BMJ Open

Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose–response meta-analysis

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To cite: Kennedy OJ, Roderick P, Buchanan R, *et al*. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose–response meta-analysis. *BMJ Open* 2017;**7**:e013739. doi:10.1136/bmjopen-2016-013739

► Prepublication history and additional material are available. To view please visit the journal (http://dx.doi.org/ 10.1136/bmjopen-2016-013739).

Received 3 August 2016
Revised 30 January 2017
Accepted 6 March 2017

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ABSTRACT

Objectives To examine the association between coffee, including caffeinated and decaffeinated coffee, with hepatocellular carcinoma (HCC) and assess the influence of HCC aetiology and pre-existing liver disease.

Design We performed a systematic review and meta-analysis. We calculated relative risks (RRs) of HCC according to caffeinated and decaffeinated coffee consumption using a random-effects dose–response meta-analysis. We tested for modification of the effect estimate by HCC aetiology and pre-existing liver disease. We judged the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

Results We found 18 cohorts, involving 2 272 642 participants and 2905 cases, and 8 case–control studies, involving 1825 cases and 4652 controls. An extra two cups per day of coffee was associated with a 35% reduction in the risk of HCC (RR 0.65, 95% CI 0.59 to 0.72). The inverse association was weaker for cohorts (RR 0.71, 95% CI 0.65 to 0.77), which were generally of higher quality than case–control studies (RR 0.53, 95% CI 0.41 to 0.69). There was evidence that the association was not significantly altered by stage of liver disease or the presence/absence of high alcohol consumption, high body mass index, type 2 diabetes mellitus, smoking, or hepatitis B and C viruses. An extra two cups of caffeinated and decaffeinated coffee (2 and 3 cohort studies, respectively) were associated with reductions of 27% (RR 0.73, 95% CI 0.63 to 0.85) and 14% (RR 0.86, 95% CI 0.74 to 1.00) in the risk of HCC. However, due to a lack of randomised controlled trials, potential publication bias and there being no accepted definition of coffee, the quality of evidence under the GRADE criteria was 'very low'.

Conclusions Increased consumption of caffeinated coffee and, to a lesser extent, decaffeinated coffee are associated with reduced risk of HCC, including in pre-existing liver disease. These findings are important given the increasing incidence of HCC globally and its poor prognosis.

Strengths and limitations of this study

- This is the first meta-analysis to calculate the relative risks (RRs) of hepatocellular carcinoma (HCC) for 1–5 cups of coffee per day, which may be useful in the design of a coffee-based intervention for evaluation in a clinical trial.
- This is the first meta-analysis to investigate the influence of all the main HCC risk factors on the association between coffee and HCC.
- This is the first meta-analysis to calculate the RR of HCC for decaffeinated coffee consumption.
- There was heterogeneity between the studies included in the meta-analysis.
- Many studies did not specify coffee caffeine content.

INTRODUCTION

Primary liver cancer is the sixth most commonly diagnosed cancer worldwide, and because of its poor prognosis the second leading cause of cancer death.[1 2] Hepatocellular carcinoma (HCC) is the dominant histological subtype accounting for 85%–90% of cases.[3] HCC most commonly develops in people with cirrhosis due to chronic viral hepatitis B (HBV) or hepatitis C (HCV), excess alcohol consumption, and/or non-alcoholic fatty liver disease.[3] Non-alcoholic steatohepatitis (NASH), which is rapidly increasing worldwide, can lead to the development of HCC in the absence of cirrhosis.[4] The incidence of liver cancer is increasing due to changes in these underlying risks, and by 2030 the number of new cases annually will have risen by around 50% to over 1.2 million.[5] The burden of liver cancer is highest in East and South-East Asia, with China alone accounting for 50% of cases worldwide.[2] Only 10%–37% of patients diagnosed with HCC are eligible for potentially curative tumour resection (partial hepatectomy).[6] Thus, prognosis remains poor, with a 5-year overall survival rate of 18%.[7]

Coffee is a popular drink in most countries, with approximately 2.25 billion cups consumed daily.[8] It is a complex mixture of biologically active molecules, including caffeine, chlorogenic acid and diterpenes.[9]

These compounds possess antioxidant, anti-inflammatory, antifibrotic and anticarcinogenic properties, which may explain the observational data that coffee drinkers have lower rates of chronic liver disease (CLD), including fibrosis, cirrhosis and HCC.[10] Reports by the World Cancer Research Fund (WCRF)[11] and the International Agency for Research on Cancer (IARC)[12] are both supportive of a protective role of coffee against HCC. In addition, a recent meta-analysis reported that the relative risk (RR) of HCC for an extra cup of coffee per day was 0.74 (95% CI 0.65 to 0.83).[13] However, to date no randomised controlled trials (RCTs) investigating a coffee intervention for preventing HCC have been performed. Challenges in designing such a trial include a lack of understanding of the effect modification by aetiology or risk factors for HCC (eg, alcohol liver disease, NASH, cirrhosis, etc). In addition, there is uncertainty as to whether all types of coffee are equally beneficial, especially given their differing chemical compositions (eg, caffeinated vs decaffeinated coffee). To help address these challenges, we have now explored, for the first time in a meta-analysis, the modification of the inverse association between coffee and HCC by key risk factors, such as HBV/HCV, high body mass index (BMI), type 2 diabetes mellitus (T2DM), smoking, alcohol consumption and the presence of CLD including cirrhosis. We also report the first meta-analysis for the association between decaffeinated coffee and HCC. Decaffeinated coffee protects against liver damage in animal studies[14] and is inversely associated with T2DM, abnormal liver function tests and cirrhosis in human observational studies.[15–17]

METHODS

The methods used were similar to those described in our earlier work[18] and are detailed below. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines; a protocol, which was prespecified but not preregistered online, is provided as online supplementary file information.

Searches and selection of studies

We performed searches of abstracts and titles in Web of Science, Embase and PubMed with the following: ('odds' OR 'risk' OR 'hazard' OR 'OR' OR 'RR' OR 'HR') AND 'coffee' AND ('liver' OR 'hepatocellular*') AND ('cancer 'OR 'carcino*' OR 'neoplas*'). The searches were run in September 2015 without restriction of date of publication. References of pertinent studies were searched manually. After removing duplicates, OK and RB independently screened the titles and abstracts of the studies found in the search. Studies that were included (1) reported an RCT, case–control study or cohort study; and (2) reported HRs, ORs or RRs with 95% CIs for HCC in adults according to consumption of coffee. Studies that were excluded (1) did not report a dose–response or give sufficient information for calculation of a dose–response (ie, this requires estimates for more than two exposure levels, or (ii) were non-English-language studies. We assumed cases of primary liver cancer to be HCC. If studies overlapped, we included the largest study or otherwise the last published study. We worked from published studies only, including abstracts, although we unsuccessfully attempted to acquire unpublished data from the authors of one study, as indicated below.

