Original Article

Green tea and gastric cancer risk: meta-analysis of epidemiologic studies

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Objective: To evaluate the association between green tea consumption and the risk of gastric cancer. **Methods:** Electronic search of the Cochrane Library, MEDLINE, EMBASE and Chinese Bio-medicine Database, which have articles published between (1966 and 2006), was conducted to select studies for this meta-analysis. **Results:** This meta-analysis included 14 epidemiologic studies, with a total number of 6123 gastric cancer cases and 134006 controls. The combined results based on all studies showed that green tea consumption was not associated with the risk of gastric cancer [odds ratio (OR) = 0.98, 95% confidence interval (CI) = 0.77-1.24]. The summary OR from all population-based case–control studies showed a minor inverse association between green tea consumption and risk of gastric cancer (OR = 0.68, 95% CI = 0.49-0.92), while no associations were noted from hospital-based case–control studies (OR = 1.12, 95% CI = 0.70-1.77) and cohort studies (OR = 1.56, 95% CI = 0.93-2.60). No associations were noted both in males (OR = 1.10, 95% CI = 0.76-1.60) and females (OR = 0.99, 95% CI = 0.64-1.51). The summary OR from seven studies suggest that the highest consumption level of green tea was more than 5 cups per day and no associations were noted (OR = 0.99, 95% CI = 0.78-1.27). **Conclusions:** The results of this meta-analysis indicated that there is no clear epidemiological evidence to support the suggestion that green tea plays a role in the prevention of gastric cancer.

Key Words: Meta-analysis, green tea, gastric cancer, case-control study, cohort study

INTRODUCTION
Gastric cancer, the second leading cause of death from cancer throughout the world, is an important health problem. A 2005 analysis of the worldwide incidence of- and mortality from cancer showed that 934,000 cases of gastric cancer occurred in 2002 and that 700,000 patients die annually from this disease.[1] As one of the most popular beverages consumed around the world, green tea, obtained from the steamed or pan-fried leaves of *Camellia sinensis*, contains polyphenolic components, which have been postulated to be protective against gastric cancer. Epigallocatechin-3-gallate is the major polyphenolic constituent of green tea.[2] Numerous animal and in vitro experiments have been carried out either on green tea or epigallocatechin-3-gallate. Although green tea polyphenols have various anticarcinogenic effects, such as strong antioxidant activity, inhibition of nitrosation and cell proliferation, and the induction of apoptosis among carcinoma cells, the molecular mechanisms of the chemopreventive effects of green tea are still uncertain.

Over the last three decades, a number of epidemiologic studies were conducted to investigate the association between green tea consumption and gastric cancer risk in humans. Two recent reviews concluded that epidemiologic studies did not provide consistent evidence to support green tea as chemopreventive agent for gastric cancer development.[3,4] No quantitative summary of the epidemiologic evidence on green tea and gastric cancer risk has ever been performed. The purpose of this meta-analysis was to evaluate the association between green tea consumption and the risk of gastric cancer.

MATERIALS AND METHODS
Literature search strategy
Search was applied to the following electronic databases: the Cochrane Library (first quarter, 2006), MEDLINE (1966 to June 2006), EMBASE (1980 to June 2006) and Chinese Bio-medicine Database (1979 to June 2006). The following key words were used: tea, gastric OR stomach, carcinoma OR cancer OR tumor. The search was done on studies conducted on human subjects, without restriction on language. The reference lists of reviews and retrieved articles were handsearched at the same time. We did not consider abstracts or unpublished reports.

Inclusion and Exclusion Criteria

We reviewed abstracts of all citations and retrieved studies. For inclusion in the meta-analysis, the identified articles have to provide information on: (i) the number of gastric cancer cases and controls studied; and/or (ii) the odds ratio (OR) or relative risk (RR) and its corresponding 95% confidence interval (CI), for highest versus non/lowest level of tea intake. Major reasons for the exclusion of studies were (i) black tea and unclear type of tea; (ii) duplicates; (iii) no usable data reported.

Data Extraction

All data were extracted independently by two reviewers (Zhou Y and Li N) according to the pre-specified selection criteria. Disagreement was resolved by discussion. The following data were extracted: study design and period, statistical methods, country, consumption level of green tea, and results of studies.

