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Serine/threonine kinase 11 (STK11) associated adnexal tumors: from biology to therapeutic impact

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Abstract

Female adnexal malignancies, while relatively uncommon, exhibit high mortality rates due to often-late diagnosis. The serine/threonine kinase 11 (*STK11*) is a tumor suppressor gene, and its inactivation or mutation often leads to an autosomal dominant genetic disorder known as Peutz-Jeghers syndrome (PJS), which is associated with ovarian and cervical cancers. *STK11*-associated adnexal tumors mostly originate from the ovary, with a low incidence rate but high metastasis rates worldwide. In addition to surgery and chemotherapy, it is necessary to optimize relevant screening policy and targeted therapy. *STK11*-associated adnexal tumors are difficult to diagnose by histopathology. Although genetic testing involves higher costs, it can serve as a primary preventive measure for high-risk populations with *STK11*-associated tumors. A more intensive screening program (MISP) is needed for individuals with significant clinical symptoms and a family history of PJS. These tumors may be adequately treated with fertility-sparing surgery in young women with lower malignant potential tumors. Prophylactic adnexectomy, chemotherapy, and immunotherapy may offer potential clinical benefits but also pose significant challenges. Therefore, surgery should be undertaken with careful and comprehensive consideration of the patient's age, reproductive history, risk of malignancy, genetic mutation lineages, post-operative complications, and other conditions. Further research is essential to develop better screening, diagnostic, and treatment strategies.

Keywords Serine/threonine kinase 11, Gynecological oncology, Genetic susceptibility

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Introduction

Female adnexal malignancies, including ovarian cancer (OC) and fallopian tube cancer (FTC), pose a significant threat to women's health globally. Among them, OC incidence rate ranks third only after cervical cancer and uterine relevant cancer, while the mortality rate of OC remains the highest among malignant tumors of the female reproductive system. Until 2020, OC was the 8th most common cancer globally among the female population, with an estimated diagnosis rate of 3.7% and a mortality rate of 4.7% among all cancers in women [1]. According to 2022 GLOBOCAN statistics for 36 cancers in 185 countries, there were 324,398 new OC cases and 206,839 OC deaths, accounting for 3.4% of incidence and

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4.8% of mortality in female patients. Age-standardized rate analysis indicated that approximately 3.8–4.3 per 100,000 females were diagnosed with OC, and 6.0–7.0 per 100,000 females died from OC [2]. In the United States, an estimated 19,680 new cases and 12,740 deaths were projected for 2024 [3]. More than 70% of OC cases are not diagnosed until the cancer has progressed to stage III or IV, thus leading to a 5-year overall survival (OS) of 47.4%. Actually, it is well-established that the prognosis of OC is strongly associated with the stages of cancer. The 5-year OS for early and middle-stage ovarian cancer can reach approximately 80-90%, whereas the 5-year OS for advanced ovarian cancer with metastasis is only about 25% [4]. Surgery, chemotherapy and targeted therapy have significantly improved the prognosis of OC in recent years [5, 6]. Additionally, the incidence and mortality rates of FTC were not accurately recorded due to the uncertain location of primary lesions [7].

Genetic susceptibility is considered a key factor in the occurrence and progression of OC. *BRCA1/2* are the most well-known genes initially identified to be associated with hereditary OC [8, 9]. The Next-Generation Sequencing (NGS) has facilitated the identification of additional genetic alterations in OC, including mutations in *TP53*, *PTEN*, *CDH1* and *STK11* [10]. *STK11*, a tumor suppressor gene located on chromosome 19p13.3 with a size of approximately 23 kb, is expressed in almost all human tissues. It is primarily responsible for the phosphorylation of at least 14 proteins, playing a crucial role in maintaining the balance of cellular energy metabolism, cell polarity, growth requirements, and consistent tumor suppression [11]. The inactivation or mutation of *STK11* usually causes an autosomal dominant genetic disease called Peutz-Jeghers syndrome (PJS), with an incidence of about 1/50,000 to 1/250,000 in live births [12]. The germline mutation rate of *STK11* in PJS patients ranges from 66 to 94%. Clinically, *STK11* mutation or inactivation and its relevant disease mainly lead to hamartomatous gastrointestinal polyps, mucocutaneous pigmentation, and the increased risk of small bowel, breast, testicular, colorectal, gastric, pancreatic, gallbladder and lung cancers. In gynecology, it often results in the sex cord tumor with annular tubules (SCTATs) in ovaries and lobular endocervical glandular hyperplasia (LEGH)/minimal deviation adenocarcinoma (MDA) in cervix [13, 14]. Cases of MDA with PJS were reported to have a poorer prognosis than non-*STK11* mutation cases do, as MDA has an aggressive clinical course [15].

The rare pathological features, differentiation patterns and poor prognosis of *STK11*-associated tumors highlight the necessity of relevant screening policy or targeted therapy in addition to surgery and chemotherapy. However, there has been limited research on these topics. This review aims to summarize the available literature about *STK11*-associated adnexal tumors, with the expectation of developing novel screening, diagnostic, and treatment strategies in gynecological oncology.

Primary situation: previous research on *STK11*-associated adnexal tumors

Brief overview of adnexal tumors: OC and FTC

OC is the 8th most common cause of deaths in female carcinoma [1]. By 2018, there were about 295,414 new cases and 184,799 deaths of OC [16]. The incidence rate of malignant solid tumors originating from fallopian tubes is still uncertain, which could be inferred to be much less than 1/10,000 with the exception of fallopian tube choriocarcinoma. Previous studies indicated an incidence rate of 0.36/100,000 to 0.41/100,000 every year, referring to approximately 300 to 400 annual cases [17]. However, recent studies suggest that about 80% of tumors classified as ovarian or peritoneal high-grade serous carcinoma may actually originate from the fimbriae of the fallopian tubes. Clinically, the uncertain definition of primary lesions can lead to divergence in diagnosis and treatment, thereby affecting prognosis.

In 2014, the World Health Organization (WHO) updated a novel classification of OC, FTC and peritoneal cancer in both clinical and pathological contexts to enhance the understanding of these malignancies [18, 19]. This update was accompanied by new surgical staging published by FIGO [19, 20]. The new FIGO staging system integrated the epithelial ovarian/fallopian tube/peritoneal carcinoma, as well as the ovarian stromal and germ cell tumors. Although the new staging system can better predict different clinical outcomes in some cases, there are still limitations in classification of FIGO III/IV stage outcomes and overlap of molecular characteristics [21–24]. Most OC cases are sporadic, with the most common pathological types being epithelial, germ cell, and sex cord stromal tumors. Epithelial ovarian cancer (EOC) includes high-grade serous carcinoma (HGSC, 70%), endometrioid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (3%), and low-grade serous carcinoma (LGSC, < 5%) [25, 26]. FTC is often diagnosed at advanced stages, mostly as HGSC, poorly-differentiated/undifferentiated carcinoma or the carcinosarcoma. Tumor cells typically exhibit a high level of chromosomal instability, similar to OC [17]. As mentioned, the incidence rate of FTC is not currently clear because the original location of carcinoma remains uncertain. Researchers discovered pre-malignant serous tubal intraepithelial carcinoma (STIC) and potentially invasive HGSC in fallopian tube specimens as early as 2001 (particularly in the fimbria) without neoplasms found in ovarian tissues during risk-reducing surgery [27]. This finding suggests that many OC-related deaths might actually result from tumors originating in the fallopian tubes, further

demonstrated by whole exome sequencing (WES) and copy number analysis [28].

