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Pathogenesis of Ovarian Cancer. Lessons from Morphology and Molecular Biology and their Clinical Implications

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Abstract

The received view of ovarian carcinogenesis is that carcinoma begins in the ovary, undergoes progressive “dedifferentiation” from a well to a poorly differentiated tumor and then spreads to the pelvic and abdominal cavities before metastasizing to distant sites. It has therefore been reasoned that survival for this highly lethal disease could be improved by developing screening methods that detect disease when it is confined to the ovary. To date, however, no prospective, randomized trial of any ovarian cancer screening test(s) has demonstrated a decrease in mortality. We believe that one of the main reasons for this is that the dogma underlying ovarian carcinogenesis is flawed. Based on studies performed in our laboratory over the last decade we have proposed a model of ovarian carcinogenesis that takes into account the diverse nature of “ovarian cancer” and correlates the clinical, pathologic and molecular features of the disease. In this model, ovarian tumors are divided into two groups designated Type I and Type II. Type I tumors are slow growing, generally confined to the ovary at diagnosis and develop from well established precursor lesions that are termed “borderline” tumors. Type I tumors include low-grade micropapillary serous carcinoma, mucinous, endometrioid, and clear cell carcinomas. They are genetically stable and are characterized by mutations in a number of different genes including *KRAS*, *BRAF*, *PTEN*, and *beta-catenin*. Type II tumors are rapidly growing, highly aggressive neoplasms for which well defined precursor lesions have not been described. Type II tumors include high-grade serous carcinoma, malignant mixed mesodermal tumors (carcinosarcomas) and undifferentiated carcinomas. This group of tumors has a high level of genetic instability and is characterized by mutation of *TP53*. The model helps to explain why current screening techniques, aimed at detecting stage I disease, have not been effective. Tumors that remain confined to the ovary for a long period of time belong to the Type I group but they account for only 25% of the malignant tumors. The vast majority of what is considered “ovarian cancer” belongs to the Type II category and these are only rarely confined to the ovary. Although the reasons for this are not entirely clear, it appears that some tumors evolve rapidly and spread to extra-ovarian sites early in their development. In addition, a significant number of Type II “ovarian carcinomas” develop outside the ovary, specifically, the peritoneum and fallopian tube, and involve the ovary secondarily. These tumors are advanced stage at their inception. Therefore, a more realistic endpoint for the early detection of ovarian carcinoma may be volume and not stage of disease. Thus, the model which correlates the clinical and pathologic features of “ovarian cancer” with the specific molecular genetic events that play a role in tumor progression can lead to a more rational approach to early detection and to more targeted therapeutic intervention.

The received view of ovarian carcinogenesis is that carcinoma begins in the ovary, undergoes progressive “dedifferentiation” from a well to a poorly differentiated tumor and then spreads to the pelvic and abdominal cavities before metastasizing to distant sites. It is also believed that since serous borderline tumors (SBTs) are rarely associated with invasive serous carcinoma they are a distinct entity unrelated to invasive carcinoma. However, SBTs sometimes progress to carcinoma and therefore some relationship must exist. In contrast, mucinous borderline tumors (MBTs) are often associated with invasive mucinous carcinoma. These disparate

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findings suggest that some borderline tumors are precursors of invasive carcinoma and others are not. In the past several years, clinicopathologic and molecular genetic analyses performed on a large number of borderline ovarian tumors and invasive carcinomas (1–4) by our research group have elucidated the relationship of borderline ovarian tumors to invasive cancer. Based on these studies a model of ovarian carcinogenesis for all the surface epithelial tumors has been proposed which reconciles the difference in the relationship of SBTs and MBTs to their respective carcinomas. The model divides surface epithelial tumors into two groups designated Type I and Type II (1,5). Type I tumors tend to be low grade, indolent neoplasms that arise from well characterized precursor lesions, specifically borderline tumors (6). The Type I group includes low-grade micropapillary serous carcinoma (MPSC), mucinous carcinoma, endometrioid carcinoma and clear cell carcinoma. In contrast, Type II tumors are aggressive and high grade from the outset and since precursor lesions have not been identified, have been said to arise *de novo* (7). Included in this group are high grade serous carcinoma, malignant mixed mesodermal tumors (MMMTs) and undifferentiated carcinomas. In addition to the clinical and pathologic differences, molecular genetic studies have shown that Type I tumors are relatively genetically stable and are characterized by a number of different mutations whereas the Type II tumors show considerable genetic instability. The mutations that characterize Type I tumors are not detected in Type II tumors whereas the vast majority of Type II tumors contain mutant p53 which is only rarely found in Type I tumors (1,8). This model does not replace the standard histopathologic classification of ovarian carcinoma, its purpose is to provide a framework for the study of ovarian carcinogenesis. The model, by drawing attention to molecular genetic pathways that play a role in tumor progression, can shed light on new approaches to early detection and novel methods of treatment.

