Racial and Ethnic Differences in Alcohol-Associated Aspartate Aminotransferase and γ-Glutamyltransferase Elevation

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Background: Recent analyses have confirmed that Hispanic and black non-Hispanic Americans are at an increased risk for death from liver cirrhosis. The reasons for this are unknown. As a common cause of cirrhosis, differing sensitivities to alcohol-related hepatocellular injury may play a role. This study compared racial and ethnic aspartate aminotransferase and γ-glutamyltransferase level elevations within alcohol-drinking categories.

Methods: A cross-sectional analysis of adult subjects from the Third National Health and Nutrition Examination Survey. Logistic regression models were used to estimate the risk for elevation of aspartate aminotransferase and γ-glutamyltransferase levels among Mexican American and black non-Hispanic subjects compared with white non-Hispanic Americans within categories of alcohol use. Adjustment was made for age, sex, exposure to hepatitis C and B, and body mass index.

Results: Among current drinkers, black non-Hispanic and Mexican Americans were more likely to have a 2-fold elevation in aspartate aminotransferase levels when compared with white non-Hispanic Americans. This was most pronounced in the highest-frequency drinkers (Mexican Americans: odds ratio, 9.1 [95% confidence interval, 3.9-21.0]; and black non-Hispanic Americans: odds ratio, 3.1 [95% confidence interval, 1.4-6.8]). No racial and ethnic differences were apparent among current abstainers. A similar pattern was found for 2-fold γ-glutamyltransferase level elevations.

Conclusions: Among current drinkers, Mexican and black non-Hispanic Americans may have an increased risk for hepatocellular injury. These results require confirmation in other study populations for whom validated measures of quantity and pattern of drinking exist.

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Recent analyses of death certificate data have demonstrated that age-adjusted cirrhosis-related mortality is higher in Hispanic and black non-Hispanic Americans compared with white non-Hispanic Americans. The reason for this is not known, and may include differences in alcohol consumption, differences in access to care, or other causes. However, to significantly influence population-based estimates for death rates, the cause or causes must be prevalent in the population. The most common causative agent is alcohol, but reliable data from the National Longitudinal Alcohol Epidemiologic Study have demonstrated that the prevalence of heavy drinking in the population is similar among various racial and ethnic groups. If alcohol were a cause of the observed differences in cirrhosis-related mortality, then alcohol use would have to represent a higher risk for cirrhosis in Hispanic and black non-Hispanic Americans. This study estimates the potential contribution of alcohol sensitivity to cirrhosis-related mortality disparities by evaluating racial and ethnic differences in the likelihood of hepatocellular injury associated with various levels of alcohol use. Aspartate aminotransferase (AST) was chosen as the primary marker for hepatocellular injury because it is relatively more specific than other liver enzymes for detecting alcohol-induced hepatocyte necrosis. A γ-glutamyltransferase (GGT) was also analyzed as an additional marker for alcohol-induced hepatotoxicity. If racial and ethnic differences exist, sensitivity to the hepatotoxic effects of alcohol would be supported as a possible independent contributor to cirrhosis-related mortality disparities.

Participants and Methods
This study was an analysis of survey data from the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was conducted by the National Center for Health Statistics in 2 phases, from October 18, 1988, through October 24, 1991, and from September 20, 1991, through October 15, 1994.
Data were collected during several sessions, including interview, examination, and laboratory components. The complex sampling design allows estimates for the noninstitutionalized, civilian, US population and for white non-Hispanic, black non-Hispanic, and Mexican Americans. Full details of the NHANES III design have been discussed elsewhere. For the AST analysis, subjects were restricted to adults (aged ≥17 years) for whom alcohol use data, AST measurement, and covariate data were available. The final sample size was 15774 persons. The GGT measurement was initiated in the later stages of NHANES III, and the sample size for this analysis was smaller as a result (n = 12288).

The outcome of primary interest was the probability of having an elevated AST level. This was defined as greater than the race- and ethnicity-adjusted 95th percentile, and greater than 2 times the adjusted 95th percentile. The 2-fold elevation was chosen because this would likely correlate more strongly with hepatic inflammation, whereas the 95th percentile cutoff may overemphasize clinically insignificant differences in race- and ethnicity-specific alcohol and AST associations. Separate analyses were conducted for each definition of AST elevation. Adjusting the 95th percentile for race and ethnicity was necessary, because black non-Hispanic, white non-Hispanic, and Mexican Americans had significantly different AST distributions (by 1-way analysis of variance on the normally distributed natural logarithm of AST). These different distributions have been detected in other study populations. Mean differences, however, were quite small (1-2 U/L after exponentiation of the mean logarithm values). The 95th percentile values were determined in the unweighted samples, because the weighting is intended to estimate means rather than medians. These differed more substantially (34, 41, and 46 U/L for white non-Hispanic, black non-Hispanic, and Mexican Americans, respectively). This may merely reflect different sample sizes, which were smaller for black non-Hispanic Americans (n = 4261) and Mexican Americans (n = 4419) than for white non-Hispanic Americans (n = 6471) (the remaining 623 subjects were members of other ethnic groups for whom results are not reported because of small sample sizes). Subjects were classified as having an elevated AST level if their measured levels were greater than 1 and 2 times their specific racial and ethnic group 95th percentiles, respectively.

