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Nationwide survey of hereditary pancreatitis in Japan

Atsushi Masamune[1] · Kazuhiro Kikuta[1] · Shin Hamada[1] · Eriko Nakano[1] ·
Kiyoshi Kume[1] · Ayano Inui[2] · Toshiaki Shimizu[3] · Yoshifumi Takeyama[4] ·
Masaki Nio[5] · Tooru Shimosegawa[1]

Abstract

Background Hereditary pancreatitis (HP) is a rare cause of chronic pancreatitis. We here report a nationwide survey to clarify the epidemiological, genetic, and clinical features of HP in Japan.

Methods Target subjects were patients with HP and their family members who had visited selected hospitals between 2005 and 2014. This study consisted of two-stage surveys; patients with HP were identified by the first questionnaire and their clinical features were assessed by the second questionnaire.

Results Two hundred seventy-one patients (153 males and 118 females) in 100 families diagnosed based on the Japanese criteria or 231 patients (131 males and 100 females) patients in 80 families based on the EUROPAC criteria were reported. Of the families undertaking genetic tests, 41% had the *PRSS1* mutations (p.R122H 33%, p.N29I 8%) and 36% had the *SPINK1* mutations (p.N34S 22%, c.194+2T>C 14%, p.P45S 1%). The mean age at symptom onset was 17.8 years. The cumulative rates of pancreatic exocrine insufficiency and diabetes mellitus were 16.1 and 5.5% at 20 years old, and 45.3 and 28.2% at 40 years, respectively. Forty-four percent of the patients underwent endoscopic treatment and/or surgery. The cumulative rate of pancreatic cancer diagnosis was 2.8% at 40 years old, 10.8% at 60 years, and 22.8% at 70 years.

Conclusions HP was characterized by early disease onset, frequent development of pancreatic exocrine insufficiency and diabetes mellitus, requirement of endoscopic treatment and/or surgery, and increased risk of pancreatic cancer. *PRSS1* and *SPINK1* mutations serve as genetic background for HP in Japan.

Keywords Chronic pancreatitis · Pancreatic cancer · Recurrent pancreatitis · Trypsin · Trypsinogen

Abbreviations
CI	Confidence interval
CP	Chronic pancreatitis
DM	Diabetes mellitus
HP	Hereditary pancreatitis
EUROPAC	European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer
PC	Pancreatic cancer
PEI	Pancreatic exocrine insufficiency
RAP	Recurrent acute pancreatitis
SD	Standard deviation

✉ Atsushi Masamune
amasamune@med.tohoku.ac.jp

1   Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

2   Department of Pediatric Hepatology and Gastroenterology, Eastern Yokohama Hospital, Yokohama, Japan

3   Department of Pediatrics, Juntendo University, Tokyo, Japan

4   Department of Surgery, Faculty of Medicine, Kindai University, Osaka, Japan

5   Department of Pediatric Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

Introduction

Hereditary pancreatitis (HP) is a rare cause of chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP), first described in 1952 [1–3]. In 1996, Whitcomb et al. [4] identified the p.R122H mutation in the cationic trypsinogen (*PRSS1*) gene as a cause of HP. Subsequently, other

pathogenic *PRSS1* mutations such as the p.N29I and p.A16 V mutations have been reported [5]. Because HP is a rare clinical entity, information about its epidemiological and clinical characteristics is rather limited. There have been two large studies from Europe reporting the clinical and genetic features of HP [6, 7]. These studies showed that most of the patients had the *PRSS1* mutations. Thereafter, a smaller study from Denmark [8] showed that HP was associated with the p.N34S mutation in the serine protease inhibitor Kazal type 1 (*SPINK1*) gene as well. Mutations in the *SPINK1* gene are thought to diminish protection against prematurely activated trypsin, and are thereby linked to trypsin-related pancreatic injury [9, 10]. Because the genetics of pancreatitis differs among different populations [11, 12], it is important to clarify the genetic and clinical features of HP in other populations, especially in East Asia. Since 2015, the Japanese government has designated HP as an intractable disease that qualifies for financial support of the medical expenses (www.nanbyou. or.jp). This study aimed to clarify the epidemiological, genetic, and clinical profiles of HP in Japan.

Methods

We conducted a two-staged postal survey. The first survey was to determine the number of patients with HP, and the second survey was conducted to obtain detailed clinical information. This study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine (article#: 2014-1-548 and 2017-1-196).

