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Risk of Pancreatic Cancer After Acute Pancreatitis: A Retrospective Analysis of the Korean National Sample Cohort

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ABSTRACT

Background: Acute pancreatitis may increase the risk of pancreatic cancer, although this association remains unclear. Therefore, we aimed to investigate this association.
Methods: We retrospectively analyzed the 2002–2019 Korean National Health Insurance Service-National Sample Cohort using 1:3 propensity score matching for sex and age (acute pancreatitis, n = 4,494; matched controls, n = 13,482). We calculated the hazard ratio (HR) for pancreatic cancer risk in patients with acute pancreatitis using Cox proportional hazards regression.
Results: Acute pancreatitis was significantly associated with an increased risk of pancreatic cancer throughout the study period (adjusted HR, 7.56 [95% confidence interval, 5.00–11.41]), which persisted for 2, 2–5, and > 5 years post-diagnosis (19.11 [9.60–38.05], 3.46 [1.35–8.33], and 2.73 [1.21–6.15], respectively). This pancreatitis-related pancreatic cancer risk became insignificant beyond 10 years of follow-up (1.24 [0.24–6.49]). Furthermore, this risk notably increased as the number of recurrent acute pancreatitis episodes increased (1 episode: 5.25 [3.31–8.33], 2 episodes: 11.35 [6.38–20.19], ≥ 3 episodes: 24.58 [13.66–44.26]).
Conclusion: Following an acute pancreatitis diagnosis, the risk of pancreatic cancer increases significantly in the initial years, with a rapid increase further accentuated with recurrent acute pancreatitis episodes. Additional study is needed to evaluate whether this increased risk of carcinogenesis is attributed to accumulated inflammation.

Keywords: Pancreatic Cancer; Acute Pancreatitis; Acute Recurrent Pancreatitis; Risk Factor

INTRODUCTION

Pancreatic cancer ranks as the 8th most common cancer in the Republic of Korea, with approximately 7,000 new cases in 2017, and it stands as the fifth most common cause of cancer-related deaths.[1] The incidence and mortality rates of pancreatic cancer are gradually increasing. Notably, the 5-year relative survival rate in 2017 was 12.2%.[2] The relative survival rate has not improved considerably over the past 20 years.[2] Early diagnosis and curative surgery are crucial elements in treating pancreatic cancer.[3] Unfortunately, effective options for the early diagnosis of pancreatic cancer are currently lacking. Therefore, understanding the risk factors is essential to facilitate early diagnosis and increase successful resection rates.

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jeong SH, Kim SH, Jang SI. Data curation: Jeong SH, Hurh K, Kim SH. Formal analysis: Hurh K, Jeong SH. Methodology: Jeong SH, Park EC, Leigh JH, Kim SH, Jang SI. Supervision: Kim SH, Jang SI. Writing - original draft: Jeong SH. Writing - review & editing: Jeong SH, Hurh K, Park EC, Leigh JH, Kim SH, Jang SI.

Acute pancreatitis is an inflammatory disease of the pancreas that develops suddenly.[4] Pancreatic cancer can induce acute pancreatitis, and the inflammatory processes within the pancreas can also contribute to the development of pancreatic cancer.[5] This is particularly true for chronic pancreatitis, which is strongly associated with pancreatic cancer.[6,7] However, the role of acute pancreatitis in pancreatic cancer is less evident.[8,9] Previous experimental studies have suggested that acute pancreatitis can cause pancreatic cancer,[10,11] whereas epidemiological studies have reported conflicting results.[12,13] Furthermore, acute pancreatitis can progress to pancreatic cancer due to genetic changes.[10,11] However, the association between acute pancreatitis and pancreatic cancer remains controversial. Moreover, the cost-effectiveness of a close follow-up after the first episode of acute pancreatitis and its potential to enable an early diagnosis of pancreatic cancer, are questionable. Therefore, it is necessary to establish a reliable estimate of the association between acute pancreatitis and pancreatic cancer through investigation and verification in a large-scale cohort study. The relationship between acute pancreatitis and pancreatic cancer in the general Korean population, based on large-scale cohort data has not been fully elucidated.[14] Therefore, we conducted this national population-based matched cohort study to investigate the risk of pancreatic cancer in patients with acute pancreatitis, compared to the risk in a matched cohort, in the general population of Korea.

