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Original Article

Dietary vitamin E intake could reduce the risk of lung cancer: evidence from a meta-analysis

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Abstract: Background: Quantification of the association between the intake of vitamin E and risk of lung cancer is still conflicting. Thus, we conducted a meta-analysis to summarize the evidence from epidemiological studies of vitamin E intake with the risk of lung cancer. Methods: Pertinent studies were identified by a search in PubMed and Web of Knowledge up to October 2014. Random-effect model was used to combine study-specific results. Publication bias was estimated using Egger's regression asymmetry test. Results: Ten articles reporting 11 studies (10 prospective studies and 1 case-control studies) involving 4434 lung cancer cases were used in this meta-analysis. The combined relative risk (RR) of lung cancer associated with vitamin E intake was 0.858 (95% CI=0.742-0.991) overall, significant protective associations were also found in America population (RR=0.862, 95% CI=0.715-0.996) and prospective studies (RR=0.913, 95% CI=0.827-0.996). No publication bias was found. Conclusions: Our analysis indicated that vitamin E intake might decrease the risk of lung cancer, especially in America.

Keywords: Vitamin E, lung cancer, meta-analysis

Introduction

Lung cancer is the leading cause of cancer mortality worldwide, with almost 1.4 million deaths per year [1]. Cigarette smoking causes 90% of all lung cancers, and although the prevalence of smoking is declining, the risk of lung cancer after smoking cessation persists and remains elevated compared with never-smokers [2]. The age-adjusted incidence rate of lung cancer was recently reported at 62.6 cases per 100,000 people per year [3]. Thus, primary prevention of lung cancer is critical. Many studies have shown that lung cancer is associated with genetic factors [4, 5], and environmental factors including tobacco use [6], alcohol consumption [7], and intake of fruit, vegetables [8] and vitamins [9, 10] can also affect the incidence of lung cancer.

Dietary antioxidants, including vitamin E intake, have been shown in laboratory studies to enhance growth restriction of cancer cells in general [11]. It has generally been acknowledged that vitamin E protects cells from oxidative DNA damage, thereby blocking carcinogenesis [12]. To date, a number of epidemiologic studies have been published exploring the relationship between vitamin E intake and lung cancer risk. However, the results of these studies are not consistent. Therefore, we conducted a meta-analysis in order to assess lung cancer risk for the highest vs. lowest categories of vitamin E intake and assess heterogeneity and publication bias among the studies we analyzed.

Methods

Search strategy

Studies were identified using a literature search of PubMed and Web of Knowledge through October 2014 and by hand-searching the reference lists of the retrieved articles. The following search terms were used: 'lung cancer' or 'lung carcinoma' combined with nutrition, diet, lifestyle, vitamin E, vitamins or tocopherol. Two investigators searched articles and reviewed all the retrieved studies independently. Disag-

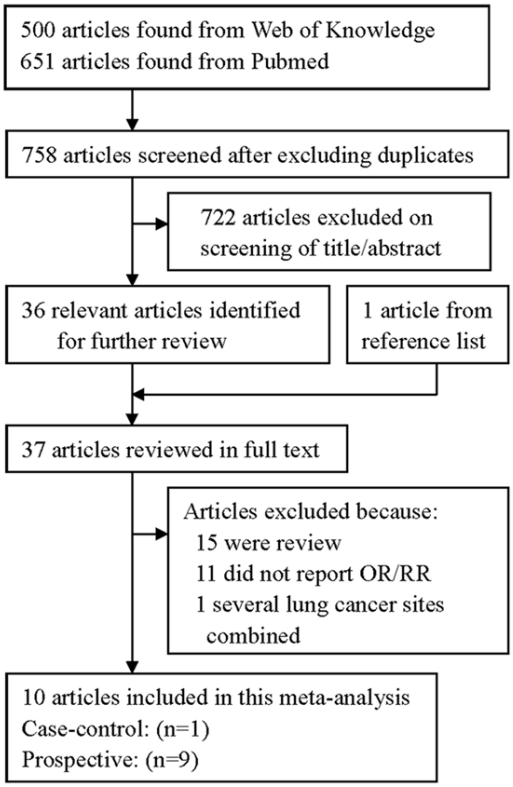

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

reements between the two investigators were resolved by consensus with a third reviewer.

Study selection

For inclusion, studies had to fulfill the following criteria: (1) have a prospective or case-control study design; (2) vitamin E intake was the independent variable of interest; (3) the dependent variable of interest was lung cancer; and (4) relative risk (RR) or odds ratio (OR) with a 95% confidence interval (CI) was provided (or data available to calculate them). If data were replicated in more than one study, we included the study with the largest number of cases. Accordingly, the following exclusion criteria were also used: (1) reviews; (2) the RR or OR with 95% CI was not available and (3) repeated or overlapped publications.

