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The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers

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Background: Coffee intake is associated with reduced risk of liver cancer and chronic liver disease as reported in previous studies, including prospective ones conducted in Asian populations where hepatitis B viruses (HBVs) and hepatitis C viruses (HCVs) are the dominant risk factors. Yet, prospective studies in Western populations with lower HBV and HCV prevalence are sparse. Also, although preparation methods affect coffee constituents, it is unknown whether different methods affect disease associations.

Methods: We evaluated the association of coffee intake with incident liver cancer and chronic liver disease mortality in 27 037 Finnish male smokers, aged 50–69, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, who recorded their coffee consumption and were followed up to 24 years for incident liver cancer or chronic liver disease mortality. Multivariate relative risks (RRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazard models.

Results: Coffee intake was inversely associated with incident liver cancer (RR per cup per day = 0.82, 95% CI: 0.73–0.93; *P*-trend across categories = 0.0007) and mortality from chronic liver disease (RR = 0.55, 95% CI: 0.48–0.63; *P*-trend < 0.0001). Inverse associations persisted in those without diabetes, HBV- and HCV-negative cases, and in analyses stratified by age, body mass index, alcohol and smoking dose. We observed similar associations for those drinking boiled or filtered coffee.

Conclusion: These findings suggest that drinking coffee may have benefits for the liver, irrespective of whether coffee was boiled or filtered.

Liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death in the world (Ferlay *et al*, 2010). Traditionally, liver cancer rates have been high in regions with endemic hepatitis B virus (HBV) infection, such as countries in sub-Saharan Africa or Asia (McGlynn *et al*, 2001). In recent times, however, rates have increased in countries with low HBV prevalence, such as those in North America and Europe (McGlynn *et al*, 2001), likely due to infection with hepatitis C virus (HCV), obesity and diabetes (El-Serag and Rudolph, 2007). As liver cancer often arises from within livers damaged by chronic liver disease over the course of many years (Siegel and Zhu, 2009), it is vital to consider both chronic liver disease and liver cancer for cancer prevention.

A number of recent studies have suggested that coffee intake benefits liver health. Coffee consumption has been reported to be inversely associated with enzymes indicative of liver disease and

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damage (Arnesen *et al*, 1986; Kono *et al*, 1994; Poikolainen and Vartiainen, 1997; Tanaka *et al*, 1998; Nakanishi *et al*, 2000; Ruhl and Everhart, 2005), fibrosis and cirrhosis in cross-sectional studies (Modi *et al*, 2010; Muriel and Arauz, 2010), and liver disease progression (Freedman *et al*, 2009). Coffee may also be associated with lower cancer risk. Several prospective cohort studies in Asian populations with high HBV prevalence observed inverse associations between high or regular coffee consumption and liver cancer (Bravi *et al*, 2007; Larsson and Wolk, 2007). Studies in Western populations with a different spectrum of liver disease risk factors are limited, although a few case–control studies in Italy and Greece and one prospective cohort study in Finland support an inverse association for coffee and liver cancer (Bravi *et al*, 2007, 2009; Larsson and Wolk, 2007; Hu *et al*, 2008). The reported inverse association may be due to the anti-proliferative properties of a number of coffee compounds such as chlorogenic acid (Iwai *et al*, 2004) and diterpenes (e.g., cafestol and kahweol; Cavin *et al*, 1998, 2002; Majer *et al*, 2005). Yet, it has also been reported that different methods of coffee preparation can influence levels of these and other compounds (Ratnayake *et al*, 1993; Urgert *et al*, 1995; Gross *et al*, 1997) and preparation method has been shown to affect associations of coffee consumption with lipid levels and blood pressure in previous studies (Jee *et al*, 2001; Noordzij *et al*, 2005). However, little is known about whether the association of coffee intake with the risk of chronic liver disease or liver cancer is affected by preparation method.

We evaluated associations between coffee intake and subsequent risk of incident liver cancer or chronic liver disease mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a prospective cohort of Finnish male smokers that also had available data on coffee preparation methods.

