Coffee Drinking and Hepatocellular Carcinoma Risk: A Meta-Analysis

Francesca Bravi,[1] Cristina Bosetti,[1] Alessandra Tavani,[1] Vincenzo Bagnardi,[2] Silvano Gallus,[1] Eva Negri,[1] Silvia Franceschi,[3] and Carlo La Vecchia[1,4]

Several studies suggest an inverse relation between coffee drinking and risk of hepatocellular carcinoma (HCC). We conducted a meta-analysis of published studies on HCC that included quantitative information on coffee consumption. Ten studies were retrieved (2,260 HCC cases), including 6 case–control studies from southern Europe and Japan (1551 cases) and 4 cohort studies from Japan (709 cases). The summary relative risk (RR) for coffee drinkers versus non-drinkers was 0.54 (95% confidence interval [CI] 0.38-0.76) for case–control studies and 0.64 (95% CI 0.56-0.74) for cohort studies. The overall RR was 0.59 (95% CI 0.49-0.72), with significant heterogeneity between studies. The overall summary RR for low or moderate coffee drinkers was 0.70 (95% CI 0.57-0.85), and that for high drinkers was 0.45 (95% CI 0.38-0.53). The summary RR for an increase of 1 cup of coffee per day was 0.77 (95% CI 0.72-0.83) from case–control studies, 0.75 (95% CI 0.65-0.85) from cohort studies, and 0.77 (95% CI 0.72-0.82) overall. The consistency of an inverse relation between coffee drinking and HCC across study design and geographic areas weighs against a major role of bias or confounding. Coffee drinking has also been related to reduced risk of other liver diseases, thus suggesting a continuum of the favorable effect of coffee on liver function. However, subjects with liver conditions may selectively reduce their coffee consumption. *Conclusion:* The present analysis provides evidence that the inverse relation between coffee and HCC is real, though inference on causality remains open to discussion. (HEPATOLOGY **2007;46:430-435.**)

Several data have been reported on a potentially favorable effect of coffee on liver function and liver diseases, including liver enzymes, cirrhosis, and hepatocellular carcinoma (HCC).[1]

Coffee consumption has been inversely related to γ-glutamyltransferase and aminotransferase activity in studies from Europe, Japan, and the United States.[1-4] Such inverse relations are stronger in high-risk subjects, particularly in heavy drinkers.[1,5-10] Coffee drinking has also been inversely related to the risk of cirrhosis—a major correlate of HCC[11-13]—in studies from North America and Europe.[14-18]

At least 11 studies conducted in southern Europe and Japan have considered the relation between coffee drinking and the risk of HCC. A Greek case–control study of 333 cases reported an age-adjusted and sex-adjusted odds ratio (OR) of 0.7 for drinkers of ≥20 cups of coffee per week compared with those who never drink coffee.[12] An Italian case–control study of 151 cases of HCC reported a multivariate OR of 0.78 for drinkers of ≥3 cups of coffee per day compared with occasional drinkers.[19] An update analysis of the Italian study,[20] including 501 HCC cases, reported an OR of 0.5 for drinkers of ≥3 cups per day compared with never drinkers, with a significant trend in risk with dose. The combined analysis of the Greek and Italian case–control studies[20] gave an OR of 0.7 for drinkers of ≥3 cups per day compared with never drinkers, with a significant trend in risk. The inverse relation was also evident among subjects with a history of infection with HBV and/or HCV. In another Italian case–control study of 250 cases, OR was 0.8 for drinkers of 1-2 cups per day, 0.4 for drinkers of 3-4 cups per day,

Abbreviations: HCC, hepatocellular carcinoma; OR, odds ratio; RR, relative risk.

From [1]Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy; [2]Dipartimento di Statistica, Università degli Studi di Milano-Bicocca, Milan, Italy; [3]International Agency for Research on Cancer, Lyon, France; and [4]Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy.

Received January 30, 2007; accepted March 5, 2007.

Supported by the Italian Association for Cancer Research, the Italian League Against Cancer, and the Italian Ministry of Research (PRIN 2005). Francesca Bravi is a Fellow of the Rosario Samanin Fund.