First-stage survey

Target subjects were patients with HP and their family members who had visited selected hospitals between January 1, 2005 and December 31, 2014. The surveyed hospitals were extracted from the Hospital Yearbook, 2012 (R&D Co, Ltd, Tokyo, Japan). The questionnaire was sent to 2375 departments of gastroenterology certified by the Japanese Society of Gastroenterology, departments of gastroenterology and pediatrics in hospitals having more than 200 beds, children's hospitals, and those who requested genetic testing for pancreatitis-associated mutations to our departments (Tohoku University and Juntendo University) between 2005 and 2014. In the first survey, a simple questionnaire was sent to each department asking the number of patients with HP who visited between 2005 and 2014.

Second-stage survey

Requests for detailed clinical information including sex, age, age at the disease onset, clinical symptoms,

treatments, and development of pancreatic cancer (PC) were sent to those departments responding that they had patients with HP between 2005 and 2014 on the first questionnaire. Information about the family history was also requested.

Diagnosis of HP

According to the Japanese diagnostic criteria [13], a diagnosis of HP could be made if the patient had RAP or CP, with a family history of two or more affected patients irrespective of generation, with at least one of the patients having no known etiological factors and, in the case of siblings only, the age at onset is before 40 years. Alternatively, a patient having the p.R122H or p.N29I mutation in the *PRSS1* gene is diagnosed as having HP even in the absence of family history of pancreatitis.

The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) trial has defined HP as there being two first-degree relatives, or three or more second-degree relatives, in two or more generations with RAP and/or CP, for which there were no predisposing factors [6]. Basically, the analyses of subjects diagnosed according to the Japanese criteria are presented unless otherwise specified.

Definitions

Pancreatic exocrine insufficiency (PEI) was diagnosed in the case of clinical steatorrhoea or the need for long-term oral pancreatic enzyme supplements. Diabetes mellitus (DM) was diagnosed if the fasting plasma glucose concentration was ≥ 126 mg/dl, casual plasma glucose ≥ 200 mg/dl, HbA1C $\geq 6.5\%$, or 2-h plasma glucose value of ≥ 200 mg/dl in 75 g oral glucose tolerance test [14].

Genetic analysis

After written informed consent was obtained, peripheral blood was collected and genomic DNA was extracted. All exons and flanking introns of the *PRSS1* and *SPINK1* genes were analyzed by Sanger sequencing as previously reported [9, 15, 16]. If no pathogenic *PRSS1* or *SPINK1* mutations were found, at least one affected family member underwent comprehensive analysis of the additional pancreatitis-associated genes including chymotrypsin C (*CTRC*) and carboxypeptidase A1 (*CPA1*) by targeted next-generation sequencing using the HaloPlex Target Enrichment System (Agilent Technologies, Santa Clara, CA, USA) [17]. If any non-synonymous or splice-site variant was identified,

Sanger sequencing was performed to confirm the presence of the variant, as previously reported [18, 19].

Statistical analysis

Data are shown as mean ± standard deviation (SD) or median with 95% confidence interval (CI). Unknown or undescribed items were excluded from the statistical analysis. Continuous variables were compared using Student's t test. The Kaplan–Meier survival analysis was used to estimate the cumulative rates of patients with PEI, DM, requirement for intervention (endoscopic treatment and/or surgery), and the diagnosis of PC. Cumulative rates over time were compared with the log-rank test according to the mutation status. A two-sided P value of less than 0.05 was considered significant. All statistical analyses were performed using the SPSS version 20.0 statistical analysis software (SPSS Inc., Chicago, IL, USA).

Results

Of 2375 departments, 1358 departments responded to the first-stage survey (response rate 57.2%). In the second-stage survey, 271 patients (153 males and 118 females) in 100 families based on the Japanese criteria or 231 patients (131 males and 100 females) in 80 families based on the EUROPAC criteria were reported. Three sporadic cases without family history of pancreatitis were diagnosed as having HP according to the Japanese diagnostic criteria due to the presence of the pathogenic PRSS1 mutations (two cases with the p.R122H mutation and one with the p.N29I mutation).

