Malignant epithelial tumors (carcinomas) are the most common ovarian cancers and also the most lethal gynecological malignancies. Based on histopathology and molecular genetic alterations, ovarian carcinomas are divided into five main types [high-grade serous (70%), endometrioid (10%), clear-cell (10%), mucinous (3%), and low-grade serous carcinomas (<5%)] that account for over 95% of cases. These types are essentially distinct diseases, as indicated by differences in epidemiological and genetic risk factors, precursor lesions, patterns of spread, and molecular events during oncogenesis, response to chemotherapy, and prognosis. For a successful specific treatment, reproducible histopathological diagnosis of the tumor cell type is critical. The five tumor types are morphologically diverse and resemble carcinomas of the uterus. Actually, recent investigations have demonstrated that a substantial number of cancers, traditionally thought to be primary ovarian tumors (particularly serous, endometrioid, and clear-cell carcinomas), originate in the fallopian tube and the endometrium and involve the ovary secondarily. This presentation summarizes recent advances in the molecular pathology which have greatly improved our understanding of the biology of ovarian carcinoma and are also relevant to patient management.

Key words: carcinomas, histopathological types, molecular genetics, ovary

Epithelial ovarian tumors are heterogeneous neoplasms which are primarily classified according to cell type into serous, mucinous, endometrioid, clear-cell, transitional, and squamous cell tumors [1, 2]. Parenthetically, none of these cells are found in the normal ovary and their development has long been attributed to mullerian ‘neometaplasia’ of the ovarian surface epithelium (mesothelium). More importantly, these tumors are further subdivided into benign, borderline (intermediate), and malignant (carcinoma) depending on the degree of cell proliferation and nuclear atypia, and the presence or absence of stromal invasion [1, 2]. Borderline tumors show epithelial proliferation greater than that seen in their benign counterparts and variable nuclear atypia; however, in contrast to carcinomas, there is absence of stromal invasion, and their prognosis is much better than that of carcinomas. Despite the lack of ovarian stromal invasion, serous borderline tumors, particularly those with exophytic growth, can implant on peritoneal surfaces and, rarely (~10% of peritoneal implants), progress to low-grade serous carcinoma (LGSC), and invade the underlying tissues. The biologic behavior of invasive peritoneal implants is similar to that of LGSC.

Malignant epithelial tumors (carcinomas) are the most common ovarian cancers accounting for 90% of cases [1, 2]. Although traditionally referred to as a single entity, ovarian cancer is not a homogeneous disease but rather a group of diseases, each with different morphology and biologic behavior. Compared with breast cancer, ovarian cancer is 10 times less common, yet is associated with a much greater number of deaths, as 75% of patients present with advanced (stage III) tumors, experience recurrence after surgery and chemotherapy and most, ultimately, die of disease. Globally, it accounts for over 100,000 women’s deaths per year, constitutes the fifth most common cause of cancer death in women in the Western world, and is the most lethal gynecological cancer [3]. Early diagnosis has been unsuccessful.

Currently, based on histopathology, immunohistochemistry, and molecular genetic analysis, at least five main types of ovarian carcinomas are identified: high-grade serous carcinomas (HGSCs; 70%), endometrioid carcinomas (EC; 10%), clear-cell carcinomas (CCC; 10%), mucinous carcinomas (MC; 3%), and LGSC (<5%) [4] (Table 1) (Figure 1). These tumors account for 98% of ovarian carcinomas, can be reproducibly diagnosed by light microscopy, and are inherently different diseases, as indicated by differences in epidemiological and genetic risk factors, precursor lesions, patterns of spread, molecular events during oncogenesis, response to chemotherapy, and prognosis.

