Cancer arising from Endometriosis and Its Clinical implications

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Suggested Reading

Nezhat’s Video-Assisted and Robotic-Assisted Laparoscopy and Hysteroscopy

EDITED BY: Camran Nezhat, Farr Nezhat, and Ceana Nezhat

CAMBRIDGE Medicine


Objectives

- Overview of endometriosis and ovarian cancer
- Pathogenesis of malignant transformation of endometriosis
- Clinical applications
- Future investigation
Chronic
Inflammatory
Estrogen-Dependent
Typically Recurrent/Progressive
Endometriosis and Epithelial Ovarian Cancer

- The malignant transformation of endometriosis was first suggested by Sampson in 1925

- **Common characteristics**
  - Metastatic – locally and distant
  - Loss of control of cell proliferation
  - Invade and damage
  - But **does not** cause Catabolic and metabolic disturbances

*Sampson JA. Endometrial carcinoma of ovary arising in endometrial tissue in that organ. Arch Surg 1925;10:1-72*
Epidemiological, Histological, and Molecular studies suggest a link between endometriosis and invasive epithelial ovarian cancer, based on frequent co-occurrence in surgical specimens, particularly the histological subgroups endometrioid, clear cell and low grade serous ovarian carcinoma.


Ovarian Clear cell carcinoma

WITH

Endometriosis

Ovarian Clear cell carcinoma

WITH

Endometriosis
Genetic mutations in HNF-1β and ARIDIA (Kato et al 2006; Wiegand et al 2010) in cancer and contiguous endometriosis

Ovarian Clear cell carcinoma WITH Endometriosis
Endometriosis and Cancer

Endometriosis and Cancer

<table>
<thead>
<tr>
<th></th>
<th>H&amp;E</th>
<th>BAF250a Expression</th>
<th>HNF-1β Expression</th>
<th>ER Expression</th>
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<tbody>
<tr>
<td>Clear-Cell Carcinoma</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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<tr>
<td>Contiguous Atypical Endometriosis</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
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<tr>
<td>Distant Endometriosis</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
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</tbody>
</table>

Endometriosis-associated ovarian cancer
Pathogenesis

- SOMATIC GENETIC MUTATIONS
- INFLAMATION
- HORMONAL
Endometriosis-associated ovarian cancer Pathogenesis

- **Somatic Genetic Mutation**
  
  - Endometriosis that appears benign already harbors **Molecular defects** and that ovarian cancer may arise within this lesion (LOH at 10q23.3 in 56% of endometriotic cysts)
Inflammation is hallmark of endometriosis

Loss of local tumor cell regulation due to chronic inflammation

- Endometriotic implant → Production of proinflammatory cytokines → Persistent exposure to these factors → disruption of homeostasis, genomic instability → abnormal proliferation

- Microenvironment of endometriotic cysts (↑free iron, ↑lipid peroxidase) induces state of oxidative stress that plays a role in malignant transformation of endometriosis
Hormonal factors

- ↑estrogen persist due to aromatase activity in microenvironment of endometriotic implant and in the ovary → alters physiologic milieu around ovarian surface → proliferation with increased chance of DNA damage and mutations.

Oxholm et al, 2007
Clinical Applications
“Average” life-time risk = 1.3%
- High-risk populations
  - BRCA mutations: 20-40%
  - Lynch Syndrome: 9%

Endometriosis = 2-3%

Median age at diagnosis is 63 years old

Most lethal gynecologic malignancy
- 21,980 newly diagnosed cases
- 14,720 deaths

>60% diagnosed in advanced stages. **Poor prognosis**

- 30% diagnosed at Stage I-II. **Better prognosis**

- 50% need another surgery *(unexpected diagnosis)*
Ovarian Cancer
Epithelial

- Screening
- Prevention
- Diagnosis
- Treatment
Ovarian Cancer Epithelial

- Screening
- Prevention
- Diagnosis
- Treatment
Prevalence of histologic types of epithelial ovarian cancer and their associated molecular genetic changes

Kurman RJ, Shih LM. Molecular Pathogenesis and Extraovarian Origin of Epithelial Ovarian Cancer. Shifting the Paradigm. Hum Pathol. 2011; 42(7):918-931
STAGE I OVARIAN CARCINOMA: DIFFERENT CLINICAL PATHOLOGIC PATTERNS

