Cancer Risk Reduction Surgery

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Conflict of Interest

Disclaimer

None
Objectives

- Evaluation of genetic risk for developing malignancy
- Understanding the role of risk reducing surgery
- Timing of risk reducing surgery
- Surgical technique
- Postoperative management
Case # 1

No effective screening test

47 year old G2P2, LMP 2 weeks ago, recently diagnosed with cancer of the right breast. ER/PR (+). Her Medical Oncologist asked her to see you because she was found to have a BRCA1 mutation.

PMH: 2 cesarean sections, PPTL

Your Recommendations??
33 year old G3P2, LMP 2 weeks ago. Using oral contraceptives. Her mother was recently diagnosed with cancer of the breast and found to have a BRCA1 mutation. The patient had site specific testing and also has the mutation.

PMH: Negative. Distance runner (BMI 20)

Your Recommendations??
Case # 3

No effective screening test

45 year old G2P2, LMP 4 weeks ago. S/P laparoscopic sigmoid colectomy. Tumor testing (+) for MSI, genetic testing (+) for MLH1 mutation.

PMH: HTN, DM, Obesity.

Your Recommendations??
Case # 4

No effective screening test

77 year old G0. Recently diagnosed with advanced breast cancer (liver and bone metastases). Currently receiving Taxotere/Adriamycin from her Medical Oncologist who ordered genetic testing which showed a BRCA 2 mutation.

PMH: HTN, CHF, DM

As her gynecologist, she wants your opinion regarding risk reducing BSO.

Your Recommendations??
Ovarian Cancer Screening

- No effective screening test

**PLCO (Prostate, Lung, Colorectal & Ovarian Cancer Screening)**
  - 34,261 women, aged 55-74 with ovaries and without symptoms
  - Randomized to no intervention vs. annual TV sono and CA-125
  - For every 1 patient found to have ovarian cancer 20 additional women had surgery.
  - No survival advantage for those women diagnosed with ovarian cancer due to screening compared to those not screened.

**ROCA (Risk of Ovarian Cancer Algorithm)** CA-125 followed by sono
  - 3,238 low risk women, ages 50-74 (USA Trial)
  - 200,000 low risk women, ages 50-74 (United Kingdom Collaborate Trial)
  - Both show specificity of 99.8 % (lack of disease)
  - Both have Positive Predictive Value of 35-37%
Syndromes Associated with Increased Risk of Gynecologic Cancer

- **Hereditary Breast & Ovarian Cancer (HBOC)**
  - BRCA1 and BRCA2
- **Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC)**
  - MLH1, MSH2, MSH6, PMS2
- **Cowden Syndrome**
  - PTEN
- **Li Fraumeni Syndrome**
  - TP53
- **Peutz-Jeghers Syndrome**
  - STK11/LKB1
Syndromes Associated with Increased Risk of Gynecologic Cancer

- Hereditary breast and ovarian without an identified genetic risk.
- 64-86% of persons with suspected hereditary predisposition to breast and ovarian cancer have not been found to have pathogenic mutation.

Tung et al. Cancer 2015;121:25-33
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<tr>
<th>Gene</th>
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<td>RAD51D-Associated Cancer Risk</td>
<td>BR  OV  CO  EN  NE  PA  GA  PR  OC</td>
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- **High Risk**
- **Elevated Risk**
## Risk of Malignancy by Gene Mutation

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<th>Gene</th>
<th>Breast</th>
<th>Ov/FT/Per</th>
<th>Uterus</th>
<th>Colon</th>
<th>Cervix</th>
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<td>Gen. Population Lifetime Risk</td>
<td>12.3%</td>
<td>1.4%</td>
<td>2.7%</td>
<td>4.8%</td>
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<td>65-85%</td>
<td>39-46%</td>
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<td>45-85%</td>
<td>10-27%</td>
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<td>MLH1</td>
<td>4-20%</td>
<td>20-54%</td>
<td>25-50%</td>
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<tr>
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<td>21-49%</td>
<td>25-50%</td>
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<td>MSH6</td>
<td>0-13.5%</td>
<td>16-71%</td>
<td>25-50%</td>
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<tr>
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<td></td>
<td>15%</td>
<td>25-50%</td>
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<td>PTEN</td>
<td>50%</td>
<td></td>
<td>19-28%</td>
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<td>TP53</td>
<td>60%</td>
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<td>STK11/LKB1</td>
<td>50%</td>
<td>21% sex cord stromal tumor</td>
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<td>10% adenoma malignum</td>
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Cancer Risk Assessment

- Cumulative risk to age 80
- Current risk
- Risk Confounders
  - Other diseases (cancer, cardiac, neurologic, etc.)
The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer

Lynn C. Hartmann, M.D., and Noralene M. Lindor, M.D.

