RESEARCH ARTICLE

Association Between Green Tea and Colorectal Cancer Risk: A Meta-analysis of 13 Case-control Studies

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Abstract

Objective: Experimental studies have suggested green tea to be a chemopreventive agent for colorectal cancer, and many studies have examined possible associations. However, the conclusions were inconsistent or even contradictory, so we performed a meta-analysis based on published case-control studies to explore if green tea is indeed a protective factor. Methods: PubMed was searched up to May 10th, 2012 for relevant studies, and references of included studies were manually searched. Finally 13 eligible studies, involving 12,636 cases and 38,419 controls were identified. After data extraction, a meta-analysis was performed using CMA v2 software. Results: The results indicated there may be a weak but not statistically significant reduced risk of colorectal cancer with high dose of green tea intake (OR=0.95, 95% CI:0.81-1.11, p=0.490.69–0.98). This protective effect was also found in all subgroups, except in American and European populations. Sensitivity analysis indicated the result to be robust. Publication bias was not detected by either funnel plot or Egger tests. Conclusion: The results of this meta-analysis indicate a weak lower tendency for colorectal cancer development with green tea consumption, but available epidemiologic data are insufficient to conclude that green tea may protect against colorectal cancer in humans.

Keywords: Green tea - colorectal cancer - colon cancer - rectal cancer - meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the leading cause of cancer mortality in western conutries (Siegel et al., 2012). China, Japan, and South Korea have experienced an increase of two to four times in the incidence of CRC during the past few decades (Sung et al., 2005), and more than 700,000 new CRC cases occur in ASEAN (the Association of Southeast Asian Nations) countries (Kimman et al., 2012). The definite mechanism of CRC development is still unclear, both environmental factors and genetic susceptibility are considered as risk factors. The incidence rate and mortality rate of CRC in many asian countries are still considerably lower than in western countries (Edwards et al., 2010), suggesting that there maybe some potential protective factors play a role in risk for CRC in this population.

Tea is a widely consumed beverage worldwide, generally consumed in the forms of green, oolong, and black tea, all of them originated from the dried leaves of plant Camellia sinensis. Of them, green tea constitutes about 20% of the world tea production, mainly consumed in China and Japan. Green tea is produced by steaming or pan-frying tea leaves, which inactivates the enzymes and prevents the oxidation of tea constituents. Green tea polyphenols have been extensively studied as cancer chemopreventive agents. The catechins are major consisted of (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC), EGCG is the most abundant and active compound that can block cancer progression (Jankun et al., 1997; Kanwar et al., 2012).

This possible cancer preventive mechanism of green tea has caught much attention in the past three decades. Many animal models have been demonstrated that the green tea catechins against carcinogenesis at different organ sites (Yang et al., 2011), and this conclusion is supported by many epidemiological studies. However, there are also some published studies had come to the meaningless or opposite conclusions, and individual studies may be underpowered to detect the effect of different tumor site of CRC. Given the inconsistent associations between consumption of green tea and the potential protection implications for CRC, we conducted a meta-analysis for deriving a more precise estimation of this association.

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Materials and Methods

Literature search

We initially identified published studies that concerned green tea consumption in relation to CRC risk by searching the PubMed up to May 10th, 2012. The following search terms were used: (1) "colorectal" or "colonic" or "rectal" or "colon" or "large bowel"; (2) "neoplasm" or "cancer"; (3) "green tea" or "catechin" or "tea"; (4) "case-control" or "case control" or "case". These search themes were combined using "and" without restrictions. Additionally, we also checked the reference lists of retrieved papers and recent reviews.

Study selection

We included studies that met all of the following criteria: (1) case-control study; (2) tested the association between green tea and CRC risk; (3) the cancer type did not contain adenocarcinoma; (4) the diagnoses of CRC was confirmed either histological, pathologically or cytological; (5) the site of cancer included colon, rectum, or colorectum; (6) the adjusted odds ratios (OR) and relevant corresponding 95% confidence intervals (CIs) were reported, for highest versus non/lowest level of green tea intake. Two investigators reviewed the eligibility of all studies according to the predetermined selection criteria independently, disagreements were resolved by consultation with the third one.

