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Chapter 1

Ovarian Cancer Genetics: Subtypes and Risk Factors

Jeff Hirst, Jennifer Crow and Andrew Godwin

Abstract

The genetics of ovarian cancer are a complex, ever evolving concept that presents hurdles in classification, diagnosis, and treatment in the clinic. Instead of common driver mutations, genomic instability is one of the hallmarks of ovarian cancer. While ovarian cancer is stratified into different clinical subtypes, there still exists extensive genetic and progressive diversity within each subtype. In high-grade serous ovarian cancer, the most common subtype, \( TP53 \) is mutated in over 90% of all patients while the next most common mutation is less than 20%. However, next-generation sequencing and biological statistics have shown that mutations within DNA repair pathways, including \( BRCA1 \) and \( BRCA2 \), are common in about 50% of all high-grade serous patients leading to the development of a breakthrough therapy of poly ADP ribose polymerase (PARP) inhibitors. This is just one example of how a better understanding of the complex genetic background of ovarian cancer can improve clinical treatment. A thorough review of ovarian cancer genetics and the effect it has on disease development, diagnosis, progression, and treatment will enhance the understanding of how to better research and treat ovarian cancer.

Keywords: genetics, subtypes, pathogenesis, \( BRCA1 \), \( BRCA2 \), \( TP53 \), risk factors

1. Introduction

Ovarian cancer is a generic term used to classify cancers involving the ovaries though they can arise from many different cell types within the Müllerian compartment. Ovarian cancer presents as a distinct subset of cancers with a wide variety of genomic variation (e.g., somatic \( TP53 \) mutations, germline \( BRCA1/2 \) mutations, copy number gains in \( BRAF \), \( CCNE1 \), \( TERC \), \( TERT \), and copy number loss of \( RB1 \) and/or \( PTEN \) as demonstrated through a Pan-Cancer analysis using The Cancer Genome Atlas (TGCA) database (Figure 1). The pathogenesis and the debate of cellular origins of ovarian cancer will be discussed in Section 4.
Ovarian cancer is a pathological and genetically diverse disease that presents many hurdles towards clinical detection and treatment. These clinical barriers have prevented significant improvement in patient survival for the past three decades. The heterogeneity of ovarian cancer is one of the driving factors limiting clinical progress. In this chapter, we will discuss the diversity of ovarian cancers and how these genetic factors effect clinical detection, progression, and treatment. A better understanding of the genetic differences in ovarian cancer will open up new areas for research and treatment.

Ovarian cancer can be classified into subclasses based on pathological and genetic observations. Each subclass has distinct genetic alterations, disease pathogenesis, tumor progression, and survival outcomes in response to therapy. Not only does each subclass behave differently, heterogeneity within specific subclasses presents challenges in regards to treatment options, drug resistance, and overall clinical response. Genetic diversity has greatly limited the development of targeted therapies, which have been successful in other cancers, such as HER2 amplified breast cancers (trastuzumab, Herceptin®), BCR-ABL fusion in chronic myelogenous leukemia (CML) or KIT mutant gastrointestinal stromal tumor (imatinib mesylate, Gleevec®), and BRAF V600E mutant melanoma, vemurafenib (Zelboraf®). However, understanding genetic vulnerabilities such as deficiencies in homologous DNA repair prompted the development of poly

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**Figure 1.** Common genetic alterations in ovarian cancer represented across pan-Cancer analysis from the TCGA. Bar graphs depict % of cases with mutations (green), amplification (red), and/or deletion of commonly dysregulated genes across a panel of cancers in the TCGA.
ADP ribose polymerase (PARP) inhibitors, a breakthrough in the treatment of specific ovarian cancer patients.

Finally, we will discuss genetic and lifestyle factors that can contribute to the development or progression of ovarian cancer. Since ovarian cancer is difficult to detect at early stages, knowing genetic and lifestyle risk factors for the development of the disease is critical. In fact, studying familial breast and ovarian cancer led to the discovery of inherited mutation in either BRCA1 or BRCA2 and improved detection of patients at risk for both cancers. While germline BRCA1/2 mutations are two of the highest risk factors for developing ovarian, other genetic and lifestyle factors have been shown to influence the risk of disease development. A more thorough understanding of the risks of ovarian cancer is needed to stratify the chances of developing ovarian cancer for each patient.

2. Classification of ovarian cancer

Ovarian cancers of epithelial cell origin account for more than 85% of all ovarian tumors when compared to tumors that arise from germ, epidermoid, stromal, and border cells [1]. Since EOCs are the most common and deadly form of ovarian cancer, we will refer to EOC as ovarian cancer for the remainder of this chapter and primarily discuss ovarian cancers of epithelial origin [2, 3]. Typically, EOC is classified into five different histological subtypes: high-grade serous (HGS), low-grade serous (LGS), endometrioid, clear cell and mucinous [3, 4] (Table 1). Low-grade and high-grade disease can typically be distinguished based on the extent of nuclear atypia and mitosis [5]. Low-grade tumors are slower growing, more genetically stable and do not respond to chemotherapy as well as the faster growing, genomically instable high-grade tumors [6–8]. High-grade serous carcinomas are the most common ovarian cancer subtype (more than 70%) followed by endometrioid, clear cell and low-grade serous [9]. Mixed ovarian cancers that represent more than one subtype are more rare, accounting for less than 1% of all ovarian cancers [10, 11]. Globally, each subtype follows a similar distribution of incidence outside of Asia, where clear cell and endometrioid tumors are more frequent compared to other locations [12]. Each subtype behaves as a discrete disease with differences in presentation, progression, mutation profile, association with hereditary cancer syndromes, and response to chemotherapy (Table 1) [13]. The 10-year survival for each subtype can be influenced by each of these factors and ranges from mucinous (87%), endometrioid (59.7%), clear cell (58.7%), to serous (24.4%) [14, 15].

