Long-Term Use of Supplemental Multivitamins, Vitamin C, Vitamin E, and Folate Does Not Reduce the Risk of Lung Cancer

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***Rationale*: Lung cancer is the leading cause of cancer-related mortality in the United States. Although supplements are used by half the population, limited information is available about their specific effect on lung cancer risk.**

***Objectives*: To explore the association of supplemental multivitamins, vitamin C, vitamin E, and folate with incident lung cancer.**

***Methods*: Prospective cohort of 77,721 men and women aged 50–76 years from Washington State in the VITAL (VITamins And Lifestyle) study. Cases were identified through the Seattle–Puget Sound SEER (Surveillance, Epidemiology, and End Results) cancer registry.**

***Measurements and Main Results*: Hazard ratios (HRs) for incident lung cancer according to 10-year average daily use of supplemental multivitamins, vitamin C, vitamin E, and folate. A total of 521 cases of lung cancer were identified. Adjusting for smoking, age, and sex, there was no inverse association with any supplement. Supplemental vitamin E was associated with a small increased risk of lung cancer (HR, 1.05 for every 100-mg/d increase in dose; 95% confidence interval [CI], 1.00–1.09; $P = 0.033$). This risk of supplemental vitamin E was largely confined to current smokers (HR, 1.11 for every 100-mg/d increase; 95% CI, 1.03–1.19; $P < 0.01$) and was greatest for non–small cell lung cancer (HR, 1.07 for every 100-mg/d increase; 95% CI, 1.02–1.12; $P = 0.004$).**

***Conclusions*: Supplemental multivitamins, vitamin C, vitamin E, and folate were not associated with a decreased risk of lung cancer. Supplemental vitamin E was associated with a small increased risk. Patients should be counseled against using these supplements to prevent lung cancer.**

Keywords: bronchial neoplasm; diet; dietary supplements; public health

Lung cancer is the leading cause of cancer-related mortality, accounting for an estimated 162,460 deaths in 2006 in the United States (1). Cigarette smoking causes 90% of all lung cancers (2), and although the prevalence of smoking is declining, the risk of lung cancer after smoking cessation persists and remains elevated compared with never-smokers (3). The Centers for Disease Control and Prevention estimated that 42% of the adult population in the United States has an increased risk of lung cancer because of current or former cigarette use (4, 5). Although there is currently a great deal of interest in using computed tomography for screening, the benefits have not been confirmed (6), and chemoprevention strategies have an even greater potential to reduce the morbidity and mortality of this disease.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung cancer is the leading cause of cancer-related mortality in the United States. Although supplements are used by half the population, limited information is available about their specific effect on lung cancer risk.

What This Study Adds to the Field

Supplemental multivitamins, vitamin C, vitamin E, and folate are unlikely to decrease the risk of developing lung cancer. Use of supplemental vitamin E at high doses for a prolonged period of time may slightly increase this risk.

Fruits and vegetables are associated with a lower incidence of lung cancer (7), but because dietary habits are difficult to change (8), there is considerable interest in supplemental vitamins for chemoprevention. Supplements are used by over half of adults in the United States (9), and a majority of them believe they are "good for health and well-being" (10). This belief that supplements are helpful, or at least safe, is controversial because there is growing evidence to the contrary and some supplements are associated with an increased risk of death (11, 12). A systematic review of randomized controlled trials found little evidence that vitamin supplementation prevents chronic disease, including cancer (13), and a National Institutes of Health (NIH) panel did not make recommendations about their use (14), noting the lack of research with "accurate and current data on the public's total intake of these nutrients."

Many food-based vitamins, including multivitamins, vitamin C, vitamin E, and folate, have been studied without consistent results in relation to the prevention of lung cancer (15–17). Randomized controlled trials that have included supplemental vitamin C and vitamin E showed no significant association (18–20), and in the case of β-carotene, have documented harmful effects (21, 22). In addition, folate supplementation has recently come under increased scrutiny given its effect on aggressive polyp formation in subjects at risk of colon cancer (23). Although there is information on possible mechanisms of these vitamins' effect on cancer (15, 24–26), epidemiologic studies in lung cancer have been mixed (27–36). A pooled analysis found no association with lung cancer and multivitamins, and total vitamin C, vitamin E, and folate, but had limited ability to detect an association with supplements (17). Most previous studies have only examined supplements dichotomously and none has examined the intensity of long-term average use.

