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Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer

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Abstract

Introduction: Hereditary pancreatitis (HP), an autosomal dominant disease typically caused by mutations in *PRSS1*, has a broad range of clinical characteristics and high cumulative risk of pancreatic cancer. We describe survival and pancreatic cancer risk in the largest HP cohort in the US.

Methods: HP probands and family members prospectively recruited from 1995 to 2013 completed medical and family history questionnaires, and provided blood for DNA testing. Overall survival (until 12/31/2015) was determined from the Social Security Death Index (SSDI), National Death Index (NDI) and family members. Cause of death was obtained from the NDI.

Results: 217 *PRSS1* carriers (181 symptomatic) formed the study cohort. The most frequently detected mutations were p.R122H (83.9%) and p.N29I (11.5%). Thirty-seven *PRSS1* carriers (30 symptomatic, 7 asymptomatic) were deceased at conclusion of the study (5 from pancreatic cancer). Median overall survival was 79.3 years (IQR 72.2–85.2). Risk of pancreatic cancer was significantly greater than age- and sex-matched SEER data (SIR 59, 95% CI 19–138), and cumulative risk was 7.2% (95% CI 0–15.4) at 70 years.

Discussion: We confirm prior observations on survival and pancreatic cancer SIR in *PRSS1* subjects. Although risk of pancreatic cancer was significantly high in these patients, its cumulative risk was much lower than previous reports.

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Keywords

Hereditary pancreatitis; PRSS1; pancreatic cancer

INTRODUCTION

Hereditary pancreatitis (HP) is a highly penetrant, autosomal dominant disorder characterized by acute pancreatitis (AP) in childhood and chronic pancreatitis (CP) in young adults. Between 65–100% of families with HP have a gain-of-function mutation in the cationic trypsinogen gene (*PRSS1*) (1–3). The two most commonly identified pathogenic *PRSS1* mutations are p.R122H and p.N29I (90%) (4, 5), while less common mutations include A16V, R122C, N29T, D22G, and K23R (4). In HP kindreds without a single causal missense variant, the genetic etiology may be more complex, such as from *PRSS1* duplication and triplication copy number variants (CNVs) (6, 7) or combinations of disease-associated variants (8).

Clinical features include abdominal pain, diabetes mellitus and exocrine pancreatic insufficiency, but the clinical presentation, natural history, complications and need for surgery varies among patients (4, 5, 9, 10). Although the overall survival in HP patients is similar to the background population, the cumulative risk of its most severe complication, pancreatic cancer, has been reported to be as high as 40% at age 70 years (10). The cause of death other than pancreatic cancer in HP patients has only been evaluated in one study (11). Moreover, no prior study has evaluated silent *PRSS1* carriers to assess if their overall survival or risk of pancreatic cancer is similar to symptomatic *PRSS1* carriers.

Several large studies of HP families from European populations were previously published, including estimates of pancreatic cancer risk (4, 11, 12). Clinical characterization of HP in the United States is limited to initial reports from the Midwest Multicenter Study Group describing the regional distribution of HP cases (13) and the clinical characteristics of 32 HP (28 *PRSS1* p.R122H) probands in a large kindred (14).

Here we describe overall survival, cause of death and risk of pancreatic cancer in both symptomatic and asymptomatic *PRSS1* carriers in a prospective HP registry in the United States. While we confirm prior clinical findings and a survival similar to the background population, we found the cumulative risk of pancreatic cancer to be much lower than previously reported, and that silent carriers are also at an increased risk of pancreatic cancer.

MATERIALS AND METHODS

The HP Study

The HP study was initiated at the University of Pittsburgh in 1995 to investigate the clinical characteristics of HP, to evaluate kindreds with known or suspected HP, and to obtain biological samples for further research. Family members were recruited under IRB protocols as described (13).

Data Collection

Structured case report forms were completed by study subjects to provide information on demographics, family history of pancreatitis and pancreatic cancer (minimally, three-generations with construction of pedigrees), alcohol and tobacco exposure, symptoms related to pancreatitis, history of diabetes and exocrine insufficiency, findings on imaging tests, treatment and surgical interventions for pancreatitis, and quality of life. Subjects are also asked to report on their family history of smoking, alcohol, diabetes mellitus and cystic fibrosis. Responses to medical questionnaires and available medical records were reviewed by a licensed physician (CU) for data entry and analyses.

