COFFEE AND LIVER HEALTH

OVERVIEW

Research suggests an inverse association between moderate coffee consumption and the risk of developing a range of liver diseases including cancer, fibrosis, cirrhosis and non-alcoholic fatty liver disease (NAFLD)[1-20]. Moderate coffee consumption is typically defined as 3-5 cups per day, based on the European Food Safety Authority's review of caffeine safety[21].

In 2016, The International Agency for Research on Cancer (IARC) published an assessment of coffee, maté, and very hot beverages[1]. Having reviewed publically available scientific evidence, the IARC Working Group found no clear association between coffee intake and cancer at any body site and suggested that coffee drinking may actually help reduce the risk of certain cancers, including liver cancer[1].
Meta-analyses have suggested that coffee consumption versus no coffee consumption is associated with up to a 40% risk reduction of liver cancer (although this is in a dose-dependent manner)[2-5].

Further information on IARC guidance can be found in our factsheet on cancer, available here

Research suggests that coffee intake is associated with a reduced risk of cirrhosis[6-9], fibrosis[8,10,11], chronic liver disease[6,10,11], and of developing NAFLD[6,12-20]. Research in patients with advanced hepatitis C-related liver disease also suggests that regular, moderate coffee consumption is associated with lower rates of disease progression[22-24].

Several possible mechanisms are under investigation to help understand whether, and to what extent, caffeine is associated with the inverse association between coffee consumption and these liver diseases; for example, the main primary caffeine metabolite, paraxanthine, appears to suppress the synthesis of CTGF (connective tissue growth factor) via a cascade of control cycles, which subsequently slows down the progression of liver fibrosis, cirrhosis and liver cancer[9,24-26]. Other suggested mechanisms include the anti-carcinogenic effects of cafestol and kahweol[27] and the possible effects of chlorogenic acids in reducing oxidative stress[28-30].

BACKGROUND INFORMATION

The European Association for the Study of the Liver estimates that approximately 29 million people in the European Union suffer from a chronic liver condition[31] and that mortality attributable to liver diseases has risen four-fold between 1970 and 2013[32].
Data suggests that cirrhosis, causes an estimated 170,000 deaths per year in Europe[31]. There are large intra-European variations, for example about 0.1% of Hungarian males die of cirrhosis every year, compared with 0.001% of Greek females[31]. Hepatitis comprises a number of

variants, and in Europe hepatitis B is estimated to affect 0.5-0.7% of the population and hepatitis C 0.13-3.26%[31].

Liver cancer is the sixth most common cause of cancer-related deaths globally, and the 14th most prevalent in Europe[33-35]. It accounts for 782,000 deaths worldwide[33-35] (47,000 deaths in Europe)[31]. 90-95% of patients with hepatic carcinoma have underlying cirrhosis[33].

COFFEE CONSUMPTION AND LIVER FUNCTION

Coffee and risk of liver cancer

In 2016, the International Agency for Research on Cancer (IARC) published an updated review of the scientific evidence related to coffee and cancer, finding no conclusive evidence for a carcinogenic effect of coffee overall, and, concluding that the research suggests an inverse association between coffee consumption and liver cancer[1].

Four meta-analyses of both prospective cohort and case control studies, looking at liver cancer, concluded that all ten of the reviewed epidemiological studies showed an inverse association between coffee consumption and liver cancer[2-5]. The results of the cohort studies included in the meta-analyses indicated a dose-response relationship between frequency of coffee consumption and a reduced risk for liver cancer.

The results from the US Multi Ethnic Cohort study also suggest that coffee consumption is inversely related to the incidence of hepatocellular cancer, showing a risk reduction of 38% in those who drank 2-3 cups of coffee per day and 41% in those who drank more than 4 cups[36]. Two large studies have also shown a similar association [37,38], with a risk reduction of up to 72% in the highest coffee drinkers in the EPIC study[37], and of 54% in women who drank more than 3 cups of coffee a day in the US Consortium[38]. Interestingly, the US study showed a greater effect in women compared to men[38]. Data from Finland has considered the role played by the type of coffee, concluding that coffee intake was inversely associated with incident liver cancer and mortality from chronic liver disease, irrespective of whether the coffee was boiled or filtered[39].

