The Epidemiology of Cirrhosis in the United States
A Population-based Study

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Background and Aims: Liver cirrhosis is an important public health concern in the United States and a significant source of morbidity and mortality. However, the epidemiology of cirrhosis is incompletely understood. The aims of this study were to estimate the prevalence of cirrhosis in the general US population, determine characteristics of affected Americans with a focus on health disparities, and calculate excess mortality attributable to cirrhosis.

Methods: National Health And Nutrition Examination Survey data conducted between 1999 and 2010 were used to estimate cirrhosis prevalence and factors associated with cirrhosis. The National Center for Health Statistics-linked death certificate data from the National Death Index were linked to the National Health And Nutrition Examination Survey database for the years 1999 to 2004, and attributable mortality was calculated using propensity score adjustment. Cirrhosis was ascertained by aspartate aminotransferase-to-platelet ratio of >2 and abnormal liver function tests.

Results: The prevalence of cirrhosis in the United States was approximately 0.27%, corresponding to 633,323 adults. Sixty-nine percent reported that they were unaware of having liver disease. The prevalence was higher in non-Hispanic blacks and Mexican Americans, those living below the poverty level, and those with less than a 12th grade education. Diabetes, alcohol abuse, hepatitis C and B, male sex, and older age were all independently associated with cirrhosis, with a population attributable fraction of 53.5% from viral hepatitis (mostly hepatitis C), diabetes, and alcohol abuse. Mortality was 26.4% per 2-year interval in cirrhosis compared with 8.4% in propensity-matched controls.

Conclusions: The prevalence of cirrhosis is higher than previously estimated. Many cases may be undiagnosed, and more than half are potentially preventable by controlling diabetes, alcohol abuse, and viral hepatitis. Public health efforts are needed to reduce this disease burden, particularly among racial/ethnic minorities and individuals at lower socioeconomic status.

Key Words: NHANES, mortality, prevalence, disparities

(*J Clin Gastroenterol* 2015;49:690–696)

BACKGROUND

Liver cirrhosis is an important public health concern in the United States and a significant source of morbidity and mortality. The National Center for Health Statistics (NCHS) and Centers for Disease Control (CDC) estimates that in 2009 chronic liver disease and cirrhosis represented the 12th leading cause of death overall and the fifth leading cause of death for patients aged 45 to 54 years.[1] Studies using data from death certificates estimates that there are over 30,000 deaths per year in the United States[2]; if codes for viral hepatitis and cirrhosis complications were included in these estimates, the number of deaths would increase to 60,000.[3,4]

The prevalence of cirrhosis is likely increasing, due to the aging hepatitis C cohort and rise in fatty liver disease.[5,6] However, the epidemiology of cirrhosis in the general population is poorly understood. One study reported that approximately 30,000 cases of cirrhosis are diagnosed at tertiary referral centers in the United States per year.[7] This would exclude cases that are not diagnosed, as well as those not referred to a tertiary care center. No studies have measured prevalence in the general population, although some authors estimate the number to be perhaps 400,000 individuals, based on expert opinion.[8] Several lines of evidence suggest that the true prevalence may be much higher. One population-based cross-sectional study in Italy found cirrhosis in 1.1% of adults. Cirrhosis prevalence at autopsy is approximately 5% to 10%, with two thirds of cases diagnosed premortem, suggesting that nearly a third of patients with cirrhosis remain undiagnosed.[9,10]

Although data on population demographics of cirrhosis are scarce, well-known health disparities exist within and between groups with chronic liver diseases.[11] The incidence and prevalence of viral hepatitis,[12] nonalcoholic fatty liver disease (NAFLD),[13] and survival associated with hepatocellular carcinoma[14] disproportionately affect populations by sex, race, and socioeconomic status.[15]

We hypothesized that cirrhosis is more common than previously recognized, primarily because of a large amount of undiagnosed cryptogenic cirrhosis among individuals with risk factors for NAFLD. We also hypothesized that there are significant racial/ethnic and socioeconomic disparities in the prevalence of cirrhosis. Accordingly, we aimed to estimate the prevalence of cirrhosis in the general US population and to explore demographic and clinical features of those with cirrhosis. We sought to determine the population attributable fraction (PAF) of alcohol, diabetes, and viral hepatitis as potentially preventable contributors to the prevalence of cirrhosis. Finally, we aimed to calculate mortality attributable to cirrhosis. Understanding the epidemiology of cirrhosis in the general population is an important first step in developing interventions to reduce this disease burden.

