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Review

**Mortality rate and risk factors in patients
with hereditary pancreatitis.
Uni- and multidimensional analysis.**

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Key words

Hereditary pancreatitis – Cationic trypsinogen mutation – PRSS1 – Chronic pancreatitis – Epidemiology – Pancreatic adenocarcinoma – Mortality rate – Mortality risk factors.

Running title: Mortality rate in hereditary pancreatitis.

Study Highlights

What is current knowledge

Hereditary pancreatitis (HP) is a well defined genetic disease due to the mutation of the PRSS1 gene.

HP course is associated with a high risk of pancreatic cancer: 50 to 87 times compared to the general population.

What is new here

Patients with HP do not have an excess mortality risk as compared with the general population.

The mortality risk is not higher irrespective of gender, tobacco use or diabetes mellitus compared to the general population.

Abstract

Patients with hereditary pancreatitis (HP) bear a high risk of pancreatic adenocarcinoma, but their life expectancy remains unknown.

Aim: to assess if the high risk of cancer decrease survival.

Methods: Inclusion criteria were the presence of a PRSS1 mutation with pancreatic symptoms or chronic pancreatitis in at least 2 first degree relatives or 3 second-degree relatives without another cause. Survival rates were assessed according to risk factors. Excess mortality as compared with the general French population was calculated (statistical Esteve model) over 2 periods (20-50 and 50-70 years), according to several risk factors.

Results: The cohort comprised 189 patients. PRSS1 mutations were found in 66%. Nineteen patients died at the median age of 60. Ten deaths were attributable to HP, including 8 pancreatic adenocarcinoma. Global median overall survival was 74 years (95%CI: 71-79) for the whole cohort. Presence of R122H mutation, gender, tobacco consumption in patients older than 18 and diabetes mellitus were not associated with differences in survival. Only patients with pancreatic cancer had a decreased survival ($p=0.008$). Excess mortality risk as compared to the general population was 0.02 % between 20 and 50 years, and 0.61 % between 50 and 70 years (NS). Gender, R122H mutation, diabetes or tobacco use were not associated with excess mortality in these 2 periods.

Conclusion: Despite high risk of cancer, HP patients do not have an excess mortality risk as compared with the general population, irrespective of gender, tobacco use or diabetes mellitus. These data should be brought out to patient's knowledge.

Introduction

Hereditary pancreatitis (HP) is a rare cause of chronic pancreatitis, first described by Comfort and Steinberg in 1952.¹ The origin of this disease is a genetic defect in the cationic trypsinogen PRSS1 gene on the long arm of the chromosome 7 (7q35).²⁻⁴ The first mutation, i.e. R122H, was described in 1996 by Whitcomb et al.⁵ Other mutations in this gene have then been described subsequently, such as N29I, A16V, R122C, R116C...⁶⁻⁸

Natural history of HP has been described in few series.⁹⁻¹³ Inflammatory changes begin at birth because of the genetic origin of the disease. Symptoms start during childhood and HP is a major risk for pancreatic adenocarcinoma. The ratio of standardized incidence (SIR) for pancreatic cancer was estimated between 53 and 87 in patients with HP. The risk is higher in smokers.^{11, 14-16} Physicians in charge of these patients are very often questioned about the risk of HP complications and mortality excess, but no data are hitherto available in the literature. Moreover, patient support groups are asking for scientific studies about HP-related mortality, both for psychological and financial (insurances, credits) purposes. Mortality rates have been published for patients with alcoholic chronic pancreatitis.¹⁷⁻²⁰ An excess mortality compared to the general population (35%) was shown to be mainly due to multivisceral complications of chronic alcoholic and tobacco abuse rather than to chronic pancreatitis itself.^{19, 20} Another study was carried out in 1993 in patients with non alcoholic chronic pancreatitis by Dancour et al.²¹ The authors did not demonstrate an excess risk of mortality compared to the general population.

The aims of the present study were to calculate the excess risk of mortality in HP patients compared to the French general population, according to epidemiological, genetic and clinical criteria and to search for risk factors of mortality in a cohort of HP patients based on a national census.

