Dietary carbohydrate intake and the risk of esophageal cancer: A meta-analysis

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Abstract

Purpose: Dietary carbohydrate intake had become recognized as an important risk factor for risk of esophageal cancer. This meta-analysis aimed to assess the association between dietary carbohydrate intake and the risk of esophageal cancer. Methods: Suitable databases were carefully searched. A random-effects model was used for combined the odds ratio (OR) and 95% confidence interval (CI). Stata software 14.0 was adopted for the analysis. Results: Thirteen publications were included in our study. There was significant correlation between highest category compared with lowest category of dietary carbohydrate intake and the risk of esophageal cancer (summarized OR= 0.627, 95%CI= 0.505-0.778, I2= 59.9%, P for heterogeneity = 0.001). The results in the subgroup of esophageal adenocarcinoma (summarized OR= 0.569, 95%CI= 0.417-0.777) and esophageal squamous cell carcinoma (summarized OR= 0.665, 95%CI= 0.453-0.975) were consistent with the overall result. A positive association was found in European populations, Asian populations, North American populations, instead of South American populations. Conclusions: In conclusions, dietary carbohydrate intake may have a protective effect against the risk of esophageal cancer.

Background

Cancer is a crucial health problem on a global scale that has become one of the primary causes of death. Esophageal cancer remained an indispensable cause of cancer-related deaths and had shown a dramatic increase in global morbidity by more than six times [1]. Efforts to identify lifestyle factors that may affect the risk of esophageal cancer had been ongoing and indicated that some dietary factors, such as dietary vitamins [2, 3], dietary fiber intake [4], dietary folate intake [5, 6], total iron and zinc intake [7] and so on, may affect the development of esophageal cancer. Previous studies had been published to assess the intake of carbohydrate and some cancers, such as colorectal cancer [8], breast cancer [9], prostate cancer [10] and so on, but no meta-analysis about esophageal cancer. So far, numerous researchers had explored dietary carbohydrate intake on the potential effects of esophageal cancer, but existing epidemiological data are inconsistent. Hence, we aimed to evaluate results from previous studies systematically and carefully by conducting a meta-analysis of observational studies to find: (1) whether highest versus lowest category of dietary carbohydrate intake could reduce the risk of esophageal cancer; (2) whether between-study heterogeneity or publication bias exited in our study.

Methods

This meta-analysis was carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [11].

Data source and search strategy

Two authors independently performed a literature search of PubMed, Embase, the Cochrane Library, and Wanfang Database. The search included studies published through 31 December, 2018. The associated medical subject headings and terms were ‘dietary carbohydrate’ combined with ‘esophageal cancer’ or ‘esophageal adenocarcinoma’ or ‘esophageal squamous cell carcinoma’. Divergence in the search results was resolved by discussion.

Inclusion and exclusion criteria

The studies were included in our meta-analysis if they met the following criteria: (1) observational studies; (2) studies assessing the associations between dietary carbohydrate intake and the risk of esophageal cancer; (3) studies reporting in humans; (4) available odds ratio (OR) and 95% confidence interval (CI) for highest category versus lowest category of dietary carbohydrate intake; (5) humans studies. In addition, overlapped studies or populations, conference reports, editor comments, reviews, case reports, and academic dissertations were excluded from the analysis.

Data extraction

Two authors independently extracted the following data from each eligible study: first author's name, publication year, research location, sample size, average cases age, disease type, study design, OR and 95%CI of dietary carbohydrate intake, assessment of intake, adjusted or matched for factors. Divergence in the extraction was resolved by discussion.

Statistical analysis

Association analysis between dietary carbohydrate intake and the risk of esophageal cancer was performed using a random-effects model. The effect size was estimated by calculating the summarized OR and its 95%CI [12]. The I^2 statistic was used to estimate the degree of heterogeneity among the studies [13]. Meta-regression was performed to interpret the between-group heterogeneity [14]. Furthermore, sensitivity analyses and publication biases by Egger's test [15] and Begg's funnel plots [16] were performed. All tests were two-tailed, and a p value less than 0.05 was considered statistically significant.

