Chapter

Ovarian Cancer: Molecular Classification and Targeted Therapy

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Abstract

Ovarian cancer is the deadliest gynecological cancer among women with an overall 5-year survival rate below 50% due to its asymptomatic nature, diagnosis at advanced stages, and a high recurrence rate after standard therapy in 70% of cases. Ovarian cancers are heterogenous cancers where each subtype possesses a varied morphology and biologic behavior. Accumulating evidence has identified each of these subtypes characterized with specific pathways activated in each along with specific gene alterations. For example, high-grade serous ovarian cancer is characterized by universal *TP53* mutation, mucinous ovarian cancer with *KRAS* mutation and clear cell or endometrioid ovarian cancers with *ARID1A* mutations. With the current focus of molecular-targeted therapies for cancer, such druggable markers serve as excellent targets for precision therapy and combination therapy. This chapter, provides an overview of the critical molecular pathways activated in the ovarian cancer subtypes with its druggable targets studied in ovarian cancer. We also highlight the implications of miRNAs in chemoresistance and sensitivity in the regulation of ovarian cancer.

Keywords: ovarian cancer subtypes, targeted therapy, miRNAs in ovarian cancers

1. Introduction

Ovaries are the prime female reproductive organ that produces the oocyte or the egg cell for fertilization. It is also an endocrine gland that produces the female sex hormones estrogen and progesterone responsible for ovulation and pregnancy maintenance. Some of the diseases that affect the ovaries are ovarian cysts, primary ovarian insufficiency, ovarian torsion and more recently ovarian cancer (OC). OC was first detected in the 1950s and is now one of the deadliest gynecological cancers among women [1, 2]. According to the latest Global Cancer Observatory: CANCER TODAY (GLOBOCAN 2018), the incidence and mortality rates of OC vary globally and ranks at the 8th and 7th position respectively [3]. The highest mortality rates are reported in Oceania and Europe and the lowest are from Latin America, the Caribbean and Asia [3]. OCs are also prevalent in countries with a high human development index (HDI) but with lower mortality rates due to increased diagnostic and therapeutic support [4].

Most OCs manifest post menopause and the increased incidence is reported in women older than 65 years [5]. Considering the ethnicity, non-Hispanic white women are reported to have the highest incidence and mortality rates [6]. OCs are heterogeneous cancer, hence the risk factors for each histological subtype vary. In

general, some of the major risk factors for OC include Hereditary Breast and Ovarian Cancer (HBOC) syndrome [7], Lynch syndrome [8], menopausal hormonal therapy [9, 10], endometriosis [11], IVF treatment [12], use of fertility drugs [13], late menopause [14] and null parity [15]. Interestingly, high parity [16], hysterectomy [17] and usage of hormonal contraceptive pills for prolonged periods [18] are reported to have a protective effect since these conditions confer in the suppression of ovulatory cycles [19]. The sterilization treatment, tubal ligation is also reported to reduce the risk of OCs [17, 20]. Recently reported other emerging risk factors for OCs are the use of talc powders [21], asbestos exposure [22] and pelvic inflammatory disease [23].

OCs are difficult to detect;therefore almost 60% of OC cases are diagnosed at advanced stages [24]. It is often called the "whispering cancer" or "silent cancer" due to its asymptomatic nature and late presentation [25, 26]. Late-stage OC symptoms are very nonspecific and diffuse but may include abdominal bloating or swelling, pelvic pain, increased urinary urgency, weight loss, or fatigue [27, 28]. Although a biopsy is the only reliable diagnosis for OC, screening for serum cancer antigen 125 (CA-125) levels combined with ultrasound imaging are used for women with increased risk [29]. The emerging technique of liquid biopsy is being explored for identifying serum biomarkers for early detection of OCs. It holds great promise being non-invasive and is utilized to diagnose, prognose and predict surgical outcomes. One such serum biomarker identified is the Human Epididymis Protein 4 (HE4) which is reported to have high specificity for OCs [30, 31]. 2011 FDA approved, ROMA index (risk of ovarian malignancy algorithm) deduced from HE4, CA-125 and the menopausal status is used for diagnosis and prognosis of OCs with a specificity of 90% [32–34]. Another recent 2016 FDA approved serum-based screening test, Overa also uses HE4 levels along with other serum proteins is reported to show a sensitivity of 94% along with pathological diagnosis [35]. The mutational status of multiple cancer-causing genes are also being developed as screening tests for various cancers like PapSEEK and CancerSEEK and are reported to detect OC with a specificity of 63% and 98%, respectively [36, 37].