Address reprint requests to: Francesca Bravi, Sc.D., Laboratorio di Epidemiologia, Istituto di Ricerche Farmacologiche "Mario Negri," Via Eritrea 62-20157 Milan, Italy. E-mail: bravi@marionegri.it; fax: (39) 02-33200231.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.21708

Potential conflict of interest: Nothing to report.

and 0.3 for drinkers of ≥5 cups per day.[21] In an additional Italian case–control study of 185 HCC cases, OR was 0.4 for drinkers of ≥3 cups per day compared with never drinkers, with a significant trend in risk.[22] The inverse relation was also observed among heavy alcohol drinkers and in subjects with or without serological evidence of hepatitis.[22] A Japanese case–control study of 73 cases of HCC assessed the role of coffee consumption on the risk of HCC among cases and controls with serological evidence of HCV.[23] Regular coffee drinkers (≥1 cup per day) had an OR of 0.38 compared with nondrinkers. Another Japanese case–control study included 209 cases of HCC and 3 different groups of controls (1,253 community controls, 275 hospital controls, 381 chronic liver diseases patients without HCC).[24] For coffee consumption 10 years before diagnosis, adjusted ORs for occasional use, 1-2 cups per day, and ≥3 cups per day compared with no use were 0.33, 0.27, 0.22, respectively, using community controls. Corresponding ORs were 0.86, 0.62, and 0.53 in chronic liver disease patients. In a case–control study conducted in Haimen, China, only 7 cases and 7 controls reported to drink coffee at least twice per month, with a corresponding OR of 1.08.[25]

A Japanese prospective study of 90,452 subjects followed for 10 years and including 334 HCC cases found that drinkers of ≥5 cups of coffee per day had a lower HCC risk (relative risk [RR] = 0.24) than those who almost never consumed coffee, with a significant trend in risk.[26] A pooled analysis of 2 other Japanese cohort studies, including 22,404 and 38,703 subjects followed for 9 and 6 years, respectively, and a total of 117 HCC cases, yielded a RR of 0.58 for drinkers of ≥1 cup per day compared with never drinkers.[27] The beneficial effect of coffee was also evident among subjects with a history of HBV or HCV. In another cohort investigation from Japan (the Japan Collaborative Cohort Study for Evaluation of Cancer Risk [JACC] Study),[28] including 83,966 subjects followed for up to 11 years, and 258 cases, the multivariate RR was 0.50 for regular (≥1 cup per day) coffee drinkers. The inverse relation was similar in men and women, and in subjects with and without history of liver disease.

We have combined all published data on this issue to obtain an overall quantitative estimate of the association between coffee drinking and HCC.

Materials and Methods

Search Strategy and Selection Criteria. We performed a MEDLINE search of the literature from 1966 to February 2007 using the MeSH terms "coffee" and combinations of "hepatocellular" or "liver" and "carcinoma" or "neoplasm." Additionally, the reference lists of the identified publications were cross-checked to obtain other pertinent publications. We considered articles presenting data from case–control and cohort studies that were originally published in English. We identified 11 papers: 8 case–control studies[12,19-25] and 3 cohort studies[26-28] (Table 1). Among these, Gallus et al.[20] reported data from 2 case–control studies conducted in Greece[12] and Italy[19] that we considered separately. Similarly, Shimazu et al.[27] presented data from 2 prospective cohorts that we considered as 2 different studies (cohort 1 and cohort 2). We did not include in the meta-analysis a case–control study from China[25] that did not report daily or weekly coffee consumption. When the data of a study were included in more than 1 publication, only the most recent and complete study was included in the meta-analysis.

For each study, we extracted details on study design, number of subjects (cases and controls or person-years), daily or weekly consumption of coffee, and control of confounding factors. We did not assign quality scores to studies, and no studies were excluded a priori for weakness of design or data quality.

