

## Original Article

# Association of dietary vitamin E intake with risk of lung cancer: a dose-response meta-analysis

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**Background and Objectives:** Several epidemiological studies investigating the association between dietary vitamin E intake and the risk of lung cancer have demonstrated inconsistent results. Hence, a meta-analysis was conducted to summarise evidence of the association of dietary vitamin E intake with the risk of lung cancer. **Methods and Study Design:** In this meta-analysis, a systematic literature search of PubMed and Web of Science was conducted to identify relevant studies published from 1955 to April 2015. If  $p < 0.05$  or  $I^2 > 50\%$ , a random effect model was used to estimate overall relative risks (RRs) and 95% confidence intervals (CIs). Otherwise, a fixed effect model was applied. Publication bias was estimated using the funnel plot and Egger's test. The dose-response relationship was assessed using the method of restricted cubic splines with 4 knots at percentiles 5, 35, 65, and 95 of the distribution. **Results:** The pooled RR of lung cancer for the highest versus lowest categories of dietary vitamin E intake was 0.84 (95% CI=0.76-0.93). With every 2 mg/d increase in dietary vitamin E intake, the risk of lung cancer statistically decreased by 5% (RR=0.95, 95% CI =0.91-0.99,  $p_{\text{linearity}}=0.0237$ ). **Conclusions:** Our analysis suggests that higher dietary vitamin E intake exerts a protective effect against lung cancer.

**Key Words:** vitamin E, lung cancer; dietary intake; meta-analysis; dose-response

## INTRODUCTION

Lung cancer has the highest incidence and mortality among all cancers.<sup>1</sup> It is reported that an estimated of 1.3 million newly lung cancer cases are diagnosed each year.<sup>2</sup> Furthermore, the overall survival rate of patients with lung cancer is considerably low.<sup>2</sup> More than half of patients are diagnosed with advanced lung cancer. Hence, these patients have a poor prognosis and considerably low 5-year survival rate.<sup>3</sup> Undoubtedly, it is necessary to explore preventive measures of lung cancer. The etiology of lung cancer is still not completely known, and many studies have demonstrated that genetic factors<sup>4-6</sup> and environmental factors including alcohol consumption,<sup>7</sup> tobacco use,<sup>8-10</sup> intake of fruits,<sup>11</sup> vegetables and vitamins<sup>12,13</sup> play roles in lung cancer development.

Vitamin E is a powerful lipid-soluble vitamin, which has several health benefits, including antioxidant, anti-inflammatory and neuroprotective properties.<sup>14</sup> In recent years, the use of vitamin E supplements as antioxidants has become common.<sup>15</sup> Since the early 1980s, several studies have demonstrated that antioxidants and other micronutrients such as vitamin E play preventive roles in carcinogenesis.<sup>16,17</sup> However, the results from these studies have been controversial. Roswalla et al demonstrated that vitamin E intake is a protective factor against lung cancer,<sup>13</sup> whereas other studies suggested vitamin E intake has no effect on lung cancer.<sup>18-20</sup> Moreover, Fortmann et al revealed in his study that vitamin E intake increased the risk of lung cancer.<sup>21</sup> To date, no definitive evidence has demonstrated that vitamins E can reduce the

incidence of lung cancer. For a more precise evaluation of the relationship between vitamin E intake and the risk of lung cancer, we conducted a meta-analysis of 9 prospective cohort articles covering 4,164 cases and 431,359 controls to assess the dose-response relationship of lung cancer with vitamin E intake.

## MATERIALS AND METHODS

### Search strategy

In this study, we conducted a comprehensive literature search of PubMed and Web of Science to identify potential studies with information on dietary vitamin E intake and lung cancer risk from 1955 to April 2015. We searched for English-language articles by using the following keywords separately or in combination: "lung cancer" and "vitamins" and "vitamin E" or "tocopherol". We evaluated all relevant publications including research articles and reviews to retrieve additional eligible studies. When several publications reporting on the same study population data, only that with the most complete or larg-

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Manuscript received 18 September 2015. Initial review completed 06 December 2015. Revision accepted 27 December 2015.

doi: 10.6133/apjcn.032016.04

est sample was included in our meta-analysis.

