Systematic Review and Meta-Analysis

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Green tea consumption and risk of breast cancer

A systematic review and updated meta-analysis of case-control studies

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Abstract

Background: As the most popular beverage in East Asia, green tea (GT) has various biological activities effects such as anti-mutation, anti-oxidation, and anti-tumor. In this study, we aimed to evaluate whether GT consumption could be an effective way to decrease the risk of breast cancer.

Methods: We had performed a systematic review and updated meta-analysis of published case–control studies to evaluate the association between GT intake and the risk of breast cancer. Searching strategies were performed by the following keywords "Breast cancer," "breast neoplasm," and "green tea," with derivations and different combinations. The following databases were searched: PubMed, Cochrane Library, EMBASE, Web of science, China National Knowledge Infrastructure, WanFang, and China Biology Medicine disc. Studies published in both English and Chinese were considered for inclusion. Risk of bias was assessed through the Newcastle-Ottawa Scale (NOS). All data were analyzed through using Review Manager 5.1 software.

Results: Fourteen studies fulfilled inclusion criteria for meta-analysis, yielding a total of 14,058 breast cancer patients and 15,043 control subjects. Individuals with the habit of drinking GT were found to have a negative association with the risk of future breast cancer (odds ratio 0.83; 95% confidence interval: 0.72–0.96) despite significant heterogeneity. In subgroup analyses, the negative correlation was still found in studies using registry-based controls, NOS grades ≥6 and the number of cases <500.

Conclusions: GT consumption may have a decreased incidence of breast cancer despite significant heterogeneity. However, owing to the quality of available studies, more properly designed trials are warranted to clarify the association between GT consumption and breast cancer.

Abbreviations: CBM = China Biology Medicine disc, CIs = confidence intervals, CNKI = China National Knowledge Infrastructure, GT = green tea, NOS = Newcastle-Ottawa Scale, ORs = odds ratios, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RRs = risk ratios.

Keywords: breast cancer, green tea, meta-analysis

1. Introduction

Breast cancer is one of the most common malignant tumors in the world after lung cancer. The incidence rate of breast cancer is 10.4% of all cancers, which is the leading cause of death in women aged between 20 and 50 years.[1] Epidemiological studies have shown that people in areas with a low incidence of breast cancer and then immigrate to countries with higher rates of breast cancer, will increase the incidence of breast cancer.[2] This evidence points out that environmental factors and lifestyle may play an essential role in the pathogenesis of breast cancer. Besides, there are still some regional differences in the incidence of breast cancer between different countries. Compared with the United States and European countries, some Asian countries like China and Japan have lower breast cancer mortality rates.[3]

The habit of drinking green tea (GT) is a prominent feature of the diet structure in East Asian countries. Tea, especially GT, contains lots of polyphenols, which are a mixture of polyhydroxy phenolic compounds. Many studies have confirmed that tea polyphenols have various biological activities and pharmacological effects such as antimutation, antitumor, or antioxidation.[4–6] Animal experiments have also shown that drinking tea can reduce the risk of oncology in the skin, intestine, breast, and other organs.[7–9]

Different kinds of viewpoints occurred in this filed. A cohort study of a Japanese population showed that the risk of developing tumors was significantly lower in those who drank >10 cups of GT a day (odds ratio [OR]=0.59, 95% confidence interval [CI]:0.35–0.98).[10] Conversely, a study of western women's eating habits suggested that there was no relationship between tea drinking and the risk of breast cancer.[11] Because of the significant differences in epidemiological studies on the relation-

Editor: Kou Yi.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

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Medicine (2019) 98:27(e16147)

Received: 17 February 2019 / Received in final form: 24 May 2019 / Accepted: 29 May 2019

http://dx.doi.org/10.1097/MD.0000000000016147

ship between tea consumption and risk of breast cancer in Asian and Western countries, it is difficult to obtain a reliable conclusion. In this study, we conducted an updated systematic review and meta-analysis of 14 case–control studies to further determine the relationship between the risk of breast cancer and GT consumption.

