



# Association of Coffee Intake With Reduced Incidence of Liver Cancer and Death From Chronic Liver Disease in the US Multiethnic Cohort

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This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this exercise, the learner will be able to discuss the potential hepatoprotective effects of coffee consumption on liver disease.

**BACKGROUND & AIMS:** Coffee consumption has been proposed to reduce risk for hepatocellular carcinoma (HCC) and chronic liver disease (CLD), but few data are available from prospective, US multiethnic populations. We evaluated the association of coffee intake with HCC and CLD in 162,022 African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in the US Multiethnic Cohort (MEC). **METHODS:** We collected data from the MEC, a population-based prospective cohort study of >215,000 men and women from Hawaii and California, assembled in 1993–1996. Participants reported coffee consumption and other dietary and lifestyle factors when they joined the study. During an 18-year follow-up period, there were 451 incident cases of HCC and 654 deaths from CLD. Hazard rate ratios (RRs) and 95% confidence intervals (CIs) were calculated using Cox regression, adjusting for known HCC risk factors. **RESULTS:** High levels of coffee consumption were associated with reduced risk of incident HCC and CLD mortality ( $P_{\text{trend}} \leq .0002$ ). Compared with non-coffee drinkers, those who drank 2–3 cups per day had a 38% reduction in risk for HCC (RR = 0.62; 95% CI: 0.46–0.84); those who drank  $\geq 4$  cups per day had a 41% reduction in HCC risk (RR = 0.59; 95% CI: 0.35–0.99). Compared with non-coffee drinkers, participants who consumed 2–3 cups coffee per day had a 46% reduction in risk of death from CLD (RR = 0.54; 95% CI: 0.42–0.69) and those who drank  $\geq 4$  cups per day had a 71% reduction (RR = 0.29; 95% CI: 0.17–0.50). The inverse associations were similar regardless of the participants' ethnicity, sex, body mass index, smoking status, alcohol intake, or diabetes status. **CONCLUSIONS:** Increased coffee consumption reduces the risk of HCC and CLD in multiethnic US populations.

**Keywords:** Liver Cancer; Race; Protective; Epidemiology.

The incidence of hepatocellular carcinoma (HCC) in the United States has tripled in the past 3 decades.<sup>1</sup> The health impact of the increasing incidence of HCC is compounded by its dismal prognosis, with overall 5-year survival <12%.<sup>2</sup> Among all major cancers in the US, HCC has shown the greatest annual percent increase in mortality rate during 1975–2010.<sup>3</sup> In 2013, HCC was the 7<sup>th</sup> most

common cause of cancer mortality in the United States, accounting for >21,000 deaths.<sup>3</sup> Chronic liver disease (CLD) is a major source of morbidity and mortality<sup>4</sup>; >30 million Americans have CLD and approximately 31,000 people died from it each year.<sup>5</sup>

There are marked differences in HCC incidence by race/ethnicity. Asians/Pacific Islanders and Hispanics have the highest incidence rates, at 3-fold and 2-fold higher, respectively, compared with rates among non-Hispanic whites.<sup>6</sup> The rates for Hispanics and African Americans are also the fastest rising among all racial/ethnic groups.<sup>6,7</sup> Hispanics have a CLD rate that is twice that of the white population; they also have more aggressive patterns of disease and overall worse treatment outcomes.<sup>8</sup> In 2009, CLD was the third leading cause of death for Hispanic men, ages 55–64 years.<sup>5</sup>

Coffee is a commonly consumed beverage worldwide and it may have beneficial effects on the liver. Coffee consumption has been associated with reduced liver enzymes, including alanine aminotransferase, aspartate aminotransferase, and  $\gamma$ -glutamyltransferase.<sup>9–11</sup> Coffee intake has also been associated with lower severity of liver diseases and lower rates of liver disease progression.<sup>12–14</sup> Epidemiologic studies have suggested that coffee drinking is protective against HCC and CLD.<sup>15–21</sup> However, prospective data in the US minority populations (eg, African Americans, Hispanics, Asians) are nonexistent,<sup>16,19,21</sup> and it is unclear whether coffee is protective against HCC and CLD in these populations.

In this study, we conducted a prospective analysis to examine the association of coffee drinking with the risk of incident HCC and with CLD mortality in >160,000 African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites in the Multiethnic Cohort (MEC) study.

**Abbreviations used in this paper:** BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; MEC, Multiethnic Cohort; QFFQ, Quantitative Food Frequency Questionnaire; RR, hazard rate ratio.

## Materials and Methods

### Study Population

The MEC is an ongoing population-based prospective cohort study with >215,000 men and women from Hawaii and California (mainly Los Angeles County), assembled between 1993 and 1996. The MEC was established to study dietary, environmental, and genetic risk factors for cancer and other chronic diseases. The details of the study design and baseline characteristics have been published previously.<sup>22</sup> Briefly, the cohort is comprised predominantly of African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites (aged 45–75 years at recruitment). Potential participants were identified primarily through Department of Motor Vehicles drivers' license, voter registration lists, and Health Care Financing Administration data files. The response rates were highest in Japanese Americans (51.3%), whites (47.0%), and Native Hawaiians (42.2%), and lowest in African Americans (25.5%) and Latinos (21.3%). All participants returned a self-administered baseline questionnaire that obtained information on demographic and lifestyle factors, physical activity, tobacco smoking history, diet, anthropometric measures, personal history of medical conditions, medication use, family history of cancer, and reproductive history and hormone use (women only). Between 2001 and 2006, the MEC prospectively collected blood samples from >60,000 cohort participants. The Institutional Review Boards at the University of Hawaii and at the University of Southern California approved the study protocol.

