BRCA and Genetics in Gynecologic Malignancies

Disclosures

- Advisory board
  - Iovance
  - Clovis
  - AstraZeneca
- Data monitoring committee
  - Genentech

Objectives

- Review features of common hereditary gynecologic cancer syndromes
  - BRCA
  - Lynch syndrome
- Describe approaches to hereditary cancer risk assessment and genetic testing
- Understand current and evolving landscape of genetic testing in gynecologic cancer susceptibility syndromes
BRCA and Genetics in Gynecologic Malignancies

**Sporadic**
- Later age at onset (60s or 70s)
- Little or no family history of cancer
- Single or unilateral tumors

**Inherited**
- Early age at onset (<50)
- Multiple generations with cancer
- Clustering of certain cancers (i.e. breast/ovarian)

**Autosomal dominant inheritance**

**Hereditary susceptibility to gynecologic cancers**
- Hereditary Breast-Ovarian Cancer (BRCA1/BRCA2)
  - Ovarian cancer
- Lynch syndrome (MLH1/MSH2/MSH6/PMS2/EPCAM)
  - Endometrial cancer, ovarian cancer
- Cowden syndrome (PTEN)
  - Endometrial cancer
- DICER1 syndrome (DICER1)
  - Sertoli-Leydig cell tumors of the ovary
- SMARCA4 mutations
  - Ovarian small cell carcinoma, hypercalcemic type
- Peutz-Jeghers syndrome (STK11)
  - Ovarian sex cord tumors, cervical adenoma malignum
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Suspect hereditary cancers when...

- Cancer in 2 or more relatives (on same side of the family)
- Early age of cancer diagnosis
- Multiple primary tumors
- Constellation of tumors consistent with cancer syndrome
  - Example: breast and ovarian cancers
- Family history is key!

Verify family history

Verbally reported pedigree

After review of pathology reports

Family histories are dynamic

Initial History

2 years later
Hereditary breast and ovarian cancer

Breast Cancer and Ovarian Cancer

- Sporadic
- Family clusters
- Hereditary

Genetic predisposition of ovarian cancer

2018 Estimated New Ovarian Cancer cases: 22,240

- 20-25% Hereditary disposition
- 15% Lynch syndrome
- 18-24%BRCA1
- 15-20%BRCA2
- 18-24% Other single genes
- 10%Lynch syndrome

Hereditary breast and ovarian cancer syndrome

BRCA1 and BRCA2
**BRCA and Genetics in Gynecologic Malignancies**

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**BRCA gene**
- **BRCA** genes are tumor suppressor genes
  - Function in the DNA repair process
    - Single/double strand breaks, homologous recombination
  - General population: 1 in 300 to 800 carry the mutation
  - **BRCA** mutation may be discovered in new incident case
    - In ovarian cancer, 40% have no prior family history
  - Majority of mutations are deleterious
    - Protein is non-functional
  - Over 2000 separate mutations have been identified


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**BRCA associated cancers**
- **Breast cancer**
  - ~5% of all breast cancers (20% of hereditary cases)
- **Ovarian cancer**
  - 9-24% of all epithelial ovarian cancer cases
  - Risk begins to rise at age 40 and sharply rises after age 50
- **Pancreatic cancer**
  - **BRCA** 2 carriers have a 3x increased risk and 7% lifetime risk of pancreatic cancer
- **Others**: Prostate cancer, melanoma
- Questionable association with serous uterine cancer


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**BRCA1**
- Tumor suppressor gene on chromosome 17
- Autosomal dominant transmission
- Protein has role in genomic stability
- >600 different mutations reported

Breast Cancer Information Core

**Nonsense** • **Missense** • **Splice-site**
**BRCA1 associated cancers**

- Breast cancer 50-85% (often early age at onset)
- Second primary breast cancer 40%-60%
- Ovarian cancer 15-45%
- Possible increased risk of other cancers (eg, prostate)

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**BRCA2**

- Tumor suppressor gene on chromosome 13
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~450 different mutations reported

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**BRCA2 associated cancers**

- Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)
Guidelines for BRCA testing

