PANCREATIC DISEASE

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.[3–8] Recently, several studies have reinforced this hypothesis.[9–14] However, the risk of pancreatic cancer in patients with CP varied widely from 2.3[11] to 18.5[14] 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,[10 11 13] or even on a questionnaire[12]; both acute pancreatitis, unspecified pancreatitis, and CP were analysed in several series[10–13]; and most studies were retrospective,[9–13] began in 1946,[9] or were multicentric,[9] leading to heterogeneity and possible biases. We thus aimed to determine the risk of pancreatic adenocarcinoma in a prospective, single centre, medical-surgical cohort of consecutive patients with proven CP.

PATIENTS AND METHODS

Patients

All consecutive patients with suspected CP attending the medical and surgical gastroenterological units of our institution between 1973 and the end point of this study (July 1997), who fulfilled the diagnosis criteria of CP cited below during follow up, were prospectively studied. Patients with a follow up of less than two years or a diagnosis of pancreatic cancer established during the first two years of follow up were excluded to rule out the possibility of pancreatitis revealing pancreatic adenocarcinoma.

Definitions

The diagnosis of CP was based on one or more of the following three criteria: (1) pancreatic calcifications, as evidenced by *x* ray, computed tomography scan, ultrasonography, or endoscopic ultrasonography; (2) moderate to marked pancreatic ductal lesions on endoscopic retrograde or intraoperative pancreatography ("Cambridge" criteria)[15]; (3) typical histology on an adequate surgical pancreatic specimen. CP was considered to be due to alcohol when alcohol intake exceeded 60 g/day for at least two years in the absence of other causes; CP was considered "idiopathic" when no cause was found. The date of clinical onset of CP was defined as the date when the first manifestation clearly attributable to CP occurred. The diagnosis of pancreatic adenocarcinoma had to be proved in all cases by histological examination of surgical specimens or fine needle biopsy. Special attention was paid to exclude pancreatic adenocarcinoma arising on intraductal papillary mucin producing tumours.

Study design and data collection

Patients were seen as outpatients at least once a year, or unscheduled (as outpatients or hospitalised) when symptomatic or when their disease was complicated. Special attention was paid to signs or symptoms suggestive of pancreatic cancer (pain, weight loss, jaundice, abdominal mass). Abdominal imaging and laboratory tests were performed when necessary. Patients were considered lost to follow up when they failed to attend our institution for more than one year. Person years (that is, the observation time contributed by one patient followed for one year) were calculated from the date of clinical onset of CP, and either the end point of the study, the last personal contact, the date of diagnosis of pancreatic adenocarcinoma, the date of total pancreatectomy (n=4), or death. Data were prospectively registered on a database.

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

Table 1 Clinical characteristics of the 373 patients with chronic pancreatitis (CP)

	CP patients
Median age at onset of CP (y)	40 (CI 17–67, range 5–86)
Median age at diagnosis of CP (y)	42 (CI 20–68, range 12–86)
Median duration of follow up (y)	9.2 (CI 2.2–27.2, range 2.0–34.8)
Male (%)	322 (86)
Alcoholic CP (%)	318 (85)
Alcohol consumption (g/day)*	
0 (%)	26 (7)
<20 (%)	25 (7)
20–120 (%)	140 (40)
>120 (%)	162 (46)
Tobacco consumption (pack years)†‡	
0 (%)	36 (12)
<10 (%)	24 (8)
10–40 (%)	159 (52)
>40 (%)	88 (29)
Pancreatic calcifications (%) §	308 (83)
Diabetes mellitus (%)§	202 (54)
Insulin requirement (%) §	90 (24)
Bouts of acute pancreatitis (%) §	207 (55)
Pseudocysts (%) §	171 (46)
Duodenal stenosis (%) §	69 (18)
Splenic or portal vein occlusion (%) §	77 (21)
Liver disease/cirrhosis (%) §	140 (38)/40 (11)
Biliary liver disease (%) §	51 (14)
Elective surgery for CP (%) §	222 (60)
Uncomplicated CP (%)§¶	42 (11)
Deaths (%)	61 (16)

Available data for: *353 (95%) patients; †307 (82%) patients.
‡Percentage totals exceed 100% because of rounding.
§At any time during the course of CP.
¶No acute pancreatitis, pseudocysts, duodenal stenosis, biliary liver disease, splenic or portal vein occlusion, need for pancreatic surgery, or insulin.

