Endometriosis and Cancer: What the Practitioner Needs to Know

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Endometriosis and Cancer

• Endometriosis is a common condition, possibly affecting 7-15% of women of reproductive ages
• Suggestive evidence that women with endometriosis are at elevated risks of developing certain cancers
• Issue difficult to study and relationships remain unresolved
Endometriosis and Cancer: Reasons for Concern

• Evidence that endometriosis derives from various genetic, hormonal and immunologic factors

• Malignant ovarian tumors arise in 5-10% of patients with ovarian endometriosis; frequency of other cancers is less clear

• Few clinical or epidemiologic studies that clarify long-term cancer risks
Difficulties in Assessing Relationships with Cancer Risk

• Many cases of endometriosis or leiomyomas are unrecognized
• Diagnoses may lead to increased testing and detection of cancers
• Hysterectomies and/or oophorectomies complicate evaluation
• Many studies of case-control design, raising issues of recall bias
Brinton et al. Cancer risk after a hospital discharge diagnosis of endometriosis. 
*Am J Obstet Gynecol* 1997;176:572-9

- Retrospective cohort design
- 20,686 women hospitalized for endometriosis between 1969-1983 identified through the nationwide Swedish Inpatient Register
- Linkage against the National Swedish Cancer Registry through 1989 to identify subsequent diagnoses of cancer
- Average of 11.4 years of follow-up
### Swedish Record Linkage Study: Standardized Incidence Ratios for Subsequent Cancers

<table>
<thead>
<tr>
<th></th>
<th>Obs</th>
<th>Exp</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>297</td>
<td>234.4</td>
<td>1.3</td>
<td>1.1-1.4</td>
</tr>
<tr>
<td>Ovary</td>
<td>29</td>
<td>15.1</td>
<td>1.9</td>
<td>1.3-2.8</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>48</td>
<td>35.6</td>
<td>1.4</td>
<td>1.0-1.8</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>28</td>
<td>15.7</td>
<td>1.8</td>
<td>1.2-2.6</td>
</tr>
</tbody>
</table>
Swedish Record Linkage Study: SIRs for Ovarian Cancer by Detailed Parameters

* 95% CIs exclude 1.0

Years of Follow-up

- 1-2
- 3-4
- 5-9
- 10+

Site of Origin of Endometriosis

- Ovary
- Pelvis
- Uterus

*
Swedish Record Linkage Study: Ovarian Cancer Findings

• Biologic effect suggested by high risks related to years of follow-up and site of origin
• Results complement clinical observations of synchronous events and suggest a long-term effect
• Confounding by parity or infertility possible, although not likely
Retrospective Cohort Study of Women Evaluated and Treated for Infertility

1965                         1988                             1999

• Varying causes of infertility (e.g., endometriosis, anovulation)
• Treatment regimens
• Potential confounders (e.g., parity)

12,193 patients
Detailed medical record abstraction

Death certificates
Questionnaires
Registry linkage
Cancer validation
## U.S. Study of Women Evaluated and Treated for Infertility: Cause of Infertility

<table>
<thead>
<tr>
<th>Cause of Infertility</th>
<th>Ovarian Cancers</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td>13</td>
<td>1.2 (0.6-2.5)</td>
</tr>
<tr>
<td>Anovulation</td>
<td>12</td>
<td>1.0 (0.5-2.0)</td>
</tr>
<tr>
<td>Tubal disease</td>
<td>16</td>
<td>0.8 (0.4-1.6)</td>
</tr>
<tr>
<td>Male factor</td>
<td>10</td>
<td>1.0 (0.5-2.1)</td>
</tr>
<tr>
<td>Cervical disorder</td>
<td>2</td>
<td>0.8 (0.2-3.3)</td>
</tr>
<tr>
<td>Uterine disorder</td>
<td>6</td>
<td>0.9 (0.4-2.3)</td>
</tr>
</tbody>
</table>

*RRs adjusted for age, calendar year, site and parity at follow-up*

*Brinton et al., Fertil Steril 2004; 82:405-414.*
U.S. Study of Women Evaluated and Treated for Infertility: Endometriosis and Ovarian Cancer

Among women with primary infertility (relative to women with secondary infertility)

RR (95% CI)

No
1.9 (0.9-1.4)

Yes
3.1 (1.5-6.8)

Brinton et al. Fertil Steril 82:405-414, 2004
Endometriosis and Ovarian Cancer: Results from a Pooled Analysis of Ovarian Cancer


- Pooled analysis involving 5,207 ovarian cancer cases and 7,705 controls
- Endometriosis associated with increased risk (RR=1.5, 95% CI 0.8-2.8)
- Increased risks also observed for
  - serous borderline tumors among gravid women (RR=2.6, 95% CI 1.1-6.3) - ?surveillance bias
  - endometrioid/clear cell tumors (RR=3.4, 95% CI 1.9-6.0)
Endometriosis and Ovarian Cancer

