Alcohol Consumption, Cigarette Smoking, and the Risk of Recurrent Acute and Chronic Pancreatitis

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Background: Recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) are associated with alcohol consumption and cigarette smoking. The etiology of RAP and CP is complex, and effects of alcohol and smoking may be limited to specific patient subsets. We examined the current prevalence of alcohol use and smoking and their association with RAP and CP in patients evaluated at US referral centers.

Methods: The North American Pancreatitis Study 2, a multicenter consortium of 20 US centers, prospectively enrolled 540 patients with CP, 460 patients with RAP, and 695 controls from 2000 to 2006. Using self-reported monthly alcohol consumption during the maximum lifetime drinking period, we classified subjects by drinking status: abstainer, light drinker (≤0.5 drink per day), moderate drinker (women, >0.5 to 1 drink per day; men, >0.5 to 2 drinks per day), heavy drinker (women, >1 to <5 drinks per day; men, >2 to <5 drinks per day), or very heavy drinker (≥5 drinks per day for both sexes). Smoking was classified as never, past, or current and was quantified (packs per day and pack-years).

Results: Overall, participants' mean (SD) age was 49.7 (15.4) years; 87.5% were white, and 56.5% were women. Approximately one-fourth of both controls and patients were lifetime abstainers. The prevalence of very heavy drinking among men and women was 38.4% and 11.0% for CP, 16.9% and 5.5% for RAP, and 10.0% and 3.6% for controls. Compared with abstaining and light drinking, very heavy drinking was significantly associated with CP (odds ratio, 3.10; 95% confidence interval, 1.87-5.14) after controlling for age, sex, smoking status, and body mass index. Cigarette smoking was an independent, dose-dependent risk factor for CP and RAP.

Conclusions: Very heavy alcohol consumption and smoking are independent risks for CP. A minority of patients with pancreatitis currently seen at US referral centers report very heavy drinking.

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CHRONIC PANCREATITIS (CP) is an inflammatory syndrome of the pancreas characterized by progressive parenchymal fibrosis, maldigestion, diabetes mellitus, and pain.[1] Excessive alcohol consumption has been identified as the primary etiologic factor in numerous studies of adult CP,[2-8] although fewer than 5% of heavy drinkers develop CP.[9,10] In 1978, a landmark South African study observed a dose-dependent risk of CP from alcohol consumption.[11] However, threshold levels and drinking patterns were not evaluated, and the study only included men. Other studies have suffered from similar limitations.[8] Cigarette smoking has been reported to be an independent risk factor for developing CP[8,12-14] and to increase its rate of progression.[15,16] Recently, genetic factors have been identified that also increase the risk of pancreatitis, independent of alcohol consumption or cigarette smoking.[17-21] To our knowledge, no previous study has evaluated the role of alcohol and smoking in both men and women in recurrent acute pancreatitis (RAP) and CP. Additionally, the current prevalence of alcohol consumption and smoking and their associated risk with RAP and CP in the United States is unknown.

We hypothesized that the etiology of RAP and CP is complex, and that the effects of alcohol and smoking may be limited to specific patient subsets. To further characterize the risk of RAP and CP

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in US men and women, we prospectively ascertained 1000 patients with pancreatitis and 695 controls from 20 centers with expertise in pancreatic diseases and performed adjusted analyses of alcohol consumption and cigarette smoking.

METHODS

STUDY POPULATION

The North American Pancreatitis Study 2 (NAPS2)[22] prospectively enrolled 1000 affected patients (540 with CP and 460 with RAP) using strict entry criteria and 695 controls from 20 secondary or tertiary pancreatic care centers across the United States between the years 2000 and 2006. Spouses and family members made up 61.7% of controls (34.2% and 27.5%, respectively), while the remaining controls were friends or unrelated to subjects with pancreatitis. A detailed study protocol and methods for the NAPS2 study have been published.[22] Recurrent acute pancreatitis was defined by the presence of 2 or more documented episodes of acute pancreatitis, and CP by the presence of changes primarily on imaging studies or histologic specimens. All patients meeting these criteria were eligible for inclusion. Each study center obtained approval from its institutional review board or ethics committee. Informed consent was obtained from all participants prior to their enrollment.

DRINKING CATEGORIES

Study participants completed a questionnaire with assistance from a trained study coordinator that included detailed information on alcohol consumption and smoking. Alcohol questions assessed use in terms of quantity, duration, patterns of use, and relationship with pancreatitis exacerbations as described in detail in an earlier publication.[22] *Ever drinking* was defined as a lifetime alcohol intake of more than 20 drinks. We stratified subjects into 5 drinking categories by average reported alcohol consumption in a month during the maximum lifetime drinking period (average number of drinks consumed on a drinking day and number of days per month this amount was consumed) using definitions similar to the National Health Interview Survey (NHIS).[23] Drinking categories included abstainers (no alcohol use or <20 drinks in a lifetime), light drinkers (≤0.5 drinks per day or ≤3 drinks per week), moderate drinkers (>0.5 to 1 drink per day or 4 to 7 drinks per week for women; >0.5 to 2 drinks per day or 4 to 14 drinks per week for men), heavy drinkers (>1 to <5 drinks per day or 8 to 34 drinks per week for women; >2 to <5 drinks per day or 15 to 34 drinks per week for men), and very heavy drinkers (≥5 drinks per day or ≥35 drinks per week for both sexes). A drinking category was assigned directly to 1507 subjects (88.9%), while in 141 subjects (8.3%) it was assigned after review of available responses on quantity, frequency, drinking patterns, and responses to TWEAK questions (TWEAK is an adapted acronym for the 5 questions used in the questionnaire: tolerance, worry, eye-opener, amnesia, and "kut" down).[22] A drinking category could not be assigned to 47 subjects (2.8%). Information on average daily drinking and duration was used to determine alcohol exposure (in kilograms) during the maximum lifetime drinking period.

DRINKING PATTERNS

As previously described,[22] subjects also provided the following information for each drinking phase of their life, beginning with the age of drinking onset: age phase started, pattern of drinking, age pattern changed, and average number of drinks consumed per day during each phase. The drinking patterns were categorized as follows: 1, abstinence; 2, occasional drinking (<15 drinks per month on average and no binges); 3, weekend drinking (≤6 drinks per day for up to 2 days per week); 4, moderate drinking (15 drinks per month up to 2 drinks per d); 5, heavier drinking (>2 drinks per day); and 6, binge drinking (at least 3 days in a row of heavy drinking of >6 drinks per day). The total duration of lifetime alcohol consumption and the proportion of time spent at different drinking levels were calculated using information on drinking patterns and associated ages.

