Consumption of Coffee Reduces Risk for Liver Cancer: A Meta-Analysis

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Abstract

Background & Aims: Epidemiologic studies are not identical regarding risk for liver cancer related to coffee consumption. 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. All statistical analyses were conducted with STATA (version 11.0; StataCorp, College Station, TX).

Results: 9 case-control studies and 7 cohort studies were selected in our meta-analysis. The fixed-effects summary OR for highest vs lowest intake category was 0.50 (95% CI: 0.43 - 0.59), with no significant heterogeneity across studies. Subgroup analysis was conducted by study
design, study region, gender, adjusted or unadjusted history of liver
disease. The ORs was 0.51(95% CI: 0.40-0.66) for hospital-based case-
control studies, 0.46(95% CI: 0.27-0.79) for nested case-control studies
and 0.50(95% CI: 0.39-0.63) for cohort studies. The ORs was 0.40(95%
CI: 0.28-0.57) in male and 0.60(95% CI: 0.33-1.10) in female. The ORs was
0.47(95% CI: 0.38-0.57) for Asia and 0.57(95% CI: 0.44-0.75) for Europe
studies. The ORs was 0.48(95% CI: 0.38-0.60) for adjusted a history of
liver disease and 0.53(95% CI: 0.42-0.67) for unadjusted a history of liver
disease studies.

**Conclusions:** The results of this meta-analysis suggested that coffee
consumption may be associated with reduced risk of liver cancer. Because
the small number of studies, further prospective studies are needed.

**Keywords:** coffee; liver cancer; meta-analysis.

**Introduction**

Primary liver cancer is a common malignancy tumor in worldwide. It
is the fifth common malignant tumor and third of deaths caused by
malignant tumor in men. It is the eighth common malignant tumor and
the sixth deaths caused by malignant tumors in women\(^1\). **Chronic**
infection with hepatitis B or C viruses, alcohol consumption are
considered the most important risk factors for liver cancer\(^2\)[3][4][5]. A large
number of epidemiological studies indicate that environmental factors can
affect the risk of liver cancer, the role of dietary factors in tumorigenesis
has not yet been determined\cite{6,7,8}. Therefore, change the environmental factors to prevent liver cancer has become one of the hot research in recent years.

Coffee contains many biologically active components, which with anti-tumor effect. Epidemiology has reported inconsistent findings on coffee and liver cancer. Therefore, in order to clarify the influence of coffee in liver cancer, We carried out a meta-analysis of prospective cohort studies and case-control studies on this topic.

Materials and Methods

Literature 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 OR dietry) 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:(1)case-control or cohort study;(2)the exposure of interest was the frequency of coffee consumption;(3)the
primary outcome was defined as liver cancer or HCC; (4) the relative risk (RR) estimates or odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were reports. Exclusion criteria included: (1) duplicate reports; (2) 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, study period, sample size, type of outcome, consumption of coffee, number of exposed cases, the RRs or ORs or HRs and their 95% confidence intervals (CIs) and covariates for adjustment in the analysis. All data were extracted independently by three reviewers, any disagreement was resolved by discussion among three reviewers. 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 similar the same as RR and HR, and we report all results as the OR for simplicity.\(^9\)

**Quality assessment**

The study quality was assessed by the 9-star system.\(^10\) The full score was 9 stars, Score ≥ 6 stars is considered to be high-quality research. The quality of case-control studies were assessed as follows: adequate definition of cases, representativeness of cases, selection of control, definition of control, control for the most important factor or the second
important factor, exposure assessment, same method of ascertainment for all subjects, non-response rate (Table 1). The quality of cohort studies were 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**

Statistical analyses were conducted for the included studies. We computed a pooled ORs (or RR or HRs) with 95% CI for the highest versus lowest category of coffee consumption from each study. Since various sources of heterogeneity may exist due to a variety of factors, we carried out subgroup analysis to investigate the influence of study design, study region, gender and history of liver disease in the heterogeneity. Statistical heterogeneity was evaluated through the Q test and I² statistics [11], P<0.10 was considered statistically significant [12]. If the heterogeneity was acceptable (I² <50%), a fixed effects was conducted to calculate the pooled OR; In addition, a random effect model was used. The causes of heterogeneity were investigated by subgroup analyses. To evaluated whether publication bias might affect the statistical results, we applied Egger’s test and Begg’s method to assess the bias through visual inspection of funnel plots [13][14], P<0.05 indicated bias and P>0.05
indicated no obviously publication bias. All statistical analyses were conducted with STATA (version 11.0; StataCorp, College Station, TX). P<0.05 was considered statistically significant. All statistical tests were two sided.

