Hereditary Ovarian Cancer: Why it Matters to the General OB/GYN

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Disclosures

- Consultant or Advisory Role: Pfizer
- Expert Testimony: Pfizer
- I will be discussing off-label use of oral contraceptives.
Objectives

• At the end of this course, the learner should be able to:
  
  – Identify women who should be considered for hereditary cancer risk assessment.
  
  – Choose among available options for the management of women with an inherited predisposition towards ovarian and related cancers.
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Number of New Cases</th>
<th>% Caused by Single Gene Mutations</th>
<th>Number of Inherited Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>232,340</td>
<td>7-10%</td>
<td>16,000-23,000</td>
</tr>
<tr>
<td>Lung</td>
<td>110,110</td>
<td>&lt;1%</td>
<td>&lt; 1000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>69,140</td>
<td>6%</td>
<td>4,150</td>
</tr>
<tr>
<td>Uterine</td>
<td>49,560</td>
<td>5%</td>
<td>2,475</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,240</td>
<td>10%</td>
<td>2,200</td>
</tr>
</tbody>
</table>
## Cancer Susceptibility Syndromes That May Be Encountered by Gynecologists

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast Ovarian Cancer</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>PTEN</td>
</tr>
<tr>
<td>Lynch / Hereditary Non-Polyposis Colon Cancer (HNPCC)</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis (FAP)</td>
<td>APC (Dominant)</td>
</tr>
<tr>
<td></td>
<td>MYH (Recessive)</td>
</tr>
<tr>
<td>Li-Fraumeni Syndrome</td>
<td>p53</td>
</tr>
<tr>
<td>Von Hippel-Lindau</td>
<td>VHL</td>
</tr>
</tbody>
</table>
Causes of Hereditary Susceptibility to Ovarian Cancer

Sporadic

Hereditary (~10%)

Other single genes (<5%)

BRCA1 (~70-75%)

HNPCC (~2%)

BRCA2 (~20%)
Who Is at Inherited Risk?

How do we find the 5-10% of individuals at risk in this group?
Tumor Suppressor Genes

Normal genes (prevent cancer)

1st mutation (susceptible carrier)

2nd mutation or loss (leads to cancer)
Indicators of a Possible Hereditary Cancer Syndrome

• Early age at diagnosis (e.g. breast cancer <50)
• Same type of cancer in 2 or more close relatives on the same side of the family
• Combination of cancers indicative of a specific syndrome (e.g. colon and endometrium)
• Multiple primary tumors in a single individual / bilateral disease
• Single cases of cancer in which a high proportion is inherited (e.g. high grade serous ovarian/fallopian tube ca, medullary thyroid ca)
**Hereditary vs. Sporadic Breast Cancer**

**Hereditary**
- Two or more individuals with breast cancer before age 50 or ovarian cancer at any age
- Ashkenazi individuals with breast cancer prior to 50 or ovarian cancer at any age
- Ovary, dx. 42
- Breast, dx. 43
- Breast, dx. 51

**Sporadic**
- No breast cancer diagnosed before age 50
- No ovarian cancer in lineage
- No clear pattern on either side of family
- Breast, dx. 65
Assess Family History

• Three generation pedigree is ideal, but time consuming to generate.

• Genetic Counselors and appropriately trained physician extenders can assist in this process.
Family History Screen

- Family history screen for first visit:
  - “Does anyone in your family; parents, grandparents, siblings, aunts, uncles or first cousins; have breast, ovary, uterine or colon cancer?”

- Family history screen for subsequent visits:
  - “Has any close relative been diagnosed with breast, ovarian, uterine, or colon cancer since I last saw you?”
Hereditary Breast-Ovarian Cancer Syndrome
BRCA1-Associated Cancers: Lifetime Risk

Breast cancer 50%–85% (often early age at onset)

Second primary breast cancer 40%–60%

Ovarian cancer 35%–45%

Possible increased risk of other cancers (eg, prostate)
BRCA2-Associated Cancers: Lifetime Risk

- Increased risk of prostate, laryngeal, and pancreatic cancers
- Breast cancer (40%−85%)
- Ovarian cancer (10%−27%)
- Male breast cancer (6%)
Which Patients Should be Referred for Genetic Counseling?

