Endometriosis-Associated Ovarian Cancer: Malignant Transformation of Endometriosis

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I have no disclosures.

Background
- EOC is gynecologic cancer with highest mortality in the US
  - 22,240 women dx and 14,030 deaths in 2013
- 70% of cases have serous histology
- Clear cell accounts for 12% and second-leading mortality cause from EOC
  - Genetically stable
  - Low mitotic rate
  - Lacks chromosomal instability

Sugiyama et al. Cancer 2000;88:2584-9
Crotzer et al. Gynecol Oncol 2007;105:404-8

Background
- Endometriosis considered benign, chronic gynecologic disorder
- Exact prevalence not known since many are asymptomatic and definitive dx made histologically
- Estimates
  - 10% of premenopausal women
  - 4% of postmenopausal women
  - 35-40% of women with infertility or chronic pelvic pain


Background
- Noteworthy association between endometriosis and clear cell, endometrioid EOC
  - Cohort study in Denmark (1978-1998)
  - Increased risk of EOC in women with endometriosis restricted to 2 histologies
    - Endometrioid (RR, 2.53; 95% CI 1.19-5.38)
    - Clear cell (RR, 3.37; 95% CI 1.24-9.14)


Background
- Controversy over causality of relationship
  - Invasive cancer may obliterate endometriosis
  - Endometriotic implants may be missed on histologic examination
  - Difficult to distinguish b/w endometriosis not related to cancer and endometriosis that may have undergone malignant transformation

Background

- Endometriosis shares common features with malignancies
- Can attach and adhere to other tissue
- Can invade locally and metastasize distantly
- Endometriosis unlike cancer does not have catabolic potential and is almost never fatal

Epidemiology

- Data from large cohort and case-control studies indicate association between endometriosis and increased risk of EOC is modest
- Cohort studies and case-control studies
  - Swedish National Board of Health and Welfare
  - National Swedish Cancer Registry
  - Shizouka Cancer Registry

<table>
<thead>
<tr>
<th>Author</th>
<th># of Patients</th>
<th>F/U Time (Years)</th>
<th>Overall Cancer Risk</th>
<th>EOC Cancer Risk</th>
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<td>20,686</td>
<td>&lt;0.25</td>
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Relationship Between Endometriosis and EOC: Sampson’s Criteria

- Endometriosis must be present in close proximity to tumor
- No other primary site for tumor identified
- Tissue resembling endometrial stroma surrounding glands must be present
- Scott’s additional requirement
- Histologically proven transition from endometriosis to cancer

Cohort Studies Evaluating EOC Risk in Patients with Endometriosis

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Association between history of endometriosis and the histological subtypes of ovarian cancer (Pearce et al., 2012)

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<td>OR (95% CI)</td>
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</table>
Pathology

- Common genetic alterations in allelotyping of endometriosis along with adjacent EOC
- Genetic defects only in carcinoma and not in benign epithelium

Atypical Endometriosis: Precursor to Cancer

- Cytologic atypia and hyperplasia documented in endometriosis
- May represent transition from endometriosis to cancer
- 194 cases of ovarian endometriosis
  - Cytologic atypia (severe, 3.6%; mild 22%)
  - Hyperplasia 2%
  - Severe atypia in 14 (100%) EAOC and 6 (2%) controls
  - Atypical endometriosis in 61% of EAOC and 1.7% of controls
  - Severe atypia in 29/37 (78%) EAOC cases, transition from typical to atypical endometriosis in 22 cases and transition from atypical endometriosis to cancer in 23 cases

Atypical Endometriosis

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Hyperplasia as Precursor to Cancer

- CH seen in association with cytologic atypia
- Role as independent precursor in EAOC remains elusive
- Complex hyperplasia
  - 50% of 14 EAOC cases
  - 1% of 325 controls (p<0.0001)

Pathogenesis: Genetic Alterations

- Genomic instability and clonal outgrowth are fundamental in oncogenesis
- Loss of heterozygosity (LOH)
  - 1LOH at ovarian suppressor gene loci seen in 11/40 (27.5%) of endometriosis samples
  - 2Common LOH event in 9/11 cases of ovarian endometriosis adjacent to ovarian carcinoma
  - 3LOH events accumulate as disease progresses

2Perfumo et al. Gynecol Oncol 2002;84:280-84
3Takising et al. Hum Pathol 1997;30:249-51
4Ogawa et al. Gynecol Oncol 2000;77:298-304
5Perfumo et al. Gynecol Oncol 2002;84:280-84
8Munksgaard et al. Gynecol Oncol 2012;124:164-69
PTEN

