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Acute Pancreatitis Recurrences Augment Long-Term Pancreatic Cancer Risk

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INTRODUCTION: **In animal models, inflammation caused by experimental acute pancreatitis (AP) promotes pancreatic carcinogenesis that is preventable by suppressing inflammation. Recent studies noted higher long-term risk of pancreatic ductal adenocarcinoma (PDAC) after AP. In this study, we evaluated whether the long-term PDAC risk after AP was influenced by the etiology of AP, number of recurrences, and if it was because of progression to chronic pancreatitis (CP).**

METHODS: **This retrospective study used nationwide Veterans Administration database spanning 1999–2015. A 2-year washout period was applied to exclude patients with preexisting AP and PDAC. PDAC risk was estimated in patients with AP without (AP group) and with underlying CP (APCP group) and those with CP alone (CP group) and compared with PDAC risk in patients in a control group, respectively, using cause-specific hazards model.**

RESULTS: **The final cohort comprised 7,147,859 subjects (AP-35,550 and PDAC-16,475). The cumulative PDAC risk 3–10 years after AP was higher than in controls (0.61% vs 0.18%), adjusted hazard ratio (1.7 [1.4–2.0], $P < 0.001$). Adjusted hazard ratio was 1.5 in AP group, 2.4 in the CP group, and 3.3 in APCP group. PDAC risk increased with the number of AP episodes. Elevated PDAC risk after AP was not influenced by the etiology of AP (gallstones, smoking, or alcohol).**

DISCUSSION: **There is a higher PDAC risk 3–10 years after AP irrespective of the etiology of AP, increases with the number of episodes of AP and is additive to higher PDAC risk because of CP.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C773

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INTRODUCTION

Pancreatic cancer ("pancreatic ductal adenocarcinoma" [PDAC]) is one of the leading causes of cancer mortality in the US, with an estimated 62,210 new diagnoses and 49,830 deaths in 2022 (1). Global incidence of PDAC is 8.1 cases per 100,000 person-years, and the projected burden is expected to increase (2–4). Five-year survival in PDAC remains dismal (4%–9%) and has barely improved in the past several decades despite recent advances in imaging techniques or therapy (5–10). Late onset of symptoms and rapid progression to death are the hallmarks of PDAC. Understanding the significance of a history of acute pancreatitis (AP) for pancreatic carcinogenesis might help in developing novel approaches for early detection and/or chemoprevention of PDAC.

AP is a common problem with nearly 274,000 hospitalizations in the US at an estimated cost of $2.6 billion annually (11). However, its long-term sequelae, particularly if and how it may predispose to PDAC, are not well understood. In murine models, AP promotes pancreatic carcinogenesis and accelerates development of PDAC (12–14). These effects are prevented by suppressing inflammation (12,13,15), suggesting a cardinal role of inflammation in pancreatic carcinogenesis promoted by AP. Recent epidemiologic studies from Europe have reported a higher PDAC risk for up to 10 years after AP (16,17). Whether the PDAC risk is related to smoking and heavy alcohol intake, which increase both the risk of AP and PDAC or is because of inflammatory changes associated with AP as suggested by murine studies is not well established in humans. There is good reason to suspect that inflammation has an important role in humans too because nonsteroidal antiinflammatory drugs have been found to reduce PDAC incidence in epidemiologic studies (18–20).

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In this study, we sought to confirm the higher long-term risk of PDAC after AP as reported in recent studies using a national Veteran's Administration (VA) database. We also evaluated whether the risk was related to the number of AP episodes or underlying etiologies (such as smoking and alcohol use) or because of progression to chronic pancreatitis (CP), already known to predispose to PDAC (21).

METHODS

Study design and data source

This is a retrospective cohort study of VA patients from 1999 to 2015. We used Department of Veterans Affairs inpatient and outpatient medical SAS data sets including utilization data related to all encounters within the VA system from September 1999 through December 2015. These data sets were used to ascertain detailed cohort participant's demographic characteristics, AP, chronic pancreatitis (CP), pancreatic cancer (PDAC), and other comorbidity information based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) diagnostic and procedure codes associated with inpatient and outpatient encounters.

Primary outcome

The primary outcome was pancreatic cancer, defined based on primary or secondary diagnosis codes (≥1 codes) for adenocarcinoma of pancreas (inpatient or outpatient, *ICD 9* codes 157.0–157.4, 157.8 and 157.9). The date of first *ICD 9* diagnosis code was used as the date of the PDAC diagnosis.

Primary predictor

The primary predictor variable of interest was AP, defined based on the inpatient diagnosis codes for AP (primary or secondary, *ICD 9* code 577.0). Because AP is primarily an inpatient diagnosis, only patients with inpatient diagnosis codes for AP were included in the analysis and patients with *ICD 9* code 577.0 only in outpatient settings were not included. For each patient, we looked for subsequent *ICD 9* codes (if any) to determine the frequency of recurrent AP (none/1 episode, 2 episodes, ≥3 episodes). We defined recurrent AP as a new episode of AP > 1 month after the first episode of AP, and hospital readmissions (if any) within 30 days were treated as a part of index episode. For each episode, admission date was considered as the AP diagnosis date.

Etiology of AP

Patients with AP with associated *ICD 9* codes for gallstones (ICD codes 574, 574.1, 574.3, 574.5, 574.7, 574.8, 574.9) were classified as gallstone-AP, and rest of the patients with AP without associated *ICD 9* diagnosis codes for gallstones were classified as nongallstone AP.

Chronic pancreatitis

We defined CP based on primary or secondary diagnosis codes (inpatient or outpatient, *ICD 9* codes 577.1). Similar to PDAC, the date of first *ICD 9* diagnosis code was used as the CP diagnosis date.

Covariates

Diabetes mellitus (ICD 9 code 250), presence of gallstones (*ICD* codes 574, 574.1, 574.3, 574.5, 574.7, 574.8, 574.9), history of heavy alcohol consumption (*ICD 9* codes 303.0 [alcohol dependence], 303.9 [alcohol addiction], 305.0 [acute alcohol intoxication]), smoking (based on personal history of smoking: current/past/nonsmoker), and demographic variables (age at the time of entry into the study, sex: man/woman, race: white/black/other) were also evaluated because these are known risk factors for PDAC.