Genetic Testing

Blood was collected, and buffy coats stored at -80°C . DNA was extracted and assessed for the following *PRSS1* mutations: R122H, N29I, R122C, K23R, A16V, and R116C with Sanger sequence verification (n=195) (1), clinical test reports (n=20), or obligate status (n=2).

HP Group for this Study

The cohort included subjects with a history of pancreatitis who were enrolled from 1995–2013 and an identified *PRSS1* mutation (R122H, N29I, R122C, K23R, or A16V). Subjects were classified into two groups: (1) symptomatic *PRSS1* subjects; and (2) silent *PRSS1* carriers.

Survival

Although we made attempts to follow-up for clinical outcomes, only a subset of subjects could be contacted to provide this information. Therefore, we used the Social Security Death Index (SSDI) (15) and the National Death Index (NDI) (16) through the National Center for Health Statistics (NCHS) (16) as the primary sources for an unbiased assessment of vital statistics (17–19) in a combined approach (20, 21). This approach did not rely on the ability to re-contact study participants.

We searched the SSDI with participant identifying information to identify deceased participants until March 2014 (22). To expand death information through 2015, identifying information on subjects was also submitted to the NDI. Recommendations from the NCHS (23) and Fillenbaum *et al* (24) were used to determine ‘true’ matches between NDI decedents and study subjects. Information was supplemented by reports from family members upon re-contact and obituary searches.

Cause of death codes (ICD-9 and ICD-10) for deceased participants were obtained from NDI documentation, and special attention was paid to diagnosis codes for pancreatic cancer, other cancers, and pancreatitis-related deaths.

Statistical Methods

The general cohort statistics are reported as counts and percentages, or median, range and interquartile range (IQR). Comparisons between groups were made using the Kruskal-Wallis

test for continuous data and the χ^2 test or Fisher's exact test, when applicable, for categorical data.

Time to event was estimated using the Kaplan-Meier non-parametric method. Cumulative incidence was estimated with 1-S(t) with a log-log 95% confidence interval. Subjects who did not experience the event were censored at the last known age at which they were free of the event. Survival was calculated by censoring living participants at 12/31/2015. The log-rank test was used to determine the significance of differences according to sex, mutation type, smoking status, and diabetes mellitus.

SEER age-specific (5-year interval) and sex-adjusted death rates of U.S. whites (2009–2013) for pancreatic cancer (25) were used to calculate the standardized incidence ratio. Estimates for expected number of deaths were calculated using age at December 31, 2015 or death. Statistical analyses were completed in R 3.4.0 (26) with a critical level of significance of $P < 0.05$.

RESULTS

Study Subjects

A total of 181 symptomatic *PRSS1* carriers and 36 silent carriers (had a *PRSS1* mutation but no reported history evidence of pancreatitis) were identified from the HP Study. The two most common mutations detected among the carriers were R122H (83.9%, 182/217), and N29I (11.5%, 25/217), while the remaining ~4.5% had other mutations – R112C (1.4%, 3/217), A16V (1.8%, 4/217), and R116C (1.4%, 3/217). The distribution of mutations among symptomatic and silent carriers was similar, except that A16V was not identified among silent carriers.

Of 181 symptomatic carriers, 87 (48.1%) were male and all 177 subjects who reported ethnicity/race were Caucasian/white. The median age at enrollment was 30.4 years (IQR 13.7–44.5; range <1–77) and 59/181 (33%) were minors at enrollment (< 18 years) (Figure 1A). Ever smoking or drinking was reported by 27.6% (50/181; in adults – 39.1% [50/128]) and 32% (58/181; in adults – 44.5% [57/128]) of subjects respectively. Heavy drinking (5 drinks per day) was reported by only 5 subjects.

Median age at enrollment of silent *PRSS1* carriers was 40.6 years (IQR 23.6–49.1; range 2.2–93) and 38.8% (14/36) were male. Ever smoking or drinking was reported by 8 (22.2%) and 13 (36.1%) subjects respectively, and one subject reported drinking an average of 5 drinks per day. There was no significant difference between age at enrollment, % male, ever smoking or ever drinking between silent and symptomatic carriers. Only 1 reported a cholecystectomy at age 57.

