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The association of dietary β-carotene and vitamin A intake on the risk of esophageal cancer: a meta-analysis

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ABSTRACT

Background and purpose: dietary β-carotene and vitamin A intake have shown some potential effect in the development of esophageal cancer. This meta-analysis was performed to investigate the association of β-carotene and vitamin A intake on the risk of esophageal cancer.

Methods: the PubMed, Embase, Web of Science and Wanfang Med online databases were systematically searched to collect the relevant articles regarding the impact of β-carotene and vitamin A intake on esophageal cancer risk. Pooled odds ratios (OR) with 95 % confidence intervals (CI) were combined using the Review Manager Version 5.3 software.

Results: this meta-analysis included 14 articles. The highest category of β-carotene intake may significantly reduce the risk of esophageal cancer compared with the lowest category (OR = 0.62, 95 % CI = 0.50-0.77). Similar significant results were found in American and European populations but not in other populations with β-carotene intake. An inverse association was found between vitamin A intake and

esophageal cancer risk (OR = 0.79, 95 % CI = 0.63-0.99). No potential publication bias was detected.

Conclusions: our study suggested that dietary β-carotene and vitamin A intake may reduce the risk of esophageal cancer. More relevant studies are needed to further explore this association, as there were some limitations in our analysis.

Keywords: Dietary. β-carotene. Vitamin A. Esophageal cancer. Meta-analysis.

INTRODUCTION

Esophageal cancer mainly includes esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) (1). It is the sixth most common cancer with a high incidence rate and is the third most common gastrointestinal cancer (1). Therefore, it is essential to control and prevent esophageal cancer. Genetic factors are an important factor that affects the occurrence of esophageal cancer (2,3). Furthermore, diet may also be a potential factor in the prevention of esophageal cancer (4,6). Previous studies have indicated that dietary vitamin C intake might have a protective effect against esophageal cancer (7). Cui et al. performed a meta-analysis of vitamin E intake and esophageal cancer risk. The results suggested that a higher vitamin E intake was associated with a lower esophageal cancer risk (8). Ma et al. performed a study of vitamin B intake and esophageal cancer risk and concluded that vitamins B1, B3, B6 and B9 decreased the risk of esophageal cancer (9). However, there are no published meta-analyses about β-carotene and vitamin A intake on esophageal cancer risk. The results of the many studies are conflicting about β-carotene and vitamin A intake on the effect of esophageal cancer. Therefore, this systematic review and meta-analysis was performed to investigate the exact association of β-carotene and vitamin A intake on esophageal cancer risk.

METHODS

This study was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group (10).

Literature search and selection criteria

Several databases including PubMed, Embase, Web of Science and Wanfang Med online were systematically searched using the following keywords: ('β-Carotene' OR 'vitamin A' OR 'retinol') AND ('esophageal cancer' OR 'esophageal adenocarcinoma' OR 'esophageal squamous cell carcinoma'). The time of publishing the studies was from inception to July 31st, 2019. Two investigators independently searched the articles.

The inclusion criteria were as follows: a) observational study design; b) the study populations were patients with esophageal cancer or EAC or ESCC; c) dietary factor was β-carotene and/or vitamin A intake; and d) available data of odds ratios (OR) and 95 % confidence intervals (CI) or enough data to calculate them.

The following exclusion criteria were used: a) reviews or meetings or abstracts or letter to the editor; b) overlapping articles or populations; c) animal studies; and d) no available data of OR and 95 % CI.

Data extraction and quality assessment

The detailed information that was extracted in each included study is shown in table 1. Two investigators independently completed this analysis. Inconsistent information extracted by these two investigators was resolved through discussion. The Newcastle-Ottawa-Scale (NOS) was used to evaluate the quality of each study (11) (11).

Statistical analysis

Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) was used for the statistical analyses. The overall OR and 95 % CI were pooled using the random-effect model (12). Heterogeneity was quantified with the I^2 statistic and an I^2 value greater than 50 % represented significant heterogeneity (13). Subgroup analysis and meta-regression were performed to explore the between-study heterogeneity (14). Sensitivity analysis was performed to detect the influence of a single study on the overall estimate. Publication bias was evaluated according to Egger's test (15) and funnel plot (16). Two-side $p < 0.05$ was considered to be

statistically significant.

RESULTS

Literature search and study characteristics

Figure 1 shows the flow chart for the selection process and detailed identification. In total, 14 articles (17-30) which met our inclusion criteria were included in the meta-analysis. Three articles including Mayne et al. (25), Terry et al. (27) and Tzonou et al. (29) reported both EAC and ESCC simultaneously and independently. Therefore, 15 independent studies with 3,376 cases and 12,557 participants for β-carotene intake and 13 independent studies with 2,478 cases and 9,480 participants for vitamin A intake were used for the final analysis. All 14 articles had a relatively high quality (over six stars), with an average NOS score of 7.07. Table 1 shows the baseline characteristics of all the included studies.

