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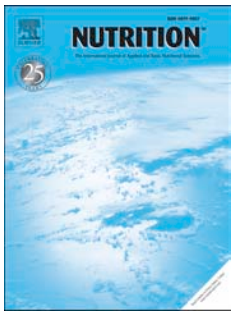


Tea consumption and lung cancer risk: a meta-analysis of case-control and cohort studies

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# Tea consumption and lung cancer risk: a meta-analysis of case-control and cohort studies

**Running heads**: Tea consumption and lung cancer risk

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**ABSTRACT**

*Objective:* Recent epidemiologic studies, especially cohort and case-control studies, have yielded inconsistent findings regarding the association between tea consumption and risk of lung cancer. This meta-analysis was conducted to assess a potential relationship between tea consumption and incidence of lung cancer worldwide.

*Methods:* A systematic literature search of PubMed, Web of Science, the Cochrane Library, Google Scholar, the Chinese Biomedical Database and Wanfang Database was conducted from 1966 to January 2014 by two investigators. All cohort studies and case-control studies that evaluated the association of tea and lung cancer were included. Summary relative risks (RR) and the corresponding 95% confidence intervals (CIs) were calculated using a random-effects model. Quality assessments were performed using the Newcastle–Ottawa Scale. Heterogeneity was assessed using the Q and $I^2$ tests, and the source of heterogeneity was detected by meta-regression analysis. Publication bias was evaluated with Egger's regression symmetry test. Subgroup analyses and sensitivity analysis were performed.

*Results:* Thirty-eight lung cancer studies (26 case-control studies and 12 cohort studies) with 59041 cases and 396664 controls were included. Overall tea consumption was significantly associated with decreased risk of lung cancer (RR 0.78, 95% CI 0.70–0.87). Subgroup analyses showed that tea consumption was associated with reduced lung cancer risk in women (RR 0.76, 95% CI 0.62–0.93), case-control studies (RR 0.72, 95% CI 0.63–0.83), Western studies (RR 0.85, 95% CI 0.75–0.97) and studies in China and Japan (RR 0.74, 95% CI 0.62–0.88). Both green tea (RR 0.75, 95% CI 0.62–0.91) and black tea (RR 0.82, 95% CI 0.71–0.94) were significantly

associated with reduced lung cancer risk. No significant association was found in men or in cohort studies.

*Conclusions:* Tea consumption may offer some protection against lung cancer.

*Keywords:* Tea; Meta-analysis; Lung cancer

## Introduction

Tea is the second most widely consumed beverage worldwide, after water [1, 2]. It is made from the leaves of plant *Camellia sinensis*. Tea, from a biological standpoint, is not a substance. It contains many bioactive components, such as catechins, flavonols, lignans, and phenolic acids. Based on handling methods and prompt processing after tea picking, tea is divided into three main types: green, black and oolong.

Recently, tea has attracted attention for its health benefits, particularly with a protective effect on various cancers [3-6]. Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death among males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths worldwide in 2011 [7]. Numerous animal and *in vitro* studies suggest that tea may have a protective effect against lung cancer initiation and its subsequent development, owing to the polyphenolic antioxidants present in tea [3, 8], by inhibiting nitrosation, cell proliferation and tumor progression, and by inducing carcinoma cell apoptosis [9].

However, epidemiological studies of the association of tea consumption and lung cancer risk have been inconsistent. In 2009, a meta-analysis by Tang et al. to assess this relationship suggested that green tea consumption but not black tea has a protective effect on lung cancer [10]. Tang also found that an increase in green tea consumption of two cups/day was associated with an 18% decreased risk of developing lung cancer [10]. However, the results should be updated. First, only studies published in the English language were included in that study. Second, since Tang's meta-analysis, eight epidemiological studies concerning the association between tea

consumption and lung cancer risk have been published, offering some new data and diverse conclusions [11-18]. Therefore, to better clarify the association between tea consumption and the risk of lung cancer, we conducted a meta-analysis that included the latest data and both English- and Chinese-language published studies.

## Methods

### *Search strategy*

A systematic literature search was carried out in PubMed, Web of Science, the Cochrane Library, Google Scholar, the Chinese Biomedical Database and Wanfang Database to identify relevant studies published in English and Chinese through January 2014. We used the search terms “tea”, “green tea”, “black tea”, “diet”, “food”, “drinking” combined with “lung cancer”, “lung neoplasm”, “lung tumor” or “lung carcinoma”.

