Pancreatic Cancer Following Acute Pancreatitis: A Population-based Matched Cohort Study

Omid Sadr-Azodi, MD, PhD[1,2,3], Viktor Oskarsson, MD, PhD[4], Andrea Discacciati, PhD[5], Per Videhult, MD[6], Johan Askling, MD, PhD[1] and Anders Ekbom, MD, PhD[1]

BACKGROUND: **Acute pancreatitis is linked to pancreatic cancer, but the direction of this association is not fully elaborated.**

METHODS: **This was a population-based cohort study including all Swedish residents diagnosed with a first-time episode of acute pancreatitis between 1997 and 2013 and corresponding matched pancreatitis-free individuals from the general population. Hazard ratios for the association between acute pancreatitis and pancreatic cancer were estimated using multivariable Cox regression models.**

RESULTS: **Overall, 49,749 individuals with acute pancreatitis and 138,750 matched individuals without acute pancreatitis were followed up for 1,192,134 person-years (median 5.3 years). A total of 769 individuals developed pancreatic cancer, of whom 536 (69.7%) had a history of acute pancreatitis. The risk of pancreatic cancer was substantially increased during the first few years after a diagnosis of acute pancreatitis but declined gradually over time, reaching a level comparable to the pancreatitis-free population after >10 years of follow-up. In those with non-gallstone-related acute pancreatitis, the risk of pancreatic cancer declined to a level comparable to the pancreatitis-free population only when follow-up time was censored for a second episode of acute pancreatitis or a diagnosis of chronic pancreatitis. Increasing number of recurrent episodes of acute pancreatitis was associated with increased risk of pancreatic cancer.**

CONCLUSION: **These findings imply a delay in the diagnosis of pre-existing pancreatic cancer, if clinically presented as acute pancreatitis. Any association between non-gallstone-related acute pancreatitis and pancreatic cancer in the long-term (>10 years) could be mediated through recurrent acute pancreatitis or chronic pancreatitis.**

SUPPLEMENTARY MATERIAL accompanies this paper at https://doi.org/10.1038/s41395-018-0255-9

Am J Gastroenterol (2018) 113:1711–1719. https://doi.org/10.1038/s41395-018-0255-9

BACKGROUND

Acute pancreatitis is linked to pancreatic cancer, but the direction of this association is not fully elaborated. It is well known that acute pancreatitis can be the earliest clinical presentation of pancreatic cancer [1], but owing to some aspects of the clinical management, a pre-existing tumor might go undetected. In an acute setting, even if contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) are performed, which have high sensitivity in detecting a tumorous mass in the pancreas [2], it might be difficult to distinguish between pancreatic inflammation due to acute pancreatitis and a pancreatic tumor [3]. It is also possible that gallstones and alcohol abuse, the most important risk factors for acute pancreatitis [4], are mistaken as the cause of the disease instead of a pre-existing pancreatic cancer. Thus, the diagnosis of a pre-existing pancreatic cancer might be delayed in some patients with acute pancreatitis. To our knowledge, only one previous study has investigated the potential delay in the diagnosis of pre-existing pancreatic cancer in patients with acute pancreatitis [5]. In that study, based on US military veterans, there was a markedly increased risk of pancreatic cancer within the first year of follow-up, which declined gradually and reached the same level as individuals without acute pancreatitis after 4 years of follow-up. However, the role of different type of pancreatitis (i.e., acute, recurrent and chronic) on pancreatic cancer development was not elaborated.

[1]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden. [2]Department of Surgery, Eskilstuna County Hospital, Eskilstuna, Sweden. [3]Center for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden. [4]Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [5]Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [6]Department of Surgery, Västerås County Hospital, Västerås, Sweden. **Correspondence:** O.S.-A. (email: omid.azodi@ki.se)
Received 6 December 2017; accepted 6 August 2018; Published online 12 October 2018

While pancreatic cancer can be the cause of acute pancreatitis, it is also plausible that inflammatory processes in the pancreas might induce pancreatic cancer development [6]. This is particularly true for chronic pancreatitis, which is strongly associated to pancreatic cancer [7], whereas the role of acute pancreatitis is less clear. Most studies to date have not been able to distinguish between different types of pancreatitis, which makes it impossible to estimate the association between acute pancreatitis, per se, and risk of pancreatic cancer [8–13]. To our knowledge, only three studies have investigated the long-term (>10 years) role of acute pancreatitis in the development of pancreatic cancer. While two Swedish studies, using regional [14] and national [15] data, showed no association between acute pancreatitis and pancreatic cancer beyond 10 years of diagnosis of acute pancreatitis; a recent study from Denmark, using national data [16], found a positive association between acute pancreatitis and pancreatic cancer beyond 10 years of diagnosis. However, the studies from Sweden had no matched reference populations, which made statistical adjustment for potential confounders impossible, whereas the study from Denmark did not explore the role of recurrent acute pancreatitis and chronic pancreatitis, developed after a first episode of acute pancreatitis, in the development of pancreatic cancer.

By using a large population-based matched cohort with a long follow-up, and by considering potentially important confounders and different types of acute pancreatitis, we aimed to investigate the short- and long-term association between acute pancreatitis and risk of pancreatic cancer.

METHODS

Study design and setting

In this population-based cohort study, the risk of pancreatic cancer in individuals (aged 18 years or older) who were hospitalized for a first-time episode of acute pancreatitis between January 1, 1997 and December 31, 2013 was compared to the corresponding risk in a matched pancreatitis-free population. Data on acute pancreatitis, pancreatic cancer and potential confounders were obtained from high-quality and validated Swedish national registers (as described below). The Swedish personal identity number, uniquely assigned to each Swedish resident, allowed for accurate linkage between registers [17]. The study was approved by the Central Ethical Review Board in Stockholm, Sweden.