Statistical Analysis

Statistical analysis was conducted using STATA 8.2 (StataCorp, College Station, Tex), $p<0.05$ was considered statistically significant. Dichotomous data were presented as OR with 95% CI. Statistical heterogeneity was measured using the Q statistic ($p<0.10$ was considered representative of significant statistical heterogeneity).[5,6] Heterogeneity was also assessed through visual examination of L'Abbe plots.[7] Fixed effects model was used when there was no heterogeneity with regard to the results of the trials. Otherwise, the random effects model was used. For dichotomous outcomes, patients with incomplete or missing data were included in sensitivity analyses by counting them as treatment failures. To establish the effect of clinical heterogeneity between studies on meta-analysis' conclusions, subgroup analysis was conducted on the basis of study design, gender, and consumption level of green tea.

Several methods were used to assess the potential for publication bias. Visual inspection of asymmetry in funnel plots was conducted.[8] The Begg rank correlation method and the Egger weighted regression method were also used to statistically assess publication bias ($p<0.10$

was considered representative of statistically significant publication bias).[8,9]

RESULTS

Study Characteristics

There were 320 papers relevant to the words used for the search (Figure 1). Through the step of title screening, 155 of these articles were excluded (31 were not in the English or Chinese Language, 61 were not epidemiologic studies, 63 were not conducted in humans). Abstracts from 165 articles were reviewed and an additional 113 trials were excluded (33 were not epidemiologic studies, 80 were not conducted in humans), leaving 52 studies for full publication review. Of these, 39 were excluded [15 were not green tea,[10-24] 21 did not report usable data,[3, 25-44] 3 were duplicates[45-47]]; thus, 13 papers and 14 studies (n=140129 participants) were found to conform to our inclusion criteria.[48-60] Fourteen studies, including four
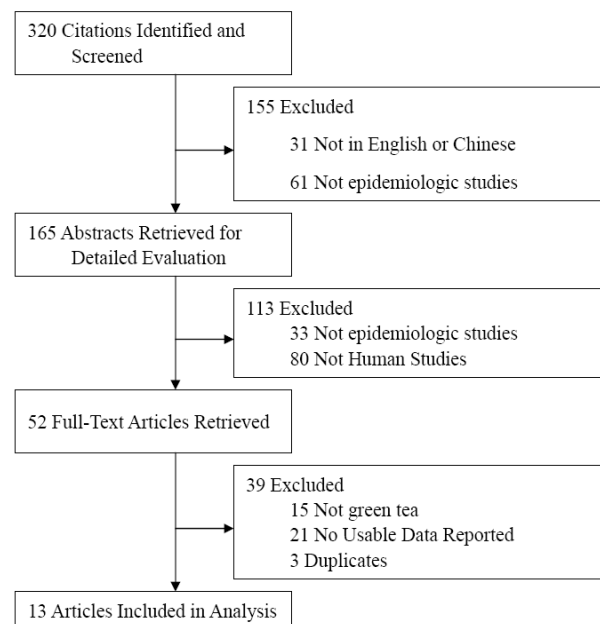

Figure 1. Studies identification, inclusion, and exclusion criteria

Table 1. Characteristics of Studies Included in the Meta-analysis

Study	Design	Study period	Country	No. of case /noncases	Lowest consumption level	Highest consumption level	Percent in lowest, highest exposure level
Kono 1988	HCC	1979-1982	Japan	139/2574	≤ 4 cups/day	10+ cups/day	54%, 10%
Kono 1988	PCC	1979-1982	Japan	139/278	≤ 4 cups/day	10+ cups/day	51%, 15%
Lee 1990	HCC	1954-1988	China	210/810	No	Yes	98%, 2%
Yu 1995	PCC	1991-1993	China	711/711	Nondrinkers	Drinkers	65%, 35%
Ji 1996	PCC	1988-1989	China	1124/1451	Nondrinker	Regular drinker	58%, 35%
Inoue 1998	HCC	1990-1995	Japan	893/21128	Rarely	7+ cups/day	6%, 11%
Galanis 1998	Cohort	1975-1980	Japan	108/11907	None	2+ cups/day	75%, 12%
Ye 1998	PCC	1994-1995	China	272/544	≤ 0.75 kg/year	> 0.75 kg/year	74%, 26%
Huang 1999	HCC	1988-1995	Japan	850/28619	Never	6+ cups/day	21%, 16%
Tsubono 2001	Cohort	1984-1992	Japan	419/26311	<1 cups/day	5+ cups/day	18%, 42%
Setiawan 2001	PCC	1995	China	133/433	Nondrinkers	3+ cups/day	58%, 12%
Nagano 2001	Cohort	1979-1981	Japan	901/38540	≤ 1 cups/day	5+ cups/day	14%, 26%
Hoshiyama 2004	Cohort	1988-1990	Japan	157/285	<1 cups/day	10+ cups/day	11%, 12%
Mu 2005	PCC	2000	China	206/415	Nondrinkers	Drinkers	52%, 44%

