SYSTEMATIC REVIEW AND META-ANALYSIS

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Inverse Association of Coffee with Liver Cancer Development: an Updated Systematic Review and Meta-Analysis

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ABSTRACT

Background & Aims: Coffee consumption has been suggested to reduce the risk for hepatocellular carcinoma (HCC). While several studies report inverse correlation with coffee drinking, others have suggested more than 2 cups of coffee every day decrease the risk of liver cancer or HCC. However, controversy exists about the exact dose that would provide protective benefit. Therefore, we aimed to carry out a systematic review and meta-analysis of all studies that investigated the association of coffee consumption and risk of HCC and/or liver cancer. Our outcomes were the evaluation of the association of coffee with HCC or liver cancer development along with the amount of coffee needed to prevent HCC or liver cancer.

Methods: We performed a PubMed/MEDLINE/EMBASE/Ovid/Google Scholar search of original articles published in English from 1996 to June 2019, on case-control or cohort or prospective studies that associated coffee with liver cancer or HCC. We calculated the relative risk (RR) of the two conditions for coffee drinking and then stratified this into increments of one cup of coffee per day. Twenty studies were identified. The analysis was performed using random effects models from the methods of DerSimonian and Laird with inverse variance weighting. The Cochrane Q and the I^2 statistics were calculated to assess heterogeneity between studies. A $p<0.10$ value for chi-square test and $I^2<20\%$ were interpreted as low-level heterogeneity. Probability of publication bias was assessed using funnel plots and with the Egger's test.

Results: The overall RR was 0.69 (95%CI 0.56-0.85; $p<0.001$) with significant heterogeneity between the studies. We performed subgroup analysis over the increments of 1 cup of coffee. Higher doses of coffee consumption were associated with a significant decrease in the risk of developing HCC or liver cancer. The funnel plot did not show significant publication bias.

Conclusions: Our systematic review and meta-analysis suggests that drinking coffee provides benefits with a reduction in the risk of HCC or liver cancer. Higher doses of coffee have higher benefits in terms of risk reduction. However, further biological and epidemiological studies are required to determine the exact mechanism and to study specific subgroups such as viral hepatitis B or C related HCC.

Key words: coffee – hepatocellular carcinoma – inverse association.

Abbreviations: CLD: chronic liver disease; ESLD: end-stage liver disease; HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease.

INTRODUCTION

The popularity of coffee continues to grow in the modern era and it is now the second most traded commodity [1]. Naturally with such wide use, the effect of coffee consumption on human health has become an important area of research. Numerous studies have tried to delineate whether whole coffee or some of the thousand compounds contained within, such as caffeine, chlorogenic acids, pentacyclic diterpenes such as kahweol and cafestol, and various antioxidants, influence human health [2]. In fact, an umbrella review by Poole et al. [3] found that coffee consumption was more often associated with benefit than harm for a variety of health outcomes including cardiovascular disease, cancer, metabolic syndrome associated conditions, as well as chronic liver disease (CLD).

The relationship between coffee consumption and liver health has been well documented for the last three decades. Initially, the effect of coffee consumption on lowering serum markers of liver injury such as gamma-glutamyl transferase and

aminotransferase levels was noted. Subsequently, numerous studies have shown a beneficial impact of coffee on delaying the progression of CLD [4-6]. These studies have not only shown an indirect effect on the amount of fibrosis development but also the rate of hepatocellular carcinoma (HCC) incidence [7, 8].

The worldwide burden of liver cancer, most of which is HCC, is already quite significant. Over 841,000 new cases were reported in 2018 making it the sixth most common cancer worldwide. Hepatocellular carcinoma was also the cause of over 781,000 deaths in 2018 making it fourth amongst all cancers worldwide [9].

Hepatocellular carcinoma usually develops in the setting of advanced fibrosis in end-stage liver disease (ESLD) and currently almost 80% of HCC cases are due to chronic viral hepatitis [10]. However, the prevalence of underlying etiologies of HCC is expected to shift and its incidence will increase in the coming years mainly due to the burgeoning epidemic of obesity and metabolic syndrome resulting in non-alcoholic fatty liver disease (NAFLD) and subsequent non-alcoholic steatohepatitis (NASH)-related cirrhosis [11]. With this impending worsening impact of HCC and the known association between coffee consumption and the reduced HCC risk [12, 13], there has been an increased focus on analyzing this relationship.