Statistical analysis

Differences were analysed using the Student's *t* test or Mann-Whitney U test as necessary for continuous data and the χ^2 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 studies[11 12] and population based cohort studies,[10 13] several of which having even challenged the hypothesis of an association between CP and pancreatic cancer.[16–20]

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,[16–20] 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.[12]

Cohort studies stand and fall by the quality of the input data.[21 22] The two large population based studies available retrieved inpatients with either acute pancreatitis, recurrent pancreatitis, CP, or even "unspecified" pancreatitis from county[10] or national[13] registers from 1965 to 1983, raising concerns about the possibility of misclassification bias. The

Table 2 Characteristics of the four patients with chronic pancreatitis (CP) and pancreatic adenocarcinoma

Sex/ age (y)	Alcohol intake (g/day)	Smoking (pack years)	Aetiology of CP (duration (months))	Pancreatic calcifications	Diabetes mellitus	Steatorrhea	Symptoms revealing pancreatic cancer	Outcome
F/43	20–120	10–40	Alcoholic (29)	Yes	No	No	Pain, weight loss, jaundice	Died at 8 months
F/54	>120	Not available	Alcoholic (38)	Yes	Yes	No	Pain, weight loss, jaundice	Died at 11 months
M/77	<20	0	Idiopathic (55)	No	No	Yes	Pain, weight loss, jaundice, duodenal stenosis	Died at 5 months
M/38	20–120	<10	Alcoholic (103)	Yes	No	Yes	Pain, weight loss, jaundice	Died at 14 months

proportion of CP patients was unknown in the earlier study.[10] In the latter,[13] CP concerned men only 2.6 times more often than women, and was diagnosed at a mean age of 53.2 years, more than a decade older than the age at diagnosis in our study and in most other reports.[9 23] Only 58% of a random sample (10%) of "CP" patients had definite diagnostic criteria of CP (as ours), the remaining having either "recurrent pain" (25%) or a "questionable" discharge diagnosis (17%).[24] Misclassifying acute pancreatitis and CP may dilute the risk of pancreatic cancer in CP patients and account for the intriguing observed risk excess in patients with one single episode of acute pancreatitis.[10 13] The finding that the risk of pancreatic cancer at 10 years remained significant in the case of alcoholism but not in CP patients further suggests the possibility of misclassification in subcohorts.[13]

The results of two previous cohort studies of CP patients are in accordance with the present study.[9 14] The latter[14] was in fact an extension of a subcohort included in the former,[9] to take into account the heterogeneity of CP patients recruited through seven centres in six countries, as attested by wide variations between the subcohorts for age at diagnosis of CP (41.7 to 51.6 years), duration of follow up (5.9 to 9.4 years), male sex (71% to 87%), alcoholic CP (68% to 82%), pancreatic calcifications (38% to 84%), diabetes (28% to 76%), pancreatic surgery (33% to 54%), deaths (14% to 47%), and pancreatic cancer (1.3% to 2.7%). Recruitment of patients began in 1946 when it was virtually impossible to diagnose CP and to distinguish it from pancreatic cancer with certainty, and only 35% and 16% of patients underwent endoscopic retrograde pancreatography and computed tomography scan, respectively.[9] Moreover, the incidence of pancreatic cancer dramatically increased several decades ago, suggesting the possibility of detection bias in this historical study.[25]

