Chapter 1

Ovarian Cancer Genetics: Subtypes and Risk Factors

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Additional information is available at the end of the chapter

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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.

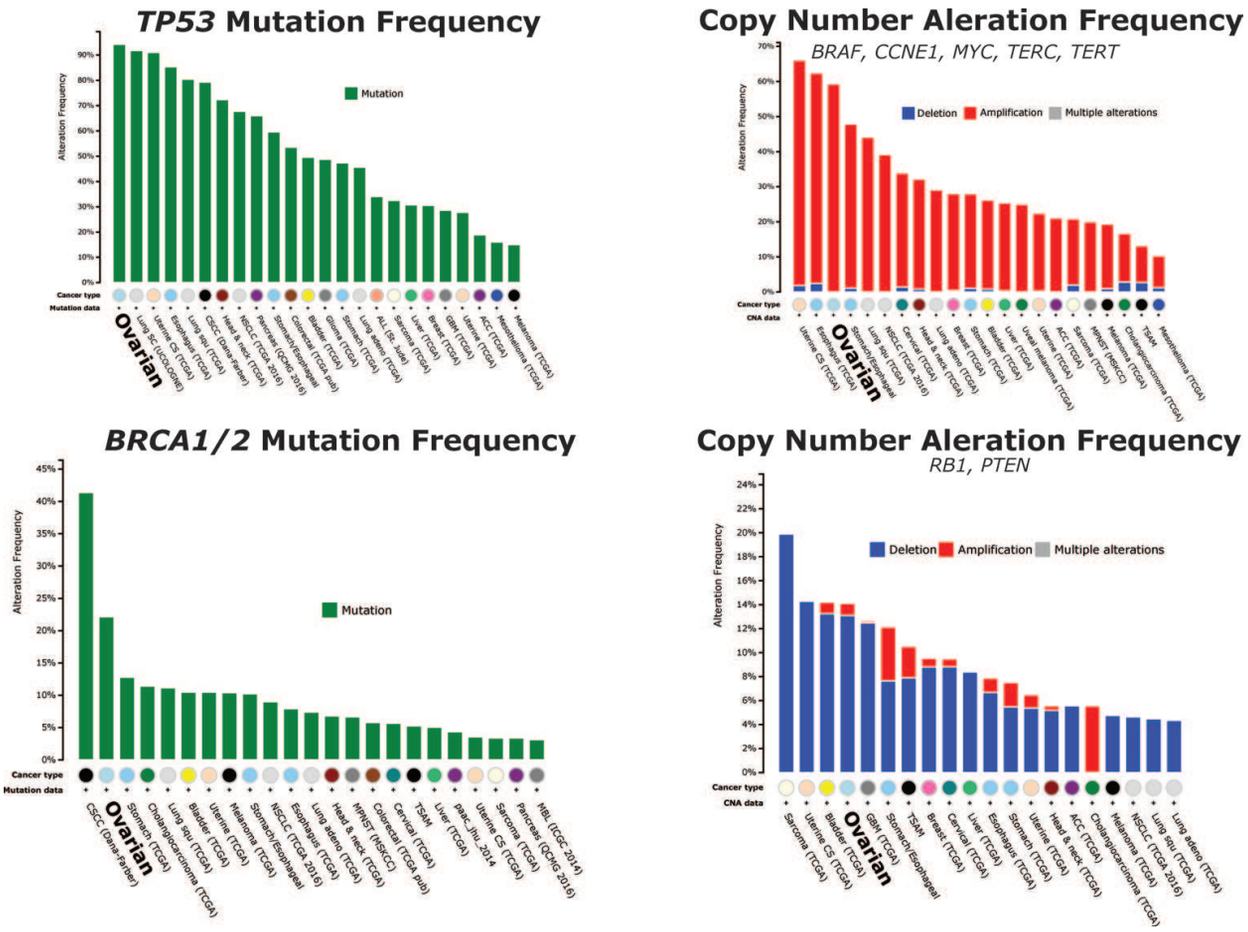

Figure 1. Common genetic alterations in ovarian cancer represented across pan-Cancer analysis from the TCGA. Bar graphs depict % of cases with mutations (green), amplification (red), and/or deletion of commonly dysregulated genes across a panel of cancers in the TCGA.

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

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, gnomically 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.

Sub Type	Mutations	Clinical Prognosis	Frequency
High-grade serous	*TP53*, *BRCA1*, *BRCA2*, *CDK12*	Often diagnosed at late stage and chromosomally unstable.	~65%
Low-grade serous	*BRAF*, *KRAS*, *NRAS*, *ERBB2*	Often diagnosed in younger patients, less aggressive, gnomically stable.	~5%
Endometrioid	*PTEN*, *CTNNB1*, *PPP2R1α*, MMR deficient	Favorable prognosis and response to chemotherapy.	~20%
Clear cell carcinoma	*PIK3CA*, *KRAS*, *PTEN*, *ARID1A*	Low response to chemotherapy and intermediate prognosis.	~5%
Mucinous	*KRAS*, *HER-2* amplification	Low response to chemotherapy.	~5%

Table 1. Subtypes of ovarian cancer.

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

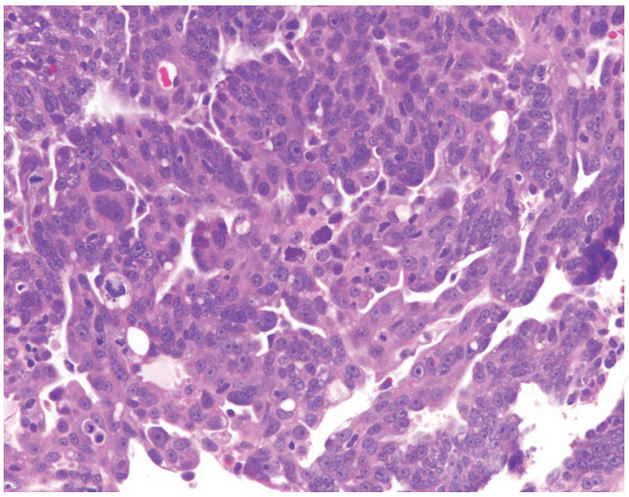

Figure 2. Representative H&E staining of high-grade serous ovarian carcinoma.

