ONCOLOGY

Tea consumption and risk of endometrial cancer: a metaanalysis

Na-Ping Tang, MD; Hua Li, MD; Yun-Liang Qiu, MD; Guo-Min Zhou, PhD; Jing Ma, PhD

OBJECTIVE: The objective of the study was to assess the association between tea consumption and endometrial cancer.

STUDY DESIGN: Studies were identified by searching PubMed and EMBASE databases and screening the references of retrieved articles. The summary relative risk (RR) with 95% confidence interval (CI) was calculated.

RESULTS: The combined RR for ever drinkers vs non/lowest drinkers was 0.85 (95% CI, 0.77–0.94). Compared with non/lowest drinkers, the summary RR was 0.88 (95% CI, 0.78–0.98) for low to moderate drinkers and 0.75 (95% CI, 0.64–0.88) for high drinkers. An increase in tea intake of 2 cups/day was associated with a 25% decreased risk of endometrial cancer. In subgroup analyses, tea consumption was significantly associated with reduced endometrial cancer risk in Asian studies and studies using interviewing techniques. Furthermore, the protective effect of green tea on endometrial cancer seemed more evident than that of black tea.

CONCLUSION: Findings from this metaanalysis suggest that tea consumption may reduce the risk of endometrial cancer. Because of the limited number of studies, further prospective studies are needed to explore the protective effect of tea on endometrial cancer.

Key words: endometrial cancer, metaanalysis, tea consumption

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Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in women. According to American Cancer Society statistics for 2008, 40100 women in the United States were expected to be diagnosed with incident endometrial cancer, and approximately 7470 women were expected to die of it.[1] Although incremental improvements are made regularly in the ways in which all treatment modalities are applied to patients with endometrial cancer, the prognosis from this disease has only marginally improved. Therefore, more and more attention has been given to primary prevention.

Tea, produced from the leaves of the plant *Camellia sinensis*, is the second most consumed beverage behind water.[2,3] Multiple lines of evidence support a protective effect of tea on various cancers.[4,5] Evidences from studies in vitro and animal suggest that tea or the active ingredient in tea, polyphenols, can reduce tumor formation, tumor size, and cellular proliferation,[6,7] probably through scavenging reactive oxygen species, inhibition of tumor initiation, and modulation of detoxification enzymes.[7] However, the results based on epidemiological studies on the association of tea consumption with endometrial cancer were inconsistent. Thus, we conducted a metaanalysis of all relevant published studies to evaluate the relationship between tea consumption and endometrial cancer.

Materials and Methods

Search strategy

We identified studies by a literature search of the PubMed and EMBASE databases (from 1966 to February 2009) with the following key words: "tea," "green tea," "black tea," "flavonoid," "catechin," "thearubigin," or "theaflavin" combined with "endometrial neoplasms," "endometrial cancer," "endometrial tumor," "endometrial carcinoma," or "uterine corpus cancer." We also reviewed reference lists of retrieved articles or preceding reviews for additional pertinent studies. No language restrictions were imposed. All searches were conducted independently by 2 authors (N.-P.T. and H.L.). The results were compared, and any questions or discrepancies were resolved through iteration and consensus.

Study selection

For inclusion in the metaanalysis, the identified articles had to fulfill the following criteria: (1) they had a cohort or case-control design; (2) the exposure of interest was tea consumption; (3) the outcome of interest was primary endometrial cancer; and (4) the risk estimates with their corresponding 95% confidence intervals (CIs) were reported (or data to calculate them).

The process of study selection was shown in Figure 1. Thirteen potentially relevant studies[8-20] were identified by searching electronic databases and reference lists of retrieved articles or preceding reviews. Five studies[8-12] were excluded because they did not report data regarding tea consumption and endometrial cancer. One study[13] was excluded because it was a du-

