	0.22	0.01	
Squamous cell carcinomas	1.00	1.02	0.95	0.92 (0.70–1.20)	0.43	0.04	0.12	0.63
Total folate								
Adenocarcinomas	1.00	1.06	1.00	1.28 (0.97–1.68)	0.04	0.17	0.91	
Small cell carcinomas	1.00	1.05	0.93	1.20 (0.83–1.75)	0.31	0.32	0.30	
Squamous cell carcinomas	1.00	0.82	0.82	0.90 (0.59–1.36)	0.68	0.11	0.24	0.51

[1]Number of lung cancer cases: 956 adenocarcinomas, 538 small cell carcinomas and 901 squamous cell carcinomas for vitamins A, C, E and folate from food-only; 652 adenocarcinomas, 263 small cell carcinomas and 359 squamous cell carcinomas for total vitamins A, C, E and folate. The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, the Netherlands Cohort Study and the Canadian National Breast Screening Study were not included in total vitamins A, C, E and folate analyses. Adjusted for the same covariates as multivariate model in Table II.

was similar to that observed for intakes of fruits or fruits and vegetables; in all these studies, associations with total vitamin C intakes were not examined. In our study, we found that total fruit, citrus fruit and β-cryptoxanthin (which is found in citrus fruits and other fruits[58]) intakes were each inversely associated with lung cancer risk.[47,48] Although we found a similar inverse association for vitamin C intake from food-only in the multivariate-adjusted analysis, the association was attenuated and not statistically significant after further adjustment for β-cryptoxanthin, while β-cryptoxanthin intake remained inversely associated with lung cancer risk. A cohort study of Chinese men reported essentially the same findings; the inverse association between vitamin C intake and lung cancer was largely explained by smoking and β-cryptoxanthin intake.[59] Moreover, in our study, vitamin C intake combining food and supplemental sources and supplemental vitamin C alone were each not associated with lung cancer risk. Thus, the inverse association between vitamin C intake from food-only and lung cancer risk probably represents the association with either β-cryptoxanthin intake or some other dietary constituents that are highly correlated with β-cryptoxanthin in fruits. This needs further exploration, as it is important to identify components in foods that may directly affect lung cancer risk.

Two previous studies that have examined the use of vitamin supplements and lung cancer risk have not found strong associations.[10,57] We found that multivitamin use was associated with a modest increase in lung cancer risk among women. Because of this, the weak inverse associations we observed for vitamin intake from food-only were attenuated or become slightly positive when we evaluated total vitamin intake, which included the intake from food and supplements in women. Multivitamin intake was not associated with lung cancer risk in men, and thus, the results for vitamin intake from food-only and total vitamin intake were similar in men. Because we analyzed multiple dietary factors within multiple strata, the positive associations we observed for multivitamin use and total vitamin A intake among women may be because of chance rather than have real biological implications.

Two clinical trials have found that folate and vitamin B12 supplementation reversed atypia among patients with bronchial squamous metaplasia, a precursor of squamous cell carcinoma of the lung.[60,61] However, few epidemiologic studies have examined folate intake in relation to lung cancer risk and these studies have not found inverse associations,[9,62] as also shown in our study. A recent case–control study has found that dietary folate intake was inversely associated with lung cancer risk among former smokers.[63] However, the association was not observed for total folate intake, which suggests that the inverse association observed for dietary folate intake may represent a beneficial effect of other cancer-preventing compounds found in fruits and vegetables rather than an effect of folate.

Our analysis had several strengths. By including only prospective cohort studies and those with validated diet assessment instruments, we minimized the possibility of bias and misclassification.

By applying uniform criteria to define the nutrient variables, if available, we minimized potential sources of heterogeneity across the studies. By pooling several studies, we had a large sample size to detect modest associations, even in analyses stratified by smoking and lung cancer cell type. Results were similar overall and, in the stratified analyses, with minimal heterogeneity across studies.

Our study also had several limitations. Because we only had data on baseline dietary intake, we were not able to assess changes in vitamin intake over time, whether from diet or supplements. Some of the studies included in our analyses did not have information on vitamin intake from multivitamins and supplements. Therefore, we had fewer studies included in the analyses of total vitamin intake than dietary intake. We also had limited power to evaluate especially high intakes of vitamins. In addition, we were not able to examine duration of vitamin supplement use.

In summary, this pooled analysis of 8 prospective studies does not suggest that intakes of vitamins A, C and E and folate reduce the risk of lung cancer. The results were similar with different analytic approaches and across studies, sex, smoking status and lung cancer cell type.

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