Data extraction

Two researchers independently extracted the following data from each study that met the criteria for inclusion: the first author's last name, year of publication, geographic locations, study design, sample source, the age range of study participants, duration of follow-up, the number of cases and participants (person-years), and RR (95% CI) for vitamin E intake and lung cancer risk. From each study, we extracted the RR that reflected the greatest degree of control for potential confounders. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

Statistical analysis

The pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI, to assess the association between vitamin E intake and the risk of lung cancer. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [13]. The I^2 was used to assess heterogeneity, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity [14], respectively. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [15]. Publication bias was evaluated using Egger regression asymmetry test [16]. A study of influence analysis [17] was conducted to describe how robust the pooled estimator was to removal of individual studies. An individual study was suspected of excessive influence if the point estimate of its omitted analysis lay outside the 95% CI of the combined analysis. All statistical analyses were conducted with STATA version 11.0 (StataCorp LP, College Station, Texas, USA). Two-tailed $P \leq 0.05$ was accepted as statistically significant.

Results

Search results and study characteristics

The search strategy identified 500 articles from PubMed and 651 from the Web of Knowledge; 36 articles were reviewed in full after reviewing the title/abstract. By studying reference lists, we identified 1 additional article. Twenty-seven of these 37 articles were subsequently excluded from the meta-analysis for various reasons. In total, 10 articles [18-27] reporting 11 studies (10 prospective studies

Table 1. Characteristics of studies on dietary vitamin E intake and lung cancer risk

Study, year	Country	Study design	Participants (cases)	Age (years)	RR (95% CI) for highest versus lowest category	Adjustment for covariates
Bandera et al. 1997	United States	Prospective	48,000 (525)	40-80	0.86 (0.67-1.09) for males 0.80 (0.52-1.23) for females	Adjusted for age, education, cigarettes/day, years smoking, and total energy intake (except calories) based on Cox Proportional Hazards Model.
Gaziano et al.2009	United States	Prospective	14,641 (50)	≥50	0.89 (0.60-1.31)	Adjusted for age, PHS cohort (original PHS I participant, new PHS participant), and randomized treatment assignment (beta-carotene, multivitamin, and either vitamin E or vitamin C); and stratified on baseline cancer.
Ocke et al. 1997	Nether-lands	Prospective	561 (54)	Case: 59.3 Control: 59.5	0.68 (0.31-1.51)	Adjusted for age, pack-years of cigarettes, and energy intake,
Slatore et al. 2008	United States	Prospective	77,721 (521)	50-76	1.19 (0.95-1.50)	Adjusted for age, sex, years smoked, pack-years, and pack-years squared.
Speizer et al. 1999	United States	Prospective	121,700 (593)	30-55	0.91 (0.70-1.20)	Age, total energy intake, smoking (past and current amount in 1980; 1±4, 5±14, 15±24, 25±34, 35±44, 45+) and age of starting to smoke.
Stefani et al. 1999	Uruguay	Case-control	981 (541)	30-89	0.50 (0.34-0.74)	Adjusted for age, residence, urban/rural status, and education, family history of a lung cancer in 1st-degree relative, body mass index, tobacco smoking (pack-yr), and total energy and total fat intakes, IQR, interquartile range.
Voorrips et al. 2000	Nether-lands	Prospective	58,279 (939)	55-69	0.77 (0.54-1.08)	Adjusted for current smoking, years of smoking cigarettes, number of cigarettes per day, highest educational level, family history of lung cancer, and age.
Wu et al. 2015	China	Prospective	72,829 (481)	40-70	0.53 (0.29-0.97)	Adjusted 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.
Yong et al. 1997	United States	Prospective	1,068 (248)	25-74	0.66 (0.45-0.96)	Adjusted for sex race, educational attainment, nonrecreabonal activity level, body masa index, family history, smoking status/pack-years of smoking, total calorie intake, and alcohol intake.
Yuan et al. 2003	China	Prospective	63,257 (482)	45-74	0.81 (0.59-1.09)	Adjusted for age at baseline, sex, dialect group, year of interview, level of education, and BMI, number of cigarettes smoked per day, number of years of smoking, and number of years since quitting smoking for former smokers.

Abbreviations: CI=Confidence interval; RR=Relative risk.

