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REVIEW

The association between green tea consumption and breast cancer risk: A systematic review and meta-analysis

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This systematic review and meta-analysis aimed to critically evaluate the relation between green tea (GT) consumption and the risk of breast cancer. Popular electronic databases were systematically searched for papers in English language. All case-control and cohort studies in addition to randomized clinical trials were included if they assessed the chemopreventive effects of GT on breast cancer. The quality of included studies was assessed using the Newcastle–Ottawa and Jadad scale. This systematic review comprised 14 studies: 9 case-control studies, 4 cohort studies, and 1 clinical trial. Odds ratio (OR) in case-control studies suggested that women in the group receiving the highest level of GT had 19% reduction in breast cancer risk compared with those who received the lowest level of GT (summary OR = 0.81, p = .031; 95% CI [0.66, 0.981]; heterogeneity, I^2 = 71.53, p < .001, random effect model; 9 studies). OR in cohort studies also showed no significant difference (OR = 0.99, p = .94; 95% CI [0.81, 1.138]; heterogeneity, I^2 = 19.06, p = .29; fixed-effect model; 4 studies). According to the only clinical trial, treatment with GT could not alter the mammographic density compared with placebo (26% vs. 25%). It cannot be concluded that GT consumption may decrease the risk of breast cancer. Due to high heterogeneity, a pooled analysis of case-control and cohort studies was not performed.

KEYWORDS

breast cancer, *Camellia sinensis*, green tea

1 | INTRODUCTION

Worldwide, the most-frequently observed neoplasm among women is breast cancer, which shows an increasing rate in many countries (Cabrera, Artacho, & Giménez, 2006; Siegel, Miller, & Jemal, 2018). Most recently published reports indicate that breast cancer is the first and second cause of cancer-induced death among women in developing and developed countries, respectively (Torre et al., 2015). Nonetheless, for many years, breast cancer was the leading cause of death even in developed countries (Boyle & Levin, 2008; Siegel et al., 2018).

Although the relationship between lifestyle-related parameters and breast cancer risk has been studied and some of them like breastfeeding, body fat, and adult attained height reached a "convincing" level but evidence indicating a relationship between some foods and breast cancer risk remains insufficient (Li et al., 2016). The lower rates of breast cancer in the Asian population who consume high levels of green tea (GT), has made the scientists to suggest a protective effect for GT against breast cancer (Schulze, Melzer, Smith, & Teschke, 2017), but the results of published epidemiological studies, which have evaluated the possible chemopreventive effects of GT in humans, are inconsistent (Inoue et al., 2008; Nagano, Kono, Preston, & Mabuchi, 2001; Shrubsole et al., 2009; Suzuki et al., 2004; Zhang, Holman, Huang, & Xie, 2006). Besides, it seems that GT extracts may be even hepatotoxic (Teschke, Zhang, Melzer, Schulze, & Eickhoff, 2014).

Generally, four different types of tea with different content of polyphenols are known. GT preparation like white tea does not lead

to fermentation or oxidation of polyphenols. However, during black tea preparation, marked amounts of polyphenols are oxidized. In this context, oolong tea is somehow between green and black tea (i.e., polyphenols are partially oxidized) (Mitscher et al., 1997; Unachukwu, Ahmed, Kavalier, Lyles, & Kennelly, 2010; Zhang et al., 2006).

The anticancer effects of GT polyphenols (i.e., catechins like epigallocatechin-3-gallate) have been supported by in vivo and in vitro studies (Cooper, Morré, & Morré, 2005a, b; Crespy & Williamson, 2004; Li, Yin, Wang, & Jiang, 2014; Satoh et al., 2002; Yang, Wang, Lu, & Picinich, 2009). It has been suggested epigallocatechin-3-gallate inhibits dihydrofolate reductase, which leads to apoptotic cell death in cancer cells (Lievers et al., 2001). However, epidemiological studies have noted controversial effects for GT from protective (Shrubsole et al., 2009; Wu, Yu, Tseng, Hankin, & Pike, 2003; Zhang et al., 2006) or null effects (Inoue et al., 2008; Nagano et al., 2001; Suzuki et al., 2004) to cancer-causing properties (Kumar et al., 2009). Low bioavailability and biotransformation in vivo are considered to be a reason leading to the contradictory results between in vitro and in vivo studies (Xiang et al., 2016).

