Citrus fruit intake and the risk of nasopharyngeal carcinoma

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ABSTRACT

Background and Objectives: Citrus fruit are suggested to be associated with reduced risk of nasopharyngeal carcinoma (NPC), but findings from epidemiologic studies have been inconsistent. We aimed to synthesize the association by conducting a meta-analysis of existing evidence. **Methods and Study Design:** Databases including Medline, EMBASE, Web of science, and the Cochrane Library were searched for eligible studies up to March 2019 using a series comprehensive searching terms. The adjusted odds ratios (ORs) of citrus fruit intake with NPC risk from each study were extracted to calculate a pooled association estimate with its 95% confidence interval (CI). **Results:** Nine studies totaling 3304 cases and 3850 controls were included in this analysis. Citrus fruit intake was significantly associated with reduced risk of NPC (OR: 0.72, 95% CI 0.58-0.91, p=0.005). In addition, this association tended to be stronger in Chinese (OR: 0.67, 95% CI 0.54-0.84, p<0.001). Dose-response analysis using cubic splines showed the risk of NPC decreased by 21% for citrus fruit intake of 4 times/week (OR: 0.79, 95% CI 0.66-0.94). **Conclusions:** The consumption of citrus fruit was associated with a significant reduced risk of NPC, especially in Chinese population.

Key Words: citrus fruit consumption, nasopharyngeal carcinoma, dose-response analysis, protective effects, meta-analysis

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a squamous-cell carcinoma that originates in the epithelial lining of the nasopharynx.[1] It is more prevalent in populations in Southeast Asia, the Arctic, and the Middle East/North Africa,[2,3] and more than 70% of new reported cases were from eastern/south-east Asia in 2012.[4] The overall age-standardized incidence rate and mortality of NPC in 2013 were 25/100,000 and 14/100,000 amongst people living in South China, higher than Caucasians from America and other western countries with the incidence rate and mortality of 1/100,000.[2,5] To date, the exact pathogenic mechanism of NPC has not been understood. However, the distinctive ethnic distribution of the carcinoma worldwide suggests that besides genetic susceptibility and Epstein-Barr virus (EBV) infection, environmental factors might be associated with the risk of NPC.[6,7]

A number of factors have been suggested to be associated with increased risk of NPC, including the consumption of Cantonese-style salted fish,[8,9] preserved vegetables,[10,11] cigarette smoking,[12] and alcohol drinking.[13] Whereas, fruit consumption has been associated with a reduced risk of NPC.[14] Citrus fruit contains a variety of antioxidants such as vitamin C, folate, and carotenoids, and other bioactive components, which are believed to have protective effects on cancer that attributed to antioxidant activities, prevention of nitrosamine formation, and other anticarcinogenic properties.[15]

Previous studies have demonstrated that citrus fruit consumption are associated with decreased risk of various cancers from gastrointestinal and urogenital systems.[16,17] Over the decades, there have been studies reported controversial association between citrus fruit consumption and the risk of NPC.[18-26] In addition, variations in geographic location, methodology, and adjustment factors across studies may have differential impacts on NPC risk, yet the directions of these impacts have not been investigated.

We conducted a meta-analysis of all published studies to evaluate the association between citrus fruit intake and NPC risk. We also quantified dose-response relations of citrus fruit intake with NPC risk.

MATERIALS AND METHODS

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[27] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group checklist.[28]

Search strategy

Databases of Medline, EMBASE, Web of science, and the Cochrane Library were searched for published studies till March 2019. The following search terms were applied to maximize sensitivity: 'diet' OR 'fruit' OR 'citrus' OR 'orange' OR 'tangerine' OR 'grapefruit' OR 'lemon' OR 'lime' and 'nasopharyngeal neoplasms' OR 'nasopharyngeal carcinoma' OR 'nasopharyngeal cancer' OR 'nasopharynx cancer' OR 'pharyngeal cancer' OR 'NPC'. We also manually searched the references listed in the retrieved articles and published systematic reviews to identify additional relevant studies. Potential unpublished studies were searched by contacting corresponding authors of relevant primary studies.