Each subtype has distinct histological protein expression patterns, mutations and even epigenetic signatures. Further classification based on molecular profiles may provide insights into improving therapy selection [16, 17]. Recent studies have helped to further stratify the genomic differences between each subtype where 12 different loci contribute to the susceptibility of serous (3q28, 4q32.3, 8q21.11, 10q24.33, 18q11.2, 22q12.1, 2q13, 8q24.1 and 12q24.31), mucinous (3q22.3 and 9q31.1) and endometrioid (5q12.3) subtypes of ovarian cancer [18]. Molecular classification has been shown to stratify low-grade diseases into separate clusters, whereas high-grade diseases have less genetic separation [19–21], indicating early pathogenesis of the disease might be the best time to molecularly phenotype or develop targeted therapies.
Within each subclass ovarian cancers are diagnosed and staged after primary cytoreductive surgery which attempts to remove any visible mass within the peritoneal cavity. The International Federation of Gynecology and Obstetrics (FIGO) have established guidelines for the staging of ovarian cancer. These guidelines are established based on disease localization from ovaries only (Stage I), pelvic extension (Stage II), peritoneum spread (Stage III), to distant metastases (Stage IV). While the 5-year relative survival for localized disease is over 90%, the majority of patients are diagnosed with regional (15%) or distant (60%) disease where the 5-year survival is 73% and 28.9% respectively [22]. While molecular characterization of each stage is still progressing, some data suggest there is a stepwise progressing in gene expression that could be exploited for enhanced staging [23].

In the next sections of this chapter we will discuss each subtype of ovarian cancer. We will focus primarily of specific genomic alterations, clinical pathogenesis, and responses to therapy.

### 2.1. High-grade serous tumors

High-grade serous tumors account for both the majority of ovarian cancer diagnoses and deaths [5, 9]. HGS tumors show a broad range of histological phenotypes with papillary, micropapillary, glandular, cribriform and trabecular structures involving columnar cells with pink cytoplasm [24, 25]. HGS is a separate disease from its LGS counterpart (and not different grades of the same neoplasm) and is identified by high mitotic index and high-grade nuclear features [5, 26] (Figure 2). HGS disease can be identified from other malignancies such as uterine cancer and endometrioid cancer through positive staining in WT-1, p53, and p16 [27–31]. The majority of HGS tumors are diagnosed at late stages when a complete resection of the tumor is difficult. In fact, less than 5% of HGS cancers are diagnosed at a Stage 1 (when the tumor is confined to the ovaries). Finally, while extremely rare, there is some evidence to support the progression of LGS or borderline tumors into high-grade disease. These cases have been identified through concurrent mutations in KRAS and TP53 in both a borderline lesion and HGS carcinoma [32]. This progression could be due to a secondary mutation of TP53 in borderline or low-grade tumors [33].

HGS tumors are associated with genomic instability [2, 34] since almost all (>95%) high-grade serous cancers have somatic TP53 mutations and over half have homologous DNA repair

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Table 1. Subtypes of ovarian cancer.
pathway deficiencies mainly represented by defects in BRCA1, BRCA2, or related proteins [35–38]. Many of these genomic alterations are similar to basal-like breast cancer, opening the opportunity for comparative studies [39]. In fact, when compared to other cancers HGS ovarian cancer had the most genomic instability when comparing copy number alterations to mutation rates [40]. Other genetic alterations that have been identified in HGS disease include cyclin E1 (CCNE1) amplifications. CCNE1 amplification in HGS disease is associated with poor prognosis and platinum resistance [41]. Likewise, HGS genomic instability leads to inactivation of tumor suppressor genes through gene breakage [42]. Loss of expression of PTEN in tumor specific cells is predictive of poor patient survival in ovarian cancer [43].

To provide an example of this, we utilized data available through TCGA to demonstrate genetic aberrations within 34 common cell cycle control genes from 316 HGS ovarian cases with complete mutation, copy number alteration, and mRNA data [44] (Figure 3). While some alterations were fairly consistent across patient samples (such as up-regulation or amplification of MYC in ~30% of cases, down-regulation of RBL2 in ~25% of cases, and up-regulation or amplification of CCNE1 in ~20% of cases) the remaining 31 queried genes had between 3 and 29% alteration rates of which there was little discernable pattern. As a comparison, TP53 is shown to be altered in most of the cases. Examples such as this demonstrate just how difficult high-grade EOC is to treat with single molecularly-targeted therapies [45, 46]. However, one of the major breakthroughs for the treatment of ovarian cancer has been the development and FDA approval of PARP inhibitors, olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula). Specifically, in BRCA deficient or other homologous repair deficient cells, PARP inhibitors induce the error prone DNA repair pathway non-homologous end joining [47]. Therefore, PARP inhibitors were investigated for efficacy in ovarian cancer due to the high number of patients with BRCA and/or homologous recombination (HR) deficient tumors [48]. Rucaparib, an oral PARP-1, -2 and -3 inhibitor, has been approved for treatment in patients with BRCA mutations (somatic or germline) who have received at least two prior chemotherapy treatments [49, 50]. Another PARP inhibitor, niraparib, was approved in early 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, regardless of the BRCA mutation status. However, in the Phase III trial of niraparib, the progression
free survival (PFS) was superior only for germline BRCA mutant patients when compared to standard of care (22 months vs. 9 months) versus BRCA competent patients compared to standard of care (9.3 months vs. 3.9 months) [51], indicating better activity in the BRCA deficient tumors. To address this limitation, our laboratory has shown that alisertib (MLN8237) can inhibit DNA double strand break repair as well as BRCA expression which sensitizes resistant tumors to treatment.

