Clinical and Genetic Characteristics of Hereditary Pancreatitis in Europe

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Background & Aims: **Hereditary pancreatitis is an autosomal dominant disease that is mostly caused by cationic trypsinogen (PRSS1) gene mutations. The aim was to determine phenotype-genotype correlations of families in Europe.** ***Methods:*** **Analysis of data obtained by the European Registry of Hereditary Pancreatitis and Pancreatic Cancer was undertaken using multilevel proportional hazards modelling.** ***Results:*** **There were 112 families in 14 countries (418 affected individuals): 58 (52%) families carried the R122H, 24 (21%) the N29I, and 5 (4%) the A16V mutation, 2 had rare mutations, and 21 (19%) had no PRSS1 mutation. The median (95% confidence interval [CI]) time to first symptoms for R122H was 10 (8, 12) years of age, 14 (11, 18) years for N29I, and 14.5 (10, 21) years for mutation negative patients ($P = 0.032$). The cumulative risk (95% CI) at 50 years of age for exocrine failure was 37.2% (28.5%, 45.8%), 47.6% (37.1%, 58.1%) for endocrine failure, and 17.5% (12.2%, 22.7%) for pancreatic resection for pain. Time to resection was significantly reduced for females ($P < 0.001$) and those with the N29I mutation ($P = 0.014$). The cumulative risk (95% CI) of pancreatic cancer was 44.0% (8.0%, 80.0%) at 70 years from symptom onset with a standardized incidence ratio of 67% (50%, 82%).** ***Conclusions:*** **Symptoms in hereditary pancreatitis start in younger patients and endpoints take longer to be reached compared with other forms of chronic pancreatitis but the cumulative levels of exocrine and endocrine failure are much higher. There is an increasingly high risk of pancreatic cancer after the age of 50 years unrelated to the genotype.**

Hereditary pancreatitis was first described by Comfort et al.[1] in 1952 as an autosomal dominant condition with 80% penetrance. Since then, well over 100 families have been described worldwide.[2–8] The natural history of the disease is incompletely described,[1–8] and as a consequence there is some uncertainty as to how it relates to the natural history of patients with alcohol-induced chronic pancreatitis and various forms of idiopathic chronic pancreatitis.[9,10] Mutation of the Protease Serine 1 (PRSS1) gene, which transcribes for cationic trypsinogen, is an important causative factor in patients with hereditary pancreatitis.[4,11] The 2 most common PRSS1 mutations are the R122H and N29I mutations[4,11] and less commonly or rarely the A16V,[12] R122C,[13] N29T,[13] D22G,[14] and K23R mutations.[15] PRSS1 mutations are unusual in the general population[4,11] and are sometimes found in patients with idiopathic chronic pancreatitis[16–19] and include variants (L104P, R116C, and C139F) that so far have not been described in hereditary pancreatitis.[18]

In a North American study, it was concluded that the R122H mutation was more aggressive, but this was based on 43 affected individuals from only 2 kindreds.[4]

Abbreviations used in this paper: EUROPAC, European Registry of Hereditary Pancreatitis and Pancreatic Cancer; SIR, standardized incidence ratio.

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No phenotypic differences between these mutations were found in a study from Germany[8] based on 75 affected individuals from 27 families (R122H = 21 and N29I = 6). There is good evidence for an increased incidence of pancreatic ductal adenocarcinoma in hereditary pancreatitis,[8,20] although this has been questioned.[5] The risk has also been said to be largely attributable to paternal transmission of the disease.[20] These studies are subject to ascertainment bias, however, and none take into account the influence of familial bias as shown by the phenotypic expression and penetrance of monozygotic twins affected with hereditary pancreatitis.[21]

To overcome ascertainment bias, families were investigated from the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) for the distribution of PRSS1 mutations and correlations between the genotype and phenotype including the risk of developing pancreatic cancer. The register contains all families known so far in 12 out of 14 European countries from which there are known families with hereditary pancreatitis. These kinds of data are hierarchical in structure because of the nesting of affected patients within families and hence are not completely independent. Multilevel modelling was therefore used to account for the variation distributed within a family as well as between families. This study was large enough and the first to use this analytical technique to investigate the relationship between biological and demographic factors of patients with hereditary pancreatitis.

Materials and Methods

Registration and Clinical Information

The EUROPAC was established with ethical committee approval in October 1997.[22] The aims of EUROPAC included the determination of the distribution of PRSS1 mutations within Europe and correlation between the genotype and phenotype of hereditary pancreatitis including the risk of developing pancreatic ductal adenocarcinoma. The diagnosis of hereditary pancreatitis in a family was made on the basis of 2 first-degree relatives or 3 or more second-degree relatives, in 2 or more generations with recurrent acute pancreatitis and/or chronic pancreatitis, for which there were no precipitating factors. A multidisciplinary "hanging" committee accepted families onto the register after consideration of all relevant clinical information. The diagnosis of recurrent acute pancreatitis and/or chronic pancreatitis was made by the referring clinician based on clinical, biochemical, and radiologic criteria.[17] After written informed consent, both affected individuals and their referring clinicians each completed detailed questionnaires. Clinically unaffected individuals from hereditary pancreatitis families were rigorously screened for symptoms of pancreatitis by questionnaire. Affected and unaffected individuals were invited to provide a sample of blood for DNA extraction and mutation analysis again after written informed consent.