METHODS

Data and study participants

In this retrospective cohort study, we analyzed data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database from 2002 to 2019. In the Republic of Korea, following the introduction of the National Health Insurance in 1989, the National Health Insurance Corporation established the National Health Information Database (NHID), a claims database designed for study purposes that stores all records of medical and long-term care services. Using data from the NHID, the National Health Insurance Corporation established a sample of the population registered in its records, which is a representative administrative database for health policy and biomedical study purposes, and made these data available to study.[15] As of 2002, 1 million participants had been selected for the National Health Insurance Corporation sample to represent the Korean population. All individuals included in this sample were followed-up until December 31, 2019, unless they were disqualified, such as immigration or death. Under the National Health Insurance single-insurer system, the National Health Insurance Corporation retains all personal information of Korean citizens, including demographic data, medical utilization records, and medical treatment information. The dataset encompasses all inpatient and outpatient medical and prescription claims, along with the codes for treatment and diagnostic procedures, and generic prescription names.

Acute pancreatitis and matched comparator cohorts

The acute pancreatitis cohort comprised all individuals diagnosed with acute pancreatitis (NHIS-NSC, 2002–2019; N = 14,989). We did not include patients with an outpatient diagnosis of acute pancreatitis as this was indicative of a follow-up consultation after admission or potential coding errors (n = 8,201).[16] Additionally, to examine the effect of acute pancreatitis in detail, we excluded patients diagnosed with chronic pancreatitis before or after their acute pancreatitis diagnosis (n = 1,218). Furthermore, to select new-onset acute pancreatitis cases, we excluded patients who had filed medical claims for acute pancreatitis

in 2002 or 2003 (i.e., implementing a 2-year washout period) as these patients might have previously been diagnosed with acute pancreatitis (n = 293). Participants with at least 1 year of follow-up were included (n = 439); the date of the first acute pancreatitis diagnosis was considered the index date. Furthermore, we excluded patients (n = 186) who underwent pancreatic cancer-related operation before the index date (Korea Classification of Operations and Major Procedures: Q7565, Q7567, Q7563, Q7571, Q7572, Q7562, Q7561, QZ964, and QZ961) or a diagnosis of pancreatic cancer (International Classification of Diseases, 10th Revision [ICD-10] code: C25). Similarly, patients younger than 19 years on the index date were excluded (n = 158). Following these exclusions, 4,494 individuals were enrolled in the acute pancreatitis group.

Furthermore, using matching propensity scores, participants in the acute pancreatitis groups were matched with participants in the control group (who had never previously been diagnosed with acute pancreatitis or pancreatic cancer). The propensity score was derived using logistic regression to calculate the probability of acute pancreatitis with covariates of sex and age. After calculating the propensity score, we performed 1:3 greedy matching using the OneToManyMTCH macro for SAS (SAS Institute Inc., Cary, NC, USA).[14,15]

Follow-up and pancreatic cancer outcomes

To investigate the risk of pancreatic cancer, we followed the participants with acute pancreatitis and their matched controls from their respective index dates until the date of pancreatic cancer diagnosis, as recorded in the NHIS-NSC. Participants with an ICD-10 code C25 were considered to have pancreatic cancer. For each participant, the final follow-up date was defined as the date of diagnosis of pancreatic cancer, the end of the study period (December 31, 2018), or the date of death.

Control variables

The possible confounding factors were variables that could affect the incidence of pancreatic cancer in patients with acute pancreatitis. These confounding factors included age, sex, social security status, residential region, disability, household income level, the Charlson Comorbidity Index (CCI), diabetes, and the year in which acute pancreatitis was diagnosed. The CCI enables the evaluation of how a participant's comorbidities may alter their mortality risk, especially in longitudinal studies; the CCI is calculated by weighing 1–6 points for 19 comorbid diseases. The comorbidity categories in the CCI score comprise myocardial, vascular, lung, endocrine, renal, gastrointestinal, cancer/immune, and neurological conditions.[17] The participants' CCI scores were calculated using the ICD-10 code for each comorbidity,[18] and participants were divided into 3 groups according to their CCI scores: 0, 1–2, and ≥ 3. Furthermore, a diagnosis of diabetes that was obtained using the ICD-10 code was included in the analysis separately. The cohort was divided into 4 age groups (19–49, 50–59, 60–69, and ≥ 70 years), accounting for the increased incidence of pancreatic cancer after the age of 50 years.[19] Residential regions were divided into 3 population density-based categories: metropolitan, city, and rural areas. The Korean National Health Insurance system covers all individuals residing within the Republic of Korea, except for medical aid beneficiaries. Additionally, the Korean government provides medical aid programs for people who cannot afford health insurance.[20] These programs encompass individuals with disabilities whose incomes are below the government-set poverty thresholds or those who have access to free government-provided inpatient and outpatient care. Consequently, medical insurance was classified into 2 categories: national health insurance and medical aid. The household income level was classified into 3 categories: low, mid, and high, according to

household-level insurance premiums. Disability was classified into 2 categories: yes and no, depending on whether the rating was determined.