AT-RISK DRINKING

Ever drinkers also completed the TWEAK questionnaire (hold version)[24,25] to characterize at-risk drinking habits. Based on the responses, a composite TWEAK score (range, 0-7) was generated for each individual.[24] Detailed information on the questions and derivation of the TWEAK score has been published previously.[22] A reference period (the months before getting pancreatitis) was used for patients with pancreatitis but not for controls. At-risk drinking was defined as a score of 3 or higher.

CIGARETTE SMOKING

Smoking status was classified as never (smoked <100 cigarettes in lifetime) or ever (smoked >100 cigarettes). Ever smokers were categorized as past or current smokers. Amount of smoking was categorized as less than 1 or 1 or more packs per day (ppd).[22] The number of pack-years of smoking was calculated from self-reported amount of smoking (average number of cigarettes smoked per day and the duration of smoking) and stratified as less than 12, 12 to 35, and more than 35 pack-years.

STATISTICAL ANALYSIS

Descriptive analyses are presented as proportions for categorical data and as mean (SD) values or medians and interquartile ranges (IQR) for continuous data. Comparisons of continuous variables between controls and patients with pancreatitis were performed using 1-way analysis of variance and Kruskal-Wallis tests where applicable. If significant results were observed, appropriate 2-group comparisons were performed using the *t* test or Mann-Whitney test. Categorical data were compared using the χ^2 test. The distributions of subjects across drinking categories, amount of smoking, and BMI (≤25, >25 to ≤30, or >30) were compared using the Cochran-Armitage test. The correlation between the drinking categories and TWEAK scores was tested using the Spearman correlation coefficient.

Multivariable logistic regression was used to assess associations of alcohol consumption and cigarette smoking with pancreatitis after controlling for the potential confounding variables of age, sex, and current or maximum body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). Data were evaluated for colinearity and interactions. For CP, we also performed stratified regression analyses for men and women; abstainers and ever drinkers; never and ever smokers; whites and blacks; and drinking categories. Age was assessed as a continuous variable; all other variables in the models were categorical variables, including alcohol (drinking categories), smoking (never or ever; never, <1, or ≥1 ppd; never, <12, 12-35, or >35 pack-years), BMI (≤25, >25 to ≤30, or >30) and sex. We used abstainers and light drinkers as the reference category for alcohol consumption. Regression models were evaluated by the goodness of fit χ^2 test. Two-sided *P* values less than .05 were considered significant. Data analysis was performed using the R Project software (www.r-project.org) and SPSS version 16 (SPSS Inc, Chicago, Illinois).

Table 1. Demographic and Selected Risk Factors[a]

Characteristic	Controls	RAP	*P* Value[b]	CP	*P* Value[c]	*P* Value[d]
			All Subjects			
Subjects, No.	695	460		540		
Age at enrollment, mean (SD), y	52.2 (14.5)	46.0 (15.8)	<.001	49.5 (15.4)	<.01	<.001
Race			.22		<.01	<.01
White	606 (87.4)	415 (90.4)		458 (85)		
Black	41 (5.9)	24 (5.2)		58 (10.8)		
Other	46 (6.6)	20 (4.4)		23 (4.3)		
Drinking category[e]			.13		<.001	<.001
Abstainer	178 (26.8)	120 (26.7)		124 (23.1)		
Light	205 (30.9)	124 (27.6)		101 (18.8)		
Moderate	153 (23.1)	106 (23.6)		108 (20.1)		
Heavy	88 (13.3)	51 (11.4)		67 (12.5)		
Very heavy	39 (5.9)	48 (10.7)		136 (25.4)		
At-risk drinking[e]	85 (12.2)	77 (16.7)	<.05	171 (31.7)	<.001	<.001
Smoking status			.20		<.001	<.001
Never	346 (50.3)	204 (44.9)		153 (28.6)		
Ever						
Past	202 (29.4)	145 (31.9)		129 (24.1)		
Current	140 (20.3)	105 (23.1)		253 (47.3)		
Smoking amount, pk-y			.06		<.001	<.001
<12	111 (17.8)	71 (17.6)		76 (16.7)		
12-35	106 (17.0)	76 (18.9)		108 (23.7)		
>35	61 (9.8)	52 (12.9)		118 (25.9)		
Smoking amount, ppd			<.01		<.001	<.001
<1	157 (23.5)	93 (20.9)		147 (28.7)		
≥1	164 (24.6)	149 (33.4)		213 (41.5)		
BMI (max)[e]			.39		<.001	<.01
Normal	128 (19.9)	89 (21.8)		132 (28.6)		
Overweight	220 (34.2)	142 (34.7)		162 (35.0)		
Obese	295 (45.9)	178 (43.5)		168 (36.4)		
			Men			
Subjects	249 (35.8)	205 (44.6)	<.01	283 (52.4)	<.001	<.05
Age at enrollment, mean (SD), y	53.2 (15.3)	47.4 (15.2)	<.001	49.6 (15.0)	<.01	.11
Race			.88		<.05	<.05
White	220 (88.7)	184 (90.2)		240 (84.8)		
Black	14 (5.6)	10 (4.9)		33 (11.7)		
Other	14 (5.6)	10 (4.9)		10 (3.5)		
Drinking category[e]			.10		<.001	<.001
Abstainer	43 (17.8)	29 (14.4)		36 (12.8)		
Light	56 (23.2)	41 (20.4)		30 (10.7)		
Moderate	84 (34.9)	77 (38.3)		73 (26.0)		
Heavy	34 (14.1)	20 (10.0)		34 (12.1)		
Very heavy	24 (10.0)	34 (16.9)		108 (38.4)		
At-risk drinking[e]	46 (18.5)	52 (25.4)	.10	125 (44.2)	<.001	<.001
Smoking status			.16		<.001	<.001
Never	108 (43.9)	75 (37.1)		55 (19.6)		
Ever						
Past	96 (39.0)	79 (39.1)		74 (26.4)		
Current	42 (17.1)	48 (23.8)		151 (53.9)		
Smoking amount, pk-y			<.05		<.001	<.001
<12	40 (17.9)	28 (15.5)		38 (15.9)		
12-35	48 (21.5)	45 (24.9)		60 (25.1)		
>35	27 (12.1)	33 (18.2)		86 (36.0)		
Smoking amount, ppd			<.05		<.001	<.001
<1	50 (21.1)	37 (18.8)		73 (27.1)		
≥1	79 (33.3)	85 (43.1)		141 (52.4)		
BMI (max)[e]			.07		<.001	<.05
Normal	20 (8.8)	35 (18.8)		59 (24.5)		
Overweight	99 (43.4)	67 (36.0)		95 (39.4)		
Obese	109 (47.8)	84 (45.2)		87 (36.1)		