### **Study selection**

We scrutinized full text of each potentially relevant paper by using the following inclusion criteria to select studies for the meta-analysis: (1) studies on dietary vitamin E intake and risk of lung cancer (2) studies included should be prospective cohort studies; (3) dietary vitamin E intake was the independent variable of interest; (4) the dependent variable of interest was lung cancer; (5) provide sufficient data for estimating an RR with a 95% CI; and (6) the studies must provide the dietary intake of vitamin E for each response category (or data available to calculate them) for dose-response analysis. The exclusion criteria were: (1) reviews; (2) the RR with 95% CI was unavailable; (3) repeated publications; and (4) studies about vitamin supplement.

### **Data extraction**

To minimise bias, 2 reviewers independently and carefully extracted information from all eligible studies meeting the inclusion criteria. Disagreements regarding eligibility of the data were resolved through consensus with a third reviewer. The following characteristics were collected from each study in the order shown: the first author's surname, publication year, country, study design, source of controls, the age range of study participants, duration of follow-up, the total number of participants and cases (person-years), the numbers of cases and controls with lung cancer, and RR (95% CI) for each category of vitamin E. From each study, we used the RR that reflected the maximum extent of control for potential confounders.

### **Statistical analysis**

The inverse variance-weighted mean of the logarithm of RR with the 95% CI was calculated to assess the association between dietary vitamin E intake and the risk of lung cancer.  $I^2$  was used to assess heterogeneity, and  $I^2$  values of 0%, 25%, 50% and 75%, respectively, represented no, low, moderate and high heterogeneity.<sup>22</sup> If  $p < 0.05$  or  $I^2 > 50\%$ , which represented significant heterogeneity, a random effects model was applied. Otherwise, a fixed effects model was applied. The potential publication bias was evaluated using Egger's test<sup>23</sup> and Funnel plots.

The method of restricted cubic splines with 4 knots at percentiles 5, 35, 65, and 95 of the distribution was adopted to assess the dose-response relationship between dietary vitamin E intake and lung cancer risk. For this method, the distribution of cases and person-years or controls, and the RRs with 95% CI with the variance estimates for at least three quantitative exposure categories are known. The median or mean intake of vitamin E in each category was assigned to the corresponding RR with 95% CI for each study. For studies that reported vitamin E by range of intake in the articles, the midpoint of the range was used. When the highest category was open-ended, we assumed the width of the category to be the same as that of the adjacent category. When the lowest category was open-ended, we set the lower boundary to zero.<sup>24,25</sup> All statistical analyses were conducted using STATA software (version 12.0; StatCorp, College Station, TX, USA). A 2-sided  $p$  value  $< 0.05$  was considered

statistically significant.

## **RESULTS**

### **Search results and study characteristics**

In total, we identified 504 and 978 articles from PubMed and Web of Science, respectively. One article was retrieved from a reference list. After excluding 847 duplicate papers, we reviewed the titles and abstracts of the remaining 636 articles and excluded an additional 596 articles. We examined the full text of the remaining 40 articles, and 28 articles were excluded for the following reasons: 1 article did not report the RR, 21 were reviews, 1 did not report the 95% CI, 6 did not report dietary vitamin E intake, and 2 were case-control studies. Finally, 9 articles reporting 11 studies<sup>13,26-33</sup> with 4,164 cases and 435,532 participants were included in our meta-analysis. The characteristics of the selected studies are presented in Table 1. Among the 11 studies, 4 studies were conducted in America, 5 in Europe, and the remaining 2 in Asia.

### **Comparison of high and low dietary vitamin E intake**

The pooled RRs were calculated to compare the highest dietary vitamin E intake with the lowest dietary vitamin E intake. Compared with the lowest intake, the highest dietary vitamin E intake was associated with a decrease risk of lung cancer (pooled RR=0.84, 95%CI=0.76-0.93,  $I^2 = 41.1\%$ ; Figure 1).

Subgroup analysis by geographic location revealed significant inverse associations of dietary vitamin E intake with lung cancer for the European and American populations (pooled RR=0.85, 95% CI=0.75-0.95), but not for the Asian population. An analysis stratified by gender revealed no significant association between dietary vitamin E intake and the risk of lung cancer in males or females. However, an inverse association between dietary vitamin E intake and the risk of lung cancer was observed in mixed population (males and females). Subgroup analysis by history of smoking revealed an inverse association of dietary vitamin E intake with the risk of lung cancer among current smokers, but not among former smokers or never smokers. The results are provided in Table 2.

### **Dose-response analysis**

Dose-response analysis revealed that the risk of lung cancer statistically decreased by 5% for every 2 mg/d increase in dietary vitamin E intake (RR=0.95, 95% CI=0.92-0.99,  $p_{\text{linearity}}=0.009$ ; Figure 2).

