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EDITORIAL

Green tea and the risk of gastric cancer: Epidemiological evidence

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Abstract

Gastric cancer (GC) is one of the leading causes of cancer death in the world. Numerous efforts are being made to find chemoprotective agents able to reduce its risk. Amongst these, green tea has been reported to have a protective effect against stomach cancer. This article aims to critically evaluate all epidemiological studies reporting an association between green tea consumption and GC risk. MEDLINE, EBSCOHOST and Google Scholar were used to search for clinical trials of green tea and its correlation to stomach cancer. Studies include cohort and case-control studies. Outcome of interests are inverse association, no association, and positive association. Seventeen epidemiologic studies were reviewed. Eleven studies were conducted in Japan, five in China, and one with Japanese descendent in Hawaii. Ten case-control studies and seven cohort studies were included. The relative risks or odds ratio of GC for the highest level of green tea consumption was compared. Seven studies suggested no association, eight an inverse association, and one a positive association. One study had shown a significantly lowered GC risk when tea was served warm to cold. Another study also showed a significantly risk with lukewarm tea. All studies that analyzed men and women separately have suggested a reduced risk in women than in men, albeit no significant difference. This review demonstrates that there is insufficient information to support green tea consumption reduces the risk of GC. More studies on the subject matter are warranted.

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Key words: Gastric cancer; Green tea; Epidemiology; Case-control study; Cohort study

Core tip: Gastric cancer (GC) is one of the leading causes of cancer death in the world. Numerous efforts are being made to find chemoprotective agents able to reduce its risk. This review demonstrates that there is insufficient information to support green tea consumption reduces the risk of GC. More studies on the subject matter are warranted.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer and second leading cause of death from cancer throughout the world. A 2011 world analysis showed that 989600 new GC cases and 738000 deaths were estimated to have

occurred in 2008[1]. The incidence of GC varies up to 10-fold across the world with the greatest percentage in China, followed by South Korea, South American countries and Japan[1]. These variations may be due to differences in environmental and lifestyle factors.

An excessive intake of protein, fat, salt or meat increases the risk of stomach cancer. Contrarily, dietary fiber, vegetables, fruit, and soy have been shown to play an important role in prevention of GC[2]. Tea, one of the most commonly consumed beverages in the world, has been reported in pre-clinical and epidemiological studies to provide protective effects against GC[3]. Green tea and its constituents have been shown to exhibit multiple health benefits[4-6]. Green tea and its bioactive constituents inhibit tumorigenesis in many animal models, including those for cancer of the skin, lung, oral cavity, esophagus, stomach, small intestine, colon, liver, pancreas, bladder, breast, and prostate[7-11].

Polyphenols, which include flavanols, flavandiols, flavonoids, and phenolic acids, constitute the most interesting group of green tea leaf components. Most green tea polyphenols (GTPs) are flavonoids. Flavonoids are phenol derivatives synthesized in substantial amounts (0.5%-1.5%) and variety (more than 4000 flavonoids identified), and widely distributed among plants[12]. The main flavonoids present in green tea are catechins. Catechins are colorless, astringent, water soluble compounds, and are readily oxidizable. Since green tea does not undergo fermentation, it contains greater amounts of various catechins than in black or oolong tea. Traces of catechins are also found in grapes, wine, and chocolate[13]. The four kinds of catechins found mainly in green tea include: (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin, (-)-epicatechin, and (-)-epigallocatechin-3-gallate (EGCG). Out of the above, EGCG accounts for more than 40% of the total catechin content. Figure 1 shows the chemical structure of the four major catechins present in green tea. EGCG is the most abundant polyphenol in green tea and has gained most attention as the active constituent responsible for the anticarcinogenic activity of this tea. One cup of brewed green tea (2.5 g of green tea leaves/200 mL of water) may contain 90 mg of EGCG[14]. In black tea, the catechins compounds such as theaflavins and thearubigins predominate. Black and green tea both contains similar amounts of flavonoids, however they differ in their chemical structure; green tea contains more catechins (simple flavonoids). Conversely, the oxidation undergone by black tea processing converts these simple flavonoids into theaflavins and thearubigins[12].