(continued)

RESULTS

Overall, the mean (SD) age for the NAPS2[22] cohort was 49.7 (15.4) years; 87.5% were white, and 56.5% were women. Controls and patients with CP were older than patients with RAP, and a greater proportion of controls were women (**Table 1**). Drinking behavior differed by sex and pancreatitis type. Heavy or very heavy drinking was reported by a much greater proportion of patients with CP than controls or patients with RAP. While approximately half of men with CP were heavy or very heavy drinkers, close to two-thirds of women with CP were self-reported abstainers or light drinkers. The demographics and distribution of drinking and smoking categories were generally similar across the top 10 centers that recruited over 80% of all participants.

Table 1. Demographic and Selected Risk Factors[a] (continued)

Characteristic	Controls	RAP	*P* Value[b]	CP	*P* Value[c]	*P* Value[d]
			Women			
Subjects	446 (64.2)	255 (55.4)	<.01	257 (47.6)	<.001	NR
Age at enrollment, mean (SD), y	51.7 (14.0)	44.9 (16.2)	<.001	49.3 (16.5)	<.05	<.01
Race			.20		.12	NR
White	386 (86.7)	231 (90.6)		218 (85.2)		
Black	27 (6.1)	14 (5.5)		25 (9.8)		
Other	32 (7.2)	10 (3.9)		13 (5.1)		
Drinking category[e]			.69		.07	NR
Abstainer	135 (32.0)	91 (36.7)		88 (34.5)		
Light	149 (35.3)	83 (33.5)		71 (27.8)		
Moderate	69 (16.4)	29 (11.7)		35 (13.7)		
Heavy	54 (12.8)	31 (12.5)		33 (12.9)		
Very heavy	15 (3.6)	14 (5.6)		28 (11.0)		
At-risk drinking[e]	39 (8.7)	25 (9.8)	.74	46 (17.9)	<.001	<.01
Smoking status			.76		<.001	<.01
Never	238 (53.8)	129 (51.2)		98 (38.4)		
Ever						
Past	106 (24.0)	66 (26.2)		55 (21.6)		
Current	98 (22.2)	57 (22.6)		102 (40.0)		
Smoking amount, pk-y			.91		<.001	<.01
<12	71 (17.7)	43 (19.4)		38 (17.6)		
12-35	58 (14.5)	31 (14.0)		48 (22.2)		
>35	34 (8.5)	19 (8.6)		32 (14.8)		
Smoking amount, ppd			.14		<.001	<.05
<1	107 (24.9)	56 (22.5)		74 (30.3)		
≥1	85 (19.8)	64 (25.7)		72 (29.5)		
BMI (max)[e]			.80		<.05	.07
Normal	108 (26.0)	54 (24.2)		73 (33.0)		
Overweight	121 (29.2)	75 (33.6)		67 (30.3)		
Obese	186 (44.8)	94 (42.2)		81 (36.7)		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CP, chronic pancreatitis; max, maximum; NR, not reported; pk-y, pack-years of smoking; ppd, packs of cigarettes per day; RAP, recurrent acute pancreatitis.

[a] Unless otherwise indicated, data are reported as number (percentage) of subjects; all proportions presented are based on effective numbers. Information was missing from the following data categories at the time of analysis: race (2 controls, 1 RAP, and 1 CP); drinking category (32 controls, 11 RAP, and 1 CP), smoking status (7 controls, 6 RAP, and 5 CP), smoking pk-y (71 controls, 57 RAP, and 85 CP); smoking, ppd (28 controls, 14 RAP, and 27 CP); and BMI (52 controls, 51 RAP, and 78 CP).

[b] Control vs RAP.

[c] Control vs CP.

[d] RAP vs CP.

[e] For the definitions of all drinking categories, see the "Methods" section. For BMI, normal (≤25), overweight (>25 to ≤30), and obese (>30).

Figure 1 illustrates the distribution of drinking categories for controls and patients with pancreatitis. Alcohol exposure (average drinks per day [**Figure 2**A], duration, and amount of alcohol consumed during the maximum lifetime drinking period) and the proportion of lifetime drinking spent at higher drinking levels (ie, levels 5 or 6) increased from light to very heavy drinkers for both controls and patients with pancreatitis.

Very heavy drinkers formed a distinct subgroup of controls and patients with pancreatitis. Alcohol exposure during the maximum lifetime drinking period in this subgroup was much higher than among the other drinking categories. These individuals also spent a higher proportion of their life engaging in heavier or binge drinking. An overlap for alcohol exposure with very heavy drinkers was observed for 10% to 20% of moderate drinkers and 15% to 30% of heavy drinkers.

Overall, the lifetime drinking duration for controls (median, 29 years; IQR, 17-38) and patients with CP (median, 27; IQR, 17-37) was higher than for patients with RAP (median, 22; IQR, 9-32). Binge drinking during any life period was reported by 4.6% of controls, 7.3% of patients with RAP, and 14.8% of patients with CP who provided responses to questions on drinking categories. Among patients with pancreatitis, most binge drinkers were either heavy drinkers (30% of RAP and 8% of CP) or very heavy drinkers (65% of RAP and 88% of CP). The proportion of time spent binge drinking by very heavy drinkers increased from controls to RAP and CP. At-risk drinking was more common for patients with CP than RAP or controls among both men and women (Table 1). A strong correlation was observed between TWEAK score and drinking categories for the entire cohort ($r=0.69$; $P<.001$) as well as among the individual groups (Figure 2B).

