

Intakes of citrus fruit and risk of esophageal cancer

A meta-analysis

Wenyue Zhao, MD^a, Lu Liu, MD^b, Shun Xu, PhD^{a,*}

Abstract

Esophageal cancer (EC) is the eighth most common cancer and the sixth most frequent cause of cancer death in the whole world. Many studies have investigated the association between citrus fruit intake and the risk of EC, but the results are inconsistent and not analyzed by category. We aimed to perform a meta-analysis of studies to evaluate the incidence between citrus fruit consumption and subtypes of esophageal cancer and derive a more precise estimation.

Through searches of PubMed, OVID, and Web of Science we updated 1988 systematic review up to April 2016. Based on an inclusion and exclusion criteria, conventional meta-analysis according to DerSimonian and Laird method was used for the pooling of the results. Random-effect models were used to calculate subgroups.

Twenty-five English articles (20 case-control studies and 5 cohort studies) comprising totally 5730 patients of esophageal cancer would be suitable for use in this study. The result indicated the inverse associations between intakes of citrus fruit and EC (relative risk [RR]=0.65, 95% confidence interval [CI] 0.56–0.75, $I^2=51.1%$, $P=.001$), Esophageal squamous cell carcinoma (ESCC) (RR=0.59, 95% CI 0.47–0.76, $I^2=60.7%$, $P=.002$), no significant relationship between citrus fruit and esophageal adenocarcinoma (EAC) (RR=0.86, 95% CI 0.74–1.01, $I^2=0.0%$, $P=.598$).

This meta-analysis indicates that intakes of citrus fruit significantly reduce the risk of ESCC and is no obvious relationship with EAC. Further studies about constituents in citrus fruit and its mechanism are warranted.

Abbreviations: BMI = body mass index, CI = confidence interval, EAC = esophageal adenocarcinoma, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, FFQ = Food Frequency Questionnaire, NOS = Newcastle-Ottawa Quality Assessment Scale, OR = odds ratio, RR = relative risk, SDM = standardized mean difference.

Keywords: citrus fruit, epidemiology, esophageal cancer, meta-analysis

1. Introduction

Esophageal cancer (EC) is the eighth most common cancer and the sixth most frequent cause of cancer death in the whole world.^[1] These cases account for >400,000 deaths worldwide and most having occurred in the southern and eastern Africa and eastern Asia.^[2] In some parts of China, the number of deaths

from esophageal cancer is 10 to 100 times that of the United States. The 5-year survival outcomes of patients with esophageal cancer only provided between 15% and 25%.^[3] It is still unclear today with the high mortality and morbidity. Many previous studies have suggested risk factors for esophageal cancer, including cigarette smoking, alcohol drinking, and body mass index,^[4] whereas the consumption of vegetables and fruits play an essential role in reducing the incidence rate of esophageal cancer.^[5]

Citrus fruits, mainly including oranges, mandarins, limes, lemons, grapefruits, and citrons, belong to the genus *Citrus* of the family Rutaceae. Citrus fruits contribute to cancer prevention, because they are being loaded with vitamin C and other antioxidant, antimutagenic, and antiproliferative constituents.^[6,7] Available experiments showed that vitamin C destroys cancer cells, suppresses tumor growth, and is cytotoxic to cancer,^[8–10] which might reduced the risk of gastric cancer, breast cancer, lung tumorigenesis, colonic tumorigenesis, hepatocarcinogenesis, bladder cancer, and pancreatic cancer.^[11–15] Since 1980s, many epidemiologic studies indicated a potential association between citrus fruit consumption and risk of esophageal cancer, but there are still conflicting results.

Esophageal cancer is divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) by histological classification. There is a clear difference in 2 subtypes, including incidence, mortality, risk factors, clinical features, genetic susceptibility, and pathogenesis.^[16] In the past decades, compared with the rising rates of EAC, the ESCC

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^a Department of Thoracic Surgery of the First Affiliated Hospital, ^b Department of Breast Surgery of the First Affiliated Hospital, China Medical University, Shenyang, China.

* Correspondence: Shun Xu, Department of Thoracic Surgery of the First Affiliated Hospital, China Medical University, Shenyang 110001, China (e-mail: Xushun610539@sina.com).

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incidence trends have been decreasing or stabilizing among men.^[17] With respect to esophageal cancer, recent experiment found different effects on risk of EAC and ESCC, but in a recently published meta-analysis took them into account without detailed statistical analysis and comprehensive original articles.^[18,19] We therefore conducted a meta-analysis of cohort and case-control studies to evaluate the incidence between citrus fruit and subtypes of esophageal cancer.

2. Materials and methods

2.1. Search strategy

A systematic literature search of the related English articles was carried out using MEDLINE database (PubMed) and journals @Ovid Full Text database and BIOSIS previews databases (OVID) by 2 independent researchers (WZ and LL). The following Medical Subject Headings (MeSH) search terms were used: (Citrus [MeSH] OR orange [MeSH] OR food OR diet OR fruit) AND (esophagus OR esophageal) AND (adenocarcinoma OR cancer OR neoplasm OR carcinoma OR tumor). We limited our search to reports on human subjects in the English language. We searched databases for articles published between 1983 (Because Brown et al published their result on the first results of EC in 1988) and April 2016. The reference lists of all retrieved articles in English were also searched to find relevant publications.

2.2. Study selection

2.2.1. Inclusion criteria. Two authors (WZ and LL) independently scanned all the relevant studies retrieved according to the prespecified criteria as the following: were original articles; used a case-control or cohort study design; presented the odds ratios (ORs)/relative risk (RR) with 95% confidence intervals (CIs).

2.2.2. Exclusion criteria. Studies were excluded with the content as the following: studies reported the same population, we chose the most complete one; combined cancer that included upper aerodigestive tract cancer; mechanistic studies, non-peer-reviewed articles, abstracts, and editorials; used other diet simultaneously that influence the result.