According to the World cancer report 2020, OC five-year survival rate is below 30% [38]. This is mainly because this cancer gets diagnosed at stage III or IV with metastasis and the recurrence rate high despite standard therapy. Cytoreductive surgery followed by chemotherapy based on cancer's surgical stage remains the gold standard treatment for OCs. The most commonly administered chemotherapy drugs are platinum derivatives e.g. cisplatin and carboplatin and are often combined with taxane-based drugs like paclitaxel or docetaxel. These drugs induce apoptosis in the tumor cells by creating double-stranded breaks in the DNA [39]. Despite chemotherapy being effective for advanced cancers in the initial phases, cancer relapses in 70% of cases due to drug resistance [40]. In the case of recurrent OCs, the second line of the chemotherapy treatment regimen is based on the platinum-free interval and the tumor's molecular profile [41]. Furthermore, the treatment options include combinations of carboplatin with gemcitabine, topotecan, vinorelbine, trabectedin, belotecan or pegylated liposomal doxorubicin [42].

Despite intensive combination chemotherapy, the survival rate decreases with chemoresistance and subsequent OC metastasis. The lack of anatomical barrier around the ovaries facilitates the dissemination of OC cells into the peritoneal cavity, metastasizing onto abdominal organs resulting in bowel obstruction, which is the major cause of OC morbidity and mortality [43, 44]. Currently, there are no preventive measures for OCs, and options for the high-risk category are prophylactic surgeries like hysterectomy (removal of the uterus) combined with bilateral salpingo-oophorectomy (removal of both ovaries and fallopian tube) or bilateral salpingectomy (removal of both fallopian tubes) [45]. Women with average risk can opt for oral contraceptive treatment [46].

Presently, there is no effective cure for advanced OC. Though these cancers vary histologically, clinical treatment therapies neglect these differences and are treated as a single disease. Each OC subtype is characterized by specific genetic mutations that deregulate specific signaling pathways that should be utilized for personalized or tailored therapeutics. Precision therapy is the need of the hour for OC treatment in improving the current survival rate. In the following sections of the chapter, we describe the various OC subtypes, their histological classification and the key molecular pathways activated in each subtype along with its druggable targets.

2. Ovarian cancer subtypes

OC neoplasms arise from distinct regions of the ovary. They are termed heterogeneous as each OC subtype is unique with varied morphology, biologic behavior and even prognosis. High throughput sequencing technologies have identified each OC subtype as distinct even on a molecular level with unique genomic characteristics. OCs are broadly classified into epithelial and non-epithelial cancers. Non-epithelial cancer comprises germ cell cancer, stromal cell cancer, and the rare small cell carcinoma. The origin of the various subtypes of OCs and the sub-classifications are depicted in **Figure 1**.

2.1 Epithelial ovarian cancer (EOC)

Epithelial ovarian cancers (EOCs) comprise 90% of all OCs and are among the most well-characterized forms of OC. EOCs are thought to arise from the epithelium, the outer lining of the ovary. EOC is an age-related disease and is considered mainly a postmenopausal disease. Based on tumor cell morphology, they are further subdivided into high grade serous ovarian carcinoma (HGSOC), low grade serous ovarian carcinoma (LGSOC), mucinous ovarian carcinoma (MOC), endometrioid carcinoma (EC), and clear-cell carcinoma (CCC). The histological image, epidemiology, molecular alterations and pathways affecting each EOC variant are outlined in **Figure 2**.

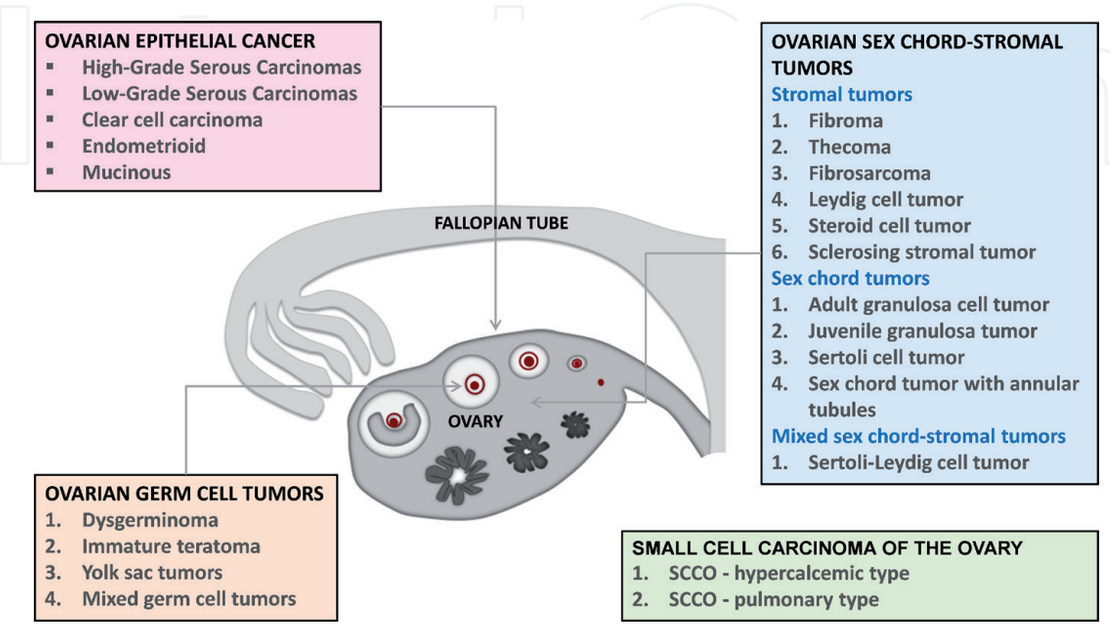
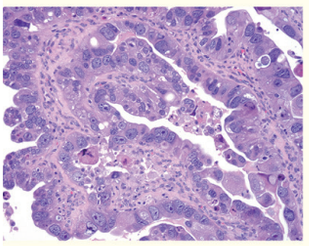