2. Materials and methods

2.1. Ethics statement

Because the data in this meta-analysis were based on previously published studies, the present study does not require ethical approval or patient consent.

2.2. Selection criteria

For inclusion of our study, trials were required to describe:

1) A case–control design, published in Chinese or English.
2) Reported ORs or risk ratios (RRs), with 95% CIs for exposure, or provide sufficient information for us to calculate them.
3) Studies that assessed the correlation between GT drinking and prevention of breast cancer risk.
4) The diagnosis of breast cancer should be made according to diagnostic criteria, and the subjects in control groups should not have any history or sign of breast cancer.

For the exclusion of our study, trials were required to met at least one of the following criteria:

1) Case reports, case series, review articles, and clinical guidelines.
2) Duplicate studies in >1 databases.
3) Incomplete literature.
4) Low-quality case–control studies (Newcastle-Ottawa Scale [NOS] score between 1 and 4).

2.3. Search strategy

To fulfill the purpose of this study, we had searched scientific articles in the following electronic databases: PubMed, Cochrane Central Register of Controlled Trials, EMBASE, Web of science, CNKI, WanFang, and CBM. All articles were published previous to September 2018. For this purpose, we search for terms related to tea, GT combined with breast neoplasm, or breast cancer with derivations and different combinations. The full search strategies used in the mentioned databases are shown in Supplementary Table 1, http://links.lww.com/MD/D72. Also, to identify scientific studies related to the topic of this systematic review, a manual search of the references from already published studies was conducted.

2.4. Study selection and data extraction

All researchers had received complete system evaluation training. Two researchers (Y-SB and Z-LZ) independently searched the literature, read the title and abstract for the first selection, and then read the full-text review to exclude nonconforming literature. Later, 2 researchers independently extracted the relevant literature which included the first author, year of the publication, study period, source of breast cancer information, country, age, sample size, tea consumption level, and compared the extracted content. If there existed any disagreement, it would be resolved by researching and discussing the literature again together. If there were still disagreements, the third researcher (R-Y) would come to fix it.

2.5. Quality assessment

Methodological quality was evaluated by using the NOS by 2 reviewers (Y-SB and Z-LZ) for assessing the risk of bias in observational studies.[12] The NOS contained 8 items that were categorized into 3 major components which were a selection of cases and controls, comparability of the groups, and ascertainment of the outcome of interest, and were evaluated using the Star system. Discrepancies between 2 reviewers were settled through discussion until a consensus was reached.

2.6. Statistical analysis

This system review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[13] The Review Manager (version 5.1) was used to analyze the association between GT consumption and the risk of breast cancer. Meta-analyses of the risk of breast cancer outcomes were carried out by generating pooled ORs with 95% CIs. The presence of heterogeneity between studies was assessed by χ^2 statistics, and the extent of inconsistency was assessed by I^2 statistics. With the I^2 statistic, $I^2 < 25\%$ was considered as low-level heterogeneity, 25% to 50% at a moderate level, and >50% as high level. Besides, we defined $P \geq .1$ and $I^2 < 50$ as an indicator that the results have a good agreement, and the fixed-effects model was employed. Whereas $I^2 > 50\%$ was defined as an indicator of striking heterogeneity between the data, and the random-effects model was employed.

To explore the heterogeneity between studies, we conducted subgroup analyses stratified by the number of cases, the source of the case groups, and NOS grades. We also elevated the impact of geographic location on the association between GT intake and the risk of breast cancer. Sensitivity analysis was performed by excluding each study individually to assess its influence on the overall result of the meta-analysis. Publication bias was detected graphically using a funnel plot of a trial's effect size against the standard error.

3. Results

3.1. Literature search and study selection

The process of how we screened and selected the trials was shown in a flow chart (Fig. 1). The initial number of our research result was 1129, of which 1075 were deemed duplicated or ineligible after screening of titles and abstracts. Another 54 reports were excluded from our final analysis for the following reasons: 29 were not case–control studies, 11 were not the breast cancer-related articles. The remaining 14 eligible cases were included in our analysis.

