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Coffee Consumption Is Associated With Response to Peginterferon and Ribavirin Therapy in Patients With Chronic Hepatitis C¹

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BACKGROUND & AIMS: High-level coffee consumption has been associated with reduced progression of pre-existing liver diseases and lower risk of hepatocellular carcinoma. However, its relationship with therapy for hepatitis C virus infection has not been evaluated. **METHODS:** Patients (n = 885) from the lead-in phase of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial recorded coffee intake before retreatment with peginterferon α -2a (180 μ g/wk) and ribavirin (1000–1200 mg/day). We assessed patients for early virologic response (2 log₁₀ reduction in level of hepatitis C virus RNA at week 12; n = 466), and undetectable hepatitis C virus RNA at weeks 20 (n = 320), 48 (end of treatment, n = 284), and 72 (sustained virologic response; n = 157). **RESULTS:** Median log₁₀ drop from baseline to week 20 was 2.0 (interquartile range [IQR], 0.6–3.9) among nondrinkers and 4.0 (IQR, 2.1–4.7) among patients that drank 3 or more cups/day of coffee (*P* trend < .0001). In unadjusted models, odds ratios and 95% confidence intervals for drinking 3 or more cups/day vs nondrinking were 3.2 (IQR, 1.9–5.3) for early virologic response, 3.1 (IQR, 1.8–5.1) for week 20 virologic response, 3.5 (IQR, 2.0–5.9) for end of treatment, and 2.7 (IQR, 1.4–5.3) for sustained virologic response (*P* trend < .0001 for all). After adjustment for age, race/ethnicity, sex, alcohol, cirrhosis, ratio of aspartate aminotransferase to alanine aminotransferase, the *IL28B* polymorphism rs12979860, dose reduction of peginterferon, and other covariates, odds ratio (95% confidence interval) for early virologic response was 2.0 (IQR, 1.1–3.6; *P* trend = .004); for week 20 virologic response was 2.1 (IQR, 1.1–3.9; *P* trend = .005); for end of treatment was 2.4 (IQR, 1.3–4.6; *P* trend = .001); and for sustained virologic response was 1.8 (IQR, 0.8–3.9; *P* trend = .034). **CONCLUSIONS:** High-level consumption of coffee (more than 3 cups per day) is an independent predictor of improved virologic response to peginterferon plus ribavirin in patients with hepatitis C.

Keywords: Liver Fibrosis; Diet; Risk Factor; Caffeine.

Approximately, 70%–80% of individuals exposed to hepatitis C virus (HCV) become chronically infected.¹ Worldwide these individuals are estimated to number between 130 and 170 million.² Treatment with peginterferon and ribavirin resolves chronic hepatitis C in about half of patients.^{3,4} However, those who fail or are unable to tolerate treatment have few current treatment options.

A number of factors affect response to therapy,⁵ including African-American race,^{6–8} presence of cirrhosis,⁸ baseline aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio,⁸ baseline serum HCV level,⁸ insulin resistance,^{9,10} particular single nucleotide polymorphisms, including rs12979860 or rs8099917 near *IL28B*,^{11–15} genotype 1 of HCV,^{8,16,17} and patients' ability to tolerate full doses of peginterferon during treatment.¹⁸

Coffee drinking has been associated with several aspects of liver health, including concentrations of the liver enzymes ALT, AST, and γ -glutamyltransferase,^{19–24} progression of pre-existing liver disease,²⁵ and hepatocellular carcinoma.^{26,27} It is not known whether coffee affects spontaneous HCV clearance or, among chronically infected individuals, patients' response to HCV therapy.²⁸

Therefore, we investigated the association between coffee intake and virologic response to peginterferon plus ribavirin treatment in the lead-in phase of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial of patients with baseline fibrosis or cirrhosis who had failed previous interferon therapy.²⁹

¹This is publication no. 72 of the HALT-C Trial.

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FFQ, food frequency questionnaire; HALT-C, Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial; HCV, hepatitis C virus; HOMA2, homeostatic model assessment score of insulin resistance; IQR, interquartile range; LDL, low-density lipoprotein.

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 0016-5085/\$36.00
 doi:10.1053/j.gastro.2011.02.061

Materials and Methods

Patient Population

As described previously,^{8,18,29,30} the lead-in phase of HALT-C enrolled 1145 HCV-positive patients who had an Ishak fibrosis score ≥ 3 , had failed previous interferon treatment, and had no evidence of hepatic decompensation or hepatocellular carcinoma. During lead-in, patients received 180 μ g per week of peginterferon α -2a and 1000 mg/day ribavirin for those weighing ≤ 75 kg and 1200 mg/day for those weighing >75 kg. Patients with declining neutrophil, platelet, or hemoglobin counts, or other adverse effects, were managed by dose reduction of peginterferon and or ribavirin.¹⁸ The amount of medication taken by each patient during the first 20 weeks was expressed as a proportion of the original prescribed dosage. The study protocol was approved by the institutional review board of each participating institution and written consent was obtained from all patients.