MATERIALS AND METHODS

Participants, follow-up and outcome ascertainment. The rationale and design of the ATBC Study have been described previously (The ATBC Cancer Prevention Study Group, 1994). In short, the ATBC Study was a randomised, double-blinded, 2×2 factorial designed, placebo-controlled trial that evaluated whether vitamin E in the form of α-tocopherol and β-carotene would reduce the risk of lung cancer. A total of 29 133 Finnish male smokers with no prior malignancy, alcoholism or other major medical problems were enrolled at baseline between 1985 and 1988. Although the trial ended on 30 April 1993, the men were further followed-up through national registers for morbidity and mortality end points.

Men diagnosed with liver cancer ($n = 194$; ICD-9 = 155 and ICD-10 = C22) were identified through the Finnish Cancer Registry, providing close to 100% case ascertainment (Korhonen *et al*, 2002). The medical records of 80% of the liver cancer cases (i.e., those diagnosed during the trial and 6 years post-intervention) were reviewed by a study physician to confirm the diagnosis of liver cancer while incident data from the remaining 20% was available only from the Finnish Cancer Registry. Follow-up time began at randomisation until the date of cancer diagnosis, death or until 31 December 2009, whichever came first. Men who died from chronic liver disease ($n = 213$; ICD-9 = 571 and ICD-10 = K70, K73 or K74) were identified through the Finnish Register of Causes of Death. The underlying cause of approximately 90% of the chronic liver disease deaths was noted as alcohol-related liver diseases. Follow-up time began at randomisation until the date of death (from chronic liver disease for the cases or other causes for the controls), incident liver cancer or until 31 December 2009, whichever came first. After excluding those who reported liver cirrhosis and who lacked information on demographics or coffee intake, we had an analytic sample of 27 037 men (93% of the cohort; Figure 1). A total of eight men were diagnosed with incident liver cancer and also died from chronic liver disease. For our study, these men were considered to have incident liver cancer but were not included in the chronic liver disease mortality category. Information on the method of coffee preparation was available for 20 737 men.

Written informed consent was provided by all participants before randomisation. The institutional review board of both the National Public Health Institute of Finland and the US National Cancer Institute approved the ATBC Study.

Data collection and laboratory analysis. At baseline, participants were asked to complete a questionnaire concerning their medical history, diet, tobacco smoking and alcohol consumption. Intake of coffee, alcohol, tea and other foods was calculated from a food

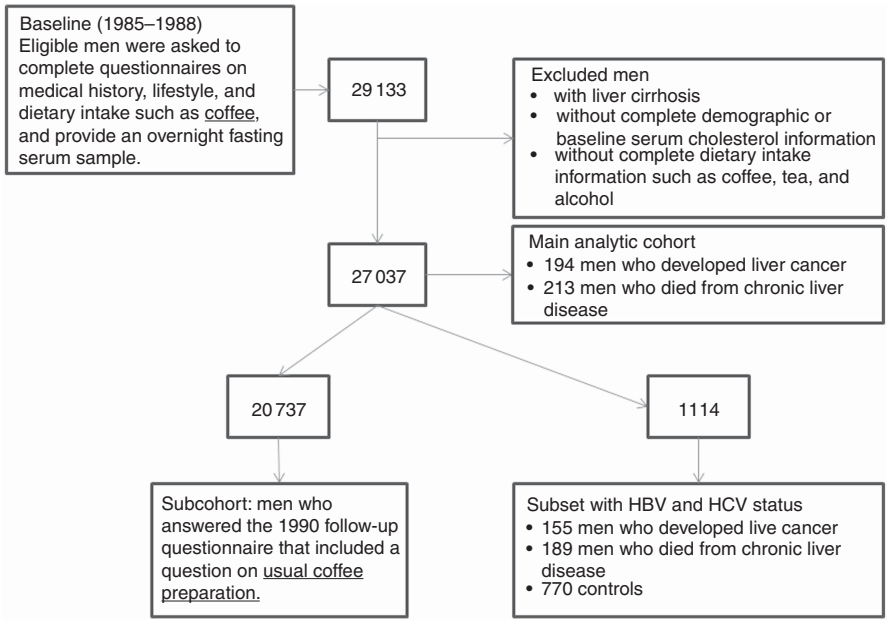

Figure 1. Diagram of analytic sample within ATBC Study.