### *Inclusion criteria*

The following inclusion criteria were used to select relevant studies for the meta-analysis: (a) cohort or case-control studies, not laboratory or animal studies; (b) the exposure factor was tea consumption; (c) the outcome of interest had to be incidence of lung cancer (small-cell lung carcinoma or non-small-cell carcinoma or both, histologically proven); (d) relative risk (RR) or odds ratio with their corresponding 95% confidence intervals (95% CI) were reported or could be calculated.

### *Data extraction and study quality assessment*

Data were extracted independently by two investigators using a collection form. Extracted data including the first author’s name, year of publication, country of origin, study period, study

`design, gender, age, sample size (cases and controls or cohort size), tea type, tea consumption, and the RR with corresponding 95% CIs were all used for meta-analysis.

The quality of each study was evaluated with Newcastle–Ottawa Scale (NOS) [19]. The included studies were judged on three aspects: the selection of study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Studies with scores of 0–4, 5–6, 7–9 stars were considered as low, moderate and high quality, respectively.

***Statistical analysis***

Our meta-analysis was performed by STATA 12.0 statistical software (Stata Corp). The RR with 95% CI was calculated using pooled data from the included studies. Statistical heterogeneity between studies was assessed with the Q test and $I^2$, and heterogeneity was considered significant when the $P$ value was less than 0.10 [20]. The pooled RR and 95% CI were calculated using a fixed-effects model if no significant heterogeneity existed between studies. Otherwise, a random-effects model was used. When statistical heterogeneity was observed, meta-regression analyses were conducted to explore how heterogeneity was influenced by sample size, case/control ratio, study design, tea types, follow-up time, and geographical region. Subgroup analyses of gender, tea type, geographical regions, study design, and smoking status were also performed. Sensitivity analysis was carried out by sequentially omitting individual studies to explore whether the results were significantly influenced by a specific study. Publication bias was evaluated with the Begg and Mazumdar adjusted rank correlation test and Egger's regression symmetry test [21, 22].

## Results

### *Characteristics of included studies and quality assessment*

The method used to select studies is shown in Fig.1. Of the 69 studies identified and screened, 5 reviews, 2 animal model studies and 5 studies of other cancers were excluded. After referring to full texts, we identified 50 epidemiologic studies published between 1966 and January 2014 that examined the potential association between lung cancer and tea consumption. Nine studies were excluded because they had data overlapping with that of other studies [23-31]. Three studies were excluded because of insufficient information to calculate the RR and 95% CI [32-34].

As a result, 38 publications recruiting 59041 cases and 396664 controls were finally enrolled in the analysis, which is shown in Table 1. Of these studies, 26 were case-control studies [11-14, 16-18, 35-53], and 12 studies [15, 54-64] were cohort studies. Among the case-control studies, 15 used population-based case-controls [12, 14, 16-18, 36-39, 42, 45, 47-50], and 11 studies used hospital-based case-controls [11, 13, 35, 40, 41, 43, 44, 46, 51-53]. Twenty-four studies were conducted in Asian countries [11-14, 16-18, 37-46, 54-56, 58-60, 64], and 14 in Western countries [15, 35, 36, 47-53, 57, 61-63]. Of all studies, 26 reported an association between specific tea types (green or black) and risk of lung cancer [11, 35-38, 40, 42, 43, 45-56, 58-63], and 19 compared the relative risk between men and women [12, 14, 15, 17, 35, 37, 42-45, 47, 49, 52, 53, 57, 59, 60, 62, 63].

The quality scores of each study are shown in Table 1. The quality scores ranged from 6 to 9: 33 studies were high quality (scored 7, 8 or 9), while the other 5 were moderate quality (scored

6).

***Risk estimation***

The RR of lung cancer risk and tea consumption for individual studies and all studies combined are shown in Fig.2. The overall results showed a significant 22% reduction in risk of lung cancer with tea consumption (RR 0.78, 95% CI 0.70–0.87). Significant heterogeneity was observed across all studies ($I^2$ = 83.3%, $P$ = 0.000). Publication bias was observed from Begg's funnel plot (Fig.3) and Egger's test ($P$ = 0.005). Sensitivity analysis showed that the pooled estimate of tea intake and lung cancer risk did not vary substantially with the exclusion of any one study, although one study by Wang et al. [15] has a large effect on the summary estimates (RR 0.77, 95% CI 0.69–0.87). The results confirmed the stability of our results.