Statistical Methods. The measure of interest was the RR for cohort studies, approximated by the OR in case–control studies, and the corresponding 95% CI. When RRs were not available in the published article, they were computed from the exposure distributions. Because the various studies used different units to measure coffee consumption, we converted these into cups per day as a standard measure. Publication bias was evaluated using funnel plots[29] and Egger's test.[30]

To compute summary RR for various levels of coffee consumption, we first calculated the study-specific estimates separately for low or moderate consumption (defined as <3 cups per day for Gallus et al.,[20] Gelatti et al.,[21] Inoue et al.,[26] and Montella et al.,[22] and as <1 cup per day for Kurozawa et al.,[28] Shimazu et al.,[27] Ohfuji et al.,[23] and Tanaka et al.[24]) and high consumption (defined as ≥3 cups per day for Gallus et al.,[20] Gelatti et al.,[21] Inoue et al.,[26] and Montella et al.[22] and as ≥1 cup per day for Kurozawa et al.,[28] Shimazu et al.,[27] Ohfuji et al.,[23] and Tanaka et al.[24]).

We computed the summary RR for coffee drinkers versus non-drinkers and for different levels of consumption by giving each study-specific RR a weight proportional to its precision (i.e., the inverse of the variance, derived, when necessary, from the reported 95% CI).[31] We calculated summary estimates for the 2 study types (case–control and cohort) separately, as well as in combination. We assessed the statistical heterogeneity among studies using the χ^2 test; results were defined as heterogeneous for P values less than 0.10.[31] We pooled the study-

Table 1. Case–Control and Cohort Studies on Coffee Consumption and HCC

Study	Country	No. of Cases	No. of Controls/Size of Cohort	Duration of Follow-up	Adjustment
Case-control studies					
Kuper et al.[12,20,*]	Greece	333	360	–	Age, sex
Gallus et al.[20,*]	Italy	501	1,552	–	Age, sex
Gelatti et al.[21,*]	Italy	250	500	–	Age, sex, alcohol drinking, HCV, HBV
Montella et al.[22,*†]	Italy	185	412	–	Age, sex, education, tobacco smoking, alcohol consumption, serological evidence of HCV and/or HBV infection
Ohfuji et al.[23]	Japan	73	253	–	Duration of liver disease, body mass index, disease severity, family history of liver disease, interferon therapy, tobacco smoking, alcohol consumption, consumption of other caffeine-containing beverages
Tanaka et al.[24,‡]	Japan	209	1,253	–	Age, sex, alcohol consumption, tobacco smoking
Cohort studies					
Inoue et al.[26]	Japan	334	90,452	10 years	Age, sex, study center, tobacco smoking, alcohol consumption, vegetable consumption, tea consumption
Shimazu et al.[27] (cohort 1)	Japan	70	22,404	9 years	Age, sex, history of liver disease, tobacco smoking, alcohol consumption
Shimazu et al.[27] (cohort 2)	Japan	47	38,703	6 years	Age, sex, history of liver disease, tobacco smoking, alcohol consumption
Kurozawa et al.[28]	Japan	258	83,966	11 years	Age, sex, education, history of diabetes and liver disease, tobacco smoking, alcohol consumption

*Hospital-based case-control study.
†OR computed from published frequencies.
‡Population-based case-control study.

specific estimates using the fixed effect model and the random effect model proposed by DerSimonian and Laird[32] when a significant heterogeneity was found.

Because some studies provided risk estimates for subjects with a history of hepatitis or liver disease[20,27,28] or serological evidence of HBV and/or HCV,[22,23] we also computed the summary RR for coffee drinkers versus non-drinkers in those subjects.

For dose–response analysis, we used the method proposed by Greenland and Longnecker[33] to estimate study-specific slopes from the natural logarithm of the RR across exposure categories, assigning to each class the dose corresponding to the midpoint of the range. Because the higher category of consumption was usually open, we considered it of the same amplitude as the preceding category. Then, we obtained the summary RR estimates by pooling the study-specific slopes, using the inverse of the corresponding variances as weights.