Patients with *greater than an approximately 20–25% chance* of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment *is recommended*:

- Women with a personal history of both breast cancer and ovarian cancer
- Women with ovarian cancer and a close relative† with ovarian cancer or premenopausal breast cancer or both
- Women with breast cancer prior to age 40 or ovarian cancer at any age who are of Ashkenazi Jewish ancestry
- Women with a close relative† with a known *BRCA1* or *BRCA2* mutation

Patients with \textit{greater than an approximate 5–10\% chance} of having an inherited predisposition to breast cancer and ovarian cancer and for whom genetic risk assessment \textit{may be helpful}:

- Women with breast cancer at age 40 years or younger
- Women with breast cancer at age 50 years or younger and a close relative\textsuperscript{†} with breast cancer at age 50 years or younger
- Women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger
- Women with ovarian, fallopian tube or primary peritoneal cancer of high grade, serous histology at any age

Prevalence of Germline $BRCA$ Mutations in Serous Ovarian Cancer

- **Risch HA, et al. AJHG 2001**
  - 56 (16.4%) of 341 unselected serous ovarian ca diagnosed in Ontario from 1995-6

  - 20 (16.5%) of 121 unselected serous ovarian ca diagnosed in Tampa area from 2000-2003

- **Alsop K, et al. JCO 2012**
  - 98 (17.1%) of 574 incident high-grade serous ovarian ca ascertained as part of the Australia Ovarian Cancer Study from 2002-2006
Prevalence of Germline BRCA Mutations in Triple Neg Breast Ca Diagnosed Prior to Age 50

  – 11 (19%) of 58 unselected TN breast cancers diagnosed prior to age 50 from two UK series

  – 13 (15%) of 86 unselected TN breast cancers diagnosed prior to age 50 presenting to a community oncology network in TX from 2005-2010
Hereditary Cancer Risk Assessment is a Process

This process should:

- Include assessment of risk, education and counseling;
- Be conducted by a physician, genetic counselor or other provider with expertise in cancer genetics;
- May include genetic testing if desired after appropriate counseling and consent is obtained.
Risk-Reduction Strategies

– Breast
  • Intensive Surveillance (Mammogram, U/S, MRI)
  • Chemoprevention (Tamoxifen, Raloxifene, Aromatase Inhibitors)
  • Risk-Reducing Surgery (Mastectomy, Oophorectomy)

– Ovary
  • Chemoprevention (Oral Contraceptives)
  • Risk-Reducing Surgery (Salpingo-Oophorectomy)
Intensive Surveillance
### Mammogram Screening in BRCA Mutation Carriers

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sensitivity</th>
<th>Invasive Cancer</th>
<th>Lymph Node Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brekelman, et al.</td>
<td>128</td>
<td>56%</td>
<td>5/9</td>
<td>56%</td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheuer, et al.</td>
<td>251</td>
<td>42%</td>
<td>5/12</td>
<td>25%</td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prospective Studies of MRI Screening for Breast Cancer in Women at with BRCA1/2 Mutations

<table>
<thead>
<tr>
<th></th>
<th>Dutch MRISC study, Kriege et al, 2004</th>
<th>Toronto, Canada, Warner et al, 2004</th>
<th>MARIBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>1909</td>
<td>236</td>
<td>649</td>
</tr>
<tr>
<td>No. of BRCA 1/2 carriers</td>
<td>354</td>
<td>236</td>
<td>120</td>
</tr>
<tr>
<td>MRI sensitivity (95% CI)</td>
<td>71.1%</td>
<td>77.3%</td>
<td>77%</td>
</tr>
<tr>
<td>MRI specificity</td>
<td>89.8%</td>
<td>95.4%</td>
<td>81%</td>
</tr>
<tr>
<td>Mammogram sensitivity</td>
<td>40%</td>
<td>36.4%</td>
<td>40%</td>
</tr>
<tr>
<td>Mammogram specificity</td>
<td>95%</td>
<td>99.8%</td>
<td>93%</td>
</tr>
</tbody>
</table>

MRI Breast Screening

Normal Mammogram
Performed at Time of MRI

MRI Detected
Occult Stage I Breast Cancer
1275 women with a BRCA1 or BRCA2 mutation

- 445 women in MRI Trial; 830 in Comparison Group
- Followed for mean of 3.2 yrs, cancer incidence estimated at 6 yrs

DCIS or Stage I
- 13.8% in MRI; 7.2% in Mammo (p=0.01)

Stage II-IV
- 1.9% in MRI; 6.6% in Mammo (p=0.02)
- HR = 0.30 (95% CI 0.12 – 0.78, p=0.008)
Chemoprevention
Oral Contraceptives in *BRCA* Mutation Carriers: Impact on Ovarian Cancer Risk

• Narod, et al. NEJM 1999
  – HR for Ovarian Ca — 0.5 (95% CI; 0.3-0.8)

• Modan, et al. NEJM 2001
  – No protective effect against Ovarian Cancer
    • Only 19 (8%) of carriers with ovarian ca used OC’s for 5 years

