Coffee consumption and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma by sex: The Liver Cancer Pooling Project

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Abstract

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Background—Coffee consumption has been reported to be inversely associated with hepatocellular carcinoma (HCC), the most common type of liver cancer. Caffeine has chemopreventive properties, but whether caffeine is responsible for the coffee-HCC association is not well studied. In addition, few studies have examined the relationship by sex, and no studies have examined whether there is an association between coffee and intrahepatic cholangiocarcinoma (ICC), the second most common type of liver cancer.

Methods—In the Liver Cancer Pooling Project, a consortium of U.S.-based cohort studies, data from 1,212,893 individuals (HCC n=860, ICC n=260) in nine cohorts were pooled. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using proportional hazards regression.

Results—Higher coffee consumption was associated with lower risk of HCC ($HR_{>3 \text{ cups/day vs. non-drinker}}$, 0.73; 95% CI, 0.53-0.99; $p_{\text{trend cups/day}}$=<0.0001). More notable reduced risk was seen among women than men ($p_{\text{interaction}}$=0.07). Women who consumed more than three cups of coffee per day were at a 54% lower risk of HCC (HR, 0.46; 95% CI, 0.26-0.81), whereas men had more modest reduced risk of HCC (HR, 0.93; 95% CI, 0.63-1.37). The associations were stronger for caffeinated coffee ($HR_{>3 \text{ cups/day vs. non-drinker}}$, 0.71, 95% CI, 0.50-1.01) than decaffeinated coffee (HR, 0.92; 95% CI, 0.55-1.54). There was no relationship between coffee consumption and ICC.

Conclusions—These findings suggest that, in a U.S. population, coffee consumption is associated with reduced risk of HCC.

Impact—Further research into specific coffee compounds and mechanisms that may account for these associations is needed.

INTRODUCTION

Primary liver cancer is the second leading cause of cancer death worldwide (1), and the seventh leading cause in the U.S. (2). Liver cancer incidence rates in the U.S. have been rising since 1980 (3), although the increase has not been significant in recent years (4). Hepatocellular carcinoma (HCC) is the dominant histologic type of liver cancer, accounting for approximately 65% of cases, while intrahepatic cholangiocarcinoma (ICC), the second most common histologic type, accounts for approximately 14% (5). HCC usually develops in the background of oxidative stress and inflammation, triggered by chronic infection with hepatitis B or C virus (HBV or HCV), excess alcohol consumption, aflatoxin exposure or obesity/diabetes (6). Based on a recent meta-analysis, potential common risk factors for HCC and ICC include chronic HBV and HCV, excessive alcohol use, and diabetes/obesity (7).

Most observational studies have shown a reduced risk of HCC associated with coffee consumption (8, 9). Caffeine, polyphenols (e.g., chlorogenic acid), and diterpenes (e.g., cafestol and kahweol) are thought to be, at least partially, responsible for this reduction in

HCC risk (10). Experimentally, caffeine has been shown to inhibit hepatic carcinogenesis (11), potentially through an antioxidant, anti-inflammatory, or radical scavenging mechanisms (12).

Age-adjusted incidence of HCC in men is approximately three times higher than in women (13). This disparity has been hypothesized to be due to the greater prevalence of most known risk factors among men. However, these differences cannot fully explain the male predominance of these tumors (14). It is possible that coffee consumption differentially affects tumor risk in men and women by influencing hormone levels (15), obesity (16), diabetes (16), or other unknown factors.

While the association between coffee drinking and incidence of HCC has been studied in Asian and European populations (8), only one study has examined the association in a U.S. population (17). Additionally, no studies have examined the association between coffee consumption and ICC.

To examine the overall and sex-specific association of coffee with HCC and ICC, and determine whether the associations varied by caffeine content, we studied the hypothesis in a project that pooled data from nine U.S.-based cohort studies.

MATERIALS AND METHODS

Study Population

The Liver Cancer Pooling Project (LCPP) has been described previously (18). Briefly, all U.S.-based cohort studies that are members of the National Cancer Institute (NCI) Cohort Consortium were invited to participate in the LCPP. Of the 14 studies that agreed to participate, nine studies contributed data on both coffee consumption and liver cancer histology: NIH-AARP Diet and Health Study (AARP) (19), Agricultural Health Study (AHS) (20), United States Radiologic Technologists (USRT) Study (21), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (22), Women's Health Study (WHS) (23), Cancer Prevention Study–II Nutrition Cohort (CPS-II) (24), Iowa Women's Health Study (IWHS) (25), Black Women's Health Study (BWHS) (26), and Women's Health Initiative (WHI) (27) (**Supplementary Table S1**).