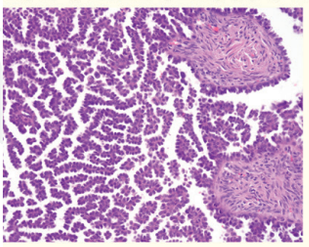
Figure 1.
Origin of the various ovarian cancer subtypes and their sub-classifications.

HIGH GRADE SEROUS OVARIAN CARCINOMA



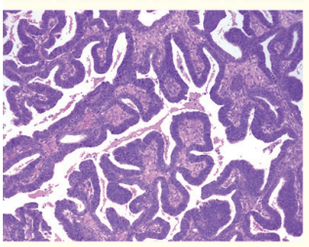
Incidence: 75% of EOCs
Age affected: >65 years
Risk factors: HBOC syndrome, Menopausal hormonal therapy
Prognosis: Poor
Chromosomal aberrations: *TP53* mutations (90%), *BRCA* mutations (<20%)
Major pathways affected: HR pathway

LOW GRADE SEROUS OVARIAN CARCINOMA



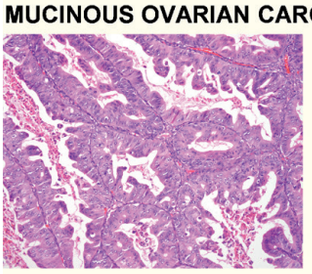
Incidence: <2% of all OCs
Age affected: mean age of 55 years
Risk factors: Menopausal hormonal therapy
Prognosis: Intermediate
Chromosomal aberrations: Mutations in *BRAF/KRAS/NRAS, ERBB2, PI3KCA, FFAR1, USP9X, EIF1AX*
Pathways affected: MAPK pathway, PI3K pathway, mTOR pathway

ENDOMETRIOID CARCINOMAS



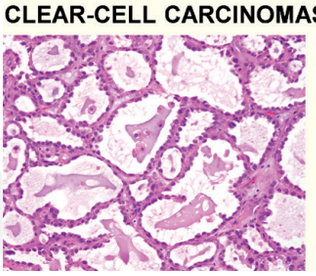
Incidence: 10% of all OCs
Age affected: 40-70 years
Risk factors: Endometriosis, menopausal hormone therapy, HBOC syndrome, Lynch syndrome and late menopause
Prognosis: Favorable
Chromosomal aberrations: Mutations in *ARID1A* (30%), *CTNNB1* (25-60%), *KRAS/BRAF* (20%), *PIK3CA* (12%) and *TP53* (25%)
Pathways affected: MAPK pathway, β-catenin signalling, PI3K/PTEN pathway

MUCINOUS OVARIAN CARCINOMA



Incidence: 2-3% of all OCs
Age affected: <40 years
Risk factors: Smoking
Prognosis: Good
Chromosomal aberrations: Mutations in *KRAS* (66%), *TP53*, *PIK3CA/PTEN, ARID1A, BRAF, CTNNB1/APC* and HER2 amplification
Pathways affected: MAPK pathway, Wnt signalling pathway, PI3K/PTEN/AKT pathway

CLEAR-CELL CARCINOMAS



Incidence: >5% of all OCs
Age affected: 50-70 years
Risk factors: Late menopause, Endometriosis
Prognosis: Intermediate
Chromosomal aberrations: Mutations in *PIK3CA (50%), ARID1A, ARID1B, SMARCA4, ERBB2, PIK3CA, PIK3R1, AKT2, PTEN, KRAS, PPP2R1A, TP53* and *TERT* promoter, *MET* gene amplification
Pathways affected: PI3K/PTEN/AKT pathway, MAPK pathway

Figure 2.
EOC subtypes: histology, epidemiology, and molecular alterations. Histology images courtesy [47].

2.1.1 High grade serous ovarian carcinoma (HGSOC)

High grade serous ovarian carcinomas (HGSOCs) are the most lethal forms of OCs and account 75% of all EOCs [48]. They are the most aggressive and chemo-resistant forms of EOCs responsible for 70–80% of OC related deaths. HGSOCs are thought to be derived from the fallopian tube [49]. These cancers are mainly diagnosed in postmenopausal women and due to its asymptomatic character presents themselves in advanced stages. Familial HBOC syndrome, and menopausal hormonal therapy predispose women towards this cancer [25, 50].

