Nutrition and Cancer

Effects of Green Tea, Black Tea, and Coffee Consumption on the Risk of Esophageal Cancer: A Systematic Review and Meta-Analysis of Observational Studies

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Epidemiological studies regarding the associations of tea and coffee consumption with esophageal cancer (EC) risk are still inconsistent and this meta-analysis was conducted to examine these associations. PubMed, ISI -Web of Science, China National Knowledge Infrastructure (CNKI), and Chinese VIP database up to October 2011 were searched and manual search for reference lists of relevant studies were conducted. Random effects model was used to pool the odds ratios (OR). Twenty-four case-control and cohort studies with 7376 EC cases were included in this meta-analysis. The pooled OR of EC was 0.77 [95% confidence intervals (95% CI): 0.57, 1.04] for highest vs. non/lowest green tea consumption; but it was statistically significant for case-control studies (OR = 0.70; 95% CI: 0.51, 0.96) and for studies conducted in China (OR = 0.64; 95% CI: 0.44, 0.95). No significant association was observed for the highest vs. non/lowest black tea consumption against EC risk (OR = 1.35; 95% CI: 0.86, 2.11). A borderline significantly inverse association of highest vs. non/lowest coffee consumption against EC risk was found (OR = 0.88; 95% CI: 0.76, 1.01). In conclusion, our data showed that both green tea and coffee consumption, but not black tea consumption, have protective effects on EC.

INTRODUCTION

Esophageal cancer (EC) is the eighth most common cancer and the sixth leading cause of cancer deaths in the world (1). An estimated 482,300 new EC cases and 406,800 deaths occurred in 2008 worldwide, and men were 3 to 4 times more likely to get EC than women. Southern and Eastern Africa and Eastern Asia had the highest rates for EC, whereas the lowest rates were observed in Western and Middle Africa and Central America (2).

Tea, second only to water, is the most popularly consumed beverage in the world and it is grown in about 30 countries and produced from the leaves of the plant *Camellia sinensis*. Tea is classified into 3 major types: green tea (nonfermented), oolong tea (half-fermented), and black tea (fermented); green tea (about 20%) and black tea (about 78%) are the main tea types consumed in the world. Worldwide interest in tea, especially green tea, as a cancer prevention agent has been increasing, as it is nontoxic and effective in a wide range of organs (3). Several meta-analyses have examined the effects of tea on cancers (4–6), and it was also hypothesized that tea consumption had a protective effect on the risk of EC. Several case-control studies (7–11) found that tea consumption could significantly decrease the risk of EC, whereas other case-control and cohort studies didn't support its role in EC prevention (12–16). Results remain inconsistent, and no quantitative analysis has ever been conducted to examine this relation.

Coffee is also popular around the world and some observational studies reported that coffee intake could significantly decrease EC risk (17–19), whereas some others didn't find any significant association between coffee and EC risk (13, 20, 21). A meta-analysis has been conducted to assess the effect of coffee consumption on EC risk (22); however, the inclusion criteria is problematic and selection bias was considerable in this study.
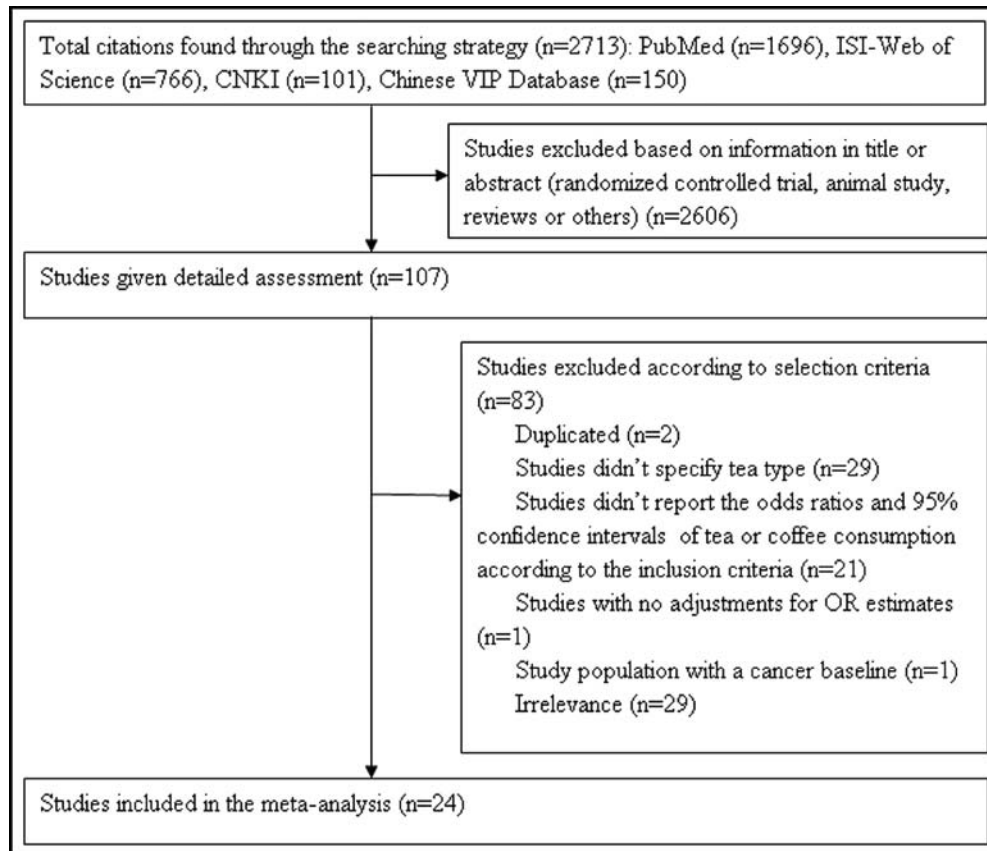
FIG. 1.   Flowchart for selection of articles.

To demonstrate the role of tea (green tea and black) and coffee consumption in EC prevention, we conducted this systematic review and meta-analysis to summarize odds ratios (OR) from cohort and case-control studies.