Exclusion criteria

Using patient encounters (inpatient and/or outpatient), we identified first and last visits for each patient. From the initial cohort of 11,798,498 patients identified in the VA healthcare system during the study period, we selected 10,519,102 patients with greater than 2 years (duration between first and last visit) in the VA system during the study period. Patients with *ICD 9* diagnoses codes for AP (*ICD 9* 577.0) from outpatient setting only without an accompanying inpatient diagnosis code for AP were not included for analysis (n = 53,509). We applied a 2-year washout period and excluded patients with AP (n = 21,016) and PDAC diagnosis (n = 10,857) within 2 years of entry into the system. Patients younger than 40 years of age (n = 2,209,434) were excluded because we had earlier reported that the risk of PDAC was extremely low in that patient subset (22).

We also excluded patients (i) in whom PDAC was diagnosed before AP (n = 406) and (ii) with pancreatic cyst (n = 19,580) based on their higher long-term risk of PDAC (23). Because this study focused on patients who developed long-term PDAC (3–10 years after AP), patients and those who developed PDAC, within 2 years after the study entry were also excluded from the analyses (n = 1,056,441). Final cohort included in the study was 7,147,859 (Figure 1).

Cohort assembly

Based on the *ICD 9* codes for AP and CP, patients were classified into 4 groups: AP without preexisting CP (AP group), preexisting CP without AP (CP group), AP with preexisting CP (APCP group), and remaining patients without AP or CP (controls). These patients were followed in time to evaluate for the risk of PDAC. For patients in the AP group and the APCP group, date of first AP diagnosis was designated as the time of study entry (T0) into respective groups. For patients in the CP group and for controls; the first outpatient or inpatient encounter after the 2 years of washout period was designated as the time of study entry. No patients in the final study cohort had AP, CP, or PDAC diagnosis in the preceding 2 years (preexisting) before inclusion into the study cohort (see Supplementary Digital Content, Figure S1, http://links.lww.com/AJG/C773).

Follow-up for those who developed PDAC ended on the date of first diagnosis of PDAC, and for those who did not develop PDAC, it was censored at the time of loss to follow-up (last visit recorded in the VA system during the study period), death, or end of the study period. Median duration of follow-up for the AP group was 7.6 years, the CP group was 8.3 years, the APCP group was 8.7 years, and the control group was 11.3 years. In this manuscript, we focused on patients who developed PDAC 3–10 years into follow-up; therefore, we accordingly calculated the incidence rate and hazard ratios (HRs).

Statistical analysis

Patient characteristics among the 4 groups were assessed using frequencies (n [%]), and age was compared using median ± interquartile range. The proportion of patients who were subsequently diagnosed to have PDAC was calculated for each group. Incidence rates for PDAC (per 1,000 person-years) were

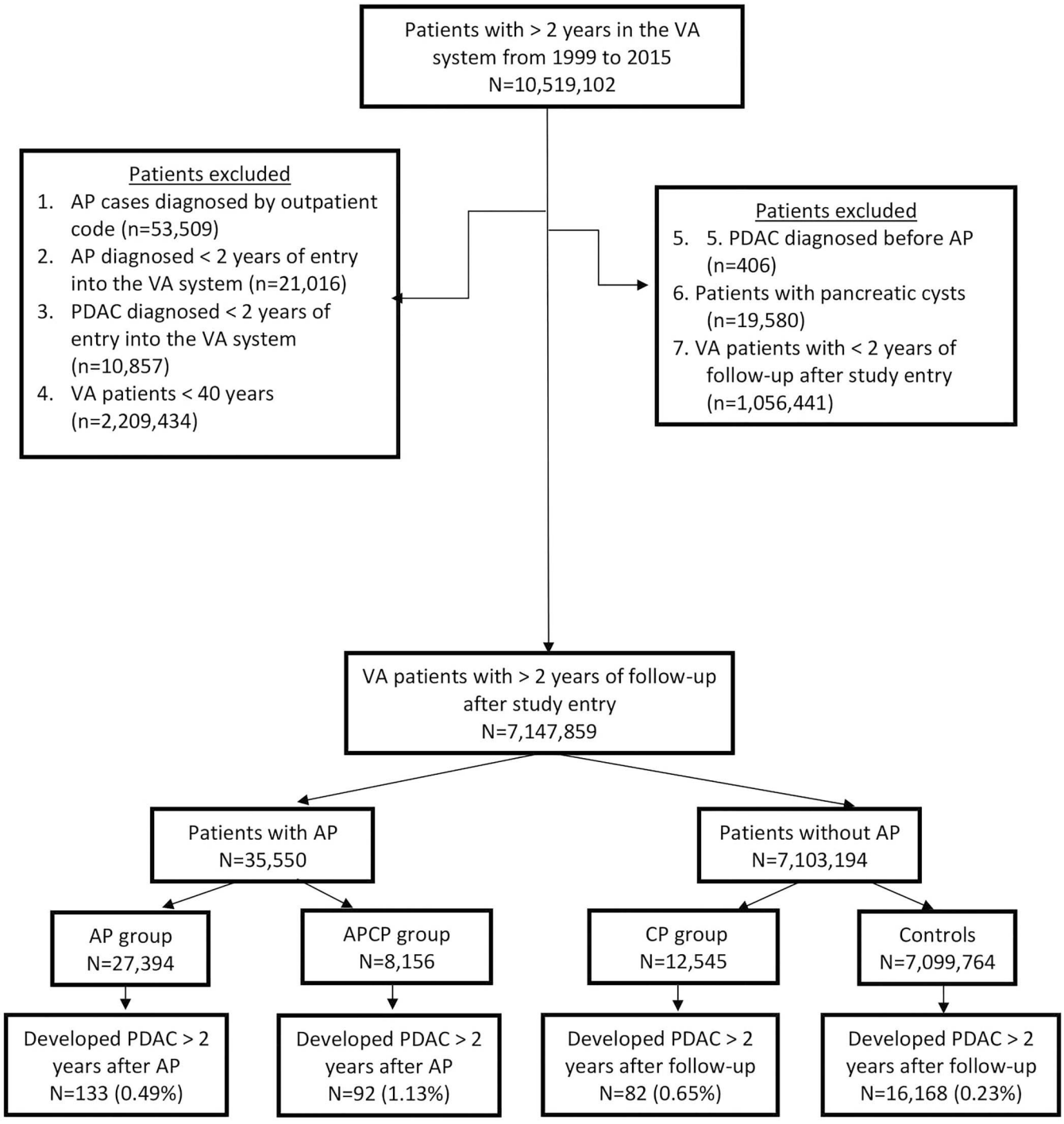

Figure 1. Flow diagram illustrating the selection of our study cohort. AP group, patients with AP without preexisting CP; CP group, patients with CP without AP; APCP group, patients with AP and preexisting CP; controls, remaining patients in the database without AP or CP. AP, acute pancreatitis; CP, chronic pancreatitis, PDAC, pancreatic ductal adenocarcinoma; VA, Veteran's Administration.

estimated and HRs unadjusted, and after adjusting for age, race, sex, smoking history, alcohol history, diabetes status and gallstone disease with 95% confidence intervals (CIs), incidence rates were calculated for the entire study duration and for each year from year 3–10. Cause-specific hazard model was fitted using Cox-regression model, and competing events were treated as censored observations. Cumulative incidence curves of PDAC were generated for the (i) 4 study groups, (ii) etiology of AP, and (iii) number of AP episodes.