The inverse association between coffee consumption and liver cancer is observed both in participants with and without a history of liver disease. For example, studies in patients with hepatitis have suggested that coffee consumption is associated with a reduced risk of hepatocellular carcinoma[40-42], with one of the studies highlighting the potential role for lifetime coffee consumption[41]. A further study has suggested that coffee consumption over 3 cups a day is associated with a decreased risk of liver cancer recurrence and provides for increased survival following liver transplantation[43].

Overall, drinking coffee has been associated with up to a 40% reduced risk of liver cancer compared to those who do not drink coffee[36-42].

Coffee and risk of other liver diseases

Coffee drinking has also been related to a reduced risk of other liver diseases. A systematic review published in 2014 suggested coffee consumption was associated with beneficial outcomes in patients with chronic liver disease, cirrhosis, hepatocellular cancer and NAFLD[6]. A 2016 review also concluded that coffee intake of more than 2 cups per day in patients with pre-existing liver disease was associated with a lower incidence of fibrosis and cirrhosis, lower hepatocellular carcinoma rates, and decreased mortality[8].

Liver fibrosis

- A review concluded that patients with higher coffee consumption display a milder course of fibrosis[11].
- Data from the US National Health and Nutrition Examination Surveys (NHANES 1999-2010) suggests that higher intakes of coffee (including decaffeinated coffee) were associated with beneficially lower levels of liver enzymes[44].
- Data from the Rotterdam Study Research also suggested that daily coffee consumption of three or more cups decreases liver stiffness (a marker of liver fibrosis)[45].
- A cross-sectional study assessing the impact of a variety of food groups suggested that tea and coffee consumption had a protective role in hepatic fibrosis independent of other risk factors[46].

Chronic liver disease

- A Scottish study suggested that coffee drinking is associated with a reduced prevalence of cirrhosis in patients with chronic liver disease[9].
- Data from the US Multi Ethnic Cohort concluded that coffee drinking was associated with a reduced incidence of chronic liver disease. Compared to non-coffee drinkers, consuming 2-3 cups per day was associated with a 46% reduction in risk of death from chronic liver disease, and greater than 4 cups a day with a 71% reduction[36].

Non-alcoholic fatty liver disease (NAFLD)

- NAFLD is a common liver disease and a major cause of cirrhosis and hepatocellular carcinoma. It is defined by presence of steatosis in 5% of hepatocytes or more in the absence of other causes of fatty liver. The metabolic syndrome is a major known risk factor for NAFLD[47].
- A North American study investigated the effects of dietary behaviour in NAFLD patients, using four continuous cycles of the National Health and Nutrition Examination Surveys (NHANES 2001-2008). It found caffeine intake to be independently associated with a lower risk of NAFLD, suggesting a potential protective effect[13].
- A 2012 study correlated coffee caffeine consumption with the prevalence and severity of NAFLD. Coffee caffeine consumption was associated with a significant reduction in risk of fibrosis among patients with non-alcoholic steatohepatitis[14].
- A Mexican case-control study looked at the antioxidant effect of coffee by measuring antioxidant enzymes and lipid peroxidation markers in patients with NAFLD, and in patients without NAFLD. They found that a high intake of coffee had a protective effect against non-

alcoholic fatty liver disease; however there was no significant difference in the antioxidant variables analyzed[15].

- Data from 728 adults in the Non-alcoholic Steatohepatitis Clinical Research Network (NASH-CRN) suggests that coffee intake was inversely associated with advanced fibrosis in patients with non-alcoholic fatty liver disease[16].
- Five further reviews found a significantly decreased risk of liver fibrosis among patients with NAFLD who drank coffee[17-19]. One of these reviews further suggested that regular coffee caffeine consumption, not total caffeine intake, was associated with a reduced risk[18].
- A further systematic review and dose response analysis concluded that coffee intake of more than 3 cups per day was associated with lower risk of NAFLD than less than 2 cups per day, and suggested that the relationship was non linear[20].