Serous Tumors

The relationship of SBTs to invasive carcinoma has puzzled investigators since the category was created by FIGO and the WHO over 30 years ago. In the past, it was not clear whether SBTs were a distinct entity unrelated to serous carcinoma or whether they represented part of a continuum of tumor progression that culminates in serous carcinoma (9–13). Until recently, the molecular genetic studies have suggested that SBTs are unrelated to serous carcinoma. (1,7,11,12,14,15)

Our initial clinicopathologic studies revealed that noninvasive serous tumors display two distinctly different morphologic phenotypes. One is characterized by a hierarchical branching pattern that we classify as an “atypical proliferative serous tumor (APST)”. This tumor behaves in a benign fashion. The other morphologic variant is characterized by a nonhierarchical, micropapillary pattern that we designate “micropapillary serous carcinoma (MPSC)”, a noninvasive carcinoma. Foci of invasion can develop in these tumors and when they overgrow the noninvasive component the tumor is classified as a low-grade micropapillary serous carcinoma.” Invasion can be extensive or focal. Focal invasion can display a variety of patterns and has traditionally been classified as “microinvasion”. The pattern that resembles micropapillary serous carcinoma is the one associated with a poor outcome (16,17). Accordingly, we classify tumors with small foci displaying a micropapillary architecture, as “microcarcinoma” to distinguish them from the other patterns of “microinvasion” which do not have an adverse effect on outcome. Data on the behavior of “microcarcinoma” are limited (16) so there are no established criteria for separating microcarcinoma from bona fide invasive low-grade micropapillary serous carcinoma. We have seen cases measuring less than 3 mm associated with a poor outcome. This is an area that clearly warrants further investigation.

Invasive low-grade MPSC nearly always displays a micropapillary architecture although on rare occasion other patterns can be observed. These include tumors with a macropapillary pattern (18,19) and therefore there is merit to the view that all these low-grade tumors should

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be classified as low-grade serous carcinoma (6). We believe the qualifier “micropapillary” is helpful to draw attention to the distinctive morphology, behavior and nature of this neoplasm that distinguishes it from the usual type of serous carcinoma which is high-grade. Invasive low-grade micropapillary serous carcinoma is characterized by small solid nests and micropapillae haphazardly infiltrating the stroma (2) (Fig 1). Psammoma bodies are often present and there is no evidence of necrosis. Cytologically, invasive low-grade MPSC is composed of a relatively uniform population of cells with small, rounded nuclei often containing a small but conspicuous nucleolus. On a scale of 1 to 3 this degree of nuclear atypia qualifies as grade 1. Mitotic activity is low and there is no evidence of abnormal mitotic figures. Multinucleation is almost absent. It has been estimated that low-grade micropapillary serous carcinomas account for approximately 10% of all serous carcinomas (6).

Compared to atypical proliferative serous tumors (APSTs) which are synonymous with the usual type of SBT, noninvasive MPSCs are more often associated with invasive as opposed to noninvasive implants. Invasive implants generally have a micropapillary architecture and resemble low-grade invasive serous carcinoma (18). Accordingly, in our opinion invasive implants are low-grade serous carcinomas and should be classified as such. Recurrences have a similar appearance. The median survival of patients following recurrence of an SBT in which the recurrent tumor looks like micropapillary serous carcinoma is the same as for women who have a low-grade serous carcinoma at presentation (20) providing further support to the view that the invasive low-grade tumors develop from atypical proliferative serous tumors and noninvasive MPSCs.

Low-grade MPSC, the prototypic Type I tumor, and its precursor lesions, APST is characterized by sequence mutations in *KRAS, BRAF* and *ERBB2* oncogenes (8,21–24). Oncogenic mutations in *BRAF, KRAS* and *ERBB2* result in constitutive activation of the mitogen activated protein kinase (MAPK) signal transduction pathway which plays a critical role in the transmission of growth signals into the nucleus and contributes to neoplastic transformation. Previous studies (21,23) have demonstrated that *KRAS* mutations at codons 12 and 13 occur in one third of invasive low-grade MPSCs and another one third of SBTs. Similarly, *BRAF* mutations at codon 600 occur in 30% of low-grade serous carcinomas and 28% of SBTs (21). These findings have been confirmed by other investigators (24,25). Mutations in *KRAS, BRAF* and *ERBB2* are mutually exclusive. Therefore mutations in any of the genes are detected in about two thirds of MPSCs and APSTs. In contrast, these genes are not mutated in high-grade serous carcinomas (21,22). Mutations of *KRAS* and *BRAF* appear to occur very early in the development of low-grade MPSC as evidenced by the demonstration that the same *KRAS* and *BRAF* mutations detected in SBTs are detected in the cystadenoma epithelium adjacent to SBTs (26). Mutations in *TP53* are very rare.

