Green tea consumption and risk of esophageal cancer: a meta-analysis of epidemiologic studies

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Abstract

Background: Green tea has shown the role of chemoprevention for cancer. Recently, several studies suggested that green tea intake may have effect on esophageal cancer risk, whereas the results were inconsistent.

Methods: We performed a meta-analysis of all English and Chinese language studies of green tea consumption and esophageal cancer risk indexed in Medline, Embase, the Science Citation Index, the Chinese Biomedical Database and Wanfang Data from 1980 to June 2012. After reviewing each study, extracting data, and evaluating heterogeneity (Chi-square-based Q test and $I^2$) and publication bias (Begg and Egger test), a meta-analysis was performed to evaluate the association between high/medium/low green tea consumption and non-drinking esophageal cancer risk. Pooled relative risk (RR) or odds ratio (OR) with 95% confidence intervals (CIs) were calculated using the fixed- or random-effect models.

Results: Ten eligible epidemiologic studies including 33731 participants and 3557 cases for esophageal cancer were included. Eight of which were case–control studies, and two were cohort studies. Overall, there were no association between high/medium/low green tea consumption and non-drinking risk of esophageal cancer (High: highest vs non-drinker: RR/OR = 0.76, 95% CI: 0.49 to 1.02. Medium: drinker vs non-drinker: RR/OR = 0.86, 95% CI: 0.70 to 1.03. Low: lowest vs non-drinker: RR/OR = 0.83, 95% CI: 0.58 to 1.08). When stratified analyses according to study design (case–control and cohort studies), country (China and Japan), participates source (population-based and hospital-based case–control), and gender (female and male), there were significant association between high/medium/low green tea consumption and non-drinking risk of esophageal cancer among female (High: RR/OR = 0.32, 95% CI: 0.10 to 0.54. Medium: RR/OR = 0.43, 95% CI: 0.21 to 0.66. Low: RR/OR = 0.45, 95% CI: 0.10 to 0.79), but not the others.

Conclusions: We did not found significant association between green tea consumption and non-drinking esophageal cancer risk, but an evidence of protective effect was observed among female.

Background

Esophageal cancer is a major concern in the world, ranking the sixth most common cause of cancer mortality [1]. Lifestyle such as cigarettes smoking, alcohol drinking and dietary habits have been suggested to be associated with the carcinogenesis of esophageal cancer [2,3]. Tea is one of the most widely consumed beverages in the world [4]. Tea is divided into three major types: green tea (non-fermented), oolong tea (half-fermented) and black tea (fermented) according to on the manufacturing process. Green tea and its constituents such as epigallocatechin-3 gallate (EGCG), epigallocatechin (EGC) and epicatechin-3 gallate (ECG) have been shown to inhibit tumorigenesis in many animal models [5,6]. There have been a number of epidemiologic studies evaluated the relation between green tea intake and esophageal cancer risk in human, but with different results. Two large case–control studies [7,8] showed the protective effect of green tea intake on esophageal cancer incidence. However, another case–control study including 883 cases showed that people who have more consumption of green tea more susceptible to esophageal cancer [9]. No quantitative attempt has been to summarize the results of studies exploring a possible association between green tea and esophageal cancer.

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Therefore, we conducted this meta-analysis to examine
the association in epidemiologic studies.

Methods
Search strategy
The electronic databases, Medline (1966 to June 2012),
Embase (1980 to June 2012), the Science Citation Index
(1945 to June 2012), the Chinese Biomedical Database
(1981 to June 2012) and Wanfang Data (1980 to June
2012) were searched for epidemiologic studies published
in English or Chinese of green tea intake in relation to
esophageal cancer risk. We used the search terms “tea,”
“food,” “diet,” “beverage,” “drinking” or “tea polyphenol”
combined with “esophageal”, “oesophageal”, or “esophag-
ous”. Firstly, the title and abstract of identified relevant
studies were used to exclude any obviously irrelevant
studies. The full-texts and tables of the remaining arti-
cles were retrieved and perused to determine the rele-
vancy of the study design and data, according to the
inclusion criteria detailed below. Additional studies were
identified by screening the reference lists of each rele-
vant study. Furthermore, reviews concerning the rele-
vant topic were retrieved from the above-mentioned
databases in order to potentially broaden the search by
identifying additional relevant publications from the
studies cited in the reviews.