### **Sensitivity analysis and publication bias**

Sensitivity analysis showed that no individual study significantly influenced the pooled effect. Symmetrical funnel plots were obtained (Figure 3). Moreover, the Egger's test showed no evidence of publication bias ( $t=1.24$ ,  $p=0.246$ ).

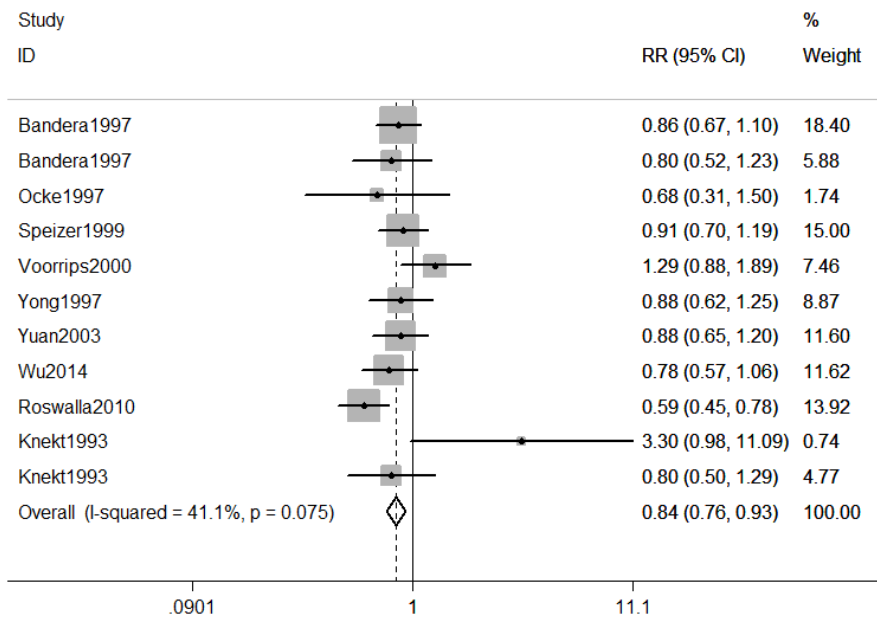
## **DISCUSSION**

Diet is reported to be associated with the aetiology of lung cancer, and antioxidant-rich foods are believed to be protective factors.<sup>34</sup> Epidemiological studies have demonstrated a significant association between antioxidant vitamin intakes and the risk of lung cancer.<sup>35</sup> However, pre-

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

First author, year	Country	Study design	Participants (cases)	Age range	Follow-up years	RR (95% CI) for highest vs lowest category	Adjustment for covariate
Bandera, 1997 <sup>26</sup>	United States	Cohort	48,000 (525)	40-80	18	0.86 (0.67-1.09) for men 0.8 (0.52-1.23) for women	Age, education, cigarettes/day, years smoking, and total energy
Speizer, 1999 <sup>29</sup>	United States	Cohort	121,700 (593)	30-55	16	0.91 (0.7-1.2)	Total energy intake, smoking and age of starting to smoke
Voorrips, 2000 <sup>30</sup>	Netherland	Cohort	58,279 (939)	55-69	7	1.29 (0.88-1.89)	Age, family history, smoking, SES, folate (quintiles), energy (continuous)
Yong, 1997 <sup>31</sup>	United States	Cohort	10,068 (248)	25-74	22	0.88 (0.62-1.25)	Sex, race, educational attainment, nonrecreabonal activity level, BMI
Yuan, 2003 <sup>32</sup>	China	Cohort	63,257 (482)	45-74	6	0.88 (0.65-1.2)	Age at baseline, sex, dialect group, year of interview, level of education, and BMI.
Knekt, 1993 <sup>27</sup>	Finnish	Cohort	5,254 (121)	>15	19	3.3 (1-11.3) for never smoker 0.8 (0.5-1.3) for current smoker	Age
Wu, 2014 <sup>13</sup>	China	Cohort	72,829 (481)	40-70	4	0.78 (0.58-1.07)	Age, average intake of total energy and the calcium-to-magnesium (Ca:Mg) ratio, ever consumption of tea, status exposed to passive
Roswalla, 2010 <sup>28</sup>	Denmark	Cohort	55,557 (721)	59.2 (case) 56.2 (control )	14	0.59 (0.44-0.77)	Intake of the three other micronutrients as well as dietary intake for the supplemental intake and supplemental intake for the dietary intake and further for smoking status (never/former/present), smoking duration, smoking intensity, possible cessation and when, passive smoking and work exposure
Ocke, 2007 <sup>33</sup>	Netherlands	Cohort	561 (54)	59.3 (case) 59.5 (control)	20	0.68 (0.31-1.51)	Age, pack-years of cigarettes, and energy intake

BMI: body mass index; SES: socioeconomic status; RR: relative risk; CI: confidence intervals.