Almost 20% of the global tea consumption comprises GT, and it has become a dietary supplement in recent years around the world. As mentioned above, it has been shown that high polyphenol content may reduce the risks of cancer and cardiovascular diseases (Cabrera et al., 2006; Schneider & Segre, 2009); however, data reported by epidemiological studies are inconsistent; thus, we evaluated the methods utilized in these studies and pooled their results to study the chemopreventive effects of GT on breast cancer using published human studies.

2 | METHODS

2.1 | Search strategy

We systematically searched electronic databases, namely, PubMed, Scopus, Web of Science, Cochrane, and ProQuest until October 3, 2017, for papers (in English) that studied the relationship between GT consumption and prevention of breast cancer in women. For this purpose, we search for terms related to *Camellia sinensis*, tea, polyphenol, diet combined with breast cancer and breast neoplasm. We scrutinized the reference list of review articles and meta-analysis studies to find relevant studies. Two reviewers independently checked all abstracts and full-text articles. The disagreement was resolved by discussion, and where no agreement was reached, an independent third-party acted as an arbiter.

2.2 | Selection criteria

All case-control and cohort studies, as well as randomized clinical trials (RCTs), were discussed in this systematic review if they studied the association between GT drinking and prevention of breast cancer.

Case-control and cohort studies were included into the meta-analysis if the odds ratio (OR) or relative risk (RR) values were calculated after adjustment for participants' age. Moreover, studies that were considered had adjusted the effect size on the basis of at least two variables of the following important variables: menarche age, nulliparous or number of births, receiving hormone replacement therapy or oral contraceptive, family history of breast cancer, and menopausal status.

RCTs were included if the effect of GT on the incidence of breast cancer was evaluated. However, as mentioned above, in vivo and in vitro studies, as well as duplicate and non-English studies, were not included.

2.3 | Quality assessment

Observational studies and clinical trials were assessed in terms of quality using the Newcastle–Ottawa Scale (NOS; Wells et al., 2015) and Jadad scale (Wells et al., 2015), respectively. The NOS comprises three items, namely, selection, comparability, and exposure or outcome. For case-control studies, case and control definition, case and control selection method, comparability of groups, data collection method, and non-response rate were assessed. Case-control studies of NOS score ≥ 7 (out of 10 points) were included in this systematic review. For cohort studies, representation of the exposed group, the selection method of nonexposed, ascertainment of exposure, lack of outcome at baseline, comparability of groups, assessment method, enough long follow-up period, and adequacy of follow-up visits were assessed. Furthermore, cohort studies of NOS score ≥ 7 (out of 13 points) were included in this systematic review.

The Jadad scale consists of three items, namely, randomization, the method of randomization, and blinding. Baseline comparability was also assessed. Two reviewers independently checked these criteria. Any disagreements were resolved by consensus or by consulting a third party.

2.4 | Data extraction

A checklist was prepared containing information such as the name of the author, year of publication, study location, study design, case and control population, follow-up duration (for cohort studies), sources of breast cancer information, dietary assessment instrument, outcome, and covariate adjustment. Data extraction was independently done by two authors.

2.5 | Outcome measures

OR estimation for case-control studies and risk or rate ratios for cohort studies were all assumed to be valid approximations of RR. Approximate risk of comparisons between groups receiving the highest and lowest levels of GT was used for the meta-analysis.

2.6 | Statistical analyses

The DerSimonian and Laird method were used to calculate a weighted average of the logarithms of RR. RR estimates were pooled using random effect model. The heterogeneity for each pooled estimate was assessed by Cochran's Q test and Begg's rank correlation test, and publication bias was assessed by Egger's regression model. Heterogeneity was considered if a $p < .1$ existed for the Q statistic. The

contribution of each study to the overall effect was assessed by sensitivity analysis.