Inclusion criteria
The following inclusion criteria were used to select rele-
vant studies for the meta-analysis: (a) human studies,
not laboratory or animal studies were included; (b) the
daily consumption of the natural green tea product, not
of green tea extracts or supplements were recorded; (c)
the outcome of interest had to be an incidence of
esophageal cancer; (d) relative risk (RR) or odds ratio
(OR) estimates with corresponding 95% CIs (or suffi-
cient information to calculate them) were reported. If
two or more studies used the same population resource
or had overlapping subjects, only the study reporting the
largest population was selected for inclusion in the
meta-analysis.

Data extraction
Two reviewers (Ping Zheng and Haiming Zheng) inde-
dependently performed the data extraction. Disagreements
were resolved by reviewers (Deng and Zhang), and a
consensus was reached for all data prior to meta-anal-
ysis. The following information was collected: the first
author’s name, publication year, the country of origin,
follow-up duration, gender, the number of participants
(cases and cohort size), measurements of green tea con-
sumption, relative risk (RR, which is a ratio of the
exposed group and non-exposed group incidence rate
and suitable for cohort/prospective study), or odds ratio
estimates (OR, which is suitable for case–control studies),
and their corresponding 95% confidence intervals (95%
CIs). We treated them as two different studies when a
study provided separate RR/OR estimates for men and
women. If a study provided several RR/ORs, we extracted
the RR/ORs reflecting the greatest degree of control for
potential interaction factors. When a study provided RR/
OR for both esophageal cancer and invasive esophageal
cancer, we used the former due to getting more cases.

Statistical analysis
To evaluate the association between green tea consump-
tion and risk of esophageal cancer, the RR/OR with 95%
CIs were calculated using pooled data from the studies.
Data pooling was carried out by using the fixed effects
model (based on the Mantel-Haenszel method) or the
random effects model (based on the Dersimonian and
Laird method) [10,11] The random effects model was
used if heterogeneity existed between the studies from
which the data was extracted; otherwise, the fixed effects
model was used. Statistical heterogeneity between stud-
ies was assessed with the Chi-square-based Q test and
I², and heterogeneity was considered significant when
the two-tailed P value was less than 0.10 [12]. I² was
used to qualify variation in RR/OR that was attributable
to heterogeneity [13]. Publication bias was estimated by
using the Begg and Mazumdar adjusted rank correlation
test and the Egger regression asymmetry test [14,15].
Finally, the statistical significance of the RR/OR was
determined by using the Z test.

Since the original data of tea consumption dose is non-
linear, we divided the level of consumption into high,
medium and low groups. We calculated the highest/lowest
level of tea consumption as high/low group to compare
with the non-drinking when the original literature pro-
vided the group of tea-drinking dose. When there is no
dose group, we use the drink group as highest/lowest level
of tea consumption respectively. We calculated the drink-
ing of tea consumption as medium group to compare with
the non-drinking when the original literature provided
the group of tea-drinking. And when there is several dose
groups, we use the combination as drink group. So we
generated three group of tea intake: highest vs non-
drinker, drinker vs non-drinker, lowest vs non-drinker.

We performed meta-analysis for all the included stud-
ies, and then made subgroup analysis according to study
design, country, participates source and gender. This
work was conducted on the basis of MOOSE guidelines
proposed by the Meta-Analysis of Observational Studies
in Epidemiology group [16]. All P values are two-tailed.
For all tests, P values < 0.10 are considered statistically
significant, except for heterogeneity. All analysis was
performed by the Stata version 11.0 software (Stata Cor-
poration, College Station, Texas).
Results
Characteristics of included studies
Ten epidemiologic studies [7-9,17-21] including 33731 participants and 3557 cases of esophageal cancer were identified according to the inclusion criteria of the meta-analysis. The characteristics of the included studies are summarized in Table 1. The publication dates in this study ranged between 1994 and 2011. Eight of them [7-9,18-21] were case–control studies (seven conducted in China and one in Iran), and the other two were cohort studies (conducted in Japan) [17]. Among eight case–control studies, seven studies were population-based.