METHODS

Data Sources

The National Health and Nutrition Examination Survey (NHANES) is an annual national survey conducted

Received for publication March 17, 2014; accepted June 27, 2014.
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by the NCHS of the CDC and Prevention (http://www.cdc.gov/nchs/nhanes.htm). Since 1999, this annual survey consists of a cross-sectional interview, examination, and laboratory data collected from a complex, multistage, stratified, clustered probability sample representative of the civilian, noninstitutionalized population. The survey was approved by the CDC and Prevention Institutional Review Board, and all participants provided written informed consent to participate. Our current analysis was performed on NHANES data collected from 1999 to 2010. Samples were weighted on the basis of age, sex, race, and ethnicity to represent the distribution of the United States.

Inclusion Criteria

Inclusion criteria were as follows: age 18 years or older, availability of complete demographics (race/ethnicity, sex, and age), clinical data (history of hypertension, type II diabetes), and social history (alcohol history, tobacco, and intravenous drug use). Additional data collected for the analysis included γ-glutamyl transpeptidase, serum iron, total iron-binding capacity, fasting glucose and insulin, triglycerides, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and 25-hydroxy-vitamin D. Ultimately, physical examination and laboratory data were available for 35,379 participants aged 18 and over. Of these, we used data on 29,906 (85%) individuals who were not pregnant, and did not have missing data on physical examination or laboratory values. Pregnant participants were excluded because etiology of abnormal liver tests in pregnancy markedly differs from the general population. In addition, approximately 8% of pregnant females will have thrombocytopenia.[16] A flowchart is shown in Figure 1.

Definitions

Cirrhosis was defined as abnormal liver function tests and an aspartate aminotransferase-to-platelet ratio (APRI) of >2. This method is supported by numerous studies in various liver diseases showing APRI to be a good predictor of cirrhosis.[17–20] The APRI was calculated as follows: (AST/upper-limit of normal)/platelet count times $\times 100$. Subjects were also required to have abnormal liver tests, to exclude those with primary hematological causes for thrombocytopenia. Based upon the published NHANES reference ranges, the following definitions were used to define APRI and abnormal liver tests: upper-limit of normal of aspartate aminotransferase (AST) used for APRI calculation was 33 IU/L. Abnormal liver functions tests were defined as alanine aminotransferase (ALT) > 40 IU/L for men and >30 IU/L for women, alkaline phosphatase >113 IU/L, and total bilirubin 1.3 mg/dL. Finally, we excluded participants with an AST or ALT > 500 IU/L, so as to not capture those with acute hepatitis but no cirrhosis. The NHANES question "Have you ever been told you have liver disease?" provided information on the proportion of patients whose cirrhosis remains undiagnosed.

Diabetes mellitus was defined as fasting blood glucose ≥ 126 or history of use of oral hypoglycemic or insulin use or both. Insulin resistance was defined as homeostasis of model assessment score of ≥ 3.0.[21]

Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 or history of antihypertensive medications.

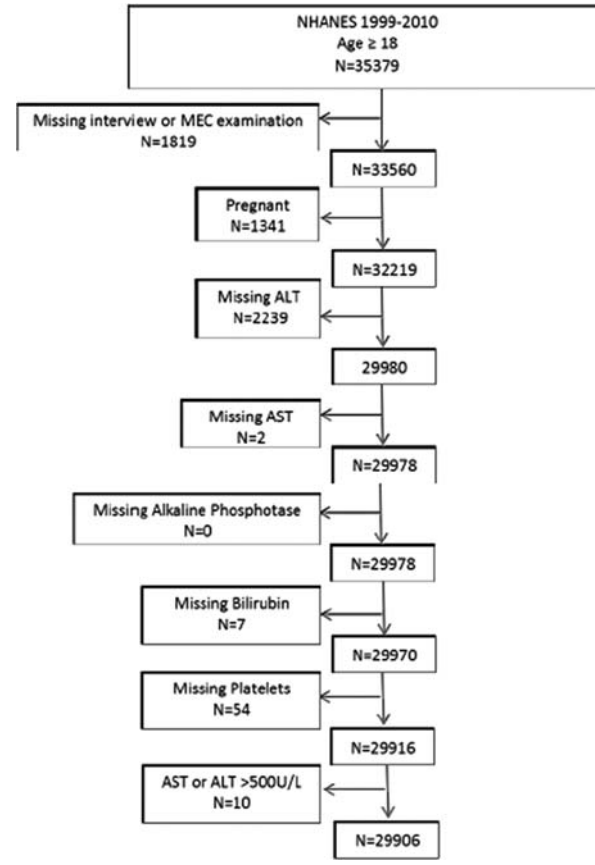

FIGURE 1. Flow diagram.

Hypercholesterolemia was defined as a total cholesterol level > 200 mg/dL, LDL level of ≥ 139 mg/dL, and HDL of ≤ 40 mg/dL for men and ≤ 50 mg/dL for women.

Obesity was defined as a BMI ≥ 30. Visceral obesity was defined as WC ≥ 102 cm for men and 88 cm for women.

