Cancer Arising from Endometriosis, Endometrioma and the Impact on Fertility: Our Theory

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NO DISCLOSER
Objectives

- Overview of endometriosis and ovarian cancer
- Pathogenesis of malignant transformation of endometriosis
- Clinical applications
- Future investigation
The malignant transformation of endometriosis was first suggested by Sampson in 1925.

Early epidemiologic studies suggested a link between endometriosis and invasive epithelial ovarian cancer, based on frequent co-occurrence in surgical specimens, particularly the histological subgroups endometrioid and clear cell ovarian carcinoma.

Sampson JA. Endometrial carcinoma of ovary arising in endometrial tissue in that organ. Arch Surg 1925;10:1-72
Overview of endometriosis and ovarian cancer

Sonographic characteristics of malignant transformation in endometrioid cysts

Figure 1 Endometrioid borderline tumor that developed in an endometrioid cyst in a 30-year-old patient. The ovarian lesion appeared as a unilocular-solid lesion (largest diameter of mass, 46 mm) with a papillary projection (height = 29 mm) (a), which was highly vascularized at power Doppler examination (b).

A. Testa et al, Ultrasound Obstet Gynecol 2011
DOI: 10.1002/uog.8970
Overview of endometriosis and ovarian cancer

Figure 1. Gross features of endometrioid adenocarcinoma associated with endometriosis of the ovary. A unilocular cyst contain inner nodules (carcinoma) is seen. The inner flat areas are also recognized (endometriosis).

Figure 4. Atypical endometriosis (left) is seen near the inner endometrioid adenocarcinoma cells. HE, x100.

T. Terada, Int J Clin Exp Pathol 2012;5(9):924-927
## Similarities between Endometriosis and Cancer

<table>
<thead>
<tr>
<th></th>
<th>Endometriosis</th>
<th>Ovarian CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menarche</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Genetic Predisposition</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Infertility</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Estrogen Exposure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BTL</td>
<td>Protective</td>
<td>Protective</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>Protective</td>
<td>Protective</td>
</tr>
<tr>
<td>Progesterone Exposure</td>
<td>Protective</td>
<td>Protective</td>
</tr>
</tbody>
</table>
Prevalence of Endometriosis in Women with Ovarian Cancer

- In a review of 15 published reports, the prevalence of endometriosis was
  - 39.2% (198/505) for clear cell
  - 21.2% (147/694) for endometrioid malignancies
  - 3.3% (39/1173) for serous type
  - 3.0% (13/436) for mucinous type ovarian cancer

Relative Risk of Ovarian Cancer in Women with Endometriosis

- In a retrospective cohort study of 20,686 women hospitalized for endometriosis, Brinton et al. found that patients with longstanding ovarian endometriosis had a high relative risk of ovarian cancer.

- Melin and colleagues later updated this report, finding that the highest risk was attributed to patients with ovarian endometriosis; there was no elevated risk for adenomyosis patients.

- Other factors associated with higher risk for ovarian cancer:
  - Longstanding endometriosis
  - Endometriosis diagnosed at younger ages

Relative Risk of Ovarian Cancer in Women with Endometriosis

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Stratified only</th>
<th>Stratified and adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
<td>OR (95% CI)*</td>
</tr>
<tr>
<td>Invasive clearance</td>
<td>1.49 (1.34–1.65)</td>
<td>&lt;0.0001</td>
<td>1.53 (1.37–1.70)</td>
</tr>
<tr>
<td>Clear-cell</td>
<td>3.73 (3.04–4.58)</td>
<td>&lt;0.0001</td>
<td>3.44 (2.78–4.27)</td>
</tr>
<tr>
<td>Endometroid</td>
<td>2.32 (1.94–2.78)</td>
<td>&lt;0.0001</td>
<td>2.20 (1.82–2.66)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.09 (0.76–1.58)</td>
<td>0.63</td>
<td>1.04 (0.71–1.51)</td>
</tr>
<tr>
<td>High-grade serous</td>
<td>1.11 (0.96–1.29)</td>
<td>0.16</td>
<td>1.16 (1.00–1.35)</td>
</tr>
<tr>
<td>Low-grade serous</td>
<td>2.02 (1.38–2.97)</td>
<td>&lt;0.0001</td>
<td>2.22 (1.48–3.31)</td>
</tr>
<tr>
<td>Borderline</td>
<td>1.26 (1.05–1.50)</td>
<td>0.012</td>
<td>1.19 (0.99–1.43)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.27 (0.97–1.67)</td>
<td>0.078</td>
<td>1.19 (0.90–1.57)</td>
</tr>
<tr>
<td>Serous</td>
<td>1.31 (1.05–1.63)</td>
<td>0.015</td>
<td>1.28 (1.02–1.61)</td>
</tr>
</tbody>
</table>