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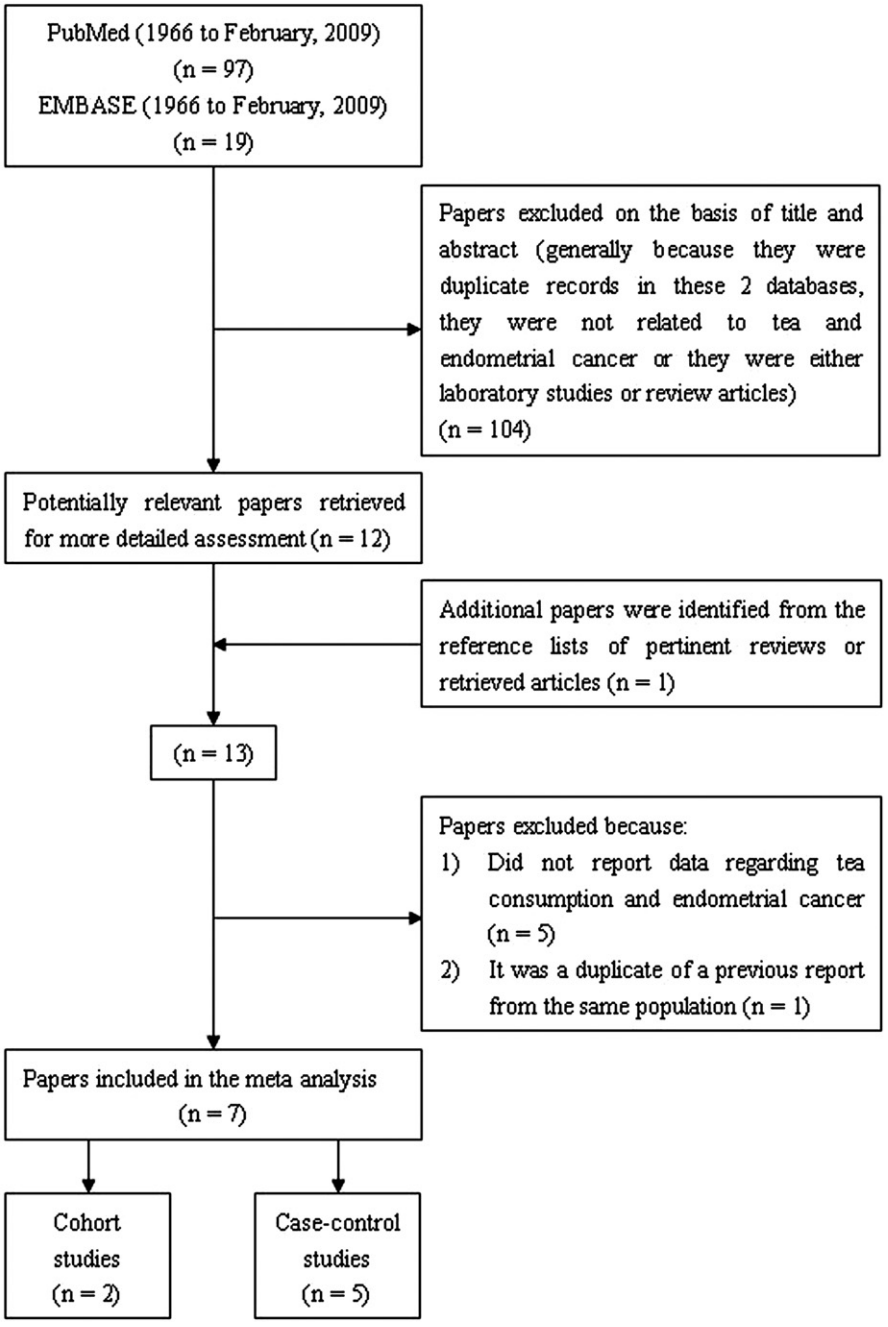
FIGURE 1
Process of study selection



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plicate of a previous report[14] from the same population. Thus, a total of 7 studies[14-20] with 2 cohort studies[15,16] and 5 case-control studies[14,17-20] were included in this metaanalysis.

Data extraction

The following data were extracted independently by 2 researchers from each study: the first author's last name, year of publication, study population, study design, type of controls for case-control studies (population- or hospital-based controls), study period, sample size (cases and controls or cohort size), exposure of tea consumption, tea type, method of tea assessment, covariates controlled for in the analysis, and the risk estimates with corresponding 95% CIs. For each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounders.

Statistical analysis

Study-specific risk estimates were extracted from each study, and log risk estimates were weighted by the inverse of their variances to obtain a pooled risk estimate. We first compared the risk of endometrial cancer in ever drinkers with non/lowest drinkers. Several studies did not report a risk estimate for ever drinkers. For these studies, a summary estimate for ever drinkers was calculated using reported risk estimate for each tea consumption category. This summary estimate was used in the metaanalysis for calculation of the overall relative risk (RR) for ever drinkers.