Race and ethnicity were classified into 4 groups as follows: (1) non-Hispanic whites; (2) non-Hispanic blacks; (3) Mexican Americans/Hispanics; and (4) Other. The "Other" category consists of Aluet, Eskimo, American Indian, Asian, and Pacific Islander.

Etiology of Cirrhosis

Excess alcohol consumption was defined as >2 drinks/d for men and >1 drink/d for women within 1 year before the completion of data collection, based on the Alcohol Use Questionnaire. Iron overload was defined as transferrin saturation >50%. Chronic hepatitis B was defined as a positive test for hepatitis B surface antigen. Participants were defined as hepatitis C virus (HCV) positive if they had a positive test for antibody to hepatitis C.

National Mortality Data

The NCHS has linked death certificate data from the National Death Index (NDI) to the NHANES database. The linked mortality files available for public use include the continuous NHANES years (1999 to 2004) and are based on a probabilistic match of NHANES participants and NDI death records. The data provide mortality follow-up from the date of survey participation through December 31, 2006; thus, follow-up is greater for participants in the

earlier years of the continuous NHANES database than for participants in the years 2003 to 2004.

Statistical Analysis

The population-weighted prevalence of cirrhosis was calculated for each 2-year period. Population-weighted prevalence was also estimated by age group, HCV status, and among individuals with abnormal liver tests.[22] Basic demographic and laboratory information for NHANES participants with and without cirrhosis was analyzed using *t* tests for continuous variables and χ^2 tests for categorical variables. Multivariate logistic regression was used to determine factors independently associated with cirrhosis. A stepwise procedure was implemented to determine the best fitting model and all meaningful interactions were assessed.

Description of the calculation and interpretation of PAF has been described in detail elsewhere.[23] PAFs for 3 exposures, namely diabetes, viral hepatitis [HCV and hepatitis B virus (HBV)], and excessive alcohol consumption, were computed using multivariate logistic regression models.[23] The PAF was calculated using the following formula:

$$\mathrm{PAF} = 1 - \sum_{i=1}^{8} \frac{\pi_i}{OR_i},$$

where $i = 1, \ldots, 8$ runs over the 8 possible exposure group combinations, with $i = 1$ representing the group of no exposure (no diabetes, viral hepatitis, or excessive alcohol consumption), and $OR_1 = 1$. The proportion of cases of cirrhosis in the *ith* exposure group is denoted by π_i and OR_i represents the adjusted odds ratio comparing the *ith* exposure group with the unexposed group. Odds ratios were estimated using logistic regression models that included and excluded potential interaction among the exposures. Results of the interaction models and main effect models were similar; for simplicity, only the noninteraction models are presented. The odds ratios were estimated following the fit of the multivariate logistic regression model adjusted for age, sex, and race/ethnicity. The PAF is then expressed as a percentage of cirrhosis cases that could be prevented by eliminating risk factors—individually or overall. Importantly, the sum of individual PAFs is more than the overall PAF. This is because, for example, if a patient has hepatitis C and still drinks alcohol in excess, eliminating the hepatitis C would reduce but not totally eliminate the probability of cirrhosis.

Mortality was measured using the linkage between NHANES 1999 to 2004 and the NDI. Cirrhosis cases were matched to controls at a 1:3 ratio via propensity scores. The control cohort was created based on propensity scores that included the entire 1999 to 2004 NHANES data set and were created with the following variables: sex, race, excess alcohol use, diabetes, education level, and income level. Effectiveness of propensity score matching was assessed and death rates were estimated at each 2-year interval between 1999 and 2004.

Weights and sampling error codes provided in the NHANES data files were used to compute nationally representative estimates and design-based SEs for those estimates that appropriately reflect the complex NHANES sampling methodology.[24] Appropriate survey procedures in the statistical package SAS 9.3 (SAS Institute, Cary, NC) were used to carry out all analyses.

TABLE 1. Population Weight Prevalence of Cirrhosis by NHANES Survey Year and Age Group

Variables	Cirrhosis	Total	Prevalence (%)
Survey year			
1999-2000	78,404	30,394,159	0.258
2001-2002	60,244	31,744,574	0.190
2003-2004	96,097	33,116,854	0.290
2005-2006	98,798	32,597,587	0.303
2007-2008	92,845	34,500,849	0.270
2009-2010	105,744	35,016,119	0.302
Age group			
< 25	3477	24,609,303	0.014
25-34	28,499	34,625,160	0.082
35-44	114,292	40,118,785	0.285
45-54	228,433	39,815,883	0.574
55-64	90,662	26,195,364	0.346
65-74	27,492	18,027,980	0.153
75 +	39,277	13,977,666	0.281
Overall	532,132	197,370,142	0.270

NHANES indicates National Health And Nutrition Examination Survey.

