

Green tea, black tea consumption and risk of endometrial cancer: a systematic review and meta-analysis

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Abstract

Background Several studies have assessed the association between green and black tea consumption and the risk of endometrial cancer (EC) and have yielded inconsistent results.

Objective The purpose of this meta-analysis is to systematically analyze the effect of green tea and black tea on EC risk.

Methods PubMed, Embase, Cochrane Library and China Biological Medicine Database were searched through February 2, 2015 to identify studies that met pre-stated inclusion criteria. Overall relative risk (RR) was estimated based on the highest and lowest levels of green/black tea

consumption. Dose–response relationships were evaluated with the data from categories of green/black tea intake in each study.

Results For green tea, the summary RR indicated that the highest green tea consumption was associated with a reduced risk of EC (RR 0.78, 95 % CI 0.66–0.92). Furthermore, an increase in green tea consumption of one cup per day was associated with an 11 % decreased risk of developing EC. (RR 0.89, 95 % CI 0.84–0.94). For black tea, no statistically significant association was observed in the meta-analysis (highest versus non/lowest, RR 0.99, 95 % CI 0.79–1.23; increment of one cup/day, RR 0.99, 95 % CI 0.94–1.03). The power of the estimate of green tea and black tea with risk of EC was 84.33 and 5.07 %, respectively. The quality of evidence for the association between green and black tea with EC risk was moderate and very low, respectively.

Conclusions The results from this meta-analysis indicate that green tea, but not black tea, may be related to a reduction of EC risk. Large population-based randomized controlled trials and large prospective cohort studies are required to obtain a definitive conclusion and determine the mechanisms underlying this association.

Q. Zhou, H. Li and J.-G. Zhou have contributed equally to this work.

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Keywords Endometrial cancer · Green tea · Black tea · Dose–response relationship · Systematic review · Meta-analysis

Introduction

In recent years, endometrial cancer (EC) has become one of the most common cancers in women, ranking as the fourth highest cause of female cancer-related deaths worldwide [1–3]. Interestingly, however, the incidence of endometrial

cancer in developed countries is at least twofold greater than that observed in developing countries, with an age-standardized annual incidence rate (ASR) of 14.7 per 100,000 women and 5.5 per 100,000 women, respectively [4]. In the United States, it is estimated that approximately 54,870 women will be diagnosed in 2015 [5]. Tea is the second most popular beverage in the world [6] and originates from the leaves of the plant *Camellia sinensis* [7]. Different processing methods result in several types of tea. Of the total amount of tea consumed worldwide, 20 % is green tea (unfermented), 78 % is black tea (fermented) and 2 % is oolong tea (a kind of tea, which is considered to be about 50 % fermented) [7]. Tea contains a wide variety of antioxidants, such as flavonoids, catechins, thearubigins and theaflavins, some of which have been reported to exert potential anti-carcinogenic properties. Growing evidence from laboratory, epidemiologic, and human intervention studies suggests that consuming tea can exert preventive effects against many types of cancers [8].

To date, only one prior meta-analysis [9] has been conducted to address whether tea consumption is associated with EC risk. That meta-analysis combined data from five case-control studies and two cohort studies and found an inverse association between ever tea intake and non/very low tea consumption. Moreover, a stratified analysis by tea type showed that green tea, but not black tea, was beneficial in a lower EC risk. However, the previous meta-analysis only considered four and two studies on green tea and black tea, respectively. Since 2009, five studies have been published [10–14], and one study was not included in the previous meta-analysis [15]; given the new evidence, we conducted a meta-analysis of observational studies with the following objectives: (1) to update the epidemiology evidence on the association between green/black tea intake and the risk of EC; (2) to quantify the dose–response association between green/black tea consumption and EC; and (3) to evaluate the statistical power of the associations found in (1) and the overall strength of the evidence presented.

Materials and methods

A prospective protocol was registered on PROSPERO (<http://www.crd.york.ac.uk/prospéro/>) with the identification number CRD42015017944. We attempted to report this meta-analysis in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [16], which are included in the online supplement material.

Date source and search strategy

We searched PubMed, Embase, Cochrane Library and China Biological Medicine Database for studies published

prior to February 2, 2015, that focused on describing the association between tea consumption and EC risk. The following key words were used in our search strategies: (“endometrial cancer” OR “endometrium cancer” OR “endometrial carcinoma” OR “endometrium carcinoma” OR “endometrial neoplasms” OR “endometrium neoplasms” OR “corpus uteri cancer” OR “corpus uteri neoplasm” OR “corpus uteri carcinoma” OR “uterus tumor” OR “uterine tumor”) AND (“Tea” OR “green tea” OR “black tea” OR “catechin” OR “theaflavin” OR “thearubigin”). In addition, we analyzed references from the original paper and review articles to identify further relevant studies. In cases of duplicated data, the most recent or most complete study was included in our analysis.