frequency questionnaire in conjunction with a validated comprehensive nutrient database. Within the questionnaire, participants were asked to indicate the average number of cups of coffee consumed per day or per week in the previous year. With the use of a colour picture booklet, participants were also asked to indicate their typical cup size. The three cup sizes most commonly used in Finland for coffee were 70, 110 and 170 g. For coffee intake, the intraclass correlation coefficient comparing food records with food use questionnaires ranged from 0.72 to 0.79 (Pietinen *et al*, 1988). Each participant also provided an overnight fasting serum sample that was stored at $-70\,^{\circ}C$. Total cholesterol was measured using an enzymatic assay (CHOD-PAP method, Boehringer Mannheim, Germany). Over the course of the trial, participants visited local centres every 4 months to complete follow-up questionnaires. In the fall of 1990 (2–5 years after randomisation), participants were asked about the usual method of preparing coffee at baseline with the following answer choices: 'usually filtered', 'usually boiled', 'usually instant' and 'I don't drink coffee'. Among these men, 71% and 21% reported filtered and boiled methods of preparation, respectively. Coffee prepared by filtered methods involves pouring water over roasted, ground coffee beans contained within a filter (nearly always paper). Coffee prepared by boiling methods involves pouring hot water onto ground coffee in a pot or cup, waiting until the grounds settle and then drinking the supernatant.

Serologic determinations were conducted in a subset of the cases (men who were diagnosed with liver cancer and men who died from chronic liver disease) and controls, frequency (2 : 1) matched by age (± 5 years) and date of blood draw (± 30 days). Testing for HBV surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc) and antibody to HCV (anti-HCV) was performed by the SAIC NCI-Frederick National Laboratory (Frederick, MD, USA). HBsAg was tested using enzyme immunoassay from Bio-Rad Laboratories (Redmond, WA, USA), and anti-HBC and anti-HCV were tested using enzyme-linked immunosorbent assays from Ortho-Clinical Diagnostics (Raritan, NJ, USA). Concordance of samples with known HBV and HCV status were perfect. Information on HBV and HCV was available in 155 men who developed liver cancer, 189 men who died from chronic liver disease, and 770 controls.

Statistical analysis. After excluding participants with missing demographic or serum data, our final analytic sample was 27 037 men. Baseline demographic, behavioural and lifestyle factors as well as serum levels of cholesterol by intake of coffee are presented. Using the USDA conversion tables, we calculated that one cup of coffee (one cup being 8 oz) was approximately 237 g. Relative risks (RR) and 95% confidence intervals (CIs) for the association of coffee intake with incident liver cancers or mortality from chronic liver disease were estimated by Cox proportional hazard regression models with person-years as the underlying time metric. We tested the proportional hazards assumption by modelling the interaction of coffee consumption with follow-up time and observed no significant deviations. We used coffee drinkers who drank <1 cup per day ($>0-<1$ cup) as the referent group. Linear trend tests across increasing number of cups of coffee were estimated by assigning each participant the median intake of his category and entering that term as a continuous variable in the regression model. In the subset with information on HBV and HCV status, odds ratios and 95% CIs were estimated by logistic regression models.

We examined risk estimates from crude and multivariable models that were adjusted for a number of known and possible confounders including: intervention arm, age (continuous), body mass index (BMI; continuous), education (elementary school or less, greater than elementary school), marital status (currently married, not currently married), history of diabetes (yes, no), years of smoking (continuous), number of cigarettes smoked per day (continuous), alcohol intake (continuous), tea intake (never drinker, up to 6 oz of tea per day, >6 oz of tea) and total serum cholesterol level (continuous). These variables were evaluated because they are either known or are suspected risk factors for liver cancer and chronic liver disease (Chuang *et al*, 2009; Souza *et al*, 2012) or were associated with coffee intake. We further adjusted for hepatitis B and C status among the subset of men with this information. As HBV and HCV are associated with both liver cancer and chronic liver disease, we also evaluated the association among HBV- and HCV-negative participants. Lag analyses were conducted by evaluating associations after removing the first 2 and 5 years of follow-up, and among the first 10 years and last 10 years of follow-up. To consider possible effect modification, we evaluated associations by subgroups defined as above or below the median for age, BMI, years of smoking, number of cigarettes smoked per day, alcohol intake and serum cholesterol. Effect modification was formally tested by using likelihood ratio tests that compared regression models with and without the cross-product term for categorical coffee intake and the categories of each examined exposure.