Statistical analysis

We first investigated the frequency and percentage of each categorical variable at each participant's baseline and performed a χ^2 test to examine the distribution of pancreatic cancer across these variables. A Cox proportional hazards model was generated for examining the association between acute pancreatitis and the risk of pancreatic cancer. All Cox proportional hazards models were fully adjusted for the covariates presented in **Table 1**. A Kaplan–Meier survival curve was used to obtain the incidence of pancreatic cancer, and the log-rank test was used to compare the Kaplan–Meier curves of the matched cohorts. Furthermore, we considered various follow-up periods (0–2, 2–5, > 5, and > 10 years) in the survival analysis, as well as the total duration to facilitate comparisons with studies from other countries. The incidence rate (IR) and its associated 95% confidence interval (CI) for pancreatic cancer were calculated using a generalized linear model with the Poisson distribution and expressed as the number of incident cases per 100,000 person-years. Person-years were calculated from the date of admission for acute pancreatitis (or the corresponding index date for matched controls) to the date of pancreatic cancer, death, or the end of the study period, whichever occurred first. The effect sizes are expressed as hazard ratios (HRs) using Cox's proportional hazards model, which includes a robust variance estimator that accounts for clustering within matched pairs.[21,22] Additionally, considering the high recurrence rate of acute pancreatitis,[23] we performed an additional analysis using the Cox proportional hazards model to determine the risk of pancreatic cancer according to the number of episodes of acute recurrent pancreatitis (0, 1, 2, ≥ 3) after adjusting for all covariates. Moreover, we performed analyses stratified by sex, age, and region to investigate the association between acute pancreatitis and the risk of pancreatic cancer. Differences were considered statistically significant for *P* values < 0.05. All data were analyzed using SAS 9.4 (SAS Institute Inc.).

Ethics statement

All data are available in the database of the Korean National Health Insurance Sharing Service (https://nhiss.nhis.or.kr) and can be provided upon reasonable request. The study protocol was approved by the Institutional Review Board of Yonsei University's Health System (approval No. 4-2022-0006; Seoul, Republic of Korea). Due to the retrospective nature of the study, the requirement for informed consent was waived.

RESULTS

Baseline characteristics

Baseline characteristics of the study sample are presented in **Table 1**. The analysis comprised a total of 17,976 participants, including 4,494 patients with an initial diagnosis of acute pancreatitis and 13,482 matched controls, of whom 115 (0.6%) developed pancreatic cancer. In the χ^2 test, a significant intergroup difference in the prevalence of pancreatic cancer was observed when the cohort was divided according to the diagnosis of acute pancreatitis. Moreover, in the univariate analysis, age, disability, the CCI score, diabetes, and year of diagnosis of acute pancreatitis were significantly associated with the risk of pancreatic cancer. Conversely, sex, household income level, region, and social security, were unassociated with the risk of pancreatic cancer.

Table 1. General characteristics of the study population based on acute pancreatitis diagnosis