Hereditary breast and ovarian cancer is a syndrome that involves an increased predisposition to breast cancer, ovarian cancer, or both and an autosomal dominant pattern of transmission. The numbers of breast-cancer diagnoses, the ages of patients at diagnosis, and the occurrence of ovarian cancer in addition to breast cancer vary among families with hereditary breast and ovarian cancer syndrome. The likelihood of detecting an underlying disease-causing mutation is highest in the most severely affected families, especially those with ovarian cancer. Disease-causing mutations in BRCA1 and BRCA2, the genes most often associated with hereditary breast and ovarian cancer syndrome, are identified in only a minority of families with suspected hereditary breast and ovarian cancer syndrome.

Risk-reducing mastectomy and risk-reducing salpingo-oophorectomy are options for the primary prevention of breast and ovarian cancers, and they have been shown in multiple studies to have efficacy. However, these procedures, which have profound effects on a woman's body, are associated with complex and emotionally charged decision making.

In this review, we address issues related to the care of women in families with hereditary breast and ovarian cancer syndrome who have not had cancer. We discuss risk assessment for breast and ovarian cancers according to the woman's age, the efficacy of risk-reducing surgery, the complications and psychosocial effects of these procedures, alternative strategies for risk management, and the best ways to facilitate individual decision making.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Breast and Ovarian Cancer Risk Assessment
Breast and Ovarian Cancer Risk Assessment

Table 5d

A method of estimating residual lifetime risk:

Based upon formula reviewed and used in Clauw et al., Cancer 109:435-51.

Information on the cumulative probability of cancer development. R(x), may be used to calculate conditional probabilities of remaining lifetime risk, (RC y | x), using the following equation:

\[ RC(y \mid x) = \frac{R(y) - R(x)}{1 - R(x)} \]

For example, for BRCA1+, if the breast cancer risk to age 80 = .448 and risk to age 60 = .223 then the remaining risk from age 60 to 80 would be calculated as \([.448 \times .223]\) divided by \([1 - .223]\) = .280 or 28.0%. This simple calculation can be done based on the cumulative penetrance figures given for BRCA1/2 in Supplementary Table S9.
Options for Risk Reduction

Increased hereditary risk

Breast Cancer

Increased surveillance: Mammography & MRI
Medical Management: Tamoxifen, Raloxifene
Surgical Management: Risk reducing mastectomy (simple, nipple sparing)

Ovarian and Fallopian Tube Cancer

Increased surveillance: Currently not effective
Medical Management: Oral contraceptives
Surgical Management: BSO, Bilateral salpingectomy, Hysterectomy, BSO

Uterine/Endometrial Cancer

Increased surveillance: Sonography, endometrial sampling
Medical Management: ??
Surgical Management: Hysterectomy, BSO
80% (64-96%) reduction in risk of developing ovarian cancer.

Perhaps a 50% reduction in breast cancer risk if performed after menopause.

PROSE* (Prevention and Observation of Surgical Endpoints) Trial in 2482 BRCA (+) patients showed a 60% reduction in all-cause mortality.

Timing: Between the age of 35-40 (perhaps age 45 in BRCA2 carriers), after completion of childbearing.

* Domchek et al. JAMA 2010;304:967-75.
Risk Reducing BSO
National Guidelines

**Bilateral Salpingo-Oophorectomy**

NCCN: “Recommend risk-reducing salpingo-oophorectomy (ideally in consultation with a gynecologic oncologist) typically between 35 and 40 years, and upon completion of child bearing.”

USPSTF: “Risk-reducing salpingo-oophorectomy decreased breast cancer incidence by 37 to 100%, ovarian cancer by 69 to 100%, and all-cause mortality by 55 to 100%.”

Society of Gynecologic Oncology: “The most proven method for the prevention of ovarian cancer in women who carry a deleterious BRCA1 or BRCA2 mutation is risk-reducing salpingo-oophorectomy. Prospective studies have reported a 70% to 85% reduction in ovarian cancer... risk-reducing salpingo-oophorectomy between the ages of 35 and 40 years is recommended for risk reduction in women at increased genetic risk of ovarian cancer. The age [at which risk-reducing salpingo-oophorectomy is performed] may also be individualized according to the earliest age of onset in the family and personal choices.”

Comments on the procedure: The procedure, usually performed laparoscopically, should include visual assessment of the abdomen and pelvis, a pelvic washing, and total bilateral salpingo-oophorectomy, including ligation of the ovarian artery and vein approximately 2 cm proximal to the ovary and tube to ensure removal of all tissue. Because of the possibility of occult cancer, including serous tubal in situ carcinoma, meticulous processing of the surgical specimen is necessary according to the SEE-FIM protocol (protocol for sectioning and extensively examining the fimbriated end).
Fallopian Tube as Source/Facilitator for Ovarian Cancer

- Pathologic findings at Risk Reducing Salpingo-oophorectomy (RRSO)
- Epithelial changes and genotoxic injury to the fallopian tube epithelium.
- Decreased incidence following tubal ligation.
Pathologic Findings at RRSO for BRCA Mutation Carriers