Table 1 Characteristic of including studies of green tea intake and incidence risk of esophageal cancer

| Study            | Country; design       | Study period | Population | Green tea intake levels OR or RR (95% CI) | Adjustments                                                                 |
|------------------|-----------------------|--------------|------------|------------------------------------------|------------------------------------------------------------------------------|
| Gao (1994)       | Shanghai China        | 1990-1993    | 902 (male:622, female: 280) cases and 1552 (male:854, female: 698) hospital-based controls | Male: drinking vs. never drinking 0.80 (0.58-1.09) 1-199g/month vs. never drinking 0.79 (0.53-1.17) >200g/month vs. never drinking 0.79 (0.56-1.13) Female: drinking vs. never drinking 0.50 (0.30-0.83) 1-199g/month vs. never drinking 0.77 (0.39-1.53) >150g/month vs. never drinking 0.34 (0.17-0.69) | Age, education, birthplace, cigarette smoking (both sexes), and alcohol intake (men only). |
| Yang (1999)      | Yangzong China        | 1998-1998    | 68 cases and 68 population- based controls | drinking vs. never drinking 0.20 (0.06- 0.67) | Age, education, cigarette smoking, and alcohol intake .                        |
| Mu (2003)        | Taixing, China        | 2000-2000    | 218 cases and 415 hospital based controls | <125g/month vs. never drinking 1.13 (0.67-1.92) 125-250g/month vs. never drinking 0.78 (0.46-1.34) >250g/month vs. never drinking 0.58 (0.35-0.97) | Age, education, cigarette smoking, and alcohol intake .                        |
| Astunobu, cohort 1 (2006) | Japan prospective cohort study | 9 years | 38 cases among 9008 residents in Miyagi prefecture | 1-2 cups/day vs. < never or occasionally 0.69 (0.17-2.91) 3-4 cups/day vs. < never or occasionally 1.58 (0.52-4.76) 5 cups/day vs. < never or occasionally 1.78 (0.66-4.82) | Age, sex, cigarette smoking, alcohol consumption, consumption of black tea, coffee |
| Astunobu, cohort 2 (2006) | Japan prospective cohort study | 7.6 years | 40 cases among 17715 residents in Miyagi prefecture | 1-2 cups/day vs. < never or occasionally 1.22 (0.47-3.19) 3-4 cups/day vs. < never or occasionally 0.85 (0.30-2.40) 5 cups/day vs. < never or occasionally 1.61 (0.71-3.66) | Age, sex, cigarette smoking, alcohol consumption, consumption of black tea, coffee |
| Wang (2007)      | China population based case control study | 2004-2006 | 355 (male:223, female: 132) cases and 408 (male:252, female: 156) population controls | Male drinking vs. never drinking 1.37 (0.95–1.98) Female: drinking vs. never drinking 0.26 (0.07–0.94) | Age (continuous), sex, cancer family history and BMI, marital status and education years. smoking, alcohol drinking. |
| Wu (2009)        | Dafeng China population based case control study | 2003-2007 | 637 (male:426, female: 211) cases and 1938 (male:1368, female: 570) Dafeng population controls | <150g/month vs. never drinking 1.0 (0.7-1.3) 125-250g/month vs. never drinking 1.0 (0.6-1.8) >250g/month vs. never drinking 1.0 (0.6-2.0) | Age , gender, education level, income, cancer family history, BMI smoking , alcohol drinking, tea temperature |
| Wu (2009)        | Ganyu China population based case control study | 2003-2007 | 883 (male:765, female: 118) cases and 1941 (male:1548, female: 393) Gany population controls | <150g/month vs. never drinking 1.1 (0.7-1.7) 125-250g/month vs. never drinking 1.0 (0.7-1.6) >250g/month vs. never drinking 1.6 (1.1–2.2) | age , gender, education level, income, cancer family history, BMI smoking , alcohol drinking, tea temperature |
| Chen (2011)      | Guangdong China hospital based case control study | 2004-2010 | 150 cases and 300 hospital based controls | <100g/month vs. never drinking 1.27(0.72-1.89) 100-250g/month vs. never drinking 0.97 (0.59-2.56) >250g/month vs. never drinking0.92 (0.49-2.32) | age, sex, education level, annual income, cancer family history, smoking and drinking status |
| Islami (2009)    | Northern Iran population based case control study | 2003-2007 | 266 cases and 386 population- based controls | Daily, weekly vs Never, <weekly 0.65 (0.32 to 1.31) | ethnicity, daily vegetable intake alcohol consumption, tobacco or opium ever use, duration of residence in rural areas, |