2.3. Data extraction

Two of the authors (WZ and LL) independently extracted the data from the primary sources. Any discrepancies between the 2 were resolved by consensus. Abstracted information included study design, institution database, date published, etc.

The following predefined variables were recorded electronically: first author, publication year, study design, the number of cases and controls or cohort size, type of citrus fruit and consumption categories, dietary assessments, the OR, or RR with the corresponding 95% CI for the highest versus lowest level of intake, the risk estimates were extracted with the greatest number of adjustments for potential confounders.

2.4. Statistical analysis

The statistical analysis was based on the Cochrane System Manual. Continuous outcome measures were used standardized mean difference and corresponding 95% CIs and results of categorical data were used odds ratio (OR) and corresponding 95% CIs. The statistical inference of the combined effect was

tested by Z test and results are considered to be significant for $P < .05$. We estimated between-study heterogeneity in each meta-analysis by the Q test and I^2 statistics. A fixed effect model was performed using Mantel-Haenszel fixed effects model^[20] if $I^2 < 50\%$ and $P > .10$, which means no heterogeneity; otherwise a random effects model as described by DerSimonian and Laird^[21,22] was used. We performed separate meta-analyses for EAC and ESCC.

Sensitivity analysis was performed to evaluate the effect of individual study and the stability of our results by omitting each study or some studies and summarizing the remaining. Funnel plot and Egger test^[23] were performed to assess publication bias. Significant publication bias was indicated when P values were $< .05$. Most of the statistical analysis was conducted using spreadsheet software (Microsoft Excel 2007, Microsoft, Redmond, WA) and statistical software (STATA, version 14.0, StataCorp, College Station, TX). A $P < .05$ was considered statistically significant.

3. Results

3.1. Studies selected and general demographics

The search strategy generated 4814 citations, of which 84 were considered of potential value. Among these 84 articles, 67 articles were further selected out by following various reasons: 48 articles did not evaluate the association of interest, 9 articles were combined cancer, 6 were published without RR/OR or 95% CI, and 4 articles studied on the same population. Eight additional articles were included from the reference review.

Thus, 25 articles, including 20 case-control studies and 5 cohort studies, were incorporated in this meta-analysis^[18,24-47] (Fig. 1). The Newcastle-Ottawa scale was used to evaluate randomized studies in this meta-analysis from selection, comparability, and outcomes, including 22 articles of high quality (final score > 6). Two authors (Z.W. and L.L.) scored for each articles independently and negotiated to get final score.

Studies were published between 1983 and 2015, which consist of 2456 ESCC (range 47–395), 1284 EAC (range 67–282), and 1990 EC (range 53–1246). Of these 25 studies, 10 were from Europe, 6 from Asia, 6 from the United States, and 3 were from the South America (Table 1). The Newcastle-Ottawa Quality Assessment Scale (NOS) scores of 25 clinical trials range from 5 to 9, with an average of approximately 7. The median score was 6.75 for case-control studies and 8 for cohort studies (Table 1).

3.2. Quantitative data synthesis

3.2.1. ESCC group. Totally, 10 case-control studies and 3 cohort studies were included in the pooled analysis between citrus fruit consumption and ESCC risk (Table 2). The pooled RR was 0.59 (95% CI, 0.47–0.76) with significant heterogeneity ($I^2 = 60.7\%$, $P = .002$). The analyses revealed a significant association for citrus fruit intake with a reduced risk of ESCC. There was no evidence of publication bias; the P values were .059 for Begg test and .064 for Egger test.

3.2.2. EAC group. Five case-control studies and 3 cohort studies were included in the pooled analysis between citrus fruit consumption and EAC risk. The pooled RR was 0.86 (95% CI, 0.74–1.01) with no heterogeneity ($I^2 = 0.0\%$, $P = .598$) (Table 3). The Egger test ($P = .071$) and the Begg test ($P = .063$) showed that there was no evidence of publication bias.

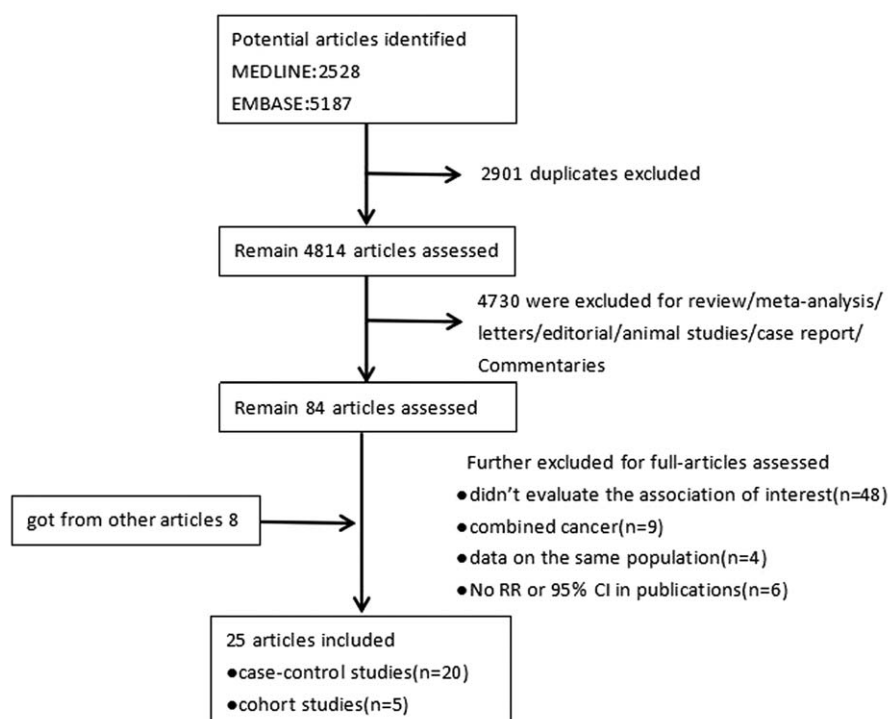


Figure 1. Flow diagram. CI = confidence interval, RR = relative risk.