Genetic background

Seventy-three of 100 (73%) HP families based on the Japanese criteria, or 59 of 80 (73.8%) families diagnosed based on the EUROPAC criteria, undertook genetic tests for the PRSS1 and SPINK1 mutations. Seventy-four percent of the families had the PRSS1 or SPINK1 mutations, but 26% of the families were negative for these mutations (Table 1). Among the families who underwent genetic analysis, 41% had the PRSS1 mutations. The p.R122H was the most common PRSS1 mutation, followed by the p.N29I mutation. Thirty-six percent of the families diagnosed according to the Japanese criteria or 29% of the families according to the EUROPAC criteria had the SPINK1 mutations. The p.N34S was the most common SPINK1 mutation, and the intronic mutation c.194+2T>C (IVS3+2T>C) was also frequently found. One family had

the SPINK1 p.P45S mutation, which was previously reported in a patient with early-onset idiopathic CP in Japan [20]. Among the families without the PRSS1 or SPINK1 mutations, one family had the p.V251M mutation in the CPA1 gene [19].

Age at symptom onset

The age at symptom onset was reported in 192 patients. Most patients developed symptoms before they were 30 years old, but some patients developed symptoms after they were 40 years old (Fig. 1). The mean (±SD) age at symptom onset was 17.8 (±13.8) years old. Forty-five (23.4%), 67 (34.9%), and 131 (68.2%) patients developed symptoms by the time they were 5, 10, and 20 years old, respectively.

We compared the age at symptom onset according to the mutation status. Information of both the mutation status and the age at the symptom onset was obtained in 144 patients (Table 2). The age at symptom onset was not different between the patients carrying the PRSS1 p.R122H mutation and those carrying the PRSS1 p.N29I mutation ($P = 0.27$), or between those carrying the SPINK1 p.N34S mutation and the SPINK1 c.194+2T>C mutation ($P = 0.57$). Patients with the PRSS1 mutations had significantly earlier symptom onset than those carrying the SPINK1 mutations ($P = 0.003$) or than those without the PRSS1 or SPINK1 mutations ($P = 0.008$). The age at symptom onset was not different between the patients with the SPINK1 mutation and those without the PRSS1 or SPINK1 mutations ($P = 0.74$).

Development of PEI

Information about the presence or absence of PEI was available in 139 patients, all with the age at PEI development or absence of PEI. Fifty-four (38.8%) had PEI with the remaining 85 patients being censored. The cumulative rate of PEI was 3.2% at 10 years of age, 16.1% at 20 years, 28.9% at 30 years, 45.3% at 40 years, 56.9% at 50 years, and 69.3% at 60 years (Fig. 2a). The overall median (95% CI) time to PEI was 42 (38, 46) years.

We compared the age at PEI onset according to the mutation status in 103 patients where both information was available. The median time to PEI was 35 (26, 44) years in the patients carrying the PRSS1 mutation ($n = 55$), 42 (28, 57) in those carrying the SPINK1 mutations ($n = 24$), and 53 years in those without the PRSS1 or SPINK1 mutations ($n = 24$) (Fig. 2b). The age at PEI onset was significantly earlier in patients carrying the PRSS1 mutations than in those without the PRSS1 or SPINK1 mutations ($P = 0.022$). Of note, patients carrying the PRSS1

Table 1 Genotypes of families with HP in Japan

	Japanese criteria	EUROPAC criteria
Number of families	100 (100%)	80 (100%)
Genotype tested	73 (73.0%)	59 (73.8%)
PRSS1 or *SPINK1* mutation positive	54 (74.0%)	41 (69.5%)
PRSS1 or *SPINK1* mutation negative	19 (26.0%)[a]	18 (30.5%)
CPA1 p.V251M	1 (1.4%)	1 (1.7%)
PRSS1 mutation positive	30 (41.1%)	25 (42.4%)
PRSS1 p.R122H	22 (30.1%)	20 (33.9%)
PRSS1 p.N29I	6 (8.2%)	4 (6.8%)
PRSS1 p.R122H/*SPINK1* p.N34S	1 (1.4%)[b]	0 (0%)
PRSS1 p.R122H/*SPINK1* c.194+2T >C	1 (1.4%)[b]	1 (1.7%)[a]
SPINK1 mutation positive	26 (35.6%)	17 (28.8%)
SPINK1 p.N34S	13 (17.8%)	9 (15.3%)
SPINK1 c.194+2T>C	7 (9.6%)	5 (8.5%)
SPINK1 p.P45S	1 (1.4%)	1 (1.7%)
SPINK1 p.N34S/c.194+2T>C	3 (4.1%)	1 (1.7%)
PRSS1 p.R122H/*SPINK1* p.N34S	1 (1.4%)[b]	0 (0%)
PRSS1 p.R122H/*SPINK1* c.194+2T>C	1 (1.4%)[b]	1 (1.7%)[a]