METHODS

Literature Search Strategy

We conducted a literature search in PubMed, ISI-Web of Science, China National Knowledge Infrastructure (CNKI), and Chinese VIP database up to October 2011, restricting to Chinese and English language. For PubMed searching the string '(tea OR polyphenol OR catechin, OR coffee OR caffeine OR beverages OR diet OR drinking) AND (esophageal OR esophagus OR oesophagus OR oesophageal) AND (cancer OR neoplasm OR tumor OR carcinoma)' was used; and for ISI-Web of Science, CNKI and VIP database, keywords *tea*, *polyphenol*, *catechin*, *coffee*, *caffeine*, *drinking*, *beverages*, together with *esophageal*, *esophagus*, *oesophagus*, *oesophageal*, *cancer*, *neoplasm*, *tumor*, *carcinoma* were used. References from the retrieved articles were reviewed to identify additional studies. Authors were contacted if we couldn't find the original articles, and two of them responded, providing their original articles. The search strategy followed the Meta-analysis of Observational Studies in

Epidemiology Guidelines (23). The flowchart for selection of articles is given in Fig. 1.

Inclusion and Exclusion Criteria

Two authors (JZ and JY) independently conducted the search and discrepancies were resolved through group discussion. Included studies needed to meet the following criteria: (a) studies were restricted to cohort or case-control study design; (b) relative risk (RR), hazard ratio (HR) or odds ratio (OR) with their corresponding 95% confidence intervals (CIs) of EC for tea (green tea or back tea) and coffee consumption were reported; (c) if the study population was duplicated in more than one study, the more recent publication was included.

Major reasons for exclusion of studies were 1) cross-sectional or experimental designs were used; 2) studies that didn't specify tea type (green or black tea); 3) duplicated studies; 4) studies with no adjusted OR, or studies that didn't report ORs or their 95% confidence intervals (95% CIs); 5) studies that only reported the OR in relation to beverage temperature; (f) and studies with a primary cancer baseline.

Data Extraction

The following data from each publication were extracted: first author's name, study design and period, country, gender, sample

size, number of events, adjusted covariates, methods of outcome assessment, methods of dietary assessment, tea type, cancer type, categories of green tea, black tea and coffee consumption, and their corresponding RRs, HRs, or ORs with 95% CIs for EC risk. The most adjusted risk estimate from each study was extracted.

Statistical Analyses

All of the statistical analyses were performed using STATA version 11.0 (StataCorp, College Station, TX). DerSimonian and Laird random-effects model, which takes into account both within- and between-study variability, was used to combine the ORs and they were weighted by the inverse of their variances. ORs from each study were transformed to their natural logarithm and the 95% CIs were used to calculate corresponding standard errors. METAN command was used to achieve the final ORs. Studies reporting ORs and their 95% CIs for both men and women were taken as two studies, and for a study in which both ESCC and EAC were reported, it was also taken as two studies. One study (24) reported ORs for people between 20~40 yr old and people above 40 yr old separately, and the ORs were pooled within the study using a random effects model.

Dose-response analyses for green tea and coffee consumption and EC was conducted according to Greenland and Longnecher (25) and Orsini et al. (26), and GLST command was used. Studies with 3 or more exposure categories were included according to this method. Variance-weighted least squares regression was used (13, 15, 20, 27, 28) to achieve the risk estimate if the number of cases or person-yr was not available. Midpoint of upper and lower boundaries was taken as the dose of the category if the study only reported the range of tea or coffee consumption; if the highest category was open-ended, we regarded it of the same amplitude as the preceding one; and the lowest boundary was set to zero if the lowest category was open. If tea consumption category was reported by gram of tea leaves, we considered 2.5 g tea leaves as approximately equivalent to one cup; and 150 mL coffee or tea consumption was regarded as one cup. Pooled ORs were achieved by pooling the study-specific slopes and weighted by the inverse of their variances. The final pooled OR was expressed as the risk of EC associated with every increment of 2 cups/day of tea or coffee consumption.

We assessed statistical heterogeneity with the Q and I^2 statistics (29). I^2 values of 25%, 50%, and 75% corresponded to cut-off points for low, moderate, and high degrees of heterogeneity. If heterogeneity was presented, subgroup analyses were conducted to examine the sources of heterogeneity. A sensitivity analysis (METANINF command) was conducted in which one study at a time was excluded to evaluate the influence of one individual study on the results. Publication bias was assessed using Begg's funnel plots and Egger's regression test (30). Asymmetry of funnel plot or P value (Egger's regression test) <0.10 was considered to possess publication bias. Trim and fill algorithm (31) was conducted if possible publication bias was found in our meta-analysis. This method was used to identify and correct for the asymmetry of funnel plot from publication bias and provide an adjusted summary effect estimate based on all the studies, including the estimated missing studies.

RESULTS

Study Characteristics

The main characteristics of the included studies in this meta-analysis are indicated in Table 1. This meta-analysis included 24 published studies, with totally 7376 EC cases, 487,894 controls in 20 case-control studies (7–12,14–16,18,19,21, 24,27,28,32–36) and 8,874,734 person-yr in 4 cohort studies (13,17,20,37). Twelve studies (7–16,27,32) and 3 studies (12,16,19) reported the associations of EC with green tea and black tea respectively, and 14 studies (13,16–21,24,28,33–37) reported the association of coffee consumption with EC risk. Three studies (13,16,19) reported both the coffee and tea consumption in relation to EC risk. Of all the identified studies, 10 were from China (7–11,14,19,24,27,32), 4 from Japan (13,15–17), 1 from Iran (12), 1 from India (21), 1 from Turkey (36), 1 from South America (35), 1 from United States (20), and 5 from Europe (18,28,33,34,37).

Green and Black Tea Consumption and EC Risk

There were 13 published articles (7–16,19,27,32) that examined the relation of EC risk with green or black tea consumption. All of the included studies were from Asia, of which 9 from China (7–11,14,19,27,32), 3 from Japan (13,15,16), and 1 from Iran (12). Only 1 study was a cohort study (13), whereas the others were all case-control studies. One study (10) with 93.3% of the tea drinkers consumed green tea was considered as green tea consumption study in this meta-analysis. Two studies (11,27) were published in Chinese.