The first green tea clinical trial with cancer patients as a phase I study using green tea capsules was performed in 1997 and later published in 2001[15]. The purpose of this study was to determine the maximum-tolerated dose, toxicity, and pharmacology of oral green tea extract. A total of 49 cancer patients with solid tumors were studies. There were two treatment arms in this two years study: 0.05-5.05 g/m^2 once daily dose and 1.0-2.2 g/m^2 three-times-daily for 6 mo. The maximum tolerated dose was 4.2 g/m^2 once daily or 1.0 g/m^2 three times a day. This study recommended that 1.0 g/m^2 for three times daily should be considered for future clinical trials and that doses studied can be taken safely for at least 6 mo[15]. Thereafter, several phase I studies on healthy volunteers have also been conducted to define the basic pharmacokinetic parameters and safety profile for oral consumption of various types of green tea preparations[16,17]. In 2003, a phase I study investigated polyphenon E™ (a defined, decaffeinated GTP mixture) in healthy individuals[18]. The study concluded that greater oral bioavailability of EGCG can be achieved by taking the polyphenon E™ capsules on an empty stomach after an overnight fast. Recent phase I studies have concluded that the consumption of green tea appears to be relatively safe (8-16 cups of green tea once a day or in divided doses twice a day for 4 wk)[3]. However, up to 2 g orally twice per day was observed to be well tolerated in patients with stage 0 to Ⅱ chronic lymphocytic leukemia[19]. Bettuzzi *et al*[20] had reported that 600 mg of daily catechin extract had a statistically significant protective effect in patients with high-grade prostate intraepithelial neoplasia. EGCG delivered in the capsule form (200 mg/d for 12 wk) has also been reported to be effective in patients with human papilloma virus-infected cervical lesions[21].

Although many clinical trials have been conducted to explore the safety and efficacy of green tea extract in cancer patients, similar studies in GC patients have not yet been executed. Over the last three decades, a number of epidemiological studies were conducted to investigate the association between green tea consumption and stomach cancer risk in human subjects[22-27]. Nonetheless, the epidemiologic studies have not yielded clear conclusions concerning the protective effects of tea consumption against cancer formation in humans. The aim of this systematic and up-to-date review was to critically evaluate all epidemiological studies published so far to report an association between green tea consumption and GC risk.

SEARCH STRATEGY AND METHODS

Database and search strategy

Research articles presented in this review includes epidemiological studies of green tea consumption in relation to GC risks. Epidemiological studies were retrieved through three computerized literature search engines: PubMed (Medline), American University of Health Science's literature database EBSCOHOST, and Google Scholar. All 5490 journals in PubMed and 32 publications in EBSCOHOST are utilized in the search. Only articles published between 1990 and 2012 were retrieved. The major descriptor key words used for the search were stomach cancer, GC, green tea, *Camellia sinensis*, EGCG, polyphenol, catechin and the minor descriptor key words used were tumor, cancer, lesion, polyp, adenocarcinoma. The identifiers used were risk, prevention, treatment, prolong disease. In addition, relevant publications retrieved from reference lists were manually searched to be included in this review. Abstracts were reviewed and studies retrieved in full.

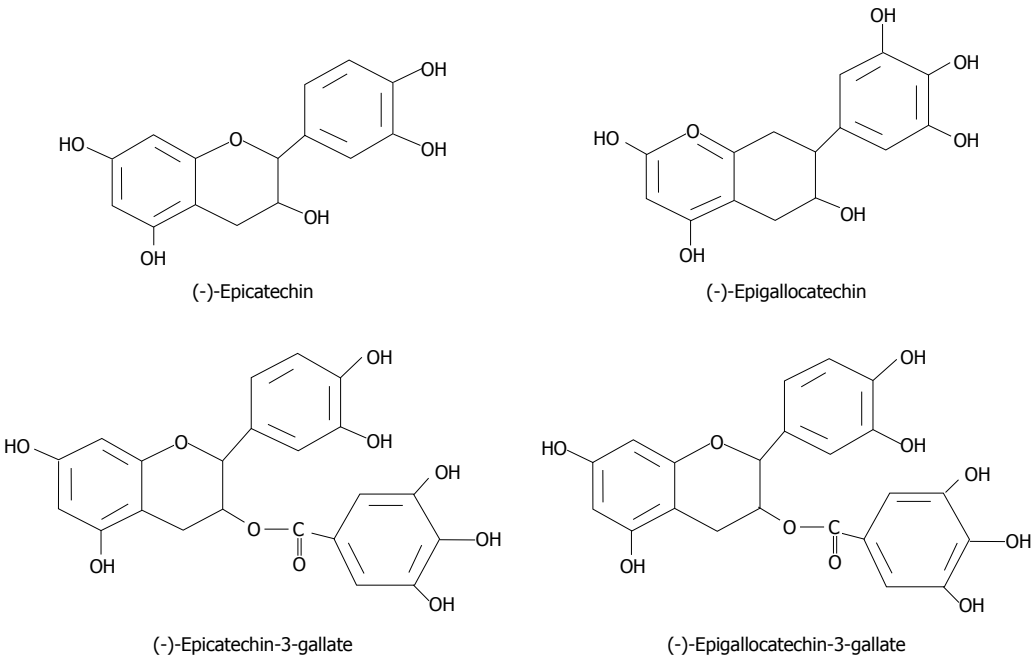

Figure 1 Structures of green tea catechins.