[a] Includes a family carrying the *CPA1* p.V251 M mutation

[b] These cases are listed in duplicate in the *PRSS1* mutation-positive and *SPINK1* mutation-positive columns
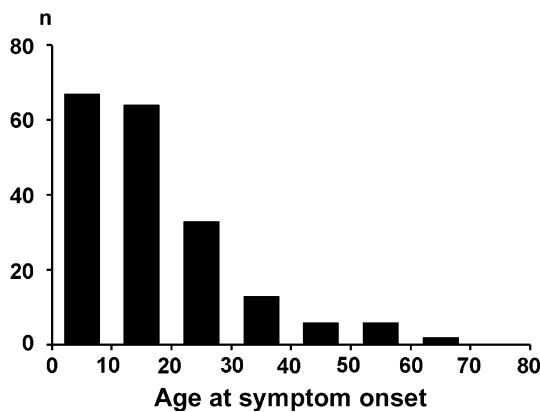
Fig. 1 Distribution of the age at symptom onset in patients with HP. *n* number of patients

p.R122H mutation developed PEI significantly earlier than those without the *PRSS1* or *SPINK1* mutations ($P = 0.015$). The age at PEI onset was not significantly different between the patients with the *PRSS1* mutations and those with the *SPINK1* mutations ($P = 0.30$).

Development of DM

Information about the presence or absence of DM was available in 139 patients, along with the age at DM onset if any. Thirty (21.6%) patients had DM with the remaining 109 patients being censored. The cumulative rate of DM was 1.6% at 10 years of age, 5.5% at 20 years, 13.2% at 30 years, 28.7% at 40 years, 36.0% at 50 years, and 53.1% at 60 years (Fig. 3a). The overall median (95% CI) time to DM was 58 (52, 64) years.

We compared the age at DM onset according to the mutation status in 104 patients where both information was available. The median time to DM was 42 (36, 48) in the patients carrying the *PRSS1* mutation ($n = 55$), 61 (40, 82) in those carrying the *SPINK1* mutations ($n = 24$), and 58 (27.8, 88.2) years in those without the *PRSS1* or *SPINK1* mutations ($n = 25$) (Fig. 3b). The age at DM onset was not significantly different among the types of mutation status. Even if the patients were stratified by the specific mutation types such as the *PRSS1* p.R122H, it was not significantly different.

Endoscopic treatments and surgery

Symptomatic CP often requires endoscopic treatment or surgery. Information about the presence or absence of endoscopic treatment and/or surgery was available in 155 patients. Sixty-eight (43.9%) patients underwent endoscopic treatment and/or surgery, with the remaining 87 patients being censored. Out of the 68 patients, 37 (54.4%) patients underwent endoscopic treatment alone, 27 (39.7%) patients underwent surgery as a first approach, and four (5.9%) patients received a step-up approach. Among the 31

Table 2 Age at disease onset according to the genotype

| Genotype	Number of patients	Age at disease onset (mean ± SD)
PRSS1 p.R122H positive	61[a, b]	12.8 ± 9.1
PRSS1 p.N29I positive	10	9.4 ± 8.6
SPINK1 p.N34S positive	25[b, c]	18.1 ± 11.9
SPINK1 c.194+2T>C positive	17[a, c]	20.7 ± 17.4
SPINK1 p.P45S positive	2	25.0 ± 0.0
CPA1 p.V251M positive	3	14.3 ± 17.0
PRSS1 mutation positive	71[a, b]	12.3 ± 9.0
SPINK1 mutation positive	41[a, b, c]	20.0 ± 14.2
PRSS1 or *SPINK1* mutation negative	32[d]	21.3 ± 17.2

[a] Includes two cases carrying *PRSS1* p.R122H and *SPINK1* c.194+2T>C mutations

