Pathogenesis of Ovarian Cancer
Lessons from Morphology and Molecular Biology

A Proposed Model with Clinical Implications

Robert J Kurman, M.D.
Key Issues

• Epithelial carcinomas of the ovary can be divided into two categories designated Type I and Type II.

• Type I carcinomas are slow growing, indolent tumors that develop from atypical proliferative (borderline) tumors.

• Type II carcinomas are rapidly growing, aggressive tumors which develop *de novo*.

• Understanding the pathogenesis of Type I and Type II carcinomas provides clues for new approaches to early detection and treatment.
Histological Classification of Ovarian Tumors

FIGO Classification
Tumors of the Ovary- 1971

Cystomas
(a) Benign cystadenomas
(b) Cystadenomas with proliferating activity of the epithelial cells and nuclear abnormalities but with no infiltrative destructive growth (low potential malignancy)
(c) Cystadencarcinomas

WHO Classification
Ovarian Tumours - 1973

Surface Epithelial-Stromal Tumors

Benign
- Cystadenoma
- Adenofibroma

Of borderline malignancy (carcinomas of LMP)
- Cystadenoma
- Adenofibroma

Malignant
- Adenocarcinoma
- Surface papillary carcinoma
- Malignant adenofibroma
Serous Borderline Tumors

The Birth of Borderline

The borderline group was carved out of the carcinoma category and defined as a noninvasive group of tumors displaying cellular proliferation and cytologic atypia.

Why was Borderline Created?

To account for

- "Intermediate" behavior between cystadenomas and frankly invasive carcinomas
- Inability to predict the outcome of an individual tumor
Histological Classification of Ovarian Tumors

WHO Classification
Ovarian Tumours - 1999

Surface Epithelial-Stromal Tumors
Benign
• Cystadenoma
• Adenofibroma

Of borderline malignancy
(carcinomas of LMP)
• Cystadenoma
• Adenofibroma

Malignant
• Adenocarcinoma
• Surface papillary carcinoma
• Malignant adenofibroma

WHO Classification
Ovarian Tumours - 2003

Surface Epithelial-Stromal Tumors
Benign
• Cystadenoma
• Adenofibroma

Borderline Tumor
• Cystadenoma
• Adenofibroma

Malignant
• Adenocarcinoma
• Surface papillary carcinoma
• Adenocarcinofibroma
 (malignant adenofibroma)
Dualistic Model of Ovarian Carcinogenesis

Type I
- Low-grade

Type II
- High-grade

Shih and Kurman
Am J Pathol 164:1511, 2004
Dualistic Model of Ovarian Carcinogenesis

Type I
- Low-grade
- Arise from precursor lesions in a stepwise fashion
  - Cystadenomas
  - Borderline Tumors

Type II
- High-grade
- Arise “de novo”

Shih and Kurman
Am J Pathol 164:1511, 2004
Dualistic Model of Ovarian Carcinogenesis

**Type I**
- Low-grade
- Arise from precursor lesions in a stepwise fashion
  - Cystadenomas
  - Borderline Tumors
- Typically present as stage I

**Type II**
- High-grade
- Arise “de novo”
- Typically present as advanced stage

*Shih and Kurman* 
*Am J Pathol 164:1511, 2004*
### Dualistic Model of Ovarian Carcinogenesis

**Type I**
- Low-grade
- Arise from precursor lesions in a stepwise fashion
  - Cystadenomas
  - Borderline Tumors
- Typically present as stage I
- Slow growing, indolent

**Type II**
- High-grade
- Arise "de novo"
- Typically present as advanced stage
- Rapid growing, aggressive

---

*Shih and Kurman*
*Am J Pathol 164:1511, 2004*
## Dualistic Model of Ovarian Carcinogenesis

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade</td>
<td>High-grade</td>
</tr>
<tr>
<td>Arise from precursor lesions in a stepwise fashion</td>
<td>Arise “de novo”</td>
</tr>
<tr>
<td>- Cystadenomas</td>
<td></td>
</tr>
<tr>
<td>- Borderline Tumors</td>
<td></td>
</tr>
<tr>
<td>Typically present as stage I</td>
<td>Typically present as advanced stage</td>
</tr>
<tr>
<td>Slow growing, indolent</td>
<td>Rapid growing, aggressive</td>
</tr>
<tr>
<td>Generally remain low-grade</td>
<td></td>
</tr>
</tbody>
</table>

Shih and Kurman
*Am J Pathol* 164:1511, 2004
Dualistic Model of Ovarian Carcinogenesis