To estimate summary RR for various levels of tea consumption, we also calculated the study-specific estimates separately for low to moderate tea consumption (defined as >0 cup/d to <2 cups/d for Zheng et al[15]; >0 cup/d to <7 cups/wk for Gao et al[17]; >0 cup/d to ≤7 cups/wk for Xu et al[14]; ≥4 cups/wk to ≤4 cups/d for Kakuta et al[19]; >4 cups/wk to <5 cups/d for Shimazu et al[16]; and >0 cup/d to ≤2 cups/d for McCann et al[20]). Estimates were also calculated for high tea consumption (defined as ≥2 cups/d for Zheng et al[15]; ≥7 cups/wk for Gao et al[17]; ≥7 cups/d for Hirose et al[18]; >7 cups/wk for Xu et al[14]; >4 cups/d for Kakuta et al[19]; ≥5 cups/d for Shimazu et al[16]; and >2 cups/d for McCann et al[20]). These study-specific estimates were then pooled using the inverse of the corresponding variances as weights.

Statistical heterogeneity among studies was assessed with the Q and I^2 statistics[21]; $P < .10$ was considered statistically significant.[22] If no heterogeneity was observed, the fixed-effect model (the Mantel-Haenszel method) was used to calculate the pooled RR; otherwise, the random-effect model (the DerSimonian and Laird method) was used.

For the dose-response metaanalysis, we used the method proposed by

TABLE 1
Characteristics of studies included in the metaanalysis

Study reference	Study design	Study population	Study period	Cases/controls or cohort	Tea consumption	Risk estimate (95% CI)	Adjustments
Zheng et al[a]	Cohort	United States	1986-1993	249/35,369	Never/monthly Weekly 1 cup/d ≥2 cups/d	1.00 1.02 (0.75–1.37) 1.29 (0.87–1.94) 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
Shimazu et al[a]	Cohort	Japan	1990-2005	117/53,724	≤4 cups/wk 1-2 cups/d 3-4 cups/d ≥5 cups/d	1.00 1.04 (0.62–1.74) 0.79 (0.47–1.35) 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 consumption, and coffee consumption
Gao et al[b]	PCC	China	1997-2002	995/1087	Never Ever <7 cups/wk ≥7 cups/d	1.00 0.82 (0.67–1.00) 1.12 (0.69–1.82) 0.78 (0.63–0.96)	Age, education, age at menarche in years, menopausal status, number of pregnancies, use of oral contraceptives, family history of cancer, and BMI
Hirose et al[a]	HCC	Japan	1990-2000	229/12,425	Never/occasional ≥7 cups/d	1.00 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[b]	PCC	China	1997-2003	1204/1212	Never Ever 1-6 cups/wk 7 cups/wk >7 cups/wk	1.00 0.80 (0.60–1.00) 1.20 (0.80–2.00) 0.70 (0.60–0.90) 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, and soy protein intake
Kakuta et al[a]	PCC	Japan	2002-2007	152/285	<4 cups/wk 5-6 cups/wk to 1 cup/d 2-3 cups/d >4 cups/d	1.00 0.77 (0.37–1.58) 0.61 (0.30–1.23) 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[a]	HCC	United States	1982-1998	541/541	Never 0.5 cups/d 1-2 cups/d >2 cups/d	1.00 0.81 (0.57–1.14) 0.89 (0.63–1.26) 0.56 (0.35–0.90)	Age, hormone replacement use, oral contraceptive use, education, smoking status, BMI, menopausal status, and coffee intake

BMI, body mass index; *CI*, confidence interval; *DM*, diabetes mellitus; *HCC*, hospital-based case-control study; *PCC*, population-based case-control study.

[a] These studies used self-administrated questionnaire for tea assessment; [b] These studies used interview for tea assessment.

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Greenland and coworkers[23,24] to calculate study-specific slopes from the correlated natural logarithm of the RR across categories of tea consumption. We attempted to place the studies on a common scale by estimating the RR for an increase in tea consumption of 2 cups/d. For each study, we calculated the median cups of tea consumption for each category by assigning the midpoint of upper and lower boundaries in each category as the average consumption. If the upper bound was not provided, we assumed that it had the same amplitude as the preceding category.[23] Because this method requires the risk estimates with their variances for at least 3 quantitative exposure categories, the study by Hirose et al[18] with only 2 categories was not included in this analysis. In addition, this method also requires that the distribution of cases and noncases (or person-time) for at least 3 quantitative exposure categories are known. For studies[15,16] that did not provide the number of cases and noncases in each consumption category, we estimated the slopes using variance-weighted least squares regression.

