



Intake of Vitamins E, C, and A and Risk of Lung Cancer

The NHANES I Epidemiologic Followup Study

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The relation between the dietary intake of vitamins E, C, and A (estimated by a 24-hour recall) and lung cancer incidence was examined in the First National Health and Nutrition Examination Survey Epidemiologic Followup Study cohort of 3,968 men and 6,100 women, aged 25–74 years. During a median follow-up period of 19 years (from 1971–1975 to 1992), 248 persons developed lung cancer. Adjusted for potential confounders using Cox proportional hazards regression methods with age as the underlying time variable, the relative risk of lung cancer for subjects in the highest quartile of vitamin C intake compared with those in the lowest quartile was 0.66 (95% confidence interval (CI) 0.45–0.96). For vitamin A intake, a protective effect was observed only for its fruit and vegetable component (carotenoids) among current smokers (relative risk = 0.49, 95% CI 0.29–0.84), but this was modified by the intensity of smoking (a statistically significant effect (relative risk = 0.33, 95% CI 0.13–0.84) was observed only for those in the lowest tertile of pack-years of smoking). The vitamin E intake-lung cancer relation was modified by the intensity of smoking with a significant protective effect confined to current smokers in the lowest tertile of pack-years of smoking (relative risk = 0.36, 95% CI 0.16–0.83). Overall, there was no additional protective effect of supplements of vitamins E, C, and A beyond that provided through dietary intake. When vitamin E, vitamin C, and carotenoid intakes were examined in combination, a strong protective effect was observed for those in the highest compared with those in the lowest quartile of all three intakes (relative risk = 0.32, 95% CI 0.14–0.74). These data provide support for a protective role of dietary vitamins E and C and of carotenoids against lung cancer risk but with a modification in effects by the intensity of cigarette exposure. While smoking avoidance is the most important behavior to reduce lung cancer risk, the daily consumption of a variety of fruits and vegetables that provides a combination of these nutrients and other potential protective factors may offer the best dietary protection against lung cancer. *Am J Epidemiol* 1997;146:231–43.

ascorbic acid; carotenoids; fruit; lung neoplasms; prospective studies; vegetables; vitamin A; vitamin E

There has been increasing interest in the role diet plays in reducing the risk of lung cancer. Vitamins E and C and the carotenoids, which have antioxidant properties, and vitamin A, which functions in cell differentiation, have been hypothesized to protect against cancer (1). Numerous studies have found an inverse association between the risk of lung cancer and the frequency of consumption of fruits and vegetables

(2), the major food sources of these nutrients. In human epidemiologic studies, the serum/plasma levels or dietary intakes of these nutrients have generally, but not always, been shown to be inversely associated with the risk of lung cancer (3–5). In recent intervention trials, however, there was no reduction in lung cancer incidence among participants given supplements of vitamin E (6), vitamin A (7), or β -carotene (6–8).

Although cigarette smoking is a major cause of lung cancer (9), few studies have examined in detail the modifying effect of the intensity of cigarette exposure on nutrients, particularly vitamins E and C, in relation to lung cancer risk. Using data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Followup Study (NHEFS), we examined the relation of intakes of dietary and supplemental vitamins E, C, and A, and that of fruits and vegetables, to subsequent risk of lung cancer, as well

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Abbreviations: CI, confidence interval; NHANES I, First National Health and Nutrition Examination Survey; NHEFS, First National Health and Nutrition Examination Survey Epidemiologic Followup Study.

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as the extent to which cigarette exposure or other risk factors modified these relations.

MATERIALS AND METHODS

The NHEFS cohort

The NHANES I, based on a probability sample of the civilian noninstitutionalized population of the United States, was conducted between 1971 and 1975 by the National Center for Health Statistics (10, 11). Groups at high risk for malnutrition (the elderly, children, women of childbearing age, and the poor) were oversampled. The first follow-up survey, the 1982-1984 NHEFS, included all persons who were 25-74 years of age at the time of the NHANES I (baseline) examination ($n = 14,407$) (12). Additional follow-up surveys were conducted in 1986 for those aged 55 years and older at baseline (13) and in 1987 (14) and in 1992 for the entire NHEFS cohort. By the end of the 1992 follow-up, 96 percent of the cohort were successfully traced with their vital status determined. Death certificates have been obtained for 98 percent of the 4,604 decedents. This analysis is based on the NHANES I subjects who were followed through 1992 in the NHEFS.

Dietary and supplemental intake of vitamins E, C, and A

Data on dietary intake were obtained at the baseline NHANES I interview. The dietary interview was conducted by trained interviewers using the 24-hour recall method. Each subject was asked to recall all foods and beverages consumed during the day preceding the interview (15). Information on food preparation methods and on portion sizes estimated with the aid of three-dimensional food models was also obtained. The intakes of calories, vitamin C (in mg), and vitamin A (in IU) from the 24-hour-recall data were estimated using food composition data from the US Department of Agriculture handbook no. 8, industry, and other sources (16).

There are a total of 1,639 single food items, including a limited number of processed or fortified products (17), in the 24-hour recalls of this cohort. We next constructed separate indices of intake of preformed vitamin A or retinol (hereafter referred to as retinol) and carotenoids by summing the vitamin A intake from the 24-hour-recall food items of their major sources (18). The intake of retinol was based on whole milk, dairy products, eggs, liver, butter, margarine (fortified with vitamin A, mostly retinyl esters, to the same level as butter), and fortified cereals, whereas carotenoid intake was based on all fruits and vegetables.

Estimates of the intake of vitamin E and polyunsaturated fatty acids were not available in the NHANES I nutrient database. Therefore, it was necessary to code all the 24-hour-recall food items reported by this cohort. Vitamin E (in mg of α -tocopherol equivalents) and polyunsaturated fatty acids (in g) values for all food items were obtained from the nutrient database (release 5, $n = 6,659$ food items) developed by the US Department of Agriculture for use in the Continuing Survey of Food Intakes by Individuals conducted in 1989-1990 (19). The values for 12 food items that were unavailable (all were reported less than 10 times, mostly one or two) were imputed from the food with greatest nutrient similarity. Using these coded values, we then estimated the intakes of vitamin E and polyunsaturated fatty acids from the 24-hour-recall data for each subject.