Variables	Total	Acute pancreatitis	Matched control	*P* value	Risk of pancreatic cancer		*P* value
					No	Yes	
Total	17,976 (100.0)	4,494 (25.0)	13,482 (75.0)		17,861 (99.4)	115 (0.6)	
Acute Pancreatitis							< 0.001
No	13,482 (75.0)				13,446 (99.7)	36 (0.3)	
Yes	4,494 (25.0)				4,415 (98.2)	79 (1.8)	
Gender				1.000			0.958
Male	10,204 (56.8)	2,551 (25.0)	7,653 (75.0)		10,139 (99.4)	65 (0.6)	
Female	7,772 (43.2)	1,943 (25.0)	5,829 (75.0)		7,722 (99.4)	50 (0.6)	
Age				1.000			< 0.001
19–49	5,980 (33.3)	1,495 (25.0)	4,485 (75.0)		5,968 (99.8)	12 (0.2)	
50–59	3,776 (21.0)	944 (25.0)	2,832 (75.0)		3,760 (99.6)	16 (0.4)	
60–69	3,064 (17.0)	766 (25.0)	2,298 (75.0)		3,033 (99.0)	31 (1.0)	
70	5,156 (28.7)	1,289 (25.0)	3,867 (75.0)		5,100 (98.9)	56 (1.1)	
Household income level				< 0.001			0.714
Low	3,989 (22.2)	1,463 (21.0)	5,502 (79.0)		3,961 (99.3)	28 (0.7)	
Mid	7,048 (39.2)	1,181 (25.5)	3,451 (74.5)		7,007 (99.4)	41 (0.6)	
High	6,939 (38.6)	1,850 (29.0)	4,529 (71.0)		6,893 (99.3)	46 (0.7)	
Region				< 0.001			0.091
Metropolitan	6,965 (38.7)	1,463 (21.0)	5,502 (79.0)		6,927 (99.5)	38 (0.5)	
City	4,632 (25.8)	1,181 (25.5)	3,451 (74.5)		4,607 (99.5)	25 (0.5)	
Rural	6,379 (35.5)	1,850 (29.0)	4,529 (71.0)		6,327 (99.2)	52 (0.8)	
Medical insurance				< 0.001			0.702
NHI	17,025 (94.7)	4,084 (24.0)	12,941 (76.0)		16,917 (99.4)	108 (0.6)	
Medical aid	951 (3.3)	410 (43.1)	541 (56.9)		944 (99.3)	7 (0.7)	
Disability				< 0.001			0.022
No	16,162 (89.9)	3,915 (24.2)	12,247 (75.8)		16,066 (99.4)	96 (0.6)	
Yes	1,814 (10.1)	579 (31.9)	1,235 (68.1)		1,795 (99.0)	19 (1.0)	
CCI				< 0.001			< 0.001
0	8,947 (49.8)	1,368 (15.3)	7,579 (84.7)		8,916 (99.7)	31 (0.3)	
1–2	7,178 (39.9)	2,183 (30.4)	4,995 (69.6)		7,116 (99.1)	63 (0.9)	
≥ 3	1,852 (10.3)	943 (51.0)	907 (49.0)		1,829 (98.9)	21 (1.1)	
Diabetes				< 0.001			0.005
No	15,641 (87.0)	3,575 (22.9)	12,066 (77.1)		15,551 (99.4)	90 (0.4)	
Yes	2,335 (13.0)	919 (39.4)	1,416 (60.6)		2,310 (98.9)	25 (0.6)	
Year of acute pancreatitis diagnosis				0.837			0.037
2004	664 (3.7)	165 (24.8)	499 (75.2)		660 (99.4)	4 (0.6)	
2005	894 (5.0)	211 (23.6)	683 (76.4)		882 (98.7)	12 (1.3)	
2006	1,056 (5.9)	248 (23.6)	805 (76.4)		1,043 (99.1)	10 (0.9)	
2007	1,103 (6.1)	267 (24.2)	836 (75.8)		1,096 (99.4)	7 (0.6)	
2008	1,098 (6.1)	266 (24.2)	832 (75.8)		1,093 (99.5)	5 (0.5)	
2009	1,223 (6.8)	294 (24.0)	929 (76.0)		1,213 (99.2)	10 (1.8)	
2010	1,132 (6.3)	281 (24.8)	851 (75.2)		1,123 (99.2)	9 (0.8)	
2011	1,351 (7.5)	328 (24.3)	1,023 (75.7)		1,342 (99.3)	9 (0.7)	
2012	1,280 (7.1)	316 (24.7)	964 (75.3)		1,272 (99.4)	8 (0.6)	
2013	1,262 (7.0)	315 (25.0)	947 (75.0)		1,255 (99.4)	7 (0.6)	
2014	1,277 (7.1)	326 (25.5)	951 (74.5)		1,269 (99.4)	8 (0.6)	
2015	1,115 (6.2)	286 (25.7)	829 (74.3)		1,105 (99.1)	10 (0.9)	
2016	1,455 (8.1)	378 (26.0)	1,077 (74.0)		1,443 (99.2)	12 (0.8)	
2017	1,521 (8.5)	408 (26.8)	1,113 (73.2)		1,519 (99.9)	2 (0.1)	
2018	1,548 (8.6)	405 (26.2)	1,143 (73.8)		1,546 (99.9)	2 (0.1)	

Values are presented as number (%).
NHI = National health insurance, CCI = Charlson Comorbidity Index.

Risk of pancreatic cancer and acute pancreatitis

During the entire follow-up period, there was a significant intergroup difference in the cumulative incidence of pancreatic cancer between the group with acute pancreatitis and the matched controls ($P < 0.001$, log-rank test; **Fig. 1**).