The finding that the risk of pancreatic cancer declined with time in population based[10 13] and case control[11] studies raises the possibility of a spurious association—pancreatic cancer masquerading as (or causing an obstructive form of) CP. This misdiagnosis bias, which was more likely to occur in older studies[9 10 13] and in studies lacking stringent diagnostic criteria for CP,[10–13] was minimised in our study and others[9 10 14] by excluding CP patients in whom pancreatic cancer was diagnosed during the first two years of follow up. This policy led to exclusion of nearly half of the cases of pancreatic cancer arising in CP patients in previous studies, further underlining the importance of this misdiagnosis bias.[9] However, this two year exclusion policy—a fortiori if a one year cut off was chosen[11–13]—might have been insufficient in studies in which pancreatic cancer was not always proven by histological examination as in our study[9–11 13] to eliminate a significant proportion of cases corresponding to slower growing tumours, such as intraductal papillary mucin producing tumours. Of note, in the most recent study, "obstructive" CP (that is, non-alcoholic, non-familial, non-idiopathic) accounted for 12% of cases, suggesting that a significant proportion of the population studied corresponded to obstructive CP caused by potentially premalignant lesions of the pancreas.[14]

Calculating person years from the date of diagnosis of CP[9–11 13] rather than the date of onset of the disease as in our study and others[14] may cause overestimation bias by obviating the first years of the disease or may lead to illegitimate exclusion of patients followed for less than two years since the date of diagnosis—particularly patients with a more indolent form of CP. Our diagnostic criteria for CP were stringent but did not exclude painless CP, which accounts for 5–10% of cases of alcoholic CP and up to 50% of cases of non-alcoholic CP.[23 26] These patients were more likely to be recruited in previous studies when pain occurred, not being due to CP but to pancreatic cancer, artificially increasing the risk of pancreatic cancer within the first two years of follow up. Even in the most recent study in which the design closely resembled ours, the diagnosis was based on so-called "typical pancreatic" pain, and "the year of clinical onset was taken as the year in which the first unmistakable episode of pain occurred".[14] Overestimation bias may also have resulted from recruitment of only inpatients with CP in all previous studies but one.[14]

The main limitation of our study was the high rate of patients lost to follow up. This is likely due to the long duration of follow up, the stringency of our definition of patients lost to follow up, and the usual low compliance of alcoholic patients which accounted for 85% of our patients. Patients lost to follow up did not differ from the remaining CP patients in their characteristics, except for a longer duration of follow up. However, even though patients lost to follow up were considered to have been followed until the end point of the study without occurrence of pancreatic adenocarcinoma (4762 patient years), the SIR of pancreatic cancer remained very high (19.0). A similar approach was used in a previous study.[9] In contrast, hypothesising that (at least) one of the seven unexplained deaths in this study were due in fact to pancreatic cancer would result in an even higher SIR of pancreatic cancer in CP patients. Another limitation of our study was the small number of observed cases of pancreatic cancer, precluding investigation of potential risk factors such as smoking.[1]

The mechanisms underlying the risk of pancreatic cancer in CP patients are unclear. Ductal epithelial hyperplasia, metaplasia and dysplasia, and Ki-ras gene mutations have been described in CP patients, suggesting an oncogenetic multistep sequence.[27] Chronic pancreatic inflammation may account for the increased risk of pancreatic cancer in the course of CP whether induced by environmental, genetic, or other causes, as is the case for other premalignant diseases.[28 29] The duration of CP may influence the magnitude of the increase in the risk of pancreatic cancer, as suggested by the estimated cumulative risk of 40% to age 70 years found in patients with hereditary CP.[30] However, only 1.1% of CP patients in our study developed a pancreatic cancer, and CP may account for only 0.1%[31] to 5%[12] of cases of pancreatic cancer compared with an attributable risk of approximately 30% for smoking.[31] For this reason, a policy of pancreatic cancer screening in CP patients does not seem to be advocated. In addition, diagnosing pancreatic cancer in CP patients remains challenging, as pancreatic cancer was almost always diagnosed at an advanced stage despite close follow up in our study and others.[32]

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