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Association between tea drinking and endometrial cancer risk: a meta-analysis

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Abstract

The meta-analysis on observational studies was conducted to explore the association of tea drinking with endometrial cancer (EC). The MEDLINE and EMBASE databases were searched until August 2018. Altogether 19 works on tea drinking that involved 6,797 EC patients and 858,780 normal controls, including 10 case control and 9 cohort studies, were enrolled. The pooled relative risk (RR) of EC for the greatest tea consumption compared with the lowest level was 0.99 (95% CI: 0.94-1.04; I2 = 53%, p for heterogeneity = 0.005). In terms of study design, pooled RRs were 0.83 (95% CI: 0.73-0.95) and 1.02 (95% CI: 0.96-1.08) for case-control and cohort studies, respectively. By study region, the pooled RRs were 1.01 (95% CI: 0.95-1.08) in Europe, 1.06 (95% CI: 0.94-1.20) in USA/Canada, and 0.80 (95% CI: 0.69-0.93) in Asia. By additional subgroup analysis, inverse association was shown in green tea (RR 0.73, 95% CI: 0.64-0.84) and black tea (RR 0.65, 95% CI: 0.46-0.92). No difference was detected in smoking status or body mass index. To sum up, although tea does not have obvious protective effect against endometrial cancer, either black tea or green tea protects against EC. Moreover, Asian studies show that tea drinking protects against EC.

Keywords: endometrial cancer; meta-analysis; observational study; risk; tea.

Practical Application: We updated the epidemiological knowledge regarding the relationship of tea drinking with the EC risk.

1 Introduction

Endometrial cancer (EC) is frequently seen among females and has a large geographic variation in incidence and mortality rates (Brocker et al., 2014; Svampane et al., 2014; Torre et al., 2015). With the increase of obesity prevalence, reduced physical activity and increased life expectancy, it is estimated that EC incidence may further increase (Gao et al., 2016). The age standardized annual incidence rate (ASR) of EC is 14.7/100,000 women among the developed countries, which increases by over twice compared with that of 5.5/100,000 women among the developing countries (Olesen et al., 2014). It is predicted that 61380 new EC patients are diagnosed in United States annually (Siegel et al., 2017).

Tea ranks the second place among the widely consumed beverages globally (Zhou et al., 2016), which potentially protects against certain types of cancers. There are various antioxidants in the tea, including catechins, flavonoids, theaflavins and thearubigins, and some of them are suggested to have possible effect against carcinogenesis (Zhou et al., 2016). The possible mechanisms are free radical scavenging, inflammation suppression, mitigated DNA damage, improved insulin sensitivity, increased sex hormone-binding globulin (SHBG) content and reduced circulating glucose and free estradiol levels (Arnlöv et al., 2004; Bag & Bag, 2018; Grosso et al., 2017a; Gunter et al., 2012; Pérez-Jiménez et al., 2010; Tej & Nayak, 2018; Yang et al., 2009).

There are some meta-analyses (Butler & Wu, 2011; Je & Park, 2015; Tang et al., 2009; Yang et al., 2015; Zhou et al., 2016) on the relationship between tea and EC incidence. However, the conclusions are controversial. Je & Park (2015) and Yang et al. (2015) reported that tea drinking was not related to the EC risk, whereas Tang NP (Tang et al., 2009) suggested that tea drinking potentially decreased the EC risk. Since 2016, new studies have been conducted, which revealed that tea consumption showed either no obvious effects (Arthur et al., 2018) or adverse effects (Gao et al., 2016) on endometrial cancer. Except that, published meta-analyses did not classify explicitly the types of tea. Herein, for updating the epidemiological knowledge regarding the relationship of tea drinking with the EC risk and for exploring the heterogeneities across diverse tea types in relation to EC, the present meta-analysis on observational studies was carried out.

2 Materials and methods

2.1 Search strategy and study selection

Eligible studies were retrieved against MEDLINE and EMBASE electronic databases from inception to July 2018 with no restrictions on language or publication status. In this meta-analysis, search terms including "(tea OR black tea OR green tea OR flavonoid OR catechin OR thearubigin OR theaflavin) AND (corpus uteri OR endometrial OR endometrium OR uterus OR uterine) AND (cancer OR carcinoma OR tumor OR tumour OR neoplasm)" were adopted. Additionally, the published reviews and all references cited in those screened studies were manually retrieved to found more related articles. Studies conforming to the following criteria were shown below: (1) types of studies: case-control or cohort studies; (2) the outcome of interest: EC incidence; (3) the exposure of interest: tea consumption without limitation on tea types. Studies with only the abstract

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available were excluded. For duplicated publications, the latest article or the article published in the more influential journal was enrolled into this study. In the research of Uccella et al. (2013), the participants were classified as 2 groups according to EC type and both groups were analyzed independently. To reduce the error of data inclusion, we classified this study as two independent studies, which were marked as Uccella et al. (2013) I and Uccella et al. (2013) II.

2.2 Data extraction

Two investigators of this article, i.e. Yu GAO and Zhihong CAO, independently performed the initial screening and extraction. Three additional investigators of this article, i.e. Yanmei ZHAO, Lihong TANG and Hongjuan ZHANG, evaluated each eligible study independently and collected related information following those meta-analysis of observational studies in epidemiology (MOOSE) guidelines (Stroup et al., 2000). Any disagreement between them was settled down via the opinion of a third investigator of this article, i.e. Fushun ZHOU, until a consensus was reached. Data below were collected from every article, including first author last name, study design, publication year, control type, origin country, research time and follow-up period, case number and control/subject number, possible confounders, relative risks (RRs) in case-control studies, hazard ratio (HR) in cohort studies, multivariable-adjusted RRs in every article, and corresponding 95% CIs regarding the relationship of coffee drinking and the EC risk.

2.3 Quality analysis

The Newcastle-Ottawa Quality Assessment Scale was adopted for assessing study quality (Stang, 2010; Wells et al., 2014), which includes one item of comparability and three items of outcome. NOS grade scores of included studies were described qualitatively in Table 1, which showed that all included studies were with high scores.

2.4 Statistical analysis

The present meta-analysis was carried out by the use of Review Manager 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Because EC is rare and its HR was close to its RR value, results were presented in the manner of RR in the present work. Forest plots were drawn to present results, in which the diamond stands for pooled RR, while the data marker size (square) was associated with the inverse of natural logarithm variance for RR in every article. The data point scattering level and CIs overlapping were inspected, meanwhile, Q and I^2 statistics were verified to evaluate heterogeneities. Typically, $I^2 \leq 25\%$ represented low heterogeneity; I^2 between 50% and 75% stood for moderate heterogeneity, while that $\geq 75\%$ suggested high heterogeneity. The random-effect model was used for analyzing pooled RRs together with the corresponding 95% CIs of the greatest compared with lowest tea consumption levels. Besides, Stata version 15.0 (StataCorp, College Station, Texas, USA) was adopted to predict potential publication bias by Egger's regression test or Begg rank correlation test. $p < 0.10$ indicated publication bias in the results.

3 Results

3.1 Study characteristics

After an initial search, 1276 articles published from inception to August 2018 were retrieved (Figure 1). After abstract and full-text

Table 1. NOS Grade of included studies in the qualitative analysis.