Study selection and data extraction

First, we performed an initial screening of the titles or abstracts, followed by a full-text review. Studies were considered eligible if they met the following criteria: (1) the experimental design included a case–control or cohort study; (2) the exposure of interest was tea intake; (3) the outcome of interest was endometrial cancer; and (4) the odds ratio (OR) or the relative risk (RR) and the corresponding 95 % confidence interval (CI) of endometrial cancer were provided for the highest and lowest levels and were adjusted for potential confounders. Two independent investigators (QZ and HL) conducted the study selection. For each included study, we extracted the following information: the first author’s last name, publication year, country of origin, study period, study design, tea intake categories, type of tea, the number of cases and controls in case–control studies or the number of cases and cohort size in cohort studies, ORs or RRs (with their 95 % confidence intervals) for each category of tea consumption and covariates used to adjust in the multivariate analysis. In cases in which the tea type was unspecified, the local tea drinking preference was used, including black tea for English-speaking countries [17] and green tea for Asian countries [18]. All data were retrieved by two independent investigators (QZ and JGZ), and any disagreements were resolved by consensus.

Quality assessment of study and evidence

The Newcastle–Ottawa Scale [19] (NOS) was used to assess the overall quality of the included studies. This scale ranged from 0 (poor) to 9 stars (excellent), and four stars were awarded for the selection of study participants, two stars for the comparability of studies based on the design or analysis, and three stars for the evaluation of exposure in case–control studies or ascertained outcomes in cohort studies. Studies with a score of 6 stars or greater were

considered high quality. Two reviewers (HM and YM) evaluated the quality of evidence using the GRADE system [20] (using GRADE profiler 3.6.1). In this system, an observational study is initially assumed to contain low-quality evidence. The score can be downgraded for five reasons (i.e., risk of bias, inconsistency, indirectness, imprecision and publication bias) and upgraded for three reasons (i.e., a large effect, presentation of a dose–response gradient or plausible confounders that did not alter the apparent treatment effect). The evidence grades were divided into the following categories: (1) high, which indicated that further research was unlikely to alter confidence in the estimated effect; (2) moderate, which indicated that further research may significantly alter confidence in or change the estimated effect; (3) low, which indicated that further research was likely to significantly alter confidence in the effect estimate and to change the estimate; and (4) very low, which indicated that any effect estimate is uncertain.

Statistical analysis

Because the incidence of endometrial cancer is low [1], the OR is mathematically similar to RR [21]. Therefore, we reported all results as RR for simplicity. Associations between green and black tea intake with EC risk were quantified by comparing the highest and lowest (the referent) categories. For the dose–response meta-analysis, we used the “generalized least squares for trend estimation” method proposed by Greenland and Longnecker [22, 23], which considers the correlation of the log RR estimates across different exposures. This method requires knowledge of the cases and cohort size/number of controls of each category and the RR with its variance estimate for at least three quantitative exposure categories. For studies that did not provide the number of cases and cohort size/number of controls in each exposure category, we estimated the slopes using “variance-weighted least-squares regression model” [22]. Tea intake values were assigned as the medium provided by the original research. For studies that did not provide a median value, we used the midpoint for closed categories and similar amplitudes as the neighbouring open-ended categories. Statistical heterogeneity among studies was assessed using the χ^2 test and was defined as a P value less than 0.10. Quantification of heterogeneity was made using the I^2 statistic [23], with low heterogeneity defined by I^2 values less than 50 % and values greater than 50 % indicative of high heterogeneity. The Begg rank correlation test [24] and Egger’s regression test [25] were used to detect publication bias, and publication bias was considered to exist when $P < 0.10$ [26]. We tried to explore the source of heterogeneity by subgroup analysis and conduct a sensitivity analysis to

investigate the influence of a single study on the overall risk estimate by omitting one study in each turn. Power calculation was performed after the studies had been collected using the methodology described by Cafri et al. [27]. Details on the macro and SAS code used are included in the online supplement material. Statistical analyses were conducted in Stata Version 12.0 (StataCorp, College Station, TX, USA). A threshold of $P < 0.05$ was considered statistically significant, unless otherwise specified.

Results

Literature search

Figure 1 shows the results obtained in the literature research and selection. We identified 372 articles from PubMed, Embase, Cochrane Library and China Biological Medicine Database that were published prior to February 2, 2015, in our initial electronic search. A manual search of the reference lists yielded an additional 2 related papers. After excluding duplicate records and studies that did not fulfill our inclusion criteria, 21 articles remained. Of these, we excluded 8 studies as follows: 4 studies [28–31] did not provide data on tea intake, 2 studies [32, 33] did not provide information on endometrial cancer, 1 study [34] was a conference abstract and overlapped with a previous article, and 1 article was found to overlap [35]. In total, 13 studies [10–13, 15, 36–42] were shown to meet the inclusion criteria and were included in the meta-analysis. Among these articles, only one study [11] provided information for both type I and type II endometrial cancer and was thus considered two comparisons.