HGSOCs are characterized by a high frequency (90%) of somatic *TP53* mutations. These mutations are present in the DNA binding domain of TP53 which

render its tumor-suppressive function inactive, leading to enhanced cell proliferation and metastasis. The drug APR-246 targeting TP53 resulting in its wild type stabilization is under clinical trial and has shown favorable results [51]. Another drug, nutlin-3a targeting MDM2, a negative regulator of TP53, has also entered clinical trials with positive outcomes [52]. Moreover, combination therapy using nutlin-3 and RG7388 (another MDM2-TP53 antagonist) have reported cytotoxic effects in various OC cell lines [53].

15–20% of HGSOC patients harbor germline mutations in *BRCA1* or *BRCA2* [48]. The *BRCA* genes are involved in the repair of double-strand DNA breaks through homologous recombination (HR). Besides, most HGSOCs with the germline *BRCA* mutation are also reported to harbor somatic mutations in other HR-related genes conferring an HR deficient (HRD) phenotype [54]. The Cancer Genome Atlas Research Network (TCGA) has reported almost 50% HGSOCs cases as HR deficient [55]. HRD conferring genes besides *BRCA1/2* include Fanconi anemia genes (*PALB2, FANCA, FANCI, FANCL, FANCC*), RAD family genes (*RAD50, RAD51, RAD51C, RAD54L*), MRN complex genes (*Mre11-Rad50-Nbs1*), and also DNA damage response genes (*ATM, ATR, CHEK1, CHEK2*) [54, 56]. This manifestation of inactivating *BRCA* gene mutations and other HRD genes confer a DNA repair-deficient phenotype leading to genomic instability [57].

One of the most remarkable developments for OC therapy has been the PARP (poly (ADP-ribose) polymerase) inhibitors. PARP is an excision repair enzyme involved in the repair of single DNA strand breaks. PARP inhibitor treatment in BRCA-deficient cancer induces synthetic lethality and cell death [58]. The PARP inhibitor olaparib has been reported to show increased progression-free survival (PFS) and is currently approved as first-line maintenance therapy for *BRCA*-mutant individuals [59, 60]. Another PARP inhibitor, niraparib, improved PFS regardless of *BRCA* or HRD status is also approved for first-line maintenance of advanced OCs [61]. CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) are also under clinical trials as maintenance and combination therapy for HGSOCs [62]. Cyclin-dependent kinase 4 and 6 (CDK4/6) are key kinases that regulate the cell cycle. CDK4/6 inhibitors hinder G1-S transition inducing cell cycle arrest at the G1 phase. PI3K/AKT and NOTCH pathways are reported to be deregulated in HGSOCs which could also be targeted via combination therapies using PI3K inhibitors or the AKT inhibitor, afuresertib [63].

One of the first targeted therapy used to treat advanced OCs is Bevacizumab, an anti-angiogenic agent that targets vascular endothelial growth factor (VEGF) [64]. Angiogenesis plays a pivotal role in tumor progression and metastasis in many malignant cancers. This drug acts by neutralizing VEGF-A, thereby inhibiting tumor growth and invasion. Bevacizumab is currently approved as a combination therapy along with platinum/taxane drugs for advanced HGSOCs and has been reported to show a significant improvement in progression-free survival [57].

2.1.2 Low grade serous ovarian carcinoma (LGSOC)

As the name suggests, LGSOCs are indolent and less aggressive tumors with relatively better prognosis than HGSOC. They are prevalent in younger women with a median age of 55 years and constitute less than 5% of all OCs [65]. Though LGSOCs are chemoresistant they are treated the same way as HGSOCs with platinum/taxane drugs. The increased survival rate in LGSOCs is attributed to its longer disease trajectory and complete resection of the tumor post-primary cytoreductive surgery [66].

LGSOCs are characterized by activation of the mitogen-activated protein kinase (MAPK) pathway in 80% cases. *KRAS* (54%), *BRAF* (33%), *NRAS* (26%), and

ERBB2, the upstream regulators of MAPK pathways are reported to be mutated, with mutations in *BRAF/KRAS* considered as good prognostic markers [67]. Due to the high prevalence of activated MAPK pathway in LGSOCs, MEK inhibitors (Trametinib, Selumetinib, Pimasertib, Binimetinib) are among the druggable targets for these cancers and some are under evaluation [65]. Recurrent mutations in *PIK3CA*, *FFAR1*, *USP9X* (11%) and *EIF1AX* (15%) are reported as driver mutations [68]. *USP9X* and *EIF1AX* are regulators of the mTOR pathway which are downstream effectors of the MAPK pathway. The use of Metformin, an inhibitor of the mTOR pathway, along with MEK inhibitor (Trametinib) has been reported to show an inhibitory effect in various LGSOCs cell lines [69]. Taken together, MEK inhibitors and Metformin are potential candidates for targeted therapies. CDK4/6 inhibitors, (ribociclib and abemaciclib) are under clinical trials for LGSOCs [65]. Endocrine therapy using letrozole, anastrozole or tamoxifen used as maintenance therapy has been reported to be beneficial in LGSOCs due to estrogen and progesterone receptors expressions [70].

