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Review

Ovarian Tumorigenesis

A Proposed Model Based on Morphological and Molecular Genetic Analysis

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The pathogenesis of ovarian carcinoma, the most lethal gynecological malignancy, is unknown because of the lack of a tumor progression model. Based on a review of recent clinicopathological and molecular studies, we propose a model for their development. In this model, surface epithelial tumors are divided into two broad categories designated type I and type II tumors that correspond to two main pathways of tumorigenesis. Type I tumors tend to be low-grade neoplasms that arise in a stepwise manner from borderline tumors whereas type II tumors are high-grade neoplasms for which morphologically recognizable precursor lesions have not been identified, so-called *de novo* development. As serous tumors are the most common surface epithelial tumors, low-grade serous carcinoma is the prototypic type I tumor and high-grade serous carcinoma is the prototypic type II tumor. In addition to low-grade serous carcinomas, type I tumors are composed of mucinous carcinomas, endometrioid carcinomas, malignant Brenner tumors, and clear cell carcinomas. Type I tumors are associated with distinct molecular changes that are rarely found in type II tumors, such as *BRAF* and *KRAS* mutations for serous tumors, *KRAS* mutations for mucinous tumors, and β-catenin and *PTEN* mutations and microsatellite instability for endometrioid tumors. Type II tumors include high-grade serous carcinoma, malignant mixed mesodermal tumors (carcinosarcoma), and undifferentiated carcinoma. There are very limited data on the molecular alterations associated with type II tumors except frequent p53 mutations in high-grade serous carcinomas and malignant mixed mesodermal tumors (carcinosarcomas). This model of carcinogenesis reconciles the relationship of borderline tumors to invasive carcinoma and provides a morphological and molecular framework for studies aimed at elucidating the pathogenesis of ovarian cancer. *(Am J Pathol 2004, 164:1511–1518)*

Ovarian cancer is the most lethal gynecological malignancy and surface epithelial tumors (carcinomas) are the most common type of ovarian cancer. Despite considerable efforts aimed at elucidating the molecular mechanisms of ovarian carcinoma, its pathogenesis is still unknown, because unlike colorectal carcinoma,[1] a progression model has not been described. Ovarian carcinomas are heterogeneous and are primarily classified by cell type into serous, mucinous, endometrioid, clear cell, and Brenner (transitional) tumors corresponding to different types of epithelia in the organs of the female reproductive tract.[2–4] The tumors in each of the categories are further subdivided into three groups, benign, malignant, and intermediate (borderline tumor) to reflect their behavior. Mucinous and endometrioid borderline tumors are often associated with invasive carcinomas but serous borderline tumors are rarely associated with serous carcinomas.[2] This latter observation as well as recent molecular genetic studies showing a very different frequency of p53 and *KRAS* mutations in serous carcinoma as compared to serous borderline tumors have led most investigators to conclude that serous borderline tumors and serous carcinomas are unrelated.[5–9] The uncertainty about the nature of the borderline group of tumors, reflected by the ambiguous term "borderline," is a major shortcoming of the current classification. Here we review recent histopathological and molecular genetic

