CHAPTER

3

Clinical Characteristics

3.1 Clinical Description

Peutz-Jeghers syndrome (PJS) is characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. The risk for gastrointestinal and extraintestinal malignancies is significantly increased. Distinct benign and malignant gonadal and gynecologic tumors can also be seen. Variable expressivity is common; for example, some affected individuals in families with PJS may have only polyps or perioral pigmentation.

Gastrointestinal polyposis. Peutz-Jeghers-type hamartomatous polyps can occur anywhere in the GI tract, but occur most commonly in the small intestine. The density of polyps is greatest in the jejunum, followed by the ileum, then the duodenum. Polyps can occur elsewhere in the GI tract, including the stomach and

large bowel. Polyps have also been reported in the renal pelvis, urinary bladder, ureters, lungs, nares, and gallbladder.

Adenomas also appear with increased prevalence throughout the gastrointestinal tract.

The malignant potential of Peutz-Jeghers-type hamartomatous polyps is unknown; however, the polyps can cause significant complications including bowel obstruction, rectal prolapse, and/or severe gastrointestinal bleeding with secondary anemia requiring multiple emergency laparotomies and bowel resections. The age of onset of symptoms from polyps is variable, with some children developing symptoms within the first few years of life. In one series, 68% of affected individuals had undergone emergency laparotomy by age 18 years. By age ten years, 30% of individuals with PJS had undergone a laparotomy [Hinds et al 2004]. One small single-center retrospective study of 15 individuals concluded that endoscopic management of small-bowel polyps in PJS using double-balloon endoscopy decreased the occurrence of urgent laparotomy by decreasing the mean number of resected polyps larger than 20 mm with each procedure [Sakamoto et al 2011].

Significant interfamilial variability in the age at which polyps first appear is observed, suggesting that the natural history of polyps in a family may be a predictor of severity for offspring. In studies from MD Anderson Cancer Center, the median age at which GI symptoms first appeared was ten years, while the median age at first polypectomy was 13 years [Amos et al 2004]. These data have prompted an earlier start date for surveillance procedures to detect and remove gastrointestinal polyps to decrease malignancy and complications of bowel obstruction [van Lier et al 2010, Latchford et al 2011].

Mucocutaneous pigmentation. Melanocytic macules (MM) are rarely present at birth; they become pronounced in most children

before the fifth year, but then may fade in puberty and adulthood. Children often present with dark blue to dark brown mucocutaneous macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa. Hyperpigmented macules on the fingers are also common. In one series, 94% of individuals with PJS had perianal MM, 73% had MM that affected the digits, 65% had MM on the buccal mucosa, and 21% had MM at other sites [Utsunomiya et al 1975].

Histologically, increased melanocytes are observed at the epidermal-dermal junction, with increased melanin in the basal cells. No malignancy risk is associated with MM.

Gonadal tumors. Females with PJS are at risk for ovarian sex cord tumors with annular tubules (SCTATs) and mucinous tumors of the ovaries and fallopian tubes. Symptoms include irregular or heavy menstrual periods and, occasionally, precocious puberty due to hyperestrogenism. SCTATs in PJS are bilateral multifocal small tumors with focal calcification and a typically benign course [Young 2005]. In contrast, sporadic SCTATs are large, unilateral, and associated with a 20% risk of malignancy.

In an Italian series of 61 females with PJS, three had ovarian cancer, one was a malignant SCTAT [Resta et al 2013]. In a Dutch series of 69 females with PJS, 2 females had malignant Sertoli cell ovarian tumors and one had ovarian small cell cancer [van Lier et al 2010].

Males occasionally develop large cell calcifying Sertoli cell tumors (LCST) of the testes derived from sperm cord cells. These tumors may secrete estrogen and can lead to gynecomastia, advanced skeletal age, and ultimately short stature, if untreated. Multifocal calcifications are typically seen on testicular ultrasound. Malignant transformation is unusual. Aromatase inhibitors help reverse the hormonal effects of Sertoli cell tumors including reduction of gynecomastia and slowing of linear bone growth and bone age

[Crocker et al 2014]. In a series including 64 males with PJS, one testicular seminoma was reported [van Lier et al 2010].

