

Coffee, Cirrhosis, and Transaminase Enzymes

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Background: A minority of persons at risk develop liver cirrhosis, but knowledge of risk modulators is sparse. Several reports suggest that coffee drinking is associated with lower cirrhosis risk.

Methods: We studied 125 580 multiethnic members of a comprehensive prepaid health care plan without known liver disease who supplied baseline data at voluntary health examinations from 1978 to 1985. Subsequently, through 2001, 330 of them were diagnosed with liver cirrhosis. Review of medical records confirmed the diagnosis of cirrhosis and ascertained probable etiology. The association of coffee drinking with cirrhosis was estimated by Cox proportional hazards models with 7 covariates. We also did a cross-sectional analysis of baseline aspartate aminotransferase and alanine aminotransferase levels, studied by logistic regression.

Results: In the cohort study, relative risks of alcoholic cirrhosis (199 subjects) for coffee drinking (vs none) were less than 1 cup per day, 0.7 (95% confidence interval [CI], 0.4-1.1); 1 to 3 cups, 0.6 (95% CI, 0.4-0.8; $P < .001$); and

4 or more cups, 0.2 (95% CI, 0.1-0.4; $P < .001$). For 131 subjects with nonalcoholic cirrhosis, relative risks were less than 1 cup, 1.2 (95% CI, 0.6-2.2); 1 to 3 cups, 1.3 (95% CI, 0.8-2.1); and 4 or more cups, 0.7 (95% CI, 0.4-1.3). These relative risks for coffee drinking were consistent in subsets. Tea drinking was unrelated to alcoholic or nonalcoholic cirrhosis. In the cross-sectional analyses, coffee drinking was related to lower prevalence of high aspartate aminotransferase and alanine aminotransferase levels; for example, the odds ratio of 4 or more cups per day (vs none) for a high aspartate aminotransferase level was 0.5 (95% CI, 0.4-0.6; $P < .001$) and for a high alanine aminotransferase level, 0.6 (95% CI, 0.6-0.7; $P < .001$), with stronger inverse relations in those who drink large quantities of alcohol.

Conclusion: These data support the hypothesis that there is an ingredient in coffee that protects against cirrhosis, especially alcoholic cirrhosis.

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LONG-TERM INGESTION OF large amounts of alcohol is the most common cause of liver cirrhosis in developed countries,¹⁻⁶ with the total lifetime ethanol dosage considered to be the key factor.⁶⁻⁹ Women may be more susceptible,^{10,11} and ethnic differences in risk have been cited.¹⁰ The amount of alcohol consumed and an individual's drinking pattern also play a role,^{2,12} so it is difficult to definitively establish independence of the demographic traits from these features. Because most long-term heavy alcohol drinkers do not develop cirrhosis,^{4,6,12} there are other predisposing traits. Other possible cofactors include genetic susceptibility, nutritional status, immune-mediated mechanisms, cigarette smoking, diet, and interactions with other hepatotoxins.^{3,4,6,7,9,10,12,13}

In 1992, we reported an inverse relation of coffee drinking to risk of liver cir-

rhosis in a 10-year cohort follow-up.¹³ That analysis involved 132 persons who had been hospitalized or who had died from cirrhosis from 1978 to 1988. The inverse coffee-cirrhosis relation was stronger for cirrhosis attributed to alcohol drinking than for non-alcohol-associated disease, but limited statistical power owing to small numbers clouded this differentiation.

An inverse relation of coffee drinking with cirrhosis has been confirmed by studies of nonfatal^{5,14,15} and fatal¹⁶ disease. A similar inverse relation of coffee drinking to primary hepatocellular carcinoma¹⁷⁻¹⁹ warrants mention because of the usual antecedent cirrhosis. There are also reports of lower blood levels of hepatocellular enzymes in coffee drinkers.²⁰⁻²² Because elevated levels of these enzymes are thought to be a sensitive marker of acute or subacute liver damage, these reports offer further indirect support for possible protection by coffee. The mechanisms for

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hypothetical protection are speculative, and it is unclear whether the inverse relation is associated more with caffeine or with some other coffee ingredient. The question of whether the inverse relation is specific (or relatively so) for alcoholic liver disease is also unresolved.

We present herein an extension of our cohort study, with a 22-year follow-up and 330 subjects who developed cirrhosis. Rigorous record review was done to verify the presence of chronic liver disease and to assign a probable primary etiology. We also present a cross-sectional analysis of baseline interrelations of coffee, alcohol, and elevated blood levels of liver enzymes.

