

Editorial

Coffee, liver enzymes, cirrhosis and liver cancer

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Several data on a potentially favourable effect of coffee on liver function and liver diseases have accumulated over the last two decades. These span from liver enzymes, to cirrhosis and to hepatocellular carcinoma, and therefore constitute a continuation not only of epidemiological data, but also of biological and clinical evidences.

Coffee consumption, in fact, has been inversely related to gamma-glutamyltransferase (GGT) activity in studies from Norway, Italy, Finland, France, Japan and the United States [1–16]. The inverse relation was particularly strong in high risk subjects, including heavy alcohol drinkers [3,4,6,8–10]. Thus, in a study of 2494 male self-defence officials from Japan [4], the geometric mean GGT was about 30% lower in subjects who drank five or more cups of coffee per day compared to nondrinkers. In another Japanese dataset [10], the inverse relation between coffee and GGT was restricted, or stronger, in alcohol drinkers.

Although GGT is a relevant indicator of cirrhosis risk, serum alanine aminotransferase (ALT) activity is a more specific marker of liver injury than GGT, and a few population-based surveys from Italy and Japan [4,10,15,16] found a similar inverse relation between coffee drinking and ALT. Furthermore, among 5944 adults in the Third US National Health and Nutrition Examination Survey conducted in 1988–94, the multivariate relative risk (RR) for elevated ALT activity (>43 U/L) was 0.56 in subjects who drank more than two cups of coffee per day compared to non-coffee drinkers [17]. The inverse relation was consistent across strata of major covariates, including indicators of liver injury and alcohol drinking. This is of specific interest, since coffee may be a substitute for alcoholic beverages on an individual and on a population level, and indicates therefore that the favourable effect of coffee cannot be

accounted for only by lower alcohol drinking in (heavy) coffee consumers.

Coffee drinking has also been inversely related to the risk of cirrhosis [18]. In a cohort study, including 59 cases from the Kaiser Permanente Medical Care Program, subjects who drank four or more cups of coffee per day had about five fold lower the risk of non coffee drinkers [19]. In the same dataset, coffee was inversely related to the risk of cirrhosis death (multivariate $RR=0.77$ for coffee drinkers versus nondrinkers [20]).

A case-control study from Italy, including 115 cases, showed an inverse relation between coffee and the risk of cirrhosis, and a favorable effect of coffee on alcohol-related cirrhosis risk [21]. Another larger Italian study, which included 274 cases and 458 controls, also showed a strong inverse relation between coffee drinking and cirrhosis, with a RR of 0.16 for drinkers of four or more cups per day compared to non-coffee drinkers. The apparent protection was consistent across strata of alcohol drinking, as well as of serum markers of hepatitis B and C [22].

In a hospital-based case-control study of digestive tract and liver diseases from Milan, Italy, including 101 cases with cirrhosis and 1538 controls, the RR was 0.77 for subjects drinking one cup of coffee per day, 0.57 for two, and 0.29 for three or more cups compared to non coffee drinkers. The RR for 40 years of coffee consumption or more was 0.45. The inverse trend in risk between cancer risk and the number of cups drunk and between cancer risk and duration of coffee drinking were both significant. [23].

Cirrhosis is a major correlate of hepatocellular carcinoma [24–27], and the relation between coffee drinking and the risk of primary liver cancer has been examined in at least two studies. An Italian case-control study [28] based on 151 cases with hepatocellular carcinoma, reported a multivariate RR of 0.78 for drinkers of ≥ 3 cups of coffee per day, compared to non coffee drinkers. In a Greek case-control

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study [26], including 333 cases, the age- and sex-adjusted RR was 0.7 for drinkers of ≥ 20 cups of coffee per week compared to non drinkers.

In an updated and combined analysis of the above mentioned Greek and Italian datasets, which included a total of 844 cases and 1912 controls, the multivariate RR was 0.7 for drinkers of three or more cups of coffee per day compared to non-coffee drinkers [29]. The apparent favourable effect of coffee consumption on hepatocellular carcinoma may be due to its inverse relation with cirrhosis, but allowance for clinical history of cirrhosis did not totally account for the inverse association in the combined analysis [29]. However, allowance for clinical history of cirrhosis may well be subject to underdiagnosis, and hence residual confounding may be present. More important, the RR for the highest level of coffee drinking was only of borderline statistical significance, and even modest residual bias or confounding could well explain the apparent inverse association.

The study by Gelatti et al. in this issue of the Journal [30], a hospital-based case-control study of 250 cases and 500 controls from northern Italy, provided additional relevant quantification of the inverse relation between coffee and hepatocellular carcinoma. Compared with non coffee drinkers, the RRs were 0.8 for drinkers of 1–2 cups per day, 0.4 for those of 3–4 cups, and 0.3 for drinkers of five or more cups per day. The inverse relation between coffee and primary liver cancer is therefore apparently stronger than in previous studies, indicating that the relation is probably real, and not due to chance alone. The combined, pooled RR from three published studies of coffee and hepatocellular carcinoma for drinkers of three or more cups of coffee per day as compared to non coffee drinkers is therefore around 0.6 (Table 1). More important, the study by Gelatti et al. provides original information on the independent effect of coffee from the major recognized risk factors for primary liver cancer. The inverse relation with coffee, in fact, was of similar magnitude in subjects negative or positive for HBV or HCV serum markers, as well as in non- or moderate drinkers and in heavy drinkers. The data were inadequate to investigate tobacco, another known liver carcinogen [26,31,32], and its potential interaction with coffee.

Table 1
Coffee consumption and primary liver cancer: findings from 3 studies

Study, Country	No. of cases: no. of control	Relative risk for coffee consumption. Cups per day:		
		Nondrinkers	1–2	≥ 3
Gallus et al., 2002, Greece and Italy [29]	834:1912	1+	1.1	0.7
Gelatti et al., 2005, Italy [30]	250:500	1+	0.8	0.4
Overall, pooled estimate	1084:2412	1+	1.0	0.6

+, Reference category.

It is conceivable that the results on cirrhosis are influenced by possible physicians' recommendation about restrictions of coffee drinking in cirrhotic patients. It is, however, unlikely that any such bias has materially influenced the findings on liver enzymes as well as on hepatocellular carcinoma, since the inverse associations for liver cancer were consistent across strata of cirrhosis and/or cirrhosis severity.

Given its effects on liver enzymes and cirrhosis, and the weight of epidemiological evidence, coffee appears therefore to have a real—though moderate—effect in reducing the risk of hepatocellular carcinoma, as suggested also by limited available data on rodents [33]. Various components of coffee have been related to such a favourable effect, including caffeine, coffee oils kahweol of cafestol, and antioxidant substances from coffee beans [34–37], but no definite evidence is available for any of these components.

Despite these uncertainties, HCC should be added to other digestive tract cancers on which a favourable role of coffee drinking has been suggested, including oral and pharyngeal, oesophageal [28,38,39] and colorectal cancers [40,41].

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