Coffee consumption and risk of hepatocellular carcinoma: a meta-analysis of cohort studies

J Li¹, M Xu², Z Cheng³, P Wang⁴, S Wei¹, X Ma¹, G Li⁵*

Abstract

Introduction

Quantities of studies investigating coffee consumption and risk of hepatocellular carcinoma have reported different findings. The aim of this study was to perform a meta-analysis of cohort studies to clarify the effect of coffee intake on risk of hepatocellular carcinoma and to conduct an exhaustive stratified analysis and dose–response analyses.

Materials and Methods

Electronic reference databases including MEDLINE, the Cochrane Controlled Trials Register, EMBASE, and Science Citation Index and PubMed (up to May 2013) were searched to identify eligible cohort studies investigating relationships between coffee consumption and risk of hepatocellular carcinoma. Study-specific relative risk estimates were pooled using a random-effects model.

Results

Ten cohort studies (including 553,088 participants and 1649 hepatocellular carcinoma cases) were included in the meta-analysis. The summary relative risk for coffee drinkers versus non-drinkers was 0.64 (95% confidence interval: 0.55, 0.75), while relative risk for lowest and highest drinkers was 0.75 (95% confidence interval: 0.65, 0.87) and 0.48 (95% confidence interval: 0.39, 0.60), respectively. An increment of one cup of coffee per day was significantly related to decreased risk of hepatocellular carcinoma (relative risk: 0.82, 95% confidence interval: 0.78, 0.87). Subgroup, sensitivity and detailed dose–response analyses indicated the robustness and insensitivity of the relationship between coffee intake and reduced risk of hepatocellular carcinoma.

Conclusion

Based on the evidence of cohort studies, the meta-analysis confirms that coffee consumption is associated with reduced risk of hepatocellular carcinoma. The inverse relationship between coffee and risk of hepatocellular carcinoma was consistent across different populations and settings.

Introduction

As one of the most widely consumed beverages in the world, coffee has many potential beneficial health effects. For example, coffee consumption has been marked to be associated with reduced risks of several chronic diseases including type 2 diabetes mellitus, Parkinson’s disease, hepatocellular diseases and gout. The relationship between coffee intake and reduced risks of cancers is a matter of concern, because coffee contains high level of anti-cancer compounds such as chlorogenic acids, cafestol and kahweol. Moreover, emerging epidemiological studies have shown promising effects of coffee on several cancers including oral cavity, colorectal, prostate, leukaemic, pancreatic cancer, etc.

Liver cancer (LC) is the most common digestive tumour nowadays. For men, it is the fifth most frequently diagnosed cancer worldwide and the second cause of death due to cancer; however for women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of death. Hepatocellular carcinoma (HCC) is the major histological subtype, accounting for 70–85% of the total LC burden worldwide and with a moderately increasing rate in North America and North Europe over the last few decades. Till date, liver cirrhosis and chronic infection with hepatitis B or C viruses are considered the most important risk factors for HCC. Some lifestyle-related factors such as alcohol consumption, obesity and diabetes are also identified to be independently associated with the risk of HCC, while no significant relation between smoking and HCC was reported.

Inverse association between coffee consumption and the risk of HCC has recently been investigated in observational studies. Moreover, several meta-analyses summarising the evidence of observational studies clarified the significant relationship between the risk of HCC and coffee intake consistently. However, all the existing meta-analyses lacked an exhaustive stratified analysis, for example, none of them investigated association between HCC and smoking, and only one study included data of alcohol drinking. Moreover, even though there were three meta-analyses reported results of dose–response analyses, little was known about the relationship between an increment of one cup of coffee and the risk of HCC.

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coffee per day and risk of HCC stratified by gender, region, history of liver disease, etc. Besides, majority of the included studies in the meta-analyses were conducted in Japan, while more observational studies in other countries had been published recently. Thus, a meta-analysis with comprehensive analysis is imperative to summarise the latest evidence till date. Provided cohort studies are considered to be hierarchically superior to case–control studies mainly in avoiding recall and selection bias. In this study we carried out a meta-analysis of prospective cohort studies to clarify the association between coffee consumption and risk of HCC.

