



Green tea consumption and hepatocellular carcinoma: a meta-analysis lacking evidence for a protective effect

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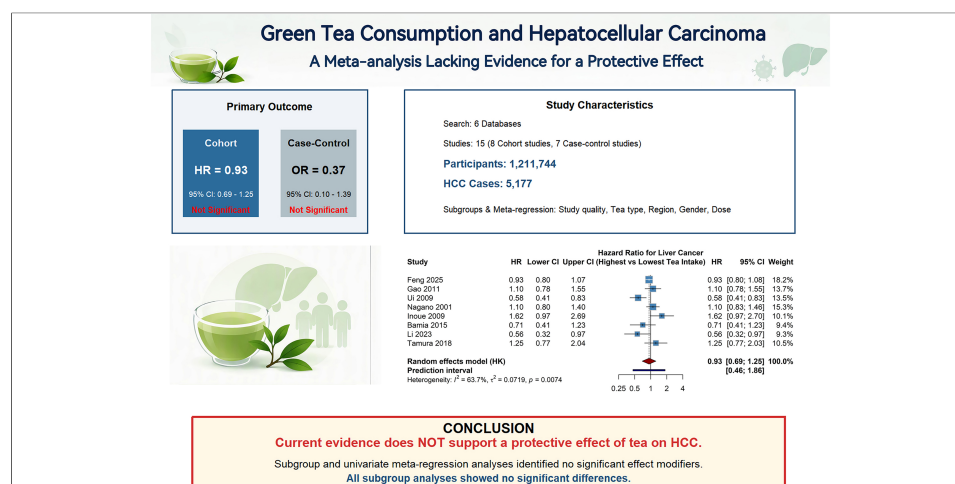
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Abstract

Aim: The association between green tea consumption and hepatocellular carcinoma (HCC) risk remains controversial. This meta-analysis aimed to quantify this association using rigorous epidemiological evidence.

Methods: Six electronic databases (PubMed, Embase, Cochrane Library, SinoMed, CNKI, and Wanfang Data) were searched for studies published up to December 2025. Study quality was assessed using the Newcastle-Ottawa Scale, and only studies with a score ≥ 6 were included. Heterogeneity was quantified by I^2 , and pooled hazard ratio (HR) and odds ratio (OR) with 95% confidence intervals (CI) were calculated using random-effects models with the Hartung-Knapp-Sidik-Jonkman method. Subgroup analyses and meta-regression were conducted by study quality, tea type, region, sex, and dose, and by adjustment for 11 potential confounders, including hepatitis B virus and body mass index. Sensitivity analysis was performed using the leave-one-out method to assess the robustness of the pooled estimates. Publication bias was examined using funnel plots, Egger's test, and Begg's test.

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Results: Fifteen studies, including 8 cohort studies and 7 case-control studies, comprising 1,211,744 participants with 5,208 HCC cases, were eligible. For cohort studies, the pooled HR for HCC associated with tea consumption was 0.93 (95%CI: 0.69-1.25). For case-control studies, the pooled OR was 0.37 (95%CI: 0.10-1.39). Neither was statistically significant. Subgroup analyses showed no significant association for any examined factor, including study quality, tea type, sex, and dose. However, a statistically significant association was observed in the European subgroup (HR = 0.41, $P = 0.0058$), although this finding was based on a single study and should be considered exploratory. Leave-one-out sensitivity analysis confirmed the robustness of the findings. No obvious publication bias was observed.

Conclusion: In the overall pooled analysis of cohort studies, current evidence, derived predominantly from East Asian populations, does not support a causative effect of tea consumption on HCC, although a modest protective effect cannot be completely ruled out based on the available data. Further rigorous studies are needed to clarify this relationship.

INTRODUCTION

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is one of the leading causes of cancer-related mortality worldwide^[1,2]. East Asia carries the highest burden of HCC, with age-standardized incidence rates ranging from 8.5 to 14.7 per 100,000 population^[3], where hepatitis B virus (HBV) infection is the predominant cause of HCC-related mortality^[4]. HCC is a complex, multifactorial disease involving interactions between genetic and environmental factors^[5-8]. In addition to well-established risk factors for HCC including HBV infection, hepatitis C virus (HCV) infection, aflatoxin exposure, and alcohol consumption^[9-11], evidence from nutritional epidemiology revealed the important role of lifestyle factors in HCC development and prevention^[12,13].

Tea is one of the most widely consumed beverages globally and is rich in polyphenolic compounds, particularly catechins. These compounds exhibit multiple potential anti-cancer biological activities, including antioxidant, anti-inflammatory, anti-proliferative, and detoxification enzyme-regulating effects^[14]. However, experimental evidence from cellular and animal studies is insufficient to establish a protective effect at the population level. Epidemiological evidence regarding the association between tea consumption and HCC risk remains inconclusive.