Several groups have performed case-control and prospective cohort studies [14-16] which have demonstrated a reduced risk of HCC with coffee consumption. Furthermore, numerous meta-analyses in recent years have combined these data to show the significance of this inverse relationship [17-21]. While it is evident from these data that an inverse relationship exists between coffee consumption and the HCC risk, it is not clear if there is an optimal dose of coffee for reducing the risk for HCC. Specifically, Kennedy et al. [18] were able to show that 2 or more cups of coffee per day had the lowest risk of HCC [18], while Bravi et al. [17] showed that high consumption, defined as 1-3 cups per day depending on the study, of coffee was associated with a lower risk of HCC development.

In this study, we aimed to perform an updated systematic review and meta-analysis of all the studies that had investigated the association between coffee consumption and the risk of HCC or liver cancer development with the additional goal of identifying an optimal dose of daily coffee with respect to HCC risk reduction.

METHODS

Eligibility criteria

The specific inclusion criteria for the systematic review and meta-analysis were: (1) original studies based on humans; (2) studies focusing on primary HCC (or liver cancer if no separate results were available); (3) studies with measures of estimate (odds ratio, confidence interval, or information sufficient to calculate them) of the association of coffee and HCC; (4) full text articles available in the English language. Reviewed studies included in our analysis were prospective cohort studies and case control studies which evaluated the association of coffee and development of HCC.

Search strategy

The search strategy was designed and conducted by the authors (A.B., P.R., S.Y., L.P., P.D., D.R., V.R.). Three reviewers, independently and in duplicate, searched PubMed, Medline, CENTRAL, EMBASE, Scopus, Web of Sciences and clinical trial registries using multiple search terms in the combination ('coffee' OR 'caffeine' OR 'diet' OR 'beverage' OR 'lifestyle' OR 'drinking') AND ('liver' OR 'carcinoma' OR 'hepatocellular' OR 'liver cancer' OR 'neoplasm' OR 'cirrhosis' OR 'liver neoplasm')) of all published articles up to June 2019. This was performed using PRISMA statement for systematic reviews and meta-analysis. All titles and abstracts were identified by the authors and screened to accrue potentially eligible studies. Then, the authors independently assessed all selected full-text manuscripts for eligibility. A manual search of the references of the selected articles was also performed to supplement the electronic search. Disagreements between 2 reviewers were resolved through consensus and after input from the third reviewer and principal investigator.

Data extraction

Six reviewers (A.B., P.R., S.Y., L.P., P.D., D.R.) independently reviewed and abstracted data from the included studies. If there were multiple reports stemming from a specific study database, data from the most robust study was extracted with other studies contributing towards the bibliography. The reviewers sorted the data separately in all stages of study collection, data extraction and quality assessment. All discrepancies found between 2 reviewers were resolved with consensus and input from other authors.

Data extracted from all the publications included study design, country, size of the cohort, follow-up duration, amount of coffee consumption, outcomes (hepatocellular carcinoma or liver cancer), risk ratio and corresponding confidence interval. Primary outcome was the association of coffee drinking and the risk of developing HCC or liver cancer. Secondary outcomes were the association of the amount of coffee with the risk of developing HCC or liver cancer.

Quantitative data synthesis

All data were analyzed by the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ; http://www.meta-analysis.com/). The final pooled risk estimates were obtained using random effects models by the methods of DerSimonian and Laird with inverse variance weighting. The prior studies have shown significant variation in the effects of coffee in terms of HCC development; therefore, the inverse variance weighting method was used. Studies with a precise estimate of the population effect size (a low variance) are assigned more weight, while studies with a less precise estimate of the population effect size (a high variance) are assigned less weight. Thus, raw data for the amount of coffee intake, events and nonevents from each study were used to calculate a crude odds ratio (OR) for each study. The Cochrane Q and the I^2 statistics were calculated to assess heterogeneity between studies. A $p<0.10$ value for chi-square test and $I^2<20\%$ were interpreted as a low-level heterogeneity. Probability of publication bias was assessed using funnel plots and with Egger's test.