2.1.3 Endometrioid carcinomas

Endometrioid carcinomas (ECs) are the second most common EOCs representing 10% of all OCs [71]. They are diagnosed in women in the age range of 40–70 years and are associated with a good prognosis. As its name suggests they are associated with endometriosis and are thought to be derived from the endometrium [72]. Endometriosis, menopausal hormone therapy, HBOC syndrome, Lynch syndrome and late menopause are some of the risk factors associated with ECs [14, 73].

One of the most mutated genes reported in ECs is *ARID1A* at a frequency of 30%. *ARID1A* is a component of the SWI/SNF chromatin remodeling complex. Targeting *ARID1A* with HDAC inhibitors have been reported to be effective in mice models harboring *ARID1A* tumor mutation [74]. *CTNNB1*, of the β-catenin signaling is also reported to be mutated at a rate of 25–60%. β-catenin signaling is a conserved pathway involved in development implicated in other epithelial cancers but its oncogenic role is less understood [75]. Other less frequent mutations are *KRAS/BRAF* (20%), which are regulators of MAPK pathways, *PIK3CA* (12%), and *TP53* (25%) [76]. *PTEN* mutations with frequent loss of heterozygosity (45–75%) is also reported [52]. *PTEN* is a tumor-suppressor gene that is a negative regulator of the PI3K pathway and is also the most mutated in the related endometrial cancers [77]. The multiple mutational spectra of ECs warrants the investigation of combination therapy using MEK inhibitors (trametinib, MEK162), TP53 activators (APR-246), and PI3K inhibitors (idelalisib, voxtalisib). Only 14% of EC cases are reported to be *BRCA* mutation carriers [78], and HBOC syndrome being one of the risk factors for ECs, PARP inhibitors are a viable option for targeted therapies.

2.1.4 Mucinous ovarian carcinomas

Mucinous carcinomas (MOCs) are a rare subset of EOCs accounting for 2–3% of all OCs. They are histologically characterized by high levels of intracellular mucin. MOCs are more prevalent in women below 40 years and unlike other EOC types, the only risk factor identified is smoking [14, 79]. Early-stage MOCs have an excellent prognosis and beyond stage II, they are addressed by standard chemotherapeutic agents with poor outcomes, as these tumors are chemoresistant.

Though rare, MOCs have been well characterized. The predominant mutation present in MOCs is *KRAS* mutations reported in 66% of cases [79, 80]. A recent large cohort study identified many other mutations in MOCs besides *KRAS* in varying degrees which are *TP53* mutation, HER2 amplification (a member of the

epidermal growth factor receptor family), *PIK3CA/PTEN* (regulator of PI3K-PTEN-AKT pathway), *BRAF* mutation, *CTNNB1/APC* mutations (regulator of Wnt-signaling pathway), and *ARID1A* mutation (a member of the SWI/SNF family) [79, 80]. One of the potential drugs for the treatment of MOCs is 5-fluorouracil. MOCs and mucinous colorectal cancer (CRC) share a similar mutational profile with unfavorable outcome [81]. 5-fluorouracil, which is currently utilized for CRC treatment has been effective in various MOC cell lines in combination with oxaliplatin [82]. Moreover, the multiple mutational spectra reported in MOCs are a great avenue for identifying the most potent target for tailored therapies. Some targeted drugs like BRAF inhibitors, PI3K inhibitors are already being investigated in various other cancer types. Combinatorial therapy using dual inhibitors is warranted for MOC treatment due to its varied mutational landscape.

2.1.5 Clear-cell carcinomas

Clear cell carcinomas (CCCs) of the ovary constitute >5% of all OCs and 10% of all EOCs [83]. The incidence rates of CCCs vary by ethnicity; the majority of the cases are reported in East Asian countries (mainly Japan) for unknown reasons [84]. They are mostly diagnosed in younger women with an option of fertility-sparing surgery before standard chemotherapy. These are chemoresistant tumors with a poor prognosis if diagnosed at an advanced stage, but most of these cases are diagnosed early with a good prognosis [83]. They are a distinct class of EOCs thought to arise from endometriosis or clear cell adenofibroma, hence they are associated with endometriosis which is thought to be the precursor for CCC manifestation and this association is considered a good prognosis [85]. Late menopause and endometriosis are considered to be the highest risk factors for developing CCCs.

The most common genomic alterations identified in CCCs are activating mutations in *PIK3CA*, a regulator of the PI3K-PTEN-AKT pathway (50%), and loss of function in *ARID1A*, component of SWI/SNF chromatin remodeling complex (50%) [86]. Other mutations reported in varying degrees are *MET* gene amplification, mutations in *ARID1B, SMARCA4*, *ERBB2, PIK3CA, PIK3R1, AKT2, PTEN, KRAS, PPP2R1A, TP53, TERT* promoter, and ZNF217 overexpression [85, 87]. Antioxidant genes like *Glutathione peroxidase 3 (GPX3)*, *glutaredoxin (GLRX),* and *superoxide dismutase 2 (SOD2)* are reported to be highly expressed in CCCs rendering them resistant to chemotherapy [88]. A recent report on the pharmacological inhibition of EZH2 for loss of function of *ARID1A* has shown considerable promise in treating CCCs [89]. The overexpression of the transcription factor ZNF217 is a poor prognostic marker. In-vitro studies in ZNF217-overexpressing cells treated with triciribine, a DNA synthesis inhibitor, have shown inhibitory effects suggesting ZNF217 be a druggable target [90]. Targeting PI3K/AKT/mTOR pathways using PI3K inhibitor (idelalisib, Voxtalisib) or mTOR pathway inhibitor (Metformin) are other viable options.

