



REVIEW

The Dualistic Model of Ovarian Carcinogenesis *Revisited, Revised, and Expanded*



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Since our proposal of a dualistic model of epithelial ovarian carcinogenesis more than a decade ago, a large number of molecular and histopathologic studies were published that have provided important insights into the origin and molecular pathogenesis of this disease. This has required that the original model be revised and expanded to incorporate these findings. The new model divides type I tumors into three groups: i) endometriosis-related tumors that include endometrioid, clear cell, and seromucinous carcinomas; ii) low-grade serous carcinomas; and iii) mucinous carcinomas and malignant Brenner tumors. As in the previous model, type II tumors are composed, for the most part, of high-grade serous carcinomas that can be further subdivided into morphologic and molecular subtypes. Type I tumors develop from benign extraovarian lesions that implant on the ovary and which can subsequently undergo malignant transformation, whereas many type II carcinomas develop from intraepithelial carcinomas in the fallopian tube and, as a result, disseminate as carcinomas that involve the ovary and extraovarian sites, which probably accounts for their clinically aggressive behavior. The new molecular genetic data, especially those derived from next-generation sequencing, further underline the heterogeneity of ovarian cancer and identify actionable mutations. The dualistic model highlights these differences between type I and type II tumors which, it can be argued, describe entirely different groups of diseases. (*Am J Pathol* 2016, 186: 733–747; <http://dx.doi.org/10.1016/j.ajpath.2015.11.011>)

More than a decade ago we proposed a dualistic model of epithelial ovarian carcinogenesis (type I and type II tumors) in an attempt to unravel the complex molecular genetic pathways involved in pathogenesis of primary ovarian carcinomas and to correlate these pathways with the histopathologic classification.¹ In the ensuing years, a large number of molecular and histopathologic studies were published that have provided important insights into the origin and development of these tumors. We are now at crossroads where pathogenesis according to morphology and molecular findings intersect. At present, our understanding of carcinogenesis and its role in tumor classification is based largely on morphology, but the importance of molecular classification is becoming increasingly apparent. The new model takes into account the current histopathologic classification and integrates it with the emerging molecular genetic findings to provide a bridge to the future (Figure 1).

Clinical Features

The salient clinicopathologic and molecular differences between type I and type II tumors are shown in Table 1. Type I carcinomas usually present as large, unilateral, cystic neoplasms. With the exception of clear cell carcinomas, which are not graded but are considered high grade, type I tumors are low grade; they therefore, not surprisingly, tend to behave in an indolent fashion. When confined to the ovary they have an excellent prognosis, but advanced stage tumors have a poor outcome. Type I tumors account for only 10% of the deaths from ovarian cancer.

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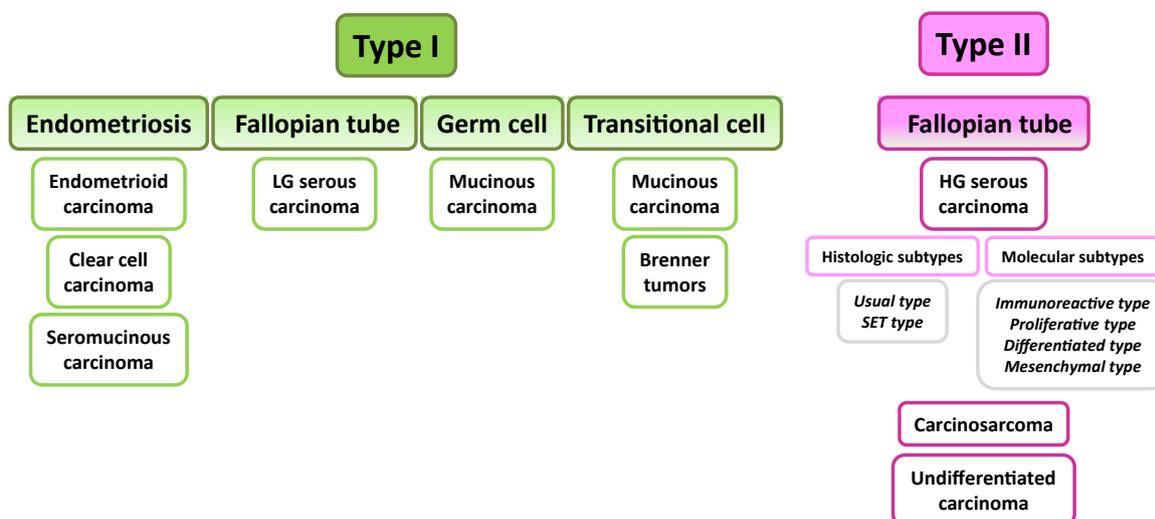


Figure 1 Expanded dualistic model of ovarian carcinogenesis. Ovarian carcinomas derive from endometrial tissue, fallopian tube tissue, germ cells, and transitional epithelium. Type I carcinomas comprise endometrioid, clear cell, LG serous, and mucinous carcinomas. Seromucinous neoplasms and malignant Brenner tumors are rare. It was recently proposed that seromucinous neoplasms be designated mixed Müllerian tumors. Type II carcinomas are largely composed of HG serous carcinoma, carcinosarcoma, and undifferentiated carcinoma. Transitional cell indicates metaplastic transitional epithelium at the tuboperitoneal junction. HG, high-grade; LG, low-grade; SET, solid pseudoendometrioid transitional.

Comprehensive staging of type I tumors is routinely performed, but, in the absence of overt extraovarian disease, the likelihood of detecting occult tumor is remote. One study of >100 women with unilateral mucinous carcinomas reported that staging failed to detect occult disease in any of these patients.²

Type II tumors present in advanced stage in >75% of cases. They are invariably high grade, develop rapidly, and are highly aggressive. The volume of tumor in the ovaries (typically both are involved) is substantially less than that of the type I tumors. However, the volume of extraovarian disease is generally much greater, often with massive disease in the omentum and mesentery, than in the type I tumors. Ascites

frequently accompanies the type II tumors but is infrequent with type I tumors. Aggressive surgery and chemotherapy have lengthened progression free survival and, to a very modest extent, of overall survival, but ultimately most patients with type II tumors succumb. These neoplasms account for 90% of the deaths from ovarian cancer.

