Green tea and stomach cancer risk : A meta-analysis

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Table of Contents

List of Tables

List of Figures

= ABSTRACT =

Green tea and stomach cancer risk : A meta-analysis

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Green tea has been suggested to have a chemopreventive effect against various cancers including stomach cancer. No attempt has been made, however, to quantitatively summarize the results of epidemiological researches on green tea consumption and stomach cancer risk so far. The aim of this study is to elucidate the relationship between green tea consumption and stomach cancer risk by meta-analysis of previously published data.

Eighteen observational studies were identified using MEDLINE, THE COCHRANE LIBRARY, RISS, and a manual search. Summary odds ratios (ORs) for the highest versus non/lowest green tea consumption levels were calculated based on fixed and random effect models. The meta-regression analysis and stratified analyses were used

to examine heterogeneity across the studies. Influence analysis was done to test robustness of the analysis.

The combined result indicates a reduced risk of stomach cancer with intake of green tea (summary OR=0.86, 95% confidence interval(CI)=0.74-1.00). The protective effect was mainly found among twelve case-control studies (summary OR=0.74, 95% CI=0.63-0.86) and among five Chinese studies (summary OR=0.61, 95% CI=0.47-0.81). Notably, subgroup analysis with six studies which reported differences between the highest and lowest consumption levels equal to or greater than 5 cups/day revealed a statistically significant protective effect (summary OR=0.68, 95% CI=0.53-0.87).

Green tea appears to play a protective role in the development of stomach cancer. The result also implies that a higher level of green tea consumption might be needed for a clear preventive effect to appear. This conclusion, however, should be interpreted with caution because various biases can affect the result of a meta-analysis of observational studies.

Key words : Green tea, Stomach cancer, Meta-analysis

1. Introduction

Cancer is the leading cause of death in Korea. According to National Statistics Office, 136 out of 100,000 people died of cancer in 2005(National Statistics Office of Korea, 2005). Although the incidence of stomach cancer has declined recently, it is still the second most commonly developing malignant neoplasm in the world(Bae, 2006). Among 99,025 new cancer patients registered in Korea in 2002, 19,970 had been diagnosed with stomach cancer(Ministry of Health & Welfare of Korea, 2002).

Risk factors for stomach cancer include infection with Helicobacter pylori, genetic factors, dietary intake and cigarette smoking(Helicobacter and Cancer Collaborative Group, 2001; Forman and Burley, 2006). Dietary intake has been suggested as an important factor in the etiology of stomach cancer, especially when explaining the geographic, socioeconomic and chronologic discrepancy in the incidence(Kelley and Duggan, 2003). Generally, salty foods, low fiber foods, foods containing nitrates, foods contaminated with fungi, bacteria or chemicals and dried or smoked foods are considered to increase the risk of stomach cancer, while whole grains, fruits, vegetables, high fiber foods, green tea and foods containing Vitamin A, calcium, folate, Vitamin C, beta carotene or selenium are considered to decrease the risk(Suh et al., 2002).

Observational studies conducted in various countries have suggested that the consumption of fruits and vegetables is associated with lowering the risk of stomach cancer(Serafini et al., 2002; Riboli and Norat, 2003; Kim et al., 2005; Lunet et al., 2006). In a recent meta-analysis conducted in Korea, intake of 100g more vegetables was associated with 0.81 fold decrease of stomach cancer risk(95% CI:0.75-0.87), and intake of 100g more fruits was associated with 0.74 fold decrease of the risk(95%CI:0.69-0.81)(Kim et al., 2002). These protective effects are supposed to be related to the antioxidants contained in fruits and vegetables(Forman and Burley, 2006), however, no significant protective effect was suggested in a meta-analysis investigating the relationship between the intake of antioxidant supplements and stomach cancer risk(Bjelakovic et al., 2004).

Tea has been known in China since 2700 BC. Soon after humans began to cultivate and process tea around the 3rd century AD, it became a daily drink(Sivasubramaniam, 2007). Tea is the most consumed beverage in the world aside from water nowadays(Kuriyama et al., 2006). Tea is generally consumed in the forms of green(20%), oolong(2%), and black (78%) teas, all of which originate from the leaves of the plant *Camellia sinensis*(Jankun et al., 1997). Among those, green tea contains many polyphenols known as catechins, such as epigallocatechin-3 gallate(EGCG),

epigallocatechin(EGC) and epicatechin-3 gallate(ECG). Black tea is produced through fermentation process, which oxidizes the catechins to theaflavins resulting in destruction of any beneficial effect(Yang and Wang, 1993).

Tea and constituents of tea have been shown to 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(Yang et al., 2002). Mechanisms which have been proposed for the biological activities of tea polyphenols include antioxidant activities, induction or inhibition of drug metabolism enzymes, inhibition of arachidonic acid metabolism, inhibition of cell proliferation, induction of apoptosis, and inhibition of DNA methyltransferase, dihydrofolate reductase(DHFR), protease, and telomerase(Yang et al., 2006).

Ahn et al. (2003) reported significant favorable responses in women with human papilloma virus infected cervical lesions treated with oral and/or topical green tea extract preparations, and Bettuzzi et al.(2006) also reported statistically significant protective effect of 600mg of daily catechin extract derived from green tea in patients with high grade prostate intraepithelial neoplasia.

Over the last three decades, a number of epidemiologic studies were conducted to

investigate the association between green tea consumption and stomach cancer risk in humans. Recent narrative reviews concluded that epidemiologic studies did not provide consistent evidence to support tea as a chemopreventive agent for stomach cancer development(Hoshiyama et al., 2005; Mu et al., 2005). There has never been any quantitative attempt, however, to summarize the results on a possible green tea-stomach cancer association. The aim of this study is to elucidate the association between green tea consumption and stomach cancer risk by meta-analysis of previously published data. This thesis presents results of meta-analysis of all published data on this topic.

2. Methods

1) Literature search

To search for observational studies of green tea consumption in relation to stomach cancer risk, we conducted a literature search using the following medical databases, MEDLINE, THE COCHRANE LIBRARY, and RISS(to search for Korean literature), restricting to English, Japanese or Korean papers published from January 1991 to May 2007. For the search, we identified articles using such medical-subject heading terms as ‘stomach neoplasms, tea or catechin’ or keywords ‘stomach cancer, gastric

cancer, green tea, catechin'. In addition, we also conducted a manual search of reference lists from the retrieved papers for further relevant publications. For Korean literature, we used keywords '위암(gastric cancer), 녹차(green tea) or 식이(diet)'.