Cigarette smoking was more prevalent among patients with CP than among controls and patients with RAP (Table 1). The prevalence and amount of smoking (**Figure 3**) increased linearly with the level of drinking in controls and patients with pancreatitis. Almost two-thirds of very heavy drinkers and 51.6% of heavy drinkers with CP reported smoking 1 or more packs per day of cigarettes compared with 13.9% of abstainers and 34.3% of light drinkers. The amount of smoking was significantly higher (among smokers) in patients with CP (26.6 pack-years; IQR, 12.0-46.0) compared with RAP subjects (19.5 pack-years; IQR, 7.9-36.1) ($P=.001$) and controls (16.2 pack-years; IQR, 6.0-32.7) ($P<.001$). Patients with CP also had significantly longer smoking duration (me-

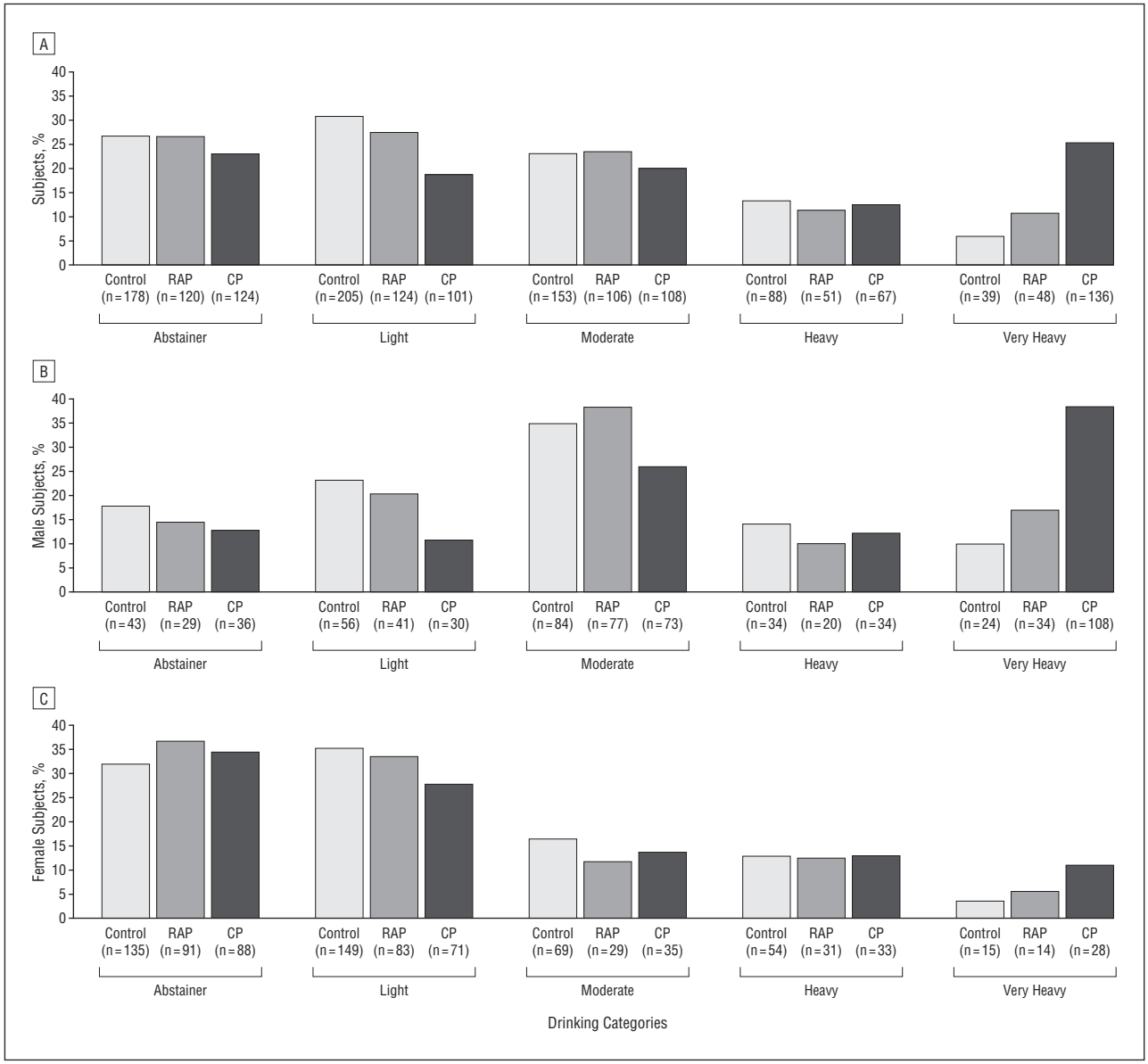

Figure 1. Distribution of drinking categories among all subjects (A), men only (B), and women only (C). Percentages are based on self-reported alcohol consumption during the maximum lifetime drinking period among controls and patients with recurrent acute pancreatitis (RAP) or chronic pancreatitis (CP). Definitions of drinking categories are detailed in the "Methods" section.

dian, 30.5 years; IQR, 19.7-39.0) than controls (median, 21.9 years; IQR, 11.4-33.1) ($P<.001$) and patients with RAP (median, 22.7 years; IQR, 12-32) ($P<.001$). Duration of smoking for patients with CP was significantly longer than for controls for all drinking categories except abstainers and light drinkers; duration of smoking for patients with CP was also significantly longer than for patients with RAP who were light or heavy drinkers.

Results for multivariable logistic regression analyses for RAP and CP are summarized in **Table 2**. In adjusted models, increasing age appeared to have a negative association with RAP (odds ratio [OR] for 10-year increase in age, 0.72; 95% confidence interval [CI], 0.65-0.79) ($P<.001$) and CP (OR for 10-year increase in age, 0.80; 95% CI, 0.73-0.89) ($P<.001$). Compared with controls, patients with RAP (OR, 1.61; 95% CI, 1.19-2.18) ($P=.002$) and CP (OR, 1.53; 95% CI, 1.13-2.07) ($P=.01$) were more often men. While heavy smoking was positively associated with RAP, alcohol consumption was not associated with RAP at any level. Compared with abstention and light drinking (after we controlled for age, sex, BMI, and smoking), very heavy alcohol consumption was significantly associated with CP (OR, 3.10; 95% CI, 1.87-5.14) ($P<.001$). The association between smoking and CP was dose-dependent.