Extraction of data and assessment of quality

We extracted the following information from each study: the first author, the date of publication, the geographic region, the design of the study, the exclusion and inclusion criteria, the estimates and adjustments, the numbers of participants (or controls) and cases, the methods of measuring exposure, and case identification. We also extracted data concerning cohort follow-up (time, losses) and whether baseline liver disease was excluded. We extracted the most rigorously adjusted effect sizes. We extracted effect sizes stratified by pre-existing CLD, smoking status, alcohol consumption, BMI, HBV and HCV status, T2DM, and type of coffee. OK extracted the data, which RB then checked. Given the low incidence of HCC, we considered ORs, RRs and HRs to be equivalent, and for simplicity we used RR to refer to all three herein. We assessed the quality of the included studies using the Newcastle-Ottawa Scale.[19] We judged the quality of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[20]

Statistical methods

Coffee and HCC

Most studies did not distinguish caffeinated versus decaffeinated coffee, so coffee was taken to be the pattern of use prevalent in the particular study population. We considered consumption in cups, where necessary[21] converting millilitres into cups of 150 mL. For each study, we calculated an RR for an extra two cups per day using dose–response data where available[22 23] or by estimating the dose–response using the method of Greenland and Longnecker.[24] The unit of an 'extra two cups' per day was selected to represent a potential coffee-based intervention, which could be used in clinical trials, and to maintain comparability with a previous meta-analysis.[25] We estimated the median consumption for each reported consumption category to be the midpoint of closed ranges and the midpoint added to the amplitude of the previous range for open ranges.[25] We assessed whether the dose–response was non-linear by a cubic spline meta-analysis.[26] We tested for statistical heterogeneity using I^2 and Cochran's Q,[27] and interpreted p values of <0.1 as statistically significant (for heterogeneity only), and we interpreted the I^2 values according to chapter 9.5.2 of the Cochrane handbook.[27] We investigated heterogeneity by meta-regression and examined the impact of individual studies by rerunning the analysis while leaving the studies out one at a time.[28] We tested for publication bias using Egger's test and a 'trim-and-fill' analysis,[29] which we used to adjust the estimate for missing studies if publication

bias was indicated. To assess the magnitude and direction of adjustment, we calculated a pooled unadjusted effect sizes for comparison with the corresponding adjusted effect size. We used random-effects models (DerSimonian-Laird) and a two-sided p value >0.05 for statistical significance. We used R (R Foundation for Statistical Computing, Vienna, Austria) with the metafor[30] and dosresmeta[31] packages for the analyses.

Effect modification by risk factors

We calculated the RRs of HCC according to coffee consumption in participants stratified by baseline CLD. We also calculated and meta-analysed RRs stratified by exposure to each of viral hepatitis status (carriers of HBV/HCV vs negative for both), BMI (highest vs lowest BMI categories), T2DM (presence vs absence), alcohol consumption (highest vs lowest categories) and smoking (current smoker vs ex/non-smoker). For these analyses, we only included studies that provided RRs for both exposed and non-exposed to the risk factors. Where available,[22 23] we used dose–response data to calculate RRs for an increase in two cups of coffee per day. Otherwise, we used the Greenland and Longnecker method,[24] where the number of exposed and non-exposed was provided[32–35] and variance-weighted least squares regression where they were not.[36–39] For each risk factor, we calculated a p value for its modifying effect on the association between coffee and HCC by meta-analysing the differences between the exposed and unexposed RRs from each study. We also calculated the τ^2 for each of these analyses.

Caffeinated and decaffeinated coffee and HCC

Where possible we extracted data separately for caffeinated and decaffeinated coffee and calculated pooled RRs of HCC per two extra cups per day of each. One study, Bamia *et al*,[21] reported RRs of HCC according to decaffeinated coffee consumption for three qualitative categories: 'non-consumers', 'consumers below the median' and 'consumers at/above the median'. We were unable to get the corresponding quantitative values after contacting the authors, so we used those reported by another publication investigating the effect of decaffeinated coffee on oesophageal cancer in the same cohort.[40] As above, we used dose–response data where available.[22] Otherwise, we calculated the dose–response using the Greenland and Longnecker method,[24] where the number of exposed and non-exposed[15] was available and variance-weighted least squares regression where they were not.[21]

RESULTS

Coffee consumption and HCC

Figure 1 shows the searches and the stages of the selection of studies. Once duplicates were removed, we screened the abstracts and titles of 181 studies. Of those, we reviewed 34 studies in their entirety. Tables 1A and 1B summarise the characteristics of the 16 studies that we included in the main meta-analysis.[15 21–23 32 33 35–39 41–45] The studies were published between 2002 and 2015. Seven were from Europe, five from Japan, two from the USA and one from each of Hong Kong and Singapore. The cohort studies primarily involved general populations (eg, randomly selected from population registries), except for Lai *et al*,[23] which included male smokers only. Total follow-ups ranged from 7[39] to 24 years,[23] and linkage to cancer registries was generally used to identify cases and exclude baseline HCC. The case–control studies were hospital-based, with only one[33] using community controls. Fifteen studies reported estimates according to 'coffee' consumption, while two and four studies, respectively, reported estimates specifically for caffeinated and decaffeinated coffee. The quality scores ranged from 4 to 8 (tables 1A and 1B) and were generally higher for cohorts (mean=6.9) compared with case–control studies (mean=5.0). A number of studies reported data from multiple cohorts or case–control studies. We extracted pooled estimates from Petrick *et al*[22] (nine cohorts) and Gallus *et al*[37] (two case–control studies) as equivalent study-specific estimates (eg, in terms of adjustments for confounders and categories of coffee consumption) were not available. We extracted separate RRs from Shimazu *et al*[39] (two cohorts). Thus, this meta-analysis included data from 18 cohorts, involving 2 272 642 participants and 2905 cases, and 8 case–control studies, involving 1825 cases and 4652 controls.