Morphologic and Molecular Features

In 2014, the World Health Organization updated the histopathologic classification of ovarian tumors.³ The morphologic features of these neoplasms are well illustrated in the

Table 1 Clinicopathologic and Molecular Features of Type I and Type II Ovarian Carcinomas

Features	Type I	Type II
Stage	Frequently early stage	Almost always advanced stage
Tumor grade	Low grade*†	High grade
Proliferative activity	Generally low	Always high
Ascites	Rare	Common
Response to chemotherapy	Fair	Good (but recur later)
Early detection	Possible	Challenging
Progression	Slow and indolent	Rapid and aggressive
Overall clinical outcome	Good	Poor
Risk factors	Endometriosis	Lifetime ovulation cycles; BRCA germline mutations
Origin	See <i>Morphologic and Molecular Features of Precursor Lesions</i>	Mostly tubal
Precursors	Atypical proliferative (borderline) tumors	Mostly STICs
Chromosomal instability	Low	High
<i>TP53</i> mutation	Infrequent	Almost always
Homologous recombination repair	Rarely defective	Frequently defective
Actionable mutations	Can be present	Rare

*Clear cell carcinoma is not graded, but many consider the tumor as high-grade.

†Occasional progression to high grade can be observed.

BRCA, breast cancer; STIC, serous tubal intraepithelial carcinoma.

World Health Organization book and in textbooks of gynecologic pathology and are therefore only briefly described in this Review. Type I tumors are composed of low-grade serous, endometrioid, clear cell, mucinous carcinomas and malignant Brenner tumors. Type II tumors include high-grade serous carcinoma (HGSC), carcinosarcoma, and undifferentiated carcinoma. In the updated model, seromucinous carcinoma was added to the type I group. It was recently proposed that a more appropriate designation for seromucinous tumors, which more accurately reflects the morphologic, immunohistochemical, and molecular features, is mixed Müllerian tumors.⁴ These comprise cystadenomas, atypical proliferative (borderline) tumors, and carcinomas. In the type II group, HGSCs were divided into two morphologic subsets: the usual type and a so-called SET variant (solid, pseudoendometrioid, transitional). HGSCs have also been subdivided on the basis of gene expression cluster analysis into four molecular subtypes termed immunoreactive, differentiated, proliferative, and mesenchymal, but a correlation with morphology has not yet been described.

The main molecular genetic feature that separates type I from type II tumors is the relative genetic stability (as reflected by global DNA copy number changes) of type I tumors compared with the marked chromosomal instability of type II tumors. In addition, ubiquitous *TP53* mutations characterize type II tumors, in contrast to their infrequency in type I tumors. The other important differences are the frequent somatic mutations involved in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (*PIK3CA*)/phosphatase and tensin homolog (*PTEN*), catenin β 1, Kirsten rat sarcoma viral oncogene homolog (*KRAS*)/B-Raf proto-oncogene, serine/threonine kinase (*BRAF*)/mitogen-activated protein (MAP) extracellular signal-related kinase (*ERK*), and AT-rich interaction domain 1A (*ARID1A*) chromatin remodeling pathways in type I carcinomas, whereas frequent abnormalities in homologous recombination repair, retinoblastoma protein, cyclin E1, forkhead box M1 (*FOXM1*), and Notch3 pathways occur in type II carcinomas (Figure 2). Although ovarian carcinomas with mixed histologic features (more than one histotype in a given tumor) can be observed, they are rare, with an estimation of <1% with the use of current diagnostic criteria and immunohistochemical staining.⁵

Type I Carcinomas

LGSCs

These tumors may be noninvasive LGSC (niLGSC) or invasive (LGSC). The niLGSC is distinguished from an atypical proliferative serous tumor (APST) according to architecture and more importantly on nuclear features. In contrast to APSTs, niLGSCs have nuclear atypia that is identical to invasive LGSC.³ Parenthetically, the 2014 World Health Organization Classification regards the terms

serous borderline tumor and atypical proliferative serous tumor as synonymous and serous borderline tumor, micropapillary variant as synonymous with niLGSC.³ We prefer APST and niLGSC and use these terms in this Review.

Unlike the other noninvasive tumors, niLGSCs are often bilateral and may be associated with extraovarian disease (implants) in up to 30% of cases.⁶ The mechanisms underlying the development of peritoneal implants (noninvasive and invasive) have bedeviled investigators for many years. Recently, it was shown that both types of implants have identical *BRAF* or *KRAS* mutation to the ovarian tumors, indicating that they are metastases.⁷ On the basis of this and other findings, the 2014 World Health Organization Classification considers invasive implants to be metastatic LGSCs.³

After surgery, approximately 10% of these tumors subsequently recur as carcinoma, almost always as low grade.^{8,9} Progression to HGSC occurs rarely.¹⁰ Studies have reported a better outcome for women whose tumors contain *BRAF* mutations than for women with *KRAS* mutations or wild-type *BRAF* and *KRAS*.^{11–13} Immunohistochemical studies have shown that *BRAF* mutations correlate with the presence of cells with abundant eosinophilic cytoplasm in the primary tumor.¹⁴ These eosinophilic cells are also found in foci of microinvasion, peritoneal implants, and lymph nodes. Furthermore, immunohistochemical studies have shown decreased expression of estrogen receptor (ER), progesterone receptor (PR), Wilms tumor 1 (WT1), and Ki-67 and increased expression of p16 in the eosinophilic cells.¹⁵ These findings and their morphologic similarity to cells in culture that are undergoing senescence suggest that the eosinophilic cells are senescent, which is consistent with the excellent outcome for women whose tumors display microinvasion and/or lymph node involvement characterized by the presence of these cells. A distinctive lesion in the fallopian tube designated papillary tubal hyperplasia is associated with APSTs.¹⁶

Endometrioid and Clear Cell Carcinomas

Most endometrioid carcinomas are well differentiated, but occasionally moderately and poorly differentiated carcinomas are observed. The frequent finding of well-differentiated areas in the moderate and poorly differentiated neoplasms suggests that the latter de-differentiated from low-grade carcinomas. In contrast to the other type I tumors, clear cell carcinomas are not graded. They are generally regarded as high grade, unlike the other type I tumors. Occasionally, both endometrioid and clear cell carcinoma components coexist in an ovarian tumor.