3.2. Characteristic of studies

The total number of women included for analysis in this review was 29,101. The publication date of these articles was between 2002 and 2016, and patients' age ranged from 32 to 71 years. The lowest number of participants was 432 (Iwasaki et al, 2010), whereas the largest group size was 9545 patients (Nagi et al, 2009).[25]

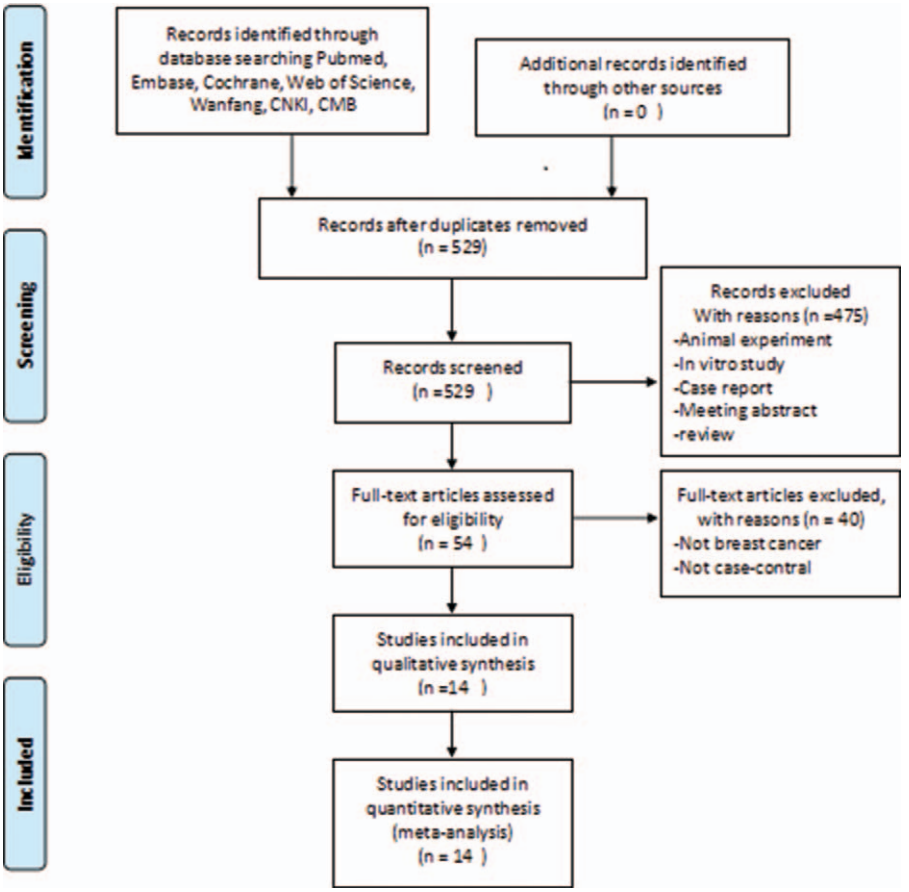

Figure 1. Flowchart of the selection of the clinical trial.

The total number of breast cancer cases in the included studies were 14,058. Of all these cases, 5384 of them having the habit of drinking GT. These cases were compared with 15,043 non-breast cancer individuals in the general population and hospital setting, of whom 6142 were drinking GT in their daily life. Of all studies, 2 studies were conducted in the United States, and the rest 12 studies were in Asia. Breast cancer was identified with hospital-based sources for 11 studies, registry for 3 studies. The details and characteristics of the included studies were listed in Table 1.[15–28] The quality of included studies was moderate or good, varying from 5 to 7 points (Table 2).

3.3. Outcomes and meta-analysis

We conducted a meta-analysis with all 14 identified studies that reported results associated with GT consumption and risk of breast cancer. The pooled summary OR was 0.83 (95% CI: 0.72–0.96) in a random-effect model for breast cancer patients, compared with non-breast cancer individuals (Fig. 2). Significant heterogeneity was seen among these studies ($P < .00001$, $I^2 = 84\%$). The present study revealed a significant protective association between GT consumption and breast cancer risk.