Outcomes

Incident primary liver cancer (defined as International Classification of Diseases, 10th edition [ICD-10] diagnostic code C22) among LCPP cohort members was ascertained by three methods: linkage to state cancer registries, medical record review, or a self-report to the parent cohort study. Cases missing histology information were excluded (n=832). Cases were then classified as HCC (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] histology codes of 8170-8175), ICC (ICD-O-3 histology codes of 8032-8033, 8041, 8050, 8070-8071, 8140-8141, 8160, 8260, 8480, 8481, 8490, and 8560), or other liver cancer (all other histology codes). Non-HCC or non-ICC cases were excluded from the analysis (n=171). The current analysis included 860 HCC cases, 260 ICC cases, and 1,211,773 non-cases.

Exposure

With the exception of WHI, all studies assessed coffee drinking over the past year (or 12 months) (**Supplementary Table S2**). WHI asked participants to report if they usually drink coffee every day. Additionally, WHI assessed only the number of caffeinated cups of coffee consumed and, thus, was not included in decaffeinated intensity or combination analyses. The remaining studies assessed caffeine content by asking participants to report caffeinated and decaffeinated coffee consumption separately or by asking participants the proportion of decaffeinated coffee consumed. Individuals were classified into mutually exclusive groups of caffeinated coffee drinkers, decaffeinated coffee drinkers, or a combination of caffeinated and decaffeinated coffee consumption. To examine trends in coffee consumption, both by caffeine content (using a stratified analysis) and overall, the number of cups of coffee, assumed to be approximately 8 ounces, per day was analyzed as: 0, >0-<1, 1-<2, 2-3, and >3 cups/day. Non-drinkers were defined as those individuals reporting little or no coffee consumption during the FFQ timeframe.

Statistical Analysis

Cox proportional hazard regression analysis was used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals for the associations of coffee consumption with HCC and ICC. The proportional hazards assumption was tested using an interaction between coffee exposure (defined as continuous and categorical) and log(time) in models that included confounders and an interaction was observed ($p<0.05$). Thus, we present the overall HRs, averaging over varying baseline hazards ratios during follow-up, and the HRs for four time periods of follow-up, based on quartiles of follow-up time for HCC and ICC. Examination of coffee consumption by these differential follow-up times did not result in notable differences among the four lengths of follow-up.

Effect measure modification by sex, cigarette smoking (evaluated as never/ever and cigarettes/day [continuous]), body mass index (BMI, kg/m^2; evaluated as continuous and dichotomous [<25 and 25]), and diabetes (yes/no) was assessed using likelihood ratio tests comparing regression models with and without a multiplicative term (28). We found no evidence of effect measure modification by smoking, BMI, or diabetes (p 0.10). However, there was some evidence of effect measure modification by sex ($p<0.10$).

Potential confounders (29) included alcohol consumption (evaluated as ever/never [referent]; drinks/day [0, >0-<1, 1-3, and >3]), smoking (evaluated as never [referent]/ former/current; cigarettes/day, pack-years, and smoking duration [all evaluated as continuous and categorized as quartiles of intake among smokers]), age at questionnaire administration (years, evaluated as continuous and categorical [<50, 50-59, 60-69, 70]), race (Caucasian [referent], African American, Asian/Pacific Islander, American Indian/ Alaskan Native, Other), sex (male [referent]/female), education (some high school or less, high school/GED, some college/vocational training, college degree [referent], post-college), and BMI (evaluated as continuous and categorical [<18.5, 18.5-<25, 25-<30, and 30 kg/m^2]). Variables remained in the adjusted model if they were associated with the exposure and outcome and the test of effect was significant ($p<0.05$) (30); age (continuous), sex, race, smoking (never/current/former and categorized cigarettes/day [0, 10, >10- 15, >15- 25, or

>25]), alcohol consumption (categorized drinks/day [0, >0-<1, 1-3, >3]), and BMI (continuous) met this criterion and were included in all final models. We adjusted for study in all models. We also created a forest plot and used fixed-effects meta-analysis to estimate a summary HR and assess heterogeneity using I^2. An I^2 of 0% indicates no heterogeneity, whereas larger values indicate increasing heterogeneity between studies (31). Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and STATA version 13 (StataCorp LP, College Station, TX). All p-values are two-sided.

Sensitivity Analyses

We examined caffeine content and intensity of coffee consumption using a model that jointly considered these terms. We also analyzed all confirmed or suspected HCC cases, which included HCC cases (ICD-O-3 histology codes of 8170-8175) and additional suspected HCC cases defined as ICD-O-3 histology codes of 8000, 8010, or missing. Finally, we conducted a meta-influence analysis for HCC, excluding one study at a time from the pooled analysis.

RESULTS

Demographic characteristics of HCC and ICC cases and non-cases are shown in **Table 1** and **Supplementary Table S3**. Compared with non-cases, individuals who developed HCC or ICC were more likely to be older, male, Asian/Pacific Islander, overweight or obese, smoke, drink heavily, and have diabetes.

