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Green Tea Consumption and Esophageal Cancer Risk: A Meta-analysis

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ABSTRACT

Background: The protective role of green tea against cancer is still unknown.

Objectives: To investigate the association between green tea consumption and esophageal cancer risk through meta-analysis.

Methods: We searched MEDLINE, EMBASE, Web of Science and Cochrane Library for studies on the relationship between green tea and esophageal cancer risk. We assessed heterogeneity (I^2) and publication bias (Begg's and Egger's tests). Pooled relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using random effects models.

Results: A total of 20 studies were included. The RRs for all studies was 0.65 (95% CI: 0.57–0.73), with $I^2 = 75.3\%$ and $P = 0$. In the subgroup analysis, the following variables showed marked heterogeneity: Asian (RR: 0.64; 95% CI: 0.56–0.73) and non-Asian countries (RR: 0.74; 95% CI: 0.45–1.03), female (RR: 0.55; 95% CI: 0.39–0.71) and male + female (RR: 0.64; 95% CI: 0.54–0.75), case–control study (RR: 0.62; 95% CI: 0.52–0.71), impact factor >3 (RR: 0.65; 95% CI: 0.56–0.75), impact factor <3 (RR: 0.64; 95% CI: 0.48–0.80), Newcastle–Ottawa Scale >7 (RR: 0.82; 95% CI: 0.66–0.97) and Newcastle–Ottawa Scale ≤7 (RR: 0.59; 95% CI: 0.49–0.68).

Conclusion: Green tea consumption could be a protective factor for esophageal cancer.

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Introduction

Esophageal cancer, one of the most common malignant tumors of the digestive system, is highly aggressive and has a poor prognosis. Since the early symptoms are subtle, it is often not diagnosed until the middle or late stages. The five-year survival rate is less than 20% (1,2) and it is the eighth leading causes of cancer-related death worldwide (3), with a mortality rate of over 400,000 per year. According to a 2012 survey, the incidence rate is 450,000 per year and rising (4). Thus, esophageal cancer is a serious threat to health.

In daily life, the consumption of tea is second only to drinking water. The main active ingredients in tea are polyphenols, which have a wide range of biological and pharmacological functions (7,8). A 2012 meta-analysis showed that although there was no significant link between drinking green tea and esophageal cancer risk, a protective effect was observed in females (5). Due to the many components of tea, there are many confounding factors that are difficult to control. In 1990, the International Agency for Research on Cancer stated that there was not enough evidence to prove that tea is a protective factor for human cancer (6). Subsequently, researchers from all over the world studied the relationship between tea and cancer. Although an epidemiological study has suggested that tea drinking may lead to esophageal carcinoma (9), no consistent conclusion has yet been reached (2). Therefore, based on past and updated studies, we conducted a meta-analysis of this relationship.

The aim of this study is to analyze the association between drinking green tea and esophageal cancer risk. It could provide a scientific and reliable basis for the prevention of esophageal cancer and the development of more effective intervention strategies to promote health.

Materials and Methods

Study Search Strategy

We included all relevant original studies published up to June 30, 2017 on the association between green tea consumption and esophageal cancer risk. Following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, we searched PubMed, EMBASE, Web of Science and the Cochrane Library (10).

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/hnuc.

*These authors contributed equally to this work.

Inclusion Criteria

The inclusion criteria were: 1) case–control or cohort studies published as original articles in English; 2) studies that investigated green tea consumption and the resulting risk of esophageal cancer; and 3) studies providing odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs), or gave sufficient data for these to be calculated. Dates were extracted and summarized by two authors independently. In case of disagreement, another author resolved this by discussion.

The following data were analyzed: first author, publication year, country, study design, gender, research cases/size, exposure range, adjustment factors, impact factor (IF), Newcastle-Ottawa Scale (NOS) and RRs or ORs with 95% CIs. If both crude RRs and adjusted RRs are available, we chose adjusted RRs.

Data Analyses

ORs with 95% CIs were assessed to determine the relationship between green tea and esophageal cancer. The most adjusted RRs and 95% CIs were estimated for the highest versus lowest green tea consumption.

