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Survival, surveillance, and genetics in patients with Peutz–Jeghers syndrome: A nationwide study

Anne Marie Jelsig[1] | Thomas van Overeem Hansen[1,2] | Lene Bjerring Gede[1] | Niels Qvist[3,4] | Lise-Lotte Christensen[5] | Charlotte Kvist Lautrup[6] | Jane Hübertz Frederiksen[1] | Lone Sunde[7,8] | Lilian Bomme Ousager[9,10] | Ken Ljungmann[11] | Birgitte Bertelsen[12] | John Gásdal Karstensen[13,14]

[1]Department of Clinical Genetics, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark

[2]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[3]Research Unit for Surgery, Odense University Hospital, Odense, Denmark

[4]University of Southern Denmark, Odense, Denmark

[5]Department of Molecular Medicine, University Hospital of Aarhus, Aarhus, Denmark

[6]Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark

[7]Department of Clinical Genetics, Aalborg University Hospital, Aarhus, Denmark

[8]Department of Clinical Medicine, Aalborg University, Aarhus, Denmark

[9]Department of Clinical Genetics, Odense University Hospital, Odense, Denmark

[10]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[11]Department of Surgery, Aarhus University Hospital, Aarhus, Denmark

[12]Center for Genomic Medicine, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark

[13]Danish Polyposis Registry, Gastrounit, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre, Denmark

[14]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence
Anne Marie Jelsig, Department of Clinical Genetics, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark.
Email: anne.marie.jelsig@regionh.dk

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Abstract

Peutz–Jeghers syndrome (PJS) is an autosomal dominant hereditary polyposis syndrome causing increased morbidity and mortality due to complications of polyposis and the development of cancer. *STK11* is the only gene known to be associated with PJS, although in 10%–15% of patients fulfilling the diagnostic criteria no pathogenic variant (PV) is identified. The primary aim of this study was to identify the genetic etiology in all known PJS patients in Denmark and to estimate the risk of cancer, effect of surveillance and overall survival. We identified 56 patients (2–83 years old) with PJS. The detection rate of PVs was 96%, including three cases of mosaicism (6%). In two patients a variant was not detected. At the age of 40 years, the probabilities of cancer and death were 21% and 16%, respectively; at the age of 70 years these probabilities were 71% and 69%. Most cases of cancer (92%) were identified between the scheduled examinations in the surveillance program. These observations emphasize

that PJS should be regarded as a general cancer predisposition syndrome, where improvement of clinical care is needed.

KEYWORDS
endoscopy, genetics, hereditary, Peutz–Jeghers syndrome, polyp, polyposis, *STK11*

1 | INTRODUCTION

Peutz–Jeghers syndrome (PJS, OMIM175200) is an autosomal dominant polyposis syndrome that has been known as a clinical entity for over a century.[1,2] The syndrome is characterized by gastrointestinal (GI)-hamartomatous polyposis, especially in the small intestines, and an increased risk of various types of cancer. Lifelong surveillance from early childhood is recommended to decrease morbidity and mortality. The risk of cancer has been shown to be age-dependent with a high cumulative risk of 75%–89% at the age of 70 years.[3,4]

The diagnosis of PJS is based on clinical criteria comprising the presence of two or more histopathological characteristic polyps (hamartomatous Peutz–Jeghers (PJ) polyps) and/or mucocutaneous pigmentations. Pigmentations are primarily located on the buccal mucosa and/or fingers, hands, and feet (Figure 1).[5]

Genetic counselling and testing are recommended. With traditional methods, such as Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA), a pathogenic variant (PV), has been detected in the serine/threonine kinase 11 gene, *STK11*, in 85%–90% of patients fulfilling the diagnostic criteria. The detection of a PV makes it possible to perform testing of family members at-risk and prenatal diagnostics.[6,7] The introduction of next generation sequencing (NGS) may increase the yield of detecting PVs as panel based NGS has a higher detection rate of mosaicism and whole genome sequencing (WGS) can detect structural variants (SVs) and/or (deep) intronic variants.