**Type I**
- Low-grade
- Arise from precursor lesions in a stepwise fashion
  - Cystadenomas
  - Borderline Tumors
- Typically present as stage I
- Slow growing, indolent
- Often remain low-grade
- Can progress to high-grade

**Type II**
- High-grade
- Arise “de novo”
- Typically present as advanced stage
- Rapid growing, aggressive

*Shih and Kurman*
*Am J Pathol 164:1511, 2004*
A “Classification” of Ovarian Carcinoma Based on Clinical, Pathologic, and Molecular Features

**Type I**
- Low-grade micropapillary serous carcinoma
- Mucinous carcinoma
- Endometrioid carcinoma
- Clear cell carcinoma
- Malignant Brenner tumor

**Type II**
- High-grade serous carcinoma
- MMMT (carcinosarcoma)

Shih and Kurman
*Am J Pathol* 164:1511, 2004
The Pathogenesis of Ovarian Cancer

Traditional View

- Ovarian cancer is regarded as a single disease and treated with one approach
- The reason is because most ovarian cancer is *serous* carcinoma
Serous Carcinogenesis - Current View

Well differentiated carcinoma *progresses* to poorly differentiated serous carcinoma.

Carcinoma *begins in the ovary (stage I)*, spreads to the pelvic (stage II) and abdominal cavities (stage III) and beyond (stage IV).
Relationship of BOTs to Invasive Carcinoma

- SBTs are rarely associated with invasive carcinoma
- SBTs are a distinct entity unrelated to invasive carcinoma
- MBTs are frequently associated with invasive carcinoma
- Are some BOTs precursors and others not?
The Pathogenesis of Ovarian Cancer

• Recent advances in understanding the pathogenesis of ovarian carcinomas come from studies of serous and mucinous borderline tumors
Can SBTs be divided into benign and malignant subtypes?

- Hierarchical Branching: 
  - Atypical Proliferative Serous Tumor

- Nonhierarchical Branching: 
  - Micropapillary Serous Carcinoma, Noninvasive

Tumors with a hierarchical pattern had significantly better outcome than those with a nonhierarchical pattern.

Noninvasive Micropapillary Serous Carcinoma

Grade 1 nuclei
Noninvasive MPSC with focus of early invasion

Invasive Low-grade MPSC
The Proposal that Noninvasive Micropapillary Tumors were Noninvasive Carcinomas
The Controversy

- Noninvasive tumors with a micropapillary pattern are variants of a borderline tumor and should not be classified as a noninvasive carcinoma because …
- there is no significant difference in the outcome of typical stage I SBTs compared to stage I noninvasive MPSCs
The Controversy

• True but…
  – As reported in the literature there is also no significant difference in the outcome of typical stage I SBTs compared to

  *Bona fide invasive stage I carcinoma which is >90%*
The Controversy

• There is no significant difference in the outcome of typical advanced stage SBTs compared to MPSCs if stratified into implant type
• Specifically, invasive implants determine behavior
  – True but…
  – virtually all studies have shown that MPSCs are significantly more often associated with invasive implants
What are Invasive Implants?
Sharp line between implant and underlying tissue

Looks like primary SBT

Irregular infiltration into underlying tissue

Looks like *well differentiated serous carcinoma*

Courtesy Debra Bell
MPSC with Invasive Implant

Ovarian tumor 1979  
Omentum 1979  
Pelvic mass 1997

Primary tumor  
Invasive implant  
Recurrent carcinoma

All look the same
MPSC with Invasive Implant (1991)

Vaginal Recurrence (1993)

Micropapillary architecture
• If something looks like a duck, walks like a duck, and quacks like a duck
• It is a duck!
• *Invasive implants are low-grade serous carcinomas*
Are Typical SBTs Ever Associated with Invasive Implants?

- for all practical purposes they are not
- Typical SBTs are *benign tumors* that have the *potential* to undergo malignant transformation to a low-grade micropapillary serous carcinoma (noninvasive or invasive)
• Reports of invasive implants associated with typical borderline tumors …
• almost certainly *missed occult areas of carcinoma* (noninvasive or invasive MPSC) in the primary SBT
• *even when the tumor was adequately sampled* (1 block/cm of the greatest tumor dimension)
• Patient with bilateral typical SBTs with implants in parametrium and pelvic peritoneum
• One block/cm of greatest tumor dimension
Bilateral Typical SBTs
Sampling 1 block/cm
Additional sections from the SBTs
Additional sections from the SBTs
Invasive Low-grade MP Serous Carcinomas
Up to 75% of **low-grade** invasive MPSCs are associated with SBTs