Data extraction

Two reviewers extracted first author's last name, year of publication, country, site of cancer, source of controls, number of cases and controls, age, gender, exposure, adjusted OR and 95% CI, adjusted estimates of risk, independently, any disagreements were resolved by consensus.

Statistical analysis

The Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey) (Borenstein et al., 2005) was used to computed pooled ORs and 95% CIs, generate forest plots, determine whether there was a statistical association, and assess heterogeneity. If heterogeneity existed, the random effects model was used, or the fixed effects model was used.

The chi-square based Cochran's Q statistic (Higgins et al., 2002) and the I^2 statistic were used to quantified evaluated heterogeneity. The I^2 statistic yields results ranged from 0 to 100% (I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2 = 50-75%, large heterogeneity; and I^2 = 75-100%, extreme heterogeneity) (Higgins et al., 2003).

In addition, we investigated the influence of a single study on the overall risk estimate by removing each study in each turn, to test the robustness of the main results. Subgroup analysis was also performed according to source of control, country, and site of cancer.

Publication bias was evaluated by visual inspection of the funnel plots of the primary outcome and the Egger weighted linear regression test (Egger et al., 1997). 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 0.05.

Results

Characteristics of included studies

Figure 1 shows flowchart of study section. Of initially 72 studies searched, 13 studies including a total of 12,636 cases and 38,419 controls were identified (Kato et al., 1990; Baron et al., 1994; Ji et al., 1997; Tavani et al., 1997; Inoue et al., 1998; Munoz et al., 1998; Slattery et al., 1999; Woolcott et al., 2002; Zhang et al., 2002; Il'yasova et al., 2003; Li et al., 2011; Wu et al., 2011; Zhang. et al., 2011). Table 1 summarized the detailed characteristics of included studies. All of included 13 studies were published in English, the cases were histological, pathologically or cytological confirmed as CRC. Controls were mainly healthy populations, and matched with age and gender, 4 were hospital-based (HB) (Tavani et al., 1997; Inoue et al., 1998; Munoz et al., 1998; Zhang et al., 2002), 9 were population-based (PB) (Kato et al., 1990; Baron et al., 1994; Ji et al., 1997; Slattery et al., 1999; Woolcott et al., 2002; Il'yasova et al., 2003; Li et al., 2011; Wu et al., 2011; Zhang. et al., 2011). There were 5 studies performed in China (Ji et al., 1997; Zhang et al., 2002; Li et al., 2011; Wu et al., 2011; Zhang. et al., 2011), two in Japan (Kato et al., 1990; Inoue et al., 1998), two in the USA (Slattery et al., 1999; Il'yasova et al., 2003), one in Sweden (Baron et al., 1994), one in Italy (Tavani et al., 1997), one in Argentina (Munoz et al., 1998), and one in Canada (Woolcott et al., 2002). All the studies reported adjusted ORs and 95% CIs and the adjusted covariates.

Green tea and risk of CRC

There was significant heterogeneity across the studies ($p<0.001$, I^2=76.9%), so the random effects was used. The overall results showed that high green tea consumption could decrease 5% risk of CRC, but there was not a statistically significant compared with non/lowest level of green tea intake (OR=0.95, 95% CI:0.81-1.11, p=0.49); when we switched to fixed model, the results showed