Data sources

The Swedish Patient Register, first introduced in 1964, has had complete national coverage on all inpatient care in Sweden since 1987. In 2001, the register was expanded to also include specialized outpatient care. The accuracy of the International Classification of Diseases (ICD) coding in the inpatient component of the Swedish Patient Register has been previously validated, with overall positive predictive values of 85–95% [18]. The validity of a diagnosis of acute pancreatitis, specifically, has also been proven to be high, with a positive predictive value of 83% for definitive disease and 98% for probable disease [19].

The Swedish Cancer Register contains, since 1958, information on all newly diagnosed cancers in Sweden. Each record includes, among others, information on tumor site (according to the most recent ICD code and translated into ICD-7 codes) and histological tumor type.

The Causes of Death Register contains information on the date of death for all deceased Swedish residents since 1952 and also has data on cause-specific death (complete to 99.2%) [20].

The Register of the Total Population was used to collect data on sex, year of birth, municipality of residence, country of birth and date of emigration. The register covers all Swedish residents since 1968 [21].

The Swedish Educational Register was used to collect data on the highest formal education by each study individual [22].

Ascertainment of exposure (acute pancreatitis) and outcome (pancreatic cancer)

Individuals who were discharged from hospital with a first-time diagnosis of acute pancreatitis (ICD-10: K85) between 1997 and 2013 were identified through the Swedish Patient Register. None of these individuals had been previously diagnosed with acute or chronic pancreatitis prior to year 1997 (see Appendix **1** for details and ICD codes). Gallstone-related acute pancreatitis was classified as episodes with gallstone-related disease (ICD-10: K800-9, K851) or gallstone-related surgery (The 7th version of the Swedish Classification of Operations and Major Procedures: JKA20-21, JKB00-01, JKE00, JKE02, JKE12, JKE18, JKE25, UJK02, UJK05) [23] within the first 3 months of the hospitalization date, either during the same hospital admission or after hospital discharge. All other episodes were classified as non-gallstone-related acute pancreatitis. Recurrent acute pancreatitis was defined as a new episode of acute pancreatitis more than 3 months after the first episode of the disease. The same time window was used to define development of chronic pancreatitis (ICD-10: K86).

Using the Swedish Cancer Register, all cases of pancreatic cancer (ICD-10: C25) in the study cohort between 1997 and 2013 were identified.

Matching procedure

For each individual with acute pancreatitis, up to 3 individuals from the Swedish background population, without a history of acute or chronic pancreatitis, were randomly matched for age, sex, calendar period and municipality of residence. The matched individuals were alive and residing in Sweden at the date of hospitalization for their index-individual with acute pancreatitis. Individuals who developed acute pancreatitis after the matching date were considered pancreatitis-free prior to their date of hospital admission and were, therefore, considered eligible for the matching procedure.

Covariates

Education level was categorized in school attainment of less than 10 years, 10–12 years and more than 12 years. Country of birth was defined as born in Sweden or born outside Sweden. A revised version of the Charlson Comorbidity Index (see Appendix **1** for details and ICD codes) was used to assess comorbidities (0, 1, 2, ≥3 comorbidities). In addition, a number of alcohol-related disorders were identified through the Swedish Patient Register to

create a proxy for alcohol abuse (see Appendix **1** for details and ICD codes).

Exclusions

Exclusions were made for individuals with (1) reused or erroneous personal identity number, (2) diagnosis of malignant tumor within 5 years before study inclusion, because of the potentially increased surveillance of these individuals in different cancer follow-up programs and (3) diagnosis of pancreatic cancer before study inclusion irrespective of its timing. Furthermore, individuals with acute pancreatitis who had a record of chronic pancreatitis within the first 3 months of follow-up were excluded, because of the high probability that they already had chronic pancreatitis misdiagnosed as acute pancreatitis.

Statistical analyses

Person-years were calculated from the date of admission for acute pancreatitis (or the corresponding index date for matched individuals) until the date of pancreatic cancer, death, emigration or end of study period (December 31, 2013), whichever occurred first. To avoid detection of pancreatic cancer through tumor diagnostics for other cancers, censoring was also made at the date of other malignant tumors (excluding non-melanoma skin cancers). Multivariable Cox regression analyses were performed to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for pancreatic cancer. Two statistical models were constructed: Model 1 included the matching variables age, sex, calendar period and municipality of residence; and Model 2 included, in addition, country of birth (Sweden, other), educational level ($<$10, 10–12, $>$12 years), the Charlson Comorbidity Index (0, 1, 2, $\geq$3) and alcohol abuse (no, yes). In a sensitivity analysis, we further included chronic obstructive pulmonary disease (as a proxy variable for smoking) and diabetes mellitus as separate variables. To estimate the potential mediating role of recurrent acute pancreatitis and chronic pancreatitis in the development of pancreatic cancer in individuals with acute pancreatitis, an additional sensitivity analysis was performed by censoring the follow-up time at the date of a second episode of acute pancreatitis or a diagnosis of chronic pancreatitis, whichever occurred first.

The proportional hazards assumption was tested by including an interaction term between follow-up time and exposure status in Model 2. Because of deviation from the proportional hazards assumption, the follow-up time was categorized into 9 categories ($\leq$2 months, $>$2–6 months, $>$6 months–1 year, $>$1–2 years, $>$2–3 years, $>$3–4 years, $>$4–5 years, $>$5–10 years, $>$10 years). Stratified analyses were performed by the type of acute pancreatitis, age, sex and calendar period. Rates of pancreatic cancer for individuals with and without acute pancreatitis were calculated for each category of follow-up time (as defined above). Due to the matching, the rates in the pancreatitis-free population were standardized to the distribution of age, sex, calendar period and municipality of residence in the pancreatitis population.

