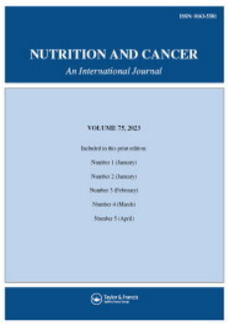

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Coffee, Green Tea Intake, and the Risk of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Several studies suggest an inverse relationship between coffee intake and risk of hepatocellular carcinoma (HCC), but the association between green tea intake and the risk of HCC is still inconclusive. We performed a meta-analysis of observational studies to clarify the association. We identified eligible studies published from January 1, 1992, to February 28, 2022, by searching PubMed, Web of Science, and EMBASE. A total of 32 studies were included in the meta-analysis. Among them, 21 studies involving 2,492,625 participants and 5980 cases of HCC reported coffee intake, 18 studies involving 1,481,647 participants and 6985 cases of HCC reported green tea intake, and seven studies reported both coffee intake and green tea intake. The results showed that a higher coffee (RR = 0.53; 95% CI: 0.47–0.59; I2 = 0.0%; Pheterogeneity = 0.634) or green tea (RR = 0.80; 95% CI: 0.67–0.95; I2 = 72.30%; Pheterogeneity < 0.001) intake may be associated with a lower risk of HCC. The same results were observed in both cohort and case-control subgroups. Our findings suggest that drinking coffee or green tea may be a potentially effective approach for the prevention or mitigation of HCC, but this still needs to be confirmed by further well-designed observational studies and clinical experimental research.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a major public health concern around the world (1). Liver cancer is the sixth most common type of cancer and the third leading cause of cancer-related death worldwide, and its incidence is increasing globally (2). According to the World Health Organization, more than one million patients will die from liver cancer by 2030 (3). HCC usually occurs in the context of oxidative stress and inflammation and is caused by chronic hepatitis B or C virus (HBV or HCV) infection, nonalcoholic fatty liver disease (NAFLD), aflatoxin exposure, excess alcohol consumption, smoking, and metabolic diseases such as obesity and diabetes (4, 5). The highest incidence of HCC is reported in East Asia and Africa, and approximately 72% of all liver cancer cases occur in Asia, with China accounting for 47% of the world's burden. In recent years, HCC incidence and mortality have been rising rapidly in the US and Europe, which may be partly due to the prevalence of obesity and diabetes (6).

Coffee and green tea are consumed in many parts of the world. Tea is the world's most popular drink other than plain water, with more than two billion cups consumed every day, followed by coffee (7, 8). According to the level of fermentation, tea can be mainly classified as three major types: green tea (non-fermented), black tea (fermented) and oolong tea (half-fermented). Among them, green tea contains a much higher level of polyphenols known as catechins, which have been shown to have anticarcinogenic effects (9). A major polyphenol of green tea, epigallocatechi-3-gallate (EGCG), has generated interest for its anti-tumor effects (10). EGCG has been

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shown to suppress the proliferation of liver cancer cells In Vitro (11). However, the molecular mechanisms of the chemopreventive effects of green tea are still uncertain. Drinking coffee or green tea is a significant component of daily life for some people. However, several epidemiological studies have shown varying results on the association between coffee or green tea intake and HCC risk (9–12). Some studies have shown a protective association between coffee or green tea intake and HCC, but others have found no such association (10, 13–16). Tanaka et al. evaluated the relationship between coffee and green tea intake and the risk of HCC in a meta-analysis in 2019 (17), and the re sults suggested that coffee intake was associated with a lower risk of HCC (RR = 0.72; 95% CI: 0.66–0.79). Green tea intake had no significant association with HCC risk (RR = 0.99; 95% CI: 0.97–1.01) in the high vs. low/no categories of green tea intake. Although many studies have shown an inverse relationship between coffee intake and HCC, the potential role of coffee and green tea intake in liver cancer prevention is still inconclusive. Therefore, we provide a comprehensive, up-to-date assessment of the relationship between coffee or green tea intake and HCC risk in the present meta-analysis.

Material and Methods

This study was registered (registration number: CRD42022313227) with the PROSPERO database before March 28, 2022 (https://www.crd.york.ac.uk/PROSPERO). The relevant literature search was conducted in the PubMed, Web of Science, and EMBASE databases from January 1, 1992, to March 28, 2022. We searched for observational studies examining the associations between coffee or green tea intake and HCC risk, and the search strategies are included in Supplemental material 1. Furthermore, we reviewed the references in the identified articles to identify more relevant studies. Our search was restricted to full-length articles published in English.

Selection Criteria

The inclusion criteria for this meta-analysis were as follows: 1) research in the form of cohort studies or case–control studies; 2) studies in which the exposure factor was coffee or green tea and included the terms caffeine or *Coffea* or chicory or coffee or green teas; 3) studies in which the outcome event was HCC (or primary liver cancer) incidence or mortality; 4) studies in which the relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs) with their corresponding 95% confidence interval (Cis) were provided or could be calculated from the data presented in the articles; and 5) animal studies, reviews, abstracts, commentaries, editorials, letters, duplicate studies, and unpublished studies were excluded. If one study was reported repeatedly, the publication with the longest follow-up time was used in the present meta-analysis.

Data Extraction

After removing duplicates, all abstracts and titles were filtered independently by two reviewers (JC Yu and D Liang) to remove irrelevant articles. We downloaded and read the full texts of the potential studies related to the selection criteria to incorporate systematic reviews. Two independent investigators (JC Yu and FD Zhou) extracted data from the included articles. Extracted data included the first author's name, year of publication, country or region in which the study was conducted, follow-up time, number of cases (or death cases), sample size, exposure measurement, comparison of intake levels, and confounders adjusted for in the models. The accuracy of the data was further confirmed by another investigator (T Wang).

Quality Assessment

Two investigators (JC YU and ZX LIU) independently assessed the methodological quality of the included studies and scored each study using the 9-point Newcastle Ottawa scale (NOS). The NOS is divided into three major domains, including selection, comparison, and outcome, accounting for four points, two points, and three points, respectively. Each included study was assessed according to the NOS and classified into low-, medium-, and high-quality studies (0–3, 4–6, 7–9, respectively) (18, 19). Any differences in the evaluation were resolved through discussion to achieve consensus, which was ultimately confirmed by another investigator (WJ Chen).