PTEN inactivation may be early event in malignant transformation of endometriosis

Mutations occur in both endometrial and ovarian carcinomas

<table>
<thead>
<tr>
<th>Histology</th>
<th>Inactivation (LOH)</th>
<th>Somatic PTEN Mutation</th>
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</thead>
<tbody>
<tr>
<td>Endometriotic Ovarian Cyst</td>
<td>13/23 (56.6%)</td>
<td>5/23 (20.8%)</td>
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<tr>
<td>Endometroid EOC</td>
<td>8/19 (42.1%)</td>
<td>4/19 (20%)</td>
</tr>
<tr>
<td>Clear Cell EOC</td>
<td>6/22 (27.3%)</td>
<td>2/22 (8.3%)</td>
</tr>
</tbody>
</table>

Sato et al. Cancer Res 2000;60:7052-

Mouse model of endometriosis and endometroid ovarian cancer

- KRAS over-expression
- PTEN knockout in ovarian surface epithelium

Resulted in endometrial morphology
Suggests potential role these genetic changes may play in malignant transformation


p53

- Mutation or loss of function critical even in development of EOC
- Not seen in endometriosis that is not associated with carcinoma
- Chromosomal loss of p53 in severe endometriosis
  - (Biscoff et al., 2002)
- p53 accumulation within endometriosis that is adjacent to carcinoma compared to endometriosis without carcinoma
  - (Nezhat et al., 2002)
- Several other series have not been able to reproduce these results

ARID1A

AT-rich interactive domain 1A gene

- Tumor suppressor gene
- Encodes for BAF250a protein
- Plays critical role in SWI-SNF complex present in all eukaryotes
- Responsible for regulating critical cellular processes and gene expression


Results
- 6 of 18 samples had somatic mutations in ARID1A
- ARID1A mutations were found in
  - 55 of 119 (46%) ovarian clear cell carcinomas
  - 10 of 33 (30%) endometroid carcinomas
  - None of 76 high-grade serous carcinomas
- IHC analysis confirmed loss of expression of BAF250 protein that correlated with ARID1A mutational status
- In 2 cases, endometriotic lesions adjacent to the tumor had the same mutations as were found in the cancer

ARID1A
- Mutations have also been found in low-grade uterine carcinomas
- Treatment strategy?
  - Loss of ARID1A activates transcriptional events that may be targetable
- Prevention strategy?
  - BAF250a expression in endometriotic lesions to identify lesions at risk of malignant transformation

Estrogen
- Aromatase
  - Catalyzes conversion of androstenedione and testosterone from ovary and adrenals to estrone and estradiol (E2)
  - Absent in endometrium
  - High concentrations in endometriotic lesions
  - Increased conversion of androgens to estrogens
  - 17β-hydroxysteroid dehydrogenase type 2
  - Converts more potent E2 to less potent estrone
  - Present in eutopic endometrium
  - Absent in endometriotic lesions
  - Result is increased levels of E2 by increased production and decreased inactivation

Endometriosis-Associated Ovarian Cancer: A Distinct Clinical Entity?
- Younger
- Diagnosed at earlier stage
- Lower grade lesions
- Better prognosis (even when adjusting for stage)

EAOC: An Entity Distinct from Other Ovarian Carcinomas
- 58 patients with EAOC nested with four age-matched non-EAOC controls
- Patients with EAOC proved to:
  - Lower stage (p<0.001)
  - Over-expression of clear cell and endometrioid histologies (p=0.0001)
  - Lower grade lesions (p=0.03)
  - Optimally debulked to no gross residual disease (p=0.0001)
  - Significantly better OS (p=0.0001)

Endometrioid Ovarian Cancer
Retrospective review of patients with endometrioid ovarian cancer
Sampson’s/Scott’s criteria to define association with endometriosis
21 patients with EAOC vs. 44 patients with EOC
EAOC patients were
- Younger
- Lower stage of disease
- Higher prevalence of low grade tumors
- More concomitant endometrial cancers (with 92% concordance in grade)
- No significant difference in survival
  (5-yr survival 44% vs. 38%, p=0.47)
- Age was the only significant predictor of survival

Retrospective Analysis of Presentation, Treatment, and Outcome
Objective
- To investigate the relationship of menopausal status and tumors arising in endometriosis

Behavior and outcome of different histologies of epithelial ovarian cancer known to arise from endometriosis were analyzed
Results

- 140 patients with complete clinical information
  - 42 (30%) clear cell carcinoma
  - 92 (65.7%) endometrioid carcinoma
  - 6 (4.3%) mixed serous, clear cell, and endometrioid carcinoma