Inclusion criteria

Only case-control studies, cohort studies, and prospective studies reporting association between green tea and stomach cancer risk were included. Articles specifying the number of GC cases and controls for case-control studies, odds ratio (OR) or relative risk (RR) and its corresponding 95%CI for highest versus non/lowest levels of tea intake are presented in this review.

Exclusion criteria

In vitro cell culture and animal studies were excluded. Papers that failed to report the number of individuals (cases and controls) involved in the study and the level of green tea consumption (amount or frequency of green tea consumed) were also excluded. Articles written in foreign languages, as well as abstracts, were excluded since the complete publications were not available for this review work.

Data extraction

All articles were read in full. From those studies finally selected, the following data were extracted: study design, study name (first author, publication year), region and study period (years), population size, green tea consumption level, OR or RR with 95%CI of the highest consumption level, and adjustments.

GREEN TEA AND GC RISK

This review included a total of 17 epidemiological studies (10 case-control studies[28-37] and 7 cohort studies[38-44] published between 1988 and 2010. Figure 2 displays a flow diagram of the procedure used to identify the studies included in this review. There were 210 papers relevant to the words used for the search. Through the steps of title screening, 125 studies were excluded (16 duplicate articles, 31 articles not in English, and 78 were not epidemiologic studies). Abstracts from 85 articles were reviewed and an additional 67 studies were excluded (33 were not epidemiologic studies, 34 were not conducted in humans), resulting in 18 articles for full publication review. Of these, 7 were excluded (5 were not green tea, 2 did not report usable data). Of the remaining 11 articles, six articles were identified from the reference lists and are included in this review. As a result, 17 articles were found to meet the inclusion criteria described above.

Eleven studies were conducted among the Japanese population in Japan[28-30,33,35,39-44], five studies were conducted among the Chinese population in China[31,32,34,36,37], and others were conducted among the Japanese-born population in Hawaii, United States[38]. All of the Chinese studies were case-control studies. RR, OR, 95%CI of the highest green tea consumption levels were included. Table 1 represents the main characteristics of the studies included in this review.

Three hospital-based case control studies were carried out in Japan[29,33] and China[37]. In all investigations, all cases were confirmed histologically and controls were free of gastrointestinal diseases. Information on green tea consumption, as well as lifestyle habits and family history, was obtained through a self-administered questionnaire before the final diagnosis. Adjustments were made for age, gender, place of residence[29], age, gender, year and season at first hospital visit, smoking and alcohol drinking status, physical exercise, intake of coffee, black tea, fruit, rice and beef[33], or age, gender, education level, and smoking status[37]. The RRs or ORs were calculated using, as reference category, subjects who drank less than 1 cup/d, or non-drinking subjects[33,37]. Although Kato *et al*[29] did not find an association between green tea