For green tea consumption, OR of the EC for highest vs. non/lowest green tea consumption was 0.77 (95% CI: 0.57, 1.04) (Fig. 2); and there was a high degree of heterogeneity ($I^2 = 72\%$, P for heterogeneity < 0.001). Sensitivity analysis indicated that the OR became statistically significant (OR = 0.72; 95% CI: 0.54, 0.97) after exclusion of Wu et al. (14). Slight publication bias was observed from Begg's funnel plot (Fig. 3) and Egger's test ($P = 0.05$). Trim and fill method didn't change the data.

Subgroup analyses of the relationship between green tea and EC risk (Table 2) found that pooled OR of EC among case-control studies was statistically significant (OR = 0.70; 95% CI: 0.51, 0.96) for green tea consumption; and for studies conducted in China, the OR was also statistically significant (OR = 0.64; 95% CI: 0.44, 0.95). In addition, the inverse association between green tea consumption and EC risk was significant for the studies, in which the ORs were adjusted for tea temperature (OR = 0.69; 95% CI: 0.49, 0.96). And studies of women showed more evident inverse association (OR = 0.32; 95% CI: 0.17, 0.59) than the overall risk estimate, and no heterogeneity was observed ($I^2 = 0$, P for heterogeneity = 0.71). However,

TABLE 1
Characteristics of studies included in this meta-analysis

Studies (references)	Country; design	Study period	Men (%)	Cancer type Cancer type	Case/control (size of cohort)	Tea consumption levels (highest vs. none/lowest)	Odds ratio (95% confidence intervals)	Adjustments
Green tea consumption								
Gao et al., men, 1994 (8)	China; CC	1990–1993	100	NR	416/654	≥200 g/month vs. nondrinker	0.79 (0.56, 1.13)	Age, education, birthplace, cigarette smoking, and alcohol intake
Gao et al., women, 1994 (8)	China; CC	1990–1993	0	NR	242/658	≥150 g/month vs. nondrinker	0.34 (0.17, 0.69)	Age, education, birthplace, and cigarette smoking
Inoue et al., 1998 (16)	Japan; CC	1990–1995	29.9	NR	185/21,128	≥7 cups/day vs. rarely	1.14 (0.55, 2.34)	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
Wang et al., 1999 (11)	China; CC	1994–1995	51.5	NR	68/68	Yes vs. no	0.20 (0.06, 0.67)	Education level, smoking, and alcohol consumption
Takezaki et al., 2000 (15)	Japan; CC	1988–1997	100	93% ESCC, 7% EAC	284/11,936	≥7 cups/day vs. occasionally or less	0.70 (0.40, 1.20)	Age, year and season of visit, smoking status, and drinking status
Gao et al., 2002 (10)	China; CC	1998–2000	62.4	NR	141/223	Yes vs. no	0.45 (0.26, 0.78)	Age, sex, smoking, alcohol drinking, tea consumption, raw vegetables, pickled vegetables, fruit, meat, soybean products, GSTT1, and GSTM1

Study	Country; Design	Year	% male	Histology	Cases/Controls	Comparison	RR (95% CI)	Adjustments
Mu et al., 2003 (27)	China; CC	2000	80	NR	218/415	≥250 g/month vs. never	0.58 (0.35, 0.97)	Age, gender, education level, smoking, eating speed, regular diet, salt consuming, and vegetable
Ishikawa et al. cohort 1, 2006 (13)	Japan; Cohort	1984–1993	100	NR	38/67,075 person-yr	≥5 cups/day vs. never	1.78 (0.66, 4.82)	Age in years, cigarette smoking, alcohol drinking, coffee consumption, and black tea consumption
Ishikawa et al. cohort 2, 2006 (13)	Japan; Cohort	1990–1998	100	NR	40/129,611 person-yr	≥5 cups/day vs. never	1.61 (0.71, 3.66)	Age in years, cigarette smoking, alcohol drinking, coffee consumption, and black tea consumption
Wang et al., 2006 (9)	China; CC	2002–2003	56.1	ESCC	107/107	Yes vs. no	0.13 (0.03, 0.62)	Family history of cancer, eating fast, utensil clean up, *H.pylori* infection and esophageal lesions
Wang et al. men, 2007 (7)	China; CC	2004–2006	100	ESCC	223/252	Yes vs. no	1.37 (0.95, 1.98)	Age, marital status and education years
Wang et al. women, 2007 (7)	China; CC	2004–2006	0	ESCC	132/156	Yes vs. no	0.26 (0.07, 0.94)	Age, marital status and education years
Wu et al. Dafeng, 2009 (14)	China; CC	2003–2007	69.7	NR	637/1938	≥250 g/month vs. never	1.00 (0.60, 2.00)	Age, gender, education level, income 10 years before, cancer family history, BMI, pack-year of smoking, alcohol drinking, tea temperature

(Continued on next page)

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TABLE 1
Characteristics of studies included in this meta-analysis (*Continued*)

Studies (references)	Country; design	Study period	Men (%)	Cancer type	Case/control (size of cohort)	Tea consumption levels (highest vs. none/lowest)	Odds ratio (95% confidence intervals)	Adjustments
Wu et al., 2009 (14)	China; CC	2003–2007	81.9	NR	883/1941	≥250 g/month vs. never	1.60 (1.10, 2.20)	Age, gender, education level, income 10 years before, cancer family history, BMI, pack-year of smoking, alcohol drinking, tea temperature
Islami et al., 2009 (12)	Iran; CC	2003–2007	49.1	ESCC	300/571	Daily vs. never	0.89 (0.38, 2.09)	Ethnicity, daily vegetable intake, alcohol consumption, tobacco or opium ever use, duration of residence in rural areas, education level, car ownership, and tea temperature
Chen et al., 2011 (32)	China; CC	2004–2010	68	ESCC	150/300	>250 g/month vs. never	0.92 (0.49, 2.32)	Age, sex, education level, annual income, cancer family history, smoking and drinking status
Black tea consumption								
Inoue et al., 1998 (16)	Japan; CC	1990–1995	29.9	NR	185/21,128	Daily vs. rarely	1.03 (0.53, 2.00)	Green tea consumption, coffee consumption, gender, age at first hospital visit, year (continuous) and season at first hospital visit, habitual alcohol drinking, regular physical exercise, fruit intake, rice intake, beef intake