Results

Our research returned 3627 articles from the above mentioned databases. Two articles were identified from the references of the relevant articles. After removing the duplicates from the different databases, 2227 articles were reviewed with titles and abstract. Then, 2191 articles were excluded due to not suitable for our analysis while reviewed the titles and/or abstract. The full texts of 36 articles were assessed. Twenty-three articles were further excluded with reasons, which showed in the Figure 1. Finally, we included 13 articles [17-29] that assessed a total of 3033 patients in our meta-analysis. The characteristics of the included studies are shown in table 1.

In our included articles, there are 5 texts (Lagergren et al. 2013, Lahmann et al. 2014, Mayne et al. 2001, Tzonou et al. 1996, Wolfgarten et al. 2001) reported both esophageal adenocarcinoma and esophageal squamous cell carcinoma about dietary carbohydrate intake. Therefore, 13 articles with 18 studies were used for the analysis.

In the results of the overall analysis, highest category versus lowest category of dietary carbohydrate intake could significantly reduce the risk of esophageal cancer (summarized OR= 0.627, 95%CI= 0.505-0.778, I^2= 59.9%, $P_{for\ heterogeneity}$ = 0.001) (Figure 2). The results in the subgroup of esophageal adenocarcinoma (summarized OR= 0.569, 95%CI= 0.417-0.777) and esophageal squamous cell carcinoma (summarized OR= 0.665, 95%CI= 0.453-0.975) were consistent with the overall result. A positive association was found in European populations, Asian populations, North American populations, instead of South American populations. When we conducted a subgroup analysis by study design, the association was significant in population-based case-control studies (PBCC), not in the hospital-based case-control studies (HBCC). The detailed results are shown in table 2.

In the publication bias assessment, the results from funnel plots (Figure 3) and Egger's test (P= 0.107) detected no publication bias. Sensitivity analyses (Figure 4) showed no single study had essential effect on the overall result.

Discussion

Numerous of studies about dietary carbohydrate intake and esophageal cancer had been published, with conflicting results. However, no meta-analysis was performed to obtain a definitive conclusion. Therefore, we conducted this study to clarify whether dietary carbohydrate intake had some inverse effects on the development of esophageal cancer. In total, our results suggested that dietary carbohydrate intake had significant association on the lower development of esophageal cancer.

In the current meta-analysis, people with higher carbohydrate intake may reduce the risk of esophageal cancer. On the one hand, carbohydrate intake was negatively correlated with fat intakes. Therefore, people who were with higher carbohydrate intake may also have lower intake of fat, then explained its inverse association with esophageal cancer [20]. On the other hand, people who were with higher intake of carbohydrate could be reflection of more plant-based food intakes, and especially fruit and vegetable, which had been confirmed having a relationship with esophageal cancer [30].

We found significant between-study heterogeneity in the whole pooled results of dietary carbohydrate intake and esophageal cancer risk. As introduced in the methods, we used meta-regression to explore the causes of heterogeneity for covariates of publication year, disease type, study design, geographic locations, assessment of intake and number of cases. Results from meta-regression suggested that no covariates increased the high between-study heterogeneity. Moreover, between-study heterogeneity also exited in the subgroup analyses by disease type, study design and geographic locations. We then used leave-one-out analysis to reduce the between-study heterogeneity. The I^2 was reduced to 47.1% when we leaved one study by Wolfgarten et al. 2001 [27] (about the esophageal adenocarcinoma study). And the pooled result about the remained 17 studies was not changed (summarized OR= 0.673, 95%CI= 0.558-0.811).

The present study still had several limitations. First, all the included studies were case-control studies. As well as known, the selection bias, recall bias and some other confounding factors cannot be excluded in the case-control studies. Hence, it is requirement for evidence from prospective cohort studies. Second, all the included studies were with English language and this may omit other languages studies. Meanwhile, the papers which had been published in the journal or online were searched and included in our analysis. Those papers which published in the meetings or unpublished were not searched. However, we did not detect any publication bias in our meta-analysis. Third, we only assessed the association between dietary total carbohydrate intake and the risk of esophageal cancer, and did not assess the association between carbohydrate type and esophageal cancer risk due to the limitation data provided in all the included original articles. Hence, more articles with detailed carbohydrate type are warranted to further assess the risk of esophageal cancer.

Conclusions

In summary, our results indicated that dietary intake of carbohydrate may contribute to the lower development of esophageal cancer. As some limitations existed in our analysis, large scale prospective studies with detailed type of dietary carbohydrate intake are needed to verify our results.

Abbreviations

OR: odds ratio; CI: confidence interval; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: All the authors consented for publication.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available in the manuscript.