3.2.3. EC group. Twenty-one case-control studies and 7 cohort studies were included in the pooled analysis between citrus fruit consumption and EC risk. The pooled RR was 0.65 (95% CI, 0.56–0.75) with low heterogeneity ($I^2=51.1\%$, $P=.001$) (Table 4). The significant inverse associations between citrus fruit intake and the risk of EC were observed. The Egger test ($P=.018$) showed that there was no evidence of publication bias.

3.3. Subgroup analysis

We performed the subgroup analysis by study design, population, number of cases, alcohol, Food Frequency Questionnaire (FFQ), study quality, smoking and cigarette, body mass index (BMI), red meat, physical activity, and fruit and vegetable to find the source of the heterogeneity. As shown in Figure 2, the pooled ORs of EAC and ESCC for prospective cohort studies, population-based case-control studies and hospital-based case-control studies were 0.78 (95% CI: 0.56, 1.10), 0.89 (95% CI: 0.71–1.11), 0.90 (95% CI: 0.61–1.23), 0.66 (95% CI: 0.49, 0.88), 0.82 (95% CI: 0.62, 1.09), and 0.50 (95% CI: 0.33, 0.75), respectively. Moreover, significant inverse associations between citrus fruit intake and the risk of ESCC were observed in cohort study (OR=0.66, 95% CI: 0.49–0.88) and hospital-based study (OR=0.82, 95% CI: 0.33,0.75), but not in population-based study (OR=0.82, 95% CI: 0.62,1.09), in >7 scores study (OR=0.56, 95% CI: 0.43,0.72), but not in <7 scores study (OR=0.70, 95% CI: 0.36, 1.37), in FFQ study (OR=0.57, 95% CI: 0.44, 0.75), but not in without FFQ study (OR=0.76, 95% CI: 0.51, 1.13), in nondrinkers (OR=0.59, 95% CI: 0.45, 0.76), not in drinkers (OR=0.55, 95% CI: 0.28, 1.08). In addition, a significant inverse association between citrus fruit intake and the risk of EAC were observed in adjusted red meat study (OR=0.63,

95% CI: 0.41, 0.96), but not in nonadjusted red meat study (OR=0.91, 95% CI: 0.77, 1.07).

3.4. Sensitivity analysis and publication bias

However, no variable were found in univariate and multivariate meta-regression analysis. In addition, we performed the sensitivity analysis by omitting 1 study at a time and further indicated that our results were stable. Egger test showed no evidence of significant publication bias for the meta-analysis on the association between citrus fruit intake and risk of ESCC, EAC, and EC, as provided in Figures 3 to 5. The Begg funnel plots did not reveal apparent asymmetry. Therefore, there were no obvious bias in these studies.

4. Discussion

This meta-analysis, including overall 25 studies, suggested that intakes of citrus fruit reduced the risk of total ESCC, as well as ESCC and EAC combined, especially in quality scores (NOS score >6) ≥ 7 studies. The inverse association with citrus fruit was esophageal cancer, possibly because of most of clinical trials were from Asia.^[27,39,47] Consumption of citrus fruit was not associated with EAC, although the estimate was based on few studies.

Many studies have investigated the mechanism that high intake of citrus fruit may reduce the risk of esophageal cancer.^[27–29] Citrus fruits have such a protective effect for cancer, because they are rich in vitamin C and secondary metabolites, such as flavonoids, alkaloids, coumarins, limonoids, carotenoids, phenol acids, and essential oils.^[6,7] These components show the effect of antioxidant, antimutagenic, and antiproliferative by inhibiting oxidation, protecting DNA from damage and stimulating

Table 1
Characteristics of studies of citrus fruit intake and the risk of esophageal cancer.

