

Tea consumption and risk of gallbladder cancer: A meta-analysis of epidemiological studies

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Abstract. Previous epidemiological studies investigating the association between tea consumption and the risk of gallbladder cancer have yielded inconsistent results. Therefore, we aimed to assess this association by conducting a meta-analysis of all available studies. A search was conducted through PubMed, Embase, Chinese Biomedical Literature Database and China Knowledge Resource Integrated Database to identify relevant studies on tea consumption and the risk of gallbladder cancer. A random-effects model was used to calculate the overall combined risk estimates. Six studies (4 case-control and 2 cohort studies), involving a total of 753 patients and 115,349 controls, were included in this meta-analysis. The overall combined odds ratio (OR) for tea consumption and gallbladder cancer was 0.67 [95% confidence interval (CI): 0.40-1.12, P=0.13]. Similar results were obtained for the high or moderate tea consumption vs. the low/non-consumption groups. However, our meta-analysis identified a significant association between tea consumption and reduced gallbladder cancer risk in women (OR=0.46, 95% CI: 0.26-0.81, P=0.008), but not in men (OR=0.43, 95% CI: 0.12-1.59, P=0.21). Therefore, the results of the present meta-analysis suggest that, according to the currently available epidemiological studies, tea consumption may reduce the risk of gallbladder cancer in women, but not in men. Further epidemiological studies are required to

determine the association between tea consumption and the risk of gallbladder cancer.

Introduction

Gallbladder cancer is a rare and highly fatal disease and is the most common malignant neoplasm of the extrahepatic biliary tract and the seventh most common gastrointestinal carcinoma (1). There were an estimated 10,310 cases of gallbladder cancer diagnosed in 2013 (2). Although gallbladder cancer remains an uncommon disease, it exhibits a high incidence in certain regions, such as Chile, where it is the most common cause of cancer-related mortality (3). We previously demonstrated the significance of lymph node metastasis (4). Although the etiology of the gallbladder cancer remains unknown, genetic, environmental and infectious factors, as well as the presence of gallstones, are considered to play important roles (5). The majority of the risk factors implicated in the development of gallbladder cancer are associated with inflammation (6).

Tea is one of the most popular beverages worldwide, second only to water, and is obtained from the steamed or pan-fried leaves of *Camellia sinensis* (7). Tea contains several polyphenols, known as catechins, such as epigallocatechin-3 gallate (EGCG), epigallocatechin (EGC) and epicatechin-3 gallate (ECG), which are considered to prevent the development of certain human diseases (8). Previous cellular and animal xenograft studies have reported that tea or its active components, EGCG, EGC and ECG, may possess antiproliferative, antimutagenic, antioxidant and antibacterial properties (9-13). In general, tea may prevent multifarious cancers at the cell and animal level. Tea was found to induce the apoptosis of GBC-SD human gallbladder carcinoma cells (14,15).

The results of epidemiological studies, such as cohort and case-control studies, investigating the association between tea consumption and gallbladder cancer risk over the last century, have been inconsistent. Certain studies reported that tea consumption significantly decreased the risk of gallbladder cancer, whereas others reported a non-significant negative correlation (16-21). However, to the best of our knowledge, there is currently no published meta-analysis investigating the

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association between tea consumption and gallbladder cancer risk.

The aim of the present study was to assess the association between tea consumption and the risk of gallbladder cancer through conducting a meta-analysis of relevant case-control and cohort studies.

Materials and methods

Literature search. A literature search was conducted through PubMed, Embase, Chinese Biomedical Literature Database (CBM) and China Knowledge Resource Integrated Database (CNKI), to identify epidemiological studies investigating the association of tea consumption with gallbladder cancer risk. As regards the outcome, the articles were identified using the Medical Subject Headings (MeSH) terms 'gallbladder neoplasm' or 'gallbladder carcinoma' or 'gallbladder cancer' and 'tea' or 'polyphenols'. As regards study design, the articles were identified using the MeSH terms 'case-control' or 'cohort' or 'prospective studies'. The reference lists of the retrieved articles were manually searched to identify potentially relevant publications. All the studies meeting the eligible criteria listed below were included in our meta-analysis.

Inclusion criteria. We reviewed the abstracts of all the identified studies. Further study selection was performed using the following inclusions: i) the exposure of interest was tea consumption; ii) the outcome of interest was gallbladder cancer; iii) the design of the study was cohort, case-control or prospective; and iv) the odds ratio (OR), relative risk or hazard ratio were reported.