[b] Includes a case with *PRSS1* p.R122H and *SPINK1* p.N34S mutation

[c] Includes three cases with *SPINK1* p.N34S and c.194+2T>C mutations

[d] Includes three cases with *CPA1* p.V251 M mutation

Fig. 2 Cumulative rates of pancreatic exocrine insufficiency (PEI) were calculated using the Kaplan–Meier method in **a** 139 patients with HP and **b** 103 patients with HP according to the mutation status (*PRSS1* mutation, *SPINK1* mutation, and absence of mutations in both genes). Censored subjects are indicated on the Kaplan–Meier curve as *tick marks*
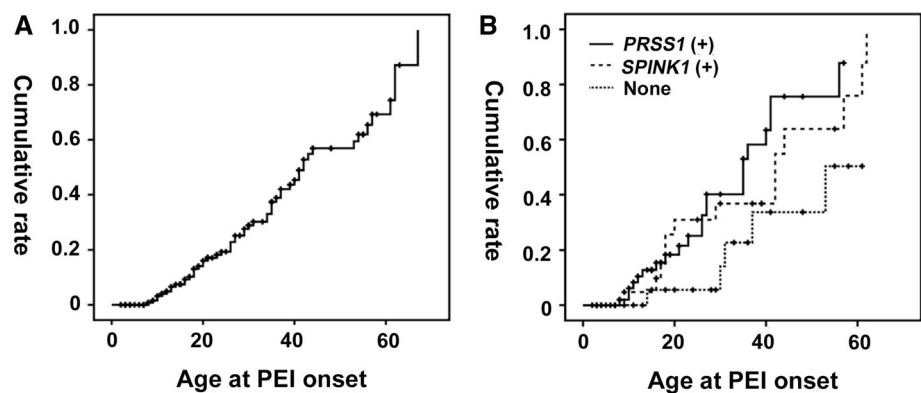
Fig. 3 Cumulative rates of diabetes mellitus (DM) were calculated using the Kaplan–Meier method in **a** 139 patients with HP and **b** 104 patients with HP according to the mutation status (*PRSS1* mutation, *SPINK1* mutation, and absence of mutations in both genes). Censored subjects are indicated on the Kaplan–Meier curve as *tick marks*
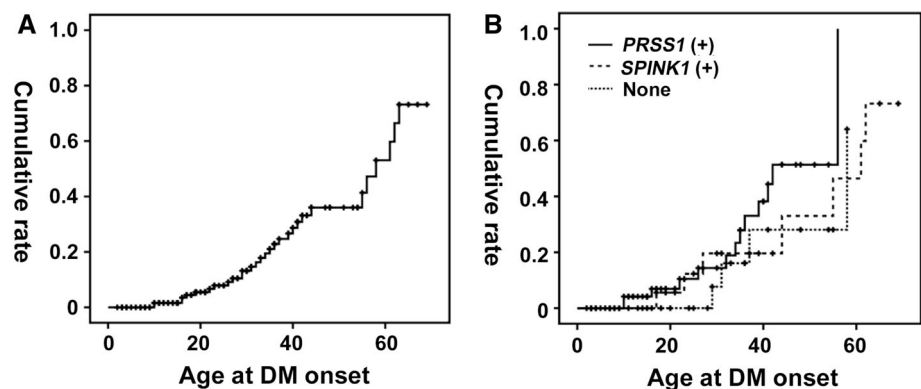
patients who received surgery, 14 underwent drainage operations such as pancreatojejunostomy (*n* = 8) and Frey procedure (*n* = 6), and two patients underwent pancreatectomy. Type of surgery was not described in 15 cases. The time of the initial intervention was not available in three patients, and the remaining 152 patients were further analyzed. The cumulative rate of intervention was 4.9% at 10 years of age, 20.5% at 20 years, 49.0% at 40 years, and 67.4% at 60 years (Fig. 4a). The overall median (95% CI)

time to intervention was 42 (30, 54) years. In the case of surgery, the cumulative rate was 2.8% at 10 years of age, 10.1% at 20 years, 25.2% at 40 years, and 28.1% at 60 years (Fig. 4b). The cumulative rates of endoscopic treatment were 2.0% at 10 years of age, 12.3% at 20 years, 29.0% at 40 years, and 43.0% at 60 years (Fig. 4c).