First author, year	Duration	Design	Location	Case	Cohort size/controls	Dietary assessment	Subtype of cancer	Exposure	Comparisons	Adjusted RR	Adjusted variables	NOS
Foschi, 2010	1991–2007	HCC	Italy and Switzerland	395	1066	78-item FFO validated	ESCC	Citrus fruits or citrus fruit juice	≥4 Portion/week vs <1 portion/week	0.42 (0.25,0.7)	Sex (where appropriate), age and study center, tobacco smoking, alcohol, education, body mass index, physical activity, and energy intake	7
Launoy, 1998	1991–1994	HCC	France	208	399	FFQ validated	ESCC	Citrus fruits	>60 vs 0–20 g/d	0.54 (0.33,0.89)	Age, interviewer, smoking, beer, aniseed aperitifs, hot Calvados, whisky, total alcohol, and total energy intake	6
Stevens, 2011	16.3 yr	Cohort	Netherlands	101	120,852	150-item FFO, validated	ESCC	Citrus fruits	156 vs 0g/d	0.54 (0.27,1.07)	Age, sex, cigarette smoking, alcohol consumption, consumption of red meat, and all other fruits.	9
Stevens, 2011	16.3 yr	Cohort	Netherlands	144	120,852	150-item FFO, validated	EAC	Citrus fruits	156 vs 0g/d	0.55 (0.31,0.98)	Age, sex, cigarette smoking, alcohol consumption, consumption of red meat, consumption of fish, total vegetable intake, and all other fruits.	9
Silvera, 2008	1993–1995	PCC	USA	206	687	104-item FFO, validated	ESCC	Citrus fruits		0.84 (0.59,1.19)	Sex, site, age, race, proxy status, income, education, usual body mass index, cigarettes, consumption of beer, wine and liquor each, and energy	8
Silvera, 2008	1993–1995	PCC	USA	282	687	104-item FFO, validated	EAC	Citrus fruits		0.94 (0.73,1.22)	Sex, site, age, race, proxy status, income, education, usual body mass index, cigarettes, consumption of beer, wine and liquor each, and energy	8
Fan, 2008	30 yr	Cohort	China	101	18,244	FFQ, NA	EC	Oranges/tangerines	3 vs 1	0.56 (0.30,1.05)	Level of education, body mass index, number of years of smoking, number of drinks consumed per day, and number of years of drinking	8
Brown, 1988	January 1, 1982 through October 31, 1984	HCC	USA	207	422	65-item FFO A	EC	Citrus fruit and juices	3 vs 1	0.5 (0.3,0.9)	Cigarettes and alcohol	5
Rolon, 1995	January 1988 and March 1991	HCC	Paraguay	131	381	50-item FFO, validated	EC	Citrus fruits	Highest vs lowest	0.8 (0.4,1.7)	Lifetime consumption of alcohol, cigarette smoking, and the design variables age group, sex, and hospital group.	6
Hajizadeh, 2011	Past 6 months	HCC	Iran	47	96	168-item FFO, validated	ESCC	Orange	3 vs 1	0.13 (0.04,0.36)	Symptomatic gastroesophageal reflux and body mass index	7
Gonzalez, 2005	6.5 yr	Cohort	10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom	67	521,457	50-item FFO, validated	EAC	Citrus fruits	4 vs 1	0.73 (0.39,1.37)	Sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, red meat intake and processed meat intake	8
Yamaji, 2008	297,651 Person-years; from 1998, until December 31, 2004	PCC	Japan	116	38,790	138-item FFO, validated	ESCC	Citrus fruits	127 vs 10g/d	0.78 (0.48,1.25)	Age and PHC area, cigarette smoking, and alcohol drinking	9
Sapkota, 2008	August 1999 and January 2003	HCC	Romania, Hungary, Poland, Russia, Slovakia, and Czech Republic	187	1110	23-item FFO, validated	ESCC	Citrus fruits	≥Once per week vs <once per month	0.76(0.46,1.28)	Age, country, sex, tobacco pack-years, education (categorical), BMI, frequency of alcohol consumption, tertiles of total vegetable, total white meat, and total red meat consumption	6
Song, 2015	April 2011 to October 2011	HCC	China	72	72	FFQ, NA	ESCC	Citrus fruits	≥1/wk vs <1/mo	0.08 (0.01,0.68)	Age, sex, education level, body mass index, intake of preserved vegetables smoking, and alcohol drinking	6

(continued)

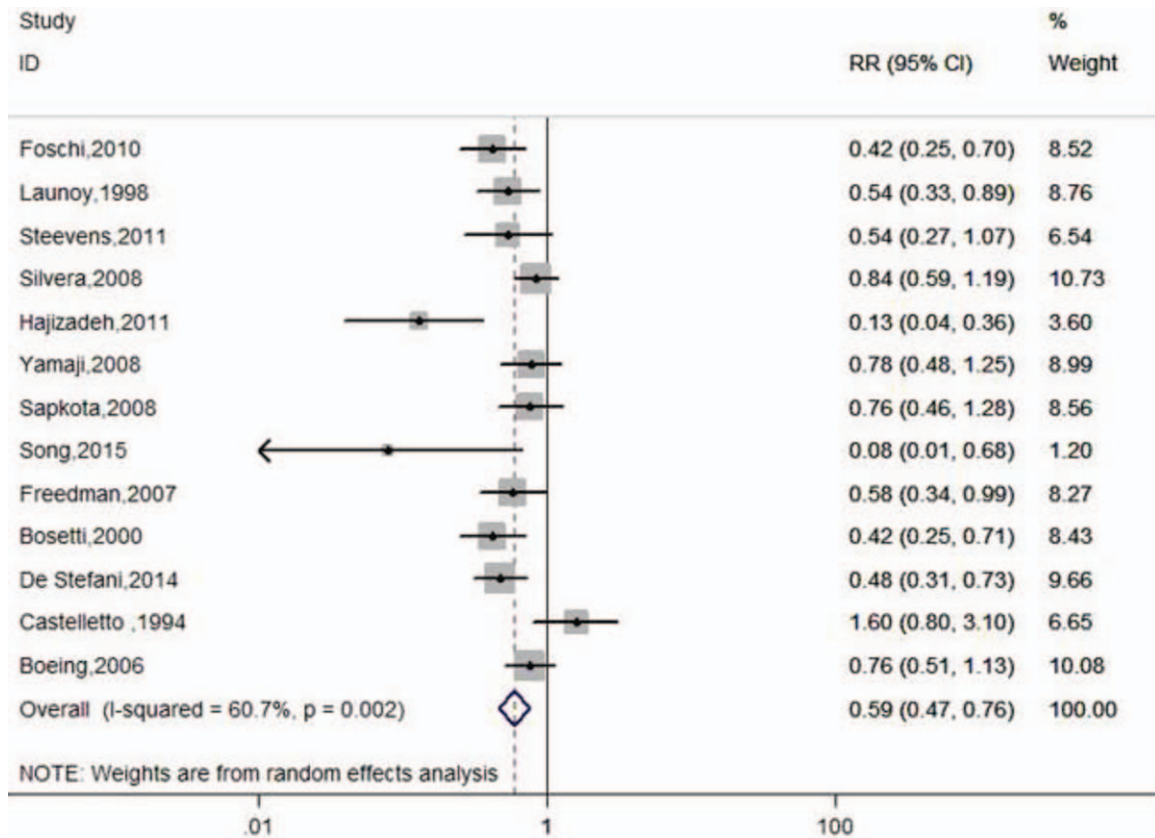
Table 1
(continued).

