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Vitamin E intake and the lung cancer risk among female nonsmokers: a report from the Shanghai Women's Health Study

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Abstract

Vitamin E includes several tocopherol isoforms which may reduce lung cancer risk, but past studies evaluating the association between vitamin E intake and lung cancer risk were inconsistent. We prospectively investigated the associations between tocopherol intake from diet and from supplements with lung cancer risk among 72,829 Chinese female nonsmokers aged 40-70 years and participating in the Shanghai Women's Health Study (SWHS). Dietary and supplement tocopherol exposure was assessed by a validated food-frequency questionnaire at baseline, and also reassessed for change in intake during follow-up. Cox proportional hazards models with time-dependent covariates were used to calculate multivariate-adjusted hazard ratios (HRs) and 95% confidence interval (CIs) for lung cancer. After 12.02 years of follow-up, 481 women were diagnosed with lung cancer. Total dietary tocopherol was inversely associated with lung cancer risk among women meeting dietary guidelines for adequate intake (AI) of tocopherol (14 mg/day or more: HR: 0.78; 95% CI 0.60-0.99; compared to the category less than AI). The protective association between dietary tocopherol intake and lung cancer was restricted to women exposed to side-stream smoke in the home and workplace (HR=0.53 (0.29-0.97), p-trend = 0.04). In contrast, vitamin E supplement use was associated with increased lung cancer risk (HR: 1.33; 95% CI 1.01-1.73), more so for lung adenocarcinoma risk (HR: 1.79; 95% CI 1.23-2.60). In summary, dietary tocopherol intake may reduce the risk of lung cancer among female non-smokers, however supplements may increase lung adenocarcinoma risk and requires further investigation.

Keywords

diet; dietary supplements; lung neoplasm; prospective study; tocopherols; women

INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide, with almost 1.4 million deaths per year.¹ Cigarette smoking is the predominant cause, exposing the airways to carcinogens and reactive oxygen and other free radicals leading to DNA damage in critical tumor suppressor genes.² However, there is a clear gender difference, with cigarette smoking accounting for 80% of the worldwide lung cancer burden in males but about 50% of the burden in females.³

Vitamin E refers to a class of essential lipid-soluble antioxidants consisting of tocopherols and tocotrienols. As the major source of vitamin E in diet, tocopherols include four isoforms (α , β , γ , and δ) differentiated by the number and position of methyl groups on the chromanol ring. Tocopherols reduce nitrite and inhibit the production of carcinogenic nitrosoamines and nitrosoamides.⁴⁻⁷ Additionally, tocopherols may inhibit carcinogenesis through inhibition of cell proliferation,⁸ induction of apoptosis,⁸ inhibition of angiogenesis,⁹ and enhancement of immune function.⁹

The relationship between dietary intake of tocopherols and lung cancer risk has been evaluated in several prospective studies,¹⁰⁻¹⁸ with the majority showing no significant association. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, a randomized, placebo-controlled trial of male smokers, reported a statistically significant protective association between total dietary tocopherol and lung cancer, but no association between α -tocopherol supplement use and lung cancer risk.^{12, 19}

The effects of tocopherols from diet and supplement use among female non-smokers are unclear. Non-smoking Asian women are among the non-smoking populations with the highest risk of lung cancer.^{20, 21} Herein, we evaluate the relationship between tocopheral exposure and lung cancer risk in the Shanghai Women's Health Study (SWHS), a prospective cohort study where over 97% of participants were non-smokers. Our results may provide further insight into the risks and benefits of tocopherol intake toward lung cancer prevention among non-smoking women.

METHODS

Study Population

The Shanghai Women's Health Study (SWHS) is a population-based, prospective cohort study based in urban Shanghai, China. Details of the study design and methods of the SWHS have been published previously.^{22, 23} Briefly, the SWHS recruited 74,942 females aged 40-70 years from 1997 to 2000. Participants resided in seven urban communities of Shanghai, and the response rate of 92.7%.

At baseline, participants completed an in-person interview using a structured questionnaire to obtain information about demographic characteristics, lifestyle, dietary habits, medical history, occupational history, and physical activity. Anthropometrics, including weight, height, and circumferences of the waist and hip, were also measured at baseline. The survey also asked participants questions about smoking habits of their husband and people at work. Exposure was classified as low exposure (never exposed or exposed to the side-stream tobacco smoke in the home or work place) and high exposure (exposed to the side-stream smoke in the home and work place). All participants provided written informed consent. The SWHS was approved by the Institutional Review Boards for human research at all participating institutes.