Patients and Methods

Data source

All patients were recruited from the French cohort of HP patients. This cohort was created by a systematic registration of patients with a known diagnosis of HP in 2005. The methods of cohort creation have already been described elsewhere.¹¹ Briefly, all the genetic laboratories involved in cationic trypsinogen (PRSS1) testing in France accepted to participate in this study and provided the data of all patients with PRSS1 gene mutations. All French pediatricians and gastroenterologists (n= 6,917) were contacted by mail. A 84% total response rate was obtained. Physicians who followed patient(s) with HP were subsequently asked to forward patients' clinical and genetic data. A complete family tree was established with the physician and the patients for all subjects, including at least three generations. Clinical diagnosis reported by patients or family members were verified in all instances by consulting the original medical records. The clinical and genetic records were entirely reviewed by one of us (VR) in each medical center. For deceased patients, index cases and their families were questioned to confirm data obtained from medical files. The agreement from the French Department for Computerized Information Security (Commission Nationale de l'Informatique et des Libertés) was obtained before study initiation on February 4th, 2005 (n° 04.555).

Inclusion criteria

Patients were included in this study if they presented symptoms related to HP: either a detected cationic trypsinogen gene mutation with clinical or morphological manifestations of pancreatitis (genetic and clinical criteria) or if they had chronic pancreatitis with a familial history (genealogical and clinical criteria). A familial history was defined by recurrent acute pancreatitis or chronic pancreatitis occurring in two first degree relatives or three or more second degree relatives, in two or more generations in the absence of precipitating factors.

Other causes of chronic pancreatitis were searched for depending on the clinical and anamnestic context in particular alcohol consumption.

Definitions

The diagnosis of chronic pancreatitis was based on the presence of at least one of the following: pancreatic calcifications as evidenced by plain radiography of the pancreatic area in three projections, CT scan, or endoscopic ultrasonography; moderate to marked pancreatic ductal lesions on pancreatography obtained by endoscopic retrograde or magnetic resonance pancreatography (Cambridge classification)²² or typical histology of an adequate surgical pancreatic specimen.

Acute pancreatitis was defined by acute abdominal pain with increased serum pancreatic enzyme levels over three times the upper limit of normal values.

Diabetes mellitus was diagnosed if a whole venous blood fasting glucose concentration was recorded ≥ 126 mg/dL (6.99 mmol/L) at at least two determinations or > 11.0 mmol/L, post prandially, at one determination. Insulin requirement was defined by the inefficacy of adequate diet (low diet of rapid sugar and fat aliments) and oral drugs in preventing hyperglycemias (biguanids, sulfonylureas, alpha-glucosidase inhibitors) in preventing hyperglycemia.

Pancreatic cancer was confirmed by consulting pathological records for all cases.

Chronic alcoholism was defined by alcohol intake exceeding 6 units/day (60g of pure alcohol per day) in males and 4 units/day (40g per day) in females for at least 2 years.²⁰ Smoking status was categorized as daily smokers if patients had smoked for at least two years (current and ex daily smokers) and non-smokers. The number of cigarettes smoked per day and duration of smoking were recorded and expressed as pack-years (pack-years of smoking were

calculated at the baseline examination as number of cigarettes per day multiplied by number of years of smoking divided by 20).

The follow-up period was defined as the delay between the date of birth and the date of the last visit or death.

Genetic data

All known mutations of the cationic trypsinogen gene (PRSS1), i.e. R122H, N29I, A16V, D22G, K23R, E79K, Q98K, R122C or R116H were considered. Molecular analyses were shared between three French molecular genetic laboratories. For single point mutation, a screening strategy was chosen by these three laboratories in order to find both known and novel variations located in the 5 exons of the PRSS1 gene and the 4 exons of SPINK1 gene by double strand direct sequencing (N=18 patients) or by a screening approach (DGGE) then replaced by DHPLC (N=173)^{23, 24} confirmed by sequencing.^{5, 25, 26} In patients deceased before 1996, PRSS1 mutations were not assessed. Thanks to analyzes of the genealogical tree, a PRSS1 mutation was searched for in the first degree relatives even if they did not have any symptoms.