Somatic inactivating mutations of *ARID1A* characterize both tumor types and activating mutations of the catenin β 1 gene (*CTNNB1* encodes β -catenin) occur in roughly 15% to 40% of ovarian endometrioid carcinomas, and mutation of this gene is associated with squamous differentiation, low tumor grade, and favorable outcome.^{17,18} In addition, inactivating mutations of *PTEN* were reported in 15% to 20% of

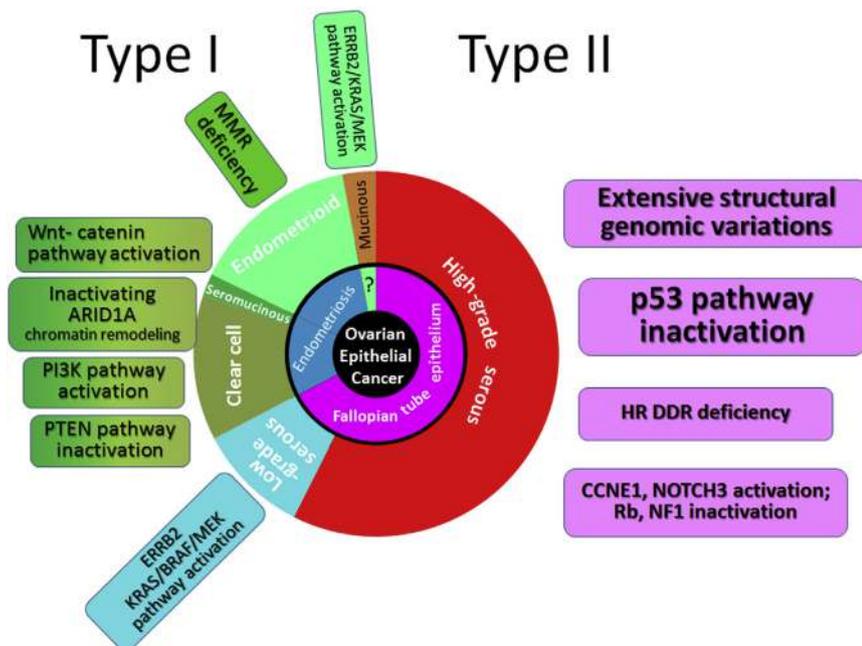


Figure 2 The revised dualistic model in the pathogenesis of ovarian epithelial cancer. Type I carcinomas comprise low-grade serous, clear cell, endometrioid, and mucinous carcinomas. Seromucinous carcinomas and malignant Brenner tumors are rare and not shown. Type II carcinomas are largely composed of high-grade serous carcinomas. Carcinosarcoma and undifferentiated carcinoma are relatively uncommon and not illustrated. The areas in individual histotypes reflect their relative prevalence. The **inner circle** indicates the likely cell of origin of the different type I and type II neoplasms. The origin of mucinous carcinomas is not well established and is discussed in the text. The molecular pathway alterations that characterize each tumor subtype are summarized in the **square boxes**. Some of the pathway abnormalities are shared by some tumor types and they are shown in **two-color fill in boxes**. ARID1A, AT-rich interaction domain 1A; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CCNE1, cyclin E1; ERB2, estrogen-related receptor β ; HR DDR, homologous recombination-mediated DNA damage repair; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein (MAP) extracellular signal-related kinase (ERK) kinase; MMR, DNA mismatch repair; NF1, nuclear factor 1; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Rb, retinoblastoma protein.

endometrioid carcinomas and in almost 10% of clear cell carcinomas.¹⁹ Activating mutations of *PIK3CA* occur in 20% of endometrioid and clear carcinomas.^{20,21} These genes are rarely mutated in other types of ovarian cancer. Inactivating mutations of *PTEN* and activating mutations of *PIK3CA* can lead to activation of the phosphatidylinositol 3-kinase signaling pathway. Less than 7% of endometrioid carcinomas have activating mutations of *KRAS* and *BRAF*.^{17,22} Microsatellite instability has also been reported in up to 20% of endometrioid carcinomas and is usually associated with loss of human mutL homolog 1 (hMLH1), human mutS homolog 2 (hMSH2), mutS homolog 6 (MSH6), and peroxide-sensitive mutant 2 (PSM2) expression. The similar molecular genetic profiles of endometrioid and clear cell carcinomas highlight their close relation and origin from endometriosis (see *Morphologic and Molecular Features of Precursor Lesions*). However, the morphology and behavior of endometrioid and clear cell carcinomas are different, so it is not surprising that, eg, canonical Wnt signaling pathway defects and microsatellite instability have not been observed with significant frequency in clear cell tumors, unlike endometrioid tumors.²³ Studies that used genetically engineered mouse models found that deletion of *ARID1A*, mimicking its somatic inactivation, is insufficient to drive ovarian tumor formation; however, codeletion of *ARID1A* and *PTEN* results in ovarian endometrioid carcinoma,²⁴ whereas codeletion of *ARID1A* and *PIK3CA* leads to formation of clear cell-like ovarian neoplasms in mice.²⁵ In addition to these molecular genetic alterations, a recent genome-wide methylation study suggested that clear cell carcinomas have a unique methylation profile compared

with the other histologic subtypes.²⁶ Pathway analyses indicate that there is an increase in promoter methylation for multiple genes in the *ER α* pathway and loss of promoter methylation for multiple genes in the hepatocyte nuclear factor 1 (HNF1) pathway, thus explaining the characteristic immunohistochemical findings in clear cell carcinomas.

TP53 mutations were described in high-grade endometrioid carcinoma with expression profiles similar to those of HGSC, but these tumors may have been misclassified, as suggested by more recent studies reporting a subset of HGSCs that display a pseudoendometrioid pattern²⁷ (see *Type II Tumors, HGSC*).

Seromucinous Carcinomas (Mixed Müllerian Carcinomas)

Most seromucinous carcinomas are noninvasive. They are generally papillary and resemble niLGSCs but, in fact, are composed of a mixture of epithelial cell types, including endometrioid and squamous cells and endocervical-type mucinous cells. Furthermore, the immunoprofile is characterized by frequent expression of ER (100%), PR (67%), cancer antigen 125 (CA125; 92%), infrequent expression of WT1 (8%), and lack of expression of cytokeratin 20 (CK20) and caudal type homeobox 2 (CDX2), an immunostaining pattern consistent with a Müllerian immunophenotype. Loss of ARID1A expression was reported in more than one-third of cases,²⁸ which is similar to the frequency in endometrioid and clear cell tumors, providing compelling evidence to include them in the group of endometriosis-related neoplasms. Note that mutation of the *ARID1A* gene or loss of its protein expression has not been found in ovarian

neoplasms other than seromucinous, clear cell, and endometrioid carcinomas. Thus, the morphologic, immunohistochemical, molecular genetic data, and frequent association with endometriosis are not consistent with a tumor that is exclusively serous and mucinous; therefore, the term seromucinous is inaccurate and misleading. It was therefore proposed that this group of tumors be designated mixed Müllerian tumors, which can be subcategorized as mixed Müllerian cystadenomas, mixed Müllerian atypical proliferative (borderline) tumors, and mixed Müllerian carcinomas.⁴