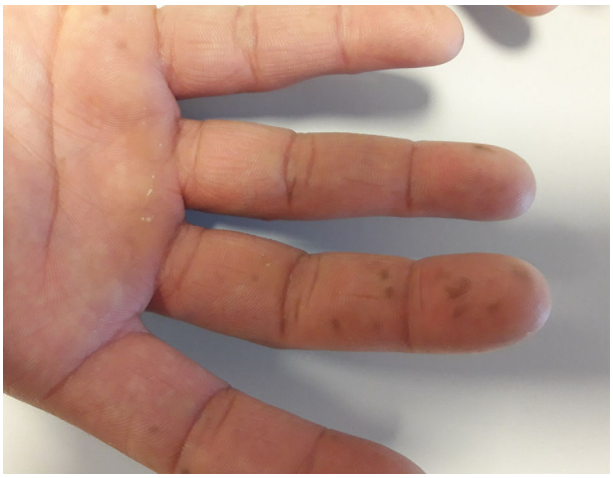


FIGURE 1 Mucocutaneous pigmentations on fingers of a patient with Peutz–Jeghers syndrome. [Colour figure can be viewed at wileyonlinelibrary.com]

The primary aim of this study was to investigate the frequency of PVs in *STK11* among Danish patients with PJS, to search for other genetic causes, and to estimate the frequency of mosaicism for a constitutional PV in *STK11* among patients with PJS. The secondary aim was to estimate the risk of cancer, effect of surveillance and overall survival.

2 | MATERIALS AND METHODS

2.1 | Identification of patients

All Danish genetic departments and laboratories reported patients with a clinical diagnosis of PJS and/or a PV in *STK11*. If the department had information about relatives, for example, children, siblings, or parents, who had been counselled or tested, these data were also collected and relatives with signs or symptoms of PJS and/or a PV in *STK11* were included. In addition, data were retrieved from The Danish Pathology Register, which comprises data from all histopathological examinations carried out in Denmark since 1997, and for some parts of Denmark even earlier. A search was performed using the Danish version of the Systematized Nomenclature of Medicine diagnostic codes for "hamartomatous polyp" and "Peutz-Jeghers syndrome." We also searched for patients who had been registered with both the terms "hamartomatous" and "polyposis" in the histopathology description. The study was approved by The Danish Patient Safety Authority (journal no. 31-1521-329), the Regional Danish Data Protection Agency (journal-no.: P-2020-557/ P-2020-696, The Capital Region of Denmark), and the National Scientific and regional Research Ethics Committee (no-2105809/H-16030776).

2.2 | Inclusion criteria

Patients fulfilling the clinical diagnostic criteria for PJS according to the *Beggs criteria* from 2010[5] were included: (1) Two or more histologically confirmed PJ-polyp in the GI tract, (2) Any number of PJ-polyps detected in one individual who has a family history of PJS within close relative(s), (3) Characteristic mucocutaneous pigmentations in an individual who has a family history of PJS within close relative(s), and/or (4) Any number of PJ-polyps in an individual who also has characteristic mucocutaneous pigmentations.

Patients were also included if they were heterozygous for a PV in *STK11* although they did not fulfil the clinical Beggs criteria. A PV was classified as a pathogenic or likely PV according to the guidelines of

American College of Medical Genetics.[8] Patients at all ages, including deceased patients, were included.

Genetic analysis: Persons were contacted and offered genetic counselling and (re)testing, if no genetic analysis had previously been performed or if previous genetic analysis had been negative. Genetic analyses were preferentially performed on DNA extracted from peripheral blood. When this was not possible because all affected relatives were deceased, the analyses were performed on DNA from formalin-fixed, paraffin-embedded non-neoplastic tissue from an affected family member. If a PV was identified in one family member, we assumed that affected relatives had the same PV.