Time-to-event analyses required an accurate date of birth as well as an accurate date for the event start. The age of symptom onset was based on patient questionnaires and supported by information from the clinician. The subsequent age of diagnosis of hereditary pancreatitis was based on information given by the clinician. The number of symptomatic attacks and hospital admissions was recorded as the number of attacks or admissions per year. The diagnosis of exocrine failure was based on standard diagnostic tests supported by the use of pancreatic enzyme supplements, and the diagnosis of diabetes mellitus was similarly based on standard tests and/or the requirement for insulin.[17] Patients were censored at age of operation if they had undergone a pancreatic resection at any time irrespective of whether they subsequently developed exocrine or endocrine failure. The type of surgery was recorded as either a resection (for pain) or as a nonresectional procedure for the complications of chronic pancreatitis. Pancreatic ductal adenocarcinoma was confirmed histologically when possible; in the absence of histological confirmation, there was a critical review of clinical and radiologic findings. Patients who had undergone pancreatic resection for benign disease of the pancreas were censored at the age of surgery because this was assumed to have significantly reduced the risk of developing cancer. Information regarding consumption of alcohol and tobacco was requested, specifically the number of units of alcohol consumed per week and the number of cigarettes smoked per day.

For deceased individuals, the diagnosis was based on independent medical records and DNA analyzed from stored tissue after consent from family members. Although all recorded clinical material was used to determine whether the individual was affected or not, specific data were analyzed only if precise details were known.

Detection of Mutations in the PRSS1 Gene

The PRSS1 gene was sequenced in both directions[9] if the commoner mutations were not detected as previously described.[12,17,23]

Statistical Analyses

Proportions of patients with events over time were estimated by using the method of Kaplan-Meier to account for censored data. Patients who did not experience the event were censored at the age when last known to be event free or at death. In multilevel modeling, 2 main explanatory covariates (gender and mutation status) were simultaneously investigated for increased or decreased risk of failure. Two binary dummy variables were created because of mutation status being a 3-level covariate: "R122H" (R122H vs. not R122H) and "N29I" (N29I vs. not N29I), using (PRSS1 mutation) "negative" patients as the baseline group. Multilevel modeling was performed for both continuous response data (with no censored data using square-root transformed response data) and censored data (using the inbuilt survival macros for the multi-level

Table 1. Patient Characteristics in the EUROPAC Study

	R122H	N29I	Negative	A16V	Not tested	Total
No. of families	58 (52%)	24 (21%)	21 (19%)	5 (4%)	4 (4%)	112 (100%)
No. of patients	222 (53%)	94 (22%)	72 (17%)	11 (3%)	19 (5%)	418 (100%) unless otherwise stated
Age (*yr*)						
N	207	76	66	11	15	N = 375
Median	37	35	40	39	40	38
Interquartile range	20–52	25–52	22–52	24–50	15–54	22–52
Range	4–90	4–79	2–81	13–61	3–66	2–90
Sex						N = 415
Male	109	45	31	2	12	199
Female	110	49	41	9	7	216
Smoking						N = 196
Never	61	16	16	4	1	98
Ever	53	24	18	3	0	98
Alcohol						N = 197
Never	53	15	13	2	0	83
Ever	57	28	22	6	1	114
Country						N = 417
Belgium	3	13	8	3	0	27
Czech Republic	0	4	4	0	0	8
Denmark	3	0	3	2	0	8
France	7	0	0	0	0	7
Germany	66	7	24	0	0	97
Hungary	2	0	0	0	0	2
Ireland	17	6	0	0	0	23
Italy	10	3	12	0	0	25
Netherlands	11	8	0	0	0	19
Norway	0	0	0	3	0	3
Poland	0	0	0	0	8	8
Sweden	3	0	0	0	6	9
Switzerland	13	0	2	1	0	16
UK	87	52	19	2	5	165
Malabsorption						N = 227
Censored	73	36	26	4	2	141
Event	48	18	14	4	2	86
Diabetes mellitus						N = 257
Censored	94	43	28	8	3	176
Event	51	19	10	1	0	81
Pancreas resection						N = 417
Censored	202	75	67	9	16	369
Event	19	19	5	2	3	48
Drainage operation						N = 417
Censored	203	88	70	9	18	388
Event	18	6	2	2	1	29
Cancer						
Censored	210	87	67	10	18	392
Event	12	7	5	1	1	26

NOTE. Age refers to the age of individuals at which data were most recently collected; the term "censored" refers to individuals with data amenable to analysis; an "event" refers to the disease or intervention taking place.

proportional hazards modelling) using MLWin 1.10. The factors of tobacco smoking and alcohol history (never vs. ever) were investigated for cancer risk in a subgroup of patients who provided this information. For cancer risk, the size of the historical cohort was estimated using person years. The expected cumulative number of cancers was calculated for the entire cohort of affected patients using published age-stratified, sex, and country-specific data according to 5-year age groups.[24] The standardized incidence ratio (SIR) was used to estimate the relative risk of cancer, defined as the ratio of observed to expected pancreatic cancers and adjusted for age and surgical intervention.

Results

At the time of censor, 527 individuals had been recruited from 14 countries of whom 418 individuals from 112 families were affected (Table 1), and most countries had referred additional families and individuals who were still undergoing genetic and clinical investi-

Table 2. Multi-level Proportional Hazards Modelling

Model	Covariate	β	se(β)	*P*
Time to symptom onset	Gender	0.071	0.136	0.60
(224 patients, 87	N29I	0.151	0.235	0.52
families)	R122H	0.443	0.206	**0.032**
Time to malabsorption (190	Gender	−0.169	0.265	0.52
patients, 84 families)	N29I	0.276	0.443	0.54
	R122H	0.352	0.391	0.37
Time to diabetes mellitus	Gender	−0.47	0.260	0.07
(218 patients, 89	N29I	0.319	0.493	0.52
families)	R122H	−0.031	0.443	0.94
Time to pancreatic resection	Gender	1.279	0.254	**<0.001**
(344 patients, 101	N29I	1.728	0.701	**0.014**
families)	R122H	0.005	0.670	1.0
Time to drainage surgery	Gender	0.343	0.259	0.19
(346 patients, 101	N29I	0.662	0.885	0.45
families)	R122H	1.006	0.762	0.19
Time to cancer (346	Gender	−0.670	0.467	0.15
patients, 101 families)	N29I	−0.532	0.981	0.59
	R122H	−0.316	0.760	0.67

NOTE. **Bold** type demonstrates the significant findings of earlier time to symptom onset by mutation status (R122H), increased risk of pancreatic resection dependent on gender (higher intervention rate in females), and reduced time to pancreatic resection by mutation status (earlier for N29I).

gation. There were 2 families with rare mutations: 1 with the R122C mutation and 1 with the N29T mutation. Excluding patients with A16V/rare mutations and those awaiting mutational analysis there were 388 patients from 103 families. There were more missing data for time-to-event analyses mostly because of the limited information obtained on deceased individuals (n = 57) and/or a missing dates of birth (n = 54).

