Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis

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Abstract

Background: Epidemiologic studies have reported inconsistent results regarding coffee consumption and the risk of liver cancer. We performed a meta-analysis of published case–control and cohort studies to investigate the association between coffee consumption and liver cancer.

Methods: We searched Medline, EMBASE, ISI Web of Science and the Cochrane library for studies published up to May 2012. We performed a meta-analysis of nine case–control studies and seven cohort studies.

Results: The summary odds ratio (OR) for high vs no/almost never drinkers was 0.50 (95% confidence interval (CI): 0.42–0.59), with no significant heterogeneity across studies (Q = 16.71; P = 0.337; I² = 10.2%). The ORs were 0.50 (95% CI: 0.40–0.63) for case–control studies and 0.48 (95% CI: 0.38–0.62) for cohort studies. The OR was 0.38 (95% CI: 0.25–0.56) in males and 0.60 (95% CI: 0.33–1.10) in females. The OR was 0.45 (95% CI: 0.36–0.56) in Asian studies and 0.57 (95% CI: 0.44–0.75) in European studies. The OR was 0.39 (95% CI: 0.28–0.54) with no adjustment for a history of liver disease and 0.54 (95% CI: 0.46–0.66) after adjustment for a history of liver disease.

Conclusions: The results of this meta-analysis suggested an inverse association between coffee consumption and liver cancer. Because of the small number of studies, further prospective studies are needed.

Keywords: Coffee, Epidemiology, Liver cancer, Meta-analysis

Background

Primary liver cancer is a common malignancy worldwide. It is the fifth most common cancer in men and the cause of a third of male cancer deaths. It is the eighth most common cancer in women and the sixth most common cause of female cancer deaths [1]. Chronic infection with hepatitis B or C viruses and alcohol consumption are considered the most important risk factors for liver cancer [2-5]. A large number of epidemiological studies indicated that environmental factors can affect the risk of liver cancer, but the role of dietary factors in tumorigenesis has not yet been determined [6-8]. Analysis of environmental factors that may be associated with liver cancer has become a popular research topic in recent years.

Coffee contains many biologically active components, some of which may have anti-tumor effects. Epidemiological studies have reported inconsistent findings on the association between coffee and liver cancer. We therefore carried out a meta-analysis of prospective cohort studies and case–control studies in order to clarify the association between coffee consumption and liver cancer.

Methods

Search strategy

We searched Medline (via PubMed; National Library of Medicine), EMBASE (Elsevier, Amsterdam, the Netherlands), ISI Web of Science (Institute for Scientific Information, Philadelphia, Pennsylvania), and the Cochrane library (Wiley, Chichester, United Kingdom) for studies published up to May 2012. Key words searched were as follows: (coffee OR caffeine OR beverages OR diet OR drinking OR lifestyle) AND (liver OR hepatocellular OR digestive) AND (cancer OR carcinoma OR tumor OR neoplasm) AND (risk). No language restrictions were applied.

Inclusion and exclusion criteria

The inclusion criteria were: case–control or cohort study; data on the frequency of coffee consumption; primary...
Table 1 Quality assessment of case–control studies included in this meta-analysis

| Study                | Adequate definition of cases | Representativeness of cases | Selection of control | Definition of control | Control for important factor or additional factor$^2$ | Exposure assessment | Same method of ascertainment for cases and controls | Nonresponse rate$^3$ | Total quality scores |
|----------------------|-----------------------------|-----------------------------|----------------------|-----------------------|-------------------------------------------------------|--------------------|---------------------------------------------------|---------------------|----------------------|
| Kuper et al. [11], 2000 | ★                            | ★                           | -                    | ★                     | -                                                     | ★                  | -                                                 | -                   | 5                    |
| Gallus et al. [12], 2002 | ★                            | ★                           | -                    | ★                     | -                                                     | ★                  | -                                                 | -                   | 6                    |
| Gelatti et al. [13], 2005 | ★                            | ★                           | -                    | ★                     | ★                                                     | -                  | -                                                 | -                   | 7                    |
| Ohfuji et al. [14], 2006 | ★                            | ★                           | -                    | ★                     | ★                                                     | -                  | -                                                 | -                   | 6                    |
| Tanaka et al. [15], 2007 | ★                            | ★                           | ★                    | ★                     | -                                                     | ★                  | -                                                 | -                   | 6                    |
| Montella et al. [16], 2007 | ★                            | ★                           | -                    | ★                     | ★                                                     | -                  | -                                                 | -                   | 6                    |
| Wakai et al. [17], 2007 | ★                            | ★                           | ★                    | ★                     | -                                                     | ★                  | -                                                 | -                   | 6                    |
| Ohish et al. [18], 2008 | ★                            | ★                           | ★                    | ★                     | ★                                                     | -                  | -                                                 | -                   | 7                    |
| Leung et al. [19], 2011 | ★                            | ★                           | -                    | ★                     | -                                                     | ★                  | ★                                                 | -                   | 5                    |