Forest plots were given. In these graphs, a square was plotted for each study whose center projection on the underlying scale corresponded to the study-specific RR. The area of the square was proportional to the inverse of the variance of the natural logarithm of the RR and thus gives a measure of the amount of statistical information available from that particular estimate. A diamond was used to plot the summary RRs, the center of which represents the RR; the extremes of the summary RRs show the 95% CIs.

Results

Figure 1 and Table 2 show the RR for coffee drinkers versus never drinkers in case–control studies, cohort studies, and overall. The combined summary RR from all studies was 0.59 (95% CI 0.49-0.72). The summary RR from case–control studies was 0.54 (95% CI 0.38-0.76). The summary RR from cohort studies was 0.64 (95% CI

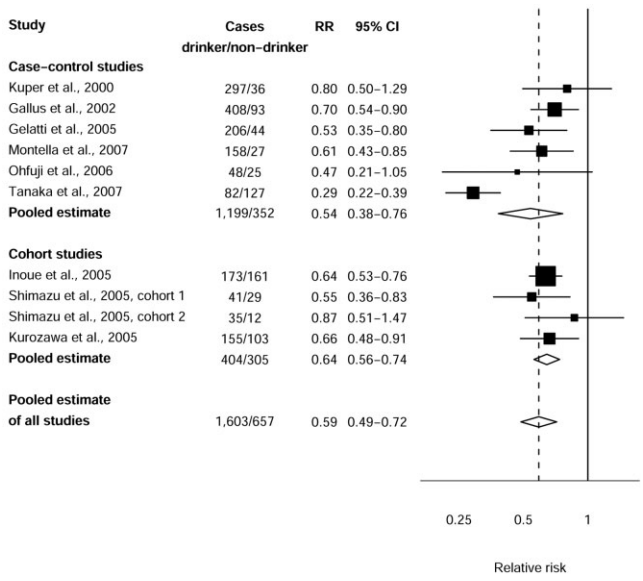

Fig. 1. Summary RRs of HCC for coffee drinkers versus non-drinkers from case–control and cohort studies.

Table 2. Summary RRs and Corresponding 95% CI for Coffee Consumption and HCC

	No. of Cases	RR (95% CI)	χ^2, df (*P* Value) for Heterogeneity
Drinkers versus non-drinkers			
All studies	2,260	0.59 (0.49–0.72)	29.56, 9 (0.001)
Case–control studies	1,551	0.54 (0.38–0.76)	24.22, 5 (0.001)
Cohort studies	709	0.64 (0.56–0.74)	1.85, 3 (0.60)
Low or moderate* drinkers versus non-drinkers			
All studies	2,260	0.70 (0.57–0.85)	20.71, 9 (0.01)
Case-control studies	1,551	0.68 (0.48–0.96)	18.00, 5 (0.003)
Cohort studies	709	0.70 (0.60–0.82)	2.69, 3 (0.44)
High† drinkers versus non-drinkers			
All studies	2,260	0.45 (0.38–0.53)	11.07, 9 (0.27)
Case-control studies	1,551	0.42 (0.32–0.55)	9.12, 5 (0.10)
Cohort studies	709	0.50 (0.38–0.66)	1.07, 3 (0.78)
Increment of 1 cup per day			
All studies	2,260	0.77 (0.72–0.82)	10.45, 9 (0.16)
Case–control studies	1,551	0.77 (0.72–0.83)	8.45, 5 (0.13)
Cohort studies	709	0.75 (0.65–0.85)	1.73, 3 (0.63)

*Low or moderate consumption was defined as <3 cups per day for Gallus et al.,[20] Gelatti et al.,[21] Inoue et al.,[26] and Montella et al.[22] and as <1 cup per day for Ohfuji et al.,[23] Tanaka et al.,[24] Kurozawa et al.,[28] and Shimazu et al.[27]

†High consumption was defined as ≥3 cups per day for Gallus et al.,[20] Gelatti et al.,[21] Inoue et al.,[26] and Montella et al.[22] and as ≥1 cup per day for Ohfuji et al.,[23] Tanaka et al.,[24] Kurozawa et al.,[28] and Shimazu et al.[27]

0.56-0.74). Significant heterogeneity was found between studies (pimarily case–control), and borderline significant heterogeneity was found between case–control and cohort study estimates ($\chi^2 = 3.49$; $P = 0.06$).