Assessment of Coffee and Tea Consumption

At the beginning of the lead-in-phase, patients completed a previously validated^{31,32} Block 98.2 food frequency questionnaire (FFQ; NutritionQuest, Berkeley, CA). Patients reported typical intake of 110 food items during the past year using 9 frequency categories ranging from "never" to "every day" and 4 categories of portion size (ie, 1 cup, 2 cups, 3–4 cups, and 5+ cups). One question assessed coffee intake and did not distinguish decaffeinated from caffeinated coffee. A second question assessed tea intake and did not distinguish black from green tea. Patients failing lead-in therapy entered the randomized phase and completed a second Block FFQ approximately 1 year after beginning the randomized phase.

For analysis, we created categorical variables of coffee (never, >0 to <1 , ≥ 1 to <3 , and ≥ 3 cups/day) and tea intake (never, >0 to <1 , ≥ 1 to <2 , and ≥ 2 cups/day). We excluded 259 patients who did not complete an FFQ and 1 patient with extreme caloric intake (>2 interquartile ranges [IQR] from the median), leaving 885 patients for the current analysis. Patients completing the FFQ were similar to those who did not, other than being more typically white (76.2% vs 65.3%; $P = .034$) and having a lower baseline AST/ALT ratio (median = 0.78 vs 0.82; $P = .0056$).

Assessment of Outcomes

Serum samples obtained from all subjects enrolled in the HALT-C Trial were tested in real-time at the University of Washington Virology Laboratory with both the quantitative Roche COBAS Amplicor HCV Monitor Test, v. 2.0 assay (lower limit of detection 600 IU/mL) and, if negative, by the Roche COBAS Amplicor HCV Test, v. 2.0 assay (Roche Molecular Systems, Branchburg, NJ) with lower limit of detection 100 IU/mL as described previously.^{8,33} HCV genotypes were determined with the

INNO-LiPA HCV II kit (Siemens Medical Solutions Diagnostics, Tarrytown, NY). Serum HCV RNA level was assessed at baseline, along with week 12, week 20, and week 48 of treatment. Early virologic response was defined as a ≥ 2 -log₁₀ decline in serum HCV RNA level at week 12. Week 20 virologic response was defined as the absence of detectable serum HCV RNA (<100 IU/mL) at week 20. Week 20, as opposed to the traditional week 24, was chosen in order to provide sufficient time to identify nonresponders for randomization into the main HALT-C trial. Patients with undetectable virus at week 20 continued to receive peginterferon plus ribavirin treatment for an additional 28 weeks (48 weeks total), at which point treatment was stopped. Sustained virologic response was defined as the absence of detectable serum HCV RNA at week 72, twenty-four weeks after the end of treatment. For analysis, we set undetectable viral levels at the detection limit (100, ie, 2 log₁₀, IU/mL).

Statistical Analysis

All tests were 2-sided and $\alpha < 0.05$ was considered to be statistically significant. Analyses were performed with SAS software (release 9.2, SAS Institute, Cary, NC). We tabulated baseline behavioral and clinical, demographic, and genetic features by categories of coffee intake. The Jonckheere-Terpstra test for trend for continuous variables and the Mantel-Haenszel test for trend for categorical variables were used to assess variation across categories of coffee intake. Variation across categories of race/ethnicity was assessed by the Pearson χ^2 test. Associations between coffee and tea intake with virologic response were determined using logistic regression. Linear trend tests were performed by assigning participants the median intake for their categories and entering that term as a continuous variable in the regression models. We present results from unadjusted crude models, along with models adjusted for continuous baseline age, AST/ALT ratio, log HCV RNA level, hemoglobin, neutrophils, platelets, and categories of sex, race/ethnicity, alcohol use at baseline, cirrhosis, HCV genotype 1, previous use of ribavirin, dose reduction of peginterferon during the first 20 weeks of treatment, and rs12979860 genotype. Additional adjustment for Short Form-36³⁴ general health, physical function, or vitality quality of life scores, pack-years of cigarettes, rs8099917 genotype, dose reduction of ribavirin during the first 20 weeks of treatment, body mass index, the homeostatic model assessment score of insulin resistance (HOMA2), total serum cholesterol, high-density lipoprotein cholesterol, or triglycerides had no appreciable effect on risk estimates for virologic response (data not shown). Additionally, we performed propensity score analysis³⁵ in order to better balance possible confounders between coffee drinkers and non-drinkers. We created a propensity score for coffee intake using the following covariates: age (continuous), sex, race/ethnicity (white, African American, Hispanic, other),

alcohol use (current, former, and never), cirrhosis at baseline, genotype 1, AST/ALT ratio (continuous), log HCV RNA level at baseline (continuous), previous use of ribavirin, hemoglobin (continuous), neutrophils (continuous), platelets (continuous), categories of peginterferon medication dose during first 20 weeks of treatment ($\geq 98\%$ – 100% , $\geq 80\%$ – $<98\%$, $\geq 60\%$ – $<80\%$, and $<60\%$), and rs12979860 genotype (TT, CT, CC). We then adjusted risk estimates for coffee with virologic response for quintiles of the propensity score using indicator variables. Risk estimates were also calculated across strata of propensity score quintiles.

We investigated possible interactions between coffee intake and number of clinical and behavioral features by examining the association between coffee and virologic response by stratum of each clinical and behavioral feature. We formally tested for effect modification by including an interaction term between each stratifying variable and continuous coffee intake in the model.