METHODS

SUBJECTS AND DATA FOR COHORT STUDY

The study protocols were approved by the institutional review board of the Kaiser Permanente Medical Care Program, Oakland, Calif. Baseline data were from health appraisal examinations²³ voluntarily taken by members of a Northern California prepaid comprehensive health care program. These members are believed to reflect the full socioeconomic spectrum of the general population except for the extremes of income.²⁴ From 1978 to 1985 a research alcohol questionnaire was completed by 125 580 adults who responded negatively to queries about presence of liver disease. These individuals comprised over 80% of all examinees; the rest consisted largely of individuals taking the examination in the absence of a special research clerk or those who were not fluent in English. The basic examination included health measurements and queries about sociodemographic status, habits, and medical history.²³ The research questionnaire included self-classified ethnicity and additional data about alcohol, coffee, and tea use in the past year (alcohol use defined as the usual number of drinks per day; coffee and tea consumption, as the usual number of cups per day).

ASCERTAINMENT OF DIAGNOSES OF CIRRHOSIS

We attempted to identify all persons among the 128 934 examinees who had a first hospital admission for cirrhosis or who died of cirrhosis after the 1978-1985 baseline examination through December 31, 2002. Excluded were persons with a primary or secondary *International Classification of Diseases, Ninth Revision (ICD-9)*,²⁵ code 571 diagnosis (chronic liver disease and cirrhosis) prior to the baseline examination. A computer search was performed for code 571 primary hospitalization discharge diagnoses in Northern California Kaiser Permanente databases and in California death indices. We also screened persons with other diagnoses considered likely to represent underlying liver cirrhosis; these included code 155.1 (malignant neoplasm of liver, primary), 456.0-456.2 (esophageal varices), 572.2 (hepatic coma), 572.3 (portal hypertension), and 572.4 (hepatorenal syndrome). The diagnosis of cirrhosis was considered confirmed if (1) there was histological confirmation by autopsy or liver biopsy, (2) there were at least 2 hospital admissions more than 12 months apart for the condition or 1 admission plus a death certificate diagnosis, (3) the diagnosis was made by a gastroenterologist, or (4) there was a compelling clinical picture. A compelling clinical picture required, in the absence of other explanations, the presence of at least 4 of the following: spider nevi, scleral icterus, palmar erythema, ascites, flapping tremor, hepatosplenomegaly, a platelet count of less than 140 000/ μ L, ultrasonographic findings of

a portal vein diameter larger than 12 mm, a serum albumin level below 3.0 g/dL (35 g/L), and an international normalized ratio prothrombin time greater than 1.5

Probable cirrhosis etiology was determined by physician investigators with the aid of computer-stored information and complete paper inpatient and outpatient medical records. Consideration was given to data about alcohol-drinking history, alcohol-related diagnoses, and clinical data at the time of diagnosis. Uncertain cases were resolved by consensus involving a gastroenterologist. The opinion of a gastroenterologist in the medical record was given considerable weight but was sometimes changed. When both chronic viral hepatitis and a history of substantial alcohol drinking were present, the probable etiology was assigned as nonalcoholic. Of 430 persons initially screened, 100 were excluded, leaving in the cohort study 330 subjects who developed cirrhosis. The largest groups excluded were (1) former health plan members with a diagnosis of cirrhosis on their death certificates but no confirmatory evidence in plan records ($n=39$), persons with transient alcoholic hepatitis ($n=38$), cases with other primary malignancy, misclassified as hepatoma ($n=9$), those with missing medical records ($n=6$), and those with other misdiagnoses ($n=7$). Of the subjects with nonalcoholic cirrhosis, 72 were judged to have chronic viral disease, 11 had biliary cirrhosis, 4 each had hemochromatosis or autoimmune disease, and 40 had cryptogenic cirrhosis. **Table 1** shows additional selected traits of the total study population and of the subjects with cirrhosis.

BASELINE LIVER ENZYMES

At baseline examinations from January 1978 through October 1979, a total of 37 620 persons had aspartate aminotransferase (AST) level determinations. From January 1978 through August 1981, 69 904 persons had alanine aminotransferase (ALT) level determinations. Except for the examination date, there were no other selection factors.