3 | RESULTS

A total of 3,664 studies were found in the preliminary search of which 3,615 studies were excluded after reading the abstract and title. From the remaining 49 studies that were assessed in detail, 35 studies were excluded due to reasons explained in Figure 1. Finally, 14 studies were chosen to be discussed in this systematic review and meta-analysis (Figure 1).

The quality of 10 case-control studies was assessed, and it was observed that all of these studies had a NOS score ≥ 7 (Inoue et al., 2008; Iwasaki et al., 2014; Iwasaki, Inoue, Sasazuki, Miura, et al., 2010; Lee et al., 2005; Li et al., 2016; Mizoo et al., 2013; Shrubsole et al., 2009; Wang et al., 2013; Wu, Tseng, Van Den Berg, & Mimi, 2003; Zhang et al., 2006); however, one of the studies had not performed adequate adjustments for confounding variables and was not included in the meta-analysis (Lee et al., 2005). Moreover, the quality of four cohort studies was assessed; all these studies had a NOS score ≥ 7 and were included in the meta-analysis (Dai et al., 2010; Iwasaki, Inoue, Sasazuki, Miura, et al., 2010; Key et al., 1999; Suzuki et al., 2004). One RCT was found that met the Jadad scale criterion (Samavat et al., 2017). Characteristics of case-control and cohort studies are summarized in Tables 1 and 2.

Nine case-control studies were selected for the meta-analysis. The calculated OR (0.81) suggests that high GT consumption resulted in reduced breast cancer risk by 19% compared with subjects who consumed GT at low levels (summary OR = 0.81, p = .031; 95% CI [0.66, 0.981]; random effect model). Marked heterogeneity was seen among studies (I^2 = 71.53, p < .001). Figure 2 displays cumulative OR in case-control studies. Funnel plot was symmetrical and Egger's regression intercept (p = .96) suggested no significant publication bias. Sensitivity analysis was conducted to identify potential possible outlier study that may affect our results. After excluding the study done by Zhang et al. (2006), heterogeneity (I^2 = 38%, p = .122) and significance level (summary OR = 0.87, p = .075) of our results decreased to a non-significant level.

Four cohort studies were chosen for the meta-analysis of the association between GT drinking and breast cancer (Figure 3). It should be noted that in one of these studies, the results of two separate cohorts were mentioned. The OR was non-significantly different between women who had the highest levels of GT consumption and those with the lowest levels of GT consumption (OR = 0.99, p = .94; 95% CI [0.81, 1.138]; fixed-effect model). Concerning the cohort studies, heterogeneity was non-significant (I^2 = 19.06, p = .29). Funnel plot was symmetrical and Egger's regression intercept (p = .47) indicated no significant publication bias.

Based on our literature search, one randomized placebo-controlled clinical trial was done by Samavat et al. (2017) to assess the effect of GT drinking on breast cancer risk. They showed that treatment with GT could not alter the mammographic density compared with placebo (26% and 25%, respectively). Subgroup (categorized based on the participants' age) analysis was also performed. It was observed that 12-month treatment with GT significantly decreased mammographic density compared with placebo (4.4% vs. 1.02%; p = .05). However, this decrease reached borderline levels in older women (p = .07).

4 | DISCUSSION

The present meta-analysis focused on the chemopreventive effects of GT consumption on breast cancer risk. It has been widely indicated that GT consumption can decrease the risk of breast cancer. In pooled analysis of case-control studies, we found an 18% decreased risk whereas analysis of cohort studies did not indicate statistical significance. Due to high heterogeneity among studies, a pooled analysis of case-control and cohort studies was not performed.

