Cancer and Liver Cancer Prevention: Is It a Fact or Just a Potential?

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In this issue of HEPATOLOGY, the article by Hu et al.[1] provides relevant information to our understanding of the relation between coffee drinking, markers of liver disease, and liver cancer risk.

First, it adds original data to our knowledge on the coffee and liver disease relationship from a cohort study of 60,323 subjects who underwent seven subsequent surveys between 1972 and 2002, and were followed-up to June 2006 (mean time of follow-up was 18 years). The study was conducted in Finland, a country with high coffee consumption.[1] Previously available data on coffee and liver cancer were based on at least 10 studies, six of which were case-control (from Greece, Italy, and Japan) and four of which were cohort investigations (all of these from Japan). Overall, the pooled relative risk (RR) was 0.54 (95% confidence interval [CI] 0.39-0.76) for case-control studies, based on 1199 coffee drinker and 352 non–coffee drinker cases, and 0.64 (95% CI 0.56-0.74) for cohort studies, based on 404 coffee drinker and 305 non–coffee drinker cases.[2] All the cohort studies, however, came from Japan, a country where coffee consumption is lower than in western countries[2] and much lower than in Finland.[1] Thus, available data from cohort studies did not allow investigation of the the dose-risk relation between coffee and liver cancer for persons who consumed >1 cup per day. The pooled RRs from Japanese cohort studies were 0.70 (95% CI 0.62-0.82) for <1 cup per day, and 0.50 (95% CI 0.38-0.66) for ≥1 cup per day.

Only data from case-control studies, mainly derived from southern Europe, allowed estimation of a pooled RR for persons who consumed ≥3 cups per day (RR = 0.42, 95% CI 0.32-0.55,[2]). This estimate is largely consistent with the RR of liver cancer for persons consuming >3 cups per day in the study by Hu et al.,[1] which was around 0.4. This consistency of the results across study designs and populations strongly supports the existence of a real inverse relation between coffee drinking and liver cancer risk.

A second important and original finding of the study by Hu et al.[1] is the observation that the inverse relation between coffee and liver cancer is independent of serum gamma-glutamyltransferase (GGT). Serum GGT levels were available only for about 63% of cases who underwent more recent surveys (from 1982-2002), and the RRs for subsequent levels of coffee consumption, further adjusted for serum GGT, were close to those unadjusted for that variable. The study was also able to consider the combined effect of coffee and GGT on liver cancer risk. Compared with heavy coffee drinkers in the three lowest quartiles of GGT, the RR was 2.7 for those who were nondrinkers or moderate coffee drinkers (<1 cup per day) on the same lowest quartiles of GGT, but rose to 11.0 for those in the highest quartile of GGT for nondrinkers or moderate coffee drinkers. Given the small number of subjects in each stratum, no CI for these estimates was given, but the pattern of risk across strata is suggestive of an independent effect of both serum GGT and coffee drinking on subsequent liver cancer risk.

Case-control studies from Italy[3-5] considered the separate effect of coffee and the two major risk factors for liver cancer, that is, clinical history of hepatitis or serum markers for hepatitis B (HBV) and C (HCV) viruses, and alcohol drinking, and reported consistent inverse relations between coffee drinking and liver cancer risk across strata of these covariates. It is now clear, therefore, that the inverse relation of coffee is independent from major established risk factors for liver cancer.

Another recognized risk factor for liver cancer is tobacco smoking,[3-5] which however tends to be directly correlated with coffee consumption, Furthermore, the association between tobacco and liver cancer is much less strong than those of HBV, HCV, and alcohol. Thus, tobacco is unlikely to exert a relevant confounding effect on the inverse relationship between coffee and liver cancer. Further, the RR provided by most studies,[2-5] including that of Hu et al.,[1] were adjusted for tobacco, and if anything, allowance for tobacco and several other variables such as education, history of diabetes, and chronic liver disease led to a stronger inverse relation with coffee.

More important, the study by Hu et al.,[1] was able to show that the inverse relation between coffee and liver cancer is similar across strata of smoking habits (current smoker versus never smoked or exsmoker), as well as of

Abbreviations: CI, confidence interval; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; RR, relative risk.