Starting with 215,251 participants, we excluded from this analysis participants who were not from the 5 major ethnic groups (N = 13,988), reporting implausible diet based on macronutrient intakes<sup>23</sup> (n = 8257) or those with a cancer diagnosis before baseline (n = 19,385). We also excluded participants with missing baseline information on coffee intake (n = 6108) and other important covariates (eg, diabetes, education, body mass index, smoking status, and alcohol intake, n = 5491). As a result, data on 162,022 participants (24.6% whites, 16.1% African Americans, 7.4% Native Hawaiians, 29.6% Japanese Americans, and 22.3% Latinos) were available for this analysis. Excluded subjects were similar to those who remained in the analyses with respect to age and distribution of HCC risk factors.

### Exposure Ascertainment

Coffee intake and other dietary information were obtained using a Quantitative Food Frequency Questionnaire (QFFQ) designed for use in this multiethnic population.<sup>22</sup> A calibration study of the QFFQ was conducted using three 24-hour recalls from a random subsample of participants selected within sex-racial/ethnic groups and revealed a high correlation between the QFFQ and 24-hour recalls for energy-adjusted nutrients.<sup>24</sup> The median correlation coefficient for coffee intake as assessed by the QFFQ and the 24-hour recalls was 0.72. Within the baseline QFFQ, participants were asked to indicate the average number of cups of regular and decaffeinated coffee, green tea, and black tea consumed per day or per week in the previous year using 9 predefined categories: from never/hardly ever to 4 or more times daily. We used information from US Department of Agriculture food composition sources (<http://ndb.nal.usda.gov/>) to calculate caffeine content in coffee, tea, and other caffeine containing food items (eg, cola beverages,

chocolate, etc.). Total caffeine intake (mg/d) was estimated by summing caffeine from regular coffee (137 mg caffeine per cup), regular tea (47 mg caffeine per cup), colas and sodas (46 mg caffeine per can or bottle), chocolate (7 mg caffeine per serving), etc. The food composition tables were maintained by the University of Hawaii Cancer Center.<sup>22</sup> Data on potential confounders, such as education level, body mass index (BMI), diabetes, smoking status and alcohol intake, were obtained from the baseline questionnaire.

### End Point Ascertainment

Incident HCC cases (International Classification of Diseases for Oncology, version 3 topographic [C22.0] and morphology codes [8170–8175]) were identified through annual linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry; these cancer registries are part of the National Cancer Institute's Surveillance, Epidemiology and End Results Program. CLD deaths (International Classification of Disease, 9<sup>th</sup> ed code 571 and International Classification of Disease, 10<sup>th</sup> ed codes K70–K76) within the cohort were determined through annual linkage to state death certificate files in California and Hawaii, and periodic linkage to the National Death Index. The follow-up rate in the cohort was 95%; National Death Index information was available for the remaining 5% of the cohort. The majority of CLD deaths in the MEC (>77%) were listed as alcoholic-related diseases and fibrosis/cirrhosis of the liver. Participants who died from HCC were not included in the CLD mortality count as the incident cases were already counted and liver cancer as a death cause was often due to metastasis from another cancer site.

### Hepatitis B and C Serology

We conducted a nested case-control study of HCC and CLD deaths within the biospecimen subcohort for serological markers of hepatitis B and C infection in blood samples of 210 cases (137 HCC cases and 73 CLD deaths) and 423 controls. All incident cases of HCC and CLD deaths with a prediagnostic blood sample were eligible for this case-control study. For each case, 2 control subjects matched to the index case by sex, race/ethnicity, study area (Hawaii or California), and age at blood draw, were selected from the biospecimen subcohort. Controls also had to be free of HCC on the date of cancer diagnosis or CLD death of the index case. The presence of hepatitis B surface antigen, anti-hepatitis B core, and anti-hepatitis C virus (Architect Assays; Abbott Laboratories, North Chicago, IL) were tested blindly without regard to case-control status.