The genetic susceptibility of OC has always been the focus of attention. Germline mutations in more than 10 genes have been associated with hereditary OC, primarily *BRCA1/2*. Studies showed that the cumulative risk for OC to age 80 years was about 44% (95% CI, 36-53%) for *BRCA1* and about 17% (95% CI, 11-25%) for *BRCA2* carriers [29]. The incidence of OC/FTC has also been correlated with hereditary diseases including Li-Fraumeni syndrome, Cowden syndrome, Lynch syndrome, diffuse gastric cancer syndrome, and PJS [13]. For example, the OC risk for PJS patients with *STK11* mutation is about 18-21% (39–44% by age 70 and 11–18% by age 70) [10]. The incidence of OC/FTC has also been correlated with hereditary diseases including Li-Fraumeni syndrome, Cowden syndrome, Lynch syndrome, diffuse gastric cancer syndrome, and PJS [30]. Despite active treatments including primary/interval debulking surgeries, chemotherapy (mostly a combination of paclitaxel and platinum), targeted therapy, and vascular endothelial growth factor (VEGF) inhibitors, the OS or progression-free survival (PFS) of female adnexal tumors have not been significantly prolonged. Therefore, more advanced and earlier screening targeting genetic susceptibility and stepped prevention for patients may be more clinically significant.

Serine/threonine kinase 11 (*STK11*) and PJS

PJS is an autosomal dominant disorder with an incidence rate of about 1/50,000 to 1/250,000 globally [12]. The clinical characteristics primarily include: (1) mucocutaneous pigmentation, which occurs in about 95% of cases at birth or early infancy; (2) the presence of two or more Peutz-Jeghers polyps (P-J polyps) confirmed by histopathology, any number of P-J polyps with a family history of the syndrome, or any number of P-J polyps with corresponding mucocutaneous pigmentation; (3) tumor susceptibility, including but not limited to gastrointestinal, colorectal, breast, and pancreatic malignancies. In 1895, Connor et al. identified a pair of twins with dark spots on the lip mucosa, one of whom died of intussusception and the other of breast cancer. In 1921, Jan Peutz observed that two boys in a Dutch family had multiple gastrointestinal polyps and mucocutaneous pigmentation, proposing that it was a familial genetic disease [14]. And in 1949, PJS was first described systematically by Jeghers [31]. Over the next half-century, studies gradually identified *STK11* as a significant cause of PJS [14]. SCTATs were firstly reported by Robert E. in 1970, and *STK11*-associated adnexal tumors were first reported in 1976 by Taxy and Battifora [32]. The discovery process is shown in Fig. 1. The cancer risk for PJS patients is about 18 times higher than that of the general population, with approximately 85% of malignant tumors occurring before