RESULTS

Table 1 presents both the population-weighted prevalence by year and age. The total prevalence of cirrhosis between 1999 and 2010 is 0.27%, which corresponds to 633,323 adults over the age of 18 with cirrhosis in the United States based on 2010 US census data.[25] The prevalence of cirrhosis steadily increased with age, and peaked at 0.57% in those between the ages of 45 to 54 years old. The peak prevalence of cirrhosis occurred later in those without HCV when compared with those with HCV, and both populations showed an increase in prevalence after age 75 years old (Fig. 2). Among those with abnormal liver tests, the overall prevalence of cirrhosis was 1.39% and peaked after 45 years old and again after 75 years old.

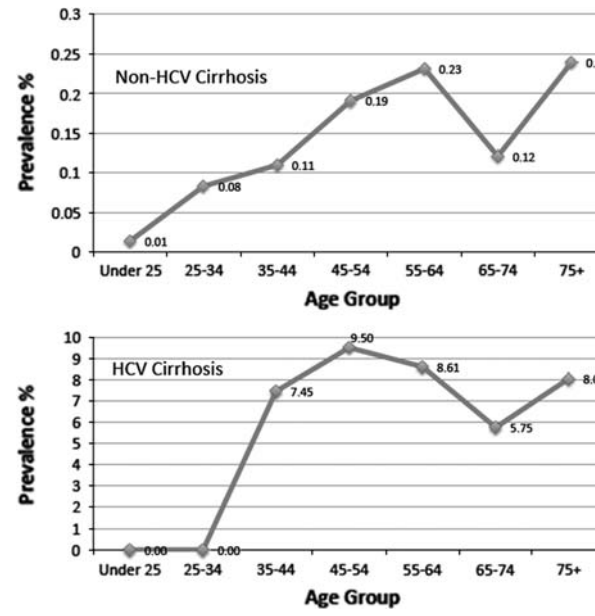

FIGURE 2. Population prevalence of cirrhosis by age group with hepatitis C virus (HCV) and without HCV.

TABLE 2. Demographic, Clinical, and Laboratory Statistics of Study Variables by Cirrhosis Status (M = median, N = sample size)