$^1$A study can be awarded a maximum of one star for each numbered item except for the item Control for most important factor or second important factor.

$^2$A maximum of two stars can be awarded for Control for most important factor or second important factor. Studies that controlled for hepatitis B virus (HBV) or HCV infection received one star, whereas studies that controlled for alcohol drinking received one additional star.

$^3$One star was awarded if there was no significant difference in the response rate between control subjects and cases in the chi-square test ($P > 0.05$).
outcome defined as liver cancer or hepatocellular carcinoma; and relative risk (RR) estimates, odds ratios (ORs) or hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs). Exclusion criteria included duplicate reports and insufficient data about coffee consumption.

Data extraction
The following data were collected from each publication: the name of the first author, year of publication, the country where the study was conducted, sex, study design, study population demographics, study period,
| Author          | Design   | Study population | Study period and outcome | Case/Control | Coffee consumption | Risk estimate (95% CI)       | Covariate adjustments                                      |
|-----------------|----------|------------------|--------------------------|--------------|--------------------|------------------------------|------------------------------------------------------------|
| Kuper et al. [11], 2000 | HCCS     | Greece           | 1995–1998 HCC incidence  | 333/360      | Nondrinkers        | 1.1 (0.5–2.6)               | Age, gender, years of schooling, HBsAg and/or anti-HCV status |
|                 |          |                  |                          |              | <20 cups/week      | 0.9 (0.4–2.5)               |                                                            |
| Gallus et al. [12], 2002 | HCCS     | Greece Italy     | 1995–1998 1984–1997 HCC incidence | 834/1912     | Nondrinkers        | 1.0                          | Age, sex, smoking, alcohol drinking, history of diabetes or hepatitis, education, BMI |
|                 |          |                  |                          |              | 1 cup/day          | 1.2 (0.9–1.6)               |                                                            |
|                 |          |                  |                          |              | 2 cup/day          | 1.0 (0.7–1.3)               |                                                            |
|                 |          |                  |                          |              | ≥2 cups/day        | 0.7 (0.5–1.0)               |                                                            |
| Shimazu et al. [20], 2005 | CS1      | Japan            | 1984–1992 Primary liver cancer incidence | 70/22404     | Nondrinkers        | 0.56 (0.33–0.97)            | Age, sex, smoking, alcohol drinking, history of liver disease |
|                 |          |                  |                          |              | occasionally       | 0.53 (0.28–1.00)           |                                                            |
| Shimazu et al. [20], 2005 | CS2      | Japan            | 1990–1997 Primary liver cancer incidence | 47/38703     | Nondrinkers        | 1.0                          | Age, sex, smoking, alcohol drinking, history of liver disease |
|                 |          |                  |                          |              | occasionally       | 1.05 (0.52–2.16)           |                                                            |
|                 |          |                  |                          |              | ≥2 cups/day        | 0.68 (0.31–1.51)           |                                                            |
| Kurozawa et al. [22], 2005 | CS       | Japan            | 1988–1999 HCC mortality  | 258/83966    | Total              | 1.0                          | Age, sex, smoking, alcohol habits, history of diabetes or liver disease, education |
|                 |          |                  |                          |              | Nondrinkers        | 0.83 (0.54–1.25)           |                                                            |
|                 |          |                  |                          |              | <1 cup/day         | 0.50 (0.31–0.79)           |                                                            |
|                 |          |                  |                          |              | ≥1 cup/day         |                             |                                                            |
|                 |          |                  |                          |              | Men                |                             |                                                            |
|                 |          |                  |                          |              | Nondrinkers        | 1.0                          | Age, sex, smoking, alcohol drinking, history of diabetes or liver disease, education |
|                 |          |                  |                          |              | <1 cup/day         | 0.91 (0.57–1.45)           |                                                            |
|                 |          |                  |                          |              | ≥1 cup/day         | 0.49 (0.28–0.85)           |                                                            |
|                 |          |                  |                          |              | Women              |                             |                                                            |
|                 |          |                  |                          |              | Nondrinkers        | 1.0                          |                                                            |
|                 |          |                  |                          |              | <1 cup/day         | 0.64 (0.27–1.51)           |                                                            |