The NHANES I dietary interview also included a nonquantitative food frequency questionnaire inquiring about the frequency of consumption (as never, daily, weekly, or less than once a week) of 13 broad food categories during the 3-month period preceding the interview (15). However, in NHANES I, not all the food items in the 24-hour recall corresponded to those in the food frequency questionnaire food categories, and there are limitations in comparing the food patterns of the two dietary assessment tools (17). Thus, to determine the food sources of vitamins E, C, and A in the diet of this cohort, we assigned the 24-hour-recall food items to the food frequency questionnaire categories based on the NHANES I food codes, as well as descriptive and nutrient content similarities. The intakes of vitamins E, C, and A from each category and the proportions of the total intake of each of these nutrients contributed by each category were computed by combining information on the number of times each food item was reported, portion size, and the concentrations of vitamins E, C, and A for each food (20).

As shown in table 1, the intake of vitamin E was distributed in varying proportions in different food categories. Fruits and vegetables contributed 18 percent to its intake (partly reflecting the contribution of the added fat and oil of some items), followed by fats/oils and butter/margarine (17 percent), eggs (12 percent), and desserts (11 percent). In contrast, fruits and vegetables alone contributed 89 percent to the intake of vitamin C, particularly those that are rich in vitamin C (63 percent). In the case of vitamin A, fruits and vegetables contributed 46 percent, particularly those that are rich in vitamin A (32 percent), whereas eggs, butter/margarine, fats/oils, whole milk, cheese/cheese dishes, dairy products, and meat/poultry contributed 36 percent to its intake.

TABLE 1. Major food sources of the 24-hour recall intake of vitamins E, C, and A in the analytical cohort (n = 10,068), First National Health and Nutrition Examination Survey (NHANES I), 1971-1975

Food category*	% of intake from 24-hour recall†		
	Vitamin E	Vitamin C	Vitamin A
Fruits/vegetables—all	17.5	88.5	45.6
Rich in vitamin A‡	6.5	16.1	32.2
Rich in vitamin C‡	5.9	62.9	15.0
Eggs	11.5	0	7.6
Desserts	11.1	0.7	3.0
Butter/margarine	9.0	0	4.7
Cereals	8.0	1.3	2.4
Fats/oil	7.8	0.03	0.2
Bread	6.0	0.2	0.8
Mixed protein dishes	5.7	3.5	4.9
Meat/poultry	4.8	0.5	15.2
Cheese/cheese dishes	1.6	0.4	2.6

* Formed by the grouping of the single food items of the 24-hour recall based on NHANES I food codes and descriptive and nutrient content similarities.

† Contribution of each food category by percentage to the overall 24-hour recall intake of each nutrient.

‡ Subcategories of all fruits/vegetables, not mutually exclusive.

The use of various types of vitamin and mineral supplements was obtained during the baseline NHANES I (1971-1975) and the 1982-1984 follow-up interviews. At baseline, only the frequency of the use of supplements, reported as never, regularly (defined as daily), and irregularly (defined as at least weekly but less than daily), was reported (21). However, data on supplement use for a subset of this cohort at the 1982-1984 interview were more detailed as it included dosage as well as the duration of use. Using this information, together with US Recommended Dietary Allowances (22) and industry information on these products during the 1971-1975 period (Annette Dickinson, Council for Responsible Nutrition, personal communication, 1994), we made the following assumptions for the content of supplements containing vitamins E, C, and A. For the multivitamin products, vitamin E = 15 IU or 10.05 mg of α -tocopherol equivalents (1 IU of *dl*- α -tocopherol acetate, the form generally available in supplements, is equal to 0.67 mg of α -tocopherol equivalents (23)), vitamin C = 60 mg, and vitamin A = 5,000 IU. For the specific products, vitamin E = 400 IU or 268 mg of α -tocopherol equivalents, vitamin C = 500 mg, and vitamin A = 10,000 IU. Thus, for the supplement users in this cohort, dosages of vitamins E, C, and A at baseline were approximated from the content of one specific or multivitamin pill or from the sum of both (for those who reported usage of both products).

Analytical cohort

Since this analysis was focused on dietary variables, subjects with inadequate or unreliable baseline dietary data were excluded. Of the 14,407 subjects in the original NHEFS cohort, the following exclusions were made sequentially: no dietary recall ($n = 3,059$); dietary information from proxies ($n = 476$) or determined as unsatisfactory by interviewers ($n = 178$) or imputed ($n = 59$); pregnant at or within 3 months prior to baseline ($n = 166$); breastfeeding at baseline ($n = 11$); missing dietary vitamin E intake because of missing gram weight/skipped foods ($n = 42$); and inconsistent vitamin supplement use ($n = 3$). A small number of subjects were in more than one of these exclusion categories. After the further exclusion of 345 subjects (3.3 percent) who had unknown vital status at all interviews from the 1982-1984, 1986, 1987, and 1992 NHEFS, a total of 10,068 subjects remained for this analysis.

Identification of cases

Incident cases of lung cancer were identified from the follow-up interviews and confirmed based on information on the hospital records and death certificates. A lung cancer case was defined as any discharge diagnosis coded 162 using the *International Classification of Diseases, Ninth Revision* (24), or a death certificate with an underlying or nonunderlying cause of death containing this code.

Data analysis

The dietary intakes of vitamins E, C, and A, retinol, and carotenoids were correlated with total calorie intake ($r = 0.63, 0.25, 0.33, 0.28,$ and 0.13 , respectively). Thus, the dietary intakes of these nutrients were adjusted for total calorie intake by computing residuals from linear regression models with total calorie intake (\log_e -transformed) as the independent variable and the absolute nutrient intake (\log_e -transformed) as the dependent variable (25). To avoid negative values for the "calorie-adjusted" nutrient intake, we added the predicted nutrient intake for the mean total calorie intake of the cohort (on the \log_e scale) as a constant to the residuals, and these were then exponentiated back to the original scale. The total intakes of vitamins E, C, and A were also constructed by summing the intakes from both supplements (using the dosages approximated as described earlier) and diet. Since the intake from supplements was not correlated with total calorie intake, only the intake from the diet was calorie adjusted.