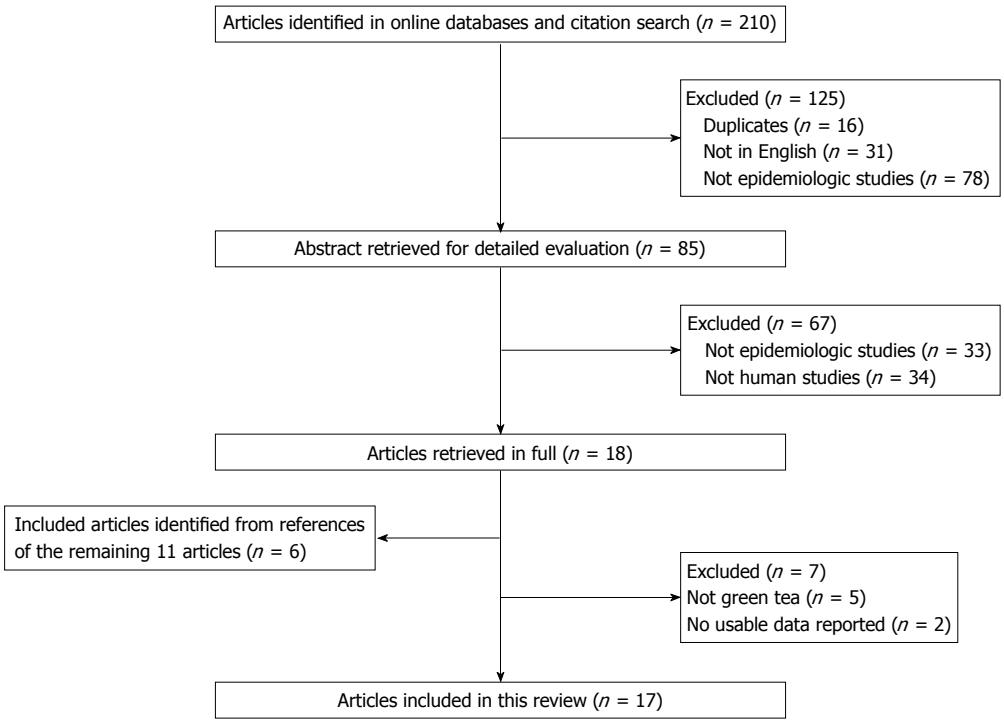

Figure 2 Flow diagram of identification of relevant studies.

consumption and GC risk, Inoue *et al*[33] and Deandrea *et al*[37] showed that the frequent consumption of green tea (≥ 7 cups/d and ≥ 750 g/year, respectively) decreased the risk of GC. Furthermore, Deandrea *et al*[37] observed a significant decrease in GC risks amongst drinkers of green tea at lukewarm temperature.

Five population-based case control studies were conducted in Japan[35] and China[31,32,34,37]. Cancer cases were confirmed pathologically[34,37], histologically[31,32] or by other methods[35]. In some epidemiological studies, controls were randomly selected[32,34,36] and matched according to age and gender[31,32,35], or study area[35]. Information was either obtained through interview[31,32,34,37] or administration of questionnaires[35]. Adjustments were made for age, education, birthplace, alcohol and cigarette usage, fresh fruit, vegetable and preserved fruit intake[31]; age, income, education among women and further adjusted for smoking and alcohol drinking among men[32]; age, gender, body mass index, cigarette smoking, and alcohol drinking[34]; and age gender, education, income, body mass index, smoking and alcohol drinking, very hot food eating habit, *Helicobacter pylori* (*H. pylori*) infection, stomach disease, family history of GC[35]. The RRs or ORs were calculated using, as reference category, non-tea drinkers[31,32,34,36] or low consumption of green tea[35]. Four of these five studies reported an inverse association between green tea consumption and the risk of GC[31,32,34,36]. The investigation conducted in Japan did not report any association[35]. Yu *et al*[31] reported that drinking warm or cold tea was associated with significant decreased GC risk compared with non-drinkers. This coincides with the findings of Deandrea *et al*[37] that there is a significant inverse association with consuming lukewarm green tea and GC risk.

Two population-hospital-based case control studies were conducted in Japan[28,30]. In both studies, cases were histologically diagnosed and hospital controls were recruited. Information from cases and hospital controls, as well as population controls, on the frequency and amount of green tea consumption was obtained by interview. Interviews were performed by the public health nurses and hospital staff[28] or by the authors and colleagues[30]. In both studies, the interview on cases and hospital controls were conducted before diagnostic procedures. The results were adjusted for age, gender, smoking, intake of mandarin oranges and other fruits[28]; and age, gender, residence, and smoking status[30]. The RRs for both studies were compared intermediate and high consumption with low consumption of green tea. Kono *et al*[28] observed a significantly decreased GC risk with high consumption of green tea (10 or more cups/d) compared to both hospital and population controls. However, Hoshiyama *et al*[30] observed a minimal to positive association in hospital and population controls.

All of the seven cohort studies were carried out among the Japanese population[38-44]. However, one was conducted in Hawaii, United States[38]. Information on the frequency and amount of green tea consumed and on other lifestyle factors was obtained by a self-administered postal questionnaire. In two of the seven cohort studies, the validity of the food frequency questionnaire was evaluated[42,44], and in two of the seven cohort studies the questionnaire was checked by interviewers[40,41]. In the study by Galanis *et al*[38] of 11907 randomly selected Japanese residents of Hawaii, 108 participants developed GC (follow-up period of 14.8 years on average). The study by Nakachi *et al*[39] on 8552 residents in Saitama Prefecture,

Table 1 Characteristics of epidemiological studies on green tea consumption and stomach cancer risk