High-grade serous carcinoma, the prototypic Type II tumor, corresponds to the usual type of ovarian serous carcinoma and accounts for approximately 90% of serous carcinomas. These tumors are composed of large masses of cells that frequently display a papillary architecture. Necrosis is a common feature. The tumor cells have large, pleomorphic nuclei, many of which are multinucleated. There is a high level of mitotic activity and abnormal mitotic figures are frequent. These tumors are considered poorly differentiated and the nuclear atypia is grade 3 (Fig 2). Studies have shown that the majority of advanced stage, high-grade serous carcinomas have mutant *TP53* (27–33) and the mutation frequency is over 80% when purified tumor samples are used for analysis (33). It has also been reported that mutant *TP53* is present in 37% of stage I and II high-grade serous carcinomas (34). In a study of very early, microscopic stage I high-grade serous carcinomas in ovaries removed prophylatically from women who were BRCA heterozygotes, over expression of p53 and mutation of *TP53* were found in these very early invasive high-grade serous carcinomas as well as in the adjacent “dysplastic” surface epithelium (35). These microscopic serous carcinomas had nuclear atypia resembling that

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found in advanced stage, high-grade serous carcinomas. It is plausible that inherited mutations in *BRCA* genes compromise DNA repair and predispose to genetic instability that may contribute to the "dysplastic changes". Although sporadic ovarian carcinomas were not analyzed in this study, the clinical and pathologic features of *BRCA*-linked ovarian carcinomas and their sporadic counterparts are indistinguishable, suggesting that their histogenesis is 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 morphologic level.

Correlation of the morphologic and molecular genetic studies elucidates some of the puzzling features of serous tumors. First, they explain the lack of association of SBTs with the usual type of serous carcinoma on the one hand and their occasional malignant behavior on the other. Thus, recognizing that the vast majority of serous tumors fall into two distinct groups is of considerable importance as it highlights the fact that the molecular genetic pathways leading to the development of low-grade micropapillary serous carcinoma and the usual type of serous carcinoma are entirely different (1). In one pathway, invasive low-grade micropapillary serous carcinoma develops from a noninvasive, i.e., *in situ* tumor which has traditionally been termed "serous borderline tumor (SBT)" (2). The progression of APST to MPSC, a noninvasive low-grade serous carcinoma, (1,23) and then to invasive low-grade carcinoma (invasive MPSC) mimics the adenoma-carcinoma sequence in colorectal carcinoma in which the carcinoma evolves through a continuum of histologically recognizable precursor lesions. (36) Progression of an APST to a noninvasive MPSC is supported by the finding of a greater level of allelic imbalance in MPSCs as compared to APSTs (23). Atypical proliferative serous tumor and noninvasive MPSC can be thought of as analogous to dysplasia and carcinoma *in situ* of the cervix. That is to say, the APST is a benign proliferative tumor that can progress to noninvasive MPSC, which is the immediate precursor of invasive low-grade micropapillary serous carcinoma. Compared to women with high-grade serous carcinoma the low-grade tumors occur at a younger age (median age 43 years compared to 61 years for the high-grade tumors) and behave in a more indolent fashion (median survival 81 months compared to 24 months for women with high-grade serous carcinoma) (6). In the second pathway, high-grade serous carcinoma is thought to develop from ovarian surface epithelium or from surface inclusion cysts (37). It is possible that the immediate precursor of high-grade serous carcinoma is an intraepithelial high-grade serous carcinoma developing in inclusion cysts but this putative *in situ* lesion has not been well characterized and therefore the origin of these tumors has been described as *de novo* (1,7). It has also been recently reported that these tumors may develop from an intraepithelial carcinoma in the fallopian tube (38,39). High-grade serous carcinomas are very aggressive and spread rapidly, accounting for their advanced stage at presentation.

It is important to emphasize that low-grade micropapillary serous carcinoma and high-grade serous carcinoma are distinctly different tumor types analogous to low-grade endometrial stromal sarcoma and "undifferentiated stromal sarcoma". This, concept of ovarian carcinogenesis is very different from the traditional view in which high-grade serous carcinomas are thought to develop progressively from well differentiated serous carcinoma. In the proposed model, high-grade serous carcinomas are high-grade from their inception and do not evolve from low-grade serous carcinomas. In fact, the low-grade tumors nearly always retain the same morphologic phenotype during the entire course of the disease which in some instances can be over 20 years.

Like high-grade serous carcinoma, other Type II tumors, specifically malignant mixed mesodermal tumors (carcinosarcomas) also demonstrate *TP53* mutations in almost all cases analyzed (40–42). Moreover, when the carcinomatous and sarcomatous components of MMMTs are analyzed for *TP53* mutation the identical mutation has been detected in both the epithelial and stromal component leading investigators to suggest that malignant mixed