The RRs of HCC according to coffee consumption are summarised in table 2, including adjustments for confounders. Most studies adjusted for age, alcohol and smoking, and a smaller number for HBV/HCV, BMI and T2DM. All the studies showed an inverse association between HCC for an extra two cups of coffee per day, although in four studies the relationship was not statistically significant. The pooled RR of HCC for an extra two cups per day across all studies for coffee was 0.65 (95% CI 0.59 to 0.72) (figure 2), for cohort studies it was 0.71 (95% CI 0.65 to 0.77) and for case–control studies 0.53 (95% CI 0.41 to 0.69). The pooled RR from studies with a quality score of 6 or above was 0.70 (95% CI 0.64 to 0.76) compared with 0.50 (95% CI 0.35 to 0.70) for those scoring below 6. The p value for non-linearity of the dose–response was not statistically significant, and the pooled RRs for different levels of consumption of up to five cups per day are illustrated in figure 3. Adjustment for confounders had minimal effect, changing the pooled RR from 0.62 (95% CI 0.53 to 0.72) (ie, unadjusted) to 0.65 (95% CI 0.59 to 0.72).

Heterogeneity and sensitivity analysis

The I^2 and the p value for Cochran's Q were 58.5% and <0.01, respectively (figure 2), which indicated 'moderate' to 'substantial' between-study heterogeneity. Heterogeneity was lower for cohorts (I^2=40.7%; p=0.09) than case–control studies (I^2=64.3%; p<0.01). In the sensitivity analysis, the RR was strongest when we excluded Hu *et al*[38] (RR 0.63, 95% CI 0.56 to 0.71) and weakest when we excluded Tanaka *et al*[33] (RR 0.68, 95% CI 0.62 to 0.74). Heterogeneity remained statistically significant

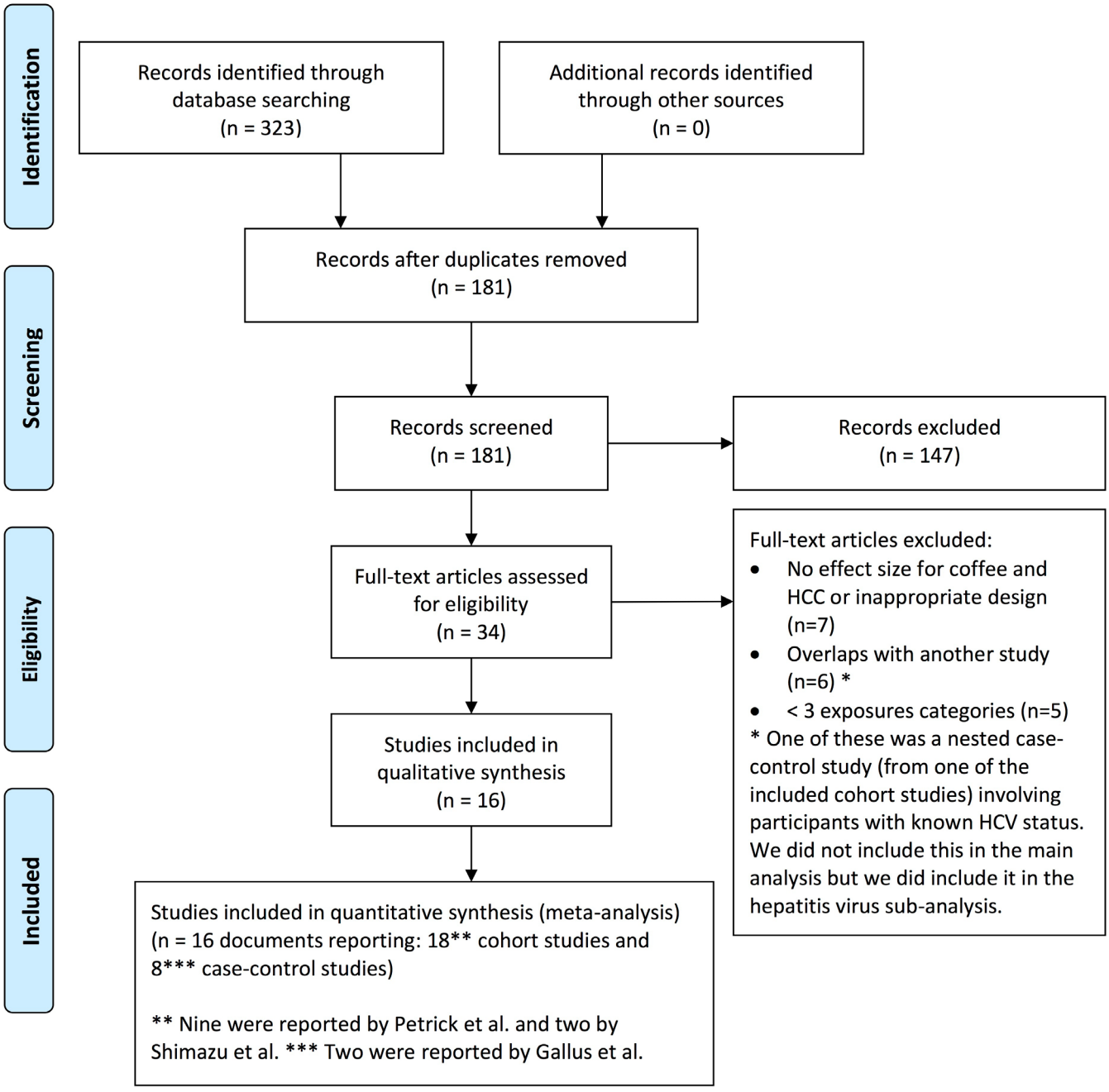

Figure 1 An illustration showing how the studies included in this meta-analysis were reviewed and selected. HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

throughout. In the meta-regression analysis, we found no statistically significant association of RR and publication year, length of follow-up (cohorts only), percentage of alcohol abstainers, age or gender.

Publication bias and quality of evidence

We found evidence of publication bias by Egger's test (p<0.0001) and visual inspection of the funnel plot as shown in figure 4. In our trim-and-fill analysis, we detected a number of 'missing' smaller studies. Calibration for missing studies pushed the effect size of coffee towards null from 0.65 (95% CI 0.59 to 0.72) to 0.71 (95% CI 0.64 to 0.79). The evidence quality that coffee protects against HCC as determined with GRADE was 'very low' (table 3).

The effect of pre-existing CLD and HCC risk factors

Three cohort studies[35 36 39] performed subgroup analyses stratified by presence/absence of baseline CLD, which was poorly defined but included cirrhosis. Data from two of those studies showed an inverse association of coffee and HCC in those with baseline CLD but not without, while the other showed an inverse association without baseline CLD only. The pooled difference between the stratified estimates was not statistically significant (p=0.87).

