Los Angeles Society of Pathology

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The Origin of Ovarian Cancer:
A Different View

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To Create a Theory

• Put together facts

• We make an interpretation of these facts

• The theory has to make sense
Fimbria

Endosalpingiosis
Mullerian metaplasia
Endometrial transport

TIC Invasion

Exfoliated tumor cells from TIC or invasive carcinoma

Mullerian inclusions
Precursor condition
Carcinoma

Ovary or Peritoneum

Surface or invasive carcinoma
To Create a Theory

• Put together facts

• We make an interpretation of these facts

• The theory has to make sense
The Fallopian Tube Proposal

- Intraepithelial carcinoma in FT
- Carcinoma in the ovary and peritoneum
- Monoclonality
Why the Origin from the Fallopian Tube is Unlikely?

- Staging
- Physiopathology
- Pathology observations
- Clonality
Staging
Carcinoma of the Fallopian Tube
558 patients

Stage I - 40%
Stage II - 30%
Stage III & IV - 30%
## Serous Ovarian Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>16%</td>
</tr>
<tr>
<td>Stage II</td>
<td>11%</td>
</tr>
<tr>
<td>Stage III</td>
<td>55%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>18%</td>
</tr>
</tbody>
</table>
STIC

97 cases

89 coexisting pelvic HGSCa

82 widely disseminated at presentation with omental/peritoneal involvement
Carcinoma of the Fallopian Tube

I Alvarado-Cabrero, R Young, E Vamvakas, and R Scully

Gyn Oncology 72:367-379, 1999
Carcinoma of the Fallopian Tube
Stage I

- A-0 Epithelium
- A-1 Lamina Propria
- A-2 Muscle
- B Bilateral (0 – 1 or 2)
- C Serosa or +Ascites
- F Fimbriated Epithelium
<table>
<thead>
<tr>
<th>Stages</th>
<th>Recurrence Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA-0, IA-1, and IB-0</td>
<td>0%</td>
</tr>
<tr>
<td>Stage IA-2</td>
<td>40%</td>
</tr>
<tr>
<td>Stages IC, and IF</td>
<td>65%</td>
</tr>
</tbody>
</table>
Physiopathology
Serous Ovarian Cancer

Stage I  16%
Stage II  11%
Stage III  55%
Stage IV  18%
Physiopathology

Pelvic inflammatory disease
Bacilli $\rightarrow$ Fallopian tube $\rightarrow$ Pelvis

vs

Malignant cells from fallopian tube $\rightarrow$ Abdomen
Spread of Ovarian Cancer
# Ovarian Cancer

<table>
<thead>
<tr>
<th>Type</th>
<th>Stage I-II</th>
<th>Stage III or IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germ cell tumors</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>Serous carcinoma</td>
<td>27%</td>
<td>73%</td>
</tr>
</tbody>
</table>
Pathology

Observations
An acceptable theory should be able to explain most of the ovarian epithelial neoplasms.
Ovarian epithelial neoplasms frequently are heterogeneous with mixed components.
Ovarian Epithelial Neoplasms

Benign and malignant are related

Endosalpingiosis and borderline serous

Endometriosis and endometrioid carcinoma

Endometriosis and borderline mixed

Serous borderline and carcinoma

Mucinous benign, borderline, and carcinoma

Borderline mixed and high-grade carcinomas
Unusual cases are the best cases to understand the development of tumors
Ovarian Epithelial Neoplasms

Are very heterogeneous tumors

Serous
Mucinous
Clear cell
Ovarian Epithelial Neoplasms

Are very heterogeneous tumors

Serous carcinoma

Intracystic

Surface papillary

Intraparenchymatous (de-novo)

Malignant serous adenofibromas
Ovarian Epithelial Neoplasms

Are very heterogeneous tumors

Mucinous Intestinal Benign-Borderline-Carcinoma

Mucinous Endocervical Serous Mucinous Borderline mixed Focal high-grade carcinoma
Ovarian Epithelial Neoplasms

Are very heterogeneous tumors

Clear cell carcinoma, pure

Associated with endometriosis

Associated with adenofibroma
Clonality
Clonality in a Lesion

Same clone $\rightarrow$ Neoplasm

Different clones $\rightarrow$ Inflammatory
Clonality in a Lesion

Rheumatoid arthritis - Monoclonal

Different samples from one neoplasm - Polyclonal
Clonality in Tumors

Two different sites

Same clone $\rightarrow$ Metastasis

Different clone $\rightarrow$ Independent Tumors
Clonality in Tumors

Two different sites

Same clone $\rightarrow$ Metastasis

Different clone $\rightarrow$ Tumor
  Progression or Heterogeneity
Interpretation of Monoclonality

In different tumors of a patient

Squamous carcinoma of the buccal mucosa
TCC of the bladder

Intraepithelial or intracavitory metastases
Interpretation of Monoclonality

In different tumors from a patient

Squamous carcinoma of the buccal mucosa
TCC of the bladder

Cells from these areas are coming from a “Patch” of cells that harbor the same clone
Currently in the H&N, bladder, and thyroid monoclonality frequently represents independent lesions
In Gyn monoclonality in some cases can not be interpreted as metastases

