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Prospective Study of Alcohol Drinking, Smoking and Pancreatitis: The Multiethnic Cohort

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Abstract

Objectives—We conducted a prospective analysis of 145,886 participants in the Multiethnic Cohort to examine the relationship of alcohol drinking and smoking with pancreatitis.

Methods—Pancreatitis cases were categorized as gallstone-related acute pancreatitis (GS AP) (N=1,065), non-GS AP (N=1,222), and recurrent acute (RAP)/chronic pancreatitis (CP) (N=523). We used the baseline questionnaire to identify alcohol intake and smoking history. Associations were estimated by hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox models.

Results—Cigarette smoking was associated with non-GS AP and RAP/CP. Moderate alcohol intake was inversely associated with all types of pancreatitis in women (HRs=0.66 to 0.81 for <1 drink/day), and with RAP/CP in men (HR=0.57; 95% CI: 0.41, 0.79 for <2 drinks/day). The risk of non-GS pancreatitis associated with current smoking was highest among men who consumed >4 drinks/day (HR=2.06; 95% CI: 1.28, 3.30), while among never-smokers, moderate drinking was associated with a reduced risk (HR=0.70; 95% CI: 0.51, 0.96). In women, drinking <2 drinks/day was associated with a reduced risk of GS-AP among never smokers (HR=0.61; 95% CI: 0.46, 0.80).

Conclusions—Smoking is a risk factor for non-GS pancreatitis. Moderate alcohol intake is protective against all types of pancreatitis in women and against RAP/CP in men.

Keywords

epidemiology; pancreatitis; alcohol; smoking

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Introduction

Pancreatitis is an inflammatory disease of the exocrine pancreas associated with inappropriate activation of digestive enzymes in the pancreas. Acute pancreatitis (AP) occurs suddenly and most often resolves within several days although a minority of cases are severe illnesses with prolonged hospitalization with a risk of death. Gallstones are the most common cause of AP, and cholecystectomy eliminates the risk of recurrent episodes[1]. The AP hospitalization in the last two decades in the United States (US) has increased 100%[2]. In 2012, AP was the third most common cause of gastrointestinal-related hospitalization in the US with 275,000 hospital admissions, incurring nearly $2.6 billion in hospitalization costs[3].

Recurrent AP (RAP), mostly non-gallstone related, can progress to chronic pancreatitis (CP) characterized by progressive pancreatic inflammation and scarring, irreversible morphologic changes, and resulting in loss of exocrine and endocrine function[4]. CP, while lower in incidence, is a serious condition which can severely impact quality of life[5] and lead to serious long-term complications including diabetes and pancreatic cancer[1]. Currently there is no available treatment for pancreatitis and no therapy to prevent recurrent episodes for non-gallstone related pancreatitis. Understanding the etiology of pancreatitis is paramount to prevent this disease.

Cigarette smoking and heavy alcohol drinking (≥ 4 drinks per day) have been associated with risk of pancreatitis[6]; since alcohol and smoking are often linked behaviors, there remain questions about the independent influence of alcohol. Data from population-based prospective studies in US multiethnic populations are scarce. Here we conducted a prospective risk factor analysis of pancreatitis, focusing on cigarette smoking and alcohol consumption among African Americans, Native Hawaiians, Japanese Americans, Latinos and whites participating in the Multiethnic Cohort (MEC) Study. The primary goal of this study, which had a large number of pancreatitis cases with smoking and alcohol data, was to investigate smoking and alcohol as cofactors of disease risk by pancreatitis subtype.

Materials and Methods

Study population

The MEC is a prospective cohort of more than 215,000 men and women, aged 45–75 years, enrolled between 1993 and 1996. The MEC study design and baseline characteristics have been described in detail previously[7]. The baseline mailed questionnaire assessed diet, lifestyle, anthropometrics, family and personal medical history, and for women menstrual and reproductive history and hormone use. Since baseline, there have been four follow-up questionnaires, and between 1995 and 2006, blood and urine specimens were collected from ~70,000 participants for biomarker and genetic studies. Incident cancers in the cohort are identified through annual linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry; these cancer registries are part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Deaths are determined through annual linkage to state death certificate files in California and Hawaii, and periodic linkage to the National Death Index.