The median age for diagnosis of any pancreatitis was 7 years (IQR 3–16; range <1–73). The age at which a diagnosis of HP was made (available in 69 subjects) was 13 years (IQR 4.5–25; range 1–66). Of these 69 subjects, the diagnosis of HP coincided (1 year) with pancreatitis diagnosis in 62.3%; in the remaining subjects, the median delay in diagnosis of

HP was 10 years (range 2–64 years). Penetrance (83.4%; 18½17) and clinical features of symptomatic carriers (not reported) were consistent with previous reports (4, 5, 27).

Survival

A total of 37/217 (16.6%; symptomatic -30/181, 15.8%; silent -7/36, 19.4%) *PRSSI* carriers were deceased as of December 31, 2015 (Figure 1B). Median time from enrollment until the time of death or December 31, 2015 for all *PRSSI* carriers was 16.25 years (range <1 – 20.6 years), and median age at death was 56.1 years (range 17.9–95.5 years). For participants alive at the conclusion of the study, median age was 43.6 years (range 13.5–88.5 years). Median overall survival was 79.3 years (IQR 72.2–85.2) (Figure 2A), which appears similar to the expected survival for whites in the United States -79.1 years in 2012 (28). Sex, type of mutation (R122H, N29I), smoking status, and diabetes mellitus were not associated with significant differences in survival.

Family members of 67.6% (25/37) of decedents were contacted (16/20, 80% with any cancer or pancreatitis-reported cause of death). Among silent carriers, family members for 71.4% (5/7) of deceased subjects were re-contacted, all of which confirmed absence of clinical evidence of pancreatitis until death.

Pancreatic Cancer

Pancreatic cancer was the confirmed cause of death in 5 individuals – 3 symptomatic carriers and 2 asymptomatic carriers (median age of death – 69 years; range 51–76 years) (Table 1). Of note, one death in the NDI was coded as prostate cancer but was diagnosed with pancreatic cancer <1 year before death at the age of 69, confirmed by medical records and pathology. The cumulative risk for death related to pancreatic cancer at 70 years was 7.2% (log-log CI 95% 0–15.4) (Figure 2B). When compared with age and sex-adjusted whites in the US population, the standard incidence rate (SIR) for pancreatic cancer in *PRSSI* carriers was significantly greater (SIR 59; 95% CI 19–138). There were no significant differences in SIR or cumulative risk between symptomatic and silent carriers.

All five subjects who developed pancreatic cancer were *PRSSI* R122H carriers and four were male. Absence of clinical manifestations of pancreatitis in both silent carriers were confirmed by first degree relatives (FDRs). All but one reported ever drinking. Two were self-reported smokers – one symptomatic carrier (age of death -74 years) smoked for 30 years (1 pack/day) and reported consuming 5 drinks/day; and one silent carrier (age of death – 69 years) smoked 1 pack per day for at least 45 years. Three subjects reported a diagnosis of diabetes. Two pancreatic cancer decedents were second-degree relatives – one silent carrier (non-drinker, non-smoker, age of death – 69 years) and one symptomatic carrier (smoker, drinker, age of death – 74 years noted above). In three pancreatic cancer subjects, *PRSSI* R122H was inherited paternally (suspected by family history), while in the remaining two it was inherited through maternal transmission (1 of 2 confirmed by testing).

Other Causes of Death

The cause of death in the remaining 32 subjects is shown in Table 1. Cause of death and absence of pancreatic cancer were confirmed in 20/32 subjects by family members who

could be re-contacted (62.5%). Non-malignant pancreatic causes of death were reported as the underlying cause of death in 29.6% (8/27) of the remaining deaths in symptomatic carriers, 75% (6/8) of which were confirmed by family members as non-malignant disease (5 by FDRs). Extrapancreatic malignancy was the underlying cause of death in 21.9% of non-pancreatic cancer deaths (7/32), 3 of which were confirmed by family members (2 by FDRs) as non-pancreatic primaries and 2 for which family members were unsure if it may have been a metastasis (Figure 3). Considering the possibility that these 7 extrapancreatic cancer deaths and the 2 unconfirmed deaths from non-malignant pancreatic disease had pancreatic primaries (14 total possible cases), the risk for pancreatic cancer may be as high as 10.9% at 70 years (95% CI 6.5–34.6%) (Supplementary Table 1). Taking the extreme assumption that all decedents had pancreatic cancer, the risk would be as high as 22.9% (95% CI 12.4–32.2%) at 70 years.