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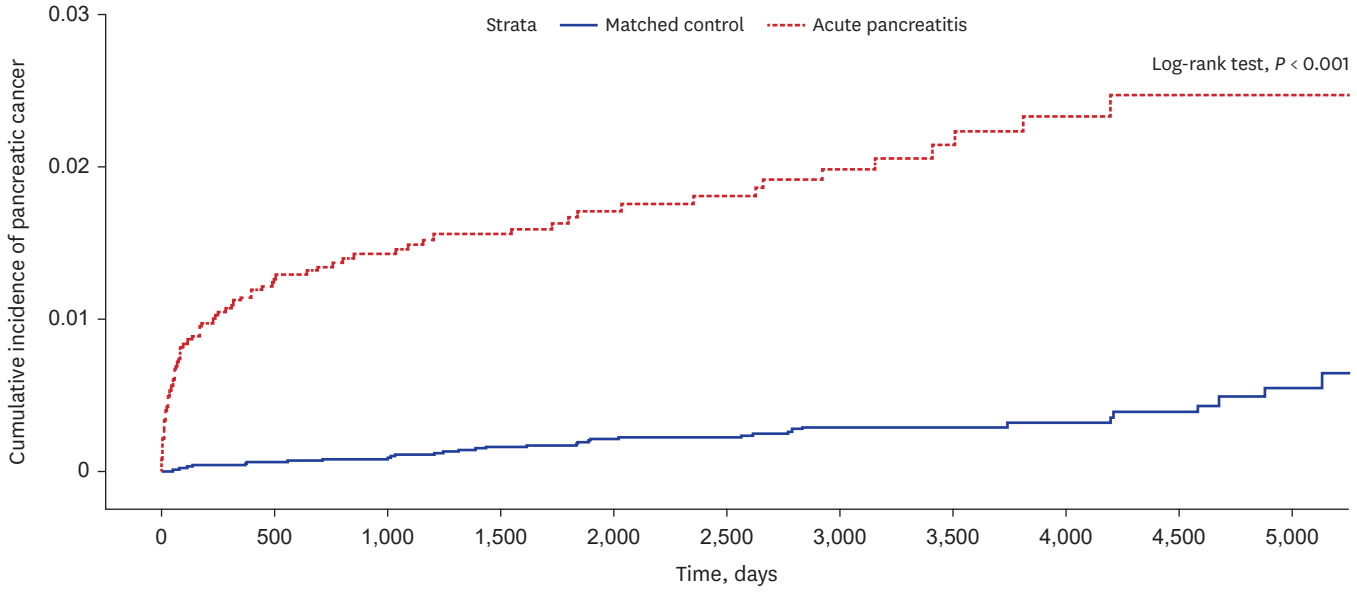

Fig. 1. Kaplan–Meier survival curves for patients with acute pancreatitis and matched controls.

Table 2 shows the results of the survival analysis using the Cox proportional hazards regression model. During the study period, patients with acute pancreatitis had an increased risk of pancreatic cancer when compared to the matched controls (adjusted HR [aHR], 7.56; 95% CI, 5.00–11.41) (**Table 2**, **Supplementary Table 1**). Notably, within the first 2 years of follow-up, patients with acute pancreatitis had the most substantial increased risk of pancreatic cancer compared with their matched controls (aHR, 19.11; 95% CI, 9.60–38.05). Patients with acute pancreatitis exhibited an increased risk of pancreatic cancer when compared to their matched controls at 2–5 years after the diagnosis of pancreatitis (aHR, 3.46; 95% CI, 1.35–8.83). Furthermore, patients with acute pancreatitis had an increased risk of pancreatic cancer compared to that in the matched controls even 5 years after their initial diagnosis of pancreatitis (aHR, 2.73; 95% CI, 1.21–6.15). However, in patients with acute pancreatitis, the risk of pancreatic cancer was similar to that of the matched controls at least 10 years after the diagnosis of pancreatitis (aHR, 1.24; 95% CI, 0.24–6.49).

Table 2. Comparative analysis of pancreatic cancer rates and association of acute pancreatitis with pancreatic cancer risk

Exposure	No. of subjects	No. of pancreatic cancer	Person-year	Incidence rate (95% CI) per 100,000 person-years	Crude HR (95% CI)	aHR[a] (95% CI)
0–2 yr						
Matched control	13,482	10	26,094.7	38.3 (20.6–71.1)	1.00	1.00
Acute pancreatitis patients	4,494	58	8,148.8	711.8 (548.9–920.2)	18.07 (9.23–35.35)	19.11 (9.60–38.05)
2–5 yr						
Matched control	12,099	10	31,190.4	32.1 (22.0–68.2)	1.00	1.00
Acute pancreatitis patients	3,630	10	8,936.3	111.9 (60.1–207.8)	3.48 (1.45–8.36)	3.46 (1.35–8.83)
> 5 yr						
Matched control	8,908	16	44,007.0	36.4 (22.3–59.3)	1.00	1.00
Acute pancreatitis patients	2,423	11	11,206.9	98.2 (54.3–177.2)	2.70 (1.25–5.83)	2.73 (1.21–6.15)
> 10 yr						
Matched control	4,259	7	11,465.9	61.1 (29.1–127.9)	1.00	1.00
Acute pancreatitis patients	1,026	2	2,827.6	70.7 (17.7–282.8)	1.16 (0.24–5.60)	1.24 (0.24–6.49)
Full cohort						
Matched control	13,482	36	101,292.2	35.5 (25.6–49.3)	1.00	1.00
Acute pancreatitis patients	4,494	79	28,292.0	279.2 (223.5–348.6)	7.37 (4.97–10.94)	7.56 (5.00–11.41)

CI = confidence interval, HR = hazard ratio, aHR = adjusted hazard ratio.
[a]All variables in **Table 1** were included in Cox proportional hazard model.