ANALYTIC METHODS FOR COHORT STUDY

Each subject was followed up until December 31, 2001, or until death, other health plan termination, or first hospitalization for cirrhosis, whichever occurred first. This yielded a total of 1 820 201 person-years of observation (mean follow-up time, 14.1 years). For age-adjusted and multivariate analyses, we used Cox proportional hazards models determined by the PHREG procedure of the SAS Users Guide (version 8; SAS Institute, Inc, Cary, NC). Most multivariate models included age ($\times 10$ years), sex, race (referent, white; black, Asian, Hispanic, or other), education (referent, no college; some college or college graduate), body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters (referent, <25 ; 25-29, or ≥ 30), alcohol (referent, never drank or <1 drink per month; <1 per day, 1-2 per day, or ≥ 3 per day), and cigarette smoking (referent, never smoked; ex-smoker, <1 pack per day, or ≥ 1 pack per day). Each covariate was included because of the apparent significant ($P<.05$) effect of alcoholic cirrhosis in stepwise regression analyses. The model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test. The analyses yielded estimates of relative risk (RR), 95% confidence intervals (CIs), and P values.

For cross-sectional liver enzyme analysis, elevated levels of AST and ALT, defined as the highest 5% for each sex, were studied by logistic regression with categories of age, race, smoking, and alcohol drinking as covariates; these models were determined for all persons in each sex and at specific reported drinking levels.

In addition to direct cross-classification, correlations of cigarette smoking and alcohol, coffee, and tea drinking were studied as Pearson correlation coefficients.

Table 1. Traits of Study Population and Subjects With Cirrhosis*

Group	Study Population†	Subjects With Cirrhosis‡	
		Alcoholic	Nonalcoholic
Total	125 580 (100)	199 (100)	131 (100)
Men	55 247 (44)	129 (65)	71 (54)
Women	70 333 (56)	70 (35)	60 (46)
Baseline age, y			
<50	88 997 (71)	98 (50)	67 (51)
50-59	18 706 (15)	51 (26)	30 (23)
≥60	17 877 (14)	47 (24)	34 (26)
Race or ethnicity			
Black	33 937 (27)	50 (27)	34 (26)
White	69 595 (55)	123 (62)	70 (53)
Asian	13 425 (11)	2 (1)	18 (14)
Hispanic	5607 (4)	18 (9)	8 (6)
Other	2776 (2)	3 (2)	1 (1)
Alcohol			
Never drank	15 038 (12)	3 (2)	19 (15)
Ex-drinker	4034 (3)	9 (5)	13 (10)
<1 Drink per month	26 588 (21)	11 (6)	27 (28)
>1 Drink per month but <1 day	46 035 (37)	26 (13)	39 (30)
1-2 Drinks per day	22 527 (18)	53 (27)	16 (12)
≥3 Drinks per day	10 005 (8)	96 (48)	7 (5)
Smoking, packs per day			
Never smoked	60 277 (48)	39 (20)	49 (38)
Ex-smoker	27 926 (22)	47 (24)	30 (23)
<1	20 890 (17)	52 (26)	27 (20)
≥1	11 398 (9)	46 (23)	16 (12)
Unknown	5089 (4)	15 (8)	9 (7)
Coffee consumption, cups per day			
Never or seldom	33 634 (27)	54 (27)	24 (18)
<1	17 576 (14)	24 (12)	17 (13)
1-3	52 351 (42)	96 (48)	68 (53)
≥4	20 504 (16)	22 (11)	18 (14)
Unknown	1415 (1)	3 (2)	3 (2)
Tea consumption, cups per day			
Never or seldom	63 504 (51)	128 (64)	63 (48)
<1	34 612 (28)	28 (14)	32 (24)
≥1	23 767 (19)	32 (16)	27 (21)
Unknown	3697 (3)	11 (6)	9 (7)

*Data are given as number (percentage). Percentages do not always add to 100% because of rounding.

†See "Subjects and Data for Cohort Study" subsection of the "Methods" section for definitions.