2) Inclusion of the studies

For inclusion in the meta-analysis, the identified articles have to meet the following criteria: (1) They have to be human studies, not laboratory or animal studies;(2) They have to provide information on (i)the number of stomach 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;(3) They have to document the daily consumption of the natural green tea product, not of the green tea extracts or supplements;(4) The outcome of interest has to be an incidence of stomach cancer;(5) Full-text article of the study has to be accessible to the author.

Initially fourteen papers in English(Kono et al., 1988; Demirer et al., 1990; Lee et al., 1990; Yu et al., 1995; Ji et al., 1996; Setiawan et al., 2001; Tsubono et al., 2001; Fujino et al., 2002; Hoshiyama et al., 2002; Sun et al., 2002; Koizumi et al., 2003; Hoshiyama et al., 2004; Sasazuki et al., 2004; Mu et al., 2005) and four papers in

Korean(Youm and Kim, 1998; Kim et al., 2002; Suh et al., 2002; Yoon, 2004) were identified with the above-mentioned search method. Three reports from Japanese Collaborative Cohort Study for Evaluation of Cancer Risk(JACC) have been published(Fujino et al., 2002; Hoshiyama et al., 2002; 2004); only a nested case control study(Hoshiyama et al., 2004) was included in the current study because the other two used death from stomach cancer instead of stomach cancer incidence as the outcome of interest. The report by Sun et al.(2002) was excluded because urinary polyphenol markers were measured instead of tea intake at the beginning of the study. The report by Demirer et al.(1990) was excluded because the type of tea was not specified. A pooled analysis of two cohort studies by Koizumi et al.(2003) included a cohort study by Tsubono et al.(2001), so we calculated crude OR for the highest green tea consumption versus the lowest level and 95% CI from the numbers shown by the authors. Two Korean reports(Kim et al., 2002; Yoon, 2004) were excluded because they were either a review article or a meta-analysis of previously published works. The report by Suh et al.(2002) was excluded because only the difference of green tea consumption between a patient group and a control group was shown. The report by Youm and Kim(1998) was excluded because it did not provide information on green tea consumption.

Six more papers in English(Kato et al., 1990; Hoshiyama and Sasaba, 1992; Galanis

et al., 1998; Inoue et al., 1998; Nakachi et al., 2000; Nagano et al., 2001) and two more papers in Korean(Lee et al., 2000; Bae et al., 2001) were identified from the reference list of the articles previously found. The report by Bae et al.(2001) was excluded because OR estimate for green tea consumption was not provided in the study. The report by Lee et al.(2000) was excluded because the amount and frequency of green tea consumption was not shown.

3) Statistical analysis

Study specific ORs/RRs and corresponding 95% CIs for highest versus non/lowest green tea consumption levels were extracted. If a study provided separate OR or RR estimates for men and women, we treated them as two different studies. For a study provides two OR or RR estimates based on hospital and population controls, we used the estimate derived from the population control. Standard errors of natural logarithm of the ORs or RRs were calculated from 95% CIs of ORs/RRs and used for the meta-analysis. Statistical computing was performed using the STATA statistical software(version 8.0; College Station, TX).

Possible heterogeneity in results across the studies was examined using the Q statistic(DerSimonian and Laird, 1986). Statistical significance for the heterogeneity

test was defined as p <0.10 rather than the conventional level of 0.05 because of the low power of this test(Hedges and Pigott, 2001). The null hypothesis that the studies are homogenous would be rejected if p is less than 0.10. When there is significant heterogeneity among study results, the random effect model was used to calculate summary OR while the fixed effect model was used to calculate summary OR among studies with homogenous results. The causes of heterogeneity were explored through both meta-regression and stratified analyses. The following variables were investigated as potential contributing factors to the heterogeneity among studies: country where the study was conducted (China, Japan and USA), study design (case-control versus cohort studies), year of publication (before 2000 versus year 2000 or later), difference between the highest measured intake level and the lowest measured intake level (≥5 cups/day versus <5 cups/day), and adjustment for other potential dietary confounders.

For calculation of the difference between the highest and lowest consumption level of green tea, all the measured consumption levels were converted to cups per day scale. Each gram of green tea consumed shown in two Chinese studies(Ji et al., 1996; Mu et al., 2005) was converted to 0.25 cup following the suggestion by Mu et al.(2005) For the study by Nagano et al.(2001), we assumed a cup of green tea would be consumed

at a time. Yu et al.(1995) reported the number of new batches of green tea used. Among those who used more than 4 batches a day, 12% brewed 1-3 cups per batch and 88% brewed more than 4 cups per batch. The cups per day consumed were calculated using the following equation: $(0.12\times2+0.88\times4)\times4 =15$.

Results of a meta-analysis may be biased if the publication of a study is dependent on the positive result. Generally studies that show a statistically significant effect of intervention are more likely to be published, more likely to be published in English, more likely to be cited by other authors, and more likely to produce multiple publications than other studies(Sterne et al., 2001). To detect a possible publication bias, Begg's funnel plot was visually explored for any asymmetry. Funnel plots are simple scatter plots of the effects estimated from individual studies on the horizontal axis against some measure of study size, which is believed to reflect the precision in the estimation, on the vertical axis(Sterne et al., 2001). In the absence of a publication bias, the funnel plot should be symmetrical with estimates from larger studies in the center, flanked equally on either side by the less precise estimates. The funnel plots would be skewed in the presence of a publication bias. To formally test a publication bias, Egger's un-weighted regression asymmetry test(Egger et al., 1997) was done. The funnel plot was considered to be asymmetrical if the intercept of Egger's regression line deviated from zero with a p value of less than 1.0. Caution has to be

paid, however, as the capacity to detect bias will be limited when meta-analyses are based on a limited number of small trials(Egger et al., 1997), which is the case in this review.

To test the robustness of the meta-analysis, influence analysis was performed. Influence of each study was estimated by deleting each in turn from the analysis and noting the degree to which the size and significance of the intervention effect change(Deeks et al., 2001).