Random effect models were used to calculate the combined ORs and 95% CIs (11). Q statistics ($p \leq 0.05$) and I^2 statistics were used to evaluate heterogeneity across the studies (12). I^2 values of 0%, 25%, 50% and 75% represented no, low, moderate and high heterogeneity, respectively (13), and an I^2 >50% was considered to indicate heterogeneity among the studies (13). Subgroup analyses were used to detect heterogeneity in gender, country, basic design, NOS, IF and adjustment for covariates (including age, birthplace, family history, alcohol intake and cigarette smoking). We conducted a sensitivity analysis to study potential sources of heterogeneity, and to identify whether one specific study significantly affected the data (14).

Publication bias was assessed by both Egger's and Begg's tests. If either p value was >0.05, we concluded that there was no significant publication bias (11,15). We used STATA 13.0 to analyze all the data, and took $p \leq 0.05$ as statistically significant.

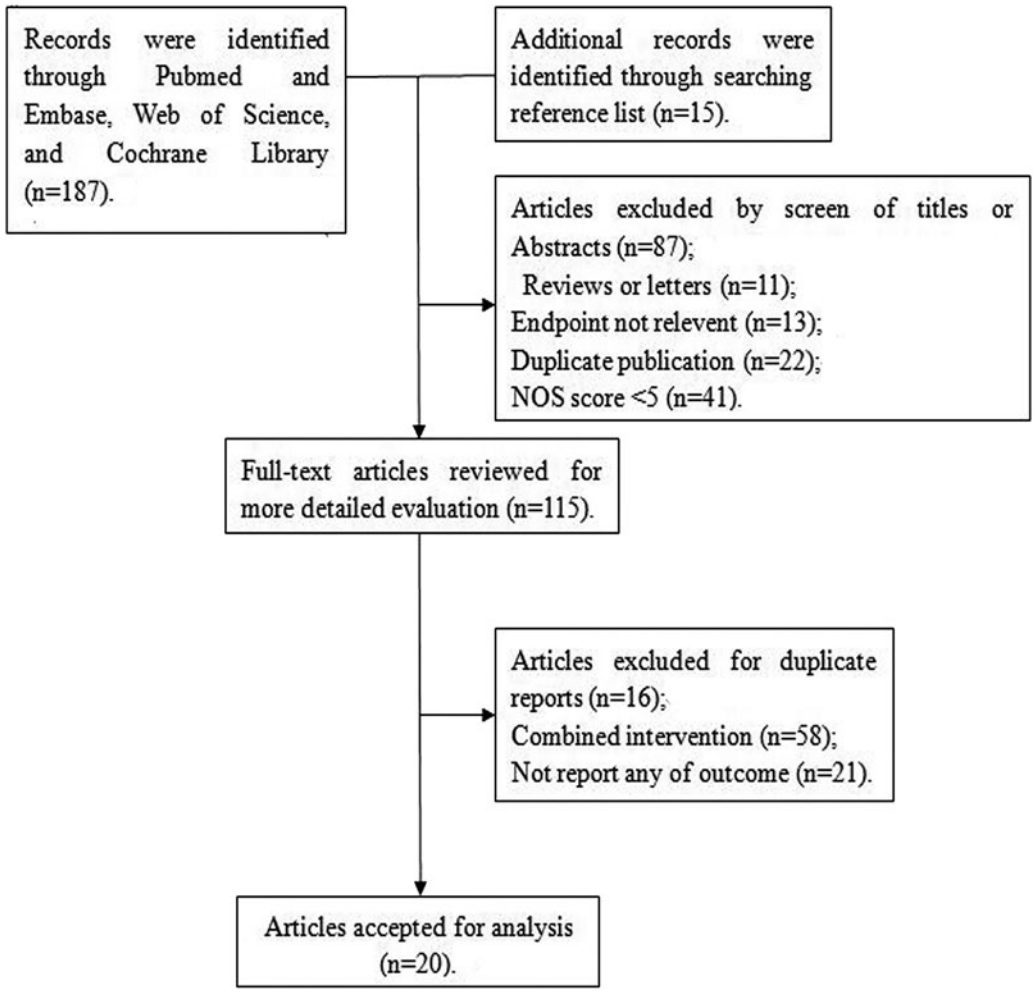

Figure 1. Search strategy and selection of studies for inclusion in the meta-analysis.