The summary estimates were stratified into: (a) regular amount or any amount, at least once a day; (b) low or up to 2 cups of coffee per day; (c) high or 3 or more cups of coffee in a day, (d) no consumption.

For the analysis, we assumed one standard cup of coffee as described by each of the journals. While some of the studies reported the amount of coffee intake in amount per cup or milliliters, others did not report the amount of coffee in each cup. Therefore, the association of an exact dose of coffee with HCC or liver cancer development could not be calculated.

Study characteristics and quality assessment

We selected data collection forms for all the studies based on the Cochrane Collaboration risk assessment tool to adhere to principles of sound methodological quality. The non-randomized studies were evaluated using the Newcastle and Ottawa scores [22]. Quality assessments were also conducted independently, and discrepancies were resolved by consensus.

RESULTS

The flow chart of selection of the studies on coffee consumption and development of HCC is shown in Fig. 1. After the initial search, it resulted in 400 studies. Thereafter, the duplicates were removed, and the remaining studies were screened. One hundred and forty-six studies were excluded based on the titles and abstracts as they were not relevant to the impact of coffee with liver cancer. Subsequently, 66 articles were assessed completely by the reviewers. The reviewers strictly followed the inclusion and exclusion criteria mentioned in the methods' section. Forty-six articles were excluded due to various reasons (duplicate study reports, no details regarding the effect of coffee in preventing liver cancer, no definite amount of coffee reported or studies not published in the English language) shown in Fig. 1. Thus, twenty were reviewed and included in the analysis as they met the inclusion criteria [14, 15, 23-40]. Table I provides the main characteristics of the selected studies. These studies were published between 2002 and 2015 across Europe, Japan, USA, Hongkong and Singapore. The included studies were case control and prospective cohort studies (Table I).

Coffee drinkers versus non-drinkers

The forest plot for the association of coffee consumption and HCC development is shown in HCC. Coffee consumption significantly decreased the risk of development of HCC or liver cancer as compared to non-drinkers (RR 0.69, 95%CI 0.56-0.85; p<0.01). There was moderate to high heterogeneity noticed based on the Q test and I^2 statistic. The majority of the included studies adjusted for age, alcohol, smoking while a few adjusted for hepatitis B or C viruses additionally. All the studies show an inverse association of coffee with HCC with a few studies showing the association was not significant.

Subsequently, we performed subgroup analysis based on the amount of coffee consumption with an increment of one cup per day. The forest plots for the various subgroups are shown in Figs. 3, 4 and 5. These showed that higher doses of coffee lead to a significantly decreased risk of HCC development. Occasional coffee drinking or up to 1 cup of coffee per day did not significantly decrease the odds of developing HCC or liver cancer (Fig. 3). Increasing the consumption of coffee to 2 cups per day offered minimal significant protection (Fig. 4).