All analyses were conducted by using SAS version 9.3 (SAS, Cary, NC). Significance tests were performed by using a 2-tailed hypothesis, and the level of significance (α) was set to 0.05. This study was approved by the Saint Louis Veterans Affairs Medical Center.

Table 1. Patient characteristics

	Controls	AP group	CP group	APCP group	All study patients[a]
N (%)	7,099,764 (100%)	27,394 (100%)	12,545 (100%)	8,156 (100%)	7,147,859 (100%)
Age in yr (median, interquartile range)	62 (53–72)	60 (54–68)	60 (53–68)	57 (51–63)	62 (53–72)
Gender					
Men	6,696,619 (94.3%)	26,076 (95.2%)	12,053 (96.1%)	7,757 (95.1%)	6,742,505 (94.3%)
Women	403,145 (5.7%)	1,318 (4.8%)	492 (3.9%)	399 (4.9%)	405,354 (5.7%)
Race					
White	557,688 (81.6%)	19,366 (71.1%)	8,736 (70.1%)	5,106 (62.9%)	5,609,996 (81.5%)
Black	965,477 (14.1%)	6,142 (22.6%)	3,199 (25.7%)	2,638 (32.5%)	977,456 (14.2%)
Other	294,627 (4.3%)	1,719 (6.3%)	528 (4.2%)	375 (4.6%)	297,249 (4.3%)
Smoking					
Current	2,213,967 (35.8%)	14,031 (51.5%)	6,804 (56.2%)	5,227 (64.4%)	2,240,029 (36.0%)
Past	1,509,042 (24.4%)	3,992 (14.7%)	1,922 (15.9%)	822 (10.1%)	1,515,778 (24.4%)
Alcohol	1,061,867 (15.0%)	12,526 (45.7%)	5,611 (44.7%)	5,388 (66.1%)	1,085,392 (15.2%)
Diabetes mellitus	2,344,016 (33.0%)	14,911 (54.4%)	6,562 (52.3%)	4,578 (56.1%)	2,370,067 (33.2%)
History of gallstones	213,987 (3.0%)	10,384 (37.9%)	1,476 (11.8%)	2,667(32.7%)	228,514 (3.2%)
PDAC	16,168 (0.23%)	133 (0.49%)	82 (0.65%)	92 (1.13%)	16,475 (0.23%)

AP, acute pancreatitis; APCP, acute pancreatitis with preexisting chronic pancreatitis; CP, chronic pancreatitis; PDAC, pancreatic cancer; age-age at the time of entry into the study.
[a]Race missing in ~4% of all pts included in the study.

RESULTS

Patient characteristics

The final cohort consisted of 7,147,859 veterans. During the study period, 35,550 veterans (0.5%) had one or more episode of AP, and PDAC was diagnosed in 16,475 veterans (0.2%). They included 133 patients in the AP group (0.5%), 82 in the CP group (0.7%), 92 in the APCP group (1.1%), and 16,168 (0.2%) in controls (Figure 1).

Patient characteristics are summarized in Table 1. Median age was 62 years (interquartile range 53–72), 82% were white, 94% were men, 36% were current smokers, 15% were heavy alcohol drinkers.

Incidence and risk of pancreatic cancer by pancreatitis status

By Cox-regression analyses, patients with AP had higher PDAC risk in following 3–10 years (adjusted HR 1.65, 95% CI 1.40–1.95 $P < 0.001$, all AP vs controls). AP was associated with higher PDAC risk even in patients with underlying CP (adjusted HR 4.71, 95% CI 3.80–5.82, $P < 0.001$ APCP group vs controls). The PDAC risk was significantly higher in APCP group than in either AP (adjusted HR 2.24, 95% CI 1.69–2.96, $P < 0.001$, APCP vs AP) or CP patient groups (adjusted HR 1.94, 95% CI 1.39–2.71, $P < 0.001$, APCP vs CP). Cumulative incidence curves of PDAC in the 4 study groups are shown in Figure 2, and the final model evaluating the PDAC risk in all 4 groups are shown in Table 2.

Supplementary Digital Content (see Table S1 and Table S2, http://links.lww.com/AJG/C773) summarizes the number of patients diagnosed to have PDAC each year during the follow-up, the incidence, and risk (HR) of PDAC diagnosis for the 4 study groups.

PDAC risk increases with more episodes of AP

Among the 35,550 patients with >2 years of follow-up after AP, 79% had one episode of AP, 13.6% had 2 episodes, and the remaining subjects had ≥3 episodes. The risk of PDAC was 0.4% in patients with 1 episode of AP, 1.1% after 2 episodes, and 2.1% in patients with ≥3 episodes of AP. Cumulative incidence plots are shown in Figure 3, demonstrating a positive relationship between the number of AP episodes and PDAC risk. Table 3 summarizes the risk (HR) of PDAC diagnosis by the number of episodes of AP.

Risk of PDAC in gallstone vs nongallstone AP

We then sought to determine if the higher risk of PDAC was intrinsic to AP or was related to the underlying etiology of AP, especially smoking and heavy alcohol intake because both are associated with higher risk of pancreatic cancer. We, therefore, compared cumulative incidence and risk of PDAC after AP in patients with gallstone and those without gallstones. As seen in Figure 4a, overall, there was no significant difference in the cumulative incidence of PDAC in patients with gallstone and nongallstone pancreatitis ($P = 0.19$). Figure 4b demonstrates that the PDAC risk after AP was similar in patients with gallstone and without gallstones even when only patients with single episode of AP were included ($P = 0.11$). The number of patients diagnosed to have PDAC each year during the follow-up, the incidence, and risk (HR) of PDAC diagnosis for the gallstone and nongallstone pancreatitis are summarized on Supplementary Digital Content (see Table S3, http://links.lww.com/AJG/C773).