Table 1. Characteristics of the studies included in the meta-analysis.

Study	Gender	Year	Design	Countries		Cases/Size	RR (95%CI)	Exposure range	Adjustment factors	IF	NOS
Gao et al. (34)	M	1994	Case–control study	China		416/658	0.79 (0.56–1.13)	≥200 g/month vs. nondrinker	Age, education, birthplace, cigarette smoking and alcohol intake.	5.4	7
	F					242/658	0.34 (0.17–0.69)	≥150 g/month vs. nondrinker	Age, education, birthplace, and cigarette smoking.		
Inoue et al. (33)	M + F	1998	Case–control study	Japan		185/21,128	1.14 (0.55–2.34)	≥7 cups/day vs. rarely	Black tea, coffee, gender, age at first hospital visit, year and season at first hospital visit, habitual alcohol drinking, regular physical exercise, fruit intake, rice intake, beef intake.	2.5	6
Wang et al. (32)	M + F	1999	Case–control study	China		68/68	0.20 (0.06–0.67)	Yes vs. no	Education level, smoking, and alcohol consumption	0	5
Takezaki et al. (31)	M + F	2000	Case–control study	Japan		284/11,936	0.70 (0.40–1.20)	≥7 cups/day vs. occasionally or less	Age, year and season of visit, smoking status, and drinking status.	2.5	6
Gao et al. (29)	M + F	2002	Case–control study	China		141/223	0.45 (0.26–0.78)	Yes vs. no	Age, sex, smoking, alcohol drinking, tea consumption, raw vegetables, pickled vegetables, fruit, meat, soybean products, GSTT1, and GSTM1.	5.9	8
Mu et al. (28)	M + F	2003	Case–control study	China		218/415	0.58 (0.35–0.97)	≥250 g/month vs. never	Age, gender, education level, smoking, eating speed, regular diet, salt consuming, and vegetable.	0	5
Ishikawa et al. (27)	M	2006	Cohort study	Japan		38/67,075 person-yr	1.78 (0.66–4.82)	≥5 cups/day vs. never	Age in years, cigarette smoking, alcohol drinking, coffee consumption, and black tea consumption.	2.5	7
	F					40/129,611person-yr	1.61 (0.71–3.66)				
Wang et al. (26)	M + F	2006	Case–control study	China		107/107	0.13 (0.03–0.62)	Yes vs. no	Family history of cancer, eating fast, utensil clean up, H. pylori infection and esophageal lesions.	3.2	7
Wang et al. (25)	M	2007	Case–control study	China		223/252	1.37 (0.95–1.98)	Yes vs. no	Age, marital status and education years.	2	6
	F					132/156	0.26 (0.07–0.94)				
Wu et al. (24)	M + F	2009	Case–control study	China	Dafeng	637/1938	1.00 (0.60–2.00)	≥250 g/month vs. never	Age, gender, education level, income 10 years before, cancer family history, BMI, pack-year of smoking, alcohol drinking, tea temperature.	5	6
					Ganyu	883/1941	1.60 (1.10–2.20)	≥250 g/month vs. never			
Islami et al. (23)	M + F	2009	Case–control study	Iran		300/571	0.89 (0.38–2.09)	Daily vs. never	Ethnicity, daily vegetable intake, alcohol consumption, tobacco or opium ever use, duration of residence in rural	19	9

(*Continued*)

Table 1. Continued.