Materials and Methods

Search strategy

MEDLINE, the Cochrane Controlled Trials Register, EMBASE, Science Citation Index and PubMed were used to search for articles (in English, up to May 2013), which described cohort studies investigating the relationship between coffee consumption and risk of HCC. In our searches, we used descriptors that included synonyms for coffee and HCC in various combinations, for example, ‘coffee or caffeine’, ‘hepatocellular or liver’ and ‘carcinoma or neoplasm’. Titles and abstracts of trials identified from the search were independently reviewed and pooled for further screening by two authors (GL and JL). Later each reviewer examined the full text of all studies independently that were identified from the title and abstract screens. Disagreement was resolved by discussion and consensus among the reviewers and a third author (PW) was available to help if consensus failed to be reached. All references related to reviews and papers retrieved by the search were also examined. Additionally, authors were tried to contact who included studies to obtain unpublished data.

Eligibility criteria

Studies were selected for analysis if they met the following criteria: (1) prospective cohort studies or nested case–control studies; (2) the exposure studied was coffee consumption or caffeine; (3) the outcome of interest was HCC, primary liver cancer (PLC) or LC; (4) RR, odds ratios (ORs) or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) (or any relevant data available to calculate these statistics) were presented.

Data extraction

Two reviewers (G.L. and J.L.) extracted data independently. The items extracted included first author’s last name, year of publication, country where the study was performed, years of study/follow-up period, number of subjects (cases, controls or cohort size), frequency of coffee consumption or caffeine intake, measures of the association (RR, HR or OR) between coffee consumption and HCC incidence and the corresponding 95% CI and confounding variables allowed in the analyses. Estimates adjusted for multiple potential confounding variables were used in all possibilities. If RRs or the corresponding 95% CIs were not provided, they were derived from available tabular data or by contacting the authors of included studies. However, if data were only available in graphic format, we imputed approximations of the statistics of interest. The study quality was assessed using the 9-star Newcastle–Ottawa Quality Assessment Scale, with which each included study was rated based on the selection of study groups, the comparability of groups and the ascertainment of exposure and outcome.

Statistical analysis

We used the generic inverse variance method to pool the summary RR for coffee drinkers versus non-drinkers and for highest/lowest coffee drinkers versus non-drinkers. The highest and lowest coffee drinkers were defined as the last and the second stratum of coffee consumption, respectively in each included study. If the study reported only data with two strata (e.g. heavy drinkers versus light drinkers), then the second stratum (i.e. heavy drinkers) would be used as both the highest and the lowest coffee data for meta-analyses.

A random effects model that did not assume homogeneity of RRs across studies was used to synthesise data by pooling the results of the included studies. Heterogeneity was evaluated through the I² statistic and the Q-test, with a value of $I^2 > 50\%$ or $P$ value $< 0.1$ taken as statistically significant heterogeneity.

If statistical heterogeneity was found to investigate the heterogeneity, we conducted subgroup analyses stratified by the following variables: geographic region, sex, smoking status, alcohol consumption, history of liver disease, follow-up period (using 10 years as a cut-off according to the mean of follow-up periods of included studies) and quality scores (considering studies of scores $> 7$ in the Newcastle–Ottawa Quality Assessment Scale as of high quality).