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

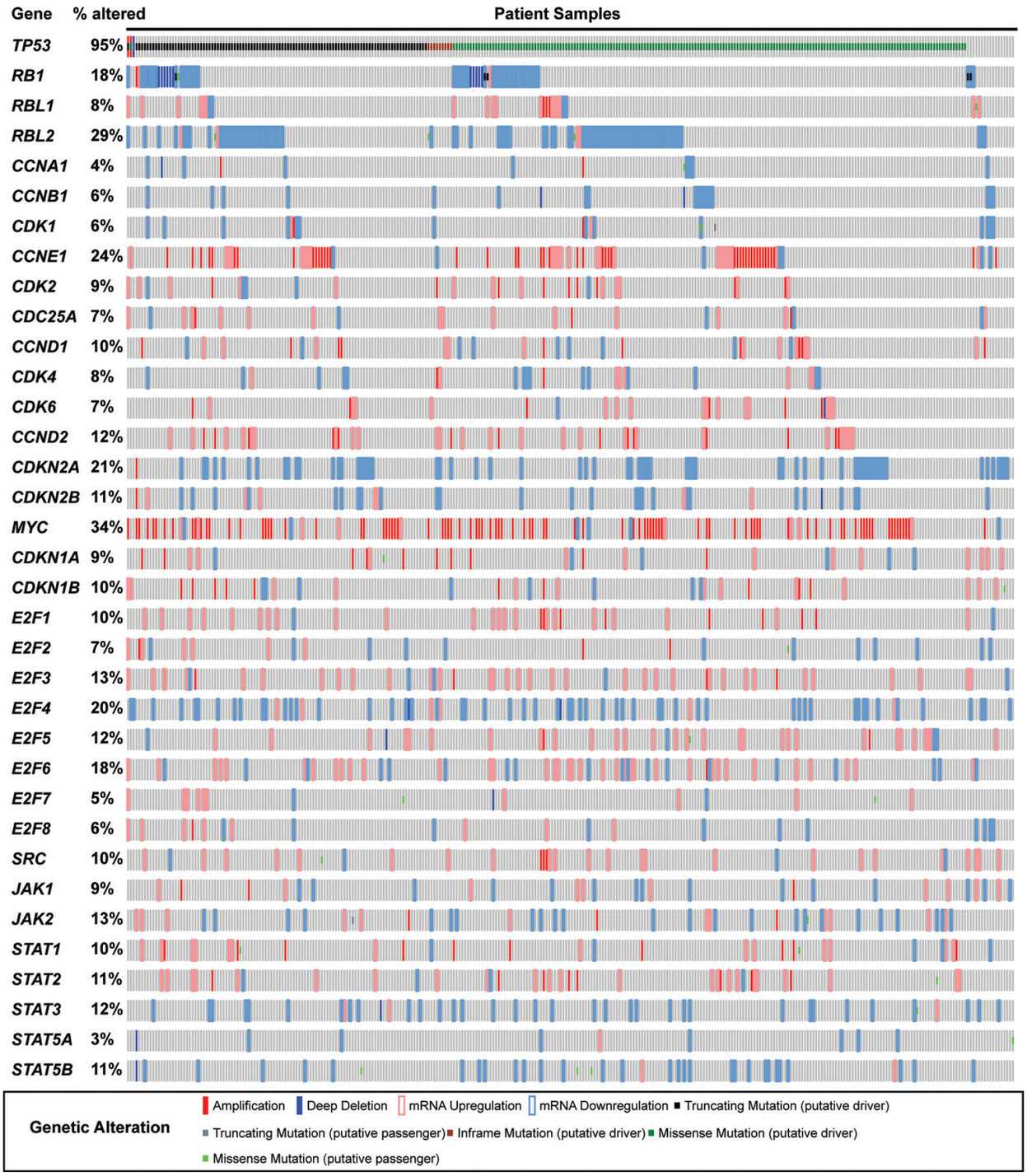

Figure 3. Genetic Dysregulation in high grade serous ovarian cancer. Data from the TCGA showing mutation, copy number alteration, and mRNA dysregulation of 34 cell cycle control genes and *TP53* alteration status (as a comparison) within 316 cases of high grade serous ovarian cancer demonstrates the overall heterogeneity of the disease.

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

cells to PARP inhibitors [52]. Using therapies to mimic different genetic phenotypes such as BRCAness has promising clinical application for ovarian cancer in trying to identify target therapies in a genetically diverse disease. Both of these therapies show that and understanding of the dynamic genes expressed in ovarian cancer can be used to mimic more sensitive disease (synthetic lethality) and improve therapy efficacy in the laboratory.

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

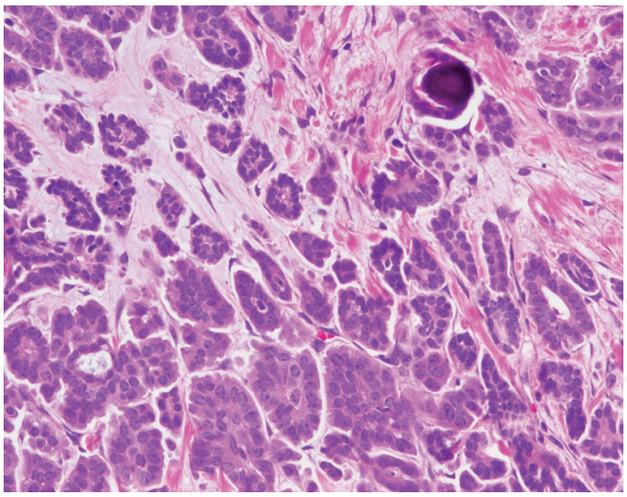

Figure 4. Representative H&E staining of low-grade serous ovarian carcinoma.

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

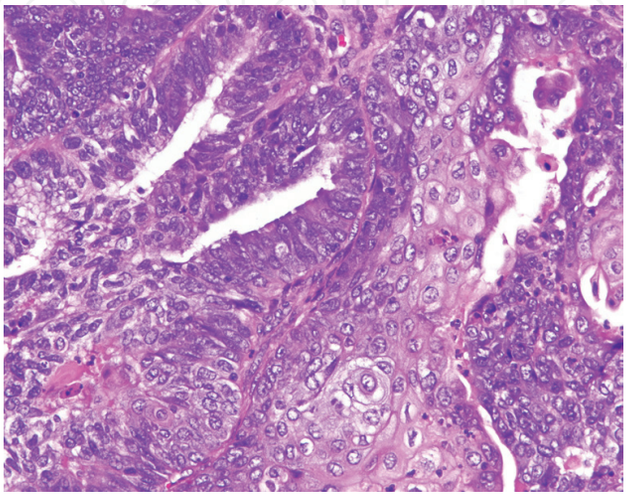

Figure 5. Representative H&E staining of endometrioid ovarian cancer.

~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

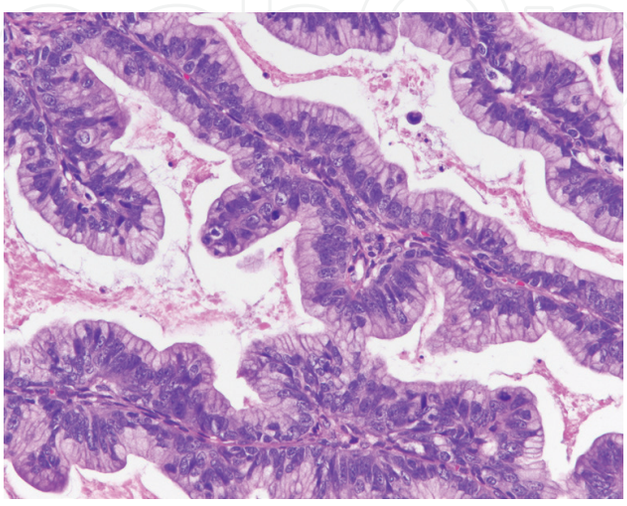

Figure 6. Representative H&E staining of mucinous ovarian cancer.

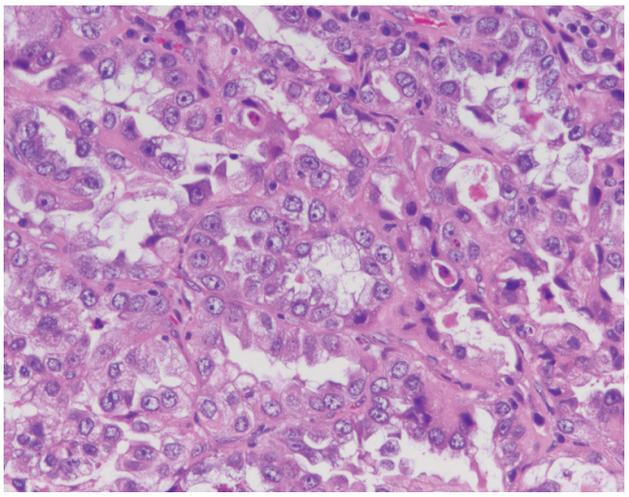

Figure 7. Representative H&E staining of ovarian clear cell carcinoma.