Results

Of the 885 patients who began full-dose peginterferon and ribavirin therapy, 85% drank coffee and 14.9% of patients drank 3 or more cups per day. At baseline, those consuming higher quantities of coffee were more likely to be white; drink alcohol and smoke cigarettes; have the CC genotype of rs12979860 (near *IL28B*); have higher hemoglobin, neutrophils, platelets, and total cholesterol; less likely to have cirrhosis at baseline; and have lower serum AST/ALT and HOMA2 score of insulin resistance ($P < .05$ for all; Table 1). Although 50.4% of noncoffee drinkers tolerated the full dose of peginterferon α -2a during treatment, 60.6% of 3 or more cups per day coffee drinkers tolerated the full dose ($P = .0015$). Among determinants of peginterferon dose reduction, 58% were due to low neutrophils and 22.6% were due to low platelets. During treatment, coffee drinkers were less likely to have a dose reduction due to either low neutrophils ($P = .016$) or platelets ($P = .059$). The relationships between coffee and clinical and demographic variables were generally similar in analyses restricted to white ($n = 674$), although we noted one difference. The association for coffee with rs8099917 genotype became statistically significant ($P = .001$).

More coffee consumption was associated with slightly higher baseline HCV RNA levels (P for trend = .007) (Table 2). Yet with increasing coffee intake, the decline in patients' serum HCV RNA level from baseline was greater and absolute levels of patients' serum HCV RNA at weeks 12 and 20 were lower (Table 2). For example, the median \log_{10} HCV RNA at week 20 was 4.6 (IQR, 2.0–5.8) for nondrinkers and 2.0 (IQR, 2.0–4.3) for those who drank 3 or more cups per day (P trend $< .0001$). Consistent results were observed for the log decrease in HCV RNA from baseline to week twelve, 1.7 (IQR, 0.7–3.6) in nondrinkers vs 3.7 (IQR, 1.8–4.2) for 3 or more cups per day

drinkers; P trend $< .0001$) and from baseline to week twenty, 2.0 (IQR, 0.6–3.9) in nondrinkers vs 4.0 (IQR, 2.1–4.7) for 3 or more cups per day drinkers; P trend $< .0001$).

Coffee drinkers were also more likely to have a virologic response according to the predefined end points (Table 3). Among nondrinkers, 45.7% had an early virologic response (≥ 2 log drop in their serum HCV RNA level at week 12), 26.3% had no detectable serum HCV RNA at week 20, 21.8% had no detectable serum at week 48, and 11.3% had a sustained virologic response. In contrast, the corresponding proportions for 3 or more cups per day coffee drinkers were 72.7%, 52.3%, 49.2%, and 25.8%, respectively. From crude logistic regression models, patients who drank 3 or more cups per day of coffee were about 3 times more likely to have a virologic response at the 4 time points of interest (Table 3). Ability to tolerate treatment had minimal effect on the relationship of coffee and virologic response. For example, the odds ratio for patients who drank 3 or more cups per day relative to nondrinkers for week 20 response changed slightly from 3.07 (crude: Table 3) to 2.92 (data not in Table) with control for peginterferon dose and the P trend remained highly statistically significant (P trend $< .0001$). Multivariate adjustment for age, sex, race/ethnicity, alcohol use, cirrhosis at baseline, genotype 1, AST/ALT ratio, log HCV RNA level at baseline, previous use of ribavirin, hemoglobin, neutrophils, platelets, peginterferon medication dose during first 20 weeks of treatment, and rs12979860 genotype, attenuated associations with coffee, although associations remained significant for each virologic response end point (Table 3). Risk estimates using propensity score methods were similar to those from multivariate adjusted models (data not shown).

In contrast to results for coffee, no effect was observed for drinking tea (P trend = .92, .96, .89, and .49 for early, week 20, week 48, and sustained virologic response, respectively).

In stratified analyses, we investigated effect modification (interaction) for week 20 HCV negativity across stratum of HCV genotype, race/ethnicity, cirrhosis at baseline, baseline AST/ALT ratio, hemoglobin, neutrophils, platelets, total cholesterol, HOMA score, Short Form-36 general health score, dose reduction of peginterferon, alcohol use, cigarette smoking, or rs12979860 genotype. Results are presented for week 20 virologic response, but were similar for early virologic response (week 12), end of treatment response (week 48), and sustained virologic response (week 72; data not shown). Risk estimates generally appeared similar in each stratum and the P values for interaction were all $> .05$ (Figure 1). For example, of the 454 patients who tolerated full dose, 43.4% had a week 20 virologic response compared with 28.5% of the 431 patients who took less than full dose. The relative benefit of coffee on virologic response was