Studies Case-control	Selection	Comparability	Exposure	NOS Grade
Bandera et al., 2010	☆☆☆☆	☆☆	☆☆	8/9
Gao et al., 2005	☆☆☆☆	☆☆	☆☆	8/9
Gao et al., 2016	☆☆☆☆	☆☆	☆☆☆	9/9
Goodman et al., 1997	☆☆☆☆	☆☆	☆☆	8/9
Hirose et al., 2007	☆☆☆	☆☆	☆☆	7/9
Jain et al., 2000	☆☆☆☆	☆☆	☆☆	8/9
Kakuta et al., 2009	☆☆☆☆	☆☆	☆☆☆	9/9
Levi et al., 1993	☆☆☆☆	☆☆	☆☆	8/9
McCann et al., 2009	☆☆☆	☆☆	☆☆	7/9
Xu et al., 2007	☆☆☆☆	☆☆	☆☆☆	9/9
Cohort study	**Selection**	**Comparability**	**Outcome**	
Arthur et al., 2018	☆☆☆☆	☆☆	☆☆☆	9/9
Giri et al., 2011	☆☆☆☆	☆☆	☆☆	8/9
Hashibe et al., 2015	☆☆☆☆	☆☆	☆☆☆	9/9
Je et al., 2011	☆☆☆☆	☆☆	☆☆☆	9/9
Shimazu et al., 2008	☆☆☆☆	☆☆	☆☆☆	9/9
Uccella et al., 2013	☆☆☆☆	☆☆	☆☆☆	9/9
Weiderpass et al., 2014	☆☆☆☆	☆☆	☆☆☆	9/9
Yang et al., 2015	☆☆☆☆	☆☆	☆☆☆	9/9
Zheng et al., 1996	☆☆☆☆	☆☆	☆☆☆	9/9

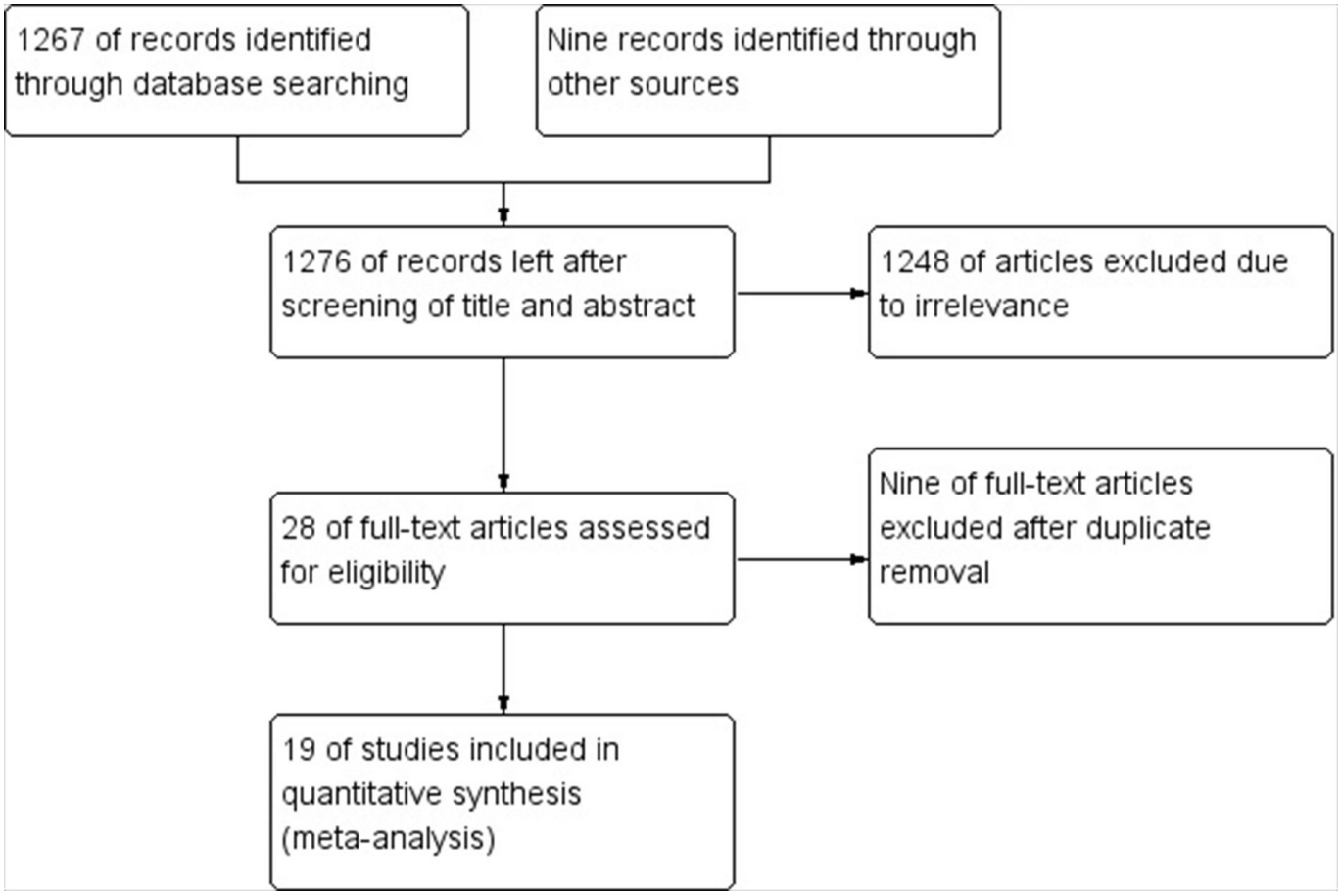

Figure1. Flow chart of meta-analysis.

screening, 19 observational studies that enrolled 12,664 incident cases of EC and 877,553 subjects were included in the analysis (Arthur et al., 2018; Bandera et al., 2010; Gao et al., 2005; Gao et al., 2016; Giri et al., 2011; Goodman et al., 1997; Hashibe et al., 2015; Hirose et al., 2007; Jain et al., 2000; Je et al., 2011; Kakuta et al., 2009; Levi et al., 1993; McCann et al., 2009; Shimazu et al., 2008; Uccella et al. 2013; Weiderpass et al. 2014; Xu et al. 2007; Yang et al. 2015; Zheng et al. 1996). Table 2 summarizes the study features. In terms of study design, 10 case-control studies (5,867 cases and 18,773 subjects) (Bandera et al., 2010; Gao et al., 2005; Gao et al., 2016; Goodman et al., 1997; Hirose et al., 2007; Jain et al., 2000; Kakuta et al., 2009; Levi et al., 1993; McCann et al., 2009; Xu et al., 2007) and 9 prospective cohort studies (6,797 cases and 858,780 subjects) (Arthur et al., 2018; Giri et al., 2011; Hashibe et al., 2015; Je et al., 2011; Shimazu et al., 2008; Uccella et al., 2013; Weiderpass et al., 2014; Yang et al., 2015; Zheng et al., 1996) on the relationship of coffee drinking and EC incidence were enrolled. Data in EC subgroup reported by Authur R et al. (2018) were enrolled into this meta-analysis. Six of those 10 case-control studies adopted population-based controls (4,699 cases and 4,979 subjects) (Bandera et al., 2010; Gao et al., 2005; Gao et al., 2016; Goodman et al., 1997; Jain et al., 2000; Xu et al., 2007) and the other four used hospital-based controls (1,168 cases and 13,794 subjects) (Hirose et al., 2007; Kakuta et al., 2009; Levi et al., 1993; McCann et al., 2009). However, fourteen studies didn't describe the type of tea precisely (Arthur et al., 2018; Bandera et al., 2010; Gao et al., 2005; Gao et al., 2016; Giri et al., 2011; Hashibe et al., 2015; Jain et al., 2000; Je et al., 2011; Levi et al., 1993; Uccella et al., 2013; Weiderpass et al., 2014; Xu et al., 2007; Yang et al., 2015; Zheng et al., 1996). Heterogeneity was observed (I^2 = 53%). However, there was no heterogeneity (I^2 = 45%) after deleting the study of Kakuta Y *et al*. 2008.