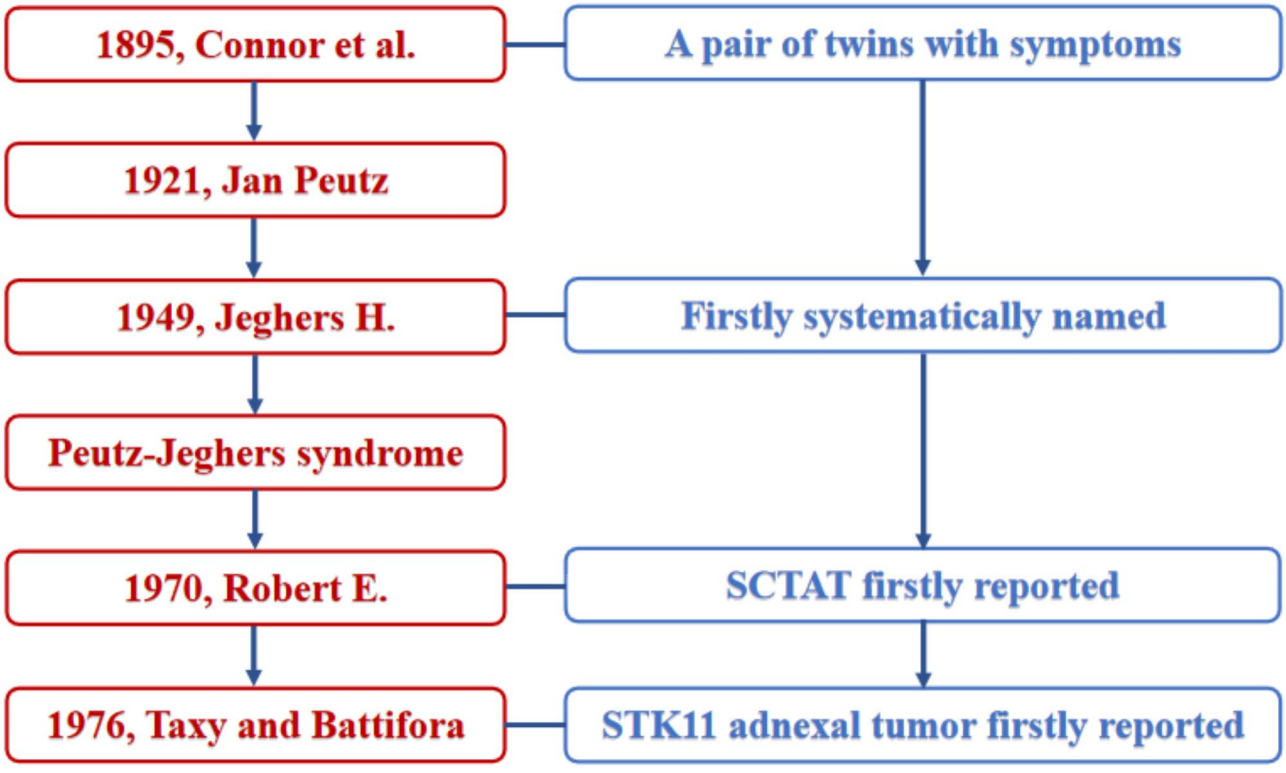

Fig. 1 Discovery process of *STK11*-associated adnexal tumors

the age of 70. In gynecological diseases, PJS is considered a promoting factor for SCTATs, MDA, and LEGH, as previously mentioned. Therefore, the spectrum of adnexal tumors that may occur in PJS patients should be noted. SCTATs and MDA occupy the vast majority of the PJS-associated gynecological oncology. *STK11*-associated FTC is rarely reported. Additionally, ovarian tumors associated with PJS include a small number of Sertoli-Leydig cell tumors (SLCT), granulosa cell tumors (GCT), and mucinous tumors, which are rarely reported. The morphological characteristics of mucinous tumors are similar to lobular cervical gland hyperplasia, and the tumor cells exhibit gastric mucinous epithelial differentiation [33]. Among these, SCTATs are most likely to be complicated with PJS, with about 36% of SCTAT cases reported, and 20% progressing to malignancy [12, 34]. In a multi-center study, researchers obtained 22 *STK11*-associated adnexal tumors to fully elucidate their clinicopathologic and genomic features, detecting an association with PJS in nearly 50% of cases [35]. This suggests that PJS, *STK11* mutation and relevant adnexal tumors are closely linked. Therefore, focusing on adnexal tumors in PJS patients or those associated with *STK11* mutation is of great clinical significance.

About 66-94% of PJS cases have been attributed to germline mutations in the *STK11* gene [14]. *STK11* consists of 9 coding exons and 1 non-coding exon, with an mRNA size of approximately 3.0-3.3 kb. The *STK11* gene encodes the *STK11* protein kinase which contains 433 amino acids, with 3 following functional regions: (1) N-terminal non-catalytic domain; (2) the kinase catalytic domain; (3) C-terminal non-catalytic regulatory domain containing a *CAAX* box. The main causes of *STK11* inactivation or mutation include nonsense mutations, missense mutations, frameshift mutations, and splice site mutations. Basically, the *AMP*-activated protein kinase (*AMPK*) - mammalian target of rapamycin (*mTOR*) pathway, *Wnt-C-Myc* pathway, *TP53* mutation, TGF-β suppression and epithelial mesenchymal transformation (EMT) associated biomarkers (Vimentin, E/C-cadherin, Cytokeratin, etc.) are all involved in carcinogenesis of *STK11* mutation [36–39]. It is noteworthy that some loss of heterozygosity (LOH) has been observed in the chromosome 19p13.3 region, about 190 kb from *STK11*, suggesting that *STK11* inactivation/mutation is not the only tumor promoter in 19p13.3 [40, 41]. Additionally, *STK11* inactivation contributes to post-translational modifications including phosphorylation, ubiquitination, and regulation of protein abundance and function through intracellular localization, protein stability, conformation, and protein-protein interactions. For example, concurrent deletion of *PTEN* and *STK11* resulted in the development of high-grade papillary serous carcinoma with increased *mTOR* activity in OC. It has been reported that the loss of *STK11* in primary and immortal cells of *TP53* mutants induces premature cellular senescence and causes G2/M cell cycle arrest. This suggests that *STK11* may affect cell polarity and differentiation, as well as promote oncogenic transformation. Additionally, *STK11* mutation or deletion is reported to influence the metastatic potential, dormancy, anoikis, fibronectin expression of OC cells [42]. These findings are illustrated in Fig. 2. Studies on HeLa cell lines of cervical carcinoma have also indicated that the homozygous deletion (HD) locus in *STK11* remains unidentified [43]. Most studies have established correlations between *STK11* and cancers of the lung, pancreas, stomach, and colorectal regions [44–46], while *STK11*-associated gynecological oncology (GO) primarily involves SCTATs and MDA. The histomorphological characteristics of *STK11*-associated GO are rarely observed and are challenging to diagnose through histopathology alone, often requiring NGS and immunohistochemistry (IHC) results. Research on the mechanisms of *STK11*-associated GO, particularly for adnexal tumors, is limited due to its low incidence rate, indicating the need for more clinical case accumulation.

Cases, features and clinical decisions of *STK11*-associated adnexal tumors

Recent reports on *STK11*-associated adnexal tumor cases

Indeed, the perception of relevance was suggested as early as 1999, with the identification of a missense mutation and loss of LOH in OC [47]. In 2000, researchers from the Mayo Clinic analyzed specimens from two PJS-associated SCTATs, five sporadic SCTATs, and eight MDAs. They found *STK11* gene mutations (missense mutations and allelic deletions) in both PJS-associated SCTATs, along with LOH in three out of eight MDA cases in other regions of chromosome 19p13.3. In contrast, no *STK11* mutations were observed in the sporadic SCTATs and the remaining five MDA cases [48].

In 2007, a four-year-old girl with gonadotropin-independent precocious puberty and an ovarian Sertoli cell tumor (SCT) was first reported [49]. Similarly, a two-year-old girl with a SLCT was reported in 2010 [50]. This patient exhibited significant features of hamartomatous gastrointestinal polyps and pigmentation. Additionally, Yucel Cicek OS et al. reported an infertile woman with an exceptionally high anti-Mullerian hormone (AMH) level (319.63 ng/ml), confirmed to have SCTATs and PJS through IHC and gene sequencing in 2022 [51]. These three cases suggest that sexual hormone disorders might potentially be associated with the incidence rate of *STK11*-associated adnexal tumors, both in infancy and during childbearing age.

According to the clinical characteristics of PJS and *STK11* gene sequencing, the prognosis of patients may be predicted. Kwon SY et al. reported two cases of SCTATs