Additional analyses were performed in individuals who developed recurrent acute pancreatitis and/or chronic pancreatitis during the follow-up. Time-varying covariates for recurrent episodes of acute pancreatitis (0, 1, 2, $\geq$3) and chronic pancreatitis were added to the statistical models. In these models, the statistical analyses were unmatched.

To identify a high-risk population for pancreatic cancer, we stratified the cohort with acute pancreatitis in nine age groups (18–39, 40–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, $\geq$80 years). We then made two assumptions: a) lesions diagnosed within the first 2 years of follow-up were detectable at baseline and b) factors other than patient-related factors, such as hospital routines and availability of imaging techniques, affected the diagnosis of a lesion within the first 2 months of follow-up (i.e., during hospitalization and the related follow-up time). Cox regression analysis including age, sex, calendar period, education level, country of birth, type of acute pancreatitis, chronic obstructive pulmonary disease, diabetes mellitus, the Charlson Comorbidity Index and alcohol abuse were used to assess patient-related risk factors for the development of pancreatic cancer between 2 months and 2 years after hospitalization for acute pancreatitis.

The results were further stratified by tumor histology, since it is plausible that acute pancreatitis might lead to an earlier diagnosis of pancreatic cancer and result in a higher probability of surgery with curative intent and a less advanced cancer. Using multivariable logistic regression analyses, the probability of surgery with curative intent (procedures codes for pancreatic cancer with curative intent: JLC00-99) was compared in individuals with and without acute pancreatitis. Information on tumor stage was available in the Swedish Cancer Register between 2004 and 2013. Tumors were classified as localized (T-classification$<$T3) or locally advanced (T-classification$\geq$T3). Information on distant metastasis was also available. Using multivariable logistic regression analyses, the probability of having an advanced tumor extent or distant metastasis was compared in individuals with and without acute pancreatitis. *P*-value for trend was analyzed by the Wald test. Statistical significance was set at a two-sided *P*-value equal to 0.05. All statistical analyses were performed using Stata, version 14.1 (StataCorp, College Station, TX).

RESULTS

In total, 49,749 individuals with a first-time episode of acute pancreatitis and 138,750 matched individuals without the disease were included in the study (median age 62 and 61 years, respectively). Compared to the matched population, individuals with acute pancreatitis were less likely to have a higher education and more likely to have a greater number of comorbidities as well as an alcohol abuse (Table **1**). More than half of the individuals with acute pancreatitis had a non-gallstone-related episode (58.1%).

After a median follow-up of 5.32 years (total follow-up 292,192 person-years), there were 536 (1.1%) cases of pancreatic cancer among those diagnosed with acute pancreatitis (Table **2**). Of these, 175 (32.6%) were diagnosed within the first 2 months of follow-up, 304 (56.7%) between 2 months and 5 years, 42 (7.8%) between 5 and 10 years and 15 (2.9%) after more than 10 years. In the pancreatitis-free population, 233 (0.2%) had pancreatic cancer after a median follow-up of 5.51 years (total follow-up 899,942 person-years). In total, 3 (0.1%) were diagnosed within the first 2 months of follow-up, 126 (54.1%) between 2 months and 5 years,

Table 1 Distribution of baseline characteristics in the population with a first-time episode of acute pancreatitis and in the matched population without the disease (1997–2013)

	Acute pancreatitis population (*n*=49,749)	Matched population (*n*=138,750)	*P*-value[a]
Age (years), median (range)	62 (18–103)	61 (18–103)	<0.01
Age (years), *n* (%)			
18–39	7,829 (15.8)	23,032 (16.6)	<0.01
40–49	6,187 (12.4)	18,012 (13.0)	
50–59	8,402 (16.9)	23,894 (17.2)	
60–69	9,266 (18.6)	25,620 (18.5)	
70–79	8,947 (18.0)	23,980 (17.3)	
≥80	9,118 (18.3)	24,212 (17.4)	
Sex, *n* (%)			
Men	25,573 (51.4)	71,019 (51.2)	0.40
Women	24,176 (48.6)	67,731 (48.8)	
Calendar period, *n* (%)			
1997–1999	7,610 (15.3)	21,261 (15.3)	1.00
2000–2004	13,706 (27.5)	38,251 (27.6)	
2005–2009	14,467 (29.1)	40,277 (29.0)	
2010–2013	13,966 (28.1)	38,961 (28.1)	
Education (years), *n* (%)			
<10	19,561 (39.3)	47,497 (34.2)	<0.01
10–12	19,947 (40.1)	55,173 (39.8)	
>12	8,492 (17.1)	32,152 (23.2)	
Unknown	1,749 (3.5)	3,928 (2.8)	
Country of birth, *n* (%)			<0.01
Sweden	41,999 (84.4)	120,327 (86.7)	
Outside of Sweden	7,750 (15.6)	18,423 (13.3)	
Comorbidity, *n* (%)[b]			<0.01
None	31,105 (62.5)	102,666 (74.0)	
1	9,235 (18.6)	20,474 (14.8)	
2	4,504 (9.0)	8,517 (6.1)	
≥3	4,905 (9.9)	7,093 (5.1)	
Alcohol abuse, *n* (%)[c]			<0.01
No	45,198 (90.9)	135,159 (97.4)	
Yes	4,551 (9.1)	3,591 (2.6)	
Type of acute pancreatitis, *n* (%)			
Gallstone-related	20,818 (41.9)	—	
Non-gallstone related	28,931 (58.1)	—	

[a]For categorical variables, the *P*-values were calculated by the χ^2-test. For continuous variables (age), the *P*-values were calculated by the Mann–Whitney U-test
[b]According to the Charlson Comorbidity Index (see Appendix **1** for details)
[c]Based on a number of codes for alcohol-related disorders in the International Classification of Diseases (see Appendix **1** for details)

65 (27.9%) between 5 and 10 years and 39 (16.9%) after more than 10 years.