Hepatitis C

- A prospective cohort US study recruited 766 hepatitis C-infected patients and followed them up for nearly four years[22]. A total of 229 patients showed serious disease progression, e.g. cirrhosis or 2-point increase in Ishak fibrosis score (a histological grading of progression to fibrosis, with scores ranging from 0 to 6). Tea consumption was not associated with the study outcomes. However, regular coffee consumption was statistically significantly associated with lower rates of disease progression.
- A French study developed to evaluate the impact of caffeine consumption on activity grade and fibrosis stage in patients with chronic hepatitis C found that caffeine consumption over 408 mg/day was associated with reduced histological activity in these patients[23].
- A study of patients with the Hepatitis C virus suggested that amongst those with a chronic infection, daily consumption of filtered coffee may have a beneficial effect on the stabilisation of the liver enzyme serum alanine aminotransferase (ALT)[24].
- Data from the Singapore Chinese Health Study, a population-based cohort of 63,275 adults, suggested that there was a strong dose-dependent inverse association between coffee intake and risk of non-viral hepatitis related cirrhosis. Compared to non-coffee drinkers, those who drank more than 2 cups per day had a 66% reduction in mortality risk. However, there was no association between coffee intake and hepatitis B related cirrhosis mortality[7].

If patients change their habits or diet as a result of their disease or its standard therapy, this can bias the observational study. Therefore it is important to assess whether such confounders are adequately taken into account. Case control-studies are particularly susceptible to bias, in particular when other patients are used as controls; prospective cohort studies are less susceptible to this type of bias.

POTENTIAL MECHANISMS

As per the above studies, there is some epidemiological evidence for an inverse association between coffee consumption and liver cancer. The same may be the case for liver fibrosis and

alcoholic cirrhosis. Clearly, a plausible biological mechanism is required to explain and confirm these associations.

The role of caffeine

Caffeine has been suggested as a key component in the observed associations between coffee consumption and a reduced risk of liver conditions[9,25,28,30,48]. The precise mechanisms behind this effect are unclear, however a number of potential mechanisms have been proposed.

A number of papers have suggested that caffeine, and in particular its main primary metabolite, paraxanthine, can suppress the synthesis of CTGF (connective tissue growth factor) via a cascade of control cycles, thereby slowing down the growth of this type of tissue, which in turn slows down the progression of liver fibrosis, alcoholic cirrhosis and liver cancer[10,26,30,48]. However, some of the epidemiological studies did not find an association with tea[48], which suggests that the mechanism of action might be not dependent solely on caffeine (via paraxanthine)[30,48].

It has also been suggested that caffeine may act via by blocking adenosine receptors, since the structure of caffeine mimics that of adenosine[48], in turn inhibiting activation of liver cells.

However, caffeine may not be the most important component, as other caffeinated drinks such as tea do not appear to provide similar protection against liver disease[19].

Other coffee constituents

A 2010 paper also mentions the potential role of the coffee components kahweol and cafestol in lowering the risk of liver cancer[27]. There is some evidence that they may have anti-carcinogenic properties[27].

It has also been proposed that the polyphenols found in coffee, such as chlorogenic acid, may reduce oxidative stress in the liver, in turn reducing the risk of fibrosis and development of cancers[28-30].

A 2019 literature review suggests that caffeine, trigonelline and chlorogenic acid may be important in the association between coffee consumption and a reduced risk of liver cancer, by modulating common molecular targets directly implicated in key cancer hallmarks[28]. A further 2019 review on liver cancer also suggested that the potential mechanisms include a role for compounds such as caffeine, chlorogenic acids, phenolic compounds and diterpenes, as well as potentially an improvement in insulin sensitivity and prevention of metabolic syndrome and diabetes[29].

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