Figure 1 shows the study-specific and summary HRs for coffee consumption versus no consumption and HCC risk. The fixed-effects summary HR was 0.95 (95% CI, 0.75-1.22). While no significant heterogeneity was detected between studies, the inconsistency was moderate (I^2=36.5%).

Table 2 presents the overall and stratified results by length of study follow-up for the pooled analysis. The group who consumed at least three cups of coffee per day were at 27% lower risk of HCC (HR, 0.73; 95% CI, 0.53-0.99), and there was evidence of an inverse dose-response relationship ($HR_{cups/day}$=0.90; 95% CI, 0.85-0.94). There was no association between coffee consumption and ICC.

Table 3 shows the association of coffee consumption by caffeine content with HCC and ICC. For caffeinated coffee, individuals who consumed at least three cups of coffee per day had a modestly reduced risk of HCC (HR=0.71; 95% CI, 0.50-1.01). A trend of decreased HCC risk was also observed for caffeinated coffee consumption ($HR_{cups/day}$, 0.91; 95% CI, 0.86-0.97; p_{trend}=0.002). However, little or no association was seen with decaffeinated coffee consumption ($HR_{>3\ cups\ vs.\ non-drinker}$=0.92; 95% CI, 0.55-1.54; $HR_{cups/day}$=0.93; 95% CI, 0.86-1.02; p_{trend}=0.1) or with consumption of both caffeinated and decaffeinated coffee ($HR_{>3\ cups\ vs.\ non-drinker}$=0.61; 95% CI, 0.31-1.21; $HR_{cups/day}$=0.89; 95% CI, 0.77-1.03; p_{trend}=0.1). The examination of ICC and consumption of caffeinated or decaffeinated coffee revealed null associations.

As shown in **Table 4** and **Supplementary Table S4**, there was evidence of a multiplicative interaction between coffee drinking and sex for HCC ($p_{interaction}$=0.07, χ^2=3.37 [df=1]) but not for ICC ($p_{interaction}$=0.8, χ^2=0.05 [df=1]). Comparing coffee drinkers to non-drinkers, women had a 22% decreased risk of HCC (HR=0.78; 95% CI, 0.56-1.10), while men did not (HR=1.21; 95% CI, 0.87-1.69). Among women who drank more than three cups of coffee per day, the risk of HCC was further reduced (HR=0.46; 95% CI, 0.26-0.81, p_{trend}=0.004). Men who drank more than three cups of coffee per day had little reduced risk of HCC (HR=0.93, 95% CI, 0.63-1.37) but the risk reduction associated with cups of coffee consumed per day was similar to women (p_{trend}=0.0004). The examination of coffee consumption and ICC stratified by sex found no notable associations among either men or women.

Results from a model that jointly considered caffeine content and intensity of coffee consumption were not substantially different than our main stratified model (**Supplementary Table S5**). When we examined suspected HCC cases, results did not differ from our main analysis of confirmed HCC (**Supplementary Tables S6**). Finally, the meta-influence analysis for HCC (**Supplementary Figure S1**), revealed that the AARP cohort exerted a substantial influence on the overall results. Thus, we also present our results for only the AARP cohort (**Supplementary Tables S7-S8**) and excluding the AARP cohort (**Supplementary Tables S9-S10**).

DISCUSSION

This study examined the association between coffee and risk of incident HCC and ICC, stratified by caffeine content and sex. In our analyses, stronger associations between coffee consumption and HCC were observed for women. Among women who drank more than three cups of coffee per day, we found risk reductions for HCC of 54%.

Previous studies have reported that coffee consumption is associated with a decreased risk of HCC. In a recent meta-analysis, high levels of coffee consumption (versus none) was associated with a 56% reduction in risk of liver cancer; with each one cup of coffee consumed per day, a 20% reduction in risk of HCC was observed (8). Three additional studies published since this meta-analysis also noted an inverse association between coffee consumption and HCC (17, 32, 33). In the current study, drinking more than three cups of coffee per day (versus non-drinkers) was associated with a 27% decreased risk of HCC and increasing coffee consumption by one cup per day was associated with a 10% reduction in HCC risk.

While not statistically significant, there was evidence of modest heterogeneity among studies. As a sensitivity analysis, we conducted a meta-influence analysis. In this analysis, the HR for coffee drinkers versus non-drinkers was notably different when the AARP study was dropped compared to the overall result (**Supplementary Figure S1**). The results were quite different examining the AARP cohort versus the other pooled cohorts. Individuals in the AARP cohort consuming more than three cups of coffee per day had little to no reduced risk of HCC. When the AARP cohort was excluded, individuals drinking more than three cups of coffee per day had a 59% decreased risk of HCC (**Supplementary Tables S7 and**

S9). It is unclear why estimates from the AARP cohort appear different, as cohort recruitment was very similar between the cohorts included in the LCPP (**Supplementary Table S1**). There are two possibilities. First, at the time of the AARP baseline questionnaire (1995), AARP was primarily composed of retirees. Thus, coffee consumption among retirees could be different than among workers or the general population. Alternatively, this could be due to chance. However, as AARP comprises over 45% of the LCPP study population, results stratified by cohort should be interpreted with caution.