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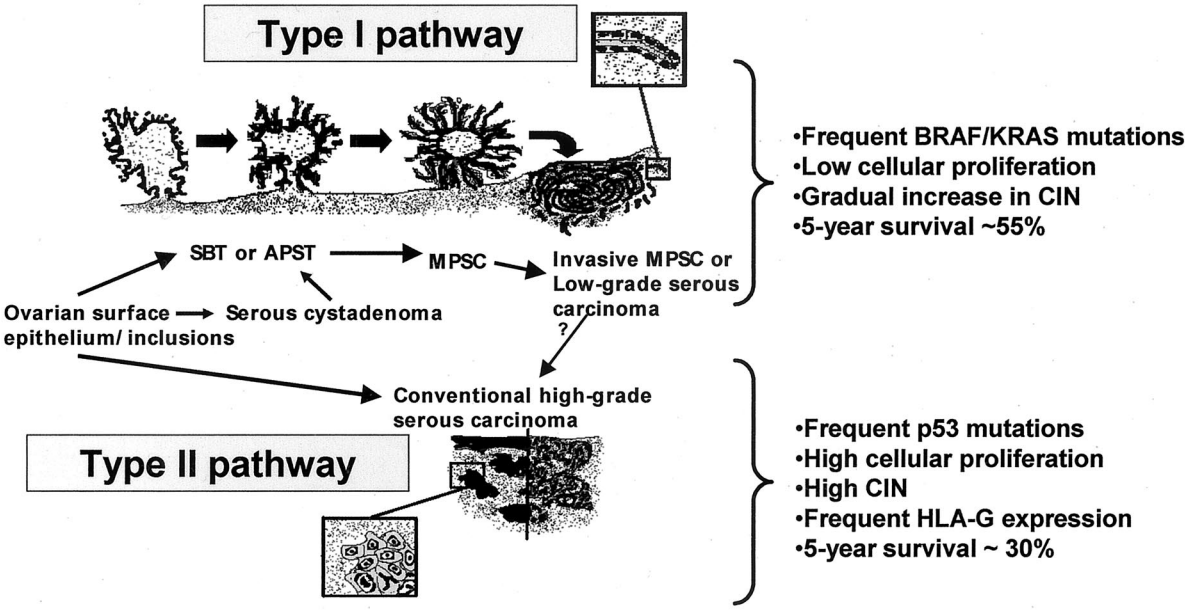

Figure 1. Schematic representation of the dualistic model depicting the development of ovarian serous carcinomas, the most common type of ovarian cancer. Low-grade serous carcinoma (MPSC) represents the prototypic type I tumor and develops in a stepwise manner from an atypical proliferative tumor through a noninvasive stage of MPSC (both of these tumors qualified as borderline) before becoming invasive. These tumors are associated with frequent *KRAS* or *BRAF* mutations. High-grade serous carcinoma represents the prototypic type II tumor and develops from the ovarian surface epithelium or inclusion cysts without morphologically recognizable intermediate stages. *KRAS* and *BRAF* mutations have been rarely found in these neoplasms. CIN, chromosomal instability.

studies to re-examine this issue and propose a model of ovarian carcinogenesis that integrates clinical, histopathological, and molecular genetic findings.

Clinical and Pathological Observations that Provide the Basis for the Proposed Model

Throughout the last 10 years, we have conducted a systematic microscopic and clinical analysis of a large number of noninvasive and invasive epithelial ovarian tumors of all histological types in an effort to delineate their pathogenesis and behavior.[2,10–12] These studies drew attention to a subset of low-grade serous tumors designated "micropapillary serous carcinoma (MPSC)" with characteristic histopathological features, low proliferative activity, and an indolent behavior that contrasts dramatically with the conventional type of serous carcinoma, an aggressive neoplasm that is high-grade and has high proliferative activity.[2,10–12] The term "MPSC" was originally proposed to distinguish the noninvasive form of this tumor from the more common noninvasive tumor, termed an "atypical proliferative serous tumor," both of which have been included under the rubric "borderline" or "low malignant potential."[10,12] Histological transitions from adenofibromas and atypical proliferative serous tumors to noninvasive MPSCs are observed in nearly 75% of cases.[13] In addition, areas of infiltrative growth (stromal invasion) immediately adjacent to the noninvasive component are found in a significant proportion of cases (Figure 1).[13] These invasive MPSCs are synonymous with low-grade serous carcinoma. The former term describes its histopathological features and the latter its clinical behavior. The histopathological findings strongly suggest that there is a morphological and biological spectrum beginning with a benign serous cystadenoma/adenofibroma, through a proliferative tumor (atypical proliferative serous tumor) to a noninvasive carcinoma (noninvasive MPSC) ending with an invasive low-grade serous carcinoma (invasive MPSC).