Statistical Methods

Stata/SE15.One and Revman5.3 software were used for data analysis, and RRs, ORs, or HRs and their corresponding 95% CIs were extracted from each study for the meta-analysis. Given the differences in exposure categories in the original studies, we obtained a summary estimate by comparing the RRs of the highest coffee or green tea intake categories with those of the lowest categories. The fixed-effects model and random-effects model were adopted to pool RRs, and

inverse variance was used in the random-effects models or fixed-effects model. Heterogeneity between studies was assessed using the Q and I^2 statistics. For the I^2 values, 25%, 50%, and 75% represented low, medium, and high levels of heterogeneity, respectively, while an I^2 >50% represented substantial heterogeneity. Subgroup analyses were performed according to study design, region, quality score, sex, and frequency to explore the sources of heterogeneity. Meta-regression was also used to explore the heterogeneity. Sensitivity analysis was performed to explore whether the inclusion of a study had a substantial impact on the results. A funnel chart was used to qualitatively evaluate publication bias. Egger's test and Begg's test were used to quantitatively evaluate publication bias, with $P<0.05$ indicating statistical significance.

Results

Search Results

We collected 2,542 records by searching the following three databases: PubMed, Web of Science, and EMBASE. After layers of screening, 21 cohort studies and 11 case–control studies met the inclusion criteria and were included in the meta-analysis. A flowchart of the literature search is presented in Figure 1.

Study Characteristics

Tables 1 and 2 present the characteristics of each study. Among the 32 studies, six were conducted in Europe, 22 were conducted in Asia, and three were conducted in the United States. After integrating all studies, a total of 2,492,625 participants and 5,980 HCC cases with coffee intake and a total of 1,481,647 participants and 6,985 HCC cases with green tea intake were included in our meta-analysis. Most of the literature quality scores were ≥ 7, while 12 studies had a quality score of ≤ 6, and no low-quality articles were found. The median scores were 6.45 for case–control studies and 6.95 for cohort studies. Most studies adjusted for potential confounding factors, including age, sex, alcohol consumption, smoking status, history of diabetes, etc.

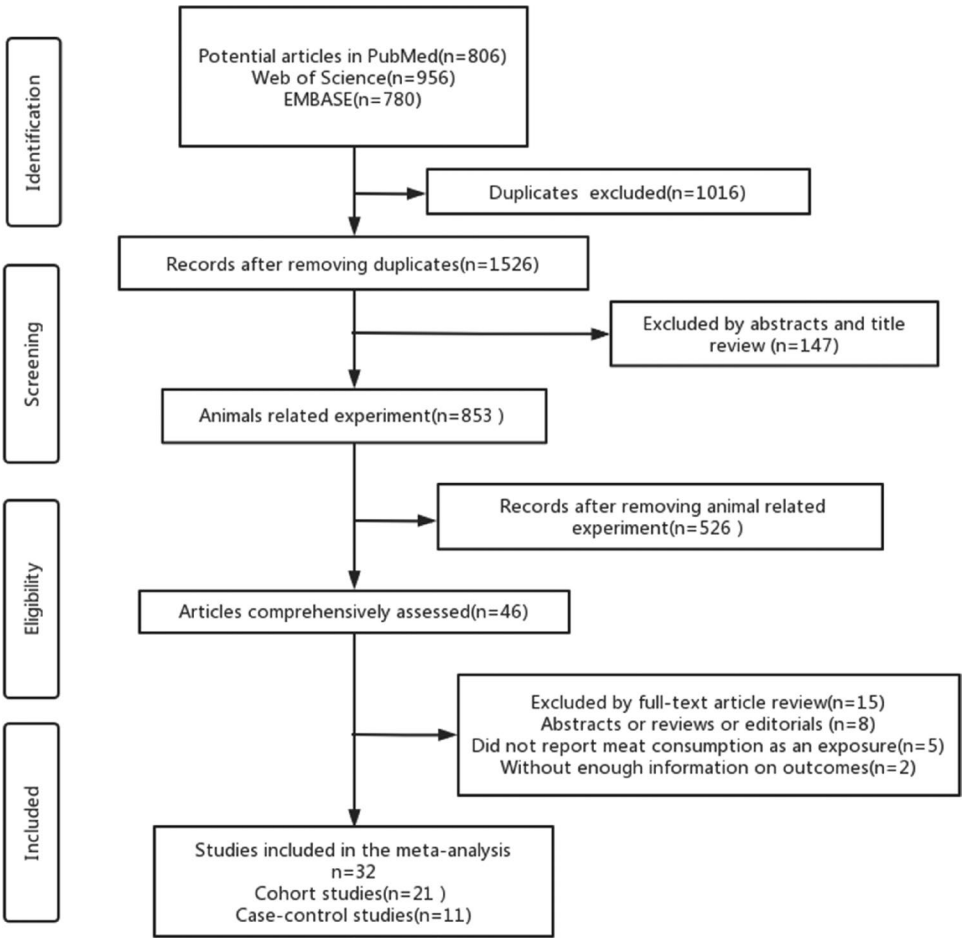

Figure 1. Flow diagram for the selection of studies.

Table 1. Main characteristics of studies on coffee intake and the risk of HCC.