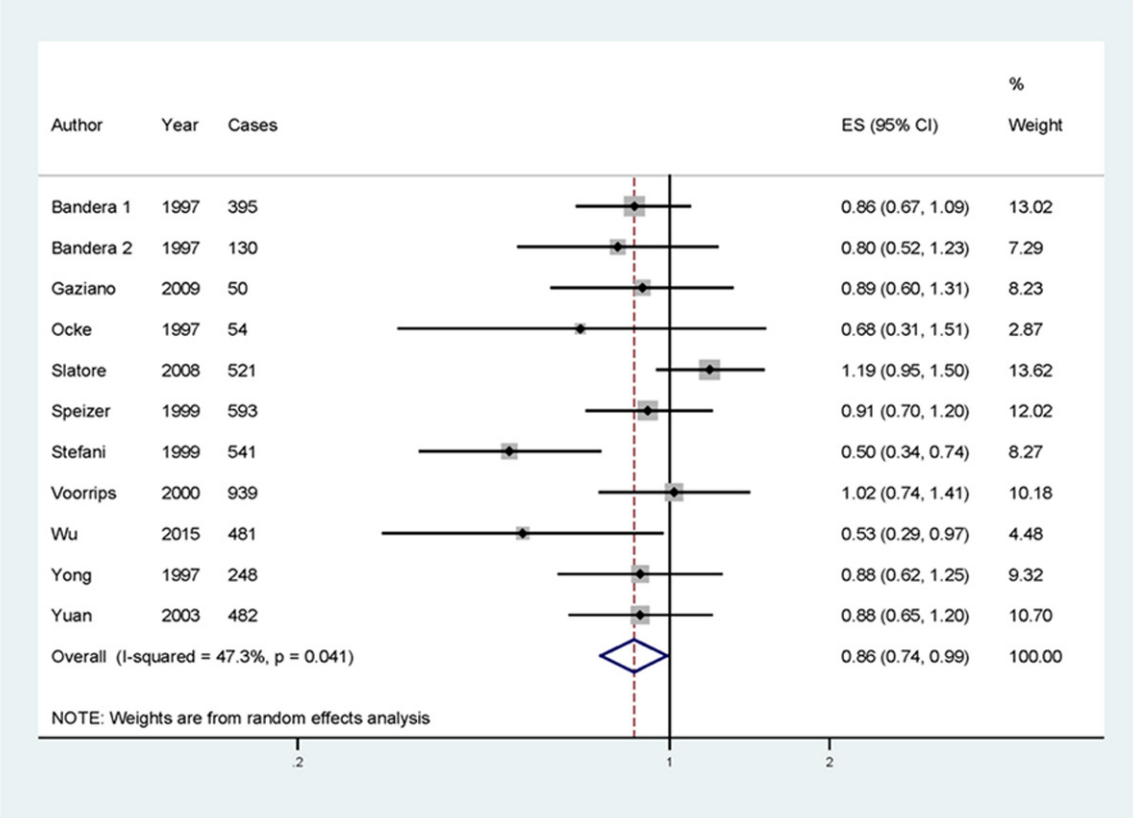

Figure 2. The forest plot between dietary vitamin E intake and lung cancer risk. White diamond denotes the pooled RR. Black squares indicate the RR in each study, with square sizes inversely proportional to the standard error of the RR. Horizontal lines represent 95% CI.

Table 2. Summary risk estimates of the association between dietary vitamin E intake and lung cancer risk

Subgroups	No. (cases)	No. studies	Risk estimate (95% CI)	Heterogeneity test	
				I^2 (%)	*P*-value
All studies	4434	11	0.858 (0.742-0.991)	47.3	0.041
Study design					
Prospective	3893	10	0.913 (0.827-0.996)	9.0	0.360
Case-control	541	1	--	--	--
Geographic locations					
America	2478	7	0.862 (0.715-0.996)	59.9	0.020
Europe	993	2	0.963 (0.714-1.298)	0.0	0.353
Asia	963	2	0.732 (0.454-1.181)	53.6	0.142

and 1 case-control studies) involving 4434 lung cancer cases were used in this meta-analysis. The detailed steps of our literature search are shown in **Figure 1**. The characteristics of these studies are presented in **Table 1**. Six studies were conducted the United States, two in the Netherlands, two in China, and one in Uruguay.

High versus low analyses

Two of the studies included in our analysis reported an inverse association of vitamin E intake with the risk of lung cancer while no significant association was reported in 9 studies. Our pooled results suggested that the highest vitamin E intake level compared to the lowest level was significantly associated with the risk of lung cancer [summary RR= 0.858, 95% CI=0.742-0.991, I^2=47.3%] (**Figure 2**). When the studies were stratified by study design, the association was also found in the prospective studies [summary RR=0.913, 95% CI=0.827-0.996]. In subgroup analyses for geographic locations, an inverse association of vitamin E intake with risk of lung cancer was