### Statistical Analysis

Regular coffee intake was categorized into: never, <1 cup daily, 1 cup daily, 2–3 cups daily, and ≥4 or more cups daily. Because of limited number of participants who drank decaffeinated coffee, it was categorized into never, ≤1 cup daily, and ≥2 or more cups daily. Caffeine intake (mg/d) was categorized using quartiles. Hazard rate ratios (RRs) and 95% confidence intervals (CIs) for HCC incidence and CLD deaths associated with coffee intake were calculated using Cox proportional hazard models. Age (in days) was used as the underlying time variable in the Cox regression starting with a participant's age at entry (baseline questionnaire completion) and ending with the earliest

of these end points: date of HCC diagnosis, date of death (from CLD or other causes for noncases), or end of follow-up. The end point ascertainment was complete through December 31, 2010 for cancer and December 31, 2012 for death, therefore, the end of follow-up was set to December 31, 2010 for HCC and December 31, 2012 for CLD analysis. Cox models were adjusted for sex and race/ethnicity (as strata variables) and education (high school graduate or less, some college, college graduate or more), BMI (<25 kg/m<sup>2</sup>, 25 to <30 kg/m<sup>2</sup>, ≥30 kg/m<sup>2</sup>), history of diabetes (yes, no), cigarette smoking status (never, former, current), and ethanol intake (0 g/d, <12 g/d, 12 to <24 g/d, ≥24 g/d). The proportional hazards assumption was tested by assessing the Schoenfeld residuals and no major violation was observed. The likelihood ratio test was used to assess statistical interaction between coffee intake with smoking status, alcohol drinking, BMI, diabetes, and hepatitis viral infection status with respect to HCC incidence or CLD mortality. The test compares models with the main effect only with models that also include interaction terms for variables of interest. All *P* values are 2-sided. Statistical analyses were performed with SAS 9.2 software (SAS Institute, Inc., Cary, NC).

## Results

After a median of 18 years of follow-up, a total of 451 incident cases of HCC (55 whites, 69 African Americans, 32 Native Hawaiians, 152 Japanese Americans, and 143 Latinos) and 654 CLD deaths (166 whites, 83 African Americans, 34 Native Hawaiians, 102 Japanese Americans, and 269 Latinos) were identified during the follow-up period among the 162,022 at-risk cohort participants (Table 1). The mean age of diagnosis for HCC was 71.7 years, ranging from 68.7 years in whites to 73.8 years in Japanese Americans. Latinos had the highest age-adjusted incidence rate of HCC across ethnic groups, followed by Native Hawaiians, Japanese Americans, African Americans, and whites. Compared with whites, the other ethnic groups had at least 2-fold higher risk of developing HCC. The mean age of CLD death was 70.7 years, ranging from 68.7 years in African Americans to 75.0 years in Japanese Americans. Latinos also had the highest rate of CLD mortality across

ethnic groups, while Japanese Americans had the lowest rate. Compared with whites, Latinos were 1.6 times more likely to die of CLD. The rates in African Americans and Native Hawaiians were similar to that of whites.

Coffee intake ranged from never/hardly ever to 4 or more cups per day, with the median intake of 1 cup per day. About 27% of the participants never/hardly ever drank coffee, 19% drank <1 cup per day, 28% drank 1 cup per day, 20% drank 2–3 cups per day, and 5% drank ≥4 cups per day (Table 2). High coffee consumption was associated with male sex, white ethnicity, higher education, current smoking status, lower BMI, nondiabetes status, and alcohol drinking (*P* < .0001). In the subset of participants with hepatitis B virus (HBV) and hepatitis C virus status, there was no difference in the levels of coffee consumption by viral hepatitis status (*P* = .78).

Table 3 shows the associations between coffee and caffeine intake and HCC incidence and CLD mortality. The risk for developing HCC decreased with increasing regular coffee (*P* trend = .0002), but not with decaffeinated coffee consumption (*P* trend = .20). Compared with non-coffee drinkers, individuals who consumed 1 cup, 2–3 cups, and ≥4 cups of coffee per day had a 13% (RR = 0.87; 95% CI: 0.67–1.11), a 38% (RR = 0.62; 95% CI: 0.46–0.84), and a 41% (RR = 0.59; 95% CI: 0.35–0.99) reduction in risk of HCC, respectively. Coffee intake was also associated with reduced risk of CLD death (*P* trend < .0001). Compared with nonconsumers, those who consumed 1 cup of coffee daily had a 15% reduction in risk of CLD death (RR = 0.85; 95% CI: 0.69–1.04), those who had 2–3 cups daily had a 46% reduction (RR = 0.54; 95% CI: 0.42–0.69), and those who had ≥4 cups daily had a 71% reduction (RR = 0.29; 95% CI: 0.17–0.50). Decaffeinated coffee intake was also inversely associated with CLD (*P* trend < .0001). The risk reductions for HCC and CLD associated with coffee drinking were similar between men and women (*P* interaction ≥ 0.34). Caffeine was associated with HCC and CLD in the age-, sex-, and ethnicity-adjusted models, but after regular coffee was included as a covariate, the association was no longer statistically significant. This was expected, as coffee