Study design and data collection

All data were collected directly by reviewing individual medical files, from questionnaires addressed to the physician in charge of the patients and by direct phone contact with the physicians. In case of missing data, the patients (or their relatives when patients were deceased) were directly contacted by phone.

Collected data included genealogical tree, general characteristics (age, gender, smoking status and number of cigarettes smoked per day, alcohol consumption as number of units of alcohol

consumed per day), PRSS1 status, symptoms (occurrence of diabetes mellitus, exocrine insufficiency, pancreatic adenocarcinoma), date and cause of death.

Statistical Analysis

General characteristics were expressed as median and range or percentages. Comparisons of variables were performed using the Kruskal–Wallis test for continuous data and the Chi2 test or the Fisher's exact test for categorical data.

For survival analysis, the end-point used was the date of last contact or death. Overall survival of the whole cohort was estimated by using the Kaplan-Meier method. Survival analysis according to gender, PRSS1 mutation status, smoking habits, occurrence of exocrine and endocrine pancreatic insufficiency and pancreatic cancer, were compared with the Logrank test. A multidimensional analysis was performed using a Cox regression analysis to search for prognostic factors of death in HP patients. The stepwise selection option was used. P values below 0.20 were considered as significant as level of entry in the model.

Excess mortality as compared with the general French population was calculated for patients older than 20 years over two periods, 20-50 (N= 94 patients) and 50-70 years (N= 46 patients). The national mortality tables for the French population were supplied by the Institut National de la Santé et de la Recherche Médicale (INSERM). These tables are based on the entire French population. The maximum likelihood method (Esteve model) was used to estimate the α risk because of the heterogeneity of the cohort for life expectancy.²⁷ The excess mortality was also calculated according to gender, tobacco use, diabetes mellitus and the presence of the main PRSS1 mutation, R122H.

Data were analyzed with the SAS 9.1 statistical software for Windows (SAS Institute Inc., Cary, NC). All statistical tests were two-sided. The critical level of statistical significance was set at $p < 0.05$.

Results

General characteristics of the cohort

The total cohort consisted of 78 families and 189 patients (104 males, 55%). The median age at inclusion was 30 years (range: 1-84). Current or ex daily smokers in the population older than 18 years represented 64 patients. The median tobacco consumption was 12 pack-years. Chronic consumption of alcohol was found in 5% of the patients. Diabetes mellitus was diagnosed in 51 patients, among them 60% required insulin and 40% only oral drugs. The median age at occurrence of endocrine pancreatic insufficiency was 38 year old [14-76]. The general characteristics of the population are summarized in Table 1.

Genetic characteristics of the cohort

A PRSS1 mutation was searched for in 180 patients and found in 125 (66%). PRSS1 mutation status was unknown in 4% because patients were deceased before 1996 and no blood sample was available. PRSS1 mutations are provided in table 1. Patients with or without detected PRSS1 mutations had the same general characteristics (Table 1).

Mortality

Nineteen patients (10%) died. Ten deaths were directly due to HP consequences including eight from pancreatic cancer (42% of deaths) and two from sepsis (one cholangitis and one sepsis after pancreatic surgery). In the remaining patients, the cause of death was not related to HP or PA: natural causes (no identifiable cause of death in 2 patients aged of 72 and 78 year old without specific symptoms at death) n=2, acute cerebral strokes n=2, car crashes n=2, breast cancer n=1, renal cell carcinoma n=1 and unknown cause of death n=1. The median age at death was 62 years [25-84] for the whole cohort and 60 years [40-79] for pts with PA.

Global median overall survival for the entire cohort was 74 years (CI95%: 71-79) (Figure 1). Gender, tobacco use in patients older than 18, exocrine and endocrine pancreatic insufficiency were not associated with significant survival differences. Only pancreatic adenocarcinoma was a risk factor of mortality ($p=0.008$). A multidimensional analysis was performed by a Cox model to search for prognostic factor of survival. Only pancreatic cancer brought out as a risk factor.