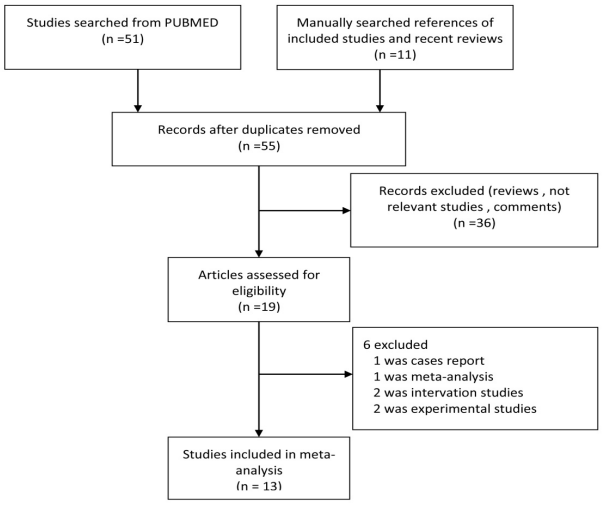

Figure 1. Flowchart of the Studies Selection Process

Table 1. Characteristics of Included Studies

Study	Country	Site of cancer	No. (Ca/Co)	Source of Co	Age(yrs,Ca/Co)	Gender (M/F,Ca:Co)	Exposure Ca	Exposure Co	Adjusted OR(95%CI)	Adjustment for covariates
Kato 1990	Japan	Colon	132/578	PB	34-80	1.49:1.88	>1 times/d	<1 times/d	0.61(0.41,0.91)	age, gender and residence
Kato 1990	Japan	Rectum	91/578	PB	34-80	1.94:1.88			1.32(0.78,2.23)	
Baron 1994	Sweden	Colon	352/512	PB	68.4±8.9/67.7±9.0	0.86:0.86	≥2 cups/d	none	0.96(0.67,1.37)	intake of fat and fiber, BMI and exercise
Baron 1994	Sweden	Rectum	217/512	PB	66.9±8.5/67.7±9.0	0.97:0.86			0.56(0.34,0.90)	
Ji 1997	China	Colon	931/1552	PB	30-74	0.93:1.15	>8500 g/m	<1 g/m	0.83(0.61,1.13)	age, income, education and smoking
Ji 1997	China	Rectum	884/1552	PB	30-74	1.10:1.15			0.68(0.49,0.95)	
Tavani 1997	Italy	Colon	2166/7057	HB	19-79(median:62)	1.19:1.27	yes	none	1.21(1.06,1.37)	age, gender, education, BMI, smoking, number of
Tavani 1997	Italy	Rectum	1364/7057	HB	19-79(median:62)	1.50:1.27			1.15(0.99,1.35)	meals,alcohol, meat, vegetables, fruit, and calories
Inoue 1998	Japan	Colon	362/21128	HB	61.1±9.6/53.9±9.5	1.43:0.43	≥7 cups/d	none	0.77(0.47,1.26)	age,gender, smoking,alcohol,exercise, and
Inoue 1998	Japan	Rectum	266/21128	HB	60.0±9.5/53.9±9.5	1.86:0.43			1.25(0.62,2.51)	intake fruit, rice,beef,coffee and black tea
Muñoz 1998	Argentina	Colorectum	190/393	HB	23-79(median:62/59)	0.88:1.05	≥1 cups/d	none	0.80(0.60,1.07)	age,gender,social class, and BMI
Slattery 1999	USA	Colon	1993/2410	PB	30-79	1.23:1.14	>1 times/d	none	0.87(0.58,1.31)	age, BMI,exercise,energy intake, sucrose, smoking and alcohol
Woolcott 2002	Canada	Colon	991/2118	PB	63.5±9.0/59.4±11.2	1.25:1.72	>5 cups/d	<1 cup/d	1.13(0.79,1.62)	age,gender, education,BMI, and intake of energy,
Woolcott 2002	Canada	Rectum	875/2118	PB	62.2±9.3/59.4±11.2	1.62:1.72			1.15(0.79,1.66)	calcium, fibre and cholesterol
Zhang 2002	China	Colorectum	102/99	HB	51.1±9.6/51.2±9.4	1.27:1.25	yes	none	0.42(0.22,0.79)	smoking,alcohol, and intake coffee
Il'yasova 2003	USA	Colon	646/1053	PB	40-80	1.06:0.97	≥2 times/d	none	1.30(0.90,1.88)	age, gender, and race
Wu 2011	China	Colorectum	421/845	PB	65.9±11.1/65.8±10.8	1.07:0.87	yes	none	2.30(1.70,3.11)	age,gender,and lifestyle habits
Zhang 2011	China	Colorectum	478/477	PB	62.4±10.8/62.2±10.6	1.41:1.38	yes	none	0.93(0.52,1.68)	age, sex, BMI, and occupation
Li 2011	China	Colorectum	175/197	PB	56.2±10.6	NA	>1 times/d	none	0.62(0.42,0.92)	education,BMI,smoking,alcohol,exercise,and energy intake