Variables	Cirrhosis Median (SE) or Frequency (%)	No Cirrhosis Median (SE) or Frequency (%)	*P*
Age (y)	51.15 (1.58), *M* = 51, N = 99	45.60 (0.22), *M* = 47, N = 29807	0.0007
Ever been told you have liver disease			< 0.0001
Yes	30 (31.3%)	902 (3.3%)	
No	66 (68.7%)	26391 (96.7%)	
Alcohol history (excess alcohol consumption)	25 (25.3%)	1816 (6.1%)	< 0.0001
Race			0.0441
White	33 (33.3%)	14340 (48.1%)	
Black	29 (29.3%)	5981 (20.1%)	
Mexican American/Hispanic	34 (34.3%)	8369 (28.1%)	
Other	3 (3.0%)	1216 (4.1%)	
Sex			< 0.0001
Male	72 (72.7%)	15000 (50.3%)	
Female	27 (27.3%)	14807 (49.7%)	
Age group			< 0.0001
< 25	3 (3.0%)	4737 (15.9%)	
25-34	5 (5.1%)	4253 (14.3%)	
35-44	16 (16.2%)	4804 (16.1%)	
45-54	41 (41.4%)	4623 (15.5%)	
55-64	21 (21.2%)	4160 (14.0%)	
65-74	6 (6.0%)	3774 (12.7%)	
75 +	7 (7.1%)	3456 (11.6%)	
Income ≤ $20,000/y	47 (50.5%)	8578 (32.5%)	0.0005
Education			0.0022
< 9th grade	17 (8.5%)	4097 (13.7%)	
9-11th grade (includes 12th grade with no diploma)	27 (13.6%)	5391 (18.1%)	
High school grad/GED or equivalent	21 (10.6%)	7284 (24.5%)	
Some college or AA	22 (11.1%)	7802 (26.2%)	
College graduate or above	12 (6.0%)	5185 (17.4%)	
Domestic partner	47 (48.0%)	16586 (57.5%)	0.0149
Poverty income ratio (PIR) ≤ 1.3	45 (48.9%)	8492 (31.0%)	0.002
Diabetes	27 (27.3%)	3639 (12.2%)	< 0.0001
IV drug use	20 (38.5%)	367 (3.0%)	< 0.0001
Current smoker	45 (46.4%)	6675 (22.6%)	< 0.0001
AST (IU/L)	152.91 (10.57), *M* = 131, N = 99	24.92 (0.09), *M* = 23, N = 29807	< 0.0001
ALT (IU/L)	131.83 (10.13), *M* = 103, N = 99	25.46 (0.12), *M* = 21, N = 29807	< 0.0001
AlkPhos (U/L)	116.66 (8.76), *M* = 104, N = 99	69.88 (0.34), *M* = 69, N = 29807	< 0.0001
Platelet count	146.62 (8.49), *M* = 133, N = 99	265.55 (0.80), *M* = 256, N = 29807	< 0.0001
Bilirubin (mg/dL)	1.11 (0.06), *M* = 1, N = 99	0.74 (0.004), *M* = 0.7, N = 29807	< 0.0001
Creatinine (mg/dL)	0.91 (0.04), *M* = 0.8, N = 99	0.88 (0.003), *M* = 0.82, N = 29807	0.3504
GGT (IU/L)	212.23 (22.75), *M* = 166, N = 99	28.43 (0.27), *M* = 20, N = 29806	< 0.0001
Iron (mg/dL)	121.41 (11.96), *M* = 110.5, N = 28	87.67 (0.54), *M* = 81, N = 12262	0.0061
TIBC (μg/dL)	356.54 (17.79), *M* = 359, N = 28	364.10 (1.39), *M* = 359, N = 12220	0.6717
HepC antibody	46 (46.5%)	505 (1.70%)	< 0.0001
HepB surface antigen	3 (3.0%)	109 (0.4%)	< 0.0001
Fasting glucose (mmol/L)	115.87 (5.41), *M* = 105, N = 50	103.19 (0.36), *M* = 98, N = 14508	0.0228
Fasting insulin (pmol/L)	23.61 (3.90), *M* = 15.7, N = 51	12.51 (0.17), *M* = 9.8, N = 14456	0.0057
Fasting triglycerides (mmol/L)	154.18 (28.18), *M* = 104.5, N = 76	147.84 (1.42), *M* = 114, N = 23960	0.8212
BMI (kg/m^2)	27.41 (0.77), *M* = 27.3, N = 96	28.23 (0.07), *M* = 27.4, N = 29211	0.2841
Waist circumference (cm)	98.54 (1.79), *M* = 97.7, N = 96	96.68 (0.20), *M* = 96.1, N = 28604	0.2869
SBP (mm Hg)	129.55 (2.47), *M* = 126.7, N = 97	122.19 (0.21), *M* = 121, N = 28558	0.004
DBP (mm Hg)	72.86 (1.57), *M* = 72, N = 97	70.83 (0.20), *M* = 70, N = 28558	0.2009
HDL (mmol/L)	54.66 (2.96), *M* = 47, N = 99	52.43 (0.19), *M* = 50, N = 29783	0.4469
LDL (mmol/L)	100.09 (5.59), *M* = 99.5, N = 46	117.42 (0.46), *M* = 113, N = 13797	0.0027
Insulin resistance (HOMA)	7.66 (1.61), *M* = 4.5, N = 50	3.41 (0.05), *M* = 2.4, N = 14435	0.0102
Components of metabolic syndrome			
Waist circumference (≥ 102 for men and ≥ 88 for women)	45 (47%)	14825 (52%)	0.5679
Fasting plasma glucose level > 110 mmol/L	15 (30%)	3098 (21.3%)	0.0375
Blood pressure > 130/85 mm Hg	20 (20.6%)	3132 (10.9%)	0.0357
Triglycerides > 150 mmol/L	16 (31.3%)	4362 (30%)	0.7604
Low HDL (< 40 mg/dL for men and < 50 mg/dL for women)	37 (37.3%)	9579 (32%)	0.7497

AA indicates Associate Degree; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; GED, General Education Development; GGT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; HOMA, Homeostasis Model Assessment; LDL, low-density lipoprotein; SBP, systolic blood pressure; TIBC, total iron-binding capacity.

Many cases of cirrhosis may be undiagnosed, as 69% indicated they had never been told they have liver disease.

Baseline descriptive characteristics are presented in Table 2. In comparison with the general population, individuals with cirrhosis tended to be older, more likely to be male, black, and not have a domestic partner. The higher prevalence of cirrhosis among blacks persisted regardless of HCV status: among HCV-positive individuals, 9% of blacks had cirrhosis compared with 7.6% of Hispanics and 7.7% of whites, and among HCV-negative individuals, 0.25% of blacks had cirrhosis compared with 0.23% of Hispanics and 0.09% of whites. The prevalence of cirrhosis declined with increasing levels of education and was higher among participants who met criteria for poverty (income < $20,000/y and poverty-to-income ratio < 1.3). A quarter of individuals with cirrhosis reported that they drink alcohol in excess during the prior year, nearly half were HCV positive, and only 3% had HBsAg positive. Compared with the general population, individuals with cirrhosis had statistically significantly higher iron, lower LDL, increased levels of fasting glucose and insulin, higher SBP, as well as higher percentage of those with diagnosis of hypertension. Individuals with cirrhosis did not differ from the general population in regards to several aspects of the metabolic syndrome, including BMI, triglyceride level, WC, DBP, and HDL.