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body mass index, besides alcohol drinking, as already reported by case-control studies from Italy and Greece.[2-5] With reference to potential information bias, recall of coffee drinking has been shown to be satisfactorily reproducible and valid.[6,7]

Thus, although all observational epidemiological studies (case-control and cohort) are prone to various sources of bias and confounding, these are unlikely to explain such a consistent inverse association as that reported between coffee and liver cancer. Likewise, it is unlikely that publication bias, that is, selective publication of studies with positive findings, may account for such a strong inverse relation. We can now, therefore, conclude that the inverse relation between coffee and liver cancer risk is real.

Various components of coffee, including caffeine, the coffee oils kahweol and cafestol, antioxidant substances from coffee beans, and chlorogenic acid, have been related to such an inverse relation, because they may favorably influence glucose metabolism and prevent hyperglycemia,[1,2,8] but no definite evidence on biologic mechanisms of the inverse relation between coffee and liver cancer is available.

Coffee drinking has been related to decreased levels of liver enzymes, including GGT and alanine aminotransferase activity,[8-11] and to reduced risk of type II diabetes,[12] which is a recognized risk factor for liver cancer.[13,14] Coffee drinking has also been inversely related to the risk of cirrhosis, with RRs around 0.2-0.3 for heavy coffee drinkers versus nondrinkers in studies conducted in Italy.[15,16] Cirrhosis is a major correlate of hepatocellular carcinoma,[17,18] but allowance for clinical history of cirrhosis did not account for the inverse association between coffee and liver cancer.[8] There is therefore a continuum of clinical and epidemiological evidence, which ranges from liver enzymes to cirrhosis to hepatocellular carcinoma, to support a favorable effect of coffee on liver function and liver diseases, including cirrhosis and also primary liver cancer.

Despite the apparent consistency of these findings, it is difficult to establish whether such an inverse relation between coffee and liver cancer is causal on the basis of observational (case-control and cohort) epidemiological studies alone. The inverse relation observed may be spurious, and attributable simply to the fact that subjects with a broad spectrum of digestive tract disorders, liver diseases, or cirrhosis may reduce their coffee consumption. Indeed, caffeine metabolism is impaired in patients with cirrhosis, who could therefore reduce coffee intake in order to avoid side effects of caffeine. Thus, bias due to reduction of coffee drinking in unhealthy subjects cannot be excluded.

However, in a study on hepatocellular carcinoma that used patients with chronic liver disease as controls,[19] a reduced risk for coffee drinkers was found, similar to that observed in studies using subjects with no liver disease as controls. Avoidance of coffee, moreover, is not commonly recommended to patients with chronic liver disease, and an inverse relation between coffee and liver cancer was also observed among subjects with self-reported[2] or serological evidence of hepatitis.[3,5] The study by Hu et al.[8] adds relevant evidence that such an inverse relation is also observed, and is indeed apparently stronger, in subjects in the highest quartile of GGT, although the interaction test between coffee consumption and serum GGT on the risk of liver cancer was far from significant.

Furthermore, the study by Hu et al.[1] provides original and important quantitative evidence that GGT levels are related to subsequent incidence of liver cancer, with an overall RR of 2.3 (95% CI 1.0-5.2). This is not surprising, because GGT is known to be directly correlated to chronic liver disease and cirrhosis, which is a major risk factor and probably a pathogenic step in liver carcinogenesis.[17,18]

It remains difficult, however, to translate the inverse relation between coffee drinking and liver cancer risk observed in epidemiological studies into potential implications for prevention of liver cancer by increasing coffee consumption. Liver cancer is the third most common cause of cancer death worldwide, with an estimated number of about 600,000 deaths per year in the early 2000s.[20] Together with avoidance of lung cancer through tobacco control, primary liver cancer is the other common neoplasm which is most largely avoidable, through HBV vaccination, control of HCV transmission, and reduction of alcohol drinking. These three measures can, in principle, avoid more than 90% of primary liver cancers worldwide. Whether coffee drinking has an additional role in liver cancer prevention remains open to discussion, but in any case any such role would be limited—if not negligible—as compared to that achievable through control of HBV, HCV, and alcohol consumption, which are the major recognized risk factors for liver cancer.

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