**Figure 1.** The forest plot between highest versus lowest categories of dietary vitamin E intake and lung cancer risk. RR: relative risk; CI: confidence intervals.

**Table 2.** Pooled risk estimates of the association between vitamin E intake and lung cancer risk

Subgroups	No. of cases	No. of studies	RR (95% CI) for highest vs lowest category	Analysis model	Heterogeneity test	
					I <sup>2</sup> (%)	p-value
All studies	4164	11	0.84 (0.76-0.93)	Fixed	41.1	0.075
Geographic locations						
America and Europe	3201	9	0.85 (0.75-0.95)	Random	52.0	0.034
Asia	963	2	0.83 (0.63-1.03)	Fixed	0	0.585
Sex						
Men	1639	5	0.95 (0.79-1.14)	Random	52	0.08
Women	1599	3	0.84 (0.70-1.01)	Fixed	0	0.736
Mixed	926	3	0.75 (0.63-0.89)	Random	57.2	0.097
History of smoking						
Never	310	5	0.88 (0.62-1.26)	Random	51.8	0.065
Current	1930	5	0.74 (0.61-0.89)	Fixed	47.9	0.087
Former	528	3	0.75 (0.54-1.05)	Random	50.4	0.109

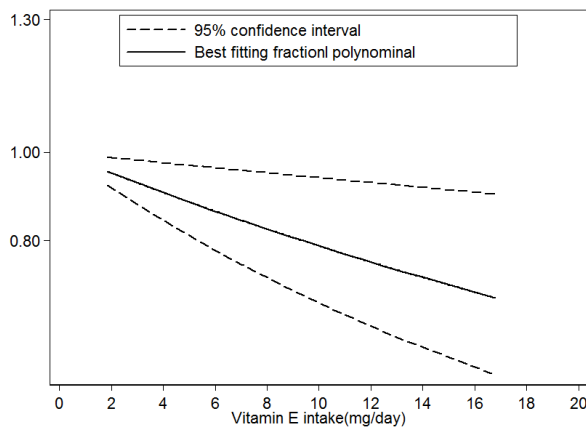
RR: Relative Risk; CI: confidence intervals.

vious studies showed controversial results. This study is the first meta-analysis of the dose-response relationship between dietary vitamin E intake and the risk of lung cancer. Our results indicated that dietary vitamin E intake was significantly associated with a reduced risk of lung cancer. Moreover, dose-response analysis revealed a linear relationship between dietary vitamin E intake and the risk of lung cancer, the risk decreased by 5% for every 2 mg/d increase in dietary vitamin E intake.

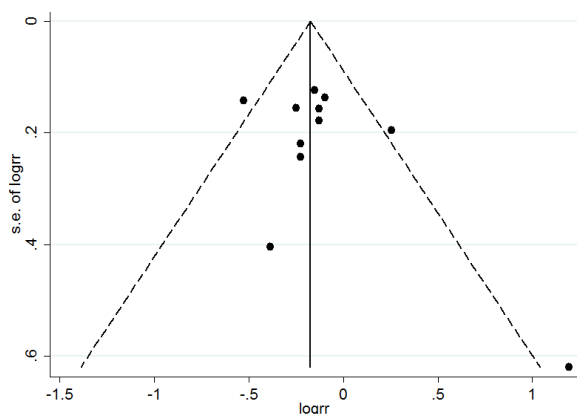
Vitamin E is a powerful lipid-soluble antioxidant<sup>36</sup> and might be effective in reducing the risk of lung cancer by reducing oxidative stress.<sup>37</sup> Li and Zhang<sup>38</sup> reported that vitamin E intake reduced the risk of gastric cancer ((RR=0.65, 95% CI=0.57-0.74). Moreover, a previous meta-analysis<sup>39</sup> indicated that high vitamin E intakes could reduce the risk of bladder cancer (RR=0.82, 95% CI=0.72-0.90). Another meta-analysis suggested that vitamin E was associated with a significant reduction in the incidence of prostate cancer (RR=0.85, 95% CI=0.73-0.96).<sup>40</sup> Our meta-analysis showed an inverse association

between dietary vitamin E intake and the risk of lung cancer, which adds new evidence for the relationship between vitamin E and the risk of cancer. More importantly, we found a linear relationship between dietary vitamin E intake and the risk of lung cancer, with the risk decreasing by 5% for every 2 mg/d increase in dietary vitamin E intake. Notably, our result differs from that of a randomised controlled trial (RCT).<sup>41</sup> Differences in the results of observational studies and RCT of vitamin E, particularly when hypotheses of RCT are null, can be attributed to numerous reasons. The most prominent reasons are the selection of an inappropriate intervention dose (too high or too low), duration (too short), timing (too late in life), or study population (people with adequate nutrition).<sup>42</sup>