Based on the distributions of the entire analytical cohort, subjects were categorized into quartiles of each

measure of nutrient intake. Estimates of the risk of lung cancer incidence for subjects in the three upper quartiles relative to those in the lowest (referent) quartile (as indicator variables) for each nutrient and for supplement users relative to nonusers (coded as 1 and 0) were derived from Cox proportional hazards regression models (26) set up by the PHREG procedure in the SAS statistical package (27). For all relative risks, 95 percent confidence intervals were computed, and all *p* values were two tailed.

Because an individual's age is strongly related to cancer risk, we used age as the underlying time metric for the Cox regression models (28). Subjects entered the cohort at the age attained at the date of their baseline interview and left the cohort at the age attained at the date of their exit from the study. For lung cancer cases, the exit date was the date of incidence, as defined by the date of first hospital admission with a lung cancer discharge diagnosis ($n = 181$) or, if unknown, the date of death reported on the death certificate ($n = 67$). For those not having a diagnosis of lung cancer (noncases), the exit date was either the date of death if they had died from other causes or the date of the last follow-up interview.

The issue of using age rather than the traditional follow-up time on study as the time scale in the analysis of data from the NHEFS has been addressed in detail by Korn et al. (29). Because a number of covariates, such as diet, are related to age at baseline, the analysis was stratified on 10-year age-at-baseline groups (<40, 40–49, 50–59, 60–69, and ≥ 70). We also examined stratified Cox regression models using follow-up time as the underlying time metric and obtained similar results. Only the age time metric results are reported. To assess the effect of the NHEFS complex sample design on the Cox regression analyses using age as the time metric, we examined additional regressions using a newly developed computer program (29) that incorporates the clustering and sample weights into the analysis. Because the results of these sample-design-weighted regressions were consistent with those of the unweighted regressions, only the unweighted estimates, which have smaller variances, are presented.

Several potential confounders derived from the baseline interview were included in the multivariate regression models as indicator variables: race (white, black, others) and educational attainment (<12, 12, >12 years, missing) that were used for oversampling in the survey design; nonrecreational physical activity level (quite inactive, moderately active, very active, missing); body mass index (weight (kg)/height (m)² in quartiles); and alcohol consumption (grams of ethanol

per day (30) in quartiles, missing). Total calorie intake (in quartiles) was also included in the model because it was significantly associated with lung cancer risk in this cohort. Information on family history of lung cancer in the subject's first degree relative (no, yes, missing) was derived from the 1982–1984 and 1992 follow-up interviews. Information on cigarette smoking was collected at baseline for a subsample of the subjects in the original NHEFS cohort. For the remaining subjects, the baseline smoking information was inferred from the detailed smoking history obtained at the 1982–1984 follow-up interview. Cigarette exposure was included in the model as indicator variables with eight mutually exclusive categories of combined smoking status and pack-years of smoking: never smokers (reference category); three categories of former smokers with pack-years in tertiles 1, 2, and 3, respectively; three categories of current smokers with pack-years in tertiles 1, 2, and 3, respectively; and subjects with either unknown smoking status or pack-years. Because the results obtained with the use of a separate indicator for missing data for smoking exposure and the other covariates were similar to those with the exclusion of subjects with missing data, only the results for the former are presented.

All models were initially run separately for men and women. However, because of the small number of lung cancer cases among women ($n = 80$) and the lack of an interaction between sex and nutrients, the final models were based on men and women combined but with the inclusion of a variable for sex (coded as 0 for men and 1 for women). Because of the lack of specific information on lung cancer prevalence at baseline, analyses were also performed after excluding the 19 lung cancer cases diagnosed within the first 2 years of follow-up. Since the exclusion of these potential pre-clinical cases did not affect the nutrient-lung cancer association in any material way, except for a reduction in statistical power, the results are presented for all cases.

Tests for trend for the age- and multivariate-adjusted relative risks were performed by assigning the integers of 0, 1, 2, and 3 to the quartiles of the nutrient variables and treating the resulting score variables as continuous in the models. Effect modifications of the nutrient-lung cancer association were examined by including interaction terms in the models and, if significant ($p < 0.05$), stratified analyses were performed. The proportional hazards assumptions for the nutrient variables (nt) were examined by including an age \times nt interaction in the regression model. There was no indication of a violation of the proportional hazards assumptions for any of the nutrients.

RESULTS

The analytical cohort of 3,968 men and 6,100 women, aged 25–74 years (median, 50 years) at baseline, was followed over a median period of 19 years (range, 0.02–22 years). Eighty-three percent of the subjects were white, 16 percent were black, and 1 percent were of other races, and 53 percent had completed 12 or more years of education. Of the 248 lung cancer cases (168 men and 80 women), 60 (24 percent) were diagnosed at age <65 years; 43 (17 percent), at 65–69 years; 47 (19 percent), at 70–74 years; and 98 (40 percent), at ≥ 75 years.

Cigarette exposure

The smoking status of the cohort was distributed as follows: 4,261 persons (42 percent) were never smokers; 1,691 (17 percent), former smokers; 3,090 (31 percent), current smokers; and 1,026 (10 percent) had unknown smoking status. As expected, compared with the noncases, a majority of the cases were smokers; 54 percent versus 30 percent were current smokers and 22 percent versus 17 percent were former smokers in contrast to 11 percent versus 43 percent who were never smokers. The risk of lung cancer was strongly dependent on cigarette smoking status; the age-adjusted relative risk of lung cancer was 4.10 (95 percent confidence interval (CI) 2.55–6.60) and 9.72 (95 percent CI 6.33–14.9) for former and current smokers, respectively, as compared with never smokers. Lung cancer risk was also related to both the intensity and duration of cigarette exposure, as represented by the pack-years of smoking (calculated as the product of the number of packs per day (1 pack = 20 cigarettes) and the number of years smoked). The age-adjusted relative risks corresponding to the tertiles of pack-years of smoking were 2.29 (95 percent CI 1.15–4.57), 5.14 (95 percent CI 2.56–10.3), and 6.92 (95 percent CI 3.29–14.5) for former smokers and 6.43 (95 percent CI 3.93–10.5), 11.3 (95 percent CI 6.84–18.6), and 21.0 (95 percent CI 12.7–34.9) for

current smokers, respectively, as compared with never smokers, thus showing the expected dose-response for cigarette exposure.