PDAC risk after AP in smokers and heavy alcohol drinkers

Among the controls (veterans without AP or CP), PDAC risk was higher in current smokers (adjusted HR 1.43, 95% CI 1.38–1.48,

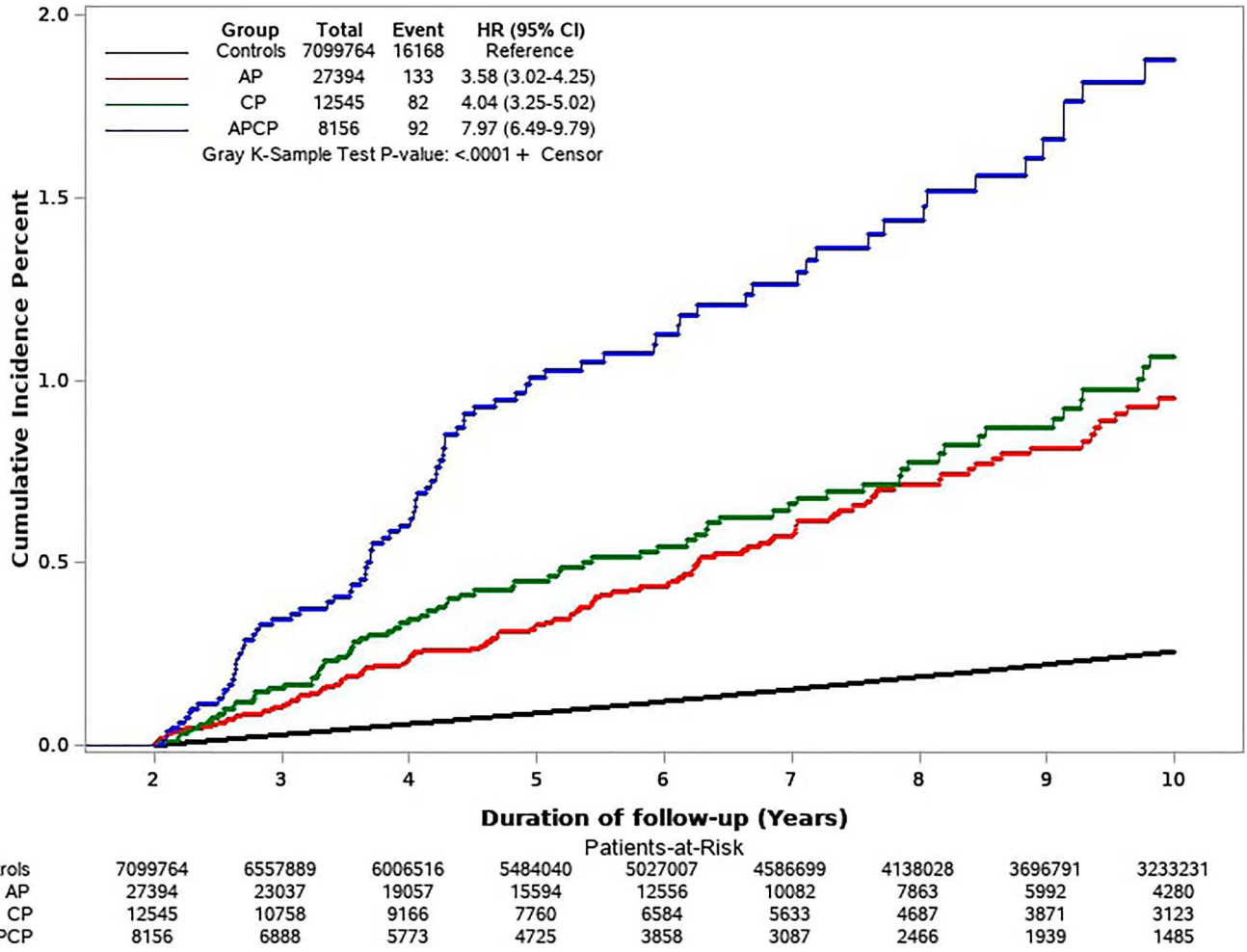

Figure 2. Cumulative incidence of pancreatic cancer in controls, AP group, CP group, and the APCP group. Hazard ratios presented on the figures are unadjusted hazard ratios from Cox-proportional model. Adjusted HRs with 95% CI from Cox-proportional model and the corresponding *P* values are listed in the appropriate sections of the manuscript. Gray K-sample test *P* value is for comparing the cumulative incidence between the groups. $P < 0.001$ AP group vs controls. $P < 0.001$ APCP group vs CP group. AP, acute pancreatitis; APCP, AP with preexisting CP; CI, confidence interval; CP, chronic pancreatitis; HRs, hazard ratios.

$P < 0.001$) and heavy alcoholic drinkers (adjusted HR 1.22, 95% CI 1.17–1.28, $P < 0.001$) (see Supplementary Digital Content, Table S4A and Table S4B, http://links.lww.com/AJG/C773). Patients with AP had a higher PDAC risk vs controls in both nonsmokers (adjusted HR 1.73, 95% CI 1.28–2.35, $P < 0.001$) and current smokers (adjusted HR 1.94, 95% CI 1.53–2.45, $P < 0.001$). This PDAC risk after AP was also increased in both nonalcoholics (adjusted HR 1.61, 95% CI 1.27–2.04, $P < 0.001$) and heavy alcoholic drinkers (adjusted HR 2.27, 95% CI 1.76–2.93, $P < 0.001$). Table 4 illustrates the independent predictors for PDAC among AP patients.

Figure 5 compares the cumulative incidence of PDAC after AP among nonsmoker/nonalcoholics with current smokers, alcoholics, and subjects who are smokers and alcoholics. The cumulative incidence and risk of PDAC was similarly increased after AP irrespective of etiology. After AP, the cumulative incidence and risk of PDAC was identical in nonsmokers vs current smokers ($P = 0.55$) and in nonalcoholics vs heavy alcoholic drinkers ($P = 0.38$) as illustrated on Supplementary Digital Content (see Figure S2A and Figure S2B, http://links.lww.com/AJG/C773).

Sensitivity analysis

We performed the following several sensitivity analyses to evaluate the robustness of our study findings.