To determine factors independently associated with cirrhosis, multivariate analysis was performed based on variables that had significant associations in univariate analyses (Table 3). The presence of diabetes mellitus, older age, male sex, excess alcohol consumption, HBV, and HCV were all independently associated with cirrhosis. Although not statistically significant, MA/Hispanics and blacks trended toward a greater risk of cirrhosis when compared with whites.

PAF

See Figure 3 for PAF. Under our model, eliminating viral hepatitis (hepatitis C and B), diabetes, and excess alcohol consumption, would eliminate roughly 53.5% of cirrhosis cases. Taken individually, eliminating diabetes, alcohol, and viral hepatitis would eliminate approximately 14.6%, 17.1%, and 46.6% of cirrhosis cases.

Mortality

Overall mortality was higher in individuals with cirrhosis, compared with propensity score matched controls. The mean proportion of deaths per 2-year interval was 26.4% (95% confidence interval, 3%-50%) among those with cirrhosis, compared with 8.4% (95% confidence interval, 3%-13%) among controls.

TABLE 3. Multivariable Logistic Regression Results for Factors Associated With Cirrhosis

Variables*	Odds Ratio	95% CI	*P*
Sex	2.44	1.43-4.16	0.001
Age	1.02	1.003-1.04	0.0207
Race			0.1041
Black	1.65	0.93-2.92	0.0877
Hispanic	1.87	0.96-3.64	0.0656
HCV	50.16	27.7-90.8	< 0.0001
HBV	7.4	1.80-30.34	0.0055
Diabetes	2.59	1.40-4.78	0.0025
Excess alcohol use	2.61	1.26-5.39	0.0096

*Reference level: sex = female; race = white; HCV = no; HBV = no; diabetes = no; excess alcohol use = no.

CI indicates confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus.

DISCUSSION

This is the first study to estimate the prevalence of cirrhosis in the general population. We found an overall prevalence of 0.27% in adults; based on 2010 US census this would correspond to 633,323 Americans adults afflicted with liver cirrhosis.

The prevalence of cirrhosis has a bimodal age distribution, peaking during the fourth and fifth decade and then again after age 75. As expected, hepatitis C, alcohol, and diabetes play a large role in the epidemiology of cirrhosis, accounting for 53.5% of cases.

As we had hypothesized, health disparities do exist in the epidemiology of cirrhosis. Participants who met criteria for poverty and those with lower educational attainment had a higher prevalence rate of cirrhosis compared with the general population. This appears to largely explained by higher rates of obesity and diabetes,[24,26,27] intravenous drug use, HCV,[28] and alcohol use,[29] as income was no longer significant in multivariate analysis. In addition, non-Hispanic blacks had higher prevalence rates of cirrhosis compared with MA/Hispanics and non-Hispanic whites. Identification of these disparities allows public health professionals to target populations at particular risk of this potentially life-threatening condition and apply screening programs and interventions to lessen the burden of this disease.

Our analysis revealed a few unanticipated findings. First, nearly 70% of participants with cirrhosis replied that they have never been told they have liver disease. Although some of these individuals may simply have forgotten or been confused about the question, this raises the possibility of a large number of undiagnosed cases of cirrhosis. Second, the prevalence of cirrhosis in non-Hispanic blacks is higher than other racial/ethnic groups.

This was unexpected given historically this population has had lower prevalence of cirrhosis, slower histologic progression to cirrhosis, have lower ALT, and less piecemeal necrosis.[11,30–33] This finding must be carefully interpreted as non-Hispanic black race was not statistically significant in multivariable regression analysis and our cohort consisted of a limited number of cirrhotics. Although reasons for this disparity appear multifactorial, the stepwise regression analysis identified HCV as the strongest predictor of cirrhosis and the variable that primarily explained the same variation in cirrhosis as did race. The available data on hepatic fibrosis and cirrhosis based on race are not completely understood as the evidence is inconclusive.[32,34] African Americans with HCV are less eligible for treatment and when treated have lower rates of treatment response indicating a population that is at risk of further fibrosis progression.[35,36] In addition, the rate of hepatocellular carcinoma among African Americans is 2-fold higher than whites.[35,37,38] Moreover, a recent multistate markov model showed the rate of hepatic fibrosis progression did not differ by race between African Americans and white Americans.[34,39] These results highlight that all racial/ethnic groups, especially non-Hispanic blacks, may benefit from improving access-to-care and screening for cirrhosis. Further research into the role of race in hepatic fibrosis progression is needed as well. Third, diabetes mellitus and LDL were the only