76 PATIENTS WITH STAGE I OVARIAN CARCINOMA UNDERWENT SURGICAL STAGING AND CYTOREDUCTION

Fertil Steril 2007;88(4):906-10
<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Ovarian Serous CA (n=22)</th>
<th>Ovarian Endometrioid CA (n=40)</th>
<th>Ovarian Clear Cell CA (n=10)</th>
<th>Mixed endometrioid / clear cell CA (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>61.05</td>
<td>52.9</td>
<td>58.6</td>
<td>52.2</td>
</tr>
<tr>
<td>Asymptomatic pelvic mass</td>
<td>13</td>
<td>3</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Symptomatic pelvic mass</td>
<td>2</td>
<td>19</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal Vaginal bleeding</td>
<td>1</td>
<td>19</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>H/o breast CA</td>
<td>8</td>
<td>--</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>BRCA mutations, tested</td>
<td>4</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ascites</td>
<td>2</td>
<td>--</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Pathology</td>
<td>Serous n (%)</td>
<td>Endometrioid n (%)</td>
<td>Clear cell n (%)</td>
<td>Mixed endometrioid and clear cell n (%)</td>
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<tr>
<td>---------------------------------</td>
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<td>------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Total</td>
<td>22 (30)</td>
<td>40 (53)</td>
<td>10 (13)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Bilateral ovarian tumors</td>
<td>11 (14)</td>
<td>3 (4)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Ovarian endometriotic cyst</td>
<td>1 (1.3)</td>
<td><strong>29 (72)</strong></td>
<td><strong>7 (70)</strong></td>
<td><strong>3 (75)</strong></td>
</tr>
<tr>
<td>Pelvic endometriosis</td>
<td>1 (1.3)</td>
<td><strong>14 (40)</strong></td>
<td><strong>1 (10)</strong></td>
<td><strong>1 (25)</strong></td>
</tr>
<tr>
<td>Pathology</td>
<td>Serous n (%)</td>
<td>Endometrioid n (%)</td>
<td>Clear cell n (%)</td>
<td>Mixed endometrioid and clear cell n (%)</td>
</tr>
<tr>
<td>-----------------------------------</td>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>1 (1.3)</td>
<td>17 (22)</td>
<td>1 (1.3)</td>
<td>--</td>
</tr>
<tr>
<td>Endometrial polyp / Hyperplasia</td>
<td>3 (4)</td>
<td>11 (14)</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4 (5.3)</td>
<td>28 (36)</td>
<td>3 (4.3)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>
Results

- **Nonserous ovarian** carcinomas comprised over \( \frac{2}{3} \) of the stage I ovarian carcinomas
- Most patients with **serous** carcinoma presented with **asymptomatic** pelvic masses
- Nonserous carcinomas presented with **pelvic pain, abnormal vaginal bleeding**, with or without a pelvic mass
- **Endometrial abnormalities 36\%**
- (Hyperplasia and carcinoma)
Ovarian Cancer Epithelial

- Screening
- Prevention
- Diagnosis
- Treatment
Endometriomas Classifications

- A Clinical and histologic classification of endometriomas

Most endometriomas are composed of endometrial implants, which invade a functional cyst.


Most endometriomas are composed of endometrial implants, which invade a functional cyst.

Hormonal therapy that suppresses the Ovulation which Decreases the rate of Ovarian endometrioma formation.


# Summary of combined oral contraceptive (COC) use and risk of cancer

<table>
<thead>
<tr>
<th>Studied relation</th>
<th>Reference</th>
<th>Type</th>
<th>Level of evidence</th>
<th>Material</th>
<th>Main findings</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of COC in relation to risk of epithelial ovarian</td>
<td>Beral et al. [2008]</td>
<td>Meta-analysis</td>
<td>2</td>
<td>23,257 cases 87,303 controls</td>
<td>• Decreased risk in COC ever users&lt;br&gt;• A more pronounced effect by duration of use</td>
<td>0.73 (0.70–0.76)</td>
</tr>
<tr>
<td>cancer</td>
<td>Havrilesky et al. [2013]</td>
<td>Systematic review/meta-analysis</td>
<td></td>
<td>657,055 women, 3,981,072 women years</td>
<td>• The protective effect lasts at least 30 years after use</td>
<td>0.73 (0.66–0.81)</td>
</tr>
<tr>
<td></td>
<td>Hannaford et al. [2007]</td>
<td>Prospective cohort</td>
<td>2</td>
<td>46,000 women 744,000 women years</td>
<td>• Decreased risk in COC ever-users&lt;br&gt;• A more pronounced effect by duration of use</td>
<td>0.54 (0.40–0.71)</td>
</tr>
<tr>
<td></td>
<td>Vessey and Painter [2006]</td>
<td>Prospective cohort</td>
<td>2</td>
<td>17,032 women, 540,000 women years</td>
<td>• The protective effect lasts at least 15–20 years</td>
<td>0.5 (0.3–0.7)</td>
</tr>
</tbody>
</table>
2 prospective cohort studies

- Nurses’ Health Study (121,700 US RNs, aged 30-55)
- Nurses’ Health Study II (116,430 US RNs, aged 25-42)

Hazard ratios (HR) and 95% CI adjusted for known and suspected ovarian cancer risk factors
Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses’ Health Studies