Table 1A Details of the cohort studies meeting the inclusion criteria

Cohort study	Country	Population characteristics (age)	Cohort (% men)	Baseline exposure ascertainment	Outcome	Outcome ascertainment	Follow-up years	Cases (rate/1000)	NOS quality score
Inoue *et al*[36]	Japan	Gen pop (40–69)*	90 452 (48)	FFQ	HCC	Cancer registry, death records, medical records	9.7 (average)	334 (3.7)	7
Kurozawa *et al*[35]	Japan	Gen pop (40–79)*; HCC deaths within first 2 years excluded	110 688 (42)	FFQ	HCC death	Death records	9–11 (total)	258 (2.3)	7
Shimazu *et al* (cohort 1)[39]	Japan	Gen pop (≥40)*	22 404 (47)	FFQ	PLC	Cancer registry, death records, medical records	9 (total)	70 (3.1)	6
Shimazu *et al* (cohort 2)[39]	Japan	Gen pop (40–64)*	38 703 (49)	FFQ	PLC	Cancer registry, death records, medical records	7 (total)	47 (1.2)	6
Hu *et al*[38]	Finland	Gen pop (25–74)*	60 323 (49)	FFQ	PLC	Cancer registry	19.3 (median)	128 (2.1)	8
Johnson *et al*[41]	Singapore	Gen pop (45–74)*	61 321 (44)	FFQ	HCC	Cancer registry and death records	NA	362 (5.9)	8
Lai *et al*[23]	Finland	Male smokers (50–69) from an RCT into lung cancer*; self-reported cirrhosis excluded at baseline	27 037 (100)	FFQ	LC	Cancer registry	18.2 (median)	194 (7.2)	6
Bamia *et al*[21]	Europe **	Gen pop (25–70)*	486 799 (30)	FFQ	HCC	Cancer registry, death records, health insurance records and mail/telephone	11 (median)	201 (0.4)	7
Setiawan *et al*[15]	USA	Gen pop (45–75)*	162 022 (47)	FFQ	HCC	Cancer registry	18 (median)	451 (2.8)	7
Petrick *et al*[22]	USA	Gen pop (<50–≥70)*	1 212 893 (41)	FFQ	HCC	Cancer registry, medical records, self-reporting	Variable	860 (0.7)	6

*Participants with a diagnosis of HCC were excluded at baseline.
**Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and UK.
FFQ, food frequency questionnaire; HCC, hepatocellular carcinoma; LC, liver cancer; NA, not applicable; NOS, Newcastle-Ottawa Scale; PLC, primary liver cancer; RCT, randomised controlled trial.

Table 1B Details of the case–control studies meeting the inclusion criteria

Case–control study	Country	Case selection	N (% men) and age of cases	Control selection	N (% men) and age of controls	Measurement of coffee consumption	Outcome	NOS quality score
Gallus *et al* (study 1)[37]	Italy	Hospital	501 (75) aged 20–75 (median 60)	Patients with non-cancer disorders in same hospital and from same catchment area	1552 (74) aged 18–75 (median 56)	FFQ	HCC	5
Gallus *et al* (study 2)[37]	Greece	Hospital	333 (85) aged 31–79 (median 65)	Patients with non-cancer disorders in same hospital	360 (83) aged 24–79 (median 65)	FFQ	HCC	5
Gelatti *et al*[42]	Italy	Hospital	250 (82) aged less than 80 (mean 63.8)	Patients without liver disease in same hospital	500 aged less than 80 (mean 64.1)	FFQ	HCC	7
Ohfuji *et al*[43]	Japan	Attending hospital for HCV follow-up	73 (47) (mean age 68.9)	Attending hospital for HCV follow-up	253 (52) (mean age 68.3)	FFQ	HCC	5
Tanaka *et al*[33]	Japan	Hospital	209 (68) aged 40–79 (mean 67)	Community controls randomly selected	1308 (50) (mean 57)	FFQ	HCC	4
Montella *et al*[32]	Italy	Hospital	185 (81) aged 43–84 (median 66)	Patients in same hospital	412 (68) aged 40–82 (median 65)	FFQ	HCC	5
Leung *et al*[45]	Hong Kong	Attending hospital for HBV follow-up	109 (79) aged ≤39 to ≥60	Attending hospital for HBV follow-up	125 (82) aged ≤39 to ≥60	FFQ	HCC	5
Stucker *et al*[44]	France	Hospital	165 (100) aged <75	Patients without liver disease in same hospital	142 (100) aged <75	FFQ	HCC	4

FFQ, food frequency questionnaire; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NOS, Newcastle-Ottawa Scale.

Table 2 The associations reported by the studies meeting the inclusion criteria for the main coffee–HCC meta-analysis

