

Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project

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Abstract

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 (HR) and 95% confidence intervals (CI) were estimated using proportional hazards regression.

Results: Higher coffee consumption was associated with lower risk of HCC (HR_{>3 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 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 association 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. *Cancer Epidemiol Biomarkers Prev*; 24(9); 1398–406. ©2015 AACR.

Introduction

Primary liver cancer is the second leading cause of cancer-related death worldwide (1), and the seventh leading cause in the United States (2). Liver cancer incidence rates in the United States 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). On the basis of a recent meta-analysis, potential common risk

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factors for HCC and ICC include chronic HBV and HCV, excessive alcohol use, and obesity/diabetes (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.

Although 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). In addition, 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 (Supplementary Table S1): NIH-AARP Diet and Health Study (AARP; ref. 19), Agricultural Health Study (AHS; ref. 20), United States Radiologic Technologists Study (USRTS; ref. 21), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; ref. 22), Women's Health Study (WHS; ref. 23), Cancer Prevention Study-II Nutrition Cohort (CPS-II; ref. 24), Iowa Women's Health Study (IWHS; ref. 25), Black Women's Health Study (BWHS; ref. 26), and Women's Health Initiative (WHI; ref. 27).

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. In addition, 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 (HR) and 95% confidence intervals (CI) 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/m²; 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 ($P \geq 0.10$). 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, >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 [white (referent), black, 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, ≥30 kg/m²)]. Variables remained in the adjusted model if they were associated with the exposure and outcome and the test of effect was significant ($P < 0.05$; ref. 30); age (continuous), sex, race, smoking [never/current/former and categorized cigarettes/day (0, ≤10, >10–≤15, >15–≤25, >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) and STATA version 13 (StataCorp LP). 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. Com-

pared 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). Although 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 ($HR_{\text{cups/day}}$, 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 ($HR_{\text{cups/day}}$, 0.91; 95% CI,

Table 1. Characteristics of participants in the LCPP by case status

	Non-cases (N = 1,211,773) N (%)	HCC (N = 860) N (%)	ICC (N = 260) N (%)
Person-years	11,861,098	5,333	1,705
Age at entry, y			
<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
BMI, 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
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

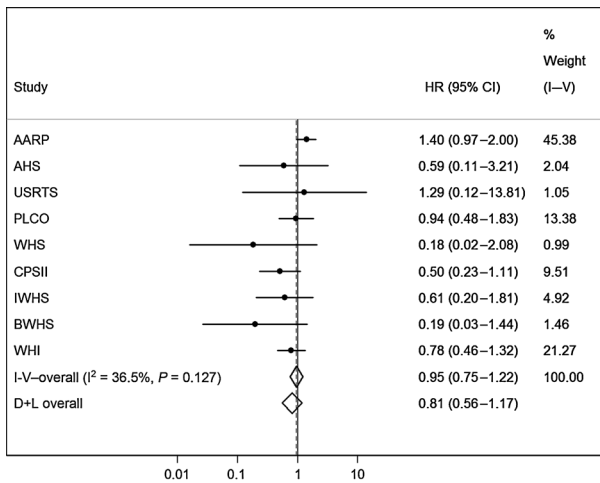


Figure 1. Study-specific and summary HR and 95% CI of coffee consumption versus no consumption for hepatocellular carcinoma, LCPP.

0.86-0.97; $P_{\text{trend}} = 0.002$). However, little or no association was seen with decaffeinated coffee consumption ($\text{HR}_{>3 \text{ cups vs. non-drinker}}$, 0.92; 95% CI, 0.55-1.54; $\text{HR}_{\text{cups/day}}$, 0.93; 95% CI, 0.86-1.02; $P_{\text{trend}} = 0.1$) or with consumption of both caffeinated and decaffeinated coffee ($\text{HR}_{>3 \text{ cups vs. non-drinker}}$, 0.61; 95% CI, 0.31-1.21; $\text{HR}_{\text{cups/day}}$, 0.89; 95% CI, 0.77-1.03; $P_{\text{trend}} = 0.1$). 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 [$P_{\text{interaction}} = 0.07$, $\chi^2 = 3.37$ (df = 1)] but not for ICC [$P_{\text{interaction}} = 0.8$, $\chi^2 = 0.05$ (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, $P_{\text{trend}} = 0.004$). 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 ($P_{\text{trend}} = 0.0004$). 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 Table S6). Finally, the meta-influence analysis for HCC (Supplementary Fig. 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 and S8) and excluding the AARP cohort (Supplementary Tables S9 and 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 (vs. none) were 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 liver cancer was

Table 2. Adjusted^a HR and 95% CI for associations between coffee consumption and HCC and ICC incidence by follow-up time, LCPP

Coffee consumption	Non-case, N	HCC					
		Case, N	Overall	0-3.6 y	3.7-6.7 y	6.4-8.8 y	≥8.9 y
			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_{trend}^b			<0.0001	0.02	0.006	0.1	0.02
Coffee consumption	Non-case, N	ICC					
		Case, N	Overall	0-3.6 y	3.7-6.7 y	6.8-9.2 y	≥9.3 y
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
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_{trend}^b			0.9	0.6	0.1	0.04	0.8

^aAdjusted 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), and alcohol (non-drinker, and >0-<1, 1-3, >3).

