Inherited Gyn Cancers and Opportunities for Prevention

Let Every Woman Know
Saturday February 5\textsuperscript{th}, 2022

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Inherited Gyn Cancers

- We know more every day....

**Endometrium**
- Lynch/MMR genes, BRCA1/2?

**Cervical Cancer**
- DICER1, PJS

**Ovary/Fallopian Tube**
- BRCA1/2, RAD51C/D, BRIP1, PALB2, TP53, Lynch MMR genes, DICER1, SMARCA4, PJS, CHEK2?, ATM?, BARD1?, NBN?, RAD50, MUTYH?

**Myometrium**
- Rb (LMS)
Ovarian Cancer in 2022

- More than 21,000 new cases
- Family history remains the most important risk factor
  - Risk in general population: 1-2%
  - Risk in mutation carriers: up to 50%
- No screening test
- Most common type: high grade serous carcinoma
  - Peritoneal surface malignancy
Ovarian Cancer

Why is it still such a deadly disease?

• Rare to have symptoms of early-stage ovarian cancer

• Rapid and early spread of cancer throughout the abdomen and pelvis

• No reliable test to find it early enough

PREVENTION IS KEY TO SAVING LIVES
Family History Matters

- **Lineage**
- **Age of onset**
- **Details on treatment**
- **Red Flags**
  - Ovarian cancer
  - Early onset breast cancer
  - Male breast cancer
  - Multiple primary (ex bilateral) breast cancer
  - Many relatives affected over multiple generations
  - Breast and ovarian cancers
  - Ashkenazi descent

<table>
<thead>
<tr>
<th>Gene</th>
<th>Conditions</th>
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<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td>Breast, Ovarian, Pancreas, Prostate, Uterine*</td>
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<tr>
<td><strong>BRCA2</strong></td>
<td>Breast, Ovarian, Male breast cancer, Prostate, Melanoma</td>
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<tr>
<td><em><em>BRIP1, RAD51C/D, BARD1</em>, PALB2</em>**</td>
<td>Ovarian</td>
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<tr>
<td><strong>ATM, CHEK2, PALB2, NBN</strong></td>
<td>Breast</td>
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<td><strong>Lynch syndrome:</strong> MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Colon, Endometrial, Ovarian, Stomach, Small bowel, Pancreas, GU</td>
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Inherited Ovarian Cancer

- ~15-20% of ovarian cancer is inherited through known genetic mutations

- If we identified every individual with a predisposing mutation, we could prevent up to 4,200 of the 21,000 annual cases in the US

- Studying high risk women had shed light on the origins of the disease

Slide courtesy of Dr. Doug Levine
Identification of the High Risk Patient

- All people with high grade serous ovarian cancer should be referred for genetic testing
  - If a mutation is identified, all close blood relatives should be screened
  - If the affected individual is deceased, start with the closest relative
**BRCA1 and BRCA2**

- **BRCA1**
  - Highest risk of ovarian cancer ~40%
  - Earlier onset

- **BRCA2**
  - Ovarian cancer risk ~20%
  - Male breast cancer

Moderate Penetrance Genes

- **BRIP1**
  - Cumulative life time risk 4-13%
  - Crosses population risk age 45-49

- **RAD51D**
  - Cumulative life time risk 6-14%
  - Crosses population risk age 45-49

- **RAD51C**
  - Cumulative life time risk 6-14%
  - Crosses population risk age 55-59

Song et al. J Clin Oncol. 2015
Lynch Syndrome

MLH1, MSH2, MSH6, PMS2, EPCAM

Lifetime risk of ovarian cancer up to ~15%
Lifetime risk of endometrial cancer up to ~70%

Median age of diagnosis = 46 and 42 years for endometrial and ovarian cancer respectively
Serous Tubal Intraepithelial Carcinoma (STIC)

• Precursor lesion to high grade serous carcinoma

• Identified in the **fallopian tubes** of:
  - 5-15% of high-risk women undergoing risk reducing surgery
  - 80% of women with **BRCA** associated ovarian cancer
  - 60% of women with sporadic ovarian cancer