A panel of genes in which PVs are associated with an increased risk of polyposis and colorectal cancer, including *STK11*, was analyzed by NGS (Illumina Technology). The sequencing analysis enabled detection of single nucleotide variants in the coding regions and ±50 bp of surrounding intronic regions, as well as detection of copy number variants (CNVs). If a PV was not revealed, WGS (Illumina Technology) was performed with alignment and variant call using Burrows–Wheeler Aligner and Genome Analysis Toolkit pipeline, respectively (reference genome: hg19). Data were analyzed for genomic SVs and CNVs with the software CNVkit, CNVnator, Manta, and Lumpy.

Clinical data: Data on all PJS patients, both deceased and alive, were retrieved from registers and medical records. Data from all relevant departments, including surgical, pediatric, oncological, and dermatological departments, were collected.

End of follow-up: The study ended December 31, 2021 and mean age and so forth were calculated by this date.

Statistics: The point prevalence for 2021 was calculated based on the total Danish population retrieved from Statistics Denmark (5,843,347 residents) as of December 31st, 2021. Descriptive data are presented in absolute numbers and proportions (%). Incidence and mortality rates with 95% confidence intervals (CIs) were estimated using a Poisson regression model and probabilities of cancer were estimated with Kaplan–Meier analysis. For patients who had been diagnosed with cancer, the time to event was not truncated at any age. For cancer incidence, the time intervals in the models were the time between birth and first cancer diagnosis, and for patients who had not been diagnosed with cancer the time intervals in the models were the time between birth and December 31, 2021, date of death, or date of loss of follow up, whichever came first. The association statistics were done using SAS enterprise Guide (Version 7.1; SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Patient characteristics

The total number of patients with PJS identified in Denmark was 56 (females: 21, males: 35) belonging to 35 families. Of the 56 patients, one did not fulfil the Beggs criteria, but had a PV in *STK11* and this patient was under 10 years of age. Twenty-one patients were deceased. The mean age of patients alive at December 31st, 2021 was 35 years (range: 1–83 years, median 33.5 years) with five patients being younger than 8 years of age, where GI-surveillance begins in Denmark. The point prevalence of PJS in the Danish population was estimated to 0.6 per 100,000 persons. Further background data are presented in Table 1.

3.2 | Diagnosis and first symptoms

For patients, who were diagnosed due to symptoms or signs of PJS, the mean age at diagnosis was 25 years (1–67 years) with small bowel invagination due to polyps being the most frequent followed by rectal bleeding (Table S2). Most patients had or had had mucocutaneous pigmentation especially on the lips; in five patients the presence of pigmentations led to the diagnosis. The age at diagnosis varied

TABLE 1 Patient characteristics.

	No of patients	Mean age in years (range)	Median age (years)
Total number of patients (male:female)	56 (35:21)		
Number of families	35		
Deceased and age at death (male:female)	21 (14:7)	50 (31–70)	50
Alive (male:female)	35 (21:14)	35 (1–83)	34
No affected parent/affected parent/unknown	24/20/12		
Number of PJ-polyps			
<10	16		
10–30	12		
31–100	18		
>100	3		
Mucocutaneous pigmentations	41 (87%)		
Testicular Sertoli Leydig tumors	3[a] (9%)		

Abbreviations: PJ, Peutz–Jeghers; PV, pathogenic variant.

[a]The total number of men examined for testicular abnormalities is unknown.

considerably with some patients being diagnosed in the first years of life, while others had a later debut and milder symptoms.

3.3 | GI polyps

In all patients who had undergone endoscopic surveillance, intestinal PJ-polyps had been detected. These were primarily located in the small intestines. The polyp burden (the cumulative number of polyps) varied from approximately 10 to several hundreds. The youngest person to be diagnosed with a PJ-polyp was 1 year of age. A few patients had extraintestinal polyps including cervical, vaginal, and gallbladder PJ-polyps.