Study characteristics

Table 1 shows the characteristics extracted from the included studies. These studies were published between 1992 and 2014. Six studies were conducted primarily in the USA [11–14, 39, 42], five were conducted in Asia (China and Japan) [36–38, 40, 41], and two were conducted in Europe (Sweden and Italy) [10, 15]. Seven studies [14, 15, 36–39, 41] had a case–control design, comprising 3915 cases and 21880 controls; among them, four were population-based case–control studies, and the other three were hospital-based case–control studies. Six studies [10–13, 40, 42] had a cohort design and comprised 2151 cases and 267,885 participants. The number of participants ranged from 67,470 in the Nurses’ Health Study (NHS) [12] to 23,356 in the Iowa Women’s Health Study (IWHS) [11]. Seven studies used food-frequency questionnaires (FFQ) to assess tea intake, and the remaining studies used other questionnaires. In some case–control studies, the Body

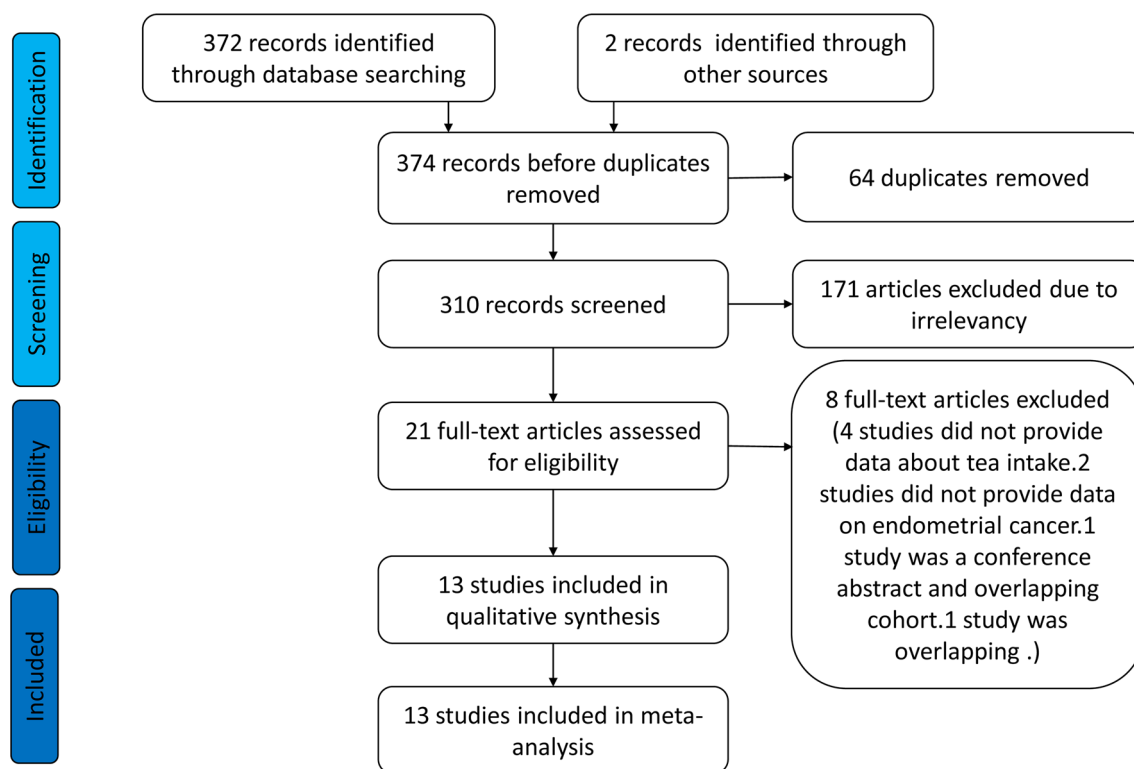


Fig. 1 Flowchart of the literature search and study selection

Mass Index (BMI) of case group was higher than that of control group. And many cases were ascertained through cancer registries (see online supplemental material). Ten comparisons focused on black tea intake [10–15, 39, 41, 42], and six comparisons [14, 36–38, 40, 41] focused on green tea. The NOS scores (Table 2) ranged from five to nine. Eight of the thirteen studies were determined to have relatively high quality (over 6 stars), and the mean NOS score was 7.08 stars (standard deviation 1.26).

Green tea consumption

A total of six studies [14, 36–38, 40, 41], including five case–control studies and one cohort study, were included in the meta-analysis on green tea intake and EC risk. The estimated relative risk of EC for the highest green tea consumption compared with the lowest green tea intake was determined to be 0.78 (95 % CI 0.66–0.92), with no statistically significant heterogeneity observed among the studies ($P = 0.16$, $I^2 = 35.7\%$; Fig. 2). When divided by study location, the one study conducted in the USA had a RR of 0.76 (95 % CI 0.48–1.22), whereas the other five studies, which were conducted in Asia, had a RR of 0.79 (95 % CI 0.66–0.94). When divided by study design, the RR of the sole cohort study was determined to be 0.75 (95 % CI 0.43–1.30), whereas the summary RR value for

the five case–control studies was 0.79 (95 % CI 0.66–0.94). Sensitivity analyses revealed that the summary RR ranged from 0.75 (95 % CI 0.63–0.88) (excluding the study of Hirose et al. [37]) to 0.81 (95 % CI 0.69–0.96) (excluding the study of Kakuta et al. [38]). Additionally, specific studies were excluded to evaluate the reliability and stability of our conclusions. Excluding the following groups of studies separately did not alter our results: 3 low-quality studies, 2 studies with sample sizes less than one thousand, 4 studies that did not adjust for total energy, 4 studies that did not adjust for diabetes and 3 studies that did not adjust for hormone therapy. Excluding the 4 studies that did not adjust for physical activity provided a non-statistically significant result, but the statistical power was only 6.79 % (Table 3). Dose–response analysis showed that an increase in green tea consumption of one cup per day was statistically significantly associated with a 11 % decrease in the risk of developing EC (RR, 0.89; 95 % CI 0.84–0.94) (Fig. 3).