Study	Coffee (cups per day, unless specified)	Participants	Cases (cumulative rate/1000)	Adjusted RR (95% CI)	Adjustments
Cohort studies					
Inoue *et al*[36]	Almost never	29 423	161 (5.5)	1 (ref) *	Age, gender, alcohol, smoking, green tea, study area, green vegetable intake
	1–2/week	17 159	65 (3.8)	0.75 (0.56 to 1.01) *	
	3–4/week	10 316	36 (3.5)	0.79 (0.55 to 1.14) *	
	1–2	23 753	54 (2.3)	0.52 (0.38 to 0.73) *	
	3–4	7316	15 (2.1)	0.48 (0.28 to 0.83) *	
	≥5	2485	3 (1.2)	0.24 (0.08 to 0.77) *	
Kurozawa *et al*[35]	Non-drinkers	24 556	103 (4.2)	1 (ref) *	Age, gender, alcohol, smoking, T2DM, liver disease, education
	<1	15 259	57 (3.7)	0.83 (0.54 to 1.25) *	
	≥1	44 151	98 (2.2)	0.5 (0.31 to 0.79) *	
Shimazu *et al* (cohort 1)[39]	Never	4938	29 (5.9)	1 (ref)†	Age, gender, alcohol, smoking, liver disease
	Occasionally	9507	25 (2.6)	0.56 (0.33 to 0.97)†	
	≥1	7959	16 (2.0)	0.53 (0.28 to 1.00)†	
Shimazu *et al* (cohort 2)[39]	Never	6954	12 (1.7)	1 (ref)†	Age, gender, alcohol, smoking, liver disease
	Occasionally	14 130	21 (1.5)	1.05 (0.52 to 2.16)†	
	≥1	17 619	14 (0.8)	0.68 (0.31 to 1.51)†	
Hu *et al*[38]	0–1	6150	20 (3.3)	1 (ref) *	Age, gender, alcohol, smoking, T2DM, liver disease, education, BMI, study year
	2–3	12 681	30 (2.4)	0.66 (0.37 to 1.16) *	
	4–5	17 991	33 (1.8)	0.44 (0.25 to 0.77) *	
	6–7	13 726	28 (2.0)	0.38 (0.21 to 0.69) *	
	≥8	9775	17 (1.7)	0.32 (0.16 to 0.62) *	
Johnson *et al*[41]	Non-drinkers	119 973 (PY)	69	1 (ref) *	Age, gender, alcohol, smoking, T2DM, education, BMI, dialect group, year of recruitment, black and green tea
	0–<1	70 762 (PY)	38	0.94 (0.63 to 1.40) *	
	1–<2	236 215 (PY)	149	1.17 (0.87 to 1.56) *	
	2–<3	190 567 (PY)	92	0.78 (0.56 to 1.07) *	
	≥3	37 505 (PY)	14	0.56 (0.31 to 1.00) *	
Lai *et al*[23]	Never drinkers	667	9 (13.5)	1.35 (0.65 to 2.82)†	Age, alcohol, smoking, T2DM, education, BMI, tea, cholesterol, marital status, ATBC intervention arm§
	>0 to <1	3094	36 (11.6)	1 (ref)†	
	1 to <2	7204	60 (8.3)	0.73 (0.48 to 1.12)†	
	2 to <3	8086	47 (5.8)	0.52 (0.33 to 0.82)†	
	3 to <4	4515	22 (4.9)	0.45 (0.26 to 0.78)†	
	≥4	3471	20 (5.8)	0.53 (0.30 to 0.95)†	
	per extra cup			0.82 (0.73 to 0.93)†	
Bamia *et al*[21]	Quintile 1	98 148	47 (0.5)	1 (ref) *	Stratified for age and centre; adjusted for gender, alcohol, smoking, T2DM, education, BMI, physical activity, energy intake, tea
	Quintile 2	100 953	49 (0.5)	0.85 (0.56 to 1.29) *	
	Quintile 3	95 231	38 (0.4)	0.63 (0.39 to 1.02) *	
	Quintile 4	96 413	36 (0.4)	0.49 (0.29 to 0.82) *	
	Quintile 5	96 054	31 (0.3)	0.28 (0.16 to 0.5) *	
Setiawan *et al*[15]	Never	44 438	119 (2.7)	1 (ref)*	Age, gender, alcohol, smoking, T2DM, education, BMI, race
	<1	31 056	111 (3.6)	1.14 (0.88 to 1.48)*	
	1	45 717	137 (3.0)	0.87 (0.67 to 1.11)*	
	2–3	32 593	67 (2.1)	0.62 (0.46 to 0.84)*	
	≥4	8218	17 (2.1)	0.59 (0.35 to 0.99)*	

Continued

Table 2 Continued

Study	Coffee (cups per day, unless specified)	Participants	Cases (cumulative rate/1000)	Adjusted RR (95% CI)	Adjustments
Petrick *et al*[22]	Non-drinker >0to <1 1 to <2 2 to 3 >3 per extra cup	172 950 164 977 179 781 370 786 161 116	85 (0.5) 138 (0.8) 149 (0.8) 255 (0.7) 97 (0.6)	1 (ref)* 1.24 (0.94 to 1.64)* 1.16 (0.88 to 1.52)* 0.89 (0.68 to 1.15)* 0.73 (0.53 to 0.99)* 0.90 (0.85 to 0.94)*	Age, gender, alcohol, smoking, BMI, race, cohort
Case–control studies		Cases	Controls		
Gallus *et al* (Italian and Greek studies combined)[37]	Non-drinkers 1 2 ≥3	129 231 292 178	256 432 582 637	1 (ref)‡ 1.2 (0.9 to 1.6)‡ 1.0 (0.7 to 1.3)‡ 0.7 (0.5 to 1.0)‡	Age, gender, alcohol, smoking, education, BMI, T2DM, hepatitis, study
Gelatti *et al*[42]	No consumption 1–2 3–4 ≥5	44 119 69 18	59 206 163 72	1 (ref)‡ 0.8 (0.4 to 1.3)‡ 0.4 (0.2 to 0.8)‡ 0.3 (0.1 to 0.7)‡	Age, gender, alcohol, HBV, HCV
Ohfuji *et al*[43]	Non-drinkers <1 ≥1	25 19 29	63 74 116	1 (ref)‡ 0.61 (0.18 to 2.03)‡ 0.38 (0.13 to 1.12)‡	Alcohol, smoking, BMI, duration of liver disease, disease severity, family history, interferon therapy, other caffeinecontaining beverage
Tanaka *et al*[33]	None Occasional 1–2 ≥3	127 53 17 12	268 496 268 221	1 (ref)‡ 0.33 (0.22 to 0.48)‡ 0.27 (0.15 to 0.48)‡ 0.22 (0.11 to 0.43)‡	Age, gender, alcohol, smoking, HBV, HCV
Montella *et al*[32]	Abstainers <14/week 14–20 21–27 ≥28	27 67 50 27 14	41 116 104 88 63	2.28 (0.99 to 5.24)‡ 1 (ref)‡ 0.54 (0.27 to 1.07)‡ 0.57 (0.25 to 1.32)‡ 0.43 (0.16 to 1.13)‡	Age, gender, alcohol, smoking, education, centre, HBV, HCV
Leung *et al*[45]	No coffee habit 1–3/week ≥4 week	86 11 12	82 17 26	1 (ref)‡ 0.58 (0.24 to 1.36)‡ 0.41 (0.19 to 0.89)‡	Age, gender, alcohol, smoking, tea, physical activity
Stucker *et al*[44]	0–1 2 >2	92 45 28	57 37 48	1 (ref)‡ 0.67 (0.3 to 1.3)‡ 0.36 (0.2 to 0.7)‡	Alcohol

*Reported as HR.
†Reported as RR.
‡Reported as OR.
§Participants were from another trial investigating vitamin E supplementation in the form of ATBC.
ATBC, α-tocopherol or β-carotene; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PY, person years; RR, relative risk; T2DM, type 2 diabetes mellitus.