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Reference	Country; Design	Period	%	Type	Cases/Controls	Comparison	OR (95% CI)	Adjustment
Islami et al., 2009 (12)	Iran; CC	2003–2007	49.1	ESCC	300/571	≥1726 mL/day vs. 0–675 mL/day	1.83 (0.93, 3.59)	Ethnicity, daily vegetable intake, alcohol consumption, tobacco or opium ever use, duration of residence in rural areas, education level, car ownership, and tea temperature
Chen et al., 2009 (32)	China_Taiwan; CC	1996–2005	100	ESCC	151/256	Yes vs. no	1.20 (0.30, 5.10)	Age, educational levels, ethnicity, source of hospital, smoking, alcohol drinking, and areca nut chewing
Coffee consumption								
La Vecchia et al., 1989 (33)	Italy; CC	1983–1988	77.5	NR	209/1944	≥3 cups/day vs. ≤ 1cup/day	0.98 (0.70, 1.37)	Age, sex, social class, education, marital status, smoking, alcohol.
Garidou et al._ESCC, 1996 (34)	Greece; CC	1989–1991	70.8	ESCC	43/200	1 cup/day vs. never	1.15 (0.84, 1.58)	Gender, age, birthplace, schooling, height, analgesics, alcohol drinking, tobacco smoking, and energy intake
Garidou et al._EAC, 1996 (34)	Greece; CC	1989–1991	73.4	EAC	56/200	1 cup/day vs. never	1.11 (0.86, 1.43)	Gender, age, birthplace, schooling, height, analgesics, alcohol drinking, tobacco smoking, and energy intake

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TABLE 1
Characteristics of studies included in this meta-analysis (*Continued*)

Studies (references)	Country; design	Study period	Men (%)	Cancer type	Case/control (size of cohort)	Tea consumption levels (highest vs. none/lowest)	Odds ratio (95% confidence intervals)	Adjustments
Inoue et al., 1998 (16)	Japan; CC	1990–1995	29.9	NR	185/21,128	≥3 cups/day vs. rarely	0.79 (0.46, 1.36)	Black tea consumption, green tea consumption, gender, age at first hospital visit, year (continuous) and season at first hospital visit, habitual alcohol drinking, regular physical exercise, fruit intake, rice intake, beef intake
Terry et al., 2000 (28)	Sweden; CC	1994–1997	83.7	EAC	185/815	>7 cups/day vs. 0–2 cups/day	0.80 (0.50, 1.40)	Age, gender, body mass index, total energy, energy adjusted alcohol, total fruit and vegetable intake, cigarette smoking, and use of antacids
Castellsague et al._men, 2000 (35)	Argentina, Brazil, Uruguay and Paraguay; CC	1986–1992	100	ESCC	550/1,198	500 mL+/day vs. never	1.19 (0.80, 1.78)	Age group, hospital, residency, years of education, average number of cigarettes/day and average amount of pure ethanol/day
Castellsague et al._women, 2000 (35)	Argentina, Brazil, Uruguay and Paraguay; CC	1986–1992	0	ESCC	144/309	500 mL+/day vs. never	1.68 (0.72, 3.93)	Age group, hospital, residency, years of education, average number of cigarettes/day and average amount of pure ethanol/day
Onuk et al., 2002 (36)	Turkey; CC	1999–2000	57.6	NR	44/100	High vs. low	0.80 (0.30, 1.60)	Tobacco use, fruit, vegetable, coffee, and pickle intake and type of bread

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Study	Location; Design	Years	%	Type	Cases/Controls	Exposure	RR (95% CI)	Adjustments
Tavani et al., 2003 (18)	Italy and Switzerland; CC	1991–1997	77.1	NR	395/1,066	>3 cups/day vs. ≤1 cups/day	0.60 (0.40, 0.90)	Age, sex, education, tobacco smoking, alcohol drinking, and intake of fruit and vegetables
Hung et al., 2004 (24)	China–Taiwan; CC	1996–2002	100	EAC	284/480	≥1 time/wk vs. <1 time/wk	20–40 yr: 0.70 (0.40, 1.20) >40 yr: 0.70 (0.40, 1.20)	Age, educational levels, ethnicity, source of hospital, smoking, alcohol drinking and areca nut chewing
Ishikawa et al., 2006 (13)	Japan; Cohort	1984–1993 for Cohort 1; 1990–1998 for Cohort 2	100	NR	78/196,686 person–yr	≥3 cups/day vs. never	0.94 (0.36, 2.45)	Age in years, cigarette smoking, alcohol drinking, green tea consumption, and black tea consumption
Naganuma et al., 2008 (17)	Japan; Cohort	1990–2003	48.2	NR	112/495,138 person–yr	≥1 cups/day vs. never	0.60 (0.37, 0.97)	Age in years, sex, body mass index, alcohol consumption, cigarette smoking, consumption of vegetables and fruit, and green tea consumption
Ganesh et al., 2009 (21)	India; CC	1989–1992	55.6	ESCC	442/1628	Yes vs. no	0.60 (0.50, 1.60)	Age, place of residence, religion and occupation, habits, dark green leafy, root vegetables, sprouts, dry fish, fresh fish, meat, and tea
Chen et al., 2009 (19)	China–Taiwan; CC	1996–2005	100	ESCC	324/702	≥1 time/wk vs. <1 time/wk	0.60 (0.40, 1.00)	Age, educational levels, ethnicity, source of hospital, smoking, alcohol drinking, and areca nut chewing

(Continued on next page)

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TABLE 1
Characteristics of studies included in this meta-analysis (*Continued*)