Age of Onset of Pancreatitis

The precise age of the onset of symptoms (and date of birth) was available in 241 of the 418 patients within 96 families. The cumulative risk of symptoms was 40.3% (95% confidence interval [CI]: 34.1%, 46.4%) at 10 years of age, 72.6% (95% CI: 67.0%, 78.2%) at 20 years, 89.2% (95% CI: 85.3%, 93.1%) at 30 years, 93.0% (95% CI: 89.7%, 96.2%) at 40 years, and 96% (95% CI: 93.3%, 98.4%) at 50 years of age. The median (95% CI) age of symptom onset of pancreatitis was 12 (10, 13) years and was similar for men (n = 109; median 12, 95% CI: 10, 16 years) and women (n = 129; median 11, 95% CI: 8, 13 years; Table 2). Fourteen patients with a minor mutation or not tested for mutation were excluded from analysis by mutation status. The median age of symptom onset was significantly reduced for R122H patients (n = 133; median 10, 95% CI: 8, 12 years) compared with N29I patients (n = 56, median 14, 95% CI: 11, 18 years) and mutation negative patients (n = 38; median 14.5, 95% CI: 10, 21 years; p=0.032; Figure 1; Table 2). It was not applicable to investigate the effects of smoking and alcohol on patients whose symptom onset occurred ≤10 years of age. The median (interquartile range) age of symptom onset for 131 patients with symptom onset aged >10 years was 20 (14–28) years, which did not differ significantly between smokers/nonsmokers and drinkers/nondrinkers.

Age of Onset of Exocrine Failure

Two hundred twenty-seven patients provided accurate data on the presence or absence of malabsorbtion (and date of birth) of whom 86 (38%) had malabsorbtion (Table 1). Of these, 201 patients (from 92 families) provided information regarding age of malabsorbtion; 60 (30%) had malabsorbtion with known age of onset and

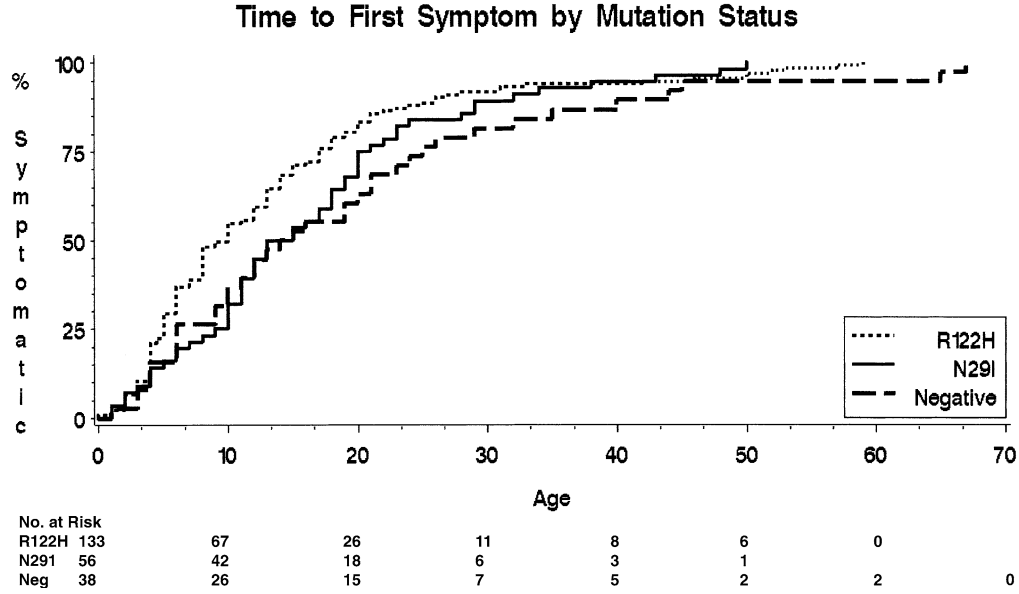

Figure 1. Time to the first onset of pancreatitis by mutation status showing that patients with the R122H mutation present at a significantly younger age.

