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# Association between vitamin C intake and lung cancer: a dose-response meta-analysis

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**Epidemiological studies evaluating the association between the intake of vitamin C and lung cancer risk have produced inconsistent results. We conducted a meta-analysis to assess the association between them. Pertinent studies were identified by a search of PubMed, Web of Knowledge and Wan Fang Med Online through December of 2013. Random-effect model was used to combine the data for analysis. Publication bias was estimated using Begg's funnel plot and Egger's regression asymmetry test. Eighteen articles reporting 21 studies involving 8938 lung cancer cases were included in this meta-analysis. Pooled results suggested that highest vitamin C intake level versus lowest level was significantly associated with the risk of lung cancer [summary relative risk (RR) = 0.829, 95%CI = 0.734–0.937, $I^2$ = 57.8%], especially in the United States and in prospective studies. A linear dose-response relationship was found, with the risk of lung cancer decreasing by 7% for every 100 mg/day increase in the intake of vitamin C [summary RR = 0.93, 95%CI = 0.88–0.98]. No publication bias was found. Our analysis suggested that the higher intake of vitamin C might have a protective effect against lung cancer, especially in the United States, although this conclusion needs to be confirmed.**

Lung cancer accounts for a significant proportion of cancer-related deaths worldwide, with an estimated 1.3 million newly diagnosed cases each year; furthermore, the overall survival rate for lung cancer patients is extremely low[1]. The age-adjusted incidence rate of lung cancer was recently reported at 62.6 cases per 100,000 people per year, and the age-adjusted death rate at 50.6 per 100,000 people per year[2]. Thus, primary prevention of lung cancer is critical. Many studies have shown that lung cancer is associated with genetic factors[3,4], and environmental factors including tobacco use[5], alcohol consumption[6], and intake of fruit, vegetables[7] and vitamins[8,9] can also affect the incidence of lung cancer.

Vitamin C is one of the most common antioxidants in fruits and vegetables, and it may exert chemopreventive effects[10]. It has generally been acknowledged that vitamin C protects cells from oxidative DNA damage, thereby blocking carcinogenesis[11]. To date, a number of epidemiologic studies have been published exploring the relationship between vitamin C intake and lung cancer risk. However, the results of these studies are not consistent. Therefore, we conducted a meta-analysis in order to (1) assess lung cancer risk for the highest vs. lowest categories of vitamin C intake; (2) assess the dose-response association of lung cancer for every 100 mg/day increment in vitamin C intake; and (3) assess heterogeneity and publication bias among the studies we analyzed.

## Methods

**Search strategy.** Studies were identified using a literature search of PubMed, Web of Knowledge and Wan Fang Med Online through December 2013, 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 C,' 'vitamins' or 'ascorbic acid'. Two investigators searched articles and reviewed all the retrieved studies independently. Disagreements 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 C intake was the independent variable of interest; (3) the dependent variable of interest was lung cancer; (4) relative risk (RR) or odds ratio (OR) with a 95% confidence interval (CI) was provided; and (5) for dose-response analysis, the intake of vitamin C for each response category must also have been 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 each category of vitamin C. 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 C 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[12]. 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[13], 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[14]. If no significant covariates were found to be heterogeneous, the "leave-one-out" sensitive analysis[15] was carried out to evaluate the key studies with substantial impact on between-study heterogeneity. Publication bias was evaluated using Begg's funnel plot[16] and Egger regression asymmetry test[17]. A study of influence analysis[18] 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.

For the dose-response analysis, the method reported by Greenland et al.[19] and Orsini et al.[20] was used to calculate study specific slopes (linear trends) based on the results across categories of vitamin C intake. The method requires that the distribution of cases and person-years or non-cases and the RR with the variance estimates for at least three quantitative exposure categories are known. When this information was not available, we estimated the slopes (linear trends) by using variance-weighted least squares regression analysis[21,22]. The median or mean level of vitamin C in each category was assigned to the corresponding RR with 95% CI for each study. When vitamin C was reported by range of intake in the paper, 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[23,24]. The dose-response results in forest plots are presented for every 100 mg/day increment in vitamin C intake. A potential curve linear dose-response relation between vitamin C and lung cancer risk was examined by using restricted cubic spline model with three knots at the 25th, 50th and 75th percentiles[25] of the distribution. A P-value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. 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.

