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Oncology

Cancer risk associated with *STK11/LKB1* germline mutations in Peutz–Jeghers syndrome patients: Results of an Italian multicenter study

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ABSTRACT

Background: Germline mutations in the *STK11/LKB1* gene cause Peutz–Jeghers syndrome, an autosomal-dominantly inherited condition characterized by mucocutaneous pigmentation, hamartomatous gastrointestinal polyposis, and an increased risk for various malignancies. We here report the results of the first Italian collaborative study on Peutz–Jeghers syndrome.
Aims: To assess cancer risks in a large homogenous cohort of patients with Peutz–Jeghers syndrome, carrying, in large majority, an identified *STK11/LKB1* mutation.
Methods: One-hundred and nineteen patients with Peutz–Jeghers syndrome, ascertained in sixteen different Italian centres, were enrolled in a retrospective cohort study. Relative and cumulative cancer risks and genotype–phenotype correlations were evaluated.

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Results: 36 malignant tumours were found in 31/119 (29 *STK11/LKB1* mutation carriers) patients. The mean age at first cancer diagnosis was 41 years. The relative overall cancer risk was 15.1 with a significantly higher risk ($p < 0.001$) in females (22.0) than in males (8.6). Highly increased relative risks were present for gastrointestinal (126.2) and gynaecological cancers (27.7), in particular for pancreatic (139.7) and cervical cancer (55.6). The Kaplan–Meier estimates for overall cumulative cancer risks were 20%, 43%, 71%, and 89%, at age 40, 50, 60 and 65 years, respectively.
Conclusion: Peutz–Jeghers syndrome entails markedly elevated cancer risks, mainly for pancreatic and cervical cancers. This study provides a helpful reference for improving current surveillance protocols.
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1. Introduction

Peutz–Jeghers syndrome (PJS) is a rare dominantly inherited disease characterized by the association of gastrointestinal hamartomatous polyposis, mucocutaneous hyperpigmentation, and an increased cancer risk at different target organs. The estimated incidence of PJS is between 1/8,300 and 1/200,000 live births and the syndrome is associated with germline mutations in the *STK11/LKB1* gene [1–3]. The gene encodes a ubiquitously expressed multitasking serine–threonine kinase, which plays a critical role in several cell functions, including proliferation, cell cycle arrest, differentiation, energy metabolism, and cell polarity [4].

Pathogenic *STK11/LKB1* mutations are usually identified in 80–94% of patients using conventional mutation screening techniques such as direct sequencing of individual exons and multiplex ligation-dependent probe amplification (MLPA). Different types of mutation have been found including small insertions, deletions, splicing defects, nonsense and missense mutations. In approximately 30% of cases partial or whole gene deletions are detected [5].

PJS causes an increased risk of gastrointestinal (GI) and non-gastrointestinal (non-GI) cancers in addition to the frequent occurrence of other rare tumour types such as those of the sex-cord with annular tubules (SCTAT) in the ovary, and sex-cord and Sertoli-cell type testicular tumours. The GI target organs showing increased cancer risk include the stomach, the small intestine, the colon and the pancreas while among non-GI cancers breast, endometrial, ovary and lung tumours are frequent.

Different studies and several meta-analyses on large cohorts of PJS patients have been reported with the aim to precisely assess cancer risk, age of onset and spectrum of malignancies in PJS patients [1,6–8]. Based on these systematic reviews of large PJS patients' series specific surveillance guidelines have been proposed although no consensus has been reached yet, due to the wide variability in cancer risk estimates.

Collaborative studies report invariably, with some exceptions, cancer risks based on surveys of heterogeneous patients' groups. Here, we report the first collaborative study on a large and homogenous Italian PJS patients' cohort carrying, in the large majority, an identified *STK11/LKB1* mutation, with the aim of assessing relative and cumulative cancer risks in this specific population.

In our PJS patient cohort the cumulative cancer risk of any cancer was nearly 90% by age 65, which is higher than what has been reported recently [1,4]. The cancer risk was especially elevated in female PJS patients. Compared with the general population and with previous reports of relative risk (RR) for cancer at specific sites, in our cohort the cancer risk was particularly increased for pancreatic cancer (RR: 139) and cervical cancer (RR: 55).