Figure 2 and Table 2 show the RRs for each case–control study and cohort study separately and overall according to low or moderate and high level of coffee consumption. The summary RR for moderate consumption of coffee was 0.70 (95% CI 0.57-0.85), wherein the RR was 0.68 (95% CI 0.48-0.96) for case–control studies and 0.70 (95% CI 0.60-0.82) for cohort studies. The summary RR for high consumption of coffee was 0.45

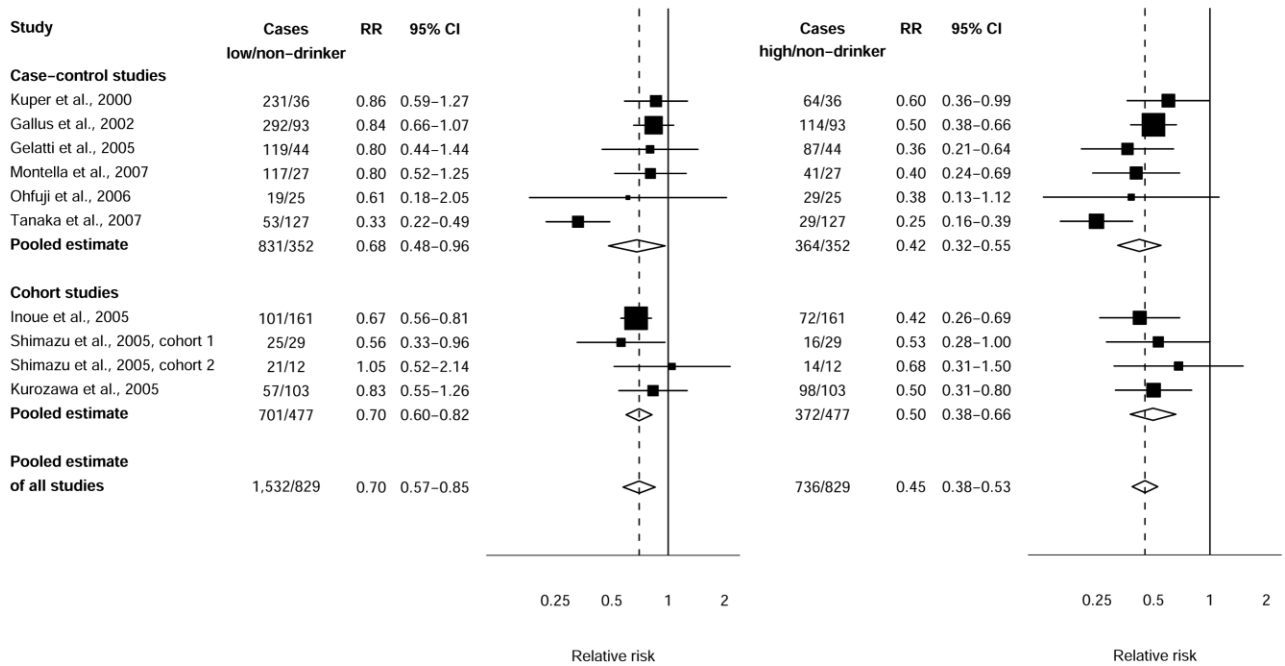

Fig. 2. Summary RRs of HCC for low or moderate and high coffee drinkers versus non-drinkers from case–control and cohort studies. (A) Low or moderate consumption was defined as <3 cups per day for Gallus et al.,[20] Gelatti et al.,[21] Inoue et al.,[26] and Montella et al.[22] and as <1 cup per day for Ohfuji et al.,[23] Tanaka et al.,[24] Kurozawa et al.,[28] and Shimazu et al.[27] (B) High consumption was defined as ≥3 cups per day for Gallus et al.,[20] Gelatti et al.,[21] Inoue et al.,[26] and Montella et al.[22] and as ≥1 cup per day for Ohfuji et al.,[23] Tanaka et al.,[24] Kurozawa et al.,[28] and Shimazu et al.[27]