- Women diagnosed with the following:
  - Epithelial ovarian, tubal, or peritoneal cancer (EOC)
  - Breast cancer
    - Diagnosed at age 45 years or less
    - Diagnosed at age 50 years or less with limited family history
    - And close relative diagnosed (<50 years) or EOC any age
    - And two or more close relatives with breast cancer
    - Two breast cancer primaries (first diagnosis before age 50)
    - Triple negative breast cancer at age 60 or less
    - Ashkenazi Jewish ethnicity
  - And close relative (<50 years) or EOC any age
  - And two or more close relatives with breast cancer
- Women unaffected with cancer with the following:
  - First degree or close relatives that meet the above criteria
  - Relative with a known BRCA mutation
  - Close relative with male breast cancer

Most informative to test an affected person
- If a harmful BRCA mutation is found, genetic counseling and cascade testing should be performed
- If this person is not available or declines, testing is appropriate with a suggestive family history
- Professional societies do not recommend testing for children (even if known mutation in family)
- Lack of risk-reduction strategies and should be deferred to adulthood
- Risks a BRCA associated cancer are extremely low

BRCA genetic testing

- Multiple panel options
  - **Will discuss specific later
- BRCA test: Classification of results
  - Positive
  - Negative
  - Variant of uncertain significance (VUS) or ambiguous
Interpreting the results: Positive
- Enhanced screening/surveillance
- Chemoprevention
- Prophylactic (risk reducing) surgery
- Cascade testing of family members

BRCA: Surveillance and risk reduction
- Breast cancer early detection/risk reduction
  - Breast awareness age 18
  - Clinical breast exam every 6-12 months starting age 25
  - MRI age 25-29y
  - MRI and mammography 30-75y
  - Individual management after age 75
  - Consider prophylactic mastectomy
    - Reduces breast cancer risk by ~90-95%
    - Consider chemoprevention (tamoxifen)
  - Possible screening for pancreatic cancer and melanoma

BRCA: Surveillance and risk reduction
- Ovarian cancer risk reduction
  - Bilateral salpingo-oophorectomy by age 35-40y
    - May delay to 45 with BRCA2
    - Pathology protocol with washings and serial sectioning
    - Residual risk of peritoneal cancer is ~1-6%
    - May reduce risk of breast cancer
  - Surveillance with annual transvaginal ultrasound with concurrent serum CA-125 (if decline/delay surgery)
    - No data to support reduction in mortality
  - Consider oral contraceptives
    - Reduce risk of ovarian cancer by ~50%
  - Discussion of risks versus benefits

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NCCN guidelines Genetic/Genodermatological High Risk Assessment: Breast and Ovarian v.1.2017
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**BRCA associated ovarian cancers**
- BRCA2 tend to have better prognosis/outcomes
- Germline or somatic BRCA mutations: PARP inhibitor maintenance therapy after frontline chemotherapy
- Treatment strategies
  - Recurrence
  - Maintenance

**Surveillance recommendations**

**Males**
- Breast cancer early detection
  - Breast self examination age 35
  - Clinical breast exam every 12 months starting age 35
- Prostate cancer early detection
  - PSA and digital rectal exam starting 45
  - Stronger recommendation for BRCA2 than for BRCA1 mutation carriers
- Possible screening for pancreatic cancer and melanoma

**Interpreting the results: Negative**
- If a close relative has tested positive, a negative result means the person does not carry that harmful mutation and cannot pass it on; general population risk
- If tested person has a suggestive family history, but tests negative, it may be a result of an as-yet unknown harmful mutation that has not been identified. There is a low likelihood of missing a known harmful mutation
- May be the result of a mutation in a non BRCA gene
Interpreting the results: VUS

- A change in BRCA1 or BRCA2 that has not been previously associated with cancer
- May occur in ~10% of women undergoing BRCA testing
  - Unclear prevalence in population
  - Unclear impact on protein function
  - Unclear association with disease
- Increased testing rates will help reclassify these results
  - Important to keep records

Lynch Syndrome

Hereditary susceptibility to colorectal cancer

Adapted from Burt RW et al. Prevention and Early Detection of CRC, 1996
Genetic features of Lynch Syndrome

- Genes: DNA mismatch repair (MMR) family
  - Mutations lead to microsatellite instability (MSI)
  - MMR proteins are missing (IHC useful), normally present
  - If protein is absent, gene is not being expressed
  - Mutation or methylation
  - Majority due to MLH1