Mucinous Carcinomas

Most mucinous carcinomas are well differentiated; moderate and poorly differentiated tumors are relatively uncommon. Typically, mucinous carcinomas are quite heterogeneous, containing areas of cystadenoma and atypical proliferative tumor intimately admixed with areas of carcinoma. A recent study that used next-generation sequencing found that *KRAS*-activating mutation is the most common single molecular genetic alteration in mucinous carcinomas, occurring in 65% of cases.²⁹ Interestingly, mutations in *KRAS*, *BRAF*, and/or *ERBB2* amplification are present in >90% of mucinous carcinomas, indicating frequent *RAS/MEK* pathway activation in this neoplasm. Another study identified mutations in a novel gene, *RNF43*.³⁰ By combining the discovery and validation sets, 6 of 29 mucinous carcinomas (21%) were found to harbor the inactivating mutations of *RNF43*, a zinc finger-dependent E3 ubiquitin protein ligase, suggesting that *RNF43* inactivation may characterize a proportion of mucinous cancers.³⁰ In contrast to other type I ovarian carcinomas, *TP53* mutation is frequent in mucinous carcinomas, being present in approximately one-half of cases.^{29,30} Interestingly, in contrast to serous, endometrioid, and clear cell tumors, mucinous tumors do not express ER or PR, which is consistent with our proposal that they are non-Müllerian-derived tumors. However, paired box 8 (PAX8), a Müllerian marker, is expressed in approximately 50% of mucinous tumors. We have postulated that the nongerm cell mucinous tumors develop from Brenner tumors, which are in turn derived from nests of transitional epithelium at or near the tuboperitoneal junction. Accordingly, a possible explanation for expression of PAX8 by a substantial number of mucinous tumors may be that in the region of the tuboperitoneal junction, where Müllerian-derived tubal epithelium is in close contact with the mesothelium of the tubal serosa and ovarian surface epithelium, overlapping PAX8 expression may occur in both Müllerian and non-Müllerian epithelium.^{31,32}

Brenner Tumors

Brenner tumors are composed of nests of transitional-type epithelium surrounded by a fibromatous stroma. Typically, the nests of transitional epithelium have a central cystic

cavity lined by mucinous epithelium. Most Brenner tumors are benign, less commonly atypical proliferative, and rarely malignant, and consequently a comprehensive molecular analysis of malignant Brenner tumors has not been performed. There have only been a few immunohistochemical and molecular genetic studies of benign and atypical proliferative Brenner tumors. p16 immunostaining was shown to be positive in the epithelial component of 12 of 13 benign Brenner tumors (92%) but completely negative in 7 atypical proliferative Brenner tumors. Fluorescence *in situ* hybridization identified homozygous deletion of *CDKN2A*, the gene encoding p16, in the epithelial component of all atypical proliferative tumors, but it was retained in all benign tumors. Two *PIK3CA* mutations were found in the stromal component in 2 of 20 benign Brenner tumors (5%) but not in the epithelial component. However, one *KRAS* mutation and two *PIK3CA* mutations were detected in the epithelial component of two atypical proliferative tumors (29%).³³ These findings suggest that loss of *CDKN2A* may play a role in progression of benign to atypical proliferative Brenner tumors.

Type II Carcinomas

HGSC

Recent morphologic studies correlated with germline breast cancer gene (*BRCA*) mutations studies have provided evidence that HGSC is more heterogeneous than previously thought.^{27,34} The usual type of HGSC is composed of solid masses of cells with slit-like spaces and papillary, glandular, and cribriform patterns often accompanied by necrosis. Another type is composed of solid masses of cells that simulate endometrioid and transitional cell carcinomas. These latter carcinomas, however, have an identical immunoprofile to HGSC, including p53, PTEN, WT1 reactivity and a similar frequency of *TP53* mutations, supporting their classification as HGSC.³⁵ To distinguish these tumors from the usual HGSC, it was proposed that they be classified as the SET variant.²⁷ Compared with the usual type of HGSC, the SET tumors have a greater number of tumor-infiltrating lymphocytes and a higher mitotic index.

Correlating the two types of HGSC with germline *BRCA1* mutations reveals substantial differences. Compared with the usual HGSC, the SET tumors were substantially more frequently associated with *BRCA1* mutations but less frequently associated with serous tubal intraepithelial carcinomas (STICs; see *Morphologic and Molecular Features of Precursor Lesions*). It was also reported that SET tumors occurred in younger women than the usual-type HGSC and had a better clinical outcome.³⁴ The latter observation may be due to greater chemosensitivity of these neoplasms (deficiency in homologous recombination repair), because it was previously reported that ovarian transitional cell carcinomas are more chemosensitive than are HGSCs and have better survival.³⁶ The Cancer Genome Atlas project

analyzed genome-wide sequence mutation, mRNA and protein expression, miRNA expression, promoter methylation, and DNA copy number in a large number of HGSCs and reported that they were characterized by *TP53* mutations in almost all tumors.³⁷ Although the number of somatic mutations per case in HGSC is similar to most solid malignant neoplasms, interestingly, unlike the latter, somatic mutations in mutated genes other than *TP53* occurred in no >5% of the ovarian HGSCs. Substantial focal DNA copy number aberrations and promoter methylation events that involved 168 genes were also found. Amplification of *CCNE1* was another frequent finding.³⁷ Analyses delineated four ovarian cancer transcriptional subtypes, three miRNA subtypes, four promoter methylation subtypes, and a transcriptional signature associated with survival duration. In addition, *NOTCH3* and *FOXM1* signaling were found to be involved in HGSC pathophysiology.³⁷ More recently, the results of The Cancer Genome Atlas (TCGA) study were largely verified in another genome-wide report.³⁸

Among these various molecular findings, those that are most characteristic of HGSC are widespread DNA copy number or structural aberrations and *TP53* mutation. TCGA project reported that >96% of HGSCs have *TP53* mutations; however, a study by five gynecologic pathologists who reviewed the negative *TP53* cases from TCGA study found that all of the negative tumors except for one were histologically misclassified. The one exception contained a homozygous deletion of the gene, indicating that all properly classified HGSCs have a *TP53* abnormality, which is almost always a mutation.³⁹ In addition to widespread copy number alterations, which reflect the history of genomic instability, and ubiquitous *TP53* mutations, other common threads in HGSCs include *CCNE1* amplification, germline and somatic mutation of *BRCA1/2*, and other aberrations in pathways that regulate homologous recombination DNA damage repair pathways.³⁸ HGSCs showing *BRCA1/2* deficiency are characterized by more extensive DNA copy number alterations, and they usually do not harbor *CCNE1* amplification and vice versa.³⁸

A gene expression analysis of >300 HGSCs identified four molecular subtypes⁴⁰ that were subsequently validated in TCGA study and termed immunoreactive, differentiated, proliferative, and mesenchymal on the basis of gene expression in the clusters (Figure 1).³⁷ These molecular subtypes were associated with distinct clinical outcomes.^{41,42} In one study, it was shown that survival differed significantly between the subtypes and was best for the immunoreactive subtype, a finding consistent with the histopathologic observation that HGSCs with large numbers of tumor-infiltrating lymphocytes are associated with a better outcome. Another study reported that *BRCA1* disruptions were associated with the immunoreactive subtype.⁴³ It is postulated that these subtypes may reflect distinct patterns of oncogene activation. These studies suggest that high-grade serous carcinogenesis is initiated by disruption of DNA

repair, followed by chromosomal instability, copy number change, and segregation into molecular subtypes.