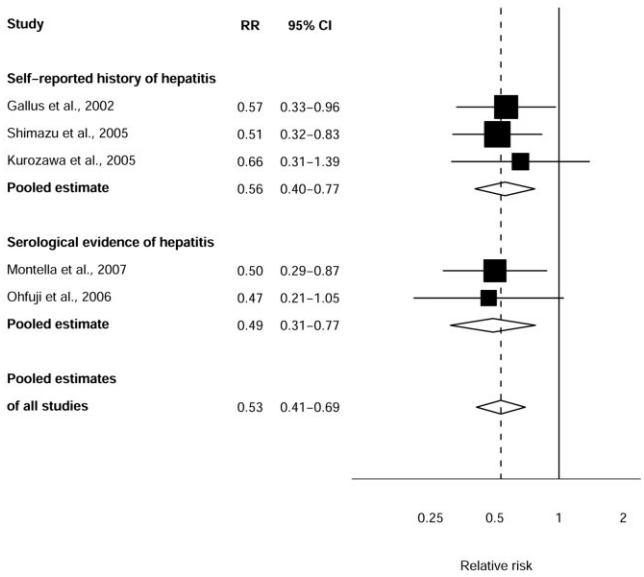

Fig. 3. Summary RRs of HCC for coffee drinkers versus non-drinkers among carriers of HBV and/or HCV or other chronic liver diseases.

(95% CI 0.38-0.53), wherein the RR was 0.42 (95% CI 0.32-0.55) for case–control studies and 0.50 (95% CI 0.38-0.66) for cohort studies. No significant heterogeneity was found between studies or study types for high and low coffee consumption.

Table 2 also gives the summary RRs for an increment of 1 cup per day of coffee. These were 0.77 (95% CI 0.72-0.82) for all studies combined, 0.77 (95% CI 0.72-0.83) for case–control studies, and 0.75 (95% CI 0.65-0.85) for cohort studies.

Figure 3 gives RR for coffee drinkers versus non-drinkers among subjects with clinical history or serological evidence of hepatitis. The summary RRs were 0.56 (95% CI 0.40-0.77) for those reporting information on history of hepatitis, 0.49 (95% CI 0.31-0.77) for those with serological evidence of hepatitis, and 0.53 (95% CI 0.41-0.69) overall.

Discussion

In the present meta-analysis, we observed a 41% reduction in the risk of HCC among coffee drinkers compared with never drinkers, with similar results from case–control and prospective studies. Moreover, the apparent favorable effect of coffee drinking was found both in studies from southern Europe,[12,19-22] where coffee is widely consumed, and from Japan,[23,24,26-28] where coffee consumption is less frequent, and in subjects with chronic liver disease.

Animal models and cell culture systems have indicated that some coffee compounds—including diterpenes, cafestol, and kahweol—may act as blocking agents via modulation of multiple enzymes involved in carcinogenic detoxification.[34,35] They also modify the xenotoxic metabolism via induction of glutathione-*S*-transferase and inhibition of *N*-acetyltransferase.[36] Other components of coffee, including caffeine and antioxidant substances from coffee beans, have been related to favorable modifications in liver enzymes such as γ-glutamyltransferase and aminotransferase activities.[1-4]

Coffee has also been related to reduced risk of liver disease and cirrhosis,[14-18,37] a major risk factor or pathogenic step in the process of liver carcinogenesis.[11-13] The beneficial effect of coffee consumption on HCC may be due to its inverse relation with cirrhosis, although allowance for clinical history of cirrhosis did not totally account for the inverse association. Thus, there seems to be a continuum of the favorable effect of coffee on liver enzymes, cirrhosis, and HCC.