The main predictor for AST elevation was race and ethnicity, and analyses were stratified by alcohol use categories. Adjustment was made for age, sex, hepatitis C antibody positivity, hepatitis B surface antigen positivity, and body mass index. Racial and ethnic groups included black non-Hispanic, Mexican, and white non-Hispanic Americans. For all risk estimates, the white non-Hispanic group was used as a reference. Alcohol use categories were frequency measures determined from a simple summation from the response to 3 questions in the NHANES III household interview. These questions determined how many times in the past 30 days the following had been consumed: (1) beer or lite beer; (2) wine, wine coolers, sangria, or champagne; and (3) hard liquor, such as tequila, gin, vodka, scotch, rum, whiskey, and liqueurs. To make population estimates for categories of alcohol use, several classifications were constructed. These included abstainers and frequencies of 1 to 9, 10 to 29, and 30 or greater drinking episodes. Age and body mass index (calculated as the weight in kilograms divided by the square of height in meters) were approximately normally distributed and were included as continuous variables. Hepatitis C antibody and hepatitis B surface antigen were considered positive for positive and indeterminate results.

Multivariate logistic regression models were analyzed to provide odds ratios (ORs) for AST level elevation for the racial and ethnic groups, adjusting for the remaining covariates. Analyses were stratified by alcohol use category. Interactions of race and ethnicity with the remaining covariates were analyzed and were largely insignificant (race and ethnicity with sex, P = .95; race and ethnicity with body mass index, P = .39; and race and ethnicity with hepatitis C antibody, P = .86). The exception was the interaction of race and ethnicity with hepatitis B surface antigen (P = .01). On closer inspection, this was because few Mexican Americans were positive for the hepatitis B surface antigen, none of whom had a 2-fold AST level elevation. This interaction was not included in the analyses.

An AST level elevation is not a specific marker for alcohol-induced hepatitis. However, more specific markers, such as the AST–alanine aminotransferase ratio, would not be sufficiently sensitive for use in this population-based sample. For example, of 15774 subjects, only 24 had an alanine aminotransferase level greater than the 95th percentile coupled with an AST–alanine aminotransferase ratio of at least 2. To provide additional epidemiologic evidence for or against racial and ethnic differences in sensitivity to the hepatotoxic effects of alcohol, an additional analysis was performed on the odds for a 2-fold or greater elevation in GGT level. For the overall sample, a wide racial and ethnic variation in the distribution of GGT levels was found (95th percentile: 68 U/L in white non-Hispanic Americans, 94 U/L in Mexican Americans, and 107 U/L in black non-Hispanic Americans). Because of this large variation, GGT elevation was not adjusted for racial and ethnic differences in enzyme distribution, and was defined as a level of 2 times the overall population 95th percentile. The 95th percentile was equal to 88 U/L. While this decision increased the overall probability for a GGT elevation among non-Hispanic black and Mexican Americans, the pattern of GGT elevation within alcohol strata was of greater interest than the actual magnitude of the increased risk. A pattern of increasing risk for black non-Hispanic and Mexican Americans in more frequent drinking strata would support the hypothesis of racial and ethnic differences in alcohol sensitivity, and the absence of such a pattern would provide evidence against differences in hepatic sensitivity to alcohol. The GGT level was not measured at the start of NHANES III, and was only available for a portion of the adult population. This incomplete sampling resulted in multiple NHANES III strata containing data on GGT from only one primary sampling unit. To complete the analysis, the first observations from such strata were collapsed into a second primary sampling unit. For this reason, the confidence intervals resulting from the GGT analysis may not accurately reflect the range of possible values in the population, and should be considered exploratory. The point estimates, however, were valid for the US population. Logistic regression was used to measure ORs for elevated GGT level using the same approach and same covariates as described for AST level elevation.

Intercooled Stata, version 7 (Stata Corp, College Station, Tex), was used for all analyses, with appropriate person-level weighting and adjustment for the complex survey design.

Sample characteristics from the analysis of AST differences are listed in Table 1. Demographically, white non-Hispanic subjects were older and Mexican Americans had a slightly higher proportion of men. Racial and ethnic representation within the various drinking categories differed statistically but was clinically similar, although among current drinkers, Mexican Americans were somewhat less likely to drink frequently.