Undifferentiated Carcinoma

These are uncommon tumors that show none of the characteristic features of HGSC or high-grade endometrioid carcinoma. At present, it is not clear whether these are distinct tumors or variants of poorly differentiated HGSCs or high-grade endometrioid carcinomas. They assume a gene expression pattern close to mesenchymal rather than epithelial cells. We are not aware of any molecular studies specifically evaluating undifferentiated carcinomas.

Carcinosarcoma (Malignant Mixed Müllerian Tumor)

Carcinosarcoma is a biphasic tumor composed of carcinoma and sarcoma. The two components are distinct but typically intermixed. Several studies have shown that the epithelial and mesenchymal components are clonal; therefore, most investigators are of the opinion that these are high-grade carcinomas that have undergone sarcomatoid differentiation.⁴⁴ Carcinosarcomas share several molecular genetic abnormalities with HGSC, including *TP53* mutations and *CDKN2A* overexpression.⁴⁵

Primary Peritoneal Carcinoma

These tumors almost always resemble HGSC, and most investigators regard them as HGSCs in which little or no tumor involves the ovary. We are not aware of molecular studies specifically evaluating these tumors.

In summary, data are now emerging to indicate that type II tumors are more heterogeneous than previously suspected, although the differences appear to be more subtle than those in the type I tumors.

Functional Aspects of the Molecular Genetic Aberrations in Different Histotypes

The individual molecular genetic alterations that are present in different histotypes of ovarian carcinoma were described in the sections above. These changes can be summarized as abnormalities that affect distinct molecular cancer pathways (Figure 1). In general, type I neoplasms are characterized by activation in the *ERBB2/KRAS/BRAF/MEK* pathway, *PI3K/AKT* pathway, and Wnt pathway, and inactivation in the *PTEN* pathway, *ARID1A*-related chromatin remodeling, and mismatch repair mechanism, either because of sequence mutations and/or gene amplification/deletion. In contrast, type II neoplasms are mainly characterized by inactivation of the *p53*-related pathways, and activation in the cyclin E1, *Notch3*, and *FOXM1* pathways. In addition, at least one-third of type II cancers exhibit deficiency in homologous recombination-mediated DNA damage repair. Tumor cells with deficiency in homologous recombination DNA damage

repair tend to use error-prone non-homologous end joining (including alternative non-homologous end joining) to repair DNA, leading to exaggerated structure variations in their genomes. Similarly, inactivation of the p53 pathway and activation of the cyclin E1 pathway also indirectly contribute to chromosomal instability that is the cardinal molecular feature of the type II ovarian cancers.

Morphologic and Molecular Features of Precursor Lesions

One of the main features that led us to parse epithelial ovarian cancers into type I and type II groups was the relation of the different histologic subtypes to precursor lesions. Specifically, type I carcinomas were found to develop from well-established benign precursor lesions, notably borderline or atypical proliferative tumors, simulating the adenoma/carcinoma sequence of colorectal carcinoma. In contrast, type II tumors were thought to develop *de novo* from the ovarian surface epithelium, because no apparent precursor lesion had been identified. In the past few years, studies have shown that many type II carcinomas develop from an intraepithelial carcinoma in the fallopian tube, generally located in the fimbria and designated as STIC.

Type I

LGSC

LGSCs (Table 2) evolve from APSTs in a step-wise fashion and are characterized by sequence mutations in the *KRAS*, *BRAF*, and *ERBB2* oncogenes, which result in constitutive activation of the MAP kinase signal transduction pathway.^{46–48} Studies have implicated a hyperplastic lesion in the fallopian tube, designated papillary tubal hyperplasia as the precursor of APSTs.¹⁶ The MAP kinase pathway plays a critical role in the transmission of growth signals into the nucleus and ultimately contributes to neoplastic transformation. *KRAS* mutations at codons 12 and 13 occur

in one-third of APSTs and LGSCs, and *BRAF* mutations at codon 600 occur in another one-third of APSTs but less commonly in LGSCs.^{46,49} Mutations of *ERBB2* occur in <5% of these tumors; neuroblastoma RAS (NRAS) viral oncogene homolog gene mutations are also detected in a small percentage of LGSCs.^{49,50} Mutations in *KRAS*, *BRAF*, and *ERBB2* are mutually exclusive and consequently are detected in approximately two-thirds of APSTs and LGSCs. They appear to occur early in the development of these tumors, as evidenced by the finding of *KRAS* and *BRAF* mutations in the benign cystadenoma epithelium adjacent to APSTs.⁵¹ Pure serous cystadenomas do not harbor these mutations, supporting the interpretation that these mutations are critical in initiating the LGSC pathway. In addition, mutation of NRAS may also be involved in progression in a small number of cases.⁵⁰

It is difficult to reconcile the disparate role of *BRAF* mutation in the pathogenesis of these tumors, because, on the one hand, it leads to senescence, and, on the other hand, it is involved in tumor initiation and occasionally progression to LGSC. We postulate that *BRAF* mutation, such as *KRAS* mutation, is required for tumor initiation, because mutations in both genes have multiple tumor-promoting effects, including up-regulation of glucose transporter-1, an essential surface protein that results in an increase in glucose metabolism required for tumor transformation.⁵² Once an APST develops, the epithelial cells may initiate a mechanism to restrain tumor progression as occurs in many benign neoplasms. This may explain why *BRAF*-mutated advanced-stage LGSCs are much less common than are *BRAF*-mutated advanced stage APSTs.^{12,13,53} Despite this restraining mechanism, a few tumors do progress, possibly as a result of hemizygous ch1p36 loss or homozygous or hemizygous deletions of ch9p21 and perhaps others, because these losses are much more common in LGSC than in APSTs.⁴⁷ The ch1p36 region contains several candidate tumor suppressor genes, including miR-34a, which is required for activation of the DNA damage response and is the direct p53 target that mediates tumor suppressor functions.^{54,55} Likewise, the ch9p21 region corresponding to the

Table 2 Potential Precursors of Type I and Type II Tumors

Tumor	Precursor site of origin	Potential precursor lesion	Immediate precursor
Invasive LGSC	Fallopian tube	Papillary tubal hyperplasia	Atypical proliferative tumor/noninvasive LGSC
Endometrioid	Endometrium	Endometriosis	Atypical proliferative tumor
Clear cell	Endometrium	Endometriosis	Atypical proliferative tumor/noninvasive
Seromucinous	Endometrium	Endometriosis	Atypical proliferative tumor/noninvasive
Mucinous	Tuboperitoneal junction	Transitional epithelium	Atypical proliferative tumor/intraepithelial carcinoma
Mucinous	Ovarian	Mature teratoma	Mucinous epithelium
Brenner	Tuboperitoneal junction	Transitional epithelium	Transitional epithelium
HGSC	Fallopian tube	STIC	STIC
Undifferentiated carcinoma	? Fallopian tube	? STIC	? STIC
Carcinosarcoma	Fallopian tube	STIC	STIC
Primary peritoneal carcinoma	Fallopian tube	STIC	STIC

?, possible; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; STIC, serous tubal intraepithelial carcinoma.