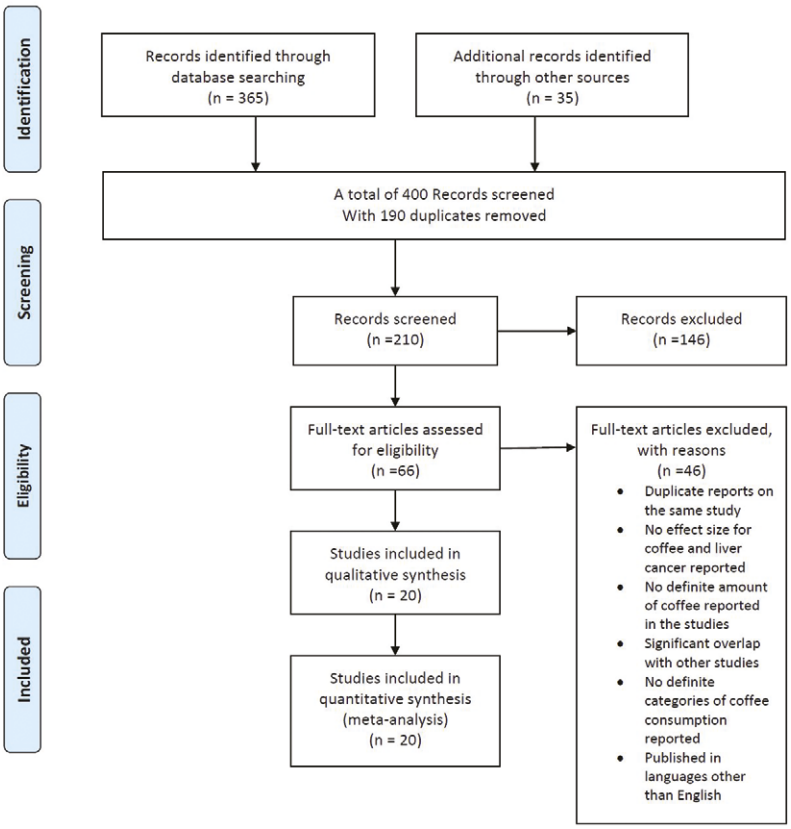

Fig. 1. PRISMA flow diagram

Table I. The main characteristics of the selected studies.

Study	Country	Type of Study	Case Cohort	Control	Exposure evaluation	Outcome evaluation	Cases
Kuper et al. [35]	Greece	Case Control	Hospitalized population	Non cancer hospital pts.	Questionnaire	Medical records	333 cases
Gallus et al. (2 Cohorts) [24]	Italy, Greece	Case Control	Hospitalized cohort	Non cancer hospital pts.	Questionnaire	Medical Records	834 cases
Gelatti et al.[15]	Italy	Case Control	Hospitalized cohort	No liver disease hospital pts.	Questionnaire	Medical Records	250 cases
Shimazu et al. [31]	Japan	Prospective Cohort	General population		Questionnaire	Medical records	117 cases
Kurozawa et al. [29]	Japan	Cohort	General Population		Questionnaire	Registry	258 cases
Montella et al. [27]	Italy	Case Control	Hospitalized patients	Hospital patients	Questionnaire	Medical records	185 cases
Ohfuji et al. [33]	Japan	Case Control	Hospital Patients	Hospital patients	Questionnaire	Hospital records	73 cases
Inoue et al.[30]	Japan	Cohort study	General population		Questionnaire	Cancer registry	334 cases
Johnson et al.[32]	Singapore	Cohort study	General Population		Questionnaire	Cancer registry, death records	362 cases
Leung et al. [34]	Hongkong	Case Control	Hospital Follow up	Hospital (HBV) follow up	Questionnaire	Medical records	109 cases
Jang et al. [37]	Korea	Case Control	Hospital based	Chronic liver disease patients	Questionnaire	Medical records	258 cases
Michikawa et al. [38]	Japan	Cohort	General population		Questionnaire	Medical records	104 cases
Lai et al. [39]	Finland	Cohort	Male smokers	Male smokers	Questionnaire	Cancer registry	194 cases
Bamia et al. [25]	Europe	Cohort	General population		Questionnaire	Cancer registry, death records, health insurance	201 cases
Setiawan et al. [14]	USA	Cohort	General population		Questionnaire	Cancer registry	451 cases
Petrick et al. [26]	USA	Cohort	General Population		Questionnaire	Cancer registry, medical records	860 cases
Tamura et al. [23]	Japan	Cohort	General population		Questionnaire	Cancer registry	172 cases
Tanaka et al. [28]	Japan	Case control	Hospital	Community control	Questionnaire	Cancer registry, death records, health insurance	1308 cases
Tran et al.[40]	UK	Cohort	General population		Questionnaire	Cancer registry	88 cases
Hu et al.[36]	Finland	Cohort	General population		Questionnaire	Cancer registry, Medical records	128 cases