OR, odds ratio; RR, relative risk; CI, confidence interval.
case–control (PCC) [7-9,18,20,21]. Besides, the other was hospital-based case–control (HCC) [19]. In addition, there were two studies [7,18] provided gender-specific OR estimates and 95% CIs for the association between green tea consumption and esophageal cancer risk.

### Meta-Analysis of categories of consumption

Three categories of consumption have been generated: high (Figure 1, Figure 2, Table 2), medium (Figure 3, Figure 4, Table 3), low (Figure 5, Figure 6, Table 4).

### Meta-Analysis of Case–control studies

Eight case–control studies were included. Of which, two studies [7,18] presented the OR and CIs for female and male respectively, and one study for participants from two different areas. All of them were treated as two studies when analysed.

In the meta-analysis, green tea consumption was found to be associated with a significantly lower risk of esophageal cancer in high group (RR/OR = 0.72, 95% CI: 0.45 to 0.98, Table 2). The $P$ value of heterogeneity chi-squared test was < 0.01, and the corresponding $I^2$ statistic was 76%, suggesting variability between studies. The $P$ values for the Begg's and the Egger's tests were $P = 0.07$ and $P = 0.02$, respectively, suggesting the probability of publication bias.

The results in Medium and low group were not statistically significant (respectively: RR/OR = 0.85, 95% CI: 0.67 to 1.02, Table 3. RR/OR = 0.82, 95% CI: 0.56 to 1.09, Table 4). The $P$ value of heterogeneity chi-squared
test were all < 0.01. The corresponding $I^2$ statistic were 65%, 72%. The $P$ value for the Begg’s test and Egger’s test were 0.03 and 0.02, 0.07 and 0.01, respectively.

**Meta-Analysis of Cohort studies**

Two cohort studies were included [17]. The association between green tea consumption and the risk of esophageal cancer were all not statistically significant (high/medium/low respectively: RR/OR = 1.67, 95% CI: 0.46 to 2.87, Table 2. RR/OR = 1.14, 95% CI: 0.70 to 1.03, Table 3. RR/OR = 0.96, 95% CI: 0.01 to 1.92, Table 4).

The $P$ value of heterogeneity chi-squared test were 0.90, 0.90 and 0.59, respectively. The corresponding $I^2$ statistic were all 0.0%, indicating a low variability between studies. The $P$ value for the Begg’s test and Egger’s test were 1.00 and not applicable, 0.26 and 0.17, 0.07 and 0.01, respectively.

**Combined and Subgroup Analysis**

Furthermore, we performed the combined analysis of case–control and cohort studies. The association between green tea consumption and non-drinking risk of esophageal cancer were not statistically significant in three group (High: RR/OR = 0.76, 95% CI: 0.49 to 1.02, Table 2. Medium: RR/OR = 0.86, 95% CI: 0.70 to 1.03, Table 3. Low: RR/OR = 0.83, 95% CI: 0.58 to 1.08, Table 4.). The $P$ value of heterogeneity chi-squared test were all < 0.01. The corresponding $I^2$ statistic were 73%, 56%, 66%, respectively. The $P$ value for the Begg’s test and Egger’s test were 0.37 and 0.16, 0.24 and 0.22, 0.16 and 0.03, respectively. Overall, no association was found between green tea consumption and non-drinking risk of esophageal cancer.

When stratified by country, we did not found association between green tea consumption and non-drinking risk of esophageal cancer in China, Japan and Northern Iran (Tables 2, 3, 4).