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Risk of pancreatic cancer and acute recurrent pancreatitis

Table 3 shows the results of the survival rate analysis according to the acute recurrent pancreatitis during the entire follow-up period using the Cox proportional hazards regression model. During the entire study period, the risk of pancreatic cancer increased as the number of episodes of acute recurrent pancreatitis increased compared to matched controls (1 episode: aHR, 5.25; 95% CI, 3.31–8.33; 2 episodes: aHR, 11.35; 95% CI, 6.38–20.19; ≥ 3 episodes: aHR, 24.58; 95% CI, 13.66–44.26).

Table 3. Cox proportional hazard regression analysis results for acute recurrent pancreatitis and pancreatic cancer risk

Variables	Risk of pancreatic cancer
	aHR[b] (95% CI)
Acute recurrent pancreatitis[a]	
None	1.00
1	5.25 (3.31–8.33)
2	11.35 (6.38–20.19)
≥ 3	24.58 (13.66–44.26)

aHR = adjusted hazard ratio, CI = confidence interval.
[a]Number of episodes of acute pancreatitis since first diagnosis of acute pancreatitis.
[b]All variables in **Table 1** were included in Cox proportional hazard model.

Subgroup analysis for pancreatic cancer risk, stratified by sex, age, and region

Table 4 shows the results of subgroup analyses stratified by sex, age, and region. Compared with patients without acute pancreatitis, male patients with acute pancreatitis had a 9.45 times higher risk of pancreatic cancer (aHR, 9.45; 95% CI, 5.27–16.95). Moreover, patients with acute pancreatitis aged 60–69 years had a 33.93 times higher risk of pancreatic cancer (aHR, 33.93; 95% CI, 4.17–275.86). Furthermore, participants with acute pancreatitis residing in rural areas had an 8.93 times higher risk of pancreatic cancer (aHR, 8.93; 95% CI, 4.71–16.92).

Table 4. Association between acute pancreatitis and the risk of pancreatic cancer stratified by independent variables

Variables	aHR[a]	Risk of pancreatic cancer
		aHR[a] (95% CI)
Sex		
Male	1.00	9.45 (5.27–16.95)
Female	1.00	5.63 (3.10–10.23)
Age		
19–49	1.00	33.25 (9.77–113.14)
50–59	1.00	7.37 (2.37–22.91)
60–69	1.00	33.93 (4.17–275.86)
≥ 70	1.00	3.97 (2.30–6.85)
Region		
Metropolitan	1.00	6.86 (3.39–13.90)
City	1.00	6.80 (2.87–16.13)
Rural	1.00	8.93 (4.71–16.92)

aHR = adjusted hazard ratio, CI = confidence interval.
[a]All variables in **Table 1** were included in Cox proportional hazard model.

DISCUSSION

In our nationwide cohort study, after adjusting for several confounding factors, the relative risk of pancreatic cancer increased significantly during the first few years following an acute pancreatitis diagnosis, with the most pronounced elevation observed during the first 2 years. However, this risk gradually decreased over time, ultimately aligning with the risk found in the matched general population after > 10 years. Specifically, our findings highlighted an elevated

incidence of pancreatic cancer in patients with acute pancreatitis, reaching 279.2 during the overall study period, and 711.8, 111.9, 98.2, and 70.7 per 100,000 person-years within 0–2, 2–5, > 5, and > 10 years, respectively, after a diagnosis of acute pancreatitis. Moreover, patients with acute pancreatitis were 7.56 times more likely to develop pancreatic cancer during the entire study period, with elevations of 19.11, 3.46, 2.73, and 1.24 times within 0–2, 2–5, > 5, and > 10 years, respectively, post-acute pancreatitis diagnosis. Furthermore, as the number of episodes of acute recurrent pancreatitis increased, the risk of pancreatic cancer escalated rapidly. Specifically, compared to the matched cohort over the entire study period, the likelihood of developing pancreatic cancer in patients hospitalized for acute pancreatitis 1, 2, and 3 or more times were 5.25, 11.35, and 24.58 times higher, respectively.

Our results suggest that acute pancreatitis may be an independent risk factor for pancreatic cancer. One study evaluated the association between acute pancreatitis and the risk of pancreatic cancer in the Korean population aged over 40 years.[14] However, to our knowledge, our study is the first to investigate this association in the entire Korean population.