Figure 3. Genetic Dysregulation in high grade serous ovarian cancer. Data from the TCGA showing mutation, copy number alteration, and mRNA dysregulation of 34 cell cycle control genes and TP53 alteration status (as a comparison) within 316 cases of high grade serous ovarian cancer demonstrates the overall heterogeneity of the disease.
To add to this hurdle, while HGS tumors are initially responsive to platinum-chemotherapy, most patients’ tumors recur which are resistant to standard chemotherapy, thus limiting treatment options for these women. The deficiencies in DNA repair pathways associate with widespread copy number alterations and make HGS cancer initially sensitive to platinum-based chemotherapy (and PARP inhibitors) but develop therapy resistance. Specifically the genomic instability can drive changes that reverse the initial sensitivity to PARP inhibitors through reversion of BRCA1/2 mutants to wild-type function [42, 53]. Similar to PARP inhibitors, patients with BRCA mutations are initially more sensitive to chemotherapy; however, reversion of the BRCA1/2 mutations promotes cisplatin resistance [53, 54]. Further, specific expression of many different genes such as ABC1 [55–59], ABC2 [60, 61], and GSH1 [62, 63] correlate to disease progression and drug resistance. The expression of mesenchymal genes such as SNAIL, SLUG, and TWIST through the epithelial to mesenchymal transitions (EMT) promotes chemotherapy resistance [64, 65]. EMT is a dynamic cellular process that can be transferred from on cell to the next through many cellular pathways including extracellular vesicles [66, 67]. Since EMT is a dynamic process, therapies that reverse the process and promote the expression of epithelial genes are an intriguing area for drug development to reverse cell growth into more sensitive phenotypes [68]. The relative success of PARP inhibitors and lack of clinical efficacy of more specific targeted therapies shows the value of identifying and exploiting the underlining molecular vulnerabilities of ovarian cancer.

2.2. Low-grade serous and borderline tumors

Low-grade serous (LGS) account for approximately 10% serous tumors. LGS tumors are more common in younger patients with an average age at diagnosis of 55.5 years compared to 62.6 years for their high-grade counterpart. LGS ovarian cancer is more commonly diagnosed at early stages, with bilateral involvement, and without invasive potential [69]. Patients with non-invasive tumors have a significantly higher 7-year survival (95.3%) compared to those with invasive tumors (66%) [70, 71]. LGS tumors appear with extensive papillary features and psammoma bodies, uniform round to oval nuclei, evenly distrusted chromosomes, and ~10 mitoses/HPF (Figure 4).

When compared to high-grade disease, LGS tumors are typically slower growing and have more frequent mutations in KRAS, BRAF, and ERBB2, and tend to lack TP53 mutations [72–74]. Mutations in KRAS, BRAF, and ERBB2 in LGS tumors are mutually exclusive. However, each gene mutation are signatures of activated mitogen-activated protein kinase (MAPK) pathways. MAPK activation is higher in LGS compared to HSG and correlates with paclitaxel sensitivity and an improved 5-year survival [75]. Along with having functional p53, LGS tumors have a more stable genome with less rearrangements, mutations, and tumor heterogeneity [76]. However, due to more competent DNA repair pathways, LGS tumors do not respond...
to front-line chemotherapy as well as HGS tumors [77]. Consequently, a patient with optimal debulking surgery with minimal residual tumor is the best predictor of survival [78]. The involvement of MAPK regulation of cell cycle is thought to be strongly associated with LGS chemoresistance [75], but in turn provides a potential subpopulation for targeted therapeutic development [79]. Selumetinib, a MEK1/2 inhibitor, showed some activity in recurrent LSG, leading to further investigation of MAPK pathway inhibitors for the treatment of LSG [80].

LGS tumors are thought to be borderline tumors formed step-wise from the ovarian surface [73]. Borderline tumors are epithelial tumors that appear to represent and intermediates step between benign cystadenomas and adenocarcinomas with histological features such as cellular atypia without stromal invasion. Progression of LGS tumors from borderline tumors is also thought be from recurrence of undetected borderline tumors [81–83]. While borderline tumors can be diagnosed as either serous or endometrioid the majority of such cases are diagnosed as serous tumors [26]. Borderline tumors account for ~15% of all ovarian cancer diagnoses with a large percent of cases diagnoses at early stage (~75%) and a high rate of overall survival [84]. Diagnosis at an early age (mean age of ~45 years) and minimal invasive disease are primary factors for the favorable survival [26]. While rare, invasive borderline tumors (Stages II-IV) account for the majority of deaths in borderline tumor patients [85]. Borderline tumors have a similar activation of MAPK compared to LGS tumors [75], but a higher frequency in BRAF mutations [86]. BRAF mutations are more common in early stage tumors as well as in late stage tumors that do not recur in the patient [87]. However, it is possible many LGS progress independent of borderline tumors and the pathogenesis of LGS requires further elucidation [88].