Numerous epidemiological studies have explored the association between tea consumption and HCC risk. Most of these studies examined tea consumption as one component of a broader dietary pattern, with relatively few focusing on tea as an independent exposure. Among existing studies, certain case-control and prospective cohort studies reported a significant inverse association between green tea or black tea consumption and reduced HCC risk^[15,16], whereas others found no statistically significant association^[17,18]. Inconsistent results have also been observed in specific populations, such as individuals with concomitant hepatitis virus infection or excessive alcohol consumption. This heterogeneity may be attributed to differences in study design, tea type, dose-response relationship, confounding factor control, and baseline liver disease status across study populations. Thus, whether tea consumption is an independent protective factor against HCC remains controversial. This meta-analysis aimed to synthesize current epidemiological evidence, quantitatively evaluate the strength of the association between tea consumption and HCC, and explore effect modification by tea type, sex, dose, and study quality through subgroup analyses.

METHODS

Literature search strategy

The literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement. Six electronic databases (PubMed, Embase, Cochrane Library, SinoMed, CNKI, and Wanfang Data) were systematically searched, supplemented by manual search of gray literature including dissertations and conference proceedings. Original research papers investigating the association between HCC risk and tea intake, published before December 15, 2025, were eligible for inclusion. The full search strategies for all databases are provided in [Supplementary Table 1](#). The full search strategy for PubMed was as follows: (“Liver Neoplasms”[Mesh] OR “Hepatocellular Carcinoma”[Mesh]) AND (“Tea”[Mesh] OR “Tea, Green”[Mesh] OR “Tea, Black”[Mesh]) OR (liver cancer OR hepatoma OR hepatic neoplasm) AND (tea OR green tea OR black tea OR tea polyphenol OR catechin). Similar strategies were adapted for other databases. This review was registered in Prospective Register of Systematic Reviews (PROSPERO) (CRD420261343011).

Inclusion and exclusion criteria

Studies were eligible for inclusion if they met all the following criteria: (1) published in English or Chinese; (2) publicly available population-based cohort studies or case-control studies investigating the association between tea consumption and HCC; (3) HCC cases in the study were confirmed by pathological examination or imaging diagnosis, or through validated cancer registries/International Classification of Diseases (ICD) coding systems with established diagnostic accuracy; (4) original studies provided data on the association between tea intake and HCC risk, including odds ratio (OR) or hazard ratio (HR) with corresponding 95% confidence interval (CI), or sufficient data to calculate the above effect estimates; (5) only studies with HCC as the target outcome were included. Studies were excluded based on the following criteria: (1) reviews, meta-analyses, conference abstracts and other types of studies without original primary data; (2) non-population-based studies including animal experiments and *in vitro* cell experiments; (3) studies with a sample size of less than 10; (4) studies with incomplete or erroneous data that cannot be corrected or supplemented; (5) for multiple publications from the same research team based on the same study population, only the study with the largest sample size and longest follow-up duration was included to avoid duplicate data bias.

Study selection and data extraction

Literature screening was performed independently by two trained researchers (Ling ST, Xie LZ) according to the pre-specified inclusion and exclusion criteria. Irrelevant records were first excluded based on title and abstract screening. The remaining potentially eligible records were subsequently evaluated via full-text review to determine the final inclusion. Disagreements between the two researchers were resolved by discussion; if no consensus was reached, a third senior researcher was consulted for final adjudication.

Two researchers independently assessed the methodological quality of the included cohort studies and case-control studies using the Newcastle-Ottawa Scale (NOS). Detailed evaluation criteria are provided in [Supplementary Table 2](#). The NOS evaluates studies from three dimensions: selection of study participants, comparability between study groups, and ascertainment of exposure or outcome, with a maximum score of 9. An adapted version of the NOS was used, allowing 0.5-point increments for individual criteria to better discriminate between studies that partially met specific criteria; this adaptation was pre-specified in the study protocol and applied consistently by two independent reviewers. Only studies with a total score of ≥ 6 were included; studies were categorized as high (H: ≥ 8), medium (M: 7.5), or low (L: 6 to < 7.5) quality based on NOS scores. The average of the scores assigned by the two independent reviewers was adopted as the final score, rounded to one decimal place. If the score difference between the two reviewers was ≥ 1 point, a third researcher was invited for arbitration.

Data extraction was similarly conducted independently by two researchers. The extracted information included: first author, publication year, country/region, study design, sample size, participant baseline characteristics, tea type and exposure assessment, definition of outcome events, effect estimates (HR or OR with 95%CI), and adjustment for confounders. For studies reporting multiple effect estimates, the estimate from the most fully adjusted model was selected for the primary meta-analysis. When multiple exposure contrasts were available, the comparison of the highest versus the lowest dose category was used. If several follow-up durations were reported, the estimate with the longest follow-up was selected. The detailed data extraction form is shown in [Supplementary Table 3](#). Disagreements during data extraction were resolved using the same procedure as for literature screening.

