

# Coffee is good for the liver

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**ABSTRACT** The intake of coffee and caffeine has been shown epidemiologically to be associated with improved liver function tests, mainly in the form of alanine transaminase and gamma glutamyl transferase, a reduction in the incidence of cirrhosis and hepatocellular carcinoma. These observations suggest that coffee drinking is protective to the liver. Hepatocellular carcinoma is a common tumour worldwide and amenable to both primary and secondary preventive strategies. Surveillance for hepatocellular carcinoma by six-monthly alpha fetoprotein and ultrasound scanning in patients with cirrhosis is essential.

**KEYWORDS** Coffee, caffeine, cirrhosis, liver enzymes, hepatocellular carcinoma

**LIST OF ABBREVIATIONS** Alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), hepatocellular carcinoma (HCC), non alcoholic fatty liver disease (NAFLD)

**DECLARATION OF INTERESTS** The authors have no interests to declare, other than one of us enjoys coffee!

Published online December 2005

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## BACKGROUND

Earlier this year, a paper in the *Journal of Hepatology* reported an inverse relationship between coffee drinking and hepatocellular carcinoma.<sup>1</sup> Whilst we are used to hearing short-lived claims linking food and disease, the relationship between coffee and liver disease seems reasonably evidence-based.

Primary liver cancer or HCC is the fifth most common cancer worldwide, with approximately one million deaths per year. The incidence of HCC varies markedly geographically, and continues to rise, especially in the Far East and China where there is a high prevalence of hepatitis B and C.

The most important risk factor for the development of HCC is the presence of liver cirrhosis, the most common causes of which are chronic hepatitis B and C infection, alcohol abuse, iron overload and obesity. As with most cancers, other environmental factors also play a significant role in HCC, including tobacco smoking, diabetes mellitus and obesity. Hepatocellular carcinoma is associated with high mortality as the majority of patients have progressive/extensive disease at the time of clinical presentation.

Several recent publications have identified an inverse association between coffee consumption and HCC as well as a beneficial influence on liver function and cirrhosis incidence.

## COFFEE AND LIVER ENZYMES

Coffee drinking has an inverse relationship to GGT production in the liver. The induction of GGT that occurs with alcohol is inhibited by coffee and thus may protect the liver against damage from alcohol excess. A study from Japan examined coffee consumption and serum GGT levels in 12,687 healthy volunteers. Increased coffee consumption was strongly and independently associated with decreased GGT activity amongst males ( $p < 0.0001$ ), especially amongst those with documented alcohol excess. In contrast, however, only a weak association between coffee intake and lower GGT levels was demonstrated in females in this study. A similar effect on the serum transaminases was also identified.

Another study reported on a cohort of 5,944 participants in the Third US National Health and Nutrition Examination Survey from 1988–1994 who had at least of one of the following: excess alcohol intake, obesity, viral hepatitis, iron overload or impaired glucose metabolism.<sup>2</sup> Increased serum ALT was found in 8.7% and analysis showed that lower ALT levels were associated with higher coffee and caffeine intake. Comparing those in the highest caffeine quintile with those in the lowest the odds ratio was 0.31 (95% confidence interval 0.16–0.61). The effect of coffee and caffeine was seen across the different subgroups.

## COFFEE AND CIRRHOSIS

Whilst coffee consumption might improve liver enzymes in at risk subjects, does it confer protection against cirrhosis? The answer to this is probably yes. There have been a number of studies identifying an inverse relationship between coffee consumption and cirrhosis. A Norwegian study looking at a 17-year follow-up of 5,130 adults who underwent screening for cardiovascular disease found less cirrhosis in coffee drinkers.<sup>3</sup> It does appear therefore that the influence of coffee on liver function tests is not just a biochemical phenomenon, but is also protective.

## COFFEE AND HEPATOCELLULAR CARCENOMA

In addition to the paper mentioned initially,<sup>1</sup> reporting less HCC in coffee drinkers, there have been a number of earlier reports examining the relationship between coffee and HCC.

In 1998, La Vecchia *et al.*<sup>5</sup> examined 151 cases of HCC and reported an odds ratio of 0.78 for people who regularly drank >3 cups of coffee per day compared with non-coffee drinkers. A similar result was reported by Kuper *et al.* who examined 333 cases of HCC and generated an odds ratio of 0.7 for people who had a coffee consumption of >20 cups per week compared with non-coffee drinkers.

