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CLINICAL—PANCREAS

Acute Pancreatitis and Pancreatic Cancer Risk: A Nationwide Matched-Cohort Study in Denmark

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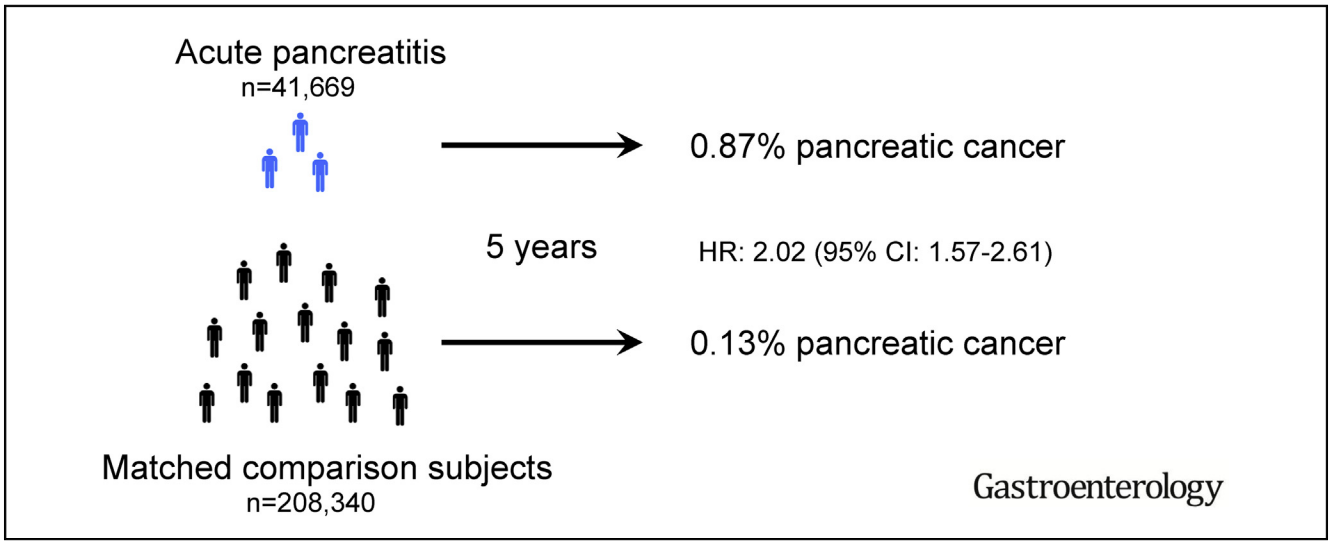

BACKGROUND & AIMS: Acute pancreatitis may be a risk factor for pancreatic cancer; however, findings from studies on this association are conflicting. We investigated the association between acute pancreatitis and increased risk of pancreatic cancer. **METHODS:** We conducted a nationwide, population-based, matched cohort study of all patients admitted to a hospital in Denmark with a diagnosis of acute pancreatitis from January 1, 1980, through October 31, 2012. As many as 5 individuals from the general population without acute pancreatitis were matched for age and sex to each patient with acute pancreatitis. Pancreatic cancer risk was expressed as hazard ratios (HRs) with 95% confidence intervals (CIs), calculated using the Cox proportional hazards model. Cox models were stratified by age, sex, and year of pancreatitis diagnosis and adjusted for alcohol- and smoking-related conditions, and Charlson Comorbidity Index score. **RESULTS:** We included 41,669 patients diagnosed with incident acute pancreatitis and 208,340 comparison individuals. Patients with acute pancreatitis had an increased risk of pancreatic cancer compared with the age- and sex-matched general population throughout the follow-up period. The risk decreased over time but remained high after more than 5 years of follow-up (adjusted HR 2.02; 95% CI 1.57–2.61). Two- and 5-year absolute risks of pancreatic cancer among patients with acute pancreatitis were 0.70% (95% CI 0.62%–0.78%) and 0.87% (95% CI 0.78%–0.97), respectively. **CONCLUSIONS:** In a nationwide, population-based, matched cohort study, we observed an association between a diagnosis of acute pancreatitis and long-term risk of pancreatic cancer.

Keywords: Pancreas; Etiology; Epidemiology; Risk Factor.

Pancreatic cancer remains a major cause of cancer-related death worldwide and is associated with a dismal prognosis.[1,2] Curative-intent surgery offers the only chance of survival from pancreatic cancer. However, fewer than 20% of patients are eligible for resection at the time of diagnosis due to locally advanced or metastatic disease.[1] To facilitate early diagnosis and thus increase resection rates of pancreatic cancer, knowledge on risk factors is essential.