Statistical analysis

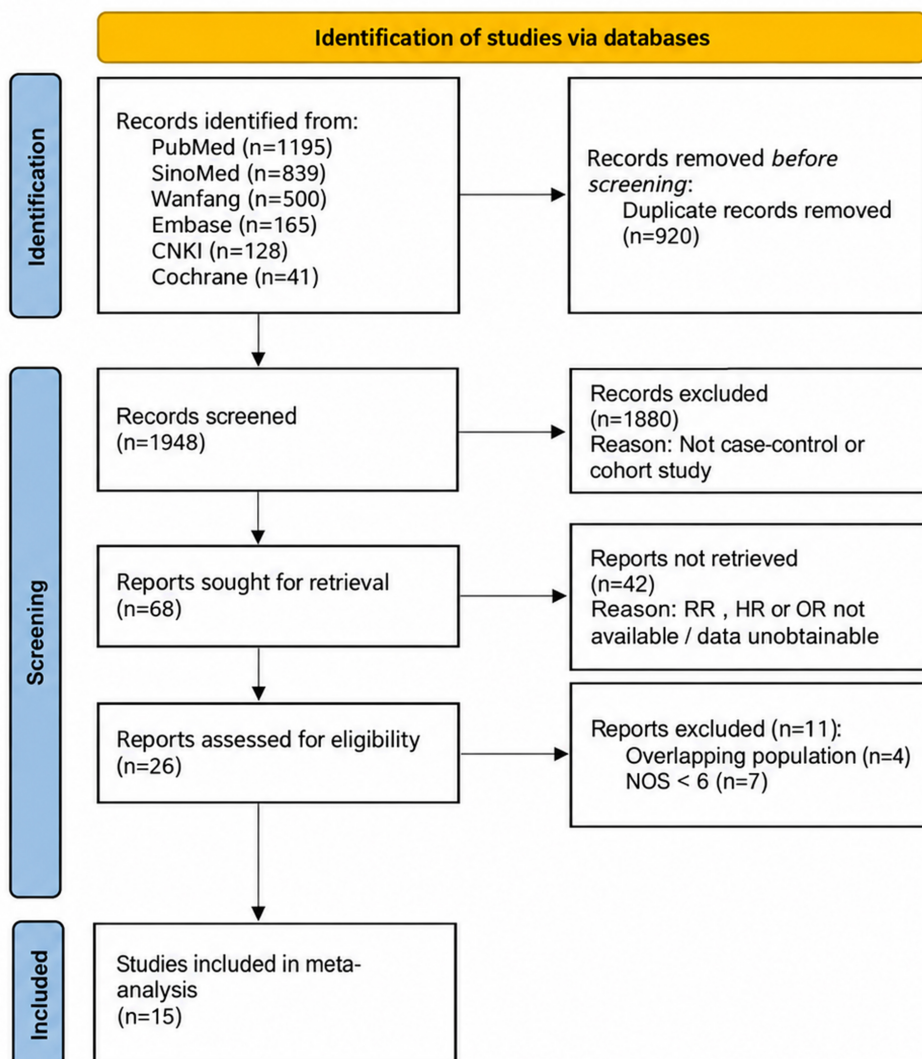
All statistical analyses were conducted using the metafor package (v4.8-0) in R (v4.5.3). Effect estimates were extracted separately for cohort studies and case-control studies. For cohort studies, we extracted HR or risk ratios (RR) as reported; for case-control studies, we used OR. No overall pooled estimate combining both study designs was calculated. Instead, subgroup analyses were performed in cohort studies.

Heterogeneity was evaluated using the Q test and I^2 statistic. Given expected between-study heterogeneity and the relatively small number of studies (≤ 10 per analysis), a random-effects model was applied for all pooled analyses. The Hartung-Knapp-Sidik-Jonkman (HKSJ) method was used as the primary approach, as the DerSimonian-Laird (DL) method often yields inflated type I error rates when the number of studies is small^[19].

To explore potential effect modifiers and sources of heterogeneity, we performed subgroup analyses and univariate meta-regression for cohort studies stratified by predefined covariates: study quality, tea type, geographic region, sex, and dose category (the latter based on within-study tertiles without cross-study standardization). Given the limited number of studies ($k = 8$), these analyses were exploratory and underpowered; no multivariable meta-regression was performed. Random-effects models with the Hartung-Knapp adjustment were used for all analyses; meta-regression additionally estimated the proportion of between-study variance explained (R^2) by each covariate.

Categorical trend analysis was performed for cohort studies using a within-study categorization approach. Tea consumption levels in each study were classified into three ordered categories (low, medium, high) based on the reported dose groups, with the lowest category as the reference. For studies reporting three or more dose groups, effect estimates for the low, medium, and high groups were extracted. For studies reporting only two dose levels, only the low and high groups were extracted. Pooled effect estimates for each dose level were then calculated using random-effects models. To evaluate the trend across exposure categories, ordinal scores (1, 2, 3) were assigned to low, medium, and high levels, and meta-regression was performed. P -value for the slope was reported as the trend P -value.

To examine whether control for key confounders affected the overall estimates, subgroup analyses were stratified by whether individual studies had adjusted for each of the following predefined covariates: body mass index (BMI), coffee consumption, diabetes, education, family history of liver cancer, HBV infection, HCV infection, income, liver disease, physical activity, and sex. For each covariate, studies were classified into “Adjusted” (the factor included in multivariable adjustment) and “Not adjusted” (the factor not adjusted for). Pooled effect sizes (HR) with 95% CIs were calculated using random-effects models. When only one study was available in a subgroup, the estimate was presented descriptively. Interaction between subgroups was tested using meta-regression ($P < 0.05$ indicating significant modification). This analysis was restricted to cohort studies due to the limited number of case-control studies.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only**Figure 1.** Four-stage flowchart of study selection according to the PRISMA Statement. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Sensitivity analysis was performed using the leave-one-out method. Publication bias was evaluated by funnel plot, Egger's regression test, and Begg's rank correlation test ($P < 0.05$ indicating significant publication bias).