Individuals with acute pancreatitis had an increased risk of pancreatic cancer compared to pancreatitis-free individuals. The magnitude of the HR was the highest within the first 2 months of the diagnosis of acute pancreatitis (HR 172.84; 95% CI: 54.85–544.66) and declined gradually over time, reaching a level comparable to the pancreatitis-free population after >10 years of follow-up (HR 1.27; 95% CI: 0.69–2.33) (Table 2, Fig. 1). Further adjustment for chronic obstructive pulmonary disease and diabetes mellitus had negligible influence on the results (Appendix **2**). The results were, however, attenuated after censoring the follow-up time for a second episode of acute pancreatitis or a diagnosis of chronic pancreatitis (e.g., HR 0.68; 95% CI: 0.28–1.67 for >10 years of follow-up) (Table 2).

When stratifying the analyses over the type of acute pancreatitis, the HRs of pancreatic cancer following a diagnosis of gallstone-related acute pancreatitis remained increased during the first 4 years of follow-up and dropped to a level comparable to the pancreatitis-free population thereafter (Table 3). The corresponding HRs following a diagnosis of non-gallstone-related acute pancreatitis remained increased throughout the entire follow-up period, even though its magnitude declined steadily over time, reaching a HR of 2.02 (95% CI: 1.03-3.97) after >10 years of follow-up. However, after censoring the follow-up time for a second episode of acute pancreatitis or a diagnosis of chronic pancreatitis, the risk reached a similar level of that in the matched population (HR 0.86; 95% CI: 0.28–2.60). Stratification for sex, age or calendar period did not change the HRs in a meaningful way (Appendix **3**-**5**).

In total, 8116 persons developed a second episode of acute pancreatitis, with a median time of 0.8 years (range 91 days–16.4 years) between the first and the second diagnosis. Among these, 99 (1.2%) developed pancreatic cancer. The risk of pancreatic cancer was excessively increased within the first 2 years of follow-up after a recurrent episode of acute pancreatitis (Table 4). Although substantially lower, the risk remained increased after 2 years of follow-up, particularly in those with three or more episodes of acute pancreatitis (HR 7.47; 95% CI: 4.16–13.42). This risk declined (HR 4.44; 95% CI: 1.81–10.89), but remained statistically significant, after censoring for a diagnosis of chronic pancreatitis.

In total, 2363 individuals with acute pancreatitis developed chronic pancreatitis after a median follow-up of 2.66 years (range 91 days–16.9 years), among whom 58 (2.5%) developed pancreatic cancer. The HR of pancreatic cancer was the highest within the first 2 years of the diagnosis of chronic pancreatitis (HR 103.59; 95% CI: 69.25–154.98) and declined substantially thereafter (HR 4.29; 95% CI: 1.97–9.33) (Table 5).

The risk of pancreatic cancer between 2 months and 2 years after hospitalization for acute pancreatitis was highest in individuals aged 60–64 (1.0%), 65–69 (0.9%) and 70–74 (0.9%) years of age (with risk estimates ranging between 0.04% and 0.6% for all other age groups); and we, therefore, restricted the analysis of patient-related risk factors to individuals aged 60 to 74 years. In a multivariable analysis of these individuals, although not

Table 2 Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for pancreatic cancer in individuals with acute pancreatitis compared with matched individuals without the disease

	Total population (main analysis)				Total population (censoring of follow-up at recurrent acute pancreatitis or chronic pancreatitis)		
	Acute pancreatitis population (n=49,749)	Matched population (n=138,750)	HR (95% CI)[a]	HR (95% CI)[b]	Acute pancreatitis population (n=49,749)	Matched population (n=138,750)	HR (95% CI)[b]
	Number of events/ person-years	Number of events/ person-years			Number of events/ person-years	Number of events/ person-years	
Follow-up time							
0–2 months	175/7,787	3/22,602	169.27 (54.07–529.92)[c]	172.84 (54.85–544.66)[c]	174/7,789	3/22,603	171.64 (54.46–540.94)[c]
2–6 months	93/14,736	9/43,927	30.80 (15.54–61.03)[c]	30.84 (15.39–61.80)[c]	84/14,414	9/43,019	27.82 (13.83–55.99)[c]
6 months–1 year	73/21,439	22/64,494	10.01 (6.21–16.12)[c]	9.92 (6.09–16.14)[c]	49/19,865	21/59,574	6.95 (4.12–11.75)[c]
1–2 years	64/38,475	32/116,377	6.05 (3.98–9.21)[c]	5.78 (3.73–8.95)[c]	32/34,122	29/103,851	3.25 (1.91–5.55)[c]
2–3 years	34/33,857	19/102,898	5.43 (3.10–9.53)[c]	5.43 (3.01–9.80)[c]	13/29,008	14/88,841	2.73 (1.19–6.29)[d]
3–4 years	22/29,744	25/90,784	2.69 (1.52–4.78)[c]	2.68 (1.50–4.76)[c]	15/24,895	21/76,693	2.24 (1.17–4.32)[d]
4–5 years	18/25,894	19/79,551	2.91 (1.53–5.54)[c]	2.70 (1.37–5.30)[c]	15/21,346	16/62,226	2.80 (1.34–5.81)[c]
5–10 years	42/85,411	65/266,929	2.02 (1.37–2.98)[c]	1.91 (1.30–2.82)[c]	27/68,695	52/216,387	1.62 (1.02–2.57)[d]
>10 years	15/34,849	39/112,380	1.24 (0.68–2.25)	1.27 (0.69–2.33)	6/27,516	26/88,089	0.68 (0.28–1.67)