Table 1. Association of Coffee Intake With Baseline Variables

Variables	Nondrinkers	Coffee consumption			P for trend ^a
		>0 to <1 cups/day	≥1 to <3 cups/day	≥3 cups/day	
n (%)	133 (15.0)	253 (28.6)	367 (41.5)	132 (14.9)	
Coffee intake (cups/day), median (IQR)	0	0.16 (0.03–0.5)	2 (1–2)	3.5 (3.5–3.5)	
Age (y), median (IQR)	48 (45–53)	49 (46–55)	49 (46–54)	49 (46–53)	.47
Female sex, n (%)	38 (28.6)	74 (29.3)	102 (27.8)	30 (22.7)	.22
Race/ethnicity, n (%)					
White	96 (72.2)	163 (64.4)	296 (80.7)	119 (90.2)	<.0001
African American	24 (18.1)	53 (21.0)	35 (9.5)	2 (1.5)	
Hispanic	7 (5.3)	32 (12.7)	28 (7.6)	7 (5.3)	
Other	6 (4.5)	5 (2.0)	8 (2.2)	4 (3.0)	
Current alcohol drinker, ^b n (%)	19 (14.4)	38 (15.0)	82 (22.5)	28 (21.2)	<.0001
Pack-years of cigarettes, median (IQR)	2.7 (0–14.0)	3.0 (0–14.5)	10.5 (1.2–25.0)	20.8 (4.3–34.8)	<.0001
Baseline HOMA2 score, ^b median (IQR)	4.7 (3.0–8.5)	4.2 (2.8–6.6)	4.0 (2.7–6.4)	3.7 (2.2–5.6)	.001
Serum total cholesterol (mg/dL), ^b median (IQR)	162 (143–185)	169 (146–190)	174 (158–196)	176 (152–202)	<.0001
Serum HDL cholesterol (mg/dL), ^b median (IQR)	40 (32–49)	43 (35–52)	41 (34–51)	37 (32–46)	.14
Serum triglyceride (mg/dL), median (IQR)	118 (76–182)	102 (78–138)	109 (75–166)	108 (79–161)	.62
General Health SF-36 score, median (IQR)	62 (40–77)	62 (47–77)	62 (42–77)	57 (40–77)	.23
Physical Function SF-36 score, ^b median (IQR)	85 (60–100)	90 (65–100)	85 (60–100)	85 (55–95)	.58
Vitality SF-36 score, median (IQR)	60 (40–80)	60 (40–75)	55 (35–75)	50 (30–70)	.002
Cirrhosis on biopsy, n (%)	52 (39.1)	109 (43.1)	123 (33.5)	39 (29.6)	.004
HCV genotype 1, n (%)	121 (91.0)	227 (89.7)	333 (90.7)	108 (81.8)	.05
AST/ALT, median (IQR)	0.82 (0.66–1.04)	0.83 (0.68–1.02)	0.75 (0.63–0.93)	0.70 (0.61–0.86)	<.0001
Previous use of ribavirin, n (%)	91 (68.4)	181 (71.5)	256 (69.8)	92 (69.7)	.86
Hemoglobin (g/dL), median (IQR)	15.1 (13.8–15.9)	15.1 (14.0–15.8)	15.2 (14.2–16.3)	15.4 (14.4–16.3)	.004
Platelets ($\times 1000/mm^3$), median (IQR)	159 (115–208)	154 (115–205)	168 (127–211)	170 (133–216.5)	.01
Neutrophils ($\times 1000/mm^3$), median (IQR)	2.9 (2.1–3.6)	2.7 (2.2–3.5)	3.1 (2.4–3.9)	3.4 (2.7–4.5)	<.0001
Peginterferon α -2a dose (% maximum), n (%)					
≥98%–100%	67 (50.4)	106 (41.9)	201 (54.8)	80 (60.6)	.0015
≥80%–<98%	24 (18.1)	64 (25.3)	72 (19.6)	24 (18.2)	
≥60%–<80%	23 (17.3)	37 (14.6)	41 (11.2)	14 (10.6)	
<60%	19 (14.3)	46 (18.2)	53 (14.4)	14 (10.6)	
Ribavirin dose (% maximum), n (%)					
≥98%–100%	67 (50.4)	113 (44.7)	182 (49.6)	63 (47.7)	.50
≥80%–<98%	23 (17.3)	62 (24.5)	77 (21.0)	27 (20.5)	
≥60%–<80%	16 (12.0)	38 (15.0)	64 (17.4)	21 (15.9)	
<60%	27 (20.3)	40 (15.8)	44 (12.0)	21 (15.9)	
rs12979860 genotype (IL28B), ^b n (%)					
TT	29 (24.0)	55 (24.6)	59 (17.9)	14 (12.0)	.0007
CT	69 (57.0)	115 (51.3)	184 (55.8)	64 (54.7)	
CC	23 (19.0)	54 (24.1)	87 (26.4)	39 (33.3)	
rs8099917 genotype (IL28B), ^b n (%)					
TT	57 (46.7)	117 (52.2)	166 (50.2)	68 (58.1)	.078
GT	53 (43.4)	90 (40.2)	145 (43.8)	45 (38.5)	
GG	12 (9.8)	17 (7.6)	20 (6.0)	4 (3.4)	

AST/ALT, aspartate aminotransferase/alanine aminotransferase; HCV, hepatitis C virus; HDL, high-density lipoprotein; HOMA2, homeostatic model assessment score of insulin resistance; IQR, interquartile range; SF-36, Short Form-36.

^aMantel-Haenszel test for trend for categorical variables; Jonckheere-Terpstra test for trend for continuous variables; and χ^2 test for race/ethnicity.