***Meta-regression analysis***

Meta-regression analysis revealed that geographical region may be a possible source of heterogeneity (Table 2). Sample size, case/control ratio, study design, tea types, and follow-up time were not major contributors to the observed heterogeneity.

***Subgroup analyses***

***Study design***

Significant association between tea consumption and lung cancer risk existed in case-control studies (RR 0.72, 95% CI 0.63–0.83) (Table 3). However, no significant association was found in cohort studies (RR 0.91, 95% CI 0.77–1.08) (Table 2). Significant heterogeneity was found among studies without publication bias (cohort studies: $I^2$ = 78.2%, $P$ = 0.000; case-control studies: $I^2$ = 82.5%, $P$ = 0.000).

***Tea type***

As shown in Table 3, significant association was found between consumption of green tea (RR 0.75, 95% CI 0.62–0.91) and black tea (RR 0.82, 95% CI 0.71–0.94) and lung cancer risk. There was severe heterogeneity (green tea: $I^2$ = 73.4%, $P$ = 0.000; black tea: $I^2$ = 87.8%, $P$ = 0.000) and no evidence of publication bias (green tea: Egger's test: $P$ = 0.376; black tea: Egger's test: $P$ = 0.631)

***Geographical regions***

The results indicated that tea consumption was associated with decreased lung cancer risk both in Western studies (RR 0.85, 95% CI 0.75–0.97) and studies in China and Japan (RR 0.74, 95% CI 0.62–0.88) (Table 3).

***Gender***

In stratified analyses by gender, a protective effect of tea consumption on lung cancer was observed in women (RR 0.76, 95% CI 0.62–0.93) but not in men (RR 0.88, 95% CI 0.72–1.07) (Table 3). There was significant heterogeneity among studies (male: $I^2$ = 79.1%, $P$ = 0.000; female: $I^2$ = 78.6%, $P$ = 0.000). Significant publication bias was observed in female populations but not in male populations (Egger's test: $P$ = 0.286 and $P$ = 0.044, respectively).

***Smoking status***

No significant association was found between tea intake and lung cancer risk either in smokers (RR 0.79, 95% CI 0.59–1.07) or in non-smokers (RR 0.88, 95% CI 0.72–1.07). Significant heterogeneity was observed both in smokers and in non-smokers ($I^2$ = 54.3%, $P$ = 0.032; and $I^2$ = 75.1%, $P$ = 0.000, respectively).

**Discussion**

The present meta-analysis is a quantitative systematic analysis of the association between tea consumption and lung cancer risk based on published results from 12 prospective studies and 26 case-control studies. Our results suggested that tea consumption was associated with a decreased risk of lung cancer.

In our meta-analysis, tea-drinking populations in Western countries and in China and Japan, the association between tea intake and risk of lung cancer is significant. When subgroup analyses were conducted by tea type, our meta-analysis showed that both green tea (RR 0.75, 95% CI 0.62–0.91) and black tea (RR 0.82, 95% CI 0.71–0.94) consumption are associated with a lower risk of lung cancer. The Western population prefers to consume black tea, which accounts for only 18% of total tea consumption [65]. However, in China and Japan, more than 90% of tea drinkers consumed green tea [10]. Green tea is produced by steaming or pan-frying fresh tea leaves, which inactivates the enzymes and prevents polyphenol oxidation [66, 67]. Therefore, green tea is a rich source of flavonoids, the predominant being catechins [67]; (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin, (−)-epicatechin-3-gallate, and (−)-epicatechin are the four major catechins. Black tea, in contrast, undergoes fermentation, by which catechins are converted to theaflavins and thearubigins [68, 69]. Green tea has a higher catechin content than black tea [70, 71], which might contribute to its beneficial effects on cancer. EGCG is the major green tea catechin [65]. Studies demonstrate that EGCG might play an important role in cancer prevention [70-73]. For green tea, our result is consistent with Tang et al. [10]; however, they found that black tea consumption was not statistically significantly

associated with reduced risk of lung cancer. The reason may be related with data used in meta-analysis: Tang et al. [10] conducted their meta-analysis based on adjusted data, whereas ours was based on crude data.