2. Materials and methods

The study was designed as a retrospective cohort study. A total of 119 PJS patients ascertained through sixteen different specialized centres throughout Italy were enrolled in the study between 1997 and 2009. All patients signed an informed consent to participate to this study and the entire study was approved by the local Ethical Board for Human Experimentation Review of University Hospital of Bari. All 119 patients were included in the analysis if they fulfilled the diagnostic clinical criteria for PJS [8,9], and/or they were carriers of the familial disease-causing mutation. Clinical diagnosis was made according to the following clinical criteria [8], with a patient being considered affected in presence of any one of the following:

1. Two or more histologically confirmed Peutz–Jeghers polyps
2. Any number of Peutz–Jeghers polyps detected in one individual who has a family history of PJS in close relative(s)
3. Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in close relative(s)
4. Any number of Peutz–Jeghers polyps in an individual who also has characteristic mucocutaneous pigmentation.

Polyps were considered as confirmed Peutz–Jeghers polyps when they showed the characteristic histological features, represented by a frond-like elongated epithelial component and cystic gland dilatation extending into the sub-mucosa or muscularis propria, and arborising smooth muscle extending into polyp fronds [8].

Patients carrying the familial mutation were considered affected, independent of matching the clinical criteria.

The clinical data collected from patients, detailed information on the mutation analysis protocol and the statistical analyses applied are reported in the supporting info available online (Appendix A).

3. Results

Data on 119 PJS patients (58 males, 48.7%), of which 99 had an identified *STK11/LKB1* mutation, were available for analysis. Among 119 patients a total of 71 patients were classified as familial and derived from 27 families while 48 were sporadic cases. The median age at diagnosis of PJS was 17 years (range 1–50). At the closing date of the study, the median age of the 108 patients still alive was 36 (range 3–65 years) while the median age of the 11 patients deceased was 50 (range 31–62 years). A total of 117/119 patients had Peutz–Jeghers polyps. GI polyps other than Peutz–Jeghers polyps (namely, adenomatous, tubulo-villous, hyperplastic, inflammatory, mixed) were also detected in 22/119 (18.5%) patients. Non-Peutz–Jeghers polyps were not included in criteria for clinical diagnosis. The clinical and molecular data of the 119 PJS patients are detailed in Appendix B, as supplementary file available online.

3.1. STK11/LKB1 mutation spectrum

Germline mutation screening of the *STK11/LKB1* gene was performed in 69 of the 75 probands (23/27 familial probands and 46/48 sporadic probands). A disease-causing mutation was detected in 65/69 probands (mutation detection rate 94.2%). The mutation identified in this patients' cohort is listed in Fig. 1. In particular, the causative mutation was identified in 20/23 familial and in