Study selection

An initial screen of titles and abstracts of the identified studies was conducted for eligibility. Full text of the relevant publications were retrieved based on the following study eligibility criteria: (1) the primary outcome was NPC; (2) the exposure was citrus fruit consumption (including oranges, tangerines, grapefruits, lemons and limes, administered alone or in combination); (3) odds ratios (ORs) and its 95% confidence intervals (CIs) for the association between citrus fruit intake and NPC risk (or sufficient data to calculate them) was reported; and (4) potential confounders were controlled by matching or multivariable analysis in the studies. If data were duplicated in more than one study, only the most updated data were chosen for analysis. Two investigators (X.-X.F. and X.T.) assessed the studies independently, and any discrepancies were resolved by group discussion among all co-authors until a consensus was reached.

Data extraction and quality assessment

Data were extracted independently by two investigators (X.-X.F. and X.T.) using a standardized form. The data included: study characteristics (first author, publication year, country, study design), participant characteristics (the number of cases/subjects, sex distribution, age range or mean age), dietary assessment methods, comparison of exposure level and their effects estimates, diagnosis method of NPC, and variables adjusted in the analysis. If a study provided several risk estimates, the maximum adjusted estimate was used. When ORs were not available, crude effect estimates and 95% CIs were calculated using the primary data. As one study did not report any association for the highest category of citrus fruit intake, we used the OR from the adjacent category.[23]

The quality of the studies was assessed using the Newcastle-Ottawa scale (NOS) based on the selection of study groups (four criteria), the comparability of study groups (one criterion), and the assessment of the exposure (three criteria).[29] Each study was assigned 0-9 points. A study was regarded high in quality if it was scored 6 or more, and those scored less than 6 were considered low quality.[30] Any discrepancies in data extraction and quality assessment were resolved through group discussion.

Statistical analysis

Pooled ORs with the corresponding 95% CIs were calculated to measure the strength of the association between citrus fruit intake and the risk of NPC. Heterogeneity across the studies was evaluated by the DerSimonian and Laird's Q statistic ($p<0.10$ indicated statistically significant heterogeneity) and I^2 statistic (values of 25%, 50% and 75% were defined to represent low, moderate and high heterogeneity, respectively).[31,32] Random-effects model was used to calculate the pooled ORs when substantial heterogeneity was detected; while the fixed-effects model was adopted otherwise.[33] Forest plot was generated to visualize the ORs and the 95% CIs across studies. The source of heterogeneity was explored with stratification and meta-regression analyses by geographic location (China vs not China), sources of controls (population-based vs hospital-based), diagnosis method (pathology reports vs the clinicians), smoking status (adjusted vs not adjusted), alcohol drinking (adjusted vs not adjusted), and quality score (high vs low).

In addition, we assessed the potential dose-response relation between citrus fruit intake and the risk of NPC using the method proposed by Greenland and Longnecker.[34] Within each study, the median or mean citrus fruit intake in each category was assigned to the corresponding OR estimate. The midpoint of the upper and lower bounds in each citrus fruit category was utilized if median or mean was not reported in the study. The open-ended categories were assumed to have the same amplitude as the adjacent categories. A restricted cubic spline model with 3 fixed knots at 10%, 50%, and 90% through the total distribution of the reported intake and the generalized least-squares regression were used to estimate the nonlinear association.[35]

Sensitivity analyses were performed by removing one study at a time to examine whether the overall result was affected significantly by any single study. Publication bias was evaluated by using visual inspection of a funnel plot, and additionally evaluated statistically with Egger and Begg's tests.[36,37]

All analyses were conducted by using Stata version 10.0 (Stata Corporation, College Station, TX, USA). All p values were 2-tailed with a statistically significance level of 0.05.

RESULTS

Search results

A total of 2558 citations were obtained from the initial search, of which 904 were from Medline, 640 from EMBASE, 989 from Web of Science, and 25 from the Cochrane Library. Fifty-five full texts were potentially eligible after removing duplicates and screening titles or abstracts. Of these, nine studies met the selection criteria and were included in the present meta-analysis (Figure 1; Supplemental Table 1).[18-26]

Study characteristics

The main characteristics of included studies are summarized in Table 1. Of the nine studies, five were conducted in China, two in Europe, one in the United States, and one in North Africa. The study samples ranged from 135 to 1967, giving a total of 7154 participants composed of 3304 NPC cases. All studies consisted of both sexes and the proportion of males varied between 50.0% and 79.3%. As to controls, five studies were population-based,[18-21,25] and the others were hospital-based.[22-24,26] Citrus fruit intake was assessed by food frequency questionnaires (FFQ) in all studies via self-administrated survey19 or face-to-face interviews.[18,20-26] NPC was ascertained based on pathological diagnosis in eight studies,18-[21,23-26] or on clinical diagnosis in one.[22] All of the studies were matched or adjusted for age, and other factors included sex,[18,20-26] smoking status,[19,21,24-26] education,[21,24-26] exposure to potential toxic substances,[21,22,24,25] energy intake,[19,24-26] residence,[20,23,26] alcohol drinking,[19,26] chronic ear and nose condition,[21,24] and NPC family history.[25] Overall, eight studies out of nine were of high quality, with a score of ≥6.