OR—odds ratio. *Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other). †Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other), and adjusted for duration of oral contraceptive use (never, <2 years, 2–4.99 years, 5–9.99 years, ≥10 years), and parity (0, 1, 2, 3, ≥4 children).

Table 3: Association between history of endometriosis and the histological subtypes of ovarian cancer

Relative Risk of Ovarian Cancer in Women with Endometriosis

Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis

Kim HS et al, 2014

- Meta-analysis

- Studies between 1990 and 2012

- 20 case–control and 15 cohort studies
  - 444,255 patients

- Ovarian cancer risk by endometriosis and clinicopathologic characteristics evaluated using risk ratio (RR) or standard incidence ratio (SIR)

- Prognosis investigated using hazard ratio (HR) with 95% confidence interval (CI)
Results

- **Endometriosis increases ovarian cancer risk:**
  - Case–control or two-arm cohort studies (RR, 1.265)
  - Single-arm cohort studies (SIR, 1.797)
Stage I–II disease, grade 1 disease and nulliparity were more common in EAOC (RRs, 1.959, 1.319 and 1.327)

Endometrioid and clear cell carcinomas were more common in EAOC (RRs, 1.759 and 2.606)

Serous carcinoma was less frequent in EAOC than in non-EAOC (RR, 0.733)
Results

- Progression free survival was not different between EAOC and non-EAOC. *(HR, 1.023; 95% CI, 0.712-1.470)*

- EAOC was associated with better overall survival than non-EAOC. *(HR, 0.778)*
Conclusion

- “There is a recognized association between endometriosis and clear cell, low-grade serous and endometrioid ovarian cancer, but the overall risk of ovarian cancer amongst women with endometriosis remains low, with a relative risk ranging from 1.3 to 1.9, which means that at worst the life-time risk of ovarian cancer is increased from ~1 in 100 to 2 in 100.”

Johnson & Hummelshoj, for the WES Montpellier Consortium, *Hum Reprod* 2013
Endometriosis associated with the increased risk of ovarian cancer:
- including early-stage disease
- low-grade disease
- specific histology (endometrioid, clear cell carcinoma)

Endometriosis may not affect disease progression after the onset of ovarian cancer
Objectives

- Overview of endometriosis and ovarian cancer
- Pathogenesis of malignant transformation of endometriosis
- Clinical applications
- Future investigation
Features shared by endometriosis and cancer

- Ability to evade apoptosis
- Macrophage-mediated inflammation
- Stem cell-like undifferentiation
- Angiogenic potential

Pollaco et al. *Gynecological Endocrinology*, 2012
DOI: 10.3109/09513590.2011.650761
Features shared by endometriosis and cancer

Pollaco et al. *Gynecological Endocrinology*, 2012
DOI: 10.3109/09513590.2011.650761
Endometriosis-associated ovarian cancer Pathogenesis

- GENETIC

- Endometriosis that appears benign already harbors genetic defects and that ovarian cancer may arise within this lesion
  
  - Several groups have performed allelotyping of endometriosis along with adjacent ovarian carcinoma and found common genetic alterations e.g. PTEN gene mutation

  - Genetic mutations in HNF-1β and ARIDIA are known to be related with the onset of endometrioid or clear cell carcinoma from endometriosis (Kato et al 2006; Wiegand et al 2010)

  - Nezhat et al (2002) suggested alterations in bcl-2 and p53 may be involved in the malignant transformation of endometriotic cysts
**INFLAMMATORY**

- Inflammation is hallmark of endometriosis
  - Endometriotic implant $\rightarrow$ Production of proinflammatory cytokines $\rightarrow$ Persistent exposure to these factors $\rightarrow$ disruption of homeostasis, genomic instability $\rightarrow$ 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 in microenvironment of endometriotic implant in the ovary → alters physiologic milieu around ovarian surface → proliferation with increased chance of DNA damage and mutations.

