Gynecologic management of women with inherited risk of gynecologic cancer

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I have nothing to disclose

Key Recommendations

- Take a basic family history
- Refer to a multidisciplinary hereditary women’s cancer risk center if available
- Provide follow up care and support for early menopause
- Identify family members who may benefit from testing

Who Should be Considered for Hereditary Cancer Risk Assessment: HBOC Syndrome?

- Young age
- Multigenerational cancers
- Personal history of non-mucinous ovarian cancer or breast cancer under age 50
- Multiple cancers, bilateral breast
- Male breast cancer
- Ashkenazi Jewish
An inherited gene accounts for 20% of epithelial ovarian cancer and 10% of breast cancer.

#### Hereditary breast ovarian cancer genetic risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ovarian cancer (Lifetime risk%)</th>
<th>Breast cancer</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>40%</td>
<td>49-57%</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>18%</td>
<td>49-57%</td>
<td></td>
</tr>
<tr>
<td>Lynch</td>
<td>4%-24%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Palb2, Chek, ATM,</td>
<td>44%, 325,30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51c, RAD51D, BRIp1</td>
<td>10%-15%</td>
<td></td>
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</tr>
</tbody>
</table>

#### Eleven Genes associated with Ovarian cancer

- BRCA1
- BRCA2
- BRIP1
- PALB2
- BARD1
- RAD51C
- RAD51D
- Lynch: MLH1, MSH2, MSH6, PMS2

Norquist, JAMA oncology, 2016

#### Ovarian and Breast Cancer risk by gene and decade of life

<table>
<thead>
<tr>
<th>Age</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 30</td>
<td>2.2%</td>
<td>1%</td>
<td>10%</td>
<td>6.6%</td>
</tr>
<tr>
<td>At 40</td>
<td>8.7%</td>
<td>2.4%</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>At 50</td>
<td>22%</td>
<td>7.4%</td>
<td>44%</td>
<td>35%</td>
</tr>
<tr>
<td>At 60</td>
<td>39%</td>
<td>16%</td>
<td>54%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Chen, JCO 2007
American Women with Breast Cancer

- Hispanic: 3.5% BRCA1
- US Ashkenazi Jews: 8.3% BRCA1
- African American: 1.3% BRCA1
- African American, with breast cancer age <35: 16.7% BRCA1
- Asian: 0.5% BRCA1

John, E. JAMA: 2007, 2869

Ethnicity | Breast cancer | Breast cancer under age 40 | Ovarian cancer |
---|---|---|---|
Ashkenazi | 10% | 30-35% | 41% |
Non-Ashkenazi | 2% | 10% | 10-15% |


Pathologic Features of BRCA1 cancer

- Triple negative breast cancer: < age 50, with any family history: 29% BRCA1
  < age 40: 23% BRCA1
- Tubal cancer: 28% BRCA
- Non-mucinous ovarian cancer: 16-21% BRCA

Cass, I GynOnc, in press
Lakhani, S Ci Can Res: 2005

Strategies for inherited cancer risk reduction

- Surveillance
- Chemo-prevention
- Surgery
- Targeted therapy

Ultrasound
Mammogram
Breast MRI

OCPs
Tamoxifen

BRCA
Mastectomy
Tubal ligation
Salpingectomy
Bilateral oophorectomy

PARP inhibitor
Platinum
Oral contraceptive pills

- OR = 0.58 (95% CL 0.46 to 0.73)
- Risk reduction for BRCA1 and BRCA2
- Greater reduction of risk with years of use (3-6)
- No clear increased risk of breast cancer

Moorman, JCO 2012
Iodice, Euro Jl of Cancer, 2010
Kostsopoulos, Breast Can Research 2014

Tubal ligation

RR 0.43 in BRCA1
OR 0.39 in BRCA1
Risk reduction not confirmed in BRCA2

Antoniou, 2009
Narod, 2003

Surveillance

UK Familial ovarian cancer screening study
- women at 10% risk: annual CA 125 and ultrasound
- 26% stage IIIC as compared with 86.7% in unscreened
- PPV 25.5%
- overall survival: 72 vs 48.4mo

UKCTOCS: Ovarian cancer screening and mortality
- Not significant difference in mortality, was significant when prevalent cases were excluded.

Rosenthal, JCO 2015
Jacob JAMA onc 2016

RISK OF OVARIAN CANCER TRIAL ROCA-KP

- Women with BRCA1 or BRCA2
- Over age 30
- Choosing surveillance

Standard arm
- CA 125 and Ultrasound q 6mths

CA 125 and HE4 q 4mths with ROCA testing
The FDA is alerting women about the risks associated with the use of tests being marketed as ovarian cancer screening tests. The Agency is especially concerned about delaying effective preventive treatments for women who show no symptoms, but who are still at increased risk for developing ovarian cancer. Based on currently available information, the FDA recommends against using currently offered tests to screen for ovarian cancer.