Ref.	Region and observation period	Study population[1]	Green tea consumption levels[2]	RR or OR (95%CI)[3]	Direction of association	Adjustments
Case-control studies						
Kono *et al*[28], 1988	Kyushu, Japan, 1979-1982	139 GC cases 2574 HC 278 PC	≤ 4 cups/d 5-9 cups/d ≥ 10 cups/d	HC: 0.5 (0.3-1.1) PC: 0.3 (0.1-0.7)	Inverse (significant) with high consumption	Age, gender, cigarette smoking, mandarin oranges and other fruits
Kato *et al*[29], 1990	Aichi, Japan, 1985-1989	427 GC cases 3014 HC	1-4 cup/d ≥ 5 cups/d	Males: 1.01 (0.70-1.47) Females: 0.81 (0.51-1.27)	None	Age, gender, residence (metropolitan area in Aichi prefecture, other areas of Aichi prefecture, and other prefectures)
Hoyoshima *et al*[30], 1992	Saitama, Japan, 1984-1990	294 GC cases 202 HC 294 PC	≤ 4 cups/d 5-7 cups/d ≥ 8 cups/d	HC: 1.3 (0.8-2.1) PC: 0.8 (0.5-1.3)	Minimal to positive	Age, gender, residence, cigarette smoking
Yu *et al*[31], 1995	Shanghai, China, 1991-1993	711 GC cases 711 matched PC	Non drinkers Drinkers	Temperature: 0.71 (0.54-0.93) Boiling hot: 1.18 (0.75-1.86) Hot: 0.63 (0.46-0.87) Warm/cold: 0.51 (0.29-0.91)	Inverse (significant with warm/ cold green tea)	Age, education, birthplace, alcohol drinking, cigarette smoking, intake of fresh fruit, vegetables and preserved fruit
Ji *et al*[32], 1996	Shanghai, China, 1988-1989	1124 GC cases 1451 matched PC	Non drinkers Males: ≤ 1200 g/yr ≤ 2000 g/yr ≤ 3000 g/yr Females: ≤ 1200 g/yr > 1200 g/yr	Males: 0.76 (0.55-1.27) Females: 0.81(0.46-1.43)	Inverse	Age, income, and education among women; further adjusted for smoking and alcohol drinking among men
Inoue *et al*[33], 1998	Nagoya, Japan, 1990-1995	893 GC cases 21128 HC	Rarely ≥ 7 cups/ d	0.69 (0.48-1.00)	Inverse	Age, gender, year and season at first hospital visit, habitual smoking, habitual alcohol drinking, regular physical exercise, intake of coffee, black tea, fruit, rice and beef
Setiawan *et al*[34], 2001	Yangzhong, China, 1995	133 GC cases 433 PC	Non drinkers 1-21 cups/wk > 21 cups/wk	0.39 (0.15-1.01)	Inverse (significant)	Age, gender, body mass index, cigarette smoking, alcohol drinking
Hoshiyama *et al*[35], 2004	Japan, 1988-1990	157 GC cases 285 PC	< 1 cup/d 1-2 cups/d 3-4 cups/d 5-9 cups/d ≥ 10 cups/d	1.20 (0.6-2.5)	None	Age, gender, cigarette smoking, *H. pylori* infection, history of peptic ulcer, family history of stomach cancer, educational level, consumption of rice, miso soup, green-yellow vegetables, white vegetables, fruits, preference for salty foods
Mu *et al*[36], 2005	Taixing, China, 2000	206 GC cases 415 PC	Non-drinkers > 250 g/mo	0.39 (0.17-0.91)	Inverse	Age, gender, education, income, body mass index, cigarette smoking, alcohol drinking, very hot food eating habit, *H. pylori* infection, stomach disease, family history of stomach cancer
Deandrea *et al*[37], 2010	Harbin, China, 1987-1989	266 GC cases 533 HC	Non-drinkers < 750 g/ yr ≥ 750 g/yr	Temperature: 0.87 (0.60-1.25) Hot: 1.27 (0.85-1.90) Lukewarm: 0.19 (0.07-0.49)	Inverse (significant with lukewarm green tea)	Age, gender, education level, cigarette smoking
Prospective cohort studies						
Galanis *et al*[38], 1998	Hawaii, Unites States, 1975-1994	108 GC cases 11907 Japanese residents	Non-drinkers 1 cup/d > 2 cups/d	1.5 (0.9-2.3) Males: 1. 6 (0.9-2.9) Females: 1.3 (0.6-2.6)	Positive	Age, gender, years of education and Japanese place of birth
Nakachi *et al*[39], 2000	Saitama, Japan	488 GC cases 8552 adults	≤ 3 cups/d 4-9 cups/d ≥ 10 cups/d	0.59 (0.35-0.98) Males: 0.54 (0.22-1.34) Females: 0.57 (0.34-0.98)	Inverse	Cigarette smoking, alcohol drinking, intake of green and yellow vegetables, intake of rice
Tsubono *et al*[40], 2001	Miyagi, Japan, 1984-1992	419 GC cases 26311 adults	< 1 cups/d 1-2 cups/d 3-4 cups/d ≥ 5 cups/d	1.2 (0.9-1.6) Males: 1.5 (1.0-2.1) Females: 0.8 (0.5-1.3)	None	Age, gender, type of health insurance, history of peptic ulcer, cigarette smoking, alcohol consumption, consumption of rice, black tea, coffee, meat, green or yellow vegetables, pickled vegetables, other vegetables, fruits and bean-paste soup
Nagano *et al*[41], 2001	Hiroshima Nagasaki, Japan, 1979-1981	901 GC cases 37639 adults	0-1 cups/d 2-4 cups/d ≥ 5 cups/d	0.95 (0.76-1.2)	None	Age, gender, city of residence, radiation exposure, cigarette smoking, alcohol drinking, body mass index, education level

