Risks of a Range of Alcohol Intake on Hepatitis C-Related Fibrosis

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Heavy alcohol use contributes to liver disease in the setting of chronic hepatitis C virus (HCV) infection. Whether this is true for light or moderate alcohol use has not been demonstrated. Light alcohol use has survival benefits at a population level and is practiced by most patients with chronic HCV infection. In this study, 800 patients with HCV undergoing liver biopsy at three sites had detailed alcohol histories recorded and the relationship between alcohol and hepatic fibrosis was assessed. On univariate analysis, heavy alcohol use (>50 g/day) was associated with an increase in mean fibrosis ($P = .01$). Such an association could not be demonstrated for light and moderate alcohol use. For each category of alcohol intake (none, light, moderate, and heavy), a spectrum of fibrosis was observed. On multivariate analysis, age, serum alanine aminotransferase (ALT), and histological inflammation were the independent predictors of fibrosis ($P = <.0001, .0003, <.0001$, respectively). In conclusion, heavy alcohol use exerts a greater effect on fibrosis than light or moderate use. There is a range of fibrosis at each level of alcohol use. Age, serum ALT, and inflammation are independently associated with fibrosis in multivariate analysis, highlighting the fact that variables other than alcohol intake predominate in the production of hepatic fibrosis. (HEPATOLOGY 2004;39:826–834.)

Hepatitis C virus (HCV) is the primary cause of cirrhosis leading to liver transplantation in the United States[1] and Europe.[2] Many patients chronically infected with HCV, however, never develop serious liver disease. Epidemiological studies have shown that certain patient-related variables are associated with worse liver disease. In general, these have included: older age at HCV acquisition, heavy alcohol consumption, and male gender.[3] Longer duration of HCV infection, more histological inflammation, and elevated serum liver enzymes have also been found to correlate with liver fibrosis in a number of studies.[4–7] The proportion of patients progressing to cirrhosis varies widely, based on the group examined, from 22% after 20 years of infection in studies from liver clinics, to 4% in blood donor series.[8,9] Thus, disease progression clearly depends on a variety of factors.

Heavy alcohol consumption has been found in many studies to contribute to the progression of HCV-related liver disease. Patients with HCV are generally counseled by their physicians to abstain from drinking alcohol,[10] despite the fact that light alcohol intake, which most patients practice, has not been shown to lead to worse liver disease. Additionally, there is increasing evidence that light alcohol consumption bestows significant health benefits.[11,12] As such, we sought to address how deleterious different amounts of alcohol intake are to patients with chronic HCV.

This issue has not been settled to date, despite many studies that have examined the additive effect of alcohol to HCV-associated liver disease. Each study has had limitations, and none have clearly demonstrated how much alcohol is harmful to the liver. Limitations have included grouping subjects by fixed categories of alcohol intake, with an inability to examine intake within the categories.[3,4,13] Also, case-control methodology has often been used, with cases typically having decompensated cirrhosis and controls having little liver disease.[14,15] Most studies were retrospective,[13–15] although a few have been prospective.[5]

Abbreviations: HCV, hepatitis C virus; ALT, alanine aminotransferase; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; IDU, injection drug use.

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The contribution of light or even moderate alcohol intake has infrequently been examined. Studies which have examined this issue[5,16,17] have had conflicting results, with some finding no relationship between alcohol intake and fibrosis overall,[5] and others suggesting that such a relationship exists.[16,17] There is no consensus about a level of alcohol that increases the risk of liver disease progression. The specifics of these relationships, however, are important in daily practice for patient counseling.

To overcome these limitations, we conducted a cross-sectional study of alcohol intake up to the time of a liver biopsy. Current and past alcohol use was quantified. Consecutive patients were enrolled at three centers over 5 years. All patients had daily alcohol intake calculated by the same method, allowing the full range to be examined. Histological outcomes were used. Our aims were: 1) to evaluate whether there is a "safe" level of alcohol intake, and whether alcohol has a dose-effect on fibrosis; 2) to define the spectrum of liver injury in patients who consume the same amount of alcohol; and 3) to compare the contribution of alcohol to fibrosis with that of other common clinical predictors. In doing so, we hoped to clarify the degree to which alcohol contributes to HCV-related liver injury.