Citrus fruit intake and NPC

Among the nine studies, four reported a significantly decreased risk of NPC associated with citrus fruit intake,[18,20,21,24] and the comparison of exposure level and their effects estimates in each primary study were show in Supplemental Table 2. Significant heterogeneity was observed across the studies (I^2=51.6%; pheterogeneity = 0.04). Pooled OR was 0.72 (95% CI 0.58-0.91, p=0.005) for the highest relative to the lowest citrus fruit intake using the random-effects model (Figure 2). In the dose-response analysis using cubic splines, the risk of NPC decreased by 21% with increasing intake of citrus fruit up to 4 times/week (OR: 0.79, 95% CI 0.66-0.94, Figure 3). No benefit was apparent when increasing intake above this value.

When stratified by geographic location, studies conducted in China tended to report a stronger association of citrus fruit intake with NPC risk (OR: 0.67, 95% CI 0.54-0.84, p<0.001), whereas the association was nonsignificant in other populations (OR: 0.84, 95% CI 0.50-1.42, p=0.515). Subgroup analysis across other study and participant characteristics found these factors did not significantly alter the shape of the association (Table 2). Sensitivity analysis and publication bias

Sensitivity analyses showed that the pooled ORs for NPC ranged from 0.67 (95% CI 0.57-0.80) when the study conducted by Feng et al.[22] was excluded to 0.76 (95% CI 0.59-0.97) when the study conducted by Yuan et al.21 was excluded, which indicate that the results of the present meta-analysis remained stable (Supplemental Table 3). No publication bias was suggested, either by the funnel plot or by statistical tests (Begg's test, p=0.60; and Egger's test p=0.91; Supplemental Figure 1).

DISCUSSION

The findings from the present meta-analysis suggested that high intake of citrus fruit was associated with a significant decreased risk of NPC. In addition, a significant dose-responsive relation was observed, which indicating a reduction risk of 21% NPC for citrus fruit intake of

4 times/week. The results also showed that studies conducted in China tended to report a stronger association.

The association between citrus fruit intake and cancers have been examined. For example, Wang et al. noted that a decreased risk of esophageal cancer was associated with higher intake of citrus fruit (OR: 0.63, 95% CI 0.52-0.75) in a meta-analysis of 6 cohort studies and 13 case-control studies.[38] Similarly, a decreased risk of 50% was confirmed by Bravi et al for oral and pharyngeal cancer among those with highest quintile intakes of citrus fruit after adjustment of age, sex, center (Italy, Switzerland), education, year of interview, BMI, tobacco smoking, alcohol drinking and energy intake.[39] Citrus fruit has been shown to be protective as well for pancreatic cancer and breast cancer.[40,41] The present results showed that higher consumption of citrus fruit was associated with a reduced risk of NPC, adding in the evidence that citrus fruit intake would have a protective effect on cancer development.

Our finding of a decreased NPC risk with high citrus fruit intake is biologically plausible, and the potential mechanisms are consistent with numerous proposed mechanisms whereby citrus fruit decrease risk for cancers because of the similar pathogenesis. Citrus fruits are rich in multiple cancer chemopreventive agents, including antioxidants, limonoids and furocoumarins. As principal antioxidants, vitamin C may play a role in the prevention of different malignant diseases development including NPC by blocking the metabolic activation of carcinogens, stimulating the immune function, and preventing oxidative stress.[42,43] Besides decreasing oxidative damage to DNA, carotenoids and folate are implicated in the etiology of cancer via effects on inhibition of cell proliferation and differentiation, repair and methylation of DNA and scavenging free radicals.[44,45] Moreover, as prominent phytochemicals in citrus fruit, limonoids appear to possess substantial antineoplastic activity against chemically induced cancers,[46] as animal experiment has demonstrated that limonoids were positively correlated with the induction of Glutathione S-transferase (GST) activity to catalyzes the conjugation of glutathione with electrophilic xenobiotics that induce activated carcinogens.[47] Notably, furanocoumarins had been indicated to exhibit several antiproliferative activities against the growth of cancer cells through modulation of several molecular pathways, such as upregulation of the signal transducer and activator of transcription 3, phosphatidylinositol-3-kinase/protein kinase B, nuclear factor-κB, and mitogen-activated protein kinase expression.[48]

