Hereditary Ovarian Cancers

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Center for Cancer Risk Assessment
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An Overview of Our Discussion Today

• What are the functions of the ovaries?
• What are the types of ovarian cancer?
• Symptoms and screening options
• What is the difference between sporadic versus hereditary (ovarian) cancer
• Describe hereditary ovarian cancer syndromes
• Who is a candidates for genetic counseling and testing?
• Discuss the benefits and limitations of genetics testing
The **ovaries** are an important part of the female reproductive system. They have 2 functions:

1. They produce the hormones, including estrogen, that trigger menstruation.
2. They also release at least one egg each month for possible fertilization.
How big (or small) is an ovary?
Are there screening tests for ovarian cancer?

There are no recommended screening tests that are effective at diagnosing ovarian cancer at an early/treatable stage

- Transvaginal ultrasounds and CA-125
  - Are offered to high-risk women
  - Has led to more testing and more surgeries, but has not lowered the mortality caused by ovarian cancer
  - Not specific enough
  - Not sensitive enough
  - We need something better
What does it mean to have ovarian cancer?

Ovarian cancer = invasive tumors that originate in the ovary

These include tumors that start at the Fallopian tube or in the peritoneal cavity

Most common = epithelial ovarian cancer

Serous, Endometrioid, Mucinous, Clear Cell

Non-epithelial ovarian cancer/tumor

Germ cell tumors (teratomas, dysgerminoma)

Sex-chord/stromal tumors (Sertoli-Leydig)

Mixed mesodermal tumors

Borderline ovarian tumors
Symptoms of Ovarian cancer

• Bloating
• Pelvic or abdominal pain
• Trouble eating or feeling full quickly
• Urinary symptoms such as urgency (always feeling like you have to go) or frequency (having to go often)

These symptoms are also commonly caused by benign (non-cancerous) diseases and by cancers of other organs. When they are caused by ovarian cancer, they tend to be persistent.
Risk Factors for Ovarian Cancer

- **Age.** Ovarian cancer can occur at any age but is most common in women ages 50 to 60 years.

- **Inherited gene mutations.** A small percentage of ovarian cancers are caused by gene mutations you inherit from your parents.

- **Family history of ovarian cancer.** People with two or more close relatives with ovarian cancer have an increased risk of the disease.

- **Estrogen hormone replacement therapy,** especially with long-term use and in large doses (oestrogen only or combination, but it’s not a large risk)

- **Age when menstruation started and ended.** Beginning menstruation at an early age or starting menopause at a later age, or both, *may* increase the risk of ovarian cancer.

Adapted from cancer.org
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Adapted from cancer.org
All cancer **IS** genetic!

- Cancer is caused by mistakes that accumulate in genes (DNA) in **one to several cells** of the body that leads to uncontrolled cell division & growth (i.e. a tumor)

But, **not** all cancer is hereditary!

Hereditary cancer means an individual was born with a gene mutation in **every cell** of their body that increases their chances of developing cancer in their lifetime
Let me explain…

All cancer is GENETIC
All cancer is GENETIC
All cancer is GENETIC
All cancer is GENETIC
But only *some* cancers are hereditary
What percent of cancers is due to an inherited gene mutation?

- **Only 5-10%** of individuals with cancer have an identifiable hereditary gene mutation.
What does Sporadic cancer look like? 
(70%)

- Not a strong family history of cancer
- Relatives are diagnosed at older/common ages
- Cancers are happening due to other (more common) risk factors:
  - Skin cancers: sun exposure
  - Lung cancer: smokers
  - Colon cancer: obesity, Chron’s disease

This slide is adapted from March of Dimes “Genetics and Primary Care” Education Initiative
What do Hereditary cancer families look like? (5-10%)

- Multiple affected individuals across multiple generations
- Younger ages of onset (often <45-50 years)
- Individuals with multiple primaries
- Rare tumors and unique combinations of cancers in the family:
  - Breast (male or female) and ovarian
  - Colon, uterine, ovarian and stomach cancer
Pedigree #1