3. Results

Eighteen studies(Kono et al., 1988; Kato et al., 1990; Hoshiyama and Sasaba, 1992; Yu et al., 1995; Ji et al., 1996; Galanis et al., 1998; Inoue et al., 1998; Nakachi et al., 2000; Nagano et al., 2001; Setiawan et al., 2001; Tsubono et al., 2001; Koizumi et al., 2003; Hoshiyama et al., 2004; Sasazuki et al., 2004; Mu et al., 2005) [each result from 3 papers(Kato et al., 1990; Ji et al., 1996; Sasazuki et al., 2004) which reported separate values for males and females was treated as the result from one study] were included in the meta-analysis on green tea consumption in relation to stomach cancer risk. There were six cohort studies(Galanis et al., 1998; Nakachi et al., 2000; Nagano

et al., 2001; Tsubono et al., 2001; Koizumi et al., 2003; Sasazuki et al., 2004), one population based nested case-control study(Hoshiyama et al., 2004), seven population based case-control studies(Kono et al., 1988; Hoshiyama and Sasaba, 1992; Yu et al., 1995; Ji et al., 1996; Setiawan et al., 2001; Mu et al., 2005), and four hospital based case-control studies(Kato et al., 1990; Hoshiyama and Sasaba, 1992; Inoue et al., 1998). Twelve studies were conducted among Japanese population in Japan(Kono et al., 1988; Kato et al., 1990; Hoshiyama and Sasaba, 1992; Inoue et al., 1998; Nakachi et al., 2000; Nagano et al., 2001; Tsubono et al., 2001; Koizumi et al., 2003; Hoshiyama et al., 2004; Sasazuki et al., 2004), five studies were conducted among Chinese population in China(Yu et al., 1995; Ji et al., 1996; Setiawan et al., 2001; Mu et al., 2005), and the other was conducted among the Japanese born in Hawaii, USA(Galanis et al., 1998). No Korean study met the inclusion criteria. All Chinese studies were case-control studies. Table 1 presents the characteristics of the studies used in the analysis.

In addition to three studies(Kato et al., 1990; Ji et al., 1996; Sasazuki et al., 2004) which reported two separate ORs/RRs for each gender, four more studies(Yu et al., 1995; Galanis et al., 1998; Inoue et al., 1998; Tsubono et al., 2001) provided enough information for the calculation of gender specific risk. While three of them reported gender specific ORs/RRs derived from multivariate analyses, Inoue M et al.(1998)

only provided the numbers of cases and controls for each gender. Crude OR was calculated from the numbers given in the study to assess the gender specific risk.

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

Author, Year	Design	Region, Country	No. of cases/ No. of Noncases	No. of exposure level	Lowest consumption level	Highest consumption level	RR/OR (95%CI) for the highest versus the lowest level	Adjustments
Galanis DJ, 1998	Cohort	Hawaii, USA	108/11799 64 men 44 women	3	None	≥2 cups/day	1.5 (0.9-2.3) 1.6 (0.9-2.9) 1.3 (0.6-2.6)	Age, gender, education, Japanese birth place
Nakachi K, 2000	Cohort	Saitama, Japan	140/8412	3	≤3 cups/day	≥10 cups/day	0.69 (0.23-1.88)	Age, cigarette smoking, alcohol, intake of green and yellow vegetables and rice
Tsubono Y, 2001	Cohort	Miyagi, Japan	419/25892 296 men 123 women	4	<1 cup/day	≥5 cups/day	1.2 (0.9-1.6) 1.5 (1.0-2.1) 1.1 (0.6-2.0)	Age, gender, health insurance, history of peptic ulcer, cigarette smoking, alcohol, intake of rice, black tea, coffee, meat, vegetables, fruits, and bean-paste soup
Nagano J, 2001	Cohort	Hiroshima & Nagasaki, Japan	901/37639	3	<1 time/day	≥5 times/day	0.95 (0.76-1.20)	Age, gender, city, radiation exposure, cigarette smoking, alcohol, BMI, education, calendar time
Koizumi Y, 2003	Cohort	Japan	314/39290	4	< 1 cup/day	≥5 cups/day	1.19 (0.89-1.59)*	None
Sasazuki S, 2004	Cohort	Japan	892/72051 665 men 227 women	4	<1 cup/day	≥5 cups/day	 0.97 (0.77-1.22)** 0.70 (0.47-1.05)**	Age, area, cigarette smoking
Kono S, 1988	Case-control	Saga, Japan	139/278	3	≤4 cups/day	≥10 cups/day	0.36 (0.16-0.80)†	None
Kato I, 1990	Case-control Hospital based	Aichi, Japan	427/3014 289 men 138 women	3	< 1 cup/day	≥5 cups/day	 1.01 (0.70-1.47) 0.81 (0.51-1.27)	Age, residence
Hoshiyama Y, 1992	Case-control	Saitama, Japan	294/294	3	≤4 cups/day	≥8 cups/day	0.8 (0.5-1.3)	Age, gender, cigarette smoking, region
Yu G, 1995	Case-control	Shanghai, China	711/711 453 men 258 women	3	None	≥4 new batches/day (≥15 cups/day)	0.54 (0.33-0.88) 0.53 (0.31-0.90) 0.44 (0.07-2.97)	Age, gender, region, education, birth place, cigarette smoking, alcohol

Ji BT, 1996	Case-control	Shanghai, China	1124/1451 684 men 345 women	5	None	> 3000 g/yr (> 2 cups/day) > 1200 g/yr (> 1 cup/day)	0.76 (0.55-1.27) 0.81 (0.46-1.43)	Age, income Cigarette smoking, alcohol for men Education for women
Inoue M, 1998	Case-control Hospital based	Nagoya, Japan	869/21128 613 men 280 women	5	Rarely	≥7 cups/day	0.69 (0.48-1.00) 0.98 (0.80-1.20)‡ 1.09 (0.79-1.49)‡	Age, gender, cigarette smoking, physical exercise, intake of coffee, black tea, fruits, rice and beef, years and season of hospital visit
Setiawan VW, 2001	Case-control	Yangzhong, China	132/423	3	None	>21 cups/wk (>3 cups/day)	0.39 (0.15-1.01)	Age, gender, education, BMI, cigarette smoking, alcohol
Hoshiyama Y, 2004	Nested case-control	Japan	151/265	5	<1 cup/day	≥10 cups/day	1.2 (0.6-2.5)	Age, gender, cigarette smoking, H.pylori infection, history of peptic ulcer, family history of gastric cancer, education, intake of rice, miso soup, green and yellow vegetables, white vegetables, and fruits, preference for salty foods
Mu LN, 2005	Case-control	Taixing, China	193/397	4	None	≥250 g/month (≥2 cups/day)	0.39 (0.17-0.91)	Age, gender, cigarette smoking, alcohol, education, BMI, H.pylori infection, history of stomach disease, family history of gastric cancer, very hot food consumption

Case-control studies are population based unless otherwise specified

* Among two cohorts reported in the article, crude RR and 95%CI was calculated from the numbers from the previously unpublished cohort 2

**ORs were the results of a pooled analysis of two cohorts reported in the study

†Crude OR and 95%CI were calculated from the numbers shown on the study

‡Crude ORs and 95%CIs were calculated from the numbers given in the study for men and women respectively

The overall result, which was presented in Figure 1, showed a statistically significant, 14% reduction in risk of stomach cancer with high green tea consumption (summary OR=0.86, 95% CI =0.74-1.00). There was a significant heterogeneity across the studies (Q=34.98, p=0.06).