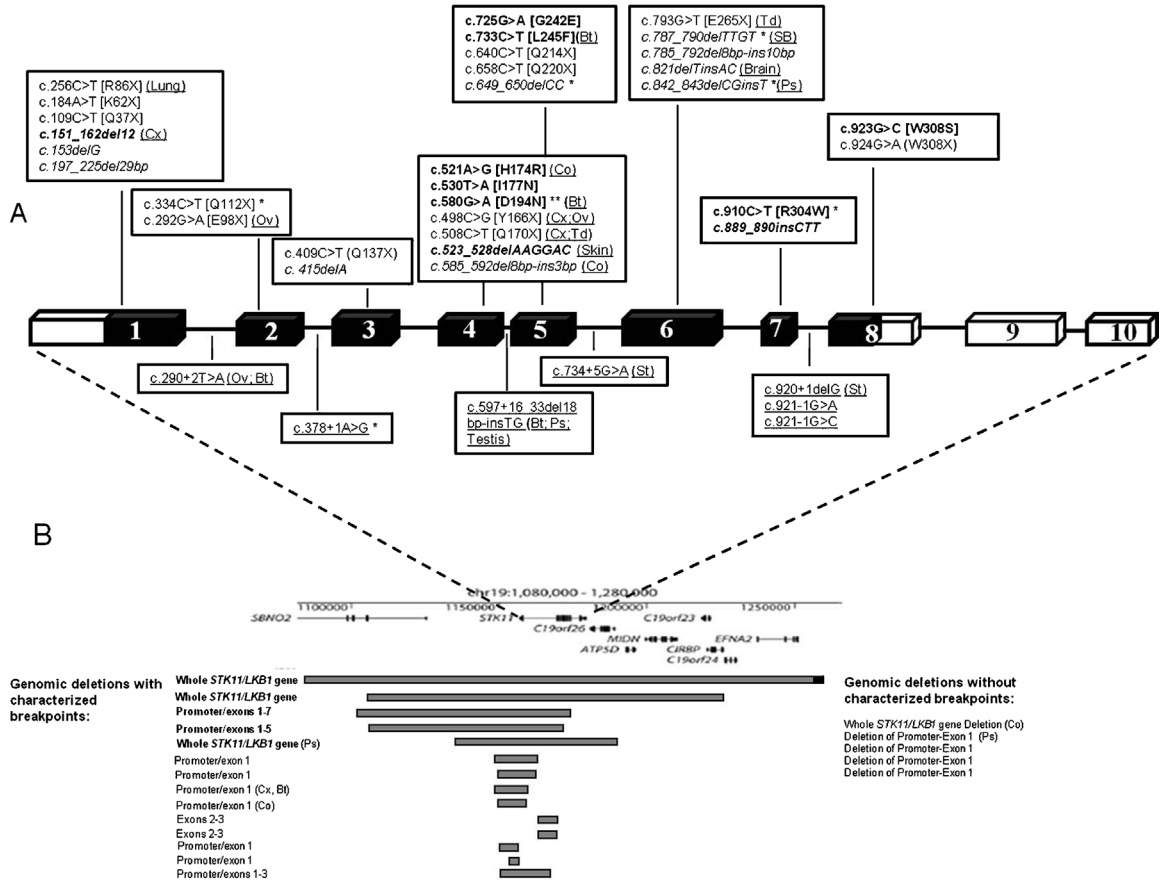

Fig. 1. Distribution of *STK11/LKB1* mutations in Italian patients with Peutz–Jeghers syndrome. (A) Black boxes indicate the exons encoding for the kinase domain. Nonsense mutations are in normal font, missense mutations are in bold. In italic out-of-frame insertion/deletion/indel mutations. In bold and italic in-frame insertions/deletions. Intronic mutations causing defective splicing are underlined. * = mutation occurring in two unrelated probands; ** = mutation occurring in three unrelated probands. In parenthesis, next to each mutation, the Peutz–Jeghers-syndrome-related tumours diagnosed in patients carrying the mutation (Co, Colon; Cx, Cervix; Bt, Breast; Ov, Ovary; Ps, Pancreas; SB, small bowel). (B) Whole and partial genomic deletions identified in patients with Peutz–Jeghers syndrome. For the 14 deletions with identified breakpoints (on the left of the figure), the length of the grey bar indicates the approximate extension of each deletion. In bold, deletions removing multiple genes in addition to *STK11/LKB1*. As above, next to each deletion, the cancers diagnosed in patients harbouring the deletion.

45/46 sporadic cases. Nineteen probands had large partial or whole-gene deletions, while the remaining 46 mutations were nucleotide substitutions, small insertions/deletions or a combination of both (indels). Among these 46 mutations, one recurred in three unrelated probands, six recurred in 2 unrelated probands, and 33 were unique, for a total of 38 different small mutations identified. Fig. 1 shows the distribution and the type of all 39 identified small mutations and all 19 genomic deletions. Among the 38 small mutations, 21 were truncating (9 frameshift mutations and 12 nonsense substitutions), leading to the creation of premature stop codons, 7 disrupted intronic splice sites, and 10 were non-truncating changes (one in-frame insertion, two in-frame deletions, and seven missense substitutions leading to non-conservative amino acid changes) [10,11]. While all mutations were falling within the coding region spanning from exon 1 and exon 8, the distribution of mutations was non random, since both truncating and non-truncating mutations appear to cluster in exons 4–6, which encodes for the kinase domain of the *STK11/LKB1* polypeptide [11]. Most genomic deletions encompass *STK11/LKB1* exon 1 and its upstream sequences, while deletions affecting the remaining exons or removing the whole *STK11/LKB1* gene seem to occur less frequently (Fig. 1). The breakpoints were characterized in 14/19 genomic deletions [5]. Genetic testing was extended to the probands' relatives, allowing to confirm the presence of the causative mutation in 34 at-risk individuals. Thus, a total of 99/119 patients (83.1%) were carriers of an identified *STK11/LKB1* mutation in our cohort (20 familial probands, 34 relatives, and 45 sporadic cases).