3.2 Highest versus lowest tea consumption

For determining the tea intake influence on EC incidence, the comparison of highest and lowest coffee consumption was performed. As shown in Figure 2, the pooled RR for EC regarding the greatest versus lowest tea intake levels was 0.99 (95%CI: 0.94-1.04). The pooled RR was 0.83 (95% CI: 0.73-0.95) for case-control studies, while that was 1.02 (95% CI: 0.96-1.08) for cohort studies upon stratification by the study design (Figure 3). The pooled RRs were different when the studies were stratified according to study region (Figure 4). The pooled RR for EC in Europe [1.01 (95% CI: 0.95-1.08)] was similar to that in USA/Canada [1.06 (95% CI: 0.94-1.20)]. However, pooled RR in Japan was 0.80 (95% CI: 0.69-0.93). Thus, tea didn't show definite protective effects on endometrial cancer. However, after stratification by study design, tea showed protective effects in case-controlled

Table 2. The main characteristics of the included studies concerning tea consumption and endometrial cancer risk.

Studies	Study design	Country	Study period/ follow-up	Cases/ Subjects	Tea type	Tea consumption	Relative risk (95% CI)	Adjustment for covariates
Case-Control Studies								
Bandera et al., 2010	Population-based case-control (EDGE Study)	USA	2001-2005	417/395	Tea, including green tea.	0 (ref)	1.00	Age, BMI, education, race, age at menarche, menopausal status and age at menopause, parity, OC use, HRT use, smoking, addition of milk/cream/non-dairy creamer
						≤ 1 cup/day	2.24 (1.29-3.88)	
						> 1 cups/day	1.77 (0.96-3.28)	
Gao et al., 2005	Population-based case-control	China	1997-2002	995/1087	Tea, including black tea and green tea.	No tea drinking	1.00	Age, education, age at menarche, menopause status, parity, OC use, family history of malignant tumour, BMI
						Tea drinking	0.82 (0.67-1.00)	
Gao et al., 2016	Population-based case-control (SECS study)	China	1997-2003	1199/1212	Not mentioned.	Regular tea drinking	1.00	Age, BMI, physical activity, total meat intake, oral contraceptive use, intra-uterine device use, parity, menopause status, menstruation span (year), history of diabetes, history of endometrial hyperplasia, family history of colorectal, breast or endometrial cancers
						Not regular tea drinking	1.29 (1.06-1.57)	
Goodman et al., 1997	Population-based case-control study	USA	1985-1993	332/511	Tea, including black tea and green tea.	Quartile 1 (low)	1.1	Pregnancy history, oral contraceptive pill use, history of diabetes, BMI, fat calories
						Quartile 2	1.1	
						Quartile 3	1.1	
						Quartile 4 (high)	1.1	
Hirose et al., 2007	Hospital-based case-control	Japan	1990-2000	229/12,425	Japanese tea	occasional or non-drinkers	1.00	Age, BMI, year, motivation for consultation, parity, age at first delivery, smoking, drinking, type of breakfast, fondness for salty and fatty foods, fruit, vegetables, beef, fish, carrots, exercise
						7 cups or more per day	1.33 (95% CI: 0.75-2.35)	
Jain et al., 2000	Population-based case-control	Canada	1994-1998	552/562	Not mentioned.	Quartile 1 (low)	1.00	Age, BMI, education, if ever smoked, history of diabetes, HRT, OC use, live births, age at menarche, total energy intake

Table 2. Continued...

Studies	Study design	Country	Study period/ follow-up	Cases/ Subjects	Tea type	Tea consumption	Relative risk (95% CI)	Adjustment for covariates
						Quartile 2	1.21 (0.87-1.68)	
						Quartile 3	1.17 (0.79-1.73)	
						Quartile 4 (high)	0.99 (0.68-1.45)	
Kakuta et al., 2009	Hospital-based case-control	Japan	2002-2007	152/285	Green tea	< 4 cups/week	1.00 (referent)	Age, area of residence, BMI, education, number of pregnancies, menopausal status, smoking status, diabetes mellitus, total calorie intake in kcal, miso soup consumption, tofu consumption, and coffee consumption
						5-6 cups/week–1 cup/day	0.77 (0.37-1.58)	
						2-3 cups/day	0.61 (0.30-1.23)	
						> 4 cups/day	0.33 (0.15-0.75)	
Levi et al., 1993	Hospital-based case-control	Italy and Switzerland	1988-1991	274/572	Not mentioned.	Tertile 1 (ref)	1.00	Age, study centre
						Tertile 2	1.84	
						Tertile 3	-	
McCann et al., 2009	Hospital-based case-control	USA	1982-1998	513/512	Black tea	No (ref)	1.00	Age, hormone replacement use, oral contraceptive use, education, smoking status, body mass index, menopausal status and each beverage mutually adjusted for other beverages
						0.5 cup/day	0.81 (0.57-1.14)	
						1-2 cups/day	0.89 (0.63-1.26)	
						> 2 cups/day	0.56 (0.35-0.90)	
Xu et al., 2007	Population-based case-control (SECS study)	China	1997-2003	1204/1212	Tea, including black tea, green tea, and other type.	Never	1.0	Age, education, menopausal status, years of menstruation, number of pregnancies, diagnosis of diabetes, alcohol consumption, body mass index, physical activity, energy intake, total fruit and vegetable intake, and soy protein intake
						Ever	0.8 (0.6-1.0)	
Cohort Studies								

Table 2. Continued...