β-carotene intake and the risk of esophageal cancer

The highest category of β-carotene intake may significantly reduce the risk of esophageal cancer compared with the lowest category (OR = 0.62, 95 % CI = 0.50-0.77), with significant heterogeneity (I^2 = 70.8 %, $p_{for\ heterogeneity}$ < 0.001) (Fig. 2). Similar significant results were found both in EAC (OR = 0.61, 95 % CI = 0.45-0.82) and ESCC (OR = 0.62, 95 % CI = 0.43-0.88) (Fig. 2). The subgroup analysis by geographic location showed an inverse association in American (OR = 0.65, 95 % CI = 0.48-0.89) and European populations (OR = 0.45, 95 % CI = 0.34-0.59), but not in other populations. The results did not change in population-based case-control studies (PBCC) or hospital-based case-control studies (HBCC). The detailed results are shown in table 2. Sensitivity analysis was performed by omitting one study in turn and no single study had an impact on the overall estimate (Supplementary Fig. 1). Publication bias was not detected according to the Egger's test (p = 0.252) and funnel plot (Supplementary Fig. 2).

Vitamin A intake and the risk of esophageal cancer

An inverse association between vitamin A intake and esophageal cancer risk (OR =

0.79, 95 % CI = 0.63-0.99) was found, with significant heterogeneity (I^2 = 71.5 %, $p_{for\ heterogeneity}$ < 0.001) (Fig. 3). However, according to the subgroup analysis by disease type, the association was only significant for EAC (OR = 0.58, 95 % CI = 0.47-0.73) and not for ESCC (OR = 0.85, 95 % CI = 0.56-1.30). Hierarchical analysis by study design was performed, and the OR in PBCC and HBCC was 0.60 (95 % CI = 0.44-0.81) and 0.94 (95 % CI = 0.71-1.25), respectively. A significant result was only found in American populations (OR = 0.63, 95 % CI = 0.51-0.77), but not in other populations. The detailed results are shown in table 2. Sensitivity analysis by omitting one study in turn was performed and no single study had an impact on the overall estimate (Supplementary Fig. 3). Publication bias were not found according to the Egger's test (p = 0.344) and funnel plot (Supplementary Fig. 4).

DISCUSSION

Findings from the current study suggested that β-carotene intake could significantly decrease the risk of esophageal cancer. Inverse associations were found between β-carotene intake and the subtypes of esophageal cancer of EAC and ESCC. Furthermore, a significant association was found in American and European populations, but not in other populations. Vitamin A intake could reduce the risk of esophageal cancer in the overall analysis. A significant association was only found between vitamin A intake and EAC, but not for ESCC. A decreased risk of esophageal cancer was also found in American populations and not other populations.

β-carotene and vitamin A intake had been linked with some cancers. Zhang et al. performed a meta-analysis of vitamin A intake and pancreatic cancer risk. This study indicated that dietary vitamin A intake may be inversely associated with the risk of pancreatic cancer (31). A meta-analysis of 19 publications suggested that the high category of dietary β-carotene and vitamin A intake could reduce the risk of lung cancer (32). In our study, a significant decreased association was found between esophageal cancer and β-carotene intake, as well as vitamin A intake. Previous meta-analyses have already confirmed the inverse association of vitamin C and vitamin E on esophageal cancer risk. Vitamins A, C and E act as scavengers of reactive oxygen species and may protect esophageal cells from oxidative damage and DNA

destruction (33). Furthermore, vitamin A, C and E are important to prevent the endogenous synthesis of N-nitroso compounds, which are potential carcinogens in the esophagus (34). This may be why vitamin A can reduce the risk of esophageal cancer.

A significant heterogeneity (β-carotene: I^2 = 70.8 %, $p_{for\ heterogeneity} < 0.011$; vitamin A: I^2 = 71.5 %, $p_{for\ heterogeneity} < 0.011$) was found in the overall results. Between-study heterogeneity is common in a meta-analysis and the exploration of the sources of heterogeneity is an essential part of these studies. We used meta-regression to explore the causes of heterogeneity for covariates of publication year, study design, geographic locations disease type and number of cases. According to our results, no covariate had an essential effect on this high heterogeneity, either in the β-carotene group or in the vitamin A group. Subgroup analyses were also performed as shown in table 2 and there was heterogeneity in some subgroups. Therefore, other factors such as genetics, environment or the interaction of genetic and environmental factors may also contribute to between-study heterogeneity.