Black tea consumption

A total of nine studies [10–15, 39, 41, 42] involving four case–control studies and five cohort studies were included in the meta-analysis on black tea intake and EC risk. The summary relative risk estimate of EC for the highest black

Table 1 Characteristics of studies in the meta-analysis of tea (green and black) and endometrial cancer risk

References	Country	Period	Study design	Cases/cohort size or controls	Tea type	Lowest consumption	Highest consumption	RR or OR (95 % CI)	Adjustments
Vecchia et al. [15]	Italy	1983–1990	HPC	567/6141	Black	None	>1 cup/day	1.4 (1.2–1.7)	Age, area of residence, education, smoking, coffee consumption
Zheng et al. [42]	USA	1986–1993	cohort	249/35,369	Black	Never/monthly	≥2 cups/day	0.76 (0.45–1.27)	Age, education, smoking status, pack-years of smoking, physical activity, all fruit and vegetable intake, waist/hip ratio, family history of cancer, age at menarche, age at menopause, and age at first pregnancy
Gao et al. [36]	China	1997–2002	PCC	995/1087	Green	None	≥7 cups/week	0.78 (0.63–0.96)	Age, education, age at menarche, menopausal status, number of pregnancies, use of oral contraceptives, family history of cancer and BMI
Hirose et al. [37]	Japan	1990–2000	HCC	229/12,425	Green	Never or occasional	≥7 cups/day	1.33 (0.75–2.35)	Age, year, motivation for consultation, parity, age at first delivery, smoking, drinking, type of breakfast, fondness of salty and fatty foods, fruit, vegetable, beef, fish, carrot, exercise and BMI
Xu et al. [41]	China	1997–2003	PCC	1042/1035	Green	Never/monthly	>7 cups/week	0.80 (0.40–1.70)	Age, education, menopausal status, years of menstruation, number of pregnancies, diagnosis of diabetes, alcohol consumption, BMI, physical activity, energy intake, total fruit and vegetable intake, soy protein intake
Shimazu et al. [40]	Japan	1990–2005	cohort	117/53,724	Green	4 days/week	≥5 cups/day	0.75 (0.44–1.30)	Age, study area, BMI, menopausal status, age at menopause, use of exogenous female hormones, smoking status, green vegetable consumption, beef consumption, pork and coffee consumption
Kakuta et al. [38]	Japan	2002–2007	PCC	152/285	Green	<4 cups/week	>4 cups/day	0.33 (0.15–0.75)	BMI, education, number of pregnancies, menopausal status, smoking status, DM, total calorie intake, miso soup intake, tofu intake, and coffee intake
McCann et al. [39]	USA	1982–1998	HCC	513/512	Black	None	>2 cups/day	0.56 (0.35–0.90)	Age, hormone replacement use, oral contraceptive use, education, smoking status, BMI, menopausal status and coffee consumption
Bandera et al. [14]	USA	2001–2005	PCC	417/395	Black Green	None None	>1 cup/day >1 cup/day	1.77 (0.96–3.28) 0.76 (0.48–1.21)	Age, education, race, age at menarche, menopausal status and age at menopause for post-menopausal women, parity, OC use, HRT use, BMI, smoking status, milk, cream, or non-dairy creamer added in tea
Giri et al. [13]	USA	1993–2005	cohort	427/45,696	Black	Non-daily	≥4 cups/day	1.10 (0.61–1.97)	Age, ethnicity, unopposed estrogen use, progestin + estrogen use, smoking and BMI
Je et al. [12]	USA	1980–2006	cohort	672/67,470	Black	<1 cup/day	≥4 cups/day	1.06 (0.77–1.46)	Age, BMI, age at menopause, age at menarche, parity and age at last birth, parity, duration of oral contraceptive use, post-menopausal hormone use, pack-years of smoking, alcohol intake and total energy intake

Table 1 continued

References	Country	Period	Study design	Cases/cohort size or controls	Tea type	Lowest consumption	Highest consumption	RR or OR (95 % CI)	Adjustments
Uccella et al. [11]	USA	1986–2005	cohort	471/23,356	Black	Never or <1/month	>5 cups/week	0.95 (0.74–1.22) (Type I) 1.26 (0.65–2.43) (Type II)	Age, diabetes, duration of HT use, hypertension, age at menarche, age at menopause, quartiles of body mass index, waist-to-hip ratio, smoking status, pack-years of smoking, total energy and alcohol use
Weiderpass et al. [10]	Sweden	1991–2009	cohort	144/42,270	Black	None	>1 cup/day	0.71 (0.38–1.33)	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

BMI Body Mass Index, *HCC* hospital-based case-control study, *PCC* population-based case-control study

tea consumption compared with the lowest black tea intake was shown to be 0.99 (95 % CI 0.79–1.23) (Fig. 2), with statistically significant heterogeneity observed among the studies ($P = 0.003$, $I^2 = 64.2\%$). Exploration of heterogeneity by subgroup analysis revealed that the observed RRs were similar across the subgroups when they were divided by study location, study design, NOS score and following adjustment for menopausal or hormone therapy (Fig. 4); further, testing for subgroup differences showed no statistical significance among the subgroups. Importantly, only cohort study subgroups and studies of NOS that scored more than 6 stars displayed low heterogeneity (Table 4). Sensitivity analyses revealed that the RR values ranged from 0.92 (95 % CI 0.76–1.12) (excluding the study of Vecchia et al. [15]) to 1.06 (95 % CI 0.87–1.29) (excluding the study of Mccann et al. [39]). Dose–response analysis showed that an increase in black tea consumption of one cup per day did not affect the risk of EC development (RR 0.99; 95 % CI 0.94–1.03) (Fig. 3).