Studies	Study design	Country	Study period/ follow-up	Cases/ Subjects	Tea type	Tea consumption	Relative risk (95% CI)	Adjustment for covariates
Arthur et al., 2018	Cohort (CSDLH cohort)	Canada	1992-2010/ 12.2 years	180/2608 (The data in the subcohort of endometrial cancer were included in the meta-analysis.)	Not mentioned.	None	1.00	Age at entry, education, pack years of smoking, alcohol intake, total calories, BMI, physical activity, age at menarche, parity, breastfeeding, menopausal status, HRT use, oral contraceptive use, family history of breast cancer in a first degree relative.
						> 0 - ≤ 1	1.50 (0.99-2.27)	
						> 1 - ≤ 2	0.84 (0.48-1.47)	
						> 2 - ≤ 3	1.50 (0.81-2.77)	
						> 3	1.49 (0.80-2.78)	
Giri et al., 2011	Cohort (WHI OS study)	USA	1993-2005/ 7.5 years	427/45,696	Not mentioned.	Non-daily tea consumption	1.00 (ref)	Age, ethnicity, unopposed oestrogen use, combined oestrogen-progestin use, smoking, BMI. This study was restricted to postmenopausal women.
						≥ 4 cups/day	1.10 (0.61-1.97)	
Hashibe et al., 2015	Cohort (PLOC cohort)	USA	Recruited in1992-2001, until May 2011/ more than 10 years	254/ 32392	Not mentioned.	Per cup	1.09 (1.00–1.19)	Smoking status (never/former/ current), smoking frequency (cigarettes er day categories), smoking duration (years of smoking categories), time since stopping smoking for past smokers (years categories), and drinking frequency (drinks per day categories)
						< 1 Cup per day	1.00	
						≥ 1 Cups per day	1.24 (0.95-1.63)	
Je et al., 2011	Cohort (NHS)	USA	1980-2006/ 26 years	672/67,470	Not mentioned.	< 1 cup/month	1.00	Age, BMI, age at menarche, age at menopause, parity and age at last birth, duration of OC use, PMH use, alcohol, pack years of smoking, total energy intake
						1 cup/month to < 1 cup/day	1.18 (0.94-1.49)	
						1 cup/day	1.39 (1.06-1.84)	
						≥ 2 cups/day	1.20 (0.88-1.63)	
Shimazu et al., 2008	Cohort (JPHC study)	Japan	1990-2005/ 15 years	117/53,724	Green tea	≤ 4 cups/week (ref)	1.00	Age, BMI, study area, menopausal status, age at menopause, parity, use of exogenous female hormones, smoking status, green vegetables, beef, pork

Table 2. Continued...

Studies	Study design	Country	Study period/ follow-up	Cases/ Subjects	Tea type	Tea consumption	Relative risk (95% CI)	Adjustment for covariates
						1-2 cups/day	1.04 (0.62-1.74)	
						3-4 cups/day	0.79 (0.47-1.35)	
						5 or more cups/ da	0.75 (0.44-1.30)	
Uccella et al., 2013	Cohort (IWHS study)	USA	1986-2005/ 20 years	542/23,356 471 Type I and 71 Type II	Not mentioned.	Type I		Age, diabetes, duration of HRT use, hypertension, age at menarche, age at menopause, BMI, waist-to-hip ratio, smoking status, pack-years of smoking, total energy and alcohol use
						Never or < once per month	1.00 (reference)	
						1-3 cups a month	0.87 (0.66, 1.15)	
						1-4 cups a week	0.89 (0.69, 1.15)	
						5+ cups a week	0.95 (0.74, 1.22)	
						Type II		
						Never or < once per month	1.00 (reference)	
						1-3 cups a month	1.28 (0.65, 2.52)	
						1-4 cups a week	1.23 (0.65, 2.34)	
						5+ cups a week	1.26 (0.65, 2.43)	
Weiderpass et al., 2014	Cohort	Sweden	1991-2009/ 19 years	144/42270	Not mentioned.	0 cup	1 (reference)	Age, education, duration of hormonal contraceptive use, parity, duration of breastfeeding, smoking status and number of cigarettes/day, menopausal status, body mass index, and diabetes mellitus
						1 cup	1.10 (0.76-1.59)	
						> 1 cup	0.71 (0.38-1.33)	
Yang et al., 2015	Cohort (MWS) and meta-analysis	England and Scotland	Recruited in1996-2001/ followed for an average of 9.3 years	4067/556289	Not mentioned.	< 1 cups/d	1.04 (0.96, 1.14)	Region, socioeconomic status, height, are at menarche, parity, duration of oral contraceptive use, age and status of menopause at study baseline, duration of hormone therapy for menopause, BMI, smoking, alcohol consumption, strenuous exercise, coffee consumption, and other non-alcoholic fluid intake
						1-2 cups/d	1.00 (0.94, 1.07)	
						3-4 cups/d	1.05 (1.00, 1.11)	

Table 2. Continued...

Studies	Study design	Country	Study period/ follow-up	Cases/ Subjects	Tea type	Tea consumption	Relative risk (95% CI)	Adjustment for covariates
						≥ 5 cups/d	1.01 (0.95, 1.08)	
Zheng et al., 1996	Cohort	USA	January 1986 to December 31, 1993/ followed for 8 years	394/ 34975	Not mentioned.	Never/ monthly	1.00	Age, education, smoking status, pack-years of cigarette smoking, physical activity, all fruit and vegetable intake, waist/hip circumference ratio, family history of cancer among female relatives, total energy intake, alcohol cosumptio, age at menarche, age at menopause, age at first pregnancy
						Weekly	1.02 (0.75-1.37)	
						1 cup/day	1.29 (0.87-1.94)	
						≥ 2 cups/day	0.76 (0.45-1.27)	

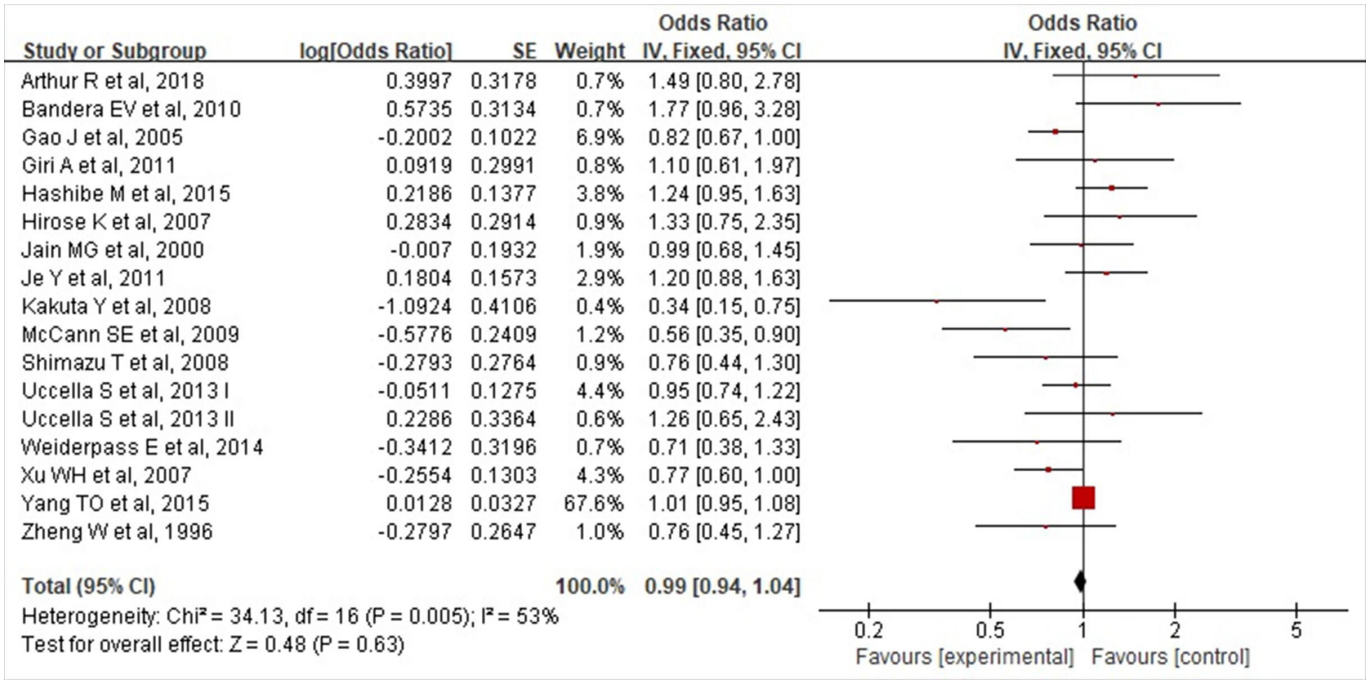

Figure 2. Forest plot of total tea intake and relative risk of endometrial cancer.