The association between tea intake and breast cancer risk was inconsistent among epidemiological studies. The main reason was that studies performed in the USA or Europe actually investigated black tea, which has low levels of polyphenols. A meta-analysis found no

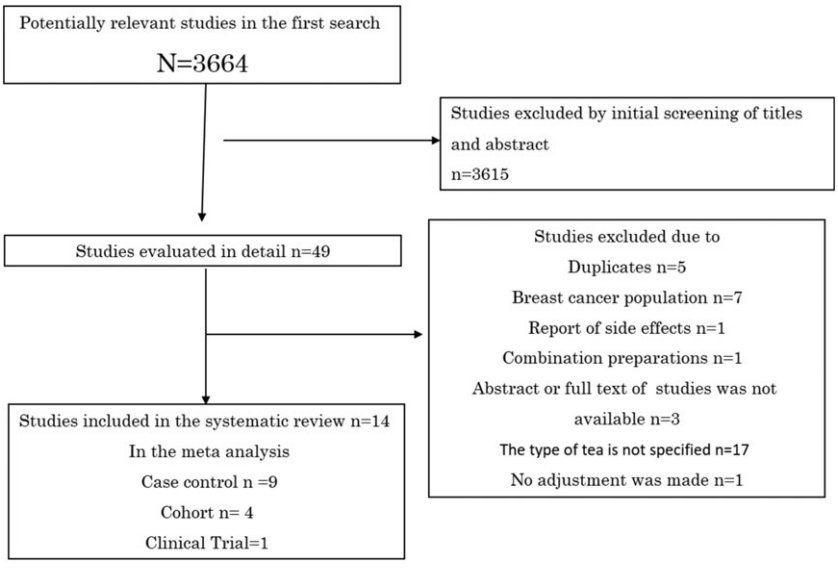

FIGURE 1 Search strategy of the study

TABLE 1 Characteristics of nine case-control studies included in this systematic review

Author	Year	Country	Study design	Case	Control	Sources of breast cancer information	Dietary instrument	Comparison groups (highest vs. lowest)	Outcome	Covariate adjustment
Li, M.	2016	Hong Kong	Case control	756	789	Hospital based	Standardized questionnaire	>3 cups/day vs. <1 cup/day	No association between tea drinking >3 cups/day and breast cancer risk OR = 1.53 (95% CI [0.71, 3.28])	Age menarche age parity age at first birth HRT family history BMI
Wang, L.	2013	Taiwan	Case control	157	314	Hospital based	FFQ	≥1 cup/day vs. <1 cup/day	No association between breast cancer and GT consumption, OR = 0.65 (95% CI [0.44, 0.97])	Perceived stress alcohol drinking smoking physical activity dietary factors education level menarche age HRT
Mizoo, T.	2013	Japan	Case control	472	464	Hospital based	Self-administered questionnaire	≥4 times/week vs. <1 time/week	Only 2–3 times/week; GT intake had a protective effect OR = 0.63 (95% CI [0.43, 0.93])	BMI alcohol drinking food intake (green and yellow vegetables, meat, egg, fish, milk, soy, fruits, and mushrooms) beverage (coffee and GT) physical activity menarche age education parity
Iwasaki, M.	2010	Japan	Nested case control	144	288	Hospitals and registry based	FFQ	<5 cups/day ≥5 cups/day	No significant association between GT consumption and breast cancer risk. p = .42	menarche age menopausal status age at menopause parity age at first birth nulliparous BMI alcohol drinking
Iwasaki, M.	2013	Japan	Case control	405	405	Hospital based	FFQ	>600 ml/day vs. <120 ml/day	No association between GT drinking >600 ml/day vs. <120 ml/day and breast cancer risk OR = 1.27 (95% CI [0.75, 2.14])	menopausal status parity family history smoking status physical activity vitamin supplement, oolong tea, black tea, coffee and canned coffee consumption
Shrubsole, MJ.	2009	China	Case control	3,554	3,474	Registry	FFQ	Ever[a] vs. never	Never: Ref Regularly: OR = 0.88 (95% CI [0.79, 0.98])	age, study phase education family history