**Table 1.** Hepatocellular Carcinoma Incidence and Chronic Liver Disease Mortality Rates in the Multiethnic Cohort

|                                     | White       | African American | Native Hawaiian  | Japanese American | Latino           | All        |
|-------------------------------------|-------------|------------------|------------------|-------------------|------------------|------------|
| No. at risk participants            | 39,927      | 26,071           | 11,948           | 47,934            | 36,142           | 162,022    |
| No. hepatocellular carcinoma cases  | 55          | 69               | 32               | 152               | 143              | 451        |
| Age at diagnosis, y, mean (SD)      | 68.7 (8.1)  | 70.5 (9.0)       | 71.2 (8.5)       | 73.8 (8.0)        | 71.2 (7.0)       | 71.7 (8.1) |
| Incidence rates <sup>a</sup>        | 7.9         | 15.6             | 20.3             | 16.7              | 22.0             |            |
| Age-adjusted RR (95% CI)            | 1.00 (Ref)  | 2.04 (1.43–2.91) | 2.35 (1.52–3.63) | 2.09 (1.50–2.78)  | 2.57 (1.88–3.52) |            |
| No. of chronic liver disease deaths | 166         | 83               | 34               | 102               | 269              | 654        |
| Age at death, y, mean (SD)          | 70.1 (9.1)  | 68.7 (9.8)       | 68.9 (9.0)       | 75.0 (8.4)        | 70.2 (8.0)       | 70.7 (8.8) |
| Mortality rates <sup>a</sup>        | 23.8        | 19.6             | 20.2             | 9.8               | 38.5             |            |
| Age-adjusted RR (95% CI)            | 1.00 (ref.) | 0.78 (0.60–1.02) | 0.80 (0.55–1.16) | 0.47 (0.37–0.61)  | 1.62 (1.34–1.97) |            |

<sup>a</sup>Per 100,000 and age-adjusted to the US 2000 standard population.

**Table 2.** Baseline Characteristics of the at Risk Cohort Participants by Coffee Intake

| Characteristics <sup>a</sup>       | Regular coffee intake |      |                             |      |                            |      |                               |      |                            |      |
|------------------------------------|-----------------------|------|-----------------------------|------|----------------------------|------|-------------------------------|------|----------------------------|------|
|                                    | Never (n = 44,438)    |      | <1 Cup per day (n = 31,056) |      | 1 Cup per day (n = 45,717) |      | 2–3 Cups per day (n = 32,593) |      | ≥4 Cups per day (n = 8218) |      |
| Age at cohort entry, y, mean (SD)  | 59.5 (9.0)            |      | 59.1 (8.8)                  |      | 60.7 (8.7)                 |      | 58.1 (8.5)                    |      | 56.5 (8.0)                 |      |
|                                    | n                     | %    | n                           | %    | n                          | %    | n                             | %    | n                          | %    |
| Sex                                |                       |      |                             |      |                            |      |                               |      |                            |      |
| Male                               | 18,069                | 40.7 | 15,391                      | 49.6 | 21,009                     | 45.9 | 16,450                        | 50.5 | 4682                       | 57.0 |
| Female                             | 26,369                | 59.3 | 15,665                      | 50.4 | 24,708                     | 54.1 | 16,143                        | 49.5 | 3536                       | 43.0 |
| Race/ethnicity                     |                       |      |                             |      |                            |      |                               |      |                            |      |
| White                              | 11,094                | 25.0 | 5776                        | 18.6 | 9895                       | 21.6 | 9976                          | 30.6 | 3186                       | 38.8 |
| African American                   | 9453                  | 21.3 | 6033                        | 19.4 | 6809                       | 14.9 | 3195                          | 9.8  | 581                        | 7.1  |
| Native Hawaiian                    | 3689                  | 8.3  | 2537                        | 8.2  | 3211                       | 7.0  | 1983                          | 6.1  | 528                        | 6.4  |
| Japanese American                  | 11,459                | 25.8 | 9088                        | 29.3 | 14,757                     | 32.3 | 10,221                        | 31.4 | 2409                       | 29.3 |
| Latino                             | 8743                  | 19.7 | 7622                        | 24.5 | 11,045                     | 24.2 | 7218                          | 22.2 | 1514                       | 18.4 |
| Education                          |                       |      |                             |      |                            |      |                               |      |                            |      |
| High school graduate or less       | 18,403                | 41.4 | 14,060                      | 45.3 | 21,813                     | 47.7 | 12,359                        | 37.9 | 2909                       | 35.4 |
| Some college                       | 13,058                | 29.4 | 8950                        | 28.8 | 13,363                     | 29.2 | 10,283                        | 31.6 | 2638                       | 32.1 |
| College graduate or more           | 12,977                | 29.2 | 8046                        | 25.9 | 10,541                     | 23.1 | 9951                          | 30.5 | 2671                       | 32.5 |
| Smoking status                     |                       |      |                             |      |                            |      |                               |      |                            |      |
| Never                              | 23,746                | 53.4 | 14,765                      | 47.5 | 19,744                     | 43.2 | 11,287                        | 34.6 | 1685                       | 20.5 |
| Past                               | 16,314                | 36.7 | 12,073                      | 38.9 | 18,707                     | 40.9 | 14,056                        | 43.1 | 3139                       | 38.2 |
| Current                            | 4378                  | 9.9  | 4218                        | 13.6 | 7266                       | 15.9 | 7250                          | 22.2 | 3394                       | 41.3 |
| Body mass index, kg/m <sup>2</sup> |                       |      |                             |      |                            |      |                               |      |                            |      |
| <25                                | 18,790                | 42.3 | 11,791                      | 38.0 | 19,433                     | 42.5 | 13,786                        | 42.3 | 3532                       | 43.0 |
| 25 to <30                          | 16,267                | 36.6 | 12,278                      | 39.5 | 17,788                     | 38.9 | 12,980                        | 39.8 | 3247                       | 39.5 |
| ≥30                                | 9381                  | 21.1 | 6987                        | 22.5 | 8496                       | 18.6 | 5827                          | 17.9 | 1439                       | 17.5 |
| Diabetes                           |                       |      |                             |      |                            |      |                               |      |                            |      |
| No                                 | 38,795                | 87.3 | 27,308                      | 87.9 | 40,606                     | 88.8 | 29,545                        | 90.6 | 7546                       | 91.8 |
| Yes                                | 5643                  | 12.7 | 3748                        | 12.1 | 5111                       | 11.2 | 3048                          | 9.4  | 672                        | 8.2  |
| Alcohol, g/d                       |                       |      |                             |      |                            |      |                               |      |                            |      |
| None                               | 27,308                | 61.5 | 15,020                      | 48.4 | 21,138                     | 46.2 | 13,915                        | 42.7 | 3745                       | 45.6 |
| <12                                | 11,259                | 25.3 | 10,601                      | 34.1 | 14,211                     | 31.1 | 10,978                        | 33.7 | 2530                       | 30.8 |
| 12 to <24                          | 2398                  | 5.4  | 2359                        | 7.6  | 3782                       | 8.3  | 3146                          | 9.6  | 716                        | 8.7  |
| ≥24                                | 3473                  | 7.8  | 3076                        | 9.9  | 6586                       | 14.4 | 4554                          | 14.0 | 1227                       | 14.9 |
| Hepatitis B or C <sup>b</sup>      |                       |      |                             |      |                            |      |                               |      |                            |      |
| No                                 | 125                   | 80.1 | 87                          | 75.0 | 171                        | 79.9 | 88                            | 81.5 | 21                         | 77.8 |
| Yes                                | 31                    | 19.9 | 29                          | 25.0 | 43                         | 20.1 | 20                            | 18.5 | 6                          | 22.2 |