^bP value for trend of continuous variable.

Table 3. Adjusted^a HR and 95% CI for associations between coffee consumption and HCC and ICC incidence by caffeine content, LCPP

	Non-case, N	HCC		ICC	
		Case, N	HR (95% CI)	Case, N	HR (95% CI)
Caffeinated coffee					
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)
<i>P</i> _{trend} ^b			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^c					
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)
<i>P</i> _{trend} ^b			0.1		0.6
Combination coffee					
Non-drinker ^c	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^c					
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)
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)
<i>P</i> _{trend} ^b			0.1		0.9

^aAdjusted 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), and alcohol (non-drinker, and >0-<1, 1-3, >3 drinks/day).

^b*P* value for trend of continuous variable.

^cWHI excluded from analysis, due to lack of information about decaffeinated coffee consumption.

observed (8). Three additional studies published since this meta-analysis also noted an inverse association between coffee consumption and HCC (17, 32, 33). In this study, drinking more than three cups of coffee per day (vs. 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.

Although 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 with the overall result (Supplementary Fig. 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 with a reduced 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 this 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% to 67% reduced risk of HCC (Supplementary Tables 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 United States (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).

Table 4. Adjusted^a HR and 95% CI for associations between coffee consumption and HCC by sex, smoking status, BMI, and diabetes, LCPP

Coffee consumption	Men			Women		
	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)
<i>P</i> _{trend} ^b			0.0004			0.004
Coffee consumption	Non-smokers			Smokers		
	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)
<i>P</i> _{trend} ^b			0.1			0.0005
Coffee consumption	BMI <25 kg/m ²			BMI ≥25 kg/m ²		
	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)
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)
<i>P</i> _{trend} ^b			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)
<i>P</i> _{trend} ^b			<0.0001			0.2

^aAdjusted 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), and alcohol (non-drinker, and >0-<1, 1-3, >3 drinks/day).

^b*P* value for trend of continuous variable.

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 of 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). In addition, 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 this report, the EPIC study noted inverse, monotonic associations between coffee and HCC among caffeinated coffee consumption ($P_{\text{trend}} = 0.009$) but not decaffeinated coffee ($P_{\text{trend}} = 0.5$; ref. 33). Although 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 this 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 this 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 toward the null (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 with 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 nested case-control 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). In addition, 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 prooxidative 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 with 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. In addition, previous studies have primarily been conducted in Europe and Asia (8), where coffee brew and preparation methods are different than in the United States.