2.2 Sex cord-stromal tumors (SCSTs)

The rare ovarian sex cord-stromal tumors (SCSTs) constitute 8% of all OCs and are diagnosed in broad age groups with mixed prognosis [91]. These neoplasms originate from the stromal cells and/or the sex chord cells of the ovary, which are involved in the endocrine function of producing the female sex hormones, therefore unlike EOCs, they present with hormone-related disorders. Certain hereditary cancer syndromes predispose patients towards SCST. Based on the WHO classification of OCs, the various subtypes of SCSTs with their incidence, risk factors, prognosis, and molecular alterations are outlined in **Table 1** [92].

SCST subtypes	Incidence rates	Incident age groups	Risk factors	Prognosis	Chromatic alteration
Stromal tumors					
Fibroma	4% of all OCs	~ 40 years	Meigs' syndrome	Good	
Thecoma	0.5–1% of all OCs	26–86 years		Poor	*FOXL2* (~21%)
Fibrosarcoma		20–73 years		Poor	
Leydig cell tumor	0.1% of all SCST	Post-menopausal women		Good	
Steroid cell tumor	0.1% of all SCST	~ 43 years	Cushing syndrome	Good	
Sclerosing stromal tumor	>0.1% of all SCST	<30 years		Good	
Sex-chord tumors					
Adult granulosa cell tumor	5% of all OCs, 70% of all SCSTs	24–84 years	Peutz Jeghers syndrome, Potters syndrome	Poor	*FOXL2* mutation (> 95%), *TERT* mutations (~40%), AKT1 amplification (~60%)
Juvenile granulosa tumor	5% of all GCTs	8–45 years	Ollier disease, Maffucci disease	Good	AKT1 amplification (~60%), *GNAS* mutations (~30%)
Sertoli cell tumor		2–76 years	Peutz Jeghers syndrome	Good	
Sex chord tumor with annular tubules	1.4% of all SCST	5–39 years	Peutz Jeghers syndrome	Favorable	
Mixed sex chord-stromal tumors					
Sertoli-Leydig cell tumor	0.5% of all OCs	>30 years	Dicer syndrome	Good	Germline and somatic *DICER1* mutations (60%)

Table 1.
Sex cord-stromal tumors subtypes: epidemiology, and molecular alterations.

Due to the rarity of these tumor types, the molecular characteristics of only a few of these subtypes are reported. The cancers arising in the ovary's granulosa cells are the most common in this group comprising 2–5% of all OCs [93]. Granulosa cells are somatic cells involved in folliculogenesis and ovulation, the variant adult granulosa cell tumors (AGCTs), which are estradiol producing are the most common in this group constituting 70% of all SCSTs [94]. Inhibin, a gonadal hormone secreted by granulosa cells, is reported to be elevated in GCT patients [95]. Inhibin level and CA-125 are utilized as a diagnostic biomarker to assess disease progression in GCTs [96]. 97% of AGCTs are characterized by the ubiquitous presence of *FOXL2* mutations, a component of the TGFβ pathway [95]. The pleiotropic TGFβ pathway is reported to be deregulated in many cancers conferring chemoresistance and metastasis [97]. Moreover, *TERT* promoter mutations are reported in 40% of recurrent AGCT cases with poor prognosis [98]. Few small cohort studies of AGCTs, and juvenile granulosa cell tumors (JGCTs), have reported amplification in

AKT leading to possible dysregulations in PI3K/AKT pathways [99, 100]. Activating GNAS mutations involved in tumor invasion are reported in 30% of JGCTs with aggressive nature [101]. The notch signaling pathway is also reported to be altered in GCTs [102]. Estrogen producing thecomas, composed of pure stromal cells are also reported to harbor *FOXL2* mutation at a rate of 21% [103]. Sertoli-Leydig cell tumors (SLCTs), which belong to mixed-sex chord and stromal cells are androgen-secreting tumors that induce varying degrees of virilization (male physical characteristics) [104]. Mutation in *DICER1*, an endoribonuclease involved in microRNA biogenesis, is reported with a high frequency of 88% in undifferentiated SLCTs [105].