Excess mortality risk in HP patients as compared to the general population was 0.02 % between 20 and 50 years (N=90 patients), and 0.61 % between 50 and 70 years (N= 29 patients) (NS). According to gender, corresponding figures were 0.04 % and 1 % in males (NS), and 0.09 % and 0% in females (NS). R122H mutation and tobacco use were not associated with increased death rate in any of the 2 periods.

Discussion

The present study is the first one to provide mortality analysis in patients with HP. It assessed mortality rates compared with the general population and searched for risk factors of mortality. The overall median survival was 74 years. HP patients did not have an excess mortality rate compared to the general population. These results were similar according to gender, mutation status (presence of the R122H mutation), diabetes mellitus or tobacco use. The only risk factor of mortality was the occurrence of cancer. Pancreatic adenocarcinoma was the first cause of death in HP population.

This historical cohort was created in 2005; methods have been published elsewhere.¹¹ Genealogical trees were established for each family in three generations to reduce the selection bias and the risk to miss patients in a family. All the index cases have been interviewed directly or by phone when data were missing in the medical file. Causes of deaths were searched for and all but one were known. Each cause of death was confirmed by analysing medical files or asking directly the physician in charge of the patient. This methodology allowed us to assess the excess mortality in this population. The maximum likelihood approach (the Estève model) was used for two periods.²⁷ The other methods of calculation of crude survival corrected for independent causes of death are subject to various biases when the population is heterogeneous for life expectancy or for the duration of follow up, as in the HP cohort. The proposed maximum likelihood approach eliminates these biases by enabling relevant adjustment for covariates which influence survival.

Several series dealing with mortality were already published in the setting of alcoholic chronic pancreatitis.¹⁷⁻²⁰ The crude mortality rate was 28.8-35% with a similar observation time (median 6.3-9.8 years). All series reported that alcoholics with chronic pancreatitis have an excess mortality compared to the general population with an excess in mortality of 36%

after 20 years.^{17, 20} The reported risk factors were more likely to be related to chronic alcoholic and tobacco consumption than to chronic pancreatitis itself. The main causes of death were alcohol or tobacco related cancers (i.e. oesophagus), liver cirrhosis or hepatocellular carcinoma and also severe infections and postoperative mortality. Chronic pancreatitis itself was the direct cause of death in only 19% of the patients, at variance with the extrapancreatic consequences of chronic alcoholism or smoking habits (53% of the deaths).^{17, 19, 20, 28} Lowenfels et al. evaluated survival among 2015 subjects with chronic pancreatitis treated at seven centers located in six countries in a cohort of patients with alcoholic and non alcoholic chronic pancreatitis.²⁹ Smoking (hazard ratio: 1.4; 95% CI: 1.0-1.9), drinking (hazard ratio: 1.6; 95% CI: 1.2-2.2), or development of cirrhosis (hazard ratio: 2.5; 95% CI: 2.0-3.2) increased the risk of death during the observation period. Others studies clarified the role of chronic pancreatitis itself on mortality, comparing alcoholic and non alcoholic aetiologies.²¹ Dancour et al. compared mortality and risk factors in 37 patients with non alcoholic chronic pancreatitis (NACP) to 319 patients with alcoholic chronic pancreatitis (ACP). The overall survival for NACP was similar compared to the general population but was higher compared with patients with ACP. The excess mortality for ACP was 6%, 11% and 20% after 5, 10 and 15 years of natural course, respectively. The rate of deaths was 15% (versus 2% for NACP) after 15 years of follow up.²¹ Others series reported a higher survival (15%) in patients with NACP than in those with ACP.³⁰ The death rate at 10 years was 10% in the NACP compared to 35% in those with ACP (no chronic pancreatitis related death).³¹ Even if rigorous comparison between these two groups is not easy because of the heterogeneity of the follow up of the NACP patients. Chronic pancreatitis itself had no major influence on prognosis.