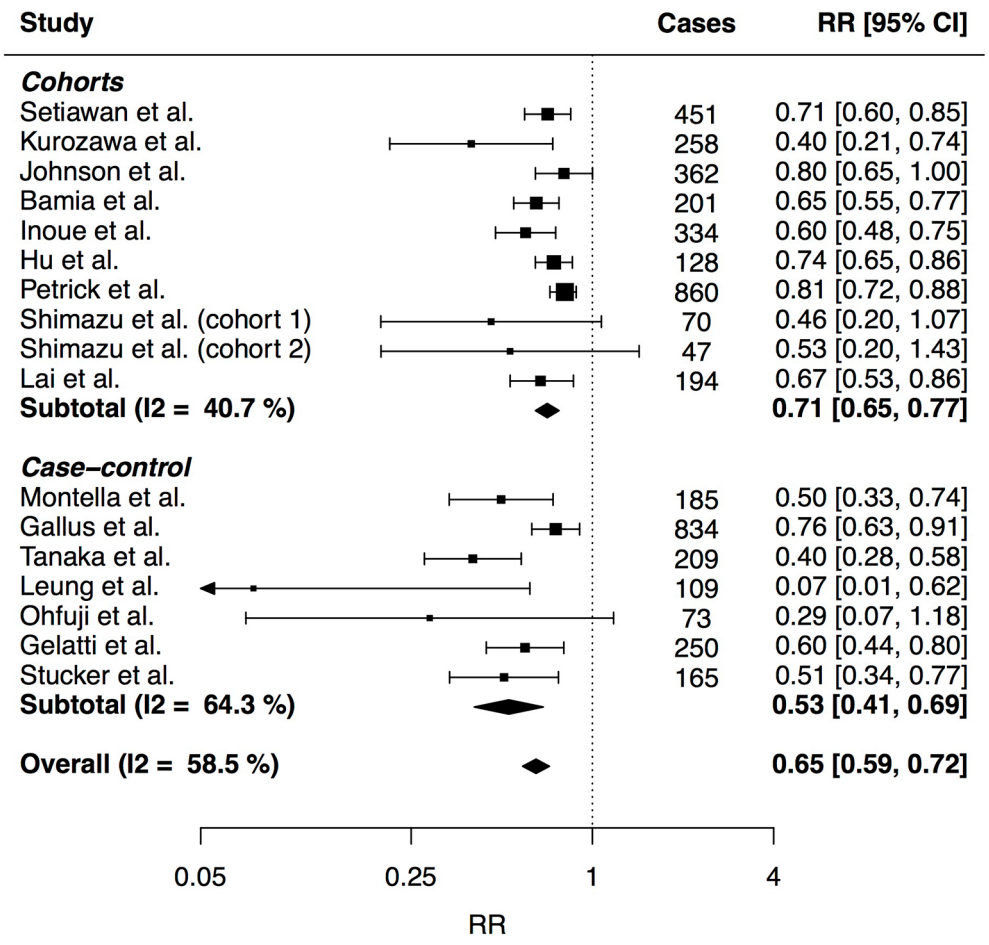

Figure 2 A forest plot illustrating RRs of HCC for an extra two cups of coffee per day. The RRs as reported by the individual studies are shown as squares. The sizes of the squares represent the weightings in the random-effects model. The pooled RRs (from cohorts, case–control studies and all studies) are shown as diamonds. HCC, hepatocellular carcinoma; RR, relative risks.

Data from a fourth (case–control) study[33] showed statistically significant inverse associations between coffee and HCC, both when cases were compared with community controls and controls with CLD, 22% of whom had cirrhosis. Three other case–control studies[37 43 45] showed inverse associations between coffee and HCC using only controls with liver disease.

Results from the investigation into the influence of risk factors on the association between coffee and HCC are presented as online supplementary file information. In summary, there was no statistically significant difference in the associations between coffee and HCC according to viral hepatitis status, smoking, BMI, T2DM or alcohol consumption.

Caffeinated and decaffeinated coffee

Four studies reported RRs of HCC specifically for decaffeinated coffee consumption.[15 21 22 32] No single study reported a statistically significant association between HCC and decaffeinated coffee consumption. Three cohort studies,[15 21 22] involving approximately 750 000 participants and 800 cases, reported dose–response RRs or RRs for >2 consumption categories. The pooled RR of HCC for two extra cups per day was 0.86 (95% CI 0.74 to 1.00; three studies). Only two studies, involving approximately 850 000 participants and 900 cases, reported RRs of HCC according to caffeinated coffee consumption in a manner suitable for dose–response analysis.[15 22] The pooled RR of HCC for an extra two cups of caffeinated coffee was 0.73 (95% CI 0.63 to 0.85).

DISCUSSION

In our meta-analysis of 18 cohort studies, involving 2 272 642 participants and 2905 cases, and 8 case–control studies, involving 1825 cases and 4652 controls, increasing coffee consumption by two cups per day was associated with a 35% reduction in the risk of HCC (RR 0.65; 95% CI 0.59 to 0.72). This is similar to previous meta-analyses.[13 25] In a subset of studies, the association was not significantly different in participants with pre-existing CLD at baseline, some of whom had cirrhosis. This is an important finding as the absolute risk of HCC in cirrhosis is high but may be more than halved by five cups per day of coffee compared with none (figure 3). The association was also not significantly different for the main exposures

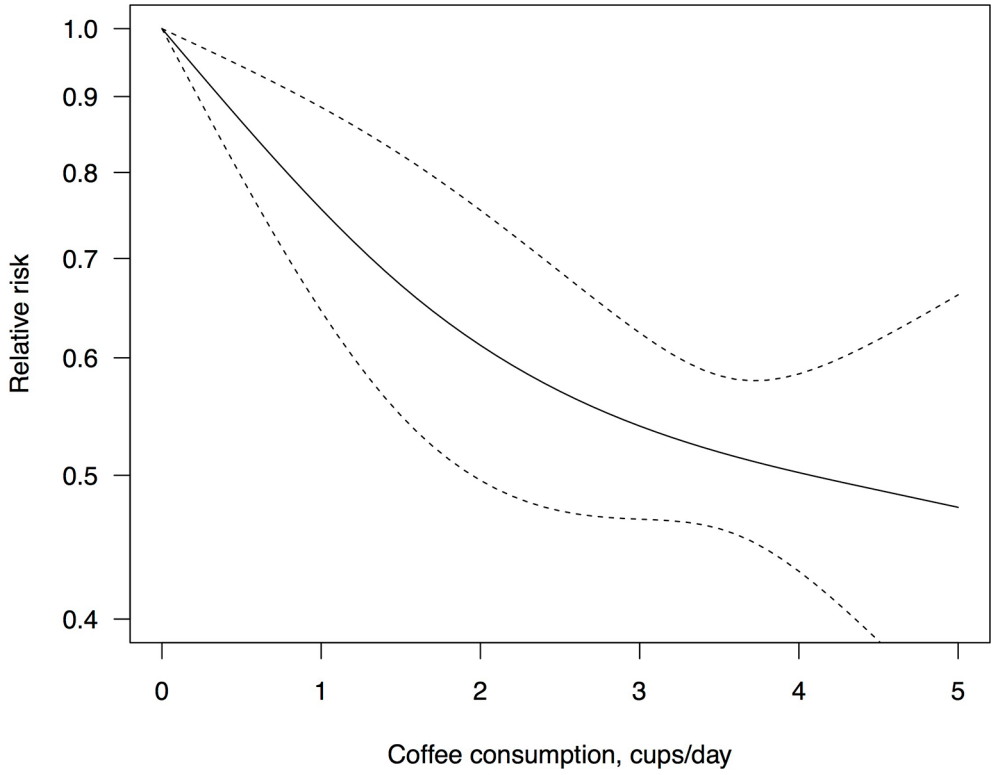

Figure 3 Results of a cubic spline dose–response meta-analysis of the association between coffee and hepatocellular carcinoma.