Author (year)	Country	Duration of follow-up (years)	Study design	Cases number and sex	Sample size/ controls and sex	Exposure measurements	Coffee consumption frequency	Relative risk (95%CI)	Adjustments	Quality score
Tamura et al. (20) (2018)	Japan	16	Prospective cohort	172 (106 men and 66 women)	30,824 (14,240 men and 16,584 women)	FFQ	Nondrinkers <Once/day Once/ day ≥Twice/day	1.00 0.65 (0.46, 0.93) 0.63 (0.39, 1.02) 0.40 (0.20, 0.79)	Age, sex, ethanol intake , smoking status, BMI, education, total energy intake, physical activity, and medical history of diabetes mellitus.	8
Park et al. (21) (2018)	US	19	Prospective cohort	670 (men/ women)	167,720 (men/ women)	FFQ	None 1-3 cups/month 1-6 cups/week 1 cup/day 2-3 cups/day ≥4 cups/day	1.00 1.10 (0.76, 1.58) 0.97 (0.71, 1.32) 0.88 (0.68, 1.15) 0.64 (0.48, 0.85) 0.57 (0.38, 0.87)	Age, body mass index, education, alcohol intake, physical activity, history of diabetes, family history of corresponding cancer, and menopausal status and menopausal hormone therapy for women only	8
Bamia et al. (22) (2015)	10 European countries	11	Prospective cohort	201 (133 men and 68 women)	486,799 (men/ women)	FFQ	Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	1.00 0.85 (0.56, 1.29) 0.63 (0.39, 1.02) 0.49 (0.29, 0.82) 0.28 (0.16, 0.5)	Sex, diabetes mellitus, education, BMI, tobacco smoking, alcohol drinking, physical activity, energy intake	7
Petrick et al. (23) (2015)	US	10-22	Prospective cohort	860 (618 men and 242 women)	1,212,893 (men/ women)	FFQ	Never Ever >0-<1cups/day 1-<2 cups/day 2-3 cups/day >3 cups/day	1.00 1.00 (0.79, 1.27) 1.24 (0.94, 1.64) 1.16 (0.88, 1.52) 0.89 (0.68, 1.15) 0.73 (0.53, 0.99)	Age, race, BMI, smoking status, cigarette smoking intensity, alcohol drinking	6
Setiawan et al. (24) (2014)	US	18	Prospective cohort	451 (men/ women)	162,022 (75,601 men and 86,421 women)	FFQ	Never <1 cup per day 1 cup per day 2-3 cups per day ≥ 4 cups per day	1.00 1.14 (0.88, 1.48) 0.87 (0.67, 1.11) 0.62 (0.46, 0.84) 0.59 (0.35, 0.99)	Age, sex, and race/ethnicity education, BMI, alcohol intake, smoking status, diabetes	7
Lai et al. (25) (2013)	Finnish	18	Prospective cohort	194 (men)	20,737 (men)	FFQ	Never >0-<1 cups/day 1-<2 cups/day 2-<3 cups/day 3-<4 cups/day ≥ 4 cups/day	1.35 (0.65 ,2.82) 1.00 0.73 (0.48, 1.12) 0.52 (0.33, 0.82) 0.45 (0.26, 0.78) 0.53 (0.30, 0.95)	Age , BMI , education, marital status , history of diabetes, years of smoking , cigarettes smoked per day , alcohol, tea intake and serum cholesterol	6
Johnson et al. (26) (2011)	Singapore	13	Prospective cohort	362 (men/ women)	61,321 (men/ women)	FFQ	Never >0-<1 cups/day 1-<2 cups/day 2-<3 cups/day ≥ 3 cups/day	1.00 0.94 (0.63, 1.40) 1.17 (0.87, 1.56) 0.78 (0.56, 1.07) 0.56 (0.31, 1.00)	Age, gender, dialect group, year of recruitment, BMI, level of education, alcoholic, cigarette smoking, black tea and green tea intake, and history of diabetes	8
Leung et al. (27) (2010)	China	3	Case-Control	109 (86 men and 23 women)	125 (102 men and 23 women)	FFQ	<1 time/week 1-3 times/week ≥ 4 times/week	1.00 0.58 (0.24, 1.36) 0.41 (0.19, 0.89)	Age, gender, alcohol, smoking, tea, physical activity	7
Inoue et al. (28) (2009)	Japan	13	Prospective cohort	110 (73 men and 37 women)	18,815 (6,414 men and 12,401 women)	Self-administered questionnaire	Never <1 cups/day 1-2 cups/day ≥ 3 cups/day	1.00 0.67 (0.42, 1.07) 0.49 (0.27, 0.91) 0.54 (0.21, 1.39)	Sex, age , area , smoking status, weekly ethanol intake, BMI, history of diabetes mellitus , , serum ALT level , HCV infection status , and HBV infection status	7
Hu et al. (29) (2008)	Finnish	19	Prospective cohort	128 (men/ women)	60,323 (29,286 men and 31,037 women)	FFQ	0-1cups/day 2-3 cups/day 4-5 cups/day 6-7 cups/day ≥ 8 cups/day	1.00 0.66 (0.37, 1.16) 0.44 (0.25, 0.77) 0.38 (0.21, 0.69) 0.32 (0.16, 0.62)	Age, sex, study year, alcohol consumption, education, smoking, diabetes and chronic liver disease and BMI.	7