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Study design	Case	Control	Sources of breast cancer information	Dietary instrument	Comparison groups (highest vs. lowest)	Outcome	Covariate adjustment
									Premenopausal: Regularly: OR = 0.87 (95% CI [0.76, 1]) Postmenopausal: Regularly: OR = 0.88 (95% CI [0.74, 1.04])	a history of fibroadenoma menarche age parity age at first birth menopause age physical activity waist/hip ratio total energy, fruit, vegetable, and fat intake
Inoue M.	2008	Singapore	Nested case control	380	662	Registry	24 hr food recalls	Daily vs. none or <weekly	No association between GT and breast cancer risk	Age education BMI menarche age parity black tea consumption
Zhang, M.	2007	China	Case control	1,009	1,009	Hospital based	Structured questionnaire	At least twice/day vs. never or seldom	No association between GT intake and breast cancer risk	location education BMI number of children breastfed menopausal status OCP use HRT benign breast diseases Family history total energy, soy, vegetables and fruits intake passive smoking alcohol and coffee drinking physical activity
Wu, A. H.	2003	USA Chinese, Japanese, or Filipino women	Case control	501	594	Registry	Structured questionnaire	>0.85.7 ml/day vs. non-drinker	A significant association between amount of GT consumption and breast cancer risk	age ethnicity location employment status Education menarche age BMI total caloric, intake of soy, dark green vegetable intake menopausal status HRT smoking alcohol drinking physical activity family history

Note. BMI = body mass index; FFQ = food frequency questionnaire; GT = green tea; HRT = hormone replacement therapy; OCP = oral contraceptive pill.

[a]Ever: drank tea regularly as at least twice per week for at least 3 months continuously.

TABLE 2 Characteristics of four cohort studies included in this systematic review

Author	Year	Country	Study design	Case	Study population	Follow up duration	Source of breast cancer information	Dietary instrument	Comparison groups	Relative risk (CI)	Covariate adjustment
Iwasaki, M.	2010	Japan	Cohort I (1990–1994) Cohort II (1995–1998)	581 350	53,793 43,639	13.6 years 9.5 years	Population based	Dietary records for 28 days (7-day dietary records in four seasons) or 14 days	≥5 cups/day vs. <1 cup/day	No association between tea consumption and breast cancer risk	location menarche age menopause age menopausal status parity age at first birth BMI alcohol intake smoking status physical activity HRT family history Oolong tea, black tea, coffee, and canned coffee intake
Dai, Q.	2010	China	Cohort	614	74,942	7.3 years	Population based	Structured questionnaire	Regular[a] vs. non-regular	No association between tea consumption and breast cancer risk	Education statue income family history history of fibroadenoma BMI WHR physically activity smoking status passive smoking alcohol drinking menarche age age at first live birth menopausal status menopause age HRT total energy, fruits, red meat, fish vegetables, ginseng, and isoflavones intake
Suzuki, Y.	2004	Japan	Cohort I (1984) Cohort II (1990)	103 119	14,409 20,595	9 years 7 years	Population based	Self-administered questionnaires	≥5 cups/day vs. <1 cups/day	No association between tea consumption and breast cancer risk in both cohorts	health insurance menarche age age at first birth menopausal status parity family history smoking alcohol drinking body mass index black tea and coffee consumption

(Continues)

TABLE 2 (Continued)

Author	Year	Country	Study design	Case	Study population	Follow up duration	Source of breast cancer information	Dietary instrument	Comparison groups	Relative risk (CI)	Covariate adjustment
Key, T. J.	1999	Japan	Cohort 1969–1970 1979–1980	427	34,759	Until 1993	Population based	Dietary questionnaire	≥5/day vs. ≤ 1/day	No association between tea consumption and breast cancer risk	year city age at the time of bombings radiation dose menarche age parity BMI

Note. BMI = body mass index; HRT = hormone replacement therapy; WHR = waist-to-hip ratio.