When stratified by participates source, we found a significant association between high green tea consumption and non-drinking esophageal cancer risk among PCC (RR/OR = 0.71; 95% CI: 0.43-0.98, $P < 0.01$ for heterogeneity, $I^2 = 78$%), but not the HCC (RR/OR = 0.92; 95%
CI: 0.49-2.32, with only one study, Table 2). We did not find association between medium/low green tea consumption and non-drinking risk of esophageal cancer in PCC and HCC.

There were two studies [7,18] provided gender-specific RR estimates and 95% CIs for the association between green tea consumption and esophageal cancer risk, therefore we also made stratified analysis by gender. The results of meta-analysis showed that there were significant association between high/medium/low green tea consumption and non-drinking risk of esophageal cancer among female (High: RR/OR = 0.32, 95% CI: 0.10 to 0.54, \( P = 0.75 \) for heterogeneity, Table 2. Medium: RR/OR = 0.43, 95% CI: 0.21 to 0.66, \( P = 0.35 \) for heterogeneity, Table 3. Low: RR/OR = 0.45, 95% CI: 0.10 to 0.79, \( P = 0.16 \) for heterogeneity, Table 4), but not the male.

Sensitivity analysis
Sensitivity analysis has been carried out by excluding one study from others step by step in each group. They did not alter the original results.

Discussion
Our meta-analysis of epidemiologic studies did not found significant association between high/medium/low green tea consumption and non-drinking esophageal cancer risk, while an evidence of protective effect was observed among female.

However, there are only two cases of case–control in female studies which existed all in China, this result can lead to selection bias. In addition, the positive results are more easily published, making publication bias generated. All that makes worthy of further consideration about female results. If excluding these factors, some
other reason should be considered of the impact among female.

Sex hormone may be an explanation for why female experiencing significantly a lower risk of esophageal cancer when take high level green tea. A sex hormone-mediated pathway may be involved in esophageal carcinogenesis, which was supported by two experimental studies [22,23]. A suppressing effect of estrogen and a promoting effect of androgen were shown in the experimental induction of esophageal cancer by the administration of chemical carcinogen [22]. Meanwhile, the growth rate of metastatic squamous cell carcinoma of the esophagus was inhibited by estrogen and enhanced by testosterone, respectively [23]. Additional studies are warranted to explain and confirm this preliminary evidence.

There have been a number of experimental and clinical studies suggesting drinking beverages at high temperatures to be a cause of esophageal cancer. The facts that more tumors were showed and larger size of esophagus papillomas were rapidly increased when the temperature at 70°C and above was reported by a previous experimental study [24]. In our meta-analysis, two included studies [9,19] both found that drinking tea at high temperature significantly increases risk of esophageal cancer incidence. However, the two studies had different definition for high or normal temperature of green tea drinking, which make it difficult to be stratified for further analysis.

Three studies [9,17,19] included in the meta-analysis have investigated the effects of green tea drinking and dose response relationship. No dose–response relationship was observed among the two studies [17,19]. In the study conducted by Wu [9], higher monthly consumption of tea (P for trend = 0.07) and usually drinking tea in high concentration (P for trend = 0.01) showed a positive tendency with cancer risk for ever drinker after adjusting for tea temperature. We have analysed data by grouping high/medium/low intake. However, we have not found it is effective between green tea consumption and non-drinking in esophageal cancer risk.

The protective effect of high green tea consumption on esophageal cancer was observed among case–control
Table 4 Risk estimates of low green tea consumption with esophageal cancer by sex, geographic region and type of epidemiologic studies