The MEC participants older than 65 years were linked to Centers for Medicare Services (CMS) claims (1999–2012) using Social Security number, sex, and date of birth, and 93% of these participants were successfully linked[8]. California participants were also linked to the Office of Statewide Health Planning and Development Hospital Discharge Data (1993–2012). The University of Southern California's and the University of Hawaii's Institutional Review Boards approved this study.

For this study, participants with a diagnosis of pancreatic cancer identified via tumor registries or pancreatitis identified via the California hospital discharge data (N=361) before cohort entry were excluded. We also excluded participants (N=26,070) who were not from the five major ethnic groups or who had missing baseline information on pancreatitis risk factors and important covariates (*i.e.*, body mass index, smoking history, diabetes, alcohol intake, and education level). HI participants who were not Medicare members (N=14,035) or who were not fee-for-service (FFS) members were excluded (N=28,438), as we had no opportunity to discover a pancreatitis diagnosis in this group. A total of 145,886 eligible participants were available for analysis.

Case ascertainment

Pancreatitis cases in California and Hawaii were ascertained from the Medicare hospitalization claim files (MedPAR) between 1999 and 2012 among fee-for-service (FFS) participants using the principal diagnosis and the first diagnosis in the claim with an International Classification of Diseases (ICD), 9th Revision, code 577.0 for acute pancreatitis (AP) or 577.1 for chronic pancreatitis (CP). For California participants, particularly among the non-FFS participants, we also utilized the California Hospital Discharge Data (CHDD) between 1993 and 2012 to identify cases using the same codes as above. Pancreatitis cases were categorized as AP if they had one AP hospitalization, RAP if they had more than one AP hospitalization more than 30 days apart, and CP if they had one CP hospitalization regardless of whether they had an AP episode or not. We further divided the AP group into gallstone and non-gallstone related types using ICD-9 codes for gallstone (574.x) from the same pancreatitis hospitalization claim and procedure codes for cholecystectomy [ICD-9: 51.2x and Current Procedural Terminology (CPT) codes: 47480, 47490, 47562, 47563, 47564, 47600, 47605, 47610, 47612, 47620, 56340, 56341, 56342]. 89% of AP cases had cholecystectomy within 90 days of the AP hospitalization date. For each pancreatitis case, the date of the first occurrence of a hospitalization claim where pancreatitis was the principal diagnosis was used as the event date. A total of 2,814 cases were identified through 2012; 4 cases were excluded because we could not identify eligible non-cases for the risk set using the criteria below.

Exposure assessment

Data on alcohol intake, smoking history, anthropometry, physician-diagnosed type 2 diabetes and demographic factors were obtained from the baseline questionnaire. Consumption of alcoholic beverages during the year preceding the baseline questionnaire was assessed by consumption frequency questions. Alcoholic drinks were classified into regular beer light beer, red wine/pink wine (including champagne and sake) and hard liquor. Nine intake categories ranged from "never" to "4 or more times per day" and information on

usual serving size was also requested. Mean daily alcohol intake was calculated using our extensive food composition table[7]. The total intake of alcohol was expressed in grams per day, and it was calculated by multiplying the volume of a drink by the percentage of alcohol content. In men, total alcohol intake was categorized as non-drinkers, <24, 24–≤48, and >48 g ethanol/day, and in women as non-drinkers, <12, 12–<24, and ≥24 g ethanol/day.

Smoking status was categorized as never, past, and current, and for past and current, they were further stratified by <20 and ≥20 pack years. Body mass index (BMI) was calculated as weight in kg divided by height in m^2.