Patients and Methods

Patients

In all, 948 consecutive patients who consented to enrollment made up the study cohort. Patients were enrolled at the time of a liver biopsy performed by collaborating investigators for staging of HCV disease at the Veterans Affairs and U.C.S.F. Medical Centers in San Francisco and the Scripps Clinic in La Jolla, California. None of the patients had received prior anti-HCV therapy. Patients with clinically decompensated cirrhosis or contraindications to liver biopsy were not enrolled. Enrollment occurred between July 1997 and May 2002. The study was approved by local institutional review boards. Following written, informed consent, patients completed questionnaires, generally at the time of liver biopsy. From this initial group, 148 patients were excluded from analysis for the following reasons: incomplete alcohol data (124), human immunodeficiency virus (HIV) infection (12), prior solid organ transplantation (7), other coexisting liver disease (5), leaving 800 in whom data analyses were performed.

Questionnaire

Study questionnaires included demographic information and risk factors for HCV acquisition. Complete injection drug use and blood transfusion histories were obtained. Other potential exposures to HCV were also recorded.

Alcohol Quantification

Alcohol consumption was assessed in detail. Beer, wine, and liquor consumption were quantified individually from patients' typical quantity, frequency, and duration of use, based on previously validated questionnaire items.[18] Years of consumption of each of the three alcohol types were estimated from 0–25. The number of drinks consumed over a patient's lifetime was multiplied by the alcohol content (each drink estimated to contain the equivalent of 10 g of pure ethanol), giving lifetime alcohol consumption in grams of ethanol. To attempt to address age bias (older patients having more years to drink, and thus a higher lifetime intake), lifetime alcohol was then divided by the length of time a respondent had drunk any alcohol, yielding an average consumption over the span of drinking (in grams per day). This average consumption is referred to as "alcohol intake."

Subjects enrolled at the San Francisco sites were also asked the "CAGE" questions, the most commonly used alcohol abuse screening questions.[19] The screen is considered "positive," *i.e.*, possibly indicative of alcohol abuse, if two or more of the four questions are answered in the affirmative.[20] All patients were asked if they felt that they had ever had "a drinking problem," and when they had last had an alcoholic beverage.

Diagnosis of HCV Infection

All patients tested positive for specific HCV antibodies by second or third generation enzyme-linked immunosorbent assay (ELISA; Abbott Laboratories, Chicago, IL, or ORTHO ELISA, Ortho-Biotech, Raritan, NJ), had detectable serum HCV RNA by polymerase chain reaction (PCR)-based methodology, and had liver histology compatible with chronic hepatitis C disease. Quantitative viral load and genotype were available in most patients. HCV RNA was quantified by branched DNA assay (Quantiplex, v. 2, Chiron, Emeryville, CA), or by RT-PCR (AMPLICOR Roche Diagnostic Systems, Branchburg, NJ; and National Genetics Institute, Los Angeles, CA). To allow comparison of different quantitative assays, we separated viremia into three classes or textiles, as described previously[21]: class 1 – low viremia, less than the 33.3rd percentile of the data; class 2 – intermediate viremia, between the 33.3rd and the 66.6th percentiles; class 3 – high viremia, above the 66.6th percentile. HCV genotyping was performed by standard methodology (INNO-LiPA, second generation, Innogenetics, Zwijnaarde, Belgium).

Liver Biopsies

Liver histology was assessed by staff pathologists at each of the three institutions involved. At the V.A.M.C. and U.C.S.F., the Batts-Ludwig classification system was used,[22] and in San Diego the Metavir scoring system[23] was used, both of which employ a single score for both inflammation and fibrosis. Since fibrosis score was the primary outcome variable in this study, fibrosis in a sample of Scripps biopsies was rescored in a blinded fashion at the S.F.V.A.M.C., and scoring between sites was found to be equivalent (kappa index 0.86, 95% CI 0.73–0.99).

Serum Assays

Serum alanine aminotransferase (ALT), HCV genotype, and viral load were obtained when available within 6 months of questionnaire completion. ALT was defined as "elevated" if its value closest to the time of liver biopsy was above the upper limit of the normal range at each site (San Diego 50 U/l, SFVAMC 56 U/l, UCSF 59 U/l).

