Coffee and Liver – Long Way To Go

Abstract 1

Johnson S, Koh WP, Wang R, Govindarajan S, Yu MC, Yuan JM. Coffee consumption and reduced risk of hepatocellular carcinoma: Findings from the Singapore Chinese Health Study. *Cancer Causes Control*. 2011; 22:503–510.

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Background: Coffee consumption has been associated with reduced markers of hepatic cell damage, reduced risk of chronic liver disease, and cirrhosis across a variety of populations. Data on the association between coffee consumption and risk of hepatocellular carcinoma (HCC), especially in high-risk populations, are sparse. **Methods:** This study examines the relationship between coffee and caffeine consumption, and the risk of developing HCC within the Singapore Chinese Health Study, a prospective cohort of 63,257 middle-aged and older Chinese men and women, a relatively high-risk population for HCC. Baseline data on coffee consumption and other dietary and lifestyle factors were collected through in-person interviews at enrollment between 1993 and 1998. **Results:** As of 31 December 2006, 362 cohort participants had developed HCC. High-levels of coffee or caffeine consumption were associated with reduced risk of HCC (P for trend <0.05). Compared with nondrinkers of coffee, individuals who consumed three or more cups of coffee per day experienced a statistically significant 44% reduction in risk of HCC (hazard ratio 0.56, 95% confidence interval, 0.31–1.00, $P = 0.049$) after adjustment for potential confounders and tea consumption. **Conclusion:** These data suggest that coffee consumption may reduce the risk of developing HCC in Chinese in Singapore.

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Abbreviations: HCC: Hepatocellular carcinoma; IQR: interquartile range; CC: Caffeine consumption; NAFLD: Nonalcoholic fatty liver disease; NHANES: National Health and Nutrition Examination Surveys; CHC: Chronic hepatitis C; LDL: Low-density lipoprotein

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Abstract 2

Freedman ND, Curto TM, Lindsay KL, Wright EC, Sinha R, Everhart JE; HALT-C TRIAL GROUP. Coffee consumption is associated with response to peginterferon and ribavirin therapy in patients with chronic hepatitis C. *Gastroenterology*. 2011;140:1961–1969.

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Background & aims: High-level coffee consumption has been associated with reduced progression of pre-existing liver diseases and lower risk of hepatocellular carcinoma. However, its relationship with therapy for hepatitis C virus infection has not been evaluated. **Methods:** Patients ($n = 885$) from the lead-in phase of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial recorded coffee intake before retreatment with peginterferon α -2a (180 μ g/wk) and ribavirin (1000–1200 mg/day). We assessed patients for early virologic response (2 $\log_{10}$ reduction in level of hepatitis C virus RNA at week 12; $n = 466$), and undetectable hepatitis C virus RNA at weeks 20 ($n = 320$), 48 (end of treatment, $n = 284$), and 72 (sustained virologic response; $n = 157$). **Results:** Median $\log_{10}$ drop from baseline to week 20 was 2.0 (interquartile range [IQR], 0.6–3.9) among nondrinkers and 4.0 (IQR, 2.1–4.7) among patients that drank 3 or more cups/day of coffee (P trend <0.0001). After adjustment for age, race/ethnicity, sex, alcohol, cirrhosis, ratio of aspartate aminotransferase to alanine aminotransferase, the IL28B polymorphism rs12979860, dose reduction of peginterferon, and other covariates, odds ratios for drinking 3 or more cups/day vs nondrinking were 2.0 (95% confidence interval [CI]: 1.1–3.6; P trend = 0.004) for early virologic response, 2.1 (95% CI: 1.1–3.9; P trend = 0.005) for week 20 virologic response, 2.4 (95% CI: 1.3–4.6; P trend = 0.001) for end of treatment, and 1.8 (95% CI: 0.8–3.9; P trend = 0.034) for sustained virologic response. **Conclusions:** High-level consumption of coffee (more than 3 cups per day) is an independent predictor of improved virologic response to peginterferon plus ribavirin in patients with hepatitis C.

Abstract 3

Molloy JW, Calcagno CJ, Williams CD, Jones FJ, Torres DM, Harrison SA. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology*. 2012;55:429–436.

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Coffee caffeine consumption (CC) is associated with reduced hepatic fibrosis in patients with chronic liver diseases, such as hepatitis C. The association of CC with nonalcoholic fatty liver disease (NAFLD) has not been established. The aim of this study was to correlate CC with the prevalence and severity of NAFLD. Patients involved in a previously published NAFLD prevalence study, as well as additional NASH patients identified in the Brooke Army Medical Center Hepatology clinic, were queried about their caffeine intake. A validated questionnaire for CC was utilized to assess for a relationship between caffeine and four groups: ultrasound negative (controls), bland steatosis/not-NASH, NASH stage 0–1, and NASH stage 2–4. A total of 306 patients responded to the CC questionnaire. Average milligrams of total caffeine/coffee CC per day in controls, bland steatosis/not-NASH, NASH stage 0–1, and NASH stage 2–4 were 307/228, 229/160, 351/255, and 252/152, respectively. When comparing patients with bland steatosis/not-NASH to those with NASH stage 0–1, there was a significant difference in CC between the two groups ($P = 0.005$). Additionally, when comparing patients with NASH stage 0–1 to those with NASH stage 2–4, there was a significant difference in coffee CC ($P = 0.016$). Spearman's rank correlation analysis further supported a negative relationship between coffee CC and hepatic fibrosis ($r = -0.215$; $P = 0.035$). **Conclusion:** Coffee CC is associated with a significant reduction in risk of fibrosis among NASH patients.