Ohishi et al. (8) (2008)	Japan	44	Case-Control	224 (136 men and 88 women)	644 (387 men and 257 women)	Self-administered questionnaire	Never Daily	1.00 0.40 (0.16, 1.02)	Hepatitis virus infection, alcohol consumption, smoking habit, BMI, diabetes mellitus, and radiation dose to the liver	6
Tanaka et al. (30) (2007)	Japan	3	Case-Control	209 (141 men and 68 women)	1,308 community controls (656 men and 652 women), 275 hospital controls (180 men and 95 women), and 381 CLD patients (205 men and 176 women)	Interview survey and Self-administered questionnaire	Never <1 cups/day 1-2 cups/day ≥ 3 cups/day	1.00 0.31 (0.21, 0.46) 0.11 (0.06, 0.21) 0.10 (0.04, 0.24)	Sex, age, heavy drinking history, and smoking. HBsAg or anti-HCV	7
Wakai et al. (31) (2007)	Japan	11	Case-Control	96 (men/ women)	3,444 (men/women)	Self-administered questionnaire	Never <1 cups/day ≥ 1 cups/day	1.00 0.77 (0.45, 1.32) 0.49 (0.25, 0.96)	Age, sex, anti-HCV-antibody Seropositivity, area, smoking and drinking habits, and history of diabetes mellitus and liver disease	8
Montella et al. (32) (2007)	Italy	3	Case-Control	185 (149 men and 36 women)	412 (281 men and 131 women)	FFQ	Abstainers <14 cups/week 14–20 cups/week 21–27 cups/week ≥28 cups/week	2.28 (0.99, 5.24) 1.00 0.54 (0.27, 1.07) 0.57 (0.25,1.32) 0.43 (0.16, 1.13)	Age, gender, alcohol, smoking, education, center, HBV, HCV	6
Ohfuji et al. (33) (2006)	Japan	4	Case-Control	73 (men/ women)	253 (men/women)	Self-administered questionnaire	Never <1 cups/day ≥ 1 cups/day	1.00 0.61 (0.18, 2.03) 0.38 (0.13, 1.12)	Duration from first identification of liver disease, body mass index at first identification of liver disease, disease severity at first OCUH visit, family history of liver disease, interferon therapy, smoking, alcohol drinking, and other caffeine-containing beverage	7
Inoue et al. (34) (2005)	Japan	10	Prospective cohort	334 (men/ women)	90,452 (men/ women)	FFQ	Never 1-2 days/week 3-4 days/week 1-2 cups/day 3-4 cups/day ≥ 5 cups/day	1.00 0.75 (0.56, 1.01) 0.79 (0.55, 1.14) 0.52 (0.38, 0.73) 0.48 (0.28, 0.83) 0.24 (0.08, 0.77)	Age, study area, smoking status, ethanol intake, green vegetable intake and green tea intake	7
Shimazu et al. (35) (2005)	Japan	9	Prospective cohort 1	70 (50 men and 20 women)	22,404 (10,588 men and 11,816 women)	FFQ	Never Occasionally ≥ 1 cups/day	1.00 0.56 (0.33, 0.97) 0.53 (0.28, 1.00)	Age, gender, history of liver disease, alcohol consumption and smoking status	6
Shimazu et al. (35) (2005)	Japan	6	Prospective cohort 2	47 (41 men and 6 women)	38,703 (18,869 men and 19,834 women)	FFQ	Never Occasionally ≥ 1 cups/day	1.00 1.05 (0.52, 2.16) 0.68 (0.31, 1.51)	Age, gender, history of liver disease, alcohol consumption and smoking status	6
Kurozawa et al. (36) (2005)	Japan	11	Prospective cohort	401 (287 men and 114 women)	110,688 (46,399 men and 64,289 women)	Self-administered questionnaire	Never <1 cups/day ≥ 1 cups/day	1.00 0.83 (0.54,1.25) 0.50 (0.31, 0.79)	Age, gender, educational status, history of diabetes and liver diseases, smoking and alcohol habits	7
Gelatti et al. (37) (2005)	Italy	9	Case-Control	250 (204 men and 46 women)	500 (408 men and 92 women)	FFQ	No consumption 1–2 cups/day 3–4 cups/day ≥5 cups/day	1.00 0.8 (0.4, 1.3) 0.4 (0.2, 0.8) 0.3 (0.1, 0.7)	Age, gender, alcohol, HBV, HCV	6
Gallus et al. (38) (2002)	Italian and Greek studies combined	14	Case-Control	834 (661 men and 173 women)	1,912 (1,439 men and 473 women)	FFQ	Non-drinkers 1 cups/day 2 cups/day ≥3 cups/day	1.00 1.2 (0.9, 1.6) 1.0 (0.7, 1.3) 0.7 (0.5, 1.0)	Age, gender, alcohol, smoking, education, BMI, T2DM, hepatitis, study	6

FFQ: food frequency questionnaire, BMI: body mass index.
In the studies by Kurozowa et al., the number of HCC cases recorded are the number of patients who died from their hepatocellular carcinoma, the rest recorded the incidence of hepatocellular carcinoma.

Table 2. Main characteristics of studies on green tea intake and the risk of HCC.