CDKN2A/B locus encodes three well-known tumor suppressor proteins, p14 (Arf), p16, and p15, that inhibit cyclin-dependent kinase. Thus, deletions or silencing of miR-34a and *CDKN2A/B* loci may abrogate the checkpoint on mutations and permit some APSTs to progress to LGSCs. In this regard, it was reported that p16 expression levels are significantly decreased in LGSCs compared with in APSTs.⁵⁶

Endometrioid and Clear Cell Carcinoma

These tumors may be pure or admixed with their corresponding atypical proliferative tumors, suggesting that like LGSCs they develop from atypical proliferative tumors. In addition, both the carcinomas and atypical proliferative tumors are frequently associated with endometriosis. This association was described for several decades and has now been supported by molecular genetic studies. Inactivating mutation of *ARID1A*, a tumor suppressor gene involved in switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling, was detected in up to 50% of clear cell carcinomas and 30% of endometrioid carcinomas.^{21,57,58} Moreover, mutation and loss of expression of this gene was found in the endometriotic epithelium in endometriomas immediately adjacent to endometrioid and clear cell carcinomas but not in the epithelium in the endometriotic cysts more distant from the carcinoma.^{57,58} Somatic mutations of *PTEN* were also found in endometrioid and clear cell carcinomas and in endometriotic cysts, lending further support to endometriotic cysts as precursors of these neoplasms.⁵⁹

Seromucinous Carcinoma (Mixed Müllerian Carcinoma)

Evidence is persuasive that these tumors are derived from endometriosis, because approximately one-third are associated with endometriosis, which is similar to the frequency found in endometrioid and clear cell carcinomas.⁶⁰ In addition, seromucinous tumors are cytokeratin (CK)7⁺, CK20⁻, CDX2⁻, WT1⁻ and usually express ER and PR, which closely resembles the immunoprofiles of endometrioid and clear cell tumors. In contrast, intestinal-type mucinous tumors do not express ER and PR.⁶¹ Thus, three tumors, endometrioid, clear cell, and seromucinous carcinomas, all appear to be derived from endometriosis, and we refer to them as endometriosis-related neoplasms.

Mucinous Carcinoma and Malignant Brenner Tumor

Mucinous carcinomas typically display considerable heterogeneity, with foci of mucinous cystadenoma admixed with atypical proliferative tumor and obvious carcinoma. Laser capture microdissection studies have shown the identical *KRAS* mutation in all three components (adenoma, atypical proliferative, and carcinoma), supporting their clonal relation and thereby providing strong evidence that mucinous cystadenomas are the precursor lesions^{62,63}; the origin of mucinous cystadenomas, however, is not clear. A minority were found to develop from mucinous epithelium in teratomas, but most mucinous cystadenomas are not

associated with teratomas. It was proposed that these non-germ cell mucinous tumors are derived from Brenner tumors.⁶⁴

Mucinous tumors are typically large, whereas Brenner tumors tend to be smaller. Accordingly, it was suggested that expansion of the mucinous epithelium in the Brenner tumor leads to the development of a cystadenoma, which then compresses and obliterates the Brenner tumor.⁶⁴ This hypothesis was supported by a recent study showing that, in combined Brenner and mucinous tumors, the Brenner and mucinous components are clonally related.⁶⁵ It was argued that Brenner tumors arise from nests of transitional epithelium, so-called Walthard cell nests, which can be found adjacent to the fallopian tubes and ovaries at a site termed the tuboperitoneal junction.⁶ Meticulous sectioning of this region has found a relatively high frequency of nests of transitional metaplasia, which for all practical purposes are Walthard cell nests. Because they are small, they are easily missed in routine sampling.⁶ Accordingly, evidence is good that some mucinous neoplasms arise from teratomas and that others develop from Brenner tumors. This does not exclude the possibility that some mucinous tumors arise from other sources, but, at present, no data indicate what those sources might be.

Type II

HGSC

One of the main advances in our understanding of the pathogenesis of ovarian cancer that occurred in the past few years was the recognition that many HGSCs may develop from a precursor lesion in the fallopian tube, designated STIC (Table 2). This finding was first described in women at high risk of developing ovarian cancer or who had *BRCA* germline mutations, when they underwent risk-reducing salpingo-oophorectomy (RRSO).^{66–69} Interestingly, similar lesions were not detected in the ovary. This was surprising, because it had been assumed that the precursor of ovarian carcinoma would be in the ovary, although multiple studies in the past three decades failed to find a convincing ovarian precursor lesion. The detection of the lesion in the fallopian tube was due to the introduction of a new method of sampling the fallopian tube in which the entire fallopian tube, with particular attention to the fimbria, was sectioned, the so called sectioning and extensively examining the fimbria technique.⁷⁰ Subsequently, STICs were detected in 50% to 60% of women with sporadic HGSC when the fallopian tubes were completely processed with the sectioning and extensively examining the fimbria protocol.^{71,72} It has been argued that STIC may be a metastasis rather than a precursor of HGSC, but accumulating evidence supports STIC as a precursor lesion for at least many ovarian HGSCs. Briefly, STICs are detected in the absence of an ovarian carcinoma in women at high risk who are undergoing RRSO as noted earlier. More recently, incidental STICs were reported in women undergoing

hysterectomy and bilateral salpingo-oophorectomy for nonprophylactic reasons, who were not known to have *BRCA* mutations in both selected^{73,74} and unselected series.^{75–77} Other data that support STIC as a precursor are that, in women with a concomitant HGSC in the ovary and a STIC, the identical *TP53* mutation is found in both lesions.⁷⁸ In addition, STICs, compared with the concomitant ovarian tumor, have shorter telomeres,⁷⁹ and shortened telomeres are one of the earliest molecular changes in carcinogenesis. Finally, in molecularly engineered mouse models, inactivation of *BRCA*, *TP53*, and *PTEN* leads to the development of STICs and ovarian HGSC. When salpingectomy is performed at an early age, no cancers develop, whereas neither oophorectomy nor hysterectomy prevents the development of cancer.⁸⁰ A recent epidemiologic study showed that in women who had prior salpingectomy, the risk of developing HGSC was significantly decreased compared with that of women with intact fallopian tubes, further supporting the tubal origin of HGSC.^{81,82}

The diagnostic criteria of STIC are based on morphologic features and immunostaining profiles, which are summarized in a previous report.⁸³ Because STIC is a carcinoma confined to the epithelium, one would expect there to be lesions that are precursors of it; indeed, cytologic atypia in tubal epithelium that falls short of STIC was described and termed serous tubal intraepithelial lesions or tubal intraepithelial lesions in transition. In addition, stretches of normal tubal epithelium that express p53 and termed p53 signatures were reported,⁸⁴ but the significance, if any, of serous tubal intraepithelial lesions and p53 signatures and their relation to STIC have yet to be established.