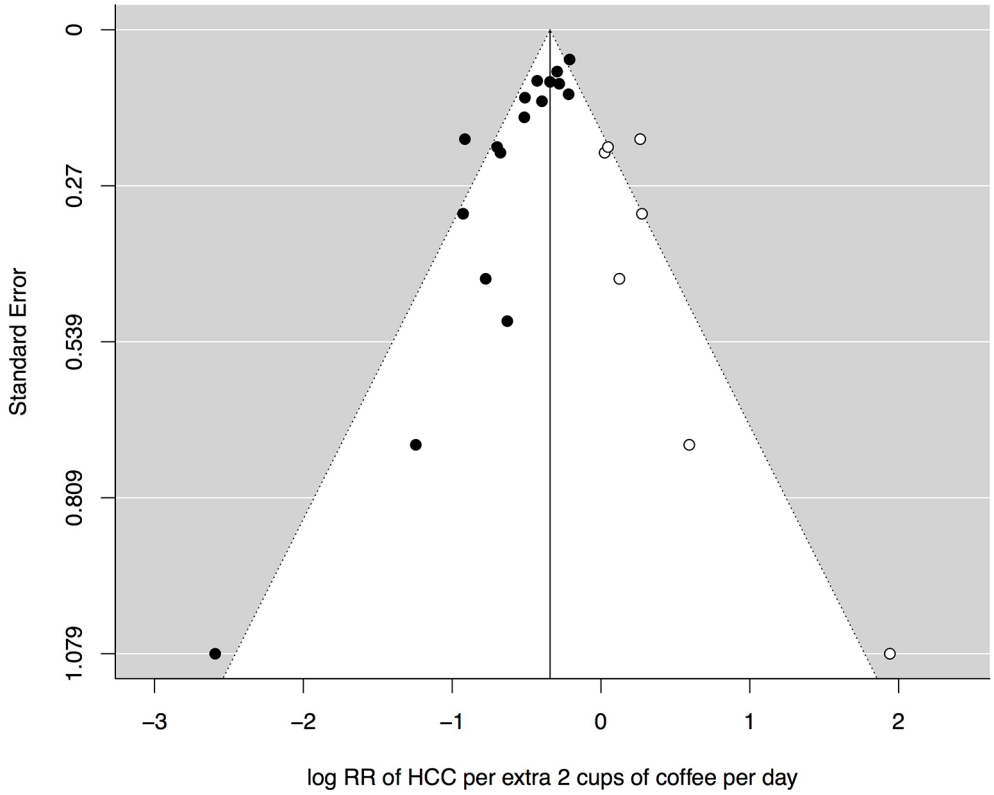

Figure 4 Filled funnel plot for the risk of HCC per extra two cups of coffee daily. Black circles represent the included studies found by our search, while white circles represent the 'missing' unpublished studies detected in the trim-and-fill analysis. HCC, hepatocellular carcinoma; RR, relative risk.

Table 3 GRADE summary of findings table

An extra two cups of coffee per day for preventing HCC

Patient or population: risk of HCC
Setting: primary/secondary care
Intervention: two extra cups of coffee per day
Comparison: usual coffee consumption

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no coffee	Risk with coffee				
HCC assessed with: cancer registries, death records and medical records	High 50 per 1000	33 per 1000 (30 to 36)	RR 0.65 (0.59 to 0.72)	1825 cases, 2905 controls, 2115/1 683 071 exposed, 654/399 566 unexposed (26 observational studies)	⊕◯◯◯ VERY LOW†	The RR corresponds to two extra cups of coffee per day.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†The quality of evidence rating was downgraded because of (1) risk of bias, (2) indirectness and (3) publication bias.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCC, hepatocellular carcinoma.

for HCC: high alcohol consumption, smoking, high BMI, T2DM and HBV/HCV.[46] Data from the few studies that specified coffee type showed that increasing caffeinated and decaffeinated coffee consumption by two cups per day was associated with reductions of 27% (RR 0.73, 95% CI 0.63 to 0.85) and 14% (RR 0.86, 95% CI 0.74 to 1.00) in the risk of HCC. This is the strongest evidence to date of an association between decaffeinated coffee and HCC. It may be important for developing coffee as a lifestyle intervention in CLD, as decaffeinated coffee might be more acceptable to those who do not drink coffee or who limit their coffee consumption because of caffeine-related symptoms. However, the benefits of decaffeinated coffee appear to be smaller and less certain than for caffeinated coffee.

Other major strengths of this meta-analysis are the systematic approach used to calculate a dose–response between coffee and HCC and the inclusion of a large number of participants and cases, representing a range of demographic groups (eg, gender, nationality, etc) and the main risk factors for HCC. We did not detect effect modification by baseline CLD and HCC aetiology, although our analysis was limited by the small number of studies that provided the necessary data for these analyses.

The main limitation is that all the included studies were observational, and thus we cannot infer causation. Observational studies are susceptible to bias and confounding, and case–control studies are at particular risk of selection and information bias. In the case–control studies, cases were mostly from hospital admissions or clinic records, which may not be representative of all HCC. Not all patients with HCC are admitted to hospitals, and individual factors associated with likelihood to attend clinic and/or to participate in a research study may be associated with coffee consumption or other risk factors (and confounders) for HCC. In addition, because of the need to interview participants, dead cases were not included.

The use of hospital controls in all except one study may also have introduced bias. First, there are associations between coffee drinking and a large number of other health conditions.[47] Second, hospitals vary in the scale of their catchment areas and so hospital controls may not be representative of the populations from which cases arose, especially in areas where HCC care is highly specialised.

Among the cohorts, some studies used primary liver cancer as an outcome, whereas others used HCC. All but one cohort study used cancer registries to identify cases, sometimes in combination with death records. Cancer registries are more robust for ascertainment than death records.

