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Dietary and supplementary vitamin C intake and the risk of lung cancer: A meta-analysis of cohort studies

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Abstract. Previous cohort studies reported inconsistent findings regarding the association between dietary or supplementary vitamin C intake and lung cancer risk. These associations were investigated by conducting a meta-analysis of cohort studies. The PubMed and EMBASE databases were utilized, using keywords related to the topic from inception to April 15, 2022. Pooled effect sizes, such as relative risk (RR) or hazard ratio (HR) with 95% confidence intervals (CIs), were calculated using a random-effects model. A total of 20 cohort studies from 13 articles were included in the final analysis. In a meta-analysis of all studies, there was no significant association between dietary or supplementary vitamin C intake and lung cancer risk (RR/HR, 0.90; 95% CI, 0.80-1.01; I^2=56.4%; n=20). In the subgroup meta-analysis by the source of vitamin C, dietary vitamin C intake decreased the risk of lung cancer (RR/HR, 0.82; 95% CI, 0.73-0.92; I^2=42.5%; n=14), whereas there was no association between supplementary vitamin C intake and lung cancer risk (RR/HR, 1.01; 95% CI, 0.84-1.22; n=4). The present meta-analysis of cohort studies found that dietary vitamin C intake is beneficial for preventing lung cancer, whereas its supplementary intake does not have a beneficial effect.

Introduction

In recent decades, lung cancer has been the leading cause of cancer death worldwide (1,2). According to the GLOBOCAN report in 2020, the number of new cases of lung cancer was >2.2 million, accounting for 11.4% of all cancer cases and ranking second worldwide; the number of deaths from lung cancer was nearly 1.8 million, accounting for 18% of all cancer deaths and ranking first worldwide (3). Identification of modifiable risk factors for lung cancer can help prevent this deadly malignancy. Current epidemiological data suggest that tobacco use is the most probable cause which leads to lung cancer (4). On the other hand, high consumption of fruit and vegetables (5) rich in vitamins and various antioxidants decreases the risk of lung cancer (6-11).

Vitamin C has been reported to have a protective effect against the risk of lung cancer (12,13). More specifically, vitamin C is an important antioxidant regulator (14) that traps free radicals and reactive oxygen molecules (15), which in turn protects cells from oxidative DNA damage, thereby preventing cancer initiation (16).

Previous observational epidemiological studies have reported inconsistent findings regarding the association between vitamin C intake and the risk of lung cancer. Several observational studies have reported that high consumption of dietary vitamin C is associated with a decreased risk of the lung cancer (15,17,18). For example, studies by Yong *et al* (6) in 1997, Voorrips *et al* in 2000 (19) and Yuan *et al* (20) in 2003 reported that vitamin C intake reduced the risk of lung cancer by 34, 23 and 19%, respectively. Additionally, it has been reported that supplementary vitamin C intake reduces the risk of lung cancer (10,21,22). However, other observational studies have reported that there is no association between vitamin C (dietary and/or supplementary) intake and the risk of lung cancer (19,20,23-25). Previous studies reported that vitamin C intake even increased the risk of lung cancer (26-29).

Previous meta-analyses of cohort studies have also reported inconsistent findings based on the source of vitamin C: dietary or supplementation. Meta-analyses conducted by Cho *et al* (12) in 2006, Luo *et al* (13) in 2014 and Fu *et al* (30) in 2021 showed that dietary vitamin C intake significantly reduced the risk of lung cancer by 20, 17 and 16%, respectively. On the contrary, the study of Cho *et al* (12) showed that no association between

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total vitamin C intake (dietary plus supplementary) and the risk of lung cancer. Fu *et al* (30) also showed no association between supplementary vitamin C intake and the risk of lung cancer.

The aim of the present study was to investigate the association between dietary or supplementary vitamin C intake and the risk of lung cancer using a comprehensive meta-analysis of cohort studies and subgroup meta-analyses by various factors, specifically the source of vitamin C (dietary or supplementary).

Materials and methods

Literature search strategy. An extensive research was conducted for eligible studies published from inception to April 15, 2022, in two core databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/) and EMBASE (https://www.embase.com/landing?status=grey). Both the National Library of Medicine and Medical Subject Heading (MeSH) terms were used and a wide range of free-text search terms to identify as numerous relevant articles as possible. A PICO framework was used to determine the search terms associated with the topic as follows: 'P' stands for population, which, in the present study, was 'general population'; 'I' for intervention (exposure in this study), which was 'dietary or supplementary intake of vitamin C'; 'C' for comparison, which was 'little or no intake of vitamin C'; and 'O' for outcome, which was 'incidence of lung cancer.' Using Boolean operators along with all selected MeSH and free-text terms, the following search term was created: (vitamin C or ascorbic acid) and (lung cancer or lung neoplasms). The language of the publications was limited to English.

Selection criteria. The cohort studies that were selected (i) investigated the association between vitamin C intake (dietary or supplementary) and the risk of lung cancer, and (ii) reported outcome measures using adjusted relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs). When multiple studies used data from the same study, the most comprehensive analysis was included.

Selection of relevant studies and data extraction. Based on the selection criteria, two authors (Dung V Dung and Xuan Quy Luu) independently evaluated the eligibility of the studies that could potentially be included in the meta-analysis. Discrepancies between evaluators were resolved by a third author (Seung-Kwon Myung). The following data was extracted on the general characteristics of the included studies: Year of publication, name of first author, region (period of enrollment), characteristics of the population (number of participants, sex and age), follow-up period, type of vitamin C intake, outcomes, number of lung cancer cases, RR/HR with 95% CI and adjusted variables.