Stratified models for CP are summarized in **Table 3**. Very heavy drinking was significantly associated with CP in men, ever smokers, whites, and blacks. A dose-dependent relationship between smoking and CP was noted for men, women, ever drinkers, and whites. When we tested for interaction between drinking categories and smoking (never/ever or amount), a nonsignificant main effect was seen for the interaction term. However, a trend for interactive relationship between drinking and smoking was ob-

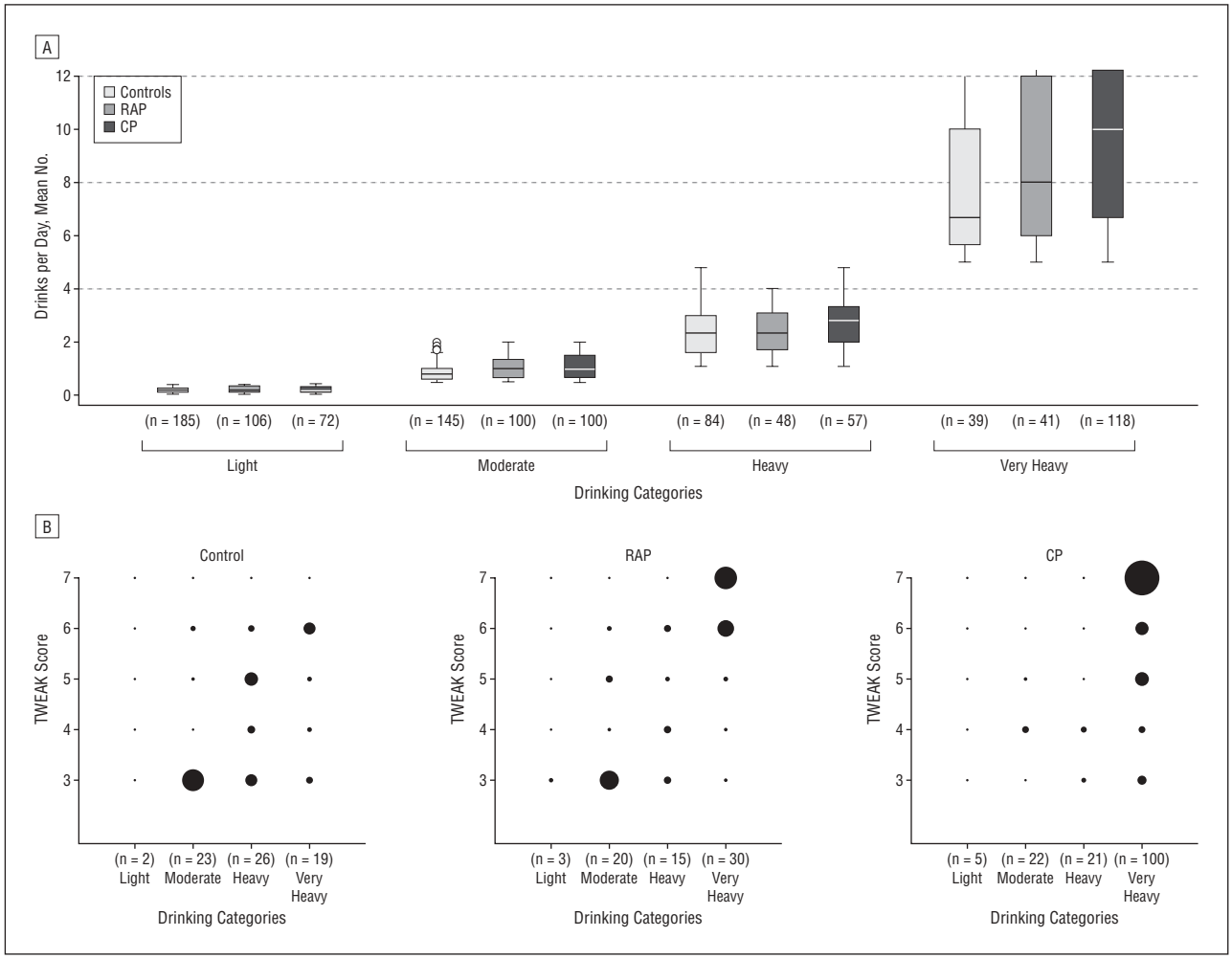

Figure 2. Distribution of self-reported alcohol consumption (A) and at-risk drinking behavior (B). Definitions of drinking categories are detailed in the "Methods" section. A, Alcohol consumption (average drinks per day) among controls and patients with recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) stratified by drinking categories. Data are presented as medians and interquartile ranges (IQR). Error bars represent data falling 1.5 IQR above and below the 25th and 75th percentiles, and open circles represent outliers. B, At-risk drinking behavior (defined as a TWEAK score[22] of 3 or higher) among controls and patients with RAP and CP. All subjects with a TWEAK score lower than 3 and subjects who were assigned a drinking category are not shown in the figure.

served in stratified models. Among ever smokers, the odds of a patient with CP being a very heavy drinker were almost 5 times greater than the odds of being an abstainer or light drinker (Table 3). In stratified models for drinking categories, after controlling for age, sex, and maximum BMI, we found that the ORs for heavy smoking associated with CP increased with the level of drinking (**Table 4**). Among heavy or very heavy drinkers, the odds of a patient with CP being a heavy smoker (>35 pack-years) were 13 times greater than those of being a never smoker. A similar observation was noted when smoking was used in the models as ever vs never (data not shown) or as packs per day (Table 4). The trends were stronger for pack-years of smoking than for packs per day, indicating that the duration of smoking is important in addition to the amount of cigarettes smoked per day.

COMMENT

To our knowledge, this is the largest US study of risk factors for RAP and CP to date. We observed a smaller than expected relationship of alcohol consumption and pancreatitis and confirmed a significant association of very heavy alcohol consumption and cigarette smoking with CP. Our study is the first to our knowledge to demonstrate that a significant increase in the risk of CP occurs only at or above the threshold of 5 alcoholic drinks per day. Contrary to previous studies,[2,4-8] only 38.4% of men and 11% of women with CP were very heavy drinkers. Although heavy smokers tended to be heavy drinkers, smoking itself was a significant risk factor for pancreatitis.

Accurate quantification of alcohol consumption and its relationship to disease risk is a challenge in any observational study. We used drinking category definitions similar to those used in the NHIS[23] US general population survey and the recommendations of other government agencies,[26] although we divided the NHIS heavier drinking category into heavy and very heavy to perform more precise comparisons. Self-reported alcohol intake during the maximum lifetime drinking period served as primary data to create drinking categories. This criterion was chosen for subject classification, rather than total lifetime alcohol consumption, to reflect the time of highest alcohol-associated risk. Furthermore, use of lifetime alcohol