Considering the low prevalence of smoking in this cohort (n=2,113, 2.8%), we decided to include only those women who never smoked (n=72,829). Additional exclusions included: (1) a previous diagnosis of cancer before enrollment (n=1,527); (2) loss to follow-up shortly after enrollment (n=5); (3) diagnosis of cancer in situ during follow-up (n=67); (4) a cancer diagnosis that could not be confirmed (n=15); (5) death from cancer with no cancer type or diagnosis date (n=106); (6) extreme values for total energy intake (<500 or >4,000 kcal/d) (n=13); (7) or missing data for any of the covariates of interests (n=6,030). After these exclusions, a total of 65,066 participants remained.

Assessment of Dietary Intake

Dietary information was collected using a validated semi-quantitative food-frequency questionnaire (FFQ) at baseline and at first follow-up conducted 2-3 years after baseline.²³ The FFQ included 77 food items encompassing about 90% of commonly consumed food items in urban Shanghai in 1996.²³ The validity and reproducibility of the questionnaire used in the SWHS has been described.²³ During the in-person interview, each participant was first asked how often, on average, she consumed a specific food or food group during the 12-month time period prior to the interview. Possible responses included: daily, weekly, monthly, yearly, or never. A follow-up question asked about the amount consumed in liang (1 liang=50g) per unit of time. Each participant was also asked about whether he or she had taken vitamin supplements (A, B, C, or E; a multivitamin; or calcium) at least 3 times per week continuously for more than 2 months. Our validation study showed that the validity of the FFQ was at least as good as that of the FFQ used in other major cohort studies.²⁴ The correlation coefficient between Vitamin E estimated by FFQ compared to the means of the 24-hour dietary recalls (the recalls were conducted twice per month during a 12-month period) was $r=0.49$.²³ Although the correlation is typical when comparing FFQ to 24-hour diet recall assessment estimates²³, we attempted to improve the assessment of usual dietary intake by FFQ in our analysis by averaging the intakes from the baseline FFQ and the FFQ completed 2-3 years after baseline which has recently become available for analysis from the SWHS.²⁵ For persons who reported having diabetes or cardiovascular disease diagnosed between the two FFQ surveys, only baseline dietary intake was used as the exposure ($n=5,450$, 7.5%). Total energy and nutrient intakes for each food were calculated by multiplying the amount of food consumed by the energy or nutrient content per gram of the food, as obtained from the Chinese Food Composition Tables.²⁶ Total dietary consumption of each nutrient was calculated by summing the nutrients from all food items reported in the FFQ.

Follow-up and Cancer Identification

Cohort members were followed for diagnosis of cancer by in-person follow-up surveys every 2-3 years, and annual record linkage with databases from the population-based Shanghai Cancer Registry, Shanghai Vital Statistics Registry, and Shanghai Resident Registry. The SWHS underwent four in-person follow-up surveys between 2000 and 2011 to ascertain changes in health status, with survey response rates for the first (2000-2002), second (2002-2004), third (2004-2007), and fourth (2008-2011) surveys were 99.8%, 98.7%, 96.7%, and 92.0%, respectively. All possible cancer diagnoses were verified through home visits and a review of medical charts by a panel of oncologists. Lung cancer was defined under code 162 as per the International Classification of Disease - 9th revision. Histological groups of lung cancer cases with sufficient sample size for analysis were classified as adenocarcinoma or non-adenocarcinoma according to the morphology code of International Classification of Diseases for Oncology-2nd edition (ICD-O-2, 8140/3).

Statistical Analysis

Dietary tocopherol was categorized into tertiles, with the lowest tertile of intake serving as the reference group. Tests for linear trend were performed by assigning an ordinal value (1,

2, and 3) to each category and treating it as a continuous variable in the regression model. A second categorization of dietary tocopherol intake used the recommendation of the Chinese Nutrient Society, which advises an adequate intake (AI) of tocopherol for adults at 14 mg/day or more.²⁷ Current vitamin E and multivitamin supplement use was categorized as Yes/No and treated as a time-dependent variable using a counting process approach to capture the changes in vitamin E and multivitamin supplement intakes during the follow-up period.²⁸

Person-years of follow-up time were calculated for each participant from the date of the baseline interview to the date of cancer diagnosis, death, loss to follow-up, or December 31, 2010, whichever date occurred first. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with age as the time scale. The proportional hazards assumption was examined by evaluation of the interaction between exposure and survival time in the models, and we found no violations of the model assumptions.