<sup>a</sup>All characteristics were significantly different at  $P < .0001$  across coffee intake categories, except for the hepatitis B or C viral infection ( $P = .78$ ), as tested by 2-sided  $\chi^2$  test for categorical measures.

<sup>b</sup>Based on the MEC subcohort case-control samples.

**Table 3.** Association of Coffee and Caffeine Intake With Hepatocellular Carcinoma Incidence and Chronic Liver Disease Mortality in the Multiethnic Cohort

|                                    | No. of cases | Person years | RR <sup>a</sup> (95% CI) | RR <sup>b</sup> (95% CI) |
|------------------------------------|--------------|--------------|--------------------------|--------------------------|
| Hepatocellular carcinoma           |              |              |                          |                          |
| Regular coffee, cups/d             |              |              |                          |                          |
| Never                              | 119          | 665,161      | 1.00 (Ref)               | 1.00 (Ref)               |
| <1                                 | 111          | 466,122      | 1.18 (0.91–1.53)         | 1.14 (0.88–1.48)         |
| 1                                  | 137          | 683,898      | 0.97 (0.76–1.24)         | 0.87 (0.67–1.11)         |
| 2–3                                | 67           | 499,003      | 0.73 (0.54–0.99)         | 0.62 (0.46–0.84)         |
| ≥4                                 | 17           | 125,473      | 0.81 (0.48–1.34)         | 0.59 (0.35–0.99)         |
| <i>P</i> trend                     |              |              | .03                      | .0002                    |
| Decaffeinated coffee, cups/d       |              |              |                          |                          |
| Never                              | 287          | 1,517,706    | 1.00 (Ref)               | 1.00 (Ref)               |
| ≤1                                 | 128          | 706,852      | 0.93 (0.75–1.14)         | 0.87 (0.70–1.08)         |
| ≥2                                 | 21           | 113,110      | 0.96 (0.62–1.50)         | 0.86 (0.55–1.34)         |
| <i>P</i> trend                     |              |              | .54                      | .20                      |
| Quartiles of caffeine intake, mg/d |              |              |                          |                          |
| 0 to <51.76                        | 113          | 604,036      | 1.00 (Ref)               | 1.00 (Ref)               |
| 51.76 to <140.37                   | 137          | 606,866      | 1.16 (0.91–1.49)         | 1.04 (0.78–1.39)         |
| 140.37 to <326.15                  | 118          | 608,780      | 0.99 (0.76–1.29)         | 0.92 (0.64–1.32)         |
| ≥326.15                            | 83           | 619,975      | 0.76 (0.57–1.02)         | 0.72 (0.36–1.44)         |
| <i>P</i> trend                     |              |              | .04                      | .45                      |
| Chronic liver disease              |              |              |                          |                          |
| Regular coffee, cups/d             |              |              |                          |                          |
| Never                              | 184          | 714,697      | 1.00 (Ref)               | 1.00 (Ref)               |
| <1                                 | 163          | 501,530      | 1.20 (0.97–1.48)         | 1.14 (0.92–1.41)         |
| 1                                  | 202          | 733,422      | 0.99 (0.81–1.21)         | 0.85 (0.69–1.04)         |
| 2–3                                | 91           | 535,769      | 0.64 (0.49–0.82)         | 0.54 (0.42–0.69)         |
| ≥4                                 | 14           | 134,527      | 0.40 (0.23–0.70)         | 0.29 (0.17–0.50)         |
| <i>P</i> trend                     |              |              | <.0001                   | <.0001                   |
| Decaffeinated coffee, cups/d       |              |              |                          |                          |
| Never                              | 441          | 1,628,980    | 1.00 (Ref)               | 1.00 (Ref)               |
| ≤1                                 | 156          | 759,666      | 0.74 (0.62–0.89)         | 0.71 (0.59–0.85)         |
| ≥2                                 | 21           | 121,735      | 0.58 (0.37–0.90)         | 0.54 (0.35–0.85)         |
| <i>P</i> trend                     |              |              | .0001                    | <.0001                   |
| Quartiles of caffeine intake, mg/d |              |              |                          |                          |
| 0 to <51.76                        | 165          | 648,897      | 1.00 (Ref)               | 1.00 (Ref)               |
| 51.76 to <140.37                   | 209          | 651,811      | 1.20 (0.98–1.48)         | 1.09 (0.87–1.38)         |
| 140.37 to <326.15                  | 172          | 653,736      | 0.98 (0.79–1.21)         | 0.95 (0.71–1.27)         |
| ≥326.15                            | 108          | 665,501      | 0.63 (0.49–0.81)         | 0.98 (0.57–1.67)         |
| <i>P</i> trend                     |              |              | <.0001                   | .72                      |