Variables Examined

Demographic characteristics analyzed included age, gender, race, and military veteran status. Disease-associated variables included: risk factor for HCV acquisition (injection drug use (IDU), blood transfusion, or neither); estimated age at infection and duration of infection; HCV genotype and viral load. Age at infection was estimated as in other studies[3–5,13,16] as first exposure to IDU or blood transfusion and duration of infection was estimated from this time to the date of liver biopsy. Year of first IDU was used if both risk factors were present; if neither were present, duration of infection and age at infection were not estimated. Fibrosis progression was calculated as in other studies[3] as fibrosis score divided by duration of infection, when duration could be estimated. Alcohol-associated variables included: alcohol intake (in grams/day); time since last alcohol consumption; self-report of having had an "alcohol problem"; and "CAGE score." "Light" intake was defined as 0–20 g/day, "moderate" as 20.1–50 g/day, and "heavy" as >50 g/day, based on previous studies.[3,24] Demographic, histological, alcohol, and HCV-associated data were gathered prospectively.

Statistical Analysis

Although fibrosis scores were not normally distributed, an approximate sample size calculation was based on a *t* test comparison of fibrosis scores in two levels of alcohol consumption. Data from previous studies[3] shows a standard deviation (SD) of ~1.33 for fibrosis score. Group sizes of 100 would provide power of 0.80 using a two-tailed alpha of 0.05 to detect differences as small as 0.53 in mean fibrosis scores. Data are expressed as percentages for categorical variables; means, and SDs for normally distributed continuous variables; and medians with 95% upper and lower confidence intervals (CI) for variables which were not normally distributed (Table 1). Fibrosis was included as integer fibrosis score (0–4), rather than grouped (*e.g.*, 0–2 vs. 3–4 or "present" vs. "absent"), in each model. Demographic and histological variables and serum assays were compared across levels of fibrosis. Before fitting a continuous predictor variable as a linear term into a model, it was divided into quartiles and its relationship to the outcome variable was examined. Linear terms were then included in models only where appropriate. Chi-square tests were performed on discrete variables and Kruskal-Wallis tests on continuous variables to examine relationships between descriptive statistics by site (Table 1). Other tests were performed as noted.

Associations between predictor variables and cirrhosis were analyzed using standard logistic regression models. The associations between predictor variables and fibrosis level were modeled using proportional odds logistic regression models. These models express the effects of predictor variables in terms of odds ratios that reflect the odds of being one fibrosis level higher as a function of a one unit change in the predictor variable. This model assumes effects of a predictor variable are constant across the levels of a fibrosis outcome. This assumption is tested with a score test.[25] Variables showing associations with fibrosis in univariate analysis (significance level $P < .20$) were included in multivariate proportional odds models. In these models, only patients with values for all predictors were included.

Results

Study Population

In all, 800 patients were included in the analysis. Patients differed by center with regard to multiple characteristics (Table 1). Data not shown in Table 1 include: injection drug use history was present in 73% of S.F.V.A.M.C. patients, 72% from U.C.S.F., and 48% from La Jolla; blood transfusion history alone was present in 8%, 13%, and 29%, respectively ($P < .0001$ for differences in risk factors by sites). Of the total, 643 (80%) had one or both risk factors, and so had duration of infection estimated. All 277 patients from S.F.V.A.M.C. were military veterans, as were 17 U.C.S.F. patients, and 5 La Jolla patients.

Median fibrosis progression for the cohort overall was 0.061 U/year, 95% CI 0.057–0.064. Mean fibrosis score was 1.56 U, SD 1.18. Median inflammation score at each site was 2; median fibrosis score was 1 at U.C.S.F. and La Jolla, and 2 at S.F.V.A.M.C. Elevated ALT value was