In the Gellati study,<sup>1</sup> which was case-controlled, and included 250 cases of HCC along with 500 controls, a dose relationship was found. The odds ratio compared with non-coffee drinkers was 0.8 for 1–2 cups per day, 0.4 for 3–4 cups per day and 0.3 for those drinking five or more cups. The inverse association was present regardless of the aetiology. This protective dose-related effect has also been suggested by recent work by Inoue *et al.* who conducted a large-scale population based cohort study in Japan, with the most protection being seen in those drinking five or more cups per day.<sup>5</sup>

## COFFEE: MECHANISM OF ACTION

The mechanism by which coffee protects liver function and prevents HCC is unclear. Reduction of HCC may be by reducing the development of cirrhosis, the dominant risk factor. The pathogenesis of the mechanisms underlying such hepatic protection remains to be determined. Caffeine seems to have a major role in the normalisation of liver enzymes in the USA study<sup>2</sup> but whether other coffee components such as kahweol and cafestol are important is unknown. These components influence such enzymes as gamma-glutamylcysteine synthetase, N-acetyltransferase and glutathione S-transferase involved in chemoprotection. In addition, induction of the cytochrome P450 system, which occurs with alcohol consumption and tobacco use, has been shown to be reduced with regular coffee intake.

## DIET AND CHEMOPROTECTION

Links between cancer and environmental influences are continually being sought, in particularly links with diet. Indeed, coffee itself has been implicated in pancreatic, bladder and colorectal malignancy. However, the evidence for a protective effect of coffee on the liver seems both consistent and logical. Protection from injury, as evidenced by lowering serum markers of hepatic injury, such as the transaminases, might account for the lower incidence of cirrhosis and thereby reduced HCC. Coffee is not alone in being implicated in chemoprotection against HCC. Green leafy vegetables, such as broccoli, cauliflower and Brussels sprouts, contain isothiocyanates and have also been reported to protect from HCC.<sup>6</sup>

Kurozawa *et al.* examined the dietary habits and the incidence of HCC in over 1,000,000 volunteers.<sup>7</sup> Interestingly, the regular intake of eggs was associated with an increased risk of HCC, while coffee and pickle intake were shown to have a significant inverse relationship.

## OTHER PREVENTIVE MEASURES IN HCC

Dietary manipulation as protection against HCC is only one approach to this global health problem. Other prevention strategies can be divided into primary or secondary.

### Primary prevention

Primary prevention is defined as prevention of known risk factors from triggering the carcinogenic process. In the case of HCC prevention, this would involve reducing the established risk factors, such as aflatoxin from foodstuffs, reducing alcohol abuse and preventing hepatitis B and C infection. This is obviously the most attractive form of protection if an effective strategy can be devised. Prevention of chronic hepatitis B infection by mass infant vaccination in high-risk groups has proven extremely effective. For example a program to vaccinate in infancy with catch-up vaccination in older children in Alaska Natives dramatically reduced hepatitis B infection. Similar success in reducing hepatitis B, and HCC, in children has been reported in Taiwan. No vaccine is currently available against hepatitis C but strategies to reduce transmission such as screening blood donations are likely to be highly effective. Similar strategies to reduce alcohol abuse and reduce levels of obesity are urgently needed but are proving difficult. Obesity is rapidly increasing and is accompanied by a rapidly rising prevalence of NAFLD, the end stage of which is cirrhosis.

### Secondary prevention

Secondary prevention strategies should be aimed to prevent HCC in patients with liver disease and would include treatment of viral hepatitis, alcohol abstinence

in alcoholic liver disease, venesection in haemochromatosis, and weight loss in NAFLD. If good evidence that dietary manipulation such as drinking coffee or eating certain types of vegetables is beneficial can be produced then this will be an important advance in managing patients with liver disease. The papers cited earlier do suggest that coffee drinking is likely to be protective to the liver but long-term randomised controlled trials of coffee intake to prove this are likely to be difficult. However dose-response effects of coffee on markers of liver injury in patients with chronic liver disorders such as hepatitis C or NAFLD would be simple to do and worthwhile. Meanwhile consideration should be given to encourage patients with chronic liver disease who do not drink coffee, to start.

### Surveillance

Patients with cirrhosis are at increased risk of HCC, but are usually beyond treatment by the time HCC causes clinical features. Early detection of developing HCC by

six-monthly ultrasonography and blood alpha-fetoprotein measurements may allow successful liver transplantation.<sup>8</sup> Surveillance in patients with cirrhosis, especially if potential transplant candidates, is essential.

### KEYPOINTS

- Coffee and caffeine intake are associated with better liver enzymes.
- Coffee intake is inversely associated with cirrhosis.
- Coffee intake is inversely associated with HCC.
- Primary prevention of HCC with strategies such as hepatitis B vaccination in at risk groups is highly effective.
- Further research into the effect of coffee, caffeine and other dietary components in liver disease are required.

### FURTHER READING

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