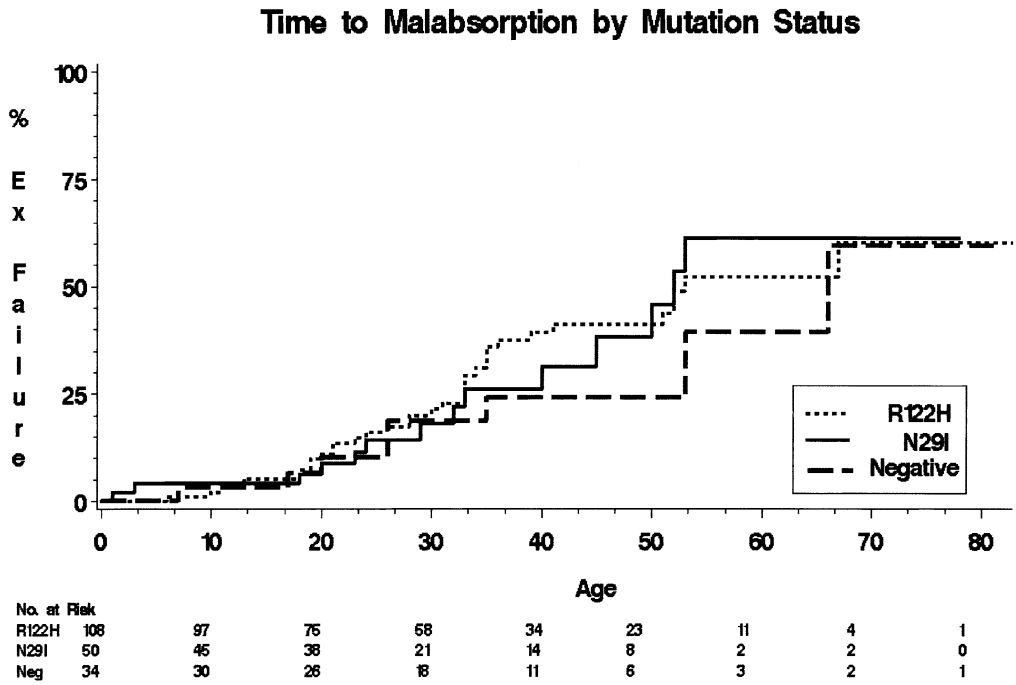

Figure 2. Time to the detection of exocrine failure showing no significant differences by mutation status.

the remaining 141 patients were censored. The cumulative risk of pancreatic exocrine failure was 2.0% (95% CI: 0.1%, 4.0%) at 10 years of age, 8.4% (95% CI: 4.3%, 12.5%) at 20 years, 20.2% (95% CI: 13.9%, 26.6%) at 30 years, 33.6% (95% CI: 25.4%, 41.8%) at 40 years, 37.2% (95% CI: 28.5%, 45.8%) at 50 years, 51.3% (95% CI: 40.3%, 62.3%) at 60 years, and 60.2% (95% CI: 45.9%, 74.5%) at 70 years of age. The median (95% CI) time to malabsorbtion was 53 (52, −years) years of age and was not significantly different between men (n = 87; median 53, 95% CI: 45, −years) and women (n = 112; median 66, 95% CI: 51, −years) (Table 2). In the analysis by mutation status, 9 patients were excluded because of minor mutations. The median (95% CI) time to the onset of malabsorbtion was 53 (39, −years) years of age for R122H patients (n = 108), 52 (45, −) years of age for N29I patients (n = 50), and 66 (53, −years) years of age for mutation negative (n = 34) patients (Figure 2). Differences in the age of onset of pancreatic exocrine insufficiency were not significantly influenced by either gender or mutation status (Table 2). The cumulative risk of pancreatic exocrine failure from symptom onset for the 180 patients with complete information and whose symptoms occurred before failure was 11.9% (95% CI: 6.8%, 17.0%) at 10 years after symptom onset, 28.2% (95% CI: 20.0%, 36.5%) at 20 years, 45.6% (95% CI: 34.8%, 56.3%) at 30 years, and 65% (95% CI: 52.5%, 77.5%) at 40 years from symptom onset.

Age of Onset of Endocrine Failure

There were 257 patients with accurate data regarding the presence or absence of diabetes mellitus (and date of birth) of whom 81 (32%) had diabetes (Table 1). Of these, 232 patients (from 98 families) provided information regarding the timing of the development or absence of diabetes; 60 (26%) had diabetes attributable to natural progression of the disease, the remaining 172 patients being censored. The cumulative risk of endocrine failure was 1.3% (95% CI: 0.0%, 2.9%) at 10 years of age, 4.4% (95% CI: 1.6%, 7.2%) at 20 years, 8.5% (95% CI: 4.3%, 12.7%) at 30 years, 21.1% (95% CI: 14.1%, 28.1%) at 40 years, 47.6% (95% CI: 37.1%, 58.1%) at 50 years, 60.2% (95% CI: 48.2%, 72.1%) at 60 years, 68.6% (95% CI: 54.5%, 82.7%) at 70 years, and 79.1% (95% CI: 59.9%, 98.3%) at 80 years of age. The overall median (95% CI) time to diabetes mellitus was 53 (47, 65) years of age, somewhat reduced for men (n = 102; median 47, 95% CI: 44, 56 years) compared with women (n = 128; median 68, 95% CI: 49, −years) ($P = 0.074$; Table 2). In the analysis by mutation status, 9 patients were excluded because of minor mutations and three because of incomplete mutation analysis. The median (95% CI) time to the onset of diabetes mellitus was 51 (45, 68) years of age in R122H patients (n = 129), 46 (44, 59) years of age in N29I patients (n = 56), and 55 (40, −years) years of age in mutation negative (n = 35) patients (Figure 3). Differences in the age of onset of diabetes mellitus were not significantly influenced by

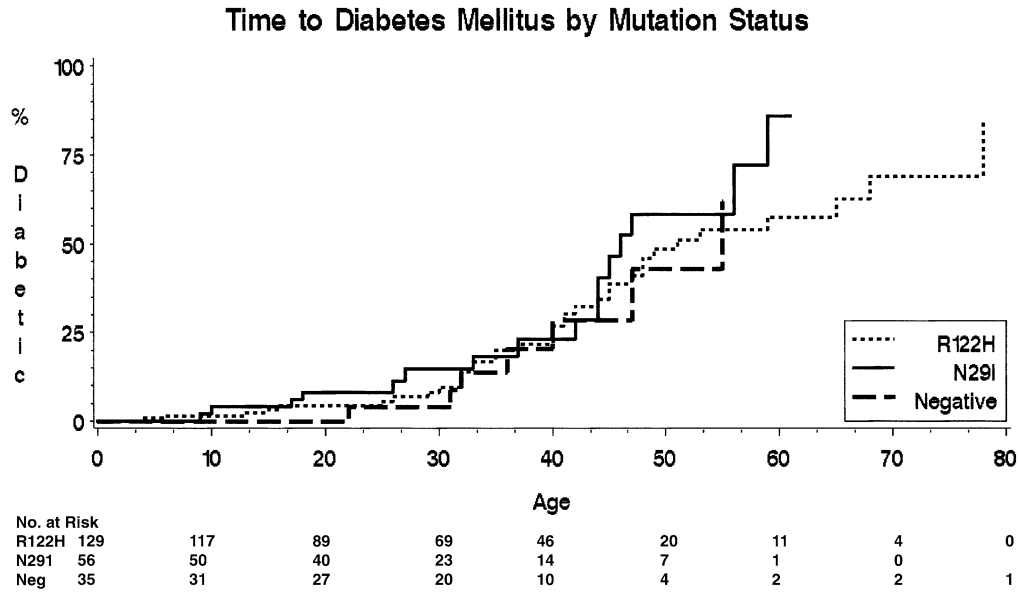

Figure 3. Time to the detection of endocrine failure showing no significant differences by mutation status.