Study	Gender	Year	Design	Countries	Cases/Size	RR (95%CI)	Exposure range	Adjustment factors	IF	NOS
								areas, education level, car ownership, and tea temperature.		
Chen et al. (20)	M + F	2011	Case–control study	China	150/300	0.92 (0.49–2.32)	>250 g/month vs. never	Age, sex, education level, annual income, cancer family history, smoking and drinking status.	5	6
Hu et al (35)	M + F	1994	Case–control study	China	196/392	3.9 (1.7–9.1)	3000 (g/yr) vs. never	Smoking, alcohol drinking, income, occupation.	5.4	7
Gao et al. (21)	M + F	2009	Case–control study	China	600/1514	1.68 (1.19–2.39)	3750 ∼ 24750 (g/yr) vs. .never	Age, smoking, alcohol drinking, diet, geographic region, water source, other.	2	5
Chen et al. (22)	M + F	2009	Case–control study	China	299/612	0.50 (0.30–1.00)	Yes vs. no	Age, smoking, alcohol drinking, consumption of Areca, educational levels, ethnicity, source of hospital.	3.4	6
Sun et al. (30)	M + F	2002	Case–control study	China	42/772	0.87 (0.38–2.02)	Yes vs. no	Age, smoking, alcohol drinking, diet, other.	4.8	7
Nechuta S et al. (19)	F	2012	Cohort study	China	56/69,310	0.77 (0.57–1.03)	≥150 g/mo vs. never	Age, marital status, education, occupation, BMI, exercise, fruit and vegetable intake, meat intake, diabetes, and family history of digestive system cancer.	6.9	8
Zamora-Ros R et al. (17)	M + F	2014	Cohort study	Ten European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom)	339/442,143	0.74 (0.51–1.08)	≥178.6 (ml/d) vs. never	Educational level, smoking status and intensity, physical activity, energy intake, and daily consumption of fruit, vegetables, red and processed meat and coffee and tea mutually.	6.5	8
Oze I et al. (18)	M + F	2014	Case–control study	Japan	434/961	1.31 (0.95–1.81)	≥3 cups/day vs. Less than daily	Age, sex, coffee and green tea intake, alcohol consumption, cumulative smoking, fruit and vegetable intake, BMI, occupation and frequency of rice intake.	6.5	6
Dar NA et al. (16)	M + F	2015	Case–control study	India	73/2367	2.60 (1.68–4.02)	>1250ml/d vs. ≤500 ml/d	age, ethnicity, place of residence, income, sex education, the wealth score, fruit and vegetable intake (logarithmic scale), ever use of bidi, gutka, and alcohol, and cumulative use of hookah, cigarette and nass.	6.5	7

BMI: body mass index; CI: confidence interval; F: female; IF: impact factor; M: male; NOS: Newcastle–Ottawa Scale; RR: relative risk.

Results

Literature Search

We initially identified 187 relevant studies, published between 1994 and 2015. These were screened according to the inclusion criteria to leave a final selection of 20 (16–35). Figure 1 illustrates the retrieval process.

Study Characteristics

Of the 20 studies that met the inclusion criteria, 17 were case–control studies and three were cohort studies; 19 were conducted in Asia (including 13 in China, four in Japan, one in India and one in Iran) and one in Europe. The total number of subjects was 755,108, including 6103 cases of esophageal cancer. The RRs of all studies were adjusted. In most studies, age, sex, family history, education, alcohol intake and cigarette smoking were corrected. We conducted NOS on the studies, with a score of 5–9. The basic characteristics are summarized in Table 1.

Main Results

The summary RR for all studies was 0.65 (95% CI: 0.57–0.73), with high heterogeneity (I^2 = 75.3% and $p = 0$, Figure 2). This indicates that green tea intake is a protective factor for the risk of esophageal cancer.

Subgroup Analyses

To investigate the sources of heterogeneity, we conducted a subgroup analysis of the relationship between green tea consumption and esophageal cancer. The