Oxholm et al, 2007
Clinical Applications
The patient is a 29yo P0 who was found to have a left 2.6x3.6cm ovarian cyst (dermoid vs endometrima) during her evaluation for infertility for one year.

Ob/Gyn History: Para 0, regular menstrual cycles, mild dysmenorrhea. Not obese or overweight. Denies any STDs or pelvic infections.

No Past Medical or Surgical
Case Presentation

- She had laparoscopy, left ovarian cystectomy for a presumed dermoid cyst, and dilation and curettage.
- Laparoscopy: Pelvic endometriosis.
- Pathology
  - Left Ovarian Cyst: Well-differentiated endometrioid adenocarcinoma
  - Endometrial Curetttings: Proliferative Endometrium, polypoid fragments of endometrium with complex endometrial hyperplasia with marked atypia
After consulted with Gyn Oncologist and Neg. Metastatic W/U

Laparoscopic Robotic assisted surgical staging followed by chemotherapy, Taxol & Carb.

Successful Spontaneous pregnancy x 2

NED X4 Years.
195 cases of malignant tumors arising from endometriosis

- **Sites**
  - Ovary: 78.7%
  - Extragonal sites: 21.3%

- **Types of malignancies**
  - Endometrioid carcinoma
  - Clear cell carcinoma
  - Carcinosarcoma
  - Adenosarcoma

Heaps J, Nieberg R, Berek J
Malignant Neoplasms Arising in Endometriosis
Obstet Gynecol. 1990 Jun;74(6):1023-8
Nezhat et al

- 15 pts with infiltrating endometriosis of bladder
- Laparoscopic segmental cystectomy
- 1 pt diagnosed with endometriosis on frozen section
- Final pathology: adenosarcoma of bladder
- 2 previous surgeries showed bladder endometriosis on biopsy

Nezhat C, Malik S, Osias J, Nezhat F, Nezhat C

Laparoscopic management of 15 patients with infiltrating endometriosis of the bladder and a case of primary intravesical endometrioid adenosarcoma

Fertil and Steril 2002;78(4):872-875
Clinical Applications

- **Ovarian cancer**
  - 2\textsuperscript{nd} most common gynecologic malignancy in developed countries

- **in the U.S.**
  - 22,000 new cases
  - 14,000 cancer-related deaths expected from ovarian cancer in 2013

- **lifetime risk is 1:70 and the average age at diagnosis of ovarian cancer in the US is 63 years old**

30% diagnosed at Stage I ..... Better prognosis

However 50% ovarian cancers diagnosed early stage need another surgery (unexpected diagnosis) and most are Endometrioid and Clear cell carcinoma

>60% diagnosed in advanced stages (majority are papillary serous). Poor prognosis
Pathogenesis

Dualistic model for ovarian carcinogenesis

- **Type I tumors** (low-grade serous, endometrioid, clear cell, mucinous)
  - Indolent, present in stage 1
  - KRAS or BRAF mutations

- **Type II tumors** (high-grade serous, high grade endometrioid, malignant mixed mesodermal tumors)
  - Aggressive, advanced stage at dx
  - TP53 mutations
Endometriosis-associated ovarian cancer Risk Factors

- Long-standing endometriosis
- Endometriosis diagnosed at an early age
- Endometriosis associated with infertility and/or history of infertility treatment
- Ovarian endometriomas
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
Endometriosis-associated ovarian cancer Screening