Studies (references)	Country; design	Study period	Men (%)	Cancer type	Case/control (size of cohort)	Tea consumption levels (highest vs. none/lowest)	Odds ratio (95% confidence intervals)	Adjustments
Ren et al. ESCC, 2010 (20)	United States; Cohort	1995–2003	59.5	ESCC	123,305/2,584,953 person-yr	>3 cups/day vs. <1 cup/day	1.53 (0.83, 2.82)	Age, sex, tobacco smoking, alcohol drinking, BMI, education, ethnicity, usual physical activity throughout the day, vigorous physical activity and daily intake of fruit, vegetables, red meat, white meat, and calories
Ren et al. EAC, 2010 (20)	United States; Cohort	1995–2003	59.5	EAC	305/2,584,953 person-yr	>3 cups/day vs. <1 cup/day	0.81 (0.57, 1.16)	Age, sex, tobacco smoking, alcohol drinking, BMI, education, ethnicity, usual physical activity throughout the day, vigorous physical activity and daily intake of fruit, vegetables, red meat, white meat and calories
Tverdal et al., 2011 (37)	Norway; Cohort	1985–1999	48	ESCC	96/5,597,957 person-yr	>9 cups/day vs. 1–4 cups/day [a]	0.97 (0.50, 1.88)	Sex, daily smoking, body mass index and education

NR = not reported; CC = case-control study; ESCC = esophageal squamous cell carcinoma; EAC = esophageal adenocarcinoma.
[a]Highest *vs.* second lowest category as reference group of this study was the second lowest category.

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TABLE 2
Subgroup analyses of the included studies for the associations of green tea and coffee consumption with esophageal cancer risk

Subgroup	No. of studies	Odds ratio	95% confidence intervals	Heterogeneity I^2 (%)	P	Degree
		Green tea consumption				
All studies	16	0.77	0.57, 1.04	72	< 0.001	Moderate
Case-control studies	14	0.70	0.51, 0.96	73.8	< 0.001	Moderate
Population-based case-control studies	11	0.64	0.43, 0.95	79.3	< 0.001	High
Hospital-based case-control studies	3	0.86	0.58, 1.25	0	0.563	Low
From China	11	0.64	0.44, 0.95	79.4	< 0.001	High
Out of China	3	0.85	0.57, 1.25	0	< 0.001	Low
Prospective cohort studies	2	1.68	0.89, 3.16	0	< 0.001	Low
China	11	0.64	0.44, 0.95	79.4	< 0.001	High
Japan	4	1.1	0.71, 1.72	29.7	0.234	Moderate
Iran	1	0.89	0.38, 2.09			
Histology						
ESCC	5	0.66	0.33, 1.33	71.5	0.007	Moderate
NR	11	0.79	0.56, 1.12	74	< 0.001	Moderate
Gender						
Men	5	1.07	0.75, 1.52	54	0.069	Moderate
Women	2	0.32	0.17, 0.59	0	0.71	Low
Both	9	0.70	0.45, 1.10	75.4	< 0.001	High
Adjusted for tea temperature	3	0.69	0.49, 0.96	69.9	< 0.001	Moderate
Not adjusted for tea temperature	13	1.27	0.88, 1.85	28.5	0.247	Moderate
Adjusted for alcohol drinking or smoking	13	0.81	0.59, 1.09	68.8	< 0.001	Moderate
Not adjusted for alcohol drinking or smoking	3	0.41	0.08, 1.98	85.5	0.001	High
Coffee consumption						
All studies	17	0.88	0.76, 1.01	38.4	0.055	Moderate
Case-control studies	12	0.88	0.74, 1.04	44.8	0.046	Moderate
Prospective cohort studies	5	0.88	0.65, 1.19	31.3	0.213	Moderate
Asia	7	0.67	0.55, 0.82	0	0.952	Low
Europe	6	0.95	0.78, 1.15	38.5	0.149	Moderate
Others	4	1.13	0.82, 1.57	40.3	0.17	Moderate
Histology						
ESCC	8	1.00	0.80, 1.25	44.1	0.084	Moderate
EAC	3	0.88	0.67, 1.17	55.5	0.106	Moderate
NR	6	0.69	0.56, 0.87	0	0.869	Low
Gender						
Men	4	0.82	0.58, 1.15	48.6	0.12	Moderate
Women	1	1.68	0.72, 3.93			
Both	12	0.88	0.75, 1.04	36.6	0.098	Moderate
Adjusted for alcohol drinking or smoking	16	0.89	0.77, 1.03	37.6	0.064	Moderate
Not adjusted for alcohol drinking or smoking	1	0.6	0.50, 1.60			
Adjusted for energy	5	1.04	0.86, 1.25	21.1	0.28	Low
Not adjusted for energy	12	0.80	0.67, 0.94	25.5	0.193	Moderate

NR = not reported; ESCC = esophageal squamous cell carcinoma; EAC = esophageal adenocarcinoma.
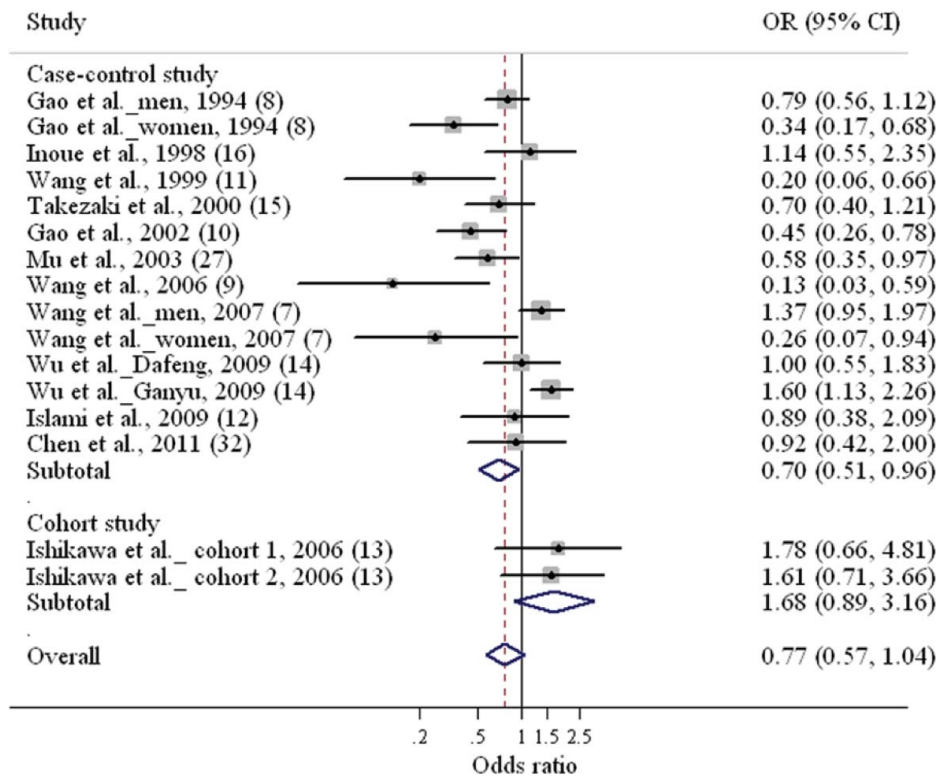
FIG. 2.   Pooled odds ratio (OR) of esophageal cancer for highest vs. non/lowest green tea consumption. Square indicates adjusted OR from each study and square size indicates the study-specific weight. The unshaded diamond reflects the pooled OR and its 95% confidence intervals (CIs). The horizontal line indicates 95% of each study (Color figure available online).