Declarations: The authors declare that they have no competing interests.

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Authors' contributions: FX and WL drafted the manuscript. FX, WL and XQG carried out the literature quality evaluation and extracted the related data. XQG performed the statistical. FX and WL conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of the included studies.

Study, year	Design	Age	Participants, Cases	Country	Disease type	Assessment of intake	OR (95%CI) Highest vs. lowest	Adjusted for or matched for
Chen et al. 2002	PBCC	62.3±12.4	573, 124	United States	Esophageal adenocarcinoma	HHHQ	0.4(0.2-0.9)	Age, age squared, sex, respondent type, BMI, alcohol use, tobacco use, education, family history of cancers, and vitamin supplement use
De Stefani et al. 2006	HBCC	40-89	1170, 234	Uruguay	Esophageal squamous cell carcinoma	FFQ	0.74(0.47-1.17)	Age, sex, residence, urban/rural status, birthplace, education, body mass index, smoking status, years since quit smoking, number of cigarettes smoked per day, alcohol drinking, mate consumption, and total energy intake.
De Stefani et al. 1999	HBCC	NA	459, 66	Uruguay	Esophageal cancer	FFQ	0.8(0.5-1.1)	Age, sex, residence, urban/rural status, education, BMI, tobacco smoking, total alcohol intake and total energy intake
Jessri et al. 2011	HBCC	40-75	143, 47	Iran	Esophageal squamous cell carcinoma	FFQ	0.22(0.05-0.84)	Age, sex, reflux, BMI, smoking, physical activity, and education
Lagergren et al. 2013	PBCC	<80	1008, 188	Sweden	Esophageal adenocarcinoma	FFQ	0.68(0.40-1.16)	Age, sex, reflux, BMI, smoking, alcohol consumption, education grade, and total energy intake
Lagergren et al.	PBCC	<80	987, 167	Sweden	Esophageal squamous cell carcinoma	FFQ	1.05(0.61-1.80)	Age, sex, reflux, BMI, smoking,

2013								alcohol consumption, education grade, and total energy intake
Lahmann et al. 2014	PBCC	18-79	1778, 88	Australia	Esophageal adenocarcinoma	FFQ	0.79(0.49-1.25)	Age, sex, education, BMI, smoking, physical activity, alcohol intake, NSAID, diabetes, total fruit intake (except for fiber), red meat, processed meat, and total energy
Lahmann et al. 2014	PBCC	18-79	1717, 227	Australia	Esophageal squamous cell carcinoma	FFQ	0.46(0.28-0.75)	Age, sex, education, BMI, smoking, physical activity, alcohol intake, NSAID, diabetes, total fruit intake (except for fiber), red meat, processed meat, and total energy
Li et al. 2017	PBCC	30-79	2527, 500	United States	Esophageal adenocarcinoma	FFQ	0.93(0.56-1.54)	Age, sex, race, study indicator, BMI, fruits and vegetables intake, cigarette smoking, GERD frequency and total energy intake.
Mayne et al. 2001	PBCC	30-80	969, 282	United States	Esophageal adenocarcinoma	FFQ	0.34(0.20-0.58)	Age, site, sex, race, proxy status, BMI, income, education, smoking, and alcohol consumption
Mayne et al. 2001	PBCC	30-80	893, 206	United States	Esophageal squamous cell carcinoma	FFQ	0.68(0.37-1.25)	Age, site, sex, race, proxy status, BMI, income, education, smoking, and alcohol consumption
Mulholland	PBCC	64±11	480,	Ireland	Esophageal	FFQ	0.39(0.16-	Age, sex,