3.4 | Genetic analysis

Genetic analyses were attempted in 11 patients who had not been genetically tested previously ($n = 8$) or where previous *STK11* analysis had not identified a PV ($n = 3$). Of these patients, four were found to have a PV in *STK11* and in additionally two patients, mosaicism for a PV in *STK11* was identified. See also Table 2. In three patients, all deceased, no biological material was available for genetic analysis. In two patients, who both were diagnosed with PJS due to intestinal hamartomatous polyps only, no PV was identified in *STK11* or in other genes related to polyposis syndromes or increased risk of CRC (*APC*, *AXIN2*, *BMPR1A*, *EPCAM*, *GREM1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NTHL1*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *SMAD4*, *STK11*). WGS was performed in DNA from blood in one of the patients, and in the other patient genetic analysis of *STK11* was performed on tissue from one of the PJ-polyps—with normal results.

Twenty-nine different PVs were detected in 30 families; two families had the same PV. The PVs in *STK11* are presented in Table S1. The variants were located throughout the gene and comprised both frameshift, missense, and splice site variants, as well as larger deletions encompassing several exons. In the patients, where mosaicism was detected, the PV could be seen in 10%–21% of reads in blood using NGS. We found no indication of genotype-phenotype correlations, as various types of cancer at all ages were seen in patients with various types of variants.

TABLE 2 Genetic analysis.

	Number of patients	Number of families
PV in *STK11*	51 (96%)	30 (93%)
Mosaicism for a PV in *STK11*	3 (6%)	3 (10%)
Genetic analysis not possible	3 (5%)	3 (9%)
No PV detected	2 (4%)	2 (6%)
Single nucleotide variant	26 (87%)	26 (87%)
Larger copy number variants	4 (13%)	4 (13%)

Abbreviation: PV, pathogenic variant.

3.5 | Patients without a PV in STK11

In two patients a PV in *STK11* was not detected. Both patients were more than 50 years of age, had not had mucocutaneous pigmentations, and had no affected family members, including healthy grown-up children. They both fulfilled the clinical criteria of PJS solely due to intestinal polyps: One had four PJ-polyps in the small intestine, and one had several PJ-polyps in the colon. Revision of the histopathology of one or more of the polyps by a pathologist with experience in the field, confirmed that these polyps were PJ-polyps.

3.6 | Cancer types and incidence

Nineteen patients (30–74 years) were diagnosed with a total of 24 malignant tumors at various anatomical sites (Table 3). Cancer in the GI tract ($n = 13$) was most frequent (54% of all cancers), including colorectal ($n = 4$) and pancreato-biliary cancer ($n = 5$). Fifteen patients eventually died of disseminated cancer. The average time from cancer diagnosis to death was 10 months (few days to 47 months) with five patients living less than 1 month after diagnosis. The histopathology showed adenocarcinoma in all cases except for a follicular thyroid cancer, a neuroendocrine lung tumor, a squamous cell penile cancer, and two superficially spreading malignant melanomas. The cervical cancers were adenoma malignum.

Two cases of cancers were detected by examination as part of regular PJS-surveillance (CRC and pancreatic). Twelve patients were

TABLE 3 Cancer occurrence and surveillance.

	Number	Mean age (range)	Median age (years)
Total number of cancers	24	46 (30–64)[a]	43[a]
Patients with cancer	19	46 (30–64)	43
Cancer as cause of death	15	50 (31–74)	45
Patients with more than one cancer	4		
Localization			
Cholangiocarcinoma	2	62 (60–63)	
Colorectal	4	41 (34–61)	35
Gynecological	4	39 (36–42)	63
Other upper GI	3	48 (35–64)	
Pancreatic cancer	3	62 (43–74)	63
Pulmonary	3	46	45
Other (penile, ileum, thyroid, malignant melanoma)	5	–	–

[a]Age at diagnosis.

TABLE 4 Cancer and surveillance.

	Number of patients
Cancer diagnosed by examination at regular PJS surveillance	2
Cancer diagnosed because of symptoms (cancer type not included in surveillance)[a]	10
Cancer diagnosed because of symptoms (cancer type included in surveillance)	2
Patient not in surveillance at time of diagnosis (PJS diagnosis not known)	6
Unknown	4

[a]The types of cancer comprised: pancreatic, cholangiocarcinoma, cervical (adenoma malignum), ovarian, uterine, penile, and pulmonary. From 2020 surveillance for pancreatic cancer was included in surveillance program.

diagnosed with cancer, while they followed recommended surveillance (Table 4).