The association of supplemental vitamin use with lung cancer remains uncertain. To address the NIH panel's concerns re-

(*Received in original form September 20, 2007; accepted in final form November 7, 2007*)

Supported by grant CA74846 from the National Cancer Institute.

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Am J Respir Crit Care Med Vol 177. pp 524–530, 2008
Originally Published in Press as DOI: 10.1164/rccm.200709-1398OC on November 7, 2007
Internet address: www.atsjournals.org

garding supplements (14), we used the VITAL (VITamins And Lifestyle) cohort, designed to specifically examine the association between supplement use and cancer in the general population, to evaluate the relationship between the long-term average intake of supplemental multivitamins, vitamin C, vitamin E, and folate on the risk of incident lung cancer. Given the detrimental effect of supplemental carotenoids in randomized controlled trials (21, 22) and the low use of β-carotene supplementation in this population, we did not study these supplements for this analysis. Some of the results of these analyses have been previously reported in the form of an abstract (37).

METHODS

Subject Recruitment

The methods used in the VITAL cohort study have been described (38). Men and women were eligible if they were aged 50 to 76 years and lived in the area covered by the Seattle–Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry. Using a commercial list, we mailed 364,418 questionnaires from October 2000–December 2002. A total of 77,719 (21.3%) participants returned questionnaires and passed eligibility and quality-control checks. Baseline data were obtained from a 24-page self-administered questionnaire that included items on supplement use, diet, medical history, personal characteristics, and cancer risks. The Institutional Review Board of the Fred Hutchinson Cancer Research Center approved the protocol.

Outcome Assessment

Participants were monitored for lung cancer occurring from baseline through December 31, 2005, by linking the cohort to the Seattle–Puget Sound SEER registry. Cases were ascertained through all hospitals in the area, offices of pathologists, oncologists, and radiotherapists, and from state death certificates. The SEER registry has been shown to have accurate and complete data collection (39) and is reliable for lung cancer histology (40).

Linkage was conducted in December 2006, at which time registry data were 99.7% complete. We excluded participants with a previous diagnosis of lung cancer reported at baseline or for whom this datum was missing (n = 588). We also excluded those whose lung cancer was first diagnosed on a death certificate only (n = 3) and those whose lung cancer morphology was lymphoma (n = 2).

For each subject, the censored date was the earliest date of withdrawal from the study (0.03%), death (3.02%), a move out of the SEER catchment area (4.57%), or last date of SEER diagnoses for remaining subjects (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 subjects had multiple diagnoses of lung cancer, we used the time to first primary diagnosis.

Measurement of Supplement Use

The VITAL supplement questionnaire is a valid and reliable indicator of supplement consumption (41). Respondents reported supplemental vitamin use, including multivitamins, vitamin C, vitamin E, and folate, during the 10 years before baseline. Supplement use was categorized as current, past, or never use with questions about the frequency (times per week), dose per day, and duration of use over the previous 10 years. For multivitamin use, 10-year intake was expressed as pills per week over the 10 years (years/10 × days per week). Average daily intake over the previous 10 years of supplemental vitamin C, vitamin E, and folate was estimated by summing intake from individual supplements and intake from multivitamins in the 10-year period, where intake from each nutrient was computed as follows: (years/10 × days per week/7 × dose per day). The vitamin content of each individual's multivitamin was estimated from the *Physician's Desk Reference for Non-Prescription Drugs* (42) and/or inquiry to manufacturers. Because the DL-α-tocopheryl acetate form of vitamin E was used by over 90% of the VITAL cohort, we used dl-α-tocopheryl acetate as the default form of supplemental vitamin E converted as follows: international units (IU) of vitamin E from DL-α-tocopherol acetate = mg DL-α-tocopherol acetate.