As far as we know, this is the first meta-analysis of β-carotene and vitamin A intake with esophageal cancer risk. Our study included more cases and participants than one single study and therefore, obtained a more exact conclusion. Despite this, there were still some limitations. Firstly, a dose-response analysis of β-carotene and vitamin A intake on esophageal cancer risk was not performed as there was not enough detail of the amount of β-carotene and vitamin A intake in the single study. Secondly, all the included studies had a case-control design. This may cause some selection bias and recall bias. Hence, further studies with a cohort design are warranted to confirm these results. Thirdly, we only found an inverse association between β-carotene intake and esophageal cancer risk in American and European populations, but not in other populations. Meanwhile, the association between vitamin A intake and esophageal cancer risk was only significant in American populations. This may be caused by the few studies and cases included in other populations. Fourth, subgroup analysis by sex was not performed as few studies had sufficient detailed data, which limited the conclusion in this regard.

CONCLUSIONS

In conclusion, our study suggested that dietary β-carotene and vitamin A intake may reduce the risk of esophageal cancer. More relevant studies are needed to further explore this association, as some limitations existed in our analysis.

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Table 1. Characteristics of all included studies

Study, year	*Country*	*Age*	*Participants, cases*	*Study design*	*Disease type*	*Vitamins*	*Quality score*	*Assessment of intake*	*Category*	*OR (95 %CI)*	*Adjusted for or matc*
Chen et al. 2002	United States	62.3 ± 12.4	573, 124	PBCC	EAC	β-carotene Vitamin A	7	HHHQ	Q4 *vs* Q1	β-carotene: 0.6 (0.3-1.2) Vitamin A 0.5 (0.3-1.0)	Age, age squared, se respondent type, BM use, tobacco use, ed family history of can vitamin supplement
De Stefani et al. 1999	Uruguay	NA	459, 66	HBCC	Esophageal cancer	β-carotene Vitamin A	6	FFQ	Highest *vs* lowest	β-carotene: 1.1 (0.8-1.5) Vitamin A: 0.9 (0.7-1.4)	Age, sex, residence, urban/rural status, e BMI, tobacco smokin alcohol intake and to intake
De Stefani et al. 2006	Uruguay	40-89	1,170, 234	HBCC	ESCC	β-carotene Vitamin A	7	FFQ	Q4 *vs* Q1	β-carotene: 0.78 (0.49-1.24) Vitamin A:	Age, sex, residence, urban/rural status, b education, body mas smoking status, year

										0.66 (0.42-1.05)	quitting smoking, nu cigarettes smoked p alcohol drinking, me consumption and to intake
Decarli et al. 1987	Italy	32-74	453, 105	HBCC	Esophageal cancer	β-carotene Vitamin A	6	FFQ	> 150 *vs* ≤ 100	β-carotene: 0.23 (0.12-0.46) Vitamin A: 2.27 (1.13-4.52)	Age, sex, education, class, body mass ind alcohol and tobacco consumption
Franceschi et al. 2000	Italy	39-77	1,047, 304	HBCC	ESCC	β-carotene Vitamin A	7	FFQ	Q5 *vs* Q1	β-carotene: 0.4 (0.2-0.7) Vitamin A: 1.9 (1.1-3.1)	Age, gender, area of education, physical a BMI, tobacco smokin drinking and non-alc energy
Graham et al. 1990	United States	NA	342, 178	PBCC	Esophageal	β-carotene Vitamin A	7	FFQ	Q4 *vs* Q1	β-carotene: 0.66 (0.36-	Age, sex, education, and alcohol ingestio

					cancer					1.23) Vitamin A: 0.60 (0.32- 1.12)	
Ibiebele et al. 2013	Australia	18-79	857, 288	HBCC	EAC	β-carotene	8	FFQ	Q4 *vs* Q1	β-carotene: 0.81 (0.53- 1.22)	Gender, age, educat esophageal reflux sy lifetime alcoholic dri pack-years of smoki use, supplement use (ever/never) and tot (log-transformed)
Jessri et al. 2011	Iran	40-75	143, 47	HBCC	ESCC	β-carotene Vitamin A	8	SFFQ	T3 *vs* T1	β-carotene: 1.07 (0.81- 2.13) Vitamin A: 0.72 (0.38- 2.12)	Age, sex, reflux, BMI physical activity, and education
Mayne et al.	United	30-80	969,	PBCC	EAC	β-carotene	7	FFQ	Q4 *vs* Q1	β-carotene:	Age, site, sex, race, p

2001	States		282			Vitamin A				0.43 (0.32-0.59) Vitamin A: 0.47 (0.34-0.66)	status, BMI, income, education, smoking alcohol consumption
Mayne et al. 2001	United States	30-80	893, 206	PBCC	ESCC	β-carotene Vitamin A	7	FFQ	Q4 *vs* Q1	β-carotene: 0.43 (0.29-0.63) Vitamin A: 0.53 (0.36-0.79)	Age, site, sex, race, p status, BMI, income, education, smoking alcohol consumption
Tang et al. 2014	China	61 ± 11.4	739, 359	HBCC	Esophageal cancer	β-carotene	8	SFFQ	> 9,800 *vs* < 4,530 μg	β-carotene: 0.96 (0.65-1.40)	Age, gender, educat body mass index, tot intake, smoking stat drinking and family h cancer in first-degre
Terry et al. 2000	Sweden	< 80	1,000, 185	PBCC	EAC	β-carotene	8	FFQ	Q4 *vs* Q1	β-carotene: 0.5 (0.3-0.8)	Age (5-year age grou body mass index (qu

