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REVIEW

Refractory fallopian tube carcinoma – current perspectives in pathogenesis and management

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Abstract: Fallopian tube carcinoma (FTC) is considered a rare malignancy, but recent evidence shows that its incidence may have been underestimated. Risk-reducing salpingo-oophorectomy (RRSO) in *breast cancer susceptibility gene (BRCA)*-positive women has provided a unique opportunity to study the pathogenesis of FTC and ovarian carcinomas. Newer data now suggest that most high-grade serous cancers of the ovary originate in the fimbrial end of the fallopian tube. Due to the presumed rarity of FTC, most current and more recent ovarian cancer clinical trials have now included patients with FTC. The treatment guidelines recommend similar overall management and that the same chemotherapy regimens be used for epithelial ovarian cancers and FTC.

Keywords: high grade serous cancers, serous tubal intraepithelial carcinomas, fallopian tube carcinoma

Introduction

Fewer than 500 patients are diagnosed with fallopian tube carcinoma (FTC) every year, representing about 0.2% of cancers diagnosed in women in the United States annually.[1] The incidence rate of FTC is between 3.72 and 4.1 per one million women in the United States.[1,2] The incidence rate is higher in Caucasian women than in women of African American, Hispanic, or Asian descent.[1] Recent evidence shows that the incidence of FTC may have been grossly underestimated.[3] In this article, we will highlight the recent literature and understanding of the pathogenesis of FTC that explains the underestimation of its incidence, and the current perspectives in the management of FTC.

Pathogenesis

The origin of epithelial ovarian cancer (EOC) was thought to be the neoplastic transformation of cells in the cortical inclusion cysts of the ovary.[4–6] The incessant ovulation theory postulated that there is a stepwise accumulation of genetic mutations in the ovarian epithelial lining as a result of repeated damage and repair during ovulation, leading to EOC.[6–9] However, it has never been demonstrated conclusively that there exists a precursor lesion in the ovary that progresses to high-grade serous cancer (HGSC).[10,11] Another hypothesis is that HGSC originates, not from the surface of the ovary but, from the epithelial layer of the neighboring fimbrial end of the fallopian tube.[3–5,8,12–27] Newer data now suggest that HGSC of ovary, primary peritoneal carcinoma (PPC), and FTC have similar pathogenesis and molecular biomarkers and that these cancers should more accurately be called pelvic serous carcinomas.[14,28] The epidemiological

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data also support a common etiology of ovarian, fallopian, and primary peritoneal cancers. There are racial, ethnic, and geographic similarities in the incidence of these three cancers, and the higher incidence of all three cancers in non-Hispanic white women further suggests a common origin.[2]

In general, most epithelial cancers in the body arise as a consequence of a series of events and progress from a benign epithelium to an invasive cancer.[18] A proposed stepwise sequence to the development of invasive cancers in the fallopian tube is shown in Figure 1.[4,8,16,19,29]

The earliest abnormality noted in the fallopian tube epithelium is called secretory cell outgrowth (SCOUT). SCOUTs are discretely localized alterations commonly containing an altered expression of multiple genes within a histologically benign tubal epithelium. Immunohistochemistry shows low expression of *paired box 2 (PAX2)*, low Ki67 index, and, in most cases, no *tumor protein p53 (TP53)* gene mutations.[19] Next, somatic tumor protein 53 (p53) mutations arising from deoxyribonucleic acid (DNA) damage appear in the benign tubal epithelium, with foci of strong p53 immunostaining, termed "p53 signatures".[30] The "p53 signature" is defined as 12 or more consecutive cells with strongly positive p53 nuclear staining within a benign-appearing epithelium.[15,16,18] In the presence of a p53 signature, proliferative lesions appear, which are called serous tubal intraepithelial lesions (STILs)[31] or transitional intraepithelial lesions of the tube (TILTs).[22] These lesions are dysplastic and give rise to serous tubal intraepithelial carcinoma (STIC), also called tubal intraepithelial carcinoma (TIC), which is a precursor for invasive cancer.[4,8,31] STIC is composed of secreting cells in the distal fallopian tube, with cytologic atypia, a high proliferative index, and strong nuclear staining for p53.[17] The pathogenesis of HGSC from ovarian surface epithelium is unclear as a similar step-wise carcinogenic sequence has never been identified. Recent observations show that STIC may be a precursor lesion for most fallopian tube, ovarian, and peritoneal HGSCs.[5,8,14,25]