Our findings are consistent with those from previous studies evaluating the association between acute pancreatitis and pancreatic cancer.[14,16,24-26] Korean patients with acute pancreatitis aged > 40 years had approximately 63 times higher risk of developing pancreatic cancer in the first 2 months and approximately 8.46 times in 1–2 years. Notably, this risk gradually decreased over time. After 10 years, no significant difference was observed compared to the population without acute pancreatitis.[14] In the Netherlands, pancreatic cancer was approximately 9 times more likely to be diagnosed during a 47-month follow-up period after a diagnosis of acute pancreatitis.[24] In Taiwan, pancreatic cancer was 3.72 times more likely to be diagnosed during the 5-year follow-up period after an acute diagnosis of acute pancreatitis.[25] Furthermore, a study from Sweden showed that the likelihood of being diagnosed with pancreatic cancer in the first 2 months after the first diagnosis of acute pancreatitis was 171.64 times, gradually decreased to 1.62 times between 5 and 10 years, and was the same as that of the population without pancreatitis after 10 years.[26] However, a study conducted in Denmark showed that the likelihood of being diagnosed with pancreatic cancer after a diagnosis of pancreatitis was 19.28 and 2.21 times higher in the first 2 months and over 10 years post-diagnosis, respectively.[16]

In our study, the risk of pancreatic cancer after acute pancreatitis differed slightly from previously reported rates. While our study reported significantly higher or lower incidence rates of pancreatic cancer post-acute pancreatitis than those reported in the literature, similar trends were noted as the risk of pancreatic cancer gradually converged with that of the general population 10 years after diagnosis of acute pancreatitis.[14] Therefore, the abovementioned differences in our results might have been due to differences in study design, follow-up duration, or patient ethnicities.[14,16,24-26]

Additionally, our findings show that the risk of pancreatic cancer increases with the number of episodes of acute recurrent pancreatitis, suggesting its role as an independent risk factor for pancreatic cancer. In our study, the rate of recurrence of acute pancreatitis was approximately 24.9% (**Supplementary Table 2**), consistent with previous study reporting recurrence rates of approximately 10–30%.[27] Furthermore, our results may support previous findings indicating that recurrent acute pancreatitis is a potential independent risk factor for pancreatic cancer development.[26,28,29]

The mechanisms supporting the association between acute pancreatitis and pancreatic cancer are unclear; however, various pathogenic mechanisms purportedly include processes related to chronic inflammation, such as increased cell cycles, DNA damage, release of growth factors, and subsequent activation of embryonic signaling pathways.[5,30,31] In chronic pancreatitis, the relationship with pancreatic cancer has been clearly demonstrated,[8,9] and acute pancreatitis is often a precursor of chronic pancreatitis. Patients with severe acute pancreatitis, although asymptomatic, can exhibit several signs of pancreatitis before their initial hospitalization. It is difficult to clinically distinguish between acute and chronic pancreatitis, and an accurate diagnosis is often made through continuous patient follow-up.[32] Pancreatic cancer mimics pancreatitis before a definite diagnosis, that is, pancreatic cancer itself may be the etiology of pancreatic cancer after acute pancreatitis.[33] Therefore, the role of acute pancreatitis in the development of pancreatic cancer remains unclear, and additional study is needed to reveal the exact underlying mechanism.

Furthermore, as the number of episodes of acute recurrent pancreatitis increases, the risk of developing pancreatic cancer increases, corroborating previous studies.[16,26,28] In other words, our results indirectly demonstrate that repeated bouts of acute inflammation can further promote carcinogenesis. Previous studies have reported that persistent inflammatory processes in the pancreas may trigger the development of pancreatic cancer.[24] Given the existing evidence linking acute pancreatitis, recurrent acute pancreatitis, chronic pancreatitis, and pancreatic cancer,[26] further studies evaluating the factors related to recurrent acute pancreatitis among patients with acute pancreatitis are warranted. This approach will enable to identification of specific factors leading to pancreatic cancer and inform early intervention strategies.

In our study, participants with acute pancreatitis who were men, aged 60–69 years, or residing in rural regions had a higher risk of developing pancreatic cancer. This highly correlated result in men may be attributed to the higher alcohol and tobacco consumption among men compared with women, in the Republic of Korea,[34,35] and is positively correlated with tobacco and alcohol consumption,[36-38] which are well-established risk factors.[39] However, the abovementioned association was not found in a Danish study that evaluated the relationship between smoking in acute pancreatitis and pancreatic cancer.[16] Therefore, additional study is needed to determine why the risk of pancreatic cancer is high in men with acute pancreatitis. In addition, patients with acute pancreatitis aged 60–69 years had a high risk for pancreatic cancer. This association might be attributed to fact that, in the Republic of Korea, the highest incidence (37.2%) of pancreatic cancer is depicted among individuals in their 60s.Notably, our study showed a similar trend in patients with acute pancreatitis,[40] a trend consistent with findings from previous studies.[26] Furthermore, in our study, young patients aged 19–49 years with acute pancreatitis had a high risk of developing pancreatic cancer. Previous studies have reported elevated risks of hospitalization for recurrent acute pancreatitis in this younger population.[41] The elevated risks of pancreatic cancer in cases of recurrent acute pancreatitis, as depicted in our study, may support these results. However, future study should focus on the association between age and the risk of pancreatic cancer in patients with acute pancreatitis. Moreover, the elevated association between patients with acute pancreatitis living in rural areas and pancreatic cancer is likely due to the imbalance between the quality of treatment and the treatment needs in rural areas.[42] Furthermore, a high body mass index (BMI) is a known risk factor for pancreatic cancer.[43] In the republic of Korea, rural residents tend to have higher BMIs than those of urban residents,[44] which could have contributed to the increased incidence of pancreatic cancer among rural residents with acute pancreatitis.