Low-grade serous carcinomas typically pursue an indolent course that may last more than 20 years.[12,13] Approximately 50 to 60% of patients ultimately succumb because of widespread intra-abdominal carcinomatosis but the tumor maintains its low-grade appearance and low proliferative index throughout its course (Silva et al, 1997 and unpublished data).[13] This contrasts with conventional high-grade serous carcinoma that presents as a clinically aggressive neoplasm that spreads rapidly and is associated with a poor outcome. Analysis of mucinous, endometrioid, clear cell carcinomas, and malignant Brenner tumors reveals that they are often associated with cystadenomas, borderline tumors, and intraepithelial carcinomas.[2] Furthermore, it has been long recognized that endometrioid carcinoma and clear cell carcinoma are associated with endometriosis in the ovary or pelvis in 15 to 50% of cases[14,15] leading investigators to propose that endometriosis is a precursor of these tumors. Rarely, a high-grade serous carcinoma is associated with ovarian endometriosis but this is viewed as an independent, coincidental finding; a causal relationship of endometriosis and serous carcinoma has never been proposed. A recent clinical study using serial transvaginal ultrasonography has shown that ~50% of ovarian carcinomas develop from pre-existing cystic lesions whereas the remaining 50% develop in ovaries without apparent abnormality on ultrasound.[16] The former group

Table 1. Precursors and Molecular Genetic Alterations of Type I Tumors of the Ovary

Type I tumors	Precursors*	Known molecular genetic alterations
Low-grade serous carcinoma (invasive MPSC)	Serous cystadenoma/adenofibroma Atypical proliferative serous tumor Noninvasive MPSC	*BRAF* and *KRAS* mutations (~67%)
Mucinous carcinoma	Mucinous cystadenoma Atypical proliferative mucinous tumor Intraepithelial carcinoma	*KRAS* mutations (>60%)
Endometrioid carcinoma	Endometriosis Endometrioid adenofibroma Atypical proliferative endometrioid tumor Intraepithelial carcinoma	LOH or mutations in *PTEN* (20%) β-catenin gene mutations (16–54%) *KRAS* mutations (4–5%) Microsatellite instability (13–50%)
Clear cell carcinoma	Endometriosis Clear cell adenofibroma Atypical proliferative clear cell tumor Intraepithelial carcinoma	*KRAS* mutations (5–16%) Microsatellite instability (~13%) TGF-β RII mutation (66%)†
Malignant Brenner (transitional) tumor	Brenner tumor Atypical proliferative Brenner tumor	Not yet identified

Abbreviation: MPSC, micropapillary serous carcinoma; LOH, loss of heterozygosity; TGF, transforming growth factor.
*Atypical proliferative serous tumors and noninvasive MPSC have been termed "borderline" tumors in the literature. Similarly for mucinous, endometrioid, clear cell, and Brenner tumors, atypical proliferative tumor and intraepithelial carcinoma have been combined and designated "borderline tumor" in the literature.
†Based on preliminary results analyzing three cases.[57]

was composed mainly of mucinous, endometrioid, clear cell carcinomas, and borderline tumors whereas the latter group was composed almost exclusively of high-grade serous carcinomas. This distribution corresponds to the type I and II tumors described below.

A Proposed Model of Ovarian Carcinogenesis

Our clinicopathological and molecular genetic studies provide the basis for a proposed model of ovarian carcinogenesis in which there are two main pathways of tumorigenesis, corresponding to the development of type I and type II tumors (Tables 1 and 2). It should be emphasized that the terms, type I and type II, describe pathways of tumorigenesis and are not specific histopathological terms. Type I tumors (low-grade serous carcinoma, mucinous carcinoma, endometrioid carcinoma, malignant Brenner tumor, and clear cell carcinoma) develop in a stepwise manner from well-recognized precursors, namely borderline tumors that in turn develop from cystadenomas and adenofibromas (Figure 1 and Table 1).[5] The latter benign tumors appear to develop from the surface epithelium or inclusion cysts in the case of serous and mucinous tumors and from endometriosis or endometriomas in the case of endometrioid and clear cell tumors. Type I tumors are slow growing as evidenced by the observation that they are large and often confined to the ovary at diagnosis. In contrast, type II tumors are high-grade at presentation. Type II carcinomas include what are currently classified as high-grade serous carcinoma (moderately and poorly differentiated), malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinoma (Figure 1 and Table 2). In addition, it is likely that some high-grade serous and undifferentiated carcinoma containing cells with clear cytoplasm have been classified as clear cell carcinoma and would be included in this group. Although malignant mixed mesodermal tumors (carcinosarcomas) were once thought to be mixed tumors comprised of carcinoma and sarcoma, recent studies have demonstrated that they are monoclonal.[17,18] Accordingly, these tumors are now regarded as high-grade carcinomas with metaplastic sarcomatous elements. Type II carcinomas are rarely associated with morphologically recognizable precursor lesions and it has been proposed that they develop *de novo* from the surface epithelium or inclusion cysts of the ovary.[7] They evolve rapidly, metastasize early in their course, and are highly aggressive. It is likely that the apparent *de novo* conventional high-grade serous carcinoma does develop in a stepwise manner but precursor lesions have not yet been elucidated molecularly or morphologically (Figure 1). Presumably, this is because of rapid transit from inception as a microscopic carcinoma to a clinically diagnosed neoplasm. This is supported by