RESULTS

COFFEE DRINKING AND RISK OF CIRRHOSIS

With increasing coffee intake a strong progressive inverse relation to risk of alcoholic cirrhosis was evident (**Table 2**). There was no significant ($P < .05$) inverse relation of coffee intake to nonalcoholic cirrhosis. The RR per cup of coffee per day for alcoholic cirrhosis was 0.78 (95% CI, 0.71-0.85); for nonalcoholic cirrhosis it was 0.92 (95% CI, 0.84-1.02). Among subgroups of subjects with nonalcoholic cirrhosis, coffee had a similar, weak, nonstatistically significant inverse relation to risk of either viral hepatitis-associated cirrhosis or to miscellaneous other cirrhosis; the RR per cup per day for both was 0.9 (95% CI, 0.8-1.1). Multivar-

Table 2. Adjusted* Relative Risk of Cirrhosis According to Whether an Individual Drinks Coffee or Tea

Coffee or Tea, Cups per Day	Subjects With Cirrhosis	
	Alcoholic	Nonalcoholic
Coffee		
Never or seldom	1.0	1.0
<1	0.7 (0.4-1.1)	1.2 (0.6-2.2)
1-3	0.6 (0.4-0.8)†	1.3 (0.8-2.1)
≥4	0.2 (0.1-0.4)†	0.7 (0.4-1.3)
Per cup of coffee per day‡	0.8 (0.7-0.9)†	0.9 (0.8-1.0)
Tea		
Never or seldom	1.0	1.0
<1	0.6 (0.4-1.0)§	1.0 (0.7-1.6)
≥1	1.0 (0.7-1.5)	1.1 (0.7-1.7)
Per cup of tea per day‡	0.9 (0.8-1.1)	1.0 (0.9-1.2)

*By Cox proportional hazards models adjusted for sex, race or ethnicity, smoking, alcohol use, education, and body mass index. Values in parentheses are 95% confidence intervals.

† $P < .001$.

‡Continuous with following values assigned: never or seldom = 0, less than 1 cup per day = 0.5, 1 to 3 cups per day = 2, 4 to 6 cups per day = 5, and more than 6 cups per day = 7.

§ $P < .05$.

||Number of subjects reporting drinking 1 or more cups of tea per day, 23 735.

iate regressions with coffee categorized for the 72 subjects with hepatitis showed the following RRs vs non-coffee drinkers: for 1 to 3 cups per day the RR was 1.2 (95% CI, 0.7-2.2; $P = .52$); for 4 or more cups per day the RR was 0.7 (95% CI, 0.3-1.5; $P = .32$). Tea intake was unrelated to either alcoholic or nonalcoholic cirrhosis (Table 2).

The inverse relation between coffee and alcoholic cirrhosis showed general consistency in subgroups of sex, ethnicity, age, and BMI category (data not shown). There was no diminution in the lower risk associated with coffee drinking, with increasing intervals between collection of coffee data and cirrhosis diagnosis; RR for more than 4 cups per day vs no coffee at less than 5 years (39 subjects) was 0.2 (95% CI, 0.6-0.5), at 5 to 9 years (59 subjects) it was 0.3 (95% CI, 0.1-0.8), and at more than 10 years (81 subjects) it was 0.2 (95% CI, 0.1-0.5).

The goodness-of-fit test results for alcoholic cirrhosis were satisfactory ($\chi^2 = 4.62$; $P = .71$).

RISK OF CIRRHOSIS ASSOCIATED WITH COVARIATES

The risk of both alcoholic and nonalcoholic cirrhosis was higher with increasing age, male sex, smoking, and a BMI of 30 kg/m² or greater, whereas persons with more education had a lower risk of both (**Table 3**). Asian ethnicity was inversely related and Hispanic ethnicity positively related to alcoholic cirrhosis. Perhaps partially an artifact of classification, intake of large quantities of alcohol was related only to alcoholic cirrhosis.

CORRELATIONS OF HABITS

Coffee drinking was positively correlated with smoking (Pearson correlation coefficient, 0.32) and alcohol drinking (coefficient, 0.18) and was weakly inversely corre-

lated with tea drinking (coefficient, -0.07). The correlation coefficient of smoking with alcohol was 0.30 . These correlations were similar for men and for women (data not shown). Coffee drinking was weakly correlated with BMI ($+0.06$) and unrelated to education (-0.01). Persons who reported drinking 4 or more cups of coffee per day composed 16.3% of all examinees but included substantially disproportionate numbers of heavy smokers and alcohol drinkers. For example, 21.9% (4733 of 21 596) of these heavier coffee drinkers reported smoking at least 1 pack per day (vs 9.2% of all examinees) and 12.2% (2659 of 21 569) reported consuming a least 3 alcoholic drinks per day (vs 8.2% of all examinees).