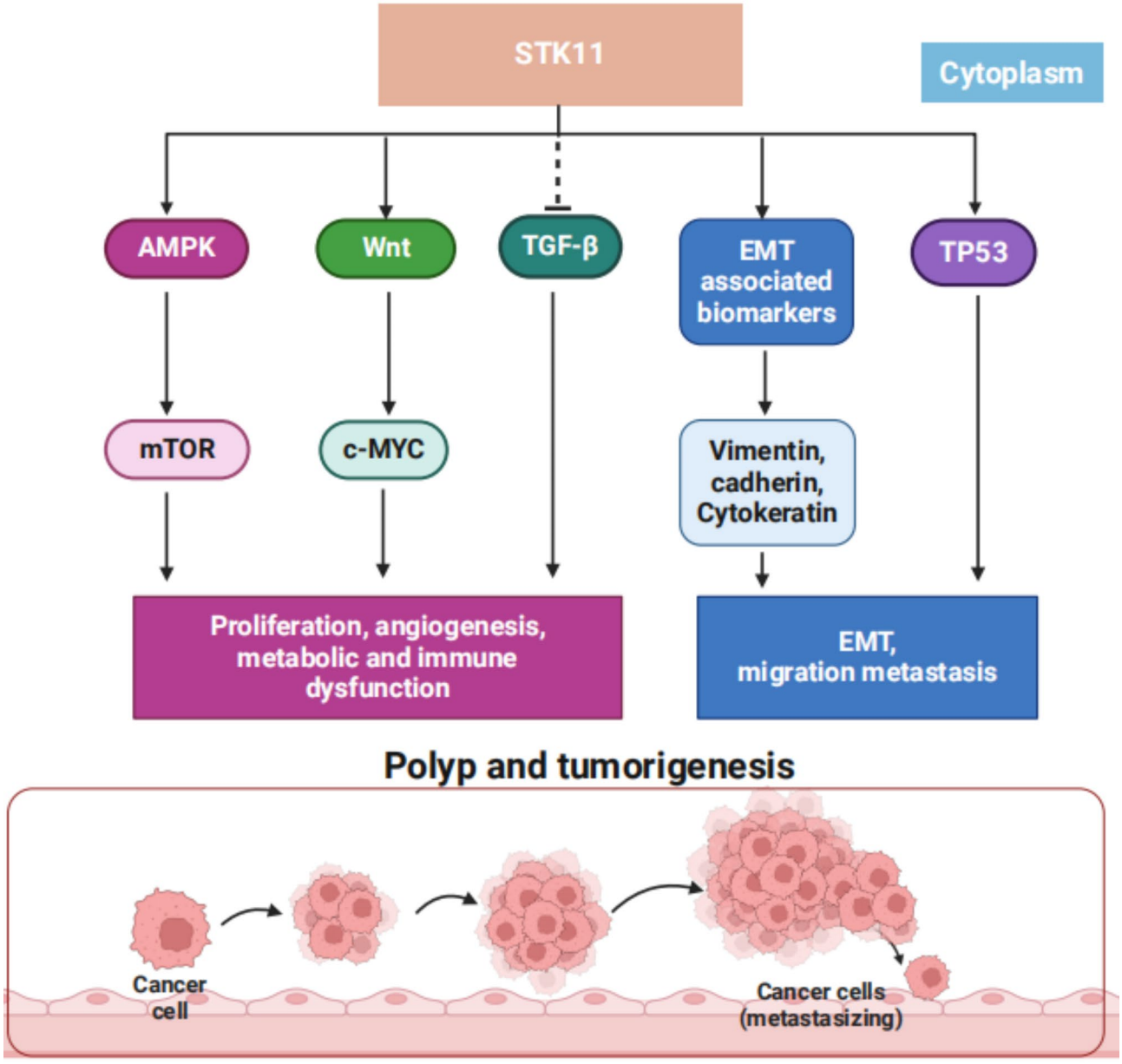

Fig. 2 Signaling pathways associated with carcinogenesis of *STK11*-mutation. The *AMP*-activated protein kinase (*AMPK*) - mammalian target of rapamycin (*mTOR*) pathway, *Wnt-C-Myc* pathway, *TP53* mutation, TGF-β suppression and epithelial mesenchymal transformation (EMT) associated biomarkers (Vimentin, E/C-cadherin, Cytokeratin, etc.) are all involved in carcinogenesis of *STK11* mutation

in 2012 [52]. Case 1 involved a 36-year-old woman with ovarian mucinous cystadenoma (MCA) accompanied by SCTATs and bladder involvement. P-J polyps and a family history of P-J polyps and colon cancer were evident from medical records. Despite receiving a combination of chemo-radiation therapy and three cycles of irinotecan and cisplatin, the patient expired one year after radical surgery. In contrast, Case 2 had a much better prognosis, likely due to comparatively mild clinical features with only a history of colonoscopic polypectomy.

Other cases reported over the past five years include: (1) a pyloric gland-phenotype ovarian mucinous tumor with histomorphology similar to LEGH detected in a 47-year-old postmenopausal woman in 2017 [33, 53]; (2) a 59-year-old woman with concurrent endometrial adenocarcinoma and ovarian granulosa cell tumor (GCT) in 2018 [54]; (3) a 24-year-old woman described as having a composite synchronous cervical malignancy comprising LEGH, MDA, and gastric-type adenocarcinoma (GTA), also found with a serous tubal intraepithelial lesion (STIL) in her right fallopian tube, reported in India

in 2019 [55]; (4) the first globally reported case of bilateral PJS-associated SCTATs combined with unilateral adult GCT in China in 2023 [56]. All four cases demonstrated germline/somatic mutations of the *STK11* gene and were reported primarily due to their extremely rare histopathology. It should be noted that primary *STK11*-associated FTC might be overlooked or misdiagnosed as other malignancies, although there are no relevant case reports. The clinical, histopathological, and genetic information of all the above cases are summarized in Table 1.

Combining the findings from the above cases, the characteristics of patients with *STK11*-associated adnexal tumors can be summarized as follows: (1) mass in the adnexal region, with the majority being SCTATs; (2) typical presentation of PJS; (3) sexual hormone disturbance; and (4) other non-specific clinical manifestations.

Screening of *STK11* associated adnexal tumor

According to the US Surveillance, Epidemiology, and End Results (SEER) database, the risk of ovarian cancer (OC) in the general population is approximately 1-2%. The 2022 NCCN guidelines list the OC risk in carriers of pathogenic or likely pathogenic mutations in OC susceptibility genes [57]. Although an OC risk of 18-21% and a total gynecological oncology (GO) risk of 9-21% have been reported in individuals with *STK11* mutations, previous guidelines did not routinely include *STK11* in genetic/familial risk assessments. Furthermore, the risk of GO by the age of 60 is approximately 13% in carriers of pathogenic variants (PV) and likely pathogenic variants (LPV) of *STK11* [10, 13]. Compared with the extensive screening recommended by the NCCN guidelines for women aged 18–60 years (beginning at age 18–20), the American College of Gastroenterology (ACG) defines an initial screening age of 25 (with an average diagnosis age of 28) for *STK11*-associated OC [58]. However, both the ACG and the European Society of Digestive Oncology (ESDO) guidelines for hereditary gastrointestinal cancer recommend a baseline screening age of 8 when relevant polyps are found [58, 59]. Considering these results, a screening age of ≥ 8 or even earlier for adnexal tumors may be considered when the following complications are present: (1) multiple polyps confirmed by endoscopy or previous surgery (especially hamartomatous polyps); (2) pigmentation on the skin or mucous membranes, particularly on the lips, buccal mucosa, or digits; (3) confirmed hereditary features and a family history of Peutz-Jeghers syndrome (PJS). In principle, these conditions also apply