Author (year)	Country	Duration of follow-up (years)	Study design	Cases number and sex	Sample size/ controls and sex	Exposure measurements	Tea consumption frequency	Relative risk (95%CI)	Adjustments	Quality score
Li et al. (39) (2019)	China	4	Cohort	1,874 (men/ women)	455,981 (men/ women)	Interviewer-administered questionnaire	Less than weekly Weekly Daily ≤2.0 g Daily 2.1–4.0 g Daily >4.0 g	1.00 1.00 (0.83, 1.21) 0.98 (0.83, 1.15) 1.05 (0.89, 1.23) 0.98 (0.82, 1.18)	Age, sex, and study area, education, occupation, marital status, household Income, physical activity intakes of red meat, fresh fruits and vegetables, BMI, prevalent diabetes	7
Tamura et al. (20) (2018)	Japan	16	Cohort	172 (106 men and 66 women)	30,824 (14,240 men and 16,584 women)	FFQ	Nondrinkers < Once/day Once/day 2–3 times/day ≥4 times/day	1.00 1.36 (0.8, 2.16) 1.08 (0.6, 1.94) 0.75 (0.5, 1.11) 1.25 (0.7, 2.04)	Age, sex, ethanol intake, smoking status, body mass index, education, total energy intake, physical activity, and medical history of diabetes mellitus	8
Bamia et al. (22) (2015)	10 European countries	11	Cohort	201 (133 men and 68 women)	486,799 (men/ women)	FFQ	Category 1 Category 2 Category 3 Category 4 Category 5	1.00 1.05 (0.68, 1.63) 0.98 (0.63, 1.53) 0.71 (0.41, 1.23) 0.41 (0.22, 0.78)	Sex, diabetes mellitus, education, BMI, tobacco smoking, alcohol drinking, physical activity, energy intake	7
Butler et al. (40) 2015	China	15	Cohort	214 men	18,244 men	Baseline interview and Follow-up questionnaires	Never 0–2 cups/day 3–4 cups/day 5 cups/day	1.00 0.66 (0.38, 1.14) 0.82 (0.47, 1.43) 0.98 (0.57, 1.68)	Age, BMI, education smoking status alcohol intake hepatitis B surface antigen serological status	6
Nechuta et al. (41) (2012)	China	14	Cohort	134 (women)	69,310 (women)	FFQ	Never 0–2 cups/day 3–4 cups/day 5 cups/day	1.00 1.17 (0.62, 2.2) 1.03 (0.56, 1.89) 0.44 (0.18, 1.08)	Age, marital status, education, occupation, BMI, exercise, fruit and vegetable intake, meat intake, diabetes, family	8
Johnson et al. (26) (2011)	Singapore	13	Cohort	362 (men/ women)	61,321 (men/ women)	FFQ	Non-drinkers drinkers	1.00 0.98 (0.76, 1.26)	Age, gender, dialect group, year of recruitment, BMI, level of education, alcoholic, cigarette smoking, black tea and green tea intake, and history of diabetes	8
Li et al. (42) (2011)	China	3	Case-Control	204 (159 men and 45 women)	415 (287 men and 128 women)	Interviewer based questionnaire	0–2 cups/day 3–4 cups/day 5 cups/day	1.21 (0.62, 2.36) 0.76 (0.38, 1.51) 0.55 (0.28, 1.09)	Age, gender, education, income, BMI, family history, pack-year, alcohol drinking and HBSAg	7
Ui et al. (43) (2009)	Japan	7	Cohort	247 (164 men and 83 women)	41,761 (19,748 men and 22,013 women)	FFQ	<1 cup/day 1-2 cups/day 3-4 cups/day ≥ 5 cups/day	1.00 0.78 (0.54, 1.12) 0.98 (0.69, 1.37) 0.58 (0.41, 0.83)	Age, sex, alcohol consumption, coffee consumption, vegetables consumption, dairy products consumption fruit	8
Inoue et al. (28) (2009)	Japan	13	Cohort	110 (73 men and 37 women)	18,815 (6,414 men and 12,401 women)	Self-administered questionnaire	<3 cups/day 3-4 cups/day ≥5 cups/day	1.00 1.62 (0.97, 2.69) 1.44 (0.84, 2.45)	Sex, age , area , smoking status, weekly ethanol intake, BMI, history of diabetes mellitus , , serum ALT level , HCV infection status , and HBV infection status	7
Wang et al. (44) (2008)	China	14	Cohort	1,803 (1,536 men and 267 women)	89,789 (men/ women)	Self-administered questionnaire	At least 4 times/ week	0.74 (0.43, 1.28)	Age, surface antigen of hepatitis B virus, occupation, history of hepatitis, family history of liver cancer, smoking, and alcohol drinking	6

Wang et al. (11) (2008)	China	3	Case-Control	215 (men/ women)	215 (men/ women)	Self-administered questionnaire	Never Low Moderate High	0.23 (0.14, 0.38)	Age, gender, education, income, BMI, family history, pack-year, alcohol drinking and HBSAg.	5
Iso et al. (9) (2007)	Japan	14	Cohort	602 (men/ women)	99,510 (men/ women)	Self-administered questionnaire	Man ≤4/week 1-3/day ≥4/day Woman ≤4/week 1-3/day ≥4/day	1.00 0.68 (0.49, 0.94) 0.89 (0.69, 1.16) 1.00 0.69 (0.44-1.08) 0.85 (0.59-1.23)	Age, sex, ethanol intake, smoking status, body mass index, education, total energy intake, physical activity, and medical history of diabetes mellitus	8
Ohfuji et al. (33) (2006)	Japan	4	Case-Control	73 (men/ women)	253 (men/ women)	Self-administered questionnaire	≤1 cup/day 2 cup/day ≥3 cup/day	1.00 5.90 (1.32, 26.3) 4.08 (1.20, 13.9)	BMI, family history of liver disease, interferon, therapy, smoking, alcohol drinking, and other caffeine-containing beverage	6
Shimazu et al. (35) (2005)	Japan	9	Cohort 1	70 (50 men and 20 women)	22,404 (10,588 men and 11,816 women)	FFQ	≤2 cups/day 3-4 cups/day	1.00 1.20 (0.75, 1.94)	Age, gender, history of liver disease, alcohol consumption and smoking status	6
Shimazu et al. (35) (2005)	Japan	6	Cohort 2	47 (41 men and 6 women)	38,703 (18,869 men and 19,834 women)	FFQ	≤2 cups/day 3-4 cups/day ≥5 cups/day	1.00 1.20 (0.75, 1.94) 0.90 (0.56, 1.44)	Age, gender, history of liver disease, alcohol consumption and smoking status	6
Mu et al. (45) (2003)	China	4	Case–control	204 (men/ women)	211 (men/ women)	Self-administered questionnaire	Never 0–2 cups/day 3-4 cups/day ≥5 cups/day	1.00 1.07 (0.61, 1.86) 0.93 (0.55, 1.60) 0.58 (0.34, 1.00)	Age, sex, alcohol consumption, smoking status, BMI, education	6
Nagano et al. (46) (2001)	Japan	15	Cohort	418 (260 men and 158 women)	38,540 (14,873 men and 23,667 women)	Self-administered questionnaire	0-1 times/day 2-4 times/day ≥5 times/day	1.00 1.1 (0.80, 1.40) 0.95 (0.69, 1.30)	Age, gender, radiation dose, smoking status, drinking history, BMI, education	7
Nakachi et al. (47) (2000)	Japan	11	Cohort	35 (men/ women)	8,552 (men/ women)	Self-administered questionnaire	≤3 cups/day ≥10 cups/day	1.00 0.53 (0.17, 1.57)	Age, cigarette smoking, alcohol consumption	6

FFQ: food frequency questionnaire, BMI: body mass index.

In the studies by Iso et al., Wang et al. (cohort), Wang et al. (case-control), the number of HCC cases recorded are the number of patients who died from their hepatocellular carcinoma, the rest recorded the incidence of hepatocellular carcinoma.