A sensitivity analysis was performed by applying a fixed effects model. Furthermore, to make the probability statement of a beneficial risk of HCC related to coffee, another sensitivity analysis based on a hierarchical Bayesian random effects model using a ‘non-informative’ prior distribution was conducted. The summary statistics were acquired from the posterior distribution of the Bayesian analysis, presenting as a pooled RR with 95% associated credible interval (CrI). We fitted the models in WinBUGS using 100,000 Markov chain Monte Carlo cycles with two chains of simulations, a burn-in of 10,000 and thin of 10. Convergence was assessed using the Gelman…


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All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
# Coffee consumption and risk of hepatocellular carcinoma: A meta-analysis of cohort studies


**Competing interests:** none declared. Conflict of interests: none declared.

All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

## Table 1 Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>No. of cases/controls</th>
<th>Study period</th>
<th>Coffee consumption</th>
<th>RR/HR/OR(95%CI)</th>
<th>Adjustment factors</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoue 2005</td>
<td>Japan</td>
<td>334/90,452</td>
<td>1990-2001</td>
<td>never</td>
<td>0.79 (0.56-1.10)</td>
<td>Age, sex, study centre, tobacco smoking, alcohol drinking, vegetables consumption, tea drinking</td>
<td>7</td>
</tr>
<tr>
<td>Kurozawa 2005</td>
<td>Japan</td>
<td>258/83,966</td>
<td>1988-1999</td>
<td>almost never</td>
<td>0.83 (0.54-1.25)</td>
<td>Age, sex, education, history of diabetes and liver disease, alcohol drinking</td>
<td>8</td>
</tr>
<tr>
<td>Shimazu 2005 Cohort 1</td>
<td>Japan</td>
<td>70/22,404</td>
<td>1984-1992</td>
<td>never</td>
<td>0.50 (0.31-0.79)</td>
<td>Age, sex, history of liver disease, alcohol drinking</td>
<td>9</td>
</tr>
<tr>
<td>Shimazu 2005 Cohort 2</td>
<td>Japan</td>
<td>47/28,703</td>
<td>1990-1997</td>
<td>occasionally</td>
<td>0.58 (0.36-0.96)</td>
<td>Age, sex, history of liver disease, alcohol drinking</td>
<td>8</td>
</tr>
<tr>
<td>Shimazu 2005</td>
<td>Japan</td>
<td>96/110,792</td>
<td>1988-1999</td>
<td>never</td>
<td>0.77 (0.45-1.32)</td>
<td>Age, sex, study year, alcohol drinking, education, diabetes and chronic liver disease</td>
<td>6</td>
</tr>
<tr>
<td>Wakai 2007</td>
<td>Japan</td>
<td>128/60,323</td>
<td>1987-2002</td>
<td>never</td>
<td>0.49 (0.25-0.96)</td>
<td>Age, sex, study year, alcohol drinking, education, diabetes and chronic liver disease</td>
<td>7</td>
</tr>
<tr>
<td>Ohishi 2008</td>
<td>Japan</td>
<td>139/472</td>
<td>1999-2002</td>
<td>never</td>
<td>0.40 (0.16-1.02)</td>
<td>Hepatitis virus infection, alcohol consumption, smoking habit, BMI, diabetes mellitus and radiation dose to the liver</td>
<td>7</td>
</tr>
</tbody>
</table>
### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study period</th>
<th>No. of cases/controls</th>
<th>Coffee consumption</th>
<th>RR/HR/OR (95%CI)</th>
<th>Adjustment factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoue 2009</td>
<td>Japan</td>
<td>1994-2006</td>
<td>110/18,815</td>
<td>almost never</td>
<td>Reference</td>
<td>Age, sex, study centre, alcohol consumption, BMI, body mass index, diabetes mellitus, serum ALT level, HCV infection, HBV infection, hepatitis C virus infection, coffee consumption, tea drinking, history of diabetes, alcohol consumption, smoking status, history of diabetes, alcohol consumption, smoking status.</td>
</tr>
<tr>
<td>Johnson 2011</td>
<td>Singapore</td>
<td>1993-2006</td>
<td>362/63,257</td>
<td>&lt;1 cup/day</td>
<td>0.94 (0.63-1.34)</td>
<td>Age, sex, study year, BMI, body mass index, diabetes mellitus, tea drinking, smoking status, alcohol drinking, history of diabetes, alcohol consumption, smoking status.</td>
</tr>
<tr>
<td>Michikawa 2012</td>
<td>Japan</td>
<td>2000-2008</td>
<td>104/17,654</td>
<td>almost never</td>
<td>Reference</td>
<td>Age, sex, study centre, alcohol consumption, BMI, body mass index, diabetes mellitus, serum ALT level, HCV infection, HBV infection, hepatitis C virus infection, coffee consumption, tea drinking, history of diabetes, alcohol consumption, smoking status, history of diabetes, alcohol consumption, smoking status.</td>
</tr>
</tbody>
</table>