											and cigarette smokir past and current)
Terry et al. 2000	Sweden	< 80	980, 165	PBCC	ESCC	β-carotene	8	FFQ	Q4 *vs* Q1	β-carotene: 0.6 (0.4-1.0)	Age (5-year age grou body mass index (qu and cigarette smokir past and current)
Tuyns et al. 1987	France	NA	2,718, 743	PBCC	Esophag eal cancer	β-carotene Vitamin A	7	FFQ	Highest *vs* lowest	β-carotene: 0.47 (0.29-0.72) Vitamin A: 1.03 (0.67-1.60)	Age, alcohol consum tobacco smoking
Tzonou et al. 1996	Greece	NA	256, 56	HBCC	EAC	Vitamin A	7	FFQ	Highest *vs* lowest	Vitamin A: 0.62 (0.46-0.83)	Age, sex, birth place schooling, height, ar coffee drinking, alco tobacco smoking an intake
Tzonou et al.	Greece	NA	243,	HBCC	ESCC	Vitamin A	7	FFQ	Highest	Vitamin A:	Age, sex, birth place

1996			43						*vs* lowest	0.94 (0.69-1.28)	schooling, height, ar coffee drinking, alco tobacco smoking an intake
Zhang et al. 1997	United States	NA	214, 90	HBCC	EAC	β-carotene Vitamin A	6	HHHQ	Q4 *vs* Q1	β-carotene: 0.8 (0.6-1.2) Vitamin A: 0.8 (0.5-1.2)	Age, sex, race, educa smoking, alcohol int and total dietary int calories

OR: odds ratio; CI: confidence intervals; PBCC: population-based case-control study; HBCC: hospital-based case-control study; NA: not available; HHHQ: health habits and history questionnaire; FFQ: food frequency questionnaire; SFFQ: semi-quantitative food frequency questionnaire; BMI: body mass index; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; Q5: quartile 5; Q4: quartile 4; Q1: quartile 1; T3: tertile 3; T1: tertile 1.

Table 2. Summary results of β-carotene and vitamin A intake on the risk of esophageal cancer

	β-Carotene				*Vitamin A*			
Sub-groups	Studies, n	OR (95 % CI)	I^2 (%)	p-$_{heterogeneity}$	Studies, n	OR (95 % CI)	I^2 (%)	p-$_{heterogeneity}$
All studies	15	0.62 (0.50-0.77)	70.8	< 0.001	13	0.79 (0.63-0.99)	71.5	< 0.001
Disease type								
EAC	5	0.61 (0.45-0.82)	58.8	0.045	4	0.58 (0.47-0.73)	25.8	0.257

ESCC	5	0.62 (0.43-0.88)	64.1	0.025	5	0.85 (0.56-1.30)	75.8	0.002
Study design								
PBCC	7	0.49 (0.41-0.58)	0.0	0.790	5	0.60 (0.44-0.81)	53.9	0.070
HBCC	8	0.74 (0.56-0.99)	70.9	0.001	8	0.94 (0.71-1.25)	69.8	0.002
Geographic location								
America	7	0.65 (0.48-0.89)	75.1	< 0.001	7	0.63 (0.51-0.77)	37.4	0.143
Europe	5	0.45 (0.34-0.59)	29.6	0.224	5	1.14 (0.74-1.74)	81.1	< 0.001
Asia	2	1.00 (0.74-1.35)	0.0	0.730	1	-	-	-
Oceania	1	-	-	-	-	-	-	-

EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; OR: odds ratio; CI: confidence intervals; PBCC: population-based case-control studies; HBCC: hospital-based case-control studies.