Calorie-adjusted dietary intake

With the exception of retinol, the mean dietary intakes of vitamins E, C, and A (all food sources), carotenoids, and fruits and vegetables, adjusted for age and calorie intake, were significantly lower among the lung cancer cases than among the noncases (table 2). The age- and multivariate-adjusted relative risks of lung cancer according to quartiles of calorie-adjusted dietary intake of vitamins E, C, and A are shown in table 3. There was an indication of an inverse association between vitamin E intake and lung cancer risk ($p = 0.04$ for trend), but this was attenuated after the adjustment for potential confounders. Similar results were observed for the intake of vitamin A. When vitamin A intake was further examined in terms of its separate components, lung cancer risk was decreased with an increased intake of carotenoids but was increased with an increased intake of retinol. The inverse trend in relative risks for carotenoids ($p = 0.007$) was, however, reduced and no longer significant after multivariate adjustment. An inverse association with lung cancer risk that remained significant after multivariate adjustment was observed for vitamin C intake: relative risks of 0.85 (95 percent CI 0.60–1.19), 0.67 (95 percent CI 0.47–0.96), and 0.66 (95 percent CI 0.45–0.96) for those in quartiles 2–4, respectively, as compared with those in the lowest quartile.

Supplement intake

The regular use of multivitamins was reported by 15 percent, vitamin C by 5 percent, vitamin E by 3 percent, and vitamin A by 1 percent of this cohort. Regular usage of these supplements among the cases

TABLE 2. Comparison of the dietary intake of selected nutrients between cases and noncases of lung cancer, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, from 1971–1975 to 1992

	Nutrient					
	Vitamin E (mg of α -tocopherol equivalent)	Vitamin C (mg)	Vitamin A (IU)	Retinol (IU)*	Carotenoids (IU)†	Fruits/vegetables (g)
Cases ($n = 248$)	6.03 \pm 0.35‡	64.18 \pm 5.06	4,382.35 \pm 546.82	2,032.01 \pm 470.65	1,659.02 \pm 259.73	253.02 \pm 18.93
Noncases ($n = 9,820$)	6.30 \pm 0.05	82.21 \pm 0.80	4,960.19 \pm 86.44	1,854.91 \pm 74.40	2,274.45 \pm 41.06	342.15 \pm 2.99

* Calculated by summing the vitamin A intake from the 24-hour-recall food items of whole milk, dairy products, eggs, liver, butter, margarine, and fortified cereals.

† Calculated by summing the vitamin A intake from the 24-hour-recall food items of fruits and vegetables.

‡ Mean \pm standard error, age and calorie adjusted. All differences in nutrient intake between cases and noncases are significant at $p < 0.05$, except for intake of retinol.

TABLE 3. Relative risk of lung cancer according to quartiles of dietary intake of vitamins E, C, and A, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, from 1971-1975 to 1992

Quartiles*	No. of cases/noncases	Age adjusted†	Multivariate‡
Vitamin E (mg of α-tocopherol equivalent)			
1	77/2,440	1.00§	1.00
2	61/2,456	0.77 (0.55-1.08)¶	0.91 (0.65-1.29)
3	53/2,464	0.65 (0.45-0.92)	0.77 (0.54-1.10)
4	57/2,460	0.73 (0.52-1.03)	0.88 (0.62-1.25)
<i>p</i> , trend		0.04	0.30
Vitamin A (IU)			
1	65/2,452	1.00	1.00
2	62/2,455	0.84 (0.59-1.19)	0.98 (0.68-1.39)
3	64/2,453	0.86 (0.61-1.22)	0.98 (0.69-1.40)
4	57/2,460	0.78 (0.54-1.12)	1.01 (0.70-1.45)
<i>p</i> , trend		0.21	0.97
Retinol (IU)#			
1	54/2,463	1.00	1.00
2	66/2,451	1.11 (0.78-1.60)	1.20 (0.83-1.73)
3	61/2,456	0.93 (0.64-1.34)	0.99 (0.68-1.45)
4	67/2,450	1.22 (0.85-1.76)	1.25 (0.85-1.84)
<i>p</i> , trend		0.49	0.45
Carotenoids (IU)**			
1	87/2,430	1.00	1.00
2	49/2,468	0.53 (0.37-0.75)	0.56 (0.46-0.94)
3	59/2,458	0.66 (0.47-0.92)	0.78 (0.56-1.10)
4	53/2,464	0.59 (0.42-0.83)	0.74 (0.52-1.06)
<i>p</i> , trend		0.007	0.14
Vitamin C (mg)			
1	86/2,431	1.00	1.00
2	60/2,457	0.70 (0.50-0.97)	0.85 (0.60-1.19)
3	55/2,462	0.56 (0.40-0.78)	0.67 (0.47-0.96)
4	47/2,470	0.53 (0.37-0.76)	0.66 (0.45-0.96)
<i>p</i> , trend		0.0001	0.01

* Quartiles of dietary intake (calorie adjusted, as described in the text) based on overall distribution: <3.69, 3.69-5.10, 5.11-6.71, >6.71 mg for vitamin E; <1,699.63, 1,699.63-2,824.26, 2,824.27-5,110.76, >5,110.76 IU for vitamin A (all sources); <399.34, 399.34-859.37, 859.38-1,641.59, >1,641.59 IU for retinol; <206.20, 206.20-723.56, 723.57-2,289.87, >2,289.87 IU for carotenoids; <23.07, 23.07-54.29, 54.30-113.05, >113.05 mg for vitamin C.

† Relative risk from a proportional hazards model with exit age as the underlying time variable, stratified by baseline age and adjusted for sex.

‡ Relative risk adjusted for sex, race, educational attainment, nonrecreational activity level, body mass index, family history, smoking status/pack-years of smoking, total calorie intake, and alcohol intake.