Several mechanisms might explain the inverse association between dietary vitamin E intake and the risk of lung cancer. First, vitamin E is a powerful antioxidant<sup>43</sup> with anti-inflammatory<sup>44</sup> properties that protect cells and DNA from reactive radicals. Second, vitamin E may reduce nitrite and inhibit the production of carcinogenic nitro-



**Figure 2.** Dose-response relationship between dietary vitamin E intake and the risk of lung cancer



**Figure 3.** Funnel plot for publication bias of dietary vitamin E intake and the risk of lung cancer.

soamides and nitrosoamines.<sup>45,46</sup> Additionally, vitamin E may prevent carcinogenesis by down regulating the nuclear factor (NF)- $\kappa$ B signalling pathway to inhibit cell proliferation and angiogenesis, inducing apoptosis.<sup>47-50</sup>

Subgroup analysis by history of smoking revealed that higher dietary vitamin E intakes were associated with a reduced risk of lung cancer in current smokers, but not in former smokers or never smokers. Smoking has been strongly implicated as a risk factor for lung cancer. Epidemiological studies have demonstrated that the major pathological mechanism of the association of smoking with lung cancer is exposure to side stream smoking increasing oxidative stress.<sup>51,52</sup> Hence, the antioxidant properties of vitamin E may explain the reduction of the risk of lung cancer risk observed in current smokers.

Subgroup analysis by gender revealed no significant association between dietary vitamin E intake and the risk of lung cancer in males or females. However, an inverse association was observed between dietary vitamin E intake and the risk of lung cancer among the mixed population, although this conclusion should be interpreted cautiously because of the insufficient sample size. This issue should be clarified by conducting better-designed studies with a larger sample size. We also found that dietary vitamin E intake was inversely associated with the risk of lung cancer for the American and European populations. However, dietary vitamin E intakes were found to be marginally significantly associated with the risk of lung

cancer for the Asian population (pooled RR=0.84, 95% CI=0.7-1.01). We hypothesise that this marginally significantly association is caused by the insufficient sample size, because only 2 studies were conducted in Asia. Another reason for the difference in the geographic location subgroups is that dietary sources of vitamin E vary among ethnic groups and cultures. In the Western diet, the major dietary sources of vitamin E are soybeans and soybean oil, which contain a high proportion of  $\gamma$ -tocopherol.<sup>53</sup> By contrast, in the Asian population, the main sources are leafy greens and eggs, which contain high quantities of  $\alpha$ -tocopherol.<sup>54</sup> Compared with  $\alpha$ -tocopherol,  $\gamma$ -tocopherol may have unique mechanistic characteristics, such as anti-inflammatory activities, including inhibition of cyclooxygenase activity, which might make an important contribution to the effect of vitamin E on reduced lung cancer risk.<sup>51</sup>

The present study has several advantages. First, our study firstly reported the dose-response meta-analysis to assess the association between dietary vitamin E intake and lung cancer risk. Second, all included studies were cohort studies, which are effective in identifying causal relationships and can measure exposure more precisely. Moreover, no publication bias was observed, suggesting that the pooled results might be unbiased, and subgroup analysis was applied to evaluate the role of dietary vitamin E intakes under certain conditions.

The present analysis also has some limitations. First, the included studies were limited to America, Europe and Asia. Therefore, the conclusions should be applied cautiously for other regions. Second, the present studies included did not report the association between vitamin E intakes and different histological types of lung cancer. Therefore, we could not conduct the stratified analysis by histological type.

### Conclusion

The results of this meta-analysis suggest that dietary vitamin E intake is significantly associated with a reduced risk of lung cancer. Dose-response analysis suggests that the estimated risk reduction for lung cancer is 5% for every 2 mg/d increase in dietary vitamin E intake. It should be noted that the findings needs to be confirmed further by larger prospective studies.

### AUTHOR DISCLOSURES

None of the authors have any personal or financial conflicts of interest to declare.

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