Power analysis and quality of evidence

Power calculations were performed post hoc after all of the studies had been collected using the methodology described by Cafri et al. A power of 84.33 % was determined to detect an RR of 0.78 for the highest green tea consumption compared with the lowest green tea intake and 5.07 % for an RR of 0.99 for the highest black tea consumption compared with the lowest black tea intake. Outcomes in this meta-analysis were evaluated using the GRADE system (Table 5). For green tea, the quality of evidence was determined to be moderate, which was primarily associated with the presence of a dose–response relationship. For black tea, the quality of evidence was very low, which was mainly attributed to serious inconsistency and imprecision between studies.

Publication bias

For green tea intake, there was little evidence of publication bias, as indicated by the Begg rank correlation test ($P = 0.707$) and the Egger linear regression test ($P = 0.763$). For black tea intake, there was also no evidence of significant publication bias, as indicated by the Begg rank correlation test ($P = 0.99$) and the Egger linear regression test ($P = 0.127$).

Discussion

In this meta-analysis, we found that a higher consumption of green tea was associated with a lower risk of EC. Furthermore, an increase in green tea consumption of one cup

Table 2 Quality assessment according to the Newcastle–Ottawa scale

References	Country	Selection	Comparability	Outcome/exposure	Score
Vecchia et al. [15]	Italy	3	1	2	6
Zheng et al. [42]	USA	3	1	2	6
Gao et al. [36]	China	4	1	1	7
Hirose et al. [37]	Japan	4	1	1	6
Xu et al. [41]	China	4	2	1	7
Shimazu et al. [48]	Japan	4	2	3	9
Kakuta et al. [38]	Japan	4	1	1	6
McCann et al. [39]	USA	4	2	2	8
Bandera et al. [14]	USA	2	2	1	5
Giri et al. [13]	USA	4	2	2	8
Je et al. [12]	USA	2	2	3	7
Uccella et al. [11]	USA	4	2	2	8
Weiderpass et al. [10]	Sweden	4	2	3	9

per day was statistically significantly associated with an 11 % decrease in the risk of developing EC. In contrast, the consumption of black tea was not shown to have a protective effect against EC.

Heterogeneity is often a concern in meta-analysis; however, we observed little evidence of heterogeneity surrounding the estimate of green tea and EC risk. In contrast, statistically significant heterogeneity was observed among the studies that focused on black tea and EC risk, and subgroup analyses were conducted to further explore this heterogeneity. The observed heterogeneity could partly be explained by study design and NOS score status, stratification by study design revealed 83 % heterogeneity in case–control studies and 0 % heterogeneity in cohort studies. The high heterogeneity observed in the case–control studies may be due in part to the high likelihood of recall and selection biases and to the differential misclassification of exposure, as information on tea consumption was collected after a patient was diagnosed. Furthermore, when a NOS score of six was used to define the quality of studies, 65 % heterogeneity was found in low-quality studies (fewer than six stars), which was in contrast to the 23 % heterogeneity observed in high-quality studies (more than six stars). Together, our results suggest that the quality of primary studies plays an important role in the level of heterogeneity generated in meta-analysis.

A number of potential mechanisms of action have been proposed to account for the cancer-preventive effects of tea and tea constituents. Tea contains large amounts of caffeine and has been shown to induce glutathione-S-transferases, a phase II enzyme that is responsible for the inactivation of dietary and environmental carcinogens [43]. Additionally, and more relevant to the hormonal etiology of endometrial cancer, caffeine has also been shown to affect steroid hormone levels and has been reported to display an inverse association with free estradiol [44] and

plasma-free testosterone [45] and a positive association with plasma estrone and sex hormone-binding globulin (SHBG) [44, 45]. In addition, tea contains a number of antioxidants, such as catechins, that could affect carcinogenesis. Indeed, previous studies have demonstrated that epigallocatechin gallate, the major catechin in green tea, can induce apoptosis and cell cycle arrest in human carcinoma cells [46] and can inhibit the estrogen-induced activation of endometrial cells [47]. Tea catechins have also been shown to scavenge relevant reactive oxygen and nitrogen species, such as superoxide, peroxy radicals, and singlet oxygen [48]. Thus, if the beneficial effect of tea on EC risk comes primarily from the tea catechins, the relative lack of risk reduction associated with black tea consumption can be explained by the much lower level of catechins in black tea than in green tea (up to tenfold difference in catechin contents) [6]. Furthermore, previous studies have also reported a protective effect of tea–gene interaction on EC. For example, Xu et al. [41] found that tea consumption can modify the association of CYP19A1 polymorphisms rs1065779, rs752760, and rs1870050 with endometrial cancer. An inverse association of tea consumption and EC risk was highly evident in individuals with an Asp/Asp genotype of the SHBG Asp327Asn polymorphism, with a particular emphasis observed in premenopausal women [35].