Targeting Activin A of the TGFβ pathway and aromatase, a downstream target of FOXL2 has been reported promising for targeted therapies [106, 107]. *TERT* promoter mutations are present in various cancer types and are reported to activate the oncogenic MAPK pathway; targeting this pathway using MEK inhibitors (trametinib, MEK162) are potential treatment options [108]. Besides, other druggable pathways for GCTs include PI3K and NOTCH pathways. Identifying drugs targeting DICER1 is warranted which could provide novel modalities for tailored therapies for SLCTs.

2.3 Ovarian germ cell tumors (OGCTs)

Ovarian germ cell tumors (OGCTs) of the ovary are rare ovarian neoplasms comprising 2–3% of all OCs [109]. These histologically variant heterogeneous neoplasms arise in the egg or ovum, the ovary's primordial germ cell. They primarily manifest in young and adolescent women with excellent prognosis if diagnosed in earlier stages [110]. These tumors are chemosensitive allowing fertility-sparing surgery in most cases [111]. A recent small cohort study reported a low mutational burden in OGCTs explaining their chemosensitive disposition [112]. OGCTs are classified into dysgerminomas, immature teratomas, yolk sac tumors, and mixed germ cell tumors in order of their frequency. Embryonal carcinomas, choriocarcinomas, and malignant struma ovarii tumors are other very rare forms of OGCTs [113]. The understudied, very rare mixed germ cell tumors are the only aggressive OGCT subtype with poor prognosis [114]. There are no risk factors identified for OGCTs but certain genetic diseases like Turner's syndrome, Triple X syndrome, and Swyer syndrome are reported to be high-risk factors for dysgerminomas [115]. The incidence rate, prognosis, risk factors, and their molecular characteristics are outlined in **Table 2**.

OGCT subtypes	Incidence rates	Incident age groups	Prognosis	Chromatic alteration
Dysgerminoma	40% of OGCTs	19–23 years	Good	*KIT* mutation (30–50%), 12p amplifications harboring *KRAS* (80%)
Immature teratoma	~35% of OGCTs	18–36 years	Good	
Yolk sac tumors	15% of OGCTs	15–40 years	Good	*PIK3CA* or *AKT1* mutation (72%), 12p amplifications harboring *KRAS* (60%)
Mixed germ cell tumors	5% of OGCTs	<20 years	Poor	12p amplifications harboring *KRAS* (~40%)

Table 2.
Ovarian germ cell tumors subtypes: epidemiology and molecular alterations.

SCCO subtypes	Incidence rates	Incident age groups	Prognosis	Chromatic alteration
SCCO-hypercalcemic type	<1% of all OCs	<40 years	Poor	*SMARCA* mutation (90%)
SCCO- pulmonary type	<1% of all OCs	<59 years	Poor	None reported

Table 3.
Small cell carcinoma of the ovary subtypes: Epidemiology, and molecular alterations.

The most frequent mutations reported in OGCTs are *KIT* mutations and 12p amplification, which harbor KRAS [112]. The OGCT subtype, dysgerminomas harbor 12p amplification and *KIT* mutation at a frequency of 80% and 30–50%, respectively [116]. *KIT* is a proto-oncogene involved in PI3K/AKT/mTOR, JAK/STAT and MAPK pathways [117], whereas the oncogene *KRAS* is involved in the tumor development pathway of Ras/Raf/MEK/ERK pathway [118]. The aneuploid, yolk sac tumors are reported to harbor PI3K and AKT1 mutations, besides *KRAS* altering PI3K/AKT/mTOR pathway. The TGFβ/BMP and Wnt/β-catenin signaling pathways are also reported to be activated in yolk sac tumors [116]. Few druggable targets of these pathways like AKT inhibitor (afuresertib) and MEK inhibitor (trametinib) are already under clinical trials for various OCs [119].

2.4 Small cell carcinoma of the ovary (SCCO)

Small cell carcinoma of the ovary (SCCO) is a group of extremely rare OCs accounting for <1% of all OCs [120]. Their biology is poorly understood as their cellular lineage is unknown. Based on histologic characterization, SCCO is classified into hypercalcemic type (SCCO-HT), which is chemoresistant and pulmonary type (SCCO-PT) which is chemo-sensitive. These are highly malignant cancers with an average survival of 5.7 years. The incidence rate, prognosis, risk factors and molecular characteristics are outlined in **Table 3**.

One of the significant mutations identified in 90% of cases of SCCOHT is germline or somatic mutations of *SMARCA4* [121]. *SMARCA4* mutation is considered one of the hallmarks of SCCOHT, it is a key component of the switching/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex [122, 123]. The loss of function of *SMARCA4* leads to the upregulation of EZH2, the catalytic subunit of the PRC2 complex which is utilized as a druggable target for SCCOHT [124]. Targeting EZH2 using tazemetostat has reported antiproliferative and antitumor effects in SCCOHT cell lines [125]. Moreover, a recent study has reported oncolytic viruses' effect on SCCOHT derived cell line BIN-1 in reducing its proliferation >75%, which holds promise in developing targeted therapies [126]. Some of the broad categories of drugs being investigated for SCCOHT and some of which are already in clinical trials, include tyrosine kinase inhibitors, immune checkpoint inhibitors and HDAC inhibitors [127]. There are no studies reported on the molecular characterization and pathogenesis of SCCO-PT due to its rarity.