^bData not available for all participants: alcohol drinking available for 881 patients; serum total cholesterol for 847; serum high-density lipoprotein cholesterol for 845; HOMA2 score for 857; Physical Function SF-36 score for 884 patients; rs12979860 genotype for 792 patients; rs8099917 genotype for 794 patients.

similar in these two groups (odds ratio = 1.26 for full dose and 1.18 for lower dose) despite the absolute difference in response. The relationships between coffee and virologic responses were also very similar in analyses restricted to white patients. Specifically, there was a statistically significant increase in week 20 virological re-

sponse per cup increase in coffee consumption among white patients. Associations between coffee intake and virologic response were apparent in patients with both fibrosis and cirrhosis at baseline; although stronger in those with fibrosis. Finally, risk estimates for coffee appeared stronger in patients with the less favorable IL28B

Table 2. Association of Coffee Intake With Log Hepatitis C Virus RNA Level

Variables	Nondrinkers	Coffee consumption			P for trend ^a
		>0 to <1 cups/day	≥1 to <3 cups/day	≥3 cups/day	
n (%) ^b	133 (15.0)	253 (28.6)	367 (41.5)	132 (14.9)	
Baseline Log HCV RNA level, median (IQR)	6.4 (6.1–6.7)	6.4 (6.1–6.8)	6.5 (6.1–6.8)	6.6 (6.2–6.9)	.007
Week 12 Log HCV RNA level, median (IQR)	4.3 (2.8–5.7)	4.8 (2.8–5.7)	3.6 (2.0–5.6)	2.8 (2.0–4.6)	<.0001
Week 20 Log HCV RNA level, median (IQR)	4.6 (2.0–5.8)	4.5 (2.0–5.9)	2.8 (2.0–5.5)	2.0 (2.0–4.3)	<.0001
Log decrease, baseline to week 12, median (IQR)	1.7 (0.7–3.6)	1.6 (0.7–3.5)	2.8 (0.9–4.0)	3.7 (1.8–4.2)	<.0001
Log decrease, baseline to week 20, median (IQR)	2.0 (0.6–3.9)	1.9 (0.6–3.9)	3.2 (1.0–4.4)	4.0 (2.1–4.7)	<.0001

HCV, hepatitis C virus; IQR, interquartile range.

^aJonckheere-Terpstra test for trend.

^bLog HCV RNA level was available for 885 patients at baseline, 860 patients at week 12, and 846 patients at week 20.

rs12979860 TT or CT genotype, although again, differences in risk estimates were not statistically significant.

We were unable to determine coffee intake during lead-in therapy. But for patients failing lead-in therapy, coffee intake was assessed on a second occasion, 18 months after baseline, ie, 12 months after these patients had been randomized to low-dose peginterferon or no treatment. Median coffee intake was the same (1 cup per day) at baseline and at the second time point for patients in both randomization groups. The weighted κ for the 2 assessments was .58 overall ($P < .0001$), .54 in those receiving treatment ($P < .0001$), and .63 in those receiving no-treatment ($P < .0001$), indicating good agreement.

Discussion

In patients with advanced HCV-related chronic liver disease in the HALT-C trial receiving peginterferon plus ribavirin treatment, 3 or more cups per day coffee

drinkers were 3 times more likely to have a virologic response than nondrinkers. Associations were attenuated but persisted after adjustment for a wide range of behavioral, clinical, and genetic features, suggesting an effect independent of other known risk factors. In contrast to results for coffee, no effect was observed for tea drinking.

Coffee intake has been associated with lower level of liver enzymes, reduced progression of chronic liver disease,²⁵ and reduced incidence of hepatocellular carcinoma.^{26,27} Because few other data on the association of coffee drinking with virologic response are available, the association observed here needs replication in other studies.

A number of risk factors have previously been associated with virologic response in HALT-C and in other studies,^{5,8,12,14,15,18,25} including African-American race, presence of cirrhosis, AST/ALT ratio, serum HCV RNA level, particular genotypes near the *IL28B* gene, and ability to tolerate full doses of peginterferon during treat-