It should be noted that citrus fruit appeared to have protective trend on NPC in Chinese populations. Familial NPC, which is common in China, was linked to higher susceptibility to genetic locus mutation,[49] which warrants further investigation, as most of the studies ascertained in this meta-analysis did not provide information regarding the family history of nasopharyngeal cancer. Higher intakes of fruit has been show to attenuate the genetic predisposition to obesity,[50] which is associated with increased risk of NPC in a prospective cohort study from Israel and two case-control studies from Zhejiang and Guangdong, China.[51] On the other hand, preserved foods such as Cantonese salted fish, preserved vegetables and eggs, which are consumed frequently in south China, contain higher nitrosamines that were postulated as carcinogenic in the development of NPC over time.[52] Thus, the protective effect of citrus fruit on NPC risk via prevention of nitrosamine formation is more likely to be detected among Chinese. Finally, citrus extracts has been indicated to have inhibitory effects on EBV early antigen activation induced by the tumor promoter in an in vitro experiment.[53] The epidemiology of childhood EBV infection is different in Chinese and other populations, and most children in the developing countries are infected with EBV before the age of three.[54] Therefore, the effect of citrus fruit could be different depending on the timing of EBV infection.

The limitations of this meta-analysis should be noted. First, the present study was based on case-control studies and are susceptible to the inherent recall bias and selection bias, which may overstate the association.[55] However, the quantitative analyses in our study were based on a large number of participants and most studies were evaluated to be high quality using the NOS,[29] which suggested the results were quite robust. Second, the associations across studies are heterogeneous, indicating differences in study regions, source of controls, and adjusted confounders; however, stratified analyses by these factors did not affect the association of citrus fruit intake with NPC risk in the present meta-analysis. Third, our inability to standardize citrus fruit intake in all of the included studies might have biased the results, although the likelihood should be small because the reference group and the highest citrus fruit intake group were similar in most primary studies. Fourth, residual or unknown confounders could not be completely excluded. For example, higher fruit intakes is more likely to related to certain healthy behaviors that would bias the true associations.[56] Fifth, possible measurement errors in the dietary assessment using FFQ that represent a subjective approximation of past dietary behaviors rather than an assessment of absolute intakes in the included studies may affect the effect estimates, but the directions of these impacts are unpredictable. Sixth, although no publication bias was suggested visually or statistically, it cannot be fully ruled out.

Conclusion

In summary, this meta-analysis suggested that citrus fruit intake was significantly associated with a lower risk of NPC, particularly in Chinese populations. Further well-designed cohort studies and randomized controlled trials including other populations are warranted to confirm the impact of citrus fruit on NPC risks.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Characteristics of studies on citrus fruit intake and NPC risk

First author, year	Country	Study design	Case/controls (n)	Sex (%male)	Age (years)	Dietary assessment	Diagnosis method	Adjustments	Quality score†
Chen et al, 1997 [18]	China	Case-control (PCC)	104/104	50.0	≤55	FFQ-33 face-to-face interview	Pathology reports	Age, sex	5
Farrow et al, 1998 [19]	USA	Case-control (PCC)	133/212	67.5	18-74	FFQ-100 self-administrated survey	Pathology reports	Age, alcohol consumption, cigarette smoking, total caloric intake	6
Armstrong et al, 1998 [20]	China	Case-control (PCC)	282/282	69.1	45 (mean)	FFQ-55 face-to-face interview	Pathology reports	Age, sex, residence, marital status	7
Yuan et al, 2000 [21]	China	Case-control (PCC)	935/1032	69.5	15-74	FFQ-38 face-to-face interview	Pathology reports	Age, gender, level of education, cigarette smoking, exposure to smoke from heated rapeseed oil and burning coal during cooking, occupational exposure to chemical fumes , history of chronic ear and nose condition	7
Feng et al, 2007 [22]	North Africa	Case-control (HCC)	636/615	69.5	15-81	FFQ face-to-face interview	The clinicians	Sex, center, age, socio-economic status variables, exposure to toxic substances	8
Nešić1 et al, 2010 [23]	Serbia	Case-control (HCC)	45/90	64.4	NR	FFQ-100 face-to-face interview	Pathology reports	Age, sex, residence	6
Liu et al, 2012 [24]	China	Case-control (HCC)	600/600	74.7	47 (mean)	FFQ-78 face-to-face interview	Pathology reviews	Age, gender, BMI, educational level, marital status, occupation, household income, occupational, domestic exposure to potential toxic substances, chronic rhinitis history, smoking status, passive smoking, daily energy intake, energy-adjusted intakes of other food groups	7
Hsu et al, 2012 [25]	China	Case-control (PCC)	371/321	69.4	≤75	FFQ-66 face-to-face interview	Pathology reports	Age, gender, ethnicity, educational level, NPC family history, total calories intake, years of cigarette smoking, exposures to formaldehyde and wood dust	7
Polesel et al, 2013 [26]	Italy	Case-control (HCC)	198/594	79.3	18-76	FFQ-78 face-to-face interview	Pathology reports	Center, sex, age, place of living, year of interview, education, tobacco smoking, alcohol drinking, non-alcohol energy	7