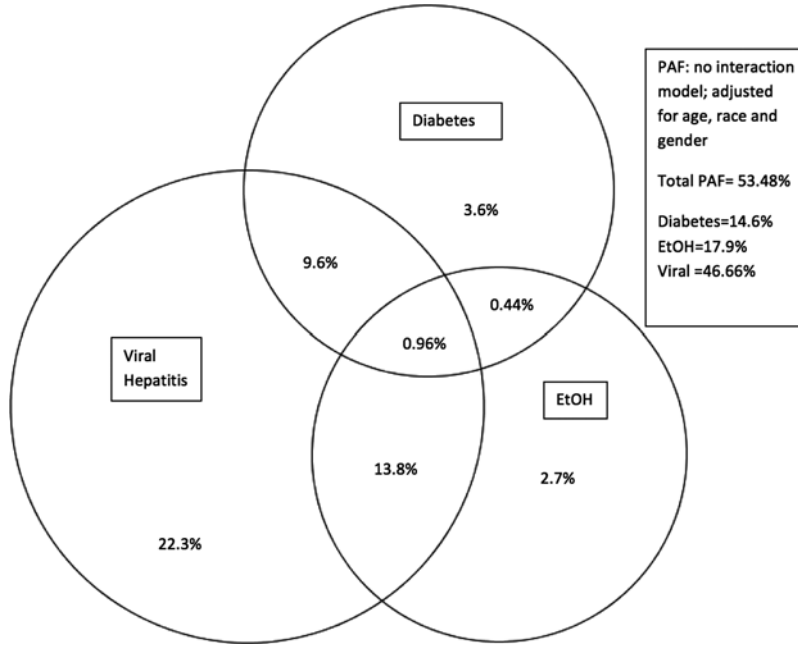

FIGURE 3. Population attributable fraction of cirrhosis by diabetes, excessive alcohol consumption, and viral hepatitis.

factors in the metabolic syndrome associated with cirrhosis. Hypertension, hypercholesterolemia, WC, and obesity did not persist in further multivariable regression. This was also unexpected given that the changing face of chronic liver disease is one toward NAFLD and away from viral hepatitis.[40]

Several limitations of our study must be considered. First, the APRI has not been validated in the general population, significantly limiting its specificity in identifying cirrhosis. The limited specificity of APRI in the general population may explain why 69% of cirrhotic cases have remained undiagnosed. In addition, APRI may misclassify patients with mild liver disease as cirrhotics. However, the APRI has been validated as a noninvasive measure of cirrhosis in multiple disease states including viral hepatitis, alcoholic liver disease, NAFLD, and others, with area under the receiver-operating characteristic curve values of 0.76 to 0.94.[17–20] Furthermore, the large role of HCV, diabetes mellitus, alcohol, male predominance, and increased mortality of cirrhotic cases in our study suggests that our ascertainment method is valid. Most importantly, the absence of a perfect gold-standard noninvasive test for cirrhosis makes other methods of ascertainment unfeasible. Second, the small number of cases of cirrhosis limits the statistical power to detect small differences versus controls and warrants caution when extrapolating to the to the entire US population. Third, NHANES is a cross-sectional study and does not serve to investigate a sample population over time. For example, the association between diabetes and cirrhosis could be causative in either direction. Fourth, the true prevalence is probably higher than we report given that the population studied excluding prisoners, immigrants, and military veterans.

In conclusion, our study estimates the prevalence of cirrhosis to be 0.27% of the general US population, suggesting that 633,323 American adults are afflicted with liver cirrhosis at any given time. Non-Hispanic blacks have higher prevalence of cirrhosis than other races/ethnicities. Hepatitis C, alcohol, diabetes mellitus, and male sex play a significant role in the prevalence of cirrhosis. These findings can serve to guide future public health efforts aimed at controlling the burden of cirrhosis.