RESULTS

Literature search results and screening process

A total of 2,868 records were retrieved. After removing 920 duplicates, 1,948 records remained for title and abstract screening. After excluding 1,880 ineligible records, 68 underwent full-text review, of which 42 were excluded. After further excluding 4 studies with overlapping populations and 7 low-quality studies, 15 studies were finally included [Figure 1].

Included studies

A total of 15 studies (8 cohort studies and 7 case-control studies) were included in this meta-analysis. Among them, 14 were peer-reviewed articles published in academic journals, and one was a doctoral dissertation from Fudan University^[20]. Geographically, 13 studies were conducted in Asia (9 in China, 4 in Japan), and 2

were carried out in Europe (1 in Italy, 1 multinational study). The total sample size was 1,211,744 participants, including 5,208 HCC cases, with individual study sample sizes ranging from 200 to 482,292.

Regarding exposure factors, among the 15 included studies, 10 assessed green tea consumption, 4 assessed unspecified tea types, 4 assessed mixed tea, 3 assessed black tea, 2 assessed other tea types (including oolong or herbal tea), and 1 assessed jasmine tea. Since several studies reported on more than one tea type, the sum of these counts exceeds the total number of studies. For subgroup analyses stratified by tea type, each study was classified according to its primary tea type of interest as defined in the original study, ensuring that each study contributed only one effect estimate to a given subgroup analysis to preserve statistical independence. Exposure assessment was performed using self-administered Food Frequency Questionnaires (FFQs) in seven studies, face-to-face interviews in seven studies, and urinary biomarker measurement in one study. For liver cancer diagnosis, 6 studies adopted pathological examination or combined imaging and clinical diagnosis as the confirmation criteria, and 9 studies determined outcomes based on cancer registration systems or ICD coding. In these 9 studies, the registry- or ICD-based outcome ascertainment was derived from well-validated cancer registries or hospital record systems, where HCC diagnoses were originally confirmed by pathological examination or imaging in clinical practice. All included studies adjusted for confounding factors including smoking and alcohol consumption. Eleven studies further adjusted for sex, seven for education, and twelve for HBV or HCV infection status.

For methodological quality assessment, based on the NOS, the average score of included cohort studies was 8.0, and the average score of case-control studies was 7.2, indicating high overall quality of the included studies. The baseline characteristics of all included studies are detailed in [Table 1](#).

Meta-analysis of tea consumption and HCC risk

Using the HKSJ method, cohort studies showed no statistically significant association between tea consumption and HCC risk, with a pooled HR of 0.93 (95%CI: 0.69-1.25). Heterogeneity among cohort studies was substantial ($I^2 = 63.7\%$, $\tau^2 = 0.072$, $P = 0.0074$); therefore, a random-effects model was used [[Figure 2](#)]. Given the substantial heterogeneity ($I^2 = 91.9\%$) and very wide CI, the case-control results should be interpreted with extreme caution and are presented here as a sensitivity analysis only, not as primary evidence [[Supplementary Figure 1](#)]. Due to the substantial differences in study design and effect estimates, no overall pooled estimate combining both designs was calculated.

Exploration of heterogeneity and sensitivity analyses

Given the substantial heterogeneity observed in the overall meta-analysis (cohort studies: $I^2 = 63.7\%$; case-control studies: $I^2 = 91.9\%$), subgroup analyses were performed for cohort studies stratified by study quality, tea type, geographic region, sex, and dose level [[Table 2](#) and [Supplementary Figures 2-6](#)]. In most subgroups, no statistically significant association was observed ($P > 0.05$). However, the European subgroup, which included only a single study (Bamia *et al.*), showed a potential protective effect (HR = 0.41, 95%CI: 0.22-0.77, $P = 0.0058$)^[18]. Given that this finding is derived from only one study and has a very wide CI, it should be interpreted as exploratory rather than confirmatory. This finding requires replication in larger, multi-center European cohorts. Heterogeneity remained high in most subgroups (I^2 range: 51.8%-92.8%). The Baujat plot [[Supplementary Figure 7](#)] further explored individual study contributions to overall heterogeneity.

Univariate meta-regression analyses were further performed to formally test whether the five prespecified covariates explained the heterogeneity among cohort studies [[Table 3](#)]. None of the examined factors - geographic region, NOS score, tea type, sex, or dose level - was significantly associated with the effect estimates (all $P > 0.05$). The R^2 values were 0 for most covariates, indicating that these factors individually accounted for little to none of the observed between-study variance.