Overall Meta-Analysis of the Effect of Coffee and Green Tea Intake on HCC Risk

Twenty-one studies investigated the association between coffee intake and HCC risk, including thirteen cohort studies (10, 13–15, 28, 40, 41, 44, 48–51) and eight case–control studies (18–23, 26, 43). No heterogeneity was observed (Q = 17.23; I^2=0.00%; Table 3), so the fixed-effects model was chosen for analysis. We found that a higher coffee intake was associated with a lower risk of HCC (RR = 0.53; 95% CI: 0.47–0.59; $P_{heterogeneity}$=0.634; Figure 2A). The association between green tea intake and HCC risk was evaluated in eighteen studies, with fourteen cohort studies (9–12, 14–16, 24, 27, 34, 35, 48, 50) and four case–control studies included (19, 25, 29, 36). Considering the moderate heterogeneity (Q = 61.38; I^2=72.30%; Table 3), the random-effects model was chosen to analyze the association, and the results indicated that a higher intake of green tea was associated with a lower risk of HCC (RR = 0.80; 95% CI: 0.67–0.95; $P_{heterogeneity}$<0.001; Figure 2B).

Subgroup Analysis

The results of the subgroup analysis (Table 3) suggested that a higher coffee intake was associated with a lower risk of HCC among case–control studies (RR = 0.57; 95% CI: 0.49–0.67; I^2=0.0%; $P_{heterogeneity}$=0.659) and cohort studies (RR = 0.48; 95% CI: 0.41–0.57; I^2=0.0%; $P_{heterogeneity}$=0.606). Regarding green tea intake, subgroup analyses suggested a decreased HCC risk in both case–control (RR = 0.55; 95% CI: 0.25, 1.20; I^2=92.00%; $P_{heterogeneity}$<0.001) and cohort studies (RR = 0.89; 95% CI: 0.77–1.03; I^2=44.10%; $P_{heterogeneity}$=0.039). In the subgroup analysis of different regions (Table 3), a lower risk of HCC was found among Asian populations (RR = 0.54; 95% CI: 0.47–0.63; I^2=0.0%; $P_{heterogeneity}$=0.897) and European/American populations (RR = 0.51; 95% CI: 0.43–0.61; I^2=25.90%; $P_{heterogeneity}$=0.205) with coffee intake. Subgroup analysis of green tea intake suggested a significant effect in Chinese populations (RR = 0.66; 95% CI: 0.39–0.92; I^2=82.10%; $P_{heterogeneity}$<0.001), which indicated that a higher green tea intake was associated with a lower risk of HCC but not in Japanese populations

Table 3. Subgroup analysis for the association between coffee or green tea intake and the risk of HCC.

			Heterogeneity			Model
Analysis	No. of studies	RR(95%CI)	χ^2	I^2	P	
Coffee	21	0.53(0.47, 0.59)	17.23	0.00%	0.634	F
Study design						
Case-control	8	0.57(0.49, 0.67)	5.00	0.00%	0.659	F
Cohort	13	0.48(0.41, 0.57)	10.11	0.00%	0.606	F
Region						
Asian	11	0.54(0.47, 0.63)	4.91	0.00%	0.897	F
Europe/USA	10	0.51(0.43, 0.61)	12.13	25.90%	0.205	F
Quality score						
<7	8	0.58(0.47, 0.72)	4.21	0.00%	0.755	F
≥7	13	0.51(0.45, 1.10)	12.23	1.80%	0.428	F
Sex						
Men	5	0.42(0.30, 0.58)	2.76	0.00%	0.599	F
Women	4	0.60(0.33, 1.01)	0.94	0.00%	0.815	F
Frequency						
>0–<1cups/day	11	0.78(0.60, 1.00)	42.69	76.60%	<0.001	F
1–<2 cups/day	12	0.73(0.56, 0.94)	68.83	84.30%	<0.001	F
2–<3 cups/day	9	0.72(0.62, 0.83)	11.60	31.00%	0.170	F
≥ 3 cups/day	13	0.52(0.42, 0.63)	21.11	43.10%	0.049	F
Green tea	18	0.80(0.67, 0.95)	61.38	72.30%	<0.001	R
Study design						
Case-control	4	0.55(0.25, 1.20)	37.40	92.00%	<0.001	R
Cohort	14	0.89(0.77, 1.03)	23.26	44.10%	0.039	R
Region						
China	7	0.60(0.39, 0.92)	33.45	82.10%	<0.001	R
Japan	9	0.97(0.81, 1.16)	15.91	49.70%	0.044	R
Quality score						
<7	8	0.73(0.49, 1.08)	38.87	82.00%	<0.001	R
≥7	10	0.85(0.71, 1.03)	22.47	60.00%	0.007	R
Sex						
Men	5	0.89(0.79, 1.00)	3.41	0.00%	0.492	R
Women	5	0.76(0.57, 1.01)	6.07	34.10%	0.194	R
Frequency						
0–<2 cups/day	8	0.98(0.78, 1.25)	9.84	28.80%	0.198	R
2–<4 cups/day	11	1.01(0.85, 1.19)	15.00	33.20%	0.133	R
≥4 cups/day	12	0.79(0.64, 0.96)	22.07	50.20%	0.024	R

No: number; RR: relative risk; R: the random-effects model; F: the fixed-effects model.

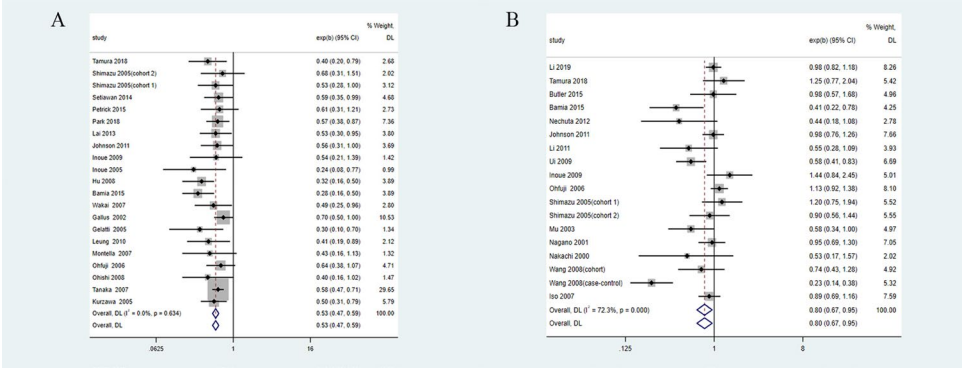

Figure 2. Forest plots of coffee or green tea intake and the risk of HCC.