DISCUSSION

This study represents the largest prospectively ascertained cohort of HP in the United States. A core *PRSSI* mutation was detected in over 90% of families meeting criteria for HP, with a high penetrance. Overall survival in *PRSSI* carriers appears to be similar to the general population. Although pancreatic cancer risk in *PRSSI* carriers was similar to previous reports (SIR 59; CI 95% 19–138), the estimated cumulative risk for death related to pancreatic cancer at age 70 years was much lower (7.2%, log-log CI 95% 0–15.4).

Internationally, the majority of *PRSSI* kindreds have been identified in the USA (13, 29, 30) and Europe (4, 31, 32), though few have also been reported from Japan (33), South America (34, 35), and Thailand (36). To date, HP has not been reported in patients of African ancestry. As in previous reports, the most common *PRSSI* mutations identified were R122H (83.9%) and N29I (11.5% of *PRSSI* HP cases) (1, 3). Previous reports have demonstrated that gene x gene interactions confer an increased risk for CP, such as through co-inheritance of defects in CFTR bicarbonate conductance and variants in *SPINK1* (37, 38). However, preliminary genetic analysis suggested a low power in this study to determine the influence of co-existing variants in *SPINK1*, *CTRC*, and *CFTR* on survival and pancreatic cancer risk in *PRSSI* carriers. With respect to cancer risk, a recent study of mouse models of pancreatic chronic inflammation found that all mice lacking pancreatic TP53 developed pancreatic cancer, compared to none of the TP53 wildtype mice (39), suggesting that inflammation alone is not sufficient to cause pancreatic cancer. Furthermore, another HP study found that the grade of dysplasia and number of PanIN lesions in HP pancreata does not correlate with age, smoking, calcifications, fibrosis, or inflammation (40). Together, these findings suggest that additional genetic variants in patients with chronic pancreatitis may modify risk for pancreatic cancer.

In contrast to CP of all etiologies (41, 42), like previous reports, the survival of *PRSSI* carriers in our study appears to be similar to the general population (11). Cancer was the most frequent cause of death in *PRSSI* carriers (32.4%), of which less than half (42%) were from pancreatic cancer (41, 43). Interestingly, non-malignant pancreatic disease was mentioned on death reports as the second most common cause (21.6%), followed by

cardiovascular disease (13.5%), which was different than the only other report on HP causes of death (11).

The SIR for pancreatic cancer in this cohort is similar to data reported by Lowenfels, *et al.* in 1997 (SIR 53; 95% CI 23–105)(10), but somewhat lower than the SIR report by the French in 2009 (SIR 87, 95% CI 42–113) (44). No significant difference in SIR was noted between symptomatic and silent *PRSSI* carriers. This finding supports alternative cancer risk mechanisms or the presence of subclinical disease in silent carriers, contributing to inflammation and oncogenesis. Moreover, identification of related individuals with pancreatic cancer suggests the presence of additional genetic factors that may modify familial risk.

Pancreatic cancer is the most dreaded complication of HP -in fact, the risk of pancreatic cancer in previous reports ranges from 18.8–40% by age 70 years (4, 10, 44). Such a high risk has a significant impact not only on patients and their families, but can also influence decision making by physicians and patients. Interestingly, we found the cumulative risk of pancreatic cancer at age 70 years to be much lower than the initial estimate (10), with a more precise estimate reflected by a tighter CI (7.2%; 95% CI 0–15.4).