Ca, cacer; Co, control; OR, odd ratio; CI, confidence interval; PB, population-based; HB, hospital-based; d, day; m, month; NA, not available; BMI, body mass index

Table 2. Subgroup Analyses According to Potential Sources of Heterogeneity

Subgroups		Number of studies	Meta-analyses ORs	95% CIs	p value	Model	Heterogeneity I^2	p value
Site of cancer	Colon	8	0.96	0.08-1.16	0.69	random	61.08	0.01
	Rectum	6	0.96	0.73-1.26	0.77	random	67.72	0.01
	Colorectum	5	0.87	0.48-1.58	0.65	random	90.96	<0.001
Source of control	Population-based	9	0.95	0.75-1.20	0.67	random	79.09	<0.001
	Hospital-based	4	0.96	0.77-1.19	0.69	random	72.14	<0.001
Country for study	Asia	7	0.87	0.62-1.22	0.43	random	83.87	<0.001
	America	4	1.01	0.86-1.18	0.90	fixed	29.32	0.23
	Europe	2	1.03	0.84-1.27	0.75	random	69.75	0.02

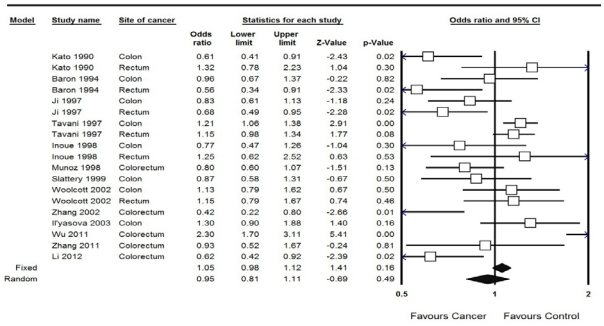

Figure 2. Forest Plot of Odds Ratios and 95% CI of Colorectal Cancer from Studies of Highest Versus Lowest/none Green Tea Intake

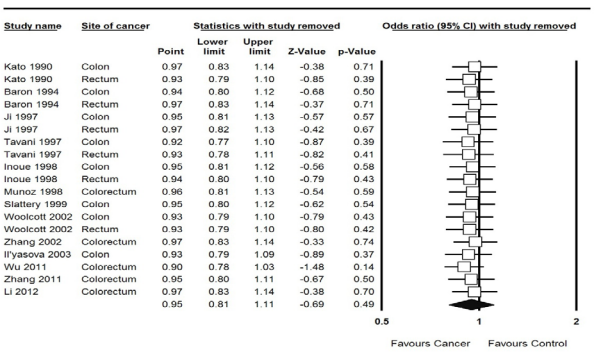

Figure 3. Forest Plot of Sensitivity Analysis by Omitting Each Study in Each Turn

high green tea consumption could increase 1.05 times risk of CRC, but the difference also without statistically significant compared with non/lowest level of green tea intake (OR=1.05, 95% CI:0.98-1.12, p=0.16) (Figure 2).

When we stratified the studies by site of cancer, results were consistent within the overall, the OR was 0.96 (95%CI: 0.08-1.16, p=0.69) for colon cancer, was 0.96 (95%CI: 0.73-1.26, p=0.77) for rectal cancer, was 0.87 (95%CI: 0.48-1.58, p=0.65) for colorectal cancer (Table 2). When we stratified studies by source of control, both population-based (OR=0.95, 95% CI: 0.75-1.20, p=0.67) and hospial based (OR=0.96, 95% CI: 0.77-1.19, p=0.69) were consistent within the overall (Table 2). When we stratified the studies by country, the studies conducted in Asia (OR=0.87, 95%CI= 0.62-1.22, p=0.43) was opposite to those conducted in America (OR=1.01, 95%CI= 0.86-1.18, p=0.90) and Europe (OR=1.03, 95%CI= 0.84-1.27, p=0.75) (Table 2).