Table 1. Distribution of Variables by Site*

	La Jolla	U.C.S.F.	S.F.V.A.M.C.	*P*
Number of patients	324	199	277	
Age (years, mean ± S.D.)	47 ± 7	47 ± 7	50 ± 7	<.0001
Gender (M/F)	218/106	126/73	269/8	<.0001
Ethnicity				<.0001
African-American	2%	9%	23%	
Asian-American	4%	7%	1%	
Caucasian	78%	69%	64%	
Latino-American	11%	4%	6%	
Other ethnicity	5%	11%	6%	
Age at infection (years, mean ± S.D.)[1]	22 ± 8	24 ± 8	24 ± 8	0.0004
Duration of infection (years, mean ± S.D.)[1]	22 ± 9	24 ± 8	25 ± 8	0.0002
CAGE ≥ 2/4	N/A	94 (48%)	180 (65%)	0.0002
Alcohol problem	78 (26%)	78 (41%)	177 (64%)	<.0001
Alcohol >50 g/d	13%	30%	47%	<.0001
Alcohol overall [g/d, median, (95% C.I.)]	8.6, (6.9–11.9)	17.3, (11.7–24.3)	46.2, (36.2–56.0)	<.0001
Alcohol-men [g/d, median, (95% C.I.)]	14.2, (9.6–15.5)	24.0, (16.1–35.7)	46.7, (36.6–56.0)	<.0001
Alcohol-women [g/d, median, (95% C.I.)]	3.4, (2.2–6.7)	7.5, (4.4–16.9)	2.0, (1.1–64.3)	0.08
Elevated ALT[2]	85%	55%	67%	<.0001
Genotype				0.008
1	61%	65%	70%	
2	13%	18%	13%	
3	18%	14%	13%	
Mixed/other	8%	3%	4%	
Viral load (tertiles)[3]				<.0001
Lowest	27%	44%	34%	
Middle	27%	32%	35%	
Upper	46%	23%	31%	
Histological inflammation (mean, ± S.D.)	1.70 ± 0.93	1.71 ± 0.78	1.70 ± 0.70	0.97
Histological fibrosis (mean, ± S.D.)	1.56 ± 1.27	1.36 ± 1.16	1.73 ± 1.24	0.006
Fibrosis score				0.01
0	70 (22%)	56 (28%)	51 (18%)	
1	114 (35%)	57 (29%)	75 (27%)	
2	69 (21%)	56 (28%)	82 (30%)	
3	32 (10%)	18 (9%)	36 (13%)	
4	39 (12%)	12 (6%)	33 (12%)	
Fibrosis progression [u/yr, median, (95% C.I.)]	0.06, (0.05–0.07)	0.05, (0.04–0.06)	0.06, (0.06–0.07)	0.03

*All variables available in >98% of patients, except as noted: [1]Estimated in 80%; [2]available in 94%; [3]available in 85%.

associated with inflammation score on a patient's liver biopsy (Mann Whitney $P < .0001$).

Alcohol Consumption

Mean alcohol intake overall was 41.6 g/day (~4 alcoholic beverages per day), but was not normally distributed, with a median of 17.4 g/day (range: 0–284). Overall, 230 patients (29%) had consumed >50 g/day over their years of drinking. Alcohol intake was highly correlated with a "positive CAGE screen" (median 74 g/day in those with a positive CAGE, 6 g/day in those with a negative CAGE, $P < .0001$) and with self-report of an "alcohol problem" (66 g/day vs. 6 g/day, $P < .0001$); 68% of patients reported abstaining from alcohol for ≥6 months prior to liver biopsy, 28% for 1–6 months, 4% for <1 month.

Alcohol intake correlated with age at biopsy (Spearman rank correlation .095, 95% CI 0.03–0.16, $P = .007$), but did not correlate with ALT value (Spearman $P = .20$) or with inflammation score on liver biopsy (Spearman $P = .84$).

Variables Associated With Fibrosis Stage

Univariate correlations between various predictor variables and fibrosis are shown in Table 2. Patient ethnicity ($P = .32$–$.88$, for each race), risk factor for HCV acquisition ($P = .36$–$.67$), and HCV genotype ($P = .25$–$.69$) did not correlate with fibrosis in univariate analysis.

Association Between Alcohol and Fibrosis

Significant alcohol use, as measured by a self-report of an "alcohol problem," or a positive CAGE screen, or alcohol use in the top 25% of patients (>59 g/day) compared to the lowest 25% (<4 g/day) was associated with increased fibrosis (Table 2). There was not a significant association between alcohol and mean fibrosis ($P = .08$) or mean fibrosis progression ($P = .62$) overall. Also, (Ta-