Statistical tests were two-sided and considered statistically significant at P-value <0.05. All analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

After a median follow-up time of 18.2 years, 194 men developed liver cancer and 213 men died from chronic liver disease. Coffee intake ranged from 0 to 4 or more cups per day, with a median level of 2.3 cups per day (interquartile range = 1.8–3.2 cups per day); approximately 2.5% of the participants were non-drinkers. At baseline, men were generally similar in age, BMI, the number of years smoked, the number of cigarettes smoked per day and proportion of those with a history of diabetes across categories of coffee consumption (Table 1). In contrast, men who consumed more coffee tended to be less educated, drink less alcohol, drink less tea and have higher serum cholesterol levels. A notable proportion of men, 64%, reported drinking no tea. Among the subset of men with information on hepatitis B and C status, the prevalence of HBsAg was 0.8% and the prevalence of HCV seropositivity was 1.6%.

Associations were similar in both crude and multivariate adjusted models. In multivariate models, the risks for incident liver cancer and mortality from chronic liver disease decreased with increasing coffee consumption (RR per cup per day = 0.82, 95% CI: 0.73–0.93 and RR per cup per day = 0.55, 95% CI: 0.48–0.63, respectively; Table 2). For liver cancer, associations were similar for those drinking $2-<3$ cups ($2-<3$ cups per day *vs* $>0-<1$ cup per day RR = 0.44, 95% CI: 0.26–0.77) or more per day ($\geqslant 4$ cups per day *vs* $>0-<1$ cup per day RR = 0.53, 95% CI = 0.30–0.95). In a sensitivity analysis, we restricted the analysis to only hepatocellular carcinoma cases ($n = 140$ cases) and observed similar estimates. In contrast, for chronic liver disease mortality, the RR became progressively lower with higher intake; men who drank >4 cups per day were at a significantly decreased risk (RR = 0.07, 95% CI = 0.03–0.15, P-value trend <0.0001). The association remained similar in analysis restricted to men without a reported history of diabetes. In the subset of men with information on HBV and HCV, associations did not appreciably change when we adjusted for HBV and HCV, or when the analysis were restricted to those lacking HBsAg (men diagnosed with liver cancer: 98.7%; men who died from chronic liver disease: 99.6%; controls: 99.2%), or HCV (93.7%, 96.8%, 99.6%, of cases and controls, respectively; Supplementary Table 1).

To account for the possibility that any underlying disease may influence coffee consumption, lag analyses were performed. Associations were similar after removing the first two (incident

Table 1. Selected baseline characteristics of men by level of coffee consumption, ATBC Study

	Never drinkers		0–<1 cup per day		1–<2 cups per day		2–<3 cups per day		3–<4 cups per day		⩾4 cups per day	
No. of participants	**667**		**3094**		**7204**		**8086**		**4515**		**3471**	
	%	**Median (IQR)**	**%**	**Median (IQR)**	**%**	**Median (IQR)**	**%**	**Median (IQR)**	**%**	**Median (IQR)**	**%**	**Median (IQR)**
Randomisation group												
Placebo	28.9%		24.9%		25.0%		25.0%		24.8%		25.8%	
AT	23.5%		25.2%		24.7%		25.2%		25.2%		25.0%	
BC	21.4%		25.2%		25.6%		24.1%		25.3%		25.3%	
ATBC	26.1%		24.6%		24.6%		25.8%		24.7%		23.9%	
Age, years		57 (53–61)		57 (54–61)		57 (53–62)		57 (53–61)		56 (52–60)		55 (52–59)
BMI, kg m^{-2}		25.5 (23.0–28.2)		26.1 (23.7–28.6)		25.9 (23.7–28.5)		25.9 (23.8–28.4)		26.0 (23.7–28.6)		26.1 (23.8–28.5)
Greater than elementary school	24.7%		27.8%		24.7%		20.0%		18.6%		17.2%	
Currently married	73.3%		74.7%		79.7%		83.5%		83.9%		82.6%	
Age when starting to smoke, years		19 (17–20)		19 (17–21)		19 (17–21)		19 (17–21)		19 (17–20)		18 (16–20)
Years of smoking		37 (31–42)		37 (30–42)		37 (31–42)		36 (31–42)		36 (31–41)		36 (32–41)
Total no. of cigarettes per day		20 (15–25)		20 (12–25)		20 (15–25)		20 (15–25)		20 (15–25)		20 (20–30)
Alcohol (g day^{-1})		15.92 (4.10–32.39)		18.82 (6.50–36.95)		12.99 (3.85–27.86)		10.09 (2.19–23.83)		8.77 (1.83–22.86)		7.22 (1.11–19.41)
Non-tea drinkers	38.8%		39.6%		57.1%		68.4%		74.5%		81.6%	
Serum cholesterol, mmol l^{-1}		5.94 (5.21–6.67)		6.06 (5.39–6.82)		6.15 (5.41–6.91)		6.20 (5.48–6.97)		6.22 (5.51–7.04)		6.20 (5.47–7.02)
History of diabetes mellitus, *n*, %	5.0%		5.0%		4.2%		3.7%		4.3%		4.3%	
Hepatitis B surface antigen positive[a]	0%		0%		1.8%		0.5%		0.8%		0%	
Hepatitis B core antigen positive[a]	0%		10.1%		7.3%		5.5%		7.0%		5.7%	
Hepatitis C positive[a]	0%		1.0%		0.9%		0%		0%		0%	