To further evaluate the association between the risk of breast cancer and GT consumption, subgroup analyses were adopted. The stratification are based on the geographic location, source of case group, NOS grades and number of cases (Table 3). No significant difference was found between cases and control for the prevalence of breast cancer in Asia or North America separately. Three of studies using registry-based controls reported negative correlation (OR: 0.84; 95% CI: 0.73–0.98) with low heterogeneity ($P = .18$, $I^2 = 41\%$), whereas the other hospital-based controls reported no significant association (OR: 0.84; 95% CI: 0.69–1.02) with significant heterogeneity ($P < .00001$, $I^2 = 87\%$). A negative correlation was founded between the risk of breast cancer and GT intake in subgroup analyses by the number of cases <500 (OR: 0.83; 95% CI: 0.74–0.93), and with low heterogeneity ($P = 0.31$, $I^2 = 15\%$). Compared with the group of which NOS grades were <6, the group with NOS grades ≥6 reported inverse association (OR: 0.87; 95% CI: 0.80–0.94), and the heterogeneity decreased a lot ($P = 0.49$, $I^2 = 0\%$).

Sensitivity analysis was also performed to detect the influence of individual study on the pooled estimate by omitting 1 study from the pooled analysis each time. The exclusion of each single study did not significantly change the pooled OR, and the ORs ranged from 0.80 (95% CI: 0.70–0.93) after excluding the study by Li et al, 2016, to 0.89 (95% CI: 0.56–0.95) after excluding the study by Zhang et al, 2007. In general, this meta-analysis showed that the association between GT consumption and the risk of breast cancer was relatively stable.

3.4. Assessment of publication bias

To some extent, this visual inspection of the funnel plot indicated the existence of publication bias (Fig. 3).

Table 1

Study included in this systematic review.

Study	Location	Study period	Source of breast cancer Information	Number of case Subjects	Mean age of Case	Number of control subjects	Mean age of control	Tea consumption Level	Outcome
Tao et al, 2002[28]	China	1999	Hospital-based	356	51.98±11.38	925	56.43±11.21	60 g/month-300 g/month	GT intake had a protective effect
Li et al, 2014[15]	China	2012–2013	Hospital-based	464	46.78±10.36	464	46.58±10.84	≤1 cup/day-≥3 cup/day	GT intake had a protective effect
Inoue et al, 2008[16]	Singapore	2012–2013	Registry	380	55.8±7.6	662	55.8±8.0	Daily-never/<weekly	No association between GT intake and breast cancer risk
Zhang et al, 2007[23]	China	2004–2005	Hospital-based	1009	48.4±10.3	1009	48.4±10.3	Never-≥twice/day	No association between GT intake and breast cancer risk
Wu et al, 2003[21]	USA	1995–1998	Registry	501	—	594	—	Never-≥85.7 mL/day	GT intake had a protective effect
Li et al, 2016[18]	HongKong	2011–2014	Hospital-based	756	—	789	53.5	≤1 cup/day–≥3 cups/day	No association between GT intake and breast cancer risk
Wang et al, 2013[20]	Taiwan	2009–2011	Hospital-based	157	—	314	—	≤1 cup/day-≥1 cup/day	No association between GT intake and breast cancer risk
Mizoo et al, 2013[26]	Japan	2010–2011	Hospital-based	472	54.72±12.45	464	53.56±11.00	≤1 times/wk–≥4 times/wk	GT intake had a protective effect
Iwasaki et al, 2010[27]	Japan	1990–2002	Hospital-based	144	52	288	52	≤5 cups/week–≥5 cups/day	No association between GT intake and breast cancer risk
Iwasaki et al, 2014[17]	Japan	1990–2002	Hospital-based	369	54.0	369	53.5	>600 mL/day–<120 mL/day	No association between GT intake and breast cancer risk
Nagi et al, 2009[25]	USA	1998–2001	Hospital-based	5059	—	4486	—	Never-≥3 cups/wk	No association between GT intake and breast cancer risk
Shrubsole et al, 2009[19]	China	1996–2005	Registry	3554	49.7±8.3	3474	50.0±8.9	Never-ever	GT intake had a protective effect
Li et al, 2011[24]	China	2009–2010	Hospital-based	540	56.2±10.6	540	56.2±10.6	≤500 g/year–≥1000 g/year	No association between GT intake and breast cancer risk
Yuan et al, 2005[22]	Singapore	1994–1999	Hospital-based	297	59.7±7.8	665	59.7±7.8	Never-≥1 time/wk	GT intake had a protective effect

GT = green tea.