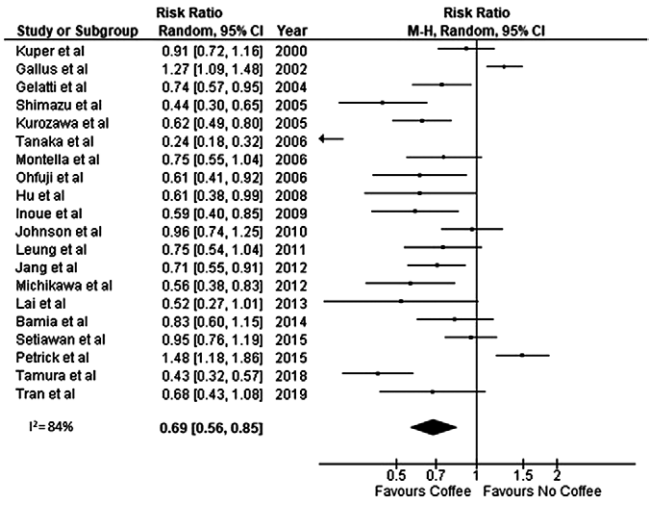

Fig. 2. Forrest plot showing any amount of coffee consumptation and risk of development of HCC/Liver cancer.

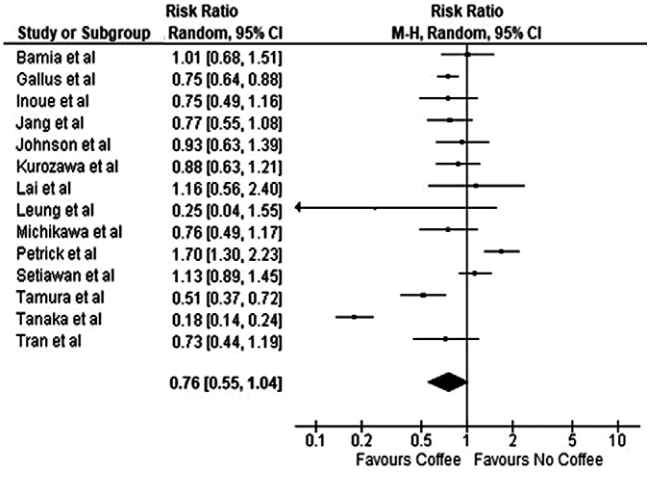

Fig. 3. Forrest plot showing coffee consumptation (up to 1 cup per day) and risk of development of HCC/Liver cancer.

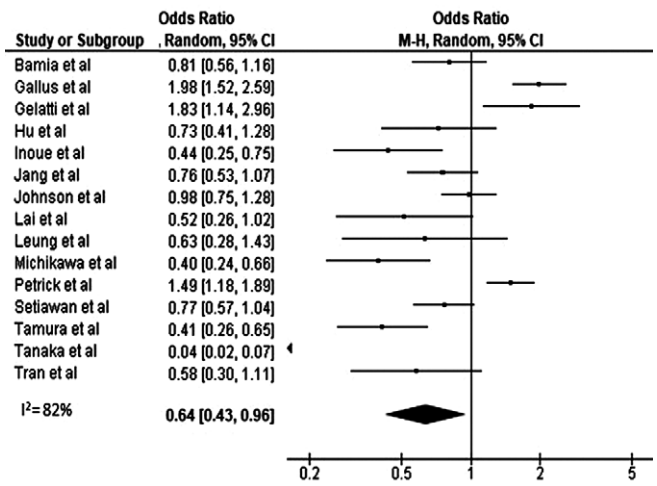

Fig. 4. Forrest plot showing coffee consumption (2 cup per day) and risk of development of HCC/Liver cancer.

However, more than 3 cups of coffee significantly decreased the odds of developing HCC or liver cancer (Fig. 5). Based on the I2 statistics, there was moderate to high level of heterogeneity in each of the subgroups.

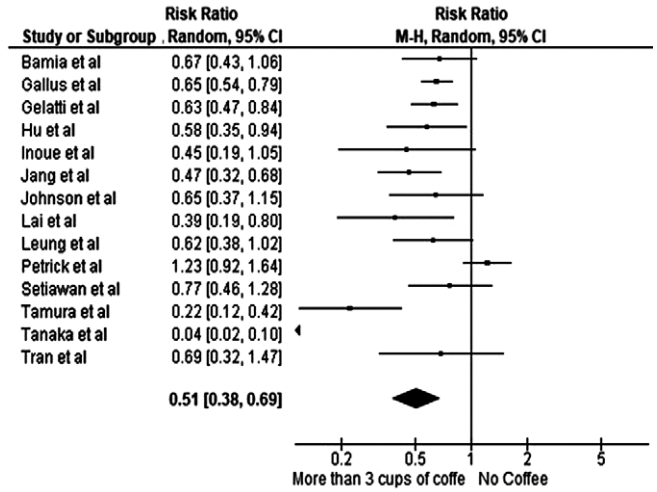

Fig. 5. Forrest plot showing coffee consumptation (3 or more than 3 cup per day) and risk of development of HCC/Liver cancer.