The recent meta-analysis also reported that coffee consumption was associated a reduce risk of HCC in both men and women (8). This meta-analysis included two previous studies that reported coffee consumption among men was associated with a greater risk reduction of HCC (34, 35) and three studies that did not report a difference (36-38). In the current study, we saw coffee consumption was associated with a decreased risk of HCC, which was stronger among women. However, in the analysis stratified by cohort, the association of coffee-HCC by sex was quite different by cohort. In the AARP cohort, women with higher coffee consumption had a possible 23% decreased risk of HCC, but men did not. Conversely, in the other cohorts, men and women had a 52-67% reduced risk of HCC (**Supplementary Table S8 and S10**). Differences between previous studies and our study could partially be due to geographic differences, variability in coffee brew or preparation methods, bioavailability of coffee compounds, or chance.

Studies have shown that coffee brew and preparation methods vary widely by geographic location, even within the U.S. (39). The amounts of various compounds retained in coffee are highly dependent on the method of brewing (40). For example, boiled, Turkish, and French press methods retain the highest amounts of cafestol and kahweol, whereas negligible amounts are found in instant, drip filtered, or percolated coffee (41). Brewing strength (i.e., the concentration of coffee grounds per liter of water used for brewing) also affects the levels of cafestol and kahweol found in various coffee brewing methods (41). Preparation of coffee with added milk or creamer could also potentially affect the bioavailability of coffee compounds. A recent study, using 10% milk or non-dairy creamer, found no differences in bioavailability in phenolic coffee compounds (42), but another study, using instant coffee dissolved in only milk, found a 28% reduction in urinary excretion of chlorogenic acid (43). This suggests that consuming milk and coffee together could affect the bioavailability of compounds found in coffee.

Coffee is a mixture of many different compounds, such as carbohydrates, lipids, vitamins, alkaloids, nitrogenous molecules, and polyphenolic compounds (44). Animal studies have also provided support for the potential chemopreventive effect of coffee. For example, a murine study found that coffee decreased the incidence of tumors, including hepatocellular adenomas, and increased energy expenditure (45). The primary compounds in coffee that have been identified as possibly having chemopreventive effects include diterpenes (i.e., cafestol and kahweol), chlorogenic acid, and caffeine (40). Diterpenes are lipids that have been shown to inhibit phase I activating enzyme expression and enzymatic activity, induce phase II detoxifying enzymes, and regulate the Nrf2/ARE signaling pathway (10, 12, 40). Chlorogenic acid is a polyphenol that has been shown to increase activity of phase II detoxifying enzymes via the Nrf2/ARE signaling pathway (46). Caffeine intake increases

metabolic rate and energy expenditure, and thus caffeine may regulate weight and reduce the risk of developing metabolic syndrome (12, 47). Additionally, caffeine may contribute to the antioxidant capacity of coffee (10, 12). A recent study from the European Prospective Investigation into Cancer and Nutrition (EPIC) found a 72% lower risk of HCC associated with high levels of coffee consumption (33). Consistent with the current report, the EPIC study noted inverse, monotonic associations between coffee and HCC among caffeinated coffee consumption (p_{trend}=0.009) but not decaffeinated coffee (p_{trend}=0.5) (33). While previous studies have reported an association between tea (33, 48), but not other types of caffeinated beverages (e.g., soda), and reductions in HCC risk (11), we were unable to evaluate tea or soda consumption in the present study.

Potential risk reduction of HCC due to coffee consumption is likely due to long-term consumption rather than transient exposure (12). Studies to date, including the current report, may not adequately captured long-term coffee consumption. All of the parent studies in the LCPP assessed coffee consumption for the 12 months prior to study baseline or less, which is the exposure included in the current report. This was assumed to be indicative of adult coffee consumption. However, there are a number of reasons, particularly due to health concerns, that may lead individuals to alter their coffee consumption, specifically caffeinated coffee (49). Thus, misclassification of long term exposure status could result from having only a single, self-reported measurement at study baseline, which does not account for the within person variability over time. However, we believe that this form of misclassification would likely be nondifferential with respect to liver cancer, and we would expect any potential bias to attenuate the estimates of risk, biasing them towards the null hypothesis (29). Therefore, the null results found for the overall association between coffee drinkers, versus non-drinkers, and HCC could potentially be due to misclassification. For instance, individuals classified as non-drinkers could have formerly been heavy coffee drinkers, which could be a potential explanation as to why among individuals consuming lower levels of coffee (<2 cups/day) we observed an increased risk of HCC, compared to non-drinkers. This is primarily being driven by the NIH-AARP study, where individuals may have altered their coffee consumption after retiring from the workforce.