The crude incidence of cancer in patients with PJS, calculated over a total of 2.216 person years, was 8.57 per 1000 person years (95% CI 5.47–13.44), 8.56 in males and 8.58 in females. The cumulative incidence of cancer at the age of 40 years was 21% (95% CI 8.2–34.5), while the cumulative incidence of cancer was 71% (95% CI 50.9–90.4) at the age of 70 years (Figure 2).

3.7 | Mortality and causes of death

By December 31, 2021, 21 PJS patients were deceased. The mean age at death was 49 years (25–77 years). Fifteen patients died of cancer, three patients died of other causes (mean age 88 years) and three patients died of unknown causes (mean age 58 years).

The crude all-cause mortality rate for persons with PJS, calculated over a total of 2.301 person-years was 9.12 per 1000 person-years (95% CI 5.95–13.99) with no significant differences between sexes. Kaplan–Meier curves for all-cause mortality are presented in Figure 3.

4 | DISCUSSION

In this study, we have provided data on the phenotype and genotype of all known patients with PJS in Denmark. The detection rate of PVs was 96%, including three cases of mosaicism (6%). We found a high, age-depending probability of cancer and mortality. And, strikingly, most cancers were identified between the scheduled examinations in the surveillance program. These results lead to several considerations.

4.1 | Considerations on genetics

In 1997, *STK11* was found to be associated with PJS and subsequently several studies have detected PVs in this gene in most patients with PJS.[4,9] However, as a PV in *STK11* was not identified in all patients with PJS when applying traditional sequencing methods, locus heterogeneity has been proposed.[10–12] A considerable, yet unsuccessful, effort has been made to identify other candidate genes.[13] The variant detection rate increased when MLPA was introduced to detect CNVs around 2005.[14] However, in 10%–15% of patients, a PV in *STK11* was still not detected. In 2016, the first report of mosaicism for a PV in *STK11* was published[15] and this was followed by Butel-Simoes et al.[16] and our own case report in 2021.[17] In the present study, we found that 82% of the Danish patients carried a PV that could be detected with Sanger sequencing, while larger CNVs were identified in 13%. In further 6% of the patients, deep sequencing of DNA from blood or PJ-polyp tissue identified mosaicism for a PV, increasing the detection rate to 96%.

Our study suggests that patients with the full spectrum of PJS features have a detectable PV in *STK11* when applying newer methods. It was notable that a broader screening with WGS did not increase the detection rate, corroborating that variants in *STK11* are the only cause of PJS. The two patients in which a PV in *STK11* was not identified, did not present with the "classic" PJS phenotype: they had no affected relatives and they had not had any mucocutaneous manifestations. Furthermore, they were diagnosed in adulthood and fulfilled the clinical criteria with a relatively low number of intestinal PJ-polyps. Although mosaicism and technical limitations cannot be ruled out, one could speculate whether they indeed have PJS. It may also be considered whether the clinical criteria are too broad when patients with two PJ-polyps and neither other features nor a family history, are diagnosed with PJS.

4.2 | Cancer risk and mortality

In our study the cumulative probability of cancer increased from 21% at the age of 40 years to 71% at the age of 70 years. Previous studies have calculated a similar high, age depending, cumulative risk of cancer: Hearle et al. found a cumulative risk of 31% by age 40 years and 85% by age 70 years. Resta et al. also found a cumulative cancer incidence at age 40 years at 20% and at age 65 years, 89%.[3,4,18,19]

As demonstrated in Figure 2, females tended to be diagnosed with cancer at an earlier age compared with males. Approximately 50% of females had been diagnosed with cancer by the age of 45 years. In our study this can be explained by the occurrence of gynecological cancer which typically was diagnosed around 40 years of age. The trend of female PJS patients developing cancer earlier than in men, was also found in Resta et al.[3]

Several different types of cancer at various anatomical sites were seen in the patients. This emphasizes that PJS is a more global tumor predisposition syndrome not only related to CRC. Notably, we did not observe any patients with breast cancer although the risk has been reported to be sixfold increased.[4] The reason for this is probably the small number of female patients included and that a significant part of woman died early of gynecological cancer.