Covariates

Tobacco. Smokers were individuals who smoked at least one cigarette per day for at least a year and smoking status was defined as never, current, quit 10 years or more, or quit fewer than 10 years ago, as of the date of questionnaire completion. Duration of smoking was estimated by the reported number of years smoked, and intensity by the usual number of cigarettes smoked per day. Smokers reported the age they started.

Additional covariates. Known risks for lung cancer were assessed. Socioeconomic and anthropomorphic factors included self-reported age, sex, race, marital status, and education, and were assessed as part of the baseline questionnaire. Previous history of cancer and self-report of physician-diagnosed chronic obstructive pulmonary disease (COPD) and/or asthma was recorded. A family history of lung cancer was categorized as none or at least one first-degree relative with lung cancer. Body mass index (BMI) was calculated from the respondent's current weight and height, measured as kg/m^2.

Daily servings of fruit and vegetables excluding potatoes were assessed. These dietary values were assessed by a food frequency questionnaire (FFQ) that was an adaptation of FFQs developed for the Women's Health Initiative and other studies (43–45), with the addition of highly supplemented foods. The measurement properties of earlier versions of this questionnaire have been published (43). We analyzed total dietary vitamin C, vitamin E, and folate.

Analysis

All statistical analyses were performed using Stata SE-9 (StataCorp, College Station, TX). We used Cox regression to estimate the hazard ratios (HRs) for associations of supplemental multivitamin, vitamin C, vitamin E, and folate use with lung cancer. Robust standard errors were used to eliminate traditional proportional hazards assumptions. Age was the time variable, with left truncation for age at baseline (which adjusts for age) and censoring (right truncation) as above. Subjects with missing data on supplemental vitamin use or other covariates in the model were excluded from analysis. *A priori* we analyzed the smoking variables to develop a model to best control for the confounding of tobacco. 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 when started smoking) at a $P = 0.05$ level. Our final model includes years smoked, pack-years, and a squared pack-years term. We also decided *a priori* to include age and sex in the model. Finally, we evaluated whether COPD, previous history of cancer, family history of lung cancer, education, BMI, and daily fruit and vegetable servings were confounders of the supplement–lung cancer associations in models with age, sex, and the smoking variables. None substantively changed our point estimates or level of statistical significance for supplement use, so were not included as covariates in the final analysis.

Supplemental multivitamin, vitamin C, vitamin E, and folate use was analyzed by categories of use and as indicator variables to estimate HRs for lung cancer by level of use. We categorized the exposures into four groups: never use and tertiles of use based on the distribution in the entire cohort. We treated the 10-year average supplement use as a continuous variable to assess for trends in lung cancer risk.

We also examined the associations between different lung cancer morphologies and supplemental vitamins, as well as examining for differences of the supplement–lung cancer associations by subgroups defined by smoking status. Likelihood ratio tests were conducted to assess the interaction between supplements, analyzed as continuous variables, and the subgroups. *P* values for interaction were obtained to compare the fit of the models with and without the interaction terms.

RESULTS

A total of 77,126 subjects met inclusion criteria and were monitored for a mean of 4.05 years (SD, 0.78 yr). Five hundred twenty-one subjects developed lung cancer. Non–small cell lung cancer (NSCLC) accounted for 75% of the total as follows: adenocarcinoma (n = 174 [33.4%]), squamous cell (n = 93 [17.9%]), large cell (n = 10 [1.9%]), and NSCLC not otherwise specified (NOS) (n = 114 [21.9%]). Small cell lung cancer (SCLC)

accounted for 14% of the total lung cancers. Other lung cancers, mostly comprising carcinomas not otherwise specified and carcinoid/neuroendocrine tumors, accounted for 11% of the total.

Demographic and lifestyle factors with the associated HRs for lung cancer are listed in Table 1. In comparison to never-smokers, smoking status was associated with increased lung cancer risk. Subjects who smoked more in terms of both duration and intensity had an increased risk of lung cancer. After adjusting for age, sex, and tobacco use, education, prior history of cancer, COPD, a family history of lung cancer, and BMI were associated with lung cancer (Table 1).