First author, year	Duration	Design	Location	Case	Cohort size/controls	Dietary assessment	Subtype of cancer	Exposure	Comparisons	Adjusted RR	Adjusted variables	NOS
Freedman, 2007	4.5 yr	Cohort	USA	103	490,802	124-Item FFQ, validated	ESCC	Citrus fruits	3 vs 1	0.58 (0.34,0.99)	Sex, age at entry into cohort, BMI, education, alcohol intake, cigarette-smoke-dose, vigorous physical activity, usual activity throughout the day, and total energy	7
Freedman, 2007	4.5 yr	Cohort	USA	213	490,802	124-Item FFQ, validated	EAC	Citrus fruits	3 vs 1	0.96 (0.69,1.3)	Sex, age at entry into cohort, BMI, education, alcohol intake, cigarette-smoke-dose, vigorous physical activity, usual activity throughout the day, and total energy	7
Bosetti, 2000	1992–1997	HCC	Italy	304	743	78-Item FFQ, validated	ESCC	Citrus fruits	5 vs 1	0.42 (0.25,0.71)	Age, sex, area of residence, education, tobacco smoking, alcohol drinking, and nonalcohol energy	7
De Stefani, 2014	1997–2000	HCC	Uruguay	234	936	64-Item FFQ, NA	ESCC	Citrus fruits	3 vs 1	0.48 (0.31,0.73)	Age, sex, residence education, monthly income, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, mate consumption, and total energy intake	7
Chen, 2002	1992–1994	PCC	USA	124	449	DHQ, validated	EAC	Citrus fruit and juices	4 vs 1	0.48 (0.21,1.1)	Age, sex, energy intake, respondent type BMI, alcohol use, tobacco use, education, family history, and vitamin supplement use for both types of cancer, and for age squared for esophageal adenocarcinoma	5
Cheng, 1995	March 1989 to December 1990	HCC	China	53	406	FFQ, NA	EC	Citrus fruits	Daily vs up to 3 times a week	0.59 (0.23,1.52)	Sex, age, educational attainment, and each other	7
Terry, 2000	Between 1 December 1994 and 31 December 1997–2014	PCC	Sweden	185	815	63-Item FFQ, validated	EAC	Citrus fruits	2.0–21.0 vs 0–0.6 serving/wk	0.9 (0.5,1.6)	Age, sex, body mass index, total energy, energy adjusted alcohol, total fruit and vegetable intake, cigarette smoking, and use of antioxidants	7
Levi, 2000	Between 1992 and 1999	HCC	Switzerland	101	327	79-Item FFQ, NA	EC	Citrus fruits	Q3 VS Q1	0.22 (0.09,0.54)	Age, sex, education, alcohol, and nonalcoholic total energy intake	7
Tuytens, 1983	from 1975 to 1980	PCC	France	1246	1976	DHQ, validated	EC	—	Yes VS no	0.62 (0.5,0.77)	Age, alcohol consumption, tobacco smoking, and urban or rural residence	5
Castelleto, 1994	May 1986 to June 1989	HCC	Argentina	131	262	50-Item FFQ, validated	ESCC	Citrus fruits	Q3 VS Q1	1.6 (0.8,3.1)	Design variables, age, sex, hospital, education, average number of cigarettes/day, alcohol consumption barbecued meat, potatoes, raw vegetables, cooked vegetables	6
Brown, 1995	During 1986 through 1989	PCC	United States	174	750	60-Item FFQ, NA	EAC	Citrus fruits	Q4 VS Q1	0.7 (0.06,7.65)	Age, area, smoking, liquor use, income, calories from food, and BMI	7
Zhang, 1997	1 November 1992 to 1 November 1994	HCC	United States	95	132	DHQ, NA	EAC	Citrus fruits	Q4 VS Q1	0.9 (0.61,1.32)	Age, sex, race, education, total dietary intake of calories, pack-years of smoking, alcohol use, and BMI	8
Boeing, 2006	5.8 yr	Cohort	European	352	2,182,560	DHQ, NA	ESCC	Citrus fruits	Q5 VS Q1	0.76 (0.51,1.13)	Age, sex, center, BMI, energy from fat sources, energy from nonfat sources, education, smoking status categories	8
Li, 2010	from 1995 to 2003	PCC	Japan	151	329,985	40-Item FFQ, validated	EC	Citrus	Q3 VS Q1	0.71 (0.43,1.16)	Age (continuous variable), sex (for total participants), job status, year of education, BMI, physical activity, energy intake, cigarette, alcohol	9

BMI = body mass index, CI = confidence interval, DHQ = dietary history questionnaire, EAC = esophageal adenocarcinoma, FFQ = Food Frequency Questionnaire, HB = hospital-based, HHHO = Health Habits and History Questionnaire, NA = not available, NOS = Newcastle-Ottawa quality assessment scale, NSAD = nonsteroidal anti-inflammatory drugs, PB = population-based, SRR = summary relative risk.