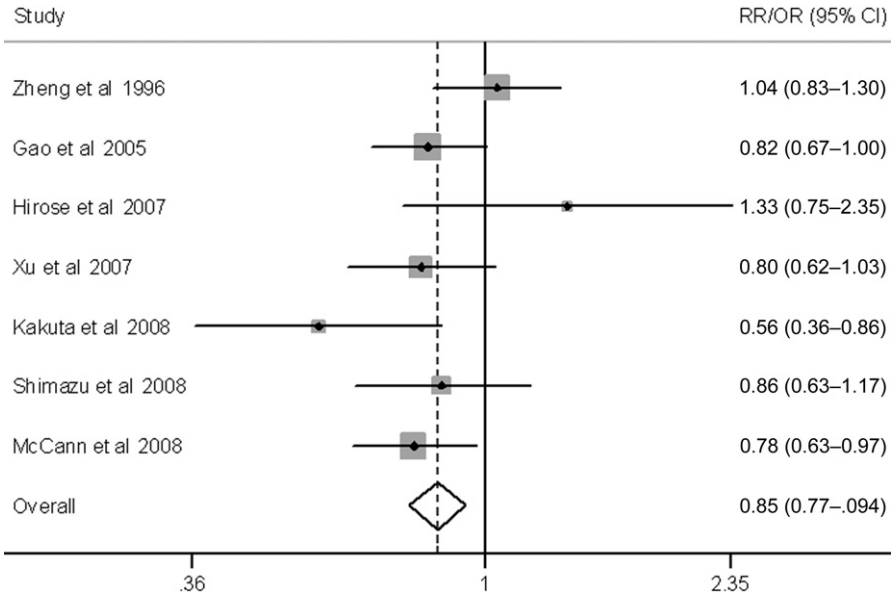
A sensitivity analysis in which 1 study at a time removed and the rest analyzed was conducted to evaluate whether the results could have been affected significantly by a single study. Publication bias was assessed through visual inspection of funnel plots, and the Egger's regression asymmetry test with $P < .10$ was considered representative of statistically significant publication bias.[25] All statistical analyses were conducted using Stata (version 9.2; StataCorp, College Station, TX).

RESULTS

Seven published studies (2 cohort studies and 5 case-control studies) regarding the association between tea consumption and risk of endometrial cancer were included in our metaanalysis (Table 1). Of these studies, 2 were conducted in the United States,[15,20] 2 in China,[14,17] and 3 in Japan.[16,18,19] Among case-control studies, 3 used population-base controls[14,17,19] and 2 used hospital-based controls.[18,20]

Risk estimates for ever drinkers vs non/lowest drinkers are shown in Figure 2 and Table 2. The summary RR of endometrial cancer from all studies was 0.85 (95% CI, 0.77–0.94). There was no statistically significant heterogeneity across the studies ($Q = 10.15$; $P = .118$; $I^2 = 40.9$). The summary RRs from the

FIGURE 2
Summary RRs of endometrial cancer for ever tea consumption vs non/lowest tea consumption



Squares indicated study-specific risk estimates (size of square reflects the study-statistical weight); *horizontal lines* indicate 95% confidence intervals; *diamond* indicates summary relative risk estimate with its corresponding 95% confidence interval.

CI, confidence interval; *OR*, odds ratio; *RR*, relative risk.

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cohort studies and all case-control studies were 0.97 (95% CI, 0.81–1.17) and 0.80 (95% CI, 0.77–0.94), respectively.

Figure 3 and Table 2 show the RRs for cohort studies and case-control studies separately and overall according to low to moderate and high level of tea consumption. The summary RR for low to moderate consumption of tea was 0.88 (95% CI, 0.78–0.98). No statistically significant heterogeneity was noted across the studies ($Q = 7.68$; $P = .175$; $I^2 = 34.9$). The summary RR was 1.05 (95% CI, 0.85–1.28) for cohort and 0.81 (95% CI, 0.71–0.93) for case-control studies. The pooled RR for high consumption of tea was 0.75 (95% CI, 0.64–0.88), with no significant heterogeneity between studies ($Q = 9.50$; $P = .148$; $I^2 = 36.8$). The RRs were 0.76 (95% CI, 0.52–1.10) for cohort studies and 0.72 (95% CI, 0.51–1.02) for case-control studies.