Cohort studies are considered preferable to case-control studies in the hierarchy of scientific evidence. Our results showed that significant association existed in case-control studies, but not in cohort studies. The results may be related to the difference of study design types and sample size. There are 94548 participants in case-control studies, while 361157 participants are included in cohort studies.

Several potential limitations of our meta-analysis should be considered in interpreting the results. First, only articles published in English and Chinese were included in our meta-analysis. Literature in other languages and gray literature could not be included. Second, our results are likely to be affected by the ambiguous definition of tea exposure, which is mostly assessed regarding the number of cups of tea consumed daily or weekly. However, cup size may vary considerably across the included studies. Therefore, we did not conduct a dose-response analysis of tea consumption. Third, the duration of tea drinking may also have a potential effect on lung cancer risk. However, few of the studies included in this meta-analysis provided data on the association between duration of tea drinking and lung cancer risk. Fourth, studies included were mainly conducted in Japan, China, Europe, and the United States; therefore, the data should be extrapolated to other populations with caution. Finally, methodological differences, as well as confounding factors and biases, inherent in cohort and case-control studies may have an influence on our results.

## Conclusion

Our meta-analysis revealed that tea consumption may have a protective effect on lung cancer. Further prospective cohort studies are needed to obtain a definitive conclusion and to determine the mechanisms underlying this association.

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**Figure legends**

**Fig. 1.** Diagrammatic representation of the process followed in the selection of studies.

**Fig. 2.** Association between tea consumption and risk of lung cancer. RR, relative risks; CI, confidence interval.

**Fig. 3.** Begg's funnel plot of studies on tea consumption and lung cancer risk. RR, relative risks.

**Table legends**

**Table 1 Study characteristics of published studies on tea consumption and lung cancer risk**

PCC, population-based case-control study; HCC, hospital-based case-control study; RR, relative risks; CI, confidence interval; US, United States; UK, United Kingdom; —, no data to show RR of men or women for tea consumption and lung cancer risk.

**Table 2 Meta-regression analysis**

**Table 3 Subgroup analyses of tea intake and lung cancer risk**

RR, relative risks; CI, confidence interval.

**Table 1 Study characteristics of published studies on tea consumption and lung cancer risk**

| Study | Study period | Gender (having RR) | Country | Study design | Cases/controls or cohort | Tea type | RR (95%CI) | NOS score (stars) |
|---|---|---|---|---|---|---|---|---|
| Xu 2013 [18] | 2006-2012 | — | China | PCC | 1225/1234 | Tea | 0.47 (0.34–0.63) | 7 |
| Zhang 2012 [17] | 1997-2006 | Male, Female | China | PCC | 426/60973 | Tea | 0.97 (0.74–1.26) | 8 |
| Lin 2012 [14] | 2006-2010 | Female | China | PCC | 226/269 | Tea | 0.43 (0.28–0.66) | 7 |
| Lin 2012 [11] | 2004-2008 | — | Taiwan China | HCC | 170/340 | Green | 0.16 (0.04–0.28) | 7 |
| Ganesh 2011 [13] | 1981-1983 | — | India | HCC | 408/1383 | Tea | 0.22 (0.10–0.51) | 6 |
| Chen 2010 [12] | 2006-2010 | Female | China | PCC | 573/573 | Tea | 0.98 (0.77–1.25) | 8 |
| Wang 2009 [15] | 1992-1995 | Female | US | Cohort | 25501/12376 | Tea | 1.01 (0.94–1.09) | 7 |
| Wang 2009 [16] | 2002-2007 | — | China | PCC | 363/363 | Tea | 0.60 (0.41–0.87) | 7 |
| Li 2008 [59] | 1995-2001 | Male, Female | Japan | Cohort | 302/41440 | Green | 1.16 (0.93–1.39) | 8 |