(~3%) 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

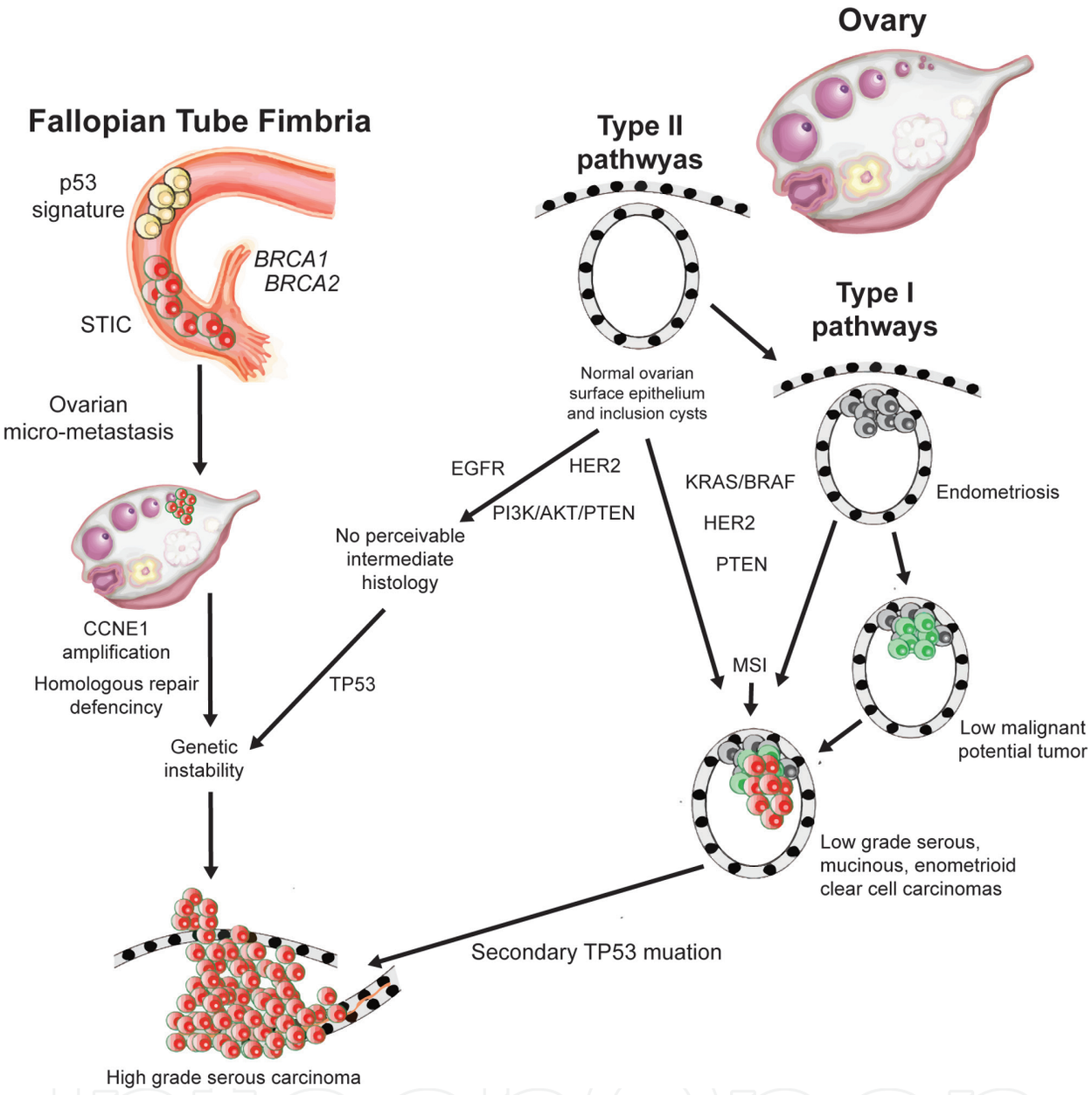

Figure 8. Pathogenesis pathways of ovarian cancer. Schematic representation of the prevailing theories behind ovarian cancer development.

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 carries [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 *BRCA1* and more than 1700 unique *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 *BRCA1* or *BRCA2* is important for risk assessment and determining medical management for patients. Most subtypes of ovarian cancer have been linked to *BRCA1* or *BRCA2* germline mutations but the development of HGS disease is the most common in these women carriers [223]. *BRCA1* and *BRCA2* mutations are more common in Ashkenazi Jewish women [206, 224, 225] due to the three common Jewish founder mutations *BRCA1* c.5266dup (5382insC) and *BRCA1* c.68_69del (185delAG) and *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 *BRCA2* c.771_775del and the rarer *BRCA1* c.5074G > A [226]. Despite having a higher risk for developing ovarian cancer, *BRCA1/2* carriers have a better clinical outcome in terms of survival, with *BRCA2* carriers having a more favorable outcome than *BRCA1* carriers [54]. This

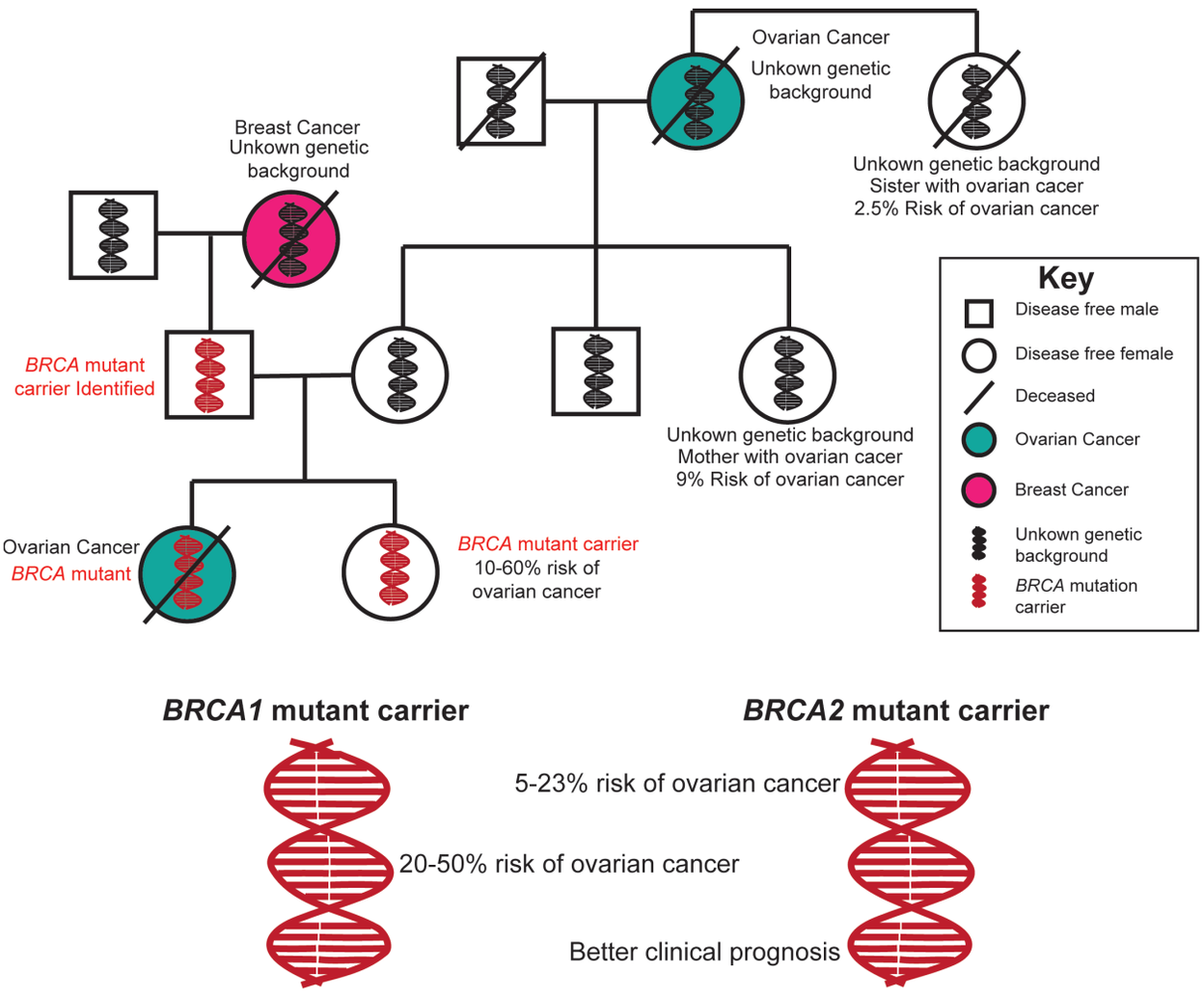

Figure 9. Hereditary ovarian cancer and BRCA mutations. Pedigree descripting "BRCAness" and risk of ovarian cancer (top). The relative risk and prognosis for women with germline *BRCA1/2* mutations.

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 HGS 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 (*RSPO1*) and 6p22.1 (*GPX6*) mutations increased the risk of serous ovarian cancer in *BRCA* carriers [231]. *BRCA1* mutation carries 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*, *CHECK2*, *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

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 reached 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] [250]. 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 women 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 the 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 *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 *TP53* mutation in high-grade serous ovarian cancer (96% of cases), which to date is undruggable, and the previously mentioned *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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References

[1] Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: The size of the problem. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2006;**20**(2): 207-225

[2] Braicu EI et al. Role of histological type on surgical outcome and survival following radical primary tumour debulking of epithelial ovarian, fallopian tube and peritoneal cancers. British Journal of Cancer. 2011;**105**(12):1818-1824

[3] Seidman JD et al. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. International Journal of Gynecological Pathology. 2004;**23**(1):41-44

[4] Gershenson DM. The heterogeneity of epithelial ovarian cancer: Getting it right. Cancer. 2010;**116**(6):1400-1402

[5] Malpica A et al. Grading ovarian serous carcinoma using a two-tier system. The American Journal of Surgical Pathology. 2004;**28**(4):496-504

[6] Iwabuchi H et al. Genetic analysis of benign, low-grade, and high-grade ovarian tumors. Cancer Research. 1995;**55**(24):6172-6180

[7] Oswald AJ, Gourley C. Low-grade epithelial ovarian cancer: A number of distinct clinical entities? Current Opinion in Oncology. 2015;**27**(5):412-419

[8] Groen RS, Gershenson DM, Fader AN. Updates and emerging therapies for rare epithelial ovarian cancers: One size no longer fits all. Gynecologic Oncology. 2015;**136**(2):373-383

[9] Kurman RJ. Origin and molecular pathogenesis of ovarian high-grade serous carcinoma. Annals of Oncology. 2013;**24**(Suppl 10):x16-x21

[10] Taylor J, McCluggage WG. Ovarian seromucinous carcinoma: Report of a series of a newly categorized and uncommon neoplasm. The American Journal of Surgical Pathology. 2015;**39**(7):983-992

[11] Mackenzie R et al. Morphological and molecular characteristics of mixed epithelial ovarian cancers. The American Journal of Surgical Pathology. 2015;**39**(11):1548

[12] Coburn SB et al. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. International Journal of Cancer. 2017;**140**(11):2451-2460