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention; BMI = body mass index; IQR = interquartile range.
[a]Available in 770 controls.

liver cancer: RR per cup per day = 0.81, 95% CI: 0.72–0.92; chronic liver disease mortality: RR = 0.57, 95% CI: 0.50–0.66) and 5 years of follow-up (incident liver cancer: RR = 0.81, 95% CI: 0.71–0.92; chronic liver disease mortality: RR = 0.56, 95% CI: 0.48–0.65) and in cases occurring during the first 10 years (incident liver cancer: RR = 0.81, 95% CI: 0.66–0.98; chronic liver disease mortality: RR = 0.53, 95% CI: 0.44–0.64) or last 10 years (incident liver cancer: RR = 0.83, 95% CI: 0.71–0.96; chronic liver disease mortality: RR = 0.57, 95% CI: 0.48–0.69) of follow-up.

We evaluated whether associations of coffee intake with incident liver cancer and chronic liver disease mortality varied by a number of risk factors including age, BMI, years of smoking, number of cigarettes smoked per day, alcohol intake and serum cholesterol. For incident liver cancer, we observed modest differences between some subgroups. For example, associations for coffee drinking appeared to be somewhat weaker among those who were younger (<57 years; RR per cup per day = 0.94, 95% CI: 0.80–1.10), had a lower BMI (<26 kg m^{-2}; RR per cup per day = 0.93, 95% CI: 0.76–1.12) and smoked for a shorter number of years (36 years; RR per cup per day = 0.93, 95% CI: 0.77–1.13) than those who were older (RR = 0.73, 95% CI: 0.61–0.86), had a higher BMI (RR = 0.77, 95% CI: 0.67–0.90) and smoked for a longer period of time (RR = 0.76, 955 CI: 0.66–0.89). However, these potential differences were not statistically significant (all *P*-for-interaction > 0.07) and thus likely due to chance. For chronic liver disease mortality, we observed little difference across each stratifying variable, and again we observed no statistical evidence for an interaction (all *P*-for-interaction > 0.09) (Supplementary Tables 2 and 3).

We also examined whether associations varied by coffee preparation methods. Boiling (about 21%) and filtering (about 71%) were the two most common methods of coffee preparation

Table 2. Association of coffee consumption with incident liver cancer and mortality from chronic liver disease, ATBC Study (Presented as RRs and 95% CIs)