Hoshiyama *et al*[42], 2002	Japan (nationwide), 1988-1997	359 GC deaths 72851 adults	< 1 cups/d 1-2 cups/d 3-4 cups/d 5-9 cups/d ⩾ 10 cups/d	Men: 1.0 (0.5-2.0) Women: 0.7 (0.3-2.0)	None	Age, smoking, history of peptic ulcer, family history, consumption of rice, miso soup, green-yellow vegetables, fruits and preference for salty foods
Fujino *et al*[43], 2002	Japan (nationwide), 1988-1990	379 GC deaths 328030 adults	Everyday ⩽ 3 times/d > 3 times/d	Males: 1.11 (0.75-1.63) Females: 1.43 (0.78-2.62)	None	Age, gender, cigarette smoking, alcohol drinking, diet, sporting activities, medical history, education level
Sasazuki *et al*[44], 2004	Japan (nationwide) Cohort Ⅰ: 1990-2001 Cohort Ⅱ: 1993-1999	892 GC cases 72943 adults	< 1 cups/d 1-2 cups/d 3-4 cups/d ⩾ 5 cups/d	Males: 0.97 (0.77-1.22) Females: 0.70 (0.47-1.05)	None	Age, area, cigarette smoking, consumption of fruit, green-yellow vegetables, fish gut, miso soup, rice, black tea and coffee

[1]Number of gastric cancer (GC) cases observed over the study period; [2]Frequency of green tea consumption reported in each study; [3]Relative risk (RR) or odds ratio (OR) for the highest green tea (GT) consumption level studies. HC: Hospital controls; PC: Population controls; *H. pylori*: *Helicobacter pylori*.

Table 2 Summary of findings: Number of epidemiological studies with its reported direction of association between green tea consumption and gastric cancer risk

Study design	Direction of association			
	Negative/inverse	None	Positive	Total
Case-control studies	7	3	0	10
Cohort studies	1	5	1	7
Total	8	8	1	17

Japan found 488 deaths from GC (follow-up period of 11 years). In the study by Tsubono *et al*[40] on 26311 residents of the Miyagi Prefecture, 419 participants developed GC (follow-up period of 9 years). Nagano *et al*[41] examined 37639 atomic bomb survivors, and of those 901 participants developed GC (follow-up period of 15 years). In the study by Hoshiyama *et al*[42] on 72851 Japanese residents, 359 subjects died of GC (follow-up period of 7 years). In the study by Fujino *et al*[43] on 328030 Japanese residents, 345 subjects died of cancer (follow-up period of 7 years). Finally, in the study conducted by Sasazuki *et al*[44] of 72943 Japanese residents, 892 participants developed GC (follow-up period of (follow-up period of 10 years). In all cohorts studies, some adjustments were made: age[38-44], gender[38-41,44], years of education[38,41,43], cigarette smoking (for men only)[38-44], alcohol consumption (for men only)[39-41,43], place of birth[38], history of peptic ulcer[40,42], body mass index[41], coffee consumption and several other foodstuffs[39,40,42,43]. RRs of the highest green tea consumption levels were included instead for all consumption levels. In all studies, some adjustments were made: gender, age, years of education, cigarette smoking, alcohol consumption, place of birth, family history of GC, body mass index, coffee consumption and several other foodstuffs. The RRs were calculated using, as reference category, either non-drinkers[38] or the lowest level of green tea consumption[39-44]. In the first cohort study, Galanis *et al*[38] reported a non-significant increased risk of GC associated with green tea consumption. In contrast, Nakachi *et al*[39] reported a slight inverse association between green tea consumption and GC risks. The other five cohort studies found no association between green tea consumption and GC incidence[40-44].