• No other ovarian pre-cancerous lesion has been found in any other site
The Fallopian Tube Hypothesis

Image credit: Carolyn Hrubran, NCI.org.
• Premalignant serous proliferations (ESPs, or “pre-STICs”) with TP53 mutations identified in the tubal fimbriae → Exfoliated ESPs may subsequently undergo malignant transformation in the peritoneum

• TP53 mutation remains the precursor “event”

• Timing of dissemination uncertain

Goal: intervene BEFORE malignant transformation, BEFORE precursor escape

Soong et al, Gyn Oncol 2019.
Ovarian Cancer Risk Reduction: Strategies and Advancements
Risk Reducing Salpingo-Oophorectomy (RRSO)

- Removal of both ovaries and fallopian tubes
- Minimally invasive surgery (laparoscopic)
- Importance of pathology review
  - SEE-FIM (Sectioning and Extensively Examining the Fimbriated End)
RRSO in BRCA Mutation Carriers

- 80 – 90% decreased risk ovarian cancer
- Decrease in all cause mortality
- Possible decreased risk of breast cancer (thought to be most significant for BRCA2 mutations carriers)

Kauff et al. NEJM. 2002.
Rebbeck et al. NEJM. 2002.
Kauff et al. JCO. 2007.
Domcheck et al. JAMA. 2010.
Recommendations for RRSO

• **BRCA1 mutation carriers**
  • 11-21% risk of ovarian cancer by age 50
  • Recommend consideration of RRSO beginning at age **35** (should complete by age 40)

• **BRCA2 mutation carriers**
  • 2-3% risk of ovarian cancer by age 50
  • Recommend consideration of RRSO beginning at age **40** (should complete by age 45-50)

• **Moderate penetrance mutations**
  • BRIP1, RAD51C, RAD51D, possibly RAD51B mutation carriers
  • Discuss the risks and benefits of performing RRSO between ages **45-50**

*Risk of OC may be higher for all genes depending on family history of OC

→ Increasing benefit to RRSO

First-degree relative OC

Population risk of OC

RRSO threshold

Level of Evidence to Support Increased Risk of OC and RRSO

Age at RRSO
- No recommendations for RRSO at this time
- Insufficient data
- Controversial
- Age 45-50 years
- Completion of childbearing, not earlier than mid-30s
- Age 35-40 years, can defer to age 40-45 years for BRCA2
The Role of Concurrent Hysterectomy

- **Reduced risk of uterine cancer**
  - Lynch Syndrome
    - High risk of uterine cancer, recommended
  - Data limited *for BRCA*
    - *BRCA 1*: likely modest increased risk (~2-5%), more aggressive subtypes
    - *BRCA 2*: Newer data suggests small increased risk

- **Safer hormone replacement options**
  - Estrogen only HRT is safer from a breast cancer standpoint

- **Must balance with surgical risks**
Impact of RRSO

• **Infertility**
  – Can be mitigated with Assisted Reproductive Technology (ex. IVF)

• **Surgical Menopause**
  – Quality of life:
    • Vaginal dryness, reduced interest in sex, sleep disturbances, impaired sexual function, hot flashes
  – Health implications:
    • CV disease, bone health, lipid levels, etc
  – Can be mitigated to a degree with HRT
Premature Menopause is Unacceptable to Some

– Many patients will delay (or even decline) RRSO due to concerns about menopause:

- In a large trial of patients with BRCA mutations (GOG199), 36% opted not to undergo RRSO

- Only 60-70% of BRCA mutation carriers are estimated to have undergone RRSO and only 43% of those <40 years