* N/A: no data could be extracted.

#### Sensitivity analyses

A sensitivity analysis applying a fixed effects model indicated the robustness of the results of relationship between coffee consumption and HCC (RR = 0.64, 95% CI: 0.55, 0.75 for drinkers; RR = 0.75, 95% CI: 0.65, 0.87 for lowest coffee drinkers; RR = 0.48, 95% CI: 0.39, 0.60 for highest coffee drinkers).

When Bayesian meta-analyses were applied using a ‘non-informative’ prior distribution (gamma distribution for the between-study variance), the pooled RR was 0.65 (95% CrI: 0.54, 0.75) for drinkers, 0.75 (95% CrI: 0.63, 0.88) for lowest drinkers and 0.48 (95% CrI: 0.38, 0.61) for highest drinkers versus non-drinkers, which were consistent with results of the classical approach (Table 3). The posterior probabilities of a beneficial risk of HCC associated with coffee intake (i.e. RR < 1) was very approximately 1, with all the probabilities >0.99. Similar results were found when the uniform distribution of the between-study SD was used, indicating the robustness of the results of Bayesian analyses.

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a significant association between risk of HCC and each increased cup of coffee in Japan\textsuperscript{17,18,20,22–25} (RR=0.72, 95% CI: 0.65, 0.79). The RR for participants without history of liver diseases was marginally significant\textsuperscript{22,25} (RR = 0.61, 95% CI: 0.37, 1.00, \( P = 0.051 \)), while the RR was 0.68 (95% CI: 0.53, 0.87)\textsuperscript{17,22,25} for subjects with history of liver diseases. With regard to gender-specific dose–response analysis, results from three studies\textsuperscript{20,22,28} showed a significant relationship with decreased risk of HCC for males (RR=0.81, 95% CI: 0.76, 0.87), whereas the association was not significant for females (RR=0.90, 95% CI: 0.80, 1.02).

Publication bias

There was no evidence of publication bias in the studies of coffee consumption and HCC for drinkers (Figure 4; Begg \( P = 0.93 \), Egger \( P = 0.28 \)), for lowest drinkers (Figure 5; Begg \( P = 0.25 \), Egger \( P = 0.32 \)) and for highest drinkers (Figure 6; Begg \( P = 0.13 \), Egger \( P = 0.15 \)) versus non-drinkers.

Discussion

The authors have referenced some of their own studies in this systematic review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

The findings of current meta-analyses from 10 cohort studies demonstrated the risk of HCC for the coffee drinkers, highest drinkers and lowest drinkers was approximately 36%, 52%, 25% lower than the non-drinkers, respectively. These results were similar to other meta-analyses that included both cohort and case–control studies\textsuperscript{27,29}. No significant heterogeneity was found between studies.
Table 2 Subgroup analysis for associations between HCC and coffee drinkers versus non-drinkers