The search only involved studies conducted on humans and the publication language was restricted to English and Chinese. If publications were duplicated or shared in more than one study using a different language, we selected the most recent edition and English.

Data extraction. Two reviewers (G.W.Z. and J.H.) independently extracted data on the characteristics of the eligible studies retrieved from the databases according to the above mentioned selection criteria, using a standardized data extraction form. The following data were recorded: author name, study design, country, sample size, study period, exposure to tea consumption and study results. Any disagreements were resolved through discussion and consensus with a third author (Z.J.W.).

Statistical analyses. OR with 95% confidence interval (CI) was used as a common measure of the association between tea consumption and the risk of gallbladder cancer across studies. For the purposes of the present analysis, tea consumption was coded as a three-level indicator variable, with non/low, moderate and high consumption (Table I). We investigated possible heterogeneity in the results across the studies using the Cochran's Q test. The I^2 statistic, which is a quantitative measure of inconsistency across publications, was also used (22). Studies with an I^2 statistic of 25-50, 50-75 and >75% were considered to exhibit low, moderate and high heterogeneity, respectively (22). The random-effects model was used when significant (moderate and high) heterogeneity

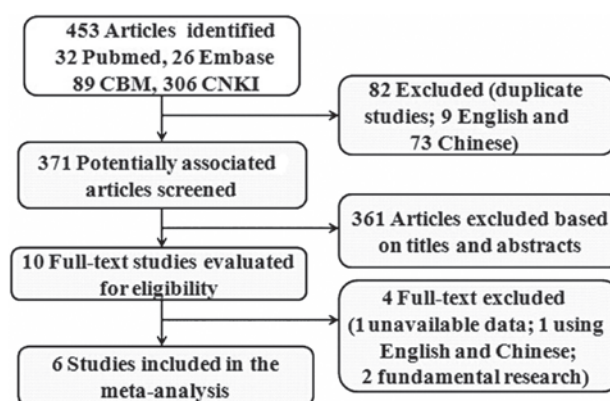


Figure 1. Flow chart of the literature search and study selection process.

was observed among studies (23). Potential publication bias was assessed by visually inspecting the Begg's funnel plots. $P < 0.05$ was considered to indicate a statistically significant difference. All the statistical analyses were performed using Review Manager software, version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Identification of relevant studies. Our meta-analysis included a total of 6 studies [4 case-control (17,19-21) and 2 cohort studies (16,18)] published between 1987 and 2012. The literature search and selection process is summarized in Fig. 1. The four databases (PubMed, Embase, CBM and CNKI) and the search through the bibliographies of relevant articles yielded 453 articles. A total of 82 articles were excluded due to being duplicate studies. The remaining 371 articles were reviewed; of these, the majority were excluded following title and abstract review (reviews, letters, or studies not relevant to our meta-analysis were excluded), leaving 10 studies for full-text review. A further 2 studies were excluded [one study with unavailable data for analysis (24) and one study published using English and Chinese (25)]. Following fundamental research exclusion of another 2 studies (14,15), a total of 6 studies were included in our present meta-analysis.

Study characteristics. The characteristics of the 6 studies included in this meta-analysis are summarized in Table I. The case/control sample size of the studies ranged between 41/184 and 368/69,310. Among these studies, 1 study only enrolled a female population (16). The definition of tea consumption level (high/moderate vs. low/non-consumption) are also reported in Table I.

Tea consumption and the risk of gallbladder cancer. A total of 6 studies were included in the meta-analysis investigating the association between tea consumption and the risk of gallbladder cancer. Overall, no significant association was observed between tea consumption and gallbladder cancer risk (OR=0.67, 95% CI: 0.40-1.12, $P=0.13$) in a random-effects model. There was significant heterogeneity among the studies ($I^2=82\%$; $P<0.0001$) (Fig. 2). Subsequently, sensitivity analyses were conducted to identify the potential source of heterogeneity and to assess the effect of different exclusion

Table I. Characteristics of the studies included in the meta-analysis.