Despite the consistency of these results, it is difficult to determine causality on the basis of these observational studies alone. The inverse relation observed may in fact be spurious and due to the fact that subjects with a broad spectrum of digestive tract diseases, liver disorders, and cirrhosis may reduce their coffee consumption. The observation that high coffee drinkers in various populations (ie, subjects drinking ≥3 cups per day in Europe, but only ≥1 in Japan) have similar reduced risks may support this selective reduction of coffee drinking by subjects with digestive tract complaints. Avoidance of coffee is, however, not routinely recommended to patients with chronic liver disease, and an inverse relation was observed among subjects with self-reported or serological evidence of hepatitis. Moreover, in a study that also used patients with chronic liver disease as controls,[24] a similar reduced risk was found.

Observational studies included in this meta-analysis are prone to various other sources of bias and confounding. An important problem concerns the assessment of coffee intake, based on patients' self-reporting. However, recall of coffee drinking has been shown satisfactorily reproducible and valid.[38,39] The observation of an inverse relation between coffee and HCC in case-control and cohort studies, and in populations from southern Europe and Japan weighs against a major role of information or selection bias in these studies. Allowance for confounding factors varied among the studies considered in this meta-analysis. However, the fact that the inverse relation persisted after allowance for major risk factors for HCC, including history or serological evidence of hepatitis B and C, cirrhosis and other liver diseases, social class indicators, alcohol drinking and tobacco smoking, reassures against major role of confounding or modifying effect. Publication bias is also possible, with selective reporting of favorable findings. We did not search for unpublished data or abstracts, given the difficulties in their interpretations. However, no significant asymmetry was present in the

funnel plot, an additional indicator of the validity of the results.

In conclusion, the results of this meta-analysis provide quantitative evidence of an inverse relation between coffee drinking and liver cancer, the third-most common cause of cancer death worldwide after lung and stomach, with about 600,000 deaths in 2002.[40] However, the interpretation of this association remains unclear, and the consequent inference of causality and worldwide public health implications remains open to discussion.

Acknowledgment: We thank Mrs. M. P. Bonifacino for editorial assistance and Martin Plummer from the International Agency for Research on Cancer, Lyon, France, for providing the R function to plot the graphs.