Table 2

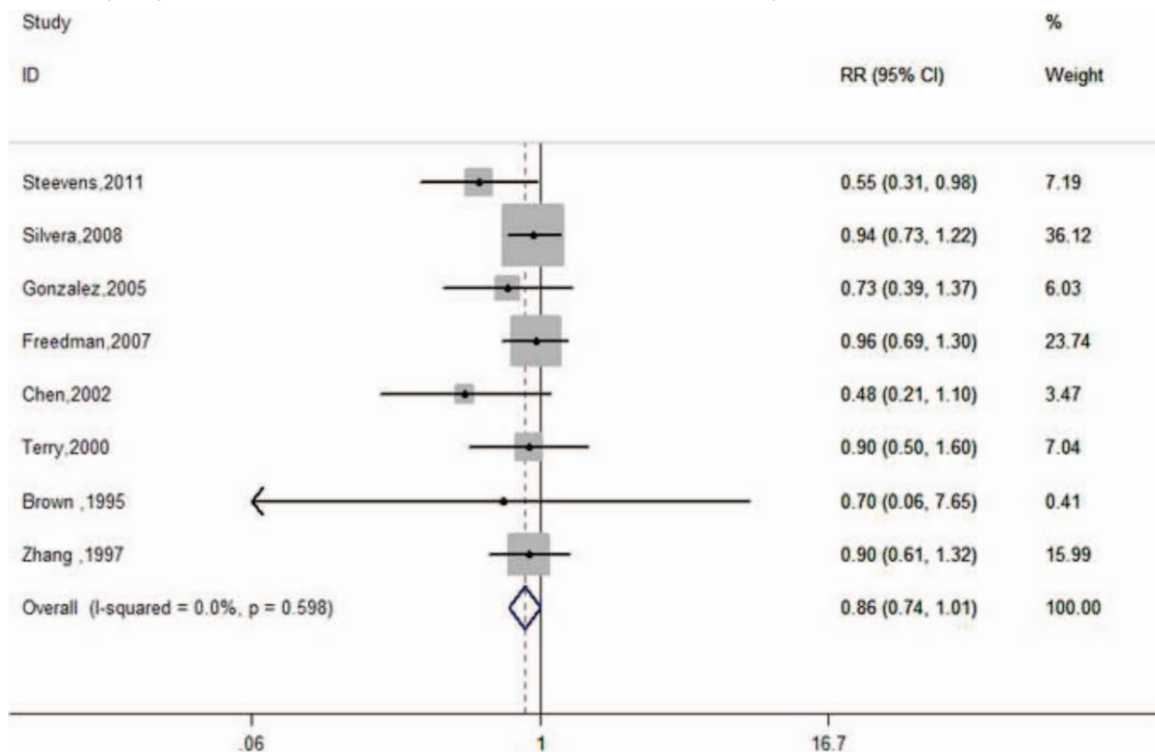
Forest plots investigating the association of citrus fruit intake and the risk of esophageal squamous cell carcinoma (ESCC).



CI = confidence interval, RR = relative risk.

Table 3

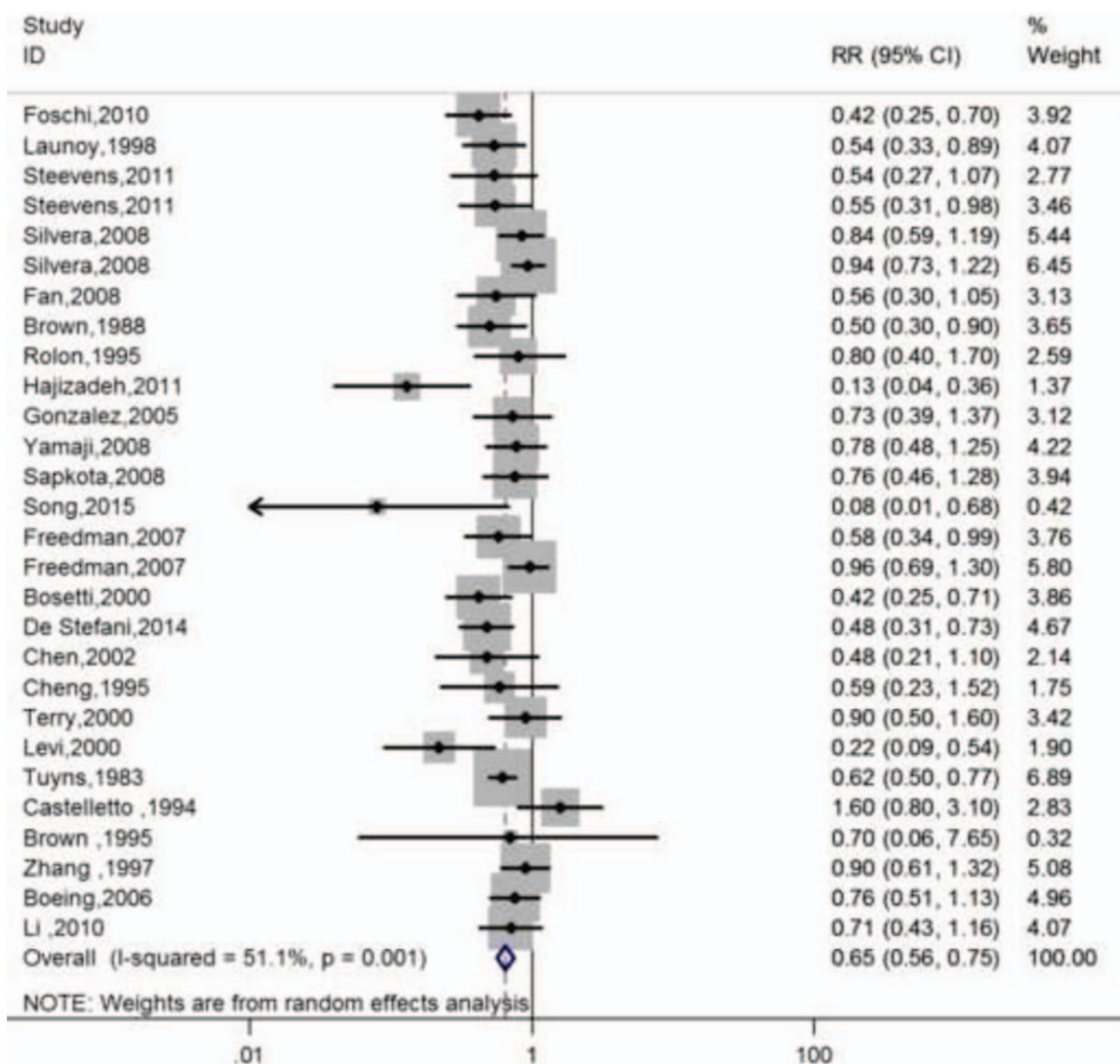
Forest plots investigating the association of citrus fruit intake and the risk of esophageal adenocarcinoma (EAC).