mutation status (Table 2). The cumulative risk of pancreatic endocrine failure from symptom onset for the 199 patients with complete information and whose symptoms occurred before failure was 5.1% (95% CI: 1.9%, 8.4%) at 10 years after symptom onset, 18.4% (95% CI: 11.5%, 25.2%) at 20 years, 30.7% (95% CI: 20.8%, 40.6%) at 30 years, 49.9% (95%CI: 36.3%, 63.4%) at 40 years, and 70.8% (95% CI: 54.3%, 87.2%) at 50 years from symptom onset.

Hospital Admission Rates

Data on the number of attacks and admissions to hospital each year were reported by 195 (47%) patients with a maximum of 52 attacks and five admissions to hospital (Table 3). The majority of patients (n = 158,85% of 186 patients with information regarding attack duration) reported that the attacks lasted ≤7 days. Multilevel modeling showed that the number of attacks was not significantly influenced by gender ($P = 0.165$)

Table 3. Details of the Number of Attacks and Hospital Admissions per Year and the Cumulative Number of Patients With Increasing Duration of Each of the Periods of Attack Requiring Hospitalization in Days

	R122H	N29I	Negative	A16V	Not tested	Total
Attacks						
N	115	38	32	8	2	195
Median (*per year*)	2	1.43	1.33	0.49	4.2	1.88
Interquartile range	0.68–4	0.59–3	1–3	0.16–0.59	-	0.63–3
Range	0.04–12	0–52	0–5	0.08–12	0.13–8.3	0–52
Admissions						
N	99	42	32	9	2	184
Median (*per year*)	0.33	0.19	0.64	0.16	0.34	0.30
Interquartile range	0.06–1	0.05–0.55	0.16–1.33	0.12–0.25	-	0.08–1
Range	0–5	0–3	0–4	0.08–0.33	0.13–0.55	0–5

	Duration of attack (*days*)	Cumulative number of patients
Attacks	≤2	35
N	≤3	51
Median (per year)	≤4	92
Interquartile range	≤5	141
Range	≤6	144
Admissions	≤7	158
N	≤14	170
Median (per year)	≤21	176
Interquartile range	≤28	181
Range	≤56	186

or mutation status (N29I $P = 0.535$; R122H $P = 0.204$). Similarly, the number of admissions to hospital was not significantly influenced by gender ($P = 0.153$). The hospital admission rate for the R122H patients was not significantly different from that of mutation negative patients ($P = 0.105$) but was significantly reduced for N29I patients ($P = 0.005$).

Surgery

Surgical procedures were reported for 81 (19%) of 417 affected individuals of whom 48 (59%) had a pancreatic resection (Table 1). Time to resection was known for 370 patients (from 111 families) including 328 censored patients and 42 (11%) patients who had a pancreatic resection. Patients were censored at age of any other surgical procedure. The overall cumulative risk of pancreatic resection was 0.6% (95% CI: 0.0%, 1.3%) at 10 years of age, 2.5% (95% CI: 0.8%, 4.1%) at 20 years, 8.3% (95% CI: 5.1%, 11.5%) at 30 years, 11.4% (95% CI: 7.6%, 15.3%) at 40 years, 17.5% (95% CI: 12.2%, 22.7%) at 50 years, and 21.5% (95% CI: 14.1%, 28.9%) at 70 years of age. There were 13 (7.4%) resections in 175 men and 29 (15.2%) resections in 192 women (3 patients with missing gender were excluded). Time to resection was significantly reduced for women ($P < 0.001$; Table 2). The cumulative risk of pancreatic resection was increased for women compared with men: 3.6% versus 1.3% at 20 years of age, 11.6% versus 5.1% at 30 years, 16.8% versus 5.9% at 40 years, 24.3% versus 10.5% at 50 years, and 24.3% versus 20.4% at 70 years. Twenty-three patients with a minor mutation or not tested for mutation were excluded from analysis by mutation. The time to resection was significantly reduced for patients with the N29I mutation (n = 75) compared with R122H (n = 206) and mutation negative (n = 66) patients ($P = 0.014$; Table 2). The cumulative risk of pancreatic resection was increased for N29I patients compared with R122H and negative patients: 34.7% versus 12.6% versus 13.2% at 50 years of age. The cumulative risk of pancreatic resection from symptom onset for the 232 patients with complete information and whose symptoms occurred prior to surgery was 7.0% (95% CI: 3.6%, 10.5%) at 10 years after symptom onset, 15.2% (95% CI: 9.7%, 20.6%) at 20 years, 16.2% (95% CI: 10.5%, 21.9%) at 30 years, 26.2% (95% CI: 17.1%, 35.3%) at 40 years, 29.6% (95% CI: 18.8%, 40.4%) at 50 years, and 36.6% (95% CI: 20.3%, 52.9%) at 60 years from symptom onset. Twenty-nine (36%) of the 81 reported procedures were pancreatic drainage operations. The time to operation was known for 375 patients (from 111 families): 347 censored patients and 28 (7%) patients who had a pancreatic drainage procedure. The cumulative risk of pancreatic drainage surgery from symptom onset for the 233 patients with complete information and whose symptoms occurred prior to surgery was 6.2% (95% CI: 2.9%, 9.6%) at 10 years after symptom onset, 11.8% (95% CI: 6.7%, 16.8%) at 20 years, 16.6% (95% CI: 9.9%, 23.3%) at 30 years, and 35.6% (95% CI: 11.5%, 59.8%) at 60 years from symptom onset.