[13] Vaughan S et al. Rethinking ovarian cancer: Recommendations for improving outcomes. Nature Reviews. Cancer. 2011;**11**(10):719-725

[14] Cress RD et al. Characteristics of long-term survivors of epithelial ovarian cancer. Obstetrics and Gynecology. 2015;**126**(3):491-497

[15] Jung ES et al. Mucinous adenocarcinoma involving the ovary: Comparative evaluation of the classification algorithms using tumor size and laterality. Journal of Korean Medical Science. 2010;**25**(2):220-225

[16] Bentink S et al. Angiogenic mRNA and microRNA gene expression signature predicts a novel subtype of serous ovarian cancer. PLoS One. 2012;**7**(2):e30269

[17] Tothill RW et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clinical Cancer Research. 2008;**14**(16):5198-5208

[18] Phelan CM et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nature Genetics. 2017;**49**(5):680-691

[19] Winterhoff B et al. Molecular classification of high grade endometrioid and clear cell ovarian cancer using TCGA gene expression signatures. Gynecologic Oncology. 2016;**141**(1):95-100

[20] Madore J et al. Characterization of the molecular differences between ovarian endometrioid carcinoma and ovarian serous carcinoma. The Journal of Pathology. 2010;**220**(3):392-400

[21] Pamula-Pilat J et al. Gene expression profiles in three histologic types, clear-cell, endometrioid and serous ovarian carcinomas. Journal of Biological Regulators and Homeostatic Agents. 2014;**28**(4):659-674

[22] Howlader N et al. SEER Cancer Statistics Review, 1975-2012. Bethesda, MD: National Cancer Institute; 2015

[23] Chang CM et al. Gene set-based functionome analysis of pathogenesis in epithelial ovarian serous carcinoma and the molecular features in different FIGO stages. International Journal of Molecular Sciences. 2016;**17**(6)

[24] Burks RT, Sherman ME, Kurman RJ. Micropapillary serous carcinoma of the ovary. A distinctive low-grade carcinoma related to serous borderline tumors. The American Journal of Surgical Pathology. 1996;**20**(11):1319-1330

[25] Seidman JD, Kurman RJ. Subclassification of serous borderline tumors of the ovary into benign and malignant types. A clinicopathologic study of 65 advanced stage cases. The American Journal of Surgical Pathology. 1996;**20**(11):1331-1345

[26] Malpica A et al. Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma. The American Journal of Surgical Pathology. 2007;**31**(8):1168-1174

[27] O'Neill CJ et al. High-grade ovarian serous carcinoma exhibits significantly higher p16 expression than low-grade serous carcinoma and serous borderline tumour. Histopathology. 2007;**50**(6):773-779

[28] Lee SH et al. Genetic alteration and immunohistochemical staining patterns of ovarian high-grade serous adenocarcinoma with special emphasis on p53 immnnostaining pattern. Pathology International. 2013;**63**(5):252-259

[29] Vereczkey I et al. Molecular characterization of 103 ovarian serous and mucinous tumors. Pathology Oncology Research. 2011;**17**(3):551-559

[30] Al-Hussaini M et al. WT-1 assists in distinguishing ovarian from uterine serous carcinoma and in distinguishing between serous and endometrioid ovarian carcinoma. Histopathology. 2004;**44**(2):109-115

[31] O'Neill CJ et al. An immunohistochemical comparison between low-grade and high-grade ovarian serous carcinomas: Significantly higher expression of p53, MIB1, BCL2, HER-2/neu, and C-KIT in high-grade neoplasms. The American Journal of Surgical Pathology. 2005;**29**(8):1034-1041

[32] Dehari R et al. The development of high-grade serous carcinoma from atypical proliferative (borderline) serous tumors and low-grade micropapillary serous carcinoma: A morphologic and molecular genetic analysis. The American Journal of Surgical Pathology. 2007;**31**(7):1007-1012

[33] Boyd C, McCluggage WG. Low-grade ovarian serous neoplasms (low-grade serous carcinoma and serous borderline tumor) associated with high-grade serous carcinoma or undifferentiated carcinoma: Report of a series of cases of an unusual phenomenon. The American Journal of Surgical Pathology. 2012;**36**(3):368-375

[34] Gorringe KL et al. High-resolution single nucleotide polymorphism array analysis of epithelial ovarian cancer reveals numerous microdeletions and amplifications. Clinical Cancer Research. 2007;**13**(16):4731-4739

[35] Ahmed AA et al. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. The Journal of Pathology. 2010;**221**(1):49-56

[36] Network TCGAR. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;**474**(7353):609-615

[37] Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nature Reviews Cancer. 2004;**4**(10):814-819

[38] Jazaeri AA et al. Gene expression profiles of BRCA1-linked, BRCA2-linked, and sporadic ovarian cancers. Journal of the National Cancer Institute. 2002;**94**(13):990-1000

[39] Network TCGA. Comprehensive molecular portraits of human breast tumours. Nature. 2012;**490**(7418):61-70

[40] Ciriello G et al. Emerging landscape of oncogenic signatures across human cancers. Nature Genetics. 2013;**45**(10):1127-1133

[41] Nakayama N et al. Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer. Cancer. 2010;**116**(11):2621-2634

[42] Patch AM et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015;**521**(7553):489-494

[43] Martins FC et al. Combined image and genomic analysis of high-grade serous ovarian cancer reveals PTEN loss as a common driver event and prognostic classifier. Genome Biology. 2014;**15**(12):526

[44] Integrated genomic analyses of ovarian carcinoma. Nature. 2011;**474**(7353):609-615

[45] Singer G et al. Diverse tumorigenic pathways in ovarian serous carcinoma. The American Journal of Pathology. 2002;**160**(4):1223-1228

[46] Salani R et al. Assessment of TP53 mutation using purified tissue samples of ovarian serous carcinomas reveals a higher mutation rate than previously reported and does not correlate with drug resistance. International Journal of Gynecological Cancer. 2008;**18**(3):487-491

[47] Fong PC et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. The New England Journal of Medicine. 2009;**361**(2):123-134

[48] Audeh MW et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: A proof-of-concept trial. Lancet. 2010;**376**(9737):245-251

[49] Jenner ZB, Sood AK, Coleman RL. Evaluation of rucaparib and companion diagnostics in the PARP inhibitor landscape for recurrent ovarian cancer therapy. Future Oncology. 2016;**12**(12):1439-1456

[50] Drew Y et al. Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer. British Journal of Cancer. 2016;**114**(7):723-730

[51] Mirza MR et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. The New England Journal of Medicine. 2016

[52] Do TV et al. Aurora a kinase regulates non-homologous end-joining and poly(ADP-ribose) polymerase function in ovarian carcinoma cells. Oncotarget. 2017

[53] Sakai W et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature. 2008;**451**(7182):1116-1120

[54] Bolton KL et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;**307**(4):382-390

[55] Eyre R et al. Reversing paclitaxel resistance in ovarian cancer cells via inhibition of the ABCB1 expressing side population. Tumour Biology. 2014;**35**(10):9879-9892

[56] Sun KX et al. MicroRNA-186 induces sensitivity of ovarian cancer cells to paclitaxel and cisplatin by targeting ABCB1. Journal of Ovarian Research. 2015;**8**:80

[57] Wang SQ et al. Afatinib reverses multidrug resistance in ovarian cancer via dually inhibiting ATP binding cassette subfamily B member 1. Oncotarget. 2015;**6**(28):26142-26160

[58] Johnatty SE et al. ABCB1 (MDR 1) polymorphisms and progression-free survival among women with ovarian cancer following paclitaxel/carboplatin chemotherapy. Clinical Cancer Research. 2008;**14**(17):5594-5601

[59] Vaidyanathan A et al. ABCB1 (MDR1) induction defines a common resistance mechanism in paclitaxel- and olaparib-resistant ovarian cancer cells. British Journal of Cancer. 2016;**115**(4):431-441

[60] Surowiak P et al. ABCC2 (MRP2, cMOAT) can be localized in the nuclear membrane of ovarian carcinomas and correlates with resistance to Cisplatin and clinical outcome. Clinical Cancer Research. 2006;**12**(23):7149-7158

[61] Tian C et al. Common variants in ABCB1, ABCC2 and ABCG2 genes and clinical outcomes among women with advanced stage ovarian cancer treated with platinum and taxane-based chemotherapy: A Gynecologic oncology group study. Gynecologic Oncology. 2012;**124**(3):575-581

[62] Hamaguchi K et al. Cross-resistance to diverse drugs is associated with primary cisplatin resistance in ovarian cancer cell lines. Cancer Research. 1993;**53**(21):5225-5232

[63] Godwin AK et al. High resistance to cisplatin in human ovarian cancer cell lines is associated with marked increase of glutathione synthesis. Proceedings of the National Academy of Sciences of the United States of America. 1992;**89**(7):3070-3074