  – After 6 or more years of use: OR = 0.62 (95% CI, 0.35-1.09)
Oral Contraceptives in BRCA Mutation Carriers: Impact on Breast Cancer Risk

- Narod S, et al. JNCI 2002
  - OC’s may be associated with an increased risk of breast ca in BRCA1 mutations carrier (OR 1.20; 95%CI 1.02-1.40)

- Brohet RM, et al. JCO 2007
  - ↑ breast ca risk with ever use of OC (HR 1.47; 95% CI: 1.16 – 1.87)
  - Longer duration of use, especially prior to first pregnancy, was associated with increased risk.
Risk-Reducing Surgery
Risk-Reducing Salpingo-Oophorectomy

Kauff ND, et al. NEJM. 2002; 346:1609-15
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Ovarian Cancer</th>
<th>Breast Cancer HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauff, et al.</td>
<td>Prospective</td>
<td>98</td>
<td>HR = 0.15</td>
<td>HR = 0.32</td>
</tr>
<tr>
<td>NEJM 2002</td>
<td></td>
<td></td>
<td>(95% CI: 0.02-1.31)</td>
<td>(95% CI: 0.08-1.20)</td>
</tr>
<tr>
<td>Rebbeck, et al.</td>
<td>Retrospective</td>
<td>259</td>
<td>HR = 0.04</td>
<td>HR = 0.53</td>
</tr>
<tr>
<td>NEJM 2002</td>
<td></td>
<td></td>
<td>(95% CI: 0.01-0.16)</td>
<td>(95% CI: 0.33-0.84)</td>
</tr>
<tr>
<td>Rutter, et al.</td>
<td>Retrospective</td>
<td>251</td>
<td>OR = 0.29</td>
<td></td>
</tr>
<tr>
<td>JNCI 2003</td>
<td></td>
<td></td>
<td>(95% CI: 0.12-0.73)</td>
<td></td>
</tr>
<tr>
<td>Finch, et al.</td>
<td>Combined</td>
<td>1045</td>
<td>HR = 0.20</td>
<td></td>
</tr>
<tr>
<td>JAMA 2006</td>
<td></td>
<td></td>
<td>(95% CI: 0.07-0.58)</td>
<td></td>
</tr>
<tr>
<td>Kauff, et al.</td>
<td>Prospective</td>
<td>881</td>
<td>HR = 0.12</td>
<td>HR = 0.53</td>
</tr>
<tr>
<td>JCO 2008</td>
<td></td>
<td></td>
<td>(95% CI: 0.03-0.41)</td>
<td>(95% CI: 0.29-0.96)</td>
</tr>
<tr>
<td>Domchek, et al.</td>
<td>Combined</td>
<td>939</td>
<td>HR = 0.14</td>
<td>HR = 0.54</td>
</tr>
<tr>
<td>JAMA 2010</td>
<td></td>
<td></td>
<td>(95% CI: 0.04-0.59)</td>
<td>(95% CI: 0.37-0.79)</td>
</tr>
</tbody>
</table>
Mutations in *BRCA1* and *BRCA2* Cause Distinct Cancer Susceptibility Syndromes

- **Breast Cancer**
  - *BRCA1*: 10-24% ER positive
  - *BRCA2*: 65-79% ER positive

- **Ovarian Cancer**
  - *BRCA1*: 34-46% risk (to age 70)
  - *BRCA2*: 10-27% risk (to age 70)
Risk of *BRCA*-associated Gynecologic Cancer following RRSO

<table>
<thead>
<tr>
<th></th>
<th>RRSO N</th>
<th>Cancers</th>
<th>Surveillance N</th>
<th>Cancers</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA1 &amp; BRCA2</em></td>
<td>509</td>
<td>3</td>
<td>283</td>
<td>12</td>
<td>0.12</td>
<td>0.03 – 0.41</td>
<td>0.001</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
<td>325</td>
<td>3</td>
<td>173</td>
<td>10</td>
<td>0.15</td>
<td>0.04 – 0.56</td>
<td>0.005</td>
</tr>
<tr>
<td><em>BRCA2</em></td>
<td>184</td>
<td>0</td>
<td>110</td>
<td>2</td>
<td>0.00</td>
<td>Not Estimable</td>
<td></td>
</tr>
</tbody>
</table>

## Risk of BRCA-associated Breast Cancer following RRSO

<table>
<thead>
<tr>
<th></th>
<th>RRSO</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Cancers</td>
</tr>
<tr>
<td><strong>BRCA1 &amp; BRCA2</strong></td>
<td>303</td>
<td>19</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>190</td>
<td>15</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>113</td>
<td>4</td>
</tr>
</tbody>
</table>