Given the wide array of measurement categories reported among studies, we also conducted dose-response analysis of tea consumption for endometrial cancer risk (Figure 4 and Table 2). Our data in-

TABLE 2
Summary risk estimates and 95% CIs for tea consumption and endometrial cancer risk

				Heterogeneity test		
Variables	**Study, n**	**Cases, n**	**RR (95% CI)**	**Q**	***P***	**I^2, %**
Ever drinkers vs non/lowest drinkers						
All studies	7	3487	0.85 (0.77–0.94)	10.15	.118	40.9
Cohort studies	2	366	0.97 (0.81–1.17)	0.98	.323	0.0
Case-control studies	5	3121	0.80 (0.77–0.94)	5.80	.215	31.0
Low to moderate drinkers vs non/lowest drinkers						
All studies	6	3258	0.88 (0.78–0.98)	7.68	.175	34.9
Cohort studies	2	366	1.05 (0.85–1.28)	0.78	.378	0.0
Case-control studies	4	2892	0.81 (0.71–0.93)	2.62	.454	0.0
High drinkers vs non/lowest drinkers						
All studies	7	3487	0.75 (0.64–0.88)	9.50	.148	36.8
Cohort studies	2	366	0.76 (0.52–1.10)	0.00	.972	0.0
Case-control studies	5	3121	0.72 (0.51–1.02)[a]	9.49	.050	57.9
Increment of 2 cups/d						
All studies	6	3258	0.75 (0.63–0.88)[a]	9.33	.097	46.4
Cohort studies	2	366	0.90 (0.77–1.05)	0.07	.793	0.0
Case-control studies	4	2892	0.66 (0.69–0.87)	2.26	.520	0.0

CI, confidence interval; *RR*, relative risk.

[a] Random-effect model.

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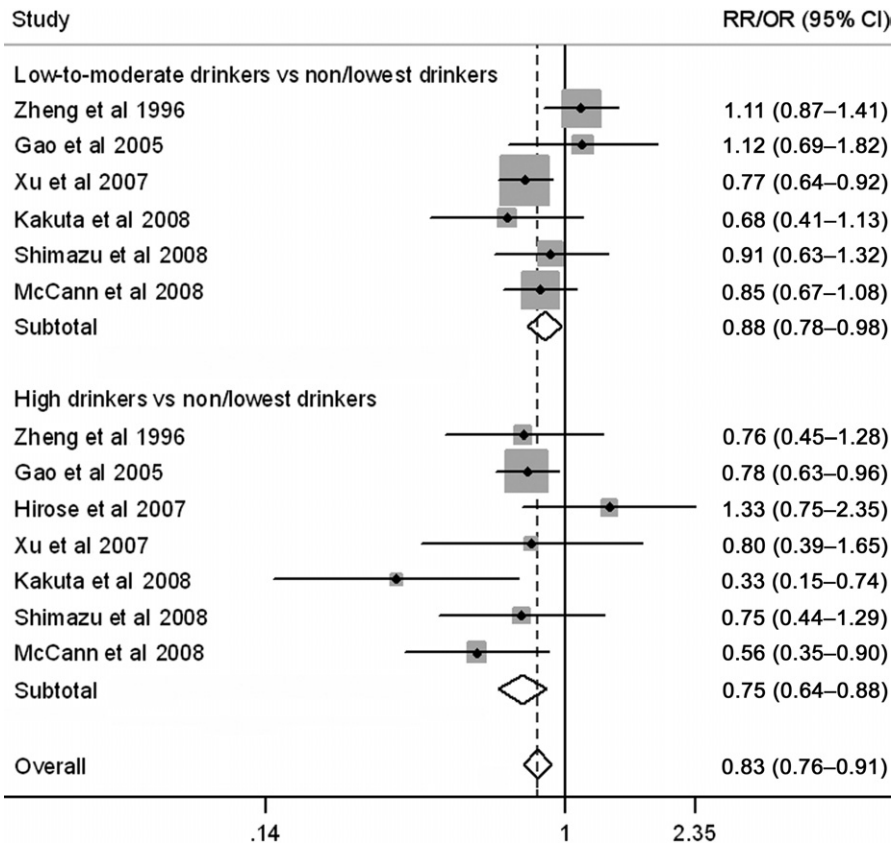
dicated that an increase in tea consumption of 2 cups/d was statistically significantly associated with a 25% decreased risk of developing endometrial cancer (RR, 0.75; 95% CI, 0.63–0.88). The RRs were 0.90 (95% CI, 0.77–1.05) for cohort studies and 0.66 (95% CI, 0.69–0.87) for case-control studies.