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mesodermal tumors are in essence variants of carcinoma. The finding that MMMts have a very high rate of *TP53* mutations similar to that of high-grade serous carcinoma has additional implications. Thus, when high grade tumors that show clear-cut evidence of endometrioid, mucinous, or clear cell carcinoma differentiation are excluded, the remaining group of tumors, namely high-grade serous carcinomas, adenocarcinomas NOS, and MMMTs have similar molecular genetic profiles (Vang et al unpublished data). Also the group of tumors that pathologists routinely classify as high-grade serous carcinoma is quite different in their appearance from what is classified as "uterine serous carcinoma". Uterine serous carcinoma has a relatively limited morphologic phenotype restricted to tumors with a clear-cut "low-grade architecture (papillary or glandular) combined with high grade (grade 3) nuclei. In contrast, the morphologic phenotype of ovarian high-grade serous carcinoma is much broader. Some resemble uterine serous carcinoma but the majority does not. Instead these tumors display large masses and nests of cells with slit-like spaces. Papillary and glandular patterns are frequently not evident. Extensive areas of necrosis and fibrosis are frequently encountered. In short, many of these high-grade carcinomas are poorly differentiated adenocarcinomas or undifferentiated carcinomas without the slightest evidence of "serous" differentiation. As presently used "moderate to poorly differentiated "or "high-grade serous carcinoma" is a "waste basket" category for high grade carcinomas that show no clear-cut evidence of endometrioid, mucinous or clear cell differentiation. The tumors in the Type II group appear to have a similar behavior. Thus, despite the morphologic diversity, from a molecular genetic standpoint they are similar. In the future it may be more appropriate to include all of these poorly differentiated/ undifferentiated carcinomas into a single category of "anaplastic carcinoma".

This proposed model of carcinogenesis is the first step in trying to unravel what is a highly complex process. For example, studies have shown that on rare occasion low-grade serous tumors are associated with high-grade serous carcinomas (Fig 3) (43,44). In a recent analysis of tumors in which a high-grade serous carcinoma was immediately adjacent to an APST we found the identical *KRAS* mutation in both components of the tumor indicating that they had a shared lineage (44). These findings suggest that on rare occasion APSTs and low-grade micropapillary serous carcinomas may progress to high-grade serous carcinomas. Interestingly, none of these high-grade tumors had a *TP53* mutation. Only six cases were studied but since over 80% of high-grade serous carcinomas contain *TP53* mutations, the absence of a *TP53* mutation in the high-grade serous carcinomas associated with APSTs raises the possibility that these high grade serous carcinomas develop along a different pathway than the usual high-grade serous carcinoma that is not associated with an APST (44).

We have also recently studied a group of moderately differentiated serous carcinomas, characterized by the presence of grade 2 nuclei that were not associated with an APST or noninvasive MPSC (Fig 4). Architecturally, several displayed a micropapillary pattern simulating low-grade serous carcinoma but to date all have had *TP53* mutations and lacked mutations of *KRAS, BRAF,* or *ERBB2* (unpublished data). These findings suggest that high-grade serous carcinomas with grade 2 nuclei may develop along yet another pathway that is different from the one described for the more common high-grade serous carcinoma with grade 3 nuclei. Since many of these tumors displayed a micropapillary architecture it is conceivable that they developed from a subset of low-grade serous carcinomas that lacked mutations of *KRAS, BRAF* and *ERBB2*. Subsequent acquisition of a *TP53* mutation could lead to genetic instability which in turn contributed to the increased level of nuclear atypia (grade 2). Accordingly, our preliminary findings suggest that although there is a dominant pathway for the development of most high-grade serous carcinomas, there are other pathways that account for the morphologic diversity displayed by this group of neoplasms. A schema depicting these different pathways is shown in Figure 5.

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Finally, given the utility of the two-tier grading system in separating low- and high-grade serous carcinomas with different clinical behaviors (6) and presumably would require different treatment, establishment of a cut-point between low- and high tumors is imperative. The distinction at either end of the spectrum is straight forward. Thus, low-grade tumors have small, uniform (grade 1) nuclei whereas high-grade tumors have highly pleomorphic, often multinucleated (grade 3) nuclei. Mitotic activity is low in the low-grade tumors and high in the high-grade tumors. However, tumors with nuclei and mitotic levels that are intermediate between low- and high-grade, i.e. moderately differentiated tumors with grade 2 nuclei do occur. Are these tumors low- or high grade using a two tier grading system? As has been discussed these grade 2 tumors have *TP53* mutations and lack mutant *KRAS* and *BRAF* which provides strong molecular genetic evidence that they are high-grade. This has important clinical implications since at the present time some oncologists consider stage I, grade 2 tumors low-grade and do no administer adjuvant chemotherapy whereas patients with grade 3 tumors receive adjuvant chemotherapy.

Mucinous Tumors

Mucinous tumors share some similarities with serous tumors but also have profound differences. Like SBTs, survival for women with stage I MBTs is 100% but based on the literature, survival with advanced stage tumors is only 50% compared to 70% for advanced stage SBTs. In addition, it has been reported that 80% of advanced stage MBTs are associated with pseudomyxoma peritonei (PMP). It is now well established that PMP results from a ruptured mucinous appendiceal adenoma and that the ovarian involvement is secondary (45–47). It has also been shown that metastatic mucinous carcinomas from the upper gastrointestinal tract including the biliary tract, pancreas and cervix can metastasize to the ovary and simulate a primary ovarian mucinous tumor. When mucinous tumors associated with PMP and metastatic mucinous carcinomas that masquerade as primary ovarian tumors are excluded from consideration, it becomes apparent that MBTs unlike SBTs never spread beyond the ovary.