2.3. Endometrioid tumors

Endometrioid tumors account for about 10–20% of all ovarian cancers. Their morphology is described as having a smooth outer surface with solid, cystic areas inside while the pathological phenotype involves high amounts of proliferative cells that resemble squamous or endometrioid differentiations with secretory cell features. Tumors contain cystic spaces lined by gastrointestinal-type mucinous epithelium with stratification and may form filiform papillae with at least minimal stromal support. Histologic review find that endometrioid tumors possess
nuclei that are slightly larger than cystadenomas; mitotic activity is present; goblet cells and sometimes Paneth cells (most commonly found in the small intestine) are present, but stromal invasion is absent [89, 90] (Figure 5). Endometrioid ovarian tumors are histologically similar to endometrial neoplasms. In fact, approximately one third of all endometrioid cases experience synchronous endometrial carcinoma or endometrial hyperplasia. This is not surprising given that endometrioid tumors are believed to arise from endometrial precursor cells and/or transformed endometrioses, possibly from back flow during menstruation that implants onto the ovarian surface epithelium [91–95].

The 5-year survival rate for endometrioid tumors is between 40 and 80%, and the 10-year survival is promising at ~60%. This is mostly due to early stage presentation of the disease; however, there is no survival difference when matched with serous patients of the same age and stage of diagnosis [96, 97]. Likewise, with serous tumors, endometrioid tumors can be both high- and low-grade with similar growth patterns distinguishing the two [98]. High-grade endometrioid tumors are very similar to HGS tumors in terms of genome instability and response to chemotherapy [99]. The primary treatment regimen consists of surgical debulking followed by platinum-based chemotherapy. Mutation profiles of endometrioid tumors reveal frequent activating mutations in CTNNB1 and PIK3CA [100, 101], as well as ARID1A (which helped link their origin to endometriosis) [102]. PTEN is altered in ~20% of endometrioid tumors, and to a lesser extent KRAS and BRAF [103, 104]. Given this mutational profile, it has been hypothesized that a subset of endometrioid tumors may be responsive to mTOR inhibitors; however, results of Phase I and II trials have shown minimal increases in overall response rate [105]. Ongoing studies emphasize a need for better molecular screening to identify individuals who could potentially benefit from a limited number of targeted therapies.

2.4. Mucinous ovarian cancer

Mucinous ovarian cancer (MOC) are primarily unilateral, can be very large (mean size of 10 cm and can range up to 48 cm) [106–108], and are diagnosed at early stages (most are stage I or II). Invasive disease accounts for less than 10% of all MOC cases [108, 109]. Mucinous ovarian tumors are rare when compared to other subtypes with reports of the overall incidence ranging from

Figure 5. Representative H&E staining of endometrioid ovarian cancer.
-12% [110] to as low as 3% [3, 111]. Patients with invasive disease (FIGO Stage III or IV) have higher risk of death and shorter survival than patients with early disease (FIGO Stage I or II) [112]. The pathological definition of MOC dictates intracytoplasmic mucin is mandatory, although many mucinous tumors lack obvious apical mucin in large parts of tumor, thereby imparting an endometrioid appearance. Mucinous tumors are often heterogeneous contain endocervical-like or intestinal-like cells with gastric superficial/foveolar and pyloric cells, enterochromaffin cells, argyrophil cells, and Paneth cells (Figure 6). While cytokeratin 7 and 20 staining is used to define MOC pathologically, it is limited in distinguishing primary ovarian tumors from secondary metastases of gastrointestinal tumors [113, 114]. Secondary pathological markers such as SATB2, CDX2, and PAX8 have potential to help diagnose MOCs [115–117].

While the overall survival for mucinous ovarian disease is high due to the majority of cases being diagnosed at early stage, invasive disease has a worse clinical outcome [118] and low response rates to chemotherapy due to the high expression of genes involved in drug resistance, including the ABC transporters [119]. Mucinous disease is mostly thought to originate from the gastrointestinal tract [120], though the molecular mechanisms of the disease are still not fully elucidated. KRAS mutations, which are found in other ovarian cancer subtypes, are the most common genetic alterations found in MOC [29, 121, 122], followed by HER2 amplifications [123]. Other mutations such as BRAF, TP53, and CDKN2A have been reported in MOC [124].

Extensive clinical studies of MOC are difficult to perform due to low number of cases and complex diagnosis and lead to early trial terminations such as GOG241 [125]. Small trials have shown that HER2 amplifications in recurrent MOC are a potential therapeutic target with trastuzumab [126]. While most ovarian cancer trials of HER2 inhibitors have shown limited efficacy, the prevalence of HER2 amplifications in MOC disease to other subtypes makes it a prospect for preselection if enough patients can be recruited [127].