Pancreatic Cancer

Pancreatic cancer was diagnosed in 26 (6%) of all the 418 affected patients (Table 1). Fifteen patients had histologically confirmed pancreatic ductal adenocarcinoma, and the diagnosis in the remainder was based on unequivocal clinical and radiological information (including lack of long-term survival). Pancreatic cancer occurred in 14 patients (13 families) with the R122H mutation, 7 patients (6 families) with the N29I mutation, 4 patients (4 families) with no PRSS1 mutation, and 1 patient (1 family) with the A16V mutation. The disease was inherited from the father in 6 patients, 2 with the R122H mutation (2 families) and 4 with the N29I mutation (3 families). Of the 6 other patients with disease inherited from the mother, 3 had the R122H mutation (3 families) and 3 had no PRSS1 mutation (3 families). Three hundred seventy-five patients (from 111 families) with follow-up data were observed over an observation period of 14,064 person years with 20 (5%) pancreatic cancers being detected (1 cancer per 703 person years follow-up). The average age and follow-up of censored noncancer patients was 35 (range 2-90, interquartile range 20-50) years. The overall cumulative risk of pancreatic cancer was 0% to 30 years, 0.5% (95% CI: 0.0%, 1.3%) at 40 years of age, 3.4% (95% CI: 0.4%, 6.5%) at 50 years, 9.8% (95% CI: 3.6%, 16.0%) at 60 years, 18.8% (95% CI: 8.6%, 29.0%) at 70 years, and 33.3% (95% CI: 19.0%, 47.5%) at 80 years. Time to cancer did not significantly differ between men and women (Table 2). Twenty-six patients with a minor mutation or not tested for mutation were excluded from analysis by mutation. Time to cancer was not significantly influenced by mutation status (Figure 4, Table 2). The cumulative risk of pancreatic cancer from symptom onset for the 233 patients with complete information and whose symptoms occurred before cancer was 1.5% (95% CI: 0%, 3.6%) at 20 years after symptom onset, 2.5% (95% CI: 0%, 5.3%) at 30 years, 8.5% (95% CI: 1.4%, 15.7%) at 40 years, 14.6% (95% CI: 1.3%, 28.0%) at 50 years, 25.3% (95% CI: 2.5%, 48.1%) at 60 years, and 44.0% (95% CI: 8.0%, 80.0%) at 70 years from symptom onset.

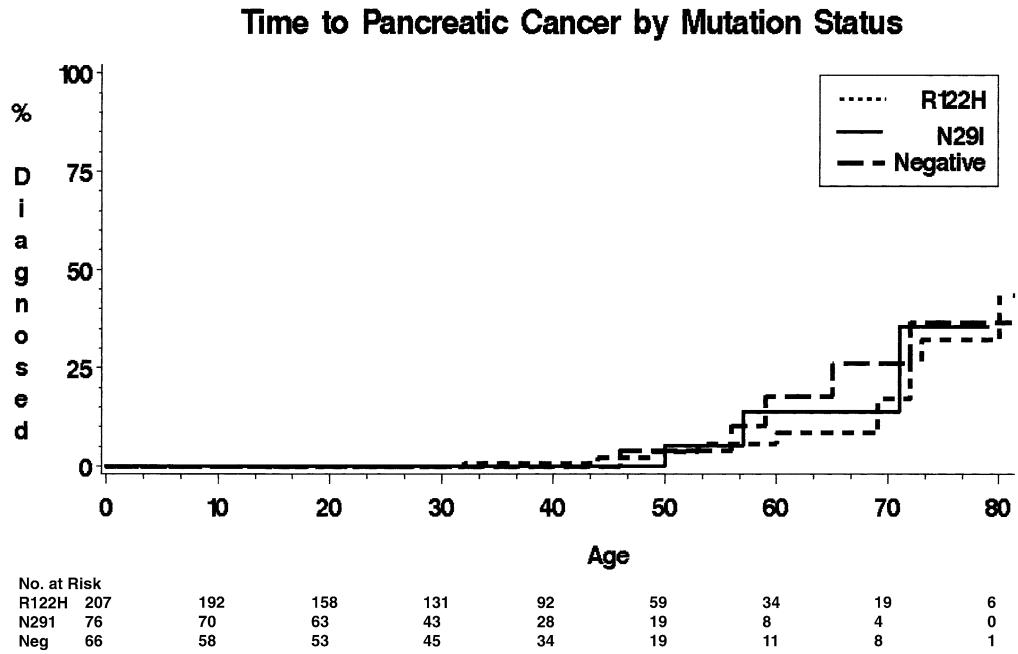

Figure 4. Time to pancreatic cancer showing no significant differences by mutation status.

One hundred ninety-two patients (from 84 families) provided a complete smoking and alcohol history: 95 (49%) patients reported a history of smoking, 111 (58%) reported consuming alcohol, and 77 (40%) patients reported both. Seventeen of these 192 patients had pancreatic cancer diagnosed with an age range of 32 to 80 years. Six (6%) non-smokers and 11 (12%) smokers were diagnosed with pancreatic cancer with a median (range) age of 71 (41–72) and 56 (32–80) years, respectively. Five (6%) nonalcohol drinkers and 12 (11%) alcohol drinkers were diagnosed with pancreatic cancer with a median (range) age of 72 (41–80) and 54 (32–72) years, respectively. Eight of the 26 patients with pancreatic cancer reported a history of both smoking and alcohol consumption (including 4 who smoked $\geq$40 cigarettes per day and 1 heavy drinker) and were diagnosed with an age range of 32 to 69 years. The SIR adjusted for age, nationality, and surgical intervention was 67 (95% CI: 50, 82). The SIR for men, 72 (95% CI: 46, 97), was higher than for women, 60 (95% CI: 37, 83).