(RR = 0.97; 95% CI: 0.81–1.16; I^2=49.70%; $P_{heterogeneity}$=0.044). In terms of different intake frequencies of coffee or green tea, a substantial association was found in coffee intake frequencies of 1 to <2 cups/day (RR = 0.73; 95% CI: 0.56–0.94; I^2=84.30%; $P_{heterogeneity}$<0.001), 2 to <3 cups/day (RR = 0.72; 95% CI: 0.62–0.83; I^2=31.00%; $P_{heterogeneity}$<0.001), and ≥ 3 cups/day (RR = 0.52, 95% CI: 0.42–0.63; I^2=43.10%; $P_{heterogeneity}$=0.049). For green tea, subgroup analysis of frequency suggested a significant association between green tea intake and HCC risk at ≥ 4 cups/day (RR = 0.79; 95% CI: 0.64–0.96; I^2=50.20%; $P_{heterogeneity}$=0.024). Subgroup analysis results based on different quality scores and sexes are shown in Table 3.

Meta-Regression Analysis

We conducted a meta-regression analysis on coffee intake and HCC risk and observed that design, region, quality score, and sex were not related to the heterogeneity (P = 0.157, 0.665, 0.366, 0.329, respectively, Supplemental Figure 1), but frequency (P = 0.024, Supplemental Figure 1) was associated with the heterogeneity. When the meta-regression analysis was based on green tea intake and HCC risk, the study design, region, quality score, sex, and frequency were not related to the heterogeneity (P = 0.115, 0.079, 0.728, 0.348, 0.154, respectively, Supplemental Figure 2).

Sensitivity Analysis

To test the stability of the association and possible sources of statistical heterogeneity, sensitivity analyses were conducted on coffee intake and HCC risk by excluding studies one by one. After any one of the studies was excluded, the pooled RRs (95% CIs) fluctuated between 0.51 (95% CI: 0.45–0.59) and 0.55 (95% CI: 0.49–0.61), which was essentially consistent with the pooled RRs of the nonexcluded studies. This suggests that the results of this study were stable and reliable. Similarly, we conducted sensitivity analyses on tea intake and HCC risk. The results showed that the pooled risk estimates changed significantly, ranging from 0.72 (95% CI: 0.58–0.89) to 0.81 (95% CI: 0.68–0.97), which indicated that the overall RR was not substantially influenced by the individual studies.

Publication Bias Analysis

When we analyzed coffee intake and HCC risk, we found evidence of publication bias by Egger's test (P = 0.002), Begg's test (P = 0.023), and visual inspection of the funnel plot, as shown in Figure 3. There may be publication bias in the reporting of the results on green tea consumption and HCC risk according to Begg's test (P = 0.063), although the funnel plot (Figure 3) was visually symmetrical and Egger's test indicated no publication bias (P = 0.215).

Discussion

At present, most of the evidence of the correlation between coffee or green tea intake and HCC is mainly based on epidemiological studies, and randomized controlled trial studies have not been conducted. Therefore, this meta-analysis only included observational studies. The associations of coffee and green tea intake with HCC risk were systematically investigated. Our meta-analysis included a large sample size (2,492,685 participants and 5,980 HCC cases for coffee intake; 1,481,647 participants and 6,985 HCC cases for tea intake), participants from a wide variety of populations (Asia and Europe/USA), and a long time span (from 1992 to 2022), which enhanced the statistical power to detect possible associations. We also conducted meta-regression analyses and subgroup analyses to identify potential sources of heterogeneity,

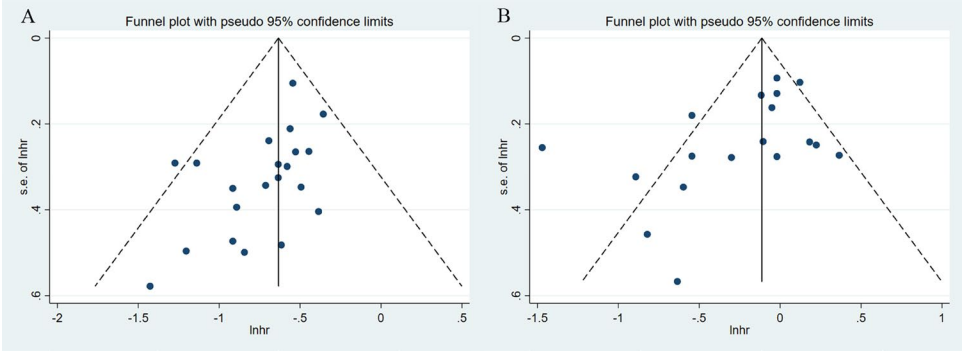

Figure 3. Funnel plots of coffee or green tea intake and the risk of HCC.

thus providing updated comprehensive quantitative evidence of the association between coffee or green tea intake and HCC risk. The present study found that a higher intake of coffee or green tea was associated with a lower risk of HCC. A coffee intake of ≥1 cups/day showed statistical significance with a lower risk of HCC compared to not drinking coffee. A green tea intake of ≥4 cups/day showed statistical significance with a lower risk of HCC compared to not drinking green tea.