Table 3. Association Between Coffee Intake and Virologic Response

	Continuous (cup/day)	Nondrinkers	Coffee consumption			P for trend
			>0 to <1 cups/day	≥1 to <3 cups/day	≥3 cups/day	
n (%)	885 (100)	133 (15.0)	253 (28.6)	367 (41.5)	132 (14.9)	
Week 12, log drop ≥2, n (%)	466 (54.2)	59 (45.7)	109 (44.7)	205 (57.1)	93 (72.7)	
Crude OR (95% CI)	1.33 (1.20–1.48)	1.00 (ref)	0.96 (0.62–1.47)	1.58 (1.05–2.37)	3.15 (1.87–5.31)	<.0001
Multivariate adjusted ^a	1.21 (1.07–1.37)	1.00 (ref)	0.88 (0.54–1.45)	1.26 (0.79–2.01)	1.97 (1.08–3.61)	.0039
Week 20 response, n (%)	320 (36.2)	35 (26.3)	73 (28.9)	143 (39.0)	69 (52.3)	
Crude OR (95% CI)	1.29 (1.18–1.42)	1.00 (ref)	1.14 (0.71–1.82)	1.79 (1.15–2.77)	3.07 (1.83–5.13)	<.0001
Multivariate adjusted ^a OR	1.20 (1.07–1.36)	1.00 (ref)	1.03 (0.58–1.81)	1.45 (0.86–2.45)	2.10 (1.12–3.93)	.0047
Week 48 response, n (%)	284 (32.1)	29 (21.8)	61 (24.1)	129 (35.2)	65 (49.2)	
Crude OR (95% CI)	1.32 (1.20–1.45)	1.00 (ref)	1.14 (0.69–1.88)	1.94 (1.22–3.09)	3.48 (2.04–5.94)	<.0001
Multivariate adjusted ^a OR	1.22 (1.08–1.37)	1.00 (ref)	1.07 (0.59–1.94)	1.61 (0.93–2.77)	2.42 (1.28–4.60)	.0011
SVR, n (%)	157 (17.7)	15 (11.3)	32 (12.7)	76 (20.7)	34 (25.8)	
Crude OR (95% CI)	1.20 (1.08–1.34)	1.00 (ref)	1.14 (0.59–2.19)	2.06 (1.14–3.72)	2.73 (1.41–5.30)	<.0001
Multivariate adjusted ^a	1.11 (0.97–1.26)	1.00 (ref)	1.03 (0.49–2.17)	1.69 (0.86–3.34)	1.80 (0.83–3.94)	.034

CI, confidence interval; OR, odds ratio; SVR, sustained virologic response.

^aAdjusted for age (continuous), sex, race/ethnicity (white, African American, Hispanic, Other), alcohol use (current, former, and never), cirrhosis at baseline, genotype 1, aspartate aminotransferase/alanine aminotransferase ratio (continuous), log hepatitis C virus RNA level at baseline (continuous), previous use of ribavirin, hemoglobin (continuous), neutrophils (continuous), platelets (continuous), categories of peginterferon medication dose during first 20 weeks of treatment (≥98%–100%, ≥80%–<98%, ≥60%–<80%, and <60%), and rs12979860 genotype (TT, CT, CC).