**Results**

**Study Characteristics**

Figure 1 shows the process of selecting studies for the meta-analysis. Fifteen observational articles regarding the association between coffee consumption and the risk of liver cancer were included in our meta-analysis (Table 3). There were 9 case-control studies\cite{15,16,20,21,22,23,24,26} \cite{29} and 7 cohort studies (2 of those were nested in a cohort article)\cite{17,18,19,25,27,28}. Of the selected studies, 11 were conducted in Asia (9 in Japan\cite{17,18,19,21,22,24,26,27}, 1 in Singapore\cite{28} and 1 in Hong Kong\cite{29}) and 5 in Europe (1 in Finland\cite{25}, 2 in Italy\cite{20,23}, 1 in Greece\cite{15}, 1 in Italy and Greece\cite{16}). Among case-control studies, 7 were hospital-based case-control studies\cite{15,16,20,21,22,23,29}, 2 were nested case-control studies\cite{24,26}.

**Highest vs lowest intake category**

Meta-analysis of risk estimates of liver cancer incidence for the highest compared with the lowest coffee consumption category could be conducted from 9 case-control studies and 7 cohort studies. Our results showed a 50% reduction in risk of liver cancer with highest intake of
coffee (summary OR: 0.50; 95% CI: 0.43 -0.59) (Figure 2). There was no significant heterogeneity across studies (Q=15.12, P=0.443, I²=0.8% ). There was no evidence of significant publication bias from Egger’s (P=0.095) test and Begg’s (P=0.192) test (Figure 3).

**Subgroup analysis**

The results of subgroup analyses by study design, study region, gender. Subgroup analysis was conducted by study design, hospital-based case-control studies (OR: 0.51, 95% CI: 0.40-0.66), nested case-control studies (OR: 0.46, 95% CI: 0.27-0.79), and cohort studies (OR: 0.50, 95% CI: 0.39-0.63) (Figure 4).

Subgroup analysis was conducted by gender, only four studies were included in the analysis. Studies in male (OR: 0.40, 95% CI: 0.28-0.57), studies in female (OR: 0.60, 95% CI: 0.33-1.10), there was no heterogeneity among the 4 studies (Q=3.80, P=0.80, I²=0.0%), and no publication bias was found (P=0.66).

When stratified analysis was conducted by study region, a statistical significant protective effect of coffee consumption on liver cancer was observed in Asia (OR: 0.47, 95% CI: 0.38-0.57), in Europe (OR: 0.57, 95% CI: 0.44-0.75) (Figure 5).

Stratifying analysis was conducted by adjusted or unadjusted history of liver disease, a statistical significant protective effect of coffee consumption on liver cancer was observed adjusted a history of liver
disease (OR: 0.48, 95% CI: 0.38-0.60), unadjusted a history of liver disease (OR: 0.53, 95% CI: 0.42-0.67).

Discussion

To our knowledge, coffee consumption has an important role in the development of liver cancer, but evidence from observational studies is inconsistent. The results of the meta-analysis from 7 prospective studies and 9 case-control studies suggest that high coffee consumption have a protective effect on liver cancer. The data found a significant reduction in the risk of liver cancer of 50% in highest coffee drinkers as compared with lowest ones.

There are several potential mechanisms through which high consumption of coffee may reduce the risk of liver cancer. Coffee contains a variety of chemical composition 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\cite{30}\cite{31}\cite{32}. Caffeine has strong antioxidant properties\cite{33}. In an animal experiment, caffeine significantly reduce the incidence of chemically induced hepatocellular carcinoma in rat\cite{34}. Furthermore, cafestol and kahweol have been shown to be anti-carcinogenic effect\cite{35}\cite{36}. Cafestol and kahweol against aflatoxin B1-induced genotoxicity have been demonstrated\cite{37}. In addition, study by
Feng R has shown that chlorogenic acids can scavenge reactive oxygen species and has anti-tumor effect\[38\]. These studies suggest that ingredients of coffee may play an important role in the protection against the occurrence and development of liver cancer.

Our meta-analysis had some merits. First, the total cases included in this meta-analysis was substantial (n=3697 liver cancer cases). The summary ORs with highest compared with the lowest coffee consumption category for risk of liver cancer were consistent with those previously published meta-analysis (n=2260 liver cancer cases)\[39\]. Second, we found little evidence of publication bias in our meta-analysis. Third, there are a comprehensive search of literature on the association between coffee consumption and liver cancer risk before May 2012.

Our meta-analysis have several limitations. First, we used the highest and lowest coffee consumption levels as measures of exposure, we were not able to obtain that the different amount of coffee consumption itself increase liver cancer risk. Second, misclassification bias should be considered. The data are that each study presented coffee consumption in different units (cups/week, cups/day, day/week, drinkers/day, times/week). Therefore, differential misclassification could bias the results. Third, because liver cancer is a multifactorial disease, it is uncertain whether other factors may have influenced the Analysis results. Fourth, the study areas covered in our meta-analysis include Asia (Japan, China, Hong Kong)
and Europe (Finland, Greece, Italy). Therefore, the value of our results is limited for other areas (Africa, America and Oceania). Fifth, potential publication bias might influenced the results, despite no publication bias was indicated from both funnel plot and Egger’s test.