The conventional pathologic classification of pelvic serous cancers mostly as ovarian cancer has contributed to the underreporting of FTCs. FTC is diagnosed only when there is no mass in the ovary or endometrium.[14] The presence of a dominant tubal mass and a precursor lesion in the fallopian tube is a prerequisite for classification of a tumor's origin in the fallopian tube, while the presence of a precursor lesion is not a requirement to diagnose a tumor of ovarian origin.[5] Similarly, PPC is diagnosed only when no mass is found on the ovary, fallopian tube, or endometrium. The convention has been to classify serous tumors in the pelvis as ovarian cancer when the origin is unclear.[3] This has led to significant underreporting of fallopian tube cancers as many cases of FTC also had tumors on the surface of the ovary and therefore, were classified as serous ovarian cancers.[3,23]

Figure 1 A proposed stepwise progression to invasive cancer in the fallopian tube.
Abbreviations: p53, tumor protein 53; SCOUT, secretory cell outgrowths; STIC, serous tubal intraepithelial carcinoma; STIL, serous tubal intraepithelial lesion; TILT, transitional intraepithelial lesions of the tube.

Molecular pathways

Advances in molecular diagnostics have led to the discovery of different mechanisms driving the EOC histological subtypes.[17,32] Type 1 tumors include clear cell, mucinous, and low-grade serous and endometrioid tumors.[8,17] These tumors show mutations in the mismatch repair genes, *Kirsten rat sarcoma vial oncogene homolog (KRAS)*, *v-raf murine sarcoma viral oncogene homolog B (BRAF)*, *catenin (cadherin-associated protein), beta 1, 88kDa (CTNNB)*, *phosphatidylinositol-4,5-biphosphate 3-kinase, catalytic subunit alpha (PIK3CA)*, *adenine-thymine (AT)-rich interactive domain-containing protein 1A (ARIDIA)*, *protein phosphatase 2, regulatory subunit A,* alpha (*PPP2R1A)*, and *phosphatase and tensin homolog (PTEN)*.[12,17,20] These tumors have a slow stepwise progression from cortical inclusion cysts to invasive cancer.[4,8,12,18] In contrast, type 2 ovarian tumors harbor mutations (as shown in figure 2) in the *TP53* gene and are usually HGSC or (some) high-grade endometrioid tumors.[12,17] These tumors are aggressive, usually present in advanced stages, and have a worse prognosis.

Tumor suppressor p53 inactivation is detected in more than 95% of cases of HGSC.[12] Studies reporting the p53 staining of the normal ovarian epithelium in patients with ovarian cancer or those at high risk of ovarian cancer (*breast cancer susceptibility gene [BRCA]*-positive) have been mixed, with some authors reporting the presence of p53 staining while others finding no evidence of p53 staining on the surface epithelium of the ovary.[11,15,33] In *BRCA*-positive patients who underwent risk-reducing salpingo-oophorectomies (RRSO), a p53 signature was found in 38% of examined fallopian tubes, while none of the cortical inclusion cysts had a p53 signature, suggesting a fallopian origin to these cancers.[15]

Gene expression profiling of HGSC has shown a close correlation to normal fallopian tube epithelium, rather than ovarian epithelium.[26,34] Molecular studies have also shown that the different histologies of ovarian cancer have distinct gene expression profiles. While HGSC most closely