In the era of personalized cancer medicine, reproducible histopathological diagnosis of tumor cell type is a sine qua non condition for successful treatment. For instance, it has been found that different tumor types respond differently to chemotherapy. The poor response rate of CCC (15%) contrasts notably with that of HGSCs (80%), resulting in a lower 5-year survival for clear cell compared with HGSC in patients with
Table 1. Ovarian carcinoma: clinical and molecular features of the five most common types

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HGSC</th>
<th>LGSC</th>
<th>MC</th>
<th>EC</th>
<th>CCC</th>
</tr>
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<tbody>
<tr>
<td>BRCA1/2</td>
<td>?</td>
<td>?</td>
<td>HNPCC*</td>
<td>Atypical endometriosis</td>
<td>Atypical endometriosis</td>
</tr>
<tr>
<td>Tubal intraepithelial carcinoma</td>
<td>Serous borderline tumor</td>
<td>Cystadenoma/borderline tumor?</td>
<td>Usually confined to ovary</td>
<td>Usually confined to pelvis</td>
<td></td>
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<tr>
<td>Very early transcoelomic spread</td>
<td>Transcoelomic spread</td>
<td>Usually confined to ovary</td>
<td>PTEN, ARID1A</td>
<td>HNF1, ARID1A</td>
<td></td>
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<tr>
<td>BRCA, p53</td>
<td>BRAF, KRAS</td>
<td>KRAS, HER2</td>
<td>High</td>
<td>Low</td>
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<td>High</td>
<td>Intermediate</td>
<td>Low</td>
<td>Favorable</td>
<td>Favorable</td>
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HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; EC, endometrioid carcinoma; CCC, clear-cell carcinoma.

*Hereditary nonpolyposis colorectal carcinoma.

Figure 1. Representative examples of the five main types of ovarian carcinoma, which together account for 98% of cases: (A) high-grade serous carcinoma; (B) low-grade serous carcinoma; (C) mucinous carcinoma; (D) endometrioid carcinoma; and (E) clear-cell carcinoma. From [4].
advanced stage tumors (20% versus 30%) [5, 6]. The clear cell and mucinous types, in particular, are candidates for clinical trials to identify more active therapy than what is presently used [7].

The fact that one tumor type (HGSC) accounts for over two-thirds of cases, does not justify classifying ovarian carcinomas into only two types, lumping together the other four (endometrioid, clear cell, mucinous, and LGSCs) as ‘type 1 carcinomas’ [8]. In fact, the latter tumors are clinically, morphologically, and molecularly distinct diseases that individually bear resemblance neither to HGSC nor to each other. Thus, classifying ovarian carcinomas into just two types ('types I and II') [8] is artificial and limits progress in understanding the biology or improving the management of the less common types of ovarian carcinomas.

Although the mesothelial origin cannot be excluded, there is now compelling evidence that a number of what have been thought to be primary ovarian cancers are actually originated in other pelvic organs and involve the ovary secondarily. In fact, it has been proposed that HGSC arise from precursor epithelial lesions in the distal fimbriated end of the fallopian tube [9–15], whereas endometrioid and CCC originate from ovarian endometriosis (Figure 2) [16, 17]. This presentation summarizes recent advances in the molecular pathology which have greatly improved our understanding of the biology of ovarian carcinoma and are also relevant to patient management.

**serous carcinomas**

It is now accepted that HGSC and LGSC are fundamentally different tumor types, and consequently, different diseases [17]. LGSC are associated in most cases with a serous borderline component, carry KRAS and BRAF mutations, and are unrelated to TP53 mutations and BRCA abnormalities [18, 19]. In contrast, HGSCs are not associated with serous borderline tumors and typically exhibit TP53 mutations and BRCA abnormalities.

**high-grade serous carcinomas**

These are the most common ovarian carcinomas and most patients present with advanced stage disease (~80%); tumors confined to the ovary at diagnosis are distinctly uncommon (<10%).

Microscopically, HGSC show papillary and solid growth with slit-like glandular lumens. The tumor cells are typically of intermediate size, with scattered bizarre mononuclear giant cells exhibiting prominent nucleoli (Figure 1A). In contrast to LGSCs, these tumors show more than threefold variation in nuclear size. Also, mitotic activity greater than 12/10 high-power microscopic fields (HPFs) favors a diagnosis of HGSC [4, 20].

Most HGSCs immunoreact for p53, BRCA1, WT1, and p16. They also exhibit a proliferation index as indicated by an increased nuclear expression of Ki-67. Estrogen receptor (ER) is expressed in approximately two-thirds of cases of HGSC [21].