When we omited one study in each turn, the ORs between 0.90 to 0.97, the p value between 0.14 to 0.74, that indicated the main result was robustness (Figure 3).

Publication bias

Based on visualization of the funnel plot (Figure 4), it was symmetrical, that indicated there was no publication bias existed. This was confirmed by Egger linear regression (intercept =-1.94, p=0.06).

Discussion

This meta-analysis evaluated the association between green tea consumption and CRC risk, based on 13 published case-control studies. The overall result showed that indicated that high green tea consumption could weakly reduction the risk of CRC, but the association without statistically significant. Sensivity analysis by

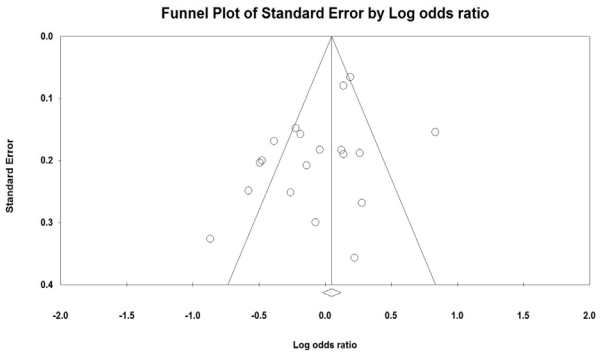

Figure 4. Funnel Plot Based on Odds Ratio for Association Between Green Tea and Colorectal Cancer

omiting individual studies and switching effect models were both supported the overall result was robust. The subgroup analyses results by stratifying the studies according to site of cancer, source of control, and country were consistent with overall result. However, the studies performed in Asia (China and Japan) indicated a weakly reduction trend, while in America (Argentina, USA, and Canada) and in Europe (Sweden and Italy) showed a weakly increase trend. That may indicated green tea is benefit for Asia people, mainly in China and Japan.

Compared with the previous meta-analysis published in 2006 by Sun et al (Sun et al., 2006), our meta-analysis included 6 eligible case-control studies before 2006 (Baron et al., 1994; Tavani et al., 1997; Munoz et al., 1998; Slattery et al., 1999; Woolcott et al., 2002; Il'yasova et al., 2003) and 3 after 2006 (Li et al., 2011; Wu et al., 2011; Zhang. et al., 2011). In addition, their results showed that high green tea consumption had a statistically significant reduction risk of CRC in overall result (OR=0.74, 95%CI= 0.63-0.86) and in conlon cancer (OR=0.74, 95%CI= 0.60-0.93), but not consistent in rectal cancer (OR=0.98, 95%CI= 0.61-1.60). The trend is similar with our result, but statistically significant was disappeared. The major strength of our study was that we used adjusted ORs instead of primary data, as we know, that can provide more precise and credible result.

Does green tea can decrease the CRC risk? Results from a human experimental randomized controlled trail support the hypothesis of a protective role of green tea for the chemoprevention of metachronous colorectal adenomas (Shimizu et al., 2008). Another randomized, placebo controlled, multicentre trial to investigate the effect of green tea extract nutriprevention of metachronous colon adenomas in the elderly population is undergoing (Stingl et al., 2011), whether it can obtain a significant result is still unkown. For colorectal adenomas is unlike CRC, so the high quality andomized, placebo controlled trials for CRC are necessary to performed.

There were also some limations of our meta-analysis. First of all, heterogeneity cannot be ruled out, neither in overall or subgroup analyses, and the protective effect of green tea was changed into susceptible factor in fixed model. If there were no heterogeneity existed, we could not kown how the result would be. Second, although no publication bias detected, there were six trails beyonded the guidelines (Figure 4), we could not find the reason and to explore it. And the non-Englishstudies could not be reviewed because of the language barrier. Lastly, for we could not extract the data of dose of green tea consumption and risk of CRC, that a dose-respone analysis could not perform to assess the relationship more precisely.

In summary, there is insufficient information from case-control studies to conclude that green tea can be linked to the prevention of CRC in humans.

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