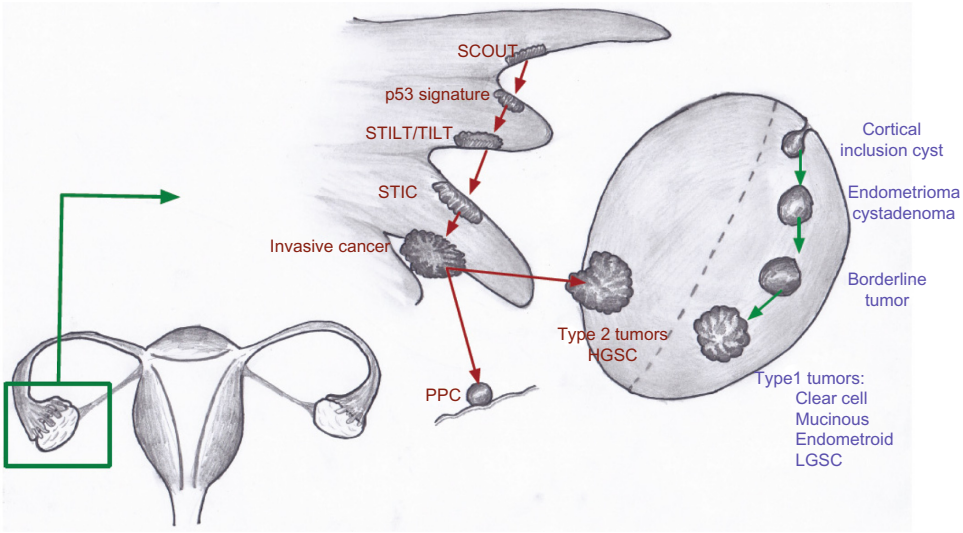

Figure 2 Proposed models for the development of type I and type 2 tumors of the ovary.
Notes: Type I tumors develop from cortical inclusion cysts on the surface of the ovary. Type 2 tumors develop in the fimbriae of the adjacent fallopian tube before being implanted on the surface of the ovary or the adjacent peritoneum.
Abbreviations: HGSC, high-grade serous cancer; LGSC, low-grade serous cancer; p53, tumor protein 53; PPC, primary peritoneal cancer; SCOUT, secretory cell outgrowths; STIC, serous tubal intraepithelial carcinoma; STILT, serous tubal intraepithelial lesions of the tube; TILT, transitional intraepithelial lesions of the tube.

correlates with normal fallopian tube epithelium, mucinous carcinomas correlate with colonic epithelium; endometrioid and clear cell carcinomas correlate with the endometrium and carry different and specific marker genes.[34] *Amylase, alpha 2B (AMY2B)* and *chitinase-3-like protein 1 (CHI3L1)* have been shown to be upregulated in serous ovarian cancer and normal fallopian tube epithelium. Endometrioid genes, like *fibroblast growth factor homologous factor 9* (*FHF9)*, *stratifin (SFN)*, *metallothionein 1G (MT1G)*, and *Indian hedgehog (IHH),* have been shown to be expressed in normal endometrium. *Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)*, *lectin, galactoside-binding, soluble, 4 (LGALS4)*, and *trefoil factor 2 (TFF2)* were all shown to be distinctly expressed in mucinous carcinomas and to be upregulated in normal colon.[34] *ARID1A* mutations are frequent in clear cell and endometrioid ovarian cancer but not in HGSC.[35,36] The same mutation is found in the majority of uterine endometrioid carcinomas.[37]

Evidence of tubal origin of ovarian cancer

RRSO in *BRCA*-positive and other high-risk women has provided a unique opportunity to study the pathogenesis of ovarian carcinomas, PPC, and FTC.[17,18,27,38] There has never been a clear precursor lesion of EOC found on the surface of the ovary in patients undergoing RRSO, in spite of data from thousands of patients at high risk of ovarian cancers (*BRCA*-positive) who have undergone this procedure. The Sectioning and Extensively Examining the Fimbriated End (SEE-FIM) protocol, used for a more detailed examination of the fallopian tubes in RRSO specimens, has led to an improved understanding of the pathogenesis of pelvis serous cancers.[39,40]

Retrospective studies

In patients with *BRCA* mutation who underwent RRSO, thorough examination of the fallopian tube revealed a tubal source 57%–100% of the time when a tumor was identified.[8,13,18,38,40,41] In unselected women undergoing RRSO, a tubal origin was found 36%–47% of the time.[14,28] Similarly, in a retrospective analysis of 51 patients from a single institution, 56% of patients who were originally classified as having a PPC were found to have STIC in the fallopian tubes.[42] In another retrospective review, six out of 76 patients with *BRCA1* mutation undergoing RRSO were found to have microscopic cancers. Four of these six patients had a tumor in the fallopian tube, one in the ovary, and the other was in the peritoneal washings.[43] In the same study, 78% of patients with *BRCA* mutations who had stage I to II cancers were found to have a dominant ovarian mass. These data suggest that although HGSC initiation may occur in the fallopian tube, tumor growth and progression may be favored in the ovary, which could be due to a more favorable microenvironment in the ovary.[43]

In a prospective study of 360 high-risk patients who underwent RRSO, the pathology review included SEE-FIM of the fallopian tube to identify the primary site of disease. In this study, there were two tubal, two ovarian, and four noninvasive STICs, supporting the fallopian tube as a likely

site of origin of many pelvic HGSCs.[27] In patients who had HGSCs involving the ovary without evidence of a concurrent fallopian tube lesion, it is possible that the fallopian tube was not the only site of tumor initiation.