2.5. Ovarian clear cell carcinoma

Ovarian clear cell carcinoma (CCC) accounts for approximately 5% of all ovarian cancer patients in the United States; however, it is more common in Asian women (~11%) than in African American.

Figure 6. Representative H&E staining of mucinous ovarian cancer.
or Caucasian (~5%) women [3, 128, 129]. CCCs are generally large (can grow over 15 cm), unilateral tumors that display only papillary, tubulocystic, and solid architectures with hobnail cells containing clear cytoplasm (Figure 7). While the pathogenesis of CCC is unknown, gene expression studies indicate clear cell ovarian cancer does not cluster with other ovarian cancers and more closely resembles lung cancers, endometriosis, and renal cell carcinoma [99, 130–132]. In terms of molecular mechanisms, CCCs are complex at the genomic level and can have mutations in ARID1A, PIK3CA, KRAS and PTEN [133, 134]: ARID1A is mutated in ~50% and PIK3CA mutated in ~33% of patient tumor samples [102, 135]. In contrast, CCCs are usually wild-type for TP53 and have a lower frequency of BRCA1 and BRCA2 mutations [136, 137].

Clinically, CCCs are typically diagnosed at an early stage; however, they are less responsive to front-line platinum-based chemotherapy, especially at later FIGO stages. When compared to matched serous disease, early stage CCC (I-II) had a better overall survival than serous, but late stage CCC (III-IV) had a worse prognosis than both serous [138] and endometrioid adenocarcinoma [137]. Interestingly, some evidence suggests that drug response can be correlated to CD44-10v isoform expression [139]. Like endometrioid, clinical trials aimed at treating CCC include mTOR inhibitors, including a Phase II trial investigating the addition of temsirolimus to standard first-line chemotherapy (NCT01196429). Additionally, CCC is characterized by overexpression of the pro-inflammatory cytokine IL-6, which could prove to be an alternative therapeutic target [140].

3. Ovarian cancer pathogenesis

EOCs were, for years, believed to arise primarily from the ovarian surface epithelium. However, two novel hypotheses for the pathogenesis of HGS ovarian cancer have been proposed. In the first mechanism, genetic alterations occurring within the normal ovarian surface epithelium or inclusion cysts which either proceed via a high-grade pathway with no perceivable intermediate histology or a low-grade pathway encompassing several, benign and non-invasive steps (Figure 8). This first hypothesis was established in the 1970s and proposed that
ovarian surface epithelial cells underwent repeated stress through multiple rounds of ovulation, leading to inflammation, DNA damage, and the initiation of tumorigenesis [141]. This hypothesis was in part supported by evidence on the decreased risk of ovarian cancer with the use of oral contraceptives, which inhibit complete ovulation [142, 143]. Other evidence supported the correlation between the number of lifetime ovulation cycles and the increase in ovarian cancer incidence [144]. Likewise, ovarian cancers are rare in other primates which have fewer ovulations cycles than humans [145]. However, ovarian tumors are more common in hens which have been induced to frequently ovulate [146, 147]. To further study the incessant ovulation theory, additional animal models will clearly be needed. In fact, Godwin and colleagues were some of the first investigators to establish ovarian surface epithelial cultures from rat and human ovaries and use model incessant ovulation in vitro as a mechanism for transformation and tumorigenesis [148–161]. Inactivation of p53 and Rb1 in mouse ovarian surface cells also led to tumorigenic transformation [162].

The second theory, which has gain much traction over the past decade, describes a progression model in which ovarian cancer precursors develop in the fimbria from occult serous tubal intraepithelial carcinoma (STIC), prior to metastasis to the ovary [163, 164]. Due to the aggressive nature of HGS tumors and the presence of early genomic instability, it is hypothesized that HGS ovarian tumors are instead metastatic lesions from the fallopian tube epithelial cells (Figure 8). To reduce the risk of HGS ovarian cancer in women BRCA mutation carriers it is beneficial to undergo a bilateral salpingo-oophorectomy (removal of both the ovaries along with the fallopian tubes) instead of just an oophorectomy (removal of only the ovaries) [165, 166]. The primary risk reduction for ovarian cancer following salpingo-oophorectomy was found to be serous disease [167]. Not only did these studies suggest a fallopian origin for serous disease, the use of salpingo-oophorectomy for preventative treatment for high-risk patients gave researchers and pathologist tissue to study and search for early ovarian cancer or precursor lesions. Microdissection of the fallopian tube epithelium following salpingo-oophorectomy from patients with a disposition to ovarian cancer showed lesions with BRCA and TP53 alterations that resemble HGS tumors [168–171]. To follow-up, extensive evaluation of both the fallopian tube and ovarian surface from BRCA mutant patients also showed common precursor lesions in the fimbria and not the ovarian surface [164, 172–174]. In genetic mouse models, conditional inactivation of commonly mutated ovarian cancer genes (BRCA1, TP53 and RB1) in ovarian surface epithelium cells leads to the formation of leiomyosarcomas and not HGSC following implantation into the mouse bursal sack [175]. Along with genetic alterations, fallopian lesions from BRCA patients showed gene expression profiles that mimicked HGS cancers [176]. Immortalization of human fallopian tube secretory epithelial cells (using hTERT and SV40 large T antigen) were transformed in vivo and in vitro by oncogenic RAS or MYC [177]. In contrast to ovarian surface epithelial cells, the inactivation of Brca, Tp53 or Pten in Pax8 over expressing mouse fallopian tubal secretory cells led to the development of HGSC [178]. Other genomic alterations common in HGS disease such as CCNE1 amplification and other copy number alterations are also found in STIC lesions and might be an early step in the progression of HGS ovarian cancer [179, 180]. For example, CCNE1 amplifications are common in both tubal lesions and HGS tumors, while centrosome amplification is more pronounced in HGS disease, indicating CCNE1 copy number gain is an early step in tumorigenesis that later promotes centrosome amplification [181]. However, some evidence exists to show an independent clonal evolution between tubular lesions and
the patient’s synchronous carcinoma, indicating small number of fallopian tube lesions may be micrometastases from uterine endometrioid carcinomas [182].