REFERENCES

1. Heron M. Deaths: leading causes for 2009. *Natl Vital Stat Rep*. 2012;61:1–96.
2. Vong S, Bell BP. Chronic liver disease mortality in the United States, 1990-1998. *Hepatology*. 2004;39:476–483.
3. Kim WR, Brown RS Jr, Terrault NA, et al. Burden of liver disease in the United States: summary of a workshop. *Hepatology*. 2002;36:227–242.
4. Asrani SK, Larson JJ, Yawn B, et al. Underestimation of liver-related mortality in the United States. *Gastroenterology*. 2013;145:375–382, e1–2.
5. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*. 2010;138:513–521, e1–6.
6. Davis GL, Roberts WL. The healthcare burden imposed by liver disease in aging Baby Boomers. *Curr Gastroenterol Rep*. 2010;12:1–6.
7. Bell BP, Manos MM, Zaman A, et al. The epidemiology of newly diagnosed chronic liver disease in gastroenterology practices in the United States: results from population-based surveillance. *Am J Gastroenterol*. 2008;103:2727–2736; quiz 2737.
8. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet*. 2008;371:838–851.
9. Graudal N, Leth P, Marbjerg L, et al. Characteristics of cirrhosis undiagnosed during life: a comparative analysis of 73 undiagnosed cases and 149 diagnosed cases of cirrhosis, detected in 4929 consecutive autopsies. *J Intern Med*. 1991;230:165–171.
10. Giarelli L, Melato M, Laurino L, et al. Occurrence of liver cirrhosis among autopsies in Trieste. *IARC Sci Publ*. 1991;112:37–43.
11. Nguyen GC, Thuluvath PJ. Racial disparity in liver disease: biological, cultural, or socioeconomic factors. *Hepatology*. 2008;47:1058–1066.

12. Wise M, Bialek S, Finelli L, et al. Changing trends in hepatitis C-related mortality in the United States, 1995-2004. *Hepatology*. 2008;47:1128–1135.
13. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*. 2004;40:1387–1395.
14. Davila JA, El-Serag HB. Racial differences in survival of hepatocellular carcinoma in the United States: a population-based study. *Clin Gastroenterol Hepatol*. 2006;4:104–110; quiz 4–5.
15. Guy J, Yee HF Jr. Health disparities in liver disease: time to take notice and take action. *Hepatology*. 2009;50:309–313.
16. Kadir RA, McLintock C. Thrombocytopenia and disorders of platelet function in pregnancy. *Semin Thromb Hemost*. 2011;37:640–652.
17. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38:518–526.
18. Cales P, Laine F, Boursier J, et al. Comparison of blood tests for liver fibrosis specific or not to NAFLD. *J Hepatol*. 2009;50:165–173.
19. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cardenas E, et al. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol*. 2008;7:350–357.
20. Lieber CS, Weiss DG, Morgan TR, et al. Aspartate aminotransferase to platelet ratio index in patients with alcoholic liver fibrosis. *Am J Gastroenterol*. 2006;101:1500–1508.
21. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care*. 2000;23:57–63.
22. Heeringa S, West BT, Berglund PA. *Applied Survey Data Analysis*. Boca Raton, FL: Chapman & Hall/CRC; 2010.
23. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88:15–19.
24. NCHS. NHANES Analytic and Reporting Guidelines. 2005.
25. US Census Bureau. 2010 Census Briefs: Age and sex composition. Washington, DC: Government Printing Office. Retrieved from http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf.
26. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. *JAMA*. 2001;286:1195–1200.
27. Hsu CC, Lee CH, Wahlqvist ML, et al. Poverty increases type 2 diabetes incidence and inequality of care despite universal health coverage. *Diabetes Care*. 2012;35:2286–2292.
28. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med*. 2014;160:293–300.
29. Baumann M, Spitz E, Guillemin F, et al. Associations of social and material deprivation with tobacco, alcohol, and psychotropic drug use, and gender: a population-based study. *Int J Health Geogr*. 2007;6:1–12.
30. Wiley TE, Brown J, Chan J. Hepatitis C infection in African Americans: its natural history and histological progression. *Am J Gastroenterol*. 2002;97:700–706.
31. Kallwitz ER, Guzman G, TenCate V, et al. The histologic spectrum of liver disease in African-American, non-Hispanic white, and Hispanic obesity surgery patients. *Am J Gastroenterol*. 2009;104:64–69.
32. Kohla M, Iwata S, Ea R, et al. Histological versus clinical cirrhosis in chronic hepatitis C: does race/ethnicity really matter? *Dig Dis Sci*. 2012;57:771–776.
33. Crosse K, Umeadi OG, Anania FA, et al. Racial differences in liver inflammation and fibrosis related to chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2004;2:463–468.
34. Forde KA, Tanapanpanit O, Rajender Reddy K. Hepatitis B and C in African Americans: current status and continued challenges. *Clin Gastroenterol Hepatol*. 2013;88:15–19.
35. Pearlman BL. Hepatitis C virus infection in African Americans. *Clin Infect Dis*. 2006;42:82–91.
36. Melia MT, Muir AJ, McCone J, et al. Racial differences in hepatitis C treatment eligibility. *Hepatology*. 2011;54:70–78.
37. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med*. 1999;340:745–750.
38. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology*. 2004;127:S27–S34.
39. Terrault NA, Im K, Boylan R, et al. Fibrosis progression in African Americans and Caucasian Americans with chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2008;6:1403–1411.
40. Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol*. 2011;9:524–530 e1; quiz e60.