While the pooled analysis included information on the major confounders (e.g., smoking and alcohol consumption), it did not include information on other potential confounders, such as HBV and HCV status, for all individuals. However, hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (anti-HCV) were assessed in a case-control study nested within this study. Among the HCC cases tested (n=151), 39 (25.8%) were positive for anti-HCV and 5 (3.3%) were positive for HBsAg. Among the matched controls (n=375), 10 (2.7%) were positive for anti-HCV and 3 (0.8%) were positive for HBsAg. We examined the association between HCV and HBV status and coffee drinking, and found no association (data not shown). Additionally, the LCPP did not obtain and harmonize information on other dietary factors (e.g., total energy intake) that may be potential confounders as well. These results may also not be generalizable to non-white or Hispanic populations, as the cohorts included in this analysis were primarily composed of white, non-Hispanic participants.

Although not statistically significant, the analyses stratified by smoking, BMI, and diabetes are intriguing. In each of these models, higher coffee consumption was associated with a

lower risk of HCC in the absence of smoking, overweight/obesity, or diabetes. This suggests that if coffee is working through an antioxidant, anti-inflammatory, or radical scavenging mechanism (12), it functions primarily at lower levels of oxidative stress and inflammation. However, in the presence of smoking, diabetes, or overweight/obesity, the potential risk reduction benefits from coffee could be overwhelmed by these highly pro-oxidative and inflammatory mechanisms (50).

This study had a large sample size to evaluate the association between coffee consumption and liver cancer incidence by subtype: HCC and ICC, although the number of ICC cases in this pooled analysis remained limited. The large sample size of the LCPP, compared to previous studies, also allowed us to stratify by caffeine content of coffee and sex; however, the number of cases for the stratified analyses is still relatively small. Additionally, previous studies have primarily been conducted in Europe and Asia (8), where coffee brew and preparation methods are different than in the U.S.

In conclusion, our finding of an inverse association between coffee consumption and HCC suggests that coffee consumption may modestly reduce the risk of HCC in the U.S. Further research is needed to elucidate the role of coffee consumption, including method of brew and preparation, in relation to HCC in the U.S.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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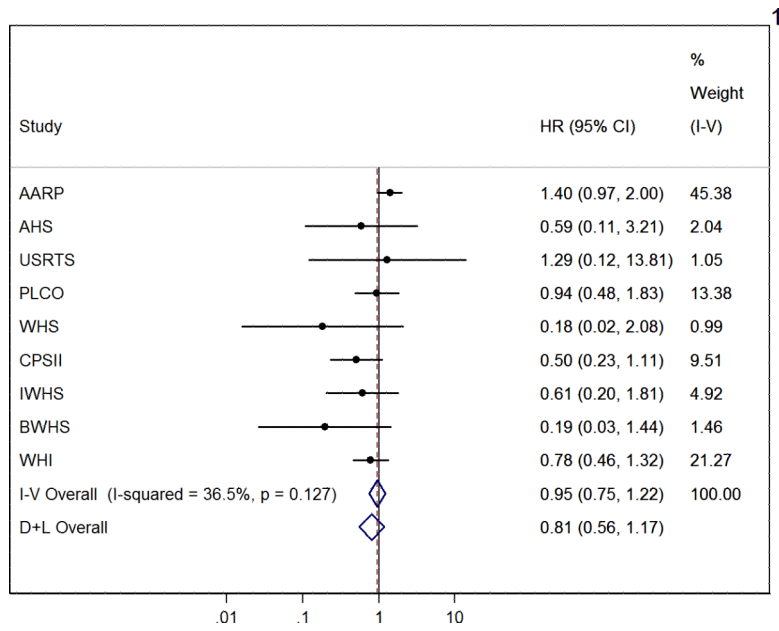
Figure 1.
Study-specific and Summary Hazard Ration (HR) and 95% Confidence Interval (CI) of Coffee Consumption versus No Consumption for Hepatocellular Carcinoma, Liver Cancer Pooling Project.

Table 1

Characteristics of participants in the Liver Cancer Pooling Project by case status.