|                 |          |                  |                          |              | ≥1 cup/day         | 0.51 (0.20–1.31)           |                                                            |
| Inoue et al. [21], 2005 | CS       | Japan            | 1990–2001 HCC incidence  | 334/90452    | Men and women      | 1.0                          | Age, sex, study area, ethanol intake, green vegetable, green tea and smoking |
|                 |          |                  |                          |              | Almost never       |                             |                                                            |
|                 |          |                  |                          |              | 1–2 day/week       | 0.75 (0.56–1.01)           |                                                            |
|                 |          |                  |                          |              | 3–4 day/week       | 0.79 (0.55–1.14)           |                                                            |
|                 |          |                  |                          |              | 1–2 cups/day       | 0.52 (0.38–0.73)           |                                                            |
|                 |          |                  |                          |              | 3–4 cups/day       | 0.48 (0.28–0.83)           |                                                            |
|                 |          |                  |                          |              | ≥2 cups/day        | 0.24 (0.08–0.77)           |                                                            |
| Study                  | Country | Women | Men                        | Nondrinkers | Taxa Measure | HCCS | HCC incidence | Age, sex, alcohol drinking, HBV and/or HCV infection |
|-----------------------|---------|-------|---------------------------|-------------|--------------|------|---------------|---------------------------------------------------|
| Gelatti et al. [13], 2005 | HCCS Italy | 1994–2003 HCC incidence | 250/500       | Nondrinkers | 1.0 | Age, sex, alcohol drinking, HBV and/or HCV infection |
|                        |         |       | Almost never               | 1.0         |              |      |              |                                                   |
|                        |         |       | 1–2 day/week               | 0.77 (0.43–1.37) |              |      |              |                                                   |
|                        |         |       | 3–4 day/week               | 0.89 (0.43–1.84) |              |      |              |                                                   |
|                        |         |       | 1–2 cups/day               | 0.43 (0.20–0.90) |              |      |              |                                                   |
|                        |         |       | 3–4 cups/day               | 0.89 (0.31–2.59) |              |      |              |                                                   |
|                        |         |       | ≥5 cups/day                | ———         |              |      |              |                                                   |
| Ohfuji et al. [14], 2006 | HCCS Japan | 2001–2002 HCC incidence | 73/253       | Nondrinkers | 1.0 | Age, sex, smoking, alcohol drinking, time since first identification of liver disease, BMI, disease severity, family history of liver disease, interferon therapy |
|                        |         |       | <1 cup/day                 | 0.61 (0.18–2.03) |              |      |              |                                                   |
|                        |         |       | ≥1 cup/day                 | 0.38 (0.13–1.12) |              |      |              |                                                   |
| Tanaka et al. [15], 2007 | PCCS Japan | 2001–2004 HCC incidence | 209/1253     | Nondrinkers | 1.0 | Age, sex, smoking status, heavy alcohol drinking, |
|                        |         |       | occasionally               | 0.33 (0.22–0.48) |              |      |              |                                                   |
|                        |         |       | 1–2 cups/day               | 0.27 (0.15–0.48) |              |      |              |                                                   |
|                        |         |       | ≥3 cups/day                | 0.22 (0.11–0.43) |              |      |              |                                                   |
| Montella et al. [16], 2007 | HCCS Italy | 1999–2002 HCC incidence | 185/412      | Abstainers | 2.28 (0.99–5.24) | 1.0 | Age, sex, alcohol drinking, HBV and/or HCV infection, education, smoking, alcohol drinking |
|                        |         |       | <14 cups/week              | 1.0         |              |      |              |                                                   |
|                        |         |       | 14–20 cups/week            | 0.54 (0.27–1.07) |              |      |              |                                                   |
|                        |         |       | 21–27 cups/week            | 0.57 (0.25–1.32) |              |      |              |                                                   |
|                        |         |       | ≥28 cups/week              | 0.43 (0.16–1.13) |              |      |              |                                                   |
| Wakai et al. [17], 2007 | NCCS Japan | 1988–1990 HCC incidence | 96/3444      | Nondrinkers | 1.0 | Age, sex, smoking, alcohol drinking, consumption of areca, educational levels, ethnicity, source of hospital |
|                        |         |       | <1 cup/day                 | 0.77 (0.45–1.32) |              |      |              |                                                   |
|                        |         |       | ≥1 cup/day                 | 0.49 (0.25–0.96) |              |      |              |                                                   |
Table 3 Characteristics of studies included in the meta-analysis (Continued)