Table 1 2014 FIGO staging system for ovarian/fallopian tube/peritoneal carcinoma

Researcher	Time	Pathology	Mutation locus	PJS associated Symptoms
Massa G et al.	2007	SCT	*STK11* exon 1 c.130 A > T;p.Lys44X	☐ Associated family history ☐ Associated polyps found ☐ Associated pigmentation
Howell L et al.	2010	SLCT	*STK11* exons 4–8 *STK11* deletion	☑ Associated family history ☑ Associated polyps found ☑ Associated pigmentation
Kwon SY et al. ***Case1***	2013	MCA & SCTATs	*STK11* exon 3 frame shift mutation	☑ Associated family history ☑ Associated polyps found ☑ Associated pigmentation
Kwon SY et al. ***Case2***	2013	MDA & SCTATs	None	☐ Associated family history ☑ Associated polyps found ☑ Associated pigmentation
Kim EN et al.	2017	Mucinous OC [a]	*STK11* exons 1–7 c.1-?_920+?del	☐ Associated family history ☑ Associated polyps found ☑ Associated pigmentation
Choi YJ et al.	2018	aGCT & EAC	*STK11* germline mutation c.339delG; p.L113fs	☐ Associated family history ☐ Associated polyps found ☐ Associated pigmentation
Neyaz A et al.	2019	STIL [b]	Not detected	☐ Associated family history ☑ Associated polyps found ☑ Associated pigmentation
Yucel Cicek OS et al.	2022	SCTATs	*STK11* exon 5 p.Asp207Glufs*76 (c.621_633del)	☐ Associated family history ☑ Associated polyps found [c] ☑ Associated pigmentation
Feng YY et al.	2023	aGCT & SCTATs	*STK11* germline mutation	☑ Associated family history ☑ Associated polyps found ☑ Associated pigmentation

Abbreviations: MCA, mucinous cystadenoma; SCTATs, sex cord tumor with annular tubules; MDA, minimal deviation adenocarcinoma; LEGH, lobular endocervical glandular hyperplasia; SCT, Sertoli cell tumor; SLCT, Sertoli-Leyding cell tumor; aGCT, adult granulosa cell tumor; EAC, endometrial adenocarcinoma; STIL, serous tubal intraepithelial lesion. **Notes**: [a]This case was reported as the pyloric gland-phenotype mucinous OC resembling LEGH; [b] This case was reported as the pyloric gland-phenotype mucinous OC resembling LEGH; [c] A history of intestinal polyp surgery performed 20 years ago

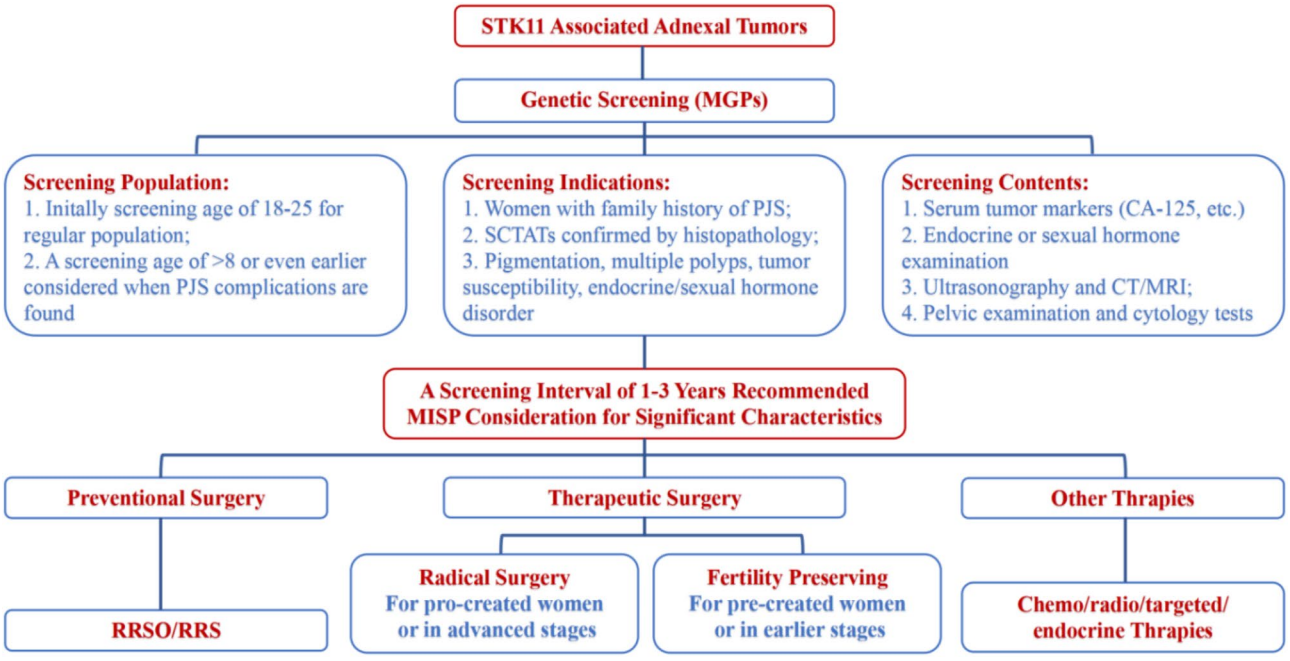

Fig. 3 Screening and Therapeutic Strategies of *STK11*-Associated Tumors. Abbreviations: MGPs, multiple-gene panels; PJS, Peutz-Jeghers syndrome; SCTATs, sex cord tumor with annular tubules; MISP, more intensive screening program; RRSO, risk-reducing salpingo-oophorectomy; RRS, risk-reducing salpingectomy

to the targeted screening population specified in previous guidelines, except for the earlier screening age.

The screening protocol consists of pelvic examination (PE), ultrasonography (US), CA-125 and Pap smear (or cervical cytology testing). CA-125 has lower specificity compared to other tumor markers such as human epididymis protein 4 (HE4) or the Risk of Ovarian Malignancy Algorithm (ROMA) index for the diagnosis of OC and FTC. Magnetic resonance imaging (MRI) is recommended when US indicates intra-pelvic lesions where the possibility of malignancy cannot be ruled out. Generally, a screening interval of 1–3 years is appropriate. However, most individuals without a relevant family history would not typically undergo these examinations or standardized digestive endoscopy at an early age. Therefore, a more intensive screening program (MISP) should be implemented for individuals with a family history of PJS, significant pigmentation, sexual hormone or endocrine disorders (especially during infancy or toddler periods). MISP could be defined as a more comprehensive screening protocol, including PE, US, tumor markers, and cytology tests, with a closer screening interval of 1 year. Additionally, MRI, gastroscopy, and colonoscopy should be conducted for further diagnosis if necessary, as shown in Fig. 3 [58]. For the female population aged 2–8 who are not suitable for PE, trans-vaginal US, or endoscopy, genetic testing might be appropriate. Sexual hormone disorders and endocrine diseases such as diabetes could also be considered as indicators and prognosis predictors for *STK11*-associated adnexal tumors, as *STK11/RB1* replication stress has been demonstrated to be linked to PARP inhibitor (PARPi) and WEE1 inhibitor activity [60].