Table 1. Baseline characteristics of included studies

No.	Author (year)	Area	Study design	Participation (n)	Cases (n)	Male (%)	Median age (range)	Median follow-up (years)	Main tea type	Exposure assessment method	Adjustment factors	Quality (NOS)
1	Feng <i>et al.</i> , 2025 ^[17]	China	Prospective cohort	482,292	398	41.1	52 (30-79)	10.1	Mixed	Interview	①②③④⑤⑥⑦⑧⑨⑩⑪⑫	H
2	Ui <i>et al.</i> , 2009 ^[15]	Japan	Prospective cohort	41,761	247	47.3	59 (40-79)	9	Green tea	FFQ	①②③⑫⑬	L
3	Nagano <i>et al.</i> , 2001 ^[21]	Japan	Prospective cohort	38,540	418	38.6	55 (40-69)	10	Green tea	Questionnaire	①②③⑥⑭	L
4	Inoue <i>et al.</i> , 2009 ^[22]	Japan	Prospective cohort	18,815	110	34.1	55 (40-69)	12.7	Green tea	FFQ	①②④⑤⑥⑩⑬⑮	H
5	Bamia <i>et al.</i> , 2015 ^[18]	10 European countries	Prospective cohort	450,921	201	41.1	48 (25-70)	11	Mixed	FFQ	①②③⑥⑨⑩⑫⑬	H
6	Gao, 2011 ^[20]	China	Prospective cohort	61,500	111	100	57 (40-74)	11.8	Mixed	Questionnaire	①②③④⑥⑦⑨⑪⑫⑰	H
7	Li <i>et al.</i> , 2023 ^[23]	China	Prospective cohort	71,841	253	0	55 (40-70)	18.1	Mixed	Interview	①②③⑥⑦⑨⑪⑫⑰	H
8	Tamura <i>et al.</i> , 2018 ^[24]	Japan	Prospective cohort	30,824	62	46.2	55 (35-79)	16	Green tea	FFQ	①②③⑥⑨⑫	L
9	Butler <i>et al.</i> , 2015 ^[25]	China	Nested case-control	1,278	211	100	55 (45-64)	NA	Green tea	Urinary biomarker	④⑪	M
10	Duan and Zhang, 2018 ^[26]	China	Case-control	794	330	81.2/76.1	54 (20-80)	NA	NR	Interview	③④⑧⑪	L
11	Lin <i>et al.</i> , 2017 ^[27]	China	Case-control	1,818	757	87.3/87.9	55 (35-70)	NA	NR	Interview	④⑧⑮	M
12	Song <i>et al.</i> , 2014 ^[28]	China	Case-control	200	100	86/86	51 (35-70)	NA	NR	Interview	④⑧	L
13	Liu <i>et al.</i> , 2025 ^[29]	China	Case-control	9,944	1,621	76.3/71.9	≥ 18	NA	Mixed	Interview	①②③④⑤⑥⑦⑧	M
14	Li <i>et al.</i> , 2011 ^[30]	China	Case-control	619	204	76.0/64.1	≥ 20	NA	Green tea	Interview	①②③④⑥⑦⑧	M
15	Montella <i>et al.</i> , 2007 ^[31]	Italy	Case-control	597	185	80.5/68.2	66 (43-84)	NA	NR	FFQ	①②③④⑤	M

For case-control studies, gender was presented as % male in cases/% male in controls. Quality assessment based on NOS scores: ≥ 8 = H (high quality); 7.5 = M (medium quality); ≥ 6 and < 7.5 = L (low quality). Adjustment factors: All studies adjusted for smoking and alcohol consumption. Additional adjusted confounders are listed below: ① Age, ② Sex, ③ Education, ④ HBsAg/HBV infection, ⑤ HCV infection, ⑥ BMI, ⑦ Income, ⑧ Family history of liver cancer, ⑨ Physical activity, ⑩ Diabetes, ⑪ Cirrhosis, ⑫ Diet/energy intake, ⑬ Coffee intake, ⑭ Radiation exposure, ⑮ ALT level, ⑯ Occupation, ⑰ Gallstones. ALT: Alanine aminotransferase; BMI: body mass index; FFQ: food frequency questionnaire; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; NA: not applicable; NOS: Newcastle-Ottawa Scale; NR: not reported.

Sensitivity analysis using the leave-one-out method showed that after excluding each study individually, the pooled HR for cohort studies varied from 0.88 (95%CI: 0.66-1.17) to 1.00 (95%CI: 0.78-1.29) [Supplementary Table 4]. None of these recalculated pooled estimates reached statistical significance (all $P > 0.05$), confirming the robustness of the null association.

