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

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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 2,905 cases, and 8 case–control studies, involving 1,825 cases and 4,652 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.

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.5 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.
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. Reports by the World Cancer Research Fund (WCRF) and the International Agency for Research on Cancer (IARC) 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). 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 and is inversely associated with T2DM, abnormal liver function tests and cirrhosis in human observational studies.

**METHODS**

The methods used were similar to those described in our earlier work 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 ‘carcinoma’* OR ‘neoplasia’*). 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. We judged the quality of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

**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 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 or by estimating the dose–response using the method of Greenland and Longnecker. 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. 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. We assessed whether the dose–response was non-linear by a cubic spline meta-analysis. We tested for statistical heterogeneity using I² and Cochran’s Q and interpreted p values of <0.1 as statistically significant (for heterogeneity only), and we interpreted the I² values according to chapter 9.5.2 of the Cochrane handbook. 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. We tested for publication bias using Egger’s test and a ‘trim-and-fill’ analysis, 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 size 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 and dosresmeta 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, 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, where the number of exposed and non-exposed was provided, and variance-weighted least squares regression where they were not. 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 t² 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, 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. As above, we used dose–response data where available. Otherwise, we calculated the dose–response using the Greenland and Longnecker method, where the number of exposed and non-exposed was available and variance-weighted least squares regression where they were not.

**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. 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, which included male smokers only. Total follow-ups ranged from 7 to 24 years, 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 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 (nine cohorts) and Gallus et al (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 (two cohorts). Thus, this meta-analysis included data from 18 cohorts, involving 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 I² 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 (I²=40.7%; p=0.09) than case–control studies (I²=64.3%; p<0.01). In the sensitivity analysis, the RR was strongest when we excluded Hu et al (RR 0.63, 95% CI 0.56 to 0.71) and weakest when we excluded Tanaka et al (RR 0.68, 95% CI 0.62 to 0.74). Heterogeneity remained statistically significant.
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 studies35-36 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).

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**Figure 1** An illustration showing how the studies included in this meta-analysis were reviewed and selected. HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
## 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)* | 90452 (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 | 110688 (42) | FFQ | HCC death | Death records | 9–11 (total) | 258 (2.3) | 7 |
| Shimazu et al (cohort 1)\(^{29}\) | Japan | Gen pop (≥40)* | 22404 (47) | FFQ | PLC | Cancer registry, death records, medical records | 9 (total) | 70 (3.1) | 6 |
| Shimazu et al (cohort 2)\(^{29}\) | Japan | Gen pop (40–64)* | 38703 (49) | FFQ | PLC | Cancer registry, death records, medical records | 7 (total) | 47 (1.2) | 6 |
| Hu et al\(^{38}\) | Finland | Gen pop (25–74)* | 60323 (49) | FFQ | PLC | Cancer registry | 19.3 (median) | 128 (2.1) | 8 |
| Johnson et al\(^{41}\) | Singapore | Gen pop (45–74)* | 61321 (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 | 27037 (100) | FFQ | LC | Cancer registry | 18.2 (median) | 194 (7.2) | 6 |
| Bamia et al\(^{21}\) | Europe ** | Gen pop (25–70)* | 486799 (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)* | 162022 (47) | FFQ | HCC | Cancer registry | 18 (median) | 451 (2.8) | 7 |
| Petrick et al\(^{22}\) | USA | Gen pop (<50–≥70)* | 1212893 (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) | 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) | 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                |
| Gelati et al     | 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     | 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     | Japan   | Hospital                | 209 (68) aged 40–79 (mean 67) | Community controls randomly selected | 1308 (50) (mean 57) | FFQ                              | HCC     | 4                |
| Montella et al   | 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      | 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    | 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<sup>36</sup>      | Almost never                           | 29 423       | 161 (5.5)                     | 1 (ref)<sup>1</sup>  | *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                            | 23 753                                 | 54 (2.3)     | 0.52 (0.38 to 0.73)          | *                    |             |
| 3                            | 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<sup>25</sup>   | Non-drinkers                           | 24 556       | 103 (4.2)                     | 1 (ref)<sup>1</sup>  | *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)     | 0.6 (0.31 to 0.79)           | *                    |             |
| Shimazu et al (cohort 1)<sup>39</sup> | Never                      | 4938         | 29 (5.9)                      | 1 (ref)<sup>1</sup>  | *Age, gender, alcohol, smoking, liver disease* |
| Occasionally                 | 9507                                   | 25 (2.6)     | 0.56 (0.33 to 0.97)<sup>1</sup> | *                    |             |
| ≥1                           | 7959                                   | 16 (2.0)     | 0.53 (0.28 to 1.00)<sup>1</sup> | *                    |             |
| Shimazu et al (cohort 2)<sup>39</sup> | Never                      | 6954         | 12 (1.7)                      | 1 (ref)<sup>1</sup>  | *Age, gender, alcohol, smoking, liver disease* |
| Occasionally                 | 14 130                                 | 21 (1.5)     | 1.05 (0.52 to 2.16)<sup>1</sup> | *                    |             |
| ≥1                           | 17 619                                 | 14 (0.8)     | 0.68 (0.31 to 1.51)<sup>1</sup> | *                    |             |
| Hu et al<sup>38</sup>         | 0–1                                    | 6150         | 20 (3.3)                      | 1 (ref)<sup>1</sup>  | *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<sup>41</sup>   | Non-drinkers                           | 119 737 (PY) | 69                            | 1 (ref)<sup>1</sup>  | *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<sup>23</sup>       | Never drinkers                         | 667          | 9 (13.5)                      | 1.35 (0.65 to 2.82)<sup>1</sup> | *Age, alcohol, smoking, T2DM, education, BMI, tea, cholesterol, marital status, ATBC intervention arm§* |
| >0 to <1                     | 3094                                   | 36 (11.6)    | 1 (ref)<sup>1</sup>          | *                    |             |
| 1 to <2                      | 7204                                   | 60 (8.3)     | 0.73 (0.48 to 1.12)<sup>1</sup> | *                    |             |
| 2 to <3                      | 8086                                   | 47 (5.8)     | 0.52 (0.33 to 0.82)<sup>1</sup> | *                    |             |
| 3 to <4                      | 4515                                   | 22 (4.9)     | 0.45 (0.26 to 0.78)<sup>1</sup> | *                    |             |
| ≥4                          | 3471                                   | 20 (5.8)     | 0.53 (0.30 to 0.95)<sup>1</sup> | *                    |             |
| per extra cup                |                                        |              |                               |                      | *Stratified for age and center; adjusted for gender, alcohol, smoking, T2DM, education, BMI, physical activity, energy intake, tea* |
| Bamia et al<sup>11</sup>     | Quintile 1                             | 98 148       | 47 (0.5)                      | 1 (ref)<sup>1</sup>  | *Age, gender, alcohol, smoking, T2DM, education, BMI, race* |
|                             | Quintile 2                             | 100 953      | 49 (0.5)                      | 0.85 (0.56 to 1.29)<sup>1</sup> | *                 |
|                             | Quintile 3                             | 95 231       | 38 (0.4)                      | 0.63 (0.39 to 1.02)<sup>1</sup> | *                 |
|                             | Quintile 4                             | 96 413       | 36 (0.4)                      | 0.49 (0.29 to 0.82)<sup>1</sup> | *                 |
|                             | Quintile 5                             | 96 054       | 31 (0.3)                      | 0.28 (0.16 to 0.5)<sup>1</sup> | *                 |
| Setiawan et al<sup>55</sup> | Never                                  | 44 438       | 119 (2.7)                     | 1 (ref)<sup>1</sup>  | *Age, gender, alcohol, smoking, T2DM, education, BMI* |
| <1                          | 31 056                                 | 111 (3.6)    | 1.14 (0.88 to 1.48)<sup>1</sup> | *                    |             |
| 1                           | 45 717                                 | 137 (3.0)    | 0.87 (0.67 to 1.11)<sup>1</sup> | *                    |             |
| 2–3                         | 32 593                                 | 67 (2.1)     | 0.62 (0.46 to 0.84)<sup>1</sup> | *                    |             |
| ≥4                          | 8218                                   | 17 (2.1)     | 0.59 (0.35 to 0.99)<sup>1</sup> | *                    |             |