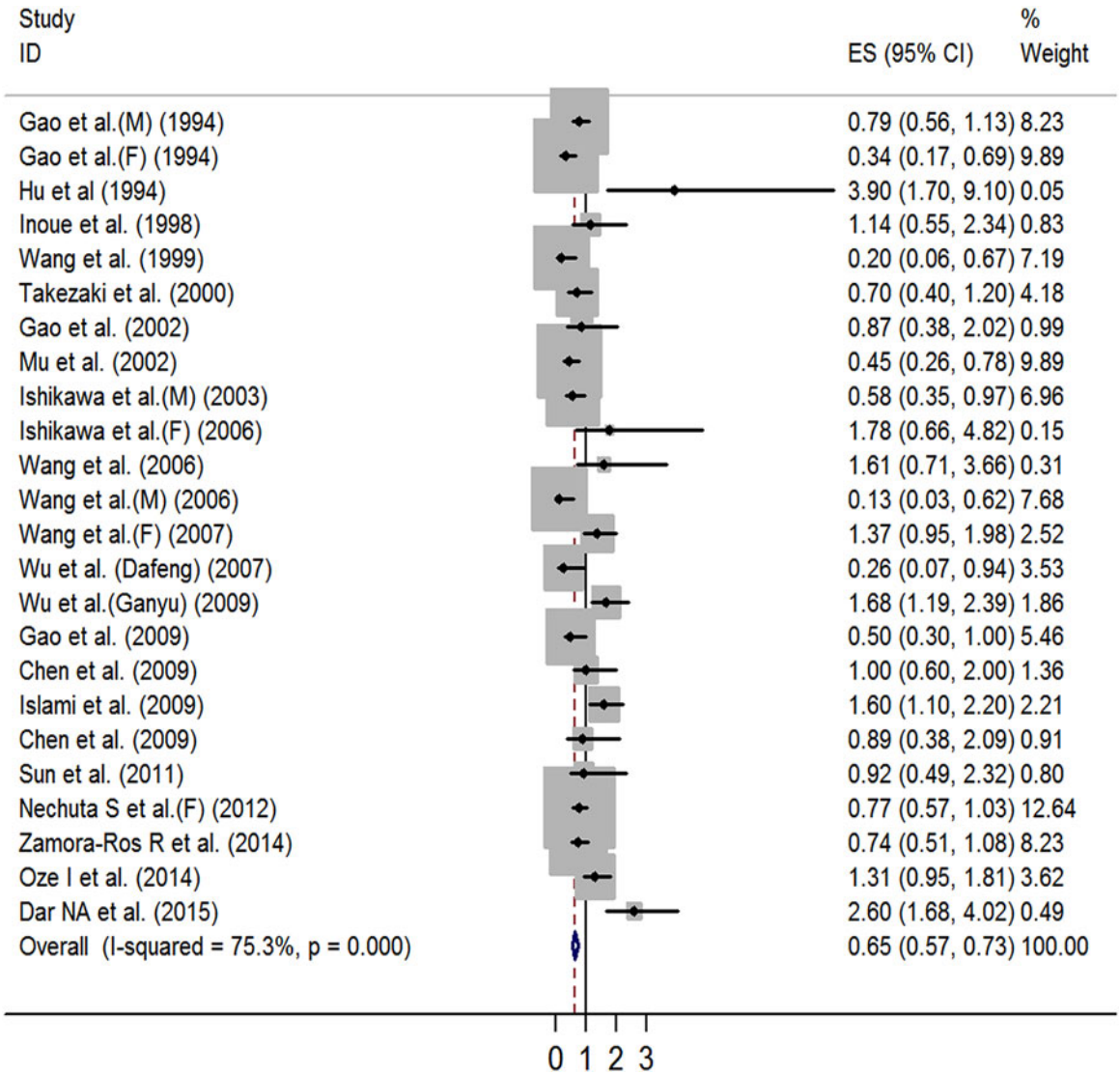

Figure 2. Forest plot of relative risks (RRs) with 95% CI, examining the association between green tea consumption and esophageal cancer risk in a random-effects model.

subgroups we analyzed included: countries (Asian or non-Asian), gender (male, female or male + female), research design (case-control study or cohort study), IF (>3 or <3), NOS (>7 or ≤7) and adjustment for covariates (age, birthplace, family history, alcohol intake and cigarette smoking). In the subgroup analysis, the following variables showed a marked heterogeneity: Asian (RR: 0.64; 95% CI: 0.56–0.73) and non-Asian countries (RR: 0.74; 95% CI: 0.45–1.03), female (RR: 0.55; 95% CI: 0.39–0.71) and male + female (RR: 0.64; 95% CI: 0.54–0.75), case–control study (RR: 0.62; 95% CI: 0.52–0.71), IF >3 (RR: 0.65; 95% CI: 0.56–0.75), IF < 3 (RR: 0.64; 95% CI: 0.48–0.80), NOS > 7 (RR: 0.82; 95% CI: 0.66–0.97) and NOS ≤ 7 (RR: 0.59; 95% CI: 0.49–0.68). In addition, there was significant heterogeneity among the subgroups of adjustment for covariates. The results of subgroup analysis are shown in Table 2.