Incident liver cancer								
	Never drinkers	>0–<1 cupper day	1–<2 cups per day	2–<3 cups per day	3–<4 cups per day	⩾4 cups per day	*P*-trend	Cups per day
No. of cases/all	9/667	36/3094	60/7204	47/8086	22/4515	20/3471		
Unadjusted	1.24 0.60–2.58	1.00 Reference	0.68 0.45–1.03	0.45 0.29–0.70	0.37 0.22–0.63	0.44 0.26–0.77	<0.0001	0.78 0.70–0.88
Multivariable[a]	1.35 0.65–2.82	1.00 Reference	0.73 0.48–1.12	0.52 0.33–0.82	0.45 0.26–0.78	0.53 0.30–0.95	0.0007	0.82 0.73–0.93
Mortality from chronic liver disease								
	Never drinkers	>0–<1 cup per day	1–<2 cups per day	2–<3 cups per day	3–<4 cups per day	⩾4 cups per day	*P*-trend	Cups per day
No. of cases/all	10/667	75/3094	68/7204	39/8086	15/4515	6/3471		
Unadjusted	0.66 0.34–1.27	1.00 Reference	0.37 0.27–0.52	0.18 0.13–0.27	0.12 0.07–0.22	0.07 0.03–0.15	<0.0001	0.52 0.46–0.59
Multivariable[a]	0.73 0.38–1.42	1.00 Reference	0.44 0.31–0.62	0.23 0.15–0.35	0.15 0.08–0.26	0.08 0.03–0.18	<0.0001	0.55 0.48–0.63

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention; BMI = body mass index.
[a]Adjusted for ATBC intervention arm (categorical), age (continuous), BMI (continuous), education (elementary school education or less, higher than elementary school education), marital status (currently married, not), history of diabetes (yes, no), years of smoking (continuous), cigarettes smoked per day (continuous), alcohol (continuous), tea intake (non-drinkers, drink up to 6 oz, drink >6 oz) and serum cholesterol (continuous).

among the 20 737 men with information on coffee preparation. These 20 737 men were similar to the overall analytic sample of 27 037 men in terms of baseline characteristics including age, BMI, education, smoking, alcohol intake and history of diabetes. This yielded 130 men who were diagnosed with incident liver cancer and 109 men who died from chronic liver disease who had reported drinking boiled or filtered coffee. The results for consumption of boiled and filtered coffee were similar in this subcohort: for liver cancer, total consumption (cups per day) RR = 0.83 (95% CI: 0.72–0.95), boiled coffee RR = 0.85 (95% CI: 0.65–1.11), filtered coffee RR = 0.82 (95% CI: 0.69–0.98); for chronic liver disease mortality, total consumption (cups per day) RR = 0.55 (95% CI: 0.47–0.65), boiled coffee RR = 0.62 (95% CI: 0.43–0.88), filtered coffee RR = 0.50 (95% CI: 0.40–0.63; Table 3).

DISCUSSION

In this prospective cohort of Finnish male smokers with low prevalence of HBV and HCV, we found those who consumed more coffee had a lower risk of incident liver cancer and mortality from chronic liver disease. Relative to coffee drinkers who drank <1 cup per day, men who drank >2 cups per day had a nearly 50% reduction in risk for liver cancer, whereas for mortality from chronic liver disease, the reduction was over 90% for men who drank >4 cups per day. These notable inverse associations were stable during the follow-up period, and observed even among those without any history of diabetes and within different strata such as age, BMI and serum cholesterol levels. Although both alcohol and smoking are risk factors for chronic liver disease and liver cancer (Fan and Farrell, 2009; Altamirano and Bataller, 2010), adjustment for alcohol and smoking had little effect on our risk estimates. Furthermore, neither smoking duration nor intensity modified the association of coffee with liver cancer or chronic liver disease and results were similar in men who drank low and high amounts of alcohol.

The very strong nature of the observed inverse associations of coffee with incident liver cancer and chronic liver disease mortality may raise questions about the plausibility of these observations. However, findings of an inverse association of coffee intake with both liver cancer and chronic liver disease have been reported in previous studies and are consistent with the literature. Coffee intake has been reported by several cross-sectional studies to be inversely associated with serum liver enzymes gamma-glutamyltransferase (Arnesen *et al*, 1986; Kono *et al*, 1994; Poikolainen and Vartiainen, 1997; Tanaka *et al*, 1998; Nakanishi *et al*, 2000), alanine aminotransferase and aspartate aminotransferase (Ruhl and Everhart, 2005), which are markers of liver injury. Coffee intake was also associated inversely with liver cirrhosis in two large US prospective cohort studies (Tverdal and Skurtveit, 2003; Klatsky *et al*, 2006). For liver cancer, inverse associations with coffee intake have been observed in case–control studies based in Italy, Greece and Japan (Bravi *et al*, 2007, 2009; Larsson and Wolk, 2007) as well as prospective cohort studies in Asia (Bravi *et al*, 2007, 2009; Larsson and Wolk, 2007; Johnson *et al*, 2011; Yu *et al*, 2011) and one in Finland (Hu *et al*, 2008).