| Study                     | Year   | Country | Incidence Period | HCC Incidence | Total Age, sex, education, study year, diabetes and chronic liver disease BMI and during follow up. |
|---------------------------|--------|---------|------------------|----------------|--------------------------------------------------------------------------------------------------|
| Hu et al. [23], 2008      | CS     | Finland | 1997–2002        | 128/60323      | Alcohol drinking, education, area, smoking, alcohol drinking, BMI and during follow up.           |
|                           |        |         |                  |                | 0–1 cup/day: 1.0                                      |
|                           |        |         |                  |                | 2–3 cups/day: 0.66 (0.37–1.16)                        |
|                           |        |         |                  |                | 4–5 cups/day: 0.44 (0.25–0.77)                        |
|                           |        |         |                  |                | 6–7 cups/day: 0.38 (0.21–0.69)                        |
|                           |        |         |                  |                | 28+ cups/day: 0.32 (0.16–0.62)                         |
|                           |        |         |                  |                | Men: 0–1 cup/day: 1.0                                  |
|                           |        |         |                  |                | 2–3 cups/day: 0.68 (0.35–1.31)                        |
|                           |        |         |                  |                | 4–5 cups/day: 0.35 (0.18–0.71)                        |
|                           |        |         |                  |                | 6–7 cups/day: 0.31 (0.15–0.63)                        |
|                           |        |         |                  |                | 28+ cups/day: 0.28 (0.13–0.61)                         |
|                           |        |         |                  |                | Women: 0–1 cup/day: 1.0                               |
|                           |        |         |                  |                | 2–3 cups/day: 0.62 (0.19–2.04)                        |
|                           |        |         |                  |                | 4–5 cups/day: 0.60 (0.20–1.82)                        |
|                           |        |         |                  |                | 6–7 cups/day: 0.58 (0.19–1.82)                        |
|                           |        |         |                  |                | 28+ cups/day: 0.41 (0.10–1.70)                         |
| Ohishi et al. [18], 2008  | NCCS   | Japan   | 1999–2002        | 224/644        | Diabetes mellitus, smoking habits, radiation dose to the liver                                    |
|                           |        |         |                  |                | Nondrinkers: 1.0                                      |
|                           |        |         |                  |                | Daily: 0.40 (0.16–1.02)                               |
| Inoue et al. [24], 2009   | CS     | Japan   | 1993–1994        | 110/18815      | Hepatitis virus infection, alcohol consumption, BMI, diabetes mellitus, and smoking habits       |
|                           |        |         |                  |                | Total: 1.0                                            |
|                           |        |         |                  |                | Almost never: 1.0                                     |
|                           |        |         |                  |                | <1 cup/day: 0.67 (0.42–1.07)                          |
|                           |        |         |                  |                | 1–2 cups/day: 0.49 (0.27–0.91)                        |
|                           |        |         |                  |                | 2+3 cups/day: 0.54 (0.21–1.39)                        |
|                           |        |         |                  |                | Women: Almost never: 1.0                             |
|                           |        |         |                  |                | <1 cup/day: 0.79 (0.46–1.37)                          |
|                           |        |         |                  |                | 1–2 cups/day: 0.37 (0.17–0.81)                        |
|                           |        |         |                  |                | 2+3 cups/day: 0.32 (0.10–1.10)                        |
| Sang et al. BMC Gastroenterology 2013, 13:34 |        |         |                  |  | |
Table 3 Characteristics of studies included in the meta-analysis (Continued)