After adjustment, 10-year average use of supplemental multivitamins, vitamin C, and folate was not associated with lung cancer for any category of intake or continuously (Table 2). There was no association for any level of vitamin E and lung cancer risk, but when examining the risk of lung cancer by the continuous variable of average 10-year intake of vitamin E, there was a significantly elevated HR (1.05; 95% confidence interval [CI], 1.00–1.09 per 100 mg/d; $P = 0\ 0.03$). After adjusting for intake of vitamin E from food sources, the point estimate for supplemental vitamin E was unchanged (HR, 1.04; 95% CI, 1.00–1.09; $P = 0.08$), although the results were no longer significant. The HRs for supplemental vitamin C and folate did not substantially change when adjusted for dietary intake.

When we examined the relationship between supplements and lung cancer morphologies, multivitamins, vitamin C, and folate were not associated with NSCLC, SCLC, or other lung cancers (Table 3). Although supplemental vitamin E was not associated with an increased risk of NSCLC when analyzed by dose categories, it was associated with an increased risk when

TABLE 1. CHARACTERISTICS OF COHORT AND LUNG CANCER CASES

Characteristic	Noncases* (*n = 76,605*)	Cases* (*n = 521*)	Adjusted Hazard Ratio (*95% CI*)
Smoking Variables			
Smoking status			
Never	36,399 (48.1)	42 (8.1)	1.00 Reference
Former, quit ⩾10 yr	28,140 (37.2)	226 (43.8)	5.77 (4.14–8.02)†
Former, quit <10 yr	4,941 (6.5)	93 (18.0)	17.94 (12.44–25.89)†
Current	6,269 (8.3)	155 (30.0)	23.96 (17.01–33.75)†
Pack-years‡	13.4 ± 21.1	43.2 ± 27.9	1.34 (per 10) (1.32–1.37)†
Years of smoking‡	11.9 ± 15.0	33.3 ± 14.2	2.12 (per 10) (1.99–2.26)†
Demographic Factors			
Age at baseline, yr	61.9 ± 7.4	67.0 ± 6.8	1.06 (1.05–1.08)§
Sex, female	39,849 (52.0)	224 (43.0)	1.02 (0.85–1.22)‖
Race			
White	70,146 (93.2)	473 (93.9)	1.00 Reference
Black	970 (1.3)	5 (1.0)	0.91 (0.37–2.21)¶
Other	4,174 (5.5)	26 (5.2)	1.18 (0.79–1.75)¶
Currently married	56,492 (75.1)	349 (68.7)	0.93 (0.76–1.14)¶
Education**			
Grade school/some HS	2,596 (3.5)	49 (9.7)	1.00 Reference
HS graduate/GED	12,476 (16.6)	139 (27.4)	0.94 (0.67–1.30)¶
Some college/tech school	28,835 (38.3)	200 (39.5)	0.72 (0.53–0.99)¶
College graduate	18,498 (24.6)	95 (18.8)	0.79 (0.56–1.12)¶
Advanced degree	12,904 (17.1)	24 (4.7)	0.39 (0.24–0.63)¶
Medical History			
Prior cancer	10,761 (14.1)	121 (23.3)	1.38 (1.12–1.70)¶
COPD	2,667 (3.5)	80 (15.4)	1.45 (1.13–1.87)¶
Asthma	7,482 (9.8)	59 (11.4)	1.09 (0.83–1.44)¶
Family history lung cancer††	9,522 (12.6)	104 (20.3)	1.49 (1.20–1.86)¶
Lifestyle Factors			
BMI category, kg/m^2‡‡			
Underweight (<18.5)	654 (0.9)	14 (2.7)	1.59 (0.88–2.89)¶
Normal (18.5–24.9)	24,383 (31.8)	182 (34.9)	1.00 Reference
Overweight (25–29.9)	29,852 (39.0)	206 (39.5)	0.86 (0.70–1.05)¶
Obese (⩾30)	17,930 (23.4)	92 (17.7)	0.66 (0.51–0.85)¶
Fruit/vegetables (servings/d)**			
First quartile (0–2)	17,250 (24.8)	134 (30.0)	1.00 Reference
Second quartile (2.1–3.2)	17,486 (25.1)	130 (29.0)	1.08 (0.85–1.38)¶
Third quartile (3.3–5.0)	17,383 (25.0)	100 (22.3)	0.91 (0.70–1.19)¶
Fourth quartile (>5.1)	17,489 (25.1)	84 (18.8)	0.90 (0.68–1.19)¶

Definition of abbreviations: BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HS = high school.