Quality assessment. The methodological quality of the individual cohort studies using the Newcastle-Ottawa Scale (31) was evaluated (n=13). The evaluated items were as follows: i) Selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and outcome of interest that was not present at the start of the study); ii) comparability (control for important and additional factors); and iii) outcome (assessment of outcome, follow-up long enough for outcomes to occur, and adequacy of follow-up of cohorts). Each cohort study could be awarded a maximum of one point for each numbered item within the selection and outcome categories, whereas a maximum of two points could be given for the comparability category. Individual studies were classified as low (average score or lower) or high quality (higher than the average score).

Main analysis and subgroup analyses. In the main analysis, the association between vitamin C intake (dietary or supplementary) and the risk of lung cancer using adjusted RRs or HRs with 95% CIs was investigated. A subgroup meta-analyses by region was also performed (Europe, United States and Asia), source of vitamin C (dietary, supplementary, or both), follow-up period (≤10 years or >10 years), sex (only male, only female, or both) and number of participants (<30,000 participants, 30,000-60,000 participants, or >60,000 participants), and quality of study (high or low).

Statistical analysis. From individual studies, the adjusted RRs or HRs were used and their 95% CIs to calculate the pooled effect size with a 95% CI. Because individual studies involved different populations, a random-effects model was chosen with the Der Simonian and Laird method (32). To examine the heterogeneity in results across studies, Higgins I^2 was used, which measures the percentage of total variation across studies. If I^2 was <0, it was set to zero. I^2 ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity); if I^2 is >50%, substantial heterogeneity exists (33).

Publication bias was evaluated using Begg's funnel plot and Egger's test. If publication bias existed, the Begg's funnel plot was asymmetrical, or the P-value of the Egger's test was <0.05. When the two tests showed inconsistent results, the results from the Egger's test were adopted because the funnel plot relies on visual inspection, which might be misleading (34). Statistical analyses were conducted using the Stata SE software package (version 17.0; StataCorp LP).

Results

Selection of relevant studies. A flow diagram of the selection process of the relevant studies is demonstrated in Fig. 1. A total of 1,588 articles were identified by searching the databases. After removing 345 duplicate articles, titles and abstracts were reviewed of 1,243 articles, and subsequently 1,218 articles that did not meet the predetermined selection criteria were excluded. After reviewing the full texts of the remaining 25 articles, 12 articles were excluded for the following reasons: Identical population (n=1), irrelevance (n=8), and insufficient data (n=3). Ultimately, 20 cohort studies from the remaining 13 articles were included in the final analysis.

General characteristics of studies. The general characteristics of the included studies are shown in Table I. From the 20 cohort studies, a total of 808,587 participants were identified, including 7,227 lung cancer patients (6,8,17-20,23-29). The individual studies were conducted in the United States (n=12), Europe (n=4), and Asia (n=4). All participants were aged between 25-80 years. The mean follow-up period ranged from 4-20 years.