50

OV 80

50

Lung 77

83

50 43

50 49

58 56
Pedigree #2

- Pedigree Diagram:
  - Pedigree Branches with Numbers:
    - OV 50
    - CO 43
    - CO 44
    - OV 48
    - 83
    - 50
    - 49
    - 58
    - 56

- Yellow Highlights:
  - OV 50
  - CO 43
  - OV 48

- Arrow Indicating Direction:
  - Arrow pointing from CO 44 to 83

- Pedigree Structure:
  - Branching Family Tree Model

- Pedigree #2 Information:
  - OV 50
  - CO 43
  - CO 44
  - OV 48
  - 83
  - 50
  - 49
  - 58
  - 56
Pedigree #3

Familial

- CO 73
- Lung 68
- 83

- Lung 53
- 50

- CO 74
- 50

- 50
- 49
- 58
- 56
Purpose: Classification > Intervention

Assessment

- Family Hx
  - Sporadic: Low
  - Familial: Moderate
  - Hereditary: High

Risk Classification

- Sporadic: Low
- Familial: Moderate
- Hereditary: High

Intervention

- Standard screening/prevention recommendations
- Personalized screening/prevention recommendations
- Referral for genetic evaluation with personalized screening/prevention recommendations

This slide is adapted from March of Dimes “Genetics and Primary Care” Education Initiative
What percent of people with ovarian cancer have a gene mutation that was inherited?

- About **10 - 25%** percent of women diagnosed with ovarian cancer have a mutation in a gene.

Image: Ambry Genetics
Do you know any genes that increase ovarian cancer risk?
BRCA1, BRCA2 genes: the most common
<table>
<thead>
<tr>
<th>GENE(S)</th>
<th>ASSOCIATED CANCERS*</th>
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<tbody>
<tr>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>APC</td>
<td>✓</td>
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<tr>
<td>ATM</td>
<td>✓</td>
</tr>
<tr>
<td>BARD1</td>
<td>✓</td>
</tr>
<tr>
<td>BRCA1, BRCA2</td>
<td>✓</td>
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<tr>
<td>BRIP1</td>
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<tr>
<td>DICER1</td>
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</tr>
<tr>
<td>EPCAM, MLH1, MSH2, MSH6, PMS2</td>
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</tr>
<tr>
<td>GREM1, POLD1, POLE</td>
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<tr>
<td>HOXB13</td>
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<tr>
<td>MRE11A</td>
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<td>NF1</td>
<td>✓</td>
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<td>PALB2</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>TP53</td>
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</tbody>
</table>
Genes associated with Ovarian Cancer risk

High Risk
- BRCA1 (40-60%)
- BRCA2 (15-30%)
- RAD51D (15%)
- MLH1 (4-12%)
- MSH2/EPCAM (4-12%)

Moderate/Low/? Risk
- BRIP1 (6%)
- RAD51C (7%)
- MSH6 (?)
- PMS2 (?)
- TP53 (?)
- NF1 (?)
- PALB2 (?)
- BARD1 (?)
Genes with guideline recommendations

BRCA1- RRSO between 35-40 y
BRCA2- RRSO between 40-45 y

RAD51D- Consider RRSO at 45-50 y, or earlier based on family hx

STK11 (Peutz-Jeghers syndrome) – Pelvic exam (starting ages 18-20 y for non-epithelial ovarian cancers)

Hereditary Breast and Ovarian Cancer syndrome
Genes with NCCN guidelines recommendations (cont.)

MLH1, MSH2/ EPCAM, MSH6, PMS2 (Lynch syndrome)-
RRSO when childbearing complete, or depending on family history; no data to support routine T U/S or CA-125, but may be considered at clinician’s discretion

BRIP1 – Consider RRSO at 45-50 y, or earlier based on family hx

RAD51C- consider RRSO at 45-50 y, or earlier based on family hx
Genes WITHOUT recommendations

- PALB2
- CHEK2
- TP53
- NF1
- DICER1

May change in the future

Based on family history
Who should consider Genetic Counseling?