Abstract 4

Birerdinc A, Stepanova M, Pawloski L, Younossi ZM. Caffeine is protective in patients with nonalcoholic fatty liver disease. *Aliment. Pharmacol Ther.* 2012;35:76–82. Center for Liver Disease and Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, USA; School of Systems Biology, College of Science, George Mason University, Fairfax, VA, USA; and Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA.

Background: Nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, is the most common cause of primary liver disease. Although recent studies have found that coffee drinking is protective against end stage chronic liver disease, there are scarce caffeine intake data in NAFLD specifically. **Aim:** To investigate the effects of dietary behavior in NAFLD patients, using four continuous cycles of the National Health and Nutrition Examination Surveys (NHANES 2001–2008). **Methods:** Using data from four continuous cycles of NHANES, dietary intake questionnaires that list 62 nutrition components. Logistic regression was used to identify independent predictors of NAFLD among nutrition components after adjustment for potential

clinical confounders. All analyses were run using SAS 9.1 and SUDAAN 10.0 (SAS Institute Inc., Cary, NC, USA). **Results:** Of the 62 nutrient components used for the univariate analysis, 38% were significant (P -value <0.05) in NAFLD with caffeine consumption being higher in the control group (P -value <0.001). The multivariate analysis using demographics, clinical parameters and nutritional components found five factors independently associated with NAFLD [African American Race (P -value <0.001); Male gender (P -value <0.001); Obesity (BMI ≥ 30) (P -value <0.001); Caffeine intake (mg) (P -value <0.001) and total plain water consumption (g) (P -value ≤ 0.02)]. **Conclusions:** Our analysis shows that caffeine intake is independently associated with a lower risk for NAFLD suggesting a potential protective effect. These data necessitate further research to elucidate the mechanism by which caffeine can protect against NAFLD.

COMMENTS

Although, beneficial health effects of coffee are controversial, a large population-based study found that increased coffee intake decreased all-cause mortality, largely due to a reduced rate of cardiovascular death.¹ As far as the liver disease is concerned, population-based studies have shown lower risk of raised transaminases and chronic liver disease with higher caffeine consumption (>2 cups per day).^{2,3} In addition, coffee has been reported to reduce the risk of advanced liver disease and its complications including hepatocellular carcinoma (HCC).⁴ Recent data has suggested that the higher caffeine consumption is associated with lower rates of progression of fibrosis in patients with chronic liver disease, particularly those related to alcohol and chronic hepatitis C (CHC).⁵ Relationship of hepatic fibrosis with coffee consumption is significant in view of the fact that the reduction of fibrosis progression in chronic liver disease would potentially help prevent the associated complications of cirrhosis and HCC.

The Singapore Chinese Health Study⁶ (Abstract 1) evaluated the relationship between coffee and caffeine consumption, and the risk of developing HCC in a prospective cohort of 63,257 middle-aged and older Chinese men and women, a relatively high-risk population for HCC. Baseline data on coffee consumption and other dietary and lifestyle factors were collected through in-person interviews at enrollment. Out of 63,257 subjects enrolled in five years, 362 participants had developed HCC. High-levels of coffee or caffeine consumption were associated with reduced risk of HCC (P for trend <0.05). Compared with nondrinkers of coffee, individuals who consumed three or more cups of coffee per day experienced a statistically significant 44% reduction in risk of HCC (hazard ratio 0.56, 95% confidence interval, 0.31–1.00, $P = .049$) after adjustment for potential confounders and tea consumption.

Most of the earlier data on the association of coffee and HCC are available from low prevalence areas. The results

from the present study are significant to confirm that coffee consumption may reduce the risk of developing HCC even in population with higher risk of developing HCC.⁶ Coffee has more than a 1,000 compounds, with caffeine being the major constituent. It is postulated that the liver-protecting properties of coffee come from two of the coffee oils (called dipterenes): cafestol and kahweol. Even though the exact mechanism is unknown, animal studies suggest that some of the coffee compounds including cafestol, and kahweol, may act as blocking agents via modulation of multiple enzymes involved in carcinogenic detoxification.^{7,8} They also modify the xenotoxic metabolism via induction of glutathione-S-transferase and inhibition of N-acetyltransferase.⁹ Coffee has also been found to reduce the risk of hepatic fibrosis and cirrhosis, a major risk in the process of liver carcinogenesis.⁴ Thus, the beneficial effect of coffee consumption on HCC may also be due to its inverse relation with hepatic fibrosis and cirrhosis.