	Non-Cases (N=1,211,773)		Hepatocellular Carcinoma (N=860)		Intrahepatic Cholangiocarcinoma (N=260)	
	N	(%)	N	(%)	N	(%)
Person-Years	**11,861,098**		**5,333**		**1,705**	
Age at Entry (years)						
<50	118,974	(9.8)	9	(1.0)	0	(0.0)
50-59	359,330	(29.7)	160	(18.6)	56	(21.5)
60-69	587,608	(48.5)	573	(66.6)	165	(63.5)
70	145,861	(12.0)	118	(13.7)	39	(15.0)
Sex						
Male	491,326	(40.5)	618	(71.9)	134	(51.5)
Female	720,447	(59.5)	242	(28.1)	126	(48.5)
Race						
White	1,050,854	(87.4)	702	(83.1)	229	(88.4)
Black	105,350	(8.8)	54	(6.4)	10	(3.9)
Other	45,878	(3.8)	89	(10.5)	20	(7.7)
Missing	9,691		15		1	
Body Mass Index (kg/m^2)						
<18.5	11,884	(1.0)	8	(1.0)	1	(0.4)
18.5-24.9	438,398	(37.0)	190	(22.8)	69	(27.3)
25-29.9	468,971	(39.6)	343	(41.1)	112	(44.3)
30	265,683	(22.4)	293	(35.1)	71	(28.1)
Missing	26,837		26		7	
Education						
Some High School or less	69,879	(6.0)	89	(10.7)	19	(7.4)
High School	235,132	(20.0)	183	(22.0)	49	(19.1)
Some College/Vocational	419,629	(35.7)	280	(33.7)	84	(32.7)
College Degree	222,206	(18.9)	143	(17.2)	63	(24.5)
Graduate Degree	227,373	(19.4)	136	(16.4)	42	(16.3)
Missing	37,554		29		3	
Diabetes						
No	1,121,080	(92.8)	620	(72.4)	228	(87.7)
Yes	86,506	(7.2)	236	(27.6)	32	(12.3)
Missing	4,187		4		0	
Alcohol (drinks/day)						
Non-Drinker	306,409	(26.5)	255	(31.9)	61	(24.9)
>0-<1 drink	638,748	(55.1)	347	(43.4)	129	(52.7)
1-3 drinks	152,062	(13.1)	96	(12.0)	31	(12.7)
>3 drinks	61,187	(5.3)	101	(12.6)	24	(9.8)
Missing	53,367		61		15	

	Non-Cases (N=1,211,773)		Hepatocellular Carcinoma (N=860)		Intrahepatic Cholangiocarcinoma (N=260)	
	N	(%)	N	(%)	N	(%)
Cigarette Smoking Status						
Non-Smoker	530,557	(44.8)	248	(29.7)	92	(35.9)
Former Smoker	471,702	(39.8)	412	(49.4)	120	(46.9)
Current Smoker	182,506	(15.4)	174	(20.9)	44	(17.2)
Missing	27,008		26		4	

Table 2

Adjusted[*] Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Associations Between Coffee Consumption and Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Incidence by Follow-Up Time, Liver Cancer Pooling Project.

			Hepatocellular Carcinoma				
			Overall	0-3.6 years	3.7-6.7 years	6.4-8.8 years	8.9 years
Coffee Consumption	Non-case N	Case N	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Non-Drinker	172,865	85	1.00	1.00	1.00	1.00	1.00
Ever	901,622	650	1.00 (0.79, 1.27)	1.05 (0.65, 1.68)	0.77 (0.50, 1.19)	1.13 (0.68, 1.87)	1.12 (0.69, 1.82)
Cups/day							
>0-<1	164,839	138	1.24 (0.94, 1.64)	1.43 (0.83, 2.48)	0.95 (0.56, 1.60)	1.33 (0.75, 2.37)	1.31 (0.72, 2.40)
1-<2	179,632	149	1.16 (0.88, 1.52)	0.91 (0.51, 1.63)	0.99 (0.59, 1.64)	1.31 (0.74, 2.32)	1.50 (0.87, 2.59)
2-3	370,531	255	0.89 (0.68, 1.15)	1.09 (0.65, 1.81)	0.61 (0.38, 1.00)	0.88 (0.51, 1.53)	1.05 (0.62, 1.77)
>3	161,019	97	0.73 (0.53, 0.99)	0.67 (0.35, 1.26)	0.57 (0.32, 1.03)	0.99 (0.54, 1.82)	0.72 (0.39, 1.36)
Continuous, cups/day			0.90 (0.85, 0.94)	0.89 (0.81, 0.98)	0.87 (0.78, 0.96)	0.93 (0.85, 1.02)	0.89 (0.81, 0.98)
p for trend[†]			<0.0001	0.02	0.006	0.1	0.02