**In conclusion**, this study combining OR estimates from studies on the relationship between coffee consumption and liver cancer incidence. The results of this meta-analysis suggested that coffee consumption may be associated with reduced risk of liver cancer.

**Conflict of interest**

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

**Authors’ contributions**

LXS and BC designed the research; LXS and XHL did the literature search; LXS and MJ analyzed the data and interpreted results; LXS and BC wrote the paper; All authors approved the final manuscript.

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Reference


Potential relevant articles identified for retrieval (n=226)

Articles excluded by screening of titles or abstracts (n=147)

Potential relevant articles were selected in this meta-analysis (n=79)

Articles excluded because they were review articles, laboratory studies or did not provide sufficient information (n=64).

Final articles included in this meta-analysis (n=15, 2 cohort studies were nested in a cohort article)

- Cohort studies (n=7)
- Case-control studies (n=9)

Figure 1: Process of study selection in the meta-analysis.
Figure 2. Risk estimates from studies assessing the association high coffee consumption (highest versus non/lowest) and liver cancer risk.
Figure 3 Begg’s Funnel Plot of coffee consumption and risk of liver cancer
Figure 4 Forest plot of coffee consumption (highest versus non/lowest) and risk of liver cancer.
### Table 1

<table>
<thead>
<tr>
<th>Study ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuper et al.[2000]</td>
<td>0.90 (0.40, 2.50)</td>
<td>3.14</td>
</tr>
<tr>
<td>Gallus et al.[2002]</td>
<td>0.70 (0.50, 1.00)</td>
<td>21.95</td>
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<tr>
<td>Gelatti et al.[2005]</td>
<td>0.30 (0.10, 0.70)</td>
<td>2.79</td>
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<tr>
<td>Montella et al.[2007]</td>
<td>0.43 (0.16, 1.13)</td>
<td>2.76</td>
</tr>
<tr>
<td>Hu et al.[2008]</td>
<td>0.32 (0.16, 0.62)</td>
<td>5.75</td>
</tr>
<tr>
<td>Subtotal (I-squared = 43.6%, p = 0.131)</td>
<td>0.57 (0.44, 0.75)</td>
<td>36.39</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shimazu et al.[2005][1]</td>
<td>0.53 (0.28, 1.00)</td>
<td>6.51</td>
</tr>
<tr>
<td>Shimazu et al.[2005][2]</td>
<td>0.68 (0.31, 1.51)</td>
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</tr>
<tr>
<td>Inoue et al.[2005]</td>
<td>0.48 (0.28, 0.83)</td>
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<tr>
<td>Kurozawa et al.[2005]</td>
<td>0.50 (0.31, 0.79)</td>
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<td>Ohfuji et al.[2006]</td>
<td>0.38 (0.13, 1.12)</td>
<td>2.27</td>
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<td>Tanaka et al.[2007]</td>
<td>0.22 (0.11, 0.43)</td>
<td>5.67</td>
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<td>Wakai et al.[2007]</td>
<td>0.49 (0.25, 0.96)</td>
<td>5.83</td>
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<tr>
<td>Ohishi et al.[2008]</td>
<td>0.40 (0.16, 1.02)</td>
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<tr>
<td>Inoue et al.[2009]</td>
<td>0.54 (0.21, 1.39)</td>
<td>2.95</td>
</tr>
<tr>
<td>Johnson et al.[2011]</td>
<td>0.56 (0.31, 1.00)</td>
<td>7.69</td>
</tr>
<tr>
<td>Leung et al.[2011]</td>
<td>0.41 (0.19, 0.89)</td>
<td>4.42</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.760)</td>
<td>0.47 (0.38, 0.57)</td>
<td>63.61</td>
</tr>
</tbody>
</table>

| Heterogeneity between groups: p = 0.235 | Overall (I-squared = 0.8%, p = 0.443) | 0.50 (0.43, 0.59) | 100.00 |

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**Figure 5** Forest plot of coffee consumption (highest versus non/lowest) and risk of liver cancer.
Additional files provided with this submission:

Additional file 1: Table 1.doc, 48K
http://www.biomedcentral.com/imedia/1983702967668903/supp1.doc
Additional file 2: Table 2.doc, 36K
http://www.biomedcentral.com/imedia/5233183137668903/supp2.doc
Additional file 3: Table 3.doc, 78K
http://www.biomedcentral.com/imedia/1838816583766890/supp3.doc
Additional file 4: Table 4.doc, 52K
http://www.biomedcentral.com/imedia/1350571027766890/supp4.doc