BMI: body Mass Index; FFQ: food frequency questionnaires; HCC: hospital-based case-control study; NPC: nasopharyngeal carcinoma; NR: not reported; PCC: population-based case–control study.
†Study quality was assessed based on the validated Newcastle-Ottawa scale; studies with ≥6 were considered high-quality and low otherwise.[30]

Table 2. Stratified analysis of the association between citrus fruit intake and NPC†

Subgroup	n	Case/controls (n)	Pooled OR	95% CI	p	
					p_h†	p_h‡
Geographic location						
China	5	2292/2339	0.67	0.54, 0.84	0.13	0.32
Not China	4	1012/1511	0.84	0.50, 1.42	0.09	
Sources of controls						0.46
Population-based	5	1825/1951	0.67	0.53, 0.86	0.13	
Hospital-based	4	1479/1899	0.81	0.50, 1.32	0.04	
Diagnosis method						NP
Pathology reports	8	2668/3235	0.67	0.57, 0.80	0.30	
The clinicians	1	636/615	1.50	0.90, 2.60	NA	
Smoking status						0.94
Adjusted	5	2237/2759	0.72	0.56, 0.91	0.21	
Not adjusted	4	1067/1091	0.72	0.43, 1.21	0.01	
Alcohol drinking						>0.99
Adjusted	2	331/806	0.73	0.48, 1.10	0.83	
Not adjusted	7	2973/3044	0.72	0.55, 0.96	0.01	
Quality score§						NP
High	8	3200/3746	0.74	0.56, 0.97	0.02	
Low	1	104/104	0.66	0.50, 0.89	NA	

CI: confidence interval; NA: not applicable (because only one study); NP: meta-regression was not possible; NPC: nasopharyngeal carcinoma; OR: odds ratio.

†ph values were for heterogeneity within a subgroup.

‡ph values were for heterogeneity between subgroups by meta-regression.

§Study quality was assessed based on the validated Newcastle-Ottawa scale; studies with ≥6 were considered high-quality and low otherwise.[30]