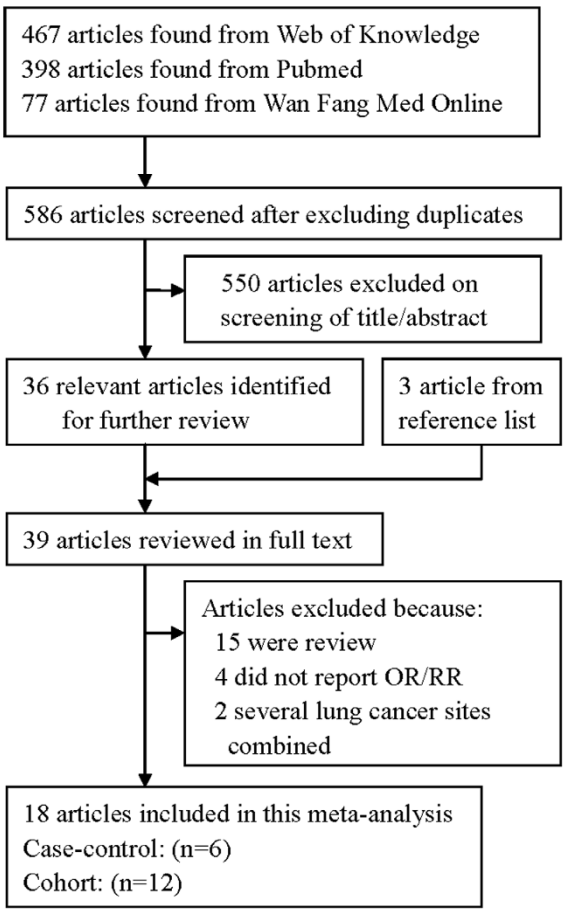


**Figure 1 | The flow diagram of screened, excluded, and analyzed publications.**

## Results

**Search results and study characteristics.** The search strategy identified 398 articles from Pubmed, 77 from Wan Fang Med Online and 467 from the Web of Knowledge; 36 articles were reviewed in full after reviewing the title/abstract. By studying reference lists, we identified 3 additional articles. Twenty-one of these 39 articles were subsequently excluded from the meta-analysis for various reasons. In total, 18 articles[26–43] reporting 21 studies (14 prospective studies and 7 case-control studies) involving 8938 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. Fifteen studies were conducted in the United States, two in the Netherlands, two in China, one in Canada and one in Uruguay.

**Analysis of high versus low vitamin C.** Six of the studies included in our analysis reported an inverse association of vitamin C intake with the risk of lung cancer. No significant association was reported in 13 studies, while 2 studies reported that high vitamin C intake could increase the risk of lung cancer. Our pooled results suggested that the highest vitamin C intake level compared to the lowest level was significantly associated with the risk of lung cancer [summary RR = 0.829, 95%CI = 0.734–0.937, $I^2$ = 57.8%] (Figure 2).

When the studies were stratified by study design, the association was also found in the prospective studies [summary RR = 0.829, 95%CI = 0.729–0.942] but not in the case-control studies. In subgroup analyses for geographic locations, an inverse association of vitamin C intake with risk of lung cancer was found in the United States [summary RR = 0.849, 95%CI = 0.735–0.982], but not in Europe or Asia. When we conducted the subgroup analysis by sex, a significant association was found in males [summary RR = 0.740, 95%CI = 0.631–0.868], but not in females. Furthermore, with stratification for histological type, associations were found with both squamous cell carcinoma and adenocarcinoma. Details results are summarized in Table 2.