Table 2 presents the results of the stratified meta-analyses. When stratified by country (Japan versus China), results were homogenous among five Chinese studies (p=0.43) with significant risk reduction of 39% (Summary OR=0.61, 95% CI=0.47-0.81). Results from twelve Japanese studies were marginally homogenous (p=0.10) with non-significant risk reduction of 6% (Summary OR=0.94, 95% CI=0.85-1.04).

Statistically significant inverse association between green tea intake and stomach cancer was observed only in eleven case-control studies (Summary OR=0.74, 95% CI=0.63-0.86), and their results were consistent to each other(p=0.20) (Figure 2). Results from seven cohort studies showed consistency (p=0.13), but they failed to support the association (Summary OR=1.03, 95% CI=0.92-1.16).

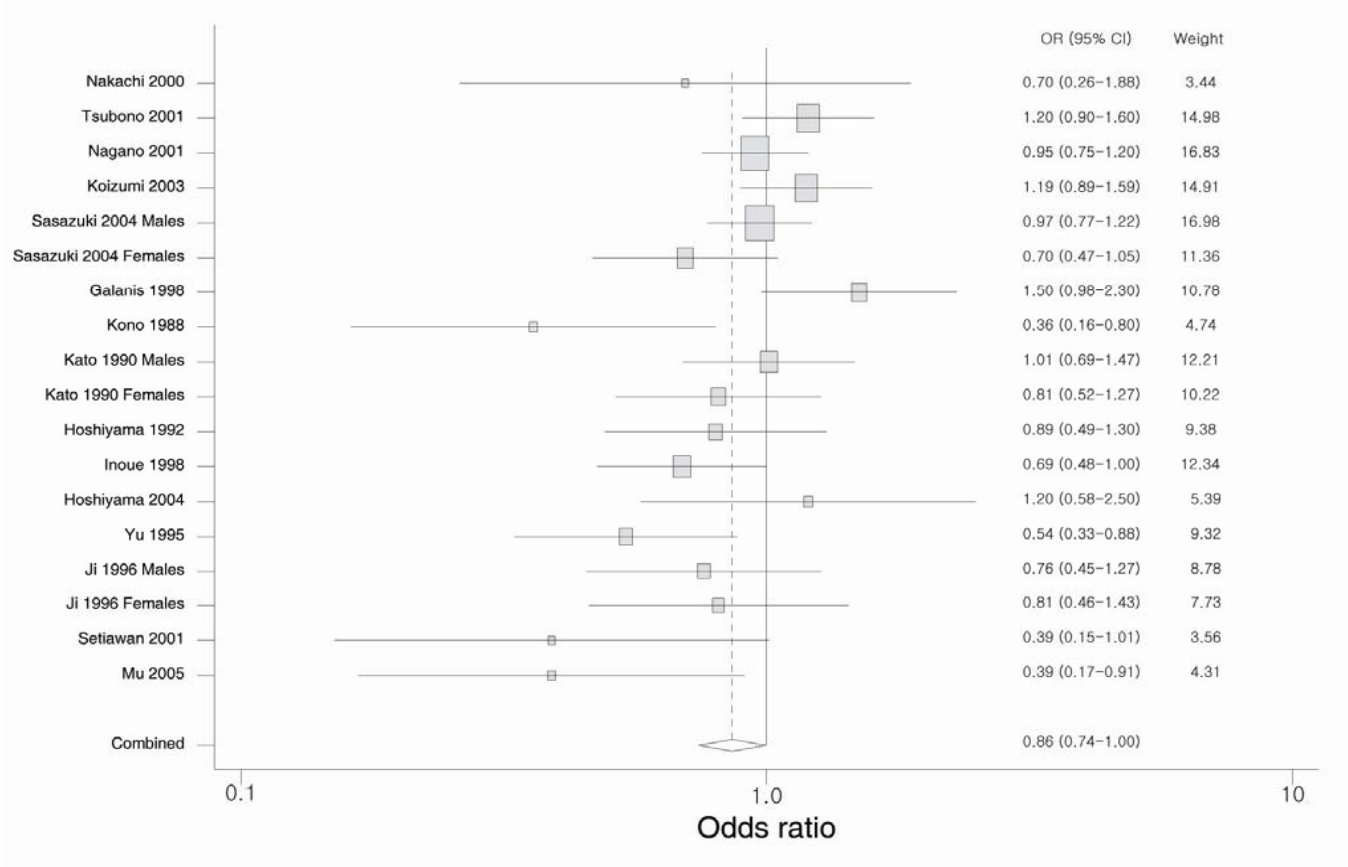

Figure 1. Forest plot of odds ratios from eighteen observational studies on green tea consumption and stomach cancer
The black square and horizontal line correspond to the odds ratio and 95% confidence intervals. The are of the black squares reflects the weight each trial contributes to the meta-analysis. The diamond at the bottom of the graph represents the combined odds ratio and its 95% confidence interval, indicating 14% reduction in the risk of stomach cancer. The solid vertical line corresponds to no effect of green tea consumption (odds ratio 1.0), the dotted vertical line to the combined odds ratio (0.86). The graph was produced in STATA.

Table 2. Meta-analysis of green tea consumption and stomach cancer risk

Category of studies	Subgroup	No. of studies	Summary OR (95% CI)*	P for heterogeneity
All studies	NA	18	0.86 (0.74-1.00)	0.06
Country	China studies	5	0.61 (0.47-0.81)	0.43
	Japan studies	12	0.92 (0.80-1.05)	0.10
Study design	Case control studies	11	0.74 (0.63-0.86)	0.20
	Cohort studies	7	1.03 (0.92-1.16)	0.13
Gender	Males	7	1.00 (0.82-1.24)	0.02
	Females	7	0.89 (0.74-1.07)	0.53
Year of publication	Published before 2000	9	0.80 (0.63-1.00)	0.06
	Published on and after 2000	9	0.93 (0.77-1.12)	0.06
Difference between the highest and lowest consumption level	Less than 5	12	0.94 (0.81-1.10)	0.04
	5 or more	6	0.68 (0.54-0.85)	0.30

* Estimates of the summary ORs and 95% CIs were based on either random effect model if the studies included are heterogeneous(i.e. p for heterogeneity is less than 0.10), or fixed effect model if the studies included are homogenous(i.e. p for heterogeneity is equal to or more than 0.10).