[64] Kajiyama H et al. Chemoresistance to paclitaxel induces epithelial-mesenchymal transition and enhances metastatic potential for epithelial ovarian carcinoma cells. International Journal of Oncology. 2007;**31**(2):277-283

[65] Haslehurst AM et al. EMT transcription factors snail and slug directly contribute to cisplatin resistance in ovarian cancer. BMC Cancer. 2012;**12**:91

[66] Crow J et al. Exosomes as mediators of platinum resistance in ovarian cancer. Oncotarget. 2017

[67] Au Yeung CL et al. Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1. Nature Communications. 2016;**7**:11150

[68] Yew KH et al. Epimorphin-induced MET sensitizes ovarian cancer cells to platinum. PLoS One. 2013;**8**(9):e72637

[69] Vang R, Shih I-M, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: Pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Advances in Anatomic Pathology. 2009;**16**(5):267-282

[70] Bell KA, Smith Sehdev AE, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumors (borderline) and micropapillary serous carcinomas. The American Journal of Surgical Pathology. 2001;**25**(4):419-432

[71] Gershenson DM, Silva EG. Serous ovarian tumors of low malignant potential with peritoneal implants. Cancer. 1990;**65**(3):578-585

[72] Singer G et al. Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. Journal of the National Cancer Institute. 2003;**95**(6):484-486

[73] Singer G et al. Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian

carcinogenesis: A mutational analysis with immunohistochemical correlation. The American Journal of Surgical Pathology. 2005;**29**(2):218-224

[74] Hunter SM et al. Molecular profiling of low grade serous ovarian tumours identifies novel candidate driver genes. Oncotarget. 2015;**6**(35):37663-37677

[75] Hsu CY et al. Characterization of active mitogen-activated protein kinase in ovarian serous carcinomas. Clinical Cancer Research. 2004;**10**(19):6432-6436

[76] Tone AA et al. Intratumoral heterogeneity in a minority of ovarian low-grade serous carcinomas. BMC Cancer. 2014;**14**:982

[77] Gershenson DM et al. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecologic Oncology. 2009;**114**(1):48-52

[78] Crane EK et al. The role of secondary cytoreduction in low-grade serous ovarian cancer or peritoneal cancer. Gynecologic Oncology. 2015;**136**(1):25-29

[79] Della Pepa C et al. Low grade serous ovarian carcinoma: From the molecular characterization to the best therapeutic strategy. Cancer Treatment Reviews. 2015;**41**(2):136-143

[80] Farley J et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: An open-label, single-arm, phase 2 study. The Lancet Oncology. 2013;**14**(2):134-140

[81] Nikrui N. Survey of clinical behavior of patients with borderline epithelial tumors of the ovary. Gynecologic Oncology. 1981;**12**(1):107-119

[82] Hogg R et al. Microinvasion links ovarian serous borderline tumor and grade 1 invasive carcinoma. Gynecologic Oncology. 2007;**106**(1):44-51

[83] Okoye E, Euscher ED, Malpica A. Ovarian low-grade serous carcinoma: A clinicopathologic study of 33 cases with primary surgery performed at a single institution. The American Journal of Surgical Pathology. 2016;**40**(5):627-635

[84] Sherman ME et al. Survival among women with borderline ovarian tumors and ovarian carcinoma: A population-based analysis. Cancer. 2004;**100**(5):1045-1052

[85] Kaern J, Trope CG, Abeler VM. A retrospective study of 370 borderline tumors of the ovary treated at the Norwegian radium hospital from 1970 to 1982. A review of clinicopathologic features and treatment modalities. Cancer. 1993;**71**(5):1810-1820

[86] Malpica A, Wong KK. The molecular pathology of ovarian serous borderline tumors. Annals of Oncology. 2016;**27**(Suppl 1):i16-i19

[87] Zeppernick F et al. BRAF mutation is associated with a specific cell type with features suggestive of senescence in ovarian serous borderline (atypical proliferative) tumors. The American Journal of Surgical Pathology. 2014;**38**(12):1603-1611

[88] Ahn G et al. Low-grade serous carcinoma of the ovary: Clinicopathologic analysis of 52 invasive cases and identification of a possible noninvasive intermediate lesion. The American Journal of Surgical Pathology. 2016;**40**(9):1165-1176

[89] Brown J, Frumovitz M. Mucinous tumors of the ovary: Current thoughts on diagnosis and management. Current Oncology Reports. 2014;**16**(6):389

[90] Chiesa AG et al. Ovarian intestinal type mucinous borderline tumors: Are we ready for a nomenclature change? International Journal of Gynecological Pathology. 2010;**29**(2): 108-112

[91] Sampson JA. Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. Archives of Surgery. 1925;**10**(1):1-72

[92] Vercellini P et al. Site of origin of epithelial ovarian cancer: The endometriosis connection. BJOG. 2000;**107**(9):1155-1157

[93] Keita M et al. Endometrioid ovarian cancer and endometriotic cells exhibit the same alteration in the expression of interleukin-1 receptor II: To a link between endometriosis and endometrioid ovarian cancer. The Journal of Obstetrics and Gynaecology Research. 2011;**37**(2):99-107

[94] Wang Y et al. Tubal origin of ovarian endometriosis and clear cell and endometrioid carcinoma. American Journal of Cancer Research. 2015;**5**(3):869-879

[95] Prowse AH et al. Molecular genetic evidence that endometriosis is a precursor of ovarian cancer. International Journal of Cancer. 2006;**119**(3):556-562

[96] Zwart J, Geisler JP, Geisler HE. Five-year survival in patients with endometrioid carcinoma of the ovary versus those with serous carcinoma. European Journal of Gynaecological Oncology. 1998;**19**(3):225-228

[97] Bouchard-Fortier G et al. Endometrioid carcinoma of the ovary: Outcomes compared to serous carcinoma after 10 years of follow-up. Journal of Obstetrics and Gynaecology Canada. 2017;**39**(1):34-41

[98] Mangili G et al. Unraveling the two entities of endometrioid ovarian cancer: A single center clinical experience. Gynecologic Oncology. 2012;**126**(3):403-407

[99] Schwartz DR et al. Gene expression in ovarian cancer reflects both morphology and biological behavior, distinguishing clear cell from other poor-prognosis ovarian carcinomas. Cancer Research. 2002;**62**(16):4722-4729

[100] Schwartz DR et al. Novel candidate targets of beta-catenin/T-cell factor signaling identified by gene expression profiling of ovarian endometrioid adenocarcinomas. Cancer Research. 2003;**63**(11):2913-2922

[101] McConechy MK et al. Ovarian and endometrial endometrioid carcinomas have distinct CTNNB1 and PTEN mutation profiles. Modern Pathology. 2014;**27**(1):128-134

[102] Wiegand KC et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. The New England Journal of Medicine. 2010;**363**(16):1532-1543

[103] Obata K et al. Frequent PTEN/MMAC mutations in endometrioid but not serous or mucinous epithelial ovarian tumors. Cancer Research. 1998;**58**(10):2095-2097

[104] Coward JI, Middleton K, Murphy F. New perspectives on targeted therapy in ovarian cancer. International Journal of Women's Health. 2015;**7**:189-203

[105] Mabuchi S et al. The PI3K/AKT/mTOR pathway as a therapeutic target in ovarian cancer. Gynecologic Oncology. 2015;**137**(1):173-179

[106] Riopel MA, Ronnett BM, Kurman RJ. Evaluation of diagnostic criteria and behavior of ovarian intestinal-type mucinous tumors: Atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive, and metastatic carcinomas. The American Journal of Surgical Pathology. 1999;**23**(6):617-635

[107] Lee KR, Young RH. The distinction between primary and metastatic mucinous carcinomas of the ovary: Gross and histologic findings in 50 cases. The American Journal of Surgical Pathology. 2003;**27**(3):281-292

[108] Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: Incidence in routine practice with a new approach to improve intraoperative diagnosis. The American Journal of Surgical Pathology. 2003;**27**(7):985-993

[109] Leitao MM Jr et al. Clinicopathologic analysis of early-stage sporadic ovarian carcinoma. The American Journal of Surgical Pathology. 2004;**28**(2):147-159

[110] Schiavone MB et al. Natural history and outcome of mucinous carcinoma of the ovary. American Journal of Obstetrics and Gynecology. 2011;**205**(5):480. e1-480. e8

[111] Kobel M et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. International Journal of Gynecological Pathology. 2010;**29**(3):203-211

[112] Simons M et al. Relatively poor survival of mucinous ovarian carcinoma in advanced stage: A systematic review and meta-analysis. International Journal of Gynecological Cancer. 2017;**27**(4):651-658

[113] Vang R et al. Cytokeratins 7 and 20 in primary and secondary mucinous tumors of the ovary: Analysis of coordinate immunohistochemical expression profiles and staining distribution in 179 cases. The American Journal of Surgical Pathology. 2006;**30**(9):1130-1139