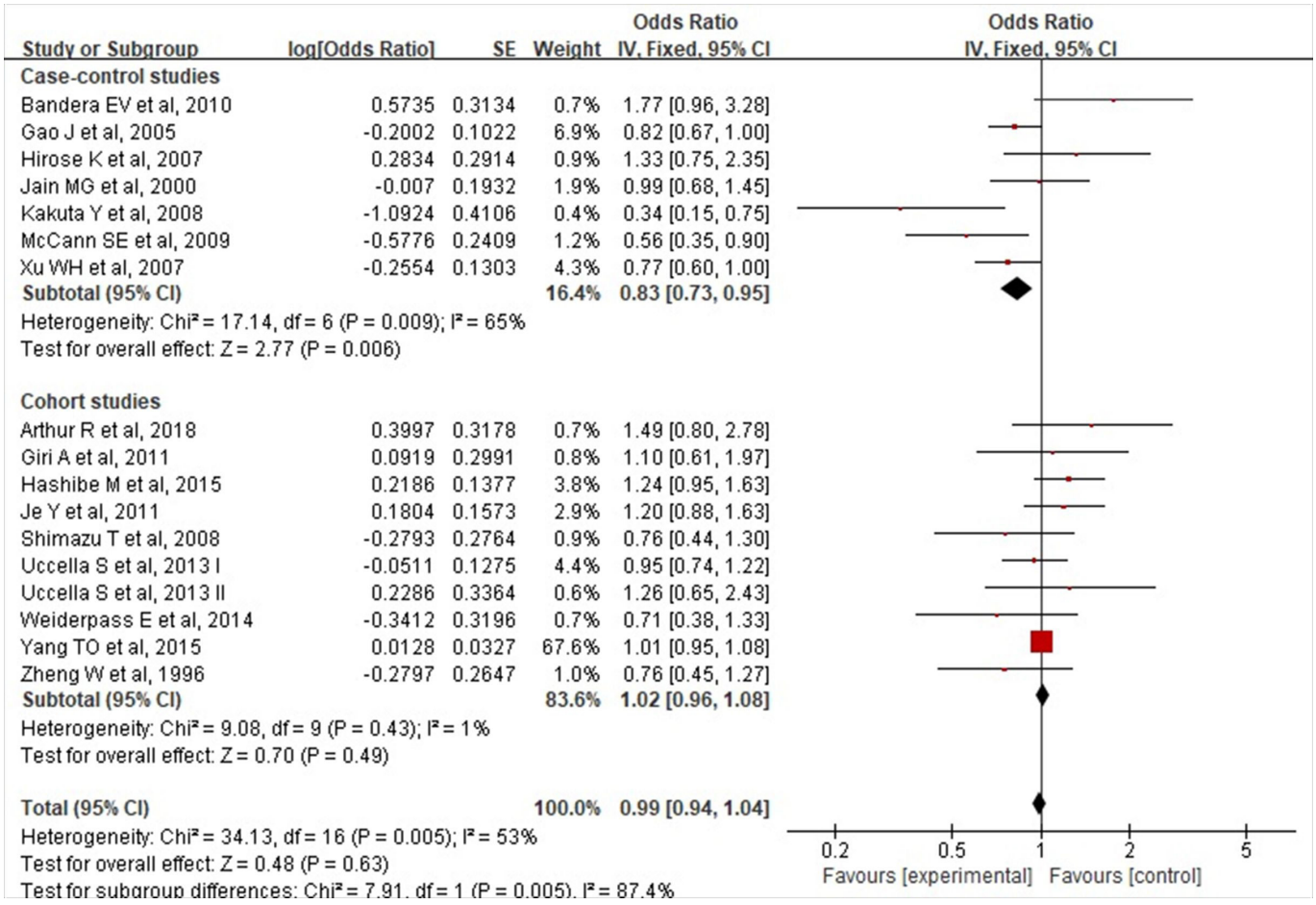

Figure 3. Forest plot of total tea intake and relative risk of endometrial cancer, stratifying by study design.