The traditional view that HGSC arise exclusively from ovarian surface epithelium or epithelial inclusion cysts has been recently challenged by the identification, in women with BRCA1 or BRCA2 germline mutations, of tubal intraepithelial carcinoma (TIC) in the distal fimbriated end of the fallopian tube as the probable precursor of advanced HGSC [9, 10, 13]. Cytologically, the cells of TIC show secretory differentiation [13] and resemble those of HGSC. TIC shows immunohistochemical evidence of double-stranded DNA damage, as indicated by nuclear staining for gamma-H2AX [15]. Like HGSC, TIC diffusely and strongly expresses p53 and the Ki-67 proliferation index is usually markedly elevated (mean labeling index, 72%; range: 40%–95%) [15]. p16 and WT-1 may also be expressed. Furthermore, the finding of identical TP53 mutations in both TIC and concomitant tumors classified as ovarian in origin [12] indicates a clonal relationship between

![Figure 2. Classification of gynecological cancers based on origin and mutations. From [4].](image-url)
them and suggests that the distal fallopian tube (fimbria) is an important site for the initiation of HGSC. Nevertheless, implantation of tubal-type epithelium into the ovary (endosalpingiosis) or mesothelial surface invaginations (inclusion cysts) may explain the origin of those HGSC lacking TIC. Currently, the relative proportion of HGSC of ovarian and tubal derivation is unknown mainly in advanced stage cancers. However, extensive examination of the fallopian tubes in HGSC (ovarian, tubal, or pelvic) shows involvement of the endosalpinx in 70% and TIC in ~50% of the cases [12].

Women with germline mutations in BRCA1 or BRCA2 have a 30%–70% risk of developing ovarian cancer by the age of 70, mainly HGSC [22]. Carcinomas arising in patients with germline BRCA1 or BRCA2 mutations are almost invariably of high-grade serous type. BRCA1 and BRCA2 are essential components of the homologous recombination DNA system required to repair DNA double-strand breaks (DSB) [23]. Like TP53 mutations, BRCA inactivation seems to be a consistent genetic alteration of HGSC [24, 25].

The discovery of TICs in risk-reducing salpingo-oophorectomy specimens from women with known BRCA mutations and/or a strong family history of ovarian cancer has resulted in extensive research into the role of the fallopian tube in pelvic serous carcinogenesis [9–15]. Early studies revealed small foci of strongly p53-immunoreactive cells in largely histologically normal fallopian tube epithelium [13]. These foci, which predominate in the distal portion of the fallopian tube, have been designated ‘p53 signatures’. Like TIC, p53 signatures are comprised exclusively of secretory cells (at least 12 consecutive immunoreactive cells), and the majority exhibit evidence of DNA damage by immunoreaction for gamma-H2AX [13, 15]. About 57% of p53 signatures contain TP53 mutations [13]; however, Ki-67 proliferation index is low (mean, 3%). p53 signatures probably represent early clonal expansion short of neoplastic proliferation [26] and, surprisingly, are found in both women with and without BRCA1 or BRCA2 mutations at the same frequency (10%–38% versus 17%–33%, respectively) [13]. TP53 mutation is an early event in the genesis of HGSC, occurring in p53 signature foci and leading to TIC in the distal fallopian tube. BRCA1 mutation also occurs early in the development of TIC but after TP53 mutation [26].

Although a substantial number of HGSC may not arise from the ovary, and the term “ovarian cancer” would not be pathogenetically precise in every case, ovarian involvement is the rule in almost all cases. Furthermore, in view of the rarity of HGSC associated with tubal tumor masses, it is unlikely that all HGSC originate in the fallopian tube. Thus, the term HGSC of ovary should be kept until the different origins of the ovarian tumors are better understood. Terms like “mullerian” or “pelvic” would create confusion for patients, physicians, and medical investigators.