Over 90% of these SBTs display a **micropapillary** pattern

**Conclusion** - SBTs with a micropapillary pattern (noninvasive MPSCs) are the **immediate precursors of low-grade invasive MPSCs**

Smith Sedhev et al  

Malpica et al  
*Amer J Surg Pathol* 28:496-504,2004
Behavior of Advanced Stage LG-Invasive MPSCs Compared to SBTs that Recur as LG-Invasive MPSCs

- **Group 1** - LG-Invas MPSC (n=112) vs
- **Group 2** - SBTs recurring as LG – Invas MPSC (n=41)
- Survival **Group 1** - 82 months
- Survival **Group 2** – 192 months
- Survival **Group 2** (from relapse as MPSC to death) – 83 months

Shvartsman et al – Unpublished data
Low-grade (invasive micropapillary serous) CA

High-grade (conventional serous) CA

are characterized by distinctive molecular genetic changes
## Frequency of KRAS/BRAF and p53 Mutations in Ovarian Serous Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>KRAS/BRAF</th>
<th>p53</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBT *</td>
<td>31/51 (61%)</td>
<td>2/25 (8%)</td>
</tr>
<tr>
<td>Low-grade Serous Ca</td>
<td>15/22 (68%)</td>
<td>1/12 (8%)</td>
</tr>
</tbody>
</table>

* Includes Atypical Prolif Tumor and noninvasive MPSC

I-M Shih et al.
# Frequency of KRAS/BRAF and p53 Mutations in Ovarian Serous Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>KRAS/BRAF (Freq)</th>
<th>p53 (Freq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBT *</td>
<td>31/51 (61%)</td>
<td>2/25 (8%)</td>
</tr>
<tr>
<td>Low-grade Serous Ca</td>
<td>15/22 (68%)</td>
<td>1/12 (8%)</td>
</tr>
</tbody>
</table>
| High-grade Serous Ca| 1/140 (<1%)      | 98/140 (70%) | **

*p53 mutation rate is 82% on purified epithelial cells from tumor samples*
Gene expression profiles in SBT, LG MPSC and HG serous carcinoma

- Gilks et al., *Gynecol Oncol*, 96:684, 2005
- Hampton et al., *Oncogene*, 24:1053, 2005
- Birrer et al., *Cancer Res*, 65:10602, 2005

SBT and LG MPSC have similar profiles distinct from HG ser CA
What is the Pathogenesis of Low-grade Micropapillary Serous Carcinoma?
Serous Cystadenoma Containing a Small Atypical Proliferative Serous Tumor (APST)

Before

After

(Borderline tumor)

(Cyst)

(Cancer Res, 64:6915, 2004)
Mutations of KRAS and BRAF Precede the Development of APSTs

Serous cystadenoma adjacent to APST

BRAF mutation
Codon 599, T1796A

APST in Serous cystadenoma

BRAF mutation
Codon 599, T1796A

(Cancer Res, 64:6915, 2004)
Pathogenesis of Low Grade Micropapillary Serous Carcinoma

- APST
- Noninvasive LG MPSC
- Noninvasive LG MPSC with focus of invasion
- Invasive LG MPSC
What is the Origin of High-grade Serous carcinoma?
The Usual Type of Serous Carcinoma

Is high-grade and rarely associated with SBTs
High-grade Serous Carcinoma Pathogenesis

- The precursors of high-grade serous carcinomas are not well characterized.
- It has been proposed that they develop "de novo" from the surface epithelium or inclusion cysts.

Bell DA, Scully RE
Cancer 73:1859-64, 1994
Development of Conventional (high-grade) serous carcinoma

Mutation of p53 is a very early event in the development of high-grade serous carcinoma

Courtesy Jeff Boyd
Dual Pathways of Serous Carcinogenesis
Early Events

Low-grade pathway  High-grade pathway

Low-grade serous carcinoma  High-grade serous carcinoma

KRAS or BRAF Mutation  p53 Mutation
Low-grade pathway

Borderline → Low-grade carcinoma
High-grade pathway

Low-grade pathway

Cystadenoma

APST

MPSC

SBT

Low-grade carcinoma

Inclusion cyst

High-grade carcinoma

High-grade pathway
Grade is a Defining Feature of Invasive Serous Carcinomas

• Serous carcinoma can be divided into two distinct types
  – Low-grade micropapillary serous carcinoma
  – High-grade serous carcinoma

• Not an issue of progression, these are distinct and separate tumor types
Grading of Serous Carcinoma