Statistical analysis

As the time of diagnosis was not measured precisely, but was based on hospital admission date, we used a Cox proportional hazards model for interval data based on a logistic model with a complementary log-log link[9]. For each case, we constructed the set of at-risk individuals (alive and without a pancreatitis diagnosis at the date of index case's diagnosis) matched on ethnicity, sex, exact birth year, study area (CA or HI), and if a case was identified via Medicare, length of Medicare coverage (± 1 year). Participants with a history of cholecystectomy, identified either from baseline questionnaire or claims, were not eligible to be selected as controls for GS AP risk set. The associations of alcohol intake and smoking with pancreatitis were estimated by the hazard ratio (HRs) and its 95% confidence interval (CI) adjusted for education (high school or less, some college, college graduate or higher), BMI (continuous), history of diabetes (no/yes), and vigorous activity (hours/day continuous). Tests for trend were performed by entering the ordinal values (i.e., 1,2,3) representing categories of alcohol intake as continuous variables in the models. Interaction between smoking and alcohol drinking was assessed using the Wald test for the cross-product terms between the two variables. We performed sensitivity analyses by excluding cases diagnosed within 1 year of cohort entry and by including Medicare FFS participants only. All analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC). All P values were two-sided.

Results

A total of 2,810 pancreatitis cases were included in the analysis with the following breakdown: 1,065 gallstone-related (GS) AP (37.9%), 1,222 non-GS AP (43.5%), and 523 RAP/CP (18.6%). The average duration from cohort entry to the first hospitalization was 10.1 years. The characteristics of pancreatitis cases are shown in Table 1. The mean ages of the GS AP, non-GS AP, and RAP/CP hospitalization were 73.8, 73.3, and 71.5 years, respectively. Age at cohort entry was similar across groups. African Americans (26.4%) and Latinos (37.9%) contributed the largest number of cases because these groups were mainly from California and we were able to utilize CHDD in addition to Medicare for case identification.

Table 2 shows the baseline characteristics of the study population by alcohol drinking level. In the cohort, 38% men and 62% women were nondrinkers. The majority of alcohol drinkers in this study were whites. Among men and women, those in higher alcohol categories were more likely to smoke. The nondrinkers were likely to be obese and to self-report a diagnosis

of diabetes. The distribution of education levels was roughly similar across the categories of alcohol intake.

Table 3 shows the association of smoking and alcohol consumption with pancreatitis type by sex. In men, smoking status was not associated with GS AP, while it was strongly associated with non-GS AP and RAP/CP. The association with smoking was statistically significant only for current smokers (HR=1.87; 95% CI: 1.44, 2.43 for non-GS AP and HR=1.72; 95% CI: 1.12, 2.66 for RAP/CP). Alcohol intake was not associated with non-GS AP; however, moderate drinking (<24 ethanol g/day or <2 drinks/day) was associated with a lower risk of RAP/CP (HR=0.57; 95% CI: 0.41, 0.79). Heavy drinking (>48 ethanol g/day or >4 drinks/day) tended to be associated with an elevated risk of RAP/CP; however, this association did not reach statistical significance (HR=1.50; 95% CI: 0.94, 2.39).

In women, smoking was strongly associated with non-GS and RAP/CP, particularly among current smokers who smoked ≥20 pack years (HR for non-GS=2.01; 95% CI: 1.45, 2.80 and HR for RAP/CP=3.22; 95% CI: 2.12, 4.87). Past smokers who smoked ≥20 pack years also had elevated risks of non-GS AP (HR=1.83; 95% CI: 1.34, 2.50) and RAP/CP (HR=1.75; 95% CI: 1.07, 2.85). Alcohol intake was associated with a lower risk of GS-AP. Moderate alcohol intake (<12 ethanol g/day or <1 drink/day) was significantly associated with lower risk of non-GS AP (HR=0.81; 95% CI: 0.67, 0.97) and RAP/CP (HR=0.66; 95% CI: 0.49, 0.87).

We examined the joint effects between alcohol intake and smoking status on risk of pancreatitis in men and in women (Table 4). Because of the limited number of cases in certain strata, particularly among heavy alcohol consumption, we collapsed the non-GS and RAP/CP as one group (non-GS pancreatitis). In men and taking never smokers who did not drink as the reference category, never smokers who drank ≤48 ethanol g/day had lower risks of non-GS pancreatitis (HR=0.70; 95% CI: 0.51, 0.96). Current smokers had increased risks of non-GS pancreatitis regardless of their drinking habit, and the highest risk was observed among those who drank >48 ethanol g/day (HR=2.06; 95% CI: 1.28, 3.30). The tests for interaction between alcohol intake and smoking were not statistically significant (GS AP, P=0.46 and non-GS pancreatitis, P=0.22).