Abbreviations: HCC, hospital-based case–control; PCC, population-based case–control.

cohort studies, six population-based case–control studies, and four hospital-based case–control studies were included in the meta-analysis on green tea consumption and gastric cancer risk. Characteristics of studies included in this meta-analysis are presented in Table 1.

Quantitative Data Synthesis

The combined results based on all studies showed that green tea consumption was not associated with the risk of gastric cancer (OR = 0.98, 95% CI = 0.77-1.24). Conflicting results were observed in population-based case–control studies versus hospital-based case–control studies and cohort studies. The summary OR from all population-based case–control studies showed a minor inverse association between green tea consumption and the risk of gastric cancer (OR = 0.68, 95% CI = 0.49-0.92), while no associations were noted from hospital-based case–control studies (OR = 1.12, 95% CI = 0.70-1.77) and cohort studies (OR = 1.56, 95% CI = 0.93-2.60) (Figure 2). Subgroup analysis was also conducted on the basis of gender and consumption level of green tea. No associations were noted both in male (OR = 1.10, 95% CI = 0.76-1.60) and female (OR = 0.99, 95% CI = 0.64-1.51). The summary OR from seven studies indicated that the highest consumption level of green tea was more than 5 cups per day and no associations were noted (OR = 0.99, 95% CI = 0.78-1.27).[49,52,54,56,58,60]

Statistically significant heterogeneity was observed between trials for all analysis with the Q statistic ($p<0.001$). In addition, L'Abbe plots did show evidence of heterogeneity. Review of funnel plots could not rule out the potential for publication bias for all analysis. Publication bias was not evident when the Begg rank correlation method ($p=.74$) and the Egger weighted regression method ($p=.60$) were used.

DISCUSSION

Although numerous experimental studies have demonstrated the inhibitory effects of green tea and tea polyphenols on gastric cancer, epidemiological studies evaluated above yield contradictory findings. In this meta-analysis, we have examined the strengths and weaknesses of these studies in order to clarify whether a relationship exists between green tea intake and gastric cancer risk.

The results of population-based case–control studies and cohort studies present considerably different impressions. Such conflicting results are often seen in cancer epidemiologic studies. In case-control studies, there may be a problem with the reliability of the information, because information that exposes the past history is collected after cancer is diagnosed. Epidemiological studies have found that patients with gastric cancer decrease their consumption of tea two years before the diagnosis and that the accuracy of the recall of an earlier diet is strongly influenced by the recent diet.[13] This bias would partly explain the difference in the findings between prospective and case–control studies.