**Dose-response analysis.** For dose-response analysis, data from fourteen studies[29,32–43] comprising 6607 cases were used for vitamin C intake and lung cancer risk. We found no evidence of statistically significant departure from linearity ($P$ for nonlinearity = 0.24). Our dose-response analysis of vitamin C indicated that an increase in vitamin C intake of 100 mg/day was statistically significantly associated with a 7% decrease in the risk of developing lung cancer (summary RR = 0.93, 95%CI = 0.88–0.98; Figure 3).

**Sources of heterogeneity.** As shown in Figure 2, evidence of heterogeneity ($I^2$ = 57.8%, $P_{heterogeneity}$ = 0.001) was found in the pooled results. However, univariate meta-regression analysis, with the covariates of publication year, study design, geographic locations, sex and sources of controls showed no covariate having a significant impact on between-study heterogeneity. The key contributor to this high between-study heterogeneity assessed by the leave-one-out analysis was one study conducted by Speizer et al. (1999). After excluding this study, heterogeneity was reduced to $I^2$ = 48.2%, and the summary RR for lung cancer was 0.805 (95%CI = 0.719–0.903).

**Influence analysis and publication bias.** Influence analysis showed that no individual study exerted excessive influence on the association of vitamin C intake and lung cancer risk. Begg's funnel plot (Figure 4) and Egger's test ($P$ = 0.654) showed no evidence of

Table 1 | Characteristics of studies on vitamin C 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 (PNCC) | 48,000 (525) | 40–80 | 0.63(0.53–0.88) for males<br>0.88(0.57–1.37) for females | Adjusted for age, education, cigarettes/day, years smoking, and total energy intake (except calories) based on Cox Proportional Hazards Model. |
| Candelora et al. 1992 | United States | Case-control (PCC) | 387 (124) | Case: 71.9<br>Control: 69.8 | 0.5(0.3–1.0) | Adjusted for age, education (≤8 and >8 grades), and total calories. |
| Feskanich et al. 2000 | United States | Prospective | 125,061 (793) | 30–75 | 1.04(0.71–1.53) for males<br>0.82(0.62–1.10) for females | Adjusted for age, follow-up cycle, smoking status, years since quitting among past smokers, cigarettes smoked/day among current smokers, age at start of smoking, total energy intake, and availability of diet data after baseline measure. |
| Fontham et al. 1988 | United States | Case-control (HCC) | 2,527 (1,253) | <40-≥70 | 0.67(0.53–0.84) | Adjusted in logistic regression model for age, race, sex, and pack years of cigarette use. |
| Gaziano et al. 2009 | United States | Prospective | 14,641 (50) | ≥50 | 0.95(0.64–1.39) | 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. |
| Jain et al. 1990 | Canada | Case-control (PCC) | 1,611 (839) | 20–75 | 1.08(0.86–1.36) | Adjusted for cumulative cigarette smoking |
| Hinds et al. 1984 | United States | Case-control (PCC) | 991 (364) | ≥30 | 0.77(0.42–1.39) | Adjustment by multiple logistic regression for age, ethnicity, cholesterol intake, occupational status, vitamin A intake, pack-years of cigarette smoking, and sex where appropriate. |
| Le Marchand et al. 1989 | United States | Case-control (PCC) | 1,197 (332) | 30–85 | 0.50(0.28–0.90) for males<br>2.50(1.12–5.59) for females | Adjusted for age, ethnicity, smoking status, pack-years of cigarette smoking, cholesterol intake (for males only), and intakes of other nutrients in the table. |
| Neuhouser et al. 2003 | United States | Prospective | 14,120 (742) | Case: 60.4<br>Control: 57.6 | 0.66(0.47–0.94) | Adjusted for sex, age, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center. |
| Ocke et al. 1997 | Netherlands | Prospective | 561 (54) | Case: 59.3<br>Control: 59.5 | 0.46(0.24–0.88) | Adjusted for age, pack-years of cigarettes, and energy intake, |
| Slatore et al. 2008 | United States | Prospective | 77,721 (521) | 50–76 | 0.97(0.76–1.23) | Adjusted for age, sex, years smoked, pack-years, and pack-years squared. |
| Speizer et al. 1999 | United States | Prospective | 121,700 (593) | 30–55 | 1.35(1.00–1.80) | 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 (HCC) | 981 (541) | 30–89 | 1.03(0.70–1.52) | Adjusted for age, residence, urban/rural status, 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. |
| Steinmetz et al. 1993 | United States | Prospective | 41,837 (179) | 55–69 | 0.81(0.46–1.43) | Adjusted by inclusion of continuous variables for age, energy intake, and pack-years of smoking in multivariale logistic regression models. |
| Takata et al. 2013 | China | Prospective | 61,491 (359) | 40–74 | 0.84(0.61–1.16) | Adjusted for age, years of smoking, the number of cigarettes smoked per day, current smoking status, total caloric intake, education, BMI category, ever consumption of tea, history of chronic bronchitis, and family history of lung cancer among first-degree relatives. |
| Voorrips et al. 2000 | Netherlands | 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. |
| 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: BMI = body mass index; CI = confidence interval; PNCC = population-based nested case–control study; HCC = hospital-based case–control study; PCC = population-based case–control study; RR = relative risk.