| Study                     | Design          | Region          | Time Period        | Cases/Control | Ratios (95% CI)        |
|---------------------------|-----------------|-----------------|--------------------|---------------|------------------------|
| Johnson et al. [25], 2011 | CS              | Chinese         | 1993–2006 HCC incidence | 362/61321     | 1–2 cups/day 0.92 (0.36–2.38) |
|                           |                 |                 |                    |               | ≥3 cups/day 0.69 (0.11–4.22) |
|                           |                 |                 |                    |               | Nondrinkers 1.0 |
|                           |                 |                 |                    |               | 0–<1 drinkers/day 0.94 (0.63–1.40) |
|                           |                 |                 |                    |               | 1–<2 drinkers/day 1.17 (0.87–1.56) |
|                           |                 |                 |                    |               | 2–<3 drinkers/day 0.78 (0.56–1.07) |
|                           |                 |                 |                    |               | ≥3 drinkers/day 0.56 (0.31–1.00) |
| Leung et al. [19], 2011   | HCCS            | Hong Kong       | 2007–2008 HCC incidence | 109/125       | <1 time/week 1.0 |
|                           |                 |                 |                    |               | 1–3 times/week 0.58 (0.24–1.36) |
|                           |                 |                 |                    |               | ≥4 times/week 0.41 (0.19–0.89) |

ALT: alanine aminotransferase; BMI: body mass index; CI: confidence interval; HbsAg: hepatitis B surface antigen; HCCS: hospital-based case–control study; PCCS: population-based case–control study; NCCS: nested case–control study; CS: cohort study; HCC: hepatocellular carcinoma.
sample size, type of outcome, consumption of coffee, number of exposed cases, the RRs or ORs or HRs and their 95%CIs, and covariates adjusted in the analysis. All data were extracted independently by three reviewers, and any disagreement was resolved by discussion between them. If results were published more than once, the results from the most recent one were selected. Because liver cancer is rare, the OR was assumed to be the same as RR and HR, and all results are reported as OR for simplicity [9].

Quality assessment
The study quality was assessed by the 9-star Newcastle-Ottawa Scale [10]. A full score is 9 stars, and a score ≥ 6 stars is considered to be high quality. The quality of case–control studies was assessed as follows: adequate definition of cases, representativeness of cases, selection of controls, definition of controls, control for the most important factor or the second important factor, exposure assessment, same method of ascertainment for all subjects, and non-response rate (Table 1). The quality of cohort studies was assessed as follows: representativeness of the exposed cohort, selection of the unexposed cohort, ascertainment of exposure, outcome of interest not present at start of study, control for the most important factor or the second important factor, outcome assessment, follow-up long enough for outcomes to occur, adequacy of follow-up of cohorts (Table 2).

Statistical analysis
For the included studies, we determined pooled ORs (or RRs or HRs) with 95% CI for the highest versus lowest category of coffee consumption from each study. Since various sources of heterogeneity may exist owing
to a variety of factors, we carried out subgroup analysis to investigate the influence of study design, study region, sex and history of liver disease on the heterogeneity.

Statistical heterogeneity was evaluated through the Q test and $I^2$ statistic [26]; $P < 0.10$ was considered statistically significant [27]. If the heterogeneity was acceptable ($I^2 < 50\%$), a fixed effects analysis was conducted to calculate the pooled OR. In addition, a random effects model was used. The causes of heterogeneity were investigated by subgroup analyses. To evaluate whether publication bias might affect the statistical results, we applied Egger’s test and Begg’s method to assess bias through visual inspection of funnel plots [28,29]; all statistical analyses were conducted using STATA (version 11.0; StataCorp, College Station, TX, USA). All statistical tests were 2-sided.

Results

Study characteristics

Figure 1 shows the process of selecting studies for the meta-analysis. Sixteen observational articles examining the association between coffee consumption and the risk of liver cancer were included in our meta-analysis (Table 3) [11-25]. There were nine case–control studies [11-19] and seven cohort studies (two of these were nested in a cohort article) [20-25]. Of the selected studies, 11 were conducted in Asia (nine in Japan [14,15,17,18,20-22,24], one in Singapore [25], one in Hong Kong [19]) and five in Europe (one in Finland [23], two in Italy [13,16], one in Greece [11], one in Italy and Greece [12]). Among case–control studies, seven were hospital-based case–control studies [11-19,1], and two were nested case–control studies [17,18].