In female never smokers and taking never smokers who did not drink as the reference category, drinking <24 ethanol g/day or <2 drinks/day was associated with reduced GS-AP risk (HR=0.61; 95% CI: 0.46, 0.80). Among past smokers, non-drinkers had higher risks of non-GS pancreatitis (HR=1.39; 95% CI: 1.16, 1.66) compared to those who did not smoke and drink. Female current smokers had increased risks of non-GS pancreatitis regardless of their drinking habit, with the highest risk of non-GS pancreatitis observed among non-drinkers (HR=1.88; 95% CI: 1.50, 2.37) followed by those who drank 2 or more drinks/day (HR=1.67; 95% CI: 1.03, 2.71). The tests for interaction between alcohol intake and smoking were not statistically significant (GS AP, P=0.50 and non-GS pancreatitis, P=0.71).

Results from the sensitivity analysis excluding cases diagnosed within 1 year of cohort entry (N=108) were similar (data not shown). Results from the Medicare only analysis were also similar. Associations between risk factors and pancreatitis types were generally consistent

across racial/ethnic groups (Supplemental Tables 1–2); however, many of these sub-group comparisons were based on small numbers.

Discussion

To our knowledge, our study is the largest population-based prospective analysis of alcohol and smoking for pancreatitis in the United States. We found that smoking was an independent risk factor for non-GS pancreatitis in men and women, and that moderate alcohol drinking was associated with reduced risks of all pancreatitis subtypes in women and RAP/CP in men.

Consistent with previous studies[10–13], we found that smoking was not associated with GS AP in both men and women, while it was significantly associated with non-GS and RAP/CP, indicating different pathophysiological mechanisms for these subtypes. Increased risk of non-GS and RAP/CP was particularly strong in female current smokers who had smoked for 20 or more pack years.

Heavy alcohol consumption has been associated with risk of pancreatitis in men; the association in women has been less consistent[14–16]. In our study, heavy alcohol consumption (>4 drinks per day) did not significantly increase the risk of pancreatitis in men, but moderate drinking (~2 drinks or less daily) was associated with lower risk of RAP/CP. Among women, moderate drinking (~ 1 drink daily) was significantly associated with lower risk of all subtypes of pancreatitis. Surprisingly, in our study, increasing alcohol intake was inversely associated with GS AP in women. Moderate alcohol consumption has been linked to a lower risk of gallstone disease[17] and cholecystectomy[18]. Women are almost twice as likely as men to form stones and undergo cholecystectomy[19]. It is possible that moderate drinking protects against pancreatitis in women, particularly GS-related pancreatitis.

Smoking and alcohol are cofactors that increase the risk of pancreatitis[1]. We found the risk of non-GS pancreatitis associated with current smoking was highest among men who consumed >4 alcoholic drinks per day. Interestingly, we found that among never-smokers, moderate alcohol drinking was associated with reduced risk of non-GS pancreatitis in men and reduced risk of GS-AP in women.

Our observations that there is a decreased risk of pancreatitis with moderate alcohol consumption for both men and women could be related to findings in experimental animal models showing that ethanol feeding inhibits the activation of the pro-inflammatory transcription factor, nuclear factor-κB in the pancreas[20]; and that ethanol feeding upregulates a protective endoplasmic reticulum stress response via the transcription factor spliced X-box binding protein 1[21–24].

In experimental models, ethanol intake promotes the development of pancreatitis only when a second stressor for pancreatitis is present[20]. In the case of the present study, the second stressor could be current smoking.