3.2. Cancer spectrum and relative and cumulative cancer risks

A total of 36 malignant tumours were diagnosed in 31 (29 *STK11/LKB1* mutation carriers) of the 119 PJS patients included in the study (Appendix B and Table 1). Five patients had metachronous primary cancers in different target organs. The mean age at first

Table 1
Characteristics of the Italian cohort of patients with Peutz–Jeghers syndrome.

Patients enrolled	
Total	119 (100%)
Male	58 (48.7%)
Age at the end of follow-up (2009)	
Median age (range) patients alive (n = 108)	36.5 (3–65) years
Median age (range) of patients at death (n = 11)	50.0 (31–62) years
Family history	
Familial patients with Peutz–Jeghers syndrome	71/119 (59.7%)
Sporadic patients with Peutz–Jeghers syndrome	48/119 (40.3%)
STK11/LKB1 mutation carriers	99/119 (83.1%)
Patients with cancers[a]	31/119 (26.0%)

[a] Five patients had two independent cancers, so 36 cancers were detected in 31 patients.

Table 2
Relative cancer risks in patients with Peutz–Jeghers syndrome.

Site	RR
Any cancer	15.1 (CI 10.5–21.2)
Males	8.6 (CI 4.2–15.7)
Females	22.0 (CI 14.1–32.7)
Breast	12.5 (CI 5.1–26.0)
Cervix	55.6 (CI 17.7–134.0)
Gynaecological cancers	27.7 (CI 11.3–57.6)
Colorectal	13.5 (CI 4.3–32.5)
Males	11.2 (CI 1.9–37.0)
Females	17.0 (CI 2.8–56.0)
Pancreas	139.7 (CI 61.1–276.4)
Males	88.6 (CI 22.6–241.6)
Females	245.4 (CI 78.0–591.9)
Gastrointestinal cancers	126.2 (CI 73.3–203.4)
Males	90.4 (CI 39.6–178.9)
Females	192.8 (CI 89.5–366.1)

RR, relative risk; CI, confidence intervals.

cancer diagnosis was 41 years (range 18–64). In Table 1 we show in details the frequency of cancer at all organ sites diagnosed at least once in our patient cohort. The gastrointestinal tract and the breast were the most frequent sites of malignancy. Among cancers diagnosed in our PJS patients' set there were 15 gastrointestinal cancers (seven pancreatic, four colorectal, one small intestinal, three gastric), 7 gynaecological cancers (four cervical and three ovarian), six breast cancers, two thyroid cancers, and one each of liver cancer, skin cancer, brain cancer and testis cancer. Three cancers (one gastric, one pancreatic and one breast cancer) occurred in patients who did not have an *STK11/LKB1* mutation identified. Out of the three ovarian cancers, one was a malignant SCTAT. Three of the four cervical cancers were mucinous adenocarcinomas, whereas the histopathological type of the remaining one was not known.