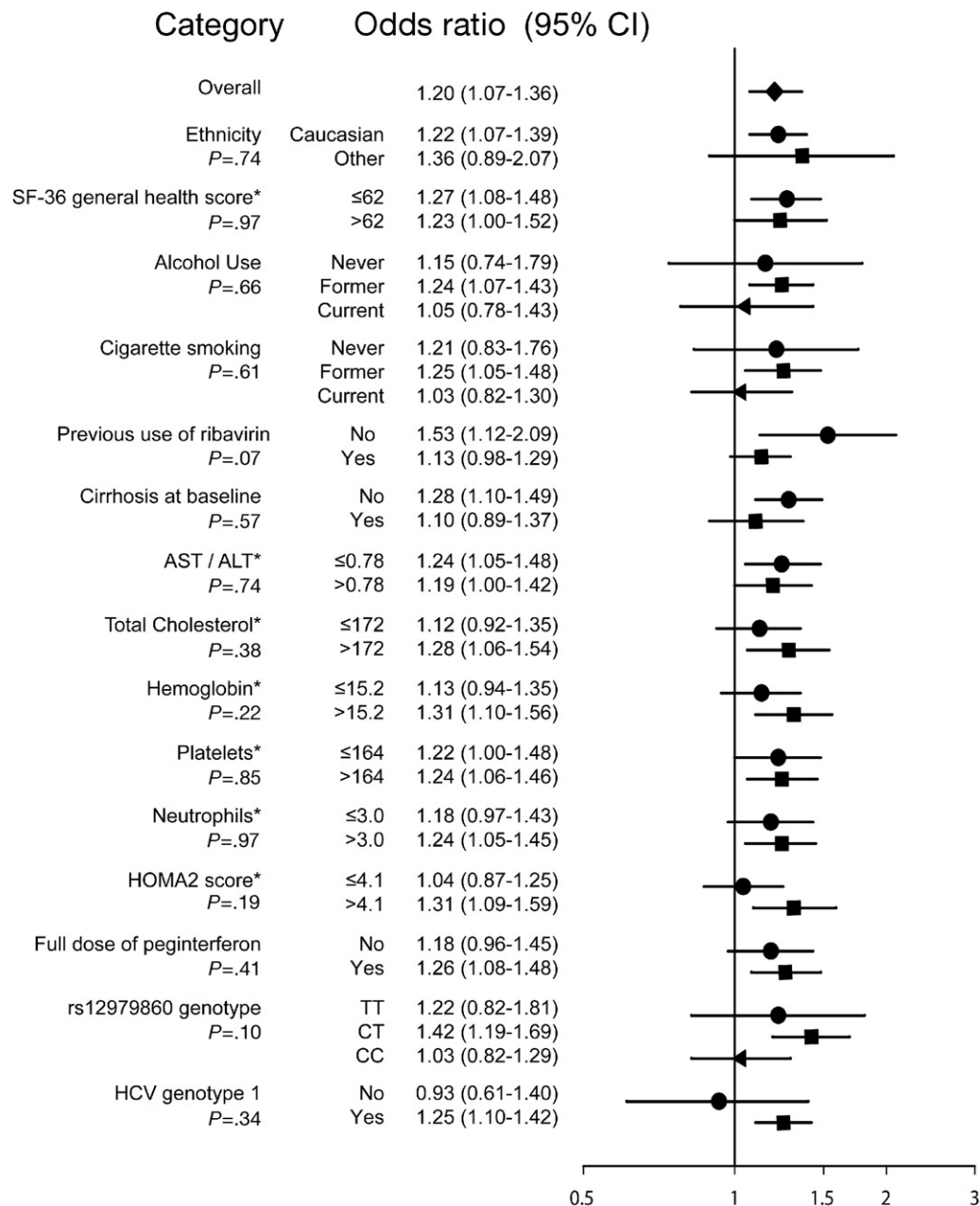


Figure 1. Stratified analysis of the association of baseline coffee intake with week 20 virologic response in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. Odds ratios shown are for an increase in coffee consumption of 1 drink per day and are adjusted for age (continuous), sex, race/ethnicity (white, African American, Hispanic, other), alcohol use (current, former, and never), cirrhosis at baseline, genotype 1, aspartate aminotransferase to alanine aminotransferase (AST/ALT) ratio (continuous), log hepatitis C virus (HCV) RNA level at baseline (continuous), previous use of ribavirin, hemoglobin (continuous), neutrophils (continuous), platelets (continuous), categories of peginterferon medication dose during first 20 weeks of treatment ($\geq 98\%$ –100%, $\geq 80\%$ – $<98\%$, $\geq 60\%$ – $<80\%$, and $<60\%$), and rs12979860 genotype (TT, CT, CC). Median values were used to define cut-points for the starred characteristics. Black diamond indicates the overall point estimate. Black circles, squares, and triangles represent the point estimate for each indicated subgroup. Horizontal lines represent 95% confidence intervals (CI). The solid vertical line indicates an odds ratio of 1. *P* values are for the interaction between coffee intake and each stratifying variable and are taken from the Wald-test for the cross-product term of each stratifying variable and continuous coffee intake.

ment. Intriguingly, coffee was modestly associated with nearly all of these factors. African Americans in our study tended to drink less coffee than white patients, and coffee drinking was associated with lower AST/ALT ratio, ability to tolerate full doses of peginterferon α -2a during treatment, and particular genotypes of single nucleotide

polymorphisms near to the *IL28B* gene, which have recently been linked to virologic response.^{11–15} Yet, the association for coffee persisted after adjustment for these and other potential confounders and was similar across strata of each of these risk factors, eg, a similar effect for coffee on virologic response was observed for both

those receiving a full dose of peginterferon and those having a dose reduction. These results suggest that coffee drinkers had a better response to treatment that was independent of other risk factors, including higher tolerance for peginterferon treatment.

Associations between coffee and features associated with virologic response raise the possibility of reverse causality, ie, sicker patients were less likely to drink coffee and, in this way, less likely to respond to treatment. But in HALT-C, patients drinking coffee reported a worse quality of life on the Short Form-36 quality of life questionnaire than nondrinkers. Quality of life was also not associated with virologic response. As in all observational studies, we cannot exclude unmeasured or residual confounding as an explanation for our results. Observed associations could also simply be due to chance.

Coffee has >1000 compounds, any one of which could be involved in virologic response. One major constituent of coffee is caffeine. Although we could not distinguish caffeinated from decaffeinated coffee in our study, we found no association with consumption of black or green tea. Fewer individuals consumed tea in our study and tea contains less caffeine than coffee. It is unlikely that coffee and its constituents have a direct antiviral effect. If so, HCV RNA levels at baseline would have been expected to be lower with greater coffee consumption. In fact, baseline levels were actually higher with greater consumption (Table 2). More likely coffee would have a facilitating effect on response to peginterferon and ribavirin treatment by a mechanism yet to be understood. It is intriguing that the C allele of rs12979860 near the *IL28B* gene has been associated with higher baseline viral levels, lower levels of interferon-stimulated gene expression, and better treatment response.^{14,36,37} The *IL28B* genotype effect on virologic response may be through the Janus activating kinase/signal transducer and activation of transcription signaling pathway.³⁸ Recently published results potentially link kahweol, a diterpene in coffee, to Janus activating kinase/signal transducer and activation of transcription signaling,³⁹ suggesting one of many possible mechanisms for the observed association in our study.

A number of studies have linked high serum total and low-density lipoprotein (LDL) cholesterol with increased virologic response to peginterferon plus ribavirin therapy.^{40–42} LDL has also been recently posited to mediate, at least partly, the effect of the rs12979860 C allele.^{41,43} Coffee intake was associated with higher serum total cholesterol in our study and has also been linked to higher serum total cholesterol and LDL in past observational and interventional studies.⁴⁴ Adjustment for total cholesterol, however, did not affect risk estimates in the current analysis. We lacked assessment of LDL.

Alternatively, insulin resistance has been associated with poor virologic response in a number of previous studies.^{9,10} Consistent with previous studies of type 2

diabetes,^{45,46} coffee intake was inversely associated with insulin resistance in HALT-C. Adjustment for HOMA2 score did not affect risk estimates for coffee with virologic response in the current analysis.

