Risk of pancreatic adenocarcinoma in chronic pancreatitis

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Background: The risk of pancreatic cancer in patients with chronic pancreatitis (CP) is difficult to assess. Previous studies, mostly case control studies or studies relying on data case registers, reported relative risks varying from 2.3 to 18.5.

Methods: We studied a prospective, single centre, medical-surgical cohort of 373 consecutive patients (322 (86%) men, median age 40 years) with proven CP (alcoholic origin 85%) and a follow up of at least two years (median follow up 9.2 years; range 2.0–34.8) in order to exclude pancreatitis revealing pancreatic cancer. We calculated the age and sex standardised incidence ratio (SIR) as the ratio of the number of observed cases of pancreatic cancer in this cohort to the number of expected cases, as provided by the French National Cancer Register.

Results: Four cases of pancreatic adenocarcinoma (1.1% of patients) were observed in 3437 patient years (expected number of cases 0.15; SIR 26.7, 95% confidence interval (CI) 7.3–68.3; p=0.00002). In a second analysis in which patients lost to follow up were considered to be followed up until the end point without having developed pancreatic adenocarcinoma (4762 patient years), SIR was 19.0 (CI 5.2–48.8; p=0.00007).

Conclusion: Patients with CP have a markedly increased risk of pancreatic cancer compared with the general population.

The aetiology of pancreatic cancer remains largely elusive. Smoking, the only consistent environmental risk factor, is associated with an approximately threefold increase in the risk of pancreatic cancer,1 and less than 5% of cases of pancreatic cancer are thought to be related to familial (genetic) factors.2

Anecdotal case reports and short case control studies have suggested that chronic pancreatitis (CP) is a risk factor for pancreatic cancer.3 However, the risk of pancreatic cancer in patients with CP varied widely from 2.3 to 18.5 in these studies, raising methodological concerns. In most, the diagnosis of pancreatic cancer (mostly without histological confirmation) or pancreatitis relied on data in inpatient, cancer, or death registers,8–11 or even on a questionnaire12; both acute pancreatitis, unspecified pancreatitis, and CP were analysed in the same study. Smoking, the only consistent environmental risk factor, is associated with a threefold increase in the risk of pancreatic cancer,1 and less than 5% of cases of pancreatic cancer are thought to be related to familial (genetic) factors.2

Abbreviations: CP, chronic pancreatitis; SIR, standardised incidence ratio.

References
Statistical analysis
Differences were analysed using the Student’s t test or Mann-Whitney U test as necessary for continuous data and the χ² test or Fisher’s exact test as necessary for categorical data. We used age stratified (according to five year age groups) and sex specific data on the incidence of cancer in France (French National Cancer Register, period 1983–87) to determine the expected number of cases of pancreatic cancer in the cohort. The ratio of the observed number of cases of pancreatic cancer in the cohort of CP patients to the expected number of cases (standardised incidence ratio (SIR)) was used to estimate the relative risk. The 95% confidence interval (CI) for the SIR was calculated assuming that the observed cases of pancreatic cancer followed a Poisson distribution. Data were analysed with SAS 6.12 (SAS Institute Inc., Cary, North Carolina, USA). All statistical tests were two sided. Statistical significance was set at p<0.05.

RESULTS
Patient characteristics
Among the 567 patients with suspected CP attending the medical and surgical gastroenterological units of our institution, 500 fulfilled the diagnostic criteria of CP and were prospectively studied. Among them, 127 patients (25%) followed up for less than two years after the onset of CP were excluded from the present analysis. Table 1 presents the characteristics of the remaining 373 patients (3437 patient years). Mean alcohol consumption of drinkers at the time of diagnosis of CP was 170 g/day. Mean cumulative tobacco consumption of smokers at the time of diagnosis of CP was 35 pack years. The causes of non-alcoholic CP were hereditary CP (n=6), abdominal radiotherapy (n=3), inflammatory bowel disease (n=1), and Sjögren’s syndrome (n=1); CP was classified as “idiopathic” in the remaining 40 (11%) cases. The 118 patients (32%) lost to follow up did not differ from the remaining CP patients in their characteristics, except for a longer duration of follow up (median follow up 10.0 years; CI 2.2–27.2; range 2.0–31.3).

Risk of pancreatic adenocarcinoma
Sixty one patients (16%) died within the follow up period: 10 patients died from liver disease, 11 from sepsis, 16 from miscellaneous causes (hypoglycaemia, pulmonary embolism, tuberculosis, stroke), and seven from unknown causes. Thirteen patients (3.5%) died from non-pancreatic cancer (head and neck, six; liver, three; oesophagus, one; colon, one; stomach, one; bladder, one). Four patients (1.1%) died from pancreatic adenocarcinoma. None had a family history of pancreatic cancer or hereditary CP (table 2). The expected number of cases of pancreatic cancer was 0.15, yielding an SIR of 26.7 (CI 7.3–68.3; p=0.00002). The cumulative incidence of pancreatic cancer was 1.1% at five years and 1.7% at 10 years. SIR was 19.0 (CI 5.2–48.8; p=0.00007) in a second analysis in which patients lost to follow up were considered to be followed up until the end point without occurrence of pancreatic cancer (4762 patient years; expected number of cases of pancreatic cancer 0.21).

DISCUSSION
This single centre, medical-surgical, prospective cohort study confirms that the risk of pancreatic cancer is markedly increased in CP patients compared with age and sex matched controls. We found a much higher risk than in most case control studies11–14 and population based cohort studies,15–19 several of which having even challenged the hypothesis of an association between CP and pancreatic cancer.20–25

Assessing the true risk of pancreatic cancer in CP patients is hampered by several potential biases. Most case control studies reported risks that did not reach statistical significance because of wide CI values,24–25 or relied on interviews of patients with pancreatic cancer, thus suggesting the possibility of recall bias and subsequent overestimation of risk as these patients may have been more sensitised than controls towards recalling past episodes of pancreatitis.26

Cohort studies stand and fall by the quality of the input data.22 27 The two large population based studies available retrieved inpatients with either acute pancreatitis, recurrent pancreatitis, CP, or even “unspecified” pancreatitis from county28 or national29 registers from 1965 to 1983, raising concerns about the possibility of misclassification bias. The
A sample (10%) of “CP” patients had definite diagnostic criteria arising in CP patients in previous studies, further underlining led to exclusion of nearly half of the cases of pancreatic cancer diagnosed during the first two years of follow up. This policy studies misdiagnosis bias, which was more likely to occur in older the possibility of a spurious association—pancreatic cancer and CP. Our diagnostic criteria for CP were stringent but did not of diagnosis—particularly patients with a more indolent form of the disease or may lead to illegitimate exclu-

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