Risk of Pancreatic Cancer After a Primary Episode of Acute Pancreatitis

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Objective: Acute pancreatitis may be the first manifestation of pancreatic cancer. The aim of this study was to assess the risk of pancreatic cancer after a first episode of acute pancreatitis.

Methods: Between March 2004 and March 2007, all consecutive patients with a first episode of acute pancreatitis were prospectively registered. Follow-up was based on hospital records audit, radiological imaging, and patient questionnaires. Outcome was stratified based on the development of chronic pancreatitis.

Results: We included 731 patients. The median follow-up time was 55 months. Progression to chronic pancreatitis was diagnosed in 51 patients (7.0%). In this group, the incidence rate per 1000 person-years for developing pancreatic cancer was 9.0 (95% confidence interval, 2.3–35.7). In the group of 680 patients who did not develop chronic pancreatitis, the incidence rate per 1000 person-years for developing pancreatic cancer in this group was 1.1 (95% confidence interval, 0.3–3.3). Hence, the rate ratio of pancreatic cancer was almost 9 times higher in patients who developed chronic pancreatitis compared with those who did not ($P = 0.049$).

Conclusions: Although a first episode of acute pancreatitis may be related to pancreatic cancer, this risk is mainly present in patients who progress to chronic pancreatitis.

Key Words: pancreas, pancreatic cancer, malignancy, acute pancreatitis

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Pancreatic cancer has a 5-year relative survival rate of 6% and is 1 of the 5 most lethal malignancies.[1,2] Prevention and early diagnosis of pancreatic cancer are therefore of utmost importance. A 9-fold increased risk of pancreatic cancer after acute pancreatitis has been reported.[3] The pathophysiologic association between pancreatic cancer and acute pancreatitis is still under debate.[3,4] It has been proposed that recurrent episodes of acute pancreatitis lead to chronic pancreatitis.[5] Chronic pancreatitis is a known risk factor for pancreatic cancer.[5] Another theory is that pancreatic cancer results in ductal obstruction and acute pancreatitis.[6] Various studies suggest that acute pancreatitis may progress to pancreatic cancer owing to genetic alterations.[7,8] The association between acute pancreatitis and pancreatic cancer is, however, contentious, and it remains questionable whether close follow-up after a first episode of acute pancreatitis is (cost-)effective and will result in earlier diagnosis of pancreatic cancer. Given the fact that acute pancreatitis is the most common gastrointestinal cause for acute hospitalization in the United States, with doubling incidence since 1988, acute pancreatitis might be an important risk factor for pancreatic cancer.[5,9–11]

The aim of this study was to identify those patients who develop pancreatic cancer after a first episode of acute pancreatitis and determine the risk of pancreatic cancer.

MATERIALS AND METHODS

Between March 2004 and March 2007, all consecutive patients with a first episode of acute pancreatitis were prospectively registered as part of 2 randomized controlled trials in 8 Dutch university medical centers and 7 major teaching hospitals.[12,13] Acute pancreatitis was defined as typical abdominal pain and serum amylase or lipase levels elevated at least 3 times the institutional upper limit of normal or characteristic imaging findings of acute pancreatitis.

None of the patients had a history of chronic pancreatitis upon inclusion. Within the first days of admission, predicted severity of acute pancreatitis was assessed using the Acute Physiology and Chronic Health Evaluation II score. During follow-up, patients were considered to have chronic pancreatitis if they fulfilled the modified diagnostic criteria for definite chronic pancreatitis according to the M-ANNHEIM classification. Follow-up was based on hospital records audit, radiological imaging, and patient questionnaires. Endpoints were death or the diagnosis of pancreatic cancer. The last questionnaire was sent in June 2011, and the hospital records audit for all survivors was censored at April first 2010. We recorded: (1) all hospitalizations and interventions for pancreatic disease; (2) current complaints (abdominal pain and steatorrhea); (3) relevant medical conditions (such as diabetes mellitus and chronic pancreatitis); and (4) medication usage. For the complete method of follow-up, see Ahmed Ali et al.[14]

Diagnosis of Pancreatic Cancer

Pancreatic cancer was suspected when: (1) During follow-up, the presence of pancreatic cancer was noted in hospital records. (2) Cancer-related death was reported. In these patients, we evaluated if pancreatic cancer was the cause of death, based on hospital records. (3) In case of all-cause mortality, we attempted to recall the cause of death and whether or not it was related to pancreatic cancer. (4) Patients had pancreatic surgery, in which case we evaluated the reason for surgery and the outcome of the surgical procedure. (5) When pancreatic cancer was suspected based on computed tomography (CT) examinations. Therefore, all CT images were reviewed for the presence of pancreatic cancer by an abdominal radiologist specialized in pancreatic imaging.