INVERSE RELATION OF BLOOD LEVELS OF LIVER ENZYMES TO COFFEE DRINKING

As expected, mean blood levels of AST and ALT were progressively higher with heavier alcohol intake, as follows. For lifelong abstainers, the AST level was 20.5 U/L and the ALT level was 15.9 U/L; for ex-drinkers, the AST level was 22.6 U/L and the ALT was level, 18.9 U/L; for those who consumed less than 1 drink per month, the AST level was 20.6 U/L and the ALT level was 16.3 U/L; for those had more than 1 drink per month but less than 1 drink per day, the AST level was 21.0 U/L and the ALT level was 16.7 U/L; for those who had 1 to 2 drinks per day, the AST level was 23.2 U/L and the ALT level was 19.1 U/L; and for those who had 3 or more drinks per day, the AST level was 30.8 U/L and the ALT level was 25.8 U/L.

The mean AST level was 20.1 U/L in men and 24.7 U/L in women; the mean ALT level was 22.4 U/L in men and 14.1 U/L in women. We elected to study the highest 5% of each sex as a definition of high AST and ALT levels. These cutoff points were an AST level of 45 U/L or higher in men or 34 U/L or higher in women, and an ALT level of 52 U/L or higher in men or 31 U/L or higher in women. Comparing heavy alcohol drinkers (≥ 3 drinks per day) with abstainers in logistic regression models demonstrated statistically significant ($P < .001$) increased prevalence of high values: an odds ratio for the AST level of 3.9 U/L (95% CI, 2.9-4.8) and for the ALT level of 2.2 U/L (95% CI, 2.0-2.6). In logistic models stratified by alcohol intake we found a substantial inverse relation of coffee drinking to prevalence of high AST and ALT levels within the alcohol intake strata (**Table 4**). This inverse relation of coffee to elevated enzyme levels was strongest in heavier alcohol drinkers (Table 4).

COMMENT

Our data showed a robust inverse relation of coffee drinking to risk of alcoholic cirrhosis, independent of several potential confounders. In contrast, there was no statistically significant relation of coffee drinking to risk of non-alcoholic cirrhosis. The positive correlations of coffee drinking with traits related to increased cirrhosis risk, such as alcohol intake, smoking, and BMI, indicate that residual confounding for these traits would more likely result in a positive—not an inverse—coffee-cirrhosis relation. One analysis of potential confounders of health

Table 3. Adjusted* Relative Risk of Cirrhosis According to Selected Covariates

Covariate (Referent)	Subjects With Cirrhosis	
	Alcoholic	Nonalcoholic
Age ($\times 10$ y)	1.4 (1.3-1.5)†	1.2 (1.1-1.4)‡
Men (women)	1.3 (0.9-1.8)	1.6 (1.1-2.4)‡
Black (white)	0.7 (0.5-1.0)	0.7 (0.5-1.1)
Asian (white)	0.2 (0.05-0.8)§	1.3 (0.8-2.4)
Hispanic (white)	1.9 (1.1-3.2)§	1.1 (0.5-2.3)
Smoke ≥ 1 pack per day (never)	3.3 (2.1-5.1)‡	2.0 (1.1-3.6)§
Consume ≥ 3 alcoholic drinks per day (never plus < 1 per month)	21.2 (11.5-38.6)†	1.0 (0.5-1.9)
College graduate (no college)	0.5 (0.3-0.7)†	0.5 (0.3-0.8)‡
BMI ≥ 30 (< 25)	1.6 (1.1-2.3)§	1.7 (1.0-2.8)§

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

*By Cox proportional hazards models including sex, ethnicity, coffee, alcohol, education, and BMI. Data are given as relative risk (95% confidence interval).

† $P < .001$.

‡ $P < .01$.

§ $P < .05$.

studies of coffee consumption²⁶ led to the conclusion that only smoking and sex were of importance. Another report²⁷ showed a positive correlation among long-term alcoholic subjects between alcohol and caffeine intake, similar to those of persons with and without a family history of alcoholism; those authors inferred the likely presence of a behavioral rather than a genetic interaction between these behaviors. These considerations, in concert with the strength of the inverse coffee-alcoholic cirrhosis association, make confounding by associated habits an unlikely explanation.