A number of clinical and pathological observations link primary mucinous carcinomas of the ovary to mucinous borderline tumors (MBTs). The mean size of MBTs and mucinous carcinomas is the same at diagnosis (18 cm). The large size of mucinous carcinomas and their unilateral presentation underscores the fact that they grow slowly. Mucinous carcinomas at the time of their diagnosis are nearly always well differentiated and merge with areas of borderline tumor and mucinous cystadenoma. In fact, it is not unusual to find a focus of carcinoma growing within a tumor that is for the most part a MBT. Cytologic atypia within the noninvasive component can range from minimal to marked, leading investigators to subclassify borderline tumors into atypical proliferative and intraepithelial carcinoma based on the degree of cytologic atypia. These findings strongly suggest that mucinous carcinoma develops slowly, in a stepwise fashion from benign precursors. This conclusion is supported by molecular genetic studies which have shown that the most common molecular genetic alteration in MBTs and mucinous carcinomas is a point mutation of *KRAS* (25,48,49). An increasing frequency of *KRAS* mutations at codons 12 and 13 has been described in cystadenomas, MBTs and mucinous carcinomas, respectively (12,48–51). In addition, mucinous carcinoma and the adjacent mucinous cystadenoma and borderline tumor share the same *KRAS* mutation (50). Besides *KRAS*, other genetic alterations in ovarian mucinous tumors have not been reported.

Endometrioid and Clear Cell Tumors

There has not been a single well documented case of a borderline endometrioid or clear cell tumor associated with malignant behavior since the category was first introduced in the early 1970s supporting the view that these are benign proliferative tumors. Nonetheless, they are frequently associated with their malignant counterparts. As with the mucinous tumors, the

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endometrioid and clear cell carcinomas tend to be large (mean diameter 15 cm), unilateral and frequent transitions between the proliferative tumor and the carcinoma are observed. Only a few molecular genetic studies of these tumors have been performed. These are discussed in greater detail in the accompanying article in this Symposium by Dr Kathleen Cho. Briefly, mutations of *KRAS* and *BRAF* have been reported in approximately 10% of endometrioid carcinomas (21,25,49,52–54) and mutation of the tumor suppressor, *PTEN*, in 20% of endometrioid carcinomas, which rises to 46% in the tumors with 10q23 loss of heterozygosity (55). 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 (55–60). Furthermore, mutations of *beta-catenin* have been detected in more than 60% of ovarian endometerioid carcinomas (grade I) and their precursor lesions, endometrioid borderline tumors (61). These molecular genetic findings together with the morphological data demonstrating a frequent association of endometriosis with endometrioid adenofibromas and atypical proliferative endometrioid tumorss adjacent to invasive well-differentiated endometrioid carcinoma provide evidence of stepwise tumor progression in the development of endometrioid carcinoma (62. The critical role of the genetic changes in PTEN and KRAS is highlighted by a recent report showing that inactivation of PTEN and an activating mutation of KRAS are sufficient to induce the development of ovarian endometrioid carcinoma in a mouse model (63). More recently, inactivation of the *Wnt/beta-catenin* and the *PI3K/Pten* pathways has been reported to be sufficient to induce endometrioid carcinoma in a engineered mouse model (64).

Clear cell carcinomas display clinical, morphologic and molecular genetic changes that are shared with, but also differ from, tumors in the Type I and II groups suggesting that clear cell carcinomas develop along an independent pathway. For example, although they tend to be diagnosed in stage I, clear cell carcinomas present more often as advanced stage tumors than the other neoplasms in the Type I group. Also, although they tend to be large at diagnosis, they typically are high grade whereas other Type I tumors are low grade. As compared to other types of ovarian epithelial tumors, the main molecular genetic changes associated with ovarian clear cell borderline tumors and clear cell carcinomas remain to be identified. Although several molecular genetic changes have been reported in clear cell tumors, most studies have analyzed a limited number of cases and therefore the true prevalence of those changes is not known. Microsatellite instability is present in endometrioid and clear cell carcinoma but is only rarely detected in serous and mucinous tumors (62,65,66). This finding supports the view that endometriosis is the common precursor for both endometrioid and clear cell carcinoma (62). Mutations in *KRAS*, *BRAF* and *TP53* are present in some clear cell carcinomas but their frequency is low (25). Thus, although mutations have been identified in clear cell carcinomas they differ from those found in the other Type I tumors. Finally, unlike Type II tumors but similar the Type I tumors, they are relatively genetically stable.