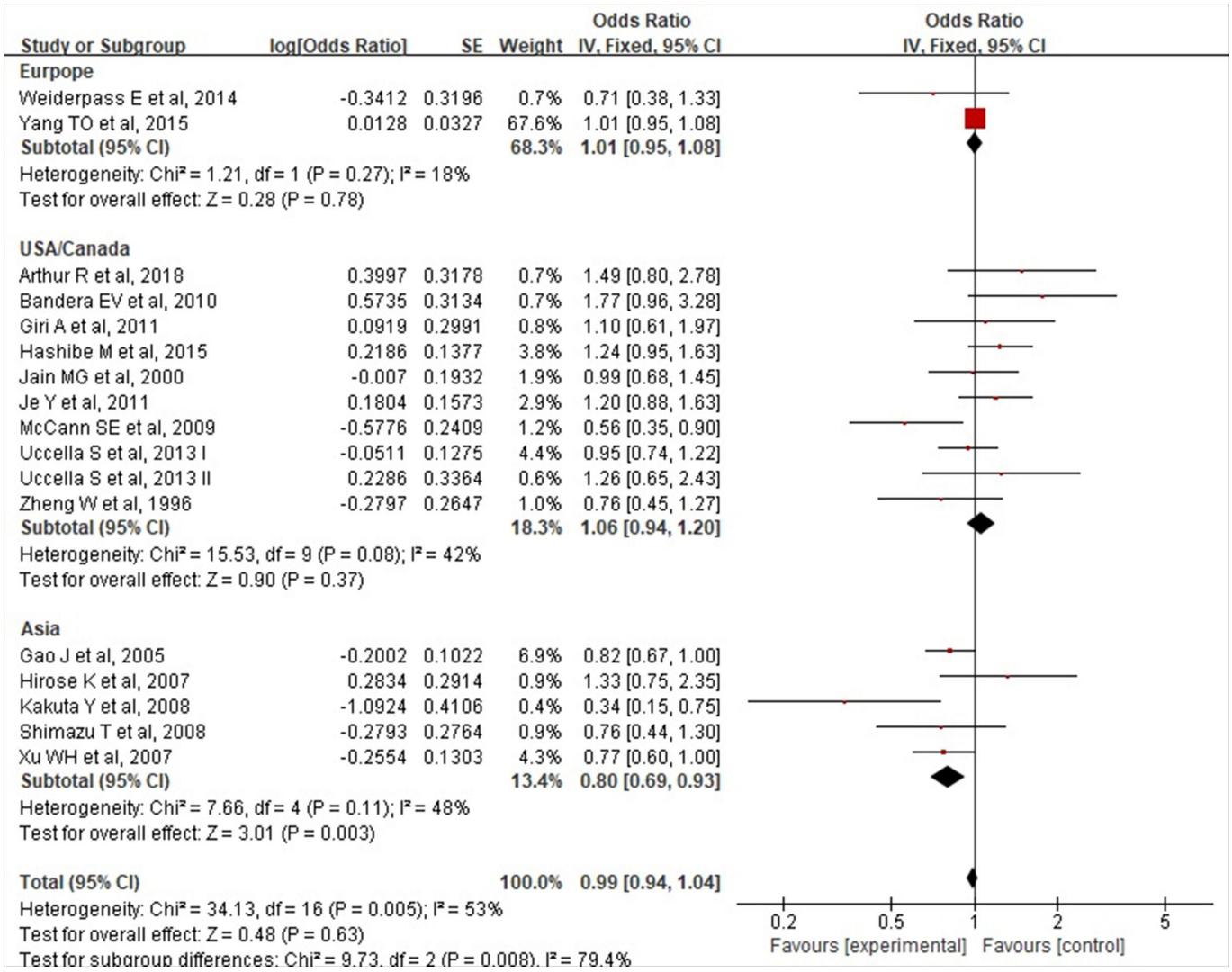

Figure 4. Forest plot of total tea intake and relative risk of endometrial cancer, stratifying by regions.

studies; and after stratification by study region, protective effects of tea were observed in Asia, but not in Europe or USA/Canada.

3.3 Subgroup analysis

The association of diverse tea types with EC incidence was examined. There were 4 articles reporting the relationship of green tea drinking with the incidence of EC, with pooled RR of 0.73 (95% CI: 0.64-0.84) (Figure 5). Three studies reported that there was association between black tea and EC incidence. The pooled RR was 0.65 (95% CI: 0.46-0.92). There were 2 articles reporting that other tea types were linked with the incidence of EC. The pooled RR was 1.72 (95% CI: 0.89-3.35). Our data suggested that reduced risks of EC were related with both green and black tea, but not with other types of tea.

There were 3 articles reporting that tea drinking was connected with the incidence of EC among participants with diverse BMI. The pooled RRs for higher and lower BMI were 1.06 (95% CI: 0.90-1.24) and 0.97 (95% CI: 0.85-1.09) (Figure 6). Two studies reported a link between tea intake and EC risk in subjects with different smoking status. The pooled RR for never smokers was 0.95 (95% CI: 0.88-1.04), and that for ever smokers was 1.07 (95% CI: 0.84-1.36) (Figure 7). Thus, both different BMI and different smoking status showed uncertain relationship with EC risks.

3.4 Publication bias

There was no obvious publication bias upon Egger's regression test (P = 0.632) or Begg correlation test (P = 0.705) or from funnel plot (Figure 8).

4 Discussion

Altogether 19 observational studies were enrolled into the present meta-analysis, including 10 case-control studies along with 9 cohort studies, involving 877,553 normal controls and 12,664 patients. This meta-analysis showed that tea had no protective effect against EC, which is consistent with other meta-analysis (Yang et al., 2015).

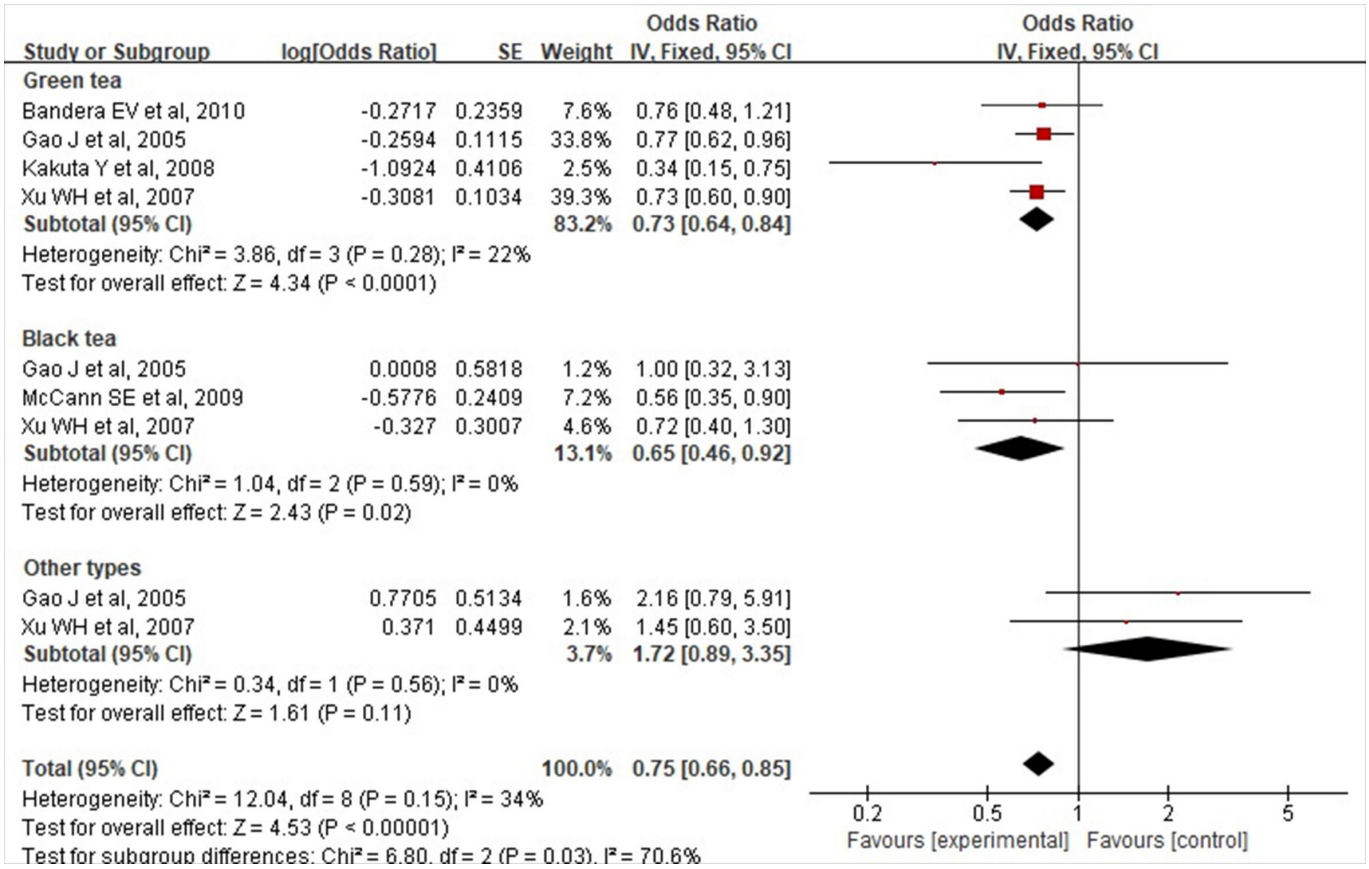

Figure 5. Forest plot of different tea types and relative risk of endometrial cancer.