CI = confidence interval, RR = relative risk.

Table 4

Forest plots investigating the association of citrus fruit intake and the risk of Esophageal cancer (EC).



CI = confidence interval, RR = relative risk.

apoptosis to cancer line.^[6,7] Recent study found that the antitumor effects of citrus fruit were derived from inhibitory effect on epithelial-to-mesenchymal transition and interfering with the canonical transforming growth factor- β 1-drosophila mothers against decapentaplegic protein-Snail/Slug axis.^[48] But some studies indicate that too much antioxidant supplementation increased overall mortality from cancers, which may explain the result of the nonsignificant inverse associations between EAC and citrus fruit. Based on the completely distinctive in etiological and pathological characteristics,^[18] we can come to conclusion that different subtypes of esophageal cancer have been effected distinctively by citrus fruit.

In view of the increasing incidence of EC and the difficulty of operation, prevention of esophageal cancer is particularly important. The existing methods to prevent esophageal cancer mainly include higher intake of vitamin C, antioxidant, anthocyanidin, and dietary fiber.^[9,10] The factors that increased

the risk of esophageal cancer included alcohol intake, red meat, and diabetes mellitus.^[49-51] Citrus fruit are rich in vitamin C, vitamin E, antioxidant, and flavonoids that make people more clearly aware of how to intake above substances in daily life.

As for confounding, only 2 studies included in the meta-analysis did not control for smoking and alcohol drinking,^[30,39] the major risk factors for esophageal cancer. However, the risk estimates for the relation of citrus fruit intake with the risk of cancer from such studies did not materially differ from studies that were properly adjusted. Because dietary intake is basically constant, desirable eating habits seem particularly important. Studies have linked Mediterranean diet with a reduced risk of cancer,^[52] which may guide people a reasonable diet. From a public health perspective, increasing consumption of citrus fruit was very effective for esophageal cancer prevention. In addition, present researches indicated that citrus fruit benefits on endothelial function, protection against the risk of renal stone

study	EAC				ESCC			
	n	Heterogeneity			n	Heterogeneity		
		RR(95%CI)	P	I ²		RR(95%CI)	P	I ²
Design								
Cohort	3	0.78(0.56,1.10)	0.154	31.8%	3	0.66(0.49,0.88)	0.005	0.0%
PCC	4	0.89(0.71,1.11)	0.294	0.00%	2	0.82(0.62,1.09)	0.165	0.0%
HCC	1	0.9(0.61,1.23)	0.593	-	8	0.5(0.33,0.75)	0.001	69.9%
Popilation								
USA	5	0.91(0.76,1.08)	0.281	0.0%	2	0.74(0.52,1.04)		0.0%
European	3	0.71(0.5,1.0)	0.050	0.0%	5	0.76(0.51,1.13)		-
Asian					3	0.24(0.05,1.13)		83.1%
South America					2	0.85(0.26,2.76)		88.5%
Number of cases								
≥200	8	0.86(0.74,1.01)	0.065	0.0%	11	0.64(0.53,0.79)	0.00	46.6%
<200					2	0.12(0.04,0.13)	0.00	0.0%
Study quality								
≥7 Scores	8	0.86(0.74,1.01)	0.065	0.0%	9	0.56(0.43,0.72)	0.00	56.2%
<7 scores					4	0.70(0.36,1.37)	0.296	72.3%
FFQ								
Yes	6	0.88(0.74,1.05)	0.145	0.0%	12	0.57(0.44,0.75)	0.00	62.6%
No	2	0.8(0.57,1.14)	0.223	45%	1	0.76(0.51,1.13)	0.176	-
Adjusted Confounders								
Alcohol								
Yes	6	0.83(0.68,1.00)	0.053	0.0%	10	0.59(0.45,0.76)	0.000	51.1%
No	2	0.94(0.73,1.21)	0.617	0.0%	3	0.55(0.28,1.08)	0.081	80.3%

Figure 2. Subgroup analyses of citrus intake and risk of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), sensitivity analysis, and meta-regression analysis. BMI = body mass index.

formation, and reduction in risk of cardiovascular disease and stroke.^[53–55]

Several limitations exist in this meta-analysis described as follows. First, the original studies use the different diet assessment methods, which cannot compare the result with each other in some degree and unavoidably cause measurement errors. The measurement errors occurred when some original studies used a nonvalidated FFQ to evaluate the consumption of citrus fruit and esophageal cancer, which may lead to decrease the relativity of

dietary habit with cancer risk. In fact, the relationship between citrus fruit and esophageal cancer is stronger than the result. Second, publication bias was observed across studies, because some original studies with negative result were more difficult to publish and all studies included are in English. Some studies, furthermore, did not provide the raw data, which is partly responsible for bias. In this meta-analysis, little publication bias was found by Egger weighted regression method about EAC and consumption of citrus fruit because there are not enough EAC