Implications of the Model for Early Detection and Treatment

An appreciation of ovarian carcinogenesis based on this model sheds light on potential new approaches to early detection and treatment. First, the model, by dividing ovarian cancer into two broad groups, Type I and Type II, draws attention to the fact that ovarian cancer is a heterogeneous group of diseases that not only behave differently but also develop differently. Screening with pelvic examination and transvaginal ultrasound is reasonable for Type I carcinomas because they develop slowly from well characterized precursors (borderline tumors) and remain confined to the ovary while growing to a large size. However, Type I carcinomas constitute only 25% of ovarian cancers so these approaches are inadequate for large scale screening of “ovarian cancer”. The vast majority of ovarian cancers are Type II tumors which are high-grade, advanced stage at presentation, rapidly growing, and highly aggressive. Current approaches to screening, namely serum CA125 assays and transvaginal ultrasound

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have not assisted in the detection of these tumors at an early stage. The likely explanation is that these are genetically unstable tumors that transit rapidly from the ovary to extra-ovarian sites and therefore the time for detecting these tumors while still confined to the ovary (stage I) is very brief. Furthermore, a substantial number of Type II carcinomas appear to develop in the fallopian tube (39) and peritoneum and involve the ovary secondarily. It is well recognized that serous carcinomas identical to ovarian serous carcinomas can develop following bilateral salpingo oophorectomy. Also many cases of serous carcinoma extensively involving the pelvic and abdominal cavities have only minimal ovarian involvement but are classified as ovarian if the ovarian tumor is greater than 5 mm. This is clearly an arbitrary decision in assigning origin to the ovary. In any event, these tumors are advanced stage at their inception. It is therefore apparent that early detection of these tumors is extraordinarily difficult since there is no morphologically characterized precursor lesion. Despite these formidable difficulties, strategies can be developed to enhance early detection and improve survival. Clues can be gleaned from advances in the surgical treatment of ovarian cancer. It is well recognized that the most important prognostic indicator is not stage but the volume of residual disease following cytoreductive surgery. As surgical techniques have evolved, what constitutes optimal cytoreduction has shifted from <2cm to <1.5cm to <1cm. With each reduction in the amount of residual disease that is considered optimal, survival has improved (67). The smaller the tumor volume the more effective chemotherapy will be. Therefore the current approach to evaluating screening tests should be shifted from detection of stage I tumors to detection of “minimal ovarian carcinoma” irrespective of stage. “Minimal ovarian carcinoma” can be defined as microscopic to 1 cm. As technology advances and the sensitivity of assays is improved, the definition of what constitutes “minimal” can be changed.

The ultimate goal of early detection, given the lack of morphologically recognizable precursor lesions for the Type II tumors, is the identification of biomarkers that precede the development of these precursors. It has been shown that mutations of *TP53* are currently the most common molecular genetic change in Type II tumors (33). Moreover, mutation of *TP53* occurs very early in the genesis of these neoplasms. In fact they have been observed in intraepithelial neoplasia in the fallopian tube fimbria of BRCA patients (38,39). Importantly, *TP53* mutations are inherited during cancer evolution and contribute to the transformed state. As a result, the initiating genetic changes are retained in both the primary and recurrent tumors. Furthermore, it is likely that the tumor DNA containing mutant *TP53* DNA or polypeptides released from these tumors can be detected in body fluids. Accordingly, a test that detects mutant *TP53* in the blood could be very useful in early detection.

The proposed model for ovarian carcinogenesis also has important implications for targeted treatment. With the characterization of specific genetic changes that occur early in the development of Type II tumors, treatment could be administered using drugs that target the pathways affected by the mutations, for example mutant *TP53*. Therapeutic options would be offered based on the presence of these biomarkers alone. A precedent for this approach currently exists for women who are identified as having BRCA mutations, many of whom choose to undergo prophylactic bilateral salpingo oophorectomy and hysterectomy.

Type I tumors present different challenges as compared to Type II tumors because they tend to be localized and indolent. Since Type I tumors are slow growing and therefore therapeutic agents that are effective against Type II tumors are not as effective against Type I tumors. For example, Type I carcinomas harbor several mutations in protein kinases and therefore the pathways that they control could be amenable to inhibitor treatment or targeted by immunotherapy. In many Type I carcinomas, there is constitutive activation of the MAPK signaling pathway due to mutations in either *KRAS* or *BRAF* genes, the upstream regulators of *MAPK*. Accordingly, *BRAF* inhibitors and other *MAPK* inhibitors should be evaluated to determine whether they could prolong disease-free interval and overall survival in patients with

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advanced-stage Type I tumors. The mutated biomarker sequences might also be specifically targeted by immunotherapy since the mutated sequence is non-self and its expression is restricted to the tumor cells.