<sup>a</sup>Adjusted for age, sex, and race/ethnicity.

<sup>b</sup>Further adjusted for education (high school graduate or less, some college, college graduate or more), BMI (<25, 25 to <30, ≥30 kg/m<sup>2</sup>), alcohol intake (0, <12, 12 to <24, ≥24 ethanol g/d), smoking status (never, former, current), and diabetes (no/yes). For decaffeinated coffee and caffeine intake, additionally adjusted for regular coffee intake (Never, <1 cup/day, 1 cup/day, 2–3 cups/day, ≥4 cups/day).

and caffeine were highly correlated. Intakes of other caffeine-containing beverages, such as green and black tea, were not associated with HCC incidence or CLD mortality (data not shown).

The associations between coffee and HCC incidence and CLD death by race/ethnicity are presented in Table 4. Increasing coffee intake, particularly ≥2 cups per day, was associated with reduced HCC incidence and CLD mortality in most ethnic groups, with no significant heterogeneity observed (*P* interaction ≥ .35).

We conducted a sensitivity analysis by excluding HCC cases (*n* = 45) or CLD deaths (*n* = 75) occurring within 2 years after cohort entry. The inverse associations between coffee intake and risk of incident HCC (*P* trend = .002) and CLD death (*P* trend < .0001) remained statistically

significant. Compared with participants who did not drink coffee, those who drank ≥2 cups daily had a 33% reduction in risk of HCC (RR = 0.67; 95% CI: 0.49–0.90) and a 46% reduction in risk of CLD death (RR = 0.54; 95% CI: 0.42–0.69).

We also examined whether associations of coffee intake with incident HCC and CLD mortality varied by known risk factors, and found no significant interaction between coffee intake and smoking status, alcohol intake, diabetes, and hepatitis viral infection status for CLD and HCC (all *P*s for interaction ≥ .11).

## Discussion

In this prospective cohort of multiethnic US populations, we found that increasing coffee consumption was



**Table 4.** Association of Regular Coffee Intake With Hepatocellular Carcinoma Incidence and Chronic Liver Disease Mortality by Race/Ethnicity