Table 2

Quality assessment of included studies according to the Newcastle-Ottawa Scale.

Item/study	Tao et al, 2002[28]	Li et al, 2014[15]	Inoue et al, 2008[16]	Zhang et al, 2007[23]	Wu et al, 2003[21]	Li et al, 2016[18]	Wang et al, 2013[20]	Mizoo et al, 2013[26]	Iwasaki et al, 2010[27]	Iwasaki et al, 2013[17]	Nagi et al, 2009[25]	Shrubsole et al, 2009[19]	Li et al, 2011[24]	Yuan et al, 2005[22]
Adequate definition of cases	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Represent activeness of cases	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Selection of control subjects	*	—	*	—	*	—	—	—	—	—	—	*	—	—
Definition of control subjects	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Control for important factor or additional factor	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Expose assessment	—	—	*	—	—	—	—	*	—	—	—	*	—	—
Same method of ascertainment for all subjects	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Non-response rate	—	—	—	—	—	—	—	—	—	—	—	—	—	—

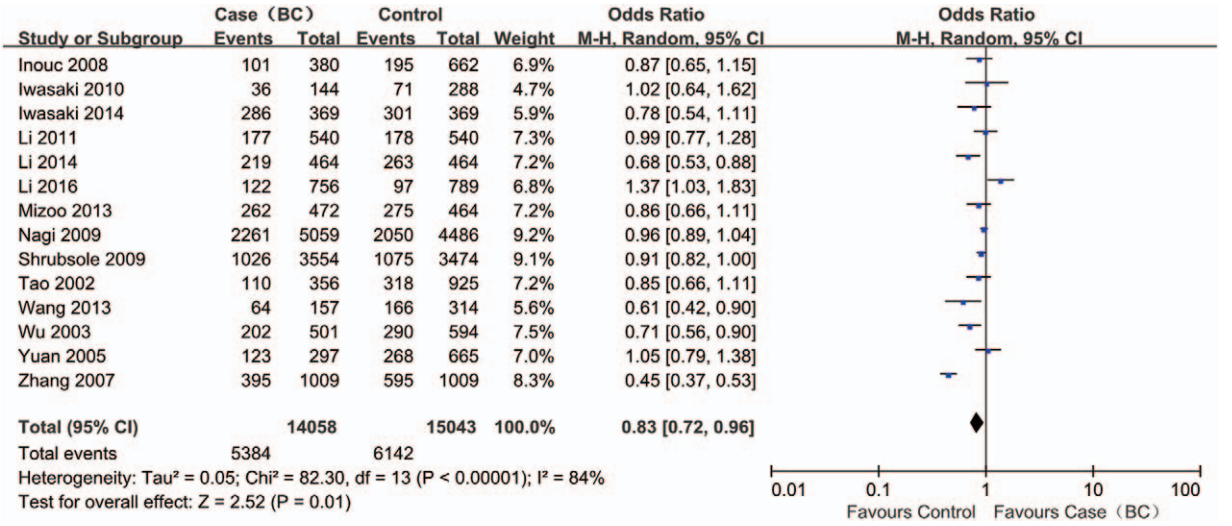

Figure 2. Forest plot of green tea consumption and risk of Breast cancer.

Table 3

Subgroup analysis of the association between green tea intake and the risk of breast cancer.