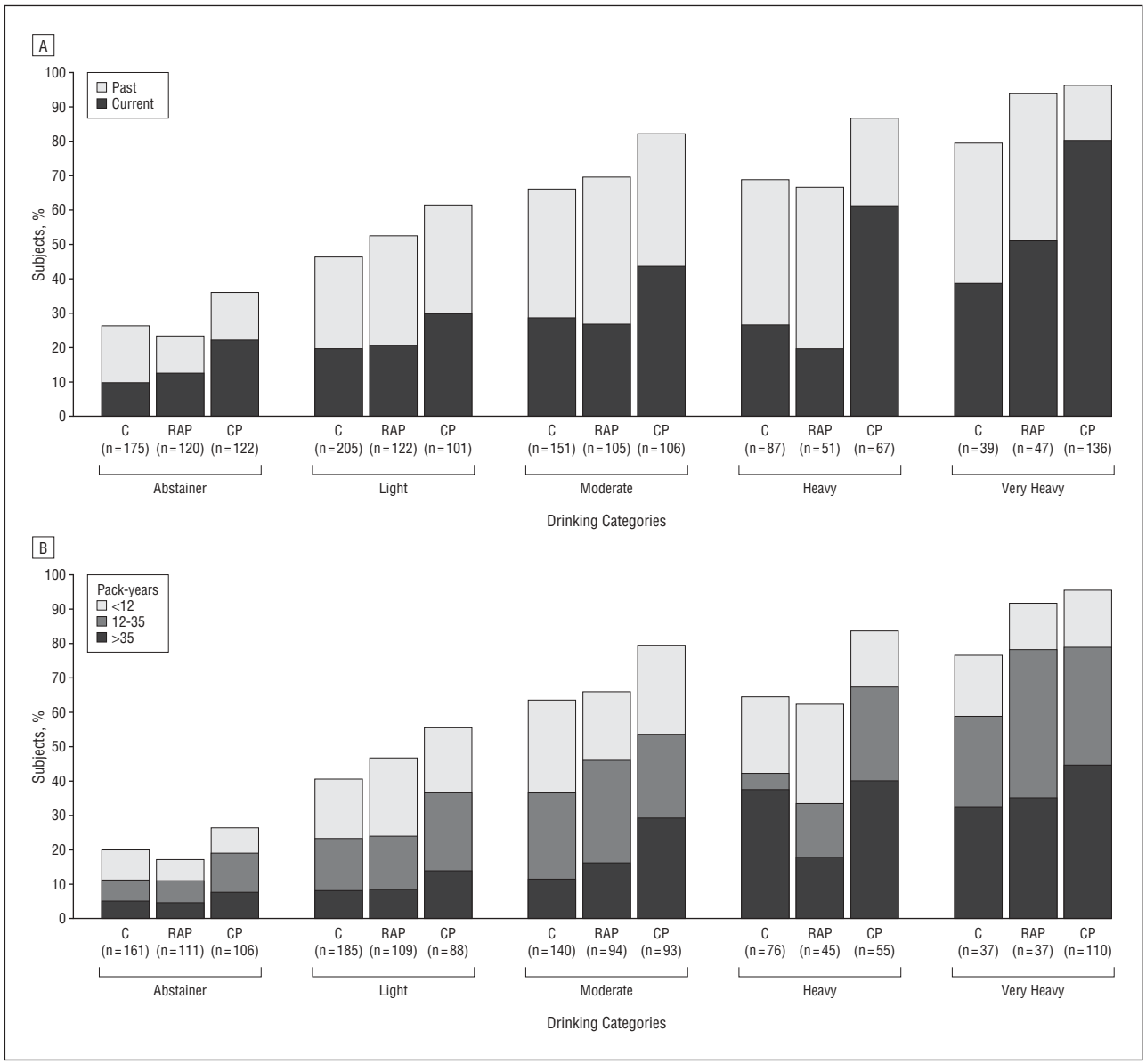

Figure 3. Distribution of self-reported smoking status (A) and amount (B) stratified by drinking categories. All proportions are based on effective numbers, and never smokers account for the proportions not reflected in the graphs. C indicates control group; CP, chronic pancreatitis group; RAP, recurrent acute pancreatitis group.

consumption criteria would classify older individuals with small amounts of daily alcohol consumption over many years in the same risk category as younger individuals who consumed alcohol more heavily for a few years (eg, 100 kg of alcohol can be consumed in 11.6 years at 2 drinks per day or in only 4.6 years at 5 drinks per day).

During the maximum lifetime drinking period, only about one-fourth of patients with CP reported alcohol consumption in amounts typically associated with CP. To avoid underestimating heavy drinking, we analyzed our data using several cutoffs. When we included subjects in the moderate and heavy drinking categories whose alcohol exposure during the maximum lifetime drinking period overlapped with very heavy drinkers, the proportion of very heavy drinkers increased to 9.8% of controls, 13.8% of patients with RAP, and 31.7% of the CP group. Positing a lower threshold for heavy drinking (ie, >14 drinks per week for men and >7 drinks per week for women), we found that the proportion of heavy or very heavy drinkers among patients with CP was 37.9% (50.5% men, 23.9% women). Positing the presence of either an overlap of alcohol exposure during the maximum lifetime drinking period or at-risk or binge drinking, we found that the proportion of very heavy drinkers increased to 17.4% among controls, 21.7% among patients with RAP, and 40.2% (58.3% men, 20.2% women) among participants with CP. Using only average number of drinks on drinking days and omitting frequency increased the proportion of subjects drinking 5 or more drinks on a drinking day to 41.6% (57.2% men, 19.7% women) for patients with CP. However, such criteria classify an infrequent drinker who consumes 5 or more drinks on a drinking day as a very heavy drinker and classifies a large proportion of controls (24.1% overall, 39.1% men

Table 2. Multivariable Logistic Regression Analyses Showing Associations of Alcohol Consumption and Smoking With RAP and CP[a]

Characteristic	RAP (n=364 [79.1%])[b] OR (95% CI)	*P* Value	CP (n=416 [77.0%])[b] OR (95% CI)	*P* Value
Alcohol use				
Abstainer or light	1 [Reference]		1 [Reference]	
Moderate	0.82 (0.57-1.18)	.29	0.81 (0.56-1.18)	.27
Heavy	0.70 (0.45-1.10)	.12	0.83 (0.54-1.29)	.41
Very heavy	1.16 (0.64-2.09)	.62	3.10 (1.87-5.14)	<.001
Smoking status, pk-y				
Never	1 [Reference]		1 [Reference]	
<12	0.96 (0.65-1.41)	.83	1.34 (0.90-2.01)	.14
12-35	1.44 (0.97-2.13)	.07	2.15 (1.46-3.17)	<.001
>35	1.91 (1.17-3.11)	.01	4.59 (2.91-7.25)	<.001
BMI (max)				
Normal	1 [Reference]		1 [Reference]	
Overweight	0.88 (0.60-1.31)	.53	0.70 (0.48-1.01)	.06
Obese	0.91 (0.63-1.32)	.63	0.51 (0.36-0.74)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CP, chronic pancreatitis; max, maximum; OR, odds ratio; pk-y, pack-years of smoking; RAP, recurrent acute pancreatitis.