Smoking & Cigarette								
Yes	5	0.88(0.74,1.05)	0.15	0.0%	7	0.72(0.57,0.93)	0.011	45.5%
No	3	0.8(0.57,1.13)	0.212	0.0%	6	0.42(0.28,0.64)	0.000	58.4%
BMI								
Yes	5	0.87(0.7,1.08)	0.193	28.5%	5	0.66(0.54,0.81)	0.000	0.0%
No	3	0.86(0.69,1.08)	0.191	0.0%	8	0.52(0.34,0.79)	0.003	73.5%
Red Meat								
Yes	2	0.63(0.41,0.96)	0.03	0.0%	5	0.66(0.53,0.82)	0.000	0.0%
No	6	0.91(0.77,1.07)	0.256	0.0%	8	0.52(0.35,0.79)	0.002	73.5%
Physical activity								
Yes	2	0.91(0.68,1.20)	0.504	0.0%	5	0.6(0.47,0.76)	0.00	26.1%
No	6	0.85(0.7,1.02)	0.077	0.0%	8	0.57(0.37,0.86)	0.08	71.7%
Fruit & vegetable								
Yes	3	0.71(0.5,1.00)	0.050	0.0%	7	0.7(0.47,0.76)	0.035	56.4%
no	5	0.91(0.76,1.08)	0.281	0.0%	6	0.49(0.34,0.71)	0.000	65.1%

Figure 2. (Continued)

cases included. In addition, a significant heterogeneity was observed in ESCC, which influence reliability of summary RR estimates. But we had no way to unite the duration of follow-up, types and quality of original articles, study populations, confounders, and so on. Moreover, most original studies only provided frequency of consumption, but not provided quantitative assessment of citrus fruit intake, with no information on the portion size. Therefore, we could not analyze the dose-risk

relation between citrus fruit and esophageal cancers, given the lack of information in the categorization in some studies, and the heterogeneity in the categorization across some others. Finally, the inadequate adjustment for confounders in observational studies was another limitation, which included less intakes of smoking, alcohol drinking, higher intake of vegetable, less BMI, and better physical activity. The confounders may make us overestimate the relationship between citrus fruit and esophageal

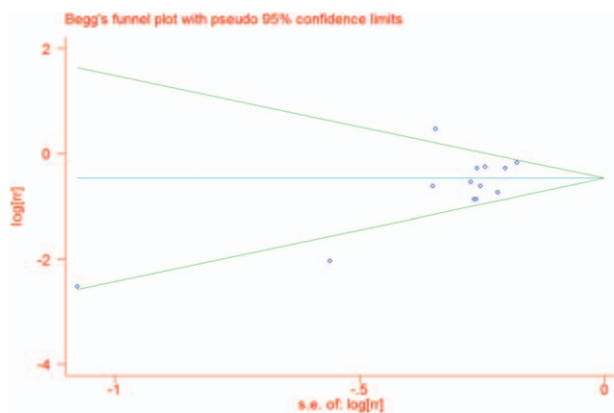


Figure 3. Begg funnel plot of studies evaluating the association between citrus fruit intake and esophageal adenocarcinoma (EAC) risks with 95% confidence limits. OR=odds ratio, SE=standard error.

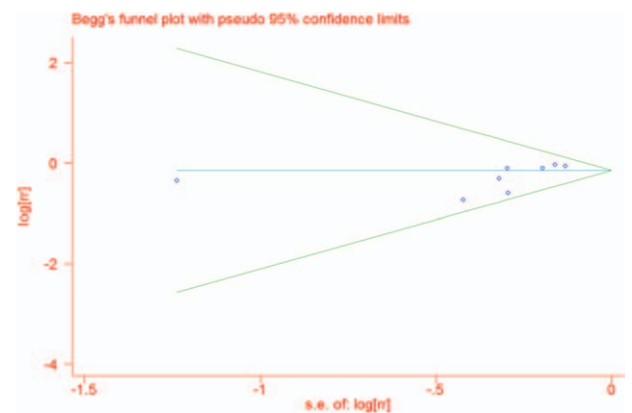


Figure 4. Begg funnel plot of studies evaluating the association between citrus fruit intake and esophageal squamous cell carcinoma (ESCC) risks with 95% confidence limits. OR=odds ratio, SE=standard error.

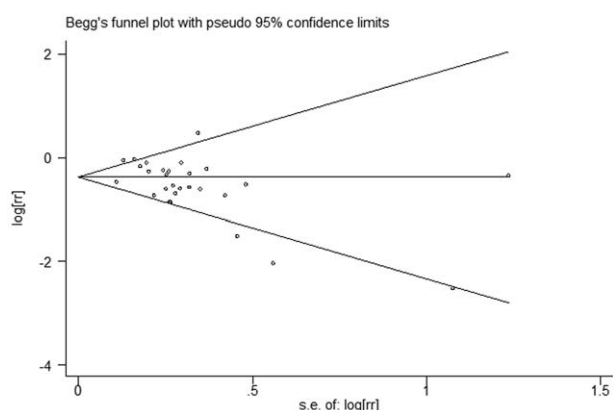


Figure 5. Begg funnel plot of studies evaluating the association between citrus fruit intake and esophageal cancer (EC) risks with 95% confidence limits. OR=odds ratio, SE=standard error.

cancer. However, most of articles in this meta-analysis restricted these confounders.

This meta-analysis shows that citrus fruit intake is associated inversely with the risk of EC and ESCC, no significant association with EAC. However, the association should be considered with some caution because of the measurement errors, confounders, and heterogeneity. Further studies are warranted to find which constituents in citrus fruit prevent esophageal cancer and its mechanism.

Author contributions

Conceptualization: W. Zhao.

Data curation: W. Zhao.

Formal analysis: L. Liu, S. Xu, W. Zhao.

Funding acquisition: L. Liu, S. Xu.

Methodology: W. Zhao.

Project administration: W. Zhao.

Resources: W. Zhao.

Software: W. Zhao.

Supervision: W. Zhao.

Validation: W. Zhao.

Visualization: W. Zhao.

Writing – original draft: W. Zhao.

Writing – review & editing: W. Zhao.

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