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

**HBOC related genes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ovary</th>
<th>uterus</th>
<th>Cervix</th>
<th>Other gyn</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>40%</td>
<td></td>
<td></td>
<td></td>
<td>49-57%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>18%</td>
<td></td>
<td></td>
<td></td>
<td>49-57%</td>
</tr>
<tr>
<td>RAD51D</td>
<td>10-15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>? nonconfirmed</td>
<td></td>
<td></td>
<td></td>
<td>58%</td>
</tr>
<tr>
<td>CHEK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48%</td>
</tr>
<tr>
<td>ATM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52%</td>
</tr>
</tbody>
</table>

Powell, 2015
Other genes associated with ovarian cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ovary</th>
<th>uterus</th>
<th>Cervix</th>
<th>colon</th>
<th>Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch</td>
<td>MLH1</td>
<td>4-20%</td>
<td>20-54%</td>
<td>4%</td>
<td>20-54%</td>
</tr>
<tr>
<td></td>
<td>MLH2</td>
<td>7-15%</td>
<td>21-49%</td>
<td>48%</td>
<td>21-49%</td>
</tr>
<tr>
<td></td>
<td>MSH6</td>
<td>0-13.5%</td>
<td>16-71%</td>
<td>12-31%</td>
<td>16-71%</td>
</tr>
<tr>
<td></td>
<td>PMS2</td>
<td>small</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
<td>19-28%</td>
<td>19-28%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11/LKB1</td>
<td>21%</td>
<td>Sex cord stromal tumors</td>
<td>10% Adenoma malignum</td>
<td>10% Adenoma malignum</td>
</tr>
<tr>
<td>Other</td>
<td>DICER1</td>
<td>Sertoli-leydig</td>
<td>Small cell carcinoma</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>SMARCA4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ovarian and Breast Cancer risk by gene and decade of life

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ovarian Cancer</th>
<th>Risk</th>
<th>Breast Cancer</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>At age 30</td>
<td>BRCA1</td>
<td>2.2%</td>
<td>BRCA2</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>10%</td>
<td>BRCA1</td>
<td>6.6%</td>
</tr>
<tr>
<td>By age 40</td>
<td>2.2%</td>
<td>1%</td>
<td>10%</td>
<td>6.6%</td>
</tr>
<tr>
<td>By age 50</td>
<td>8.7%</td>
<td>2.4%</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>By age 60</td>
<td>22%</td>
<td>7.4%</td>
<td>44%</td>
<td>35%</td>
</tr>
<tr>
<td>By age 70</td>
<td>39%</td>
<td>16%</td>
<td>54%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Powell, 2015

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

Don’t be fooled

- Families with few females
- Families with females with early hysterectomy
- Adoption
- Paternal as well as maternal history
- Need to test an affected relative
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, 2889

Likelihood of being a BRCA carrier by personal cancer history

<table>
<thead>
<tr>
<th>Personal Cancer History</th>
<th>BRCA1 Carrier Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Ashkenazi Breast cancer Breast cancer &lt;40yrs Ovarian cancer</td>
<td>2% &lt;10% 10-15%</td>
</tr>
<tr>
<td>Ashkenazi Breast cancer Breast cancer &lt;40 yrs Ovarian cancer</td>
<td>10% 30-35% 41%</td>
</tr>
</tbody>
</table>


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 Cl Can Res: 2005

Strategies for ovarian cancer risk reduction

Woman with BRCA mutation

Surveillance
Chemoprevention
CA125, Ultrasound
OCPs
RRSO, salpingectomy, BTL
Surgery
**Lifestyle modification for ovarian cancer**

Ovarian cancer risk reduction
- Parity > 4 breastfeeding

No association
- BMI, alcohol, age at menarche, first birth under age 30

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**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
  - age < 25, BRCA1
  - prolonged use
  - increase in early breast cancer, in BRCA1

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

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**Tubal ligation**

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

Antoniou, 2009
Narod, 2003

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**Surveillance**

- UK Familial ovarian cancer screening study
  - 3563 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
  - 60% of those with stage 1 had Lynch syndrome
  - All screen negative cancers, were BRCA related

Rosenthal, JCO 2013
**Surveillance: ROCA testing**

- Post-menopausal women, ave risk
- 4051 women, 11 year follow up
- CA 125 q 4mths, with ultrasound for abnormals.
- PPV 40%

Lu K, Cancer, 2013

**Symptom Diary**

- Symptoms if occurring greater than 12 times in a month were associated significantly with ovarian cancer were
  - pelvic/abdominal pain,
  - urinary urgency/frequency,
  - increased abdominal size/bloating,
  - difficulty eating/feeling full

Goff, B Cancer 2007

**Risk Reducing surgery: BSO**

- 5783 women with BRCA1 or BRCA2
- 69% reduction all cause mortality
- 77% reduction in mortality, if no prior breast cancer
- Risk per year .9% brca1 peak 50-59
- Risk per year .3% BRCA2 peak 60-69