The relative risk for any cancers was significantly higher in PJS patients than in the general Italian population (Table 2). The RR to be affected by any cancer in our cohort was 15.1 (CI 10.5–21.2) with a higher risk ($p < 0.001$) in females (22.0; CI 14.1–32.7) than in males (8.6; CI 4.2–15.7). Similarly, when cancers were analyzed regarding each specific site, RRs were significantly higher in PJS patients compared with the general Italian population (as summarized in Table 2). RR was 139.7 (CI 61.1–276.4) for pancreatic cancer, 13.5 (CI 4.3–32.5) for colorectal cancer, 12.5 (CI 5.1–26.0) for breast cancer, 55.6 (CI 17.7–134.0) for cervical cancer. Lack of statistical power prevented us to perform analysis of cancer at other sites, occurring in fewer than four cases. When analysis was performed for cancer groups, highly increased RR was shown for both gastrointestinal cancers (126.2; CI 73.3–203.4) and for gynaecological cancers (27.7; CI 11.3–57.6). The Kaplan–Meier estimates for cumulative cancer risk, considered for any cancers, at age 40, 50, 60 and 65 years were 20% (CI 12.37–31.87), 43% (CI 30.5–58.60), 71% (CI 50.99–88.84) and 89% (CI 65.47–99.07), respectively (Fig. 2A). There was a statistically significant difference in the cumulative cancer risk between males and females (log-rank test 8.72 $p = 0.0031$) (Fig. 2B). In Fig. 2C are shown the cumulative risks for GI cancers by age. Cumulative risk was 7%, 20%,44% and 55% at ages 40, 50, 60 and 65 years, respectively. Within the gastrointestinal tract, the pancreas and the colorectum were the most commonly affected sites of malignancy. The cumulative risk to develop pancreatic cancer was 2%, 4.5%, 18% and 55% at ages 40, 50, 60 and 65 years, respectively (Fig. 2D). The risk for developing colorectal cancer was 3%, 6% and 12% at ages 40, 50 and 60 years, respectively (Fig. 2E). In our PJS cohort, 6 women developed breast cancer. The lifetime cumulative risk was 12.7% at age 40 years and reached 24% by age 60 years (Fig. 2F). Seven gynaecological cancers (4 cervical and 3 ovarian carcinomas, including the malignant SCTAT) were diagnosed. The corresponding cumulative risk estimates are shown in Fig. 2G. Among these, the risk for developing cervical cancer was particularly high, reaching 14% at age 50 years and 22.7% by 65 years (Fig. 2H).

Six cancers were discovered in surveillance in 5 different patients. In two cases surveillance could not prevent patient's decease (a pancreatic cancer which was already in advanced stage when detected and a cervical cancer which was misdiagnosed as a benign cyst-like lesion at ultrasound examination so it was not promptly removed). An additional 7 cancers occurred after PJS diagnosis had already been made to the family's proband, in 7 patients who were not in regular surveillance despite proband's ascertainment. In 4 cases the cancer had a fatal outcome, whereas two cases were lost at follow-up (one testicular cancer and one lung cancer).