Age	Probability of cancer (% (95% CI))		
	Female	Male	Both
20	–	–	–
30	0	0	0
40	28.6 (4.9–52.2)	17.1 (1.8–32.3)	21.4 (8.2–34.5)
45	46.4 (18.6–74.3)	22.2 (4.9–39.6)	31.2 (15.7–46.7)
50	46.4 (18.6–74.3)	27.4 (8.5–46.4)	34.5 (18.4–50.5)
60	46.4 (18.6–74.3)	43.0 (18.2–67.7)	43.5 (25.3–61.6)
70	57.1 (28.0–86.3)	–	70.6 (50.9–90.4)
80	57.1 (28.0–86.3)	–	70.6 (50.9–90.4)

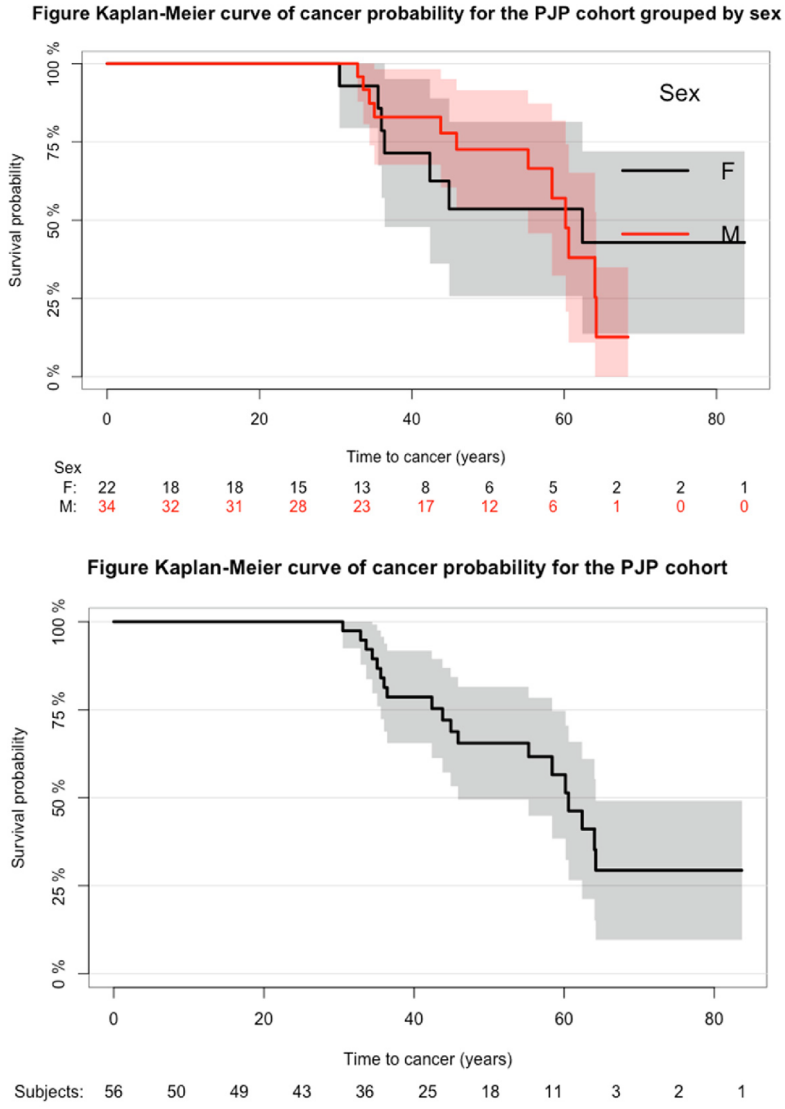


FIGURE 2 Probability of cancer. [Colour figure can be viewed at wileyonlinelibrary.com]