| Coffee intake, cups/d           | White |                          | African American |                          | Native Hawaiian |                          | Japanese American |                          | Latino |                          | P heterogeneity |
|---------------------------------|-------|--------------------------|------------------|--------------------------|-----------------|--------------------------|-------------------|--------------------------|--------|--------------------------|-----------------|
|                                 | Cases | RR <sup>a</sup> (95% CI) | Cases            | RR <sup>a</sup> (95% CI) | Cases           | RR <sup>a</sup> (95% CI) | Cases             | RR <sup>a</sup> (95% CI) | Cases  | RR <sup>a</sup> (95% CI) |                 |
| <b>Hepatocellular carcinoma</b> |       |                          |                  |                          |                 |                          |                   |                          |        |                          |                 |
| Never                           | 18    | 1.00 (Ref)               | 18               | 1.00 (Ref)               | 10              | 1.00 (Ref)               | 41                | 1.00 (Ref)               | 32     | 1.00 (Ref)               | .63             |
| <1                              | 11    | 0.98 (0.46–2.09)         | 22               | 1.54 (0.82–2.89)         | 7               | 0.89 (0.34–2.37)         | 36                | 1.04 (0.66–1.63)         | 35     | 1.18 (0.73–1.91)         |                 |
| 1                               | 15    | 0.77 (0.38–1.55)         | 18               | 1.06 (0.55–2.05)         | 13              | 0.98 (0.42–2.30)         | 49                | 0.76 (0.50–1.16)         | 42     | 0.90 (0.57–1.44)         |                 |
| >2                              | 11    | 0.36 (0.17–0.77)         | 11               | 1.03 (0.48–2.20)         | 2               | 0.19 (0.04–0.87)         | 26                | 0.51 (0.31–0.84)         | 34     | 0.90 (0.55–1.47)         |                 |
| P trend                         |       | .008                     |                  | .86                      |                 | .07                      |                   | .004                     |        | .44                      |                 |
| <b>Chronic liver disease</b>    |       |                          |                  |                          |                 |                          |                   |                          |        |                          |                 |
| Never                           | 55    | 1.00 (Ref)               | 28               | 1.00 (Ref)               | 8               | 1.00 (Ref)               | 24                | 1.00 (Ref)               | 69     | 1.00 (Ref)               | .35             |
| <1                              | 33    | 0.98 (0.64–1.52)         | 23               | 1.13 (0.65–1.98)         | 8               | 1.27 (0.47–3.41)         | 21                | 1.09 (0.60–1.96)         | 78     | 1.25 (0.90–1.73)         |                 |
| 1                               | 38    | 0.57 (0.37–0.87)         | 27               | 1.09 (0.64–1.86)         | 13              | 1.39 (0.56–3.44)         | 40                | 1.05 (0.63–1.76)         | 84     | 0.85 (0.62–1.17)         |                 |
| >2                              | 40    | 0.45 (0.30, 0.68)        | 5                | 0.32 (0.12–0.84)         | 5               | 0.73 (0.23–2.29)         | 17                | 0.58 (0.30–1.09)         | 38     | 0.47 (0.31–0.70)         |                 |
| P trend                         |       | <.0001                   |                  | .09                      |                 | .78                      |                   | .14                      |        | <.0001                   |                 |

<sup>a</sup>Adjusted for age, sex, education (high school graduate or less, some college, college graduate or more), BMI (<25, 25 to <30, ≥ 30 kg/m<sup>2</sup>), alcohol intake (0, <12, 12 to <24, ≥24 ethanol g/day), smoking status (never, former, current), and diabetes (no/yes).

associated, in a dose-dependent manner, with lower risks of incident HCC and mortality from CLD. Compared with individuals who did not drink coffee, those who drank 2–3 cups per day had a 38% reduction in risk of HCC and a 46% reduction in risk of CLD death, and those who drank ≥4 cups per day had a 41% reduction in risk of HCC and a 71% reduction in risk of CLD death. Although the numbers of cases in certain ethnic groups were small, the protective association was consistent across ethnic groups. In addition, the inverse association was observed across different categories of known HCC risk factors (ie, smoking, alcohol drinking, BMI, diabetes).

Our study is the first prospective analysis of coffee consumption and HCC risk in multiple US racial/ethnic populations. Our results are consistent with previous studies showing inverse associations between coffee intake and HCC<sup>15,17,19</sup> and CLD<sup>17,18,25</sup> and further support the hypothesis that coffee may protect against the development of CLD and HCC. The exact mechanisms by which coffee exerts its protective effects on the liver are unknown. Coffee has been associated with lower liver enzymes<sup>9–11</sup> and slower progression of liver diseases.<sup>12–14</sup> Coffee has also been inversely associated with diabetes,<sup>26,27</sup> a risk factor for HCC<sup>28</sup> and other liver diseases,<sup>29</sup> suggesting that coffee may be beneficial to the liver by reducing insulin resistance and improving glucose metabolism.<sup>26</sup> Further adjustment for diabetes in our study, however, had little effect on the coffee–HCC association.

There are thousands of compounds in coffee, including caffeine, diterpenes, potassium, niacin, magnesium, and the antioxidants chlorogenic acids and tocopherols.<sup>30</sup> The most studied coffee constituents in relation to liver function and health are caffeine, diterpenes (eg, cafestol and kahweol), and chlorogenic acids.<sup>30</sup> The potential chemopreventive effects and molecular mechanisms of these bioactive compounds against cancers and liver diseases have been discussed in detail in previous studies.<sup>16,30,31</sup> Which coffee constituents are hepatoprotective, however, remain elusive.

Our study has several strengths and limitations. The strengths include its prospective design, which minimizes temporal ambiguity and excludes the possibility of recall bias, long follow-up time, which permits lag-time analysis to assess reverse causality, multiethnic and large sample size, and comprehensive baseline risk factor data, which allow for confounder adjustment in the analysis. The limitations include coffee intake assessment by self-report at baseline that might not reflect long-term pattern of consumption. Among the participants who responded to the follow-up questionnaire administered between 2003 and 2008 and reported coffee consumption (N = 87,387), the intraclass correlation coefficient between the baseline and the follow-up questionnaires was 0.60. This imperfect correlation reflects potential exposure misclassification due to measurement error, which might have attenuated the observed associations. Another limitation is the lack of information on liver disease other than HCC at baseline. The observed inverse associations,

however, remained after lag analyses suggesting that reverse causality was an unlikely explanation for our findings. Low recruitment rates in some of the MEC ethnic groups may affect the generalizability of our results to the general population. As previously shown, however, the distribution of education level in our cohort generally resembles those reported by the US census in Hawaii and Los Angeles County for the same ethnic and age groups<sup>22</sup>; we believe that findings from this cohort are broadly generalizable. Finally, baseline data on HBV and hepatitis C virus status were unavailable for most cohort participants; consequently, we were unable to adjust for any effect of viral hepatitis on the association between coffee and HCC/CLD. However, in the subset of MEC participants with HBV and hepatitis C virus information, there was no difference in the levels of coffee consumption by viral hepatitis status.