Except where noted, all characteristics had <5% missing data and percentages are of total; numbers may not sum to 100% secondary to missing data and/or rounding.

* Values shown are number (%) or mean ± SD.

† Adjusted for age and sex.

‡ Among all participants.

§ Adjusted for years of smoking, pack-years, pack-years squared, and sex.

‖ Adjusted for years of smoking, pack-years, pack-years squared, and age.

¶ Adjusted for years of smoking, pack-years, pack-years squared, age, and sex.

** 9.1% and 14.0% of cases and controls, respectively, were missing this data.

†† Family history of lung cancer defined as 0 or ⩾1 first-degree relative with lung cancer.

‡‡ 4.9% and 5.2% of cases and controls, respectively, were missing this data.

TABLE 2. HAZARD RATIOS FOR LUNG CANCER ASSOCIATED WITH 10-YEAR USE OF SUPPLEMENTAL MULTIVITAMINS, VITAMIN C, VITAMIN E, AND FOLATE

Vitamin Use	Noncases (*n = 76,605*)	Cases (*n = 521*)	Adjusted Hazard Ratio (*95% CI*)*
Multivitamin			
No multivitamin use	26,440 (34.5)	183 (35.1)	1.00 Reference
First tertile: >0–2.8 pills/wk	15,912 (20.8)	106 (20.4)	1.21 (0.95–1.54)
Second tertile: >2.8–5.6 pills/wk	14,602 (19.1)	90 (17.3)	1.08 (0.84–1.39)
Third tertile: >5.6 pills/wk	19,641 (25.6)	142 (27.3)	0.98 (0.78–1.22)
			P trend: 0.69
Vitamin C			
No vitamin C use	20,415 (26.9)	150 (29.0)	1.00 Reference
First tertile: <60 mg/d	15,146 (19.9)	98 (18.9)	1.05 (0.81–1.35)
Second tertile: 60–322 mg/d	21,830 (28.7)	146 (28.2)	1.01 (0.80–1.27)
Third tertile: >322 mg/d	18,590 (24.5)	124 (23.9)	0.97 (0.76–1.23)
			P trend: 0.88
Vitamin E			
No vitamin E use	19,963 (26.3)	146 (28.4)	1.00 Reference
First tertile: <42 mg/d	18,676 (24.6)	115 (22.3)	0.97 (0.76–1.25)
Second tertile: 42–215 mg/d	18,604 (24.5)	93 (18.1)	0.80 (0.62–1.04)
Third tertile: >215 mg/d	18,778 (24.7)	161 (31.3)	1.19 (0.95–1.50)
			P trend: 0.03†
Folate			
No folate use	24,394 (32.1)	174 (33.6)	1.00 Reference
First tertile: < 200 μg/d	15,961 (21.0)	98 (19.0)	1.07 (0.83–1.37)
Second tertile: 2–399 μg/d	14,081 (18.5)	88 (17.0)	1.05 (0.81–1.36)
Third tertile: ⩾400 μg/d	21,619 (28.4)	157 (30.4)	0.99 (0.79–1.23)
			P trend: 0.68

Values for noncases and cases are number (%). All supplements had <5% missing data and percentages are of total; numbers may not sum to 100% secondary to missing data and/or rounding.

* Adjusted for age, sex, years smoked, pack-years, and pack-years squared.

† Hazard ratio, 1.05, for every 100 mg/day.

modeled continuously (HR, 1.07 for every 100-mg/d increase; 95% CI, 1.02–1.12; $P < 0.01$). This risk translates to a 28% increased risk of lung cancer at a dose of 400 mg/day for 10 years. We did not find an association between supplemental vitamin E and other morphologies (Table 3).