All case-control studies, principally as a result of their retrospective nature, showed selection, information and confounding bias. In almost all of these studies, selection and confounding bias was minimized (i.e. cases and controls were drawn from the same population; adjustment for certain factors). However, in hospital-based case–control studies, the controls were not free of disease. The population-based case–control study that reported an inverse association between green tea consumption and
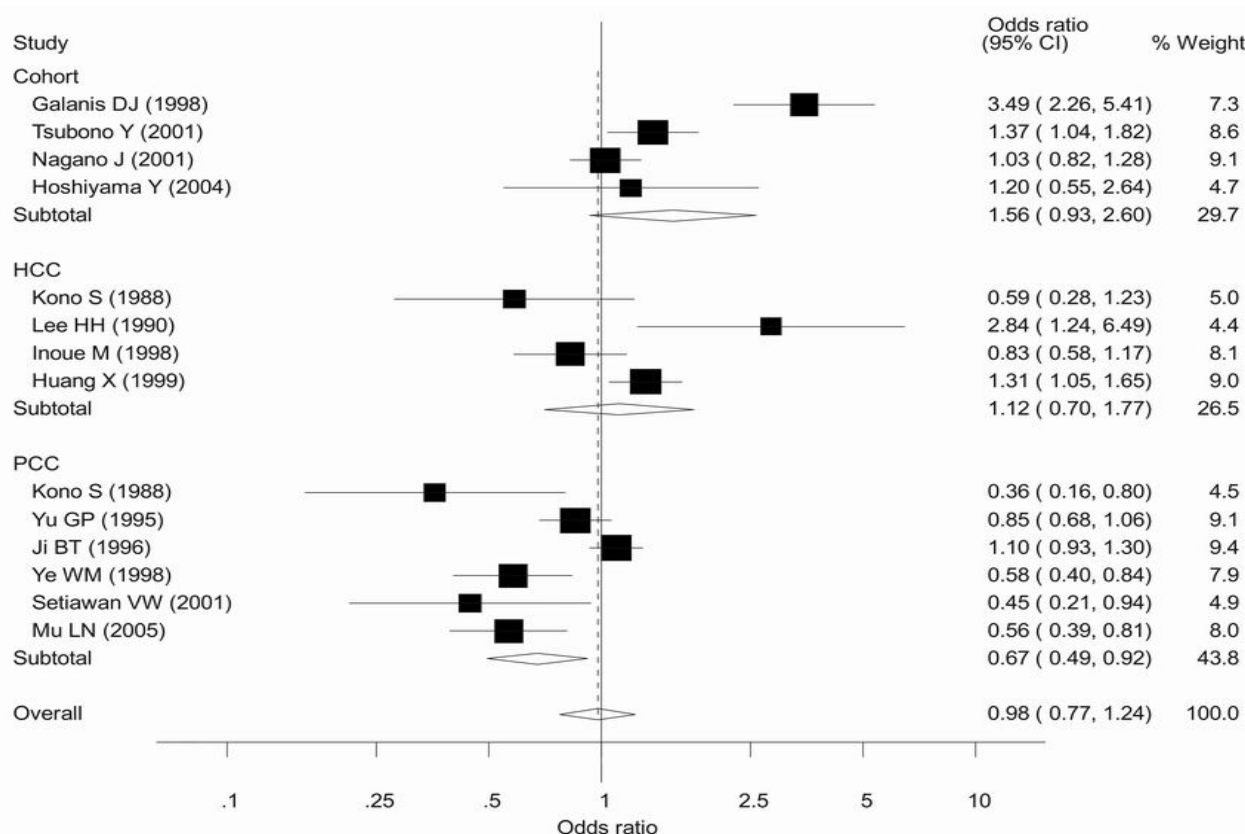

Figure 2. Meta-analysis of green tea and gastric cancer risk.
Abbreviations: HCC, hospital-based case–control; PCC, population-based case–control.

gastric cancer risk was inconclusive: no adjustments for confounding variables were performed, no quantitative information on green tea consumption was reported and, because information was obtained by a questionnaire survey, self-selection bias could not be excluded.

Our search identified four cohort studies,[53,54,56,58] which examined the association between gastric cancer risk and green tea consumption. The four cohort studies were all carried out in Japan. Information on the frequency and amount of green tea consumed and on other lifestyle factors was obtained by a self-administered postal questionnaire. In all cohort studies, some adjustments were made: sex, age, years of education, cigarette smoking, alcohol consumption, place of birth, history of peptic ulcer and stomach cancer, coffee consumption and several other foodstuffs. As a general rule, cohort studies are regarded as the most rigorous and methodologically pure for the identification, evaluation and understanding of risk factors associated with a disease. However, the value of a study depends not only on the type of design, but also on its size and overall quality. One cohort study showed limitations due to selection bias.[54]

Two statistically significant results showed that green tea has a protective effect against both adenomatous polyps and chronic gastritis, suggesting that it may be considered as a potential preventive agent for individuals at high risk of developing stomach cancer.[55, 61] One prospective nested case-control study investigated the association between prediagnostic urinary tea polyphenol markers, including epigallocatechin (EGC) and epicatechin (EC), and their respective metabolites 5-(3',4',5'-trihydroxyphenyl)-gamma-valerolactone (M4) and 5-(3',4'-dihydroxyphenyl)-gamma-valerolactone (M6), and subsequent risk of gastric and esophageal cancers among middle aged and older men in Shanghai, China. One hundred and ninety incident cases of gastric cancer and 42 cases of esophageal cancer occurring in members of the Shanghai Cohort were compared with 772 control subjects. After exclusion of cases those were diagnosed cancer under 4 years follow-up, urinary EGC positivity showed a statistically significant inverse association with gastric cancer (OR = 0.52, 95% CI = 0.28-0.97) after adjustment for *Helicobacter pylori* seropositivity, smoking, alcohol drinking, and the level of serum carotenes. The protective effect was primarily seen among subjects with low (below population median) serum carotenes. The odds ratio for EGC positivity was 0.49 (95% CI = 0.26-0.94) among subjects with low serum carotenes while the corresponding odds ratio among subjects with higher levels of serum carotenes was 1.02 (95% CI = 0.46-2.28). Similar tea polyphenol-cancer risk associations were observed when the gastric cancer and esophageal cancer sites were combined. This study provided direct evidence that tea polyphenols may act as chemopreventive agents against gastric and esophageal cancer development.[23]