Table 2. Univariate Associations With Fibrosis and Cirrhosis

	Odds Ratio for Fibrosis (lower-upper 95% CI)	*P*	Odds Ratio for Cirrhosis (lower-upper 95% CI)	*P*
Male sex	1.41 (1.05–1.90)	.02	1.59 (0.88–2.90)	.12
Military veteran	1.46 (1.12–1.90)	.004	1.25 (0.79–1.99)	.34
Age at biopsy (in quartiles)		<.0001		.003
Q2* vs. Q1	1.63 (1.14–2.32)		5.84 (2.00–17.06)	
Q3 vs. Q1	2.24 (1.56–3.22)		6.83 (2.34–19.91)	
Q4 vs. Q1	2.50 (1.73–3.61)		7.15 (2.45–20.87)	
Duration of HCV infection (in quartiles)		.006		.10
Q2* vs. Q1	1.22 (0.82–1.82)		1.08 (0.47–2.48)	
Q3 vs. Q1	1.53 (1.03–2.27)		1.46 (0.67–3.20)	
Q4 vs. Q1	1.92 (1.31–2.82)		2.19 (1.07–4.49)	
Age at infection (in quartiles)		.67		.77
Q2* vs. Q1	0.82 (0.56–1.20)		1.31 (0.64–2.67)	
Q3 vs. Q1	0.81 (0.54–1.22)		1.08 (0.49–2.38)	
Q4 vs. Q1	0.93 (0.63–1.38)		1.41 (0.68–2.91)	
HCV viral load (in tertiles)		.69		.32
Middle ⅓ vs. lower ⅓	1.10 (0.79–1.54)		0.60 (0.30–1.18)	
Upper ⅓ vs. lower ⅓	0.96 (0.69–1.33)		0.90 (0.49–1.64)	
ALT (overall)	1.005 (1.004–1.007)	<.0001	1.004 (1.002–1.007)	.0002
ALT (in quartiles)		<.0001		.005
Q2* vs. Q1	1.47 (1.02–2.11)		2.46 (1.09–5.51)	
Q3 vs. Q1	1.93 (1.34–2.79)		2.30 (1.01–5.23)	
Q4 vs. Q1	3.49 (2.41–5.07)		3.97 (1.84–8.60)	
CAGE ≥2	1.40 (1.01–1.95)	.04	1.68 (0.87–3.24)	.12
Alcohol problem	1.48 (1.14–1.91)	.003	1.64 (1.03–2.60)	.03
Alcohol intake (in quartiles)		.03		.07
Q2* vs. Q1	0.89 (0.62–1.26)		0.87 (0.43–1.76)	
Q3 vs. Q1	1.08 (0.76–1.53)		1.06 (0.54–2.08)	
Q4 vs. Q1	1.49 (1.05–2.12)		1.84 (0.99–3.42)	
Inflammation				
≥2 vs. 0-1	4.75 (3.47–6.51)	<.0001	2.56 (1.78–3.70)	<.0001

*Expressed in quartiles. Data quartiles for variables: age (years): Q1: <42, Q2: 42–47, Q3: 47–51, Q4: >51; duration of HCV infection (years): <18, 18–25, 25–30, >30; age at infection (years): <18, 18–22, 22–28, >28; ALT(U/1): <56, 56–85, 85–130, >130; alcohol intake: <3.6 g/day, 3.6–17.3, 17.3–59, >59.

ble 3) each level of alcohol intake was not associated with significantly increased mean fibrosis compared to the next higher level (*i.e.*, 0 vs. 0.1–20 g/day, 0.1–20 g/day vs. 20.1–50 g/day). Figure 1 shows the incremental effects of alcohol on fibrosis. Although overall fibrosis was greater in patients with HCV who drink heavily than in those who did not, there was a range of disease in each category of alcohol intake.

Table 3. Association Between Alcohol Intake and Fibrosis

Alcohol Intake (grams/day)	Number of Patients (%)	Mean Fibrosis (± S.D.)	Odds Ratio for Fibrosis (compared to nondrinkers)	Odds Ratio Lower to Upper 95% CI	Odds Ratio *P*
Overall:					
0	50 (6%)	1.42 ± 1.10			
0.1–20	374 (47%)	1.48 ± 1.19	1.06	0.63–1.80	0.82
20.1–50	146 (18%)	1.55 ± 1.22	1.19	0.67–2.11	0.56
50.1–80	80 (10%)	1.61 ± 1.31	1.26	0.67–2.37	0.48
>80	150 (19%)	1.84 ± 1.35	1.76	0.99–3.12	0.05
In men:					
0	28 (4%)	1.36 ± 1.10			
0.1–20	250 (41%)	1.54 ± 1.19	1.26	0.63–2.54	0.51
20.1–50	128 (21%)	1.57 ± 1.21	1.32	0.63–2.75	0.46
50.1–80	67 (11%)	1.58 ± 1.28	1.32	0.60–2.90	0.53
>80	140 (23%)	1.89 ± 1.37	2.06	0.99–4.26	0.05
In women:					
0	22 (12%)	1.50 ± 1.14			
0.1–20	124 (66%)	1.35 ± 1.20	0.79	0.35–1.77	0.56
20.1–50	18 (10%)	1.39 ± 1.24	0.86	0.28–2.63	0.80
50.1–80	13 (7%)	1.77 ± 1.48	1.39	0.41–4.73	0.62
>80	10 (5%)	1.10 ± 0.57	0.68	0.18–2.60	0.57