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>No. of cases</th>
<th>RR (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\tau^2)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>674</td>
<td>0.58 (0.47, 0.71)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td>273</td>
<td>0.64 (0.50, 0.81)</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>1159</td>
<td>0.63 (0.56, 0.70)</td>
<td>0.00</td>
</tr>
<tr>
<td>Singapore</td>
<td>362</td>
<td>0.92 (0.76, 1.10)</td>
<td>—</td>
</tr>
<tr>
<td>Finland</td>
<td>128</td>
<td>0.46 (0.34, 0.63)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Follow-up period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short(^d)</td>
<td>709</td>
<td>0.64 (0.56, 0.73)</td>
<td>0.00</td>
</tr>
<tr>
<td>Long(^d)</td>
<td>940</td>
<td>0.62 (0.47, 0.82)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>—(^e)</td>
<td>0.57 (0.40, 0.80)</td>
<td>0.05</td>
</tr>
<tr>
<td>No</td>
<td>—(^e)</td>
<td>0.57 (0.45, 0.71)</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>History of liver disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>580</td>
<td>0.59 (0.50, 0.70)</td>
<td>0.00</td>
</tr>
<tr>
<td>No</td>
<td>250</td>
<td>0.74 (0.58, 0.94)</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>—(^e)</td>
<td>0.49 (0.30, 0.82)</td>
<td>0.15</td>
</tr>
<tr>
<td>No</td>
<td>—(^e)</td>
<td>0.59 (0.39, 0.89)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Study quality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low(^f)</td>
<td>569</td>
<td>0.62 (0.53, 0.73)</td>
<td>0.00</td>
</tr>
<tr>
<td>High(^f)</td>
<td>1080</td>
<td>0.65 (0.52, 0.81)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

\(^a\)RR, relative risk; CI, confidence interval.
\(^b\)\(\tau^2\), between-study variance.
\(^c\)Not applicable because of only one study included.
\(^d\)Short period of follow-up, < 10 years; long period, < 10 years.
\(^e\)No data could be extracted.
\(^f\)Low study quality: scores of Newcastle–Ottawa Quality Assessment Scale \(\leq 7\); high study quality: scores > 7.

Table 3 Sensitivity analyses for relationship between HCC and coffee using Bayesian meta-analyses

<table>
<thead>
<tr>
<th>Meta-analysis approach</th>
<th>Drinkers versus non-drinkers</th>
<th>Lowest versus non-drinkers</th>
<th>Highest versus non-drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CrI)/CI(^a)</td>
<td>Probability of RR&lt;1</td>
<td>RR (95% CrI)/CI</td>
</tr>
<tr>
<td><strong>Bayesian analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Non-informative' prior distribution(^c)</td>
<td>0.65 (0.54-0.75)</td>
<td>&gt;0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>'Non-informative' prior distribution(^d)</td>
<td>0.64 (0.53-0.77)</td>
<td>&gt;0.99</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Classical analysis</strong></td>
<td>0.64 (0.55-0.75)</td>
<td>—</td>
<td>0.03</td>
</tr>
</tbody>
</table>

\(^a\)CrI, credible interval; CI, confidence interval.
\(^b\)\(\tau^2\), between-study variance.
\(^c\)Using gamma distribution for the between-study variance.
\(^d\)Using uniform distribution for the between-study standard deviation.

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funnel plot for coffee

HCC for the Singapore Chinese (HR = 0.56, 95% CI: 0.31, 1.00, \( P = 0.05 \))\(^2\). The discrepancy may be due to racial differences or differences in coffee drinking habits. Inverse relation between coffee and HCC was consistently found across other subgroup analyses. However, there was significant heterogeneity among studies for males, alcohol drinkers and smoking status with long periods of follow-up and of high quality (Table 2).

Bayesian meta-analyses can calculate the posterior probability that coffee intake provides a reduced risk of HCC, and explore the robustness of the analyses by comparing results from a classical approach and under different assumptions (i.e. with different distributions for between-study variance or SD)\(^3\). The significant results were consistent with the classical meta-analyses. Moreover, all the posterior probabilities of a beneficial risk of HCC in coffee drinkers and lowest/highest drinkers were approximately 1 (i.e. >0.99), which could further corroborate the positive relationship between coffee consumption and decreased risk of HCC.