**Table 1 Study characteristics of published studies on tea consumption and lung cancer risk (Continued)**

| Study | Study period | Gender (having RR) | Country | Study design | Cases/controls or cohort | Tea type | RR (95%CI) | NOS score (stars) |
|---|---|---|---|---|---|---|---|---|
| Kubik 2008 [34] | 1998-2006 | Male, Female | Czech | HCC | 1096/2996 | Green + Black | 1.00 (0.82–1.18) | 7 |
| Cui 2008 [49] | 1999-2004 | — | US | PCC | 558/837 | Black | 0.56 (0.42–0.71) | 7 |
| Zhang 2008 [41] | 2002-2006 | — | China | PCC | 505/529 | Tea | 1.16 (0.89–1.53) | 8 |
| Han 2008 [37] | 2003 | — | China | PCC | 523/1924 | Green | 0.52 (0.39–0.69) | 7 |
| Tao 2007 [40] | 2002-2006 | — | China | HCC | 47/94 | Tea | 0.72 (0.28–1.87) | 6 |
| Kuriyama 2006 [54] | 1995-2005 | — | Japan | Cohort | 16569/4901 | Green | 0.99 (0.72–1.25) | 8 |
| Bonner 2005 [36] | 1995-1996 | Male, Female | China | PCC | 122/121 | Green | 0.68 (0.24–1.12) | 7 |
| Baker 2005 [52] | 1982-1998 | Male | US | HCC | 993/986 | Black | 0.90 (0.73–1.07) | 6 |
| Khan 2004 [58] | 1984-2002 | Male, Female | Japan | Cohort | 51/3158 | Green | 0.62 (0.34–1.15) | 8 |

**Table 1 Study characteristics of published studies on tea consumption and lung cancer risk (Continued)**

| Study | Study period | Gender (having RR) | Country | Study design | Cases/controls or cohort | Tea type | RR (95%CI) | NOS score (stars) |
|---|---|---|---|---|---|---|---|---|
| Hu 2002 [48] | 1994-1997 | Female | Canada | PCC | 164/483 | Black | 0.55 (0.42–0.68) | 8 |
| Zhong 2001 [38] | 1992-1994 | Female | China | PCC | 649/675 | Green | 0.60 (0.33–0.87) | 7 |
| Hirvonen 2001 [62] | 1985-1993 | Male | Finland | Cohort | 791/27110 | Black | 0.66 (0.54–0.82) | 7 |
| Nagano 2001 [57] | 1979-1994 | — | Japan | Cohort | 436/38540 | Green | 0.78 (0.63-0.94) | 9 |
| Takezaki 2001 [45] | 1988-1997 | — | Japan | HCC | 1045/4153 | Green | 1.01 (0.84–1.19) | 7 |
| Nakachi 2000 [53] | 1986-1997 | — | Japan | Cohort | 69/8552 | Green | 0.33 (0.11–0.94) | 8 |
| Le Marchand 2000 [35] | 1992-1997 | — | US | PCC | 582/582 | Green + Black | 1.10 (0.70–1.80) | 8 |
| Nyberg 1998 [47] | 1989-1995 | — | Sweden | PCC | 124/235 | Black | 1.15 (0.64–1.65) | 8 |
| Mendilaharsu 1998 [51] | 1994-1996 | Male | Uruguay | HCC | 427/428 | Black | 0.58 (0.40–0.76) | 7 |

**Table 1 Study characteristics of published studies on tea consumption and lung cancer risk (Continued)**

| Study | Study period | Gender (having RR) | Country | Study design | Cases/controls or cohort | Tea type | RR (95%CI) | NOS score (stars) |
|---|---|---|---|---|---|---|---|---|
| Imai 1997 [63] | 1986-1990 | — | Japan | Cohort | 384/8552 | Tea | 1.41 (1.13–1.76) | 8 |
| Ko 1997 [43] | 1992-1993 | Female | Taiwan China | HCC | 106/105 | Tea | 0.40 (0.20-1.10) | 7 |
| Xu 1996 [55] | 1987-1993 | — | China | Cohort | 610/959 | Green | 0.53 (0.44–0.63) | 9 |
| Axelsson 1996 [46] | 1989-1993 | Male | Sweden | PCC | 308/504 | Black | 0.71 (0.53–0.94) | 7 |
| Goldbohm 1996 [60] | 1986-1990 | — | Netherlands | Cohort | 764/120825 | Black | 0.94 (0.78–1.10) | 8 |
| Zheng 1996 [61] | 1986-1993 | Female | US | Cohort | 312/35369 | Black | 0.99 (0.78–1.20) | 7 |
| Ohno 1995 [44] | 1988-1991 | Male, Female | Japan | PCC | 333/666 | Green | 0.67 (0.45–0.98) | 9 |
| Lei 1994 [39] | 1986 | — | China | HCC | 792/792 | Green | 0.71 (0.43–1.18) | 7 |
| Tewes 1990 [42] | 1981-1983 | Female | China | HCC | 200/200 | Green + Black | 1.51 (0.81–2.21) | 6 |