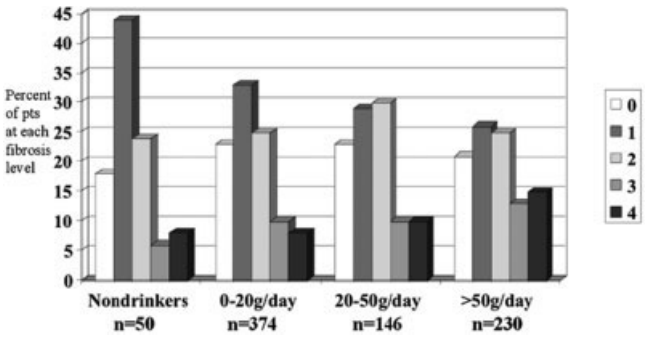

Fig. 1. Fibrosis scores by alcohol intake.

Alcohol intake was associated with a stepwise increase in mean fibrosis in the cohort overall (Table 3), and if alcohol use was dichotomized into ≥50 g/day vs. <50 g/day, there was a difference in mean fibrosis between the two groups ($P = .01$). This was not true if dichotomization was performed at lower levels of alcohol intake. Such a difference became even more statistically significant as the "cut-off" level was raised, *e.g.*, ≥80 g/day vs. <80 g/day, $P = .006$. The odds ratio for fibrosis in the listed groups (Table 3) was not increased to a statistically significant degree compared to nondrinkers until 80 g/day of alcohol were consumed. Median fibrosis progression and 95% confidence intervals by alcohol intake category: 0 g/day: 0.064 U/year (0.036–0.080); 0.1–20 g/day: 0.059 U/year (0.050–0.067); 20.1–50 g/day: 0.059 U/year (0.045–0.063); 50.1–80 g/day: 0.050 U/year (0.037–0.063); >80 g/day: 0.071 U/year (0.063–0.086). Alcohol intake did not correlate with fibrosis progression rate overall (Kruskall Wallis *P*-value .30).

Association Between Alcohol and Cirrhosis

In this study, 84 patients had cirrhosis (10.5%). Table 2 demonstrates that similar associations between predictor variables and fibrosis overall were found in those patients with cirrhosis. As with fibrosis, ethnicity, risk factor for HCV acquisition, and HCV genotype did not correlate with cirrhosis in univariate analysis (data not shown).

Women and Liver Disease/Alcohol Intake

Women drank less alcohol than men (median 5.7 g/day vs. 24.1 g/day, $P < .0001$), and had a lower mean fibrosis score than men (1.39 U vs. 1.62 U, $P = .02$), although they did not have statistically slower fibrosis progression (0.075 U/year vs. 0.081 U/year, $P = .28$). The association between alcohol intake and fibrosis was not as clear in women, however. Women did not demonstrate the same stepwise increase in mean fibrosis as men (Table 3). Only 12% of women drank >50 g/day of alcohol, but this group did not have more fibrosis than the 88% who drank less (OR fibrosis 1.15, $P = .72$) or compared to nondrinkers (OR fibrosis 0.95, $P = .92$). Fibrosis scores in women drinking >50 g/day were: Stage 0: 4; Stage 1: 11; Stage 2: 3; Stage 3: 3; Stage 4: 2.