§ Reference category.

¶ Numbers in parentheses, 95% confidence interval.

Calculated by summing the vitamin A intake from the 24-hour-recall food items of whole milk, dairy products, eggs, liver, butter, margarine, and fortified cereals.

** Calculated by summing the vitamin A intake from the 24-hour-recall food items of fruits and vegetables.

was similar to that among the noncases: multivitamins, 13 percent versus 15 percent; vitamin C, 6 percent versus 5 percent; vitamin E, 2 percent versus 3 percent; and vitamin A, 1 percent versus 1 percent. Furthermore, the regular use of vitamin supplements was associated with several socioeconomic and lifestyle

factors: female, white, and educated; non-current smoker; lower poverty level; higher physical activity level; lower body mass index; lower intakes of alcohol, cholesterol, and total and saturated fat; and higher intakes of fruits and vegetables. The percentage of irregular users was lower: 7, 2, 1, and 0.3 percent for

multivitamin and specific vitamins C, E, and A, respectively.

There was no indication of any significant protective effect against lung cancer risk for those who used multivitamin supplements or supplements for the specific vitamins E, C, and A (or their combinations) regularly or irregularly at either baseline or the 1982-1984 follow-up, or at both periods (data not shown). The magnitudes of the multivariate-adjusted relative risks of lung cancer in relation to the dietary intakes of vitamins E, C, and A (table 3) were not altered after the further adjustment for the use of multi- and specific vitamin supplements (data not shown). We next incorporated the use of vitamin supplements into the diet by forming an index of total intake rather than treating it as a potential confounder of the diet intake. Magnitudes of the relative risks of lung cancer in relation to the total intakes of vitamins E, C, and A (diet and supplements) were not appreciably different from those based on diet alone (data not shown).

Simultaneous and joint intakes of nutrients and fruits and vegetables

To further examine whether the effects of dietary intakes of vitamins E, C, and A and its components of retinol and carotenoids in relation to lung cancer risk were independent of each other, we also conducted analyses with all nutrients in the models simultaneously (data not shown). In the model that included vitamins E, C, and A (all food sources), there were no material changes in the risk estimates of each of these nutrients. Similarly, the risk estimates of vitamin E and retinol were not altered when adjusted for the effects of vitamin C and carotenoids simultaneously. Models adjusted for the dietary intake of cholesterol, total, saturated, or polyunsaturated fat, or serum cholesterol gave essentially the same results.

In this cohort, the dietary intakes of several nutrients of interest were correlated, particularly for vitamin C and carotenoids (calorie-adjusted correlation coefficient of 0.60), which may partly be attributed to common food sources. Because it would be statistically difficult to adjust the intake of vitamin C for that of carotenoids, or vice versa, by introducing them in the same model, we examined the nutrient-lung cancer associations based on the cross-classifications of the subjects on their joint intakes of these nutrients (table 4). The multivariate-adjusted relative risk of lung cancer for those in the highest quartile of all three dietary intakes of vitamins E and C and carotenoids, compared with those in the lowest quartile of all three intakes, was 0.32 (95 percent CI 0.14-0.74). Comparable, but slightly higher magnitudes of relative risks were observed for those with dietary intakes of the

following combinations of nutrients (highest vs. lowest quartile): 0.41 (95 percent CI 0.24-0.72) for vitamin C and carotenoids and 0.40 (95 percent CI 0.20-0.80) for vitamins E and C. The relative risks for other combinations of nutrients, particularly those that included retinol, were nonsignificant and were considerably less protective.

Because the dietary intake of vitamin C and carotenoids, and to a lesser extent of vitamin E, could also be a marker of fruit and vegetable consumption, they were next examined in relation to lung cancer risk. As shown in table 4, a lower risk of lung cancer was observed for those with a greater intake of fruits and vegetables; the multivariate-adjusted relative risks for those in the second to the fourth quartiles, compared with those in the lowest quartile of intake, were 0.77 (95 percent CI 0.55-1.07), 0.66 (95 percent CI 0.46-0.93), and 0.52 (95 percent CI 0.36-0.77), respectively.

Effect modifications by cigarette smoking status and alcohol consumption

Because there were few lung cancer cases among never smokers, modifications of the effects of intakes of vitamins E, C, and A and of fruits and vegetables on lung cancer risk by smoking status were examined only among current smokers and the combined category of never and former smokers (hereafter referred to as nonsmokers). As shown in table 5, a significant inverse trend of a decrease in risk of lung cancer with increased intakes of carotenoids, vitamin C, and fruits and vegetables was observed among current smokers but not among nonsmokers. In multivariate models, the linear interaction term between smoking status (coded as 0 for nonsmokers and 1 for current smokers) and dietary intake of these nutrients (\log_e -transformed) was significant only for the intake of carotenoids ($\beta = -0.10$, $p = 0.01$) and fruits and vegetables ($\beta = -0.08$, $p = 0.045$).

In this cohort, the age-adjusted relative risk of lung cancer in relation to alcohol consumption was 1.47 (95 percent CI 1.09-1.98) for those whose intake of ethanol from beer, wine, and liquor was >0.2 oz (5 g) per day compared with nondrinkers, but this effect of alcohol was reduced and was no longer significant after adjustment for cigarette exposure and other confounders (multivariate-adjusted relative risk = 1.18, 95 percent CI 0.86-1.61). Thus, because of the greater lung cancer risk-enhancing effect of cigarette smoking as compared with alcohol consumption, there is no indication of any material modification effect of alcohol on the results of this study.