Finch A, JCO 2014

**RRSO: Breast cancer risk reduction**

- RRSO under age 40
  - OR = 0.44 BRCA1
  - OR = 0.57 BRCA2

Eisen A, JCO 2005
Technique for risk reducing salpingo-oophorectomy in women with BRCA1 and BRCA2 mutations:

- Laparoscopic
- Inspection of all peritoneal surfaces, diaphragm, liver and pelvic peritoneum
- Collection of peritoneal cytology
- Resection of the entire ovary with a retroperitoneal approach, removing all adhesions with the adnexa, resection of the tube as close to the uterus as possible and gentle handling of the specimen with removal in an endoscopic bag.
- The entire tube and ovary should be submitted with micro-sectioning of the entire specimen in 2-3mm cuts.
- Attention in particular should be paid to the fimbria and immunohistochemistry staining with Ki67 and P53 for confirmation of precursor lesions.

Risk of cancer at RRSO and after

- 2,035 cases
- 3.0% STIC
- 2.7% invasive cancers

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

Finch A, Powell, GO 2014
Should Hysterectomy be performed with RRSO?

**PROS**
- Ensures removal of all tube
- Simplifies hormonal management
- Increased risk of uterine cancer with BRCA? and 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

Salpingectomy 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?
Salpingectomy

**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
- Removal of ovaries in young BRCA carriers reduces breast cancer by 50%

Salpingectomy Technique

- Inspect entire abdomen
- Peritoneal cytology
- Remove adjacent ovarian capsule
- Remove all the fimbria
- Place in an endoscopic bag for removal
- Pathology processing with SEE-FIM protocol

Long term health outcomes

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

HRT in women with BRCA mutations

PROSE study:
  - no impact on Breast cancer risk
  - may reduce the protective effect of RRSO
  - reduction still significant: HR 0.37 (CI 0.14-0.96)

427 women with BRCA1 had no increased risk of breast cancer on HRT, decreased risk on estrogen only

Rebbeck JCO 2005
Eisen JNCI 2008
Menopausal symptoms

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

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

Challenges: how to identify and test family members at risk

Finch, Fert Steril 2013
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.

FHS-7: validated questionnaire

- Did any of your first-degree relatives have breast or ovarian cancer?
- Did any of your relatives have bilateral breast cancer?
- Did any man in your family have breast cancer?
- Did any woman in your family have breast and ovarian cancer?
- Did any woman in your family have breast cancer before age 50 y?
- Do you have 2 or more relatives with breast and/or ovarian cancer?
- Do you have 2 or more relatives with breast and/or bowel cancer?

Uterine Serous Cancer related to BRCA mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Mutation testing</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Personal breast cancer history</th>
<th>BRCA1 in breast cancer subjects</th>
<th>First degree family history of breast/ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gower-Asch et al. 2003</td>
<td>9</td>
<td>Canadian</td>
<td>q common</td>
<td>0</td>
<td>0</td>
<td>6 (66.7)</td>
<td>0</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Levine et al. 2001</td>
<td>47</td>
<td>Ashkenazi Jewish</td>
<td>q founder</td>
<td>0</td>
<td>0</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Goldman et al. 2002</td>
<td>9</td>
<td>American</td>
<td>Full sequence</td>
<td>0</td>
<td>3 (33.3)</td>
<td>9 (100.0)</td>
<td>3 (33.3)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Ben-Shalom et al. 2004</td>
<td>42</td>
<td>Israeli Jewish</td>
<td>q founder</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
<td>7 (77.8)</td>
<td>3 (37.5)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Zule et al. 2008</td>
<td>39</td>
<td>Ashkenazi Jewish</td>
<td>q founder</td>
<td>7 (17.9)</td>
<td>4 (10.3)</td>
<td>15 (38.5)</td>
<td>3 (7.8)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>Pennington et al. 2013</td>
<td>151</td>
<td>American</td>
<td>BRC A panel</td>
<td>3 (2.0%)</td>
<td>0</td>
<td>22 (16.7)</td>
<td>2 (9.1)</td>
<td>40 (26.6)</td>
</tr>
</tbody>
</table>

Adapted from Lavie In t ]l of gyn cancer 2010 Pennington Cancer 2013

Occult Cancer at the time of RRSO

- Small cancers and precancers found in the tubes in 6% of patients. Precancerous changes in the tube from atypia, dysplasia to STIC.
- Fallopian tube abnormalities more common than Ovarian abnormalities.
- STIC associated with 70% of Ovarian Cancer
- Ovarian cancers rare without tubal abnormality. No pre-invasive disease.
- Recurrence of cancers is 17-47% in 5-7 years, rare if STIC.
Occult Fallopian Tube Cancer

Low power

Medium power

p53 staining (+)

Carcinoma in situ of fimbria

p53 (+)