There was no publication bias noticed in the included studies as shown in the funnel plot (Fig. 6). The shape of the funnel plot suggests an approximate symmetrical result indicating no publication bias. This was confirmed using Egger's test (p=0.23). The analysis of the funnel plot appears to suggest that the larger studies had a possible smaller variance but a possible tendency towards a higher OR value. This might raise some doubts regarding the protective effect of the coffee consumption against the occurrence of HCC/liver cancer. Therefore, it is still possible that publication bias might exist despite no statistical significance.

The studies were graded for comparability, outcome assessment using Newcastle and Ottawa scores which are also summarized in Table II.

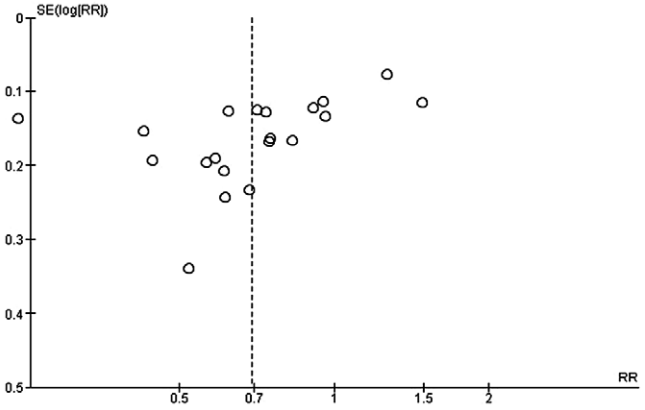

Fig. 6. Funnel plot for publication bias.

DISCUSSION

In our meta-analysis, we report a significant reduction in the risk of HCC or liver cancer among regular coffee drinkers compared with no/occasional drinkers on the basis of 20 studies including 4,710 cases of HCC or liver cancer. The reduction in the risk was proportional to the amount of coffee consistent with a real inverse association. Previous studies on the association of coffee and liver cancer also showed similar findings [17] However, multiple studies have been published on the same topic since the last meta-analysis in 2017 which necessitates an update of the results [41].

Coffee has hundreds of biologically active compounds including phenolic compounds such as chlorogenic, ferulic and cumaric acids, diterpenes caffeine, potassium and magnesium. The protective effects of coffee are postulated due to multiple ingredients. Phenolic acids and caffeine may directly impact liver carcinogenesis via inhibiting proliferation of HCC cells, suppressing progression of HCC and preventing oxidative damage to hepatocytes [42-44]. It is also postulated that coffee reduces insulin resistance and improves glucose metabolism which may also play a role in slowing the progression of liver disease [45]. The antioxidant and anti-inflammatory effects have been confirmed by *in vitro* studies and animal models [46-48]. Multiple prior studies have demonstrated protective effects of coffee on liver function ranging from improving liver chemistries to slowing the progression of liver disease [5, 49-52].

The beneficial effects of coffee in liver disease occur in a dose-dependent manner [53, 54]. Higher doses of coffee consumption are more likely to improve serum enzyme concentration, specifically aminotransferases [49, 54]. High consumption of coffee also exerts immune-boosting on NAFLD independent of antioxidant effects [53]. Aleksandrova et al. [54] reported that a higher coffee intake was associated with lower concentrations of liver-specific mitochondrial enzyme which could indirectly decrease HCC. However, it is speculated that the inverse association of coffee consumption with liver cancer could be due to the inclusion of participants with underlying liver disease who decrease coffee intake, either on the basis of physician recommendations or their own accord [17]. This argument of reverse causality was not confirmed in the prospective cohort studies [55, 56]. Aleksandrova et al. [54]