The originality of the present study is the cause of chronic pancreatitis. HP is a genetic disease and inflammatory changes begin at birth. Symptoms mainly occur during childhood

and duration of follow up is equivalent to patients' age. The natural history of HP has already been described and HP is a well known risk factor of PA.^{10-14, 16} SIR was estimated between 53 and 87 and increased in smokers. The risk of pancreatic cancer is very high because of the long delay of exposure to inflammatory changes. The present study demonstrated that in spite of this important risk, there is no excess in mortality compared to the general population. This is obviously of utmost importance to reassure patients and their families but also to allow obtaining credit and premium insurance for these patients with chronic disease. These results were expected by patient support groups to put pressure on insurance companies for decreasing very expensive sub primes.

Two main hypotheses might account for these results. Patients with HP require close medical follow up since childhood because of frequent early symptoms (pancreatic pain, acute pancreatitis, steatorrhea and diabetes mellitus). In the cohort, 27% of the patients presented diabetes. Even if long lasting diabetes has an effect on life expectancy, the early medical follow up may decrease the risk of mortality due to diabetes. They might also observe safe life habits to prevent attacks of acute pancreatitis: low fat diet, alcohol abstinence (less than 5% of chronic alcoholics in the cohort). Despite recommendations of the physicians to encourage patients to quit smoking, 64 HP patients aged more than 18 year were current or ex daily smokers. Unfortunately, the evaluation of the impact of these recommendations on the tobacco consumption habits was not possible. However, the median tobacco consumption was moderate and was not associated with chronic alcohol consumption. Patients with HP have probably a lower risk of cardiovascular diseases and alcohol-tobacco induced cancers compared to the global population.

Even if the risk of PA is higher in HP patients, patients with HP do not have an excess mortality risk as compared with the general population, irrespective of gender, tobacco use or

diabetes mellitus. These data should be brought to the knowledge of patients, insurance companies and patient support groups.

For Peer Review

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Disclosure of interests

All the authors have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) his or her actions.

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For Peer Review

Table 1. Baseline characteristics of the patients.

Characteristics	All patients N=189	Patients with PRSS1 mutations N=125	Patients without detected PRSS1 mutation N=64 ^d	p
Age at last news (years) ^a	30 [4-84]	30 [4-84]	31 [5-79]	NS
Male gender (n)	104	73	31	NS
Number of families (n)	78	50	28	
Smokers or ex smokers ^b (n), (md= 16) ^c	64/125	53/89	11/36	NS
Tobacco consumption, (pack-years) ^a	12 [1-100]	11 [1-100]	15 [1-50]	NS
Chronic alcoholism (n), (md=5) ^c	10	7	3	NS
PRSS1 mutations (n)	125	125		
- R122H	-	98		
- N29I	-	14		
- R122C	-	2		
- E79K	-	3		
- K23R	-	2		
- A16V	-	1		
- R116C	-	1		
- K170E	-	1		
- Q98K	-	1		
- 33delTCC	-	1		
- 667 tc	-	1		

^a median and [range]

^b Patients older than 18 year old (N=141/189)

^c md: missing data

^d including 9 patients deceased before 1996, in whom PRSS1 mutation could not be searched for.

Figure 1: Overall survival of the cohort.

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Table 1. Baseline characteristics of the patients.

Characteristics	All patients N=189	Patients with PRSS1 mutations N=125	Patients without detected PRSS1 mutation N=64 ^d	p
Age at last news (years) ^a	30 [4-84]	30 [4-84]	31 [5-79]	NS
Male gender (n)	104	73	31	NS
Number of families (n)	78	50	28	
Smokers or ex smokers ^b (n), (md= 16) ^c	64/125	53/89	11/36	NS
Tobacco consumption, (pack-years) ^a	12 [1-100]	11 [1-100]	15 [1-50]	NS
Chronic alcoholism (n), (md=5) ^c	10	7	3	NS
PRSS1 mutations (n)	125	125		
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- N29I	-	14		
- R122C	-	2		
- E79K	-	3		
- K23R	-	2		
- A16V	-	1		
- R116C	-	1		
- K170E	-	1		
- Q98K	-	1		
- 33delTCC	-	1		
- 667 tc	-	1		