When stratified by gender, results among men were divergent (p=0.02) while results among women were consistent (p=0.53). Both of them failed to show any significant reduction in the risk, however (Summary OR=1.00 and 0.89, 95% CI=0.82-1.24 and 0.74-1.07 respectively).

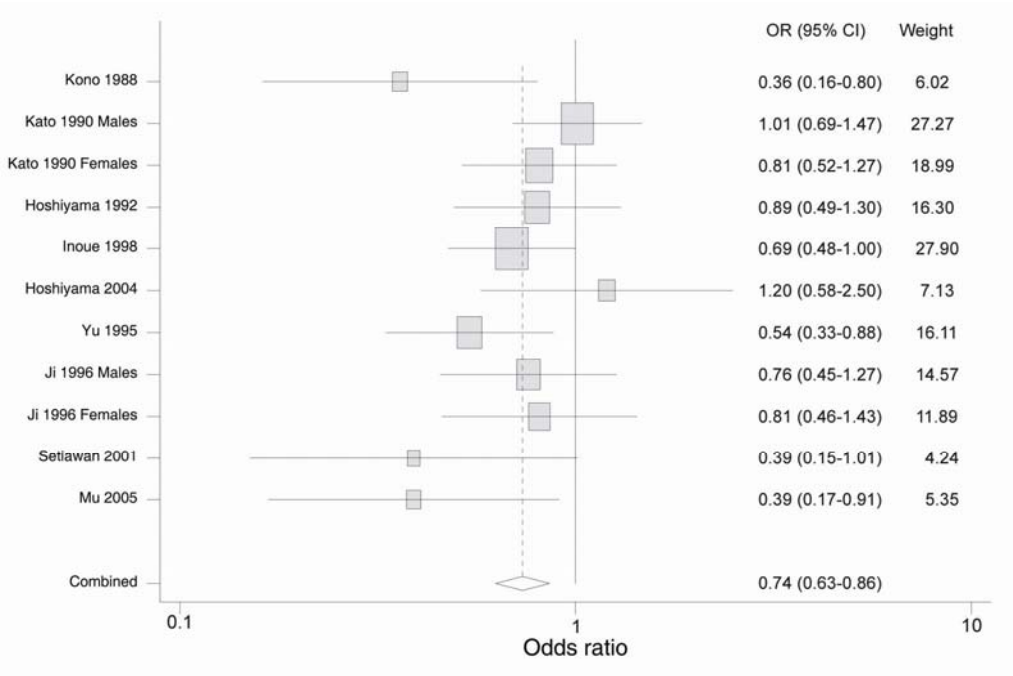

Figure 2. Forest plot of odds ratios of stomach cancer from 12 case-control studies
Combined odds ratio and its 95% CI were 0.74 (0.63-0.86). The graph was produced in STATA.

When stratified by difference between the highest and lowest green tea consumption level, results among six studies with the difference equal to or greater than 5 cups/day were consistent (p=0.30) with statistically significant risk reduction of 32% (Summary OR=0.68, 95% CI=0.54-0.85) (Figure 3). Twelve studies with the difference less than 5 cups/day showed inconsistent results (p=0.04) with non-significant risk reduction of 6% (Summary OR=0.94, 95% CI=0.81-1.10).

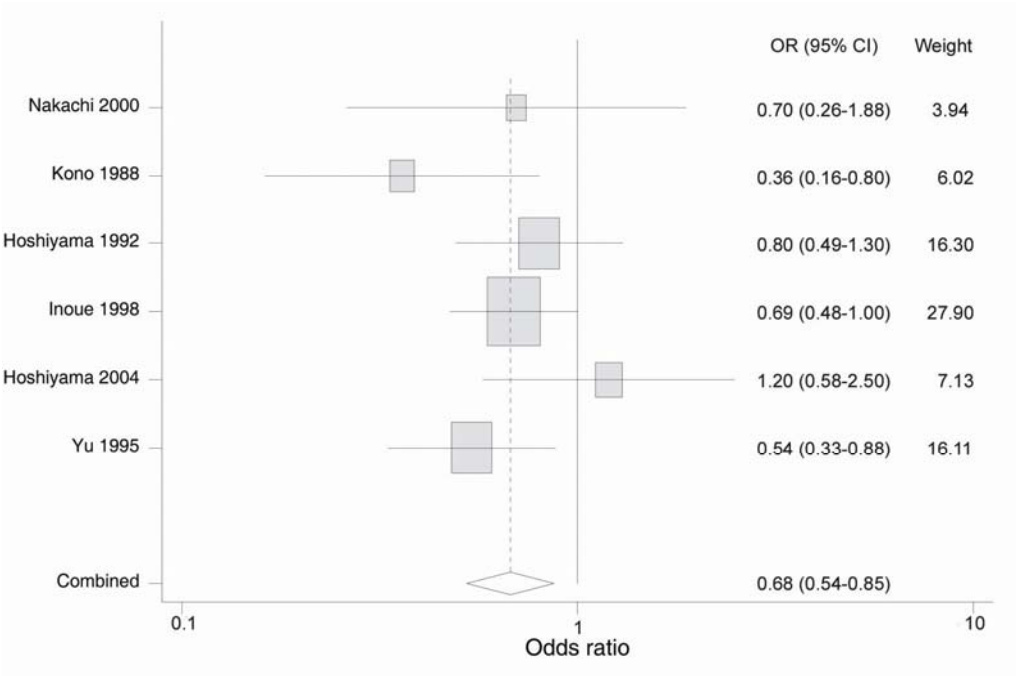

Figure 3. Forest plot of odds ratios of stomach cancer from 6 studies whose difference between the highest and the lowest green tea consumption was greater than 5 cups/day
Combined odds ratio and its 95% CI were 0.68 (0.54-0.85). The graph was produced in STATA.

Table 3 presents the result of meta-regression analysis to explore the heterogeneity. In univariate analyses, study design (p=0.00), difference between the highest and lowest green tea consumption level (p=0.01), and country where the study was conducted (p=0.01 for China vs. Japan and 0.05 for USA vs. Japan) appeared to contribute significantly to the observed heterogeneity.