et al. 2009			224		adenocarcinoma		0.98)	energy intake, smoking, BMI, education, occupation, alcohol, regular NSAID use, location, and H. pylori
Tzonou et al. 1996	HBCC	NA	256, 56	Greece	Esophageal adenocarcinoma	FFQ	0.84(0.59-1.19)	Age, sex, birth place, schooling, height, analgesics, coffee drinking, alcohol intake, tobacco smoking, and energy intake
Tzonou et al. 1996	HBCC	NA	243, 43	Greece	Esophageal squamous cell carcinoma	FFQ	1.12(0.75-1.69)	Age, sex, birth place, schooling, height, analgesics, coffee drinking, alcohol intake, tobacco smoking, and energy intake
Wolfgarten et al. 2001	PBCC	62.2±1.9	140, 40	Germany	Esophageal adenocarcinoma	FFQ	0.07(0.03-0.40)	Age, gender, height, weight, BMI and socioeconomic data such as marital status and earning capacity
Wolfgarten et al. 2001	PBCC	58.1±1.2	145, 45	Germany	Esophageal squamous cell carcinoma	FFQ	0.16(0.03-0.59)	Age, gender, height, weight, BMI and socioeconomic data such as marital status and earning capacity
Wu et al. 2007	PBCC	30-74	1514, 206	United States	Esophageal adenocarcinoma	FFQ	0.66(0.40-1.10)	Age, sex, race, birthplace, education, smoking, BMI, reflux, use of vitamins, total calories, and fat
Zhang et al. 1997	HBCC	NA	214, 90	United States	Esophageal adenocarcinoma	HHHQ	0.7(0.3-1.8)	Age, sex, race, education, smoking, alcohol intake, BMI, and total dietary intake in calories

Abbreviation: 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; BMI: Body mass index.

Table 2 Summary results about the association between dietary carbohydrate intake and esophageal cancer risk.

Subgroups	Number of studies	Number of cases	OR(95% CI)	P for trend	Heterogeneity test	
					I^2 (%)	P
Total	18	3033	0.627(0.505-0.778)	<0.001	59.9	0.001
Disease type						
Esophageal adenocarcinoma	10	1998	0.569(0.417-0.777)	<0.001	63.4	0.003
Esophageal squamous cell carcinoma	7	969	0.665(0.453-0.975)	0.037	62.8	0.013
Study design						
PBCC	12	2497	0.541(0.401-0.729)	<0.001	63.2	0.002
HBCC	6	536	0.831(0.669-1.030)	0.091	15.3	0.316
Geographic locations						
Europe	7	763	0.586(0.364-0.943)	0.028	75.5	<0.001
Asia	3	562	0.534(0.308-0.927)	0.026	53.9	0.114
North America	6	1408	0.590(0.425-0.820)	0.002	43.1	0.118
South America	2	300	0.774(0.574-1.043)	0.092	0.0	0.800

OR: odds ratio; CI: confidence interval; PBCC: population-based case-control studies; HBCC: hospital-based case-control studies