Table 2. Relative risks (RRs) of esophageal cancer in relation to green tea consumption.

Group	No. of studies	RR (95% CI)	$P_{heterogeneity}$	I^2 (%)
Country				
Asian	23	0.64 (0.56–0.73)	0	76.3
Non-Asian	1	0.74 (0.45–1.03)	0	0
Gender				
M	3	0.94 (0.69–1.19)	0.113	54.2
F	4	0.55 (0.39–0.71)	0.021	69.1
M + F	17	0.64 (0.54–0.75)	0	77.9
Design				
Case–control study	20	0.62 (0.52–0.71)	0	78.5
Cohort study	4	0.78 (0.60–0.95)	0.535	0
IF				
>3	15	0.65 (0.56–0.75)	0	76.2
<3	9	0.64 (0.48–0.80)	0	76.8
NOS				
>7	4	0.82 (0.66–0.97)	0.036	64.9
≤7	20	0.59 (0.49–0.68)	0	75.8
Adjustment for covariates				
Age				
Yes	18	0.73 (0.63–0.82)	0	74.1
No	6	0.42 (0.26–0.58)	0.003	71.6
Birthplace				
Yes	2	0.54 (0.35–0.74)	0.022	80.9
No	22	0.67 (0.58–0.76)	0	75.1
Family history				
Yes	5	0.66 (0.50–0.83)	0	84.4
No	19	0.65 (0.55–0.74)	0	73.3
Alcohol intake				
Yes	16	0.75 (0.63–0.87)	0	73.7
No	8	0.56 (0.44–0.67)	0	77.8
Cigarette smoking				
Yes	18	0.67 (0.57–0.77)	0	75.0
No	6	0.60 (0.45–0.75)	0	79.7

CI: confidence interval; F: female; IF: impact factor; M: male; NOS, Newcastle–Ottawa Scale; RR: relative risk.

Sensitivity Analysis

Sensitivity analysis was used to determine the robustness of the meta-analysis, as well as to determine the main factors that influenced the results. As can be seen in Figure 3, the effects of each study fell within the synthetic effect range: indicating that there was no single study that influenced the results more than another, and confirming that our data were rational.

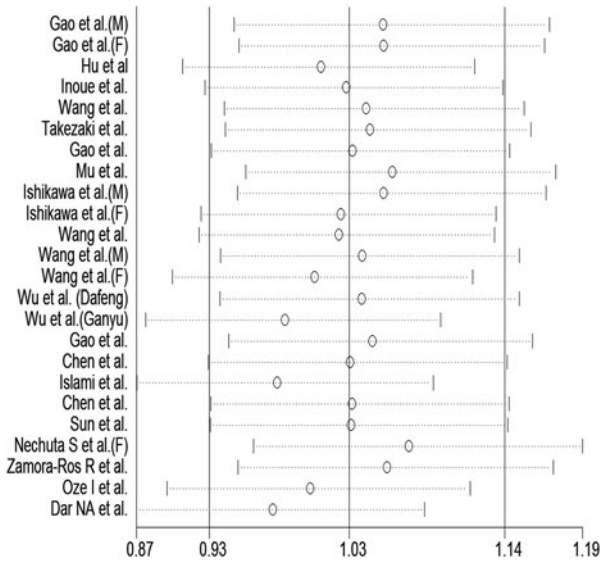

Figure 3. Sensitivity analysis of green tea consumption and esophageal cancer risk.

Regression Analysis

We used regression analysis to explore the impact of research factors and attempted to identify the sources of heterogeneity between studies. First, a meta regression analysis conducted using countries as covariates found $p = 0.179$ and $I^2 = 78.19\%$, suggesting that country could explain 78.19% of the heterogeneity. Secondly, we used gender as a covariate for meta regression analysis and found $p = 0.893$ and $I^2 = 78.75\%$. These results suggest that gender explains 78.75% of the heterogeneity. The results of the regression analysis are shown in Figures 4 and 5.