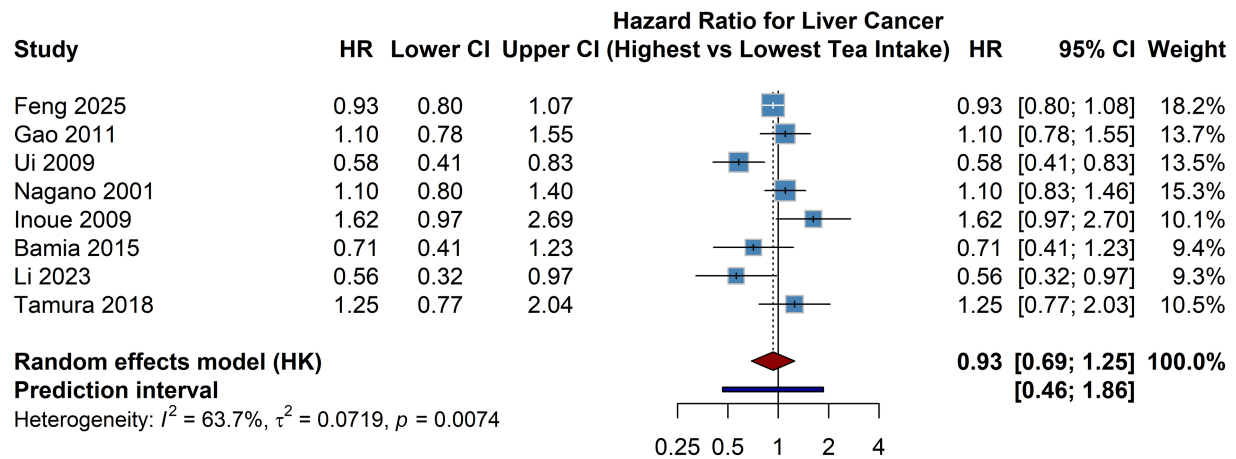


Figure 2. Forest plot of the association between tea consumption and risk of liver cancer in cohort studies; Random-effects models were fitted using the HKSJ method. CI: Confidence intervals; HKSJ: Hartung-Knapp-Sidik-Jonkman; HR: hazard ratio.

Table 2. Subgroup analysis of the association between tea consumption and HCC risk

Group	Number of studies	HR (95%CI)	P	Heterogeneity test		
				τ^2	I ² (%)	P
NOS scores						
H	5	0.84 (0.46,1.52)	0.4630	0.1508	69.5	0.0107
L	3	0.87 (0.33,2.24)	0.5806	0.1049	72.9	0.0250
Tea type						
Green tea	4	1.04 (0.52-2.08)	0.8646	0.1478	78.3	0.0031
Other tea	4	0.89 (0.62-1.28)	0.3841	0.0113	39.8	0.1730
Geographic region						
China	3	0.91 (0.46,1.80)	0.6006	0.0243	51.8	0.1258
Japan	4	0.97 (0.51,1.83)	0.8718	0.1153	72.2	0.0129
Europe	1	0.41 (0.22,0.77)	0.0058			
Gender						
Male	3	0.92 (0.39,2.15)	0.7201	0.0669	56	0.1031
Female	3	0.63 (0.19,2.04)	0.2336	0.0344	42.2	0.1777
Dose*						
Low	8	0.95 (0.85,1.06)	0.3034	0.0058	16.3	0.3014
Moderate	8	0.94 (0.78,1.14)	0.4713	0.0065	40.2	0.1108
High	8	0.86 (0.66,1.11)	0.3162	0.0962	66.7	0.0037

*Dose subgroups were stratified by exposure levels using the within-study tertile method, with no cross-study standardization of dose units. All subgroups were analyzed using random-effects models (HKSJ method). NOS scores: ≥ 8 = H (high quality); 7.5 = M (medium quality); ≥ 6 and < 7.5 = L (low quality). HKSJ: Hartung-Knapp-Sidik-Jonkman; HR: hazard ratio; NOS: Newcastle-Ottawa scale.

We further examined whether adjustment for specific confounders influenced the association between tea consumption and HCC risk. Studies were stratified by whether they adjusted for 11 pre-specified covariates: BMI, coffee consumption, diabetes, education, family history of liver cancer, HBV infection, HCV infection, income, liver disease, physical activity, and sex. Detailed adjustment factors for each included study are presented in [Supplementary Table 5](#) and [Supplementary Figures 8-16](#). For each factor, pooled effect estimates did not differ significantly between the “adjusted” and “not adjusted” subgroups (all interaction $P > 0.05$; range: 0.114-0.930). For covariates where only one study was available in a subgroup (BMI not adjusted and