CRITICAL ANALYSIS OF EPIDEMIOLOGICAL FINDINGS

Green tea contains polyphenols, powerful antioxidants that act as chemopreventive agents. EGCG is considered the major polyphenol that constitute to green tea's preventive constitute. Significant amounts of *in vitro* studies with human cancer cells as well as *in vivo* studies with animal models and have investigated the mechanism of EGCG for its anticarcinogenic properties. EGCG blocks multistage carcinogenesis by modulating a wide spectrum of signal transduction pathways, including mitogen-activated protein kinases, Janus kinase-signal transducer and activator of transcription, phosphoinositide 3-kinase/protein kinase B, Notch, nuclear factor-κB and Wnt/β-catenin, involved in cell proliferation, transformation, apoptosis, inflammation, invasion and metastasis[45]. Accumulative studies show another green tea catechin ECG can also interfere with multiple cell signaling pathways and has multiple cellular targets which are likely to interact in concert to reduce the risk of cancer[46]. Several clinical studies with human subjects have also demonstrated that consumption of green tea as well as EGCG exert beneficial effects[45]. However, epidemiologic studies are somewhat limited with mixed results. Of the 17 epidemiological studies investigated in this review, eight have no association[29,30,35,40-44], eight have inverse association[28,31-34,36,37,39], and one has positive association[38]. Table 2 provides a summary of findings. A trend observed is that decreased risk was associated with an increased green tea consumption level. The studies conducted in China showed a stronger reduction in GC among green tea drinkers than those conducted in Japan. A few authors have argued that the relative lack of subjects in Japan who do not drink green tea may have resulted in an insufficient number of non-drinkers, and this might be an explanation for the weaker association among Japanese studies[36,41,47]. In terms of study design, prospective/cohort studies are considered to be more reliable than case-controlled studies because of the large population size. However, the value of a study depends not only on the type of design, but also on the overall quality. This review identified seven cohort studies which examined the association between cancer risk and green tea consumption.

Of these, the smallest study observed an inverse association[39], whereas the five largest studies observed no association[40-44]. One study found a non-significant positive association[38].

A negative association is stronger in case-control studies than in cohort studies. Seven of the ten case-control studies have suggested an association of green tea consumption and reduced GC risk[28,31-34,36,37], whereas only one of the seven cohort studies showed a reduced GC risk[39]. These discrepancies may be partly associated with the limitations of case-control design: recall, information, selection, and confounding biases. Cancer patients may recall their dietary habits differently from healthy controls, and healthy controls are rarely representative of the population as a whole and tend to report a healthy dietary habit[36]. In retrospective studies like case control studies, the decreased consumption of green tea after abdominal symptoms due to GC may have biased the patient's recall of past consumption, resulting in underestimating the patient's true intake on green tea. Moreover, present dietary habits might influence the accuracy of recalling past dietary habits. In case-control studies, there may be a problem with the reliability of information, because information that exposes the past history is collected after cancer is diagnosed. In all studies included in this review, 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 diseases. Furthermore, self-selection bias could not be excluded because information was obtained by questionnaire survey. Only one cohort study (reporting no association between green tea consumption and GC risk) showed limitations due to selection bias[30].

The non-significant findings regarding the effects of green tea consumption on GC risk in this review contradicts the results of previous experimental studies on this topic using *in vivo* animal models and *in vitro* cancer cell lines. The experimental studies have suggested that GTPs might have a protective effect against GC due to apoptosis-inducing, antimutagenic, anti-inflammatory, and antioxidant activities. The reason for this discrepancy between the results of experimental studies and this review is unclear. However, there might be a few possible explanations. First is the difference in causative factors between the cancers in humans and animals. It is possible that green tea may be only effective against GC in certain animal species. Second, in *in vivo* studies, the doses of green tea used in animal models are much higher in comparison to human consumption. Lastly, in the context of GC, there might be a difference in the biological activities of polyphenols as an independent compound rather than green tea taken as a whole. Despite the protective role of an independent compound against the development of cancer, it is possible that the adverse effect of green tea taken as a whole is due to the interactions and complex biological mechanisms of its multiple constituents.

In this review, eight studies have analyzed men and women separately, provided RRs or ORs for each gender[18,22,28-30,32-34]. In these eight studies, men were considered to show no relation at all. Women, however, seemed to show lower risk, though there was no statistically significant difference. It should also be noted that cigarette smoking and alcohol consumption are important confounding factors. For example, in a case-control study by Tsubono *et al*[40], a protective effect of green tea consumption was observed in women, mostly non-smokers, with an OR of 0.8 and a 90%CI of 0.5-1.3. However, no protective effect was found in men, who were mostly smokers (OR = 1.5, 95%CI: 1.0-2.1). In Asia, tea drinking is commonly associated with cigarette smoking in men. Although the study by Tsubono *et al*[40] and other studies included in this review tried to correct for smoking, the interaction between these two factors is difficult to assess.