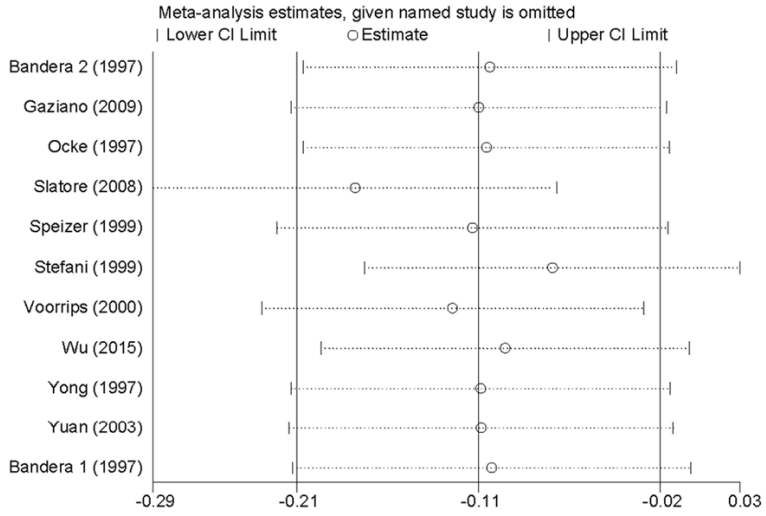

Figure 3. Analysis of influence of individual study on the pooled estimate in vitamin E intake and lung cancer risk. Open circle, the pooled OR, given named study is omitted. Horizontal lines represent the 95% CIs.

found in the America [summary RR=0.862, 95% CI=0.715-0.996], but not in Europe or Asia. Details results are summarized in **Table 2**.

Sources of heterogeneity and meta-regression

As shown in **Figure 2**, moderate between-study heterogeneity (I^2=47.3%, $P_{heterogeneity}$=0.041) was found in the pooled results. In order to explore the moderate between-study heterogeneity found in the pooled analysis, univariate meta-regression with the covariates of publication year, location where the study was conducted, study design (case-control or prospective), number of cases and degree of adjustments of covariates was performed. For the analysis between vitamin E intake and lung cancer risk, study design was found contributing significantly to the between-study heterogeneity overall (*P*=0.02). No significant findings were found in the other analysis.

Influence analysis and publication bias

Influence analysis showed that no individual study had excessive influence on the association of vitamin E intake and lung cancer (**Figure 3**). Egger's test showed no evidence of significant publication bias between vitamin E intake and lung cancer (*P*=0.147).

Discussion

Vitamin E is hypothesized to reduce the risk of cancer because of its role in quenching free radicals and reducing oxidative damage to DNA [28, 29]. Findings from this meta-analysis indicated that the highest vitamin E intake level versus the lowest level was significantly associated with the risk of lung cancer. Inverse associations were also found in prospective studies and geographic locations of the America.

We found a significant association between vitamin E intake and lung cancer in the America, from which most of the included studies (7 out of 11), and therefore most of the subjects. Only 2 studies came from Europe and 2 from Asia, in which we found no significant association, probably due to the small number of cases included. Due to this limitation, the results are applicable to the America, but cannot be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between vitamin E intake and lung cancer risk.

A paper had reported that between-study heterogeneity is common in meta-analyses [30]. Exploring potential sources of between-study heterogeneity is therefore an essential component of meta-analysis. We found a moderate degree of heterogeneity (I^2=47.3%, $P_{heterogeneity}$=0.041) in our pooled results. This might have arisen from publication year, location where the study was conducted, study design (case-control or prospective), number of cases and degree of adjustments of covariates. For the analysis between vitamin E intake and lung cancer risk, study design was found contributing significantly to the between-study heterogeneity overall (P=0.02). Thus, we conducted a subgroup analysis of study design. Only one study was case-control design, so, we did not combine the result. The between-study heterogeneity was reduced to 9.0% in prospective design.

As a meta-analysis of published observational studies, our study included a larger number of participants than others, allowing a much greater possibility of reaching reliable conclusions about the association between vitamin E

intake and lung cancer risk. However, our study has some limitations. First, although we extracted the RR that reflected the greatest degree of control for potential confounders, the extent to which they were adjusted and the possibility that the observed association was due to unmeasured or residual confounding should be considered. Second, a meta-analysis of observational studies is susceptible to potential bias inherent in the original studies, especially for case-control studies. Overstated association could be expected from the case-control studies because of recall or selection bias, and early symptoms in patients may have resulted in a change in dietary habits. However, only one study included in this meta-analysis was case-control design. Thus, the results from prospective studies might provide a more robust estimation of the associations. Third, measurement errors are important in the assessment of vitamin E intake, which can lead to overestimation of the range of intake and underestimation of the magnitude of the relationship between vitamin E and lung cancer risk [31]. Fourth, between-study heterogeneity was found in the pooled analysis, but the between-study heterogeneity was successfully explained by the subgroup analysis of study design. Finally, publication bias could be of concern in meta-analysis because of small number of studies included. Nevertheless, we found no evidence of publication bias.

In summary, results from this meta-analysis suggest that a high intake of vitamin E might have a protective effect against lung cancer, especially in the America.

Disclosure of conflict of interest

None.

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