Our results are consistent with some previous meta-analyses (8, 47). A previous meta-analysis also reported similar results for coffee intake and liver cancer risk, with a pooled RR of 0.64 (95% CI: 0.52–0.78) in eight cohorts and 0.56 (95% CI: 0.42–0.75) in eight case–control studies (9). Another meta-analysis reported that the summary RR for the highest intake (>5 cups/day) of green tea on liver cancer incidence compared with not drinking green tea was 0.62 (95% CI: 0.49–0.79) (47). Previous studies evaluated the correlation between coffee intake and the risk of HCC only in European and Japanese populations (30, 31). However, in the present meta-analysis, we included research on Asian, American, and European populations, which is the first comprehensive analysis of the relationship between coffee intake and HCC risk. In the subgroup analysis, we stratified by study design, region, quality score, sex, and frequency. We found some interesting phenomena. For coffee intake, when subgroup analyses were based on sex, the benefit of coffee intake on HCC risk was found in men, but not in women. However, this result was derived from only five studies with a small number of cases, so we could not draw a firm conclusion. In the subgroup analysis of frequency, a more obvious inverse association between coffee intake and HCC risk was found for a coffee intake frequency of ≥3 cups/day (RR = 0.52; 95% CI: 0.42–0.63) than for a frequency of 2 to <3 cups/day (RR = 0.72; 95% CI: 0.62–0.83), which was similar to an Italian case–control study (18). For green tea, when the subgroup analysis was based on region, green tea intake reduced the HCC risk in the Chinese population, but not in the Japanese population. The results are consistent with those of a previous meta-analysis (47). Differences in the preparation of green tea (steaming in Japan and dry roasting in China) can influence the type and amount of bioactive compounds in green tea, which affects their function to some extent (47). In the subgroup analysis of frequency, we found that a green tea intake frequency of ≥4 cups/day could reduce the risk of HCC, which was similar to a previous study (16).

A protective effect of coffee consumption on liver cancer is biologically plausible. coffee is a complex brew containing hundreds of biologically active compounds, including caffeine, chlorogenic acid, and diterpenes (32, 33). These compounds possess antioxidant, anti-inflammatory, antifibrotic, and anticarcinogenic properties, which may explain why coffee drinkers have lower rates of chronic liver disease (CLD), including fibrosis, cirrhosis, and HCC (37). Caffeine is a major component of coffee, and some animal-based studies reported that caffeine levels in coffee extracts were inversely related to liver injury (38, 39). Another population-based study in the United States showed that a higher intake of coffee, especially caffeine, was associated with a lower prevalence of abnormal alanine aminotransferase activity (42), which is a marker of liver injury. Green tea is mainly consumed in Asian countries, such as China and Japan, and drinking green tea has become cultural practice and even a way of life in some parts of China (45, 46). The main chemical constituents of green tea are polyphenols, of which the primary constituents are catechins, which have been shown to have antimutagenic, antigenotoxic, and anticarcinogenic activities (47). Several In Vitro and animal studies have supported the possibility that green tea has preventive effects against HCC (9, 11). However, high doses of

epigallocatechin gallate may cause toxicity in humans, and some research in mice has indicated the hepatotoxic effects of high-dose EGCG, which are attributed to increased markers of oxidative stress, including hepatic lipid peroxidation and plasma 8-isoprostane (52–55). Therefore, the association between green tea intake and the risk of HCC needs to be explored in future studies.

This meta-analysis study has several limitations. First, all the included studies were observational studies, which are susceptible to bias and confounding, so we cannot infer causation. Cohort studies are more reliable and robust than case–control studies because cohort studies are comparatively free from recall bias, selection bias, and information bias. In some case–control studies, cases and controls were mostly identified from hospital or clinical records, which may not be representative of all HCC cases. Second, the included participants estimated coffee or tea intake by selecting from a list of defined categories in food frequency questionnaires or self-administered questionnaires, and different categories may have influenced the participants' responses. There may have been differences in the cup size, caffeine content, preparation process, etc. Third, we retrieved articles that met our requirements from multiple databases, but some of eligible studies may have been missed. Each study adjusted for different factors. Many studies were adjusted for age, sex, BMI, smoking status, and alcohol consumption, but adjustments were not made for some critical confounders, such as HBV/HCV status, diabetes mellitus, and dietary energy intake (56). All these factors will affect our results to some extent. Hepatitis virus infection, the strongest risk factor for hepatocellular carcinoma, was not considered in most of the large cohort studies, which could greatly influence the summary RRs. If individuals with hepatitis virus infection tend to reduce their coffee consumption for some reason, this could produce a spurious protective association between coffee or green tea intake and HCC risk. Errors can also be made by pooling studies that adjusted for dietary energy intake with those that did not. Finally, because the publication selection was based on articles published in English and the number of relevant studies was relatively small, the data sources were not balanced. There are few data from the USA and European countries, and significant publication bias existed. Heterogeneity was observed when we assessed the association of coffee or green tea intake and HCC risk, which might have overstated the association between coffee or green tea intake and the risk of HCC. A plausible source of the heterogeneity in the results lies in the fact that the studies included in the meta-analysis differed in their approaches to measure coffee intake, follow-up cohort members, and identify cases of HCC. However, only a few factors were analyzed to explore the source of heterogeneity in the meta-regression and subgroup analyses, and some factors, such as BMI and dietary energy intake, were not included due to insufficient data. Moreover, in the subgroup analysis of sex, considering the small sample size and that the point estimate is strongly inversely related, the result may be biased, which is one of the limitations of this study.

The strengths of our meta-analysis are that we performed a much more comprehensive search between coffee or green tea intake and HCC risk and incorporated new publications and more subgroup analyses. Unlike previous meta-analyses, we also conducted meta-regression analysis to explore the heterogeneity.

In conclusion, the present study provided strong evidence that a higher level of coffee or green tea intake was associated with a lower risk of HCC. The findings of this meta-analysis indicated an inverse association between high coffee intake and HCC risk in men and an inverse association between high green tea intake and HCC risk in Chinese populations. Due to the limited available data, further large well-designed prospective studies should be performed to confirm the results.

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For this type of study formal consent and informed consent are not required. This article does not contain any studies with human subjects or animals performed by any of the authors.

Author Contribution Statement

JC Yu and WJ Chen: conceived and design of the study; JC Yu and FD Zhou: protocol of search and acquisition of data; JC YU and ZX LIU: assessed included studies quality. JC Yu and D Liang: drafting the article; All authors: revised and approval of the version to be submitted.

Data Availability Statement

The data were extracted within the published article and its supplementary files.

Disclosure Statement

No potential conflict of interest was reported by the author(s).

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