Multivariate Model of Fibrosis

A multivariate model of fibrosis was constructed (Table 4). All variables which were significantly associated with fibrosis in univariate analysis ($P < .20$) were included in initial modeling. When duration of infection was included, the model was very similar to Table 4, and duration of infection was not independently associated with fibrosis (OR 1.17, 95% CI 0.71–1.92, $P = .55$ for the upper vs. the lowest quartile). Ultimately, duration of infection was not included in the model for the following reasons: very strong association with age (Spearman rank correlation .478, 95% CI 0.44–0.56 $P < .0001$); and duration being inestimable in 184 patients, who had lower alcohol intake than those in whom duration could be estimated. The proportional odds assumption for the model (Table 4) was met, supporting its validity. Histological inflammation, serum ALT, and patient age were independent predictors of fibrosis in all models examined. Alcohol did not display an independent association with fibrosis in multivariate models.

Discussion

Heavy alcohol use has been known for some time to be associated with hepatic fibrosis stage and fibrosis progression in patients with hepatitis C. This study examines the effect of the entire range of alcohol use in three groups of patients from different medical centers who had different levels of alcohol consumption.

One important question has been: is there a "safe" level of alcohol intake in patients with chronic HCV infection? This study does not find this to be the case. We did not find a statistically significant association between alcohol intake and mean fibrosis on liver biopsy until a consumption level of 50 g/day of alcohol, and this only in univar-

Table 4. Multivariate Proportional Odds Model for Fibrosis

		Odds Ratio	Lower-Upper 95% C.I.	*P*-Value
n = 632	Male sex	1.04	0.69-1.56	.86
	Veteran	1.29	0.92-1.80	.14
	Age*–Q2 vs. Q1	1.75	1.11-2.75	.01
	Age–Q3 vs. Q1	2.97	1.87-4.72	<.0001
	Age–Q4 vs. Q1	2.67	1.67-4.25	<.0001
	ALT	1.003	1.002-1.005	.0003
	Alcohol >59 g/d†	1.39	0.99-1.95	.06
	Inflammation	3.28	2.64-4.08	<0.0001

*Age at liver biopsy, in quartiles.

†>59 g/day represents the upper quartile of alcohol use.

iate analysis. In the cohort overall, however, both mean fibrosis and the odds ratio for fibrosis increased step-wise even among patients with less than 50 g/day of alcohol consumption. The strong correlation between alcohol intake and both "CAGE" questions and self-report of having had an "alcohol problem" encourages confidence in the validity of our method of estimating alcohol intake.Thus, light and moderate alcohol intake may be playing a role in fibrosis, but even with 800 patients, our cohort size may be inadequate to demonstrate the subtle effect of low amounts of alcohol on fibrosis. A "safe" level of alcohol intake is not demonstrated. Light and moderate intake exert less of an effect on fibrosis than heavy intake, however, and may indeed have minimal or no effect. Balancing this small risk of liver disease progression against potential cardiovascular benefit may be particularly pertinent to middle-aged men, who worldwide constitute the majority of patients with HCV, and who are also at high risk for cardiovascular disease. Risk-benefit assessment should be individualized for each patient.

Previous studies that have included light drinkers have had conflicting results. One study from an Australian liver clinic used detailed alcohol histories,[5] and did not find a statistically significant relationship between light or moderate alcohol intake and fibrosis on liver biopsy. The design of that study is very similar to the present study. Two other studies including "light" drinkers used endpoints different from the current study; the first: decompensated cirrhosis, and the second: fibrosis increase on paired liver biopsies. The first, a prospective study of American inner-city injection drug users, 33% of whom were coinfected with HIV, found a step-wise, statistically significant increase in the adjusted incidence of cirrhosis when >13 g/day and >37 g/day were consumed.[16] The second, a retrospective study of Swedish patients, found increased, light alcohol consumption (median 5.7 g/day) in the 44 patients whose fibrosis worsened over time compared to the 34 patients (median 2.6 g/day) whose fibrosis did not worsen.[17] Thus, the literature to date addressing light and moderate alcohol intake in chronic HCV is conflicting, but different endpoints and patient groups make interpretation of the data difficult.

Another finding of our study is that patients with hepatitis C may have differing susceptibility to the effects of alcohol. This is accepted in alcoholic liver disease in the absence of hepatitis C,[26] where only a subset of heavy drinkers develop cirrhosis. In our study, patients with HCV who drink heavily have, on average, more liver disease than those who do not. Individual heavy drinkers, however, may have minimal liver disease, and in fact 47% of "heavy drinkers" (>50 g/day) in this study had Stage 0 or Stage 1 liver disease. Potential explanations for this somewhat surprising finding include: differential susceptibility to alcohol; different patterns of alcohol intake (*e.g.*, binge-drinking vs. habitual drinking), which were not captured fully by our questionnaire; reversal of adverse effects of alcohol with abstinence, since our patients were generally not drinking at enrollment; and misclassification of alcohol intake based on inadequate patient recall of drinking habits and/or oversimplification in our methods of alcohol assessment. Further work is needed to determine how and in whom alcohol contributes to liver disease in HCV.