It is noted by Yu *et al*[31] that among green tea drinkers, the risk of developing GC did not depend on the age when routine tea drinking started. This implied that green tea may disrupt gastric carcinogenesis at the intermediate and late stages. In addition to finding a negative association between green tea drinking and GC risk, Yu *et al*[31] noted that a lowered risk is observed when the tea was served warm/cold (boiling hot, OR = 1.18, 95%CI: 0.75-1.86; warm/cold, OR = 0.51, 95%CI: 0.29-0.91). This observation was further supported by another case-control study by Deandrea *et al*[37] (hot, OR = 1.27, 95%CI: 0.85-1.90; lukewarm, OR = 0.19, 95%CI: 0.07-0.49).

In one of the cohort studies, Galanis *et al*[38] suggested that tea might have a mutagenic effect (OR = 1.5, 95%CI: 0.9-2.3). However, the number of cases in this study was very small, and that may have resulted in the exaggerated risk estimates.

Overall, these data do not seem to suggest a protective effect of green tea on GC. The inconsistent results between the epidemiologic studies may be due to variables, such as differences in tea preparation and consumption, the methods of tea production, the bioavailability of tea compounds, and genetic variation in how the human body responds to tea consumption.

All research findings from tumor cell cultures, animal models, and epidemiological studies have shown the effects of green tea and tea polyphenols in GC prevention. However, this should be confirmed in clinical trials in order to gain more knowledge of the relationship between green tea consumption and GC risks. This review shows that the overall evidence for protective effects of green tea against cancer is inconclusive. Therefore, further epidemiologic studies and clinical trials are warranted. Adequate sample sizes, better descriptions of populations and/or clear definitions of green tea consumption may be required for conclusive studies. It is also important to consider the type of tea or its preparation (*e.g.,* short time *vs* long brewing time and hot tea *vs* iced tea) due to the marked impact of these factors on polyphenol content and concentration. It is also important to draw attention on the need of further in-depth studies on the nature and mechanisms of the active green tea compounds, on the bioavailability of the different catechins in human and

appropriate dose level to act as functional food. Further epidemiological research, designed specifically to study the effect of green tea on GC, is needed. Because many green tea drinkers brew more than one cup of tea from each batch of dried leaves, in future studies, green tea consumption should be assessed in terms of the amount of active ingredient consumed in a given period. Nevertheless, the *in vitro*, animal, and epidemiologic studies on the topic of green tea consumption and GC risks offered insightful results worthy of future research on potential cancer prevention in human.

This review has several limitations. First of all, this review only analyzed studies of the Japanese and Chinese population. Green tea is consumed mainly in Asian countries, such as China, Japan, and South Korea, it is not appropriate to generalize the findings in the study and apply it to all populations. The findings and explanations should be explored in further clinical research on a more diverse population. Second, as with most literature reviews, the results should be interpreted with caution because the highest consumption of green tea, lengths of follow-up, and questionnaire were not uniform. Although all publications included in this review adjusted for the consumption of dietary items other than green tea as much as possible, the possibility of residual confounding factors cannot be excluded. Lastly, 15 of the 17 studies investigated did not incorporate *H. pylori* infection, a strong risk factor for GC, as a confounding factor. The subjects with chronic gastritis caused by *H. pylori* infection might have limited their consumption of foods and beverages, including green tea. On the other hand, several studies have indicated positive interactions between green tea and *H. pylori*. EGCG, one of the green tea catechins, has been showed to possess significant protective effect against *H. pylori*-induced cytotoxicity in gastric epithelial cells *via* interference of the toll-like receptor 4 signaling induced by *H. pylori*[48]. Green tea or GTPs have exhibited bactericidal and/or bacteriostatic effects against *H. pylori*[49,50]. Various components of green tea have been reported to inhibit *H. pylori* infection as well as *H. pylori*-induced gastritis and gastric epithelial cell proliferation in animal models[51-53]. Chronic atrophic gastritis (CAG) represents a precancerous lesion of the stomach, and *H. pylori* infection is known to increase the risk of CAG. Shibata *et al*[54] conducted a cross-sectional study on 636 subjects livening in a farming village in Japan to examine the relationship among green tea consumption, *H. pylori* infection, and CAG. *H. pylori* infection was positively associated with the risk of CAG (OR = 3.73; 95%CI: 2.59-5.36). High green tea consumption (> 10 cups/d) was negatively associated with the risk of CAG, even after adjustment for *H. pylori* and lifestyle factors associated with green tea consumption (OR = 0.63; 95%CI: 0.43-0.93). The results support the hypothesis that green tea consumption prevents gastric preneoplasia. Hence, future epidemiological studies on green tea and GC risk should consider multivariate analysis on relationship among *H. pylori* infection sustained by cytotoxin-associated gene A-positive strains, other risk factors, and green tea consumption.

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