The outcome in this study was HCC; however, there were four studies included providing data on LC. Nevertheless, the pooled results of coffee drinkers versus non-drinkers stratified by HCC (RR = 0.69, 95% CI: 0.57, 0.83) and LC (RR = 0.57, 95% CI: 0.45, 0.71) were very similar to the result using all the included studies (Figure 1). There were three \(^7\) studies providing data on tea drinking. No significant associations were found between coffee and risk of HCC after adjusting for tea consumption\(^9\), or between tea drinking and risk of HCC after adjusting for coffee\(^7\). It may indicate that the relationship between decreased risk of HCC and coffee consumption would be biased by tea intake to some extent. However, in this study no meta-analysis taking into tea intake account was conducted for further clarification, because no sufficient information could be extracted.

It remained unclear which ingredient of coffee could protect coffee drinkers against HCC\(^4\). Biologically, there were three major components of coffee which had been considered to contribute to the beneficial effects against liver carcinogenesis: chlorogenic acids, diterpenes cafestol and kahweol and caffeine\(^16,20\). However, several studies argued that caffeine may not be related to reduced risk of HCC\(^17,20,31\), while Johnson’s study\(^21\) attested and concluded the inverse association between caffeine consumption and risk of HCC. Owing to limited information retrieved in this study, however, no meta-analysis could be performed to examine the relationship between caffeine and risk of HCC.

The significant result of dose–response analysis was similar to the findings from three previous meta-analyses\(^28,29,31\), which reported the RR of 0.57 related to two cups of coffee per day\(^3\) and the approximate RR of 0.80 associated with one cup of coffee per day\(^2\). In this study, further stratification of dose–response analyses found that males and drinkers without history of liver diseases tend to show a lower risk of HCC compared with females and drinkers.
with history of liver diseases, respectively. It may imply different beneficial effect by incremental coffee consumed per day on different gender and subjects with or without liver diseases. Nevertheless, taking into account the sample size, more research is needed to clarify the stratified dose–response analyses.

**Critical appraisal of the validity of relevant articles**

Meta-analysis had some advantages. Firstly, a comprehensive search of the literature could warrant summarising all the available evidence till date of relationship between coffee intake and risk of HCC. Secondly, the included studies were of high quality with good quality scores, thus leading to convincing results. Thirdly, detailed analyses including subgroup, sensitivity and dose–response analyses were conducted to utilise the existing evidence thoroughly.

There were also several limitations in this study. Firstly, the possibility of bias and confounding cannot be fully controlled or excluded in nutritional observational studies. For instance, it was postulated that tea drinking may bias the association between coffee and reduced risk of HCC based on the individual findings from the included cohort studies. Secondly, the results are likely to be influenced by misclassification of coffee consumption, because each study presented coffee consumption in different units (cups/week, cups/day, days/week, daily drinks, times/week). Furthermore, the majority of included studies were still from Japan, with only one study from Singapore and one from Finland. Therefore, the findings may not be generalised to other populations. Moreover, detailed information on coffee consumption (e.g. what was the method of preparation, which brewing method was chosen, it was decaffeinated or caffeinated, etc.) was not available, which may account for; at least in part the significant heterogeneity among the included studies.

**Conclusion**

The current meta-analysis confirms that coffee consumption is associated with reduced risk of HCC. The inverse relationship between coffee and decreased risk of HCC was consistent across different populations and settings.

**Clinical applicability**

Nevertheless, given the observational design and the potential confounding, the causality remains open to discussion and more better-controlled studies are warranted.

**Acknowledgement**

The authors thank Mr Yunzheng Mo for his help in writing and editing the manuscript.

**Abbreviations list**

ALT, alanine aminotransferase; BMI, body mass index; CI, confidence intervals; CrI, credible interval; HRs, hazard ratios; HCC, hepatocellular carcinoma; LC, Liver cancer; ORs, odds ratios; PLC, primary liver cancer; RR, relative risk; SD, standard deviation.

**References**