We compared the time to intervention according to the mutation status in 114 patients, where both information was available. Patients without the *PRSS1* or *SPINK1*

Fig. 4 Cumulative rates of intervention (**a**, **d**), surgery (**b**, **e**), and endoscopic treatment (**c**, **f**) were calculated using the Kaplan–Meier method in 152 (**a**–**c**) patients with HP and 114 (**d**–**f**) patients with HP according to the mutation status (*PRSS1* mutation, *SPINK1* mutation, and absence of mutations in both genes). Censored subjects are indicated on the Kaplan–Meier curve as *tick marks*
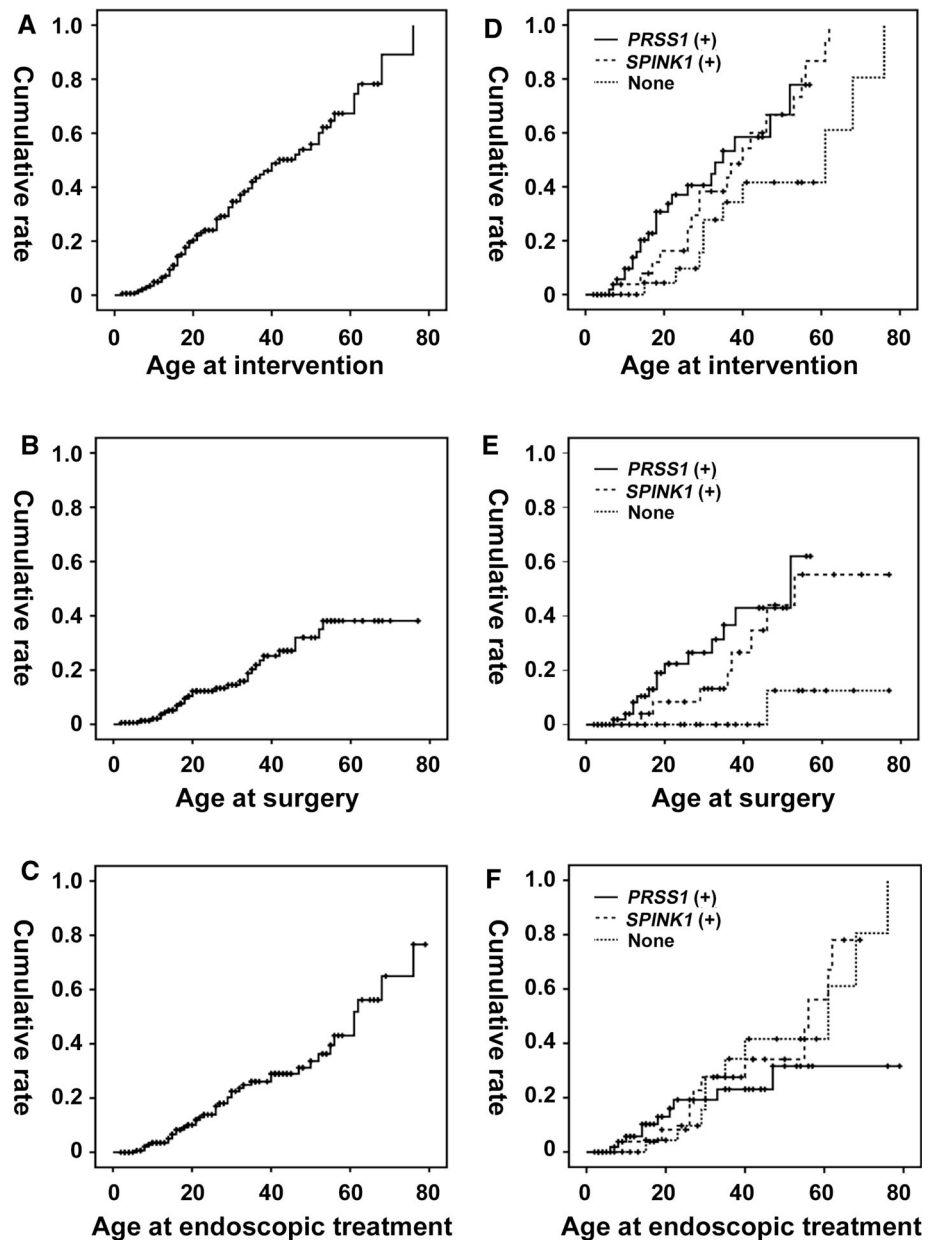
mutations ($n = 29$) had significantly longer time to intervention ($P = 0.024$ vs. *PRSS1* mutation-positive patients ($n = 56$); $P = 0.025$ vs. *SPINK1* mutation-positive patients ($n = 29$)) (Fig. 4d). This trend was more evident in the case of surgery ($P = 0.003$ vs. *PRSS1* mutation-positive patients; $P = 0.018$ vs. *SPINK1* mutation-positive patients) (Fig. 4e). Time to surgery was not different between the patients carrying the *PRSS1* mutations and those with the *SPINK1* mutations ($P = 0.31$). Time to endoscopic treatment was not significantly different among the types of mutation status (Fig. 4f).