[a]Cox regression analyses including the matching variables (age, sex, municipality of residence and calendar period)
[b]Cox regression analyses including the matching variables (age, sex, municipality of residence and calendar period), education level (<10, 10–12, >12 years), country of birth (Sweden, other), the Charlson Comorbidity Index (0, 1, 2, ≥3 comorbidities) and alcohol abuse (no, yes)
[c]P-value<0.01
[d]P-value<0.05

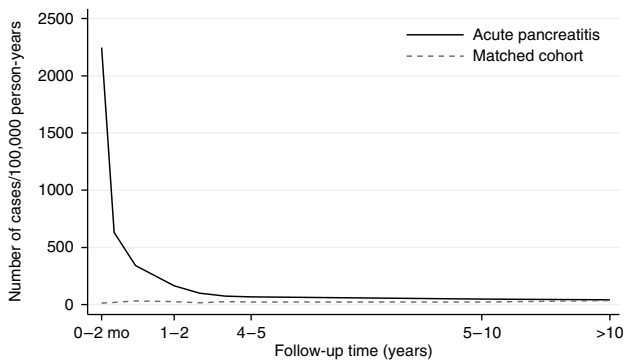

Fig. 1 Incidence rates for pancreatic cancer in individuals with acute pancreatitis (solid line) and in individuals without acute pancreatitis (dashed line), matched for sex, year of birth, calendar period and municipality of residence

statistically significant, diabetes mellitus (HR 1.87, 95% CI 0.97–3.68) and chronic obstructive pulmonary disease (HR 2.02; 95% CI 0.95-4.33) were positively associated with risk of pancreatic cancer (Appendix **6**). As expected, those with non-gallstone-related acute pancreatitis had a higher risk of pancreatic cancer than those with gallstone-related acute pancreatitis (HR 1.91; 95% CI: 1.29–2.82).

Adenocarcinoma was the most common tumor histology for pancreatic cancer (82.5% in those with acute pancreatitis, 68.2% in those without acute pancreatitis). Other tumor forms included specified types of cancers, such as sarcomas and mucinous tumors (8.1% in those with acute pancreatitis, 11.9% those without acute pancreatitis), and unspecified tumors (9.1% in those with acute pancreatitis, 18.5% in those without acute pancreatitis). Restricting the analysis to individuals with adenocarcinoma did not change the association between acute pancreatitis and risk of pancreatic cancer in a meaningful way (Appendix **7**).

The probability of surgery with curative intent was compared between individuals with and without acute pancreatitis (n=688). The analyses did not include individuals older than 80 years, since no pancreatic cancer surgery with curative intent was performed on these individuals in our data. In a multivariable model, the probability of pancreatic surgery with curative intent was highest

Table 3 Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for pancreatic cancer in individuals with acute pancreatitis compared with matched individuals without the disease, by type of acute pancreatitis

	Pancreatic cancer						
	Gallstone-related pancreatitis ($n=20,818$)	Matched population ($n=58,021$)	HR (95% CI)[a]	Non-gallstone related acute pancreatitis ($n=28,931$)	Matched population ($n=80,729$)	HR (95% CI)[a]	Censoring of follow-up at recurrent acute or chronic pancreatitis
	Number of events/ person-years	Number of events/ person-years		Number of events/ person-years	Number of events/ person-years		HR (95% CI)[a]
Follow-up time							
0–2 months	86/3,315	1/9,448	246.04 (34.23–1769.67)[b]	89/4,472	2/13,154	129.04 (31.18–533.93)[b]	126.95 (30.67–525.47)[b]
2–6 months	35/6,318	6/18,327	16.34 (6.83–39.07)[b]	58/8,418	3/25,600	60.62 (18.32–200.56)[b]	51.82 (15.51–173.12)[b]
6 months–1 year	20/9,212	9/26,844	6.42 (2.88–14.28)[b]	35/12,228	13/37,650	12.48 (6.62–23.52)[b]	9.88 (5.01–19.48)[b]
1–2 years	11/16,546	9/48,177	3.68 (1.43–9.47)[b]	53/21,928	23/68,200	7.37 (4.44–12.24)[b]	3.70 (1.91–7.16)[b]
2–3 years	9/14,550	12/42,185	2.45 (1.00–6.00)[c]	25/19,306	7/60,713	12.96 (5.43–30.94)[b]	7.36 (2.38–22.75)[b]
3–4 years	8/12,784	7/37,036	3.30 (1.21–5.03)[b]	14/16,960	18/53,743	2.54 (1.22–5.26)[c]	1.98 (0.83–4.73)
4–5 years	2/11,115	8/32,313	0.76 (0.17–3.34)	16/14,779	11/47,238	4.88 (2.23–10.71)[b]	5.26 (2.23–12.38)[b]
5–10 years	7/36,386	29/105,818	0.69 (0.30–1.59)	35/49,025	36/161,111	3.05 (1.90–4.88)[b]	2.85 (1.60–5.06)[b]
>10 years	2/14,425	13/42,039	0.41 (0.09–1.80)	13/20,423	26/70,347	2.02 (1.03–3.97)[c]	0.86 (0.28–2.60)

[a]Cox regression analyses including the matching variables (age, sex, municipality of residence and calendar period), education level (<10, 10–12, >12 years), country of birth (Sweden, other), the Charlson Comorbidity Index (0, 1, 2, ≥3 comorbidities) and alcohol abuse (no, yes)
[b]*P*-value<0.01
[c]*P*-value<0.05

when the pancreatic cancer was diagnosed within 6 months after the diagnosis of acute pancreatitis (odds ratio 2.16, 95% CI: 1.30–3.57) as compared to individuals without acute pancreatitis (Appendix **8**). This probability declined with time from the diagnosis of acute pancreatitis (p-trend < 0.01). Restricting the analyses to those with adenocarcinoma did not substantially change the results.