Our study has several advantages, including a large number of patients with histological staging of liver fibrosis, careful assessment of virologic response using a central virology laboratory, and comprehensive assessment of clinical and histologic features. Limitations include a lack of information on caffeine and coffee brewing methods and the assessment of coffee via self-report at a single time point. As such, we do not know patients' coffee intake at the time of initial treatment or whether coffee consumption was maintained during the course of the lead-in phase. However, for patients failing lead-in therapy subsequently randomized to half-dose peginterferon treatment or to no treatment, coffee consumption was similar at baseline and 18 months later (6 months after randomization). Because patients in HALT-C also had previously failed interferon therapy, it is not clear whether our results can be generalized to other patient populations, such as those with less advanced disease, those who are treatment-naïve to prior therapy, or who are being treated with newer antiviral agents.

In summary, we observed an independent association between coffee intake and virologic response to peginterferon plus ribavirin retreatment in the lead-in phase of the HALT-C trial. Future studies are needed to replicate this finding in other populations.

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Received November 20, 2010. Accepted February 18, 2011.

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Acknowledgments

The HALT-C Trial was registered with clinicaltrials.gov (NCT00006164).

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In addition to the authors of this article, the following individuals were instrumental in the planning, conduct, and/or care of patients enrolled in this study at each of the participating institutions as follows: University of Massachusetts Medical Center, Worcester, MA (Contract N01-DK-9-2326): Gyongyi Szabo, MD, Barbara F. Banner, MD, Maureen Cormier, RN, Donna Giansiracusa, RN; University of Connecticut Health Center, Farmington, CT (Grant M01RR-06192): Herbert L. Bonkovsky, MD, Gloria Borders, RN, Michelle Kelley, RN, ANP; Saint Louis University School of Medicine, St Louis, MO (Contract N01-DK-9-2324): Adrian M. Di Bisceglie, MD, Bruce Bacon, MD, Brent Neuschwander-Tetri, MD, Elizabeth M. Brunt, MD, Debra King, RN; Massachusetts General Hospital, Boston, MA (Contract N01-DK-9-2319, Grant M01RR-01066; Grant 1 UL1 RR025758-01, Harvard Clinical and Translational Science Center): Jules L. Dienstag, MD, Raymond T. Chung, MD, Andrea E. Reid, MD, Atul K. Bhan, MD, Wallis A. Molchen, David P. Lundmark; University of Colorado Denver, School of Medicine, Aurora, CO (Contract N01-DK-9-2327, Grant M01RR-00051, Grant 1 UL1 RR 025780-01): Gregory T. Everson, MD, Thomas Trouillot, MD, Marcelo Kugelman, MD, S. Russell Nash, MD, Jennifer DeSanto, RN, Carol McKinley, RN; University of California-Irvine, Irvine, CA (Contract N01-DK-9-2320, Grant M01RR-00827): Timothy R. Morgan, MD, John C. Hoefs, MD, John R. Craig, MD, M. Mazen Jamal, MD, MPH, Muhammad Sheik, MD, Choon Park, RN; University of Texas Southwestern Medical Center, Dallas, TX (Contract N01-DK-9-2321, Grant M01RR-00633, Grant 1 UL1 RR024982-01, North and Central Texas Clinical and Translational Science Initiative): William M. Lee, MD, Thomas E. Rogers, MD, Peter F. Malet, MD, Janel Shelton, Nicole Crowder, LVN, Rivka Elbein, RN, BSN, Nancy Liston, MPH; University of Southern California, Los Angeles, CA (Contract N01-DK-9-2325, Grant M01RR-00043): Sugantha Govindarajan, MD, Carol B. Jones, RN, Susan L. Milstein, RN; University of Michigan Medical Center, Ann Arbor, MI (Contract N01-DK-9-2323, Grant M01RR-00042, Grant 1 UL1 RR024986, Michigan Center for Clinical and Health Research): Anna S. Lok, MD, Robert J. Fontana, MD, Joel K. Greenson, MD, Pamela A. Richtmyer, LPN, CCRC, R. Tess Bonham, BS; Virginia Commonwealth University Health System, Richmond, VA (Contract N01-DK-9-2322, Grant M01RR-00065): Mitchell L. Shiffman, MD, Richard K. Sterling, MD, MSc, Melissa J. Contos, MD, A. Scott Mills, MD, Charlotte Hofmann, RN, Paula Smith, RN; Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD: Marc G. Ghany, MD, T. Jake Liang, MD, David Kleiner, MD, PhD, Yoon Park,

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Conflicts of interest

This author discloses the following: Dr Lindsay was a consultant and received research support from Hoffmann-La Roche, Inc. (now Genentech), during this study and is now an employee of Tibotec, Inc. (a subsidiary of Johnson and Johnson), Titusville, NJ.

The remaining authors disclose no conflicts.

Funding

This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (contract numbers are listed in the Acknowledgments). Additional support was provided by the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the National Center for Minority Health and Health Disparities and by General Clinical Research Center and Clinical and Translational Science Center grants from the National Center for Research Resources, National Institutes of Health (grant numbers are listed in the Acknowledgments). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. Additional funding to conduct this study was supplied by Hoffmann-La Roche, Inc. (now Genentech), through a Cooperative Research and Development Agreement (CRADA) with the National Institutes of Health. This research was also supported in part by the Intramural Research Program of the National Cancer Institute. The funding organizations had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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