- Relationship with endometriosis
  - 28.6% were “associated with” endometriosis (n=40)
  - 37.1% were “arising in” endometriosis (n=52)
  - 34.3% had no endometriosis (n=48)

- 42 (30%) clear cell carcinoma
- 5 (13.2%) grade = 1
- 4 (10.9%) stage 1
- 7 (16.7%) grade = 2
- 14 (33.3%) stage 2
- 13 (31.0%) grade = 3
- 23 (54.7%) stage 3

- 7 (23.3%) clear cell carcinoma
- 11 (38.9%) grade = 1
- 16 (57.1%) stage 1
- 7 (23.3%) grade = 2
- 11 (38.9%) stage 2
- 13 (45.2%) grade = 3
- 18 (62.1%) stage 3

Recurrences & Deaths by Menopausal Status

- Clear Cell
  - Pre-menopausal
    - Median F/U (months): 41 (1.99), 30 (1.105)
    - Recurrences: 1 (7.7%), 13 (44.8%)
    - Death: 1 (7.7%), 13 (44.8%)
  - Post-menopausal
    - Median F/U (months): 42.5 (4.95), 36 (1.109)
    - Recurrences: 6 (20.0%), 14 (44.5%)
    - Death: 3 (10.0%), 9 (31.0%)

- Endometrioid
  - Pre-menopausal
    - Median F/U (months): 51.5 (4.99), 36 (1.109)
    - Recurrences: 6 (20.0%), 14 (44.5%)
    - Death: 3 (10.0%), 9 (31.0%)
  - Post-menopausal
    - Median F/U (months): 51.5 (4.99), 36 (1.109)
    - Recurrences: 6 (20.0%), 14 (44.5%)
    - Death: 3 (10.0%), 9 (31.0%)

- Relationship with Endometriosis
  - Arising in Endometriosis
    - 6 (46.2%) endometrioid
    - 6 (46.2%) clear cell
    - 1 (7.7%) no endometriosis
  - Associated with Endometriosis
    - 6 (46.2%) endometrioid
    - 12 (41.4%) clear cell
    - 1 (3.5%) no endometriosis

- No endometriosis
  - 7 (17.2%) endometrioid
  - 10 (24.4%) clear cell
  - 1 (2.4%) no endometriosis

Recurrences & Deaths by Relationship with Endometriosis

- Clear Cell
  - Awaiting Endometriosis
    - Median F/U (months): 29 (1.66), 49 (1.98)
    - Recurrences: 4 (15.8%), 5 (45.4%)
    - Death: 3 (12.1%), 5 (45.4%)
  - No Endometriosis
    - Median F/U (months): 48 (10.99), 19 (1.98)
    - Recurrences: 5 (13.2%), 12 (33.3%)
    - Death: 3 (7.39), 7 (18.4%)

- Endometrioid
  - Awaiting Endometriosis
    - Median F/U (months): 51 (4.99), 19 (1.98)
    - Recurrences: 6 (13.8%), 14 (44.5%)
    - Death: 3 (7.39), 7 (18.4%)
The association of endometriosis with improved survival was slightly attenuated and no longer statistically significant after adjustment for menopausal status (p=0.07).

Case Control Study: EAOC-Serous EOC

- 67 cases and 134 controls
- 41 with endometrioid EAOC
- 26 with clear cell EAOC

Matched by age, date of dx, stage

Results

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<tr>
<th>Variable</th>
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<th>Control (n =134)</th>
<th>p value</th>
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*Difference within +/- 5 yrs of age at time of dx

Results

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5-Year DFI

Mean DFS (months):
- EAOC = 103.2
- Control = 71
p = 0.03
Conclusions

- Patients with EAOC had higher rate of synchronous EC
- No difference in demographic or tx patterns between cases and controls
- Lower rate of recurrence and improved 5-year DFI in EAOC
- No OS difference between cases and controls

Conclusions

- Association between endometriosis and EOC supported by epidemiologic research
- Molecular pathway poorly defined
- Micro-environment of endometriosis and EAOC share cytokines and mediators
  - ? Link or sharing of common signaling molecules of 2 separate lesions
- Future studies to elucidate roles of oxidative stress, inflammation and estrogen in development of EAOC
  - Impact patient counseling
  - Clinically relevant interventions, risk reduction

Future Directions

- Identification of endometriotic lesions at greatest risk of malignant transformation
- Better understanding may lead to preventative strategies for those at greatest risk of EAOC and development of novel therapies

Thank You