Our cross-sectional data about coffee drinking and high blood levels of liver enzymes are generally comparable with other reports²⁰⁻²² and inferentially support a possible protective effect of coffee against hepatocyte damage. Lower prevalence of elevated enzyme levels among coffee drinkers was not limited to heavy alcohol drinkers in our study population, but the apparent coffee effect was stronger among them. It is probable that some heavy alcohol drinkers underreport their intake. If only persons with heavy alcohol intake had elevated liver enzyme levels and hepatocyte protection by coffee, such underreporting could produce an apparent, but spurious, inverse relation of coffee to high AST and ALT levels among lighter alcohol drinkers or abstainers. However, it seems unlikely that underreporting of alcohol intake is the entire explanation, and the enzyme level relations suggest less specificity of coffee's apparent protection against acute or subacute alcohol-induced damage. It remains possible that coffee is more specifically protective against severe chronic liver disease (ie, cirrhosis) when alcohol is the noxious agent.

In other reports,^{5,16,17} specificity of the inverse coffee-cirrhosis relation for alcoholic liver disease has not been consistently found. Lower prevalence of an elevated ALT level in coffee drinkers in one report²² was similar for various high-risk groups for liver disease, such as heavy alcohol drinkers, those with chronic viral hepatitis, or obese

Table 4. High* Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) Levels by Coffee Drinking Stratified by Alcohol Intake

Alcohol Category	OR (95% CI) vs Never or Seldom Drink Coffee†		
	<1 Cup per Day	1-3 Cups per Day	≥4 Cups per Day
Highest 5% AST Level (≥45 U/L in men, ≥34 U/L in women)			
All (n = 37 620)	0.8 (0.7-0.9)‡	0.7 (0.6-0.8)§	0.5 (0.4-0.6)§
Never drank (n = 4669)	0.7 (0.4-1.2)	0.8 (0.6-1.1)	0.6 (0.3-1.0)
Ex-drinker (n = 1343)	0.9 (0.4-2.1)	0.9 (0.5-1.7)	0.4 (0.2-1.0)
<1 Drink per day (n = 22 562)	0.8 (0.7-1.0)	0.7 (0.6-0.9)‡	0.8 (0.6-1.0)
1-2 Drinks per day (n = 6836)	0.7 (0.5-1.1)	0.6 (0.5-0.8)§	0.4 (0.3-0.6)§
≥3 Drinks per day (n = 2981)	0.7 (0.5-1.0)	0.5 (0.3-0.6)§	0.3 (0.2-0.4)§
Highest 5% ALT Level (≥52 U/L in men, ≥31 U/L in women)			
All (n = 69 904)	1.0 (0.9-1.1)	0.8 (0.8-0.9)§	0.6 (0.6-0.7)§
Never drank (n = 8330)	1.1 (0.8-1.4)	0.8 (0.6-1.0)	0.8 (0.6-1.2)
Ex-drinker (n = 2025)	1.7 (0.8-3.4)	1.2 (0.7-2.1)	0.8 (0.4-1.5)
<1 Drink per day (n = 40 402)	0.9 (0.8-1.1)	0.8 (0.7-0.9)§	0.7 (0.6-0.8)§
1-2 Drinks per day (n = 12 672)	1.0 (0.8-1.4)	0.9 (0.7-1.1)	0.6 (0.4-0.8)§
≥3 Drinks per day (n = 6052)	1.1 (0.8-1.5)	0.6 (0.5-0.8)§	0.4 (0.3-0.5)§

Abbreviations: CI, confidence interval; OR, odds ratio.

*Defined as highest 5% in each sex; see "Baseline Liver Enzymes" subsection in the "Methods" section for relation to alcohol intake.

†By logistic regression models adjusted for sex; race or ethnicity; smoking; alcohol; education; and body mass index.

‡ $P < .01$.

§ $P < .001$.

|| $P < .05$.

persons. The inverse relation of coffee to hepatocellular carcinoma¹⁷⁻¹⁹ argues indirectly against specificity for alcohol-induced disease, especially because 2 of these reports^{18,19} are from Japan, where chronic viral disease plays a preponderant role in this malignancy.²⁸

The absent relation of tea drinking to cirrhosis might mean that the relation is less likely due to caffeine than to some other coffee ingredient. However, substantial tea drinking was relatively uncommon in this population, and tea typically has less caffeine per cup than coffee.²⁹ A recent report³⁰ presented data showing a similarly decreased relative risk of liver disease for caffeinated coffee as for tea, with an RR of more than 2 cups per day vs less than 1 cup per day of coffee of 0.5 (95% CI, 0.3-1.0) and of tea of 0.6 (95% CI, 0.1-2.3). As those authors stated,³⁰ the tea data lack statistical significance, but the issue of a possible relation of tea to liver disease remains open. Information about coffee and tea type was available for about 10% of our study population. Although the number of subjects with cirrhosis among that 10% was insufficient for analysis, we do know that heavier coffee drinkers in this population were less likely to drink decaffeinated coffee.²⁹ Previous reports^{5,16,22} are disparate with respect to whether the apparently protective coffee ingredient is caffeine; in our opinion this issue is quite unresolved.