**Table 1 Study characteristics of published studies on tea consumption and lung cancer risk (Continued)**

| Study | Study period | Gender (having RR) | Country | Study design | Cases/controls or cohort | Tea type | RR (95%CI) | NOS score (stars) |
|---|---|---|---|---|---|---|---|---|
| Mettlin 1989 [50] | 1982-1987 | — | US | HCC | 569/569 | Black | 0.88 (0.68–1.09) | 6 |
| Kinlen 1988 [56] | 1968-1986 | Male | UK | Cohort | 718/12868 | Tea | 1.42 (1.11–1.81) | 7 |

**Table 2 Meta-regression analysis**

| | Coefficient | SE | t | *P* | 95% CI |
|---|---|---|---|---|---|
| **Sample size** | -2.12e-06 | 3.62e-06 | -0.59 | 0.561 | -9.50e-06—5.25e-06 |
| **Case/control ratio** | 0.18 | 0.11 | 1.68 | 0.10 | -0.04—0.40 |
| **Study design** | -0.09 | 0.21 | -0.42 | 0.68 | -0.51—0.34 |
| **Tea types** | 0.16 | 0.15 | 1.13 | 0.27 | -0.13—0.46 |
| **Follow-up time** | 0.01 | 0.02 | 0.46 | 0.65 | -0.03—0.04 |
| **Geographical region** | -0.37 | 0.14 | -2.58 | 0.02 | -0.66—0.08 |

**Table 3 Subgroup analyses of tea intake and lung cancer risk**

| Study | Number of studies | RR (95% CI) | Heterogeneity test | |
|---|---|---|---|---|
| | | | *P* | $I^2$ (%) |
| All studies | 38 | 0.78 (0.70—0.87) | <0.001 | 83.3 |
| Study design | | | | |
| Prospective studies | 12 | 0.91 (0.77—1.08) | <0.001 | 78.2 |
| Case-control studies | 26 | 0.72 (0.63—0.83) | <0.001 | 82.5 |
| Tea types | | | | |
| Green tea | 16 | 0.75 (0.62—0.91) | <0.001 | 73.4 |
| Black tea | 13 | 0.82 (0.71—0.94) | <0.001 | 87.8 |

**Table 3 Subgroup analyses of tea intake and lung cancer risk (Continued)**

| Study | Number of studies | RR(95% CI) | Heterogeneity test | |
|---|---|---|---|---|
| | | | *P* | $I^2$ (%) |
| **Geographical region** | | | | |
| Western population | 24 | 0.85 (0.75—0.97) | <0.001 | 78.2 |
| China and Japan | 10 | 0.74 (0.62—0.88) | <0.001 | 82.5 |
| **Gender** | | | | |
| Male | 11 | 0.88 (0.72—1.07) | <0.001 | 79.1 |
| Female | 14 | 0.76 (0.62—0.93) | <0.001 | 78.6 |
| **Smoking status** | | | | |
| Smoking | 8 | 0.79 (0.59—1.07) | 0.032 | 54.3 |
| Non-smoking | 10 | 0.88 (0.72—1.07) | <0.001 | 75.1 |