4.3 | Effect of surveillance

The effect of surveillance on morbidity in relation to polyposis and mortality from cancer in PJS patients is in general difficult to assess; partly because long-term follow-up studies lack, and because the pathophysiological mechanism of both polyp formation and cancer is unknown. In 1999, Bosman proposed the idea of a hamartoma–adenoma–carcinoma sequence, but later studies have shown varying results to support this theory; dysplastic, adenomatous and carcinomatous changes in PJ-polyps have only rarely been described.[20–23]

In our study only two (asymptomatic) patients were diagnosed with cancer at an examination scheduled according to the recommended PJS-surveillance program, while most cancers were diagnosed because of symptoms although the patients followed surveillance (see Table 4). In a substantial number of these cases, the patients were diagnosed with a type of cancer that is not included in

FIGURE 3 Probability of survival. [Colour figure can be viewed at wileyonlinelibrary.com]

Age	Probability of survival (% (95% CI))		
	Female	Male	Both
20	1	1	1
30	1	1	1
40	76.2 (52.5–99.8)	87.5 (74.3–1.0)	83.8 (71.9–95.7)
45	59.2 (31.6–86.9)	82.6 (67.1–98.2)	74.5 (60.0–89.0)
50	50.8 (22.5–79.0)	71.9 (53.6–91.3)	64.6 (48.3–80.9)
60	50.8 (22.5–79.0)	51.3 (27.0–75.5)	52.1 (33.8–70.5)
70	50.8 (22.5–79.0)	13.3 (11.2–35.1)	30.6 (10.3–50.9)
80	16.9 (14.6–45.6)	–	10.2 (0.0–27.9)

Figure Kaplan-Meier curve of survival probability for the PJP cohort grouped by sex

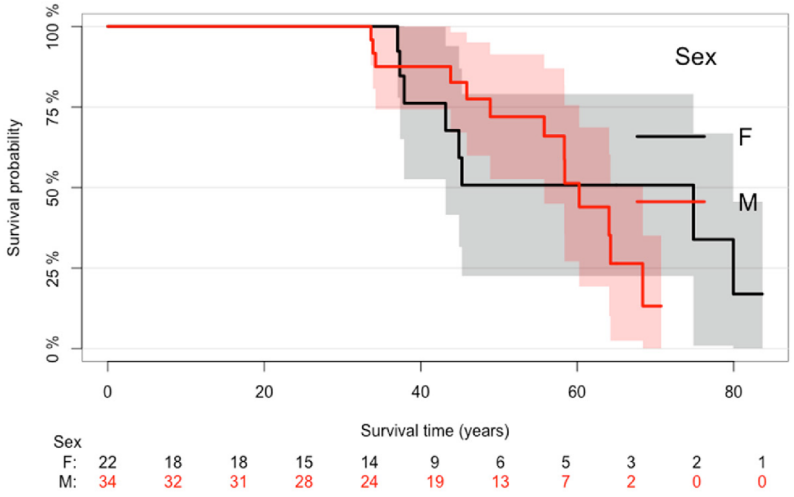
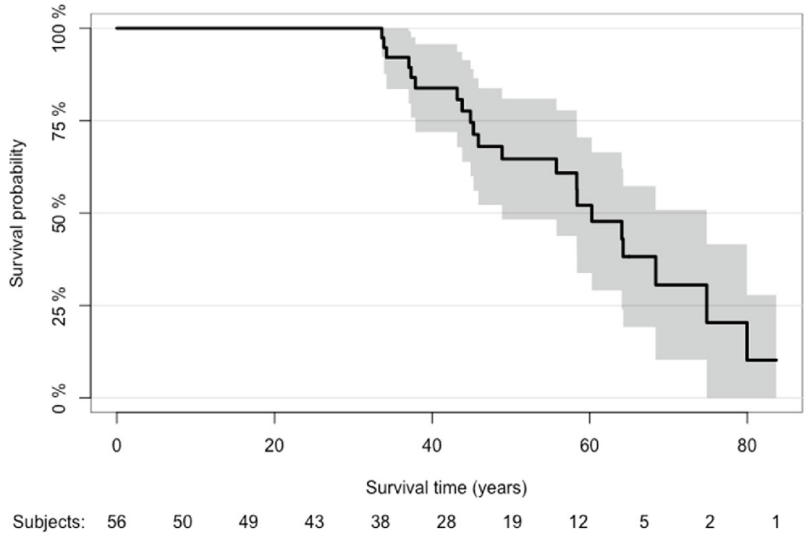