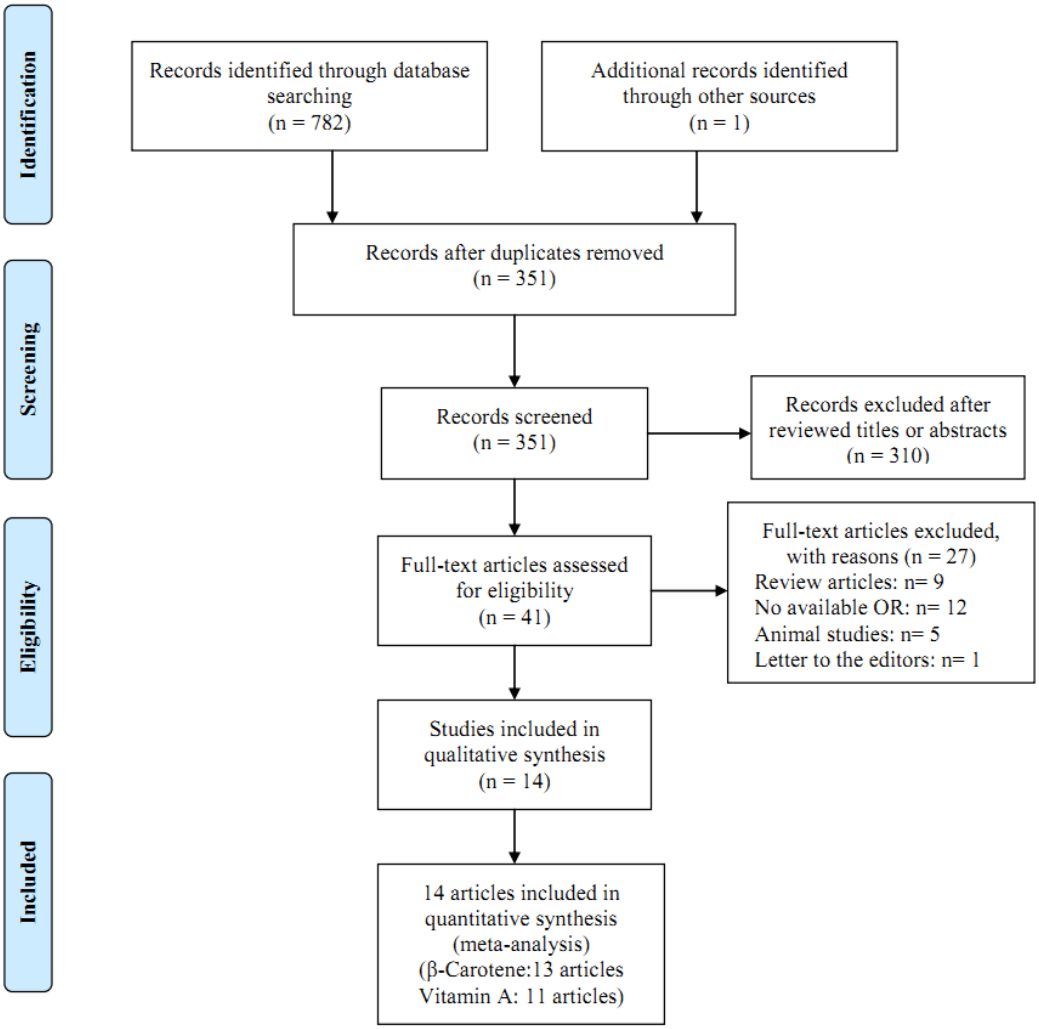


Fig. 1. Flow chart of the meta-analysis.