Our study has several strengths compared with the previously reported meta-analyses [9]. To the best of our knowledge, this is the largest systematic review and meta-analysis of observational studies on the intake of green tea/black tea and risk of EC and should thus lead to more reliable results with higher statistical power. In this meta-analysis, the power for RR value of green tea intake and EC incidence was 84.33 %, which indicates that there was sufficient evidence to clarify the inverse association between green tea and EC. Finally, there was little

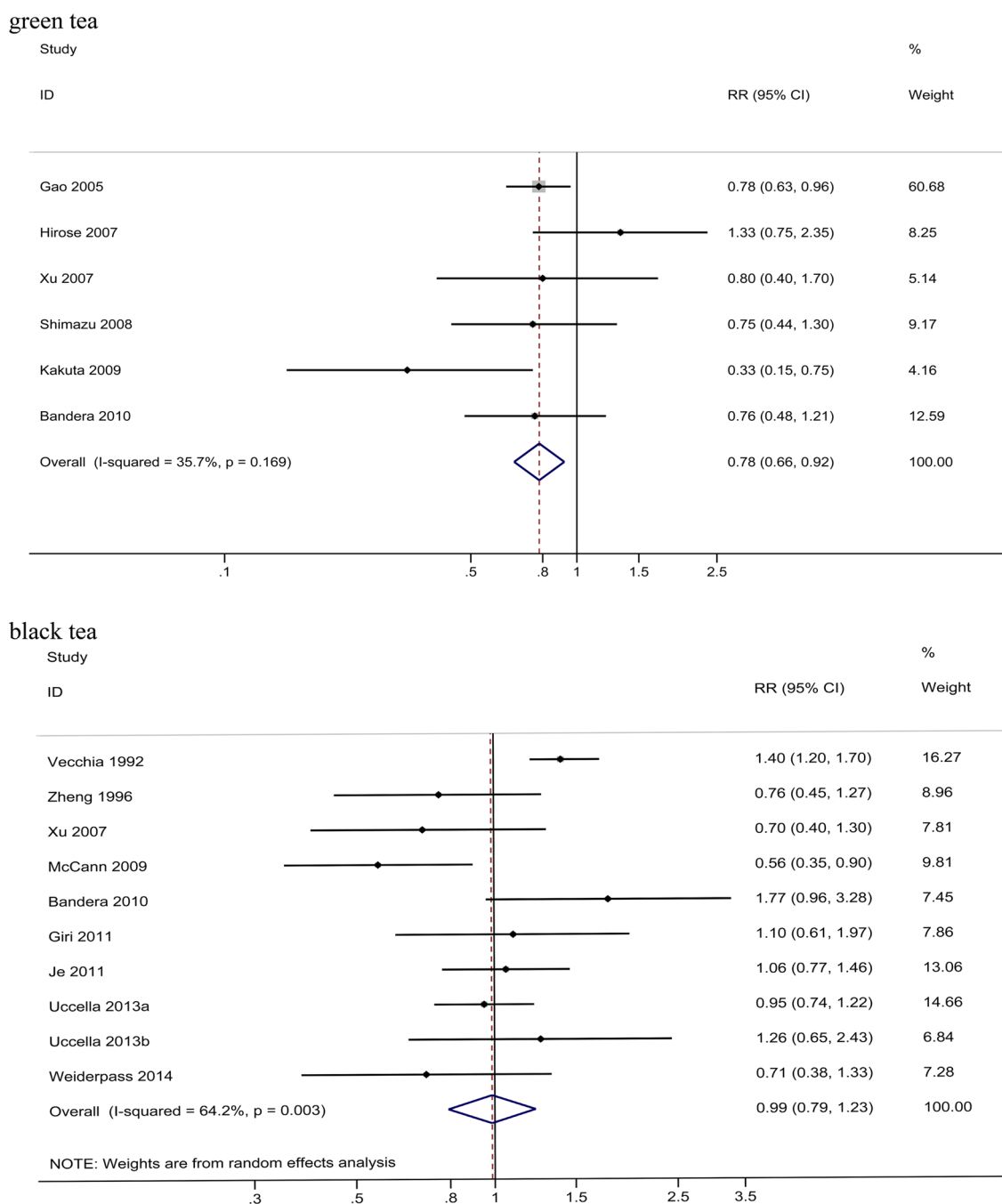


Fig. 2 Summary RRs of EC for highest versus lowest green/black tea

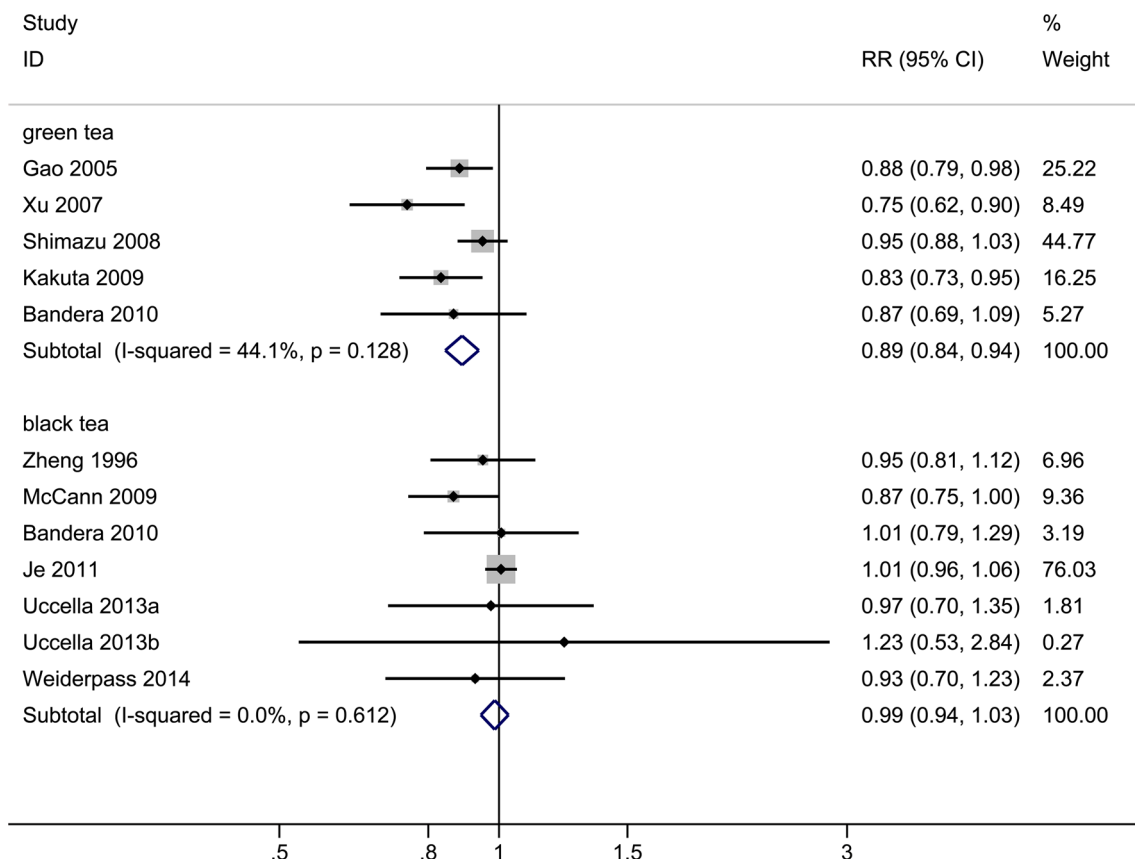
evidence of publication bias for both green/black tea consumption and EC risk studies.

