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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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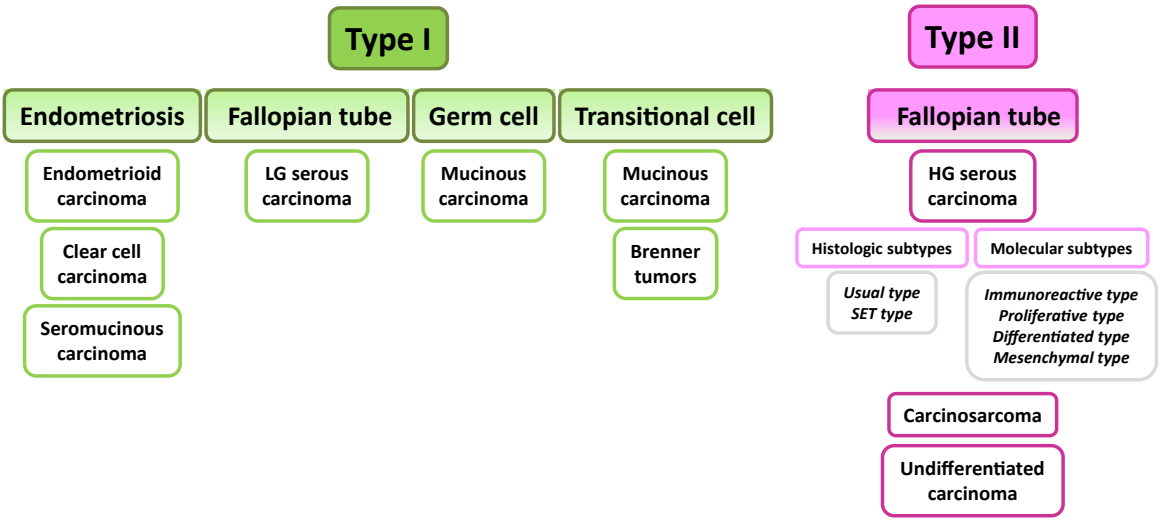

Figure 1 Expanded dualistic model of ovarian carcinogenesis. Ovarian carcinomas derive from endometrial tissue, fallopian tube tissue, germ cells, and transitional epithelium. Type I carcinomas comprise endometrioid, clear cell, LG serous, and mucinous carcinomas. Seromucinous carcinomas and malignant 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 *Morphologic and Molecular Features of Precursor Lesions*	Mostly tubal
Precursors	Atypical proliferative (borderline) tumors	Mostly STICs
Chromosomal instability	Low	High
TP53 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.