The results of subgroup analyses by tea type, study population, and tea assessment are shown in Table 3. In the subgroup analysis by tea type, we noted that green tea consumption was significantly associated with decreased risk of endometrial cancer (RR, 0.79; 95% CI, 0.69–0.90), whereas no such association was observed for black tea (RR, 0.75; 95% CI, 0.45–1.27). When subgroup analysis was conducted by study population, a statistical significant protective effect of tea consumption on endometrial cancer was observed in Asia (RR, 0.81; 95% CI, 0.71–0.93) but not the United States (RR, 0.90; 95% CI, 0.68–1.19). A subgroup analysis was also performed according to assessment method of tea consumption. Statistical significant association was observed among studies using interviewing techniques (RR, 0.81; 95% CI, 0.69–0.95) but not among studies using self-administered questionnaires (RR, 0.86; 95% CI, 0.70–1.07).

A sensitivity analysis in which 1 study was removed at a time was performed to evaluate the stability of the results. The summary RR ranged from 0.80 (95% CI, 0.72–0.90) (when excluding the study by Zheng et al[15]) to 0.87 (95% CI, 0.78–0.96) (when excluding the study by Kakuta et al[19]), indicating the stability of results. No indication of publication bias was observed from either visualization of funnel plot (Figure 5) or Egger's test ($P = .971$).

FIGURE 3
Summary RRs of endometrial cancer for low to moderate and high tea consumption vs non/lowest tea consumption



Squares indicated study-specific risk estimates (size of square reflects the study-statistical weight); *horizontal lines* indicate 95% confidence intervals; *diamond* indicates summary relative risk estimate with its corresponding 95% confidence interval.

CI, confidence interval; *OR*, odds ratio; *RR*, relative risk.

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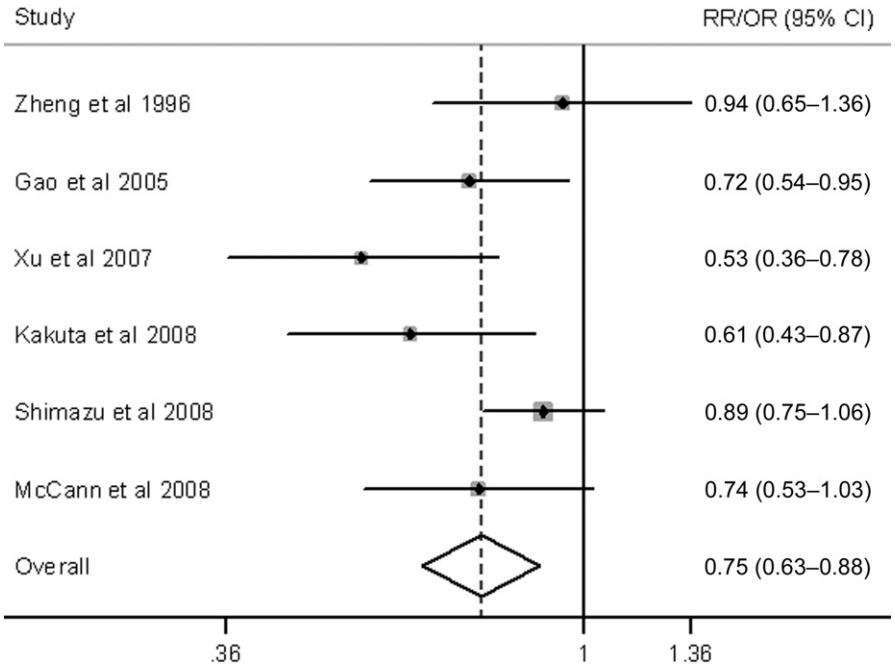
COMMENT

This metaanalysis summarized the evidence to date regarding the association between tea consumption and endometrial cancer risk, representing a pooled total of 3487 cases and 104,643 noncases. The results suggest that tea consumption was statistically significantly associated with reduced risk of endometrial caner.