3. Potential drugs for targeted therapies in OCs

Presently, targeted therapy is employed only to improve the efficacy of standard therapy in OC treatment with drugs such as bevacizumab, an anti-angiogenic agent which is licensed for use as front-line therapy for advanced OCs [57] and olaparib, a PARP inhibitor which is now approved for first-line maintenance therapy for patients with relapsed *BRCA*-mutated OCs [128]. Very recently, the combination of

bevacizumab and olaparib is FDA approved for first-line maintenance treatment in advanced OCs with HRD positive status [129].

Generic drugs being investigated for a variety of OC types are receptor tyrosine kinase (RTK) inhibitors. RTK inhibitors have been reported to be efficacious in treating a variety of malignant cancers by inhibiting tumor cell proliferation via blocking the signal transduction cascade. For e.g., Ponatinib is a multi-tyrosine kinase inhibitor that targets pathways like EGFR, FGFR, PDGFR, and VEGFR all of which are aberrantly activated in various cancer types [130]. Other RTK inhibitors being investigated for OCs are Palbociclib, Abemaciclib and Ribociclib [131, 132]. Likewise, immunotherapy using immune checkpoint inhibitors like Pembrolizumab and Nivolumab has been revolutionary in oncology research. These are monoclonal antibodies that trigger the immune T-cell activation to attack the cancer cells and Pembrolizumab is already under clinical trial for various cancer types [133, 134]. Epigenetic abnormalities being the hallmarks of cancers, epigenetic modulators like HDAC inhibitors have shown great promise as anti-cancer drugs. HDAC inhibitors like Vorinostat, Panobinostat, Quisinostat, and Trichostatin are under investigation for targeted therapies for OCs [126, 135].

4. Role of miRNAs in ovarian cancer

miRNAs are single-stranded RNA nucleotides that regulate gene expression. In the human body, they are reported to be involved in regulating around 60% of genes affecting various cellular and biological processes. Each miRNA has multiple gene targets or multiple miRNAs can act on one target gene. They can function either as an oncogene or a tumor suppressor and their expressions in cancer cells are deregulated [136]. The miRNA expression profile for each OC subtype is reported to be distinct, with a subset of miRNAs downregulated or upregulated [137]. The miRNA signatures identified in various cancer types are being investigated for their utility as cancer biomarkers in tumor diagnosis, prognosis and therapeutic outcome.

Ovarian cancer subtype	Upregulated	Downregulated	References
Serous Ovarian cancer	miR-429, miR-141, miR-200c, miR-93, miR-16, miR-20a, miR-21, miR-27a, miR-200a, miR-200b, miR-200c, miR-203, miR-205, miR-375, miR-145	miR-320c, miR-383, let-7b, miR-99a, miR-125b, miR-145, miR-100, miR-31, miR-137, miR-132, miR-26a	[138, 139]
Clear-cell carcinomas	miR-93, miR-126, miR-338, miR-200a, miR-200b, miR-30a, miR-141, miR-182, miR-200a, miR-510, miR-509,	miR-383, miR-424, miR-127, miR-155, miR-99b	[138, 139]
Mucinous ovarian carcinoma	miR-192, miR-194	—	[137]
Endometrioid carcinomas	miR-7, miR-429, miR-21, miR-29a, miR-92, miR-30c1, miR-126, miR-126, miR-29a	miR-342, miR-181a, miR-450b, miR-155, miR-25, miR-93, miR-127, miR-99b	[136–138]
Ovarian Germ cell tumors	miR-373-3p, miR-372-3p and miR-302c-3p, mir-302–367 cluster, mir-371–373 cluster, miR-146b, miR-155, miR-182	miR-199a-5p, miR-214-5p and miR-202-3p, Let-7	[139, 140]

Table 4.
Deregulated miRNAs in ovarian cancer subtypes.

The sensitivity of a cancer drug profoundly affects treatment efficacy and prognosis. miRNAs are involved in conferring chemo-sensitive or chemoresistant phenotype by regulating the drug-resistance related genes [138]. Therefore, manipulating the expression levels of specific miRNAs can aid in drug sensitivity. As previously mentioned, the sensitivity for platinum drugs varies among each OC subtype, and this profoundly affects the treatment efficacy and prognosis. Though still in its infancy, targeting miRNA holds great promise for a more customized therapeutic approach. Here, we highlight the key miRNAs reported in recent literature, which are deregulated in the various OC subtypes (**Table 4**).

5. Conclusion

The global incidence rate for OC is expected to increase by 47% by 2040 [141]. Except for the emergence of PARP inhibitors in women with HRD HGSOC tumors, the conventional treatment protocol for other OC subtypes has remained the same since the 1980s, with no significant impact on survival rates. Screening for high-grade OCs remains a challenge. With the advances in the high throughput screening technologies, the focus is warranted to shift towards translational research to treat each OC subtype for their underlying genomic aberrations.

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