We evaluated a range of possible subject characteristics, diet, and health status as potential confounders in the analysis. Final models included factors assessed at study recruitment: age (years, continuous); total energy intake (kcal/day, continuous); ever consumption of tea (yes or no); the average calcium-to-magnesium (Ca: Mg) ratio intake (calculated as calcium divided by magnesium intake, continuous),^{29, 30} status exposure to passive smoking (low or high). Further adjustment for body mass index (BMI calculated as weight in kg/m², continuous); family income level (three categories: low [$<5,000$ yuan/year], medium [5,000 to $<10,000$ yuan/year], and high [$>10,000$ yuan/year]), education level (four categories: elementary school or less, middle school, high school, and college or above), leisure time exercises (calculated by metabolic equivalent (MET)-hours per week per year, continuous), menopause status (yes or no), red meat intake (continuous), alcohol intake (yes or no), isoflavone intake (mg/day, continuous), and the ventilation condition of the kitchen did not alter our findings ($<10\%$ change in tocopherol HR) and to maintain model stability therefore were not included in the final models.

All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc, Cary, NC). All *P*-values were calculated using two-sided tests and were considered statistically significant if *P* was less than 0.05.

RESULTS

During a mean follow-up period of 12.02 years, we identified 481 incident cases of cancer of the bronchus or lung. Table 1 presents age-adjusted study population characteristics by tertile of total dietary tocopherols. Higher total dietary tocopherol intake decreased significantly with older age. Additionally, dietary tocopherol intake was significantly associated with higher BMI, more physical exercise, education, occupational category, annual family income, as well as dietary factors such as energy, red meat, and isoflavone intakes. Furthermore, greater tocopherol intake was significantly higher among women likely exposed to second-hand tobacco smoke in the home or workplace.

The associations of lung cancer with intake of tocopherol are presented in Table 2. Greater total dietary tocopherol and specific tocopherol isoforms intakes were associated with lower lung cancer risk in multivariable-adjusted models, though none of them reached statistical significance. The protective effect was stronger among women complying with suggested dietary guidelines for tocopherol intake (14 mg/day or more: HR: 0.73; 95% CI 0.54-0.99; compared to the category less than 14mg/day). In contrast, use of vitamin E supplement was significantly associated with an increase in lung cancer risk (HR: 1.33; 95% CI 1.01-1.73) (Table 2).

Dietary tocopherol intake was significantly associated with a lower lung cancer risk among women likely exposed to side-stream tobacco smoke in the home or workplace (HR: 0.53; 95% CI 0.29-0.97 for the highest tertile compared to the lowest, p-trend = 0.04) (Table 3). A similar pattern was observed among women complying with suggested dietary guidelines for tocopherol intake (Table 3). Use of vitamin E supplements, in contrast, was significantly associated with increased lung cancer risk among women likely exposed to side-stream tobacco smoke (HR=2.06 (95%CI 1.31-3.23)).

We also conducted a joint analysis to see the effects of dietary tocopherol intake with and without vitamin E supplements. Greater tocopherol intake was generally protective for lung cancer among women who did not take a supplement, with marginally significant trend tests for total tocopherol and tocopherol sub-types (β and γ and δ -tocopherols) (Supplemental Table 1). There was a significant interaction between α -tocopherol intake and taking vitamin E supplements on lung cancer risk (P interaction = 0.03), but we did not see a clear pattern or trend. Alternatively, use of vitamin E supplements was associated with greater lung cancer risk regardless of whether they had an adequate tocopherol intake, although statistical significance was lost after stratification (Supplemental Table 2).