Other studies suggest a different route of the pathogenesis of cancers, where somatic stem cells undergo oncogenic mutation and create cancer stem cells that populate tumors [183–187]. While this mechanism has been contested with evidence that cancer cell plasticity can induce a stem cell phenotype in cancer cells from differentiated tissue [188], understanding any stem cell niche in ovaries and fallopian tubes may provide insight into the pathogenesis of ovarian cancer. Both the ovarian surface epithelium and fallopian tube epithelium have stem cell niches with cells with regenerative properties that could serves as progenitor cells for ovarian cancer [189–191]. Some evidence supports there could be a stem cell niche within the junction between
the ovarian surface the fallopian tube that helps repair the damage to the ovarian surface following follicle release [192]. Notch and Wnt, canonical stem cell pathways, have been shown to regulate differentiation in fallopian tube organoids and could contribute to fallopian tube repair [193]. Fallopian stem-like cells (CD44+ and PAX8+) can be isolated from distal end of the tube and are capable of clonal growth and self-renewal [194, 195]. Since these stem cell niches are located near the areas of ovarian and fallopian surface repair and precursor lesions they could be hotspots for the development of tumors from mutations in somatic stem cells. One recent study has shown that SOX2 is overexpressed in the fallopian tubes of patients with HGS disease and in BRCA1/BRCA2 mutation carriers [196], indicating a possible stem cell precursor lesion. The role of stem cells in cancer and cancer progression will remain an influential area of research and can provide potential insight into ovarian cancer pathogenesis in the future.

Taken together, these data support that the pathogenesis of ovarian cancer is complex and thus contributes to the clinical difficulties in detecting the disease early. As our understanding of the genomic complexities of ovarian cancer continues to evolve and the cell type of origin is further defined, we should be able to use this information to improve detection at a time when disease can be cured and develop more precise therapies based on tumor profiling and precision medicine.

4. Ovarian cancer risk factors

4.1. Hereditary and genetic risk factors

Ovarian cancer risk is causally linked to both lifestyle and genetics. Firstly, hereditary ovarian cancer accounts for approximately 5–15% of all cases [197] and are often diagnosed at an earlier age than sporadic disease. Furthermore, hereditary ovarian cancer tends to be of the high-grade serous subtype [198]. Therefore, patients with a first or second-degree relative with ovarian cancer have an increased risk of developing the disease (Figure 9). Specifically, there is a 2.5% risk of ovarian cancer in woman who report a sister EOC and a 9% risk if their mother has been previously diagnosed [197]. Familial ovarian cancer was first observed in Lynch syndrome (a disease associated with familial cancer due to inherited mutations in DNA repair machinery) in the 1970s [199, 200]. Multiple group and genomic mapping studies of breast and/or ovarian cancer-prone families ultimately led to the identification of inherited mutations in BRCA1 [201] and later BRCA2 [202, 203]. The prevalence of BRCA1 or BRCA2 mutations in the populations has been estimated from 0.1–0.3%, and 0.1–0.7%, respectively, in Caucasians with European origins [204–206]. BRCA1 and BRCA2 are mutated in the germline of approximately 9–13% patients with hereditary ovarian cancer [207–209]. For mutations in BRCA1, the estimated average risk of ovarian cancers ranges from 20 to 50% [210–214]. For BRCA2, average risk estimates range from 5 to 23% [210–214]. Mutation-specific cancer risks have been reported that suggest ovarian cancer cluster region (OCCR) exist in both BRCA1 and BRCA2 [211, 215]. The prevalence and spectrum of mutations in BRCA1 and BRCA2 have been reported in single populations with the majority of reports focused on Caucasians in Europe and North America. The Consortium of Investigators of Modifiers of BRCA1 or BRCA2 (CIMBA) has assembled data on more than 26,000 BRCA1 and nearly 17,000 BRCA2 female mutation carriers from 69 centers in 49 countries on six continents [216–222]. Ongoing studies by Tim Rebbeck and the
CIMBA consortium have comprehensively evaluated the characteristics of the over 1600 unique \textit{BRCA1} and more than 1700 unique \textit{BRCA2} deleterious (disease-associated) mutations found in the carriers [215]. The most common mutation types in these genes are frameshift mutations, followed by nonsense mutations. Therefore, understanding the type of mutations in \textit{BRCA1} or \textit{BRCA2} is important for risk assessment and determining medical management for patients. Most subtypes of ovarian cancer have been linked to \textit{BRCA1} or \textit{BRCA2} germline mutations but the development of HGS disease is the most common in these women carriers [223]. \textit{BRCA1} and \textit{BRCA2} mutations are more common in Ashkenazi Jewish women [206, 224, 225] due to the three common Jewish founder mutations \textit{BRCA1} c.5266dup (5382insC) and \textit{BRCA1} c.68_69del (185delAG) and \textit{BRCA2} c.5946del (6174delT) which have long been used as a primary genetic screening test for women of Jewish descent. Other mutations that are relatively common in specific populations, referred to as founder mutations, can be used to in limited screening tests. For example, in Iceland, only two mutations have been reported: the common founder mutation \textit{BRCA2} c.771_775del and the rarer \textit{BRCA1} c.5074G > A [226]. Despite having a higher risk for developing ovarian cancer, \textit{BRCA1/2} carriers have a better clinical outcome in terms of survival, with \textit{BRCA2} carriers having a more favorable outcome than \textit{BRCA1} carriers [54]. This