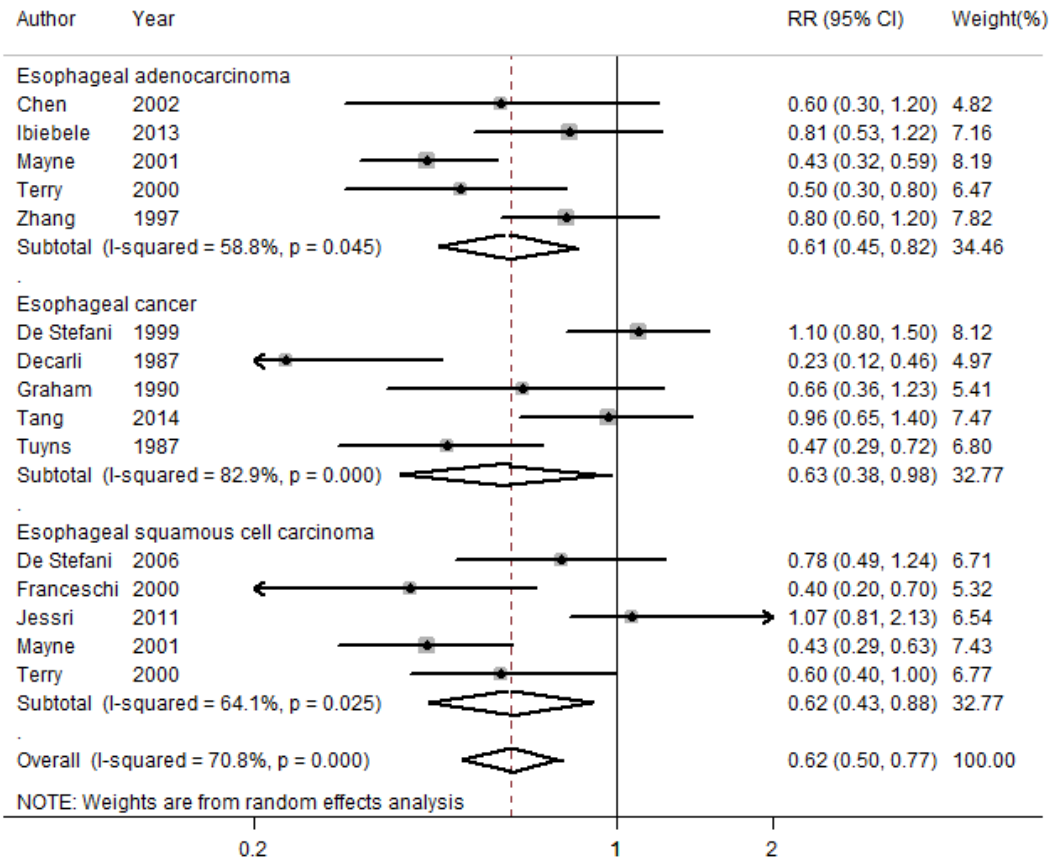


Fig. 2. Forest plot of the association between β-carotene intake and esophageal cancer risk.

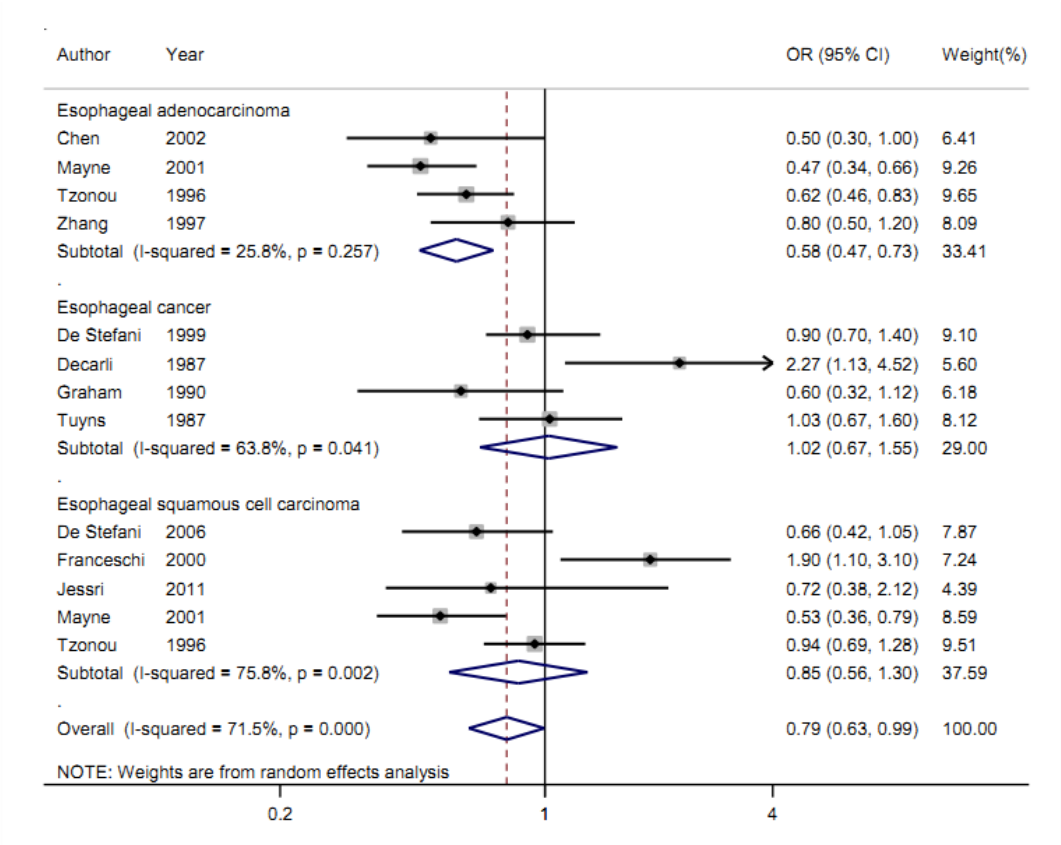
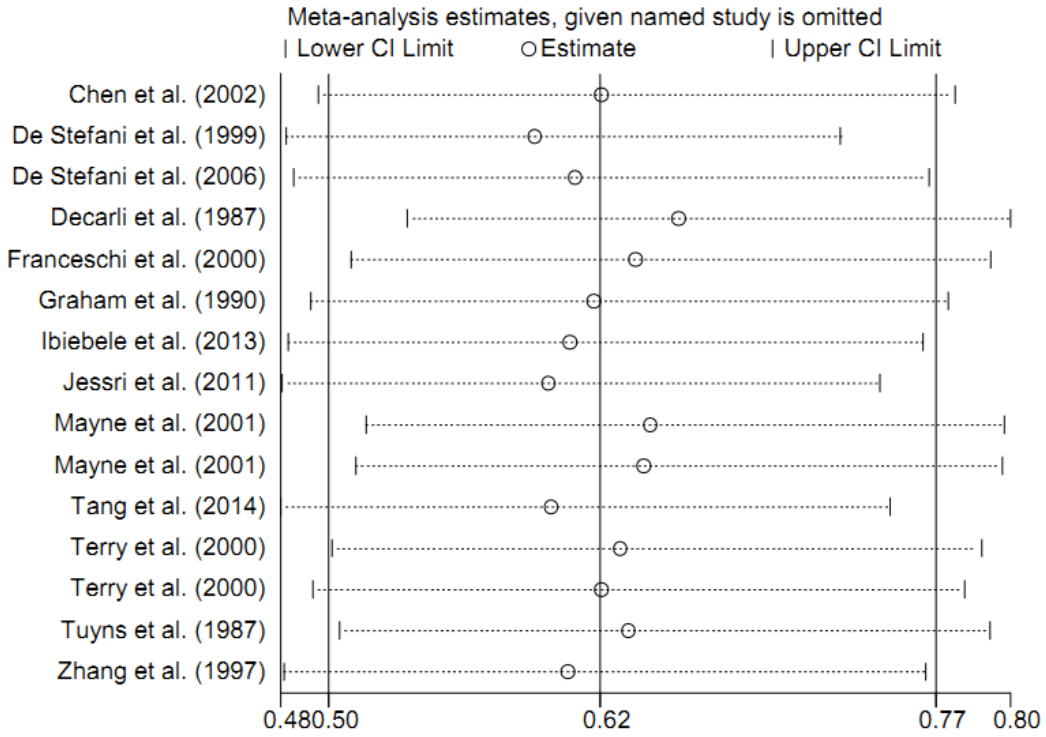
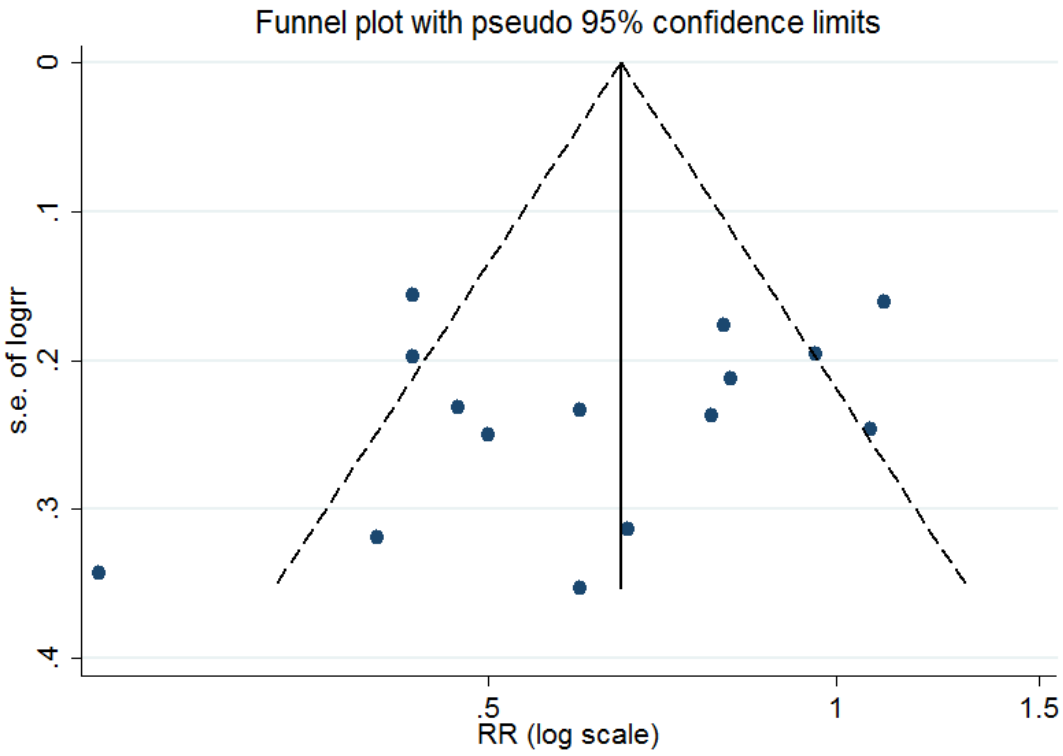