dose-response analysis didn't find significant inverse associa-
tion for every 2 cups/day increment of green tea consumption
against EC risk (OR = 0.97; 95% CI: 0.87, 1.08).

For black tea consumption, the OR of EC for highest vs.
non/lowest black tea consumption was 1.35 (95% CI: 0.86,
2.11), and there were only 3 studies (12,16,19) included in this
meta-analysis. No heterogeneity ($I^2 = 0$, P for heterogeneity
= 0.486) or publication bias (P for Egger's test = 0.925) was
observed.

Coffee Consumption and EC Risk

Fourteen studies (13,16–21,24,28,33–37) were included
regarding the relation of coffee consumption with EC
risk. Four of the included studies were cohort stud-
ies (13,17,20,37), whereas others were case-control stud-
ies (16,18,19,21,24,28,33–36). Of all the identified studies,
7 were from Asia (13,16,17,19,21,24,36), 5 from Europe
(18,28,33,34,37), 1 from the United States (20), and 1 from
South America (35). One study (37) with the second lowest
category as the reference group was also included and OR of
the highest vs. second lowest category was used for the meta-
analysis. One study (38) was excluded as no adjustment for OR
was presented. One study (39) in which the patients had head
and neck cancer baseline was excluded.

The inverse association of coffee consumption with EC risk
was marginally significant (OR = 0.88; 95% CI: 0.76, 1.01;
$I^2 = 38.4\%$, P for heterogeneity = 0.055) (Fig. 4). Sensitivity
analysis didn't change the result remarkably. Exclusion of the
study (37) with the second lowest category as the reference
group didn't significantly change the result (OR = 0.87; 95%
CI: 0.75, 1.01; $I^2 = 42\%$, P for heterogeneity = 0.039).No
publication bias was detected whether by Begg's funnel plot
(Fig. 5) or by Egger's test (P = 0.53).

Subgroup analyses showed that pooled OR was 0.67 (95%
CI: 0.55, 0.82) for studies conducted in Asia and it was more
evident than the overall risk estimate, and no heterogeneity was
found ($I^2 = 0$, P for heterogeneity = 0.952) in Asian studies.
Studies in which energy was not adjusted showed significant
inverse association of coffee consumption against EC risk (OR
= 0.80; 95% CI: 0.67, 0.94). But the dose-response analysis
didn't find significant inverse association for every 2 cups/day
increment of coffee consumption against EC (OR = 1.00; 95%
CI: 0.89, 1.12).

DISCUSSION

The present meta-analysis was the first quantitative system-
atic review regarding the associations of green tea and black
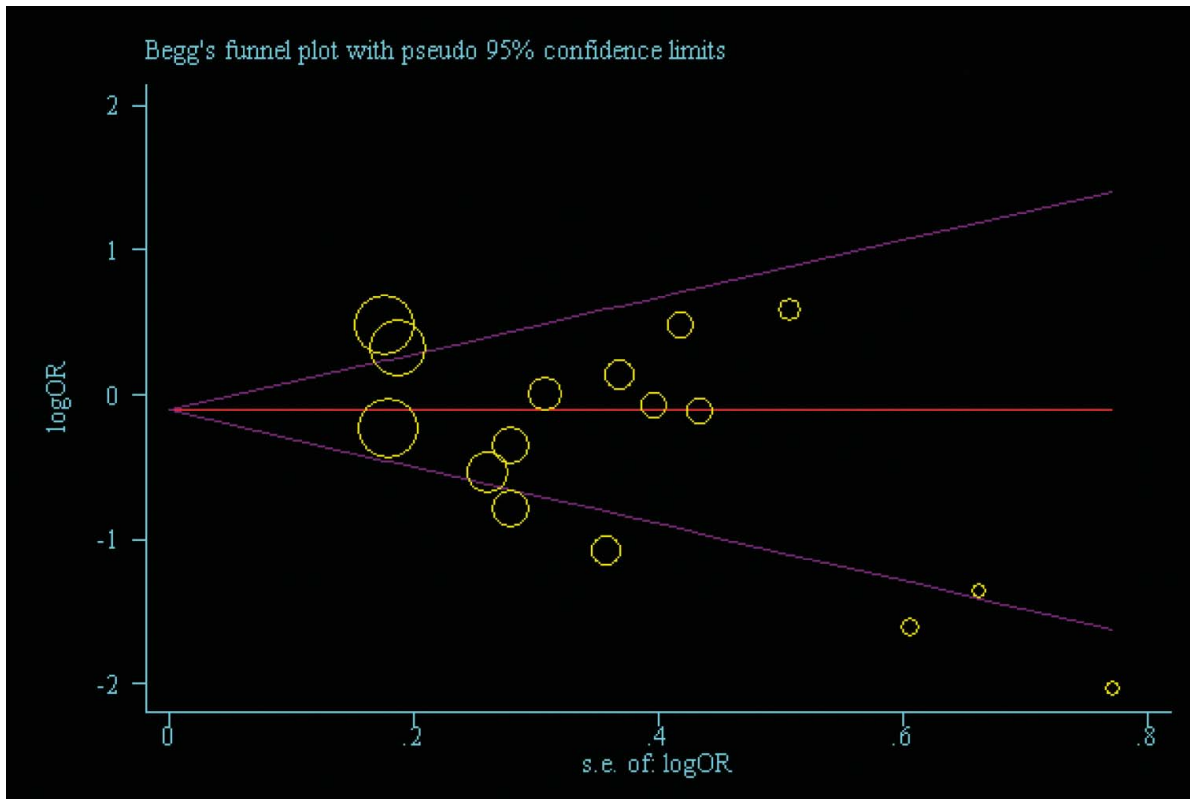tea consumption with EC risk, and this study included more