There has been extensive research into the possible biological mechanisms of the protective effect of green tea and its polyphenols on gastric cancer. Green tea and its polyphenols have also been shown to: (i) block heterocyclic aromatic amines formed during the cooking of meat which play a role in the development of gastric cancer;[62] (ii) inhibit urokinase activity, one of the most frequently over-expressed enzymes in human cancers; (iii) induce apoptosis and cell cycle arrest in human cancer cells;[63, 64] (iv) inhibit the activity of enzymes involved in important pathways that regulate cell division and proliferation (e.g. protein kinase C); (v) induce phase I and phase II metabolic enzymes that increase the formation and excretion of detoxified metabolites of carcinogens.[3,64]

There are some limitations to this meta-analysis. First, as in most meta-analyses, these results should be interpreted with caution because the highest consumption of green tea, lengths of follow-up, and questionnaire were not uniform. Although some studies adjusted for the consumption of dietary items other than green tea as much as possible, we could not exclude the possibility of residual confounding by other dietary characteristics. Second, we could not obtain information from most studies on the presence or absence of a history of infection with *Helicobacter pylori,* a strong risk factor for gastric cancer. The subjects with chronic gastritis caused by *H. pylori* infection might have limited their consumption of foods and beverages, including green tea. Third, genetic polymorphisms may also impact findings in as much as they affect the metabolism of active ingredients in tea. Nonstratification of such subsets may mask a strong effect in a subset of the population. Fourth, there were geographic biases with most of the studies on green tea conducted in China and Japan. Finally, meta-analysis remains retrospective research that is subject to the methodological deficiencies of the included studies. We minimized the likelihood of bias by developing a detailed protocol before initiating the study, by performing a meticulous search for published and unpublished studies, and by using explicit methods for study selection, data extraction, and data analysis.

Further prospective epidemiological research is needed to study the effect of green tea on adenomatous polyps and chronic gastritis, and to investigate the relationship between tea polyphenols and gastric cancer risk. In addition, future epidemiological investigations should take into account the method of preparation of green tea, as well as its strength and temperature.

In conclusion, this meta-analysis indicated that there is no clear epidemiological evidence to support the suggestion that green tea plays a role in the prevention of gastric cancer.

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Original Article

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绿茶和患胃癌风：流行病学研究的荟萃分析

目的：评价饮用绿茶和患胃癌风险的关系。**方法**：检索如下数据库：Cochrance library、MEDLINE、EMBASE 和中国生物医学文摘数据库。其中发表于 1966-2006 年之间的相关研究文章，用于此项荟萃分析。**结果**：此项荟萃分析纳入了 14 个流行病学研究，共纳入 6123 名胃癌患者和 134006 名对照。合并结果显示饮用绿茶和患胃癌风险之间没有相关性(OR=0.98, 95%CI=0.77-1.24)。以人群为基础的病例对照研究表明绿茶的饮用量和患胃癌的风险之间有很小的负相关性(OR=0.68,95%CI=0.49-0.92)，而在以医院为基础的病例对照研究 (OR=1.12, 95%CI=0.70-1.77)和 cohort 研究 (OR=1.56, 95%CI=0.93-2.60)中并没有得到类似结果。男性(OR=1.10, 95%CI=0.76-1.60)和女性(OR = 0.99, 95% CI = 0.64-1.51)均没有发现有相关性。有 7 个研究的绿茶最高饮用量为每天 5 杯以上，合并结果也未能显示饮用绿茶和患胃癌风险之间有相关性(OR=0.99, 95%CI=0.78-1.27)。**结论**：此项荟萃分析结果表明目前尚没有明确的流行病学证据支持绿茶能够预防胃癌。

关键字：荟萃分析、绿茶、胃癌、病例对照研究、cohort 研究。