Table 2. Precursors and Molecular Genetic Alterations of Type II Tumors of the Ovary

Type II tumors*	Precursors	Known molecular genetic alterations
High-grade serous carcinoma	Not yet identified	*p53* mutations (50–80%) Amplification and overepxression of *HER2/neu* gene (10%–20%) and *AKT2* gene (12%–18%) Inactivation of *p16* gene (10%–17%)
Undifferentiated carcinoma	Not yet identified	Not yet identified
Malignant mixed mesodermal tumor (carcinosarcomas)	Not yet identified	*p53* mutations (> 90%)

*Type II tumors can contain neoplastic cells with clear cytoplasm and have sometimes been classified as "clear cell carcinoma."

Table 3. Summary of Clinicopathological Features of the Prototypic Type I and Type II Tumors: Low-Grade and High-Grade Serous Carcinoma, Respectively

	Frequency	Histologic features	Precursor lesions	Clinical behavior†	Response to chemotherapy
Low grade	~25% of serous carcinomas*	Micropapillary architecture; low-grade nuclei; low mitotic index	Serous cystadenoma Serous atypical proliferative (borderline) tumor	Indolent; slow progression 5-year survival ~55%‡	Poor
High grade	~75% of serous carcinomas*	Solid nests and masses; high-grade nuclei; high mitotic index	Not known; probably from ovarian surface epithelium or inclusion cysts (*de novo*)	Aggressive; rapid progression; 5-year survival~30%	Good, although recurrence is common

*Based on a survey at the Johns Hopkins Hospital. Most patients will eventually die from the disease after a protracted clinical course.
†Advanced stage tumors.
‡See Sehdev et al.[13]

the significantly higher Ki-67 nuclear labeling (proliferation) index in conventional high-grade serous carcinomas compared to low-grade serous carcinomas (unpublished data).[19]

This dualistic model is the first step in an attempt to elucidate the molecular pathogenesis of ovarian carcinoma, but should not be construed as implying that other pathways of tumorigenesis do not exist. For example, it is not certain whether there are other subsets of type II carcinomas. Molecular profiling and epidemiological studies will be important to determine whether there are distinct subsets of type II tumors. Also it is not clear whether some low-grade serous carcinomas (type I) progress to high-grade serous carcinomas (type II). We have observed serous carcinomas with high-grade nuclei and abundant mitotic activity that display a micropapillary architecture, simulating invasive MPSC (low-grade serous carcinoma). We thought that these high-grade tumors may have arisen from invasive MPSCs (low-grade serous carcinoma) but like conventional high-grade tumors without a micropapillary architecture these tumors did not harbor *KRAS* mutations, indicating that they are not derived from invasive MPSCs (low-grade serous carcinomas) (see below).[20] These data are preliminary and do not rule out the possibility that some low-grade serous carcinomas progress to high-grade carcinomas but the findings do support the view that ovarian serous carcinomas can be graded into low- and high-grade based on nuclear rather than architectural features. Preliminary clinicopathological studies of other type I carcinomas (mucinous, endometrioid, and clear cell carcinomas) have demonstrated that some are moderately and even poorly differentiated, suggesting that some type I carcinomas can evolve from low- to high-grade neoplasms.

Molecular Evidence Supporting the Dualistic Model

Serous carcinoma is the most common type of ovarian carcinoma and therefore low-grade and high-grade serous carcinomas serve as the prototypes of type I and type II carcinomas, respectively (Table 3). Accordingly, the molecular genetic data that are being advanced in support of the dualistic model are derived mainly from studies of serous carcinoma.