In summary, this large prospective cohort study showed that coffee consumption reduces the risk of developing HCC and mortality from CLD in African Americans, Japanese Americans, Native Hawaiians, Latinos, and whites. Additional studies are warranted to clarify the protective role of specific constituents in coffee in the development of liver disease and its related mortality.

## References

1. **Altekruse SF, McGlynn KA, Reichman ME.** Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009;27:1485–1491.
2. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol* 2013;47(Suppl):S2–S6.
3. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2010, National Cancer Institute. Bethesda, MD. Available at: [http://seer.cancer.gov/csr/1975\\_2010/](http://seer.cancer.gov/csr/1975_2010/), based on November 2012 SEER data submission, posted to the SEER website, April 2013.
4. Kemmer N, Neff GW. Ethnic variations in chronic liver diseases. *Dig Dis Sci* 2008;53:1339–1344.
5. Heron M. Deaths: leading causes for 2010. *Natl Vital Stat Rep* 2013;62:1–96.
6. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: Where are we? Where do we go? *Hepatology* 2014;60:1767–1775.
7. El-Serag HB, Lau M, Eschbach K, et al. Epidemiology of hepatocellular carcinoma in Hispanics in the United States. *Arch Intern Med* 2007;167:1983–1989.
8. Carrion AF, Ghanta R, Carrasquillo O, et al. Chronic liver disease in the Hispanic population of the United States. *Clin Gastroenterol Hepatol* 2011;9:834–841; quiz e109–e110.
9. Klatsky AL, Morton C, Udaltsova N, et al. Coffee, cirrhosis, and transaminase enzymes. *Arch Intern Med* 2006;166:1190–1195.
10. Nakanishi N, Nakamura K, Nakajima K, et al. Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men. *Eur J Epidemiol* 2000;16:419–423.
11. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2005;128:24–32.
12. Molloy JW, Calcagno CJ, Williams CD, et al. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology* 2012;55:429–436.
13. **Modi AA, Feld JJ,** Park Y, et al. Increased caffeine consumption is associated with reduced hepatic fibrosis. *Hepatology* 2010;51:201–209.
14. Freedman ND, Everhart JE, Lindsay KL, et al. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology* 2009;50:1360–1369.
15. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology* 2007;132:1740–1745.
16. Saab S, Mallam D, Cox GA 2nd, et al. Impact of coffee on liver diseases: a systematic review. *Liver Int* 2014;34:495–504.
17. Lai GY, Weinstein SJ, Albanes D, et al. The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers. *Br J Cancer* 2013;109:1344–1351.
18. 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.
19. Bravi F, Bosetti C, Tavani A, et al. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol* 2013;11:1413–1421 e1.
20. Goh GB, Chow WC, Wang R, et al. Coffee, alcohol and other beverages in relation to cirrhosis mortality: The Singapore Chinese Health Study. *Hepatology* 2014;60:661–669.
21. Sang LX, Chang B, Li XH, et al. Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. *BMC Gastroenterol* 2013;13:34.
22. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol* 2000;151:346–357.
23. Nothlings U, Murphy SP, Wilkens LR, et al. Flavonols and pancreatic cancer risk: the multiethnic cohort study. *Am J Epidemiol* 2007;166:924–931.
24. Stram DO, Hankin JH, Wilkens LR, et al. Calibration of the dietary questionnaire for a multiethnic cohort in Hawaii and Los Angeles. *Am J Epidemiol* 2000;151:358–370.
25. Tverdal A, Skurtveit S. Coffee intake and mortality from liver cirrhosis. *Ann Epidemiol* 2003;13:419–423.
26. Ding M, Bhupathiraju SN, Chen M, et al. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. *Diabetes Care* 2014;37:569–586.
27. Huxley R, Lee CM, Barzi F, et al. Coffee, decaffeinated coffee, and tea consumption in relation to incident type 2 diabetes mellitus: a systematic review with meta-analysis. *Arch Intern Med* 2009;169:2053–2063.

28. Wang P, Kang D, Cao W, et al. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2012; 28:109–122.
29. Picardi A, D'Avola D, Gentilucci UV, et al. Diabetes in chronic liver disease: from old concepts to new evidence. *Diabetes Metab Res Rev* 2006;22: 274–283.
30. Torres DM, Harrison SA. Is it time to write a prescription for coffee? Coffee and liver disease. *Gastroenterology* 2013;144:670–672.
31. Bohn SK, Blomhoff R, Paur I. Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. *Mol Nutr Food Res* 2014;58: 915–930.

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**Conflicts of interest**

The authors disclose no conflicts.

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