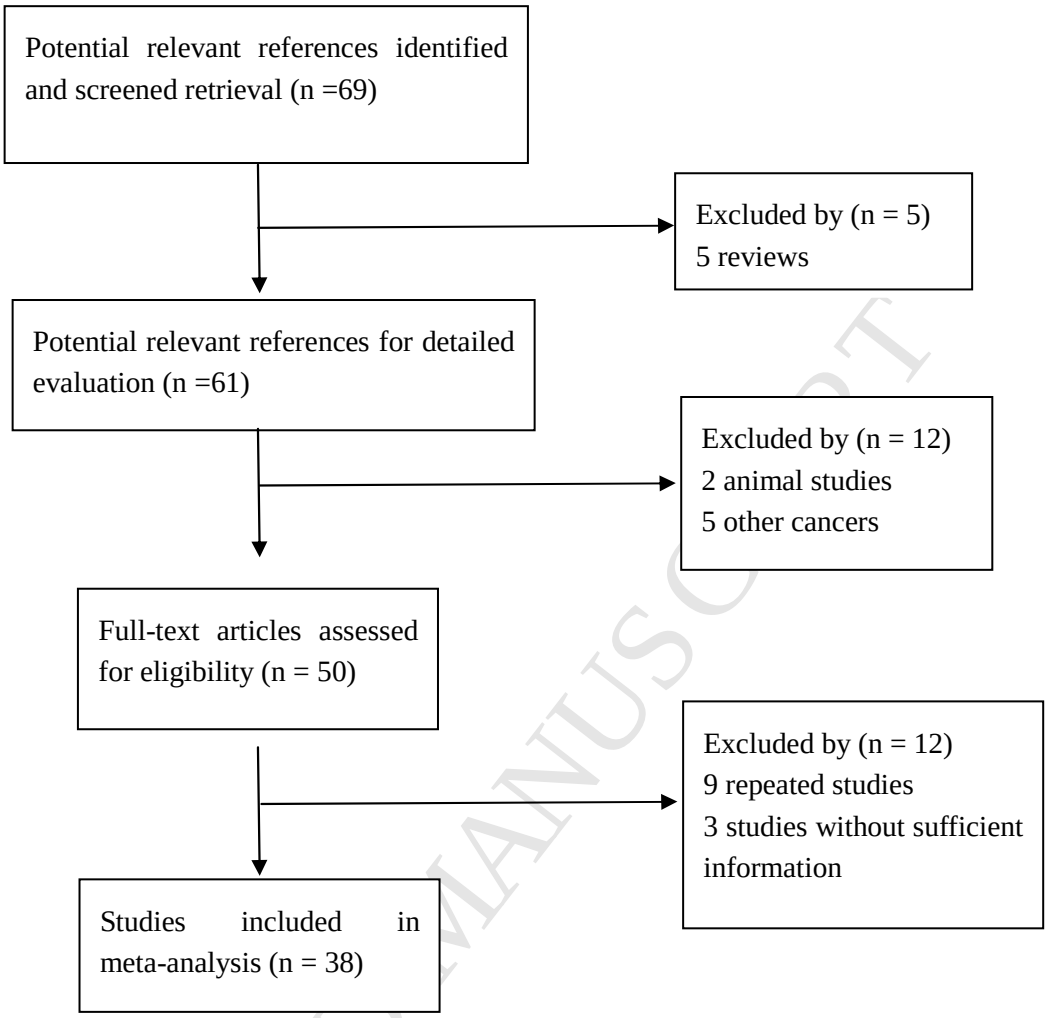


**Fig. 1.** Diagrammatic representation of the process followed in the selection of studies.

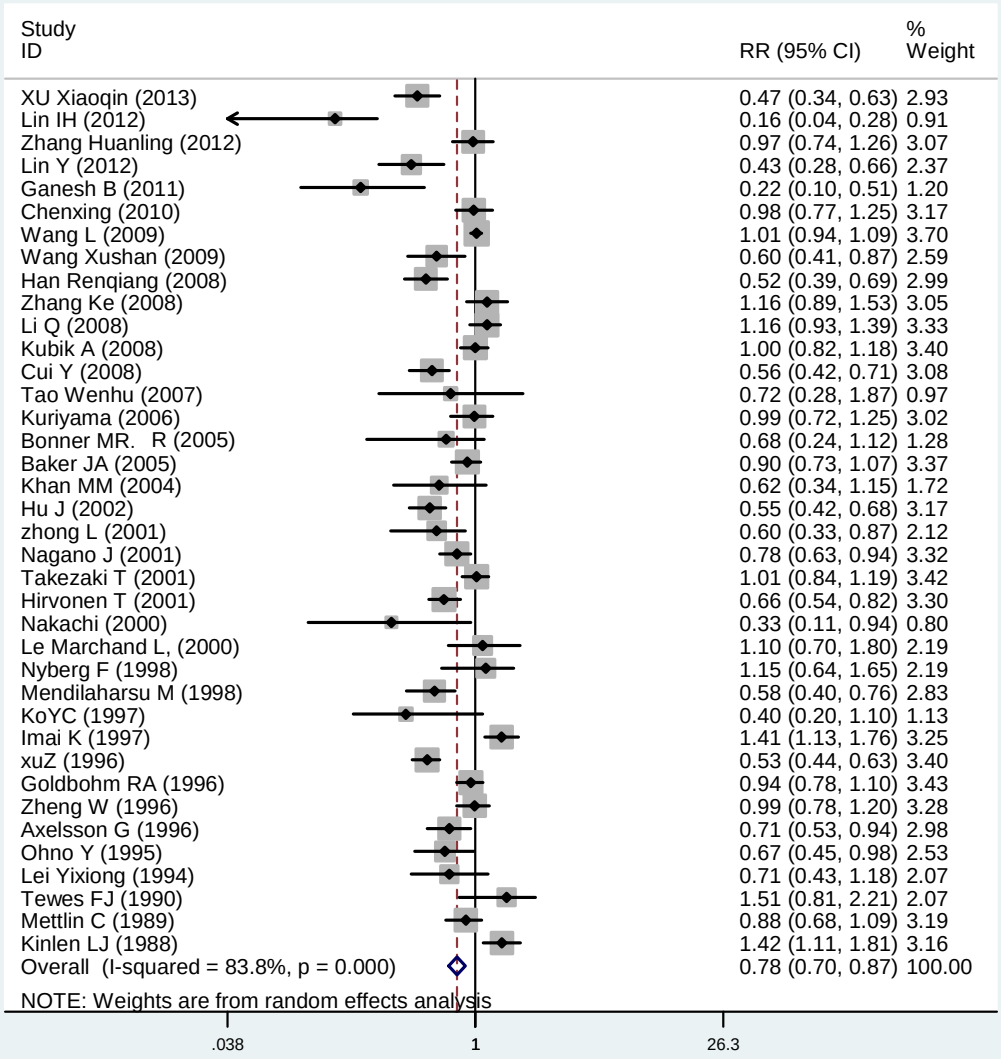


**Fig. 2.