FIG. 3. Begg's funnel plot indicating the publication bias of included studies in relation to the association of green tea consumption against esophageal cancer risk. The funnel plot is roughly symmetrical if the publication bias is not present. OR = odds ratio (Color figure available online).

comprehensive studies with regard to the relationship between coffee consumption and EC risk than previous meta-analysis (22).

For green tea consumption, all the studies were conducted in Asia. The most evident inverse association of green tea with EC risk was found in studies from China, and this might be due to higher levels of green tea consumption in Chinese population. Among the included studies, there was only 1 cohort study (including two cohorts from Japan) (13), and a statistically significant inverse association of green tea with EC risk appeared after exclusion of this study. Cohort studies possess less recall and selection bias, and so more cohort studies are warranted to further examine the association of green tea consumption with EC.

Further subgroup analyses indicated that pooled OR of EC with regard to green tea consumption for studies in women, rather than men, was statistically significant, and this was consistent with the well-known fact that men showed 3 to 4 times more likely to develop EC than women, which was possibly due to the fact that men are more likely to smoke tobacco and drink excess alcohol compared with women. However, the studies on green tea consumption and EC risk in women were rather limited, more research in relation to the association of green tea with EC risk in women are needed.

Marginally significant inverse association was observed for coffee consumption and EC risk. The association became more evident in Asian population, and this may due to Asian populations having different genetic background and responding differently to the same nutrition exposure when compared with other populations. Furthermore, the overall dietary pattern in Asia, especially in China and Japan (40), is different from that in western countries, which might contribute to the different EC risk to coffee consumption. Total energy adjustment may also affect the pooled risk estimate, as significant protective effect of coffee against EC risk was found for studies that didn't adjust for energy, whereas no significant inverse association was observed in studies that energy was adjusted. According to subgroup analyses, there was no statistically significant association of coffee intake with either esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EAC). However, studies that reported the results of ESCC and EAC separately were limited and for those studies in which EC subtype was not clarified, the inverse association of coffee intake against EC risk was significant. So the effects of coffee intake on ESCC and EAC are still inconclusive and need further confirmation.

The protective effects of tea and coffee on EC are biologically plausible. Numerous in vitro and in vivo studies (41,42) have demonstrated the role of tea as a potential cancer
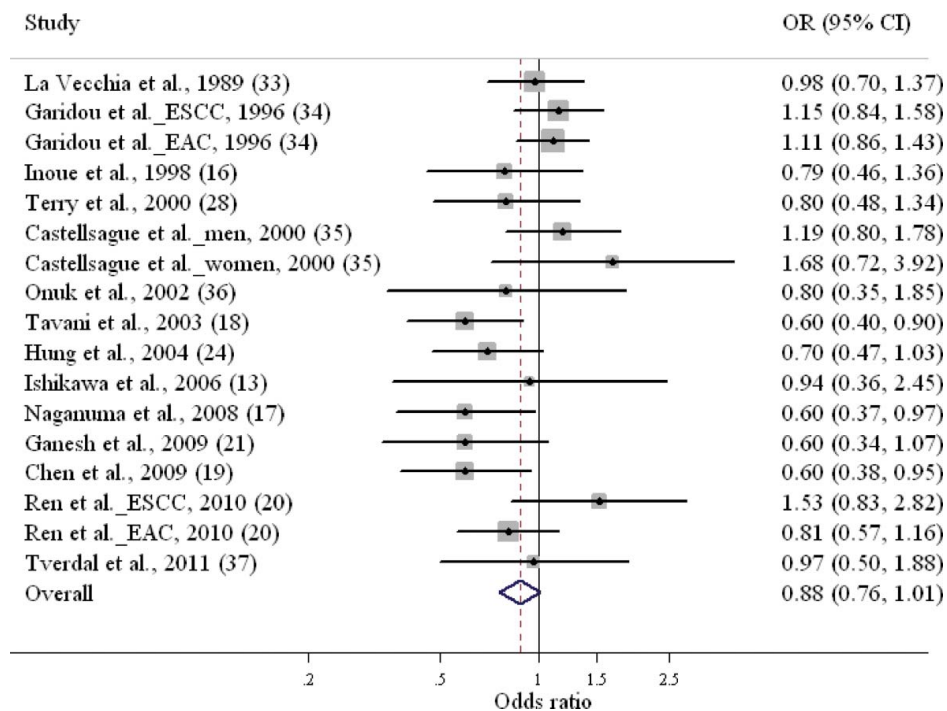
FIG. 4.   Pooled odds ratio (OR) of esophageal cancer for highest vs. non/lowest coffee consumption. Square indicates adjusted OR from each study and square size indicates the study-specific weight. The unshaded diamond reflects the pooled OR and its 95% confidence intervals (CIs). The horizontal line indicates 95% of each study (Color figure available online).

preventive agent for its antioxidative, antiinflammatory, antimicrobial, and immunostimulant effects according to experimental and epidemiological studies (43,44). Tea administration could inhibit the N-nitrosomethylbenzylamine-induced esophageal tumorigenesis in rats (45), and EC prevention activity of tea in animal model was attributed to its flavonoids and other beneficial compounds (45,46). Coffee contains numerous anticarcinogenic components, of which caffeine suppresses cell growth signal-induced activation of cyclin-dependent kinase 4 (47), whereas cafestol and kahweol could inhibit DNA damage (48). However, the mechanism for the protective effect of coffee on EC still warrants further elucidation.