PDAC risk after AP using primary inpatient diagnosis codes When AP was defined using primary inpatient diagnosis codes only, although the number of patients with AP and PDAC cases decreased, the overall finding of increased risk of PDAC in AP and APCP groups is consistent with the data presented in the manuscript (see Supplementary Digital Content, Table S5, http://links.lww.com/AJG/C773).

PDAC risk >2 years after AP. We used a minimum of 2 *ICD 9* diagnosis codes as a criterion for defining PDAC and CP diagnosis (vs one). Although the number of PDAC cases decreased in all the groups, the overall finding of the increased risk of PDAC in AP and APCP groups is consistent with the data presented in the manuscript (see Supplementary Digital Content, Table S6, http://links.lww.com/AJG/C773).

PDAC after a single episode of AP (gallstone AP vs nongallstone AP). We evaluated the risk of pancreatic cancer in patients who presented with a single episode of AP to rule out any effect of the

Table 2. Risk of pancreatic cancer by pancreatitis status[a]

	Adjusted HR	95% CI	*P* value
African-American race	1.26	1.20–1.32	<0.001
Other race	0.98	0.90–1.07	0.708
Male sex	1.53	1.36–1.72	<0.001
Age	1.04	1.03–1.04	<0.001
Current smoker	1.46	1.40–1.52	<0.001
Past smoker	0.94	0.89–0.98	0.005
Alcohol history	1.16	1.11–1.22	<0.001
Diabetes mellitus	1.72	1.66–1.78	<0.001
Gallstone disease	2.37	2.23–2.51	<0.001
AP	2.00	1.67–2.38	<0.001
APCP	4.71	3.80–5.82	<0.001
CP	3.07	2.45–3.85	<0.001

AP, acute pancreatitis without preexisting chronic pancreatitis; APCP, acute pancreatitis with preexisting chronic pancreatitis; CI, confidence interval; CP, chronic pancreatitis without any acute pancreatitis; HRs, hazard ratios.
[a]White race, female sex, nonsmokers, nonalcoholics, nondiabetics, patients without gallstone disease, and control patients without acute pancreatitis and chronic pancreatitis were taken as a reference category.

number of episodes on the gallstone AP vs nongallstone AP comparison. Using cause-specific hazard model, patients with gallstone AP showed no significant increase in the PDAC risk (HR 1.45, 95% CI 0.92–2.29, $P = 0.11$) compared with patients without nongallstone AP.

Positive and negative controls. To confirm the hypothesis that increased long-term risk of PDAC in AP is because of inflammation (and not a random association), we evaluated 2 cancers (tongue cancer-*ICD 9* code 141.9 and testicular cancer-*ICD 9* code 186.9) unrelated to AP to check whether patients with AP had an increased long-term risk of these 2 cancers. Using cause-specific hazard model, after adjusting for age, race, sex, smoking history, alcohol history, diabetes status, CP, and gallstone disease, patients with AP showed no significant difference in the risk for tongue cancer (adjusted HR 1.03, 95% CI 0.84–1.27, $P = 0.77$) and testicular cancer (adjusted HR 1.05, 95% CI 0.76–1.46, $P = 0.76$). Similarly, we also evaluated to see whether any disease condition, not known to predispose to PDAC, had any subsequent increase in the PDAC risk. For this, we compared 2 separate cohorts of patients with chronic kidney disease (*ICD 9* code 585) and patients with influenza (*ICD 9* code 487.1) without AP with the rest of the patients in the VA database without chronic kidney disease/influenza for the subsequent risk of PDAC. Using the cause-specific hazard model, after adjusting for age, race, sex, smoking history, alcohol history, diabetes status, CP, and gallstone disease, both patients with chronic kidney disease (adjusted HR 0.92, 95% CI 0.85–1.01, $P = 0.06$) and patients who were diagnosed with influenza (adjusted HR 0.94, 95% CI 0.84–1.06, $P = 0.30$) did not have any significant difference in the risk of PDAC compared with the rest of the VA patients.

DISCUSSION

In this study, using the nationwide veteran administrative database, we found an increased long-term risk (years 3–10) of PDAC after an attack of AP. In a subgroup analysis, AP was associated with a higher risk of PDAC not only in those without (AP group vs controls) but also in those with underlying CP (APCP vs CP). PDAC risk increased with the number of episodes of AP. PDAC risk after AP was comparable in patients with gallstone and nongallstones and was not influenced by smoking status or heavy alcohol intake.

PDAC can have AP as an initial presentation, likely because of an obstruction of the pancreatic duct (22,24–28). Using a cohort from VA database, we previously reported that approximately 1.4% of patients with AP were diagnosed to have PDAC in the next 2 years (22). Subsequent studies from Europe (16,17) have confirmed our findings and, in addition, noted that the higher risk of PDAC persists for 10 years or more after AP. However, these studies did not evaluate the PDAC risk in a clean cohort of patients with CP without AP to be able to determine whether the excess long-term risk of PDAC after AP was indeed because of the underlying CP or progression to CP.

We sought to determine whether the higher PDAC risk after AP was indeed because of the progression to CP or because of increased inflammation from recurrent AP which in cell culture and animal studies have been shown to promote pancreatic carcinogenesis. We also studied whether the PDAC risk was related to etiologic factors of AP (which incidentally are also known to predispose to PDAC) or because of inflammation due to AP and found that the post-AP PDAC risk was independent of the etiology of AP, especially smoking and heavy alcohol intake. We also evaluated patients with AP without CP (AP group) and with preexisting CP (APCP group) and included a group of patients with CP without AP (CP group). If the higher long-term PDAC risk after AP episode is driven by progression to CP, then the risk of PDAC in APCP group should be higher than in the AP group but no higher than in CP group. On the contrary, we found that the APCP group had significantly higher risk compared with the CP group.

The PDAC risk increased with the number of AP episodes implying that repeated bouts of acute inflammation further promote carcinogenesis. The PDAC risk was comparable in patients with and without gallstone and not influenced by the etiology of AP (smoking or heavy alcohol intake), suggesting that the higher PDAC risk in AP is largely because of AP and not because of risk factors such as smoking which are known to increase PDAC risk. The number of cases of PDAC in the cohort by Sadr-Azodi et al (17) in all groups after year 4 is extremely small and therefore precludes a definitive or meaningful interpretation. Even in our cohort despite its very large size, the number of PDAC cases in years 6–10 is rather small but much higher than in the study by Sadr-Azodi. Despite this limitation, there was a statistically significant increase in PDAC risk in patients with gallstone pancreatitis for up to 10 years after AP, and this risk was similar in magnitude to that following nongallstone AP again suggesting that AP regardless of etiology increases long-term PDAC risk.