Assuming all unconfirmed cancers and pancreatitis-related deaths were attributable to pancreatic cancer (11/37), the risk of pancreatic cancer at age 70 years only increases to 9.7% (95% CI 0.5–18). Furthermore, attributing all other confirmed cancer deaths to pancreatic cancer (14/37) increases its risk to only 10.9% (95% CI 6.4–34.6). Finally, assuming all deaths that occurred in our cohort by age 70 were from pancreatic cancer, the cumulative risk is still less than 25% (22.9%, 95% CI 12.4–32.2), which is similar to the EUROPAC estimate (Table 2) (4). There are several potential explanations for this observation – first, few subjects reached age 70 years in two of three previous studies (10, 11, 31 vs. 29 in our cohort), thereby inflating the fraction of patients with pancreatic cancer, and yielding very large CIs of the risk estimates (Table 2); second, initial estimates may have been due to referral bias or lack of genetic testing to identify milder cases; and lastly, it is also possible that new knowledge about the dangers of smoking in the past 2–3 decades may have resulted in significant lifestyle modifications, reducing the risk of cancer. Importantly, the other study with similar numbers of participants living until 70 years (31 v. 29) also found a lower cumulative incidence of 18.8% at 70 years (95% CI 8.6–29) (4), which is within the probable estimates we suggest by including deaths from other cancers and benign pancreatic diseases in our estimates. This observation is significant and should be reassuring to both patients and treating physicians. It also suggests that the actual risk estimates for pancreatic cancer in *PRSSI* subjects may be closer to risk estimates in patients with CP from other causes (5% risk over 20 years for any form of CP) (45) than previously recognized. One study suggests that CP patients with *SPINK1* or *CFTR* mutations have a higher risk for pancreatic cancer than patients with alcoholic pancreatitis (46). A higher risk of pancreatic cancer in patients with genetic pancreatitis when compared with alcohol and other forms of pancreatitis is believed to be due to longer duration of inflammatory milieu in these patients. The reason for differences in our observations from those of Midha *et al.* is unclear. These findings underscore the need for additional studies with a longer duration of follow-up to define the risk of pancreatic cancer in patients with genetic pancreatitis.

Our study has limitations. Although we used patient self-reported data as the primary source to evaluate many of the phenotypic characteristics, this information was supplemented by obtaining medical records for verification as and when feasible. To remove any bias from loss to follow-up, we used SSDI and NDI for an unbiased evaluation of pancreatic cancer and overall survival in all study participants. The potential for false and unidentified matches to National Death Index data could have been increased by the absence of social security numbers for some participants. Furthermore, It is possible that the presence of inaccurate and misclassified cause of death information on death certificates (47) could have resulted in a reduced ability to identify all deceased subjects with a diagnosis of pancreatic cancer, as suggested by the participant with pancreatic cancer whose cause of death was miscoded as prostate cancer. However, in contrast to other cancers, previous studies have shown an 87–90% agreement between pancreatic cancer diagnosis and death certificate cause of death (48, 49). Therefore, it is unlikely that inaccurate and misclassified cause of death information on death certificates (47) resulted in a reduced ability to identify all deceased subjects with a diagnosis of pancreatic cancer. Furthermore, obituary searches and family members were used to reduce both false positives and negatives in such cases. We were able to contact family members to confirm the cause of death in 80% (16/20) of patients reported to have died from any cancer or pancreatitis (Supplementary Figure 3).

In conclusion, this study confirms overall survival and an increased risk of pancreatic cancer for hereditary pancreatitis in the United States. This is the first study to evaluate survival, cause of death, and risk of pancreatic cancer in silent *PRSS1* carriers. While a high cumulative risk for pancreatic cancer in both symptomatic and silent *PRSS1* carriers was identified, this risk was much lower than previous reports, which has direct implications for risk assessment and surgical decision-making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS**1) WHAT IS CURRENT KNOWLEDGE**

- HP has significant variability in age of onset of pancreatitis, severity, and risk for complications.
- Life expectancy in HP patients is similar to the general population.
- HP patients have a high risk for pancreatic cancer—up to 40% by age 70.

2) WHAT IS NEW HERE

- We confirm survival and overall pancreatic cancer risk (SIR) for individuals with HP.
- Survival, cause of death and pancreatic cancer risk is defined in both symptomatic and silent *PRSS1* carriers.
- The cumulative risk of pancreatic cancer in *PRSS1* carriers was lower than previous estimates—7.2% (95% CI 0–15.4%) at age 70.

Figure 1:
Distribution of (A) age at enrollment and (B) age at death or the end of the study (December 31, 2015).

A KM Survival for Symptomatic and Asymptomatic *PRSS1* Carriers **B** KM Cumulative Incidence for Deaths from Pancreatic Cancer **Figure 2:**

(A) Survival and (B) cumulative incidence of pancreatic cancer for all *PRSS1* carriers. Individuals were censored at age on 12/31/2015 (A and B) or death unrelated to pancreatic malignancy (B).