We evaluated the association between tocopherol exposure and lung cancer risk by histologic subtypes, including 217 adenocarcinomas and 69 non-adenocarcinomas (i.e., squamous cell and small-cell carcinomas, excludes 195 unclassified tumors) (Supplemental Table 3). Intake of total dietary tocopherol and specific tocopherol isoforms were not significantly associated with lung adenocarcinoma or non-adenocarcinoma risk. In contrast, vitamin E supplement use was significantly associated with an increased risk of lung adenocarcinoma (HR: 1.79; 95% CI 1.23-2.60).

To minimize the potential influence of preclinical disease on our results, we excluded 45 cases diagnosed within two years of follow-up and found no appreciable change in the risk estimates. When we stratified by the median time interval between baseline and lung cancer diagnosis, the test for interaction with follow-up time did reach statistical significance (Supplemental Table 4). We also excluded the first three, four and five years of follow-up and found similar results with supplement use (Supplemental Table 5). Similarly, we assessed the effect of missing data from the second FFQ in a subset of participants by restricting the analysis to those participants whom completed both the first and second FFQ and were free of chronic disease and cancer at the second FFQ survey (n = 62,719). Again, the results were unchanged.

DISCUSSION

Our analyses found that total dietary tocopherol intake was inversely associated with lung cancer risk among women complying with suggested dietary recommendations for tocopherol intake. In contrast, vitamin E supplement use was associated with a significant increase in lung cancer risk, specific to adenocarcinomas. In addition, dietary tocopherol intake was associated with lower lung cancer risk among women reporting exposure to side-stream tobacco smoke in the home and workplace. Vitamin E supplement use remained associated with increased lung cancer risk among these passive smokers.

The four tocopherol isoforms analyzed include the most biologically active isoforms and the major sources of vitamin E in diet, serving primarily as lipid soluble antioxidants.³¹ The association between dietary tocopherol and lung cancer risk has been investigated in several prior prospective studies¹⁰⁻¹⁸ but with conflicting results. Only two prior studies^{11, 15} investigated the tocopherol and lung cancer relationship among women. Speizer et al.¹¹ found no significant association between dietary and supplement vitamin E exposure (combined) with lung cancer (relative risk (RR): 1.2; 95% CI 0.9-1.6; *P* trend=0.10) while Bandera et al.¹⁵ reported a non-significant inverse association (RR: 0.8; 95% CI 0.52-1.23; *P* trend=0.28). Furthermore, Yong et al.¹³ found no association among non-smokers in an analysis that combined both genders (RR: 0.87; 95% CI 0.49-1.60; *P* trend=0.33). In contrast, the protective association we see between total dietary tocopherol intake and lung cancer in women was consistent with an investigation from Woodson et al.¹² evaluating total dietary tocopherol at baseline with lung cancer risk among male smokers in the ATBC clinical trial.

α -Tocopherol is the most common isoform used in vitamin E supplement in the US and China.^{31, 32} However, compared to α -tocopherol, γ -tocopherol and δ -tocopherol are more abundant in the diet and more effective in trapping reactive oxygen and nitrogen species due to the unmethylated carbon at the 5-position of the chromanol ring.³¹ Experimental studies also suggest that α -tocopherol is less able to induce apoptosis compared to γ - and δ -tocopherol.³³ Differences in isoform metabolism may also be relevant³⁴ if β or γ -tocopherol levels in blood are lower than α -tocopherol levels and therefore have less hepatic toxicity.³¹ Animal studies also suggest that γ - and δ -tocopherol may be responsible for any protection against lung cancer,^{35, 36} however results from four nested case-control studies³⁷⁻⁴⁰ looking at serum β - or γ -tocopherol concentration and lung cancer have been inconclusive. We mutually controlled for these three isoforms in our multivariable models, but the direction and magnitude of risk estimates were similar to our reported results (data not shown) and we were unable to isolate a single dietary isoform protective for lung cancer risk.

Our study observed a positive association between vitamin E supplement use and lung cancer risk, especially with lung adenocarcinoma. Several randomized controlled trials and cohort studies^{10, 41-44} have examined this association, but only two studies demonstrated the results among women.^{41, 42} The Women's Health Study (WHS) found 600 international units (IU) of α -tocopherol every other day had no significant effect on the incidence of lung cancer (RR: 1.09; 95% CI 0.83-1.44; *P*=0.52).⁴² In contrast, a prospective study in California reported a RR of 0.74 (95% CI 0.46-1.18) for women comparing vitamin E

supplement users to non-users.⁴¹ These two studies included both smoking and non-smoking women.^{41, 42} It is possible that pharmacological doses of tocopherol found in supplements might affect cytochrome P450 enzyme activity or other regulatory mechanisms,⁴⁵ or that α -tocopherol from supplements interact with other tocopherols in blood to induce an effect.^{45, 46} Adenocarcinomas are the common form of lung cancer in non-smokers,²⁰ and further research is needed to understand why vitamin E supplement use may increase lung adenocarcinoma risk in non-smokers.