The present data support and advance the narrative from murine and cell culture models that acute inflammatory changes because of AP lead to molecular/cellular changes that promote carcinogenesis and are distinct from those related to CP-associated chronic inflammation and fibrosis. In several murine models, inflammation promotes cancer progression, and blocking this inflammation abrogates the carcinogenic effects (13,15). In other murine models, AP induced acinar to ductal metaplasia with oncogenic k-ras mutations (12,14). Activating oncogenic k-ras in pancreatic acinar cells during embryogenesis leads to pancreatic cancer initiation (29). The effects of AP in pancreatic

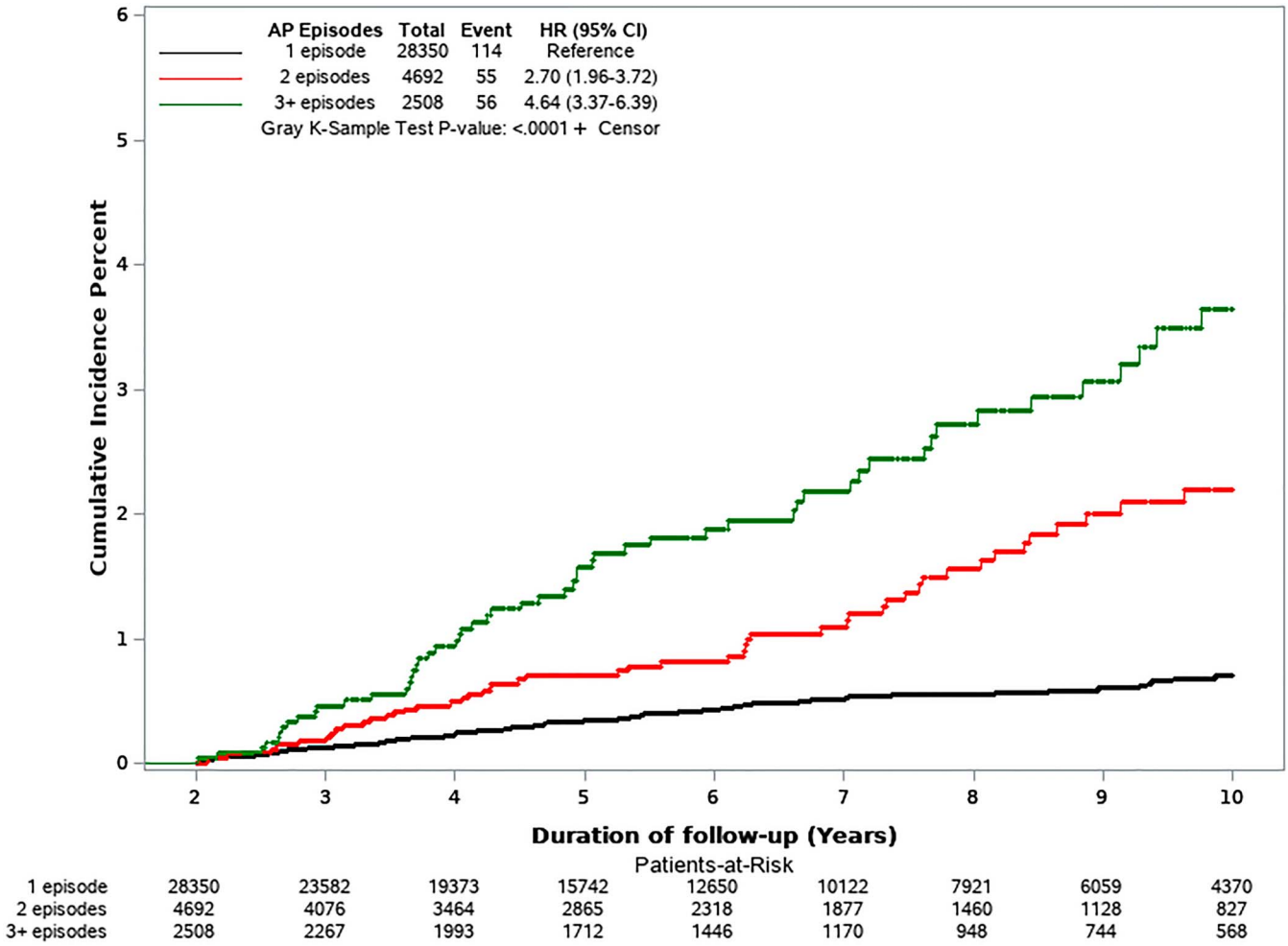

Figure 3. Cumulative incidence of pancreatic cancer based on the number of AP episodes. The trend of higher PDAC risk with increasing number of AP episodes was statistically significant as determined by Gray K-sample test *P* value for comparing the cumulative incidence between the groups. AP, acute pancreatitis; CI, confidence interval; PDAC, pancreatic ductal adenocarcinoma.

carcinogenesis are accelerated in the presence of preexisting oncogenic k-ras mutations (12). Several other biomolecular mechanisms by which AP might promote PDAC have been described, again in cell cultures and animal models. Our findings, linking recurrent AP to PDAC, make these molecular findings more relevant because potential mechanisms for the role of acute inflammation in human pancreatic carcinogenesis are likely to provide impetus for further investigation of the involved molecular pathways.

Strengths of our study include the large sample size and long duration of follow-up, exclusion of patients with pancreatic cysts, controlling for smoking (current and past smokers), heavy alcohol use status, and history of gallstones, besides also evaluating the risk of PDAC in the context of recurrent AP and CP. Although our cohort has limitations because it only represents US veteran population, the risk of PDAC was consistent with recently published studies from populations in Sweden (17) and Denmark (16). In our current dataset, the increased short-term risk (0–2

Table 3. Risk of pancreatic cancer by number of episodes of acute pancreatitis[a]

	N	PDAC n (%)	Adjusted risk	95% CI	*P* value
Controls	7,112,309	16,250 (0.23%)	Reference	—	—
1 episode	28,350	114 (0.40%)	1.28	1.05–1.57	0.016
2 episodes	4,692	55 (1.17%)	2.48	1.84–3.36	<0.001
≥3 episodes	2,508	56 (2.23%)	3.71	2.71–5.09	<0.001

CI, confidence interval; PDAC, pancreatic cancer.
[a]Versus controls (remaining patients in the database without acute or chronic pancreatitis), adjusted for age (age at the time of entry into the study), gender, race, smoking, alcohol, diabetes, gallstones, and chronic pancreatitis.