Further stratifying NSCLC into adenocarcinoma, squamous cell carcinoma, and NSCLC, NOS subtypes, no individual category of supplemental vitamin E had a statistically significant association. However, there were significant associations for squamous cell carcinoma and NSCLC, NOS when vitamin E

TABLE 3. HAZARD RATIOS FOR LUNG CANCER ASSOCIATED WITH 10-YEAR USE OF SUPPLEMENTAL MULTIVITAMINS, VITAMINS C, VITAMIN E, AND FOLATE STRATIFIED BY MORPHOLOGY

	Adjusted Hazard Ratio (*95% CI*)		
Vitamin Use	NSCLC	SCLC	Other Lung Cancers
Multivitamin			
No multivitamin use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: >0–2.8 pills/wk	1.18 (0.90–1.56)	1.34 (0.73–2.46)	1.23 (0.57–2.63)
Second tertile: >2.8–5.6 pills/wk	1.03 (0.77–1.38)	1.21 (0.63–2.31)	1.23 (0.56–2.67)
Third tertile: >5.6 pills/wk	0.99 (0.77–1.28)	0.70 (0.35–1.40)	1.23 (0.63–2.40)
	P trend: 0.84	*P* trend: 0.31	*P* trend: 0.56
Vitamin C			
No vitamin C use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: <60 mg/d	0.99 (0.73–1.33)	1.23 (0.65–2.34)	1.22 (0.56–2.66)
Second tertile: 60–322 mg/d	1.04 90.80–1.36)	0.98 (0.53–1.82)	0.77 (0.35–1.70)
Third tertile: >322 mg/d	0.97 (0.74–1.29)	0.65 (0.31–1.35)	1.37 (0.67–2.79)
	P trend: 0.74	*P* trend: 0.22	*P* trend: 0.18
Vitamin E			
No vitamin E use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: <42 mg/d	0.88 (0.66–1.19)	1.10 (0.61–1.99)	1.47 (0.72–2.98)
Second tertile: 42–215 mg/d	0.84 (0.62–1.13)	0.68 (0.34–1.38)	0.74 (0.31–1.77)
Third tertile: >215 mg/d	1.29 (0.99–1.67)	0.66 (0.33–1.31)	1.32 (0.64–2.70)
	P trend < 0.01*	*P* trend: 0.40	*P* trend: 0.98
Folate			
No folate use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: <200 μg/d	1.03 (0.77–1.37)	1.24 (0.67–2.28)	1.12 (0.52–2.40)
Second tertile: 2–399 μg/d	1.05 (0.78–1.41)	1.17 (0.61–2.24)	0.93 (0.40–2.16)
Third tertile: ⩾400 μg/d	1.03 (0.80–1.32)	0.61 (0.31–1.21)	1.20 (0.63–2.29)
	P trend: 0.37	*P* trend: 0.18	*P* trend: 0.77

Definition of abbreviations: CI = confidence interval; NSCLC = non–small cell lung cancer; SCLC = small cell lung cancer.

Values are adjusted for age, sex, years smoked, pack-years, and pack-years squared.

* Hazard ratio = 1.07 for every 100-mg/day increase.

was analyzed continuously (HR, 1.09 for every 100-mg/d increase; 95% CI, 1.00–1.18; $P = 0.04$; and HR, 1.11 for every 100-mg/d increase; 95% CI, 1.02–1.20; $P = 0.01$, respectively). The association of adenocarcinoma with supplemental vitamin E when analyzed continuously was not significant.

Table 4 summarizes the results of the association of supplemental vitamin use stratified by smoking status. Because there were few never-smokers with lung cancer, we did not analyze this group. Similar to the previous findings, we found an increased risk for every 100-mg/day increase in supplemental vitamin E (HR, 1.11; 95% CI, 1.03–1.19; $P < 0.01$) for current smokers, with an overall P value for interaction of 0.06. Current smokers in the highest dose category had a significantly increased risk of lung cancer (HR, 1.59; 95% CI, 1.05–2.41; P for trend < 0.01). We found no significant association between incident lung cancer and supplemental vitamin E for either group of former smokers. There was no significant association between groups defined by smoking status and the other supplemental vitamins. These P values for interaction were all greater than 0.05.

DISCUSSION

Using a population-based cohort, we found no evidence that use of multivitamins, supplemental vitamin C, vitamin E, or folate is associated with a lower incidence of lung cancer. These estimates were adjusted for confounding factors, including tobacco, and were consistent using different analytic techniques. In contrast to the often assumed benefits or at least lack of harm, supplemental vitamin E was associated with a small increased risk of lung cancer that was most prominent in current smokers and in those with NSCLC.