Coffee contains a large number of compounds, many of which are biologically active. The mechanisms by which coffee may possibly influence the development and progression of liver cancer and chronic liver disease could be related to the antioxidant properties of several compounds. A number of *in vitro* and *in vivo* study studies have demonstrated that chlorogenic acid, a component of green coffee beans, exhibits antioxidant, anti-inflammatory and antiproliferative properties (Saad *et al*, 1998; Iwai *et al*, 2004; Sato *et al*, 2011; Yun *et al*, 2012; Shi *et al*, 2013). Diterpenes such as cafestol and kahweol induce phase II enzyme activity and decrease chemically induced liver DNA adducts (Cavin *et al*, 1998, 2002; Huber *et al*, 2002a,b).

Table 3. Association of coffee by preparation type with incident liver cancer and mortality from chronic liver disease, ATBC Study (Presented as RRs and 95% CIs)

Incident liver cancer							
Filtered method of preparing coffee[a]	**>0–<1 cup per day**	**1–<2 cups per day**	**2–<3 cups per day**	**3–<4 cups per day**	**≥4 cups per day**	***P*-trend**	**Cups per day**
No. of cases/all	16/1467	34/4081	26/4575	9/2595	12/1931		
	1.00	0.80	0.54	0.34	0.61	0.03	0.82
	Reference	0.44–1.47	0.29–1.03	0.15–0.78	0.28–1.34		0.69–0.98
Boiled method of preparing coffee[a]	**>0 to <1 cup per day**	**1 to <2 cups per day**	**2 to <3 cups per day**	**3 to <4 cups per day**	**≥4 cups per day**	***P*-trend**	**Cups per day**
No. of cases/all	7/427	10/1016	5/1358	7/781	4/667		
	1.00	0.60	0.25	0.60	0.40	0.19	0.85
	Reference	0.23–1.57	0.08–0.80	0.21–1.75	0.12–1.40		0.65–1.11
Mortality from chronic liver disease							
Filtered method of preparing coffee[b]	**>0–<1 cup per day**	**1–<2 cups per day**	**2–<3 cups per day**	**3–<4 cups per day**	**≥4 cups per day**	***P*-trend**	**Cups per day**
No. of cases/all	28/1467	30/4081	17/4575	7/2595	2/1931		
	1.00	0.43	0.22	0.14	0.05	<0.0001	0.50
	Reference	0.25–0.73	0.12–0.40	0.06–0.33	0.01–0.22		0.40–0.63
Boiled method of preparing coffee[b]	**>0–<1 cup per day**	**1–<2 cups per day**	**2–<3 cups per day**	**3–<4 cups per day**	**≥4 cups per day**	***P*-trend**	**Cups per day**
No. of cases/all	7/427	8/1016	5/1358	2/781	2/667		
	1.00	0.52	0.26	0.16	0.19	0.005	0.62
	Reference	0.19–1.45	0.08–0.82	0.03–0.79	0.04–0.94		0.43–0.88

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention; BMI = body mass index.

[a]Adjusted for intake of coffee prepared by boiling (categorical), never drinker (yes, no), other coffee intake (yes, no), ATBC intervention arm (categorical), age (continuous), BMI (continuous), education (elementary school education or less, higher than elementary school education), marital status (currently married, not), history of diabetes (yes, no), years of smoking (continuous), cigarettes smoked per day (continuous), alcohol (continuous), tea intake (non-drinkers, drink up to 6 oz, drink >6 oz) and serum cholesterol (continuous).

[b]Adjusted for intake of coffee prepared by filtering (categorical), never drinker (yes, no), other coffee intake (yes, no), ATBC intervention arm (categorical), age (continuous), BMI (continuous), education (elementary school education or less, higher than elementary school education), marital status (currently married, not), history of diabetes (yes, no), years of smoking (continuous), cigarettes smoked per day (continuous), alcohol (continuous), tea intake (non-drinkers, drink up to 6 oz, drink >6 oz) and serum cholesterol (continuous).