Discussion

This study, which is by far the largest detailed study of hereditary pancreatitis reported to date, has confirmed that the R122H mutation of the PRSS1 gene is the commonest mutation in the disease. Nineteen percent of families had no PRSS1 mutation but had clinical features that were indistinguishable from mutation positive families, indicating that there is yet another gene of considerable importance in the pathogenesis of pancreatitis. The positive mutation rate of 81% was much higher than previously reported[25] and may be related to the strict diagnostic criteria for hereditary pancreatitis used by EUROPAC. The present study was large enough to adopt appropriate statistical modeling to account for the natural hierarchical data structure. The analysis showed that patients with the R122H mutation present on average 4–5 years earlier compared with those with the N29I mutation or those who are mutation negative and patients with the N29I mutation had a lower hospital admission rate. Moreover, women and patients with the N29I mutation underwent pancreatic resection for pain much earlier than males and those with wild-type or different PRSS1 mutations, respectively. There was also a surprising variation in the proportion of families with the N29I mutation between countries. The higher resection rate for patients with the N29I mutation does not seem consistent with the later onset of disease but may account for the reduction in hospital admissions. The possible reasons for this would include environmental and genetic factors and perhaps differences in clinical practice between countries that will be examined when recruitment of patients within each country has increased.

The focus of the present study was on affected members from families with hereditary pancreatitis accounting for the high cumulative risk of symptoms (96% at 50 years of age) in comparison to the reported penetrance of only 80%.[1,2] The incidence of exocrine and endocrine failure in hereditary pancreatitis was shown to be high, with an overall lifetime risk to 70 years for the development of malabsorbtion of 60.2% (95% CI: 45.9%,

74.5%) and 68.6% (95% CI: 54.5%, 82.7%) for diabetes mellitus. Moreover the lifetime incidence of diabetes mellitus tended to be greater in men compared with women, consistent with the trend in insulin dependent diabetes mellitus in the general population. In contrast to hereditary pancreatitis, the cumulative incidence of malabsorbtion is much lower for early-onset idiopathic pancreatitis (44%), late-onset idiopathic pancreatitis (46%), and alcoholic pancreatitis (48%).[9] Similarly, the cumulative incidence of diabetes mellitus is also much lower for early-onset idiopathic pancreatitis (32%), late-onset idiopathic pancreatitis (41%), and alcoholic pancreatitis (38%).[9]

The cumulative incidence for surgery was 21.5% (95% CI: 14.1%, 28.9%) at 70 years of age, surprisingly low compared with early-onset idiopathic pancreatitis (60%), late-onset idiopathic pancreatitis (32%), and alcoholic pancreatitis (40%).[9] The median time to exocrine insufficiency from symptom onset for hereditary pancreatitis was much longer (53 [95% CI: 51, −] years) than for early-onset idiopathic pancreatitis (26.3 years), late-onset idiopathic pancreatitis (16.9 years), and alcoholic pancreatitis (13.1 years).[9] The median time to endocrine insufficiency from symptom onset for hereditary pancreatitis was also much longer (53 [95% CI: 47, 65] years) than for early-onset idiopathic pancreatitis (27.5 years), late-onset idiopathic pancreatitis (11.9 years), and alcoholic pancreatitis (19.8 years).[9] These data clearly show a different natural history for hereditary pancreatitis compared with other forms of chronic pancreatitis. The age of onset is younger, and endpoints take longer to be reached in hereditary pancreatitis, but the cumulative levels of exocrine and endocrine failure are much higher compared with other forms of chronic pancreatitis.

Alcohol consumption has previously been shown to influence the number of painful exacerbations of pancreatitis.[9,10] The present study did not find any difference in disease severity between individuals who drink alcohol or smoke, in isolation or in combination. This does not necessarily imply that smoking and alcohol have no influence on disease expression but rather that these factors were insignificant in the context of the underlying disease process.

The present study has shown that the risk of pancreatic cancer is negligible up to the age of 50 years, but thereafter increases markedly in both sexes to 18.8% at 70 years. A previous study of patients with hereditary pancreatitis showed that 8 patients developed pancreatic cancer during 8531 person years follow-up (or 1 per 1066 person years) and yielded an estimated lifetime risk of 40%.[20] Pancreatic calcification and diabetes were found more frequently in patients who developed pancreatic cancer, compared with age- and sex-matched individuals without cancer, suggesting that the risk of pancreatic cancer was related to the severity and duration of pancreatitis.[20] A study from France found no cancers in 12 patients followed up for a mean of 15.8 years,[5] whereas 3 cancers were found in 101 (75 affected) individuals from Germany with an estimated rate of 1 per 1200 person years.[8] In the present study, the estimated rate was one cancer per 703 person years follow-up, and the cumulative risk was 44.0% at 70 years from symptom onset. In an analysis of 19 biopsy-proven cases, the median age of onset of pancreatic cancer in 11 smokers was 50 years compared with 70 years in six patients who had never smoked and a statistically significant difference was claimed.[26] The present study of 26 patients with pancreatic cancer showed a similar difference, with a median age at diagnosis of cancer of 57 years in smokers and 71 years in nonsmokers. Such a comparison, however, fails to account for any follow-up data of censored noncancer patients who may go on to develop pancreatic cancer and indicates the need for further follow-up in both cohorts. The risk of pancreatic ductal adenocarcinoma in hereditary pancreatitis was previously believed to have been dependent on the mode of disease inheritance.[20] The present study however clearly shows that the excess risk of pancreatic cancer occurs equally whether the mother or the father transmits the disease. We also report for the first time that pancreatic cancer may arise in families with any of the commoner PRSS1 mutations (R122H, N29I, and A16V) as well as in PRSS1 mutation–negative families.

Clinical trials to modify the development of pancreatitis and secondary screening to identify early pancreatic cancer may be warranted. These studies could serve as paradigms for intervention in the common form of these disease processes.