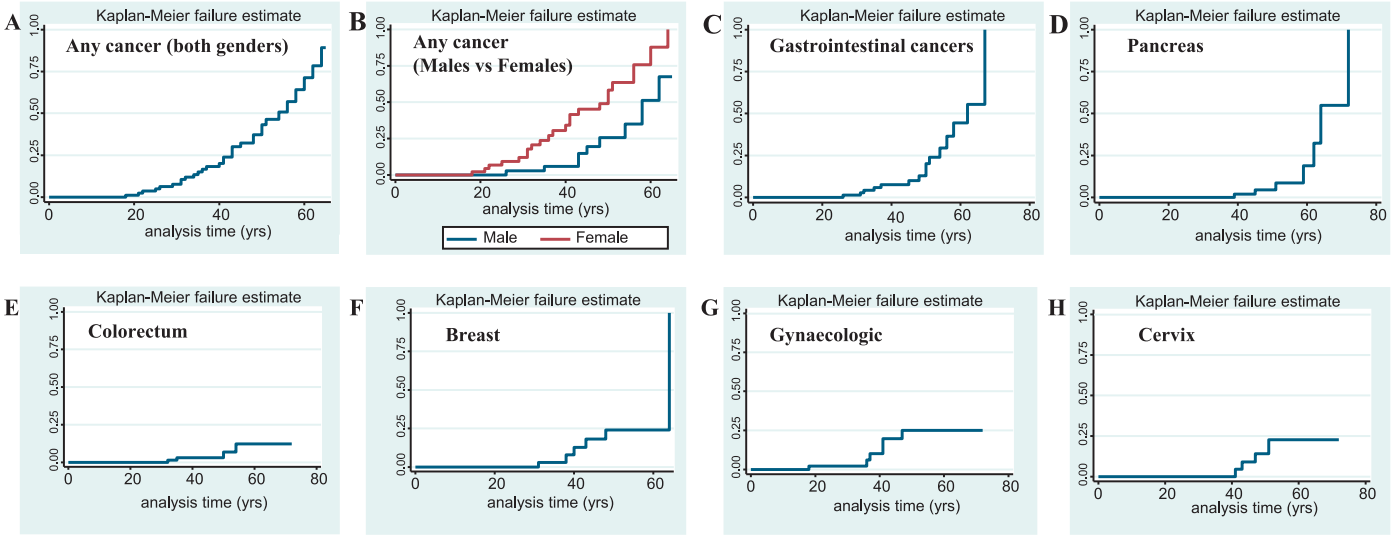

Fig. 2. Cumulative cancer risks according to age. (A) Cumulative risk for any cancer; (B) gender specific cumulative risk for any cancer; (C) cumulative risk for gastrointestinal cancers; (D) cumulative risk for pancreatic cancer; (E) cumulative risk for colorectal cancer; (F) cumulative risk for breast cancer; (G) cumulative risk for gynaecological cancers; (H) cumulative risk for cervical cancers.

3.3. Genotype–phenotype correlations

In our patients' cohort 57 different mutations were molecularly characterized. Nineteen of these mutation carriers developed a cancer of the PJS spectrum. Of these cancers 10 were diagnosed below the average age at diagnosis (41 years). There was no significant statistical association of cancer occurrence with mutation type (truncating mutations vs non-truncating mutations). However, there was a trend for higher risk for early onset cancer in patients with truncating mutations compared with patients harbouring genomic deletions ($p = 0.17$). Also, irrespective of the mutation type, early onset cancer showed a tendency to be associated with mutations localizing in exons 4–6, compared to mutations in all other coding exons although the difference did not reach statistical significance ($p = 0.09$).

4. Discussion

The present study has been conducted by the Italian Association for the study of Familial and Hereditary Gastrointestinal Tumours (AIFEG), which includes the main Italian Centres involved in the PJS ascertainment. Thus, the observed findings are representative of the clinical and biological features of clinically recognized cases of PJS in the whole country. The present study provides additional information regarding the cancer spectrum in a homogeneous cohort of PJS patients, which will help to better set up an effective preventive surveillance protocol.

Since the identification of the *STK11/LKB1* gene, several studies have demonstrated the presence of germline mutations in 80 to 94% of patients with a clinical diagnosis of Peutz–Jeghers syndrome [1,5,6]. In our study constitutional mutations were present in 94.2% of the investigated patients, thus confirming the predominant causative role of the *STK11/LKB1* gene also in the Italian population. The majority of mutations identified in this study has already been reported, but some mutations are novel and described for the first time in this paper. However, 5.8% of these selected PJS patients still lack an identifiable pathogenic mutation despite thorough molecular screening of the gene, suggesting the possible role of additional disease-causing genes and/or the failure of current techniques to detect uncommon genomic defects involving the *STK11/LKB1* locus. As reported in Fig. 1, most of the identified mutations cluster in exon 1 and exons 4–6. As far as concerns the genotype–phenotype correlations, there was no statistically significant difference in cancer occurrence between patients harbouring genomic deletions and patients carrying missense pathogenic or truncating mutations. Similarly, we found no significant association of cancer risk with pathogenic mutation localization. Furthermore, we found no significant differences between cases with *STK11/LKB1* mutations and cases where no genetic changes have been detected, similarly to previous studies [6,7].