Approximately 80% of Americans consume coffee, averaging 3.2 cups per day.³¹ On average, 80% of all caffeine is taken as coffee,²⁹ so that coffee drinking is sometimes considered a marker for caffeine intake. Because of the evident stimulatory effects of caffeine, this prominent coffee component has been much studied, but coffee is a complex substance with many potentially biologically active ingredients.³² The fact that coffee is also frequently taken with added cream, milk, sugar, or other substances adds more possibilities for health effects. Speculations²² about hepatic protection include caffeine

effects via adenosine receptor antagonists or antioxidant actions and potential adverse effects of cafestol (a fat-soluble noncaffeine component of boiled coffee) via induction of glutathione, a cellular protective factor.

The positive association of smoking to risk of alcoholic cirrhosis is clearer here than in our earlier report,¹³ with a positive, albeit weaker, relation to nonalcoholic cirrhosis. Because smoking and alcohol drinking are related habits, it is difficult to completely rule out residual confounding by alcohol amount or drinking pattern. Coffee drinking and smoking are also strongly correlated, and smoking may prolong the persistence of caffeine in the body.³³ Thus, any residual confounding related to coffee drinking would tend to produce an inverse smoking-cirrhosis relation, not the positive one we obtained.

Ascertainment of habits only at baseline time is a limitation of our study, but the probable effect of cessation or reduction of coffee drinking after baseline but before diagnosis would be to weaken, not to strengthen or produce, the inverse coffee-cirrhosis association we found. A second limitation is lack of information about changes in coffee drinking habits before baseline evaluation. Hypothetically, some persons with symptoms of undiagnosed liver disease might have reduced coffee intake or quit drinking coffee, thus spuriously increasing the risk of the non-coffee-drinking referent group. The probable result of such a phenomenon would be an apparent strong inverse coffee-cirrhosis relation only in the first years after baseline time; persistence of the inverse relation among persons with at least 10 years to diagnosis argues against this. A third limitation is the use of hospitalization and death as end points, leaving unexplored the relation of coffee drinking to milder liver disease. A fourth limitation is incomplete follow-up of the cohort, but it seems unlikely that this is systematically related to coffee drinking. Yet another limitation is the

inability to account for changes in alcohol drinking or inaccurate reporting of alcohol drinking. We have evidence that alcohol drinking habits are relatively stable in this study population.³⁴ The fact that some subjects with alcoholic cirrhosis reported lifelong abstinence and light drinking (Table 1) suggests possible underreporting. However, assuming correct diagnosis, increase or onset of drinking after baseline in some subjects could be the explanation.

The observational nature of the data and the absence of an established mechanism limit a causal interpretation. There are also no clear therapeutic implications; even if coffee is protective, the primary approach to reduction of alcoholic cirrhosis is avoidance or cessation of heavy alcohol drinking. Assuming causality, the data do suggest that coffee intake may partly explain the variability of cirrhosis risk in alcohol consumers. Basic research about hepatic coffee-ethanol interactions is warranted, but we should keep in mind that coffee might represent only one of a number of potential cirrhosis risk modulators.