Acute pancreatitis is a sudden-onset inflammatory disease of the pancreas.[3] Although experimental research suggests that acute pancreatitis can induce pancreatic

Abbreviations used in this paper: **aHR, adjusted hazard ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; DNPR, Danish National Patient Registry; ERCP, endoscopic retrograde cholangiopancreatography; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; SIR, standardized incidence ratio.**

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

The association between acute pancreatitis and pancreatic cancer have been insufficiently investigated. Previous studies on this association had severe methodological limitations.

NEW FINDINGS

Patients hospitalized with acute pancreatitis have a 2-fold increased risk of pancreatic cancer compared with the general population, even after 10 years of follow-up.

LIMITATIONS

The authors had limited information on alcohol consumption and tobacco smoking, which could have led to overestimation.

IMPACT

These findings suggest that acute pancreatitis should be considered a risk factor for subsequent development of pancreatic cancer.

cancer,[4,5] findings from epidemiological studies are conflicting.[6–9] A case-control study of approximately 2500 patients with pancreatic cancer within the US Veterans Affairs population,[6] and a British matched cohort study of approximately 6000 patients with acute pancreatitis, both observed a positive association between acute pancreatitis and pancreatic cancer.[8] However, both studies only excluded pancreatic cancer cases occurring in the first year following acute pancreatitis, which may not allow sufficient time to eliminate reverse causation or surveillance bias. Another US-based case-control study including approximately 300 patients with pancreatic cancer also found a positive association between acute pancreatitis and pancreatic cancer,[7] but did not include any lag period from acute pancreatitis to pancreatic cancer. Furthermore, all 3 studies failed to report estimates of the association at different follow-up times. In contrast, a Swedish cohort study of approximately 25,000 patients with acute pancreatitis reported no association with pancreatic cancer after more than 10 years of follow-up.[9] Thus, the association between acute pancreatitis and pancreatic cancer requires clarification.

We therefore conducted a nationwide population-based matched cohort study to examine the risk of pancreatic cancer in patients with acute pancreatitis compared with a matched comparison cohort from the general population.

Methods

Setting and Data Sources

We conducted a nationwide, population-based, matched cohort study from January 1980 through October 2013, using data from the Danish National Patient Registry (DNPR), Civil Registration System, and Danish Cancer Registry. These registries can be linked on an individual level using the Civil Personal Registration number, which is assigned to every Danish resident at birth or immigration.

The DNPR was established in 1977 and contains information on all inpatient hospitalizations to Danish public hospitals.[10] Outpatient and emergency room visits have been included since 1995. Patients are registered in the DNPR with diagnoses according to the *International Classification of Diseases* (ICD), Eighth Revision from 1977 through 1993 and ICD, 10th Revision hereafter.

The Civil Registration System, which was established in 1968, is an administrative registry containing data on variables like birth date, sex, sequential dates of migration, and vital status for every resident in Denmark.[11] The Civil Registration System is updated daily and is virtually complete.

The Danish Cancer Registry was established in 1943 and includes information on all cancers diagnosed in Denmark.[12] This registry contains information on date of diagnosis, cancer site, histology, dissemination, and other variables.

Acute Pancreatitis Cohort

From the DNPR, we identified a cohort of all individuals with an inpatient diagnosis of acute pancreatitis from January 1980 through October 2012 (n = 44,589), allowing for at least 1 year of follow-up for all patients. We applied a 3-year washout period since the start of the DNPR (1977–1979) to reduce the likelihood of including prevalent cases of acute pancreatitis. For each individual, we defined the date of the first diagnosis of acute pancreatitis as their index date. We did not include outpatient diagnoses of acute pancreatitis (n = 680), as these are most likely to represent a postadmission follow-up consultation or miscoding. We excluded patients from the acute pancreatitis cohort if they had a diagnosis of pancreatic cancer (n = 119), chronic pancreatitis/other exocrine pancreatic disease (n = 2367), or if they underwent pancreatic resection or transplantation (n = 49) before the index date. Likewise, patients younger than 18 years at the index date were also excluded (n = 385). In total, 41,669 patients were included in this study. A detailed flowchart of the study population is provided in Supplementary Figure 1.

Matched Comparison Cohort

For each patient in the acute pancreatitis cohort, we used the Civil Registration System to identify a pool of individuals from the general population with the same sex and year of birth, who were alive in Denmark on the patient's index date (ie, the date of the first acute pancreatitis diagnosis). From this pool of eligible comparison subjects, we randomly selected 5 individuals, thereby constructing a matched comparison cohort. We sampled with replacement, that is, individuals could act as comparison subjects to several patients with acute pancreatitis, but no individual could be sampled more than once to the same patient.[13] Furthermore, we required that the comparison subjects were free of acute pancreatitis, chronic pancreatitis/other exocrine pancreatic disease, and pancreatic cancer, and that they had not undergone pancreatic resection or transplantation before the index date of the patient with acute pancreatitis. We defined the index date for the comparison subjects as the date of diagnosis of the patient with acute pancreatitis to whom they were matched. Individuals in the matched comparison cohort entered the acute pancreatitis cohort if they developed acute