- Lifetime risk for ovarian cancer is 1.6% in the general population and 60% for BRCA1 and 30% for BRCA2 Carriers.
- 98% risk reduction following RRSO.
- No premalignant lesions of the ovary identified.
- STIC (serous tubal intraepithelial carcinoma) identified in fallopian tubes of 5-10% of women.
- STIC incidence is higher in BRCA1 vs. BRCA2 mutation carriers.
- p53 mutations identified in the cellular proliferation, similar to invasive HGSC.
Risk Reducing BSO
Surgical Technique

- Minimally invasive approach
- Pelvic washings with sterile saline for cytologic evaluation
- 2 cm. cephalad margin on the ovarian vessels (very close to the ureters)
- Entire tube and ovary including any peritoneal attachments/adhesions should be resected.
- Hysterectomy???
- Pathologist should be notified of the diagnosis and use the SEE-FIM Protocol.
Testing for epithelial changes in the fallopian tube.

**SEE-FIM = Sectioning and Extensive Examining the Fimbria protocol.**

Use of SEE-FIM protocol resulted in findings of tubal involvement in 70% and STC in 40-60% of unselected women diagnosed with ovarian cancer.
- Tang et al. Int J Gynecol Pathol. 2012, Mar;31(2) 103-10.
**Risk Reducing Bilateral Salpingectomy**

National Guidelines

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**Salpingectomy Alone**

NCCN: “Salpingectomy [alone] is not the standard of care and is discouraged outside a clinical trial. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer.”

Society of Gynecologic Oncology: “Salpingectomy can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years.”
Risk Reducing Hysterectomy, BSO
Surgical Technique

- For BRCA or HNPCC diagnosis
- Increased risk for serous carcinoma of the endometrium in BRCA1 patients
- Minimally invasive approach
- Pelvic washings with sterile saline for cytologic evaluation
- Pathologist should be notified of the diagnosis and use the SEE-FIM Protocol.
STIC – Serous tubal intraepithelial carcinoma

- STIC may:
  - Locally expand, invade the underlying tubal stroma, presenting as primary fallopian tube carcinoma.
  - Exfoliate onto the closely associated ovarian surface/peritoneal cavity and present as primary ovarian/peritoneal carcinoma.
  - May become entrapped in the ovary during disruption of the ovarian surface at ovulation.
STIC – Serous tubal intraepithelial carcinoma

- Recent data suggests a greater risk of developing peritoneal cancer in women found to have STIC on final pathology review at risk reducing surgery.
Ovarian/fallopian tube cancer risk reduction with opportunistic salpingectomy

- Bilateral salpingectomy at the time of hysterectomy for benign conditions or surgical sterilization
- The risk of ovarian/fallopian tube carcinoma may be reduced by 20-45%.
- The procedure does not seem to impair ovarian function or produce early menopause.


47 year old G2P2, LMP 2 weeks ago, recently diagnosed with cancer of the right breast. ER/PR (+). Her Medical Oncologist asked her to see you because she was found to have a BRCA1 mutation.

PMH: 2 cesarean sections, PPTL

Your Recommendations??
Case # 1

No effective screening test

Your Recommendations??

– Is surgery indicated?
  - What benefits and risks?
  - Type, route of surgery?
  - Management of surgical menopause symptoms?
Case # 2

33 year old G3P2, LMP 2 weeks ago. Using oral contraceptives. Her mother was recently diagnosed with cancer of the breast and found to have a BRCA1 mutation. The patient had site specific testing and also has the mutation.

PMH: Negative. Distance runner (BMI 20)

Your Recommendations??
Case # 2
No effective screening test

Your Recommendations??
  – Is surgery indicated?
    □ What benefits and risks?
    □ Timing of surgery
    □ Type, route of surgery?
    □ Management of surgical menopause symptoms?
Case # 3

No effective screening test

45 year old G2P2, LMP 4 weeks ago. S/P laparoscopic sigmoid colectomy. Tumor testing (+) for MSI, genetic testing (+) for MLH1 mutation.

PMH: HTN, DM, Obesity.

Your Recommendations??
Case # 3
No effective screening test

Your Recommendations??

- Is surgery indicated?
  - What benefits and risks?
  - Timing of surgery
  - Type, route of surgery?
  - Management of surgical menopause symptoms?
77 year old G0. Recently diagnosed with advanced breast cancer (liver and bone metastases). Currently receiving Taxotere/Adriamycin from her Medical Oncologist who ordered genetic testing which showed a BRCA 2 mutation.

PMH: HTN, CHF, DM

As her gynecologist, she wants your opinion regarding risk reducing BSO.

Your Recommendations??
Case # 4
No effective screening test

Your Recommendations??

- Is surgery indicated?
  - What benefits and risks?
  - Timing of surgery
  - Type, route of surgery?