As exposure to side-stream smoking may increase oxidative stress,^{47, 48} we carried-out a stratified analysis of tocopherols and lung cancer risk by passive smoking status. There was a significant protective trend of total dietary tocopherol intake among women highly exposed to side-stream smoke in the home and workplace, though the interaction was not statistically significant. Furthermore, vitamin E supplement significantly increased lung cancer risk among women most likely exposed to side-stream tobacco smoke. Confirmation of these novel results may suggest that dietary tocopherol, rather than supplements, is a more beneficial prevention approach for non-smoking women who live or work where smoking is prevalent.

Strengths of our investigation include a population-based prospective design, and a large sample of female non-smokers. Baseline and follow-up participation rates were exceptionally high, with repeated dietary assessments with a validated FFQ minimized measurement error or selection bias. We controlled for multiple potential confounders, including isoflavone intake and passive smoke exposure in home or workplace, kitchen ventilation, and other supplement use. Furthermore, we carried out several sensitivity analyses that excluded potential preclinical lung cancer in the first 2 years of follow-up or dietary misclassification due to missing follow-up FFQ, and found no impact on the results.

Limitations of this study also should be addressed. Vitamin E supplement capsules on the market in Shanghai vary from 20% to 39% in the proportion of α -tocopherols, with capsule weight varying from 250mg to 500mg. The FFQ did not assess the dose provided by vitamin supplements, thus vitamin supplement use was analyzed as a categorical variable (yes or no) and we could not evaluate vitamin E supplement dose-response effects with lung cancer risk.⁴⁹ Also, tocopherol from cooking oil or other non-diet sources were not measured. However, the FFQ has reasonably good correlation with data from repeated 24-hour dietary recalls (tocopherol $r=0.49$)²³, and dietary assessment error in this prospective cohort would likely be non-differential with respect to lung cancer. Thus, if anything, this error would lead to an attenuation of the true association. We had limited statistical power to investigate lung non-adenocarcinoma risk, and an expanded analysis by histology subtype should be conducted in future studies.

In summary, in this population-based prospective study, we found that greater total dietary tocopherol over the AI (14mg/day) was significantly associated with lower lung cancer risk. In contrast, vitamin E supplement use was associated with increased lung cancer risk, especially for lung adenocarcinoma or with exposure to passive smoking. The reason for differences between dietary and supplement tocopherol exposure on lung cancer requires further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Brief description of the novelty and impact

Vitamin E may reduce lung cancer risk among non-smokers, but results from prior studies of vitamin E and lung cancer were inconsistent. The authors prospectively investigated the association between vitamin E intake and lung cancer among 72,829 female non-smokers. While dietary vitamin E intake was significantly associated with lower lung cancer risk, vitamin E supplementation was significantly associated with increased lung cancer risk suggesting caution if recommending vitamin E supplements to prevent lung cancer among non-smoking women.

TABLE 1
Study population characteristics according to total dietary tocopherol intake, Shanghai Women's Health Study (1997-2010)