Category of variables	Variables of study characteristics	Number of studies	OR (95% CI)	I^2	*P* heterogeneity
Geographic location	Asia	12	0.83 (0.70–1.00)	84%	≤.00001
	North America	2	0.84 (0.64–1.13)	82%	.02
Source of the case group	Registry	3	0.84 (0.73–0.98)	41%	.18
	Hospital-based	11	0.84 (0.69–1.02)	87%	≤.00001
NOS grades	≥6	5	0.87 (0.80–0.94)	0%	.49
	<6	9	0.83 (0.66–1.06)	90%	≤.00001
Number of cases	≥500	6	0.84 (0.66–1.07)	93%	≤.00001
	<500	8	0.83 (0.74–0.93)	15%	.31

CI = confidence interval, OR = odds ratio.

4. Discussion

Since ancient times, GT had been known as a healthy drink, and it was famous for its antioxidant capacity. In animal experiments, Kathryn et al[14] had shown that GT extract or catching could inhibit the growth rate of breast cancer and reduced its invasiveness. In this study, we conducted a detailed systematic review and meta-analysis of case–control studies to evaluate the relationship between GT consumption and the risk of breast cancer.

The result of this updated systematic review had been widely indicated that GT consumption could reduce the risk of breast cancer. However, significant heterogeneity was seen among these studies. In subgroup analyses, the negative correlation was still observed in studies using registry-based controls; NOS grades ≥6 and the number of cases <500. Geographic location showed that there was no significant association. No association was found in studies using hospital-based controls, NOS grades <6, and number of cases >500.

In a meta-analysis of observational studies especially when the sizes of studies were relatively small, the issue of confounding was mainly a concern. To detect the degree to which potential confounders might have influenced the finding, a subgroup analysis was performed according to geographic location, the source of the case group, NOS grades, and number of cases. Besides, we also need to notice the study design, which will induce the difference results from the association between GT intake and the risk of breast cancer. From the perspective of epidemiology and etiology, cohort studies have more advantages because they can directly determine the relationship between disease and factors. However, because breast cancer was a chronic disease, so in practice, the cohort study was confined for it is hard to do a long follow-up with large populations. Furthermore, withdraw bias would appear because lost to follow-up was inevitable. Comparatively, case–control studies might provide some advantages in time-consuming, money-spending, and withdraw bias.

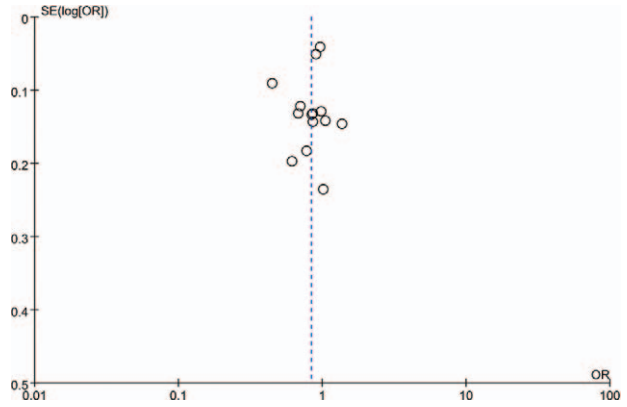

Figure 3. Funnel plot of green tea consumption and risk of breast cancer.

Here are the limitations. First, caution should be noticed about significant heterogeneity in the overall estimate provided in this study. Heterogeneity exists regarding geographic location, hospital-based controls, NOS grades <6, and number of cases >500. Even though we use the random-effect models in this meta-analysis, it is still hard to explain these differences. Second, publication bias should be brought to our attention too, for some small studies with null results would not like to publish their results. Owing to the publication bias, results of the relationship between GT consumption and the risk of breast cancer could be overestimated. Third, potential bias such as information bias or misclassification bias could not be excluded in this study because our findings are based on the result of case–control studies. Fourth, most studies in this meta-analysis did not specify the onset stage of the breast cancer, so it is hard to know whether the patients have the GT consumption before or after the onset of the breast cancer. Finally, the language other than English and Chinese might not be included in this systemic review.

In conclusion, evidence from case–control studies suggested that GT consumption might have a decreased incidence of breast cancer despite significant heterogeneity. However, owing to the small number of available clinical trials and the quality of the available studies, our results and those outcomes still need to be confirmed by large-sample and high-quality researches in the future.

Author contributions

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Writing – review & editing: Ke Wang, Yu Yan, Yu Ren.

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