A pathogenetic model that includes the stages of initiation and progression of HGSC is essential for an effective screening and treatment that takes into account biomarkers of early tumorigenesis. The model described by Bowtell [26] (Figure 3) proposes as primary events early p53 loss followed by BRCA loss leading to deficiency in homologous recombination repair of DSB, which triggers chromosomal instability (genetic chaos) and widespread copy number changes [26–28]. Secondary and tertiary events then cause global changes in gene expression followed by mutations to facilitate tumor evolution.

**low-grade serous carcinomas**

LGSC are uncommon and account for <5% of all cases of ovarian carcinoma [29]. They frequently have a noninvasive serous borderline component (with or without micropapillary pattern) and most likely represent progression of serous borderline tumors beyond microinvasion. Whereas the presence of small foci of LGSC in an ovarian borderline tumor is associated with an excellent prognosis, patients with advanced stage disease fare less favorably. Nevertheless, the disease usually follows a relatively indolent course.

Microscopically, LGSCs show small papillae of tumor cells exhibiting uniform nuclei within variable amounts of hyalinized stroma, which often contains psammoma bodies (Figure 1B).

The biomarker expression profile of LGSC is similar to that of their high-grade counterparts. Only Ki-67 immunoreaction differs substantially between the two tumor types, with median Ki-67 labeling index of 2.5% in LGSC versus 22.4% in HGSC [30]. BRAF or KRAS mutations are present in LGSCs (38% and 19%, respectively) [18, 31]. LGSCs do not show chromosomal instability and lack the complex genetic abnormalities seen in
Malignant mucinous ovarian tumors are often heterogeneous. Benign-appearing, borderline, noninvasive carcinoma, and invasive components may coexist within an individual tumor and suggest tumor progression from benign to borderline and from borderline to carcinoma [32]. The category of mucinous borderline tumor with intraepithelial carcinoma is used for those tumors that lack obvious stromal invasion but show areas, <10 mm², where the cytological features of the tumor cells are unequivocally malignant [33]. Mucinous borderline tumors with intraepithelial carcinoma have a very low risk of recurrence, of <5% [34].

Recently, MCs have been divided into two categories: (i) an ‘expansile’ type without obvious stromal invasion, but exhibiting back-to-back or complex malignant glands with minimal or no intervening stroma, and exceeding 10 mm² in area (>3 mm in each of two linear dimensions) (Figure 1C); and (ii) an ‘infiltrative’ type, showing evident stromal invasion in the form of glands, cell clusters, or individual cells, disorderly infiltrating the stroma and frequently associated with a desmoplastic stromal reaction [32, 33]. The expansile pattern of growth is associated with a more favorable prognosis than the infiltrative pattern.

The gene expression profile of MCs differs from those of serous, endometrioid, and CCC [35]. KRAS mutations, which are an early event in mucinous tumorigenesis, are frequent in ovarian MCs [36]. Primary ovarian mucinous tumors are almost always (up to 80%) immunoreactive for cytokeratin 7 (CK7) whereas colorectal adenocarcinomas are usually CK7 negative [37]. Ovarian MCs are immunoreactive for CK20 in 65% of cases, but the reaction is typically weak and focal.

Clear cell carcinomas

Endometrioid tumors of the ovary closely mimic their uterine counterparts. ECs account for 10% of all ovarian carcinomas, occur most frequently in women of perimenopausal age, and most are found at an early stage [1]. The ovarian tumors are bilateral in 28% of cases and are associated in 15%–20% of cases with carcinoma of the endometrium [2, 38]. Most ECs are low-grade adenocarcinomas and seem to arise from endometriotic cysts. Up to 42% of cases have evidence of ipsilateral ovarian or pelvic endometriosis [1, 2]. Squamous differentiation occurs in 50% of cases [1] (Figure 1D). In contrast, high-grade ECs are morphologically indistinguishable from HGSCs and often express WT1. Gene expression profiling is also similar, suggesting that high-grade EC is not a distinct tumor type [39].

It has been recognized that atypical endometriosis is the precursor lesion of endometrioid and CCC of the ovary and a direct transition from ovarian atypical endometriosis to endometrioid or CCC has been described in 15%–32% of cases [40]. In cases of ovarian EC associated with endometriosis, common genetic alterations have been encountered in the adjacent endometriosis, atypical endometriosis, and adenocarcinoma [41].