[a] Models shown are adjusted for age and sex; smoking status (pk-y); and BMI (normal, ≤25; overweight, >25 to ≤30; and obese, >30). Models using other smoking variables (ever vs never, never vs past vs current, and packs per day) and current BMI had larger sample sizes for all groups and showed similar associations.

[b] Effective sample size; the control group effective sample size was 555 (79.8%) for both comparisons.

Table 3. Multivariable Logistic Regression Analyses Showing Associations of Alcohol Consumption and Smoking With CP Subjects and Controls[a]

Characteristic	Men	Women	Ever Drinkers	Never Drinkers (Abstainers)[b]	Ever Smokers	Never Smokers	Whites	Blacks
Sample sizes, No. (%)								
Controls	197 (79.1)	358 (80.2)	431 (88.8)	145 (81.4)	307 (89.8)	302 (87.3)	485 (80)	31 (75.6)
CP	219 (77.3)	197 (76.7)	324 (77.6)	92 (74.2)	325 (85.1)	132 (86.3)	353 (77.1)	46 (79.3)
Alcohol use								
Abstainer or light	1 [Reference]	1 [Reference]	NA	NA	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	0.93 (0.53-1.64)	0.78 (0.45-1.33)	NA	NA	1.00 (0.64-1.56)	0.72 (0.38-1.35)	0.78 (0.53-1.17)	2.43 (0.32-18.49)
Heavy	0.91 (0.44-1.88)	0.86 (0.49-1.50)	NA	NA	1.06 (0.65-1.73)	0.63 (0.28-1.41)	0.76 (0.48-1.20)	2.15 (0.23-19.78)
Very heavy	4.56 (2.22-9.36)[c]	1.95 (0.90-4.24)	NA	NA	4.69 (2.76-7.97)[c]	1.37 (0.37-5.08)	2.51 (1.46-4.34)[c]	20.86 (1.38-316.13)[d]
Smoking, pk-y								
Never	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	NA	NA	1 [Reference]	1 [Reference]
<12	1.50 (0.78-2.91)	1.27 (0.76-2.11)	2.04 (1.31-3.17)[e]	0.81 (0.31-2.15)	NA	NA	1.21 (0.79-1.85)	1.20 (0.26-15.32)
12-35	2.52 (1.35-4.70)[e]	2.08 (1.26-3.44)[e]	3.29 (2.18-5.08)[c]	3.26 (1.23-8.67)[d]	NA	NA	2.04 (1.35-3.10)[e]	6.20 (0.83-46.06)
>35	8.34 (4.13-16.84)[c]	2.63 (1.39-5.01)[e]	8.07 (4.97-13.08)[c]	2.35 (0.71-7.78)	NA	NA	4.71 (2.92-7.58)[c]	4.26 (0.25-75.13)
BMI (max)								
Normal	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Overweight	0.48 (0.24-0.94)[d]	0.88 (0.55-1.41)	0.70 (0.46-1.06)	0.56 (0.25-1.23)	0.51 (0.32-0.81)[e]	1.07 (0.61-1.89)	0.79 (0.53-1.19)	0.17 (0.03-1.16)
Obese	0.39 (0.20-0.76)[c]	0.59 (0.38-0.92)[d]	0.45 (0.30-0.68)[c]	0.75 (0.36-1.56)	0.32 (0.20-0.50)[c]	0.85 (0.49-1.48)	0.64 (0.43-0.95)[d]	0.14 (0.02-0.95)[d]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CP, chronic pancreatitis; max, maximum; NA , not applicable; pk-y, pack-years of smoking.

[a] Unless otherwise noted, data are reported as odds ratios (95% confidence intervals). Models shown are adjusted for age and sex; smoking status (pk-y); and BMI (normal, ≤25; overweight, >25 to ≤30; and obese, >30). Models using other smoking variables (ever vs never, never vs past vs current, and packs per day) and current BMI had larger sample sizes for all groups and showed similar associations.

[b] For never drinkers (abstainers), the model categorizing smoking as ever vs never showed an association of ever smoking with CP (odds ratio, 1.91; 95% confidence interval, 1.11-3.31).

[c] $P \leq .001$.

[d] $P < .05$.

[e] $P < .01$.

and 15.5% women) as very heavy drinkers. Regardless of classification, the proportion of pancreatitis that can be attributed to heavy alcohol intake in our study is much lower than reported in many studies of CP.[2,4-8]

Our observation of a lower prevalence of heavy drinking among patients with CP is not completely unexpected. Most of the previous large studies of CP were based on evaluations conducted between 1960 and 1990 (compared with 2000-2006 for NAPS2[22]), when alcohol was the predominant recognized etiologic factor for CP.[2,5-7] Recently, more evidence has been accumulating for other causes of CP, including genetic mutations in *PRSS1*, *CFTR*, *SPINK1*, and chymotrypsin C genes.[17-21] Therefore, subjects without an obvious cause might be more likely to

Table 4. Multivariable Logistic Regression Findings for the Association of Smoking With CP Stratified by Drinking Categories[a]

Characteristic	Drinking Category[b]			
	Abstainer	Light	Moderate	Heavy or Very Heavy[c]
Smoking Measured in Pack-years				
Controls, No. (%)	145 (81.4)	174 (84.9)	132 (86.3)	104 (81.9)
CP, No. (%)	92 (74.2)	79 (78.2)	89 (82.4)	156 (76.8)
Smoking, pk-y				
Never	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
<12	0.81 (0.31-2.15)	1.51 (0.71-3.21)	1.87 (0.82-4.28)	3.13 (1.25-7.88)[d]
12-35	3.26 (1.23-8.67)[d]	2.31 (1.10-4.85)[d]	2.17 (0.96-4.90)	4.47 (1.93-10.34)[e]
>35	2.35 (0.71-7.78)	3.27 (1.26-8.49)[d]	7.59 (2.93-19.63)[e]	13.41 (5.23-34.4)[e]
Smoking Measured in Packs per Day				
Controls, No. (%)	151 (84.8)	186 (90.7)	139 (90.8)	114 (89.7)
CP, No. (%)	97 (78.2)	83 (82.2)	93 (86.1)	169 (83.3)
Smoking, packs per day				
Never	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
<1	1.96 (0.92-4.19)	1.31 (0.68-2.55)	2.14 (1.00-4.57)	4.50 (1.97-10.27)[e]
≥1	1.50 (0.68-3.35)	3.23 (1.63-6.39)[f]	3.20 (1.54-6.65)[f]	5.97 (2.73-13.04)[e]

Abbreviations: CP, chronic pancreatitis; pk-y, pack-years.