[a]Regular: green tea drinking of ≥3 times/week for at least 6 months.

relationship between black tea consumption and breast cancer (Sun, Yuan, Koh, & Yu, 2005). In Asian populations, where GT is routinely consumed, the results were inconsistent. Three possible explanations for this variability among the reported data are gene–nutrient, nutrient–nutrient, and stress–nutrient interactions. Concerning the gene–nutrient interaction, certain genes may modify the anticarcinogenic activity of GT polyphenols. Protective effect of regular drinking of GT on the risk of breast cancer has been shown only in women who had a highly active genotype of the angiotensin-converting enzyme gene (Yuan, Koh, Sun, Lee, & Yu, 2005). Nutrient–nutrient interaction occurs as GT polyphenols may have anticarcinogenic properties through competing with folate in the folate pathway (Inoue et al., 2008). The stress–nutrient interaction was concluded from a study in which researchers found no association between GT consumption and breast cancer, but they observed that higher stress in the absence of GT consumption was associated with a higher risk of breast cancer. It has been reported that GT intake is associated with lower psychological stress (Hozawa et al., 2009). This effect can be mainly explained by the fact that GT contains L-theanine and ascorbic acid, which can reduce blood pressure, cortisol levels, and heart rate (Brody, Preut, Schommer, & Schürmeyer, 2002; Kimura, Ozeki, Juneja, & Ohira, 2007; Wang et al., 2013).

It seems that inconsistencies among the data are consequences of different study designs. Whereas case-control studies may be influenced by recall bias, cohort studies may be affected by measurement and misclassification bias. Here, the following factors were measured in some—not all—studies that can explain the heterogeneity in case-control studies: lack of detailed data on the level of GT intake, geographic zone and conditions of GT cultivation, and methods used to brew the tea (i.e., amount of tea used, strength, temperature, and brewing time). These factors can influence polyphenols content of GT (Wu, Yu, et al., 2003). Also, different studies used various explanations (i.e., terms) for the amount and frequency of GT consumption. The above-mentioned points along with a narrow range of exposure (i.e., lack of unexposed subjects meaning that only a very small proportion of the participants were non-drinkers and individuals with a daily consumption of one cup were considered as reference group), low statistical power due to low incidence of breast cancer, or even measurement error may had led the results to null. These measures are especially important because a significant inverse dose–response relationship has been shown between increasing duration, frequency and quantity of GT consumption and breast cancer risk (Zhang et al., 2006).

In a study, the plasma levels of polyphenols were measured to investigate the relation between plasma polyphenols and GT drinking habit; based on the results, no association was found. Authors believed that because a large proportion of participants had no detectable plasma level of tea polyphenols, either it could be attributed to the poor bioavailability of these compounds or even analytical errors (Iwasaki, Inoue, Sasazuki, Sawada, et al., 2010).

Another important covariate that should be considered in future studies is the menopause status. It has been reported that GT drinking is associated with a reduced risk of breast cancer among premenopausal women but it is surprisingly associated with an increased risk among postmenopausal women. It has been suggested that GT effects might be modified by estrogen receptors (Li et al., 2016).