On the basis of the clinicopathologic differences of the usual HGSC and the SET variant and their different relations to STICs and germline *BRCA1* mutations, some investigators have proposed that HGSCs may develop along two different pathways,^{34,85} with the usual HGSC developing from a STIC and the SET variant developing either from STIC, another tubal precursor, or from elsewhere.³⁸ Indeed, a case of a SET HGSC associated with a STIC showing the same morphology suggests that there may be different types of STICs.³⁴ This is an intriguing possibility and one that requires further investigation. The likelihood that other sites, such as the ovarian surface epithelium or ovarian cortical inclusion cysts, are sources of some HGSCs cannot be entirely excluded, but at this time only limited data support this view.

Carcinosarcoma (Malignant Mixed Müllerian Tumor)

Only a few small studies focused on their association with STICs were reported, and these have shown that STICs are a precursor.^{6,86}

Primary Peritoneal Carcinoma

Studies have shown they are frequently associated with STICs.^{6,77}

Implications for Diagnosis and Treatment Based on Molecular Features

Current management of ovarian cancer is radical surgery and chemotherapy, which are directed at established cancers, not at the mechanisms by which cells become neoplastic. These modalities are costly, the benefits are limited to lengthening the interval to relapse, and they have not substantially improved overall survival in >50 years. Cure remains elusive; therefore, new approaches that are based on understanding the molecular pathogenesis of ovarian cancer are needed. These approaches should focus on strategies aimed at prevention and screening, because they have proved effective for other diseases. For example, infectious diseases are prevented by vaccines, cardiovascular disease is greatly mitigated by changes in lifestyle (diet and exercise), and cervical cancer is mitigated by both prevention (vaccines) and screening. These methods are cheaper, easier to administer, and more effective than treatment of established disease.

Screening

Over the past two decades, clinical screening trials, primarily using transvaginal ultrasonography and serum cancer antigen 125 concentrations, have not shown a survival benefit.^{87,88} Their goal was to detect stage I disease (confined to the ovary) because studies have shown 90% survival for women with stage I disease compared with 30% survival for advanced stage disease.⁸⁹ Survival differences, however, are not due to stage distribution, but to the biology of type I compared with type II tumors. Type II tumors account for 90% of the deaths from ovarian cancer and are almost nonexistent in International Federation of Gynecology and Obstetrics stage I.⁸⁹ As discussed, the earliest precursor lesion of these neoplasms is STIC, a minute, microscopic intraepithelial carcinoma in the fallopian tube. Accordingly, the earliest events in the development of HGSC occur in the fallopian tube, and therefore, at inception, HGSC is already International Federation of Gynecology and Obstetrics stage II. Moreover, the microscopic size of the STIC is below the level of detection of current screening methods. Conversely, the tumors that present in stage I are type I neoplasms, which account for 10% of deaths from ovarian cancer.⁸⁹ They present as large cystic masses that can be detected manually on pelvic examination and by transvaginal ultrasound screening. To make a substantial impact on reducing rates of mortality, the focus must be on type II tumors, and the aim of screening should be directed at detecting a tumor early in its evolution with the use of highly sensitive biomarkers. A step in this direction was recently made with the development of a highly sensitive whole exome sequencing method with the use of a panel of genes commonly mutated in ovarian carcinomas. The test was performed on liquid cervical cytology

specimens collected in the operating room at the time patients underwent resection of their ovarian neoplasms. The same mutation was detected in the liquid cytology specimen as in the tumor in 41% of 22 early- and late-stage ovarian carcinomas.⁹⁰ Although the findings are encouraging, there were only a small number of patients. Clearly, additional large-scale clinical trials must be undertaken to determine whether the test will be useful in screening. The key question to be answered is whether this, or any other biomarker assay, can detect STICs or low-volume disease.

It is important to emphasize that, unlike the precursors of the type I tumors which are benign neoplasms, STICs share many of the morphologic and molecular features of HGSC; thus, once they have acquired the ability to spread, they disseminate as carcinoma. Although STIC is confined to the epithelium, the cells tend to be discohesive; therefore, dissemination can occur in the absence of invasion.⁹¹ At present, the transit time for a STIC to disseminate to other sites is not known. In an ultrasonographic study in which investigators attempted to detect early-stage epithelial ovarian cancer in asymptomatic high-risk women, it was found that for all of the cancers detected women had normal ultrasound and physical examinations 6 to 12 months before the cancer diagnosis.⁹² Although *BRCA1* and *BRCA2* mutation carriers with incidental invasive carcinoma at RRSO are reported to have a relatively high rate of tumor recurrence despite predominantly early-stage and small-volume disease, STICs rarely recur as carcinoma and may not require adjuvant chemotherapy.⁹³ However, a more recent study of women with germline *BRCA1/2* mutations with STICs discovered at RRSO reported recurrences 4 years later, suggesting a longer transit time from STICs to recurrent HGSC.⁹⁴

Prevention

Approximately 10% of women with ovarian cancer have a genetic predisposition on the basis of germline *BRCA* mutations, and these women have an increased risk of developing HGSC. Prophylactic bilateral salpingo-oophorectomy substantially reduces their risk of ovarian cancer. Removal of the ovaries at earlier ages, however, can have detrimental effects, as shown by the Nurses' Health Study of 30,000 women which compared hysterectomy and bilateral salpingo-oophorectomy with hysterectomy with ovarian conservation. This study found no overall survival benefit from bilateral oophorectomy at any age. In fact, a significant increase was found in the rate mortality from coronary heart disease, lung cancer, colorectal cancer, and from all causes.⁹⁵ Accordingly, the recent studies that identified the potential precursor of HGSCs in the fallopian tube have led to the adoption of bilateral salpingectomy with ovarian conservation, thus preserving fertility and hormone function. For high-risk women, the time at which salpingectomy should be performed has not been well established. Incidental STICs discovered in both women at high risk and in

women undergoing surgery for benign disease found that STICs were infrequently associated with invasion or disseminated disease younger than 50 years of age.^{73,74} It therefore appears that prophylactic surgery can be safely delayed for these women until the age of 45 years. The appropriate management of women who were found to have STIC in the absence of tumor elsewhere is controversial. Although the number of these cases is small, thus far, recurrences are rare,^{93,96} suggesting that perhaps not all STICs progress to HGSC. Some investigators have therefore proposed that women diagnosed with STIC after RRSO may not require adjuvant chemotherapy, but more cases should be analyzed to reach a conclusion.⁹³