[114] Vang R et al. Ovarian mucinous tumors associated with mature cystic teratomas: Morphologic and immunohistochemical analysis identifies a subset of potential teratomatous origin that shares features of lower gastrointestinal tract mucinous tumors more commonly encountered as secondary tumors in the ovary. The American Journal of Surgical Pathology. 2007;**31**(6):854-869

[115] Vang R et al. Immunohistochemical expression of CDX2 in primary ovarian mucinous tumors and metastatic mucinous carcinomas involving the ovary: Comparison with CK20 and correlation with coordinate expression of CK7. Modern Pathology. 2006;**19**(11):1421-1428

[116] Moh M et al. SATB2 expression distinguishes ovarian metastases of colorectal and appendiceal origin from primary ovarian tumors of mucinous or endometrioid type. The American Journal of Surgical Pathology. 2016;**40**(3):419-432

[117] Ordonez NG. Value of PAX 8 immunostaining in tumor diagnosis: A review and update. Advances in Anatomic Pathology. 2012;**19**(3):140-151

[118] Hess V et al. Mucinous epithelial ovarian cancer: A separate entity requiring specific treatment. Journal of Clinical Oncology. 2004;**22**(6):1040-1044

[119] Wamunyokoli FW et al. Expression profiling of mucinous tumors of the ovary identifies genes of clinicopathologic importance. Clinical Cancer Research. 2006;**12**(3 Pt 1):690-700

[120] Zaino RJ et al. Advanced stage mucinous adenocarcinoma of the ovary is both rare and highly lethal: A Gynecologic oncology group study. Cancer. 2011;**117**(3):554-562

[121] Teer JK et al. Mutational heterogeneity in non-serous ovarian cancers. Scientific Reports. 2017;**7**(1):9728

[122] Cuatrecasas M et al. K-ras mutations in mucinous ovarian tumors: A clinicopathologic and molecular study of 95 cases. Cancer. 1997;**79**(8):1581-1586

[123] Lin WL et al. Identification of the coexisting HER2 gene amplification and novel mutations in the HER2 protein-overexpressed mucinous epithelial ovarian cancer. Annals of Surgical Oncology. 2011;**18**(8):2388-2394

[124] Ryland GL et al. Mutational landscape of mucinous ovarian carcinoma and its neoplastic precursors. Genome Medicine. 2015;**7**(1):87

[125] Gore ME et al. Multicentre trial of carboplatin/paclitaxel versus oxaliplatin/capecitabine, each with/without bevacizumab, as first line chemotherapy for patients with mucinous epithelial ovarian cancer (mEOC). American Society of Clinical Oncology. 2015;**33**:5528-5528

[126] McAlpine JN et al. HER2 overexpression and amplification is present in a subset of ovarian mucinous carcinomas and can be targeted with trastuzumab therapy. BMC Cancer. 2009;**9**:433

[127] McCaughan H et al. HER2 expression in ovarian carcinoma: Caution and complexity in biomarker analysis. Journal of Clinical Pathology. 2012;**65**(7):670-671; author reply 671-2

[128] Sugiyama T et al. Clinical characteristics of clear cell carcinoma of the ovary: A distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer. 2000;**88**(11):2584-2589

[129] Tung KH et al. Reproductive factors and epithelial ovarian cancer risk by histologic type: A multiethnic case-control study. American Journal of Epidemiology. 2003;**158**(7):629-638

[130] Kandalaft PL, Gown AM, Isacson C. The lung-restricted marker napsin a is highly expressed in clear cell carcinomas of the ovary. American Journal of Clinical Pathology. 2014;**142**(6):830-836

[131] Zorn KK et al. Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. Clinical Cancer Research. 2005;**11**(18):6422-6430

[132] Domcke S et al. Evaluating cell lines as tumour models by comparison of genomic profiles. Nature Communications. 2013;**4**:2126

[133] Tan DS et al. Genomic analysis reveals the molecular heterogeneity of ovarian clear cell carcinomas. Clinical Cancer Research. 2011;**17**(6):1521-1534

[134] Zannoni GF et al. Mutational status of KRAS, NRAS, and BRAF in primary clear cell ovarian carcinoma. Virchows Archiv. 2014;**465**(2):193-198

[135] Campbell IG et al. Mutation of the PIK3CA gene in ovarian and breast cancer. Cancer Research. 2004;**64**(21):7678-7681

[136] Alsop K et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian ovarian cancer study group. Journal of Clinical Oncology. 2012;**30**(21):2654-2663

[137] Mabuchi S, Sugiyama T, Kimura T. Clear cell carcinoma of the ovary: Molecular insights and future therapeutic perspectives. Journal of Gynecologic Oncology. 2016;**27**(3):e31

[138] Oliver KE et al. An evaluation of progression free survival and overall survival of ovarian cancer patients with clear cell carcinoma versus serous carcinoma treated with platinum therapy: An NRG oncology/Gynecologic oncology group experience. Gynecologic Oncology. 2017

[139] Sancho-Torres I et al. Clear cell carcinoma of the ovary: Characterization of its CD44 isoform repertoire. Gynecologic Oncology. 2000;**79**(2):187-195

[140] Anglesio MS et al. IL6-STAT3-HIF signaling and therapeutic response to the angiogenesis inhibitor sunitinib in ovarian clear cell cancer. Clinical Cancer Research. 2011;**17**(8):2538-2548

[141] Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? Lancet. 1971;**2**(7716):163

[142] Fleming JS et al. Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: Revisiting old hypotheses. Molecular and Cellular Endocrinology. 2006;**247**(1-2):4-21

[143] Fathalla MF. Incessant ovulation and ovarian cancer - a hypothesis re-visited. Facts, Views & Vision in ObGyn. 2013;**5**(4):292-297

[144] Banks RE et al. Circulating intercellular adhesion molecule-1 (ICAM-1), E-selectin and vascular cell adhesion molecule-1 (VCAM-1) in human malignancies. British Journal of Cancer. 1993;**68**(1):122-124

[145] Land JA. Ovulation, ovulation induction and ovarian carcinoma. Baillière's Clinical Obstetrics and Gynaecology. 1993;**7**(2):455-472

[146] Fredrickson TN. Ovarian tumors of the hen. Environmental Health Perspectives. 1987;**73**:35-51

[147] Lee J, Song G. The laying hen: An animal model for human ovarian cancer. Reproductive & Developmental Biology. 2013;**37**:41-49

[148] Godwin AK et al. Spontaneous transformation of rat ovarian surface epithelial cells: Association with cytogenetic changes and implications of repeated ovulation in the etiology of ovarian cancer. Journal of the National Cancer Institute. 1992;**84**(8):592-601

[149] Godwin AK, Testa JR, Hamilton TC. The biology of ovarian cancer development. Cancer. 1993;**71**(2 Suppl):530-536

[150] Perez RP et al. Transformation of rat ovarian epithelial and Rat-1 fibroblast cell lines by RAST24 does not influence cisplatin sensitivity. Cancer Research. 1993;**53**(16):3771-3775

[151] Testa JR et al. Spontaneous transformation of rat ovarian surface epithelial cells results in well to poorly differentiated tumors with a parallel range of cytogenetic complexity. Cancer Research. 1994;**54**(10):2778-2784

[152] Auersperg N et al. Expression of two mucin antigens in cultured human ovarian surface epithelium: Influence of a family history of ovarian cancer. American Journal of Obstetrics and Gynecology. 1995;**173**(2):558-565

[153] Godwin AK et al. Retroviral-like sequences specifically expressed in the rat ovary detect genetic differences between normal and transformed rat ovarian surface epithelial cells. Endocrinology. 1995;**136**(10):4640-4649

[154] Salazar H et al. Microscopic benign and invasive malignant neoplasms and a cancer-prone phenotype in prophylactic oophorectomies. Journal of the National Cancer Institute. 1996;**88**(24):1810-1820

[155] Dyck HG et al. Autonomy of the epithelial phenotype in human ovarian surface epithelium: Changes with neoplastic progression and with a family history of ovarian cancer. International Journal of Cancer. 1996;**69**(6):429-436

[156] Abdollahi A et al. Identification of a gene containing zinc-finger motifs based on lost expression in malignantly transformed rat ovarian surface epithelial cells. Cancer Research. 1997;**57**(10):2029-2034

[157] Abdollahi A et al. Genome scanning detects amplification of the cathepsin B gene (CtsB) in transformed rat ovarian surface epithelial cells. Journal of the Society for Gynecologic Investigation. 1999;**6**(1):32-40

[158] Kruk PA et al. Telomeric instability and reduced proliferative potential in ovarian surface epithelial cells from women with a family history of ovarian cancer. Gynecologic Oncology. 1999;**73**(2):229-236