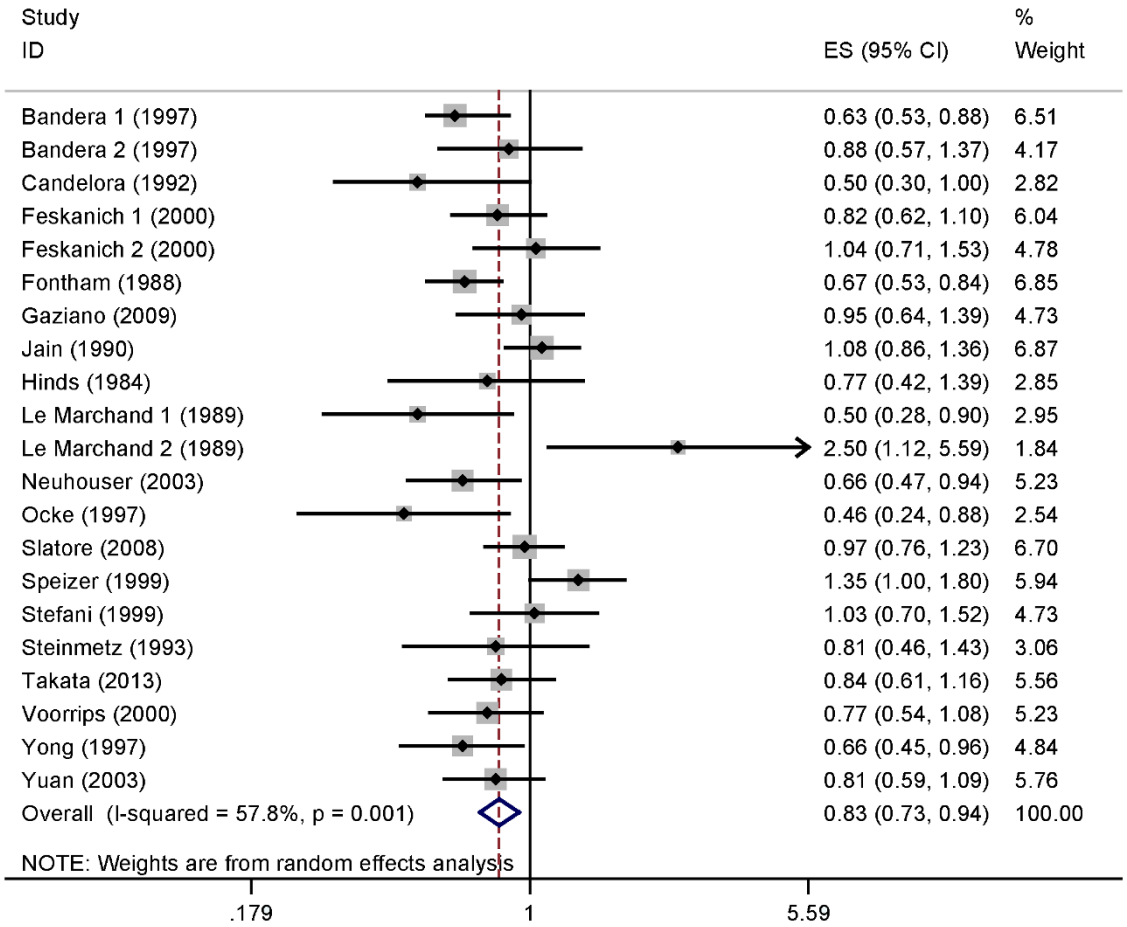


**Figure 2 | The forest plot between highest versus lowest categories of vitamin C intake and lung cancer risk.** Studies are subgrouped according to design.

Table 2 | Summary risk estimates of the association between vitamin C and lung cancer risk

| Subgroups | No. (cases) | No. studies | Risk estimate (95% CI) | Heterogeneity test $I^2$ (%) | Heterogeneity test P-value |
|---|---|---|---|---|---|
| All studies | 8938 | 21 | 0.829(0.734–0.937) | 57.8 | 0.001 |
| Study design | | | | | |
| Prospective | 5485 | 14 | 0.829(0.729–0.942) | 48.0 | 0.023 |
| Case-control | 3453 | 7 | 0.838(0.620–1.133) | 73.2 | 0.001 |
| Geographic locations | | | | | |
| America | 7104 | 17 | 0.849(0.735–0.982) | 63.4 | 0.000 |
| Europe | 993 | 2 | 0.642(0.397–1.040) | 46.8 | 0.170 |
| Asia | 841 | 2 | 0.824(0.660–1.029) | 0.0 | 0.873 |
| Sex | | | | | |
| Males | 3474 | 8 | 0.740(0.631–0.868) | 31.9 | 0.173 |
| Females | 2037 | 8 | 0.999(0.751–1.329) | 59.5 | 0.016 |
| Histological type | | | | | |
| Squamous cell carcinoma | 1009 | 3 | 0.634(0.524–0.768) | 0.0 | 0.852 |
| Adenocarcinoma | 482 | 3 | 0.713(0.549–0.926) | 0.0 | 0.632 |
| Sources of control (case-control studies) | | | | | |
| Population-based | 2184 | 7 | 0.808(0.590–1.107) | 73.4 | 0.001 |
| Hospital-based | 1794 | 2 | 0.807(0.531–1.225) | 71.4 | 0.062 |
| History of smoking | | | | | |
| Never-smokers | 262 | 3 | 1.025(0.640–1.642) | 0.0 | 0.474 |
| Current smokers | 1044 | 4 | 0.641(0.445–0.922) | 52.2 | 0.099 |
| Former smokers | 702 | 4 | 0.901(0.712–1.139) | 0.0 | 0.926 |