Conclusions

A new model for the pathogenesis of ovarian cancer based on clinical, pathological, and molecular genetic studies is proposed. In this model ovarian tumors are divided into two broad groups designated Type I and Type II. Type I tumors are slow growing, generally confined to the ovary at diagnosis and develop from well established precursor lesions that are termed "borderline" tumors. Type I tumors included low-grade micropapillary serous carcinoma, mucinous, endometrioid, and clear cell carcinomas. They are genetically stable tumors and are characterized by mutations in a number of different genes including *KRAS*, *BRAF*, *PTEN*, and *beta-catenin*. In contrast, Type II tumors are rapidly growing, highly aggressive, neoplasms for which well defined precursor lesions have not been described. The vast majority of what is considered "ovarian cancer" belongs to the Type II category. These tumors include high-grade serous carcinoma, malignant mixed mesodermal tumors (carcinosarcomas) and undifferentiated carcinomas. This group of tumors has a high level of genetic instability and is characterized by mutation of *TP53*. The model has important implications for the early detection and treatment of ovarian cancer. Specifically, it indicates that the current approach to screening, aimed at detecting stage I ovarian carcinoma, is not likely to be of benefit for Type II tumors, the vast majority of what constitutes "ovarian cancer". Type II carcinomas, are only rarely detected when the disease is confined to the ovary because those that begin in the ovary appear to spread rapidly to extraovarian sites while a substantial number of them appear to develop outside the ovary, specifically, the peritoneum and fallopian tube and involve the ovary secondarily. Therefore a more realistic endpoint for the early detection of high-grade serous ovarian carcinoma may be volume and not stage of disease. This has already been observed in the treatment setting. Knowledge of the pathogenesis of various types of ovarian cancer could also potentially lead to more targeted therapeutic interventions. In summary, this model is an initial attempt to organize our thinking about what is undoubtedly a highly complex process. Clearly, the morphologic diversity displayed by ovarian tumors indicates that a number of different molecular pathways must be operative. As our knowledge of ovarian carcinogenesis deepens, additional molecular genetic pathways will be discovered. The challenge for the future will be to elucidate and characterize them in order to customize approaches to early detection and treatment.

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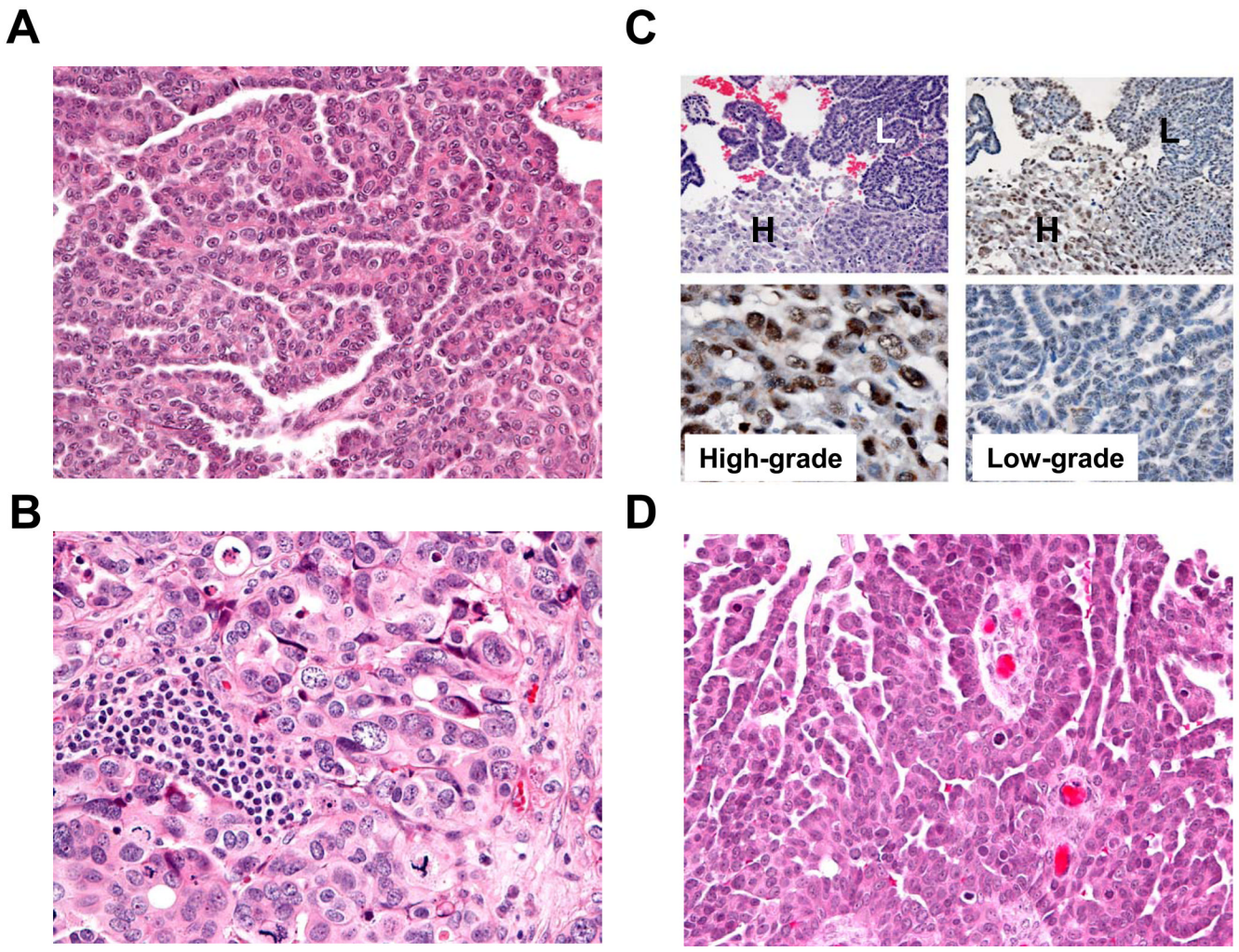