Freedman et al¹⁰ looked at an entirely new concept i.e. the effect of coffee on the response to HCV therapy in patients with CHC (Abstract 2). Interestingly they found that high-level consumption of coffee (more than 3 cups per day) was an independent predictor of improved virologic response to peginterferon plus ribavirin in patients with CHC.¹⁰ Patients ($n = 885$) from the lead-in phase of the HALT-C Trial recorded coffee intake before retreatment with peginterferon α -2a and ribavirin. The higher virological response in coffee drinkers is unlikely to be a direct antiviral effect and is more likely a facilitating effect on response to peginterferon and ribavirin treatment by a mechanism yet to be understood. The antiviral effect may be related to the link between kahweol in coffee to JAK-STAT signaling which is associated with the *IL28B* genotype effect on virological response.¹¹ Coffee intake may also cause increased virological response to therapy by increasing the serum total cholesterol and low-density lipoprotein (LDL) which has been linked with higher virological response.¹² Further, coffee intake may improve insulin resistance and thus affect the virological response.¹³

Even though coffee consumption was shown to be associated with reduced hepatic fibrosis in patients with CHC, the association with nonalcoholic fatty liver disease (NAFLD) was not well established. Molloy et al¹⁴ in a recent issue of Hepatology (Abstract 3) showed an inverse relationship between regular coffee consumption and hepatic fibrosis in patients with NAFLD with a statistically significant difference in caffeine coffee intake observed between ultrasound negative controls, bland steatosis/not-NASH patients, NASH stage 0–1 fibrosis patients, and NASH stage 2–4 fibrosis patients. Importantly, on multiple statistical analyses, the trend of increased coffee caffeine intake and decreased fibrosis remained statistically significant.¹⁴ Though patients with bland steatosis/not-NASH, as well as the control group, drank less

coffee than those patients with NASH stage 0–1 fibrosis, it was not clear what amount of coffee confers the greatest decreased risk of fibrosis. The beneficial effects of caffeine intake and association with lower risk for NAFLD suggesting a potential protective effect are reinforced in the study by Binerdinc et al¹⁵ (Abstract 4) who on evaluating dietary behavior in NAFLD patients found significantly higher caffeine consumption in the control group as compared to patients with NAFLD.

The beneficial effect of caffeine/coffee in patients with NAFLD may be related to its antioxidant activity.¹⁶ The dipterenes, kahweol and cafestol, the constituents of coffee though have been shown to have beneficial effects on glutathione metabolism; these oils have also been shown to increase cholesterol levels, a finding that may not be beneficial to patients with NAFLD.^{12,17} Caffeine also inhibits expression of connective tissue growth factor by interfering with transforming growth factor beta signaling and by up-regulating peroxisome proliferator-activated receptor gamma levels, which could explain the antifibrogenic effects of caffeine.¹⁸

While we can go on discussing as to the number of cups of coffee which are likely to provide benefit, we need to know what our cup of coffee really contains. There are various types of coffee and most commercially available coffee beverages consumed around the world are produced by the species *Coffea arabica* (Arabica) and *Coffea canephora* (Robusta) each of which has various varieties. The composition of coffee varies with the species and with the process of maturation. The caffeine content of the coffee beans depends on species and variety, from 0.6% in Laurina of *Coffea arabica* up to >4% in Robusta variety of *Coffea canephora*. The caffeine content of coffee can be reduced by decaffeination, a process which involves steam treatment of the green coffee to soften the tissues, followed by solvent extraction. The type of preparation of the cup of coffee also matters. In an espresso-type percolation, the very short time available to extract caffeine from the cellular structure leads to 75–85% extraction yield only.¹⁹

Many questions however remain unanswered before we conclude that coffee can take care of our livers. Amount of coffee, and type of coffee no doubt would be important but equally important might be the race of the population being studied for the beneficial effects of coffee. Although more than 3 cups of coffee look protective, more data on this issue are required before the protective amount of coffee is decided. Is it all caffeine or other constituents of coffee doing the job? Is it the antioxidant effect of coffee and its constituents or something else? And finally there has been lot of focus on the protective effects of coffee oils i.e. cafestol, and kahweol, most of which are filtered out in traditional American coffee, and, therefore the population may not really be exposed to them. So while we can look at our cup of coffee with exhilaration, is it the right one for our liver?

A number of studies have reported the beneficial effects of coffee on abnormal liver biochemistry, cirrhosis, hepatocellular carcinoma and NAFLD. However, the exact mechanism of these effects remains unclear as does the “dose” required to achieve these benefits.²⁰ It seems a long way to go till we get all the answers.

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