Figures

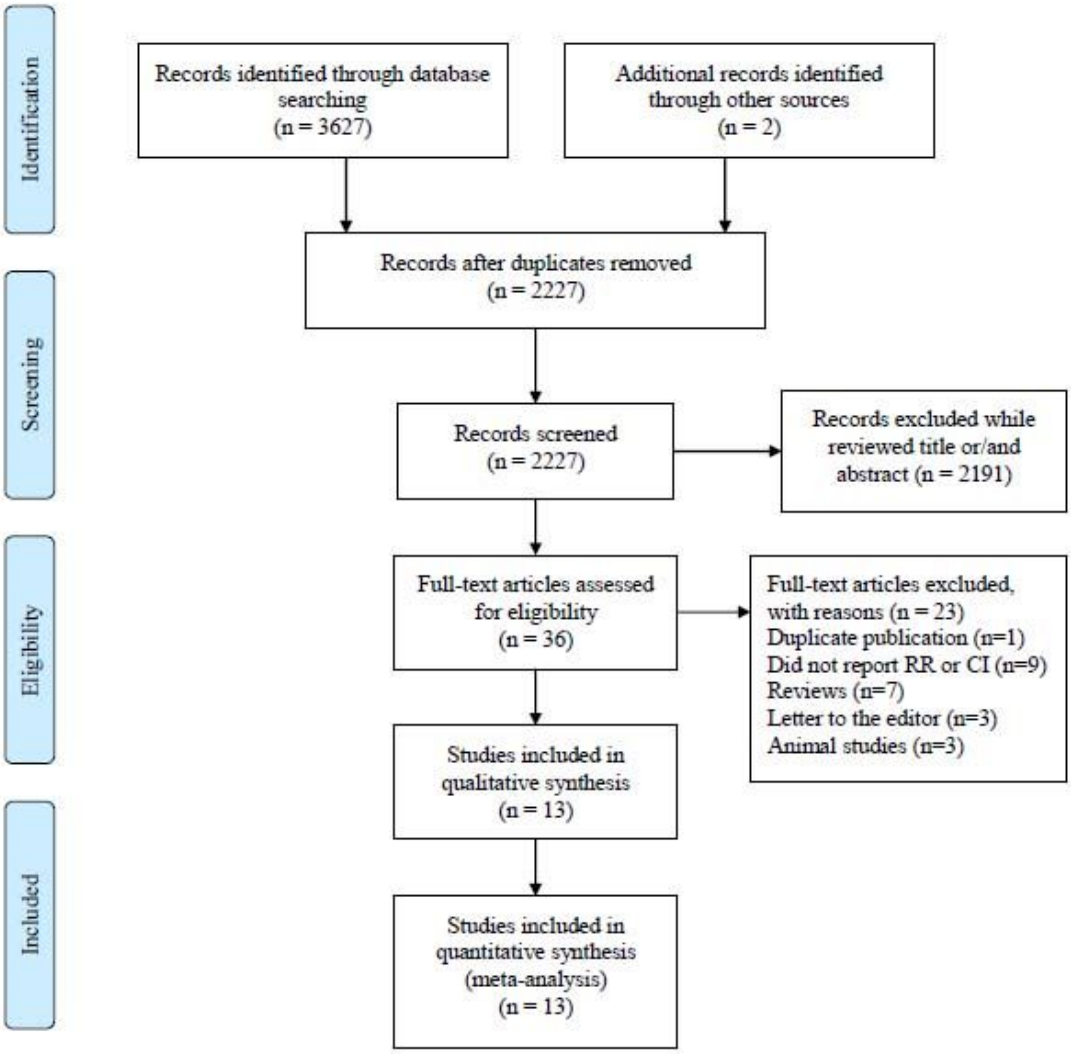

Figure 1

Flow chart of meta-analysis for exclusion/inclusion of studies.