Characteristic	Tertiles of total tocopherol intake (mg/day)			P
	T1 (<11.01)	T2 (11.01-14.87)	T3 (14.87)	
No. of participants	21688	21689	21689	
No. of lung cancer cases	200	152	129	
Age at recruitment (SD), year	53.62 (9.61)	51.90 (8.79)	51.56 (8.33)	<0.01
Mean (SE)				
Body mass index, kg/m ²	23.87 (0.02)	23.93 (0.02)	24.29 (0.02)	<0.01
Leisure time exercise, MET-h/w/y [†]	12.19 (0.18)	13.05 (0.16)	14.97 (0.15)	<0.01
Age at menopause, year [‡]	48.38 (0.04)	48.67 (0.04)	48.83 (0.04)	<0.01
Total energy intake, kcal/day	1409.35 (1.90)	1628.51 (1.89)	1892.19 (1.89)	<0.01
Red meat intake *	26.43 (0.10)	28.87 (0.10)	29.94 (0.10)	<0.01
Isoflavone intake *	12.72 (0.06)	18.51 (0.06)	26.13 (0.06)	<0.01
Calcium:Magnesium ratio *	1.59 (0.00)	1.76 (0.00)	1.89 (0.00)	<0.01
No. (%)				
Vitamin E supplement use (ever)	4099 (19.08)	5264 (24.32)	6070 (28.02)	<0.01
Multivitamin supplement use (ever)	3296 (15.35)	4247 (19.63)	4814 (22.18)	<0.01
Occupation				<0.01
Housewife	118 (0.46)	50 (0.24)	42 (0.22)	
Professional workers	5156 (24.69)	6495 (29.96)	6791 (31.03)	
Clerical workers	4457 (20.89)	4447 (20.34)	4537 (20.69)	
Manual workers	11957 (53.97)	10697 (49.45)	10319 (48.06)	
Education level				<0.01
Elementary school or less	6415 (25.05)	3849 (18.88)	3147 (16.88)	
Middle school	7978 (39.21)	8446 (38.21)	8462 (37.90)	
High school	5094 (25.07)	6354 (28.90)	6837 (30.50)	
College or above	2201 (10.67)	3040 (14.01)	3243 (14.72)	
Family income, person/year				<0.01
Low (< 5000)	7243 (31.71)	5497 (25.78)	4975 (23.98)	
Middle (5000-10000)	8583 (39.69)	8630 (39.81)	8451 (39.29)	
High (10000)	5862 (28.61)	7562 (34.41)	8263 (36.73)	
Passive smoking [§]				<0.01
Low	15704 (70.88)	14899 (69.16)	14641 (68.42)	
High	5984 (29.12)	6790 (30.84)	7048 (31.58)	
Ventilation condition of kitchen				0.95
Good	21012(96.88)	21020 (96.92)	21018 (96.93)	
Poor	674 (3.12)	669 (3.08)	671 (3.07)	
Alcohol drinking (ever)	384 (1.72)	394 (1.82)	485 (2.26)	<0.01
Tea drinking (ever)	5108 (24.42)	6567 (29.99)	7413 (33.55)	<0.01

Characteristic	Tertiles of total tocopherol intake (mg/day)			P
	T1 (<11.01)	T2 (11.01-14.87)	T3 (14.87)	
Family history of lung cancer (ever)	1002 (4.75)	1055 (4.84)	1141 (5.20)	0.09
History of lung disease (ever) ¶	2807 (12.43)	2922 (13.71)	2895 (13.75)	<0.01
Post-menopausal status	11513 (48.28)	10084 (48.43)	9902 (48.52)	0.69

All means, standard errors, or percentages for each characteristic (except age) were adjusted for age at baseline.

† Leisure time exercise: metabolic equivalent (MET)-hours per week per year.

‡ Among postmenopausal women (n=33,939).

§ Passive smoking: Low = never, or exposure to husband or working place. High = both husband and working place tobacco smoke exposure.

¶ Lung disease includes asthma, tuberculosis, and chronic bronchitis.

* Consumption of selected foods and nutrients were adjusted for energy intake using the nutrient density method. Foods expressed as per gram per 1000 kcal per day.

TABLE 2
Hazard ratios for female lung cancer associated with tocopherol intake from diet or supplements, Shanghai Women's Health Study (1997-2010)