When pancreatic cancer was suspected based on the mentioned items, the general practitioner or last attended hospital was contacted to retrieve the histopathology report to confirm the diagnosis of pancreatic cancer. Cases in which histopathology was not available were to be analyzed by an adjunction commission, formed by 4 principle investigators, to confirm the diagnosis

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pancreatic cancer. This study was conducted according to the principles of the Declaration of Helsinki.[13] All patients gave written informed consent, and the institutional review board of each participating center approved the protocol.[13]

Statistical Analysis

Normal distribution was assumed if the Kolmogorov-Smirnov test resulted in a P value of higher than 0.05. Statistical analysis was performed using the 2-sided χ^2 test, Student t test, or Mann-Whitney U test, depending on the property of the data. We calculated the risk of pancreatic cancer by means of risk ratio and incidence rate. Person-years were calculated using the total years of follow-up of all patients combined who were at risk for pancreatic cancer. We presented the outcome measures including their 95% confidence interval (CI) or interquartile range (IQR), where appropriate. A P value of less than 0.05 was considered statistically significant. All statistical analysis was performed using IBM SPSS Statistics version 19.0 (Chicago, Ill) and Stata 12 (Stata, College Station, Tex).

RESULTS

The study cohort consisted of 731 consecutive patients with a first episode of acute pancreatitis. An overview of the baseline characteristics is presented in Table 1. A total of 410 patients (56%) consented to follow-up by questionnaires with 65% response rate (n = 267). Abdominal CT was performed during follow-up in 497 patients (68%). Hospital records audit was performed for all 731 patients (100%).

TABLE 1. Baseline Variables

	Total Cohort (n = 731)
Age at admission, median (IQR), y	58 (42–71)
Sex, male, n (%)	397 (54)
Etiology acute pancreatitis, n (%)	
Biliary	395 (54)
Alcoholic	132 (18)
Medication	22 (3)
Hypertriglymic	12 (2)
Other	30 (4)
Unknown	138 (19)
Necrotizing pancreatitis	154 (21)
APACHE score, median (IQR)	6 (4–10)
ASA classification at admission, n (%)	
ASA I	320 (44)
ASA II	329 (45)
ASA III	76 (10)
ASA IV	4 (1)
Unknown	2 (0)
Diagnostic imaging, n (%)	
CT during follow-up	499 (68)
Smoking, n (%)	
Yes	43 (6)
Never	81 (11)
Stopped	138 (19)
Unknown	469 (64)
Alcohol, n (%)	
Yes	123 (17)
Never	85 (12)
Stopped	53 (7)
Unknown	470 (64)
Diabetes mellitus, n (%)	114 (16)

IQR indicates interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation.

TABLE 2. Follow-up Time

	Total Cohort (n = 731)
Survival, n (%), d	
Total	600 (82)
First 90 days	670 (92)
Follow-up time, median (IQR), mo	
Total	55 (45–64)
Survivors first 90 days	56 (47–64)
Follow-up time in person-years, median (IQR)	
Total	3081.8
Survivors first 90 days	3079.5
Patients developing chronic pancreatitis	222.9
Patients not developing chronic pancreatitis	2858.8

The median length of follow-up time for all 731 patients was 55 months (IQR, 45–64). The total length of follow-up time in person-years was 3082 years. A total of 673 patients (92%) survived the first 90 days after the onset of acute pancreatitis. A total of 599 patients (82%) were alive at the end of follow-up (see Table 2). We were able to retrieve the cause of death in 90 patients (69%). We identified 5 patients who developed pancreatic cancer during follow-up after their first episode of acute pancreatitis (0.7%). Progression to chronic pancreatitis was diagnosed in 51 patients (7.0%). Patient characteristics are depicted in Table 3.

Risk of Pancreatic Cancer in Patients With Chronic Pancreatitis

Of 51 patients who progressed to chronic pancreatitis, 2 developed pancreatic cancer after a median length of follow-up of 47 months. The risk of pancreatic cancer was 3.9%. The incidence rate per 1000 person-years was 9.0 (95% CI, 2.3–35.7). Both patients were male. The first patient was 73 years of age during the first episode of acute pancreatitis, which was of idiopathic etiology. He was readmitted twice for chronic pancreatitis until he was diagnosed with biopsy-proven pancreatic cancer (25 months after episode of acute pancreatitis), which was irresectable owing to metastatic disease. The second patient was 41 years of age during the first episode of acute pancreatitis, which was alcoholic etiology. He was readmitted 4 times for chronic pancreatitis before the diagnosis of biopsy-proven pancreatic cancer 68 months later. Unfortunately, he had metastases at the time of diagnosis and succumbed 13 months later. Patient characteristics are depicted in Table 3.