** Association between tea consumption and risk of lung cancer. RR, risk estimate; CI, confidence interval.

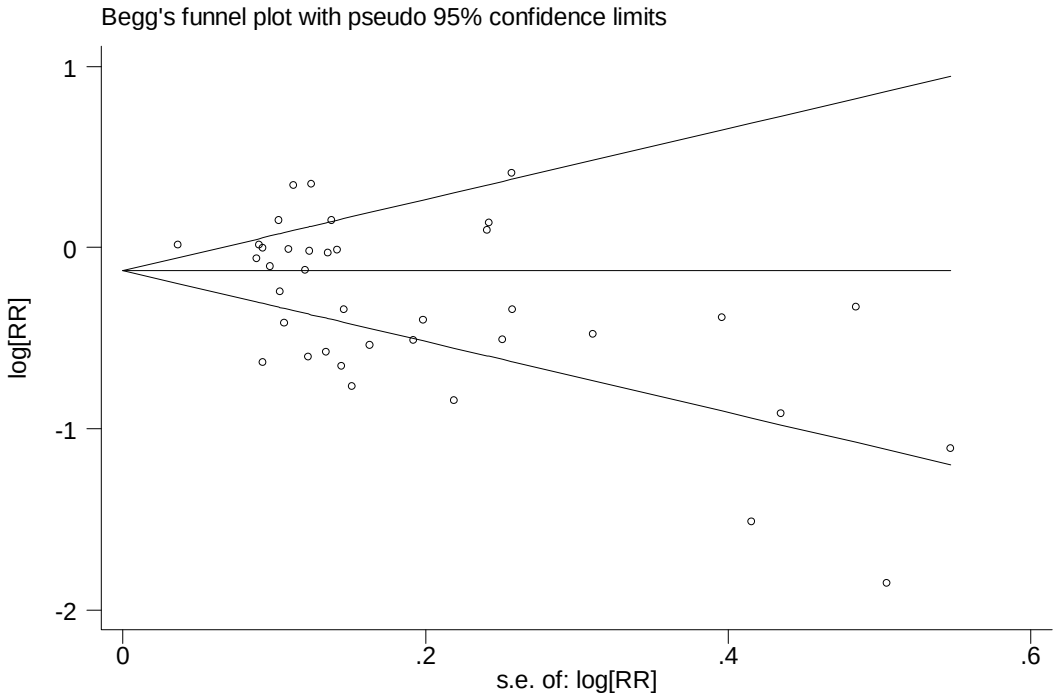


**Fig. 3.** Begg's funnel plot of studies on tea consumption and lung cancer risk. RR, risk estimate.