Malignancy. Individuals with PJS are at increased risk for intestinal and extraintestinal malignancies.

Adapted from Syngal et al [2015]

Table 1: Cumulative risk of cancers in PJS

Cancer site	General population risk (%)	Peutz Jeghers Syndrome	
		Risk (%)	Average age at diagnosis (years)
Colorectal	5	39	42-46
Stomach	<1	29	30-40
Small bowel	<1	13	37-42
Breast	12.4	32-54	37-59
Ovarian (SCTAT)	1.6	21	28
Cervix (adenoma malignum)	<1	10	34-40
Uterus	2.7	9	43
Pancreas	1.5	11-36	41-52
Testicular (Sertoli cell tumor)	<1	9	6-9
Lung	6.9	7-17	47

1. SCTAT = sex-cord tumor with annular tubules

Colorectal and gastric cancers can arise from adenomas that are commonly found in individuals with PJS. A marked increase in cancer incidence after age 50 years is notable.

Breast cancer and ovarian cancers can occur at early ages in Peutz-Jeghers syndrome. The breast cancer risk in women with PJS may approach that of women who have a pathogenic variant in *BRCA1* or *BRCA2*. Some families with PJS report relatives with

early-onset breast cancer, suggesting that some family members with a pathogenic variant may on occasion develop breast or other cancers without having symptoms from the hamartomatous polyps.

Cervical cancer. Adenoma malignum is a rare well-differentiated adenocarcinoma of the uterine cervix. Presenting symptoms include bleeding or a mucoid, watery vaginal discharge. Histologic diagnosis can be difficult on small pathologic samples. The five-year survival after surgery is 60% [Tsuda et al 2005].

3.2 Genotype-Phenotype Correlations

Data on genotype-phenotype correlation related to *STK11* pathogenic variants are conflicting. Further analysis of pooled registry data is needed to better characterize genotype-phenotype correlations and confirm malignancy risks.

In a study of 297 individuals with PJS, the type or site of the *STK11* pathogenic variant did not influence cancer risk [Lim et al 2004]. Initial reports that pathogenic variants in exon 3 [Lim et al 2004] or exon 6 [Mehenni et al 2007] were associated with an increased cancer risk have not been replicated by subsequent studies. A review of 419 affected individuals found that the variant type and site within the functional domains of the expressed protein did not affect cancer risk [Hearle et al 2006a].

In contrast, Amos et al [2004] found that individuals who had pathogenic *STK11* variants that predicted premature truncation and those who tested negative for pathogenic variants had similar ages of onset for first-reported polyps or polypectomy, and those with missense variants had later onset for these symptoms. Salloch et al [2010] similarly found that persons with pathogenic *STK11* variants that predicted premature truncation had more gastrointestinal surgeries, a higher polyp count, an earlier age of first polypectomy, and a greater risk of melanoma than persons with other pathogenic variants.

The risk for small-bowel intussusception was not influenced by *STK11* variant status [Hearle et al 2006b].

Pathogenic variants affecting protein kinase domain XI correlated with a 90% (9/10) incidence of GI polyp dysplasia compared to an 11.8% (2/17) incidence of polyp dysplasia in individuals with pathogenic variants affecting other regions of the protein [Wang et al 2014].

3.3 Penetrance

To date all reported individuals with pathogenic variants in *STK11* have shown clinical manifestations.

3.4 Nomenclature

The following terms have also been used for PJS:

- Polyp and spots syndrome
- Inherited hamartomatous polyps in association with mucocutaneous melanocyte macules
- Hutchinson Weber-Peutz syndrome
- Perioral lentiginosis (sometimes used inappropriately as a synonym for PJS)

3.5 Prevalence

Birth prevalence has not been reliably established; estimates range widely from 1:25,000 to 1:280,000 [Tchekmedyian et al 2013].

PJS can occur in any racial or ethnic group.