Study (year)	Design	Study period	Country	No. of cases/controls	Low/non-consumption	Moderate consumption	High consumption	(Refs.)
Nechuta <i>et al</i> (2012)	Cohort	1996-2000	China	83/69,310	Never	NR	Current	(16)
Yen <i>et al</i> (1987)	Case-control	1975-1979	USA	67/272	Never/occasionally/1-2 cups/day	3-4 cups/day	≥5 cups/day	(17)
Nagano <i>et al</i> (2001)	Cohort	1979-1994	Japan	122/38,540	0-1 times/day	2-4 times/day	≥5 times/day	(18)
Zhang <i>et al</i> (2006)	Case-control	1997-2001	China	368/902	Never	M: <81,600 g lifetime; F: <24,600 g lifetime	M: >81,600 g lifetime; F: <24,600 g lifetime	(19)
Zatonski <i>et al</i> (1992)	Case-control	1985-1988	Poland	72/184	Never	<6,570 lifetime drinks	>6,570 lifetime drinks	(20)
La Vecchia <i>et al</i> (1992)	Case-control	1983-1990	Italy	41/6,141	No tea consumption	NR	Tea consumption	(21)

NR, not reported; M, male; F, female.

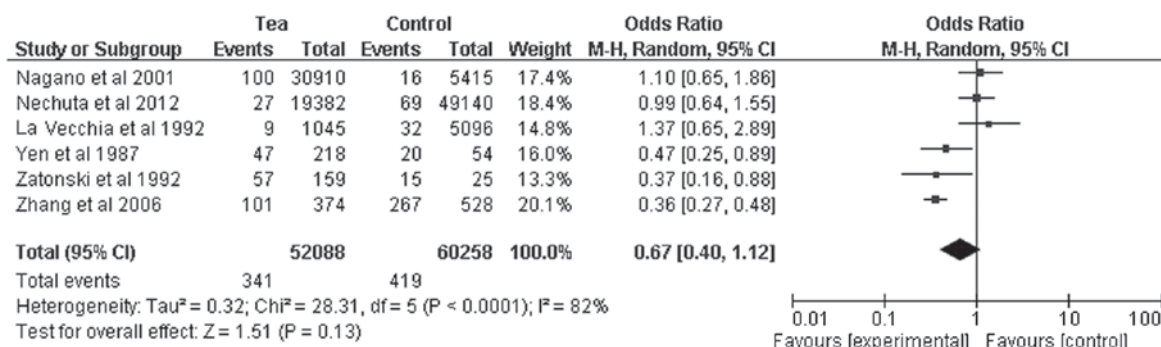


Figure 2. Forest plot showing the risk estimates from case-control and cohort studies assessing the association between tea consumption and the risk of gallbladder cancer. CI, confidence interval.

criteria on the combined estimates. Exclusion of women from studies on tea and gallbladder cancer risk yielded similar results (OR=0.62, 95% CI: 0.35-1.10, P=0.10), with significant heterogeneity (I²=81%; P=0.0003) (16). Following exclusion of 3 studies with a small sample size, the pooled results were not affected (OR=1.09, 95% CI: 0.80-1.48, P=0.60) and no significant heterogeneity was observed among the remaining studies (I²=0%; P=0.76) (17,19,20).

Levels of tea consumption and gallbladder cancer risk. We performed meta-analyses based on the level of tea consumption to investigate the effect of different tea consumption levels on gallbladder cancer risk. The results were relatively consistent and demonstrated that there was no significant difference between high/moderate vs. low/non-consumption in reducing the risk of gallbladder cancer (OR=0.57, 95% CI: 0.25-1.29, P=0.18; Fig. 3A; and OR=0.62, 95% CI: 0.33-1.14, P=0.12; Fig. 3B, respectively).

Comparison of women and men regarding tea consumption and the risk of gallbladder cancer. When studies were divided by gender, there was a significant decrease in the risk of gallbladder cancer associated with tea consumption in women (OR=0.46, 95% CI: 0.26-0.81, P=0.008; Fig. 4A). However, no association between tea consumption and the risk of gallbladder cancer was observed in men (OR=0.43, 95% CI: 0.12-1.59, P=0.21; Fig. 4B).

Publication bias. In our meta-analysis, the potential presence of publication bias was assessed by visual inspection of the Begg's funnel plots, which indicated that there was no significant publication bias (Fig. 5).

Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the association between tea consumption and

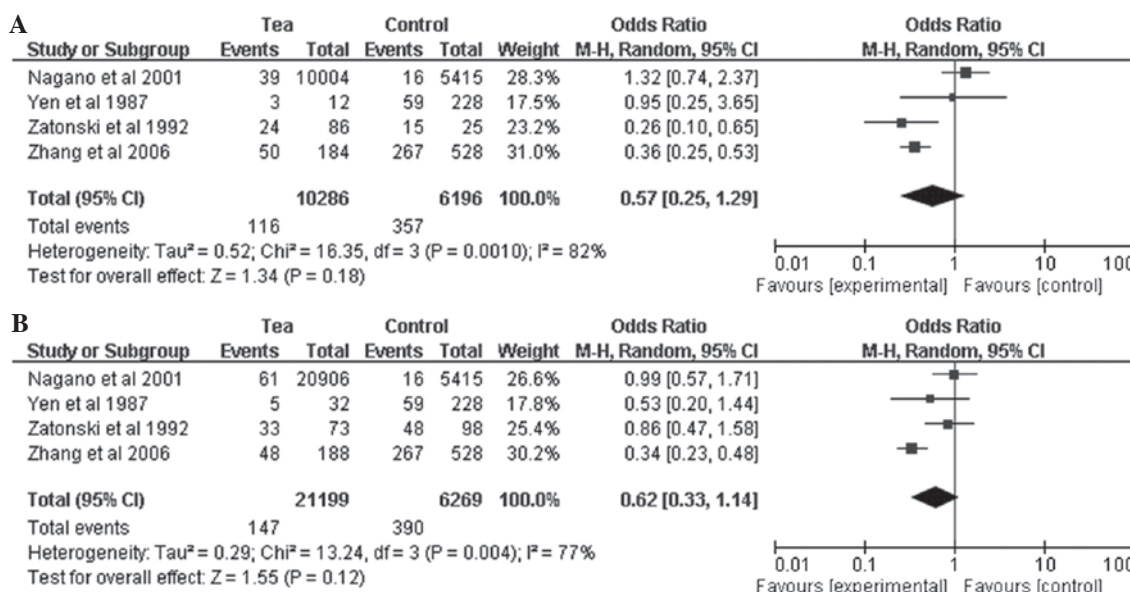


Figure 3. (A) Forest plot showing the risk estimates for high vs. low/non-consumption of tea and the risk of gallbladder cancer. (B) Forest plot showing the risk estimates for moderate vs. low/non-consumption of tea and the risk of gallbladder cancer. CI, confidence interval.

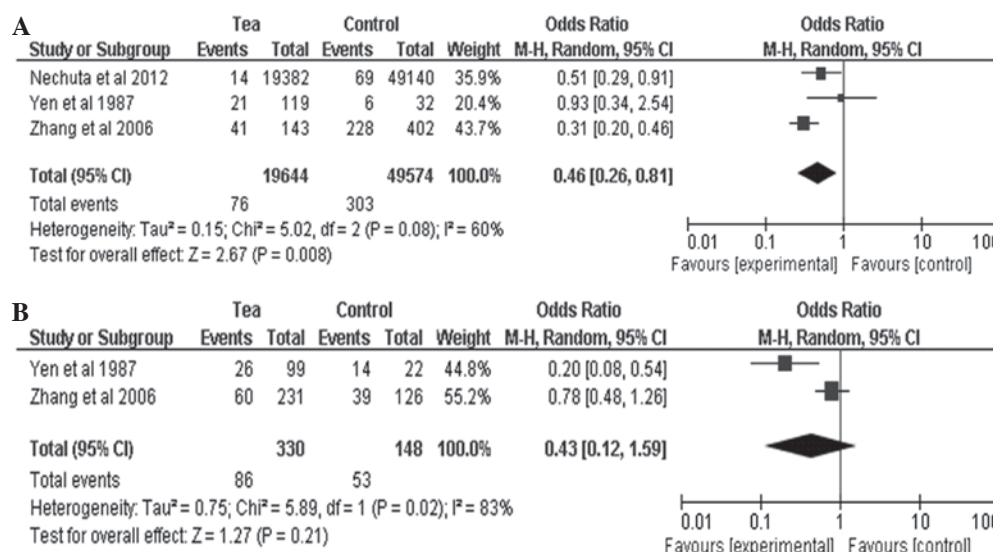


Figure 4. (A) Forest plot showing the risk estimates for tea consumption and the risk of gallbladder cancer in women. (B) Forest plot showing the risk estimates for tea consumption and the risk of gallbladder cancer in men. CI, confidence interval.