High vs Non/Almost never drinkers

A meta-analysis of risk estimates for the incidence of liver cancer for highest compared with lowest coffee consumption categories could be conducted with data from nine case–control studies and nine cohort studies. Our results showed a 50% reduction in risk of liver cancer with the highest intake of coffee (summary OR: 0.50, 95% CI: 0.42–0.59) (Figure 2). There was no significant heterogeneity across studies ($Q = 16.71, P = 0.337, I^2 = 10.2\%$). There was a symmetric funnel plot and no evidence of significant publication bias from Egger’s test ($P = 0.05$) and Begg’s test ($P = 0.096$) (Figure 3).

A sensitivity analysis for the risk of liver cancer was performed by excluding one study [22], the outcome of which was mortality. The summary OR was 0.49 (95% CI: 0.41–0.59). There was no significant heterogeneity across studies ($Q = 16.7, P = 0.272, I^2 = 16.2\%$).

Similar results were found in a subgroup analyses conducted by study design in case–control studies (OR: 0.50, 95% CI: 0.40–0.63, $Q = 12.38, P = 0.125, I^2 = 36.8\%$), and cohort studies (OR: 0.48, 95% CI: 0.38–0.62, $Q = 2.47, P = 0.676, I^2 = 0.0\%$) (Figure 4).

In a subgroup analysis conducted by sex, only four studies were included in the analysis: studies in males gave an OR of 0.38 (95% CI: 0.25–0.56, $Q = 1.83, P = 0.609, I^2 = 0.0\%$), while studies in females gave an OR of 0.60 (95% CI: 0.33–1.10, $Q = 0.94, P = 0.815, I^2 = 0.0\%$) (Table 4).

When stratified analysis was conducted by study region, a statistically significant protective effect of coffee consumption on liver cancer was observed in Asia
Stratification analysis was conducted without or with adjustment for a history of liver disease. A statistically significant protective effect of coffee consumption on liver cancer was observed with no adjustment for a history of liver disease (OR: 0.39, 95% CI: 0.28 – 0.54, Q = 5.34, P = 0.254, I² = 25.1%) and after adjustment for a history of liver disease (OR: 0.54, 95% CI: 0.46 – 0.66, Q = 8.5, P = 0.581, I² = 0.0%).

Discussion
Coffee consumption has been suggested as a protective factor in the development of liver cancer, but evidence from observational studies is inconsistent [11-25]. The results of the current meta-analysis of seven prospective and nine case–control studies suggest that there is an inverse association between coffee consumption and liver cancer among different groups according to consumption level. There were significant reductions of 50% in the risk of liver cancer with the highest consumption of coffee compared with non/almost never consumption. The meta-analyses of Bravi et al. [30] found significant reductions of 55% in the risk of liver cancer with the high drinkers compared with non-drinkers, and Larsson & wolk [31] found a risk reduction of 43% per 2 cups of coffee per day increment. Our results are consistent with these two previous articles, partly because all of the studies in these two articles are included in the our meta-analysis.

Some results in this meta-analysis were heterogeneous, because the included studies had differences in study design, study region, study sex distribution, and...
control for confounding factors. In separate analyses by study design, we found an inverse association between coffee consumption and liver cancer among hospital- based case–control studies and among cohort studies.

There was also an inverse association between coffee consumption and liver cancer among European and Asian populations, and the significant risk reduction was stronger among Asian than European populations. The different results may be explained by racial differences. Differences in coffee drinking habits may be a partial explanation for the discrepancy.

We also found an inverse association between coffee consumption and liver cancer among male and female populations, but this result was derived from only four studies with a small number of cases, so we could not draw a firm conclusion. A history of liver disease may be a risk factor for liver cancer, and after adjustment for this, a significant inverse association remained between coffee consumption and liver cancer among two subgroups.