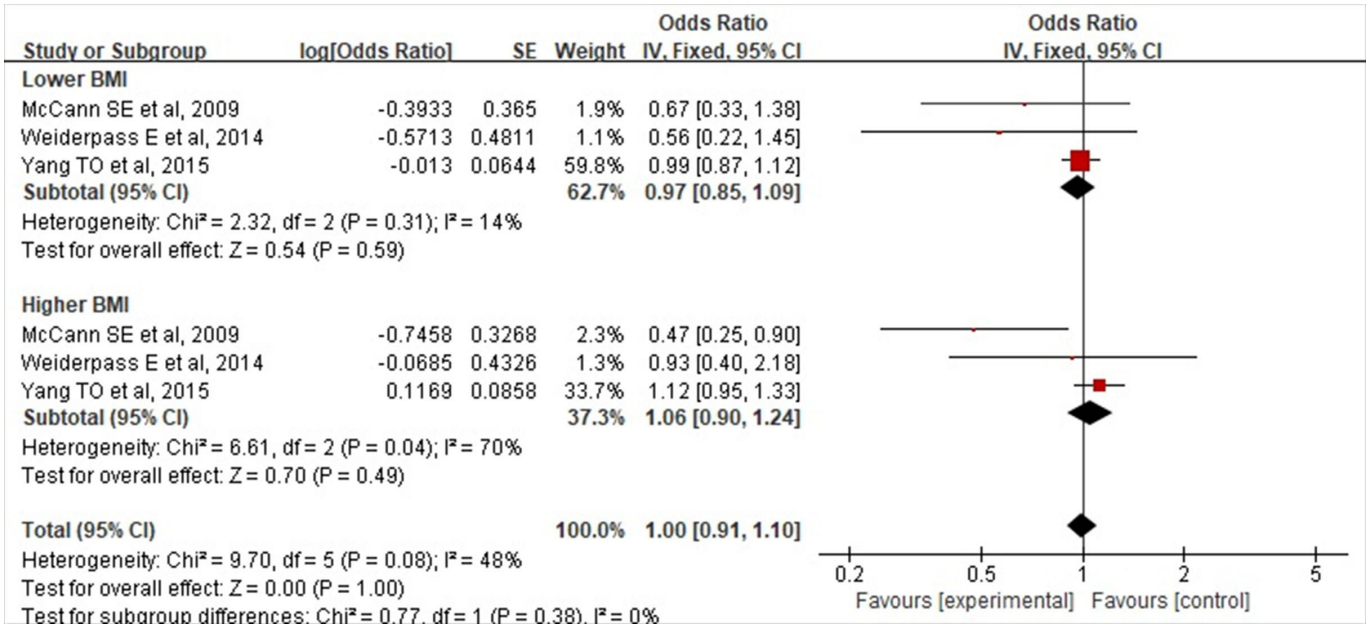

Figure 6. Forest plot of lower and higher BMI and relative risk of endometrial cancer.

Tea is among the popular beverages in the world, which is prepared from Camellia sinensis leaves (Jankun et al., 1997). Many diverse tea types have been cultivated. In terms of the global tea consumption level, black tea (fermented, 78%), green tea (unfermented, 20%) and oolong tea (2%) rank the top three places, which is considered to be about 50% fermented)

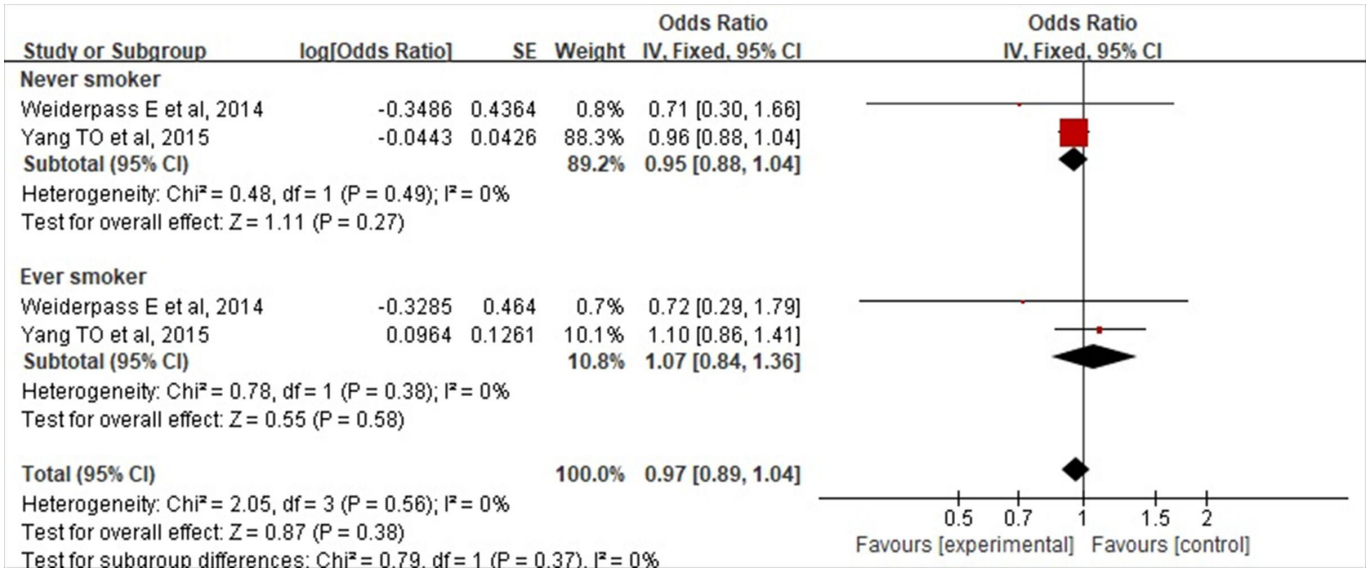

Figure 7. Forest plot of never and ever smoker and relative risk of endometrial cancer.

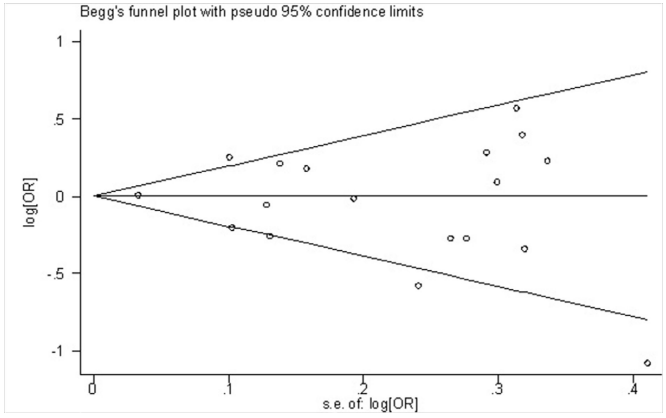

Figure 8. Funnel plot of total tea intake and relative risk of endometrial cancer.