Dietary intake (mg/day)	Range	Cases	Person years	Multivariate HR (95% CI)
Total Tocopherol [†]				
T1	< 11.01	200	259208	1.00 (ref)
T2	11.01-14.87	152	261464	0.87 (0.68-1.11)
T3	14.87	129	261352	0.78 (0.58-1.07)
<i>P</i> for trend				0.12
Total Tocopherol [†]				
< AI	<14.00	330	468142	1.00 (ref)
AI or more	14.00	151	313882	0.78(0.60-0.99)
α -tocopherol [†]				
T1	<3.39	210	258185	1.00 (ref)
T2	3.39-4.66	142	261443	0.87 (0.68-1.12)
T3	4.66	129	262395	0.90 (0.66-1.24)
<i>P</i> for trend				0.47
β and γ -tocopherol [†]				
T1	<3.35	193	259630	1.00 (ref)
T2	3.35-4.89	155	261355	0.93 (0.73-1.18)
T3	4.89	133	261039	0.79 (0.59-1.06)
<i>P</i> for trend				0.13
δ -tocopherol [†]				
T1	<2.86	197	260041	1.00 (ref)
T2	2.86-4.23	147	261410	0.83 (0.65-1.06)
T3	4.23	137	260573	0.78 (0.59-1.04)
<i>P</i> for trend				0.08
Vitamin E supplements [‡]				
No		313	595711	1.00 (ref)
Yes		168	186312	1.33 (1.01-1.73)
Multivitamin supplements [‡]				
No		337	632861	1.00 (ref)
Yes		144	149163	1.17 (0.89-1.53)

AI = adequate intake, HR=hazard ratios, 95% CI= 95% confidence intervals

[†]Adjusted for age, average intake of total energy and the calcium-to-magnesium (Ca: Mg) ratio, ever consumption of tea, status exposed to passive smoking, and ever use of vitamin E and multivitamin supplements.

[‡]Further adjusted for total dietary tocopherol and vitamin supplements use (A, B, C, calcium, and other).

TABLE 3
Effects of dietary tocopherol on lung cancer risk, by passive smoking status, Shanghai Women's Health Study (1997-2010)

Dietary intake (mg/day)	Passive smoking status*				<i>P</i> _{interaction} [§]
	Low		High		
	Cases	HR (95% CI) [†]	Cases	HR (95% CI) [†]	
Total Tocopherol					0.59
< 11.01	155	1.00 (ref)	45	1.00 (ref)	
11.01-14.87	110	0.89 (0.67-1.20)	42	0.80 (0.51-1.27)	
14.87	97	0.91 (0.63-1.32)	32	0.53 (0.29-0.97)	
<i>P</i> for trend		0.58		0.04	
Total Tocopherol					0.53
<14.00 (AI)	250	1.00 (ref)	80	1.00 (ref)	
14.00 (AI)	112	0.85 (0.63-1.15)	39	0.62 (0.39-0.99)	
α-tocopherol					0.08
<3.39	170	1.00 (ref)	40	1.00 (ref)	
3.39-4.66	95	0.77 (0.57-1.04)	47	1.14(0.72-1.81)	
4.66	97	0.99 (0.69-1.43)	32	0.74 (0.41-1.36)	
<i>P</i> for trend		0.77		0.36	
β and γ-tocopherol					0.48
<3.35	151	1.00 (ref)	42	1.00 (ref)	
3.35-4.89	109	0.91 (0.69-1.21)	46	0.96 (0.62-1.50)	
4.89	102	0.88 (0.63-1.24)	31	0.60 (0.34-1.06)	
<i>P</i> for trend		0.46		0.08	
δ-tocopherol					0.86
<2.86	151	1.00 (ref)	46	1.00 (ref)	
2.86-4.23	108	0.85 (0.64-1.13)	39	0.78 (0.50-1.23)	
4.23	103	0.85 (0.60-1.19)	34	0.63 (0.37-1.09)	
<i>P</i> for trend		0.32		0.10	
Vitamin E supplements [‡]					0.29
No	234	1.00 (ref)	79	1.00 (ref)	
Yes	128	1.07 (0.76-1.50)	40	2.06 (1.31-3.23)	
Multivitamin supplements [‡]					0.59
No	241	1.00 (ref)	96	1.00 (ref)	
Yes	121	1.33 (0.98-1.82)	23	0.84 (0.50-1.43)	

AI = adequate intake, HR = hazard ratios, 95% CI = 95% confidence intervals

* Passive smoking: Low = never, or exposure to husband or working place. High = both husband and working place tobacco smoke exposure.

[†]The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by using Cox proportional hazard models with adjustment for age, average intake of total energy and the calcium-to-magnesium (Ca: Mg) ratio, ever consumption of tea, and ever use of vitamin E and multivitamin supplements.

[‡]Further adjusted for total dietary tocopherol and vitamin supplements use (A, B, C, calcium, and other).

$\delta P_{\text{interaction}}$ was calculated by introducing an interaction term between the exposures and the status exposed to passive smoking in the regression model.