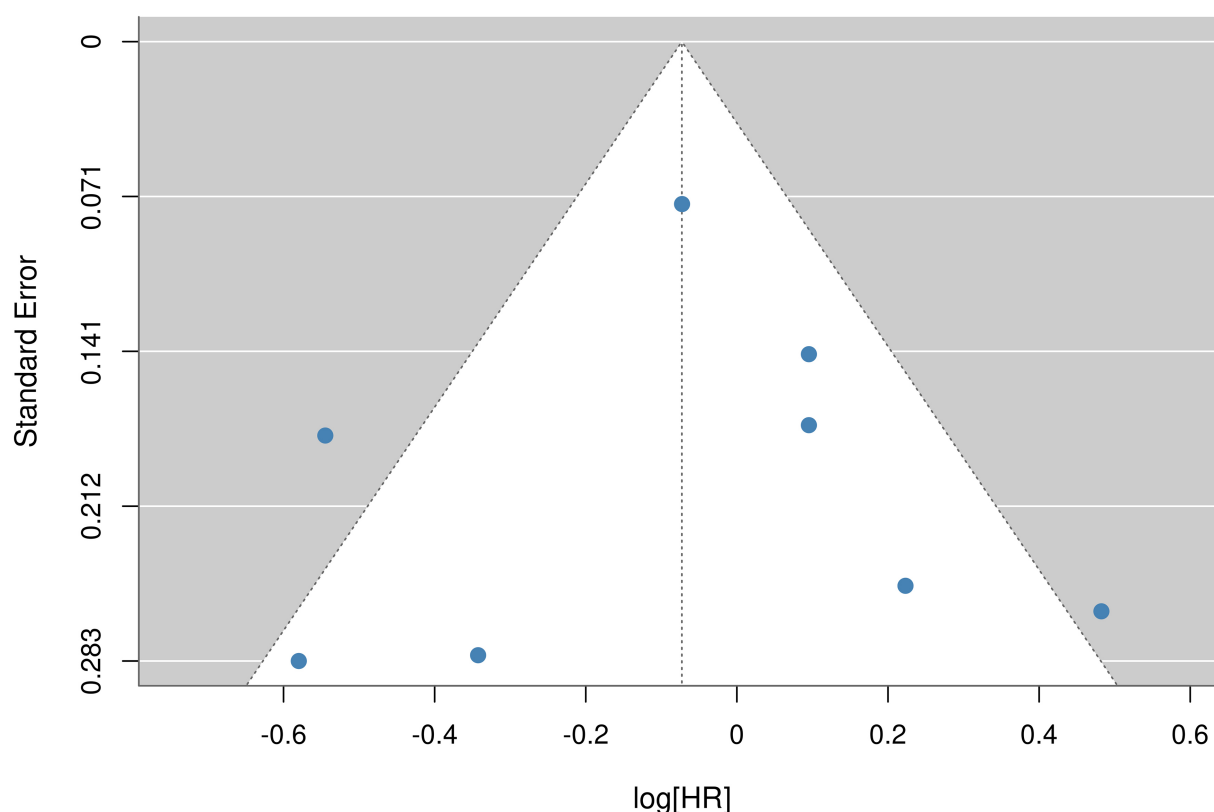


Figure 3. Funnel plot for publication bias of studies on tea consumption and liver cancer risk. The horizontal axis represents the logHR, and the vertical axis represents the SE. The vertical dashed line indicates the pooled effect estimate from the random-effects model. The diagonal dotted lines represent the 95%CI around the pooled effect. Symmetry was assessed using Egger's test ($P = 0.923$), suggesting no significant publication bias. No trim-and-fill adjustment was applied. CI: Confidence interval; log[HR]: log hazard ratio; SE: standard error.

Table 3. Univariate meta-regression analyses of study-level covariates for the association between tea consumption and hepatocellular carcinoma risk

Covariate	Subgroup (Comparison vs. Reference)	β (95%CI)*	P*	R ² (%)
Geographic region				
	Japan vs. China	0.177 (-0.588,0.942)	0.578	0
	Europe vs. China	-0.200 (-1.471,1.071)	0.702	0
NOS scores	Low vs. High	-0.024 (-0.710,0.662)	0.934	0
Tea type	Other tea vs. Green tea	-0.019 (-0.809,0.770)	0.954	0
Sex	Female vs. Male	-0.362 (-1.308,0.584)	0.348	NE [†]
Dose				
	Medium vs. Low	0 (-0.269,0.269)	1.000	0
	High vs. Low	-0.028 (-0.349,0.203)	0.590	0

*P-values and 95%CI were derived from random-effects meta-regression with Knapp-Hartung adjustment; [†]R² was not estimable for sex due to the limited number of effect sizes ($k = 6$). CI: Confidence interval; NE: not estimable; NOS: Newcastle-Ottawa Scale.

HCV adjusted), pooled estimates were not calculable (Supplementary Table 6, composite forest plot in Supplementary Figure 17). However, these subgroup comparisons should be interpreted with caution, as several subgroups contained only one or two studies, limiting statistical power.

Publication bias

Publication bias was assessed using funnel plots, Egger's regression test, and Begg's rank correlation test. Funnel plots [Figure 3] showed a generally symmetric distribution of effect sizes. Neither Egger's test ($P = 0.923$) nor Begg's test ($P = 0.720$) indicated significant publication bias.

DISCUSSION

This meta-analysis found no robust evidence for a protective effect of tea consumption against HCC. After pooling all eligible studies, no statistically significant association between tea consumption and HCC risk was observed in either cohort studies (HR = 0.93, 95%CI: 0.69-1.25) or case-control studies (OR = 0.37, 95%CI: 0.10-1.39). Subgroup analyses did not identify any consistent effect modifier (all interaction $P > 0.05$). Although a single European study suggested a potentially protective effect (HR = 0.41, 95%CI: 0.22-0.77), this result should be interpreted with caution given the limited number of studies in that subgroup. Moreover, meta-regression did not support geographic region as a significant source of heterogeneity ($P = 0.702$), suggesting that this isolated finding is likely attributable to chance or single-study influence rather than a true regional difference.