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 United States. Further research is needed to elucidate the role of coffee consumption, including method of brew and preparation, in relation to HCC in the United States.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [accessed 2014 June 2]. Available from: <http://globocan.iarc.fr>.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62:10–29.
3. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin* 2012;62:118–28.
4. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. *Am J Gastroenterol* 2014;109:542–53.
5. McGlynn KA, Tarone RE, El-Serag HB. A comparison of trends in the incidence of hepatocellular carcinoma and intrahepatic cholangiocarcinoma in the United States. *Cancer Epidemiol Biomarkers Prev* 2006;15:1198–203.
6. Ambade A, Mandrekar P. Oxidative stress and inflammation: essential partners in alcoholic liver disease. *Int J Hepatol* 2012;2012:853175.
7. Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. *J Hepatol* 2012;57:69–76.
8. Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol* 2013;11:1413–21 e1.
9. Saab S, Mallam D, Cox GA II, Tong MJ. Impact of coffee on liver diseases: a systematic review. *Liver Int* 2014;34:495–504.
10. Muriel P, Arauz J. Coffee and liver diseases. *Fitoterapia* 2010;81:297–305.
11. Cadden IS, Partovi N, Yoshida EM. Review article: possible beneficial effects of coffee on liver disease and function. *Aliment Pharmacol Ther* 2007;26:1–8.
12. Ludwig IA, Clifford MN, Lean ME, Ashihara H, Crozier A. Coffee: biochemistry and potential impact on health. *Food Funct* 2014;5:1695–717.
13. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? *Hepatology* 2014;60:1767–75.
14. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142:1264–73 e1.
15. Schliep KC, Schisterman EF, Mumford SL, Pollack AZ, Zhang C, Ye A, et al. Caffeinated beverage intake and reproductive hormones among premenopausal women in the BioCycle Study. *Am J Clin Nutr* 2012;95:488–97.
16. Takahashi S, Saito K, Jia H, Kato H. An integrated multi-omics study revealed metabolic alterations underlying the effects of coffee consumption. *PLoS ONE* 2014;9:e91134.
17. Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. *Gastroenterology* 2015;148:118–25.
18. McGlynn KA, Sahasrabudhe VV, Campbell PT, Graubard BI, Chen J, Schwartz LM, et al. Reproductive factors, exogenous hormone use and risk of liver cancer among U.S. women: results from the Liver Cancer Pooling Project. *Br J Cancer* 2015;112:1266–72.
19. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol* 2001;154:1119–25.
20. Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, et al. The Agricultural Health Study. *Environ Health Perspect* 1996;104:362–9.
21. Boice JD Jr, Mandel JS, Doody MM, Yoder RC, McGowan R. A health survey of radiologic technologists. *Cancer* 1992;69:586–98.
22. Kramer BS, Gohagan J, Prorok PC, Smart C. A National Cancer Institute sponsored screening trial for prostatic, lung, colorectal, and ovarian cancers. *Cancer* 1993;71:589–93.
23. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. *J Womens Health Gen Based Med* 2000;9:19–27.
24. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. *Cancer* 2002;94:2490–501.
25. Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. *Am J Epidemiol* 1992;136:192–200.
26. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. *J Am Med Womens Assoc* 1995;50:56–8.
27. Anderson GL, Manson J, Wallace R, Lund B, Hall D, Davis S, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol* 2003;13:S5–17.
28. Kleinbaum D. Logistic regression: a self-learning text second ed. New York: Springer; 2002.
29. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
30. Kleinbaum DG, Klein M. Survival analysis: a self-learning text. 3rd ed. New York: Springer; 2012.
31. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
32. Lai GY, Weinstein SJ, Albanes D, Taylor PR, McGlynn KA, Virtamo J, et al. The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers. *Br J Cancer* 2013;109:1344–51.
33. Bamia C, Lagiou P, Jenab M, Trichopoulou A, Fedirko V, Aleksandrova K, et al. Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: multicentre, prospective cohort study. *Int J Cancer* 2015;136:1899–908.
34. Inoue M, Kurahashi N, Iwasaki M, Shimazu T, Tanaka Y, Mizokami M, et al. Effect of coffee and green tea consumption on the risk of liver cancer: cohort analysis by hepatitis virus infection status. *Cancer Epidemiol Biomarkers Prev* 2009;18:1746–53.
35. Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, et al. Does coffee protect against hepatocellular carcinoma? *Br J Cancer* 2002;87:956–9.
36. Inoue M, Yoshimi I, Sobue T, Tsugane S, Group JS. Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan. *J Natl Cancer Inst* 2005;97:293–300.
37. Kurozawa Y, Ogimoto I, Shibata A, Nose T, Yoshimura T, Suzuki H, et al. Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan. *Br J Cancer* 2005;93:607–10.
38. Shimazu T, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, et al. Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. *Int J Cancer* 2005;116:150–4.
39. Hawkins DI, Roupe D, Coney KA. The influence of geographic subcultures in the United States. *Advances in Consumer Research* 1981;8:713–7.
40. Cavin C, Holzhaeuser D, Scharf G, Constable A, Huber WW, Schilter B. Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem Toxicol* 2002;40:1155–63.
41. Urgert R, Vanderweg G, Kosmeijerschuil TG, Vandebovenkamp P, Hovenier R, Katan MB. Levels of the cholesterol-elevating diterpenes cafestol and kahweol in various coffee brews. *J Agric Food Chem* 1995;43:2167–72.
42. Renouf M, Marmet C, Guy P, Fraering AL, Longet K, Moulin J, et al. Nondairy creamer, but not milk, delays the appearance of coffee phenolic acid equivalents in human plasma. *J Nutr* 2010;140:259–63.
43. Duarte GS, Farah A. Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans (vol 59, 7925, 2011). *J Agric Food Chem* 2011;59:10772-.
44. Spiller MA. The chemical components of coffee. In: Spiller GA, editor. *Caffeine*. Boca Raton, FL: CRC Press; 1998.

45. Stalder R, Bexter A, Wurzner HP, Luginbuhl H. A carcinogenicity study of instant coffee in Swiss mice. *Food Chem Toxicol* 1990;28: 829–37.
46. Boettler U, Volz N, Pahlke G, Teller N, Kotyczka C, Somoza V, et al. Coffees rich in chlorogenic acid or N-methylpyridinium induce chemopreventive phase II-enzymes via the Nrf2/ARE pathway *in vitro* and *in vivo*. *Mol Nutr Food Res* 2011;55:798–802.
47. Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. *J Food Sci* 2010;75: R77–87.
48. Fon Sing M, Yang WS, Gao S, Gao J, Xiang YB. Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis. *Eur J Cancer Prev* 2011;20:157–65.
49. Soroko S, Chang J, Barrett-Connor E. Reasons for changing caffeinated coffee consumption: the Rancho Bernardo Study. *J Am Coll Nutr* 1996;15:97–101.
50. Kamath S, Lip GY. Fibrinogen: biochemistry, epidemiology and determinants. *QJM* 2003;96:711–29.