In a multivariate analysis, however, difference between the highest and lowest green tea consumption level was the only factor that significantly contributed to the

heterogeneity (p=0.07 for ≥5 cups/day versus <5 cups/day). Though statistically not significant, the country where the study was conducted seemed to contribute to the heterogeneity modestly (p=0.11 for China versus Japan, p=0.50 for USA versus Japan). Study design (Cohort versus case-control), year of publication (before 2000 versus on and after 2000) and whether adjustment for potential dietary confounders was made were not obviously associated with the heterogeneity in the multivariate analysis model (p=0.38, 0.49 and 0.28 respectively).

Table 3. Meta-regression analysis of 18 observational studies

Study characteristic		Univariate analysis*		Controlling for all variables	
		Coefficient	P value	Coefficient	P value
Country	China versus Japan	-0.45	0.01	-0.29	0.11
	USA versus Japan	0.58	0.05	0.24	0.50
Study design (cohort vs. case-control)		0.35	0.00	0.26	0.38
Adjustment for dietary factors (yes vs. no)		0.00	0.99	0.15	0.28
Year of the publication (<2000 vs. ≥2000)		0.14	0.34	-0.19	0.49
Difference between highest and lowest green tea consumption level (≥5 cups/day vs. <5 cups/day)		-0.35	0.01	-0.30	0.07
Intercept				-0.87	0.51

* Univariate analysese are based on random effect models

Figure 4 presents Begg's funnel plot. Visual exploration of the plot revealed apparent asymmetry –smaller studies tended to report positive results, while larger studies reported both positive and negative results. This implies a publication bias in the reporting of results on green tea consumption and stomach cancer risk. The result of Egger's test also supported the suspicion (intercept = -2.02, p=0.01).

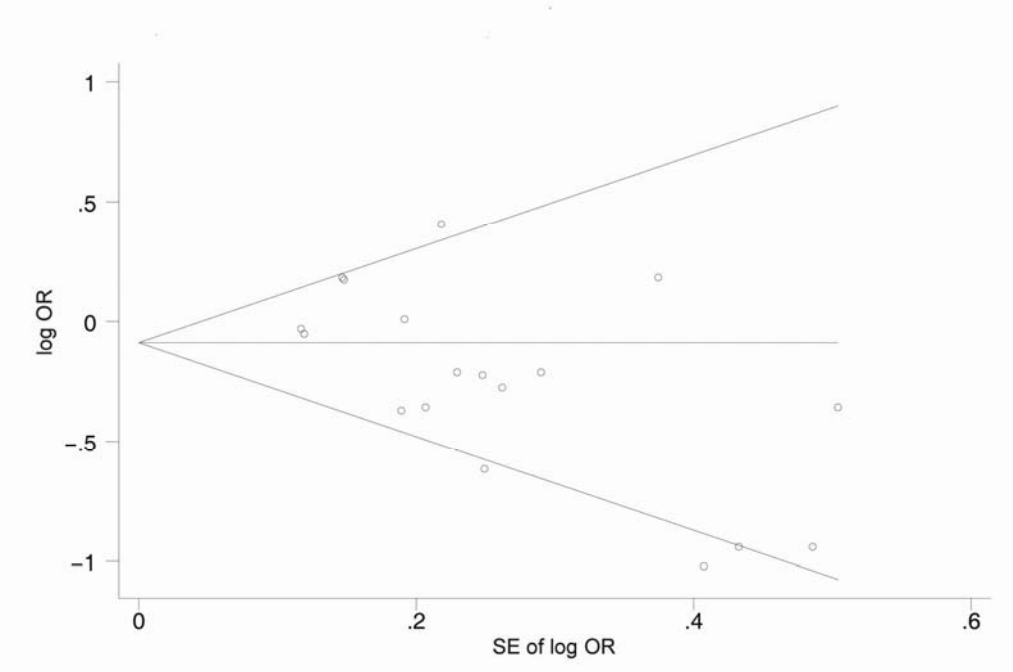

Figure 4. Begg's funnel plot of observational studies on green tea consumption and stomach cancer risk
The solid line in the center is the natural logarithm of pooled odds ratio, and two oblique lines are pseudo 95% confidence limits. The graph was produced in STATA.

Figure 5 presents results of the influence analysis. When combined odds ratios were computed omitting one study at a time, no single study seemed to dominate the meta-analysis. However, it was observed that the omission of a cohort study tended to make the estimate statistically significant, while the omission of a case-control study did not.

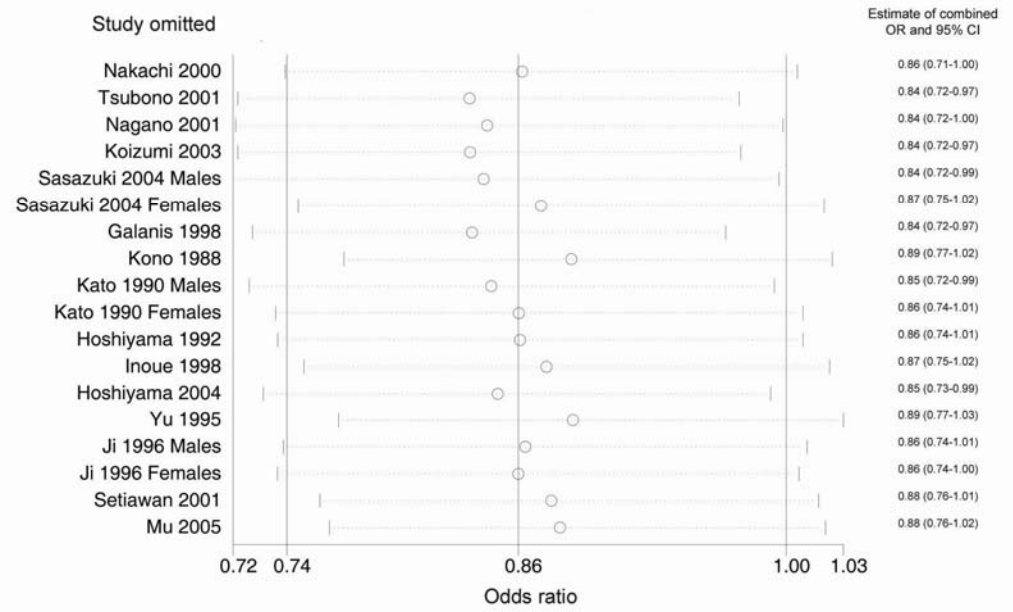

Figure 5. Influence analysis of observational studies on green tea consumption and stomach cancer risk
Open circles indicate estimates of combined odds ratio when a study was omitted. The graph was produced in STATA.