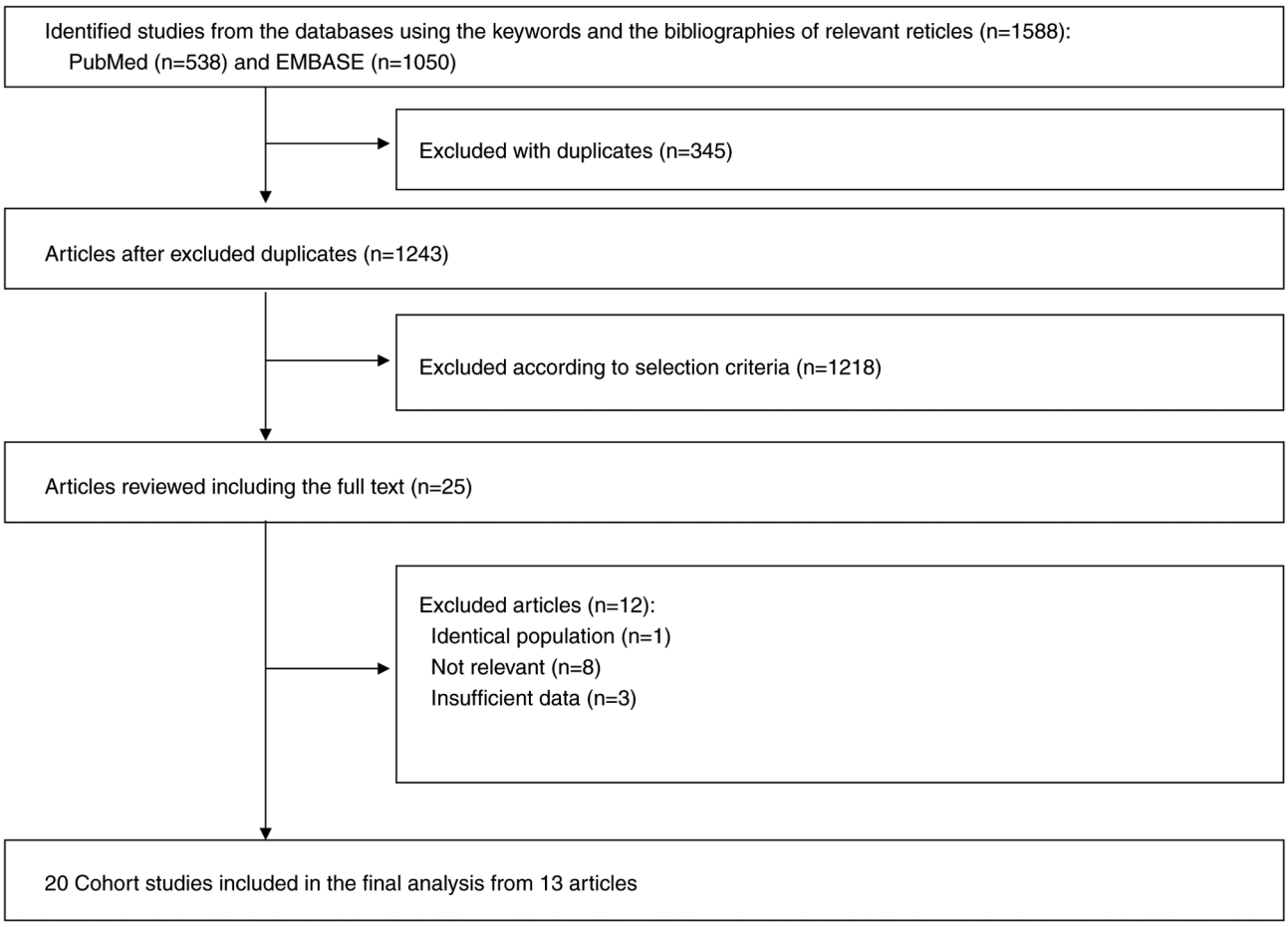

Figure 1. Flow diagram of identification of relevant studies.

Quality assessment. As shown in Table II, 14 cohort studies from eight articles were considered to be of low quality, (6,17,19,23-25,27,28) and six studies from the five remaining articles were considered to be of high quality (8,18,20,26,29).

Main analysis and subgroup meta-analyses. The findings from the main analysis and subgroup meta-analyses by the source of vitamin C are shown in Fig. 2. Overall, there was no significant association between dietary or supplementary vitamin C intake and the risk of lung cancer in the meta-analysis of all 20 cohort studies (RR/HR, 0.90; 95% CI, 0.80 to 1.01; I^2=56.4%). In the subgroup meta-analysis by the source of vitamin C, dietary vitamin C intake was associated with a decreased risk of lung cancer (RR, 0.82; 95% CI, 0.73-0.92; I^2=42.5%; n=14), whereas there was no association between supplementary vitamin C intake and the risk of lung cancer (RR, 1.01; 95% CI, 0.84-1.22; I^2=25.7%; n=4). In the subgroup meta-analysis of two cohort studies, the combination of dietary and supplementary vitamin C intake was associated with an increased risk of lung cancer (RR, 1.37; 95% CI, 1.06-1.76; I^2=0%).

Table III presents the findings of the subgroup meta-analyses based on various factors. In the subgroup meta-analysis by region, there was no significant association between vitamin C intake and lung cancer risk across regions (United States, Europe and Asia). In the subgroup meta-analysis by follow-up period, dietary or supplementary vitamin C intake decreased lung cancer risk during the follow-up period of 5 to 10 years (RR, 0.83; 95% CI, 0.74-0.94; I^2=0%; n=11). However, this beneficial effect was not observed when the follow-up period was longer than 10 years (RR, 0.94; 95% CI, 0.76-1.17; I^2=0%; n=8). As demonstrated in Fig. 3, there was no publication bias in this meta-analysis (symmetrical Begg's funnel plot; Egger's test, P=0.68).

Discussion

In the present meta-analysis of cohort studies, there was no significant association between dietary or supplementary vitamin C intake and lung cancer risk. However, in the subgroup meta-analysis by the source of vitamin C, dietary intake of vitamin C was found to be associated with a decreased risk of lung cancer, whereas no association was found between supplementary vitamin C intake and high risk of lung cancer. Notably, the combination of dietary and supplementary vitamin C intake was associated with an increased risk of lung cancer. In the subgroup meta-analysis by follow-up period, dietary or supplementary vitamin C intake was associated with a decreased risk of lung cancer among studies with 10 years or shorter follow-up periods. However, this beneficial effect was not observed among studies with follow-up periods longer than 10 years.

Although the effects of vitamin C on lung cancer development remain unclear, several potential biological mechanisms

Table I. General characteristics of cohort studies included in the analysis (n=13).