![Picture of a pedigree with BRCA1 and BRCA2 mutations highlighting the risk of ovarian cancer.](http://dx.doi.org/10.5772/intechopen.72705)

**Figure 9.** Hereditary ovarian cancer and BRCA mutations. Pedigree describing “BRCAness” and risk of ovarian cancer (top). The relative risk and prognosis for women with germline \textit{BRCA1/2} mutations.
phenomenon is thought to be due to BRCA2 carriers responding better to platinum-based chemotherapy [227]. However, the survival benefit decreases when examined over 10 years in HGSC instead of 5 years [228]. Over time, this could be possible due to secondary intragenic mutations in BRCA1 and BRCA2 that restore the wild-type reading frame (conversion back to a functional BRCA) and losing favorable responses to chemotherapy [229].

As indicated, the location of the alteration within BRCA1 or BRCA2 may vary the risk of breast and ovarian cancer [215], but other studies including genome-wide association study (GWAS) have identified several single nucleotide polymorphisms (SNPs) associated with risk of ovarian cancer for women in the general population [230]. Four of these SNP, i.e., rs10088218, rs2665390, rs717852, rs9303542, were associated with ovarian cancer risk in BRCA2 carriers, while two loci (rs10088218 and rs2665390) were associated with ovarian cancer risk in BRCA1 carriers [217]. Inherited variants in other loci along with BRCA1 or BRCA2 mutations can better predict the risk of either breast or ovarian cancer [220], indicating the need to better understand concurrent sequence variants in women with deleterious BRCA1 or BRCA2 mutations. Concurrent mutations in 1p36 (WNT4), 4q26 (SYNPO2), 9q34.2 (ABO), and 17q11.2 (ATAD5) increased risk of all EOC subtypes while 1q34.3 (RSP01) and 6p22.1 (GPX6) mutations increased the risk of serous ovarian cancer in BRCA carriers [231]. BRCA1 mutation carriers can have reduced risk with concurrent sequence variants in CASP8, i.e., the D302H polymorphism [232]. Other genetic markers of risk, such as a variant allele of KRAS at rs61764370, referred to as the KRAS-variant, which disrupts a let-7 miRNA binding site in this oncogene, is associated with sporadic and familial ovarian cancer without BRCA1/2 mutations [233]. PALB2, encoding for a BRCA2 interacting protein, has increased promoter hypermethylation which results in decreased BRCA2 function and increased risk of ovarian cancer [234]. Recent data have shown that copy number variation in BRCA1 or BRCA2 mutation carriers can either increase the risk (OR2A) or decrease the risk (CYP2A7) of ovarian cancer [235]. A better understanding of secondary genetic alteration in BRCA1/2 mutant carriers can help determine the best clinical approach for managing the risk of disease.

Genetic risk factors outside of BRCA1 or BRCA2 mutations are not as well defined but often take place in genes involved in genomic integrity, most commonly DNA mismatch repair (MMR). SNPs in the TERT locus (rs2242652 and rs10069690) were associated with decreased telomere length and increased breast and ovarian cancer risk in BRCA mutation carriers [236]. A study that sequenced 12 genes for germline mutations in patients with ovarian cancer found BARD1, BRIP1, CHEK2, MREA11, MSH6, NMN, PALB2, RAD51C, or TP53 were mutated in 24% of the 360 patients enrolled [237]. Genes within the Fanconi anemia pathway are also associated with developing ovarian cancer, including RAD51C, RAD51D, and BRIP1 [238, 239]. Other MMR genes have been associated with Lynch syndrome and ovarian cancer risk MLH1, PMS2, MSH2, and MSH6 [240–242].