4. Discussion

This meta-analysis investigated the association between green tea consumption and stomach cancer risk based on previously published researches.

The overall summary OR on green tea consumption and stomach cancer risk, based on nineteen observational studies, indicated a statistically significant 14% risk reduction in the high green tea consumption group. Substantial heterogeneity across the studies, mainly derived from the difference between the highest and the lowest consumption level, was also noted.

The reduced risk of stomach cancer in green tea drinkers was observed in studies with differences between the highest and lowest daily green tea consumption level equal to or greater than 5 cups/day(Kono et al., 1988; Hoshiyama and Sasaba, 1992; Yu et al., 1995; Nakachi et al., 2000; Hoshiyama et al., 2004). A few authors have argued that the relative lack of unexposed subjects in Japan, which resulted in an insufficient number of non-drinkers, might be an explanation for the weaker associations among Japanese researches (Nagano et al., 2001; Mu et al., 2005; Sun et al., 2006). Many studies conducted in Japan, however, failed to document green tea consumption

greater than 5 cups/day (Kato et al., 1990; Nagano et al., 2001; Tsubono et al., 2001; Koizumi et al., 2003; Sasazuki et al., 2004), even though they had enough subjects to divide the highest consumption group further. In the report by Tsubono et al.(2001), for example, 42% of subjects were included in the highest green tea consumption group(≥5 cups/day). When a meta-analysis was done with the four Japanese studies whose difference between the highest and lowest consumption level was greater than 5 cups/day (Kono et al., 1988; Hoshiyama and Sasaba, 1992; Nakachi et al., 2000; Hoshiyama et al., 2004), the summary OR and 95% CI was 0.72 and 0.53-0.97. This implies that if a large prospective study with a more detailed categorization of green tea consumption is performed, a positive result may be obtained. Moreover, in a laboratory research, the amount of ten cups of green tea per day was comparable to the concentration of green tea extract used in animal experiments that showed a protective effect in gastric carcinogenesis(Yamane et al., 1996). Dose-response relationship between green tea consumption and stomach cancer development can be presumed from these results. Further research is needed to address the issue properly.

Research design also seemed to play a major role in the heterogeneity across the studies. While the protective effect was observed among case-control studies only, prospective studies tended to show null results. A few prospective studies even showed increased risks with green tea consumption, although they were not

statistically significant(Galanis et al., 1998; Tsubono et al., 2001; Koizumi et al., 2003). Some authors suggested that tea might have a mutagenic effect(Galanis et al., 1998), but this hypothesis is contradictory to results of most laboratory research(Yang et al., 2006). The number of cases was very small for the green tea drinkers in the report by Galanis et al.(1998), and that may have resulted in the exaggerated the risk estimates. In the report by Tsubono et al.(2001), green tea drinkers were more likely to be heavy smokers compared to non-drinkers. Although cigarette smoking had been controlled in a multi-variate analysis, there is a chance that the residual confoundings may have distorted the results.

Protective effects shown by case-control studies may have been biased also. Generally, case-control studies are subject to be influenced by a recall bias, which is a form of information bias, and it could lead to a spurious association(Egger et al., 2001). Moreover, epidemiologic studies have found that patients with a gastric cancer have decreased their tea consumption two years before the diagnosis(Goldbohm et al., 1996), and that the accuracy of the recall of an earlier diet is strongly influenced by the recent diet(Willett, 1998). This bias would partly explain the difference in the findings between cohort and case-control studies.

The studies conducted in China showed a stronger reduction in stomach cancer

among green tea drinkers than those conducted in Japan or the other countries. This could be partly explained by the relative insufficiency of control groups in Japanese studies, as mentioned above. No Japanese study presented non-green tea drinkers as a reference comparison group, while all the others did. Thus the comparison had to be made between the tea drinkers and the consequent lack of power might have contributed to the null result. Another possible explanation is the difference in the production processes between Japan and the other countries. In Japan, green tea production involves a steaming process at a high temperature to keep the green color of the tea. This process may lead to changes in chemical composition and in the concentration of bioactive constituents such as vitamins C and E, which may also contribute to the preventive properties of green tea(Mu et al., 2005). Also, bioactivity of a cup of green tea differs by the amount of green tea leaves used to brew it and the frequency of renewing a tea batch in the pot(Nagano et al., 2001). Differences in tea drinking habit may be a partial explanation of the difference.

Sasazuki et al.(2004) suggested that there might be a gender-specific protective effect of green tea on stomach cancer, but the analysis of six studies(Kato et al., 1990; Yu et al., 1995; Ji et al., 1996; Galanis et al., 1998; Inoue et al., 1998; Tsubono et al., 2001; Sasazuki et al., 2004) which included gender information revealed statistically non-significant effect on both genders (estimates of OR=1.00 for males and 0.89 for

females, 95% CI=0.82-1.24 for males, 0.74-1.07 for females). Thus, gender does not seem to cause any difference in the effect of green tea on stomach cancer.

Site-specific stomach cancer incidence in accordance with green tea consumption was mentioned in four studies(Yu et al., 1995; Ji et al., 1996; Koizumi et al., 2003; Sasazuki et al., 2004) While Ji et al.(1996) and Koizumi et al.(2003) showed no difference between green tea consumption and stomach cancer risk by anatomical subsite, the other two reported a different risk pattern by subsite. Yu et al.(1995) showed a significant protective effects for pyloric tumors (OR=0.29, 95% CI=0.13-0.68), and Sasazuki et al.(2004) reported a significant effect for distal tumors among women (OR=0.53, 95% CI=0.30-0.86). Although more studies are needed to address this issue, it is possible that green tea consumption might be related to distal stomach cancers only. It is recommended that future studies take this into consideration.

Total duration of green tea drinking was considered in three Chinese studies(Yu et al., 1995; Setiawan et al., 2001; Mu et al., 2005). All of them showed a decreased risk of stomach cancer with increasing duration of green tea drinking, but failed to reach a statistical significance. The results are summarized in Table 4. These results are in concordance with the suggested dose-response relationship mentioned above. Further studies are needed to clarify this point.