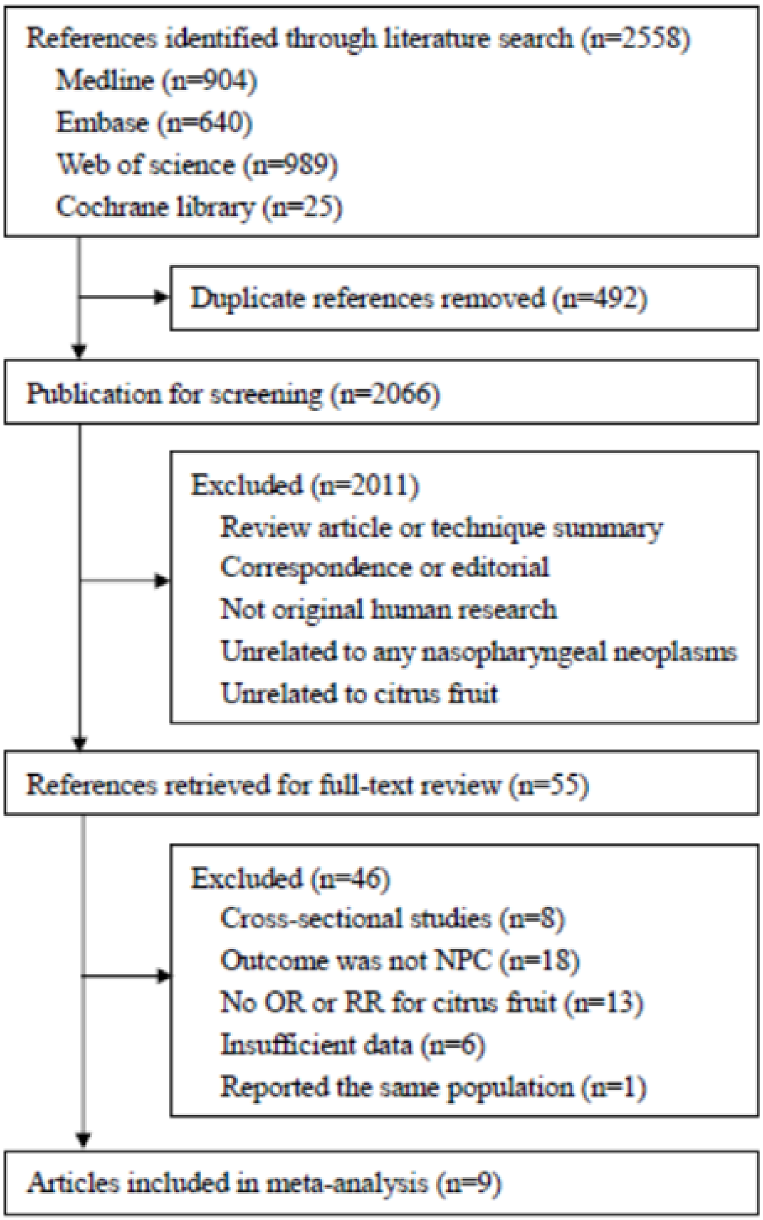


Figure 1. The flow diagram of study selection from MEDLINE (www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com/), Web of Science (http://thomsonreuters.com/web-of-science/), and the Cochrane Library (http://www.cochranelibrary.com/).

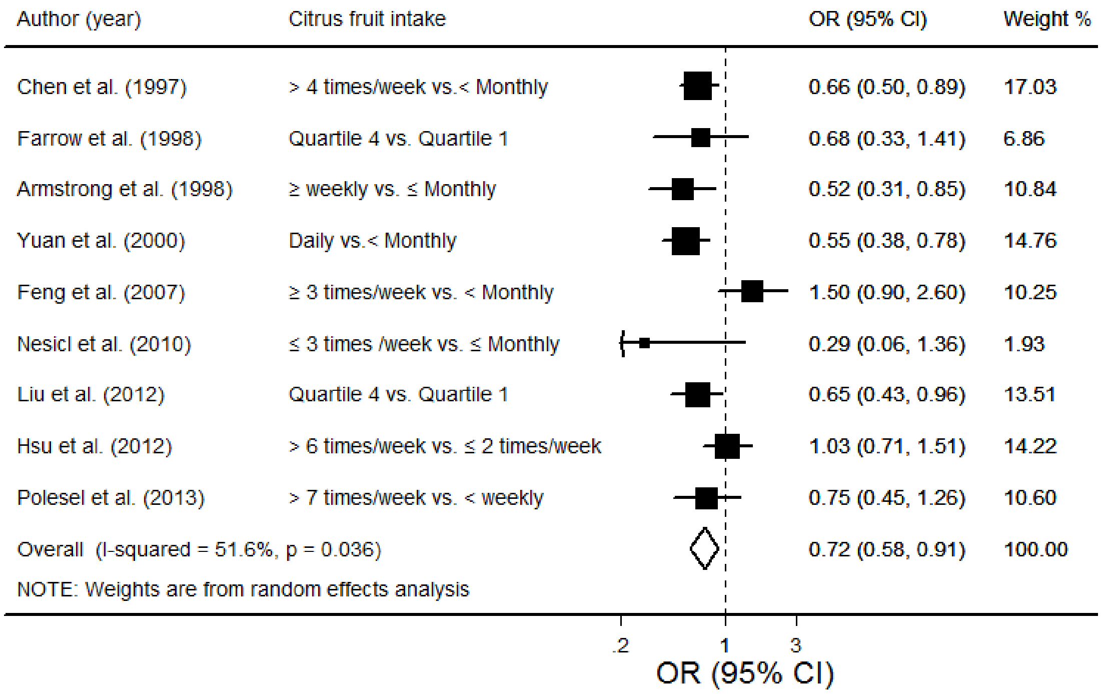


Figure 2. Forest plot on the association between citrus fruit intake (highest-versus-lowest category) and nasopharyngeal carcinoma (NPC). The boxes and lines indicate the odds ratios (ORs) and their confidence intervals (CIs) on a log scale for each study. The pooled odds ratio (OR) is represented by a diamond. The size of the black squares indicates the relative weight of each estimate. The arrow indicates that the lowest confidence interval of the OR is below the range of the axis.