**FDA safety communication Sept 7, 2016**

- 80-90% reduction in ovarian cancer
- 69% reduction all cause mortality
- NCCN guidelines recommend at age 35-40
- Breast cancer risk reduction? ≤50?
- Re-analysis of four papers, no protective effect on breast cancer, ? Small protective effect if premenopausal.

Finch A, JCO 2014
Heemskerk-Gerritsen JNCI 2015

**Risk reducing salpingo-Oophorectomy in women with BRCA1 and BRCA2 mutations: 90% reduction in ovarian cancer**

- Inspection of all peritoneal surfaces
- Collection of peritoneal cytology
- Resection of the entire tube and ovary.
- The entire tube and ovary should be submitted with micro-sectioning of the entire specimen in 2-3mm cuts.

**Risk Reducing surgery: BSO**

- Ovarian vessel ligation with a retroperitoneal approach and a 2 cm margin.
**RRSO**

- As much Fallopian tube as possible is removed.

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**Risk of cancer at RRSO and after**

- 2035 Cases
- 3.0% STIC
- 2.7% Invasive cancers

**Risk of peritoneal primary**
- 3.9% BRCA1
- 1.9% BRCA2

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**Stepwise Progression: Precursor Lesions**

- Normal FT Epithelium
- 'p53 Signature'
- TIC
- Invasive Serous Carcinoma

Attachment to ovary and development of invasive high-grade serous ovarian carcinoma (HGSOC)

Attachment to peritoneal membranes and development of primary peritoneal serous carcinoma (PPSC)

Finch A, Powell, GO 2014

Levanon JCO 2008, Lee et al
Should Hysterectomy be performed with RRSO?

**PROS**
- Ensures removal of all tube
- Simplifies hormonal management
- Increased risk of uterine cancer with BRCA1
- Tamoxifen
- Other gyn pathology

**CONS**
- Increased risk, cost, hospitalization
- No reports of cancer in cornual portion of fallopian tube
- Endometrial cancer can be detected in early stage with vaginal bleeding

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Salpingectomy with delayed oophorectomy in women with BRCA mutations

If a young woman is not ready for menopause or may even want the possibility of a child
What about removing the tube first and removing the ovaries at a later time?

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Salpingectomy with delayed oophorectomy

**Pros**
- Avoid a portion of pelvic serous cancers
- Avoid premature menopause
- Option when patient will not agree to RRSO
- Maintain option for IVF pregnancy

**Cons**
- Two stages to surgery
- Result in a delay of removing the ovaries
- May not be as effective as removing both tubes and ovaries
- No reduction in breast cancer risk

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Remove all fimbrial attachments
Long term health outcomes

- Early menopause
- Increase in osteopenia/osteoporosis – 70%
- Cardiovascular disease, hyperlipidemia – 30%
- Sexual symptom, decreased pleasure and satisfaction and increased dyspareunia.

Recommendations after RRSO

Menopausal symptoms

Hormone replacement therapy after BSO in women without breast cancer, stopping by age 45-50.

Recommendations after RRSO

- Primary peritoneal cancer:
  - ?annual pelvic exam
  - ?CA 125 q 6mths
- Bone Health
  - DXA scan at 2-3 years, then q 5 years
  - Weight bearing exercise
  - Vitamin D 1000 IU and Calcium 1500mg
- Cardiovascular disease
  - Lipids q 1-3 years if no HRT and family history

Fertility and reproduction

- Premature ovarian failure
  - Menopause at 48 vs 50
  - Increased rate of premature menopause (under age 40)
- Breast cancer
- Prenatal diagnosis:
  - PGD for those undergoing IVF
  - PND at 12-16 weeks gestation

Finch, Fert Steril 2013
Using genes to guide therapy

- 18% of ovarian cancers have germline mutations (Norquist, 2015)
- 30% of sporadic ovarian cancer had methylation of BRCA1 (Turner Nat Rev Can 2004)
- Sporadic ovarian caners also have impaired repair of DNA by the homologous recombination (HR) pathway
- Poly(ADP-ribose) polymerase (PARP) inhibitors target DNA repair

BRCA related ovarian cancer

- Improved prognosis and response to platinum
- Median survival: 55.7 vs 37.9 (Chetrit, JCO 2007)
- Improved response to liposomal doxorubicin, trabectedin, mitomycin C.
- Improved response to PARPi: HRD

PARP Inhibition

Olaparib: in BRCA mutated ovarian cancer
- Platinum sensitive: 69%RR
- Platinum resistant: 45%
- Platinum refractory: 23% (Fong, JCO 2010)

Olaparib 41% RR in BMOC vs 24% in Sporadic Olaparib maintenance in BMOC: PFS 11.2mo vs 4.8mo placebo no diff in OS
(Gelman Lanc Onc 2011 Ledermann, NEJM 2012)

The future: Population-Based Screening

Mary Claire King: Lasker Award: JAMA, 9-2014

Women do not benefit by practices that “protect” them from information regarding their own health. They should have the choice to learn if they carry an actionable mutation in BRCA1 or BRCA2.