Table II. Quality assessment of studies in the meta-analysis based on modified Newcastle-Ottawa Scale

References	Selection (maximum 4 stars)				Comparability (maximum 2 stars)	Outcome (maximum 3 stars)			Quality judgment (maximum 9 stars)
	1	2	3	4	1	1	2	3	
Kuper et al. [35]	*		*	*	**	*	*	*	********
Gallus et al. (2 Cohorts) [24]	*		*	*	**	*	*	*	********
Gelatti et al. [15]	*		*	*	**	*	*	*	********
Shimazu et al. [31]	*			*	**	*		*	*******
Kurozawa et al. [29]	*		*	*	**	*		*	*******
Montella et al. [27]	*			*	**	*		*	******
Ohfuji et al. [33]	*		*	*	**	*		*	*******
Inoue et al. [30]	*		*	*	**	*	*	*	********
Johnson et al.[32]	*		*	*	**	*	*	*	********
Leung et al. [34]	*		*	*	**	*		*	*******
Jang et al. [37]	*		*	*	*	*		*	******
Michikawa et al. [38]	*		*	*	**	*		*	*******
Lai et al.[39]	*		*	*	**	*		*	*******
Bamia et al.[25]	*		*	*	**	*		*	*******
Setiawanet al.[14]	*		*	*	**	*		*	*******
Petrick et al.l [26]	*		*	*	**	*		*	*******
Tamura et al. [23]	*		*	*	**	*	*	*	********
Tanaka et al.l [28]	*		*	*	*	*		*	*******
Tran et al. [40]	*		*	*	**	*		*	*******
Hu et al. [36]	*		*	*	**	*		*	*******

also reported that higher doses of coffee were protective against liver cancer after specifically accounting for reverse causation.

The main strengths of the study are the large number of cases with HCC or liver cancer from the included studies along with the association of the amount of coffee intake with the prevention of HCC. Risk estimates were adjusted for the impact of diabetes as a possible favorable impact of coffee on HCC development. Given the significant variation in the effect of coffee in terms of HCC development, the inverse variation model is the best fit [57]. Given the significant variation, it is important to focus on the variance to estimate the overall effect. This adds to the strength of the study. The major limitation of the study is the high heterogeneity between the included studies. The primary reason for the high heterogeneity is the inclusion of observational cohorts and case control studies. Observational studies are susceptible to bias and confounding. Case control studies evaluated patients from either hospital records or clinic evaluations and therefore, may have selection bias. Another reason would be that while some studies reported the incidence of liver cancer, others reported HCC. Additionally, other confounders could include the differences in study designs in the included studies and the non-uniform approach to the measurement of the coffee intake. This was adjusted using the random effects model which provides some protection against heterogeneity. The studies included in the meta-analysis do not take into account changes in coffee intake over the long term. Additionally, coffee consumption is a self-reported information in all the included studies which could be a potential cause of misclassification of the amount of coffee consumed in the cohorts. However, exposure misclassification is frequently nondifferential and leads to the underestimation of the association. Further, multiple studies on coffee intake have demonstrated reproducibility and validity. Some of the studies had significantly higher OR of preventing HCC or liver cancer after coffee consumption as noticed in the funnel plot. The size of the effect differs according to the study size. Petrick et al. [26] and Gallus et al. [24] had a significantly higher effect of coffee in preventing HCC or liver cancer. However, Petrick et al. [26] had a significantly higher number of retired people which might have led to the difference in the effect size. Alternatively, the possibility of chance occurrence still remains which could explain the significantly different effect sizes. Therefore, the likelihood of publication bias cannot be completely excluded.

CONCLUSIONS

Coffee has preventive effects against development of HCC. Higher doses of coffee provide an additive protective effect. This protective effect has been noticed in the general population and in patients with chronic liver disease. Further randomized studies aiming at evaluating the specific ingredients and doses to prevent HCC would be valuable.

Conflicts of interest: None to declare.

Authors' contributions: A.B., S.Y. and V.R. designed the study. A.B. and P.R. performed the statistical analysis and wrote the manuscript.

All authors participated in the search strategy, evaluated the articles' eligibility for this meta-analysis and edited the manuscript. V.K.R is the guarantor of the article.

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