			Intrahepatic Cholangiocarcinoma				
			Overall	0-3.6 years	3.7-6.7 years	6.8-9.2 years	9.3 years
Coffee Consumption	Non-case N	Case N	HR	HR	HR	HR	HR
Non-Drinker	172,865	33	1.00	1.00	1.00	1.00	1.00
Ever	901,622	199	0.93 (0.63, 1.37)	0.83 (0.39, 1.75)	1.19 (0.49, 2.85)	0.75 (0.36, 1.58)	1.05 (0.50, 2.21)
Cups/day							
>0-<1	164,839	36	1.15 (0.70, 1.89)	0.85 (0.30, 2.40)	1.18 (0.40, 3.51)	1.33 (0.54, 3.27)	1.22 (0.44, 3.39)
1-<2	179,632	33	0.79 (0.48, 1.30)	0.69 (0.26, 1.83)	1.01 (0.34, 2.97)	0.87 (0.35, 2.16)	0.60 (0.21, 1.74)
2-3	370,531	85	0.93 (0.61, 1.42)	0.86 (0.38, 1.94)	1.22 (0.47, 3.12)	0.63 (0.27, 1.47)	1.18 (0.52, 2.66)
>3	161,019	40	1.00 (0.61, 1.63)	1.12 (0.44, 2.86)	1.67 (0.61, 4.59)	0.59 (0.21, 1.67)	0.81 (0.30, 2.23)
Continuous, cups/day			1.00 (0.92, 1.08)	1.04 (0.89, 1.22)	1.12 (0.97, 1.30)	0.83 (0.69, 0.99)	0.98 (0.83, 1.15)
p for trend[†]			0.9	0.6	0.1	0.04	0.8

[*] Adjusted for: sex, age (continuous), race (white, black, other), cohort (AARP, AHS, USRT, PLCO, WHS, CPSII, IWHS, BWHS, WHI), BMI (continuous), smoking status (non-smoker, former smoker, current smoker), cigarette smoking intensity (0, 10, >10- 15, >15- 25, >25 cigarettes/day), alcohol (non-drinker, and >0-<1, 1-3, >3).

[†] P-value for trend of continuous variable.

Table 3

Adjusted [*] Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Associations Between Coffee Consumption and Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Incidence by Caffeine Content, Liver Cancer Pooling Project.

		Hepatocellular Carcinoma			Intrahepatic Cholangiocarcinoma		
Caffeinated Coffee	Non-case N	Case N	HR	95% CI	Case N	HR	95% CI
Non-Drinker	172,865	85	1.00		33	1.00	
Ever	521,438	379	1.00	(0.77 - 1.28)	119	0.91	(0.60 - 1.37)
Cups/day							
0	172,865	85	1.00		33	1.00	
>0-<1	66,120	58	1.22	(0.87 - 1.73)	17	1.32	(0.71 - 2.43)
1-<2	102,435	85	1.19	(0.87 - 1.62)	15	0.59	(0.32 - 1.10)
2-3	246,378	174	0.95	(0.72 - 1.26)	57	0.91	(0.58 - 1.43)
>3	106,505	62	0.71	(0.50 - 1.01)	30	1.08	(0.63 - 1.83)
p for trend[†]				0.002			>0.99
Decaffeinated Coffee							
Non-Drinker	172,865	85	1.00		33	1.00	
Ever	232,725	204	1.16	(0.88 - 1.53)	56	0.95	(0.59 - 1.53)
Cups/day[‡]							
0	130,187	63	1.00		18	1.00	
>0-<1	66,450	58	1.33	(0.92 - 1.91)	15	1.17	(0.58 - 2.35)
1-<2	47,791	51	1.38	(0.95 - 2.02)	10	0.94	(0.43 - 2.07)
2-3	75,840	64	0.97	(0.67 - 1.40)	20	1.11	(0.56 - 2.17)
>3	22,745	21	0.92	(0.55 - 1.54)	6	1.03	(0.39 - 2.70)
p for trend[†]				0.1			0.6
Combination Coffee							
Non-Drinker[‡]	130,187	63	1.00		18	1.00	
Ever	130,379	44	0.48	(0.29 - 0.79)	20	1.72	(0.71 - 4.16)
Cups/day[‡]							
0	130,187	63	1.00		18	1.00	
>0-<1	27,696	10	0.58	(0.28 - 1.21)	3	1.45	(0.37 - 5.68)

Caffeinated Coffee	Non-case N	Hepatocellular Carcinoma			Intrahepatic Cholangiocarcinoma		
		Case N	HR	95% CI	Case N	HR	95% CI
1-<2	27,098	10	0.52	(0.25 - 1.08)	6	2.46	(0.80 - 7.52)
2-3	45,466	11	0.33	(0.16 - 0.67)	7	1.68	(0.58 - 4.87)
>3	30,119	13	0.61	(0.31 - 1.21)	4	1.33	(0.37 - 4.78)
p for trend[†]				0.1			0.9

*
Adjusted for: sex, age (continuous), race (white, black, other), cohort (AARP, AHS, USRT, PLCO, WHS, CPSII, IWHS, BWHS, WHI), BMI (continuous), cigarette smoking intensity (cigarettes/day), smoking status (non-smoker, former smoker, current smoker), cigarette smoking intensity (0, 10, >10- 15, >15- 25, >25 cigarettes/day), alcohol (non-drinker, and >0-<1, 1-3, >3 drinks/day).

[†]P-value for trend of continuous variable.

[‡]WHI excluded from analysis, due to lack of information about decaffeinated coffee consumption.