There are several distinctive molecular changes that distinguish low-grade and high-grade serous carcinomas (Table 4). Among them, the most significant molecular genetic alterations are mutations in *BRAF* and *KRAS* oncogenes. The *RAS*, *RAF*, *MEK*, *ERK*, and *MAP* cascade is important for the transmission of growth signals into the nucleus.[21] Oncogenic mutations in *BRAF* and *KRAS* result in constitutive activation of this pathway and contribute to neoplastic transformation. Recent studies have demonstrated that *KRAS* mutations at codons 12 and 13 occur in 35% of low-grade serous carcinomas (invasive MPSCs) and 33% of borderline tumors (atypical proliferative tumor and noninvasive MPSC) but not in high-grade serous carcinomas.[5,20] Similarly, *BRAF* mutations at codon 599 occur in 30% of low-grade serous carcinomas and 28% of borderline tumors but not in high-grade serous carcinomas.[20] Mutations in *BRAF* and *KRAS*, therefore, were found in 65% of low-grade invasive serous carcinomas and in 61% of atypical proliferative tumors and noninvasive MPSCs, their putative precursors, but neither of the genes was mutated in high-grade serous carcinomas. It is of interest that *BRAF* mutations were found only in tumors with wild-type *KRAS*.[20] The mutually

Table 4. Summary of Molecular Features of Prototypic Type I and Type II Tumors: Low-Grade and High-Grade Serous Carcinoma, Respectively

	KRAS mutations	*BRAF* mutations	*BRAF* or *KRAS* mutations	*TP53* mutations	HLA-G expression	Proliferation (Ki-67) index
Low grade	35%	30%	65%	0	0	~10–15%
High grade	0	0	0	50%~80%	61%	>50%

exclusive nature of *BRAF* mutations at codon 599 and *KRAS* mutations at codons 12 and 13 in ovarian carcinoma is consistent with similar findings in melanoma and colorectal carcinoma[22,23] and lends support for the view that *BRAF* and *KRAS* mutations have an equivalent effect on tumorigenesis. Mutations of *BRAF* and *KRAS* seem to occur very early in the development of low-grade serous carcinoma as evidenced by the detection of these mutations in small atypical proliferative serous tumors but not in serous cystadenomas.[24] These data provide cogent evidence that the development of conventional high-grade serous carcinomas involves molecular mechanisms not related to mutations in *BRAF* and *RAS*.

In contrast to low-grade serous carcinoma in which mutations in *p53* are rare, mutations in *p53* are common in high-grade serous carcinomas. Most studies have shown that ~50 to 80% of advanced stage, presumably high-grade, serous carcinomas have mutant *p53*.[25–29] It has also been reported that mutant *p53* is present in 37% of stage I and II presumably high-grade serous carcinomas.[30] In a study of very early microscopic stage I serous carcinomas in ovaries removed prophylatically from women who were BRCA heterozygotes, overexpression of p53 and mutation of *p53* were found in all early invasive high-grade serous carcinomas as well as in the adjacent dysplastic surface epithelium.[31] It is likely that inherited mutations in BRCA genes predispose the ovarian surface epithelium and inclusion cysts to neoplastic transformation through an increase in genetic instability. Although sporadic ovarian carcinomas were not analyzed in this study, the clinical and pathological features of BRCA-linked ovarian carcinomas and their sporadic counterparts are indistinguishable, suggesting that their histogenesis may be similar. Thus, although the findings are preliminary, they suggest that conventional high-grade serous carcinoma, in its very earliest stage resembles advanced stage serous carcinoma at a molecular as well as at a morphological level. Similar to high-grade serous carcinoma, malignant mixed mesodermal tumors (carcinosarcomas) also demonstrate *p53* mutations in almost all cases analyzed.[32–34] It has been reported that the same *p53* mutations occur in the epithelial and the mesenchymal components.[32] Moreover, the fact that pure carcinomatous areas are often associated with sarcomatous components suggests a common derivation of both the epithelial and the mesenchymal components in these neoplasms.[35] The finding that metastases from these tumors nearly always are composed exclusively of carcinoma has led investigators to suggest that malignant mixed mesodermal tumors are metaplastic carcinomas.