We examined the impact of surgery on the time to development of PEI and DM in 139 patients, where required information was available. The median (95%CI)

time to PEI was 27 (17, 37) years in the patients who underwent surgery ($n = 25$) and 56 (43, 69) years in patients without surgery ($n = 114$). Patients who underwent surgery developed PEI earlier than those without surgery ($P < 0.001$). On the other hand, time to DM development was not different regardless of the surgery ($P = 0.62$).

Diagnosis of PC

Information about the presence or absence of PC diagnosis was available in 158 patients. PC was diagnosed in seven (4.4%) patients, five males and two females, with the

remaining 151 patients being censored. The median age at diagnosis of PC was 45 years (range, 30–65 years). Among the seven patients who developed PC, three had the *SPINK1* p.N34S mutation and one had the *PRSS1* p.R122H mutation. *PRSS1* or *SPINK1* mutations were not detected in one patient, and two patients had not undertaken genetic tests. Age at symptom onset was reported in five cases. Duration between the symptom onset and diagnosis of PC varied: simultaneously, 7, 19, 20, and 22 years. The cumulative rate of PC was 2.8% at 40 years of age, 7.1% at 50 years, 10.8% at 60 years, and 22.8% at 70 years (Fig. 5).

Discussion

There have been two major studies aimed at characterizing the clinical features of HP, both from Europe [6, 7]. In 2004, 418 patients with HP across multiple countries in Europe were characterized [6], and in 2009, 200 French patients with HP were evaluated [7]. To our knowledge, this is the first comprehensive study of HP patients outside Europe. We here collected information of 271 patients in 100 families diagnosed based on the Japanese criteria or 231 patients in 80 families based on the EUROPAC criteria. In the latest nationwide epidemiological survey of CP in Japan, the estimated number of patients with CP was 66,980 [21]. Among the 1734 CP cases reported for the second-stage survey, only 11 (0.6%) HP cases were reported. The estimated number of patients with HP was 425, corresponding to the prevalence of 0.35/100,000 persons. Our results are roughly consistent with the estimated number of patients with HP in Japan. In the French

Fig. 5 Cumulative rate of pancreatic cancer (PC) diagnosis was calculated using the Kaplan–Meier method in 158 patients with HP. Censored subjects are indicated on the Kaplan–Meier curve as *tick marks*

cohort, the nationwide prevalence of HP was 0.3/100,000 [7]. In Denmark, the estimated prevalence of HP was 0.57/100,000 for symptomatic HP patients and 0.13/100,000 for carriers of the *PRSS1* mutations [8]. The prevalence of HP in Japan, therefore, appears to be similar to that in Europe.

In this study, *PRSS1* and *SPINK1* mutations were found in 41 and 36% of the families, respectively. The proportion of *PRSS1*-associated HP was smaller in Japan than in Europe. In the EUROPAC study [6], 52% families had the *PRSS1* p.R122H, 21% had the *PRSS1* p.N29I, and 19% had no *PRSS1* mutations. In the French study [7], *PRSS1* mutations were found in 68% (p.R122H 78%, p.N29I 12%, others 10%). In Denmark, *PRSS1* mutations were found in 9/13 (69.2%) families [8]. In a recent report from Poland, *PRSS1* mutations were found in 33/41 (80.5%) patients with HP [22]. These studies indicate that most of the HP patients in Europe have *PRSS1* mutations. On the other hand, the proportion of *SPINK1*-associated HP appeared to be higher in Japan. Mutational analysis of the *SPINK1* gene was not reported in the EUROPAC study [6]. *SPINK1* mutations were found in 13% of the patients with HP in the French series, although the specific types of *SPINK1* mutations were unknown [7]. In the smaller study from Denmark, the *SPINK1* p.N34S mutation was found in 4/13 (30.8%) families, with 1 family having both the *PRSS1* p.A16 V and *SPINK1* p.N34S mutations [8]. These studies support the notion that geographical heterogeneity exists in the genetics of pancreatitis [11, 12]. The *SPINK1* c.194+2T>C mutation is a unique pancreatitis-associated mutation frequently found in East Asia including Japan [12]. This mutation causes a skipping of exon 3, resulting in the loss of the trypsin binding site in the mutated SPINK1 protein [10]. Importantly, 26% of the families had no detectable *PRSS1* or *SPINK1* mutations despite the clear family history. Except for one family carrying the *CPA1* p.V251M mutation, no pathogenic mutations in the known pancreatitis-associated genes were identified. Comprehensive whole-exosome or whole-genome analysis of these families by aid of the next-generation sequencers would lead to the identification of novel pancreatitis-associated genes.