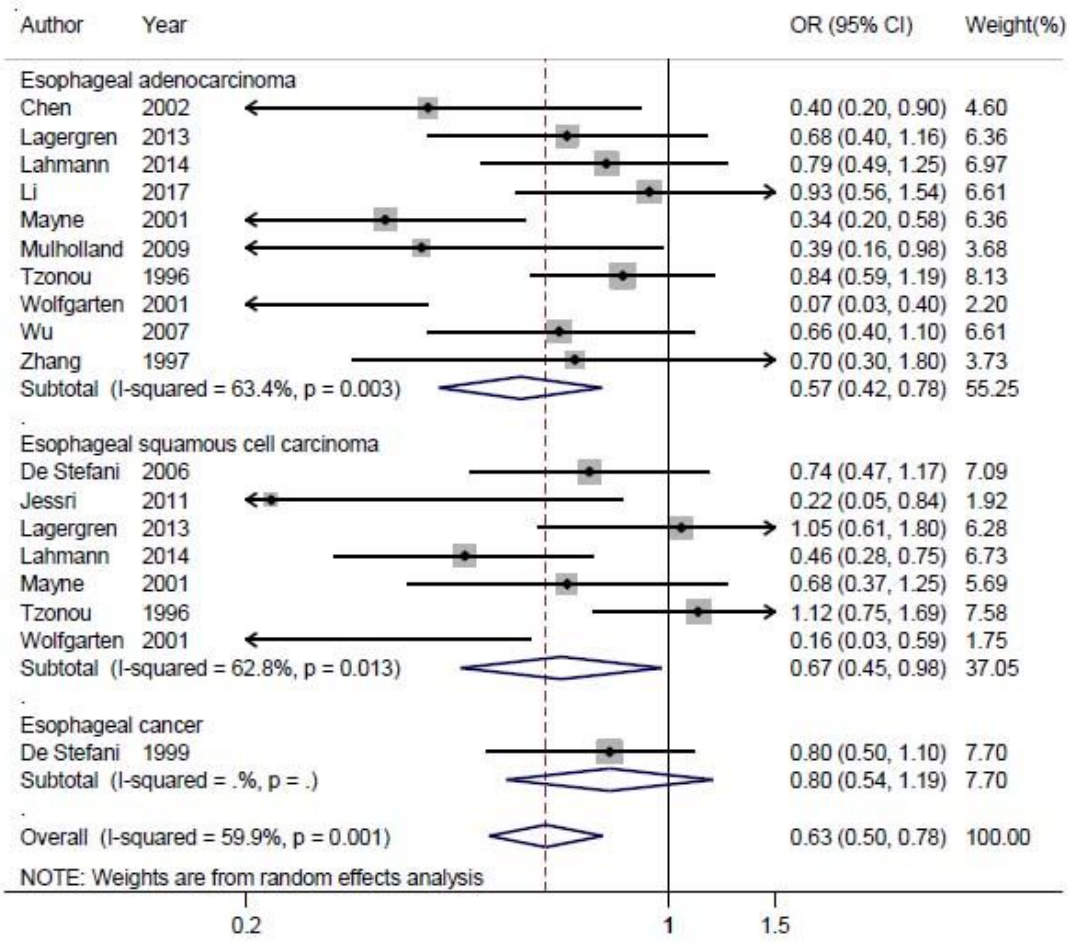

Figure 2

The forest plot of the association between dietary carbohydrate intake and esophageal cancer risk.

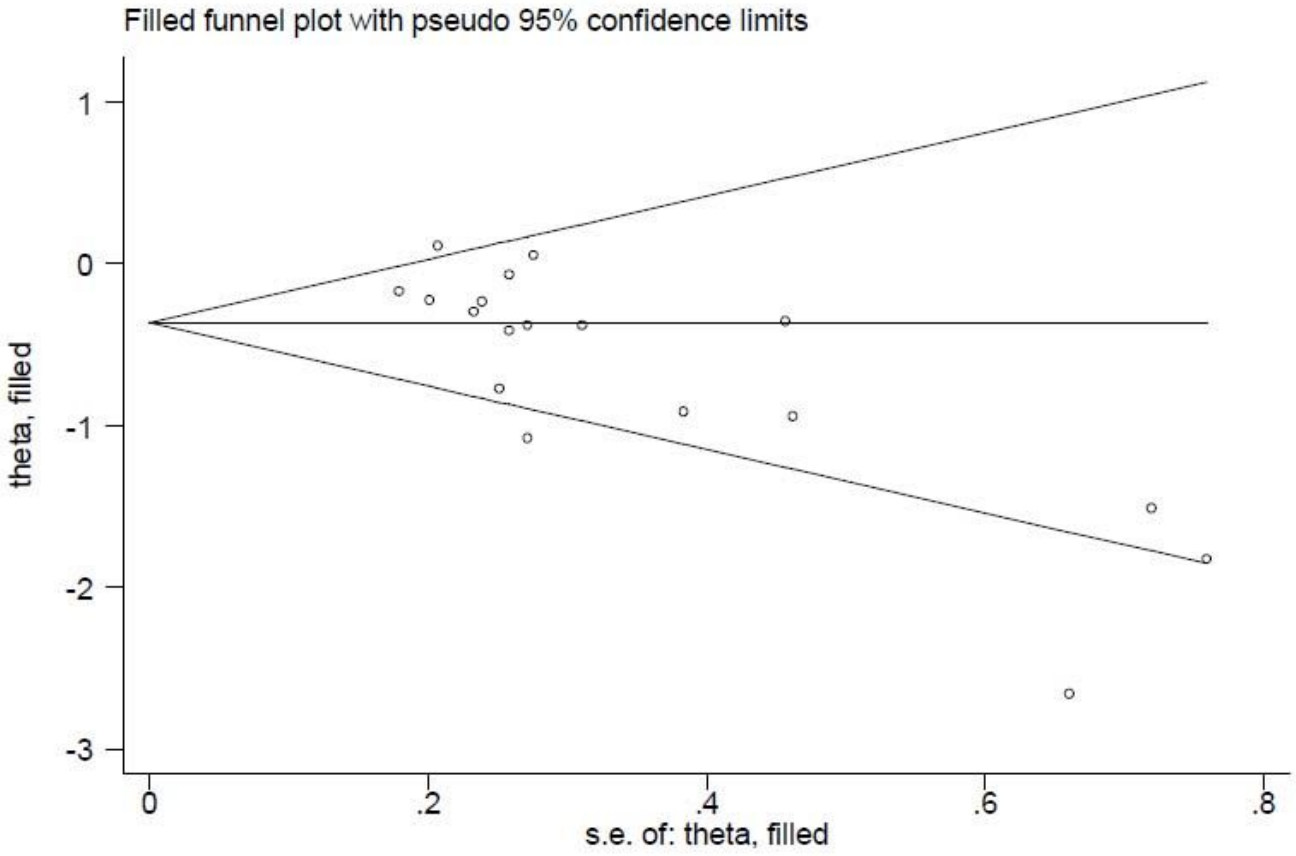

Figure 3

Funnel plot for the analysis of publication bias between dietary carbohydrate intake and esophageal cancer risk.