Figure 3:

Classification Tiers for Possible Cases of Pancreatic Cancer Five cases of pancreatic cancer we identified from death certificates or medical records. An additional 6 cases were identified as possibly pancreatic cancer according to cause of death – 2 unconfirmed extrapancreatic malignancies (brain and lung), 2 extrapancreatic malignancies for which family members were unsure of a possible pancreas primary (ovary and lung), and 2 unconfirmed non-malignant pancreatic disease. An additional 3 cancer deaths (ovary, gallbladder, stomach) were confirmed as extrapancreatic malignancies by family members.

Finally, a total of 37 deceased *PRSSI* carriers were identified, 22 of which were deceased before age 70.

*Area of circles is not to scale

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Table 1:Cause and Age of Death in *PRSS1* Carriers

Category	Underlying Cause of Death	Symptomatic (y/n)	Age at Death
Pancreatic Cancer	1 Malignant neoplasm of pancreas, unspecified [†]	yes	51
	2 Malignant neoplasm of pancreas, unspecified [†]	yes	74
	3 Malignant neoplasm of pancreas, unspecified [†]	yes	76
	4 Malignant neoplasm of pancreas ^{*†}	no	69
	5 Malignant neoplasm of pancreas, unspecified [†]	no	69
Other Cancer	6 Malignant neoplasm of unspecified part of bronchus or lung ^{†‡}	yes	51
	7 Malignant neoplasm of unspecified part of bronchus or lung	yes	79
	8 Malignant neoplasm of ovary [†]	yes	55
	9 Malignant neoplasm of ovary ^{†‡}	yes	77
	10 Malignant neoplasm of gallbladder [†]	yes	74
	11 Malignant neoplasm of stomach, unspecified [†]	no	72
	12 Malignant neoplasm of brain, unspecified	no	77
Non-malignant Pancreatic Disease	13 Acute pancreatitis, unspecified [†] Cardiovascular disease reported by family	yes	44
	14 Acute pancreatitis, unspecified [†]	yes	48
	15 Other chronic pancreatitis [†]	yes	38
	16 Other chronic pancreatitis [†]	yes	39
	17 Other chronic pancreatitis [†]	yes	44
	18 Other chronic pancreatitis	yes	48
	19 Other chronic pancreatitis [†]	yes	51
	20 Disease of pancreas, unspecified	yes	34
Cardiovascular Disease	21 Acute myocardial infarction, unspecified [†]	yes	43
	22 Atherosclerotic heart disease of native coronary artery	yes	56
	23 Heart failure [†]	yes	63
	24 Hypertensive heart disease with heart failure [†]	yes	85
	25 Acute myocardial infarction [†]	no	82
Endocrine	26 Type 1 Diabetes Mellitus with Neurological Complications [†]	yes	25
	27 Type 1 diabetes mellitus without complications [†] (and cardiovascular disease)	yes	75
	28 Hypoglycemia, Unspecified	yes	75

	Category	Underlying Cause of Death	Symptomatic (y/n)	Age at Death
29	Pulmonary	Chronic obstructive pulmonary disease, unspecified [†]	yes	85
30	Cerebrovascular	Stroke (reported by family) [†]	yes	83
31		Acute, but Ill-defined Cerebrovascular Disease	no	95
32	Renal	Chronic kidney disease, unspecified	yes	81
33		Accidental Injury	yes	17
34		Assault	yes	42
35	Other/External [†]	Accidental Poisoning	yes	44
36		Pneumonia	yes	50
37		Alcohol Abuse [†]	no	53

* Misdiagnosed as prostate cancer on death certificate

[†] Family members contacted

[†] Family members unsure if there may have been a pancreas cancer primary

Table 2:

Incidence of Pancreatic Cancer in Previous Studies

Study Population	SIR (95% CI)	CI at age 70 (95% CI)	% with a <i>PRSSI</i> Mutation	No. of Pancreatic Cancer Cases	No. at risk at age 70
This Report * USA	59 (19–138)	7.2% (0–15.4%)	100%	5	29
Lowenfels, et al. (1997) International	53 (23–105)	40% (9–71%)	Unknown	8	10
Howes, et al. (2004) EUROPAC	67 (50–82)	18.8% (8.6–29%)	78%	26	31 [†]
Rebours, et al. (2009) France	87 (42–113)	(at age 75: 53.5% [7–76%])	68%	10	11

* includes symptomatic (n=181) and silent carriers (n=36)

[†] R122H, N29I and negative *PRSSI* mutation status only