First author, year	Region (years enrolled)	Population	Follow-up Periods	Vitamin C intake (dietary or supplementary)	Outcomes and number of cases	RR/HR (95% CI)	Adjusted variables	(Refs.)
Shibata *et al*, 1992	USA (1981-1989)	24,218 men of a retirement community Mean age: 74.9 years old	8 years	Dietary Supplementary	Lung cancer (n=94)	1.11 (0.68-1.81) 1.03 (0.68-1.55)	Age and smoking	(23)
		45,941 women of a retirement community Mean age: 73.8 years old		Dietary Supplementary	Lung cancer (n=70)	0.56 (0.31-1.02) 0.72 (0.45-1.15)		
Steinmetz *et al*, 1993	USA (1986-1990)	41,837 postmenopausal women Mean age: 61.7 years old	4 years	Dietary + Supplementary	Lung cancer (n=138)	1.41 (0.87-2.30)	Age. energy intake, and pack-years of smoking in multivariable logistic regression models	(26)
Bandera *et al*, 1997	USA (1980-1987)	27,544 men from the New York State Cohort Age range: mostly 40-80 years old	8 years	Dietary	Lung cancer (n=395)	0.63 (0.53-0.88)	Age, education, cigarettes/ day, years smoking, and total energy intake (except calories) based on cox proportional hazards model	(17)
		20,456 women from the New York State Cohort Age range: mostly 40-80 years old			Lung cancer (n=130)	0.88 (0.57-1.37)		
Ocké *et al*, 1997	European (Netherlands) (1960-1990)	561 men from the town of Zutphen, the Netherlands. Age range: 52-71 years old	20 years	Dietary	Lung cancer (n=54)	0.46 (0.24-0.88)	Age, pack-years of cigarettes, and energy intake	(18)
Yong *et al*, 1997	USA (1971-1992)	10,068 persons (3,968 men and 6,100 women) from the First National Health and Nutrition Examination Survey Epidemiologic Follow up Study cohort Age range: 25-74 years old	19 years	Dietary	Lung cancer (n=248)	0.66 (0.45-0.96)	Sex, race, educational attainment, nonrecreational activity level, BMI, family history, smoking status, total calorie intake, and alcohol intake	(6)
Speizer *et al*, 1999	USA (1980-1992)	118,351 women from the Nurses' Health Study Age range: 30-69 years old	16 years	Dietary + Supplementary	Lung cancer (n=593)	1.35 (1.0-1.8)	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 (O17, 18-19, 20-21, 22+)	(27)

Table I. Continued.

First author, year	Region (years enrolled)	Population	Follow-up Periods	Vitamin C intake (dietary or supplementary)	Outcomes and number of cases	RR/HR (95% CI)	Adjusted variables	(Refs.)
Feskanich *et al*, 2000	USA (1976-1996)	47,778 men from the Health Professionals' Follow-up Study Age range: 40-75 years old	10 years	Dietary	Lung cancer (n=274)	1.04 (0.71-1.53)	n.a.	(24)
		77,283 women from the Nurses' Health Study Age range: 40-75 years old	12 years		Lung cancer (n=519)	0.82 (0.62-1.1)	n.a.	
Voorrips *et al*, 2000	European (Netherlands) (1986-1992)	58,279 men from the Netherlands Cohort Study on Diet and Cancer Age range: 55-69 years old	6.3 years	Dietary	Lung cancer (n=939)	0.77 (0.54-1.08)	Age, family history, smoking, SES, folate, and energy	(19)
Yuan *et al*, 2003	Asia Singapore) (1993-2000)	62,392 Chinese men and women in Singapore Age range: 45-74 years old	8 years	Dietary	Lung cancer (n=482)	0.81 (0.59-1.09)	Age, sex, dialect group, year of interview, level of education, BMI, r number of cigarettes smoked per day, number of years of smoking, and number of years since quitting smoking for former smokers	(20)
Slatore *et al*, 2008	USA (2000-2006)	77,126 men and women from Washington State in the VITAL study Age range: 50-76 years old	10 years	Supplementary	Lung cancer (n=521)	0.97 (0.76-1.23)	Age, sex, years smoked, pack-years, and pack-years squared	(25)
Roswall *et al*, 2010	European (Denmark) (1993-1997)	55,557 Danes from the prospective Diet, Cancer and Health study Age range: 50-64 years old	10.6 years	Supplementary Dietary	Lung cancer (n =721)	1.23 (0.93-1.62) 0.76 (0.58-0.99)	Not given	(28)
Takata *et al*, 2013	Asia (China) (2002-2009)	61,491 adult Chinese men from the Shanghai Men's Health study Age range: 40-74 years old	5.5 years	Dietary	Lung cancer (n=359)	0.84 (0.61-1.16)	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	(8)

Table I. Continued.

First author, year	Region (years enrolled)	Population	Follow-up Periods	Vitamin C intake (dietary or supplementary)	Outcomes and number of cases	RR/HR (95% CI)	Adjusted variables	(Refs.)
Narita *et al*, 2018	Asia (Japan) (1990-2013)	38,207 men from the Japan Public Health Center-based prospective study Age range: 40-69 years old	18 years	Dietary	Lung cancer men (n=1,237)	1.02 (0.79-1.32)	Age, study area, smoking status, alcohol consumption, vitamin supplements use, and energy-adjusted intakes of fish, isoflavone, vegetables, and fruits.	(29)
		41,498 women from the Japan Public Health Center-based prospective study Age range: 40-69 years old			Lung cancer women (n=453)	1.37 (0.92-2.05)		

RR, relative risk; HR, hazard ratio; CI, confident interval; NA, not available

have been proposed. Vitamin C has antioxidant properties at low serum levels, prooxidant properties at high serum levels, and is involved in the epigenetic regulation of genomic stability (35-37). High levels of reactive oxygen species (ROS), which are a subset of free radicals, are well known to damage cellular DNA and promote oncogenesis (38). Vitamin C, as a potent antioxidant, may scavenge these ROS, preventing DNA damage and oncogenesis (37). Also, at high concentrations (5-20 mM), vitamin C (ascorbate) could act as a prooxidant through the reduction of metal ions, such as Fe^{3+} (2 Fe^{3+} + Ascorbate → 2 Fe^{2+} + Dehydroascorbate), leading to the formation of ROS, such as H_2O_2. Through the Fenton reaction, H_2O_2 can produce free hydroxyl radicals (2 Fe^{2+} + 2 H_2O_2 → 2 Fe^{3+} + 2 OH· + 2 OH-) which are selectively toxic to cancer cells (36). Additionally, ten-eleven translocation (TET) promotes DNA demethylation as one of the epigenetic modifications, and loss of function in TET proteins and changes of DNA methylation can lead to genomic instability and carcinogenesis (39). Vitamin C, a cofactor of TET enzymes, is also known to directly promote DNA demethylation and alter the expression of tumor suppressors and DNA repair enzymes (39).