- Endometrial evaluation in symptomatic patients
    - 76 consecutive cases of stage I ovarian cancer
    - All nonserous ovarian carcinomas have been diagnosed from associated symptoms, such as pelvic pain with endometrial/adnexal masses or vaginal bleeding associated with underlying endometrial pathology
<table>
<thead>
<tr>
<th>Pathology</th>
<th>Serous Papillary n (%)</th>
<th>Endometrioid n (%)</th>
<th>Clear cell n (%)</th>
<th>Mixed endometrioid and clear cell n (%)</th>
<th>Total n (%)</th>
<th>P value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>22 (30)</td>
<td>40 (53)</td>
<td>10 (13)</td>
<td>4 (5)</td>
<td>76 (100)</td>
<td></td>
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<tr>
<td>Bilateral ovarian tumors</td>
<td>11 (14)</td>
<td>3 (4)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>16 (21)</td>
<td>0.00027</td>
<td>0.27</td>
</tr>
<tr>
<td>Ovarian endometriotic cyst</td>
<td>1 (1.3)</td>
<td>29 (38)</td>
<td>7 (9)</td>
<td>3 (4)</td>
<td>40 (53)</td>
<td>0.0000001</td>
<td>23.33</td>
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<tr>
<td>Pelvic endometriosis</td>
<td>1 (1.3)</td>
<td>14 (18)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>17 (22)</td>
<td>0.038</td>
<td>6.05</td>
</tr>
<tr>
<td>Pathology</td>
<td>Serous Papillary n (%)</td>
<td>Endometrioid n (%)</td>
<td>Clear cell n (%)</td>
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</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>1 (1.3)</td>
<td>17 (22)</td>
<td>1 (1.3)</td>
<td>--</td>
<td>19 (25)</td>
<td>0.0086</td>
<td>7.0</td>
</tr>
<tr>
<td>Endometrial polyp / Hyperplasia</td>
<td>3 (4)</td>
<td>11 (14)</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>16 (21)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>4 (5.3)</td>
<td>28 (36)</td>
<td>3 (4.3)</td>
<td>2 (3)</td>
<td>16 (21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

- **Nonserous ovarian** carcinomas comprised over 2/3 of the stage I ovarian carcinomas.

- Most patients with **serous papillary 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)
What Screening and Diagnostic Opportunities are Available to Practitioners for Women with Endometriosis?

- Screening for genetic mutations in ovarian cancer is just the beginning, and an emerging concept of a dual model of ovarian carcinogenesis divides ovarian carcinomas into two groups.

- High-grade serous carcinomas tend to present at an advanced stage, are associated with TP53 mutations, and likely arise from tubal epithelium.

- Low-grade serous, endometrioid, and clear cell carcinomas present at an earlier stage. These are more indolent, are associated with PTEN, BCL2 and/or ARID1A mutation, and likely arise from endometriosis.

- Currently however, there is not sufficient data to recommend mutation screening tests in patients with endometriosis.


What Screening and diagnostic Opportunities are Available to Practitioners for Women with Endometriosis?

- CA-125 has been shown to be a poor screening modality for endometriosis-associated ovarian cancers as well as non-endometriosis ovarian cancers.

- Wang et al found that CA-125 levels were lower in endometriosis-associated ovarian carcinoma compared to patients with non-endometriosis ovarian carcinoma (mean 122.9 versus 1377.5 respectively).

- Lim et al found that 32.6% of patients with early stage endometriosis-associated ovarian carcinoma demonstrated normal CA-125 levels.


What Screening and diagnostic Opportunities are Available to Practitioners for Women with Endometriosis?

**Pelvic U/S**

- useful in the identification of ovarian endometrioma with homogeneous hypoechogenic cystic features and those with mural malignant changes

- difficult to detect relatively small endocystic echogenic components with this modality

*Endometrioma with diffuse, homogenous hypoechogenic features*

*Endometrioma with mural malignant features*
What Screening and Diagnostic Opportunities are Available to Practitioners for Women with Endometriosis?

- **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

*Tanaka YO et al. Ovarian carcinoma in patients with endometriosis: MR imaging findings. Genitourinary Imaging 2000; 125*

Uterus

Left adnexa

Uterus
What Preventative Measures can be Offered to Women with Endometriosis?

When endometriosis is diagnosed, surgical resection remains the most effective treatment.
Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer

ALLA-SOFIA MELIN¹,², CECILIA LUNDHOLM¹, NINOA MALIKI¹, 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
220 cases and 416 controls entered the study

Information on hormonal and surgical treatments, and other reproductive factors was extracted from medical records according to pre-specified protocols
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

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- No statistically significant differences in cancer risk depending on types of hormonal treatment

- EXCEPT for a borderline significance for months of Danazol use (OR 1.06, 95% CI 1.00-1.12)
Strong reduction in risk of epithelial ovarian CA for:

- When endometriosis is diagnosed, surgical resection remains the most effective treatment
  - One-sided oophorectomy, multivarian analysis (OR 0.19, 95%CI 0.28-0.62)
  - Complete extirpation of endometriotic tissue (OR 0.30, 95%CI 0.25-0.55)
Life-time risk of Ovarian CA for a woman in Sweden, with *endometriosis*: 1.5%

- Risk reduction of 30% for ovarian CA if all visible endometriosis is surgically removed (ie: 95 pts in need of having radical surgery to prevent 1 case of ovarian cancer; ~ €161 500)

Life-time risk of Ovarian CA for a woman in Sweden, with *ovarian endometriosis*: 2%

- Risk reduction of 81% if affected ovary is removed (ie: 62 pts needing to have 1-sided oophorectomy to prevent 1 case of ovarian CA; ~ €105 400)
CONCLUSION

- Total extirpation of the endometriotic tissue and/or one-sided oophorectomy protects against epithelial ovarian cancer

- Current study did not show that hormonal Tx affects future risk of ovarian CA, except the possible increased risk associated with Danazol
What Preventative Measures can be Offered to Endometrioma?

- Most endometriomas are composed of endometrial implants, which invade a functional cyst
- Hormonal therapy
  - hormonal therapy alone however often fails to cause total regression of endometriomas, and is most effective following thorough surgical excision of endometriomas and associated endometriosis.
  - a review of the literature by Vercellini and colleagues comparing diligent post-operative oral contraceptive versus sporadic use demonstrated a pooled odds ratio of 0.21 (95% CI 0.11-0.40) for ovarian endometrioma recurrence
  - Koga et al presented similar findings, with GnRH agonists, OCPs, levonorgestrel IUD, and pregnancy

Endometriomas Classifications

- A Clinical and histologic classification of endometriomas

Nezhat Classification

Type 1

Primary endometrioma

- Same origin as peritoneal endometriosis
- Difficult to remove due to fibrosis
- Removed in pieces
Nezhat Classification

Type II:
Secondary endometrioma

- Follicular or luteal cyst invaded by cortical endometriosis
Nezhat Classification

- IIA: superficial endometriosis implants without penetration of cyst, thus cyst easily separable from cortex
Nezhat Classification

- IIB: endometriosis area deeper, cyst wall adherent to cortex
IIC: endometriosis is deep invading cyst and cyst wall, difficult separation between cortex and cyst
Endometriosis: Treatment of Endometriomas
What Preventative Measures can be Offered to Endometrima?

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How should we approach treatment options for women with endometriosis who are determined to be at an increased risk for ovarian cancer?

- **Treatment planning:**
  - Identification of all women with endometriosis, either surgically documented or self-reported by symptoms.
  - Careful follow up of ovarian endometriomas with imaging studies, particularly MRI when Us is suspicious, to detect any characteristics changes such as mural formation.
  - Complete surgical resection of all endometriotic foci in women undergoing surgical treatment, with tissue evaluation of ovarian endometriomas to rule out malignancy.
  - Hormonal treatment aimed at reducing the risk of recurrent endometriosis and endometriomas.
Future Studies

- While serum markers have not shown promising results, MRI imaging may be a key step in identifying women at an increased risk.
  - There is limited research examining the implications of mural nodules within endometriomas and how this finding predicts malignant transformation. Long-term follow-up is necessary to understand the timeline of transformation in patients with mural nodules, as well as the predictive value of such a discovery.

- Further research is needed to understand the genomic and immunologic pathways of endometriosis.
  - may be accomplished by larger studies with direct evaluation of endometriosis tissue.
Delineating Which Patients May be at an Increased Risk for Ovarian Cancer

- Both, the gynecologist and the general practitioner should pay special attention to patients with endometriosis and the following history:
  - Long-standing endometriosis
  - Endometriosis diagnosed at an early age
  - Endometriosis associated with infertility and/or history of infertility treatment
  - Patients with ovarian endometriomas
Conclusion

- There is now an unprecedented opportunity to develop a comprehensive plan for screening women with endometriosis for early detection and prevention of specific types of ovarian cancer.

2. Nezhat F, Pejoivc T, Reis FM, Guo SW. The Link Between Endometriosis and Ovarian Cancer: Clinical Implications. Int J Gynecol Cancer 2014. [Accepted for publication]

Thank you