[159] Roberts D et al. Decreased expression of retinol-binding proteins is associated with malignant transformation of the ovarian surface epithelium. DNA and Cell Biology. 2002;**21**(1):11-19

[160] Yang DH et al. Molecular events associated with dysplastic morphologic transformation and initiation of ovarian tumorigenicity. Cancer. 2002;**94**(9):2380-2392

[161] Roland IH et al. Loss of surface and cyst epithelial basement membranes and preneoplastic morphologic changes in prophylactic oophorectomies. Cancer. 2003;**98**(12): 2607-2623

[162] Flesken-Nikitin A et al. Induction of carcinogenesis by concurrent inactivation of p53 and Rb1 in the mouse ovarian surface epithelium. Cancer Research. 2003;**63**(13):3459-3463

[163] Kindelberger DW et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. The American Journal of Surgical Pathology. 2007;**31**(2):161-169

[164] Lee Y et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. The Journal of Pathology. 2007;**211**(1):26-35

[165] Rebbeck TR et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. The New England Journal of Medicine. 2002;**346**(21):1616-1622

[166] Olivier RI et al. Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. British Journal of Cancer. 2004;**90**(8):1492-1497

[167] Cibula D et al. Tubal ligation and the risk of ovarian cancer: Review and meta-analysis. Human Reproduction Update. 2011;**17**(1):55-67

[168] Gross AL et al. Precursor lesions of high-grade serous ovarian carcinoma: Morphological and molecular characteristics. Journal of Oncology. 2010;**2010**:126295

[169] Crum CP et al. Lessons from BRCA: The tubal fimbria emerges as an origin for pelvic serous cancer. Clinical Medicine & Research. 2007;**5**(1):35-44

[170] Callahan MJ et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. Journal of Clinical Oncology. 2007;**25**(25):3985-3990

[171] Piek JM et al. Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer. The Journal of Pathology. 2001;**195**(4):451-456

[172] Shaw PA et al. Candidate serous cancer precursors in fallopian tube epithelium of BRCA1/2 mutation carriers. Modern Pathology. 2009;**22**(9):1133-1138

[173] Medeiros F et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. The American Journal of Surgical Pathology. 2006;**30**(2):230-236

[174] Folkins AK et al. A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. Gynecologic Oncology. 2008;**109**(2):168-173

[175] Akbari MR et al. The spectrum of BRCA1 and BRCA2 mutations in breast cancer patients in the Bahamas. Clinical Genetics. 2014;**85**(1):64-67

[176] Tone AA et al. Gene expression profiles of luteal phase fallopian tube epithelium from BRCA mutation carriers resemble high-grade serous carcinoma. Clinical Cancer Research. 2008;**14**(13):4067-4078

[177] Karst AM, Levanon K, Drapkin R. Modeling high-grade serous ovarian carcinogenesis from the fallopian tube. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**(18):7547-7552

[178] Perets R et al. Transformation of the fallopian tube secretory epithelium leads to high-grade serous ovarian cancer in Brca;Tp53;Pten models. Cancer Cell. 2013;**24**(6):751-765

[179] Salvador S et al. Chromosomal instability in fallopian tube precursor lesions of serous carcinoma and frequent monoclonality of synchronous ovarian and fallopian tube mucosal serous carcinoma. Gynecologic Oncology. 2008;**110**(3):408-417

[180] Karst AM et al. Cyclin E1 deregulation occurs early in secretory cell transformation to promote formation of fallopian tube-derived high-grade serous ovarian cancers. Cancer Research. 2014;**74**(4):1141-1152

[181] Kuhn E et al. CCNE1 amplification and centrosome number abnormality in serous tubal intraepithelial carcinoma: Further evidence supporting its role as a precursor of ovarian high-grade serous carcinoma. Modern Pathology. 2016;**29**(10):1254-1261

[182] McDaniel AS et al. Next-generation sequencing of tubal intraepithelial carcinomas. JAMA Oncology. 2015;**1**(8):1128-1132

[183] Wicha MS, Liu S, Dontu G. Cancer stem cells: An old idea–a paradigm shift. Cancer Research. 2006;**66**(4):1883-1890; discussion 1895-6

[184] Marsden CG et al. Breast tumor-initiating cells isolated from patient core biopsies for study of hormone action. Methods in Molecular Biology. 2009;**590**:363-375

[185] Singh SK et al. Identification of a cancer stem cell in human brain tumors. Cancer Research. 2003;**63**(18):5821-5828

[186] Collins AT et al. Prospective identification of tumorigenic prostate cancer stem cells. Cancer Research. 2005;**65**(23):10946-10951

[187] Ricci-Vitiani L et al. Identification and expansion of human colon-cancer-initiating cells. Nature. 2007;**445**(7123):111-115

[188] Kreso A, Dick JE. Evolution of the cancer stem cell model. Cell Stem Cell. 2014;**14**(3):275-291

[189] Capel B. Ovarian epithelium regeneration by Lgr5(+) cells. Nature Cell Biology. 2014;**16**(8):743-744

[190] Ng A et al. Lgr5 marks stem/progenitor cells in ovary and tubal epithelia. Nature Cell Biology. 2014;**16**(8):745-757

[191] Bowen NJ et al. Gene expression profiling supports the hypothesis that human ovarian surface epithelia are multipotent and capable of serving as ovarian cancer initiating cells. BMC Medical Genomics. 2009;**2**:71

[192] Flesken-Nikitin A et al. Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche. Nature. 2013;**495**(7440):241-245

[193] Kessler M et al. The notch and Wnt pathways regulate stemness and differentiation in human fallopian tube organoids. Nature Communications. 2015;**6**:8989

[194] Paik DY et al. Stem-like epithelial cells are concentrated in the distal end of the fallopian tube: A site for injury and serous cancer initiation. Stem Cells. 2012;**30**(11):2487-2497

[195] Wang Y et al. Identification of quiescent, stem-like cells in the distal female reproductive tract. PLoS One. 2012;**7**(7):e40691

[196] Hellner K et al. Premalignant SOX2 overexpression in the fallopian tubes of ovarian cancer patients: Discovery and validation studies. eBioMedicine. 2016;**10**:137-149

[197] Ziogas A et al. Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention. 2000;**9**(1):103-111

[198] Bewtra C et al. Hereditary ovarian cancer: A clinicopathological study. International Journal of Gynecological Pathology. 1992;**11**(3):180-187

[199] Lynch HT, Krush AJ. Carcinoma of the breast and ovary in three families. Surgery, Gynecology & Obstetrics. 1971;**133**(4):644-648

[200] Lynch HT et al. Familial association of carcinoma of the breast and ovary. Surgery, Gynecology & Obstetrics. 1974;**138**(5):717-724

[201] Miki Y et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;**266**(5182):66-71

[202] Wooster R et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science. 1994;**265**(5181):2088-2090

[203] Wooster R et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;**378**(6559):789-792

[204] Peto J et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. Journal of the National Cancer Institute. 1999;**91**(11):943-949

[205] Whittemore AS et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic whites. Cancer Epidemiology, Biomarkers & Prevention. 2004;**13**(12):2078-2083

[206] Struewing JP et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. The New England Journal of Medicine. 1997;**336**(20):1401-1408

[207] Rubin SC et al. BRCA1, BRCA2, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: Relationship to family history and implications for genetic testing. American Journal of Obstetrics and Gynecology. 1998;**178**(4):670-677

[208] Ford D et al. Risks of cancer in BRCA1-mutation carriers. Breast cancer linkage consortium. Lancet. 1994;**343**(8899):692-695

[209] Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast cancer linkage consortium. American Journal of Human Genetics. 1995;**56**(1):265-271

[210] Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. Journal of Clinical Oncology. 2007;**25**(11):1329-1333

[211] Kuchenbaecker KB et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;**317**(23):2402-2416

[212] Antoniou A et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. American Journal of Human Genetics. 2003;**72**(5):1117-1130

[213] King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;**302**(5645):643-646

[214] Sogaard M, Kjaer SK, Gayther S. Ovarian cancer and genetic susceptibility in relation to the BRCA1 and BRCA2 genes. Occurrence, clinical importance and intervention. Acta Obstetricia et Gynecologica Scandinavica. 2006;**85**(1):93-105

[215] Rebbeck TR et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. JAMA. 2015;**313**(13):1347-1361

[216] Mavaddat N et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: Results from the consortium of investigators of modifiers of BRCA1/2 (CIMBA). Cancer Epidemiology, Biomarkers & Prevention. 2012;**21**(1):134-147

[217] Ramus SJ et al. Ovarian cancer susceptibility alleles and risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Human Mutation. 2012;**33**(4):690-702

[218] Antoniou AC et al. RAD51 135G-->C modifies breast cancer risk among BRCA2 mutation carriers: Results from a combined analysis of 19 studies. American Journal of Human Genetics. 2007;**81**(6):1186-1200