Fig. 1.
Invasive low-grade micropapillary serous carcinoma. The tumor is characterized by a micropapillary architecture and grade 1 nuclei.

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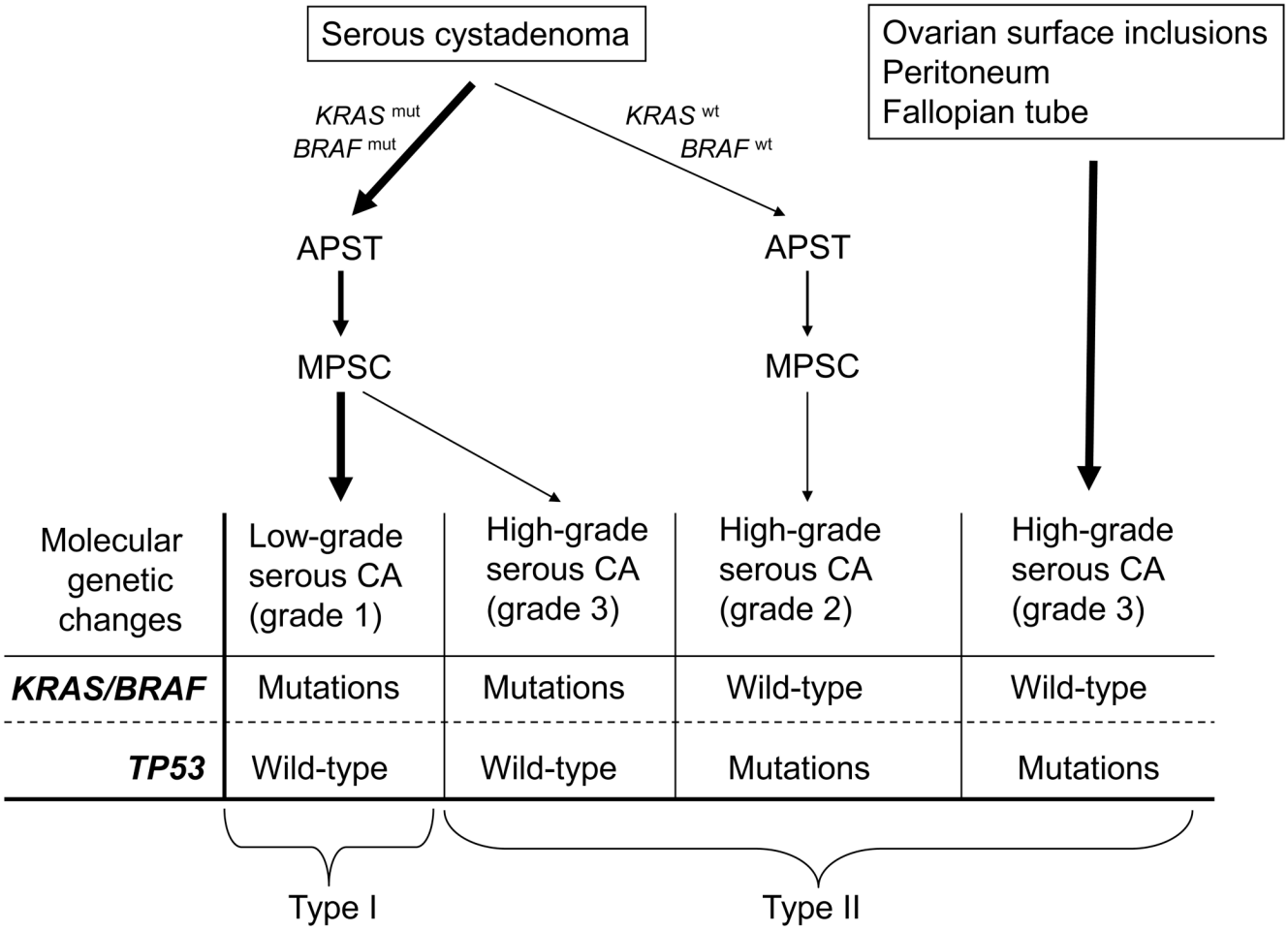

Fig. 2.

High-grade serous carcinoma. The carcinoma shows a solid growth pattern and contains large, pleomorphic nuclei (grade 3). Abnormal mitotic figures are also present.