Information on tumor stage was available for a subset of the population between 2004 and 2013 ($n=577$), of whom 116 individuals (20.1%) had a localized cancer (T classification < T3), 261 (45.2%) had a tumor with extent beyond the pancreas and 200 (34.7%) had unknown tumor size. In a multivariable model including individuals with known tumor extent, the probability of an advanced tumor extent increased with time following the diagnosis of acute pancreatitis as compared to individuals without the disease (p-trend < 0.01) (Appendix **9**). Restricting the analysis to individuals with adenocarcinoma made the association slightly stronger. There was no clear association between the timing of tumor diagnosis after acute pancreatitis and tumor metastasis (Appendix **9**).

DISCUSSION

In this population-based nationwide cohort study, the relative risk of pancreatic cancer was markedly increased during the first few years after a diagnosis of acute pancreatitis, but declined gradually over time and reached the same level as in the matched general population after >10 years of follow-up. In those with non-gallstone-related acute pancreatitis, the risk remained increased throughout the entire follow-up period, including follow-up of >10 years, but declined to the same level as the pancreatitis-free population after censoring the follow-up time for a second episode of acute pancreatitis or a diagnosis of chronic pancreatitis. Consistently, the risk of pancreatic cancer in individuals who developed recurrent acute pancreatitis and chronic pancreatitis was markedly increased within the first 2 years of follow-up and declined thereafter.

The strengths of this study included the large study population, the complete nationwide coverage of the Swedish national registries (including those of death and emigration), the accessibility of the Swedish healthcare system to all Swedish residents and the use of a randomly selected matched comparison cohort,

Table 4 Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for pancreatic cancer in individuals with recurrent acute pancreatitis compared with individuals without any history of pancreatitis

	Pancreatic cancer				
Follow-up time	**0–2 years**		**>2 years**		
	Number of events/ person-years	**HR (95% CI)[a]**	**Number of events/ person-years**	**HR (95% CI)[a]**	**HR (95% CI)[a]**
Recurrent acute pancreatitis					
None	354/75,391	17.82 (13.66–23.26)[b]	83/172,183	1.92 (1.47–2.51)[b]	1.53 (1.16–2.02)[b]
1	35/8,823	20.80 (13.60–31.83)[b]	6/14,732	1.54 (0.67–3.52)	0.81 (0.33–1.98)
2	17/3,852	28.16 (16.14–49.14)[b]	4/5,263	2.96 (1.10–7.94)[c]	1.25 (0.40–3.92)
≥3	24/3,999	44.44 (27.51–71.80) [b]	13/7,847	7.47 (4.16–13.42)[b]	4.44 (1.81–10.89)[b]
Individuals without acute pancreatitis	66/247,401	1 (Reference)	167/652,242	1 (Reference)	1 (Reference)

[a]Cox regression analyses including age (18–39, 40–49, 50–59, 60–69, 70–79, ≥80 years), sex, calendar period (1997–1999, 2000–2004, 2005–2009, 2010–2013), education level (<10, 10–12, >12 years), country of birth (Sweden, other), the Charlson Comorbidity Index (0, 1, 2, ≥3 comorbidities) and alcohol abuse (no, yes).
[a]Censoring for a diagnosis of chronic pancreatitis
[b]*P*-value<0.01
[c]*P*-value<0.05

Table 5 Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for pancreatic cancer in individuals with chronic pancreatitis compared with individuals without any history of pancreatitis

	Pancreatic cancer		
	Population developing chronic pancreatitis (n=2359)	**Population without any pancreatitis (n=138,750)**	**HR (95% CI)[a]**
	Number of events/ person-years	**Number of events/ person-years**	
Follow-up time			
0–2 years	51/3,764	66/247,401	103.59 (69.25–154.98)[b]
>2 years	7/7,287	167/652,242	4.29 (1.97–9.33)[b]

[a]Cox regression analyses including age (18–39, 40–49, 50–59, 60–69, 70–79, ≥80 years), sex, calendar period (1997–1999, 2000–2004, 2005–2009, 2010–2013), education level (<10, 10–12, >12 years), country of birth (Sweden, other), the Charlson Comorbidity Index (0, 1, 2, ≥3 comorbidities) and alcohol abuse (no, yes)
[b]*P*-value<0.01

which made it possible to control for potentially important confounders. These advantages reduce selection and confounding bias and facilitate generalizability of the results. The high accuracy of a recorded diagnosis of acute pancreatitis in the Swedish Patient Register [19] also ensures a low misclassification of the exposure. In addition, all pancreatic cancers were verified histologically in the Swedish Cancer Register, ensuring diagnostic accuracy. There were, however, some study limitations. We had no individual information on some important risk factors for pancreatic cancer, such as smoking [24] and obesity [25]. While these risk factors might play a role in the development of pancreatic cancer, a markedly increased risk of pancreatic cancer during the first few years after a diagnosis of acute pancreatitis is unlikely to be fully explained by confounding by these factors. Furthermore, some individuals with gallstone-related acute pancreatitis might have been misclassified as having a non-gallstone-related episode, and vice versa. However, based on the similar results for both disease types, especially for the first 4 years of follow-up, such misclassification should have had no meaningful impact on our findings.