The NCCN guidelines for the genetic management of OC do not recommend genetic testing for individuals under the age of 18 if the results would not impact clinical decisions [57]. Additionally, the mutation rate of *STK11* is quite low. A study in the Caribbean showed that only 4% of variant carriers had PV/LPV in *RAD51C*, *CHEK2*, *ATM*, *STK11* and *NBN*, with only 0.6% had PV/LPV in moderate risk genes including *RAD51C*, *CHEK2*, *NBN*, *STK11*, and *ATM* [61]. Therefore, gene sequencing may only be suitable for individuals with clinical characteristics of PJS at an early age (2–8 years) or with a clear family history. Germline mutations are divided into PV, LPV, variants of uncertain significance (VUS), possibly benign mutations (likely benign variants, LBV) and benign mutations (BV), based on American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) classifications [62]. Clinical interventions are generally consistent for both PV and LPV carriers. *BRCA1* and *BRCA2* were previously the primary focus of genetic testing, with some patients undergoing only *BRCA1/2* and HRD related genetic testing after diagnosis. As of 2022, the NCCN guidelines recommend screening for 21 genes, including *STK11*. A study by Kurian AW et al. indicated that from 2012 to 2019, the number of genes tested increased by 28%, while the annual number of individuals undergoing

genetic testing increased by only 2%. Of the patients tested, 87.3% had one test, 10.7% had two tests, and 2.0% had three or four tests. Most patients (71.8%) were first tested within six months of diagnosis, 24.2% more than six months after diagnosis, and only 4.0% before the diagnosis of breast cancer or OC. Among them, the number of genes tested for OC increased from 1 to 81, while the trend of genetic testing for individuals over 60 years old increased, and the testing rate for individuals under 45 years old was comparatively lower (< 15%) [63]. By 2019, multiple-gene panels (MGPs) had nearly replaced simple *BRCA1/2* testing. However, few individuals undergo genetic testing, especially before the diagnosis of diseases, as a primary prevention measure for cancer. Race, age, genetic history, and other factors must all be considered in genetic testing, which involves additional costs. Therefore, it is not entirely feasible to apply genetic testing as a screening method for the entire population. However, genetic testing might be used as a primary preventive measure for high-risk populations associated with *STK11* mutations, as mentioned above. It is more important to reduce the gap and cost of genetic testing and expand the testing population, rather than selecting more genes for testing.

Diagnosis of *STK11* associated adnexal tumor

Clinical manifestations can be an important reference for the disease. Patients with *STK11* gene anomaly usually show corresponding symptoms such as mucosal pigmentation, gastrointestinal multiple polyps and sexual hormone disorders, and with family history related to PJS in more typical cases. The most significant external manifestation of primary lesions is the hamartomatous polyps in patients, which could be distributed nearly throughout the whole digestive tract and progress quickly, with complications of intussusception, acute intestinal obstruction, hematochezia and anemia [12, 64]. The tumors do not originate only from the ovaries, but may also originate from the fallopian tubes, peritoneum, cervix or even the digestive system. Among them, primary FTC with *STK11* mutation is extremely rare while some *STK11*-associated OC or peritoneal carcinoma may originate from fallopian tubes [65].

Histopathology and genetic testing remain the gold standard for diagnosing *STK11*-associated adnexal tumor. *STK11*-associated tumors mostly occurs as SCTATs, with or without other pathological classifications of SCT, SLCT, MCA, etc. Under most situations SCTATs present as a well-defined round or oval epithelial island consisting of annular tubules with unmarked cavities. The annular structures are located within the fibrous interstitial ovary. The stroma may contain focal luteinized cells and present as focal hyalinization, which can be significant in some cases. SCTATs are usually relatively large (> 5 cm), solid, typically bilateral, and multifocal in patients with *STK11* gene anomalies or PJS [32]. The distinctive features of annular tubules and calcification are often detected. Additionally, the pathological morphology is arranged to form annular tubules, with the nuclear pole reversed near the luminal surface and transparent bodies around. Some SCTATs can also be accompanied by cytoli cell tumors, mucinous/serous epithelial tumors, mature teratomas, and other components [12]. SCTATs have been classified as sex cord-stromal tumors since 2014. However, there is controversy regarding this separate categorization because it is still uncertain whether the origin is from stem cells (mainly differentiating into sex cord) or from granulosa cells (mainly differentiating into Sertoli cells). Features of SLCT, GCT, and mucinous tumors can also be detected, as mentioned earlier.

The IHC positive index includes epithelial (AE1/AE3, CAM5.2, CK7), sex cord stromal (inhibin, calretinin, WT1) and mesothelial (calretinin, WT1, D2-40), along with hormone receptors and CD10. And FOXL2, SF1, PAX8, EMA, GATA3, TTF1 and claudin-4 usually show negative or limited expression. The desmin index could be positive [32]. The morphological characteristics of mucinous tumors were similar to cervical lobular gland hyperplasia, as tumor cells showed gastric mucinous epithelial differentiation, and MUC6 and HIK1083 could be positive [33]. Basically, the IHC expression of *STK11*-associated adnexal tumors is nonspecific. It is difficult to obtain a certain diagnosis from the IHC results of pathological specimens, and genetic testing must be applied. Although OC and FTC are often insidious diseases when diagnosed in earlier stages, they could be easier to detect when combined with *STK11* inactivation/mutation. Germline mutation of *STK11* gene is considered the main genetic cause of PJS. The main causes of *STK11* inactivation or mutation include nonsense mutations, missense mutations, frameshift mutations, and splice site mutations. Bennett JA et al. even detected *STK11* copy number variations during the molecular analysis in 15 cases of probably Wolffian-original female adnexal tumors [66].

Differential diagnosis based on clinical manifestations may be effective, but it is not the gold standard. When making a differential diagnosis, the patient's pathological characteristics and genetic testing results should be fully considered. Generally, in addition to the common characteristics of gynecological tumors (abdominal or pelvic mass, weight loss, ascites, etc.), patients with *STK11* mutation also exhibit the features associated with PJS mentioned above. Most tumors are paratubal, with about 30% showing secondary adnexal involvement. These symptoms are also nonspecific, so histopathological morphology is important for differential diagnosis. In addition to the typical features, signet ring-like cells, whorls, rhabdoid cells, squamous cells, glomeruloid cell

appearances, and bland mucinous epithelium can occasionally be seen. PJS-related SCTATs should first be differentiated from sporadic SCTATs, which are often single cases of unilateral ovary, with palpable masses and rare calcification. Subsequently, the differential diagnosis should primarily refer to female adnexal tumors of probable Wolffian origin (FATWO), sex cord stromal tumors, mesothelial neoplasms, mesonephric-like adenocarcinoma (MLA), and endometrioid carcinoma [12, 32].