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TABLE 4. Relative risk of lung cancer according to selected joint dietary intake* of vitamins E and C and of carotenoids and fruits/vegetables, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, from 1971-1975 to 1992

Joint nutrient intake† and of fruits/vegetables	No. of cases/noncases	Age adjusted‡	Multivariate§
Vitamin E + vitamin C + carotenoids¶			
Low	32/586	1.00#	1.00
Others	209/8,727	0.39 (0.27-0.56)**	0.51 (0.35-0.76)
High	7/507	0.22 (0.10-0.51)	0.32 (0.14-0.74)
<i>p</i> , trend		0.0001	0.0004
Vitamin C + carotenoids			
Low	64/1,473	1.00	1.00
Others	167/7,167	0.50 (0.38-0.67)	0.63 (0.47-0.85)
High	17/1,180	0.31 (0.18-0.54)	0.41 (0.24-0.72)
<i>p</i> , trend		0.0001	0.0003
Vitamin E + vitamin C			
Low	38/848	1.00	1.00
Others	199/8,153	0.49 (0.35-0.69)	0.63 (0.44-0.90)
High	11/819	0.28 (0.14-0.56)	0.40 (0.20-0.80)
<i>p</i> , trend		0.0001	0.003
Vitamin E + carotenoids			
Low	40/882	1.00	1.00
Others	187/7,982	0.49 (0.34-0.68)	0.60 (0.42-0.85)
High	21/956	0.46 (0.27-0.78)	0.62 (0.36-1.08)
<i>p</i> , trend		0.001	0.04
Fruits/vegetables (g) by quartile			
1	88/2,429	1.00	1.00
2	61/2,456	0.63 (0.45-0.87)	0.77 (0.55-1.07)
3	55/2,462	0.55 (0.40-0.78)	0.66 (0.46-0.93)
4	44/2,473	0.41 (0.28-0.58)	0.52 (0.36-0.77)
<i>p</i> , trend		0.0001	0.001

* Dietary intake of vitamins E and C and of carotenoids was calorie adjusted.

† Low, all nutrients in quartile 1; high, all nutrients in quartile 4; others, all nutrients in varying quartiles, based on the overall distribution.

‡ Relative risk from a proportional hazards model with exit age as the underlying time variable, stratified by baseline age and adjusted for sex.

§ Relative risk adjusted for sex, race, educational attainment, nonrecreational activity level, body mass index, family history, smoking status/pack-years of smoking, total calorie intake, and alcohol intake.

¶ Calculated by summing the vitamin A intake from the 24-hour-recall food items of fruits and vegetables.

Reference category.

** Numbers in parentheses, 95% confidence interval.

Effect modification by intensity of cigarette exposure

To further explore the effects of the intensity of cigarette exposure on the lung cancer-nutrient relation, stratified analyses were performed among current smokers. In these analyses, multivariate regression models containing indicator variables for the tertiles of pack-years of smoking and quartiles of dietary intakes of vitamins E, C, and A and of fruits and vegetables with pack-year in tertile 1 and dietary intake in quartile 1 as the reference category were constructed. Despite the small and varying number of cases in each of these

nutrient and pack-year categories, an inverse association between the intake of each of these nutrients and lung cancer risk was observed among those in the lowest tertile of pack-years of smoking (table 6). In contrast, irrespective of the level of nutrient intake, there was an increased risk of lung cancer among those in the highest tertile of pack-years of smoking. A similar pattern of lung cancer risk in relation to quartiles of intake of these nutrients (with quartile 1 as reference category) was observed when separate multivariate models were fitted for each tertile of pack-years of smoking (data not shown). In multivariate

TABLE 5. Multivariate-adjusted relative risk* of lung cancer according to quartiles of dietary intake† of vitamins E and C and of carotenoids and fruits/vegetables by smoking status, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, from 1971-1975 to 1992

Quartiles of Intake	No. of cases/ noncases	Nonsmokers‡	No. of cases/ noncases	Current smokers
Vitamin E (mg of α -tocopherol equivalents)				
1	24/1,321	1.00§	46/862	1.00
2	23/1,481	0.87 (0.48-1.55)¶	28/722	0.80 (0.49-1.31)
3	12/1,557	0.41 (0.20-0.84)	35/682	0.96 (0.61-1.53)
4	23/1,511	0.87 (0.49-1.60)	25/690	0.82 (0.50-1.37)
<i>p</i> , trend		0.33		0.60
Carotenoids (IU)#				
1	15/1,257	1.00	58/903	1.00
2	16/1,466	1.04 (0.50-2.14)	24/784	0.49 (0.30-0.81)
3	25/1,505	1.56 (0.81-3.03)	31/707	0.70 (0.44-1.10)
4	26/1,642	1.63 (0.84-3.15)	21/562	0.49 (0.29-0.84)
<i>p</i> , trend		0.08		0.02
Vitamin C (mg)				
1	15/1,262	1.00	56/899	1.00
2	21/1,406	1.49 (0.76-2.91)	31/823	0.75 (0.48-1.18)
3	23/1,545	1.27 (0.65-2.47)	27/697	0.58 (0.36-0.94)
4	23/1,657	1.37 (0.69-2.72)	20/537	0.55 (0.32-0.95)
<i>p</i> , trend		0.50		0.02
Fruits/vegetables (g)				
1	14/1,286	1.00	58/864	1.00
2	26/1,454	1.98 (1.02-3.85)	30/764	0.61 (0.39-0.96)
3	22/1,545	1.32 (0.66-2.64)	24/688	0.52 (0.32-0.85)
4	20/1,585	1.16 (0.56-2.39)	22/640	0.48 (0.28-0.82)
<i>p</i> , trend		0.85		0.002

* Relative risk from a proportional hazards model with exit age as the underlying time variable, stratified by baseline age and adjusted for sex, race, educational attainment, nonrecreational activity level, body mass index, family history, pack-years of smoking for former and current smokers, total calorie intake, and alcohol intake.

† Dietary intake of vitamins E and C and of carotenoids was calorie adjusted.

‡ Never plus former smokers.

§ Reference category.

¶ Numbers in parentheses, 95% confidence interval.

Calculated by summing the vitamin A intake from the 24-hour-recall food items of fruits and vegetables.

models, however, only the linear interaction term between pack-years of smoking and dietary intake of vitamin E ($\beta = 0.57$) and carotenoids ($\beta = 0.04$) was significant ($p < 0.05$).

DISCUSSION

In this prospective study of the NHEFS cohort, there was an inverse association between the dietary intake of vitamin C and the risk of lung cancer. There was no indication for an association between the dietary intake of vitamin A or its component of retinol and lung cancer risk. However, a protective effect was evident for its fruit and vegetable component (carotenoids) among current smokers, but this was modified by the intensity of smoking, where a statistically significant effect was observed for only those in the lowest tertile

of pack-years of smoking. The vitamin E intake-lung cancer relation was modified by the intensity of smoking, with a significant protective effect confined to current smokers who had lower pack-years of smoking.