Treatment of FTC

Due to the presumed rarity of FTC and PPC, there are no large, prospective, randomized clinical trials exclusively evaluating treatment for FTC or PPC. The National Comprehensive Cancer Network guidelines recommend similar management, and the same regimens be used for EOC, FTC, and PPC.[44] In fact, compared with the older clinical trials in ovarian cancer, most current and more recent ovarian cancer clinical trials have included patients with FTC and PPC, although they are considered distinct clinical entities.[45–55] Since the current evidence points toward a common pathogenesis for ovarian cancer, FTC, and PPC, similar treatment of these cancers is likely to be the most appropriate management of all these tumors.

First-line treatment

The first-line treatment of ovarian cancer, FTC, and PPC is a combination of a platinum agent and a taxane.[7,56] The combination of carboplatin and paclitaxel was compared with the combination of cisplatin and paclitaxel in the Gynecologic Oncology Group (COG) 158 trial. There was no statistical difference in progression-free survival (PFS) or overall survival (OS) between carboplatin and paclitaxel compared with cisplatin and paclitaxel; however, the carboplatin arm was better tolerated, with fewer nonhematologic side effects.[56]

The combination of dose-dense weekly paclitaxel and carboplatin every 3 weeks was compared with the standard regimen of both paclitaxel and carboplatin every 3 weeks, in a study done by the Japanese Gynecologic Oncology Group. The median PFS was longer in the dose-dense arm (28.0 months versus [vs] 17.2 months) (hazard ratio [HR] 0.71) (P=0.0015). The OS at 3 years was also higher in the dose-dense regimen group (72.1%) than in the conventional treatment group (65.1%) (HR 0.75) (P=0.03) However, there were more hematologic toxicities and treatment discontinuations with the dose-dense paclitaxel, although other toxicities were similar in both arms.[57] The recently reported update to this trial, with over 6 years of follow-up, showed a median overall survival greater than 100 months in the dose-dense arm.[58]

In a Phase III trial (GOG 172) evaluating intraperitoneal therapy, patients with optimally debulked, newly diagnosed ovarian cancer or PPC received intravenous paclitaxel over 24 hours and were randomized to receive either intravenous cisplatin or intraperitoneal cisplatin and intraperitoneal paclitaxel. Although the median PFS (23.8 vs 18.3 months) and OS (65.6 vs 49.7 months) were longer in the intraperitoneal arm when compared with the intravenous arm, there were significantly more grade 3 and 4 toxicities, including pain, fatigue, and gastrointestinal (GI), hematologic, and neurologic toxicities, with only 42% of patients receiving all six cycles of the assigned intraperitoneal therapy.[46] Therefore, intraperitoneal therapy should only be considered in patients with very good performance status who are willing to accept the increased toxicity of the regimen. The recently completed GOG 252 trial is evaluating a modified GOG 172 intraperitoneal regimen (which can be given in an outpatient setting) including intraperitoneal carboplatin compared with intravenous carboplatin and paclitaxel, and the results are pending (arm 1: IV paclitaxel, IV carboplatin and IV bevacizumab, arm 2: IV paclitaxel, IP carboplatin and IV bevacizumab, arm 3: IV placlitaxel, IP cisplatin, IP paclitaxel and IV bevacizumab).

The combination of docetaxel plus carboplatin[59] is another reasonable first-line option. Due to ease of administration, favorable side-effect profile, long track record, and convenience to patients, the combination of carboplatin and paclitaxel has emerged as the worldwide standard of care in the first-line treatment of advanced ovarian cancer, FTC, and PPC.[7,45]

The GOG 218 and International Collaboration on Ovarian Neoplasms (ICON) 7 trials evaluated the addition of bevacizumab to front-line chemotherapy with carboplatin and paclitaxel. There was improvement in PFS in both trials but no OS benefit.[48,49] There were more GI perforations in the patients receiving bevacizumab; however, this was not statistically different. The improved PFS was only observed among patients receiving bevacizumab with chemotherapy and as extended-maintenance treatment and in high-risk patients (36.6 months vs 28.8 months).[49]