The FATWO is considered biologically aggressive and has an overlap with *STK11* associated adnexal tumor which may lead to miss-diagnosis. Typically, FATWOs are smaller than *STK11*-associated adnexal tumors and exhibit tubular, sieve-like, and solid patterns microscopically. The cytology of FATWOs primarily consists of small epithelial cells with scant cytoplasm, oval and uniform nuclei, and infrequent mitoses. Among IHC characteristics, FATWOs are commonly positive for AE1, AE3, CAM5.2, CK7, inhibin, calretinin, WT1, D2-40, CD10, EMA, PAX8, GATA3, and MOC31, and negative for TTF1, BerEp4, CK5, and CK6. The hormone receptors (estrogen and progesterone receptors) can be positive, which is similar to the characteristics of *STK11*-associated adnexal tumors. Interestingly, the biological behavior of occurrence in extra-adnexal regions and recurrent diseases is rarely seen in FATWOs [32].

Sex cord stromal tumors (Sertoli-Leydig cell tumor, adult granulosa cell tumor, sex cord-stromal tumor, etc.) exhibit similar growth behavior and IHC profiles to *STK11*-associated adnexal tumors. However, as mentioned earlier, there is still controversy regarding the origin and differentiation trend of SCTATs. Clues for distinguishing sex cord stromal tumors include the expression status of hormonal markers and diffuse *SF1* and *FOXL2*, along with genetic alterations of *FOXL2* and *DICER1* [32, 67].

The differential diagnosis between mesothelial neoplasms and *STK11*-associated adnexal tumors primarily relies on clinical manifestations. Most mesothelial neoplasms have extra-adnexal and diffuse/multifocal peritoneal involvement, which is rarely seen in *STK11*-associated adnexal tumors. Both tumors show variable patterns and uniformly atypical epithelial cells in cytology. In terms of IHC index and molecular profiles, they can both be positive for calretinin, WT1, and D2-40, and negative for claudin-4. Immunoreactivity to estrogen receptor (ER), progesterone receptor (PR), and inhibin is comparatively less common in mesothelial neoplasms. However, alterations in *BAP1*, *CDKN2A*, *and NF2* are observed in mesothelial neoplasms. Notably, the loss of *BAP1* expression indicates peritoneal mesothelioma rather than an *STK11*-associated adnexal tumor. Recently, a particular type of mesothelial neoplasm named solid papillary mesothelial tumor (SPMT) has been discussed, characterized by alterations in *BAP1* and *CDKN2A* [32].

MLA is similar to mesonephric adenocarcinoma (MA) in morphological, IHC and molecular aspects. MLA is mainly found in the endometrium and the ovary rather than the cervix. *STK11*-associated adnexal tumors usually occur in para-adnexal soft tissues, while MLA primarily occurs in the ovaries. Tubular and ductal structures are observed in MLA, in contrast to the inter-anastomosing cords and trabeculae in a myxoid background seen in *STK11*-associated adnexal tumors. Cytologically, MLA often features crowded and overlapping cell nuclei with nuclear grooves and inconspicuous nucleoli, whereas *STK11*-associated adnexal tumors typically display only nuclear grooves. In terms of IHC, MLA is usually positive for PAX8, GATA3, and TTF1, and negative for inhibin, WT1, and hormone receptors. Conversely, *STK11*-associated adnexal tumors show opposite characteristics, with *STK11* alterations being detected [32].

It is comparatively easy to distinguish endometrioid carcinoma from *STK11*-associated adnexal tumors based on the typical original region, pathological, and cytological patterns. Endometrioid carcinoma is a type of conventional endometrioid carcinoma that may exhibit metaplastic changes (squamous, mucinous, etc.), with positivity for EMA, PAX8, and claudin-4, and negativity for WT1 and inhibin. At the molecular level, endometrioid carcinoma can show *CTNNB1* exon 3 mutations, which have not been found in *STK11*-associated adnexal tumors. Additionally, clinical features of conventional endometrioid carcinoma, endometriosis, adenofibroma, or metaplastic changes can serve as references for differential diagnosis [32].

Treatment of *STK11* associated adnexal tumor

In general, some cases of *STK11*-associated gynecological tumors occur in infancy or childbearing ages and typically exhibit lower malignancy. As a result, fertility-preserving surgery is still recommended for specific SCTAT patients. However, when these tumors are combined with other pathological types of adnexal tumors, they can become much more aggressive [65, 68]. Therefore, simple tumor resection is not recommended. Unilateral adnexectomy may also overlook additional sporadic lesions, especially in patients with *STK11* mutations, leading to a poor prognosis. Consequently, necessary lymph node resection or adnexal biopsy should be performed for suspicious lesions within the pelvic cavity or lesions with clear preoperative imaging [68].

Compared with sporadic SCTATs, *STK11*-associated SCTATs predispose to benign lesions, with approximately 1/5 undergoing malignant transformation [34]. SCTATs have been reported to be possibly related to sexual hormone (estrogen, progesterone, AMH, etc.)

disorders, presenting symptoms such as precocious puberty or amenorrhea, and are more prone to lymph node metastasis than other sex cord stromal tumors [69]. Additionally, extra-peritoneal lymph node metastasis has been frequently reported in PJS patients with gastrointestinal and pancreatic tumors. MDA is considered much more invasive in terms of lymph node metastasis and intra-peritoneal dissemination, despite being the best-differentiated cervical adenocarcinoma. These findings suggest that although *STK11*-associated adnexal tumors are better differentiated with lower malignant potential, their aggressive biological behavior may still adversely affect the prognosis. Therefore, comprehensive staging surgery, radiotherapy, chemotherapy, targeted therapy, and other treatments for some malignant and aggressive OC and FTC should be carried out in strict accordance with NCCN guidelines, especially when combined with highly malignant tumors [70]. Patients in the earlier stages or with lower-risk tumors, such as simple SCTATs, who wish to preserve fertility, could undergo fertility-preserving surgery, including unilateral adnexectomy or bilateral adnexectomy with preservation of the uterus.