Intrahepatic inflammation, serum ALT, and patient age were the independent multivariate predictors of hepatic fibrosis in this study. The multivariate odds ratio for inflammation was highly significant, whereas that for heavy alcohol intake just missed being statistically significant. The independent effect of inflammation is supported by La Jolla patients having a similar degree of hepatic fibrosis than patients at the other two sites, despite less alcohol consumption. This could be due to an aggressive immune response in La Jolla patients, supported by their statistically higher ALT. La Jolla patients clearly drank less alcohol than patients from the other two centers, but had similar fibrosis, highlighting the importance of factors other than alcohol in their disease progression.

ALT value and histological inflammation have been found to be associated with fibrosis in several other studies[6,7,27]; the inflammatory response to hepatitis C seems to contribute to disease progression. ALT and histological inflammation were highly correlated with one another in this study. The fact that neither ALT nor histological inflammation correlated with alcohol intake in univariate analysis suggests that alcohol does not act through increased inflammation in exerting an effect on fibrosis.

Most studies of risk factors for HCV progression have also found that patient age and duration of HCV infection are primary determinants of histological fibrosis.[3,28] In univariate models in this study, both age and duration of HCV infection were associated with fibrosis, but in multivariate models only age retained its significance. This may be explained by age being a better surrogate of duration of HCV infection than our estimate of HCV duration, which is based, as in most studies,[3–5,13,16] on time of first injection drug use or blood transfusion. Fibrosis may also be truly an age-dependent process, as some have suggested.[28]

It should be noted that the degree and estimated rate of histological scarring in our cohort differs from some other published studies. Poynard et al.,[3] using essentially the same system for scoring fibrosis, found a mean fibrosis score of 1.95 U in their cohort; estimated mean duration of HCV infection was 12.4 years, and the estimated mean

rate of fibrosis progression was 0.25 U/year. Our patients had less fibrosis (mean 1.56 U), and a longer duration of HCV (mean 23.7 years), leading to a slower estimated mean rate of fibrosis progression, 0.08 U/year. Our values are similar to those published from other American liver clinic studies.[29] Differences between cohorts likely reflect differences in timing of viral acquisition, host susceptibility, and environmental factors.

Studies from some years ago found that women experienced toxicity from alcohol at lower doses and had more rapidly progressive alcoholic liver disease than men.[30,31] More recent studies have generally supported these findings,[24] although some have not.[32] The importance of alcohol intake to liver disease in HCV-positive women, however, has not been reported on extensively. One of the few studies to specifically report alcohol intake by gender in patients with HCV[13] recorded the intake in 57 women only as greater or less than 40 g/day; intake >40 g/day correlated with cirrhosis. In the present study, alcohol intake was not shown to increase fibrosis in 187 women (23% of the cohort). This may be attributable to the fact that alcohol intake in women was very low, with fewer than half drinking more than 4 drinks per week (median: 5.7 g/day). Approximately 35 drinks per week were needed to demonstrate an impact on mean fibrosis overall in this study; even the 23 women who drank this much had a range of fibrosis. Firm conclusions about the risk of alcohol in women with HCV cannot be drawn from our study, but light alcohol consumption was not shown to worsen fibrosis.

In summary, we have quantified alcohol intake in 800 patients undergoing liver biopsy at three sites. A history of heavy alcohol intake correlated with a higher degree of histological fibrosis. Light or moderate drinkers did not have statistically greater fibrosis than nondrinkers, but alcohol may play a role in their liver disease. At each level of alcohol intake, there is a broad range of liver disease; successively heavier intake leads to subtle increases in risk for fibrosis. Patient age, serum ALT, and histological inflammation retained independent correlations with fibrosis in multivariate analysis, whereas heavy alcohol intake (>59 g/day) did not. The variability in natural history for a given level of alcohol intake points to a central role for immunological and/or genetic variables in HCV disease progression.

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