References

1. Comfort MW, Steinberg AG. Pedigree of a family with hereditary chronic pancreatitis. Gastroenterology 1952;21:54–63.
2. Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. Gut 1999;45:317–322.
3. Konzen KM, Perrault J, Moir C, Zinsmeister AR. Long-term follow-up of young patients with chronic hereditary or idiopathic pancreatitis. Mayo Clin Proc 1993;68:449–453.
4. Gorry MC, Garbbaizedeh D, Furey W, Gates LK, Preston RA, Aston CE, Zhang Y, Ulrich C, Ehrlich GD, Whitcomb DC. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology 1997;113:1063–1068.
5. Paolini O, Hastier P, Buckley M, Maes B, Demarquay JF, Staccini P, Bellon S, Caroli-Bosc FX, Dumas R, Delmont J. The natural history of hereditary chronic pancreatitis: a study of 12 cases compared to chronic alcoholic pancreatitis. Pancreas 1998;17:266–271.

6. Nishimori I, Kamakura M, Fujikawa-Adachi K, Morita M, Onishi S, Yokoyama K, Makino I, Ischida H, Yamamoto M, Watanabe S, Ogaw M. Mutations in exons 2 and 3 of the cationic trypsinogen gene in Japanese families with hereditary pancreatitis. Gut 1999; 44:259–263.
7. Ferec C, Raguenes O, Salomon R, Roche C, Bernard JP, Guillot M, Quere I, Faure C, Mercier B, Audrezet MP, Guillausseau PJ, Dupont C, Munnich A, Bignon JD, Le Bodic L. Mutations in the cationic trypsinogen gene and evidence for genetic heterogeneity in hereditary pancreatitis. Med Genet 1999;36:228–232.
8. Keim V, Bauer N, Teich N, Simon P, Lerch MM, Mössner J. Clinical characterization of patients with hereditary pancreatitis and mutations in the cationic trypsinogen gene. Am J Med 2001;111: 622–626.
9. Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology 1994;107:1481–1487.
10. Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology 1999;116:1132–1140.
11. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, Martin SP, Gates LK Jr, Amann ST, Toskes PP, Liddle R, McGrath K, Uomo G, Post JC, Ehrlich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996;14:141–145.
12. Witt H, Luck W, Becker M. A signal peptide cleavage site mutation in the cationic trypsinogen gene is strongly associated with chronic pancreatitis. Gastroenterology 1999;117:7–10.
13. Pfützer R, Myers E, Applebaum-Shapiro S, Finch R, Ellis I, Neoptolemos JP, Kant JA, Whitcomb DC. Novel cationic trypsinogen (PRSS1) N29T and R122C mutations cause autosomal dominant hereditary pancreatitis. Gut 2002;50:271–272.
14. Teich N, Ockenga J, Hoffmeister A, Manns M, Mössner J, Keim V. Chronic pancreatitis associated with an activation peptide mutation that facilitates trypsin activation. Gastroenterology 2000; 119:461–465.
15. Ferec C, Raguenes O, Salomon R, Roche C, Bernard JP, Guillot M, Quere I, Faure C, Mercier B, Audrezet MP, Guillausseau PJ, Dupont C, Munnich A, Bignon JD, Le Bodic L. Mutations in the cationic trypsinogen gene and evidence for genetic heterogeneity in hereditary pancreatitis. J Med Genet 1999;36:228–232.
16. Noone PG, Zhou Z, Silverman LM, Jowell PS, Knowles MR, Cohn JA. Cystic fibrosis gene mutations and pancreatitis risk: relation to epithelial ion transport and trypsin inhibitor gene mutations. Gastroenterology 2001;121:1310–1319.
17. Threadgold J, Greenhalf W, Ellis I, Howes N, Lerch MM, Simon P, Jansen J, Charnley R, Laugier R, Frulloni L, Olah A, Delhaye M, Ihse I, Schaffalitzky de Muckadell OB, Andren-Sandberg A, Imrie CW, Martinek J, Gress TM, Mountford R, Whitcomb D, Neoptolemos JP. The N34S mutation of SPINK1 (PSTI) is associated with a familial pattern of idiopathic chronic pancreatitis but does not cause the disease. Gut 2002;50:675–681.
18. Teich N, Bauer N, Mössner J, Keim V. Mutational screening of patients with non-alcoholic chronic pancreatitis: identification of further trypsinogen variants. Am J Gastroenterol 2002;97:341–346.
19. Simon P, Weiss FU, Zimmer KP, Rand S, Brinkmann B, Domschke W, Lerch MM. Spontaneous and sporadic trypsinogen mutations in idiopathic pancreatitis. JAMA 2002;288:2122.
20. Lowenfels A, Maisonneuve P, DiMagno E, Elitsur Y, Gates LK, Perrault J, Whitcomb DC. Hereditary pancreatitis and the risk of pancreatic cancer. J Natl Cancer Inst 1997;89:442–446.
21. Amann ST, Gates LK, Aston CE, Pandya A, Whitcomb DC. Expression and penetrance of the hereditary pancreatitis phenotype in monozygotic twins. Gut 2001;48:542–547.
22. Ellis I, members of the Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, the Midwest Multicenter Pancreatic Study Group and the International Association of Pancreatology. Genetic testing for hereditary pancreatitis: Guidelines for indications, counselling, consent and privacy issues. Pancreatology 2001;1:401–411.
23. Howes N, Rutherford S, O'Donnell M, Mountford R, Ellis I, Greenhalf W, Whitcomb D, Imrie C, Drumm B, Neoptolemos JP. A new polymorphism for the R122H mutation in hereditary pancreatitis. Gut 2001;48:247–250.
24. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents. Volume VIII. Lyons: International Association Research Cancer, 2003.
25. Applebaum-Shapiro SE, Finch R, Pfützer RH, Hepp LA, Gates L, Amann S, Martin S, Ulrich CD 2nd, Whitcomb DC. Hereditary pancreatitis in North America: the Pittsburgh-Midwest Multi-Center Pancreatic Study Group Study. Pancreatology 2001;1:439–443.
26. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA 2001;286: 169–170.

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