The findings of the present study, are consistent with those of previously published meta-analyses. A meta-analysis by Cho *et al* (12) of eight prospective studies in 2006 reported that dietary vitamin C intake significantly decreased the risk of lung cancer (RR, 0.80; 95% CI, 0.71-0.91), whereas there was no significant association between total vitamin C intake (dietary plus supplementary) and the risk of lung cancer (RR, 1.00; 95% CI, 0.80-1.25). Additionally, Luo *et al* (13) conducted a meta-analysis of 14 prospective cohort studies in 2014 and concluded that high dietary vitamin C intake, by consumption of fruits and vegetables, had a protective effect against lung cancer (RR, 0.83; 95% CI, 0.73-0.94). However, a subgroup meta-analysis of supplementary vitamin C alone was not conducted, and additional prospective studies have been published since this publication.

Recently, in 2021, a meta-analysis of cohort studies by Fu *et al* (30) reported findings similar to those of Cho *et al*'s meta-analysis. However, their analysis included only six cohort studies on dietary vitamin C intake and three on supplementary vitamin C intake. The present meta-analysis involved 20 cohort studies and subgroup meta-analyses according to the source of vitamin C (dietary or supplementary). Unlike previous meta-analyses, the present study's subgroup meta-analysis showed that the combination of dietary and supplementary vitamin C intake was significantly associated with a 37% increased risk of lung cancer.

There are several possible explanations for the discrepancies regarding the findings on the effects of dietary and supplementary vitamin C intake on the risk of lung cancer. The majority of commercial vitamin C supplements are synthetic. Although synthetic vitamin C supplements and food-derived dietary vitamin C are chemically identical, the effects of fruits and vegetables rich in vitamin C may differ from those of vitamin C supplements in that the combination of natural vitamin C and numerous nutrients in fruits and vegetables might have beneficial effects of reducing the risk of lung cancer (40,41). Additionally, it was found that the combination of dietary and supplementary vitamin C intake

Table II: Methodological quality of the included studies in the final analysis based on the Newcastle-Ottawa Scale for assessing the quality of cohort studies (n=13).

	Selection				Comparability	Outcome				
Cohort studies	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total	(Refs.)
Shibata *et al*, 1992	1	0	1	1	1	1	1	1	7	(23)
Steinmetz *et al*, 1993	1	1	1	1	1	1	0	2	8	(26)
Bandera *et al*, 1997	1	0	1	1	1	1	1	1	7	(17)
Ocké *et al*, 1997	1	0	1	1	1	1	1	2	8	(18)
Yong *et al*, 1997	1	0	1	1	1	1	1	1	7	(6)
Speizer *et al*, 1999	1	0	1	1	1	1	1	1	7	(27)
Feskanich *et al*, 2000	1	0	1	1	0	1	1	1	6	(24)
Voorrips *et al*, 2000	1	0	1	1	0	1	1	2	7	(19)
Yuan *et al*, 2003	1	1	1	1	1	1	1	1	8	(20)
Slatore *et al*, 2008	1	0	1	1	1	1	1	1	7	(25)
Roswall *et al*, 2010	1	1	1	1	0	1	1	0	6	(28)
Takata *et al*, 2013	1	0	1	1	1	1	1	2	8	(8)
Narita *et al*, 2018	1	0	1	1	1	1	1	2	8	(29)
								Average score=7.2		

Each study can be awarded a maximum of one point for each numbered item within the selection and exposure categories, while a maximum of two points can be given for the comparability category. 2016 Stepien *et al*'s study consists of a cohort study.