Publication Bias

Begg's and Egger's tests were performed to assess publication bias and the funnel plot symmetry was examined (Figures 6 and 7). The results from Begg's test ($Z = 1.14$, $p = 0.254$) and Egger's test ($p = 0.124$) showed no statistically significant difference, suggesting a small bias in publication.

Discussion

In a meta-analysis published in 2012, Zheng P et al. found that consumption of green tea was not associated with non-drinking esophageal cancer risk (5). In recent years,

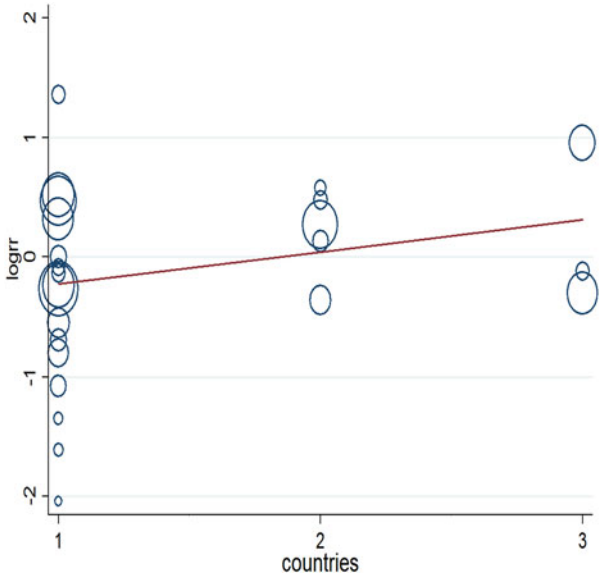

Figure 4. Meta-regulation of green tea consumption and esophageal cancer risk by using countries as covariates.

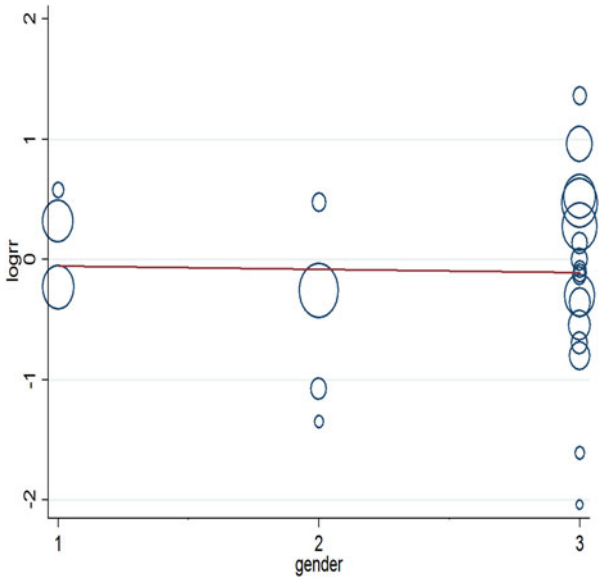

Figure 5. Meta-regulation of green tea consumption and esophageal cancer risk by using gender as covariates.

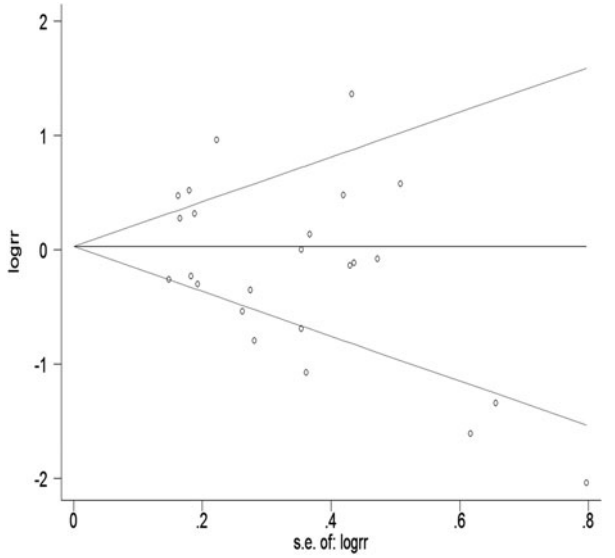

Figure 6. Egger's funnel plot assessing publication bias among the studies.