We acknowledge several limitations of our meta-analysis, including the potential misclassification of the type of tea consumed in studies that did not provide a specific tea type. In those cases, the type of tea was estimated according to local preference. However, we did not estimate the total tea intake and risk of EC because many studies have shown that black and green tea are

qualitatively different, with some studies showing that black tea does not have a beneficial effect [49, 50] and other studies finding a positive correlation between black tea consumption and the risk of cancer [51, 52]. In addition, black tea intake has been positively associated with estrogen levels, which has been established as a strong promoter of mammary carcinogenesis [53]. Second, our power for the RR value of black tea intake and EC was only observed to be 5.07 %, which suggests that the

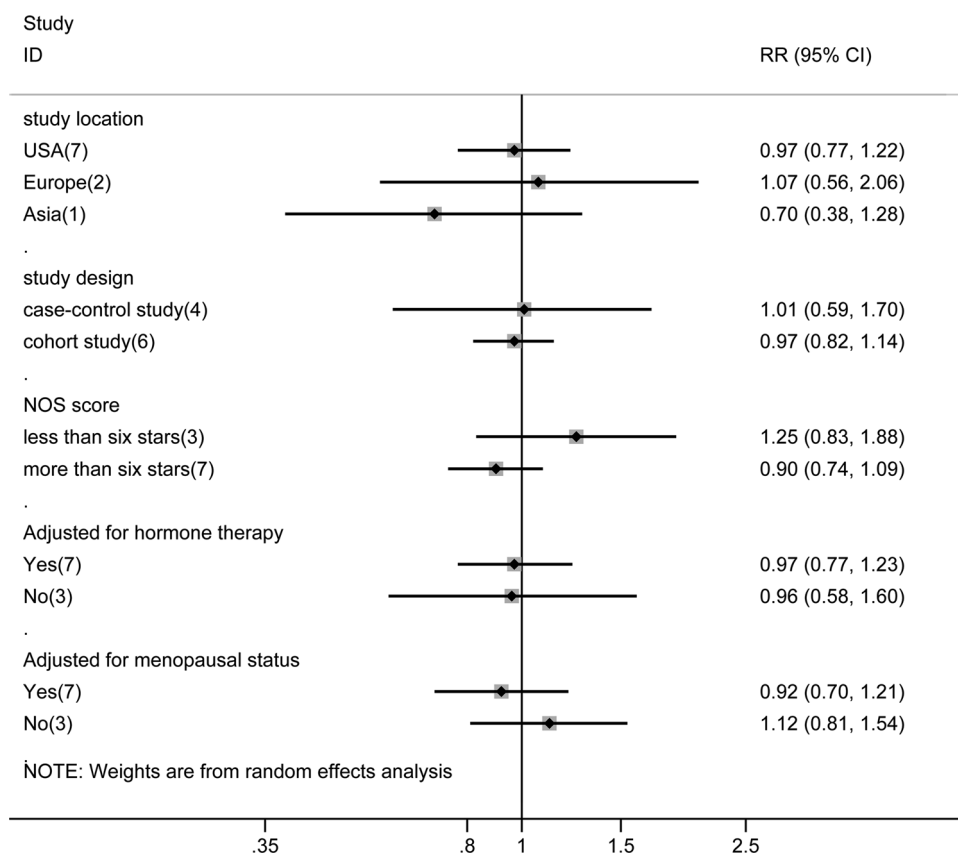
Table 3 Sensitivity analysis based on green tea consumption (highest versus lowest) and EC risk