Overall, there was no evidence of heterogeneity among the included studies on tea consumption and endometrial cancer risk. When the various studies were stratified by study design, we noted that the inverse association between tea consumption and endometrial cancer risk was more evident among case-control studies than among cohort studies. It was likely that the nonsignificant association observed among cohort studies may be due to chance because the 2 cohort studies with a small number of cases (249 cases in the study by Zheng et al,[15] and 117 cases in the study by Shimazu et al[16]) may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate.

The biologic mechanism whereby tea reduces the risk of endometrial cancer is likely to be multifactorial. The majority of established risk factors for endometrial cancer support a hormonal etiology.[26] An increased exposure to endogenous estrogen, such as early menarche, infertility, obesity, and late menopause, has been suggested to associate with increased risk of endometrial cancer.[26] Tea contains large amounts of caffeine, which has been shown to mediate changes in hormone levels including down-regulation of free estradiol and testosterone,[27,28] and up-regulation of plasma estrone and sex hormone binding globulin (SHBG).[28,29] In addition, tea contains a number of antioxidants, such as catechins, that could affect carci-

FIGURE 4
Summary RRs of endometrial cancer for an increase in tea intake of 2 cups/d



Squares indicated study-specific risk estimates (size of square reflects the study-statistical weight); *horizontal lines* indicate 95% confidence intervals; *diamond* indicates summary relative risk estimate with its corresponding 95% confidence interval.

CI, confidence interval; *OR*, odds ratio; *RR*, relative risk.

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nogenesis. Studies have demonstrated that epigallocatechin gallate, the major catechin in green tea, can significantly induce apoptosis and cell cycle arrest in human carcinoma cells.[30] It can also inhibit estrogen-induced activation of endometrial cells.[31] Tea catechins can also effectively scavenge relevant reactive oxygen and nitrogen species, including superoxide, peroxyl radicals, and singlet oxygen.[7,32] Besides caffeine and catchins, tea also contains large amounts of phytoestrogens, which have been suggested to exert a protective effect against endometrial cancer, probably because of their antiestrogenic properties.[33]

Furthermore, studies also reported a protective effect of tea-gene interaction on endometrial cancer. Xu et al[14] assessed interaction of tea consumption with CYP19A1 genetic polymorphisms in the development of endometrial cancer in a Chinese population-based case-control study. They found that tea consumption could modify the association of CYP19A1 polymorphisms rs1065779, rs752760, and rs1870050 with endometrial cancer ($P_{interaction} < .05$). Later Xu et al[13] also evaluated the potential effect of the Asp327Asn polymorphism in SHBG gene on the association between tea consumption and endometrial cancer. They found that the inverse association of tea consumption was more evi-

TABLE 3
Stratified analysis by tea type, study population and tea assessment for ever drinkers versus non/lowest drinkers

				Heterogeneity test		
Variables	**Study, n**	**Case, n**	**RR (95% CI)**	**Q**	***P***	**I^2, %**
Tea type						
Green tea	4	2468	0.79 (0.69–0.90)	2.83	.419	0.0
Black tea	2	2199	0.75 (0.45–1.27)	0.30	.586	31.0
Study population						
Asian	5	2697	0.81 (0.71–0.93)	5.90	.207	32.2
United States	2	790	0.90 (0.68–1.19)[a]	3.34	.068	70.1
Tea assessment						
Interview	2	2199	0.81 (0.69–0.95)	0.02	.881	0.0
Questionnaire	5	1288	0.86 (0.70–1.07)[a]	9.67	.046	58.6

CI, confidence interval; *RR*, relative risk.

[a] Random-effect model.

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dent for those with the Asp/Asp genotype of the SHBG Asp327Asn polymorphism, particularly premenopausal women ($P_{interaction} = .02$).

We also conducted subgroup analysis by tea types. Our data indicated that green tea but not black tea consumption was statistically significantly associated with reduced risk of endometrial cancer. It was probably because that different production technology of green and black tea may lead to the different components in them, thus to their different anticarcinogenesis properties.[34] In addition, it was also likely that the nonsignificant inverse association between black tea and endometrial cancer may be due to chance because only 2 studies were included in the analysis. Therefore, our results should be interpreted with caution.