Table 4. Stomach cancer risk and the duration of green tea drinking

Author, Year	Duration of green tea drinking	OR (95% CI)
YuG et al. 1995	Age started habitual green tea drinking (yrs)	
	< 40	0.72 (0.54-0.97)
	≥40	0.67 (0.42-1.07)
Setiawan VW et al. 2001	Tea drinking history (yrs)	
	1-21	0.70 (0.36-1.36)
	> 21	0.39 (0.15-1.01)
	P for trend	0.05
Mu LN et al. 2005	Years of green tea drinking (yrs)	
	0-15	0.60 (0.24-1.51)
	15-25	0.47 (0.20-1.12)
	≥ 25	0.64 (0.34-1.19)
	P for trend	0.10

It is known that Helicobacter pylori is an important risk factor for a stomach cancer(Helicobacter and Cancer Collaborative Group, 2001). Only two studies(Setiawan et al., 2001; Mu et al., 2005), however, controlled the bacteria infection in their analyses. Green tea has been considered to have a bacteriostatic and a bactericidal effect(Horiba et al., 1991; Yam et al., 1997), which can extend to Helicobacter pylori. Thus, the infection could have confounded the result on which a further study is needed.

It has long been known that tea has a negative impact on the absorption of nonheme iron in the diet because of its polyphenol content(Disler et al., 1975). There has been

a concern that tea consumption may cause iron deficiency anemia(Gabrielli and De Sandre, 1995). In a recent review on this matter, however, Nelson et al. concluded that there was insufficient evidence that black tea drinking was associated with iron deficiency anemia in healthy UK population(Nelson and Poulter, 2004). As green tea has more polyphenol contents compared to black tea, it is still probable that green tea may result in the iron deficiency anemia, and more studies are needed to address this issue. While drinking one to six cups of black tea per day was shown to improve the antioxidant status, the maximum intake of eight cups per day was found to minimize any risk relating to excessive caffeine consumption(Gardner et al., 2007). As green tea has less caffeine contents compared to black tea, intake of up to eight cups per day of green tea would be acceptable in terms of caffeine intake.

This meta-analysis has a few limitations. First of all, selection and information bias cannot be ruled out as this study combined results from observational studies. As the intervention cannot be randomly assigned, the selection and confounding will often distort the results of a meta-analysis(Pocock and Elbourne, 2000). This can be more prominent for preventive intervention studies like this, because they are more likely to be chosen and adhered to by people with healthier life styles(Egger et al., 2001). As shown in the stratified analysis, the protective effect of green tea was prominent among case-control studies, which could be easily misled by an information bias. In a

multivariate meta-regression analysis, however, research design was not a significant factor contributing to the heterogeneity of the studies.

Second, publication bias could have distorted the result. Tweedie et al. reported that 45% of an observed association could be due to publication bias(Tweedie et al., 1996). As published data may be systematically different from unpublished ones, reviews or meta-analyses based on published data may only reach a misleading conclusion(Thornton and Lee, 2000). Because of the asymmetric funnel plot, publication bias cannot be ruled out in this study.

Third, the studies included in this study had different categories for green tea consumption. Though odds ratio or relative risk of the highest consumption versus non/lowest consumption was used for combining the effect size, they were not uniform across the studies. This might have distorted the result.

Fourth, Chinese literature could not be reviewed because of language barrier. As results from Chinese studies tended to show protective effects, the combined effect would have been different if they were included in the study.

Last, all the studies included in the analysis had been done among Asian population.

Green tea is a popular drink in East Asia, while black tea is mostly consumed in Western countries(Sivasubramaniam, 2007). Thus, the result of this study cannot be applied to non-Asian population.

5. Conclusion

In summary, the result of this meta-analysis suggests a protective role of green tea on stomach cancer. Caution has to be paid, however, because this result might have been biased by limitations of the research design and data collection.

Subgroup analyses revealed that the difference between the measured highest and lowest green tea consumption level was found to be the most prominent factor affecting the heterogeneity of the meta-analysis. This implies that the daily consumption level might be a single most important factor in determining the preventive effect of green tea on stomach cancer. Further research focusing on higher green tea consumption level is needed to clarify the association.

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국문 요약

녹차 섭취와 위암 위험 : 메타 분석

녹차는 오래 전부터 아시아 지역에서 소비되어 온 기호식품으로 실험실 연구를 통해 이의 추출물이 위암을 포함한 암세포의 발생과 성장을 억제하는 것으로 알려져 왔다. 그렇지만 녹차 섭취와 위암 위험의 관계에 대한 다양한 역학적 연구 결과를 병합하려는 시도는 현재까지 이루어지지 않고 있다. 이 연구의 목적은 기존에 출판된 연구 결과를 토대로 메타 분석을 통하여 녹차 섭취와 위암 위험 사이의 관계를 밝히려는 것이다.

MEDLINE, THE COCHRANE LIBRARY, 한국학술정보원 데이터베이스와 이를 통해 찾은 자료의 참고 문헌을 조사하여 총 열 여덟 편의 관찰 연구를 확인하였다. 각 연구에서 녹차의 최다 섭취군과 최저 섭취군 사이의 승산비 또는 비교위험도를 병합하였으며, 통합 효과 크기는 동질성 검정 결과에 따라 고정 효과 모형 혹은 확률 효과 모형을 사용하여 계산하였다. 각 연구 사이의 이질성을 설명하기 위해서 메타 회귀 분석 및 층화 분석을 실시하였고, 결과의 확고성을 확인하기 위하여 영향력 분석을 실시하였다.

통합승산비는 0.86, 95% 신뢰구간은 0.74-1.00 으로 녹차 섭취와 위암 위험 사이에는 유의한 음의 상관 관계가 존재하였다. 녹차의 위암에 대한 보호 효과는 열 두 개의 환자-대조군 연구 (통합승산비 0.74, 95% 신뢰구간 0.63-0.86) 와 중국에서 시행된 다섯 개의 연구 (통합승산비 0.61, 95% 신뢰구간 0.47-0.81) 에서 두드러지게 나타났다. 특히 측정된 최다 녹차 섭취량과 최저 녹차 섭취량의 차이가 하루 5 잔 이상 나는 연구들에서 통계적으로 유의한 보호 효과가 확인되었다. (통합승산비 0.68, 95% 신뢰구간 0.53-0.87)

결론적으로 녹차는 위암에 대해 보호 효과를 보이는 것으로 확인되었다. 또한 이러한 효과는 많은 양의 녹차를 소비할 때 더 두드러지게 나타날 것으로 추정되었다. 그러나 관찰 연구에 대한 메타 분석의 방법론적 한계와 이 연구에서의 출판 편견의 가능성 등을 고려할 때, 이러한 결과는 조심스럽게 해석되어야 할 것이다.

중심단어 : 녹차, 위암, 메타분석