Risk of Pancreatic Cancer in Patients Without Chronic Pancreatitis

Of 680 patients who did not develop chronic pancreatitis, 3 patients (all male) developed pancreatic cancer after a median length of follow-up of 12 months. The risk of pancreatic cancer was 0.4%. The incidence rate per 1000 person-years for the development of pancreatic cancer was 1.1 (95% CI, 0.3–3.3). The first patient was 72 years of age during the first episode of acute pancreatitis, which was of idiopathic etiology. Biopsy-proven pancreatic cancer was diagnosed 52 months later. He was not eligible for

TABLE 3. Characteristics Patients With Pancreatic Cancer

	Patients With Pancreatic Cancer Who Did Not Develop Chronic Pancreatitis (n = 3)	Patients With Pancreatic Cancer Who Developed Chronic Pancreatitis (n = 2)
Age at admission, median (IQR), y	71 (56–71)	57 (41–73)
Sex, male, n (%)	3 (100)	2 (100)
Etiology acute pancreatitis, n (%)		
Biliary	1 (33)	0
Alcoholic	0	1 (50)
Idiopathic	2 (67)	1 (50)
Necrotizing acute pancreatitis, n (%)	0	0
Ascertainment of diagnosis pancreatic cancer, n (%)		
Brush	1 (33)	0
Biopsy	2 (67)	2 (10)
Time to pancreatic cancer diagnosis, median (IQR), mo	12 (4–52)	47 (25–68)
Pancreatic cancer diagnosis, n (%), mo		
<6	1 (33)	0
6–12	1 (33)	0
>12	1 (33)	2 (100)
Time to chronic pancreatitis diagnosis, median (IQR), mo	NA	7 (2–12)
Follow-up time, median (IQR), mo	17 (8–59)	66 (61 to 70)
Survival during follow-up, n (%)	0	0
Age at death, median (IQR), y	72 (58–77)	62 (47 to 76)
Time between diagnosis pancreatic cancer and death, median (IQR), mo	3 (3–4)	7.5 (2–13)
CT during follow-up	3 (100)	2 (100)
Resectable pancreatic cancer, n (%)	0	0
Reason irresectability, n (%)		
Metastatic disease	1 (33)	2 (100)
Physical condition	1 (33)	0
Metastatic disease and local irresectable tumor	1 (33)	0
Readmission, n (%)		
Cholangitis	1 (33)	0
Chronic pancreatitis	0 (100)	2 (100)
Second episode acute pancreatitis	1 (33)	0
Whipple surgery	0	0
Intervention, n (%)		
ERCP	3 (100)	1 (50)
EUS	1 (33)	0
Biliodigestive anastomosis	0	1 (50)
Other	0	1 (50)
Risk pancreatic cancer, %	0.4	3.9
Incidence rate per 1000 person-years (95% CI)	1.1 (0.3–3.3)	9.0 (2.3–35.7)

NA indicates not applicable.

resection owing to metastatic disease and died at 77 years of age, 3 months after the diagnosis of pancreatic cancer. The second patient was 71 year of age during the first episode of acute pancreatitis, which was of idiopathic etiology. Cytology-proven pancreatic cancer was diagnosed 12 months later. The patient was unfit to undergo resection owing to severe cardiovascular comorbidity. He died at 71 years of age, 5 months after the diagnosis of pancreatic cancer. The third patient was 56 years of age during the first episode of acute pancreatitis, which was of biliary etiology. He was readmitted once for a recurrent episode of acute pancreatitis before he was diagnosed with biopsy-proven pancreatic cancer 4 months later, which was irresectable owing to metastatic disease. The patient died at 57 years of age, 3 months after the diagnosis of pancreatic cancer.

Hence, the rate ratio of pancreatic cancer in patients who developed chronic pancreatitis was about 9 times higher compared with those who did not ($P = 0.049$, Table 4).

DISCUSSION

In this multicenter analysis, we found a 0.7% overall risk of pancreatic cancer during a median follow-up of 55 months after a first episode of acute pancreatitis. Patients who develop chronic pancreatitis had a 9 times higher risk of developing pancreatic cancer. The median time between the primary episode of acute pancreatitis and detection of pancreatic cancer was considerably longer for those patients who developed chronic pancreatitis compared with those who did not, respectively 47 and 12 months.