There are several limitations in the present study that should be considered when interpreting the findings. The complete ascertainment of lung cancer cases was dependent on the availability of hospital records and death certificates. In this cohort, there were 40 subjects who reported lung cancer that was unconfirmed by hospital records or death certificates. The nutrient-lung cancer relations remained essentially unchanged when analyses were repeated with these subjects treated either as cases or excluded from the cohort. Thus, it is unlikely that the findings of this

TABLE 6. Multivariate-adjusted relative risk* of lung cancer according to quartiles of dietary intake† of vitamins E and C and of carotenoids and fruits/vegetables by cigarette exposure among current smokers,‡ First National Health and Nutrition Examination Survey Epidemiologic Followup Study, from 1971–1975 to 1992

Quartiles	Tertiles of pack-years of smoking		
	≤33 (n = 45/2,126)	34–57 (n = 44/497)	≥58 (n = 44/227)
Vitamin E (mg of α-tocopherol equivalent)			
1	1.00§	0.91 (0.43–1.91)¶	1.62 (0.77–3.39)
2	0.35 (0.15–0.83)	1.22 (0.55–2.74)	1.88 (0.85–4.19)
3	0.59 (0.27–1.27)	1.05 (0.48–2.29)	2.01 (0.91–4.45)
4	0.36 (0.16–0.83)	1.11 (0.50–2.50)	2.68 (1.05–6.84)
<i>p</i> , trend#		0.0001	
Vitamin C (mg)			
1	1.00	1.70 (0.88–3.32)	3.12 (1.55–6.27)
2	0.84 (0.41–1.72)	0.89 (0.35–2.29)	2.45 (1.11–5.40)
3	0.51 (0.21–1.22)	0.92 (0.39–2.18)	2.28 (1.02–5.10)
4	0.39 (0.15–1.00)	1.64 (0.72–3.74)	1.25 (0.40–3.87)
<i>p</i> , trend		0.0001	
Carotenoids (IU)**			
1	1.00	1.57 (0.82–3.02)	2.83 (1.42–5.63)
2	0.52 (0.24–1.15)	0.85 (0.35–2.06)	1.07 (0.44–2.65)
3	0.49 (0.22–1.08)	1.23 (0.58–2.61)	2.59 (1.14–5.88)
4	0.33 (0.13–0.84)	0.70 (0.26–1.91)	2.12 (0.93–4.84)
<i>p</i> , trend		0.0001	
Fruits/vegetables (g)			
1	1.00	1.52 (0.75–3.07)	3.93 (2.01–7.70)
2	0.59 (0.28–1.26)	1.36 (0.65–2.86)	1.28 (0.48–3.60)
3	0.52 (0.22–1.21)	0.69 (0.27–1.80)	2.21 (0.98–4.99)
4	0.50 (0.20–1.22)	1.26 (0.54–2.96)	0.98 (0.35–2.73)
<i>p</i> , trend		0.0003	

* From multivariate proportional hazards regression models with exit age as the underlying time variable, stratified by baseline age and adjusted for sex, race, educational attainment, nonrecreational activity level, body mass index, family history, total calorie intake, and alcohol intake.

† Dietary intake of vitamins E and C and of carotenoids was calorie adjusted.

‡ One case and 106 noncases were excluded from this analysis because of missing data on pack-years of smoking.

§ Reference category.

¶ Numbers in parentheses, 95% confidence interval.

Test for trend was performed by assigning integers from 0 to 11 to each of the dietary intake and pack-year categories (0 for dietary intake in quartile 1 and pack-year in tertile 1 and 11 for dietary intake in quartile 4 and pack-year in tertile 3) and by treating the score variables as continuous in the model.

** Calculated by summing the vitamin A intake from the 24-hour-recall food items of fruits and vegetables.

study were biased by this potential source of misclassification of cases. There were limitations in the cigarette exposure data, especially when they were collected only at baseline for a subsample of the subjects and were inferred from the detailed smoking history obtained at the 1982–1984 follow-up interview for the remaining subjects. The validity of this approach, which has been documented for all mortality (31), was similarly observed for lung cancer. This is because cigarette smoking was a strong and independent risk factor of lung cancer in this cohort, with an expected dose-response to the pack-years of smoking among the smokers. In this study, a person's smoking status, as

with nutrient intake and other risk factors at the time of the baseline interview, was assumed to remain the same throughout the follow-up period. If considerable changes in these factors occurred, particularly with regard to the cessation of smoking, then there is a possibility that the risk of lung cancer may have been underestimated. Other than cigarette smoking, adjustment for the risk factors of sex, race, educational attainment, physical activity level, body mass index, family history, total calorie intake, and alcohol intake had only a modest effect on the magnitude of the risk of lung cancer in relation to the intake of vitamins E, C, and A, and there was no evidence for effect mod-

ification by any of these factors. The possibility that the findings were due to some other uncontrolled confounding, however, cannot be excluded.

The assessment of vitamin E intake is subject to several methodological problems because of its wide distribution in foods, with vegetable oils, whole grain cereal products, eggs, and fruits and vegetables being the major sources (32); accuracy is also dependent on the quality of the food composition database used. Consequently, the limited number of food items in the frequency-based questionnaire of some earlier studies may not adequately represent the food sources of vitamin E. In this aspect, the quantitative 24-hour-recall dietary data used in this study appeared to provide a more comprehensive estimate of the intake of vitamin E. Intakes of vitamins E, C, and A were based on a single 24-hour recall, which is known to have a high degree of intra- to interindividual variability and may not represent an individual's usual intake (33). This may result in considerable misclassification of an individual's usual intake and may have biased the observed risk estimates toward zero. However, the magnitudes of the risk estimates observed in this study were comparable to those seen in other studies in which food frequency methods were used. Thus, this may suggest that the degree of misclassification resulting from the high intraindividual variability of the 24-hour-recall intake of these nutrients is similar to the degree of misclassification resulting from the imprecision of food frequency questionnaires.