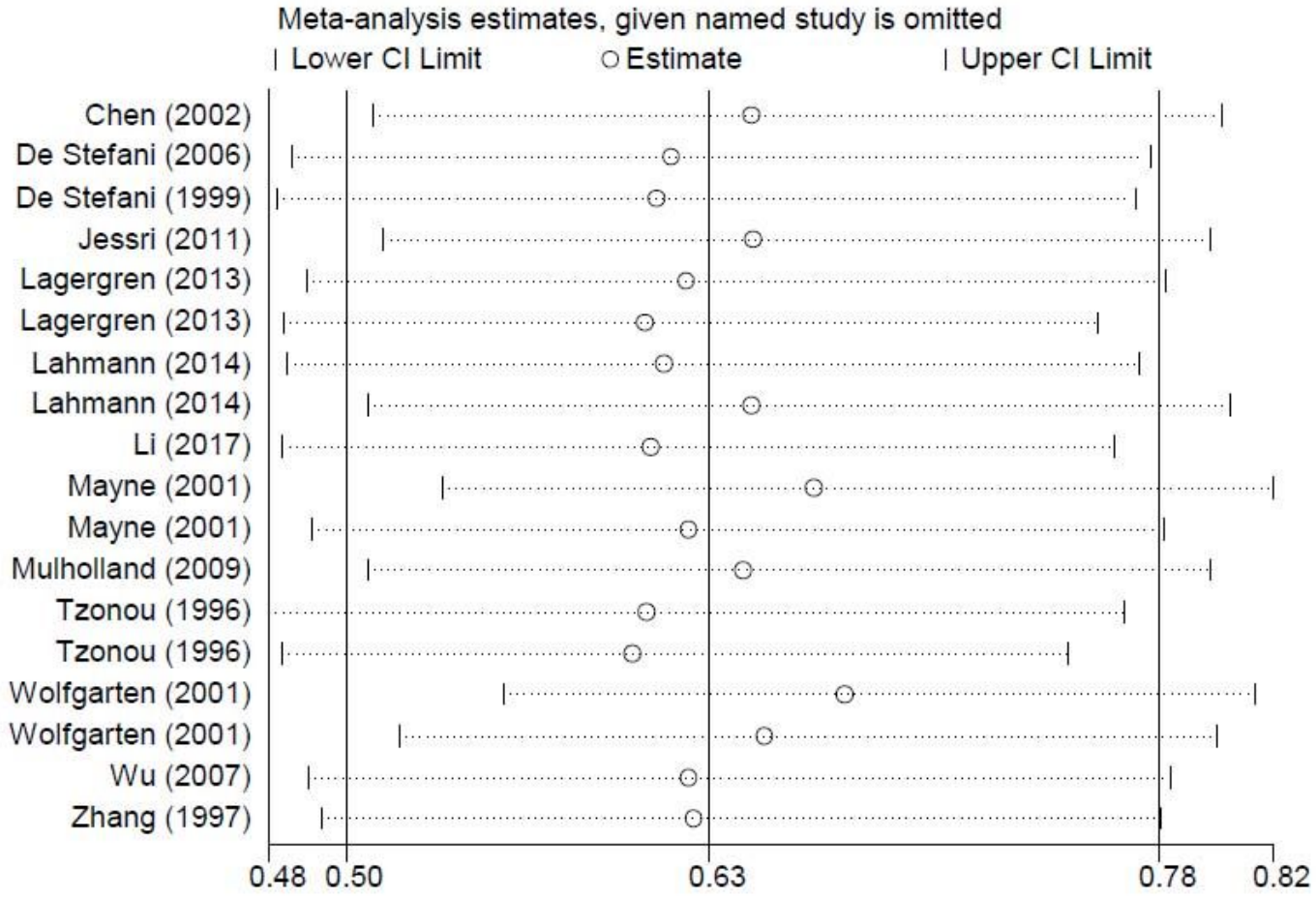

Figure 4

Sensitivity analyses between dietary carbohydrate intake and esophageal cancer risk.