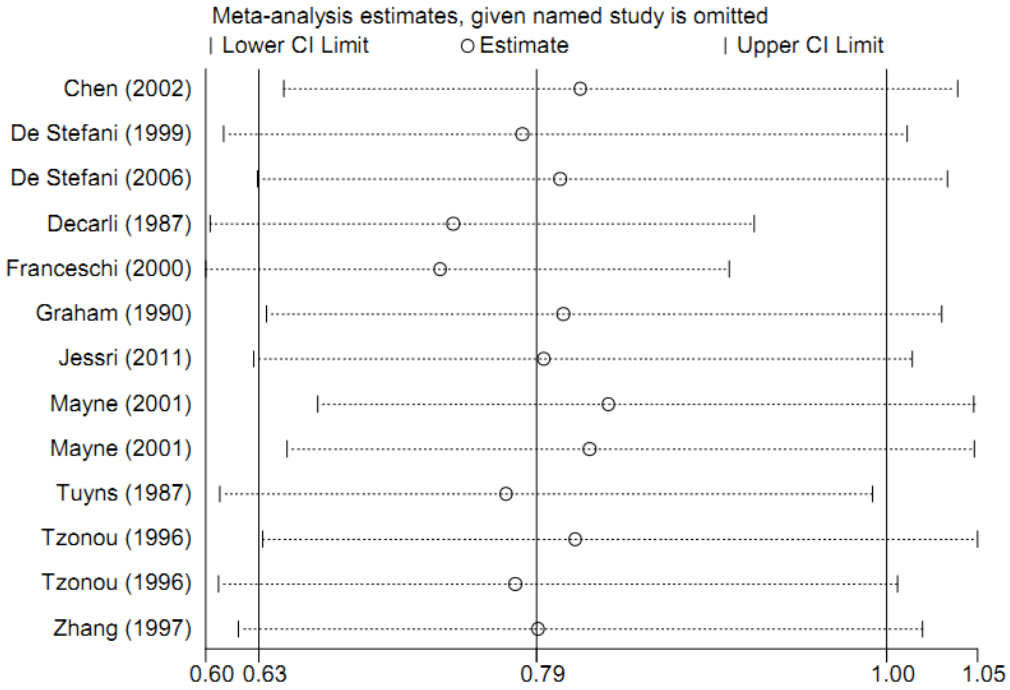
Fig. 3. Forest plot of the association between vitamin A intake and esophageal cancer risk.