Second-line treatment

Second-line treatment is determined in part by the time since the prior regimen. The platinum-free interval is an important predictor of the response to second-line treatment.[60] Patients whose cancer was controlled for greater than 6 months from the last therapy are considered to be platinum sensitive.[61] These patients are retreated with a platinum doublet, depending on their comorbidities, prior toxicities, and performance status. Carboplatin, in combination with paclitaxel (ICON4/Arbeitsgemeinschaft Gynaekologische Onkologie-Ovarian [AGO-OVAR]-2.2), gemcitabine (Intergroup trial), or PEGylated liposomal doxorubicin (PLD) (Caelyx in Platinum Sensitive Ovarian [CALYPSO]) have all been shown to be reasonable options.[62–65] In the CALYPSO trial, the combination of carboplatin and PLD was compared with the combination of carboplatin and paclitaxel. Although the

OS was not different in the two arms, patients in the PLD arm had a statistically significant improvement in PFS, the primary endpoint of the trial.[64,65] The side effect profile also favored the PLD arm.[65] Although combinations, in general, have shown an improvement in response rate (RR), PFS, and OS, there is also a higher incidence of side effects. Therefore, in patients with multiple comorbidities or poor performance status, single-agent chemotherapy is appropriate.

Patients who have a recurrence within 6 months of platinum treatment are considered to be platinum resistant.[60,61] Patients whose cancers progress while on treatment with platinum are considered to be platinum refractory, and their prognosis is very poor. Platinum agents are not recommended for these patients, and further treatment is based on underlying renal function, hepatic function, and other comorbidities. Patients usually receive sequential therapy with single agents rather than combination therapy. A Phase III trial of weekly paclitaxel was found to be as effective as a combination therapy of paclitaxel with carboplatin or topotecan, in resistant ovarian cancer.[66] In a retrospective study, PLD was shown to prolong the platinum-free interval so that patients could be resensitized to a platinum agent.[67] However, this study was small, uncontrolled, and retrospective in nature, and in the absence of prospective trials, no firm conclusions can be drawn regarding the prolongation of the platinum-free interval with PLD. Most single-agent regimens produce a RR of 10%–30%. The RRs of commonly used single-agent cytotoxic chemotherapies are reported in Table 1. Patients whose disease progresses after two or more consecutive lines of therapy should be considered refractory to platinum and are candidates for early phase clinical trials.[68]

Targeted agents

Like most other cancers, there has been an increased interest in using targeted therapies in ovarian cancer. The Gynecologic Oncology Group conducted multiple Phase II trials (GOG 170 series) evaluating targeted therapies in patients with refractory ovarian cancer, FTC, or PPC. Most of the targeted therapies tested had minimal activity in these unselected patients. Bevacizumab, aflibercept, and olaparib have been tested in ovarian cancer patients and had some antitumor activity. Other targeted agents examined in this disease, and, their RRs and PFS are shown in Table 2.

Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF) receptor, in combination with chemotherapy, is useful in both the recurrent platinum-sensitive and in the platinum-resistant setting. The addition of bevacizumab to carboplatin and gemcitabine in platinum-sensitive, recurrent pelvic serous cancers has shown an improvement in RR and PFS but a slightly higher incidence of side effects, including hypertension and arterial thrombosis;[50] however, no difference in the OS has been noted, which may be partly due to the subsequent therapy with bevacizumab in the patients who progressed on the placebo arm. In a Phase III trial of patients with platinum resistant disease (AURELIA), patients were randomized to receive investigator-selected chemotherapy (weekly paclitaxel, topotecan, or PLD) with or without bevacizumab.[69] The primary end point was Response Evaluation Criteria in Solid Tumors (RECIST)-defined PFS. Patients in the bevacizumab plus chemotherapy arm had a PFS of 5.7 months compared with 4 months in the chemotherapy-only arm (HR 0.48, 95% confidence interval [CI]: 0.38−0.60) ($P<0.001$). There were also higher RRs and complete responses in the bevacizumab arm. No OS data are available yet. There were more grade 2 or higher adverse events in the bevacizumab arm, including hypertension, proteinuria, GI perforation, and fistula formation. There were also more grade 3 or higher arterial thromboembolic events.[69] Bevacizumab has been tested in Phase II trials as a single agent and been found to have an RR of 21% to 26% and a median PFS of 4.4 months to 4.7 months and is a reasonable option.[70,71]