| Study                          | No. of studies | No. of cases | RR or OR (95% CI) | Heterogeneity | Publication bias |
|-------------------------------|----------------|--------------|-------------------|---------------|-----------------|
|                              |                |              |                   | $p$  $I^2$     |  Begg's test    | Egger's test     |
| Overall                       | 10             | 3557         | 0.83 (0.58-1.08)  | 0.00 0.66     | 0.12 0.03       |
| Country                       |                |              |                   |               |                 |                 |
| Japan                         | 2              | 78           | 0.96 (0.01-1.92)  | 0.59 0.00     | 1.00 NA         |
| China                         | 7              | 3213         | 0.85 (0.56-1.13)  | 0.00 0.75     | 0.18 0.03       |
| Northern Iran                 | 1              | 266          | 0.65 (0.32-1.31)  | NA NA         | NA NA           |
| Study design                  |                |              |                   |               |                 |                 |
| Cohort studies                | 2              | 78           | 0.96 (0.01-1.92)  | 0.59 0.00     | 1.00 NA         |
| Case control                  | 8              | 3479         | 0.82 (0.56-1.09)  | 0.00 0.72     | 0.07 0.01       |
| Participates source           |                |              |                   |               |                 |                 |
| PCC                           | 7              | 3329         | 0.78 (0.51-1.05)  | 0.00 0.73     | 0.03 0.01       |
| HCC                           | 1              | 150          | 1.27 (0.72-1.89)  | NA NA         | NA NA           |
| Gender                        |                |              |                   |               |                 |                 |
| Male                          | 2              | 845          | 1.04 (0.48-1.61)  | 0.06 0.72     | 1.00 NA         |
| Female                        | 2              | 412          | 0.45 (0.10-0.79)  | 0.16 0.49     | 1.00 NA         |

NA: not applicable; PCC: population based case control; HCC: hospital based case control.
studies and PCC, but both the heterogeneity and publication bias are significant. So the protective effect among case–control studies and PCC may be incredible. Furthermore we performed the combined analysis of case–control and cohort studies. The heterogeneity and publication bias are not significant in the overall study. So, there may be no significant association between high green tea consumption and non-drinking esophageal cancer risk in the meta-analysis.

Focus on heterogeneity and publication bias of the analyses, we found all the estimates with several studies with a large sample size are very heterogeneous, while estimates with a couple of studies and small sample size have no heterogeneity. For example, both meta-analyses of all studies (ten studies) and case–control studies (eight studies), the P for heterogeneity were < 0.01, suggesting variability between studies. However, for meta-analyses among female (two studies) or male (two studies), the P for heterogeneity were both > 0.05, suggesting a low variability between studies. When heterogeneity existed we used the random effects model to adjusted. The publication bias among case–control and PCC studies are significant in high group. The cautions for above phenomenon may be as follows: (a) Most of case–control and population-based case–control studies were performed among China [7-9,18-21], and that may cause bias. (b) Retrospective bias. (c) Positive results may be published more easily. Furthermore, we performed subgroup analysis by sex, geographic region and type of epidemiologic studies.

However, there are several disadvantages should be considered in our meta-analysis. First, publication bias in China studies or case control studies cannot be missed. The protective effect of green tea in female may be misled by a publication bias because of the female studies all from China studies or case control studies. Second, the epidemiologic studies were not much enough to be stratified for dose and temperature of green tea intake, which may mitigate the result. Third, the non-English and non-Chinese literature could not be reviewed because of the language barrier. Last, most of the studies included in the analysis had been conducted among Asian populations due to popularity of green tea in East Asia. Therefore, the results should be cautiously extrapolated to other populations.

Conclusions
The results of our meta-analysis did not found significant association between green tea consumption and non-drinking esophageal cancer risk, but an evidence of protective effect was observed among female. Additional more studies (especially the cohort studies, and studies from more countries) with careful control of interaction factors including dose and temperature of green tea intake are needed to provide a more definitive conclusion focusing on whether the routine consumption of green tea can guard against esophageal cancer.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
PZ. and HMZ carried out the literature search, selection, validity, assessment, data abstraction and data analysis respectively. PZ. and HMZ wrote the paper. XMD and YDZ had the original idea for the paper and revision of the article. All authors reviewed and approved the final draft of the paper.

Acknowledgements
Declaration of personal interests: we are indebted to the authors of the primary studies.

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Received: 23 February 2012 Accepted: 29 October 2012 Published: 21 November 2012

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doi:10.1186/1471-230X-12-165

Cite this article as: Zheng et al.: Green tea consumption and risk of esophageal cancer: a meta-analysis of epidemiologic studies. *BMC Gastroenterology* 2012, 12:165.