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

*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.
Data from a fourth (case–control) study 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 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. No single study reported a statistically significant association between HCC and decaffeinated coffee consumption. Three cohort studies, involving approximately 750000 participants and 800 cases, reported dose–response 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 850000 participants and 900 cases, reported RRs of HCC according to caffeinated coffee consumption in a manner suitable for dose–response analysis. 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 2272642 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. 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.
for HCC: high alcohol consumption, smoking, high BMI, T2DM and HBV/HCV. 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 0.90) 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. Moreover, case–control studies are susceptible to bias and confounding. The use of hospital controls in all except one study may have introduced bias. First, there are associations between coffee drinking bias. First, there are associations between coffee drinking bias and other confounders, such as smoking, alcohol consumption, BMI, T2DM and HBV/HCV. 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 use, but several did not adjust for BMI. Tobacco use and HBV/HCV were recorded in some studies, so failure to capture alcohol robustly in some studies, so failure to capture alcohol robustly in some studies, and residual confounding likely existed in all studies. 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 the effect.

Table 3   GRADE summary of findings table

| Outcomes | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|---------------------------------------|--------------------------|---------------------------------|--------------------------------|----------|
| HCC assessed with: cancer registries, death records and medical records | High | 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. |
| Safety | Risk with no coffee | Risk with coffee | | | |
| | 50 per 1000 | 33 per 1000 (30 to 36) | | | |

*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.
might underestimate the inverse association between coffee and HCC.\textsuperscript{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.\textsuperscript{86} One study used for baseline the consumption at 2 years before HCC diagnosis,\textsuperscript{32} when decades before may have been more appropriate. Another study\textsuperscript{33} 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 \textit{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 \textit{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 \textit{et al},\textsuperscript{21} Hu \textit{et al},\textsuperscript{68} and Shimazu \textit{et al}\textsuperscript{69} 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).\textsuperscript{33,38} Higher proportions of decaffeinated coffee drinkers, such as in the USA,\textsuperscript{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.\textsuperscript{49} Studies published in non-English journals may also be less rigorous and report bigger effect estimates.\textsuperscript{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,\textsuperscript{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,\textsuperscript{18,51} and several studies and a meta-analysis have reported an inverse association between coffee and cirrhosis.\textsuperscript{21} 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.\textsuperscript{52} Cafestol and kahweol increase activity of phase 2 liver enzymes, which may improve metabolism and excretion of carcinogens.\textsuperscript{33,34} and compounds including polyphenols may ameliorate oxidative DNA damage. However, cafestol and kahweol are present only in minimal quantities in instant and filtered coffee,\textsuperscript{53} and these varieties are popular in Japan and Finland, respectively, where studies included in this meta-analysis show inverse associations with HCC.\textsuperscript{33,38}

Other specific mechanisms of protection might include inhibition of hepatitis virus activity\textsuperscript{56} and prevention of T2DM.\textsuperscript{58}

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. 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. The potential harms of coffee also require further investigation, including the reported increased risk of lung cancer and bone fractures and the deleterious effect on cholesterol, which could potentially exacerbate the already increased risk of CVD associated with certain types of liver disease.

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.

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