The strengths of this study include its prospective and population-based design, racial/ethnic diversity, long follow up, large size, and detailed information on known and potential risk

factors for pancreatitis. There are also several limitations. Measurement error in self-reported alcohol is possible and may have led to some degree of non-differential misclassification of exposures. The algorithm used to identify pancreatitis cases using Medicare/CHDD claim databases has not been validated specifically in the MEC. Previous epidemiologic studies have used similar administrative databases to identify pancreatitis cases[14,25–28]; the sensitivity, specificity, and positive and negative predictive values of AP primary discharge diagnosis code are 96%, 85%, 80%, and 98%, respectively[28]. Outcome misclassification might have occurred. However, because it would be irrespective of exposures, the potential resulting bias would be toward the null. Without access to medical records, it was difficult to separate RAP from CP, and thus we combined these two groups together. In our study, we excluded the Hawaii Medicare managed care participants. While the characteristics between the MEC managed care and FFS participants were similar[8], our results still may not be generalizable to the whole cohort or managed care enrollees. We were unable to exclude prevalent pancreatitis cases in Hawaii if they were diagnosed before 1999 because we do not have access to hospital discharge data in Hawaii and Medicare files are available starting in 1999. Finally, even in our relatively large cohort, the number of cases within categories of exposures by pancreatitis types and sex were small.

In conclusion, we showed that smoking is an independent risk factor for non-GS AP and RAP/CP in men and women. Moderate alcohol intake may lower risk of RAP/CP in men and all types of pancreatitis in women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of Pancreatitis Cases in the Multiethnic Cohort

	All		GS AP		Non-GS AP		RAP/CP	
	N = 2,810	**%**	**N = 1,065**	**%**	**N = 1,222**	**%**	**N = 523**	**%**
Age at occurrence, years								
Mean (range)	73.2 (46.6–94.3)		73.8 (47.8 – 94.0)		73.3 (46.6–94.3)		71.5 (46.8–91.8)	
Year of hospitalization								
1993–1997	368	13.1	105	9.9	156	12.8	107	20.5
1998–2002	682	24.3	262	24.6	277	22.7	143	27.3
2003–2007	801	28.5	301	28.3	356	29.1	144	27.5
2008–2012	959	34.1	397	37.3	433	35.4	129	24.7
Age at cohort entry, years								
<50	216	7.7	68	6.4	113	9.2	35	6.7
50–54	309	11.0	121	11.4	109	8.9	79	15.1
55–59	508	18.1	197	18.5	229	18.7	82	15.7
60–64	585	20.8	226	21.2	252	20.6	107	20.5
65–69	626	22.3	230	21.6	279	22.8	117	22.4
≥ 70	566	20.1	223	20.9	240	19.6	103	19.7
Race/ethnicity								
White	495	17.6	185	17.4	219	17.9	91	17.4
African American	743	26.4	214	20.1	364	29.8	165	31.5
Native Hawaiian	109	3.9	45	4.2	44	3.6	20	3.8
Japanese American	399	14.2	175	16.4	161	13.2	63	12.0
Latino – US born	556	19.8	222	20.8	233	19.1	101	19.3
Latino – Mexico/South America born	508	18.1	224	21.0	201	16.4	83	15.9
Area								
Hawaii	593	21.1	243	22.8	265	21.7	85	16.3
California	2,217	78.9	822	77.2	957	78.3	438	83.7
Sex								
Male	1,168	41.6	454	42.6	508	41.6	206	39.4
Female	1,642	58.4	611	57.4	714	58.4	317	60.6

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Table 2

Baseline Characteristics by Alcohol Intake (Ethanol g/day) in the Multiethnic Cohort