In a previous study by Munigala and colleagues, the risk of pancreatic cancer was compared between US military veterans with acute pancreatitis (n=5720) and with other health conditions (n=489,784) [5]. In that study, the risk of pancreatic cancer was markedly increased within the first year after a diagnosis of acute pancreatitis (HR 66.01; 95% CI: 47.24–92.23) but declined gradually and reached a level comparable to the pancreatitis-free individuals during the fourth year of follow-up (HR 1.05; 95% CI: 0.14–7.68). In a recent study from the Netherlands, the risk of pancreatic cancer was investigated in 731 patients who had developed a first episode of acute pancreatitis [26]. Among 51 patients who developed chronic pancreatitis during the follow-up, 2 (3.9%) developed pancreatic cancer. The corresponding number among those without chronic pancreatitis was 3 pancreatic cancer cases (0.4%). In our study, we were able to distinguish between different types of acute pancreatitis. In those with gallstone-related acute pancreatitis, the elevated risk of pancreatic cancer was confined to the first 4 years of follow-up, whereas in those with non-gallstone-related acute pancreatitis, this risk was confined to the first 10 years of follow-up (and even longer, when the follow-up time was not censored for a second episode of acute pancreatitis or a diagnosis

of chronic pancreatitis). Furthermore, to our knowledge, this is the first study that has been able to examine the role of recurrent acute pancreatitis and chronic pancreatitis, developed after a first-time episode of acute pancreatitis, on pancreatic cancer development. For both conditions, the risk of pancreatic cancer increased markedly within the first 2 years of follow-up, before sharply declining. Thus, irrespective of the type of pancreatitis (acute, recurrent acute or chronic) or acute pancreatitis (gallstone-related or non-gallstone-related), there seems to be a markedly increased risk of pancreatic cancer during the first few years of diagnosis, indicating a delay in the diagnosis of a pre-existing pancreatic cancer.

Interestingly, the risk of pancreatic cancer seemed to increase with increasing number of recurrent episodes of acute pancreatitis, even after censoring the follow-up for development of chronic pancreatitis, indicating that recurring pancreatic inflammation might be an independent risk factor for pancreatic cancer.

There are several reasons why a pre-existing pancreatic cancer, if clinically presented as acute pancreatitis, might go undetected. First, even if CECT or MRI is performed, a pancreatic tumor mass might be mistaken as an inflammatory mass in the acute setting [3]. Second, it is possible that the treating physician settles for a more common disease cause, such as gallstones or alcohol abuse, than to search for a pre-existing pancreatic cancer. Third, the use of CECT or MRI is not standard in the diagnostic work-up acute pancreatitis [27–29]. While a number of patients with acute pancreatitis will still undergo such examinations during hospitalization and the related follow-up, as shown by the fact that pancreatic cancer cases diagnosed within 6 months of hospitalization were more likely to be localized and have a higher probability of surgery with curative intent, our results do highlight the need of improved diagnostic work-up in high-risk patients aged 60 to 74 years, especially in those with non-gallstone-related acute pancreatitis, a smoking history and a diagnosis of diabetes mellitus, in whom timely use of CECT or MRI could be of great importance. Such examinations should be performed earliest after an interval of 3 to 4 weeks to allow for resolution of inflammatory changes secondary to the pancreatitis episode [30].

It is biologically plausible that inflammation in the pancreas might induce pancreatic cancer, and it has even been suggested that there is a continuous relationship between benign and malignant pancreatic diseases [4]. Familial chronic pancreatitis is a strong risk factor of pancreatic cancer [31] and chronic inflammation in the pancreas might induce carcinogenic changes through mutations [32]. In experimental settings, an episode of acute pancreatitis seems to accelerate the initiation and progression of pancreatic cancer in mice expressing oncogenic KRAS [33]. Assuming that there is a causal association between acute pancreatitis and pancreatic cancer, it would be expected that the risk of pancreatic cancer is increased even in the long-term, that is, more than 10 years after diagnosis. While two population-based Swedish studies [14, 15] found no association between acute pancreatitis and pancreatic cancer when study subjects were followed for 10 years or more, a recent population-based study from Denmark found a more than two-fold increased risk of pancreatic cancer beyond 10 years of diagnosis of acute pancreatitis [16]. The studies from Sweden had a limited number of events, which did not allow for estimation of the role of different types of acute pancreatitis, and could not adjust for potential confounders [14, 15]. The finding in the Danish study is in line with that in our study before the analysis was censored for development of recurrent acute pancreatitis and/or chronic pancreatitis [16]. In our large matched study setting, we observed no association between gallstone-related acute pancreatitis and pancreatic cancer in the long-term, indicating that the short-term association is due to tumor-related ductal obstruction and/or delayed diagnosis of pre-existing pancreatic cancer. For non-gallstone-related acute pancreatitis, however, the risk of pancreatic cancer remained increased even after 10 years of follow-up; and it only declined to a level comparable to the pancreatitis-free population after censoring the follow-up for a the second episode of acute pancreatitis or a diagnosis of chronic pancreatitis. Thus, it seems that the long-term association between non-gallstone-related acute pancreatitis and pancreatitis cancer, if any, is mediated through recurrent acute pancreatitis or chronic pancreatitis. However, considering potential unmeasured and residual confounding by smoking, obesity and alcohol abuse, the magnitude of this association is most likely weaker than what was observed in our study.

In conclusion, we observed a markedly increased risk of pancreatic cancer following a first-time diagnosis of acute pancreatitis, irrespective of its type, which declined gradually over time. The same risk trend was observed for those who developed recurrent acute pancreatitis and chronic pancreatitis. These findings imply a delay in the diagnosis of pre-existing pancreatic cancer, if clinically presented as acute pancreatitis. Thus, our results give credence to the timely use of CECT or MRI in the diagnostic work-up of acute pancreatitis, especially in high-risk patients aged 60 to 74 years. They are also indicative of an association between non-gallstone-related acute pancreatitis and pancreatic cancer in the long-term, which could be mediated through recurrent acute pancreatitis or chronic pancreatitis. In support of this was he finding that increasing number of recurrent episodes of acute pancreatitis was an independent risk factor for pancreatic cancer.