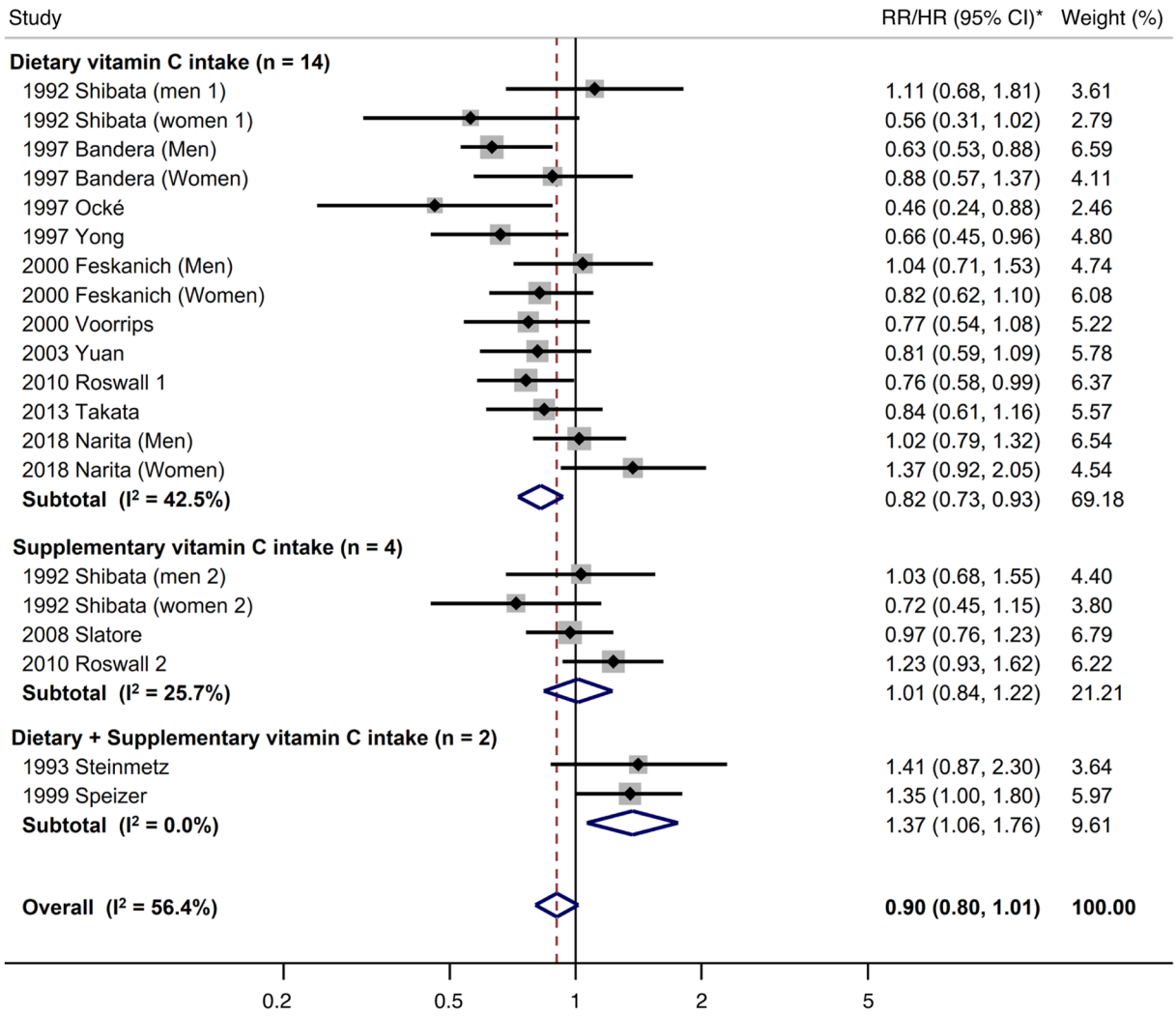

Figure 2. Association between dietary or supplementary intake of vitamin C and risk of lung cancer in a random-effects meta-analysis of cohort studies (n=20). *Random-Effects Model. RR, relative risk; HR, hazard ratio; CI, confidence interval.

significantly increased the risk of lung cancer. A possible explanation is that when provided in addition to dietary vitamin C, vitamin C supplements may act as pro-oxidants under conditions of oxidative stress, such as smoking, thereby inducing DNA damage and eventually leading to the development of lung cancer (41,42).

The present meta-analysis revealed a difference in the risk of lung cancer between food-derived, dietary vitamin C and synthetic vitamin C supplements. This implies that the diverse dietary nutrients from foods as well as vitamin C should not be directly equated to synthetic nutrient supplements in terms of beneficial effects. Although the dietary intake of nutrients from foods, such as fruits and vegetables, has shown beneficial effects in the prevention of cancer, the effects of synthetic nutrient supplements should be investigated in further randomized controlled trials (RCTs) as well as epidemiological observational studies.

The present study, to the best of the authors' knowledge, was the most comprehensive meta-analysis of cohort studies on the association between vitamin C intake and the risk of lung cancer, including subgroup meta-analyses of various factors.

However, the present study had some limitations. First, most studies included in this meta-analysis did not report the risk of lung cancer based on the specific levels of dietary vitamin C consumed by the participants. Thus, it was impossible to perform subgroup meta-analyses by dietary intake levels of vitamin C; second, although the subgroup meta-analyses revealed that dietary intake of vitamin C along with supplements increased the risk of lung cancer, only two studies were included in this analysis. Further prospective studies are warranted to confirm these findings. Third, only studies published in English were included to ensure the high quality of the included studies and accessibility of the data. If studies published in languages other than English had been included in the present study, the findings may have changed. However, this would not have significantly affected the conclusions. Fourth, this meta-analysis only included cohort studies. Regarding the effects of vitamin C supplementation, RCTs provide a higher level of evidence than cohort studies. Finally, all the included cohort studies were published before 2010. Further RCTs and meta-analyses of RCTs are warranted to confirm the association between supplementary vitamin C intake and lung cancer risk.

Table III. Association between dietary or supplementary intake of vitamin C and risk of lung cancer in subgroup meta-analyses by various factors.

Factors	No. of study	RR/HR (95% CI)	Heterogeneity, I^2 (%)
All	20	0.90 (0.80-1.01)	56.4
Region			
Europe	4	0.81 (0.58-1.14)	73.1
United States	12	0.90 (0.76-1.06)	58.5
Asia	4	0.97 (0.79-1.19)	41%
Source of vitamin C intake			
Supplementary	4	1.01 (0.84-1.22)	25.7
Dietary	14	0.82 (0.73-0.92)[a]	42.5
Dietary + Supplementary	2	1.37 (1.06-1.76)[a]	0
Follow up period			
<5 years	1	1.41 (0.87-2.29)	100
5-10 years	11	0.83 (0.74-0.94)	18.0
>10 years	8	0.94 (0.76-1.17)	71.1
Sex			
Men	8	0.85 (0.71-1.02)	50.2
Women	5	0.88 (0.72-1.08)	59.2
Both	7	0.99 (0.77-1.27)	62.4
Number of participants			
<30,000	6	0.76 (0.61-0.97)	48.3
30,000-60,000	9	0.96 (0.80-1.15)	55.4
>60,000	5	0.94 (0.78-1.13)	50.8
Quality of study			
High quality (>7 score)	6	0.95 (0.75-1.21)	59.7
Low quality (≤7 scores)	14	0.88 (0.76-1.01)	57.1

[a]Statistically significant. RR, relative risk; HR, hazard ratio; CI, confidence interval.