Although the development of PEI and DM is uncommon before the age of 20, pancreatic exocrine and endocrine insufficiency are the major clinical manifestations in adult patients with HP. Previous studies assessed the association of the mutation type and the disease severity, but the results were inconsistent. Howes et al. [6] reported that the age at onset of the first symptoms was earlier in patients with the *PRSS1* p.R122H mutation. Reborus et al. [7] reported that the clinical profiles including the time to PEI and DM were not associated with the mutation status in the *PRSS1* and *SPINK1* genes. In this study, patients with the *PRSS1* mutations had earlier onset of symptoms than those without
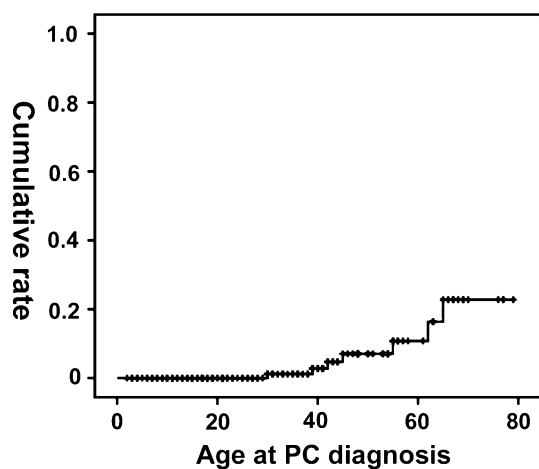
the *PRSS1* mutations. Patients with the *PRSS1* mutations developed PEI earlier than those without the *PRSS1* or *SPINK1* mutations, although the age at DM development did not significantly differ according to the mutation status. These results support the EUROPAC study [6] showing severe phenotypes in *PRSS1*-associated HP patients.

A step-up strategy has become increasingly popular for the treatment of symptomatic patients with CP [23, 24]. This strategy starts with endoscopic treatment and progresses to surgery if endoscopic treatments are unsuccessful or insufficient to resolve symptoms or prevent pancreatitis attacks. The step-up strategy has been applied for the treatment of patients with HP [25, 26]. However, the proportion of the patients who received the step-up approach was unexpectedly low in this study. Out of the 31 patients who underwent surgery, only four were treated with a step-up strategy and the remaining 27 patients received surgery as the first approach. One explanation is that 14 of the 27 patients underwent surgery before the year 2000 when endoscopic treatment was less common and the surgery-first approach was the standard intervention. On the other hand, 37 patients had been treated endoscopically without progressing further to surgery. It would be interesting to see whether patients who had received endoscopic treatment would require surgery in the future.

It is well known that HP is a significant risk factor for PC [27, 28]. In a French cohort, the cumulative rates of PC at 50, 60, and 75 years were 10, 18.7, and 53.5%, respectively [28]. In our survey, the cumulative rate of PC was 7.1% at 50 years, 10.8% at 60 years, and 22.8% at 70 years. This finding suggests that the development of CP is a key factor in determining the prognosis of HP patients. The development of PC was not restricted to the *PRSS1*-associated HP, but was also found in families carrying the *SPINK1* mutations or those without *PRSS1* or *SPINK1* mutation [29]. These results support the notion that long-term inflammation, but not the mutations by themselves, increases the risk of PC in patients with HP. Further studies are warranted to optimize the strategy to screen for the development of PC in patients with HP [30].

In conclusion, we clarified the genetic and clinical features of HP in Japan. HP was characterized by early disease onset, frequent development of PEI and DM, requirement of endoscopic treatment and/or surgery, and increased risk of PC. In addition to *PRSS1*, *SPINK1* mutations serve as genetic background for HP in Japan. Understanding of the natural history would lead to the better management including a step-up approach and improvement of the quality of life of the patients with HP. Further studies are warranted to develop screening tools and preventive measures for PC as well as specific treatments including gene therapy for this intractable disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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