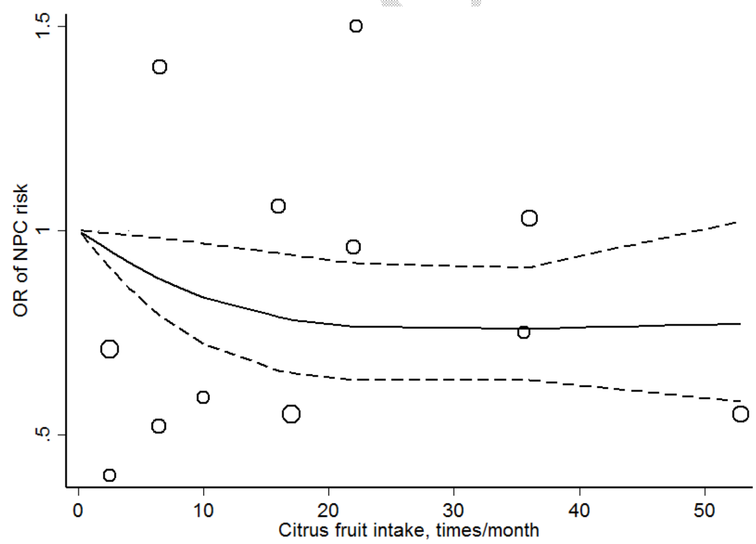
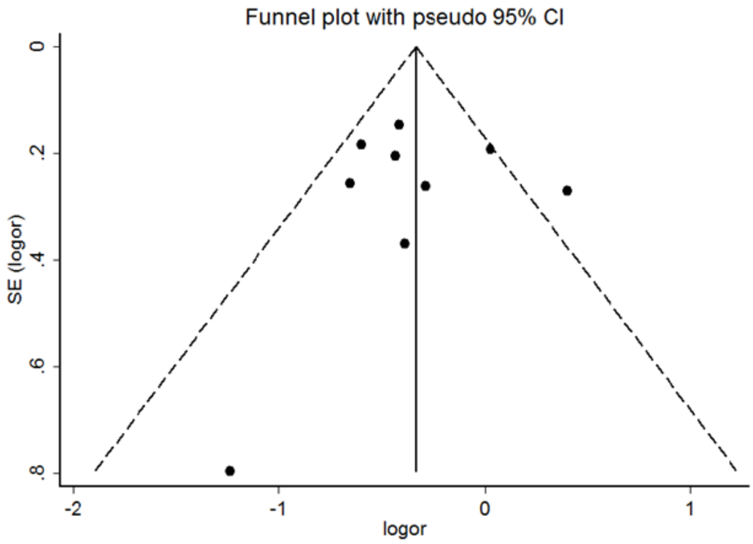


Figure 3. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the dose–response relationship between citrus fruit intake and nasopharyngeal carcinoma (NPC) risk. The circles represent ORs of varied doses in each primary study. The solid line represents best-fitting cubic spline model and the dotted lines represent 95% Cis.



Supplemental figure 1. Funnel plot of the relative risk (for highest-versus-lowest intake category) versus the standard error of the log relative risk for studies evaluating citrus fruit intake and nasopharyngeal carcinoma (NPC).

Supplementary table 1. Characteristics of studies no having OR or RR for citrus fruit in Figure 1