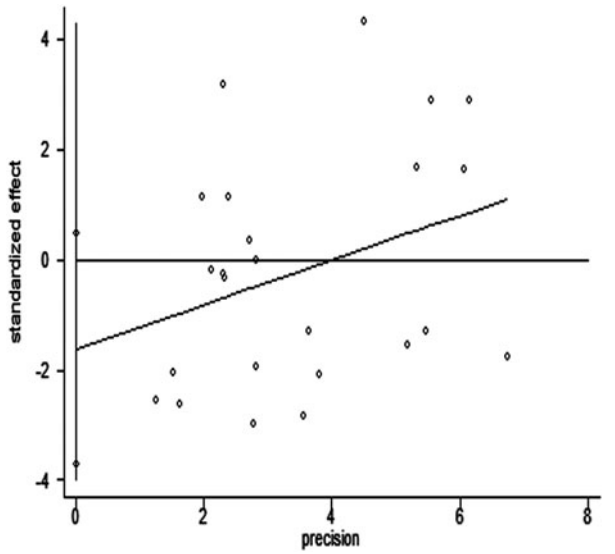

Figure 7. Begg's funnel plot assessing publication bias among the studies.

further studies on this relationship have been published, so we conducted a meta-analysis to update the field.

Although esophageal cancer is one of the most common malignant tumors of the digestive system, the pathogenesis is unclear. The disease is controlled by congenital factors, such as gene mutation and gene polymorphism, and acquired factors such as smoking, alcohol abuse and eating habits.

Tea, which is the second most common drink after water, is widely grown in more than 30 countries around the world with an annual yield of 2,500,000 tons (36). Various studies have investigated the protective effect of tea against cancer due to its antioxidant, anti-inflammatory and antitumor effects (7,8). The main active ingredients of tea are polyphenols, and the most common are epigallocatechin gallate, epigallocatechin gallate, epigallocatechin gallate and epicatechin (37). Studies have shown that epigallocatechin gallate has a significant anti-tumor effect, since it can inhibit the proliferation of cancer cells and promote their apoptosis by reducing the activity of enzymes and hindering the signal transduction pathway (38). An hour after consumption of green tea, high concentrations of catechin and theaflavins can be detected in saliva, suggesting that tea polyphenols can selectively inhibit the proliferation of oral cancer cells and induce apoptosis (39).

Different tea processing methods result in different effective ingredients and therefore different effects on esophageal cancer risk. A previous study showed that green tea, but not black tea, may be a protective factor for esophageal cancer (40). Another study proposed that there was significant isomerization of tea polyphenols at low temperatures: since yield of H_2O_2 increased with temperature, oxidation of tea polyphenols was faster at higher temperatures. Therefore, the higher the temperature of the tea, the less chance that polyphenols are able to exhibit a protective effect against cancer (41). This finding was corroborated by a study that found cold green tea was a protective factor for esophageal cancer and that the risk of esophageal cancer increased with tea temperature (42).

Some limitations in our meta-analysis should be mentioned. First of all, although the search methods used in this study are extensive, we only included research literature published in English; secondly, we did not adjust some important risk factors such as gender, family history of esophageal cancer, smoking history and drinking history; furthermore, in during the study of confounding factors, increased the difficulty of the study; finally, we did not assess the dose–response relationship between green tea intake and risk of esophageal cancer.

Some studies have shown tea polyphenols to have various properties, including anti-tumor, antioxidant and anti-inflammatory effects (7,38); however, epidemiological studies have not yet reached a consensus over its protective effects (27,33,43). The many confounding factors, including dietary habits, the composition of the tea and temperature will affect the results of the study.

Green tea is low cost and controllable, so it will become an important research target in the field of esophageal cancer. From this study, we conclude that there are risks associated with drinking hot tea, but that green tea consumption could be a protective factor against the risk of esophageal cancer, especially in later life.

Acknowledgments

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Disclosure Statement

The authors report no conflicts of interests. We confirm that none of the authors are related to authors of studies included in the meta-analysis.

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