Outcome	No. of studies	RR (95 % CI)	Heterogeneity		Statistical power (%)
			I^2 (%)	P	
All studies	6	0.78 (0.66–0.92)	35.7	0.169	84.33
Exclusion of 3 low-quality studies [14, 37, 38]	3	0.78 (0.64–0.94)	0	0.988	74.13
Exclusion of 2 studies with sample sizes less than 1000 [14, 38]	4	0.82 (0.69–0.98)	2.6	0.379	57.86
Exclusion of 4 studies that did not adjust for total energy [14, 36, 37, 40]	2	0.54 (0.31–0.92)	61.1	0.109	61.61
Exclusion of 4 studies that did not adjust for physical activity [14, 36, 38, 40]	2	1.09 (0.70–1.71)	14.43	0.280	6.79
Exclusion of 4 studies that did not adjust for diabetes [14, 36, 37, 40]	2	0.54 (0.31–0.92)	61.1	0.109	61.61
Exclusion of 3 studies that did not adjust for hormone therapy [37, 38, 41]	3	0.77 (0.65–0.93)	0	0.988	79.62

**Fig. 3** Summary RRs of EC for increasing green/black tea intake by one cup per day

estimate is unstable and indicates that more relevant studies are required to further explore this association. Third, as in all observational studies of diet and disease, the possibility of bias and confounding variables should be considered. However, to our knowledge, no clinical randomized controlled trials have been conducted to assess green/black tea consumption and EC risk. Fourth, we recognize that although most of the questionnaires used to generate tea data have been validated and shown to display reasonable

reproducibility, a potential misclassification of exposure may be unavoidable. Indeed, most of the included studies measured tea intake at baseline only, rather than updating the information. Thus, changes in tea intake during the follow-up period may result in possible misclassification. Finally, the GRADE quality of evidence for green and black tea and EC risk was moderate and very low, respectively; thus, lowering the confidence in any subsequent recommendations.

Fig. 4 Subgroup analyses of black tea intake and EC risk**Table 4** Stratified pooled RRs and 95 % CIs for black tea consumption (highest versus lowest) and EC risk

Subgroup	No. of studies	RR (95 % CI)	Heterogeneity test			<i>P</i> for interaction
			<i>Q</i>	<i>P</i>	<i>I</i> ² (%)	
Study location						
USA [11–14, 39, 42]	7	0.97 (0.77–1.22)	10.97	0.09	45	0.56
Europe [10, 15]	2	1.07 (0.56–2.06)	4.18	0.04	76	
Asia [41]	1	0.70 (0.38–1.28)	NA	NA	NA	
Study design						
Case–control study [14, 15, 39, 41]	4	1.00 (0.59–1.70)	17.65	0.00	83	0.89
Cohort study [10–13, 42]	6	0.97 (0.82–1.14)	2.92	0.71	0	
NOS score						
≤6 [14, 15, 42]	3	1.25 (0.83–1.88)	5.76	0.06	65	0.15
>6 [10–13, 39, 41]	7	0.90 (0.74–1.09)	7.81	0.25	23	
Adjusted for HT						
Yes [10–14, 39]	7	0.97 (0.77–1.23)	10.94	0.09	45.1	
No [15, 41, 42]	3	0.96 (0.58–1.60)	8.87	0.01	77.5	
Adjusted for menopausal status						
Yes [10, 11, 13, 14, 39, 41]	7	0.92 (0.70–1.21)	11.47	0.07	48	0.37
No [12, 15, 42]	3	1.12 (0.81–1.54)	6.32	0.04	68	

HT hormone therapy, NOS Newcastle–Ottawa Scale

Table 5 Assessment of quality using the GRADE system

Outcome	No. of studies	Quality assessment					Quality	Importance		
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision			Publication bias	Other considerations
Green tea [14, 36–38, 40, 41]	6	OS	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Dose–response gradient ^a	Moderate	Critical
Black tea [10–15, 39, 41, 42]	10	OS	No serious risk of bias	Serious ^b	No serious indirectness	Serious ^c	Undetected	–	Very low	Critical

OS observational studies

^a We conducted a dose–response analysis of green tea consumption and EC, and the results showed that 1 cup of green tea per day was associated with an 11 % lower incidence of EC

^b Moderate heterogeneity was detected ($P = 0.003$, $I^2 = 64.2\%$)

^c The summary RR comparing the highest and lowest boiled coffee intakes was 0.99 (95 % CI 0.79–1.23), and the power was only 5.07 %

In summary, our results suggest that the consumption of green tea, but not black tea, may have a protective effect on EC cancer risk. However, these conclusions should be considered with caution because of the inherent limitations in the described meta-analysis. Large population-based randomized controlled trials and large prospective cohort studies are required to obtain a definitive conclusion and determine the mechanisms underlying this association.

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