It has been noted that the levels of cafestol and kahweol are higher in Scandinavian-styled boiled and Turkish coffee compared with drip filtered or instant coffee (Urgert *et al*, 1995; Gross *et al*, 1997). In this study, we observed that both boiled and filtered coffee were inversely associated with chronic liver disease mortality and liver cancer, suggesting that the effects of coffee on liver cancer and chronic liver disease are likely due to components that are present in coffee prepared both ways. To our knowledge, this is the first time where the association of coffee with liver cancer and chronic liver disease was evaluated by coffee preparation method.

Alternatively, coffee may affect insulin and glucose signalling. Coffee has consistently been inversely associated with type 2 diabetes in prospective cohort studies (Agardh *et al*, 2004; Salazar-Martinez *et al*, 2004; van Dam *et al*, 2004; Yamaji *et al*, 2004; Huxley *et al*, 2009). As diabetes has consistently been associated with higher risk of liver cancer (El-Serag *et al*, 2006) and liver disease (Picardi *et al*, 2006), coffee could possibly benefit the liver through regulation of insulin secretion, improvement of glucose tolerance and other related metabolic pathways (Tunnicliffe and Shearer, 2008). However, additional adjustment for diabetes had little effect on our observed associations. Adjustment for insulin resistance in a previously published study of coffee and liver disease progression was also reported to have no effect on the association (Freedman *et al*, 2009).

Associations of coffee with incident liver cancer and mortality from chronic liver disease could also reflect underlying liver disease, as coffee intake has been associated with fibrosis and cirrhosis in previous studies and as caffeine is metabolised in the liver, those with underlying liver disease may drink less coffee. We attempted to minimise this possibility by excluding individuals with self-reported cirrhosis at baseline. In addition, the observed associations remained after lag analyses, further indicating that reverse causality was an unlikely explanation for our findings. Associations were also similar in those with both higher and lower serum cholesterol levels at baseline, which has been previously associated with liver disease and subsequent liver cancer in this and other cohorts (Cicognani *et al*, 1997; Ahn *et al*, 2009; Kitahara *et al*, 2011). Previous studies have also found inverse associations between coffee and liver disease progression among those with fibrosis at study baseline (Freedman *et al*, 2009), further suggesting that our results do not simply reflect pre-existing liver disease.

Our study has several strengths and limitations. The prospective design limits the possibility of recall bias affecting our results as participants reported their coffee intake without knowledge of their future disease occurrence. We also had a long follow-up time of 24 years permitting assessment of reverse causality through lag analyses. The extensive baseline questionnaire allowed us to adjust for a number of potential confounders such as BMI, history of diabetes, alcohol intake, and HBV and HCV status. In particular, information on coffee preparation methods allowed us to explore whether the associations between coffee intake and disease risk differed by brewing method. However, as the primary purpose of

the study was to evaluate the use of vitamin supplements on lung cancer, associations of coffee with liver cancer or chronic liver disease mortality are secondary outcomes. Yet, similarity to previous studies in Western and Asian populations lends support to our findings. Also, we did not have any information on whether intake of coffee was caffeinated or not and coffee intake was assessed at only a single time. We possessed information on HBV and HCV for only a subset of our cohort; however, the very low prevalence of these infections in this subset (99.2% and 98.5% were negative for HBsAg and HCV, respectively) suggests nearly all cases occurred in the absence of HBV and HCV infection, and as such, HBV and HCV had little effect on our risk estimates. In addition, we lacked assessment of underlying liver disease, although men with cirrhosis were excluded from the cohort at baseline and associations did not vary over 24 years of follow-up. Furthermore, the evaluation of these associations among male smokers limits our ability to generalise to other populations. Finally, it is possible that our observations, despite our consideration of a number of known and potential confounders, may be due to uncontrolled confounding or bias as is always true of observational studies.

In summary, we observed that high coffee intake was associated with a statistically significant, reduced risk of incident liver cancer and mortality from chronic liver disease in a Finnish prospective cohort study. Although different preparation methods for coffee can influence the types of compounds found in coffee, we observed that both filtered and boiled coffee were inversely associated with liver cancer and mortality from chronic liver disease. A growing body of literature supports a beneficial role for coffee in liver cancer and liver disease. Future studies will be needed to elucidate what components of coffee may contribute to these associations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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