PATIENTS DESERVE BETTER OPTIONS

WE CAN DO BETTER!
Menopause Management

• Non-hormonal options for menopausal symptoms
  – Genitourinary syndrome of menopause (ex. vaginal dryness, atrophy): moisturizers
  – Vasomotor symptoms: acupuncture, lifestyle modifications, SSRIs
• Sexual health research and increased focus on women’s sexual function
• Hormone replacement therapy
  – Highly effective at reducing side effects/health effects of surgical menopause
  – Supported by Society Gynecologic Oncology: acceptable for patients without a personal history of breast cancer
    • Prospective cohort study of 872 BRCA carriers in 80 countries
      – HRT use after RRSO was not associated with increased breast cancer risk (estrogen only after hysterectomy safest approach)

Kotsopolus et al. JAMA Onc. 2018.
Are we ready for a salpingectomy option?
The Role of Salpingectomy

• What we know now:
  – The **fallopian tube** plays a role in the development of HGSC
  – **Bilateral tubal ligation (BTL)** likely has a protective effect
    • 34% reduction in risk in a meta-analysis of 13 case-control/cohort studies
  • **Salpingectomy** is associated with decreased risk of ovarian cancer
    • Swedish cohort study including >5 million women and 30,000 cases of ovarian cancer showed a significant decrease in ovarian cancer with removal of the tubes (HR 0.65, 95% CI 0.52-0.81)

• What we still don’t know:
  – When does the lesion escape from the fallopian tube?
  – How much protection will removing the fallopian tubes provide to a high-risk person?

Early Salpingectomy Delayed Oophorectomy

• Salpingectomy can be performed as soon as childbearing complete (or sooner if IVF planned)
  – *Ovarian function preserved*
  – *Low risk procedure*

• Opportunity for SEE-FIM and inspection of the peritoneal cavity

• Ovaries can still be removed by the recommended age

• Proposed as an option for patients who decline RRSO per guidelines or as part of a clinical trial
Early Salpingectomy Delayed Oophorectomy

**PROS**
- Risk reduction without added morbidity of menopause
- Opportunity to inspect peritoneal cavity
- Pathologic evaluation of fallopian tubes
- If a STIC is identified, completion oophorectomy

**CONS**
- Degree of protection is unknown
- Diminished breast cancer risk-reduction
- Need for 2 operations
- Possibility that completion oophorectomy will not be performed
Ongoing Clinical Trials

• Women Choosing Surgical Prevention (WISP)
• Early Salpingectomy (Tubectomy) with Delayed Oophorectomy in BRCA1/2 Mutation Carriers (TUBA)
• Preventing Ovarian Cancer through Early Excision of Tubes and Late Ovarian Removal (PROTECTOR)
• A Non-Randomized Prospective Clinical Trial Comparing the Non-Inferiority of Salpingectomy to Salpingo-Oophorectomy to Reduce the Risk of Ovarian Cancer Among BRCA1 Carriers (SOROCK)
  – Oncologic endpoint
  – Currently enrolling at MSK
WISP Preliminary Results

• Premalignant disease (STIC) was identified in one subject undergoing RRSO

• No cancers diagnosed at initial surgery, between surgeries, or at completion surgery

• Quality of life outcomes:
  – Both arms had decrease in distress at 6 months (RRSO arm had greater decrease)
  – RRSO had significantly worse menopausal symptoms
  – Higher decision regret in RRSO arm, which held true regardless of use of HRT
Can we do more to prevent ovarian cancer?

OPPORTUNISTIC SALPINGECTOMY

- Average risk patients
- Removal of the fallopian tubes during any indicated abdominal or pelvic surgery
  - Sterilization – instead of “tying” the tubes
  - During any hysterectomy
  - During non-gynecologic surgery?

_This strategy is predicted to significantly reduce the number of ovarian cancers diagnosed in the general population_
In conclusion

• Genetic testing and risk-reducing surgery can be life saving!

• “Previvorship” planning is essential

• There is more work to do:
  – Expand access to genetic testing to identify ALL high-risk individuals
  – Optimize risk-reducing surgical options
  – Improving quality of life for “previvors”
  – Find opportunities to prevent in the general population
  – Develop an early detection test!
Thank you!

Of course, thank you to our courageous patients and their loved ones.

MSK Team Ovary