Several studies showed that PJS subjects are at high risk of developing cancer in various target organs [12–16], quite often at a very early age [6–8,17–19]. In more recent years, it has been increasingly recognized that the mechanisms of carcinogenesis in PJS are far more complex than originally thought, although the causative role of *STK11/LKB1* constitutional mutations in dysregulating cell proliferation and apoptosis has never been questioned. In the present study, we report the occurrence of 36 cancers in 119 PJS patients, confirming a very high RR (15.1) to develop malignancy in these patients. Throughout GI tract, pancreatic cancer showed the highest RR (139.7), which is a peculiar finding of the Italian population when compared to previous reports, reporting a luminal localization (stomach, small bowel, colorectum) in most PJS-related gastrointestinal neoplasms [6–8,14,18]. In addition, we found an excess of gynaecological cancers, with a RR of 55.6 for cervical cancers. Hence, the cumulative risk for cervical cancers is more than doubled compared to the value reported in the most recent meta-analysis of cancer risks in PJS patients [6]. Remarkably, one of the seven gynaecological cancers in our cohort was a malignant SCTAT, a very uncommon manifestation in PJS patients. Although benign SCTATs is a well-known PJS clinical feature, malignant transformation of this tumour type has always been regarded as an exceedingly rare event in these patients, as it is thus far accounted for by only three case reports [19–21]. SCTATs with malignant behaviour have never been reported previously in PJS cohorts [6–8,14–18]. Also, due to the excess of gynaecological cancer, the lifetime cumulative cancer risk and the RR for any cancer were higher in women compared to men (22.0 vs 8.6). The cumulative risk data were in accordance with previous investigations at younger age classes (<50 years), while the Kaplan–Meier cumulative risk curve showed a steeper trend beyond 50 years of age in our cohort compared to previous reports [6,8,22]. The reasons underlying such high cumulative cancer risks in Italian older patients require further investigations. Interestingly, a recent survey of Italian Lynch-Syndrome families described a lower compliance with post-testing follow-up when compared to analogous studies on Lynch-Syndrome families from other countries [23]. Such high trend in cumulative cancer risks in older patients was present for all type of cancers. Therefore, it appears unlikely that it may be caused by an underestimation of the risk for specific cancers of the PJS spectrum.

Although there is a general agreement that some sort of surveillance should be carried out in PJS patients, evidence-based guidelines have not been developed until 2009 [8], thereby leading to heterogeneity in surveillance protocols being applied across countries. In addition, the rarity of the disease still prevents extensive epidemiological studies from being performed, and a clear definition of organ-specific cancer risk from being assessed. Hence, the recommendations concerning the utility and the timing of clinical and instrumental investigations are still a matter of debate. Recently, a panel of experts proposed first line recommendations for PJS surveillance and follow-up [8]. Our results highlight the impact of pancreatic and cervical neoplasms in terms of PJS-related morbidity and mortality, as well as the non-trivial occurrence less frequent manifestations such as thyroid cancer (previously described in two case reports [24,25]) and malignant SCTAT. Although the increasing number of studies describing thyroid cancer occurrence in PJS patients at young age may suggest a close thyroid monitoring [24–26], there is no current evidence that such approach could be beneficial for these patients. The highly elevated RR for pancreatic cancer found in the present study indicates that pancreas surveillance can be considered advisable for these patients. However, there are no studies assessing the effectiveness of currently available pancreas surveillance techniques, such as endoluminal echoendoscopy. Finally, considering the very high RR for gynaecological cancers observed in our cohort, surveillance for the female genital tract in these patients should also target the potential malignant change of ovarian SCTATs.

As the patients reported in this study were enrolled before publication of international guidelines [8], surveillance protocols differed among participating centres throughout follow-up period. However, on the basis of the information available, only a minority of cancers (6/36) was diagnosed during a PJS-specific surveillance, thus indicating that the clinical management of these rare patients is still particularly difficult in our country. As a confirmation, seven cancers were diagnosed in relatives who were not in surveillance, despite a definite PJS diagnosis in the proband case. In 2001, the Italian Ministry of Health established the National Network of Rare Diseases according to which regional or inter-regional disease-specific centres should be established with the aim of fulfilling the special needs of rare disease patients. Currently, the

implementation of the regional networks has reached variable grade of completeness and no national coordination centre has been established for very rare diseases, including PJS. We believe that a nationwide research observational study could provide a frame to collect prospective information on the problems and results of prevention protocols actually proposed to PJS patients. In addition, the management of such patients poses organizational challenges as the in-charge centre must ensure the expert evaluation of medical exams in the contest of PJS natural history and the active recall for various exams. Within the frame of research collaboration, a nationwide coordination could provide a second opinion system for complex cases.

In conclusion, we show, in accord with recent surveys, that PJS patients are at significant risk of cancer at various sites with a particularly elevated risk of cervical cancer in Italian female PJS patients. While the cost-effectiveness of surveillance protocols in Italian PJS patients is difficult to be assessed, it appears to be justified considering the high risks for several cancer types reported in this study.

Conflict of interest statement

The authors disclose no existing conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2012.12.018.

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