Many of the previous studies of supplemental multivitamins, vitamin C, vitamin E, and/or folate have not found associations with lung cancer but were only able to analyze use dichotomously, as either current or no use (36, 46–48). Current use of supplemental vitamin C and folate was shown to be associated with a decreased risk of lung cancer for men only, whereas vitamin E did not affect the risk in either sex (27). Only Voorrips and colleagues analyzed longer term use of supplements; they studied 939 men with lung cancer and found no association between lung cancer and use of supplemental vitamin C and E as measured dichotomously for the previous 5 years (35). In contrast, the VITAL cohort was designed to assess the long-term intensity of supplement intake. We hypothesized that longer, higher dose exposures to supplements may be required to modify lung cancer risk and thus our measure of supplements focused on exposure over 10 years.

In addition to these observational studies, clinical trials of supplemental multivitamins, vitamin C, vitamin E, and/or folate do not suggest a benefit of supplemental vitamins for lung cancer chemoprevention. For example, a study using four different combinations of vitamin supplementation found no difference in lung cancer mortality (18). The 6-year follow-up to the Alpha Tocopherol and Beta-Carotene (ATBC) study found a relative risk of 1.03 (95% CI, 0.91–1.16) for lung cancer in the group using 50 mg/day of α-tocopherol (49). The Heart Protection Study, using a combination of antioxidant vitamins, 250 mg vitamin C, 20 mg β-carotene, and 600 mg of vitamin E, showed a nonsignificant increased lung cancer risk of relative risk (RR) 1.1 for the combination regimen (19). Likewise, the Women's Health Study showed a nonsignificant increased risk of lung cancer of 1.09 (95% CI, 0.83–1.44) using 600 IU of vitamin E (~270 mg) every other day (20).

TABLE 4. HAZARD RATIOS FOR LUNG CANCER ASSOCIATED WITH 10-YEAR USE OF SUPPLEMENTAL MULTIVITAMINS, VITAMIN C, VITAMIN E, AND FOLATE STRATIFIED BY SMOKING STATUS

	Adjusted Hazard Ratio (*95% CI*)		
Vitamin Use	Current Smokers	Former, Quit <10 yr	Former, Quit ⩾10 yr
Multivitamin			
No multivitamin use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: >0–2.8 pills/wk	1.12 (0.72–1.73)	1.29 (0.76–2.17)	1.16 (0.80–1.68)
Second tertile: >2.8–5.6 pills/wk	1.23 (0.77–1.94)	0.94 (0.52–1.72)	0.91 (0.62–1.35)
Third tertile: >5.6 pills/wk	1.02 (0.67–1.56)	0.70 (0.39–1.25)	0.96 (0.69–1.32)
	P trend: 76	*P* trend: 0.16	*P* trend: 0.60
		P for interaction: 0.41	
Vitamin C			
No vitamin C use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: <60 mg/d	1.08 (0.69–1.71)	0.73 (0.39–1.40)	1.06 (0.72–1.56)
Second tertile: 60–322 mg/d	1.24 (0.82–1.87)	0.88 (0.51–1.51)	0.83 (0.58–1.19)
Third tertile: >322 mg/d	1.05 (0.67–1.66)	0.90 (0.52–1.56)	0.92 (0.65–1.31)
	P trend: 0.53	*P* trend: 0.81	*P* trend: 1.00
		P for interaction: 0.98	
Vitamin E			
No vitamin E use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: <42 mg/d	1.06 (0.69–1.63)	0.72 (0.41–1.27)	0.90 (0.61–1.33)
Second tertile: 42–215 mg/d	0.68 (0.40–1.18)	0.80 (0.46–1.40)	0.86 (0.58–1.26)
Third tertile: >215 mg/d	1.59 (1.05–2.41)	0.77 (0.44–1.36)	1.11 (0.79–1.57)
	P trend < 0.01*	*P* trend: 0.28	*P* trend: 0.26
		P for interaction: 0.06	
Folate			
No folate use	1.00 Reference	1.00 Reference	1.00 Reference
First tertile: <200 μg/d	1.00 (0.64–1.58)	1.12 (0.65–1.93)	1.08 (0.74–1.58)
Second tertile: 2–399 μg/d	1.18 (0.74–1.90)	0.89 (0.48–1.65)	0.90 (0.60–1.35)
Third tertile: ⩾400 μg/d	1.08 (0.72–1.62)	0.76 (0.44–1.31)	0.97 (0.70–1.33)
	P trend: 0.30	*P* trend: 0.23	*P* trend: 0.90
		P for interaction: 0.29	