Despite several limitations, our findings relating the dietary intake of vitamins E, C, and A and lung cancer risk in the overall cohort are generally consistent with the literature. A decrease in lung cancer risk with an increase in dietary vitamin C intake has been reported in recent (34-36) but not earlier (37-41) studies. The null finding for dietary vitamin E intake is consistent with those observed in the few studies that have examined its relation to lung cancer risk (3, 34, 38, 42). The findings in the literature on the vitamin A-lung cancer relation have been conflicting (37-39, 43), and in studies that have differentiated between the separate components of carotenoids and retinol, an inverse association was generally observed for carotenoids (34, 36, 38, 40, 41, 44-46) but not for retinol (34, 38, 44-48). In this study, vitamin A or its preformed component of retinol was not associated with lung cancer risk and, as has been similarly reported by Shibata et al. (49), the inverse association observed for carotenoids was no longer significant after the adjustment for confounders. Although the indices of carotenoids and retinol used here were crude measures of their intake, being derived from the vitamin A activity of the fruit/vegetable and animal sources, respectively,

the fact that the reduced lung cancer risk was provided by plant rather than animal sources of vitamin A provides some support for a protective role of dietary carotenoids.

There are several possible explanations for the findings of this study. Because the intakes of vitamins E, C, and A are correlated, their estimated intakes may be indicators of consumption of fruits and vegetables, the major food sources. Alternatively, fruits and vegetables may provide a better measure of their intake, particularly that of vitamin C and the carotenoids. Numerous studies have shown an inverse association between the frequency of consumption of fruits and vegetables and cancer risk, and this is particularly consistent for lung cancer (2). In this study, the amount of fruit and vegetable intake was similarly found to be significantly and inversely associated with lung cancer risk, thus providing support for a protective effect of vitamins E and C, the carotenoids, or some other known or unknown nutritive or nonnutritive components in fruits and vegetables (50).

The protective effect against lung cancer risk, as indicated by the magnitude of the relative risk estimates, was greater for those with a high combined dietary intake of vitamins E and C and of carotenoids than for those with a high intake of each of these individual nutrients. This may be further explained by the interactive or synergistic effects of these and other nutrients, such as selenium (51), in their antioxidant action against lung cancer risk. In particular, there is *in vitro* evidence that vitamins E and C may exert their antioxidant effects synergistically at their respective lipid- and water-soluble phases and that vitamin C may have the ability to regenerate vitamin E from its oxidized state (52). Thus, it may not be just one but a combination of "balanced" proportions of the various antioxidants found in fruits and vegetables that may be most protective against lung cancer risk.

Overall, we found no indication of any beneficial effect of supplement use of vitamins E, C, and A or any additional benefit beyond that provided by the diet on lung cancer risk. These findings may reflect the low usage and the lack of information on the dosage and duration of use of vitamin supplements at baseline or, as has similarly been reported (53, 54), vitamin supplement use may merely be an indicator of a certain favorable lifestyle and diet consumption pattern.

In this study, the relation between the dietary intake of vitamin E and lung cancer risk was significantly modified by the pack-years of cigarette smoking, with a protective effect confined to current smokers who have lower pack-years of smoking. Although these observations have not been previously reported, a protective effect of dietary (47) and supplemental (48)

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vitamin E intake has been reported for nonsmokers but not for smokers. No protective effect of vitamin E, whether derived from the diet or from supplements, was seen among the heavy current smokers of this study. This finding is consistent with the recent intervention trial in Finland where no evidence of reduction in lung cancer was seen among male, middle-aged, long-term, and heavy smokers who were given a daily supplement of vitamin E for 5–8 years (6). These findings suggest that, if there is a protective effect of vitamin E against lung cancer, it may work only at the initiation or early promotional stage or that it may be effective only against lung carcinogenesis in those with low exposure to cigarettes.

The effects of cigarette smoking on the association between the indices of dietary carotenoid intake and lung cancer risk are also conflicting; some studies have found the protective effect of the index of carotene to be stronger in heavy smokers (36, 37, 45), whereas others have found a stronger protective effect in former/light smokers (35, 38, 41, 46) or in nonsmokers (34, 47, 48). Although the inconsistencies in findings among studies may be due to the small number of lung cancer cases among nonsmokers, they could also reflect the lack of adequate adjustment for smoking (49) or an effect modification by the intensity of cigarette exposure. In a case-control study conducted by Byers et al. (38), a stronger protective effect of dietary carotene was observed in men aged 60 years and older and in smokers with less cumulative lifetime cigarette exposure. In the present study, the dietary carotenoid-lung cancer relation was modified by cigarette exposure but not by age. The protective effect of carotenoids was confined to current smokers who had lower pack-years of smoking. We could not, however, address the effects of the supplemental intake of carotenoids, notably β -carotene, because of the lack of such data. Vitamin C intake, either from the diet or with the addition of supplements, was not modified by cigarette exposure. This is in contrast to the report by Knekt et al. (34) who found a stronger protective effect of vitamin C for nonsmokers than for smokers.

In conclusion, our findings are consistent with the hypothesis that increasing the dietary intakes of vitamins E and C and of carotenoids may reduce the risk of developing lung cancer. The intake of these nutrients from supplements may be beneficial for those with inadequate nutritional status but, as has been shown by the results of recent intervention trials (6–8, 55), beneficial effects from supplements remain unproven, and their usage could even be harmful for those who are well nourished and who already have an adequate supply of these nutrients from the diet. Supplemented by basic biologic research, future studies

should investigate the potential synergistic and interactive effects of nutrients against lung cancer risk and the variation in the effects of the nutrients with the extent of cigarette exposure. Although avoidance of cigarette smoking is the most effective method for reducing lung cancer risk, diet may be an important modifiable risk factor of lung cancer. In view of the greater reduction in risk of lung cancer by a combined high intake of vitamins E and C and carotenoids than by a high intake of each of these individual nutrients, a daily diet consisting of a variety of fruits and vegetables that provide a natural source of these nutrients and other potential protective factors may offer the best dietary protection against lung cancer risk.

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