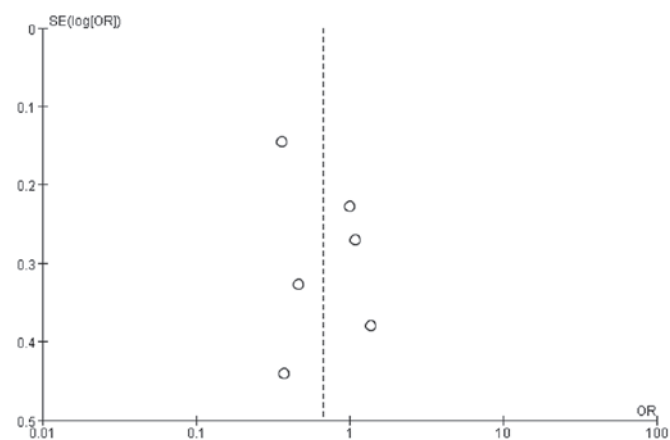


Figure 5. Funnel plot of tea consumption and the the risk of gallbladder cancer. OR, odds ratio; SE, standard error.

gallbladder cancer. This meta-analysis of epidemiological studies (4 case-control and 2 cohort studies) investigating the association between tea and gallbladder cancer risk, demonstrated that tea consumption did not reduce the risk of gallbladder cancer. Similar results were obtained for high or moderate vs. low/non-consumption. However, our meta-analysis identified a significant association between tea consumption and reduced gallbladder cancer risk in women, but not in men. The combined estimates were robust across sensitivity analyses and exhibited no publication bias.

A number of studies conducted *in vitro* and *in vivo* reported that tea may protect against different types of cancer (26-31). Therefore, several clinical and epidemiological studies were conducted, which, however, yielded conflicting results regarding tea consumption and the risk of breast (32,33),

lung (34) and renal cancer (35,36). In order to obtain more convincing results, certain meta-analyses were conducted for other types of cancer, which also yielded inconsistent results (37-40).

The results of the epidemiological studies on the association between tea consumption and the risk of gallbladder cancer included in our meta-analysis were inconsistent: 2 studies reported that tea intake decreased the risk of gallbladder cancer (17,20), 3 studies reported opposing results (16,18,21) and 1 study reported that tea intake reduced the risk of gallbladder cancer in women, but not in men (19). Therefore, we performed a meta-analysis assessing the association between tea consumption and gallbladder cancer.

Our meta-analysis found that there was a significant association between tea consumption and reduced gallbladder cancer risk in women, but not in men. There may be a reasonable explanation for this finding: Lifestyle factors, such as smoking and alcohol consumption may be responsible for the tea intake not reducing the risk of gallbladder cancer in men, due to the high prevalence of smoking and alcohol consumption among men (41,42), which may eliminate the protective effect of tea. Another possible explanation for the significant protective effect of tea in women may be relevant to the effects of tea on estrogen biosynthesis. Previous studies demonstrated that high levels of estrogens were consistently associated with a high risk of gallbladder cancer in women (43-45). Experimental data from animal and cell models suggested that tea may affect estrogen metabolism, although the detailed mechanisms underlying this effect remain unknown (46,47).

As is often the case with meta-analyses, ours had certain limitations. First, our analysis was based on 6 studies with widely variable sample sizes, which may be the origin of the heterogeneity of our meta-analysis. Although we performed a funnel plot for the outcomes, the limited number of studies makes it difficult to explain the result of publication bias. Second, certain detailed information could not be obtained, such as 2 studies that did not provide a precise record of gallbladder cancer cases (16,17), although gallbladder cancer is the most common malignant neoplasm of the extrahepatic biliary tract and accounts for the majority of extrahepatic biliary cancers (1); therefore, the studies were included in our meta-analysis. Moreover, there are several types of tea, including green, oolong and black tea, which may inhibit cancer development through different mechanisms. Therefore, our study results may not apply to all types of tea. Finally, missing and/or unpublished data may lead to bias.

In conclusion, our meta-analysis suggests that, according to the currently available epidemiological studies, tea consumption may reduce the risk of gallbladder cancer in women, but not in men. Due to the limitations of our study, further epidemiological studies are required to determine the association between tea consumption and the risk of gallbladder cancer.

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