Nevertheless, high temperature beverage drinking which could cause recurrent thermal injury to the esophageal mucosa was supposed to increase the risk of EC (49). Wu et al. (14) found that high temperature green tea consumption could significantly increase EC risk, although no significant association was observed in normal temperature groups. Hot coffee consumption was found to have a significant inverse association with EC risk, but the protective effect disappeared for very hot coffee (35). Subgroup analyses indicated that for the studies that adjusted for green tea temperature, the pooled OR of EC in relation to green tea consumption was statistically significant. So the overall protective effect of green tea per se on EC risk might be underestimated because of the effects of tea temperature. The inverse association of coffee and tea against EC risk

might be more evident if taking the beverage temperature into consideration.

This meta-analysis possesses several advantages. Firstly, there were as many as 7376 EC cases, 487,894 controls, and 8,874,734 person-yr included in this meta-analysis, and the large sample size would confer robust data to the results. Secondly, both English and Chinese articles were achieved for this meta-analysis. As green tea consumption was popular in China and most of the studies with regard to the association of green tea against EC risk were conduced in China, inclusion of studies published in Chinese would largely reduce the language bias. Thirdly, for coffee consumption, the former meta-analysis (22) only included studies that specified EC subtype (ESCC or EAC), many more studies that didn't specify EC subtype were excluded, and selection bias was considerable in the study. In contrast, our meta-analysis included all the related studies and used subgroup analyses to further examine the effects of coffee consumption on the risk of EC subtypes. Dose-response analysis in relation to coffee and ES risk was also conducted in the present study, which made the data more robust and persuasive than previous meta-analysis.

There are also some limitations in the present study. Firstly, observational studies couldn't avoid potential confounding and bias, and most of the included studies were case-control studies, which would make the results more likely attributable to recall and selection bias. Secondly, only a few studies adjusted
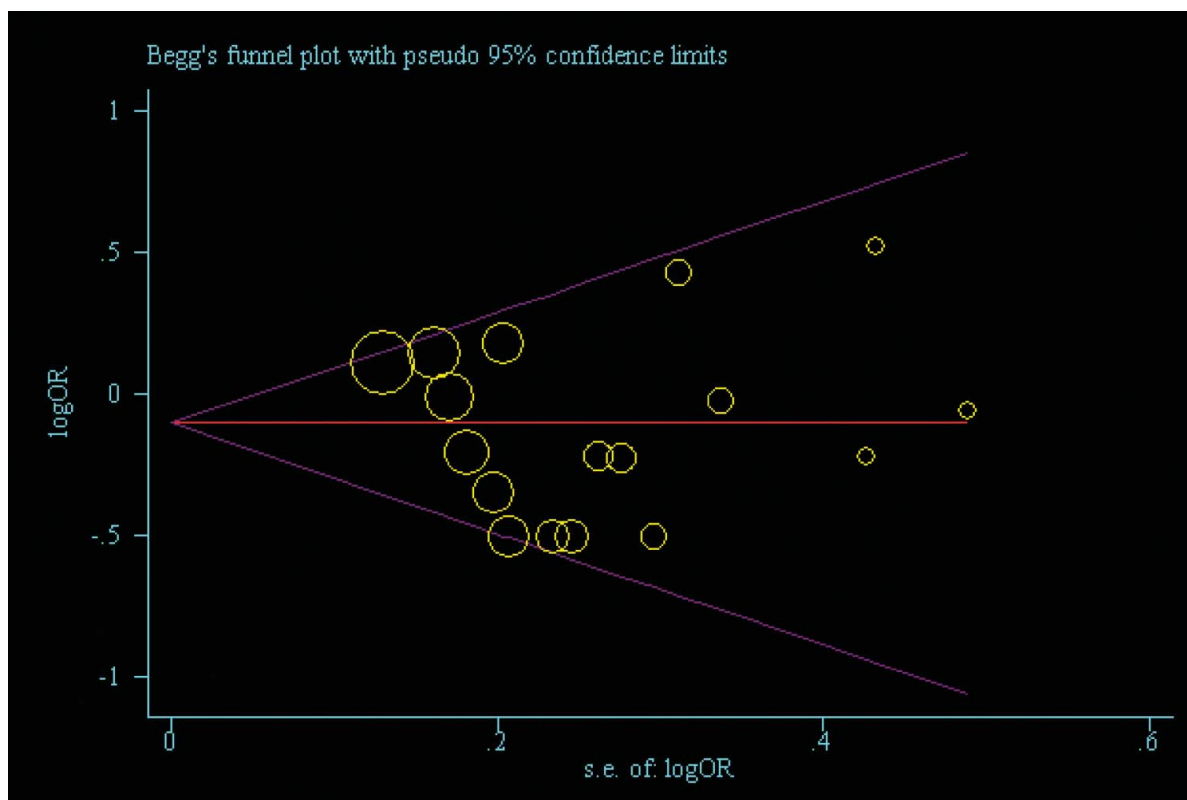
FIG. 5.   Begg's funnel plot indicating the publication bias of included studies in relation to the association of coffee consumption against esophageal cancer risk. The funnel plot is roughly symmetrical if the publication bias is not present. OR = odds ratios (Color figure available online).

for tea or coffee temperature for EC risk and this would make the results confounded by the beverage temperature. Thirdly, all the studies for tea consumption and EC risk are from Asia, especially from China, and more studies outside of Asia were warranted to further examine the role of green tea in EC prevention. In addition, for black tea consumption, many studies were excluded as they didn't specify tea type, and exclusion of these studies might bias the final results.

In conclusion, this meta-analysis indicated that green tea consumption was slightly inversely associated with EC risk, and it was more evident in Chinese population; no protective effect was found for black tea consumption. Coffee consumption showed marginally protective effect on EC, especially in Asian population. Further prospective cohort studies are warranted to examine the relationships of tea and coffee with EC risk.

ACKNOWLEDGMENTS

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