The results of the stratified regression analyses for AST differences are shown in Table 2. The ORs for AST level at the 95th percentile or greater were not signifi-
Results for the GGT analysis are shown in Table 3. Similar to the AST analysis, this also demonstrated increased risks for 2-fold GGT level elevation for Mexican Americans and black non-Hispanic Americans compared with white non-Hispanic Americans among current drinkers. The relative risk increased with increasing frequency of alcohol consumption. No increased risk was seen among abstainers. This result was surprising because of the operationalization of elevated GGT level as 2 times the overall sample 95th percentile, an approach that was anticipated to result in elevated odds for black non-Hispanic and Mexican Americans regardless of drinking status. This suggests that the differences in enzyme distribution for the overall sample are due to or strongly associated with alcohol use. As a consequence of the partial sampling of GGT in NHANES III and the analysis method, the confidence intervals provided in the table should be regarded as exploratory rather than firm and the statistical significance of the GGT differences is difficult to comment on.

*Data are given as odds ratio (95% confidence interval). The odds ratios are adjusted for age, sex, hepatitis C antibody positivity, hepatitis B surface antigen positivity, and body mass index. AST indicates aspartate aminotransferase.
†Based on the number of drinking episodes in the past 30 days.
‡Reference.
This study evaluated racial and ethnic differences in the probability of AST and GGT level elevations in the US population stratified by categories of alcohol use. The results suggest that among current drinkers, Mexican Americans and black non-Hispanic Americans may have a higher risk for hepatocellular injury when compared with white non-Hispanic Americans who drink a similar amount of alcohol. This pattern is consistent with the observed racial and ethnic differences in liver cirrhosis–related mortality in the United States.

The hypothesis that the same degree of alcohol consumption may carry a higher risk for liver injury based on an individual's racial and ethnic heritage is not new, and may be due to genetic determinants. Such a possibility is consistent with many findings regarding genetically determined susceptibility to alcohol-related morbidity and cardiovascular benefits. A recent report, for example, has demonstrated that genetic differences in alcohol dehydrogenase and aldehyde dehydrogenase levels were associated with different patterns of liver injury, pancreatitis, and esophageal cancer susceptibility. Other studies have associated alcoholic cirrhosis with HLA subtypes and protection from myocardial infarction with alcohol dehydrogenase polymorphisms.

A comparison of Japanese and US persons who abuse alcohol demonstrated different susceptibilities to liver injury. Racial differences in alcohol-associated AST levels may be due to variations in alcohol dehydrogenase, acetaldehyde dehydrogenase, or other enzymes for which race serves as a marker. Alcohol dehydrogenase and acetaldehyde dehydrogenase polymorphisms differ between black non-Hispanic and white non-Hispanic Americans; however, Mexican Americans have not been similarly examined. From an ethnic perspective, environmental factors such as diet or other culturally shared exposures might also contribute to differences in sensitivities to alcohol toxicity.

Several limitations of this analysis need to be addressed. The point estimates for 2-fold enzyme elevations have fairly wide confidence intervals. Although the estimated ORs suggest racial and ethnic differences, the true magnitude may be negligible or large. An additional limitation is the nature of the alcohol measure. This is a frequency measure rather than a quantity measure, because the serving size was not estimated. While frequency is likely correlated with quantity, it is possible that the average quantity consumed per drinking episode differs between racial and ethnic groups. If this were true, the OR estimates would be biased. The pattern of drinking is also not accurately measured. If drinking pattern affects the risk of disease and systematically differed between racial and ethnic groups, the OR estimates may again be biased. An additional source of error may lie in the differing baseline AST distributions among the groups. While statistically significant, this may not be clinically significant, amounting to mean differences of 1 to 2 U/L. The 95th percentiles differed by up to 12 U/L, which may merely reflect sample size differences between the racial and ethnic groups rather than the true distributions. If this were the case, this analysis would underestimate the ORs by erroneously assigning higher values for elevated AST level to black non-Hispanic and Mexican Americans. The GGT distributions were also higher in black non-Hispanic and Mexican Americans compared with white non-Hispanic Americans. This may have contributed to the higher odds for 2-fold GGT elevations through another mechanism, but the absence of increased risk among abstainers and the increasing odds among more frequent drinkers suggest that alcohol contributes to these differences. Finally, as with any cross-sectional study, confounding from unmeasured factors is possible. The frequency of alcohol use may be serving as a marker for an associated, but independent, cause of enzyme elevation.

In conclusion, this study supports the hypothesis that, on average, Mexican and black non-Hispanic Americans may be more susceptible to alcohol-induced hepatocellular injury than white non-Hispanic Americans. Because frequent alcohol use is prevalent in the United States, such racial and ethnic differences may contribute to disparities in cirrhosis-related mortality rates. Findings from this study require duplication in additional study populations, preferably with valid measurement of quantity and pattern of consumption.

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REFERENCES