Figure Kaplan-Meier curve of survival probability for the PJP cohort



the current surveillance program: primarily gynecological and pancreato-biliary cancers, including cholangiocarcinoma and pancreatic cancer, as well as lung cancer. In 2020, screening for pancreatic cancer with yearly MR and/or EUS was added to the Danish surveillance program, but this inclusion has been debated. Subsequently, one case of pancreatic cancer was detected during surveillance and the outcome is yet unknown. PJS is the cancer-predisposition syndrome with the highest known risk of pancreatic cancer (RR = 140), cumulative risk of 11% at age 60 years,[3,4] but larger studies have suggested little or no effect of surveillance.[24,25]

In this study, both patients with cervical cancer followed regular PJS examinations. However, adenoma malignum of the uterine cervix is not easily detected with standard methods such as SMEAR[6] which is designed for detecting squamous cell abnormalities. Thus, it is of importance that patients and gynecologists are aware of the symptoms, especially persistent watery-mucoid vaginal discharge.

Our study did not investigate the effect of surveillance on morbidity in relation to polyposis, but the purpose of surveillance is also to decrease serious surgical events such as invagination of the small intestines. This should of course be taken into consideration when evaluating the effect of a surveillance program.

4.4 | Limitations and strengths

A limitation of this study is the low number of patients included that may reduce the power of the statistical analyses. In addition, one can never exclude over-ascertainment of patients that are more affected, compared with patients that are less affected, or unaffected, and patients with a family history, that can result in overestimation of cancer and mortality risks, and of underestimation of the frequency of de novo cases, respectively. However, the strength of the study is that it was performed nationwide in Denmark, where free health care is available to all citizens, and furthermore, health care data are linked to the patients via a unique personal identifier that has been given to all citizens since 1968. Thus, our study has a high degree of completeness and a low degree of bias.

5 | CONCLUSION

When applying the newest genetic technology, a PV in *STK11* may be detectable in almost all patients with PJS (96%). Consistently with other studies, our study found that Danish patients with PJS have had a high risk of various types of cancer and a high mortality; at the age of 70 years these probabilities were 71% and 69%. Most cancer were identified between the scheduled examinations in the surveillance program. These observations emphasize that PJS should be regarded as a general cancer predisposition syndrome, where improvement of clinical care is needed.

AUTHOR CONTRIBUTIONS

Anne Marie Jelsig: Conducted the study, collected, analyzed data and wrote the manuscript. **Thomas van Overeem Hansen:** Performed genetic analysis and analyzed data. Reviewed the manuscript. **Lene Bjerring Gede:** Performed genetic analysis and analyzed data. Reviewed the manuscript. **Niels Qvist:** Collected and analyzed surgical data. **Lise-Lotte Christensen:** Collected data on patients with a pathogenic variant in the Western part of Denmark. **Charlotte Kvist Lautrup:** Collected data on patients with a pathogenic variant in the Western part of Denmark. **Jane Hübertz Frederiksen:** Department of Clinical Genetics, University Hospital of Copenhagen, Rigshospitalet, Denmark. **Lone Sunde:** Collected data on patients with a pathogenic variant in the Western part of Denmark. Reviewed the manuscript. **Lilian Bomme Ousager:** Collected data on patients with a pathogenic variant in the Western part of Denmark. **Ken Ljungmann:** Collected and analyzed surgical data. **Birgitte Bertelsen:** Collected data on patients with a pathogenic variant in the Eastern part of Denmark. Analyzed genetic data. **John Gásdal Karstensen:** Supervised the study, the methodology and edited and reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14337.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Lone Sunde https://orcid.org/0000-0002-8479-165X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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