Values are adjusted for age, sex, years smoked, pack-years, and pack-years squared.
* Hazard ratio = 1.11 for every 100-mg/day increase.

Although long-term use of multivitamins and supplemental vitamin C and folate was not associated with lung cancer, supplemental vitamin E was associated with a small increased risk. Our results show a possible U-shaped association, with subjects using a medium dose for 10 years having a decreased risk whereas those using a high dose for 10 years showed an increased risk (Table 2). Because the HR modeled continuously is significant, the mildly increased risk of 1.05 for every 100-mg/day increase in supplemental vitamin E is heavily influenced by subjects using high-dose vitamin E supplementation.

It is interesting that the HR of incident lung cancer with high doses and prolonged use of supplemental vitamin E was greater for patients with NSCLC and current smokers. Cho and colleagues did not find differences in risks for different morphologies of lung cancer or by smoking status when they examined dietary vitamin C, E, and folate (17). The ATBC study participants, all of whom were smokers at study initiation, did show a nonsignificant increased risk of lung cancer among those randomized to α-tocopherol supplementation in heavy smokers (50). Watkins and coworkers found an increased risk of lung cancer mortality for men who currently smoke and who use multivitamins along with supplemental vitamins A, C, and E (RR, 1.17; 95% CI, 1.03–1.32) (51). One possible mechanism is that, although vitamin E is considered an antioxidant, it might act as a prooxidant as well (52).

Our study has several strengths. We were able to analyze the dose–response relationship of supplement use over a long period of time, which is likely necessary for biological plausibility. Our study examines the effect of individual supplements and our measure of supplement use has been validated (41). We controlled for the strong confounding effect of tobacco and examined multiple other variables that affect the risk of incident lung cancer. Finally, the SEER database is complete and accurate.

Residual confounding might bias our results. For example, although an association with lung cancer has been reported for education and BMI, even when adjusted for tobacco exposure and/or physical activity and dietary variables (53, 54), residual confounding may still affect these results. However, when we adjusted for BMI and education, together with other potential confounders, the HRs and statistical significance for multivitamin, vitamin C, vitamin E, and folate supplementation did not substantively change. Thus, it is unlikely residual confounding significantly biases our results.

Our study has some potential limitations. Even with this very large cohort, the ability to detect a non-null result is limited to at least a 30% difference in incidence. The VITAL cohort was predominantly white and there were fewer current smokers than the proportion in the United States as a whole. Although these demographic factors may limit generalizability, they increase our internal validity by providing a wide range of supplement intensity and duration. In addition, because this is a prospective cohort study, we avoid selection bias.

Given the large population of current and former smokers at risk, the wide use of supplemental vitamins, and the extensive mortality and morbidity burden of lung cancer, evaluating the potential effects of vitamin supplementation has significant public health and resource implications. Although early detection is currently of great interest (55), it is as yet unproven (6) and chemoprevention remains an essential avenue to explore. This study of supplemental multivitamins, vitamin C, vitamin E, and folate did not show any evidence for a decreased risk of lung cancer. Indeed, increasing intake of supplemental vitamin E was associated with a slightly increased risk of lung cancer. Future studies may focus on other components of fruit and vegetables that may explain the decreased risk that has been associated with fruit and vegetables (56). Our results, in combination with other intervention and cohort studies that have not found a decreased risk of incident lung cancer for users of supplemental multivitamins, vitamin C, vitamin E, and folate, should prompt clinicians to counsel patients that these supplements are unlikely to reduce the risk of lung cancer and may be detrimental.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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