Risk-reducing salpingo-oophorectomy (RRSO) has been widely implemented in clinical practice, primarily focusing on carriers of *BRCA1/2* PV/LPV. A study involving 5783 female patients with *BRCA1/2* mutations and an average follow-up time of 5.6 years showed that the annual risk of developing peritoneal cancer after oophorectomy was 0.20% for *BRCA1* mutation carriers and 0.10% for *BRCA2* mutation carriers. Prophylactic oophorectomy resulted in an 80% risk reduction for OC, FTC, or peritoneal cancer, and a 77% reduction in all-cause mortality for *BRCA1/2* carriers, with a hazard ratio (HR) of 0.24–0.39 [71]. The data suggested that *BRCA1* mutation carriers should undergo oophorectomy at age 35, and if specific patients choose to defer RRSO and opt for risk-reducing salpingectomy (RRS) until age 40–50, the occurrence rate of OC may increase to 4.0-14.2%. Another study indicated that performing RRSO for *BRCA1* pathogenic germline variant (PGV) carriers aged 35–40 years and *BRCA2* PGV carriers aged 40–45 years could reduce the risk of OC and breast cancer [72]. Kauff et al. also demonstrated that RRSO could reduce the occurrence rate of *BRCA1*-related gynecological cancer by about 85% [73]. There is a reported absolute risk for non-epithelial OC of 10-20% among *STK11* PGVs carriers [72]. Thus, applying preventive RRSO/RRS/oophorectomy may be an important part of preventive care for OC/FTC in the specific populations mentioned above. However, preventive surgery is not routinely recommended for patients without a history of childbirth, as it may affect fertility. Additionally, the risk of mutation in *STK11* is significantly lower than in *BRCA1/2*, making the clinical benefit of RRSO/RRS/oophorectomy for *STK11* mutation carriers questionable. Nevertheless, preventive surgery might be the only surgical method for high-risk gene mutation patients and their first-degree relatives to avoid the occurrence of malignancy. No study has yet reported the clinical efficiency of preventive RRSO/RRS/oophorectomy for *STK11* mutation carriers [74]. Furthermore, RRSO/RRS can be applied as preventive surgery for women concerned about iatrogenic menopause, as it may reduce the incidence of fallopian tube-originated malignancies. However, RRSO/RRS may have limited clinical effectiveness and bring a series of female healthcare issues such as vasomotor symptoms, reduced libido, vaginal dryness, and dyspareunia. Hormone replacement therapy (HRT) can be considered after RRSO, including single estrogen therapy and combined estrogen/progesterone therapy. Studies suggest that HRT after RRSO might also reduce the risk of breast cancer or OC in women with *BRCA1/2* mutations. For uterus-preserving patients, estrogen-progestin combination therapy can significantly reduce the risk of endometrial cancer and alleviate menopausal syndrome caused by oophorectomy [75–79]. Combining the findings above, we principally recommend that the preventive surgery (RRSO/RRS/oophorectomy) for *STK11* or other gene mutation carriers for OC/FTC should be performed carefully under full and comprehensive consideration of the age, reproductive history, risk of malignancy, genetic mutation lineages, post-operative complications and other conditions of specific population. And the clinical benefit might be larger if the surgery were conducted before age of 45–50 years. Short-term postoperative HRT is also of clinical significance [79–81]. For women with *STK11* mutations who have completed childbearing, relevant studies are exploratory and require the accumulation of more clinical cases. Fertility-preserving surgery in young or nulliparous patients is applicable, while the effect of sequential salpingectomy and oophorectomy for patients who have had children remains unclear. Considering that PJS patients may develop symptoms of digestive tract tumors, associated monitoring or surgical resection may also contribute to improved patient prognosis.

A study presented a case of metastatic and recurrent non-PJS-related SCTAT with high serum estradiol and progesterone concentrations following surgery and chemotherapy. Radiotherapy (50 Gy/25 fractions) led to a significant reduction in the size of the metastatic and recurrent masses, as well as in the concentrations of estradiol and progesterone [82]. Currently, no drugs specifically targeting *STK11* or relevant clinical trials have been identified. Most clinical trials involving patients with *STK11* mutations have been conducted in non-small cell lung cancer (NSCLC) or other pathological types of cancer. However, treatments targeting biological signaling pathways such as *KRAS*, *mTOR*, and *TP53*, or in

combination with PD-1/PD-L1 inhibitors for NSCLC, have achieved significant therapeutic effects in clinical trials [83–86]. These findings provide potential possibilities and important strategies for the future treatment of *STK11*-associated gynecological tumors. Further studies are needed.

Prognosis of *STK11* associated adnexal tumor

There are few studies with large samples precisely incorporating *STK11* associated adnexal tumors and complete long-term follow-up data. In a real-world pan-cancer cohort study, *STK11* mutations have shown predictive value for the efficacy of immune checkpoint inhibitors [87]. In another study, *STK11* mutations were associated with a shorter median time to progression and OS after diagnosis (6.4 months versus 12 months, $p = 0.001$; and 20.5 months versus 29.1, $p = 0.03$) [88]. Immunotherapy appears to improve outcomes of patients with *STK11*-associated tumors. A study involving 22 patients with *STK11* adnexal tumors has shown that metastasis occurred in 11/22 (50%) patients and recurrence occurred in 12/15 (80%, mean 29 months, median 17 months) patients. In this study, 9/19 patients received adjuvant therapy and the follow-up was available for 15 patients. 4/15 (27%) were alive and well, and 6/15 (40%) were alive with disease, and 3/15 (20%) were dead of disease, and 2/15 (13%) die of other causes [35]. Another study showed SCTAT recurrence in 20% of 26 cases, with a mortality rate of 12.5%, and all deaths occurred within the first year [89]. Given the partial misdiagnosis and the small number of cases, the data may not be applicable to all populations in the real world. Additionally, influenced by MDA, PJS-related digestive tract tumors, and other complications, the prognosis of patients with *STK11* adnexal tumors fluctuated significantly, making related prognostic research challenging.

Conclusions

STK11-associated adnexal tumors, which include OC and FTC, have genetic susceptibility. The primary lesions of *STK11* tumors mostly originate from the ovary, with bilateral multifocal SCTATs featuring focal calcifications and typical benign progression being the common pathological classification. These tumors are often associated with PJS, and fertility-preserving surgery is usually recommended due to the younger onset age and lower malignant potential of the tumors. Genetic testing is essential for the prevention of *STK11*-related tumors, and a multidisciplinary approach involving significant clinical symptoms and PJS-related family history is needed. Prophylactic adnexectomy, chemotherapy, and immunotherapy may offer potential clinical benefits but also present many challenges. Therefore, surgeries should be performed carefully, considering the patient's age, reproductive history, risk of malignancy, genetic mutation lineages, postoperative complications, and other conditions.

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Author contributions
Guanxiang Huang and Wenyu Lin contributed to the conception of the study, collected, analyzed, and interpreted data from the literature, and critically revised the manuscript. Tingting Jiang, Yuanjun Cai, and Chengbin Lin performed the literature research, drafted the manuscript, and are responsible for confirming the authenticity of all the raw data. Pengming Sun contributed to the conception of the study and revised the manuscript. All authors acknowledge the above contributions.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors reviewed the article and agreed to submit the manuscript to this journal for publication.

Competing interests
The authors declare no competing interests.

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