Table 1 Response rates of single agent chemotherapies in platinum resistant and refractory setting

Drug	Response rate	Reference
Weekly paclitaxel	21%	Markman et al[83]
Gemcitabine	19%	Ferrandina et al[84] Mutch et al[85]
PEGylated liposomal doxorubicin	26%	Ferrandina et al[84] Mutch et al[85]
Pemetrexed	21%	Miller et al[86]
Nab-paclitaxel	23%	Coleman et al[87]
Topotecan	20%	Gordon et al[52]
Docetaxel	22%	Rose et al[88]
Oral etoposide	27%	Rose et al[88]
Vinorelbine	20%	Rothenberg et al[89]
Ifosfamide	12%	Markman et al[90]
Altretamine	14%	Alberts et al[91]

Abbreviation: Nab, nanoparticle albumin bound.

Table 2 Response rates and progression-free survival of selected targeted agents

Drug	ORR	PFS	Reference
Cediranib	17%	5.2 months	Matulonis et al[92]
Pazopanib	18%	17% at 6 months	Friedlander et al[93]
Temsirolimus	9%	24% at 6 months	Behbakht et al[94]
Alisertib	10%	1.9 months	Matulonis et al[95]
Dasatinib	0%	21% at 6 months	Schilder et al[54]
Patupilone	15%	3.7 months	Colombo et al[96]
Sunitinib	8%	9.9 weeks	Campos et al[97]

Abbreviations: ORR, overall response rate; PFS, progression-free survival.

Aflibercept, a VEGF trap, was found to be effective in controlling malignant ascites in a double-blind, placebo-controlled Phase II trial in patients who had received a median of four prior therapies.[72] The mean time to repeat paracentesis was significantly longer after aflibercept, 55 days vs 23 days. However, there were more grade 3 and 4 side effects, including dyspnea, fatigue, and dehydration. There were also three intestinal perforations with aflibercept.

Olaparib, a poly–adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitor has shown activity in *BRCA*-mutant ovarian cancer – patients with *BRCA* mutations have a defect in the DNA homologous recombination repair mechanism, and PARP inhibitors prevent base excision repair.[73–75] Together, these mechanisms achieve tumor cell death by preventing DNA repair via two different pathways, a process referred to as synthetic lethality. A Phase I/II trial in *BRCA* mutation-positive patients showed an RR of 40%, with a response duration of 28 weeks.[76] Other studies have shown RRs from 13% to 33%.[77,78] Even in patients with HGSC without *BRCA* mutation, the RR was 24%.[79] Olaparib has been used as maintenance therapy in platinum-sensitive relapsed ovarian cancer and found to prolong the PFS but did not add an OS benefit.[80] A Phase I study of olaparib with cediranib, a VEGF receptor tyrosine kinase inhibitor, showed an RR of 44% in recurrent ovarian cancer.[81]

Future directions

Radical fimbriectomy followed by surveillance has been suggested as an alternative to surveillance alone in high-risk *BRCA*-positive patients reluctant to undergo bilateral salpingo-oophorectomy (BSO) for risk reduction of pelvic serous carcinomas, due to concerns of prolonged menopause and other complications (like osteoporosis, vaginal atrophy, and decreased quality of life associated with menopause).[21] This approach would preserve the ovaries and consequently delay menopausal symptoms until natural menopause occurs. However, a microscopic spread of the tumor, from the fallopian tube to the ovary, may occur very early; thus, salpingectomy alone may be insufficient to protect against the development of ovarian cancer and may create a false sense of protection.[43] Therefore further evaluation of this procedure, with long-term follow-up, is necessary. The early detection of an STIC can help in the prevention of invasive ovarian cancers; however, no screening techniques are currently available to detect STIC. Endometrial cytological testing may detect early-stage ovarian, tubal, and peritoneal HGSCs and may be useful for ovarian cancer screening, but this study needs further validation.[82] The inclusion of patients with FTC, PPC, and HGSC of the ovary in clinical trials is recommended as they have similar molecular abnormalities and likely the same cell of origin. The better understanding of FTC biology will lead to improved treatment and, ultimately, improved outcomes in FTC, PPC, and HGSC.

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Disclosure

The authors report no conflicts of interest in this work.

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