(Jankun et al., 1997). Accumulated evidence shows a negative correlation between tea and risk of various cancers (Hashibe et al., 2015; Lambert, 2013; Zhou et al., 2016).

Tea may have potential anti-carcinogenic effects because tea contains antioxidants (Grosso et al., 2017b; Lambert, 2013; Zhou et al., 2016). Catechins, as an important ingredient from tea, facilitate in scavenging reactive nitrogen species (RNS) or reactive oxygen species (ROS), such as singlet oxygen, peroxyl radicals and superoxide(Nakagawa & Yokozawa, 2002). Furthermore, catechins may suppress estrogen-caused endometrial cell activation (Laschke et al., 2008) and result in cell cycle arrest and human cancer cell apoptosis (Ahmad et al., 1997). These effects of catechins could affect carcinogenesis of EC. Moreover, caffeine is suggested to cause the activation of glutathione-S-transferases, which thus possibly protects against polycyclic aromatic hydrocarbons (PAHs) (Steinkellner et al., 2005). Glutathione-S-transferase is a kind of phase II enzyme that can inactivate the carcinogens in diet and i nthe environment (Steinkellner et al., 2005). In addition, caffeine is negatively related to free estradiol (London et al., 1991) as well as the free testosterone in plasma (Ferrini & Barrett-Connor, 1996); meanwhile, it is positively related to plasma estrone together with SHBG (Ferrini & Barrett-Connor, 1996; London et al., 1991). The changes of steroid hormone levels may influence EC (Ferrini & Barrett-Connor, 1996; London et al., 1991). Besides, tea gene may contribute to the protection against EC. Xu and colleagues (Xu et al., 2007) discovered that tea drinking might change the relationship between CYP19A1 polymorphisms rs752760, rs1065779 as well as rs1870050 and EC. Besides, tea drinking is found to be related to EC incidence among subjects who have Asp/Asp genotype of SHBG Asp327Asn polymorphism (Xu et al., 2008).

In this meta-analysis, our results showed that tea had no protective effect against EC. After stratifying by study design, cohort studies did not show negative correlation between tea and EC risk, but case-controlled showed inconsistent results that the greater drinking intake level was related to the decreased incidence of EC. These results suggest that recall bias might play a role and could exaggerate the protection of tea against EC. To reduce the bias, more high quality studies, such as cohort studies, will be needed. Moreover, after stratifying by study district, studies in Asia showed protective effects of tea consumption against EC, which differed from those in Europe and USA/Canada. This may be due to the different dietary customs and tea-drinking habits. Black tea, fruit tea and herbal tea are popular in European countries, whereas black tea is more popular among North American countries (Reyes & Cornelis, 2018). Meanwhile, green, black, together with "other" teas are most popular among Asian countries (Reyes & Cornelis, 2018). In addition, the antioxidant activity of tea is weakened when milk is added (Ryan & Petit, 2010). The habit could influence the results between different districts. Different types of tea may induce different effects against risk of EC. According to our results,

drinking green tea was found to be related to the decreased EC incidence, which was consistent with other studies (Butler & Wu, 2011; Zhou et al., 2016). Zhou et al. (2016) discovered that the higher daily green tea intake level was related to the decreased incidence of EC by 11%. As a matter of fact, green tea drinking is relatively popular among Asian countries (Shimazu et al., 2008; Weiderpass et al., 2014). In the meta-analysis, included studies focused on green tea were from Asia. Meanwhile, our results also showed that consumption of black tea had protective effects against EC, which was different from other studies (Butler & Wu, 2011; Zhou et al., 2016). According to Zhou Q and colleagues (Zhou et al., 2016), drinking black tea was not significantly related to the decreased EC risk, which was possibly ascribed to the reduced catechins contents in black tea relative to those in green tea (> 10 folds in catechin levels) (Balentine et al., 1997; Zhou et al., 2016). In the current meta-analysis, only three studies (Gao et al., 2005; McCann et al., 2009; Xu et al., 2007), which all were case-controlled studies, were included to analyze the pooled RR and the 95% CIs of black tea consumption. Recall bias and less studies may induce the difference between the current meta-analysis and others (Butler & Wu, 2011; Zhou et al., 2016).

In this meta-analysis, we didn't find any correlation in subgroups of different BMI, which was similar with some studies (Weiderpass et al., 2014; Yang et al., 2015). Although it is suggested in one study (McCann et al., 2009) that, tea drinking has limited effect on decreasing the EC risk among women with a higher body weight, while a greater coffee drinking level is related to the decreased EC risk in women with normal body weight. They speculated that other phytochemicals, which were beverage specific rather than caffeine, might contribute to the benefit from tea. Tea is distinct compared with coffee because it has contained great catechins and theaflavins contents (Lakenbrink et al., 2000), which are suggested to decrease estradiol level and suppress aromatase activity (McCann et al., 2009).

Similar to BMI, no correlation was found in subgroups of different smoking status in the meta-analysis, which was inconsistent with other studies (Al-Zoughool et al., 2007; Felix et al., 2014; Lindemann et al., 2008; Polesel et al., 2009; Yang et al., 2010; Zhou et al., 2008). This difference may be associated with the few included articles into the meta-analysis. Besides, it is also reported that smoking is negatively correlated with EC incidence (Al-Zoughool et al., 2007; Felix et al., 2014; Lindemann et al., 2008; Polesel et al., 2009; Yang et al., 2010; Zhou et al., 2008). The negative correlation may be attributed to the changes of steroid metabolism and generation caused by smoking (Al-Zoughool et al., 2007).

In the meta-analysis, there were obvious heterogeneities across different articles. After deleting the data from Kakuta et al., 2009, no obvious heterogeneity was detected across different articles ($P = 0.03$, $I^2 = 45\%$). After stratifying by study design, statistically significant heterogeneity was found in case-controlled studies and little heterogeneity was found in cohort studies. After stratifying by study region and types of tea, there was little heterogeneity.

Certain limitations should be noted in this meta-analysis. Firstly, different studies focus on different types of tea, different preparation methods, different tea drinking habits and different categories of tea consumption. These differences increase the difficulty in confirming the effective components in tea. Such factors were not enrolled into this meta-analysis. Secondly, few studies were enrolled into certain subgroups. These small numbers might cause the exaggeration of results. Third, confounding factors might exist in the included studies. Different histological types of EC might lead to different responses to tea exposure. Different dietary habits, such as the intake of sugar or cream in the tea, vegetables and red meat, might also strengthen or weaken the benefit of coffee on EC incidence. Fourth, differences in methodology, trial design and statistical methods could induce heterogeneity. To reduce the heterogeneity, more cohort studies are needed.

5 Conclusions

In conclusion, tea was identified to have no protective effect against EC in our meta-analysis. However, single specific type of tea, including both green tea and black tea, had protective effects against EC. Furthermore, studies in Asia showed protective effects of tea consumption against EC. Giving those above-mentioned limitations in this meta-analysis, more large randomized controlled trials and prospective cohort studies should be conducted.

Ethical approval

The study did not include any human or animal experimentation for which ethical approval was required.

Conflict of interest

The authors declare that there is no conflict of interest.

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