Women who have taken oral contraceptive pills and women with increased parity have a substantially reduced risk of developing ovarian cancer, whereas women with germline *BRCA* mutations are at a substantially increased risk, but for the general population no other definitive risk factors were identified. As a result, it has not been possible to target a population of women who need to be screened. For many years, it was recommended that bilateral salpingo-oophorectomy be performed for women older than 40 years at the time of hysterectomy for benign disease, in an effort to reduce the future development of ovarian cancer. For these women, bilateral salpingectomy only is now being advocated.⁸² Similarly, it was recommended that salpingectomy rather than simply tubal ligation be performed for women desirous of a relatively permanent form of contraception. For the general population of women who are not known to be at high risk, other approaches besides bilateral salpingectomy should be explored. For example, as noted above, studies have shown about a 50% reduction in the risk of ovarian cancer with the use of oral contraceptive pills.⁹⁷ The mechanism by which this occurs is thought to be a reduction in the number of lifetime ovulatory cycles, because persistent ovulation has been proposed for many years to be an important event in the development of ovarian cancer. In addition, other drugs, such as statins,⁹⁸ which have been associated with a reduced risk of ovarian cancer, should be evaluated, because these drugs have relatively minimal side effects and are widely available. Statins were also recently reported in a preclinical mouse model to reduce the formation of STIC in mice.⁹⁹

Treatment

Type I tumors are mostly stage IA (confined to one ovary) and almost always low grade (except clear cell carcinoma). Removal of the affected ovary is generally curative. In contrast, metastatic type I tumors are, for the most part, chemoresistant, because of either slow proliferative activity or intrinsic mechanisms; however, because they are relatively genetically stable and contain activating mutations in genes that are actionable, targeted therapy such as kinase inhibitors may be beneficial. Moreover, those type I carcinomas that exhibit mismatch repair deficiency may benefit

from immune checkpoint inhibitors because those tumor cells produce numerous neo-antigens and are thus associated with abundant tumor-infiltrating lymphocytes due to extensive mutation load.¹⁰⁰ Those tumor-infiltrating cytotoxic T cells may potentially attack and kill tumor cells once the immune checkpoint is relieved by inhibitors. More recently, preclinical studies have found that type I tumors harboring *ARID1A* mutations are more sensitive to the treatment with the use of EZH2 inhibitor¹⁰¹ and polyADP ribose polymerase (PARP) inhibitor.¹⁰²

Although type II tumors are initially chemosensitive, as a result of their highly proliferative activity and defects in DNA repair capacity, chemoresistance almost always emerges. Recent genome-wide studies have elucidated the mechanisms underlying chemoresistance, and these may potentially lead to new therapeutic strategies that target these pathways.^{38,103} It should be noted that these new approaches may improve the progression-free survival, they are less likely to affect overall survival, underscoring the importance of early detection.

Tumors with *BRCA* abnormalities belong to a group of neoplasms that show deficiencies in homologous recombination, which is one of the main mechanisms that repair double-stranded DNA breaks. This is particularly important, because tumors with deficiencies of homologous recombination repair appear sensitive to PARP inhibitor therapy. As previously noted, the subset of women with HGSCs called the SET variant may have a more favorable prognosis than women with the usual type of HGSC, because these tumors are more sensitive to chemotherapy, particularly PARP therapy.¹⁰⁴ The mechanism for this increase in chemosensitivity is thought to result from deficiencies in homologous recombination repair. This defect may occur not only in association with germline mutant *BRCA1* but also in tumors that contain somatic *BRCA* mutations and epigenetic silencing of *BRCA* expression, and those showing *BRCA* genomic signatures or scarring (collectively, so-called BRCAness).^{38,100} The effectiveness of PARP inhibitor therapy in which *BRCA* inactivation occurs as a result of promoter methylation is likely through synthetic lethality but needs to be further explored. This has important implications because TCGA study found that one-half of all HGSCs have abnormalities in the homologous recombination repair pathway.³⁷ In addition to the therapeutic implications, recognition of the SET variant can be used to direct genetic testing to this group of individuals, as opposed to testing all women with HGSCs.²⁷

Summary

In the expanded dualistic model, type I carcinomas have now been divided into three subtypes as follows: i) endometriosis-related (endometrioid, clear cell, and seromucinous or mixed müllerian neoplasms), ii) tubal-related (low-grade serous tumors), and iii) germ cell or transitional cell-related (mucinous

and Brenner tumors). The first two groups are derived from Müllerian tissues, whereas some gastrointestinal-type mucinous tumors develop from mature teratomas in the ovary and others from an outgrowth of mucinous epithelium in Brenner tumors. The latter may develop from transitional epithelium (transitional metaplasia; i.e., Walthard cell nests) at the tuboperitoneal junction. The precursor lesions of the type I carcinomas are benign, ie, endometriosis, papillary tubal hyperplasia, and transitional epithelium, which implant on the ovary and then progress in a stepwise fashion to adenomas and atypical proliferative tumors before undergoing malignant transformation. In contrast, many type II carcinomas, at their inception, are established carcinomas (STIC) arising in the fimbria and capable of implanting on the ovary and other sites in the pelvic and abdominal cavities. This difference in the nature of the precursor lesions may explain why type I carcinomas remain confined to the ovary for long periods and have an indolent course, whereas type II carcinomas spread rapidly and are highly aggressive at their onset. Many type II carcinomas appear to be derived from tubal type epithelium and are therefore of Müllerian origin. Preliminary morphologic data suggest that they can be divided into two subsets as follows: the usual and SET variants. The usual type is more frequently associated with STICs, whereas the SET variant is more often associated with *BRCA* mutations. In addition, gene expression analysis has identified four molecular subtypes of HGSCs, termed immunoreactive, differentiated, proliferative, and mesenchymal.

In summary, recent molecular studies underline the heterogeneity of ovarian cancer, both for type I and type II tumors, demonstrating that ovarian cancer is a family of related but distinct tumors with substantial differences in molecular features, clinicopathologic characteristics, and behavior. The dramatic differences between the type I and type II tumors, in fact, argue that they describe two completely different groups of diseases. An appreciation of the different biology of these tumors should lead to a more informed approach toward prevention, diagnosis, and treatment, thereby reducing the burden of this devastating disease.

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