CONFLICTS OF INTERESTS

Guarantor of the article: Sadr Azodi, Omid

Specific author contributions: Study planning: All authors. Data collection: OSA. Interpretation of data: All authors. Statistical analysis: OSA, AD. Drafting the manuscript: OSA, VO. Critical revision of the manuscript for important intellectual content: All authors. All authors have approved the final draft.

Financial support: This study was supported by grants from the Swedish Society of Medicine, the Centre for Clinical Research Sörmland, Uppsala University and Uppsala-Örebro Research Council. None of the funders had any role in the study design, collection, analysis, interpretation or writing of the manuscript.

Potential competing interests: The authors declare that they have no potential competing interests.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Acute pancreatitis might be the earliest clinical presentation of pancreatic cancer.
- ✓ The diagnosis of pancreatic cancer in patients with acute pancreatitis might be delayed.
- ✓ The role of acute pancreatitis as a risk factor for pancreatic cancer is rarely studied.

WHAT IS NEW HERE

- ✓ The diagnosis of a pre-existing pancreatic cancer, if clinically presented as acute pancreatitis, is delayed.
- ✓ Earlier diagnosis of pancreatic cancer after a first episode of acute pancreatitis is associated with a less advanced cancer and increases the probability of surgery with curative intent.
- ✓ Non-gallstone-related acute pancreatitis was positively associated with pancreatic cancer in the long-term (more than 10 years). This association could be mediated through recurrent acute pancreatitis or chronic pancreatitis.
- ✓ Increasing number of recurrent episodes of acute pancreatitis was an independent risk factor for pancreatic cancer.

REFERENCES

1. Li S, Tian B. Acute pancreatitis in patients with pancreatic cancer: timing of surgery and survival duration. Medicine. 2017;96:e5908.
2. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol. 2014;20:7864–77.
3. Frampas E, Morla O, Regenet N, et al. A solid pancreatic mass: tumour or inflammation? Diagn Interv Imaging. 2013;94:741–55.
4. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1252–61.
5. Munigala S, Kanwal F, Xian H, et al. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. Clin Gastroenterol Hepatol. 2014;12:1143–50 e1.
6. McKay CJ, Glen P, McMillan DC. Chronic inflammation and pancreatic cancer. Best Pract Res Clin Gastroenterol. 2008;22:65–73.
7. Ekbom A, McLaughlin JK, Nyren O. Pancreatitis and the risk of pancreatic cancer. N Engl J Med. 1993;329:1502–3.
8. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, et al. Aspects of medical history and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. Int J Cancer. 1992;52:17–23.
9. Kalapothaki V, Tzonou A, Hsieh CC, et al. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. Cancer Causes Control. 1993;4:375–82.
10. Fernandez E, La Vecchia C, Porta M, et al. Pancreatitis and the risk of pancreatic cancer. Pancreas. 1995;11:185–9.
11. Hassan MM, Bondy ML, Wolff RA, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol. 2007;102:2696–707.
12. Bracci PM, Wang F, Hassan MM, et al. Pancreatitis and pancreatic cancer in two large pooled case-control studies. Cancer Causes Control. 2009;20:1723–31.
13. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23:2964–70.
14. Ekbom A, McLaughlin JK, Karlsson BM, et al. Pancreatitis and pancreatic cancer: a population-based study. J Natl Cancer Inst. 1994;86:625–7.
15. Karlson BM, Ekbom A, Josefsson S, et al. The risk of pancreatic cancer following pancreatitis: an association due to confounding? Gastroenterology. 1997;113:587–92.
16. Kirkegard J, Cronin-Fenton D, Heide-Jorgensen U, et al. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. Gastroenterology. 2018;154:1729–36.
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24:659–67.
18. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
19. Razavi D, Ljung R, Lu Y, et al. Reliability of acute pancreatitis diagnosis coding in a National Patient Register: a validation study in Sweden. Pancreatology. 2011;11:525–32.
20. The Swedish National Board of Health and Welfare. Swedish Causes of Death Register - Bortfall och kvalitet i dödsorsaksregistret. http://www.socialstyrelsen.se/register/dodsorsaksregistret/bortfallochkvalitet Accessed 6 August 2012.
21. Statistics Sweden. Register of Total Population. http://www.scb.se/Pages/SubjectArea____1954.aspx Accessed 6 August 2012.
22. Statistics Sweden. The Swedish Register of Education. http://www.scb.se/Pages/SubjectArea____3930.aspx Accessed 6 August 2012.
23. Sadr-Azodi O, Andren-Sandberg A, Orsini N, et al. Cigarette smoking, smoking cessation and acute pancreatitis: a prospective population-based study. Gut. 2012;61:262–7.
24. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;126:2394–403.
25. Michaud DS, Giovannucci E, Willett WC, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA. 2001;286:921–9.
26. Rijkers AP, Bakker OJ, Ahmed Ali U, et al. Risk of pancreatic cancer after a primary episode of acute pancreatitis. Pancreas. 2017;46:1018–22.
27. Working Party of the British Society of G, Association of Surgeons of Great B, Ireland. et al. UK guidelines for the management of acute pancreatitis. Gut. 2005;54(Suppl 3):iii1–9.
28. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400–15. 1416.
29. Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13:e1–15.
30. Cho JH, Choi JS, Hwang ET, et al. Usefulness of scheduled follow-up CT in discharged patients with acute pancreatitis. Pancreatology. 2015;15:642–6.
31. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89:442–6.
32. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010;24:349–58.
33. Carriere C, Young AL, Gunn JR, et al. Acute pancreatitis accelerates initiation and progression to pancreatic cancer in mice expressing oncogenic Kras in the nestin cell lineage. PLoS ONE. 2011;6:e27725.