	MALE				FEMALE			
	None n= 24,802	**<24 n=28,508**	**24 – 48 n=7,038**	**>48 n=4,715**	**None n= 49,916**	**<12 n=23,398**	**12 – < 24 n=3,576**	**≥24 n=3,933**
Race/ethnicity, %								
White	16.7	23.2	31.8	33.0	15.0	29.8	47.5	53.2
African American	19.2	15.3	13.3	16.5	23.9	23.2	21.3	22.4
Native Hawaiian	5.3	4.5	5.2	5.1	5.1	4.6	5.0	4.6
Japanese American	31.2	24.7	25.1	17.6	30.0	16.5	10.3	7.9
Latino – US born	14.1	16.2	14.6	16.9	12.7	15.0	10.5	8.6
Latino – Non US born	13.5	16.2	10.0	11.0	13.4	11.0	5.4	3.3
Education, %								
≥ High School	46.7	38.9	36.5	42.7	51.5	39.5	33.9	33.6
Some college	29.4	29.4	29.8	30.3	28.1	32.6	34.0	35.5
College graduate or higher	23.9	31.7	33.6	27.0	20.5	27.8	32.1	30.9
BMI (kg/m^2), %								
< 25	35.1	33.6	37.2	37.7	41.1	46.4	55.5	56.0
25 – < 30	45.7	49.5	48.7	46.3	32.7	33.5	29.2	29.5
≥ 30	19.2	16.9	14.1	16.0	26.3	20.1	15.3	14.5
Diabetes, %								
No	81.1	90.2	92.5	92.8	85.2	94.1	95.9	96.4
Yes	18.9	9.8	7.5	7.2	14.8	5.9	4.1	3.6
Smoking-Pack Years, %								
Never	33.9	32.2	22.0	17.2	63.5	51.1	34.9	26.5
Past, < 20	34.6	37.9	37.3	30.8	21.0	28.2	32.4	28.4
Past, ≥ 20	16.3	12.9	17.2	20.6	4.3	5.0	8.9	12.7
Current, < 20	7.2	9.3	10.6	11.7	7.1	10.7	13.8	16.3
Current, ≥ 20	7.9	7.7	13.0	19.7	4.1	5.1	9.9	16.1

Table 3

Associations Between Smoking and Alcohol Intake and Pancreatitis in the Multiethnic Cohort

Risk Factors	GS AP		Non-GS AP		RAP/CP	
	No. Cases	HR*(95% CI)	No. Cases	HR*(95% CI)	No. Cases	HR*(95% CI)
MALE						
Smoking						
Never	137	1.00 (ref.)	129	1.00 (ref.)	50	1.00 (ref.)
Past	263	1.22 (0.98–1.51)	255	1.21 (0.97–1.51)	112	1.25 (0.89–1.78)
Current	54	0.95 (0.68–1.32)	124	1.87 (1.44–2.43)	44	1.72 (1.12–2.66)
Smoking-Pack Years						
Never	137	1.00 (ref.)	129	1.00 (ref.)	50	1.00 (ref.)
Past, < 20	187	1.20 (0.95–1.51)	187	1.25 (0.99–1.57)	83	1.28 (0.89–1.85)
Past, ≥ 20	76	1.26 (0.93–1.70)	68	1.10 (0.80–1.50)	29	1.17 (0.72–1.90)
Current, < 20	27	0.94 (0.62–1.45)	68	1.87 (1.37–2.56)	25	1.96 (1.18–3.24)
Current, ≥ 20	27	0.95 (0.61–1.48)	56	1.87 (1.34–2.60)	19	1.47 (0.84–2.60)
Alcohol intake (ethanol g/day)						
0	193	1.00 (ref.)	210	1.00 (ref.)	98	1.00 (ref.)
< 24	202	0.91 (0.74–1.12)	216	0.85 (0.69–1.03)	66	0.57 (0.41–0.79)
24–≤ 48	37	0.77 (0.54–1.11)	38	0.70 (0.49–1.00)	16	0.59 (0.34–1.02)
> 48	22	0.68 (0.43–1.06)	44	1.06 (0.75–1.50)	26	1.50 (0.94–2.39)
p for trend		0.0411		0.3797		0.9640
FEMALE						
Smoking						
Never	354	1.00 (ref.)	358	1.00 (ref.)	152	1.00 (ref.)
Past	181	1.16 (0.96–1.41)	237	1.35 (1.13–1.61)	95	1.28 (0.97–1.68)
Current	76	1.20 (0.92–1.56)	119	1.63 (1.30–2.04)	70	2.31 (1.70–3.14)
Smoking-Pack Years						
Never	354	1.00 (ref.)	358	1.00 (ref.)	152	1.00 (ref.)
Past, < 20	146	1.11 (0.90–1.36)	184	1.27 (1.05–1.53)	74	1.20 (0.89–1.61)
Past, ≥ 20	35	1.46 (1.01–2.13)	53	1.83 (1.34–2.50)	21	1.75 (1.07–2.85)