First author, year	Country	Study design	Case/Subjects (n)	Sex (%male)	Age (years)	Exposure assessment	Diagnosis method	Adjustments
Yu et al, 1986	China	Case-control (PCC)	250/500	64.0	<35	Interview	Medical records	Age, sex
Ning et al, 1990	China	Case-control (PCC)	100/400	68.0	≤64	Interview	Pathology reports	Age, sex, race
Lee et al, 1994	Singapore	Case-control (HCC)	200/606	71.7	NR	Interview	Medical records	Age, sex, education, dialect group
Cheng et al, 1999	China	Case-control (PCC)	375/702	68.8	<75	Interview	Pathology reports	Age, sex, race, educational level, family history of NPC
Shahar et al, 2004	Malaysia	Case-control (HCC)	100/200	50.0	≥18	Interview	Medical records	Age, sex, ethnic origin
Ekburanawat et al, 2010	Thailand	Case-control (PCC)	327/654	74.0	48.1 (mean)	Interview	Pathology reports	Sex, age, geographic residence, cigarettes smoking, education
Jia et al, 2010	China	Case-control (HCC)	1387/2846	72.5	<80	Interview	Pathology reports	Age, sex, education, dialect, household type
Turkoz et al, 2011	Turkey	Case-control (PCC&HCC)	183/366	65.6	18-76	Interview	Pathology reports	Sex, age
Fachiroh et al, 2012	Thailand	Case-control (PCC)	681/1759	66.1	48.0 (mean)	Interview	Pathology reports	Sex, age group, center, education, alcohol drinking, smoking status
Hashim et al, 2012	Malaysia	Case-control (HCC)	48/96	81.3	47.5 (mean)	Interview	Medical records	Sex, age, ethnicity
Shen et al, 2012	Italy	Cohort	1533	73.3	46.1 (mean)	Interview	Medical records	Age, BMI, spouse, education, clinical stage, smoking status, alcohol intake
Belbaraka et al, 2013	Morocco	Case-control	60/120	60.0	≥25	Interview	Medical records	Age, sex, socio economic level
Yong et al, 2017	Singapore	Case-control (PCC)	290/580	81.4	21-80	Interview	Pathology reports	Sex, ethnicity, age, educational level

BMI: Body Mass Index; HCC: hospital-based case-control study; NPC: nasopharyngeal carcinoma; NR: not reported; OR: odds ratio; PCC: population-based case-control study; RR: relative risk

Supplementary table 2. Citrus fruit intake in association with NPC risk in each original study

First author, year	Comparison of exposure level	OR (95% CI)
Chen et al, 1997 [18]	<Monthly	1.00
	<weekly	NR
	1-4 times/week	NR
	>4 times/week	0.66（0.50-0.89）
Farrow et al, 1998 [19]	Quartile 1	1.00
	Quartile 2	1.02 (0.53-1.98)
	Quartile 3	0.46 (0.22-0.96)
	Quartile 4	0.68 (0.33-1.41)
Armstrong et al, 1998 [20]	≤Monthly	1.00
	<weekly	0.40 (0.24-0.69)
	≥weekly	0.52 (0.31-0.85)
Yuan et al, 2000 [21]	<Monthly	1.00
	Monthly	0.71 (0.53-0.96)
	Weekly	0.55 (0.41-0.73)
	Daily	0.55 (0.38-0.78)
Feng et al, 2007 [22]	<Monthly	1.00
	<3 times/week	1.40 (0.80-2.20)
	≥3 times/week	1.50 (0.90-2.60)
Nešić1 et al, 2010 [23]	≤Monthly	1.00
	≤3 times /week	0.29 (0.06-1.36)
Liu et al, 2012 [24]	Quartile 1	1.00
	Quartile 2	0.95 (0.67-1.35)
	Quartile 3	0.74 (0.50-1.08)
	Quartile 4	0.65 (0.43-0.96)
Hsu et al, 2012 [25]	≤2 times/week	1.00
	2-6 times/week	1.06 (0.69-1.61)
	>6 times/week	1.03 (0.71-1.51)
Polesel et al, 2013 [26]	<weekly	1.00
	1-4 times/week	0.59 (0.33-1.05)
	4-7 times/week	0.96 (0.60-1.52)
	>7 times/week	0.75 (0.45-1.26)

CI: confidence interval; NPC: nasopharyngeal carcinoma; NR: not reported; OR: odds ratio.

Supplementary Table 3. Sensitivity analysis of the association between citrus fruit intake and NPC

First author, year	Pooled OR	95% CI
Chen et al, 1997 [18]	0.74	0.56, 0.97
Farrow et al, 1998 [19]	0.73	0.57, 0.93
Armstrong et al, 1998 [20]	0.75	0.59, 0.96
Yuan et al, 2000 [21]	0.76	0.59, 0.97
Feng et al, 2007 [22]	0.67	0.57, 0.80
Nešić1 et al, 2010 [23]	0.74	0.59, 0.92
Liu et al, 2012 [24]	0.74	0.57, 0.96
Hsu et al, 2012 [25]	0.68	0.54, 0.86
Polesel et al, 2013 [26]	0.72	0.56, 0.93

CI, confidence interval; NPC, nasopharyngeal carcinoma; OR, odds ratio.