Between-study heterogeneity was substantial ($I^2 = 63.7\%$ in cohort studies, 91.9% in case-control studies), reflecting the diverse methodologies across primary studies. Meta-regression did not identify significant sources of this heterogeneity, likely due to the limited number of studies ($k = 8$), which reduces statistical power to detect true effect modifiers. This heterogeneity may partly explain why meta-analyses on this topic have reached inconsistent conclusions. Our null finding is consistent with that reported by Zhao *et al.* but differs from that reported by Li *et al.* who reported a significant inverse association for green tea (RR = 0.85, 95%CI: 0.74-0.91)^[32,33]. Several methodological issues common to observational studies of tea and HCC may contribute to these conflicting results. First, residual confounding is difficult to eliminate. Tea drinking is often correlated with healthier lifestyles, including higher education, less smoking or alcohol, and more exercise. Many primary studies have not adequately adjusted for these factors. Second, standardized quantitative measures of tea exposure, including type, dose, brewing method, and duration of drinking are lacking. Third, hepatocarcinogenesis typically requires decades of exposure, but most cohort studies may have insufficient follow-up to capture long-term risk. Moreover, as noted by a methodological review^[34], directly pooling RRs and ORs without stringent quality control can introduce bias. The present meta-analysis applied stricter inclusion criteria, including multivariable-adjusted estimates and clearly defined tea consumption metrics, to mitigate this issue.

Beyond confounding and measurement issues, biological factors also limit the potential anti-HCC effect of tea. Although experimental studies have suggested that tea polyphenols, particularly epigallocatechin gallate (EGCG), may exert anti-HCC effects through antioxidant, anti-inflammatory, and pro-apoptotic pathways^[35-42], these findings from controlled experimental conditions do not translate well to real-world settings. Several factors constrain the actual efficacy of tea consumption. First, tea polyphenols undergo extensive metabolic transformation before reaching the liver, leaving only a limited fraction of active compounds available^[43,44]. This low bioavailability fundamentally constrains the realworld anti-HCC efficacy of tea components. Second, individuals at high risk of HCC, particularly those with obesity or metabolic syndrome, not only exhibit significantly reduced absorption of EGCG^[45] but also face greater difficulty in achieving effective accumulation in liver tissue^[46]. Third, most previous mechanistic studies have relied on monolayer cell cultures to suggest potential anti-tumor effects of EGCG; however, recent evidence indicates that its activity is substantially attenuated in three-dimensional models that more closely recapitulate the *in vivo* tumor microenvironment^[47], suggesting the efficacy of EGCG may be overestimated in more complex tumor settings. Adding to the complexity, high-dose green tea extracts have also been linked to herb-induced liver injury (HILI), with causality verified via the Roussel Uclaf Causality Assessment Method (RUCAM) assessment^[48,49]. This dual role suggests that the biological impact of tea components is more complex than simple chemoprevention, which aligns with earlier editorials emphasizing that despite encouraging *in vitro* findings, clinical translation remains unproven and requires cautious interpretation^[50,51].

Several limitations should be acknowledged. First, the included case-control studies may be subject to recall and selection bias, and some cohort studies had relatively short follow-up durations, which may be insufficient to capture the long-term cumulative risk of HCC. Second, most included studies were conducted in China and Japan, with only one European study and none from Africa or the Americas. This limits the generalizability of our findings to populations with different tea consumption patterns, genetic backgrounds, or liver cancer etiologies including aflatoxin-related HCC in sub-Saharan Africa. Third, the categorical trend analysis was limited by the lack of uniform dose metrics. Because units for tea intake (cups, grams, or mL) and brewing methods varied substantially, we could not perform a robust restricted cubic spline (RCS) analysis, which requires continuous standardized dose data. We therefore used a within-study categorical trend method, which should be interpreted as exploratory. Additionally, the lack of standardized definitions for “high intake” across studies inevitably introduced non-differential exposure misclassification, which typically attenuates true associations toward the null. This represents a key methodological limitation that may partly explain the observed null findings.

In conclusion, this meta-analysis found no statistically significant association between tea consumption and HCC risk based on prospective cohort studies. Although a statistically significant association was observed in the European subgroup ($HR = 0.41$, $P = 0.0058$), this finding was based on a single study and should be considered exploratory. The case-control estimates, limited by extreme heterogeneity and imprecision, provide insufficient evidence and should not be overinterpreted. Therefore, based on current evidence, tea consumption cannot be recommended for HCC prevention, and no causative effect has been established.

DECLARATIONS

Authors' contributions

Conceptualised the study: Cao G

Contributed to the study design: Cao G, Xi Y

Led the drafting of the manuscript and analysis: Ling S, Xie L

Contributed to the interpretation of the data: Ling S, Xie L, Liu W, Cao G

Critically revised the manuscript for important intellectual content: Cao G, Liu W, Xi Y

Funding acquisition: Cao G

Visualisation: Ling S, Xie L

All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

The data generated in this study are available within the article and its [Supplementary Materials](#).

AI and AI-assisted tools statement

Not applicable.

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Conflicts of interest

Cao G is the Editor-in-Chief of the journal *Hepatoma Research*. Cao G was not involved in any stage of the editorial process, including the selection of reviewers, manuscript handling, or decision-making. The other authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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