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REFERENCES

1. Pequignot G, Tuyns AJ, Berta JL. Ascitic cirrhosis in relation to alcohol consumption. *Int J Epidemiol.* 1978;7:113-120.
2. Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. *Br Med J (Clin Res Ed).* 1981;282:263-266.
3. Smart RG, Mann RE. Alcohol and the epidemiology of liver cirrhosis. *Alcohol Health Res World.* 1992;16:217-222.
4. Corrao G, Arico S. Alcohol and liver cirrhosis: old questions and weakly explored opportunities. *Addiction.* 2000;95:1267-1270.
5. Corrao G, Zambon A, Bagnardi V, D'Amicis A, Klatsky A; Collaborative SIDECIR Group. Coffee, caffeine, and the risk of liver cirrhosis. *Ann Epidemiol.* 2001; 11:458-465.
6. Lelbach WK. Epidemiology of alcoholic liver disease. *Prog Liver Dis.* 1976;5:494-515.
7. Mezey E. Dietary fat and alcoholic liver disease. *Hepatology.* 1998;28:901-905.
8. Corrao G, Bagnardi V, Zambon A, Arico S. Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction.* 1999;94:1551-1573.
9. Lieber CS. Alcohol: its metabolism and interaction with nutrients. *Annu Rev Nutr.* 2000;20:395-430.
10. Grant BF, Dufour MC, Harford TC. Epidemiology of alcoholic liver disease. *Semin Liver Dis.* 1988;8:12-25.
11. Stinson FS, Grant BF, Dufour MC. The critical dimension of ethnicity in liver cirrhosis mortality statistics. *Alcohol Clin Exp Res.* 2001;25:1181-1187.
12. Bellentani S, Saccoccio G, Masutti F, et al. Risk factors for alcoholic liver disease. *Addict Biol.* 2000;5:261-268.
13. Klatsky AL, Armstrong MA. Alcohol, smoking, coffee, and cirrhosis. *Am J Epidemiol.* 1992;136:1248-1257.
14. Corrao G, Lepore AR, Torchio P, et al; Provincial Group for the Study of Chronic Liver Disease. The effect of drinking coffee and smoking cigarettes on the risk of cirrhosis associated with alcohol consumption: a case-control study. *Eur J Epidemiol.* 1994;10:657-664.
15. Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? *Ann Epidemiol.* 2002;12:202-205.
16. Tverdal A, Skurtveit S. Coffee intake and mortality from liver cirrhosis. *Ann Epidemiol.* 2003;13:419-423.
17. Gallus S, Bertuzzi M, Tavani A, et al. Does coffee protect against hepatocellular carcinoma? *Br J Cancer.* 2002;87:956-959.
18. Inoue M, Yoshimi I, Sobue T, Tsugane S; JPHC Group. Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan. *J Natl Cancer Inst.* 2005;97:293-300.
19. Shimazu T, Tsubono Y, Kuriyama S, et al. Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. *Int J Cancer.* 2005;10:150-154.
20. Casiglia E, Spolaore P, Ginocchio G, Ambrosio GB. Unexpected effects of coffee consumption on liver enzymes. *Eur J Epidemiol.* 1993;9:293-297.
21. Sharp DS, Everhart JE, Benowitz NL. Coffee, alcohol, and the liver. *Ann Epidemiol.* 1999;9:391-393.
22. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. *Gastroenterology.* 2005;128:28-32.
23. Collen MF, Davis LF. The multitest laboratory in health care. *J Occup Med.* 1969; 11:355-360.
24. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health.* 1992;82:703-710.
25. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977.
26. Schreiber GB, Robins M, Maffeo CE, Masters MN, Bond AP, Morganstein D. Confounders contributing to the reported associations of coffee or caffeine with disease. *Prev Med.* 1988;17:295-309.
27. Amit Z, Weiss S, Smith BR, Markevitch S. Use of caffeine-based products and tobacco in relation to the consumption of alcohol: an examination of putative relationships in a group of alcoholics in Israel. *Eur Addict Res.* 2004;10:22-28.
28. Bisceglie AM, Rustgi V, Hoofnagle JH, Dusheiko GM, Lotze MT. Hepatocellular carcinoma. *Ann Intern Med.* 1988;108:390-401.
29. Kubo Shlonsky A, Klatsky AL, Armstrong MA. Traits of persons who drink decaffeinated coffee. *Ann Epidemiol.* 2003;13:273-279.
30. Ruhl CE, Everhart JE. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. *Gastroenterology.* 2005; 129:1928-1936.
31. National Coffee Association. *National Coffee Drinking Trends*. New York, NY: National Coffee Association of USA; 2000.
32. Spiller G, ed. *The Chemical Components of Coffee*. New York, NY: Alan R Liss; 1984.
33. Joeres R, Klinker H, Heusler H, Epping J, Zilly W, Richter E. Influence of smoking on caffeine elimination in healthy volunteers and in patients with alcoholic liver cirrhosis. *Hepatology.* 1988;8:575-579.
34. Midanik LT, Klatsky AL, Armstrong MA. Changes in drinking behavior: demographic, psychosocial, and biomedical factors. *Int J Addict.* 1990;25:599-619.