Our study had several strengths. Although the use of claims data is limited, we used national cohort data representing the general Korean population. Therefore, our results can be generalized to the Korean individual-level cohorts and possibly to other populations with similar demographics, thus providing a framework for acute pancreatitis management to mitigate the risk of pancreatic cancer. In addition, unlike previous studies lacking paired reference group,[45,46] this study used propensity score matching, considering sex and age to minimize confounding factors between patients with acute pancreatitis and the control group. Therefore, compared with previous studies, this study has the advantage of addressing potential biases. Furthermore, as we included only patients with new-onset acute pancreatitis, this study provides additional evidence that new-onset acute pancreatitis is a risk factor for pancreatic cancer. We excluded participants with a prior or subsequent diagnosis of chronic pancreatitis and performed additional analyses taking into account episodes of hospitalization due to acute pancreatitis. Moreover, we investigated the relationship between the occurrence of acute pancreatitis and the risk of pancreatic cancer over time, unlike several previous studies.[12,13,24,33] As pancreatic cancer usually progresses over several years, these estimates are essential to thoroughly interpret and compare the results across multiple studies.

Nonetheless, our study has some intrinsic limitations. First, since this study used the NHIS-NSC database, the diagnosis of acute pancreatitis and pancreatic cancer was based on diagnosis codes. Therefore, coding for pancreatic cancer diagnosis may have been delayed in some patients with acute pancreatitis.[14] Consequently, the risk of developing pancreatic cancer within a few months after diagnosis may have been overestimated. Nevertheless, previous studies have validated the accuracy of medical records coding in NHIS-NSC data, reporting a 94.4% accuracy.[14] Second, due to limited information on the cause of acute pancreatitis, the etiological factors of acute pancreatitis were not fully considered in this analysis.[47] Third, due to the retrospective cohort design, certain variables, such as family history, physical activity status, BMI, and health behaviors (including smoking and drinking), which could influence the etiopathogenesis of acute pancreatic cancer, were not included.[48] Moreover, detailed medication and past histories that may have influenced the development of pancreatic cancer were not considered in the analysis. Additionally, the confounders included in the analysis may have changed over the 18-year study period. Therefore, to reduce the influence of confounding variables, we applied propensity score matching. Fourth, as suggested in previous studies, the accuracy of diagnostic information may be limited due to the inaccuracy of claims-based diagnoses.[49] Therefore, to increase the diagnostic accuracy, we investigated and analyzed both the primary and secondary diagnostic codes, and conducted the study on hospitalized for new-onset acute pancreatitis. Fifth, we could not evaluate the symptom severity of acute pancreatitis and pancreatic cancer because only the ICD-10 code was used to define participants, thus preventing us from establishing a dose relationship. Thus, the increased risk of pancreatic cancer might have been transient and might not have represented a causal association. Finally, our data did not permit an evaluation of the mechanisms that support the association between acute pancreatitis and subsequent pancreatic cancer. It is unclear whether acute pancreatitis is associated with an underlying genetic mutation predisposing to pancreatic cancer or whether such mutations increase the risk of developing pancreatic cancer.

In conclusion, using representative retrospective cohort data from the Republic of Korea this study revealed that the risk of pancreatic cancer increases after diagnosis of acute pancreatitis. After the initial diagnosis of acute pancreatitis, the risk of pancreatic cancer increased significantly in the first few years but tended to gradually decrease over time (> 10 years).

Furthermore, as the number of episodes due to acute recurrent pancreatitis increased, the risk of developing pancreatic cancer also increased rapidly. Further study is needed to evaluate whether this increased risk is responsible for carcinogenesis due to accumulated inflammation.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Association between acute pancreatitis, participant characteristics, and the risk of pancreatic cancer

Supplementary Table 2

Frequency of acute recurrent pancreatitis in patients with acute pancreatitis and their matched controls

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