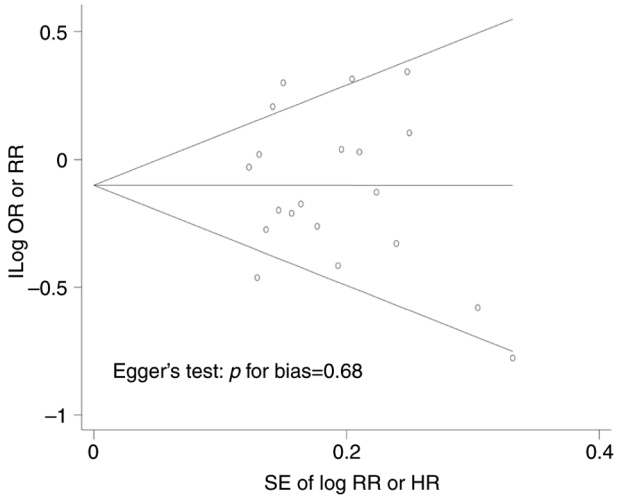

Figure 3. Begg's funnel plots and Egger's test for identifying publication bias in meta-analysis of cohort studies. RR, relative Risk; HR, hazard ratio; SE, standard error.

In conclusion, in the present meta-analysis of cohort studies it was found that the dietary intake of vitamin C is beneficial for the prevention of lung cancer, whereas its supplementary intake does not have any beneficial effect. The findings of the present study should be confirmed by further prospective studies and RCTs.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SKM and DVT conceptualized the present study, conducted investigation and data curation. SKM implemented the methodology. DVT performed formal analysis. DVT and XQL wrote the original draft. XQL and HTTT made substantial contributions to acquisition and interpretation of data. SKM, DVT and

HTTT wrote, reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript. DVT and SKM confirm the authenticity of all the raw data