In addition to p53 mutations, conventional serous carcinomas that are presumably high-grade demonstrate amplification/overexpression of HER-2/neu tyrosine kinase gene in 20 to 67%[36] and AKT2 serine/threonine kinase gene in 12 to 18% of samples analyzed.[37,38] In contrast, amplification of both genes is rare in borderline tumors. Inactivation of the p16 gene because of promoter methylation, mutation, or homozygous deletion occurs in a variety of human cancers including conventional ovarian serous carcinoma that presumably are high grade.[39] Because these are molecular genetic studies in which the tumors were described simply as "serous carcinomas," we have referred to them as "presumably high-grade" because the vast majority of serous carcinomas are high grade.

Besides molecular genetic alterations, both low-grade and high-grade serous carcinomas are characterized by distinct gene expression profiles. For example, transcriptome-wide gene expression profiling has demonstrated that human leukocyte antigen-G (HLA-G) and apolipoprotein E (apoE) are overexpressed in most high-grade serous carcinomas but rarely in low-grade serous carcinomas. HLA-G immunoreactivity, ranging from focal to diffuse, was detected in 45 of 74 (61%) high-grade ovarian serous carcinomas but in none of the 18 low-grade serous carcinomas or 26 serous borderline tumors (atypical proliferative tumors and noninvasive MPSCs) that were studied.[40] A similar correlation of HLA-G expression with behavior has been observed in large cell carcinoma.[41] A possible mechanism that explains the association of HLA-G expression with prognosis is that HLA-G seems to facilitate tumor cell evasion of the immune system by protecting malignant cells from lysis by natural killer cells.[42]

Recently, apoE expression has been detected in ovarian tumors. Besides the well-known role of apoE in cholesterol transport and in the pathogenesis of atherosclerogenesis and Alzheimer's disease, apoE may play a novel role in the development of human cancer. In ovarian carcinomas, expression of apoE is primarily confined to type II high-grade serous carcinoma because apoE immunoreactivity has been detected in 66% of high-grade but only 12% of low-grade serous carcinomas. In contrast, apoE immunoreactivity was not detected in normal ovarian surface epithelium, serous cystadenomas, serous borderline tumors, and other type I tumors (Chen, unpublished data). Inhibition of apoE expression *in vitro* induces cell-cycle arrest and apoptosis in apoE-expressing ovarian cancer cells, suggesting that apoE expression is important for their growth and survival.

The genes that are specifically expressed in other types of ovarian carcinomas remain primarily unknown. Recently, hepatocyte nuclear factor-1β and glutathione peroxidase 3 have been reported as molecular markers for ovarian clear cell carcinoma because both genes are highly expressed in ovarian clear cell carcinomas but rarely in other ovarian carcinomas.[43,44]

Finally, allelic imbalance (calculated as the number of SNP markers with allelic imbalance/total SNP markers examined) has been assessed in atypical proliferative tumors, noninvasive MPSCs, and low-grade serous carcinoma (invasive MPSC).[5] A progressive increase in the degree of allelic imbalance of chromosomes 1p, 5q, 8p, 18q, 22q, and Xp was noted when comparing atypical proliferative tumors with noninvasive and low-grade serous carcinomas (invasive MPSCs). In particular, allelic imbalance of chromosome 5q was more frequently observed in noninvasive MPSCs compared with atypical proliferative tumors and allelic imbalance of chromosome 1p was more frequently found in low-grade serous carcinoma (invasive MPSC) compared with noninvasive MPSCs. The allelic imbalance patterns in atypical prolif-

erative tumors were also found in noninvasive MPSCs containing adjacent atypical proliferative tumor components, further supporting the view that atypical proliferative tumors are the precursors of MPSCs. In contrast, all high-grade serous carcinomas including the very earliest tumors (less than 8 mm confined to one ovary) showed high levels of allelic imbalance. As allelic imbalance reflects chromosomal instability, the above findings suggest a step-wise increase in chromosomal instability in the progression to low-grade serous carcinoma in contrast to a high level of chromosomal instability in high-grade serous carcinoma even in their earliest stage of development.