- Those that have/had epithelial ovarian cancer, regardless of age of onset
- Those with a close relative with ovarian cancer
- Those with a personal/family history that has a combination of 2 or more of the following cancers:
  - Ovarian, breast, pancreatic
  - Ovarian, uterine, colon
- If you are Ashkenazi Jewish and have a personal/family history of ovarian, breast, prostate and pancreatic cancers
  - Common BRCA founder mutations (1 in 40)
We’ve Come a Long Way In Cancer Genetics

1996-2006
- Single gene testing
- Single syndrome testing

2006-2013
- Improvements in gene coverage sensitivity

2013-2018
- Multi-gene panels
- Other testing labs

Present

Courtesy of Stephanie Hicks, MS, LCGC
Genetic Counseling

• Impact on personal cancer risk and medical management
  – surveillance, surgery, medication

• Psychological implications
  – peace of mind, anxiety, vulnerability, depression, difficult decisions

• Family dynamics
  – Affect relationship with family members/can be upsetting to relatives and strain relationship (burden of disseminating information, guilt, survivor guilt, non-p/maternity)

• Insurance coverage

• Confidentiality/Insurance Issues (ie. Discrimination)
  – Health insurance/Large Employer (Protected by law)
  – Life insurance/Disability/Long Term Care (No protection)
Genetic Discrimination

• 2008 – a federal law was put into place called “Genetic Information Non-Discrimination Act” (GINA)
  • Health insurance
  • Employment
  • Some exceptions

• But this doesn’t cover everything
  – Life insurance
  – Disability policies
  – Long-term care policies
Genetic Discrimination

- A federal law was put into place called the Genetic Information Non-Discrimination Act (GINA).
- This law applies to health insurance and employment but does not cover life insurance, disability policies, or long-term care policies.

Types of Results a Patient May Receive After Genetic Testing

**NEGATIVE**

Negative for the genes tested. Important to consider if there is a known mutation in your family.

**VUS (Variant of Uncertain Significance)**

Unknown at this time if change identified is harmful.

**POSITIVE**

Positive for a gene that increases the risk of cancer.

Courtesy of Andrea Forman, MS, LCGC; Myriad Genetics Laboratories Counseling Aids
WHAT DO THESE TEST RESULTS MEAN?

**GENETIC TESTING RESULTS**

- **Negative**
- Variant of uncertain significance
- Deleterious or Suspected deleterious

**IMPLIEDATIONS**

- Medical management based on personal and family history of cancer
- Medical management based on cancer risks specific to gene mutation

Courtesy of Andrea Forman, MS, LCGC; Myriad Genetics Laboratories Counseling Aids
Can I just get my cancer testing through 23 and Me?

- Yes, but it will not be comprehensive
- In March of 2018, the FDA approved 23 and Me to report on three specific mutations that are commonly found in the Ashkenazi Jewish population
  - NOT comprehensive testing of even *BRCA1/2*, and not looking at the additional genes known to be associated with breast and ovarian cancer
  - Similarly, NOT comprehensive testing for other genes associated with hereditary ovarian cancer risk
Meet our AMAZING team!

Top row, from left: Devanshi Patel, Kristen Shannon, Carly Grant, Shelley McCormick, Linda Rodgers-Fouche
Second row, from left: Erica Blouch, Amy Mueller, Meredith Seidel, Janette Z Lawrence, Lauren Bear, Gayun Chan-Smutko
Individual pictures, from top to bottom: Kiley, Delgado, Stephanie Hicks, Margaret Emmett

Medical Co-Directors:
Leif W Ellisen, MD, PhD
Daniel Chung, MD
Thank you!