## Impact of RRSO on ER-positive vs. ER-negative Breast Cancer

*(BRCA1/BRCA2 Combined – Adjusted for Mutation Type)*

<table>
<thead>
<tr>
<th></th>
<th>ER-positive</th>
<th></th>
<th></th>
<th>ER-Negative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Events</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>Events</td>
</tr>
<tr>
<td>RRSO</td>
<td>300</td>
<td>2</td>
<td>0.22 (0.05-1.05)</td>
<td>0.058</td>
<td>14</td>
</tr>
<tr>
<td>No RRSO</td>
<td>284</td>
<td>7</td>
<td></td>
<td></td>
<td>11</td>
</tr>
</tbody>
</table>

Surgical Considerations
Primary Peritoneal Cancer Arising in an Ovarian Remnant


*Essential* to enter the retroperitoneal space to isolate the ovarian blood supply and ligate it distal to its insertion into the ovary
• Ovarian vessel ligation with a retroperitoneal approach and a 2 cm margin.
As much Fallopian tube as possible is removed.
Prevalence of Occult Cancer in Women with Mutations in *BRCA1* or *BRCA2*

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts (n)</th>
<th>Occult Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebbeck, et al. 2005</td>
<td>259</td>
<td>6 (2.3%)</td>
</tr>
<tr>
<td>Kauff, et al. 2002</td>
<td>98</td>
<td>3 (3.1%)</td>
</tr>
<tr>
<td>Leeper, et al. 2002</td>
<td>17</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Lu, et al. 2000</td>
<td>22</td>
<td>4 (18.2%)</td>
</tr>
<tr>
<td>Powell, et al. 2005</td>
<td>67</td>
<td>7 (10.4%)</td>
</tr>
<tr>
<td>Olivier, et al. 2005</td>
<td>65</td>
<td>5 (7.7%)</td>
</tr>
<tr>
<td>Finch, et al. 2006</td>
<td>490</td>
<td>11 (2.2%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>918</td>
<td>40 (4.4%)</td>
</tr>
</tbody>
</table>
What is SEE-FIM? 
(Sectioning and Extensively Examining the Fimbriated end)

- Distal 2cm of tube
  - Transect from rest of tube

- Cut into 4 pieces longitudinally
  - Section transversely every 2-3mm

- Remainder of tube
  - Section transversely every 2-3mm
Timing of Procedure

- **BRCA1**: 11-21% risk of ovarian cancer by age 50.\(^1,2\)
- **BRCA2**: 2-3% risk of ovarian cancer by age 50.\(^1,2\)
- Oophorectomy after menopause is not associated with a decrease in breast cancer risk.\(^3\)

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What is the Role of HRT?

• Increase in endocrine and sexual symptomatology is common following RRSO.¹

• Sexual symptomatology is the single biggest predictor of satisfaction with RRSO.²

• Data from WHI likely does not apply to women having premenopausal RRSO.

HRT following Risk-Reducing Salpingo-Oophorectomy


- HRT may reduce the protective effect of RRSO on breast cancer risk.
  - HR = 1.35 (95% CI, 0.16-11.58)

- RRSO with short term HRT was still associated with a profound reduction in breast cancer risk in carriers of BRCA1 and BRCA2 mutations.
  - HR = 0.37 (95% CI, 0.14-0.96)
What has RRSO taught us about the pathogenesis of BRCA-associated ovarian, fallopian tube and primary peritoneal cancer?
Ovarian Tumorigenesis – 2002

- Risk factors
  - Nulliparity
  - Early Menarche
  - Late Menopause
  - Talc

- Protective Factors
  - Pregnancy
  - Lactation
  - Oral Contraceptive Use

Drapkin and Hecht, Women’s Oncol Rev 2002
What is the Role of Risk-Reducing Salpingectomy?
Is it Reasonable to Remove Just the Fallopian Tubes for Risk-Reduction?

- We do not know the latency period from time of genetic changes in the fallopian tube to development of invasive pelvic serous cancer.
- We do not know what proportion of pelvic cancers are explained by this mechanism.
- Deferring oophorectomy will negate the benefit conferred by RRSO against breast cancer.
Challenges for the Future

• Can we better identify individuals at risk for ovarian and related cancers as well as better determine the timing and magnitude of those risks.

• Can we provide better care of sequelae of risk-reduction approaches?

• Can we make improvements in gynecologic cancer screening to allow this to become a viable alternative to risk-reduction surgery?
Challenges for the Future

• Will advances in chemoprevention approaches as well as our basic understanding of the molecular progression of ovarian and breast cancer ultimately allow us to render the surgical removal of at-risk organs obsolete?
Acknowledgements

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