In subgroup analysis by study population, we noted that significant association of tea consumption with decreased risk of endometrial cancer was observed only in Asia but not in the United States. The different observations may be explained, at least in part, by the variations of tea consumption among people in Asia and the United States. In the United States, people mainly consumed black tea, whereas in China and Japan, more than 90% of tea drinkers consumed green tea. In addition, a possible role of ethnic differences in genetic backgrounds and the environment they lived in or potential lifestyle differences should also be taken into account.

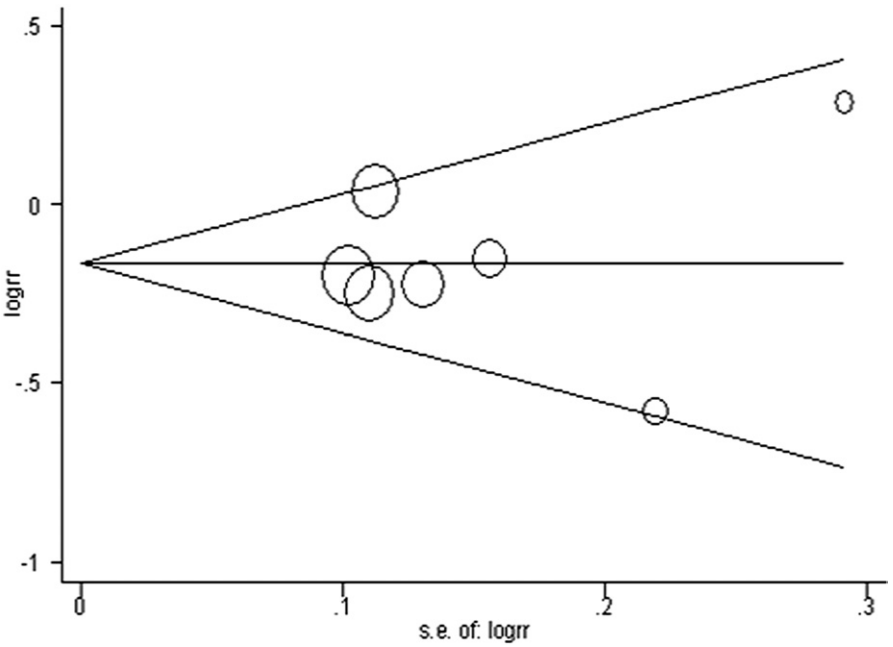
When subgroup analysis was conducted by tea assessment, we found that the inverse association between tea intake and endometrial cancer risk was stronger among studies using interviewing techniques than among studies using self-administered questionnaires. This contrast might be a consequence of response bias because of different assessment techniques or to chance alone.

Several studies have also estimated the potential effect of menopausal status on the association of tea consumption with endometrial cancer risk because the involvement of tea consumption in regulation of hormone levels.[27-29] The results from the study by Zheng et al[15] indicated that the protective effect of tea on endometrial cancer might be not significant in postmenopausal women ($P_{trend} = .47$). Their findings were consistent with the report by Gao et al[17] which also suggested that the inverse association of green tea with endometrial cancer was more evident among premenopausal women than postmenopausal women. Nevertheless, in this metaanalysis, the number of the studies on the association of tea with endometrial cancer among premenopausal or postmenopausal women was too small. Therefore, we could not draw a conclusion.

Several limitations should be taken into account when interpreting the results in our study. First, the observational studies included in this metaanalysis, even when well controlled, may have various sources of bias and confounding. Second, only published studies were included in this metaanalysis. Therefore, publication bias may have occurred although no publication bias was indicated from both visualization of the funnel plot and Egger's test. Third, our results are likely to be affected by some misclassification of tea consumption. Tea exposure is mostly assessed regarding the number of cups of tea consumed daily or weekly. However, cup size may vary considerably. Finally, studies included in this metaanalysis were major conducted in Japan, China, and the United States; therefore, the data should be extrapolated to other populations with caution.

In conclusion, the results of this metaanalysis provide evidence that tea consumption may be associated with reduced risk of endometrial cancer. Given the small number of studies, especially cohort studies, included in this metaanalysis, further prospective cohort studies with larger sample size, well-controlled confounding factors, and more accurate assessment of tea consumption are needed to affirm the protective effect of tea on endometrial cancer. ■

FIGURE 5
Begg's funnel plot with pseudo 95% confidence limits



Funnel plot indicating publication bias in the studies included in this metaanalysis. No indication of publication bias was note from both visualization of funnel plot and the Egger's test ($P = .971$).

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