Table 4

Adjusted * Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Associations Between Coffee Consumption and Hepatocellular Carcinoma by Sex, Smoking Status, Body Mass Index, and Diabetes, Liver Cancer Pooling Project.

	Men				Women			
Coffee Consumption	Non-case N	Case N	HR	95% CI	Non-case N	Case N	HR	95% CI
Non-Drinker	46,615	40	1.00		126,250	45	1.00	
Ever	393,030	490	1.21	(0.87 - 1.69)	508,592	160	0.78	(0.56 - 1.10)
Cups/day								
>0-<1	73,955	113	1.57	(1.09 - 2.25)	90,884	25	0.79	(0.47 - 1.33)
1-<2	71,352	103	1.35	(0.93 - 1.95)	108,280	46	1.01	(0.66 - 1.53)
2-3	170,339	195	1.06	(0.75 - 1.51)	200,192	60	0.71	(0.48 - 1.06)
>3	76,461	79	0.93	(0.63 - 1.37)	84,558	18	0.46	(0.26 - 0.81)
Continuous, cups/day			0.90	(0.86 - 0.96)			0.87	(0.79 - 0.96)
p for trend†				0.0004				0.004

	Non-Smokers				Smokers			
Coffee Consumption	Non-case N	Case N	HR	95% CI	Non-case N	Case N	HR	95% CI
Non-Drinker	115,235	48	1.00		57,789	37	1.00	
Ever	374,559	172	0.94	(0.68 - 1.30)	527,629	478	1.10	(0.79 - 1.55)
Cups/day								
>0-<1	87,498	39	0.91	(0.59 - 1.40)	77,356	99	1.52	(1.04 - 2.23)
1-<2	86,431	48	1.08	(0.72 - 1.62)	93,328	101	1.28	(0.87 - 1.87)
2-3	140,728	64	0.91	(0.62 - 1.33)	230,037	191	0.98	(0.68 - 1.40)
>3	47,124	12	0.52	(0.28 - 0.99)	113,988	85	0.93	(0.63 - 1.37)
Continuous, cups/day			0.93	(0.84 - 1.02)			0.91	(0.86 - 0.96)
p for trend†				0.1				0.0005

	BMI <25 kg/m²				BMI 25 kg/m²			
Coffee Consumption	Non-case N	Case N	HR	95% CI	Non-case N	Case N	HR	95% CI
Non-Drinker	67,651	25	1.00		105,214	60	1.00	
Ever	339,706	147	0.82	(0.53 - 1.25)	561,916	503	1.07	(0.81 - 1.42)

Coffee Consumption	BMI <25 kg/m²				BMI 25 kg/m²			
	Non-case N	Case N	HR	95% CI	Non-case N	Case N	HR	95% CI
Cups/day								
>0-<1	63,633	33	1.02	(0.60 - 1.72)	101,206	105	1.33	(0.96 - 1.85)
1-<2	69,237	30	0.81	(0.47 - 1.38)	110,395	119	1.30	(0.95 - 1.79)
2-3	136,149	56	0.73	(0.45 - 1.17)	234,382	199	0.95	(0.70 - 1.28)
>3	60,960	24	0.65	(0.37 - 1.14)	100,059	73	0.76	(0.53 - 1.08)
Continuous, cups/day			0.90	(0.82 - 0.99)			0.89	(0.85 - 0.94)
p for trend[†]				0.03				<0.0001

Coffee Consumption	No Diabetes				Diabetes			
	Non-case N	Case N	HR	95% CI	Non-case N	Case N	HR	95% CI
Non-Drinker	161,059	67	1.00		11,391	17	1.00	
Ever	835,624	462	0.89	(0.68 - 1.16)	63,979	188	1.41	(0.85 - 2.32)
Cups/day								
>0-<1	151,345	102	1.19	(0.87 - 1.64)	13,102	36	1.42	(0.80 - 2.54)
1-<2	165,484	104	1.02	(0.75 - 1.40)	13,769	45	1.60	(0.91 - 2.81)
2-3	344,302	174	0.75	(0.56 - 1.01)	25,558	81	1.40	(0.83 - 2.38)
>3	150,340	73	0.68	(0.48 - 0.95)	10,231	24	0.98	(0.52 - 1.83)
Continuous, cups/day			0.88	(0.83 - 0.93)			0.94	(0.87 - 1.03)
p for trend[†]				<0.0001				0.2

*
Adjusted for: age (continuous), race (white, black, other), cohort (AARP, AHS, USRT, PLCO, WHS, CPSII, IWHS, BWHS, WHI), BMI (continuous), smoking status (non-smoker, former smoker, current smoker), cigarette smoking intensity (0, 10, >10- 15, >15- 25, >25 cigarettes/day), alcohol (non-drinker, and >0-<1, 1-3, >3 drinks/day).

[†]
P-value for trend of continuous variable.