With the recent discovery of AT-rich interactive domain 1A gene (ARID1A) mutations in endometrioid and CCC as well as in adjacent endometriosis, there is renewed interest in the molecular events that occur in precursor lesions [42]. ARID1A behaves as a tumor suppressor gene. BAF250 protein, encoded by ARID1A, plays a crucial role in chromatin remodeling.

Somatic mutations of the β-catenin (CTNNB1) and PTEN genes are the most common genetic abnormalities identified in ovarian ECs [16, 43, 44]. Compared with uterine ECs, ovarian ECs have a similar frequency of β-catenin abnormalities but lower rate of microsatellite instability (MI) and PTEN alterations [44]. CTNNB1 mutations are associated with favorable outcome [45].

PTEN inactivation results in activation of the PI3K-AKT signaling pathway that inhibits apoptosis. PTEN is mutated in ~20% of ovarian ECs. The finding of LOH at 10q23 and somatic PTEN mutations in endometriotic cysts adjacent to ECs with similar genetic alterations provides additional evidence for the precursor role of endometriosis in ovarian carcinogenesis [17]. An alternative mechanism for activation of the PI3K signaling in ECs is through activating mutations of PIK3CA, which encodes the p110 catalytic subunit of PI3K.

ECs are the types most commonly encountered in patients with hereditary nonpolyposis colon cancer syndrome. The reported frequency of MI in ovarian ECs ranges from 12.5% to 19% [46, 47]. ECs are immunoreactive for vimentin, cytokeratins (CK7, 97%; CK20, 13%), epithelial membrane antigen, and estrogen and progesterone receptors.

Simultaneous carcinomas of the uterine corpus and ovary occur in 15%–20% of ovarian tumors and in ~5% of uterine tumors [2]. Both tumors are of endometrioid type in the majority of cases.

Clear cell carcinomas

CCC s account for ~10% of ovarian carcinomas and patients typically present with stage 1 or 2 diseases. Tumors are rarely bilateral. CCCs are associated with an unfavorable prognosis when they present at advanced stage [48]. As with EC, there is an association with endometriosis, and CCCs associated with endometriosis have a favorable prognosis [49].

The diagnosis of CCC is based on the following architectural and cytological findings: (a) multiple complex papillae; (b) densely hyaline basement membrane material expanding the cores of the papillae (Figure 1E); and (c) hyaline bodies, which
are present in ~25% of cases. Mitoses are less frequent than in other types of ovarian carcinomas (usually <5/10 HPFs).

CCCs lack the BRCA abnormalities, chromosomal instability, or complex karyotypes of HGSC [50]. Recently, it has been found that nearly half the CCCs (46%–57%) carry ARID1A mutations and lack BAF250 protein [42]. In two cases, ARID1A mutations and loss of BAF250α expression were found in the tumor and adjacent endometriosis but not in distant endometriosis. This finding suggests that ARID1A inactivation occurs early during malignant transformation of endometriosis [42]. CCCs are usually positive for HNF1-β (>90%) and are negative for ER and WT1 in >95% of cases [21, 30].

Hepatocyte nuclear factor-1β (HNF-1β) is upregulated in ovarian clear cell tumors, including benign, borderline tumors, and carcinomas [51]. This transcription factor facilitates glycogen synthesis and is expressed in mid-to-late secretory and gestational endometrium (Arias-Stella reaction), atypical and inflammatory endometriosis, and CCC [51]. HNF-1β regulates several specific genes of CCC, including dipeptidyl peptidase IV (glycogen synthesis), osteopontin (progesterone-regulated endometrial secretory protein), angiostatin converting enzyme 2 (ferritin induction, iron deposition, and antiapoptosis), annexin 4 (paclitaxel resistance), and UGT1A1 (detoxification) [52]. Thus, HNF-1β appears to play an important role in the pathogenesis and behavior of CCC.

disclosure

The author has declared no conflicts of interest.

references