• Large epidemiologic studies confirm clinical suspicions
• Biologically conceivable relationship given shared mechanisms for two diseases (reviewed by Ness RB, Epidemiology 2002; 11:111-117)
  ➢ Promoted by estrogen excesses, progesterone deficits
  ➢ Role for inflammatory mechanisms
• Possible histologic specificity
Linked Registry Study in Denmark

Danish Cancer Register, 1978-98
- 2,491 invasive ovarian cancers
- 860 borderline ovarian tumors
- 1,398 uterine cancers

Central Population Register (CPR)
- Subsample, comprised of 99,812 women, born after 1936, and living in Denmark in 1978, randomly selected using a 2-stage sampling design to account for age distributions of cases

Hospital Discharge Register
Hospital admissions 1977-98 and outpatient visits 1995-98
Diagnoses of:
- endometriosis, leiomyomas
- hysterectomy, oophorectomy
- tubal ligation, obesity

Additional data from CPR
- biologic vs. adopted children
- number of children
- age at first birth
Analytic Approaches

• Women followed from entry (1978) until cancer diagnosis, censoring event, or end of study (1998)
  ➢ Censoring at time of bilateral oophorectomy (for ovarian analyses), hysterectomy (uterine analyses), death, or emigration from Denmark

• Medical conditions of interest and potential confounders evaluated as time-dependent variables

• RRs, 95% CIs estimated by weighted Cox regression, overall and by histology
Relationship of Endometriosis to Gynecologic Cancers

*95% CIs exclude 1.0
## Endometriosis and Invasive Ovarian Cancer: Histology-Specific RR

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Ever Diagnosed</th>
<th>5+ years follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous (n=932)</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Mucinous (n=344)</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Endometrioid (n=300)</td>
<td>3.4*</td>
<td>2.5</td>
</tr>
<tr>
<td>Clear cell (n=123)</td>
<td>3.0*</td>
<td>3.4*</td>
</tr>
</tbody>
</table>

*95% CIs excludes 1.0
Preponderance of Endometrioid and Clear Cell Tumors: Carcinogenic Clues?

- Studies have shown atypical endometriosis to precede clear cell or endometrioid cancers
  - Alterations in tumor suppressor (e.g., \textit{PTEN}, \textit{p53}) and DNA repair (e.g., \textit{hMLH1}) genes
  - Loss of heterozygosity, partial deletions of chromosomes, clonality, and high rates of aneuploidy
Is Endometriosis Related to Sites Other than Ovarian Cancer?

- Breast Cancer
- Non-Hodgkin Lymphoma
- ?Other Sites
# U.S. Study of Women Evaluated for Infertility: Cancer Risks Among Women with Endometriosis

<table>
<thead>
<tr>
<th>Cancers</th>
<th># Cancers</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>57</td>
<td>0.8</td>
<td>0.6-1.1</td>
</tr>
<tr>
<td>NHL</td>
<td>2</td>
<td>0.7</td>
<td>0.1-4.0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>15</td>
<td>2.1</td>
<td>1.0-4.4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>7</td>
<td>3.1</td>
<td>0.9-10.7</td>
</tr>
</tbody>
</table>
Endometriosis and Breast Cancer

• Contradictory findings
  ➢ Positive studies: Swedish study, Endometriosis Association survey
  ➢ Negative studies: U.S. infertility, Iowa Women’s study, case-control studies

• Other explanations
  ➢ Possibility of shared hormonal factors
  ➢ Screening bias, non-surgical treatment effects, influence of confounding factors
Endometriosis and Non-Hodgkin Lymphoma

• Contradictory findings
  ➢ Positive studies: Swedish and Iowa studies, Endometriosis Association survey
  ➢ Negative studies: U.S. infertility study

• Other explanations
  ➢ Possible treatment effects
  ➢ Shared immunologic factors
  ➢ Environmental factors (e.g., dioxin)
Endometriosis and Cancer Risk: Summary

- Clinical and epidemiologic studies support a link between endometriosis and ovarian cancer, particularly clear cell and endometrioid cancers.
- Biologic mechanisms uncertain, but some evidence to support that endometriosis may represent a precursor for ovarian cancer.
- Attributable risk for developing ovarian cancer low.
Needed Areas for Future Research

• Role of intervening factors in link between endometriosis and ovarian cancer
  ➢ Danazol (*Cottreau et al, Clin Cancer Res 2003;9:5142-4*)
  ➢ Other co-variates

• Additional epidemiologic studies to distinguish effects of endometriosis from other risk factors
  ➢ Unresolved cancer sites: breast and thyroid cancers, NHL, melanoma