[219] Osorio A et al. DNA glycosylases involved in base excision repair may be associated with cancer risk in BRCA1 and BRCA2 mutation carriers. PLoS Genetics. 2014;**10**(4):e1004256

[220] Couch FJ et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genetics. 2013;**9**(3): e1003212

[221] Ding YC et al. A nonsynonymous polymorphism in IRS1 modifies risk of developing breast and ovarian cancers in BRCA1 and ovarian cancer in BRCA2 mutation carriers. Cancer Epidemiology, Biomarkers & Prevention. 2012;**21**(8):1362-1370

[222] Jakubowska A et al. Association of PHB 1630 C>T and MTHFR 677 C>T polymorphisms with breast and ovarian cancer risk in BRCA1/2 mutation carriers: Results from a multicenter study. British Journal of Cancer. 2012;**106**(12):2016-2024

[223] Castilla LH et al. Mutations in the BRCA1 gene in families with early-onset breast and ovarian cancer. Nature Genetics. 1994;**8**(4):387-391

[224] Tonin P et al. Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families. Nature Medicine. 1996;**2**(11):1179-1183

[225] Berman DB et al. A common mutation in BRCA2 that predisposes to a variety of cancers is found in both Jewish Ashkenazi and non-Jewish individuals. Cancer Research. 1996;**56**(15):3409-3414

[226] Bergthorsson JT et al. Identification of a novel splice-site mutation of the BRCA1 gene in two breast cancer families: Screening reveals low frequency in Icelandic breast cancer patients. Human Mutation. 1998;(Suppl 1):S195-S197

[227] Liu G et al. Differing clinical impact of BRCA1 and BRCA2 mutations in serous ovarian cancer. Pharmacogenomics. 2012;**13**(13):1523-1535

[228] Candido-dos-Reis FJ et al. Germline mutation in BRCA1 or BRCA2 and ten-year survival for women diagnosed with epithelial ovarian cancer. Clinical Cancer Research. 2015;**21**(3):652-657

[229] Gorodnova TV et al. High response rates to neoadjuvant platinum-based therapy in ovarian cancer patients carrying germ-line BRCA mutation. Cancer Letters. 2015;**369**(2):363-367

[230] Goode EL et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nature Genetics. 2010;**42**(10):874-879

[231] Kuchenbaecker KB et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nature Genetics. 2015;**47**(2):164-171

[232] Engel C et al. Association of the variants CASP8 D302H and CASP10 V410I with breast and ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Epidemiology, Biomarkers & Prevention. 2010;**19**(11):2859-2868

[233] Ratner E et al. A KRAS-variant in ovarian cancer acts as a genetic marker of cancer risk. Cancer Research. 2010;**70**(16):6509-6515

[234] Potapova A et al. Promoter hypermethylation of the PALB2 susceptibility gene in inherited and sporadic breast and ovarian cancer. Cancer Research. 2008;**68**(4):998-1002

[235] Walker LC et al. Evaluation of copy-number variants as modifiers of breast and ovarian cancer risk for BRCA1 pathogenic variant carriers. European Journal of Human Genetics. 2017;**25**(4):432-438

[236] Bojesen SE et al. Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nature Genetics. 2013;**45**(4):371-384 384e1-2

[237] Walsh T et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**(44):18032-18037

[238] Pennington KP, Swisher EM. Hereditary ovarian cancer: Beyond the usual suspects. Gynecologic Oncology. 2012;**124**(2):347-353

[239] Song H et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. Journal of Clinical Oncology. 2015;**33**(26):2901-2907

[240] Ketabi Z et al. Ovarian cancer linked to lynch syndrome typically presents as early-onset, non-serous epithelial tumors. Gynecologic Oncology. 2011;**121**(3):462-465

[241] Crispens MA. Endometrial and ovarian cancer in lynch syndrome. Clinics in Colon and Rectal Surgery. 2012;**25**(2):97-102

[242] Malander S et al. The contribution of the hereditary nonpolyposis colorectal cancer syndrome to the development of ovarian cancer. Gynecologic Oncology. 2006;**101**(2): 238-243

[243] Gwinn ML et al. Pregnancy, breast feeding, and oral contraceptives and the risk of epithelial ovarian cancer. Journal of Clinical Epidemiology. 1990;**43**(6):559-568

[244] Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses' health studies. Fertility and Sterility. 2014;**102**(1):192-198 e3

[245] Gaitskell K et al. Tubal ligation and ovarian cancer risk in a large cohort: Substantial variation by histological type. International Journal of Cancer. 2016;**138**(5):1076-1084

[246] Kauff ND et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: A multicenter, prospective study. Journal of Clinical Oncology. 2008;**26**(8):1331-1337

[247] Beral V et al. Ovarian cancer and oral contraceptives: Collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;**371**(9609):303-314

[248] Havrilesky LJ et al. Oral contraceptive pills as primary prevention for ovarian cancer: A systematic review and meta-analysis. Obstetrics and Gynecology. 2013;**122**(1):139-147

[249] Moorman PG et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: A systematic review and meta-analysis. Journal of Clinical Oncology. 2013;**31**(33):4188-4198

[250] Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: Relative and attributable risks of cardiovascular disease, cancer, and other health outcomes. Annals of Epidemiology. 2015;**25**(3):193-200

[251] Wentzensen N et al. Ovarian cancer risk factors by histologic subtype: An analysis from the ovarian cancer cohort consortium. Journal of Clinical Oncology. 2016;**34**(24):2888-2898

[252] Havrilesky LJ et al. Oral contraceptive use for the primary prevention of ovarian cancer. Evidence report/technology assessment (Full Report). 2013;**212**:1-514

[253] Hankinson SE et al. A prospective study of reproductive factors and risk of epithelial ovarian cancer. Cancer. 1995;**76**(2):284-290

[254] Adami HO et al. Parity, age at first childbirth, and risk of ovarian cancer. Lancet. 1994;**344**(8932):1250-1254

[255] Tsilidis KK et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European prospective investigation into cancer and nutrition. British Journal of Cancer. 2011;**105**(9):1436-1442

[256] Schildkraut JM et al. Age at natural menopause and the risk of epithelial ovarian cancer. Obstetrics and Gynecology. 2001;**98**(1):85-90

[257] Pearce CL et al. Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. Cancer. 2009;**115**(3):531-539

[258] Morch LS et al. Hormone therapy and ovarian cancer. JAMA. 2009;**302**(3):298-305

[259] Hildebrand JS et al. Postmenopausal hormone use and incident ovarian cancer: Associations differ by regimen. International Journal of Cancer. 2010;**127**(12):2928-2935

[260] Beral V et al. Menopausal hormone use and ovarian cancer risk: Individual participant meta-analysis of 52 epidemiological studies. Lancet. 2015;**385**(9980):1835-1842

[261] Eeles RA et al. Adjuvant hormone therapy may improve survival in epithelial ovarian cancer: Results of the AHT randomized trial. Journal of Clinical Oncology. 2015;**33**(35):4138-4144

[262] Luan NN et al. Breastfeeding and ovarian cancer risk: A meta-analysis of epidemiologic studies. The American Journal of Clinical Nutrition. 2013;**98**(4):1020-1031

[263] Beral V et al. Ovarian cancer and smoking: Individual participant meta-analysis including 28,114 women with ovarian cancer from 51 epidemiological studies. The Lancet Oncology. 2012;**13**(9):946-956

[264] Jordan SJ et al. Does smoking increase risk of ovarian cancer? A systematic review. Gynecologic Oncology. 2006;**103**(3):1122-1129

[265] Gram IT et al. Cigarette smoking and risk of histological subtypes of epithelial ovarian cancer in the EPIC cohort study. International Journal of Cancer. 2012;**130**(9):2204-2210

[266] Gwinn ML et al. Alcohol consumption and ovarian cancer risk. American Journal of Epidemiology. 1986;**123**(5):759-766

[267] Genkinger JM et al. Alcohol intake and ovarian cancer risk: A pooled analysis of 10 cohort studies. British Journal of Cancer. 2006;**94**(5):757-762

[268] Rota M et al. Alcohol drinking and epithelial ovarian cancer risk. A systematic review and meta-analysis. Gynecologic Oncology. 2012;**125**(3):758-763

[269] Olsen CM et al. Obesity and risk of ovarian cancer subtypes: Evidence from the ovarian cancer association consortium. Endocrine-Related Cancer. 2013;**20**(2):251-262

[270] Cannioto RA, Moysich KB. Epithelial ovarian cancer and recreational physical activity: A review of the epidemiological literature and implications for exercise prescription. Gynecologic Oncology. 2015;**137**(3):559-573

[271] Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. Journal of the National Cancer Institute. 1999;**91**(17):1459-1467

[272] Trabert B et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: A pooled analysis in the ovarian cancer association consortium. Journal of the National Cancer Institute. 2014;**106**(2):djt431