References

1. La Vecchia C. Coffee, liver enzymes, cirrhosis and liver cancer. J Hepatol 2005;42:444-446.
2. Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, et al. Coffee consumption and serum aminotransferases in middle-aged Japanese men. J Clin Epidemiol 2001;54:823-829.
3. Nakanishi N, Nakamura K, Nakajima K, Suzuki K, Tatara K. Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men. Eur J Epidemiol 2000;16:419-423.
4. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2005;128:24-32.
5. Casiglia E, Spolaore P, Ginocchio G, Ambrosio GB. Unexpected effects of coffee consumption on liver enzymes. Eur J Epidemiol 1993;9:293-297.
6. Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, et al. Coffee drinking and serum gamma-glutamyltransferase: an extended study of Self-Defense Officials of Japan. Ann Epidemiol 1999;9:325-331.
7. Kono S, Shinchi K, Imanishi K, Todoroki I, Hatsuse K. Coffee and serum gamma-glutamyltransferase: a study of self-defense officials in Japan. Am J Epidemiol 1994;139:723-727.
8. Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol 1997;146:1019-1024.
9. Sharp DS, Benowitz NL. Re: "Alcohol, smoking, coffee, and cirrhosis" and "Coffee and serum gamma-glutamyltransferase: a study of self-defense officials in Japan". Am J Epidemiol 1995;141:480-482.
10. Tanaka K, Tokunaga S, Kono S, Tokudome S, Akamatsu T, Moriyama T, et al. Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers. Int J Epidemiol 1998;27:438-443.
11. Adami HO, Hsing AW, McLaughlin JK, Trichopoulos D, Hacker D, Ekbom A, et al. Alcoholism and liver cirrhosis in the etiology of primary liver cancer. Int J Cancer 1992;51:898-902.
12. Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. Int J Cancer 2000;85:498-502.
13. La Vecchia C, Negri E, Cavalieri d'Oro L, Franceschi S. Liver cirrhosis and the risk of primary liver cancer. Eur J Cancer Prev 1998;7:315-320.
14. Corrao G, Lepore AR, Torchio P, Valenti M, Galatola G, D'Amicis A, et al. The effect of drinking coffee and smoking cigarettes on the risk of cirrhosis associated with alcohol consumption. A case-control study. Provincial Group for the Study of Chronic Liver Disease. Eur J Epidemiol 1994;10:657-664.
15. Corrao G, Zambon A, Bagnardi V, D'Amicis A, Klatsky A. Coffee, caffeine, and the risk of liver cirrhosis. Ann Epidemiol 2001;11:458-465.
16. Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? Ann Epidemiol 2002;12:202-205.
17. Klatsky AL, Armstrong MA. Alcohol, smoking, coffee, and cirrhosis. Am J Epidemiol 1992;136:1248-1257.
18. Klatsky AL, Armstrong MA, Friedman GD. Coffee, tea, and mortality. Ann Epidemiol 1993;3:375-381.
19. La Vecchia C, Ferraroni M, Negri E, D'Avanzo B, Decarli A, Levi F, et al. Coffee consumption and digestive tract cancers. Cancer Res 1989;49:1049-1051.
20. Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, et al. Does coffee protect against hepatocellular carcinoma? Br J Cancer 2002;87:956-959.
21. Gelatti U, Covolo L, Franceschini M, Pirali F, Tagger A, Ribero ML, et al. Coffee consumption reduces the risk of hepatocellular carcinoma independently of its aetiology: a case-control study. J Hepatol 2005;42:528-534.
22. Montella M, Polesel J, La Vecchia C, Dal Maso L, Crispo A, Crovatto M, et al. Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. Int J Cancer 2007;120:1555-1559.
23. Ohfuji S, Fukushima W, Tanaka T, Habu D, Tamori A, Sakaguchi H, et al. Coffee consumption and reduced risk of hepatocellular carcinoma among patients with chronic type C liver disease: a case-control study. Hepatol Res 2006;36:201-208.
24. Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, et al. Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan. Cancer Sci 2007;98:214-218.
25. Yu SZ, Huang XE, Koide T, Cheng G, Chen GC, Harada K, et al. Hepatitis B and C viruses infection, lifestyle and genetic polymorphisms as risk factors for hepatocellular carcinoma in Haimen, China. Jpn J Cancer Res 2002;93:1287-1292.
26. Inoue M, Yoshimi I, Sobue T, Tsugane S. Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan. J Natl Cancer Inst 2005;97:293-300.
27. Shimazu T, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, et al. Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. Int J Cancer 2005;116:150-154.
28. Kurozawa Y, Ogimoto I, Shibata A, Nose T, Yoshimura T, Suzuki H, et al. Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan. Br J Cancer 2005;93:607-610.
29. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. J Clin Epidemiol 2000;53:207-216.
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.
31. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987;9:1-30.
32. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.
33. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301-1309.
34. Cavin C, Holzhauser D, Constable A, Huggett AC, Schilter B. The coffee-specific diterpenes cafestol and kahweol protect against aflatoxin B1-induced genotoxicity through a dual mechanism. Carcinogenesis 1998;19:1369-1375.
35. Majer BJ, Hofer E, Cavin C, Lhoste E, Uhl M, Glatt HR, et al. Coffee diterpenes prevent the genotoxic effects of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and N-nitrosodimethylamine in a human derived liver cell line (HepG2). Food Chem Toxicol 2005;43:433-441.
36. Huber WW, Parzefall W. Modification of N-acetyltransferases and glutathione S-transferases by coffee components: possible relevance for cancer risk. Methods Enzymol 2005;401:307-341.
37. Kim WR. Is coffee or tea good for your liver? Nat Clin Pract Gastroenterol Hepatol 2006;3:482-483.
38. D'Avanzo B, La Vecchia C, Katsouyanni K, Negri E, Trichopoulos D. Reliability of information on cigarette smoking and beverage consumption provided by hospital controls. Epidemiology 1996;7:312-315.
39. Ferraroni M, Tavani A, Decarli A, Franceschi S, Parpinel M, Negri E, et al. Reproducibility and validity of coffee and tea consumption in Italy. Eur J Clin Nutr 2004;58:674-680.
40. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.