TABLE 4. Risk of Pancreatic Cancer

Acute Pancreatitis, Not Diagnosed With Chronic Pancreatitis (n = 680), n (%)	Acute Pancreatitis, Diagnosed With Chronic Pancreatitis (n = 51), n (%)	Risk		Incidence	
		Ratio (95% CI)	*P*	Rate Ratio (95% CI)	*P*
3 (0.4)	2 (3.9)	8.9 (1.5–52.0)	0.0036	8.6 (0.7–74.6)	0.049

Hence, it seems likely that the patients who developed chronic pancreatitis were free from pancreatic cancer at the primary episode of acute pancreatitis. Subsequently, in patients who do not develop chronic pancreatitis, pancreatic cancer could potentially have been present at diagnosis of acute pancreatitis. Screening for pancreatic cancer in our population, especially in patients who developed chronic pancreatitis, could have resulted in earlier detection of pancreatic cancer. However, the question remains whether or not these tumors would have been resectable.

The major strength of our study is the fact that the original study was designed as a randomized control trial in which the diagnosis acute pancreatitis was strictly determined. Strict conditions were set to diagnose acute pancreatitis and patients had to be free from chronic pancreatitis or pancreatic cancer. No previous study regarding the risk of pancreatic cancer after an episode acute pancreatitis met these demands. Furthermore, in our study, we only included patients after a first episode of acute pancreatitis and not patients with recurrent episodes of acute pancreatitis. Previous studies reporting on the risk of pancreatic cancer in patients with acute pancreatitis were based on hospital discharge data.[3,15] However, up to 25% of patients diagnosed with acute pancreatitis do not fulfill the diagnostic criteria and a substantial miscoding of discharge diagnosis in patients with acute and chronic pancreatitis occurs.[16,17] Furthermore, electronic data sources can erroneously misclassify patients as having pancreatic cancer.[18] In our study, patients were registered prospectively and fulfilled the criteria for acute and chronic pancreatitis, and pathology-proven pancreatic cancer.

Our study is a long-term retrospect follow-up study, and we used the person-years to determine the risk of pancreatic cancer. A sensitivity analysis excluding patients that did not survive the initial 90 days after the first episode of acute pancreatitis did not affect the results we found. This enabled us to include those patients who did not survive the initial 90 days after the first episode of acute pancreatitis. Follow-up was based on both hospital records audit and patient questionnaires. Hospital record audit was performed for all patients. Only a part of all patients consented for follow-up by questionnaires. We choose to include this information to compile a thorough database. We do not believe that this led to a form of information discrepancy because it is highly unlikely that the diagnosis of pancreatic cancer would not be included in the hospital records. Unfortunately, follow-up data beyond 2011 were not available mainly due to lost to follow-up. Because of the relatively low incidence of pancreatic cancer, only a small proportion of patients developed pancreatic cancer. Hence, we did not perform a cumulative hazard analysis or regression analysis.

Between 2004 and 2007, an average of 1808 persons was annually diagnosed with pancreatic cancer in the Netherlands.[19] The median incidence rate in the age category 45 to 75 years was 0.1 per 1000 person-years.[19] Hence, the risk of pancreatic cancer was almost 10 times higher in patients with a primary episode of acute pancreatitis. Furthermore, the risk of pancreatic cancer in patients who developed chronic pancreatitis was about 80 times higher compared with the nationwide population. This implies that patients, who endure a first episode of acute pancreatitis and especially those who develop chronic pancreatitis, are an interesting group for close follow-up or even screening for pancreatic cancer.

Because a comparison group was not available within our study design, we were not able to calculate relative risks. Owing to comparability and confounding, inclusion of an external comparison group would not have added to the appraisal of this study and would only lead to more uncertainties. However, the comparison with the nationwide population suggests a significant increased relative risk. Future studies, preferably with a prospective design, should validate our findings. A comparison group is of utmost importance.

CONCLUSIONS

In this study, we found that patients who endure a first episode of acute pancreatitis and do not progress to chronic pancreatitis have a 0.4% risk of pancreatic cancer, but those who do, have a 9-fold risk of pancreatic cancer. Screening for pancreatic cancer after a first episode of acute pancreatitis, especially in patients who progress to chronic pancreatitis, could potentially result in more curative resections and improved survival. On the other hand, it could also only prolong the lead time without a therapeutic effect. Future prospective studies are needed to validate the findings observed and could provide further insight whether or not acute pancreatitis that progresses to chronic pancreatitis is a clinical relevant risk factor for pancreatic cancer.

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