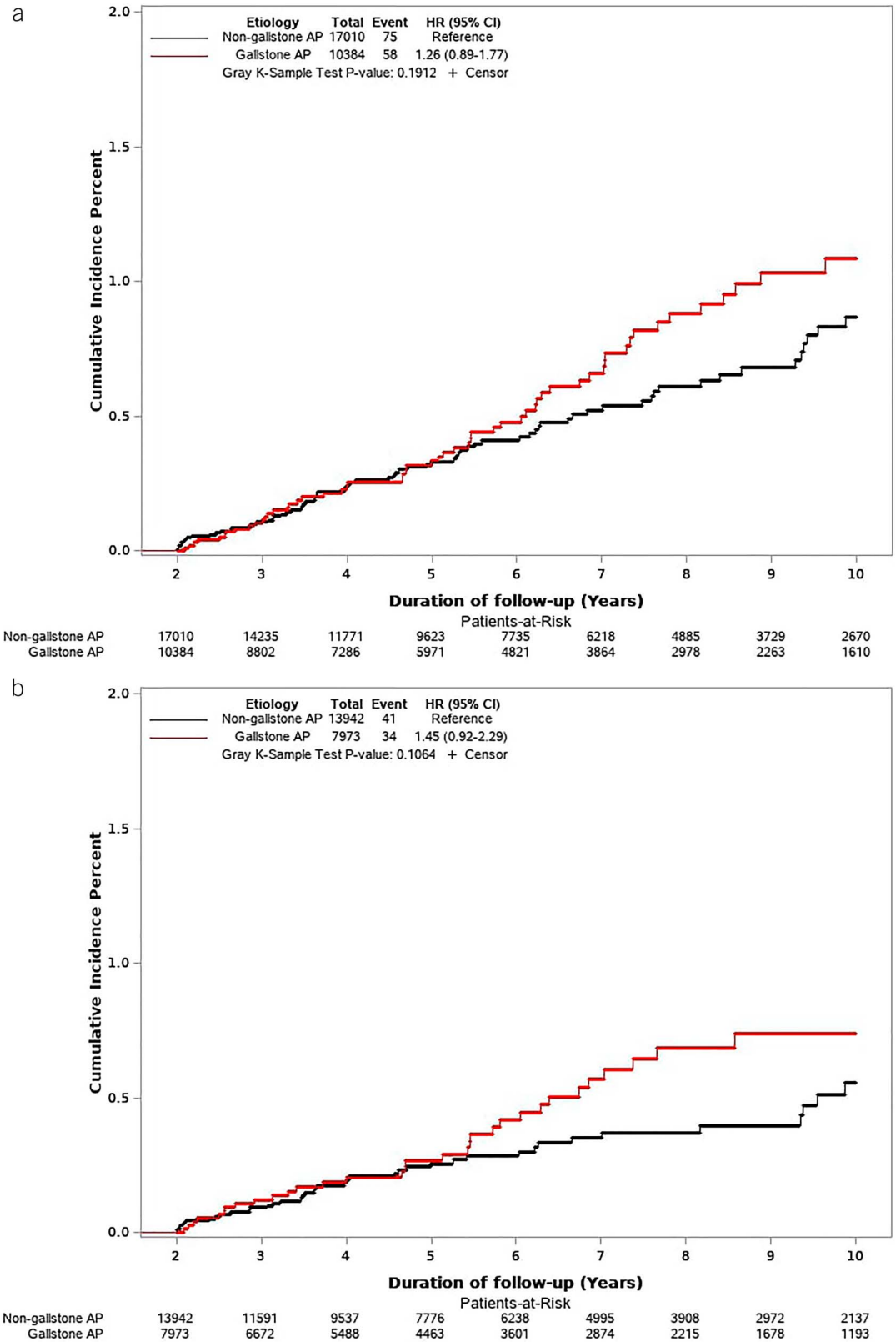

Figure 4. Cumulative incidence of pancreatic cancer after AP in patients with gallstone(s) vs those without nongallstone(s). (**a**) All patients with AP in cohort (**b**). Patients with AP with only one episode of AP. Note: There was no significant difference in PDAC risk in patients with and without gallstones. Because a difference in the number of AP episodes in the 2 groups could be a potential confounder, we evaluated and noted a similar pattern in the subset of patients with a single episode of AP. AP, acute pancreatitis; CI, confidence interval; PDAC, pancreatic ductal adenocarcinoma.

Table 4. Predictors of pancreatic cancer among acute pancreatitis patients[a]

	Adjusted HR	95% CI	*P* value
African-American race	1.60	1.05–2.44	0.027
Other race	1.02	0.49–2.13	0.954
Male sex	1.09	0.40–2.98	0.871
Age	1.04	1.02–1.05	<0.001
Current smoker	1.48	0.96–2.28	0.077
Past smoker	0.90	0.49–1.64	0.732
Alcohol	1.32	0.87–2.00	0.195
Diabetes mellitus	2.25	1.48–3.40	<0.001
Gallstone disease	1.34	0.92–1.97	0.131

CI, confidence interval; HRs, hazard ratios.
[a]White race, female sex, nonsmokers, nonalcoholics, nondiabetics, patients without gallstone disease were taken as a reference category.

years) of PDAC after AP was similar to what we had reported earlier (data not presented here) based on a smaller dataset from the VA database (22) (from 1999 to 2006) and also with the PDAC risk reported in the above-mentioned European studies (16,17). Our data are derived from one of the largest databases in the United States, has meaningful duration of follow-up (~16 years), and adequate numbers of patients with AP (>40,000) and PDAC (>11,000). We performed several sensitivity analyses to evaluate the consistency and robustness of our study findings as described in the results section (sensitivity analysis).