Risk Factors	GS AP		Non-GS AP		RAP/CP	
	No. Cases	HR*(95% CI)	No. Cases	HR*(95% CI)	No. Cases	HR*(95% CI)
Current, <20	51	1.18 (0.87–1.62)	73	1.45 (1.11–1.91)	39	1.89 (1.29–2.75)
Current, ≥ 20	25	1.24 (0.80–1.90)	46	2.01 (1.45–2.80)	31	3.22 (2.12–4.87)
Alcohol intake (ethanol g/day)						
0	444	1.00 (ref.)	475	1.00 (ref.)	224	1.00 (ref.)
< 12	137	0.69 (0.56–0.85)	182	0.81 (0.67–0.97)	72	0.66 (0.49–0.87)
12–< 24	14	0.50 (0.29–0.85)	24	0.69 (0.44–1.08)	11	0.73 (0.39–1.35)
≥ 24	16	0.52 (0.31–0. 87)	33	0.86 (0.58–1.27)	10	0.58 (0.30–1.11)
p for trend		<.0001		0.0438		0.0064

*HR adjusted for BMI, alcohol intake, smoking, diabetes, vigorous activity, and education.

Table 4

Joint associations of smoking status and alcohol intake with pancreatitis in the Multiethnic Cohort

Alcohol intake stratified by smoking status at baseline	GS-AP		Non-GS pancreatitis*	
	No. Cases	HR**(95% CI)	No. Cases	HR**(95% CI)
MALE				
Never smoker				
Non-drinker	60	1.00 (ref.)	85	1.00 (ref.)
≤ 48g daily	75	0.99 (0.69–1.41)	80	0.70 (0.51–0.96)
> 48g daily	2	0.39 (0.09–1.60)	14	1.59 (0.87–2.87)
Past smoker				
Non-drinker	118	1.34 (0.97–1.86)	173	1.28 (0.98–1.68)
≤ 48g daily	133	1.08 (0.78–1.48)	162	0.86 (0.65–1.12)
> 48g daily	12	0.76 (0.40–1.42)	32	1.30 (0.85–1.99)
Current smoker				
Non-drinker	15	0.79 (0.45–1.41)	50	1.48 (1.03–2.12)
≤ 48g daily	31	0.88 (0.56–1.39)	94	1.54 (1.13–2.09)
> 48g daily	8	1.15 (0.54–2.46)	24	2.06 (1.28–3.30)
FEMALE				
Never smoker				
Non-drinker	282	1.00 (ref.)	375	1.00 (ref.)
< 24g daily	67	0.61 (0.46–0.80)	127	0.81 (0.66–1.01)
≥ 24g daily	5	0.62 (0.25–1.51)	8	0.65 (0.30–1.38)
Past smoker				
Non-drinker	114	1.06 (0.84–1.34)	218	1.39 (1.16–1.66)
< 24g daily	60	0.86 (0.64–1.15)	99	0.97 (0.77–1.23)
≥ 24g daily	7	0.65 (0.30–1.39)	15	1.04 (0.61–1.76)
Current smoker				
Non-drinker	48	1.25 (0.90–1.72)	106	1.88 (1.50–2.37)
< 24g daily	24	0.73 (0.47–1.13)	63	1.32 (0.99–1.75)
≥ 24g daily	4	0.47 (0.17–1.28)	20	1.67 (1.03–2.71)

*This group includes Non-gallstone AP, RAP and CP.

**HR adjusted for BMI, diabetes, vigorous activity, and education.

Male: P-value for interaction = 0.4563 for GS-AP group.; P-value for interaction = 0.2203 for Non-GS-AP group.
Female: P-value for interaction = 0.4958 for GS-AP group.; P-value for interaction = 0.7061 for Non-GS-AP group.