4.2. Lifestyle risk factors

Environment and lifestyle also play a risk for developing both hereditary and sporadic ovarian cancer by either increasing or decreasing the lifetime risk of developing ovarian cancer. Like many cancers, age is a risk factor for ovarian cancer with most cases being diagnosed after the
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age of 60 and the disease being extremely rare in patients under 40 years of age [243]. As previously discussed, surgical procedures such as tubal ligation, salpingectomy and unilateral or bilateral oophorectomy have varying degrees of success for the development of ovarian cancer by removal of the organs from which the cancer develops [244, 245]. In women with a BRCA1 or BRCA2 mutation, risk-reducing salpingo-oophorectomy (RRSO) decreased the lifetime risk of developing ovarian and breast cancer [165]. In a multicenter study, RRSO was associated with an 85% reduction in BRCA1-associated gynecologic cancer risk (hazard ratio [HR] = 0.15; 95% CI, 0.04 to 0.56), while protection against BRCA2-associated gynecologic cancer (HR = 0.00; 95% CI, not estimable) was suggested, its effect did not reach statistical significance [246]. The effects of RRSO can influence risk for each subtype given the nature of development from different tissues, hence why bilateral oophorectomy has a stronger influence on the development of HGS disease, since it is believed to develop from the fallopian tubes. Lifestyle factors which influence complete cycling during menstruation have some of the strongest effects on the risk of developing ovarian cancer. This hypothesis is attributed to incessant ovulation, in which the release of eggs from the ovary, the fusion on the fallopian tube and the rebuilding of the uterine wall all contribute to pathogenesis of ovarian cancer [141, 148]. One of the most common factors which can alter complete cycling is the use of oral contraceptives [243]. The increase in use of oral contraceptives could be attributed to the decrease in ovarian cancer in the last decade. The longer use of oral contraceptives has been shown to correlate to lower risk of developing ovarian cancer [247, 248]. The risk is reduced in both BRCA wild-type and mutant carriers [249]. The risk of developing each subtype is decreased following oral contraceptive use, with the exception of clear cell carcinoma [251]. However, the associated side effects make it a poor treatment for prevention alone [252]. Another factor that can influence menstrual cycles and the risk of ovarian cancer is child birth [253], in specific the age at first birth and the number of births. In fact, it was discovered the risk of ovarian cancer decreases by approximately 10% for each 5-year increment in age at first birth [254]. Also, the number of births for a given woman has additive decrease in the risk of ovarian cancer, decreasing by about 8% for each birth [255], while the age of each woman at the onset of menopause had a weak association [129, 256].

Other lifestyle factors can influence the risk of ovarian cancer, such as hormone replacement therapy, breast feeding, obesity and inflammation. Hormone replacement therapy increases the risk of developing ovarian cancer, depending on the therapy. For instance, the use of estrogen increases the risk of developing ovarian cancer by 22%, while the combination of estrogen and progesterone only has about a 10% chance of developing ovarian cancer [257–259]. A meta-analysis showed a similar risk for developing both HGS and endometrioid ovarian cancer in menopausal women [260]. Conversely, hormone replacement given for menopause symptoms may improve survival of ovarian cancer patients [261]. Another reproductive factor is breastfeeding, in BRCA1 mutant carriers breastfeeding lead to a reduced risk of developing ovarian cancer [129, 243]. Meta-analysis also suggests the duration of lifetime breastfeeding is additive in reducing the risk of developing ovarian cancer [262]. Like many other cancers, cigarette smoking and alcohol consumption have at least some association with increasing the risk of developing ovarian cancer. Specifically, smoking is associated with an increased risk of developing clear cell and endometrial ovarian cancer but not serous [263]. Smoking increased the risk of mucinous ovarian cancer, but cessation returns can reduce the
risk over time [264] while heavy smoking (>10 packs per day) more than doubles the risk of developing ovarian cancer [265]. Alcohol consumption increased the risk of ovarian cancer, but seems to have an effect only in heavy drinkers. Consumption of more than 20 drinks per week is associated with increased risk [266] while with moderate use the risk is less pronounced or significant [267, 268]. Obesity is associated with less common subtypes of ovarian cancer and not HGS [269] and the lifetime risk decreases with recreation physical activity [270]. Finally, inflammation increases the risk of developing ovarian cancer [271] while the use of aspirin was shown to reduce risk of developing ovarian cancer from between 20 and 34% [272]. The use of other non-steroidal anti-inflammatory drugs (NSAIDs) showed a reduction in risk but was not significant.

5. Conclusion

Genetically, ovarian cancer is a heterogeneous and dynamic disease that presents several clinical and research challenges. While epithelial ovarian cancer is categorized pathologically into five basic subtypes, within each subtype exist genetic diversity that limits the development of target therapies. To add to this complexity, one of the hallmarks of serous ovarian cancer is genomic instability, which is driven by frequent \textit{TP53} mutations and deficiencies in DNA repair pathways. While this genomic alterations have led to the development of breakthrough therapies (PARP inhibitors), they also contributes to the dynamic cell growth and frequent genomic alterations and gene expression changes which contribute to the adaptation to therapy. Likewise, the pathogenesis of ovarian cancer remains a debated field with the recent insights of progression of a subset of serous ovarian cancer from fallopian tube epithelial lesions. Progression from the fallopian tube means tumors detected on the ovarian surface are already metastatic disease, leading to quick progression and limited response to therapy. Overall, while many genetic and genomic abnormalities have been identified in ovarian cancer, additional discovers are needed to (1) improve early detection of the disease (at a time when current treatment might be curative), (2) further define molecular classifiers of response to therapy, and (3) develop therapies that will be more effective across or specific to the different molecular subtypes. Other than the very common \textit{TP53} mutation in high-grade serous ovarian cancer (96% of cases), which to date is undruggable, and the previously mentioned \textit{BRCA} mutations (approximately 10–12% of ovarian cancers), only a small overall percentage of tumors from patients with this malignancy will be found to possess a specific causative mutation that can be effectively targeted therapeutically. Therefore, implementation of genomic-based medicine remains a challenge for the management of women with ovarian cancer.

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