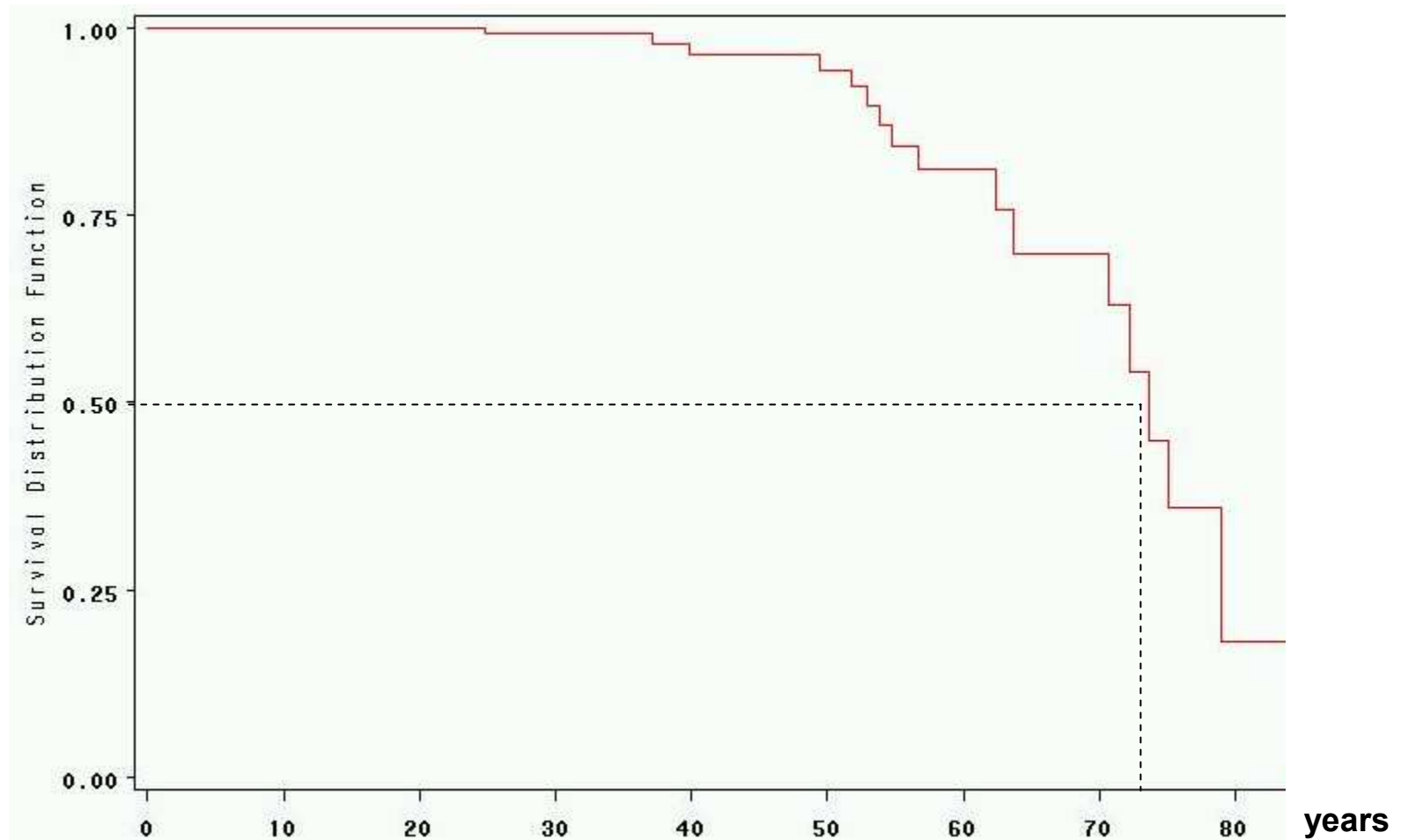
^a median and [range]

^b Patients older than 18 year old (N=141/189)

^c md: missing data

^d including 9 patients deceased before 1996, in whom PRSS1 mutation could not be searched for.

Figure 1: Global survival of the cohort



Patients nb:	189	132	96	66	41	17	9
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