There are several potential mechanisms through which high consumption of coffee may reduce the risk of liver cancer. Coffee contains a variety of chemicals including caffeine, cafestol, kahweol, and chlorogenic acids. It remains uncertain which ingredient of coffee is protective against liver cancer. Some studies have indicated that caffeine can prevent oxidative DNA damage, modify the apoptotic response and reverse cell cycle checkpoint function [32-34]. Caffeine has strong antioxidant properties [35]. In an animal experiment, caffeine significantly reduced the incidence of chemically-induced hepatocellular carcinoma in rats [36]. Furthermore, cafestol and kahweol have been shown to be anticarcinogenic [37,38]. Cafestol and kahweol have demonstrated a protective effect against aflatoxin B1-induced genotoxicity [39]. In addition, a study by Feng et al. showed that chlorogenic acids can scavenge reactive oxygen species and have an anti-tumor effect [40]. These studies suggest that ingredients in coffee may play an important role in protecting against the occurrence and development of liver cancer.

Our meta-analysis had some merits. First, the total number of cases included in this meta-analysis was substantial (n = 3622 liver cancer cases). The summary ORs of the highest compared with the lowest coffee consumption categories for risk of liver cancer were consistent with those in a previously published meta-analyses (n = 2260 liver cancer cases) [30,31]. Second, we found little evidence of publication bias in our meta-analysis. Third, we performed a comprehensive search of the literature on the association between coffee consumption and liver cancer risk up to May 2012.

Our meta-analysis had several limitations. First, we used the highest and lowest coffee consumption levels as measures of exposure, but we were not able to determine whether different amounts of coffee consumption could decrease liver cancer risk. Second, misclassification bias should be considered. Each study presented coffee consumption in different units (cups/week, cups/day, days/week, drinks/day, times/week). Therefore, differential misclassification could bias the results.

### Table 4 Pooled relative risks and 95% CI for coffee consumption and liver cancer risk

| Study | No. of studies | No. of cases | Relative risk (95% CI) | Heterogeneity |
|-------|---------------|--------------|------------------------|---------------|
|       |               |              |                        | Q  | P    | I² (%)   |               |
| High versus non/almost never intake | 16 | 3,622 | 0.50 (0.42–0.59) | 16.71 | 0.337 | 10.2% |               |
| Study design | | | | | | | |
| Cohort studies | 7 | 1,309 | 0.48 (0.38–0.62) | 2.47 | 0.676 | 0.0% |               |
| Case–control studies | 9 | 2,313 | 0.50 (0.40–0.63) | 12.38 | 0.125 | 36.8% |               |
| Study region | | | | | | | |
| Asia | 11 | 1,892 | 0.45 (0.36–0.56) | 7.86 | 0.642 | 0.0% |               |
| Europe | 5 | 1,730 | 0.57 (0.44–0.75) | 7.09 | 0.131 | 43.6% |               |
| Study gender | | | | | | | |
| Male | 4 | 583 | 0.38 (0.25–0.56) | 1.83 | 0.609 | 0.0% |               |
| Female | 4 | 247 | 0.60 (0.33–1.10) | 0.94 | 0.815 | 0.0% |               |
| Adjustment for main confounders\(^a\) | | | | | | | |
| Adjusted | 11 | 2,512 | 0.54 (0.46–0.66) | 8.5 | 0.581 | 0.0% |               |
| Unadjusted | 5 | 1,110 | 0.39 (0.28–0.54) | 5.34 | 0.254 | 25.1% |               |

\(^{a}\)main confounder: hepatitis B and hepatitis C virus infection or history of liver disease.
Third, because liver cancer is a multifactorial disease, it is uncertain whether other factors may have influenced the results. Fourth, the study areas covered in our meta-analysis only included Asia (Japan, China, Hong Kong) and Europe (Finland, Greece, Italy). Therefore, the value of our results is limited for other areas (Africa, America and Australia). Fifth, potential publication bias might have influenced the results, despite no bias indicated from either the funnel plot or Egger's test.

**Conclusion**

The results of this meta-analysis suggested that coffee consumption may be associated with a reduced risk of liver cancer. However, because of potential confounding, this finding should be treated with caution. Further better-controlled studies are needed to confirm this finding.

**Competing interests**
The authors declare no potential conflict of interest relevant to this research.

**Authors’ contributions**
LXS and BC designed the research; LXS and XHL performed the literature search; LXS, XHL and MJ analyzed the data and interpreted the results; LXS and BC wrote the paper; all authors approved the final manuscript.

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