Low-grade serous carcinoma

High-grade serous carcinoma

Invasive MPSC

Conventional Serous Carcinoma

Grade 1

Grade 3
High-grade Serous Carcinoma (HG Ser CA) Developing from an Atypical Proliferative Serous Tumor (APST)

Case A

Case B

Identical KRAS mutation in APST and HG Ser CA
No p53 mutation

(Reiko et al., in press)
Progression in the Type I Pathway
Serous Tumors

Cystadenoma

APST

Noninvasive MPSC

HG Ser CA

Invasive MPSC

Very rare event
Mucinous Borderline Tumors (MBTs)

- Survival of stage I MBTs is 100%
- Survival of advanced stage MBTs reported in the literature is 50% but
- Over 80% of advanced stage MBTs reported are associated with pseudomyxoma peritonei (PMP)
- It is now known that PMP results from a ruptured mucinous appendiceal adenoma
- Ovarian involvement is secondary
Advanced Stage (MBTs)?

• Several studies have now shown that what appear to be ovarian MBTs are in fact metastatic carcinomas

• typically from the upper GI tract (biliary tree and pancreas) or cervix
Ovarian Tumor
Ovarian Tumor

Cervical Tumor

HPV – 16 in situ hybridization
Advanced Stage (MBTs)?

- Once MBTs associated with PMP (>80%) are eliminated from consideration and
- Metastatic carcinomas involving the ovaries that masquerade as MBTs are excluded
Advanced Stage (MBTs)?

There are *none*!
The Relationship of MBTs to Mucinous Carcinoma

Molecular Studies

Molecular genetic studies using KRAS mutations as a marker

- Approximately 50% of mucinous carcinomas, MBTs and mucinous cystadenomas have KRAS mutations of codon 12 and 13
- Using laser capture microdissection the *identical* KRAS mutation is present in all three of the tumor components in the same case (mucinous cystadenoma, MBT and mucinous carcinoma)

Relationship of MBTs to Mucinous Carcinoma

- Clinical, morphologic, and molecular data suggest there is a progression
Mucinous Carcinoma

- **Mean size** of both primary mucinous carcinomas and MBTs is – *18 cm*
- Majority of primary mucinous carcinomas are **well differentiated and unilateral** at presentation
- Primary mucinous carcinomas are often **focal** developing within MBTs and mucinous cystadenomas
- Survival for stage I is >90%
Borderline Endometrioid and Clear Cell Tumors

• **Not a single well documented case associated with malignant behavior reported** since the category was introduced by FIGO in 1971 and incorporated into the WHO classification in 1973

• Frequently associated with their respective carcinomas
The Relationship of Endometrioid Adenocarcinoma To Endometrioid Borderline Tumors

Endometriosis → Atypical Endometriosis → Borderline Endometrioid Tumor → Low-grade Endometrioid Adenocarcinoma

Genetic Alterations: PTEN, K-Ras, β-catenin

Microsatellite Instability

Courtesy Kathy Cho
Endometrioid Carcinoma

- Frequently presents as a well differentiated stage Ia tumor associated with an atypical proliferative endometrioid tumor/adenofibroma
- Survival for these tumors is close to 100%
- Advanced stage tumors are relatively uncommon when classified using strict criteria
Clear Cell Carcinoma

- Poorly understood because it has not been well characterized
- In literature and based on personal experience “clear cell carcinoma” includes
  - Solid endometrioid carcinomas with extensive secretory change
  - Poorly differentiated carcinomas containing cells with clear cytoplasm
  - Classic clear cell carcinoma (tubulocystic, papillary and solid patterns)
Summary of Type I Tumors

- Low-grade
- Develop in a slow, stepwise fashion from
  - Cystadenomas
  - Atypical proliferative (borderline) tumors
- Similar to Type I endometrial carcinomas - complex hyperplasia and complex atypical hyperplasia precursors
- Typically present as stage I
- Are generally indolent and remain low-grade
- Some progress
Summary of Type II Tumors

• High-grade adenocarcinoma
  – Includes high-grade serous carcinoma, MMMT, adenocarcinoma NOS, and undifferentiated carcinoma
  – Preliminary molecular data suggests they are similar
• Arise “de novo”
• Present in advanced stage
• Highly aggressive
Dualistic Model of Ovarian Carcinogenesis

Clinical Implications

Looking to the future
Screening for Ovarian Cancer

- Understanding pathogenesis clarifies misconceptions in the current approaches to early detection
- Ovarian cancer is not a single disease
- Appreciation of diverse molecular pathways of carcinogenesis will permit more customized approaches to detection
Goal of Early Detection