This study has limitations because of its retrospective design and use of administrative data using *ICD 9* codes for PDAC, AP, and other covariates. Furthermore, our cohort of US veterans included 92% men, thereby limiting applicability to women and the general patient population. Owing to the nature of our large cohort, we could not validate the *ICD 9* codes used for identifying all patients with AP and PDAC. However, we reviewed medical charts of a random sample of 100 patients with AP and 100 patients with PDAC, and the accuracy of the *ICD-9* codes for AP

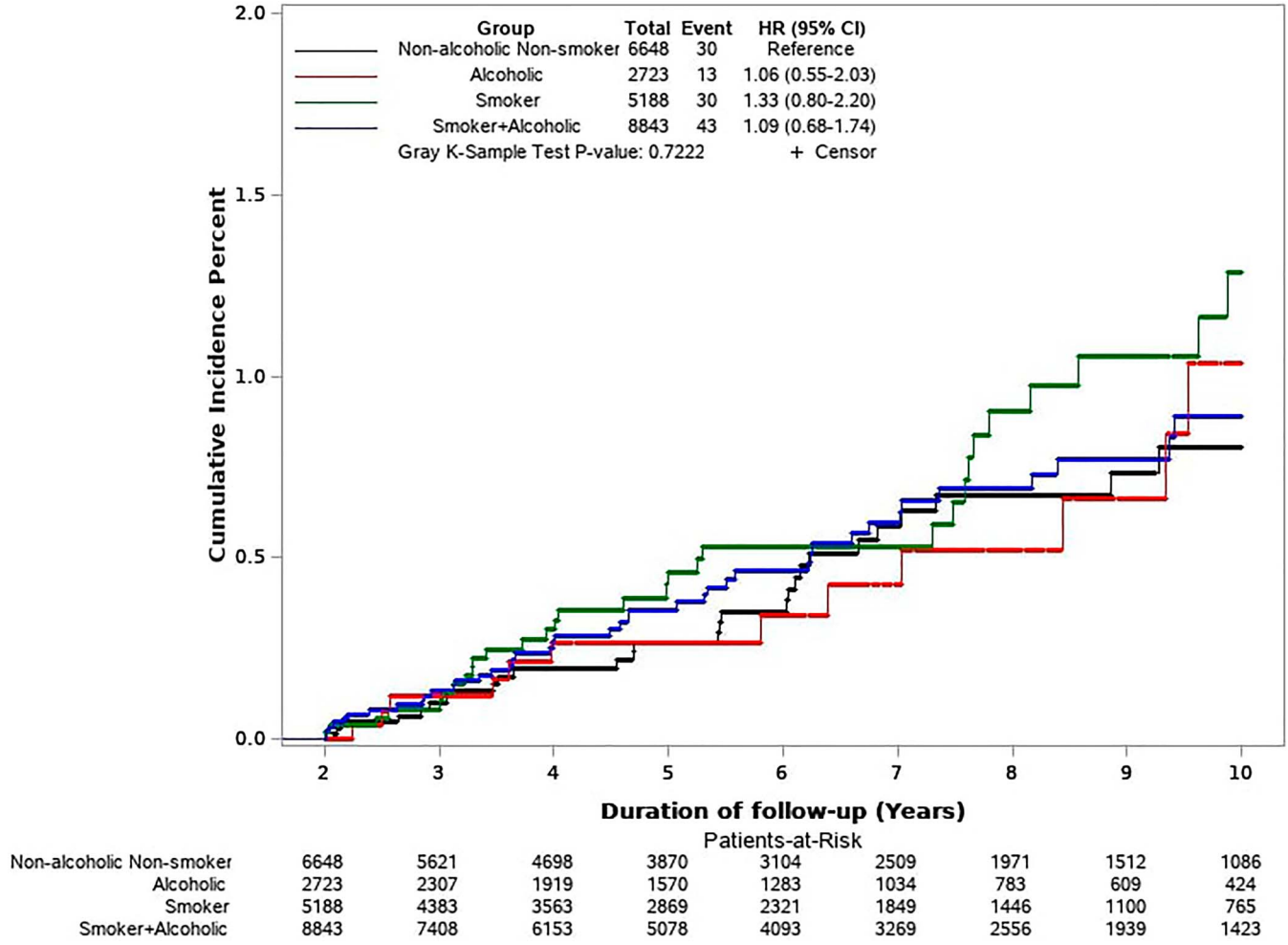

Figure 5. Cumulative incidence of pancreatic cancer after AP is uninfluenced by the etiology of AP. Note: None of the 4 groups were significantly different from each other. There was also no additive effect on PDAC risk after AP in patients who are smokers and heavy alcohol drinkers. AP, acute pancreatitis; CI, confidence interval; PDAC, pancreatic ductal adenocarcinoma.

when compared with clinical diagnosis using the Atlanta criteria (30) (minimum of 2 out of 3) was 88%, and the accuracy for PDAC was 85%. The use of *ICD 9* codes for PDAC in the VA system has also been validated (31). Owing to a lack of sufficient number of PDAC events, we were not able to analyze risk comparison for some of the individual years (beyond 10th year). Severity information for patients with AP could not be ascertained. Owing to the use of a large cohort of patients, we could not ascertain the etiology of AP from the patient charts. Gallstone pancreatitis was defined as AP with an associated *ICD 9* code for gallstone disease. Admittedly, some of those included as gallstone pancreatitis could have had AP because of another etiology and incidental gallstone disease. The prevalence of gallstone disease and alcohol history in our cohort is consistent with the previous VA studies (using a separate cohort from year 1999 to 2006) (22,32). Patients with AP, CP, and APCP were not included in the control group before their diagnosis.

In conclusion, our data provide additional evidence supporting a higher long-term PDAC risk after AP both in patients without and with underlying CP. This increased PDAC risk is intrinsic to AP and likely because of acute inflammation, increases with the number of AP episodes, is independent of the etiology of AP, and is additive with that because of CP. The findings of this study are consistent with and advance the narrative regarding cancer-promoting effects of AP, based on data from animal models and cell culture studies, and is distinct from PDAC causing and presenting with AP. Future studies are needed to confirm our findings, further evaluate the molecular pathways that are involved in promoting carcinogenesis by AP, and evaluate whether there is a potential role for pancreatic cancer surveillance in patients after AP or in certain subgroups with higher PDAC risk.

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CONFLICTS OF INTEREST

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Acute inflammation promotes pancreatic carcinogenesis in cell culture and animal models.
- ✓ Acute pancreatitis (AP) is often the initial presentation of pancreatic ductal adenocarcinoma (PDAC).
- ✓ There is higher long-term PDAC risk after AP.

WHAT IS NEW HERE

- ✓ Increased PDAC risk after AP is not influenced by the etiology of AP.
- ✓ PDAC risk after AP increases with the number of episodes of AP.
- ✓ Pancreatic cancer risk in AP is not because of progression to chronic pancreatitis because it is even higher in patients with CP who have AP.

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