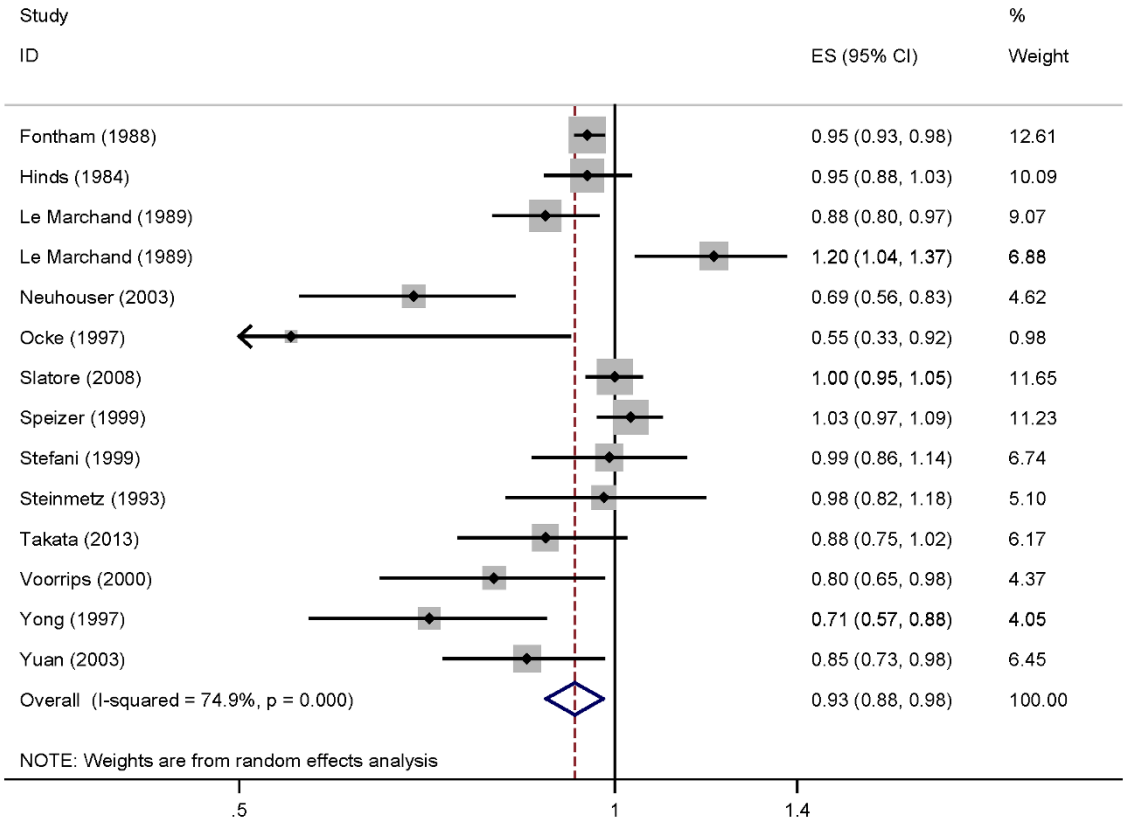


**Figure 3 | Dose-response meta-analyses of every 100 mg/day increased intake of vitamin C and the risk of lung cancer.** Squares represent study-specific RR, horizontal lines represent 95%CI and diamonds represent summary relative risks.

significant publication bias related to the association between vitamin C intake and lung cancer risk.

## Discussion

Findings from this meta-analysis indicated that the highest vitamin C intake level versus the lowest level was significantly associated with the risk of lung cancer. Inverse associations were also found in prospective studies, geographic locations of the United States and in the subgroup of males. Our dose-response analysis demonstrated a linear relationship between vitamin C intake and the risk of lung cancer, with a decrease in risk of 7% for every 100 mg/day increase in the intake of vitamin C.