• *Detect stage I ovarian carcinoma*
  • Survival of stage I disease is > 90%
  • 75-80% of ovarian carcinoma presents as advanced stage disease implying 20-25% are stage I
  • Most patients will be successfully treated by surgery
  • There will be limited need for cytotoxic chemotherapy
Detection of Stage I Ovarian Cancer

• The vast majority of “ovarian cancers” are serous carcinomas but …

• how many are stage I?
## Carcinomas Stage Distribution (n=220)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Stage I</th>
<th>Stage II-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>4%</td>
<td>96%</td>
</tr>
<tr>
<td>Mucinous</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>36%</td>
<td>64%</td>
</tr>
<tr>
<td>Brenner</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Seidman et al
## Carcinomas
### Stage Distribution
(n=220)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Stage I</th>
<th>Stage II-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serous</strong></td>
<td>4%</td>
<td>96%</td>
</tr>
<tr>
<td>Mucinous</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>36%</td>
<td>64%</td>
</tr>
<tr>
<td>Brenner</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Seidman et al
Bilaterality and Size

• Serous carcinomas tend to be small (in the ovary) and bilateral at presentation
• The bulk of the tumor is often outside of the ovary
High-grade Serous Carcinoma
High-grade Serous Carcinoma

Courtesy R Bristow
Detection of Stage I Ovarian Serous Carcinoma

• Since ovarian carcinomas are small, even when there is extraovarian spread
• They will not be detected by pelvic exam or transvaginal ultrasound
• Is it possible to detect stage I serous carcinoma?
Is Ovarian Serous Carcinoma Ever Stage I?

- Thoroughly staged, stage I serous carcinoma sent for consultation because of microscopic lesion in the omentum thought to represent mesothelial hyperplasia
Omentum
Ovary p53

Omentum p53
Is Ovarian Serous Carcinoma Ever Stage I?

- *Hardly ever!*
Other Problems

• Not all “ovarian” serous carcinomas start in the ovary
  – Serous carcinomas identical to those in the ovary can develop after bilateral salpingo oophorectomy
  – These are primary peritoneal serous carcinomas which at diagnosis are stage II or III
Other Problems

- Not all "ovarian" serous carcinomas start in the ovary
  - Small serous carcinomas detected in the fimbria of women with BRCA mutations undergoing prophylactic oophorectomy
  - Not previously recognized because fallopian tubes are not routinely serially sectioned?
  - These tumors are stage II "ovarian" carcinomas at diagnosis
Problems in the Detection of Stage I Ovarian Serous Carcinoma

Summary

• Serous carcinomas that start in the ovary spread rapidly
  – Lead time is brief and nearly always present in advanced stage
    • Cervix model does not apply
• Some serous carcinomas start in the peritoneum or fallopian tube
  – These are advanced stage at diagnosis
Detection of Stage I Ovarian Serous Carcinoma (Type II)

**Bottom Line**

- It will be virtually impossible to detect stage I serous carcinoma using presently available technology
Implications for Treatment of High-grade Serous Carcinoma (Type II Tumor)

• The most important predictor of outcome (more important than stage) is whether the tumor has been adequately debulked (optimal cytoreduction)
• Over time this has shifted from <2cm to <1.5 cm to <1cm
Successful treatment will depend on detection of minimal (microscopic to 1 cm) ovarian serous carcinoma (stage is irrelevant)

Using a panel of sensitive and specific molecular markers that precede development of morphologically recognizable precursors

Treatment will be instituted based on marker detection only
Classification of Ovarian Tumors

• Why do SBTs have an intermediate behavior?
• Because they are a heterogeneous group mainly benign (atypical proliferative) and ...
• a small number of noninvasive low-grade MPSCs which can implant (so-called invasive implants but in fact are metastatic low-grade carcinomas)
Evolution in our Understanding of Ovarian Carcinogenesis

- Creation of the borderline category was an important achievement that focused our attention on a subset of tumors that had previously been buried in the category of carcinoma.
- Over the last 30 years significant advances have elucidated our understanding of these tumors.
Evolution in our Understanding of Ovarian Carcinogenesis

• The borderline category and the concept that there is a group of tumors whose behavior is unpredictable has now outlived its usefulness and needs to be replaced
Classification of Ovarian Tumors

Cystadenoma/adenofibroma
Atypical proliferative tumor
Noninvasive (intraepithelial) carcinoma

Invasive carcinoma *(Type I)*
- Low-grade micropapillary serous
- Mucinous
- Endometrioid
- Clear cell
- Malignant Brenner tumor

High-grade carcinoma *(Type II)*

*Borderline*