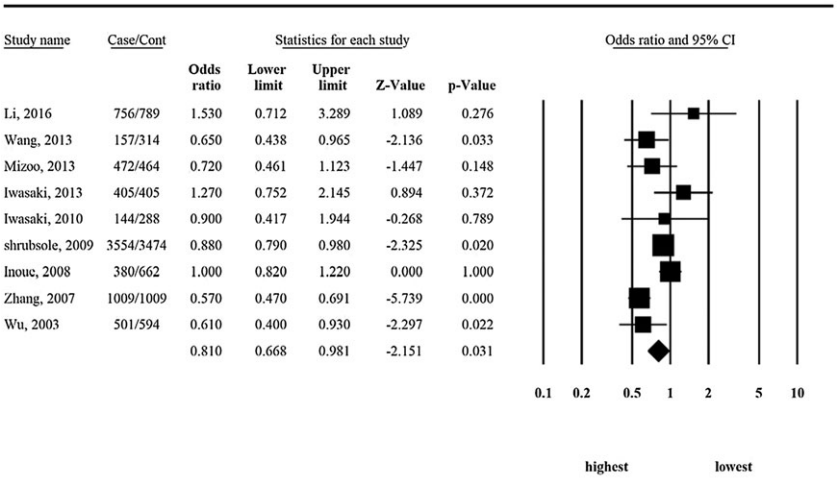

FIGURE 2 Pooled analysis of case-control studies

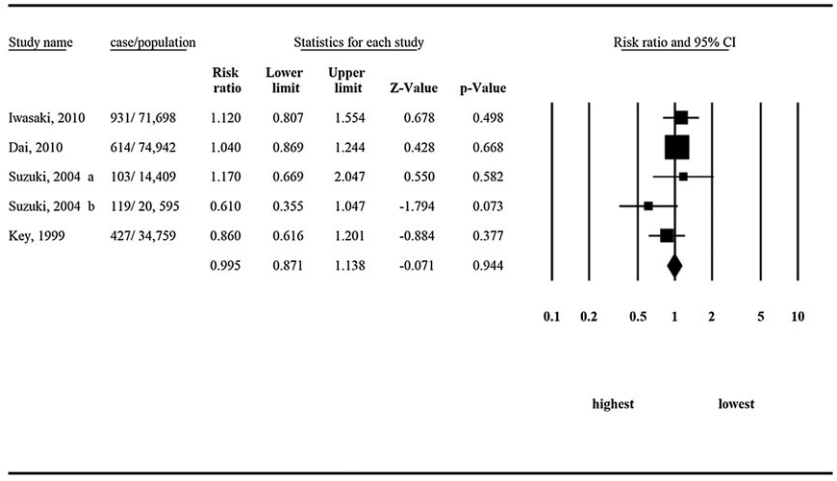

FIGURE 3 Pooled analysis of cohort studies (a and b are the results of two separate cohorts)

With regard to the above-mentioned gene–nutrient theory, the level of expression of genes associated with breast cancer is different in premenopausal and postmenopausal women (Mizoo et al., 2013). The protective effect seems to be cumulative because in premenopausal women, the years of GT drinking as well as the frequency and amount, were the main predicting factors. On the other hand, recent use and lower amounts of GT intake were the main determinants among postmenopausal women; however, a U-shaped relationship was observed between the amount of tea consumption and risk of breast cancer in both premenopausal and postmenopausal groups (Shrubsole et al., 2009). It can be also concluded that GT may primarily delay cancer progression. In other words, in premenopause patients, drinking GT delays disease onset from premenopause to postmenopause (Dai et al., 2010). Considering the misclassification of exposure that influences the cohort studies, these findings were not supported by Iwasaki, Inoue, Sasazuki, Sawada, et al. (2010).

A pooled analysis of two cohorts found no relationship between drinking GT and breast cancer (Suzuki et al., 2004). A previously reported meta-analysis found that greater GT intake is associated with a marginally diminished risk of breast cancer recurrence (Ogunleye, Xue, & Michels, 2010). Similar to our study, this meta-analysis found inconsistent results among reports with different study designs. A more recent systematic review concluded that the longevity of GT consumers is probably due to other factors like genetic or lifestyle factors (Schulze et al., 2017). Although a higher number of studies was included in our review, as compared with that published by Ogunleye et al. (2010), heterogeneity was present in results, which were mainly due to various data collection methods. Moreover, we only included studies that were controlled for at least two of four main cofounders, which can reduce the overall confounding effects. Although similar to conventional drugs, systematic review offers the most reliable evidence of efficacy (Izzo, Hoon-Kim, Radhakrishnan, & Williamson, 2016), it seems that a clinical suggestion for this issue is still vague. Together, it seems that more carefully designed clinical trials can help us to draw conclusions on the effect of drinking GT on breast cancer risk.

5 | CONCLUSION

Epidemiological studies have drawn inconsistent conclusions regarding the association between GT intake and breast cancer risk. Nonetheless, it cannot be concluded that GT consumption may decrease the risk of breast cancer. We did not find any statistically significant

reduction of breast cancer risk due to GT consumption in case-control nor cohort studies. Due to high heterogeneity, a pooled analysis of case-control and cohort studies was not performed.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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