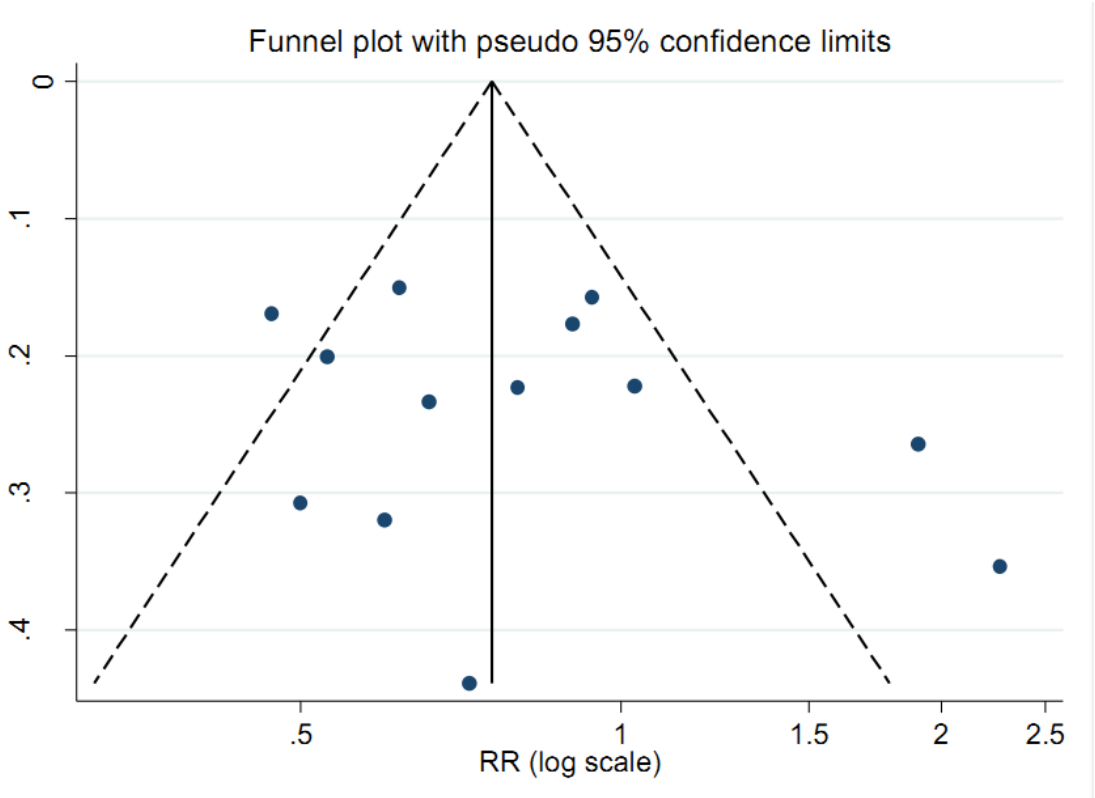
Supplementary Fig. 1. Funnel plot of the association between β-carotene intake and esophageal cancer risk.



Supplementary Fig. 2. Sensitivity analysis of the association between β-carotene intake and esophageal cancer risk.



Supplementary Fig. 3. Funnel plot of the association between vitamin A intake and esophageal cancer risk.



Supplementary Fig. 4. Sensitivity analysis of the association between vitamin A intake and esophageal cancer risk.