- Tubal ligation
  - ↓ 24% risk of ovarian CA (HR, 0.76; 95%CI 0.64-0.90)
  - Non-serous >> Serous tumors  \( p = 0.03 \)
  - Age < 35  \( p = 0.06 \)
**Hysterectomy**
- ↓ 20% risk of ovarian CA (95% CI 0.66-0.97)
- Non-serous >> Serous tumors \( p = 0.15 \)

**Oophorectomy (unilateral)**
- ↓ 30% risk of ovarian CA (95% CI 0.53-0.91)
- Non-serous ≡ Serous histology \( p = 0.60 \)
Tubal ligation

- 38% ↓ Endometrioid carcinoma
- 52% ↓ Clear cell carcinoma
- 19% ↓ High-grade serous carcinoma
The Role of the Fallopian Tube in Ovarian Cancer

High grade serous cancer

- Originates in distal fallopian tube (fimbria): unique environment

- Genetic Association
  - BCA1, BRCA2, p53
  - ≥ 70% detected in non-hereditary cases

- ~20% HGSC are + for BRCA1/2
Ovarian Cancer Epithelial

- Screening
- Prevention
- Diagnosis
- Treatment
Pelvic US

- useful in the identification of ovarian endometrioma with homogeneous hypoechogenic cystic features and those with mural malignant changes
- hyperdense mural nodules within the ovary and rapid growth of an endometrioma can be visualized on MRI – associated with malignant transformation

Endometrioma with diffuse, homogenous hypoechogenic features
- difficult to detect relatively small endocystic echogenic components with this modality

Endometrioma with mural malignant features
MRI

- more useful to both visualize endometriomas and possibly detect malignant transformation

- hyperdense mural nodules within the ovary and rapid growth of an endometrioma can be visualized on MRI – associated with malignant transformation

- In a cohort study comparing MRI findings of 10 patients with ovarian adenocarcinoma to 10 patients with benign endometriomas, Tanaka and colleagues found mural nodules in all 10 malignancies but in only 3 of the benign cases

Ovarian Cancer
Epithelial

- Screening
- Prevention
- Diagnosis
- Treatment
When endometriosis and endometrioma are diagnosed, surgical resection remains the most effective treatment.
Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer

ANNA-SOFIA MELIN¹, ², CECILIA LUNDHOLM¹, NINOA MALKI¹, MARJA-LIISA SWAHN², PÄR SPARÈN¹ & AGNETA BERGQVIST¹, ³

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, ²Department of Obstetrics and Gynecology, Karolinska University Hospital, Huddinge, and ³Department of Clinical Science and Education, Södersjukhuset, Karolinska Institute, Stockholm, Sweden

- All women with a 1st time discharge Dx of endometriosis between 1969 – 2007 in Sweden [National Swedish Patient Register]

- Identified all women Dx with epithelial ovarian cancer [National Swedish Cancer Register] at least 1 year after the endometriosis Dx

Acta Obstet Gynecol Scand. 2013
Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer

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\textsuperscript{1}Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, \textsuperscript{2}Department of Obstetrics and Gynecology, Karolinska University Hospital, Huddinge, and \textsuperscript{3}Department of Clinical Science and Education, Södersjukhuset, Karolinska Institute, Stockholm, Sweden

Strong reduction in risk of epithelial ovarian CA:

- One-sided oophorectomy involved with Endometriosis, \textit{multivariate} analysis (OR 0.19, 95\%CI 0.28-0.62) 81\% reduction.
- Complete extirpation of endometriotic tissue (OR 0.30, 95\%CI 0.25-0.55) 70\% reduction

Acta Obstet Gynecol Scand. 2013
There is now an unprecedented opportunity to develop a comprehensive plan for women with and without endometriosis for early detection and prevention of specific types of ovarian cancer.
How should we approach treatment options for women with endometriosis who are determined to be at an increased risk for ovarian cancer?

Identification of all women with endometriosis, either surgically documented or self-reported by symptoms

- **Hormonal treatment/pregnancy** aimed at reducing the risk of recurrent endometriosis and endometriomas.

- Careful follow up of ovarian endometriomas with imaging studies, particularly **MRI when Us is suspicious**, to detect any characteristics changes such as mural formation.

- **Fertility preservation**; embryo, egg or tissue preservation should be considered.
How should we approach treatment options for women with endometriosis who are determined to be at an increased risk for ovarian cancer?

- **Treatment planning:**
  - **Complete surgical resection** of all endometriotic foci in women undergoing surgical treatment, with tissue evaluation of ovarian endometriomas to rule out malignancy.
  - **Oophorectomy and Salpingectomy** should be individualized and offered based on the patient's risk and desires.
Further research is needed to understand the genomic and immunologic pathways of different mullerian tumors and endometriosis
Thank you