Ethics approval and consent to participate

Not applicable.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Glade MJ: Food, nutrition, and the prevention of cancer: A global perspective. American institute for cancer research/world cancer research fund, American institute for cancer research, 1997. Nutrition 15: 523-526, 1999.
2. World Health Organization. Cancer. https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed on December 22, 2022.
3. Sung H, Ferlay JF, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
4. Kim CH, Lee YC, Hung RJ, McNallan SR, Cote ML, Lim WY, Chang SC, Kim JH, Ugolini D, Chen Y, *et al*: Exposure to secondhand tobacco smoke and lung cancer by histological type: A pooled analysis of the international lung cancer consortium (ILCCO). Int J Cancer 135: 1918-1930, 2014.
5. Norat T, Aune D, Chan D and Romaguera D: Fruits and vegetables: Updating the epidemiologic evidence for the WCRF/AICR lifestyle recommendations for cancer prevention. Cancer Treat Res 159: 35-50, 2014.
6. Yong LC, Brown CC, Schatzkin A, Dresser CM, Slesinski MJ, Cox CS and Taylor PR: Intake of vitamins E, C, and A and risk of lung cancer. The NHANES I epidemiologic followup study. First national health and nutrition examination survey. Am J Epidemiol 146: 231-243, 1997.
7. Cheng TY, Lacroix AZ, Beresford SA, Goodman GE, Thornquist MD, Zheng Y, Chlebowski RT, Ho GY and Neuhouser ML: Vitamin D intake and lung cancer risk in the Women's health initiative. Am J Clin Nutr 98: 1002-1011, 2013.
8. Takata Y, Xiang YB, Yang G, Li H, Gao J, Cai H, Gao YT, Zheng W and Shu XO: Intakes of fruits, vegetables, and related vitamins and lung cancer risk: Results from the Shanghai Men's health study (2002-2009). Nutr Cancer 65: 51-61, 2013.
9. Redaniel MT, Gardner MP, Martin RM and Jeffreys M: The association of vitamin D supplementation with the risk of cancer in postmenopausal women. Cancer Causes Control 25: 267-271, 2014.
10. Vieira AR, Abar L, Vingeliene S, Chan DS, Aune D, Navarro-Rosenblatt D, Stevens C, Greenwood D and Norat T: Fruits, vegetables and lung cancer risk: A systematic review and meta-analysis. Ann Oncol 27: 81-96, 2016.
11. Shareck M, Rousseau MC, Koushik A, Siemiatycki J and Parent ME: Inverse association between dietary intake of selected carotenoids and vitamin C and risk of lung cancer. Front Oncol 7: 23, 2017.
12. Cho E, Hunter DJ, Spiegelman D, Albanes D, Beeson WL, van den Brandt PA, Colditz GA, Feskanich D, Folsom AR, Fraser GE, *et al*: Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: A pooled analysis of 8 prospective studies. Int J Cancer 118: 970-978, 2006.
13. Luo J, Shen L and Zheng D: Association between vitamin C intake and lung cancer: A dose-response meta-analysis. Sci Rep 4: 6161, 2014.
14. Fairfield KM and Fletcher RH: Vitamins for chronic disease prevention in adults: Scientific review. JAMA 287: 3116-3126, 2002.
15. Lee KW, Lee HJ, Surh YJ and Lee CY: Vitamin C and cancer chemoprevention: Reappraisal. Am J Clin Nutr 78: 1074-1078, 2003.
16. Pathak SK, Sharma RA, Steward WP, Mellon JK, Griffiths TR and Gescher AJ: Oxidative stress and cyclooxygenase activity in prostate carcinogenesis: Targets for chemopreventive strategies. Eur J Cancer 41: 61-70, 2005.
17. Bandera EV, Freudenheim JL, Marshall JR, Zielezny M, Priore RL, Brasure J, Baptiste M and Graham S: Diet and alcohol consumption and lung cancer risk in the New York state cohort (United States). Cancer Causes Control 8: 828-840, 1997.
18. Ocké MC, Bueno-de-Mesquita HB, Feskens EJ, van Staveren WA and Kromhout D: Repeated measurements of vegetables, fruits, beta-carotene, and vitamins C and E in relation to lung cancer. The Zutphen study. Am J Epidemiol 145: 358-365, 1997.
19. Voorrips LE, Goldbohm RA, Brants HA, van Poppel GA, Sturmans F, Hermus RJ and van den Brandt PA: A prospective cohort study on antioxidant and folate intake and male lung cancer risk. Cancer Epidemiol Biomarkers Prev 9: 357-365, 2000.
20. Yuan JM, Stram DO, Arakawa K, Lee HP and Yu MC: Dietary cryptoxanthin and reduced risk of lung cancer: The Singapore Chinese health study. Cancer Epidemiol Biomarkers Prev 12: 890-898, 2003.
21. Lee DH and Jacobs DR Jr: Interaction among heme iron, zinc, and supplemental vitamin C intake on the risk of lung cancer: Iowa Women's health study. Nutr Cancer 52: 130-137, 2005.
22. Lin J, Cook NR, Albert C, Zaharris E, Gaziano JM, Van Denburgh M, Buring JE and Manson JE: Vitamins C and E and beta carotene supplementation and cancer risk: A randomized controlled trial. J Natl Cancer Inst 101: 14-23, 2009.
23. Shibata A, Paganini-Hill A, Ross RK and Henderson BE: Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: A prospective study. Br J Cancer 66: 673-679, 1992.
24. Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, Willett WC and Colditz GA: Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. J Natl Cancer Inst 92: 1812-1823, 2000.
25. Slatore CG, Littman AJ, Au DH, Satia JA and White E: Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer. Am J Respir Crit Care Med 177: 524-530, 2008.
26. Steinmetz KA, Potter JD and Folsom AR: Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. Cancer Res 53: 536-543, 1993.
27. Speizer FE, Colditz GA, Hunter DJ, Rosner B and Hennekens C: Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). Cancer Causes Control 10: 4754-4782, 1999.
28. Roswall N, Olsen A, Christensen J, Dragsted LO, Overvad K and Tjønneland A: Source-specific effects of micronutrients in lung cancer prevention. Lung Cancer 67: 275-281, 2010.
29. Narita S, Saito E, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Ishihara J, Takachi R, Shibuya K, Inoue M, *et al*: Dietary consumption of antioxidant vitamins and subsequent lung cancer risk: The Japan public health center-based prospective study. Int J Cancer 142: 2441-2460, 2018.
30. Fu Y, Xu F, Jiang L, Miao Z, Liang X, Yang J, Larsson SC and Zheng JS: Circulating vitamin C concentration and risk of cancers: A Mendelian randomization study. BMC Med 19: 171, 2021.
31. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P: The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
32. Borenstein M, Hedges LV, Higgins JP and Rothstein HR: A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 1: 97-111, 2010.
33. Higgins JP and Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539-1558, 2002.
34. Simmonds M: Quantifying the risk of error when interpreting funnel plots. Syst Rev 4: 24, 2015.
35. Vissers MCM and Das AB: Potential mechanisms of action for vitamin c in cancer: Reviewing the evidence. Front Physiol 9: 809, 2018.
36. Villagran M, Ferreira J, Martorell M and Mardones L: The role of vitamin C in cancer prevention and therapy: A literature review. Antioxidants (Basel) 10: 1894, 2021.

37. Pawlowska E, Szczepanska J and Blasiak J: Pro- and antioxidant effects of vitamin c in cancer in correspondence to its dietary and pharmacological concentrations. Oxid Med Cell Longev 24: 7286737, 2019.
38. Singh R and Manna PP: Reactive oxygen species in cancer progression and its role in therapeutics. Explor Med 3: 43-57, 2022.
39. Brabson JP, Leesang T, Mohammad S and Cimmino L: Epigenetic regulation of genomic stability by vitamin C. Front Genet 12: 675780, 2021.
40. Myung SK, Kim Y, Ju W, Choi HJ and Bae WK: Effects of antioxidant supplements on cancer prevention: Meta-analysis of randomized controlled trials. Ann Oncol 21: 166-179, 2010.
41. Carr AC and Vissers MC: Synthetic or food-derived vitamin C-are they equally bioavailable? Nutrients 5: 4284-4304, 2013.
42. Mayne ST, Handelman GJ and Beecher G: Beta-carotene and lung cancer promotion in heavy smokers-a plausible relationship? J Natl Cancer Inst 88: 1513-1515, 1996.