The stepwise progression of borderline tumors (atypical proliferative tumor and noninvasive MPSC) to low-grade serous carcinoma (invasive MPSC) closely approximates the adenoma-carcinoma sequence in colorectal carcinoma and the progression of the other type I carcinomas, specifically mucinous and endometrioid carcinoma. In mucinous carcinoma for example, morphological transitions from cystadenoma to an atypical proliferative tumor (borderline tumor), to intraepithelial carcinoma and invasive carcinoma have been recognized for some time and an increasing frequency of *KRAS* mutations at codons 12 and 13 has been described in cystadenomas, borderline tumors, and mucinous carcinomas, respectively.[8,45–48] In addition, using microdissection, the same *KRAS* mutation has been detected in mucinous carcinoma and in the adjacent mucinous cystadenoma and borderline tumor.[45] Likewise, in endometrioid carcinomas, mutation of β-catenin has been reported in approximately one-third of cases[49,50] and mutation of *PTEN* in 20%, rising to 46% in those tumors with 10q23 loss of heterozygosity.[51] These mutations are generally detected in well-differentiated, stage I tumors with a good prognosis, suggesting that inactivation of these genes is an early event. Moreover, similar molecular genetic alterations including loss of heterozygosity at 10q23 and mutations in *PTEN* have been reported in endometriosis, atypical endometriosis, and ovarian endometrioid carcinoma in the same specimen.[51–56] The molecular genetic findings together with the morphological data showing a frequent association of endometriosis with endometrioid adenofibromas, atypical proliferative (borderline) tumors, adjacent to invasive well-differentiated endometrioid carcinoma provide evidence of stepwise tumor progression in the development of endometrioid carcinoma. Clear cell carcinoma is also frequently associated with endometriosis, clear cell adenofibromas, and clear cell atypical proliferative (borderline) tumors but molecular evidence for the stepwise progression model is lacking because molecular markers specific to clear cell neoplasms have only recently been identified.[43,44] Transforming growth factor-β receptor type II has been found to be mutated in the kinase domain in two of three clear cell carcinomas but rarely in other histological types of ovarian carcinomas.[57] Microsatellite instability is present in endometrioid and clear cell carcinoma but is only rarely detected in serous and mucinous tumors.[58,59] These findings provide further evidence of the close relationship of endometrioid and clear cell carcinoma and point to a common precursor lesion for these two neoplasms.

Conclusion

Based on morphological and molecular genetic analyses of a large series of ovarian tumors, we have proposed a tumor progression model for ovarian carcinoma. In this model, ovarian tumors are divided into two broad categories designated type I and type II. These designations refer to pathways of tumorigenesis and are not specific histopathological terms. Type I tumors include low-grade serous carcinoma, mucinous carcinoma, endometrioid carcinoma, malignant Brenner tumors, and clear cell carcinoma. Type II tumors are composed of what are currently classified as moderately and poorly differentiated serous carcinoma (high-grade serous carcinoma), malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinoma. Some of the latter may contain cells with clear cytoplasm and have therefore been classified erroneously as clear cell carcinomas. The tumorigenic pathway for type I tumors resembles the adenoma-carcinoma sequence in colorectal cancer and is characterized by clearly recognized precursor lesions, namely, cystadenoma, atypical proliferative tumor, and noninvasive carcinoma. The latter two noninvasive tumors have traditionally been combined into one category designated "borderline." Type I tumors evolve slowly and are associated with distinct molecular changes that are rarely found in type II tumors such as mutations in *BRAF* and *KRAS* for serous tumors, *KRAS* mutations for mucinous tumors, and β-catenin and *PTEN* mutations for endometrioid tumors. In contrast, type II tumors evolve rapidly, arising directly from the surface epithelium or inclusion cysts and metastasize early in their course. There are very limited data on the molecular alterations associated with type II tumors except frequent mutations of p53 in high-grade serous carcinomas and malignant mixed mesodermal tumors (carcinosarcomas). This model reconciles the inconsistency in the current classification of ovarian tumors that regards borderline tumors as a distinct entity unrelated to invasive carcinoma and provides a morphological and molecular genetic framework for future studies aimed at elucidating the pathogenesis of ovarian cancer. Unraveling the complex molecular genetic pathways involved in ovarian carcinogenesis will require correlated morphological and molecular genetic studies. Identification and characterization of the panoply of molecular changes associated with ovarian carcinogenesis will facilitate development of diagnostic tests for early detection of ovarian cancer and for the development of novel therapies aimed at blocking key growth-signaling pathways.

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