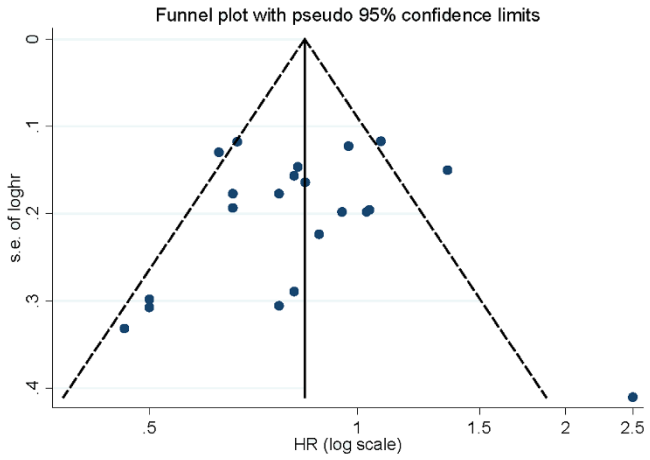


**Figure 4 | Begg's funnel plot for publication bias of vitamin C intake and lung cancer risk.**

We found a significant association between vitamin C intake and lung cancer in the United States, from which most of the included studies (17 out of 21), 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 United States, but cannot be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between vitamin C intake and lung cancer risk. As reported previously in 3 studies[26,29,33], we conclude from our meta-analysis that the relationship between vitamin C and lung cancer is restricted to males, but not in the females.

Vitamin C is hypothesized to reduce the risk of cancer because of its role in quenching free radicals and reducing oxidative damage to DNA[44–46]. Previous meta-analysis has suggested that vitamin C intake reduces the risk of colorectal adenoma (RR = 0.78, 95%CI = 0.62–0.98)[47], and that for gastric adenocarcinoma, each 20-μmol/L increase in plasma vitamin C was associated with a 14% decrease in risk (RR = 0.86; 95% CI = 0.76–0.96)[48]. Although no association was found between vitamin C intake and breast cancer in prospective studies, an inverse association of vitamin C intake with risk of breast cancer was found in case-control studies[49]. Meta-analysis has also suggested that the risk of endometrial cancer as estimated in dose-response models is reduced 15% for every 50 mg/1,000 kcal increase in intake of vitamin C (RR = 0.85; 95%CI = 0.73–0.98)[50].

Munafo and Flint reported that between-study heterogeneity is common in meta-analyses[51]. Exploring potential sources of between-study heterogeneity is therefore an essential component of meta-analysis. We found a moderate degree of heterogeneity ($I^2$ = 57.8%, $P_{heterogeneity}$ = 0.001) in our pooled results. This might have arisen from publication year, study design, geographic location, sex, sources of controls or number of cases. Thus, we used meta-regression to explore the causes of heterogeneity for covariates.

However, no covariate having a significant impact on between-study heterogeneity was found among those mentioned above. We then performed subgroup analyses by the type of study design (prospective or case-control studies), geographic locations, sex and sources of controls (population-based and hospital-based) to explore the source of heterogeneity. However, between-study heterogeneity persisted in some of the subgroups, suggesting the presence of other unknown confounding factors. The key contributor to this heterogeneity as assessed by the leave-one-out analysis was one study conducted by Speizer et al. (1999). After excluding this study, heterogeneity was reduced to $I^2 = 48.2\%$, without changing the results (RR = 0.805, 95%CI = 0.719–0.903).

We report here the first comprehensive meta-analysis of vitamin C intake and lung cancer risk based on high versus low analysis and dose-response meta-analysis. Our study included a larger number of participants than others, allowing a much greater possibility of reaching reliable conclusions about the association between vitamin C intake and lung cancer risk. There were some limitations in this meta-analysis. First, a meta-analysis of observational studies is susceptible to potential bias inherent in the original studies, especially for case-control studies. Several case-control studies were included in this meta-analysis, and no association was found between vitamin C intake and lung cancer risk in case-control studies. Second, as in any meta-analysis, the possibility of publication bias is of concern, because small studies with null results tend not to be published. However, the results obtained from Begg's funnel plot analysis and Egger's test did not provide evidence for such bias.

In summary, results from this meta-analysis suggest that a high intake of vitamin C might have a protective effect against lung cancer, especially in the United States. Dose-response analysis indicated that the estimated risk reduction in lung cancer is 7% for every 100 mg/day increase in intake of vitamin C.


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## Author contributions

J.L. and D.Z. designed the experiments; J.L., D.Z. and L.S. collected the date; J.L. and D.Z. wrote the main manuscript text and all authors reviewed the manuscript.

## Additional information

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