Residual confounding likely existed in all studies from hidden factors and misclassification of measured confounders. However, adjustment for confounders had minimal effect on the association between coffee and HCC, suggesting residual effects will be small. All studies adjusted for alcohol, but several did not adjust for BMI, T2DM and HBV/HCV. Coffee was associated with alcohol in some studies, so failure to capture alcohol robustly

might underestimate the inverse association between coffee and HCC.[15 41] The cohorts generally did not adjust for HBV/HCV despite it being a major risk factor for HCC, but prevalence was likely low and we found no evidence of an effect of HBV/HCV infection on the association between coffee and HCC.

The measurement of coffee consumption may also have introduced bias in case–control studies due to recall bias. Belief that coffee was harmful may have led to overestimation of consumption in cases. However, cases may have reduced coffee consumption because liver disease slows caffeine metabolism.[48] One study used for baseline the consumption at 2 years before HCC diagnosis,[32] when decades before may have been more appropriate. Another study[43] reported RRs of HCC according to consumption preidentification and postidentification of liver disease; the weaker preidentification estimates were used in the meta-analysis, with minimal effect on the overall pooled RR.

In the cohorts, baseline CLD may have been present in cases given the short follow-up time of some cohorts compared with the long time for HCC to develop. However, we looked at a number of cohorts that presented data stratified by baseline CLD status and found no significant effect on the association between coffee and HCC. Setiawan *et al* found that the RR of HCC for two or more cups of coffee daily compared with none remained comparable in magnitude and statistically significant when deaths in the first 2 years were excluded. Lai *et al* found that the RR of HCC for an extra cup of coffee per day was 0.81 (95% CI 0.66 to 0.98) in the first 10 years and 0.83 (95% CI 0.71 to 0.96) in the final 10 years of the study. Bamia *et al*,[21] Hu *et al*[38] and Shimazu *et al*[39] reported similar findings. Thus, drinking coffee appeared to protect against HCC in participants with varying levels of undiagnosed CLD at baseline.

Our method of estimating median consumption in the reported consumption categories may have exaggerated the effect size. There was also a lack of data in most individual studies for higher levels of coffee consumption (eg, five cups per day or above). As a result, we had limited ability to detect an upper threshold beyond which increasing consumption no longer provides any benefit with regard to the risk of HCC. This is evident from figure 3, which shows rapidly widening CIs above four cups of coffee per day.

There was statistically significant heterogeneity between the studies; in a meta-regression analysis, it was not significantly associated with publication year, length of follow-up (cohorts only), percentage of alcohol abstainers, age or gender of participants.

Heterogeneity might be due to how consumption of coffee was measured. The included studies asked participants to estimate coffee consumption, usually by selecting from a list of predefined categories in food frequency questionnaires. Different categories may have influenced participants' responses. There may be variation in the size of cups, preparation (eg, boiled vs filtered) and caffeine content; 'coffee' was taken to be the pattern of use prevalent in the particular study population. Proportions of decaffeinated coffee drinkers varied markedly and were very low in certain countries (eg, Japan and Finland).[33 38] Higher proportions of decaffeinated coffee drinkers, such as in the USA,[22] may have attenuated the overall effect size given the weaker association found here between decaffeinated coffee and HCC.

Language bias cannot be excluded as we only included English studies, although studies found in the search were mostly in English. Generally, evidence of a significant influence in meta-analyses of language bias is weak.[49] Studies published in non-English journals may also be less rigorous and report bigger effect estimates.[50] Thus, our inclusion of English studies only is not likely to have introduced significant bias. Finally, we found evidence of publication bias using Egger's test. Adjusting for smaller unpublished studies pushed the effect size towards null, but it remained statistically significant.

Our study adds to the weight of evidence considered by the IARC and WCRF that coffee is protective against HCC. However, when assessed under the GRADE criteria, the quality of evidence supporting coffee for the prevention of HCC was still 'very low'. This was mainly because of the lack of randomised trials, evidence of publication bias, and the fact that 'coffee', which has various formulations with different chemical properties, is not well defined.

Mechanism of action

As discussed in detail in previous work,[18 51] there is biological plausibility of a protective effect of coffee against HCC. The fact that we found no significant effect of aetiology albeit in a subset of studies suggests that the apparent protective mechanism acts via a common pathway, such as the development of cirrhosis. Eighty to ninety per cent of cases of HCC develop on a background of cirrhosis,[51] and several studies and a meta-analysis have reported an inverse association between coffee and cirrhosis.[18] Coffee may possess direct anticarcinogenic properties, which is supported by our finding that the association of coffee and HCC was seen in those with pre-existing CLD, including cirrhosis. Our findings suggest a central role for caffeine, given that the association was weaker for decaffeinated coffee. Caffeine reduces HCC cell proliferation.[52] Cafestol and kahweol increase activity of phase 2 liver enzymes, which may improve metabolism and excretion of carcinogens,[53 54] and compounds including polyphenols may ameliorate oxidative DNA damage. However, cafestol and kahweol are present only in minimal quantities in instant and filtered coffee,[55] and these varieties are popular in Japan and Finland, respectively, where studies included in this meta-analysis show inverse associations with HCC.[33 38] Other specific mechanisms of protection might include inhibition of hepatitis virus activity[56] and prevention of T2DM.[38]

Coffee purportedly possesses a range of health effects in addition to those on the liver, including lower incidences

of neurological diseases, various cancers and any-cause mortality.[47] However, randomised trials are needed of interventions to support patients at risk of HCC to increase coffee consumption before recommending an increase given the examples in other areas of where RCTs have shown observational data to be incorrect and the global scale and ubiquity of coffee consumption.[57] The potential harms of coffee also require further investigation, including the reported increased risk of lung cancer and bone fractures[47] and the deleterious effect on cholesterol, which could potentially exacerbate the already increased risk of CVD associated with certain types of liver disease.[58]

In summary, this study has shown that an extra two cups of coffee per day is associated with a one-third reduction in the RR of HCC. Our findings are significant given the increasing incidence of HCC and the overall poor prognosis of this condition. Randomised trials should investigate the effectiveness of increasing coffee consumption in those at risk of HCC including patients with existing CLD.

Contributors The study was conceived by all authors; The search was performed by OK. The studies were reviewed and selected by RB and OK. The quality of evidence assessment was performed by OK. The risk of bias assessment was performed by JP and OK. The data were extracted and checked by OK and RB, respectively. The statistical analysis was performed by OK. The manuscript was drafted by OK and reviewed and amended by all authors. JP is guarantor.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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