Peritoneal leiomyomatosis
Peritoneal Leiomyomatosis

A benign condition

Spontaneous regression
In Gyn monoclonality can not be interpreted as metastases

Peritoneal leiomyomatosis

Bilateral ovarian carcinomas (P53)
In Gyn monoclonoality can not be interpreted as metastases

Peritoneal leiomyomatosis

Bilateral ovarian carcinomas

Bilateral borderline tumors
## Based on Monoclonality

<table>
<thead>
<tr>
<th>Condition</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal leiomyomatosis</td>
<td>Malignant</td>
</tr>
<tr>
<td>Bilateral ovarian carcinomas</td>
<td>Metastatic-stage II</td>
</tr>
<tr>
<td>Bilateral borderline tumors</td>
<td>Metastatic-stage II</td>
</tr>
</tbody>
</table>
Monoclonality in Gyn

Cells can be from a “Patch” in the Mullerian duct
The Origin of Ovarian Cancer

Uncommitted or stem cells
Uncommitted or Stem Cells

Coelomic mesenchyma
Mullerian duct
Endosalpingiosis
Endometriosis
Endocervicosis
Stem Cell Markers

- Sox 2
- ALDH1
- CD 133
The Origin of Ovarian Cancer

Uncommitted or stem cells

Stromal-epithelial interaction
The Origin of Ovarian Cancer

Uncommitted or stem cells

Stromal epithelial interaction

Stimulated by steroid hormones
Stimulated by Steroid Hormones

- Mullerian duct
- Endometriosis and related neoplasms
- Papillary metaplastic tumor of the fallopian tube
- Microinvasion in serous LMP pregnancy
- Implants of serous LMP in pregnancy
### Steroid Hormones Inducing Ovarian Tumors in Guinea Pigs

<table>
<thead>
<tr>
<th>Steroid Hormone</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>Epithelial cysts</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Glands in the stroma</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>Papillary proliferations on ovarian surface</td>
</tr>
<tr>
<td>Estrone</td>
<td>Fibrous plaques in the peritoneum</td>
</tr>
</tbody>
</table>
The Origin of Ovarian Cancer

Uncommitted or stem cells
Stromal epithelial interaction
Stimulated by steroid hormones
Genetic changes
Multicentricity
In Gyn monoclonality can not be interpreted as metastases

Peritoneal leiomyomatosis

Bilateral ovarian carcinomas

Bilateral borderline tumors
Endometriosis

Patients with Turner Syndrome

Male patients
Case Report

Endometriosis – Associated Serous Borderline Tumor and Endometrial Stromal Sarcoma of the Ovary: A Report of a Rare Lesion in an Infant


18- month-old female infant
Multicentricity

Serous Borderline

Stage III with non invasive implants

70% never recurs
# Ovarian Serous Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>1980</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size in cm</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Stage</td>
<td>1980</td>
<td>2010</td>
</tr>
<tr>
<td>-------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Advanced</td>
<td>57%</td>
<td>62%</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Outer Tumor Surface

Smooth- 70%

Papillary- 30%
GOC Statement Regarding Salpingectomy and Ovarian Cancer Prevention

GOC Recommendations:
1. Due to its cancer prevention potential, it is recommended that physicians discuss the risks and benefits of bilateral salpingectomy with patients undergoing hysterectomy or requesting permanent, irreversible contraception.
2. Given that the total benefits and risks of this practice change have not been defined, a national ovarian cancer prevention study focused on fallopian tube removal is a GOC priority.
Knowing that most of these cancers could likely begin in the fallopian tube means that our surgical convention should be reconsidered.
The Origin of Ovarian Cancer

Serous carcinoma

Surface papillary

Intracystic

Intraparenchymatous

Malignant serous adenofibroma
STIC in HGSCa

Primary in Ovary - 29%

Primary in Peritoneum - 50%
The morphologic appearance of a neoplasm must be a direct expression of its genetic composition.
The Origin of Ovarian Cancer

Uncommitted or Stem cells

Stromal epithelial interaction

Stimulated by hormones

Induce genetic changes

Different types of Ovarian cancer

“Fere ex nihilo”
Fallopian Tube Proposal

Why FT Ca only in-situ?
No Ca on Peritoneal Surface
Only for Serous Ca
“Fere ex nihilo”

Hormonal stimulation in serous cells
Serous differentiation in stem cells in the stroma
No Ca on peritoneal surface
This can explain any ovarian tumor type
Ovarian Cancer

Identification of genetic changes

Source of new treatments

Identification of stimulating factors

Source of new treatments and possible prevention
The Origin of Ovarian Cancer

Probably more than one theory is correct

Fere ex nihilo - 99%

Fallopian tube origin - 1%
Thank You