[a] Unless otherwise indicated, data are reported as odds ratios (95% confidence intervals). Models are adjusted for age, sex, and maximum body mass index.

[b] No significant main effect was seen for the interaction term between drinking categories and smoking categories in the model containing all drinking categories. Stratified analyses were performed to assess for trends.

[c] Separate models for heavy and very heavy drinking showed stronger association for smoking (higher odds ratios) for very heavy drinkers, but the confidence intervals were large, reflecting small sample size.

[d] $P<.05$.

[e] $P<.001$.

[f] $P<.01$.

be referred to expert centers for evaluation (referral bias). Our overall lower rates of heavy drinking may also be attributed to our study's greater proportion of women compared with other studies.[2,4-8] Finally, NAPS2[22] used imaging evidence on endoscopic retrograde cholangiopancreatography or computed tomography as the primary enrollment criteria. In contrast, many previous studies of CP were conducted prior to routine clinical use of computed tomography or magnetic resonance imaging, when diagnosis relied on less sensitive techniques such as the presence of steatorrhea, diabetes mellitus, and pancreatic calcifications on abdominal radiographs. These features are commonly observed in alcoholic men who are heavy smokers.

We found the threshold drinking amount for association between alcohol use and CP to be 5 or more drinks per day. The wide spectrum of reported smoking and drinking habits in this US population allowed us to evaluate the role of alcohol and smoking in stratified analyses. Although ours is the largest study of its kind to our knowledge, the current study was not adequately powered for analysis of all important subgroups (eg, small proportion of very heavy drinkers among women, very heavy drinkers among nonsmokers, nonsmokers among very heavy drinkers, and a small number of blacks). However, our results point to important trends that should be addressed in future studies. Although there were a limited number of blacks in the NAPS2 study, the previously reported association between alcohol and CP in blacks was confirmed, suggesting racial differences in susceptibility to alcoholic pancreatitis.[14,27]

Our results confirm the association between smoking and CP[8,12,16,28] and demonstrate that this effect is dose dependent. A lack of significance for the interaction term between drinking and smoking is likely owing to coexistent heavy drinking and smoking habits as well as a low prevalence of very heavy drinking among non-smokers and heavy smoking at lower levels of drinking. However, the trend toward synergistic effect of increasing tobacco use plus alcohol use observed in this study was expected based on several observations. In our study, the primary diagnostic criteria for CP was the presence of pancreatic fibrosis. Although the biology of fibrosis is complex, it is now clear that pancreatic stellate cells are responsible for the deposition of most of the extracellular fibrotic proteins, including collagen I and II, fibronectin, and other matrix proteins.[29-31] Stellate cells are transformed from inactive to active states and proliferate in the context of injury, free radicals, proinflammatory cytokines, and other factors. The deposition of matrix proteins is driven by additional factors, including the anti-inflammatory cytokine transforming growth factor β1 and various growth factors.[29-32] Both alcohol and components of tobacco (eg, carbon monoxide) are known to have significant effects on the immune system,[33,34] but the synergistic mechanisms that lead to fibrosis in CP in humans have not yet been determined. An inverse association was observed between BMI and CP. Plausible hypotheses for this association include weight loss from malabsorption or fear of eating secondary to pain.[5,35] In addition, patients with CP were often smokers, and cigarette smoking is associated with lower weight and BMI.[36]

Potential limitations for the generalizability of our results might include the choice of controls, underreporting of alcohol consumption by study subjects, misclassification of subjects into drinking categories, misclassification of subjects into pack-year categories, higher proportion of women, and participation of expert centers for patient

enrollment. The choice of spouses, relatives, or friends as controls who may have shared drinking and smoking habits with affected participants could have introduced a conservative bias and lowered the ORs for alcohol use and smoking with pancreatitis. The prevalence of heavy or very heavy drinkers among controls was higher than in the general population.[23] However, this finding was likely owing to our use of a different reference period for creation of drinking categories (maximum lifetime drinking period rather than just the past 12 months).[23] Analysis of current drinking in our controls demonstrated that the distribution of heavier drinking was generally similar to the US general population.[23]

Self-reported alcohol consumption has been shown to be a reliable and valid measure of an individual's alcohol consumption when compared with other measures in research settings (in-person interviews and collateral reports and/or sources).[37,38] The validity of drinking category assignments in our study was confirmed by the significant correlation between the drinking categories with self-reported alcohol exposure, drinking patterns, and answers to the TWEAK questionnaire.[24,25] The sensitivity of detecting at-risk drinking in patients with CP in our study (using very heavy drinking as the reference) was slightly lower (87%), and the specificity higher (86%), than previously reported results of studies of known alcoholics.[24]

Although our study included a higher proportion of women (47.6% of CP), 35% of patients in the largest US study on idiopathic and alcoholic CP were women.[5] We performed stratified analyses for the prevalence and associations of alcohol and smoking. Therefore, a lower prevalence of very heavy drinking in our cohort cannot be explained solely on the basis of a higher proportion of women in the NAPS2 cohort.[22] Our study population was enrolled from secondary and tertiary centers with expertise in pancreatic diseases. A lower proportion of very heavy drinkers and a higher proportion of women in our study highlight the need for future studies to determine the current distribution of demographics and risk factors in the United States at a population level.

While our study confirms very heavy alcohol consumption and cigarette smoking as independent predictors of CP, it also demonstrates that the majority of CP subjects seen at US referral centers are not alcoholics and that many, in fact, are abstainers. Our results indicate that patients with CP can be stratified into 3 distinct categories: (1) those with no or minimal alcohol intake for whom alcohol is unrelated to their disease; (2) very heavy drinkers in whom alcohol and smoking may play a dominant role; and (3) moderate or heavy drinkers where alcohol might be an etiologic cofactor with smoking, other environmental factors, or genetic variables.

In conclusion, only very heavy alcohol consumption and cigarette smoking are significant independent risk factors for CP. Risk for CP from alcohol consumption occurs above a threshold level, while risk due to smoking is dose dependent. Drinking levels in subjects with RAP are similar to controls. Only a minority of patients with RAP and CP currently seen at secondary or tertiary US centers could be categorized as very heavy drinkers.

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