Lynch syndrome

- Excluded if methylation
- Germline DNA testing is required if MLH is absent and no methylation
- Abnormal IHC (absent), considered MSI high
  - 90% of Lynch syndrome tumors are MSI
  - Better prognosis
  - Therapeutic target
    - Immunotherapy

Clinical features of Lynch Syndrome

- Age of diagnosis of colorectal cancer is ~45 years
- Tumor site in proximal colon predominates
- Extracolonic cancers
  - Endometrial
  - Ovarian
  - GI tract (stomach, pancreas)
  - Urinary tract (renal, ureter)
BRCA and Genetics in Gynecologic Malignancies

Lynch syndrome risks (up to age 70)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Lynch syndrome</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer (women)</td>
<td>18-61%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>16-61%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>5-10%</td>
<td>1%</td>
</tr>
<tr>
<td>Other LS cancers</td>
<td>5-10%</td>
<td>1%</td>
</tr>
</tbody>
</table>


Family history is key

Guidelines for Lynch syndrome testing

- Personal history of endometrial or colon cancer
- Universal tumor testing with IHC
- Tumor testing on at-risk patients
  - Modified Bethesda guidelines
    - Colon or endometrial cancer less than 50 years old
    - Synchronous Lynch syndrome associated cancers
    - Colon cancer with MSI high and less than 60 years
    - Colon cancer in two or more first or second degree relatives
  - Tumor testing on tumors diagnosed prior to age 60
  - Lower costs

**Guidelines for Lynch syndrome testing**

- 1st degree relative with endometrial or colorectal cancer <60 years or at risk from systematic clinical screen
  - Pitfalls: Paucity of female family members, few individuals reaching advanced age, or family members who had hysterectomy/BSO
- Pattern of repeated generations of Lynch syndrome associated cancers
  - Especially those diagnosed <60 years
- From families with a known Lynch syndrome gene mutation
  - Regardless of degree of relation

**Approach to Lynch syndrome testing**

- All proteins present
  - MMR IHC
    - MLH1/PMS2 absent
      - Any other proteins absent
- Pos family hx
  - Consider additional testing – MSI and/or germline gene
- No family hx
  - Unlikely to be LS
    - MLH1 promoter methylation
      - Or...cut to the chase and start with germline
- Germline testing
  - Pos
    - Lynch
      - Unlikely to be LS – consider tumor seq
  - Neg
    - Lynch
      - Unlikely to be LS – consider tumor seq
  - Unlikely to be LS
    - Germline testing
      - Pos
        - Lynch
          - Unlikely to be LS – consider tumor seq
      - Neg
        - Lynch
          - Unlikely to be LS – consider tumor seq

**Lynch syndrome: Surveillance/risk reduction**

- Colon cancer
  - Colonoscopy every 1-2 years beginning at age 20-25
    - Or 2 to 5 years before earliest cancer diagnosis in family
- Genitourinary tract cancers
  - Urinalysis with cytology every 1-2 years beginning at age 25-35
- No screening but also at risk for the following tumors:
  - Pancreas, biliary tract, brain, small bowel, etc.
### Lynch syndrome: Surveillance/risk reduction

- Endometrial and ovarian cancer
  - Endometrial biopsy every 1-2 years
  - Transvaginal ultrasound every year beginning at age 30
- Chemoprevention
  - Oral hormonal therapy (OCPs, progestin therapy)
  - Levonorgestrel intrauterine device
- Prophylactic hysterectomy and bilateral salpingo-oophorectomy after completion of childbearing
  - Post-operative primary peritoneal carcinoma has been observed but magnitude of risk is unknown


### Cowden Syndrome

- Incidence: 1 in 200,000 (likely underestimated)
- Autosomal dominant inheritance
- PTEN Gene on chromosome 10q23
- Pathognomonic muco-cutaneous lesions
- Associated cancers:
  - Breast
  - Endometrial
  - Follicular thyroid
- Cancer risk management strategies

NCCN guidelines Genetic/Familial High Risk Assessment: Breast and Ovarian v.1.2017
Pilarski et al. JNCI; 2013;105:1607-1616

### Evolution of genetic testing

<table>
<thead>
<tr>
<th>Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990's</td>
<td>Single gene tests</td>
</tr>
<tr>
<td>2012</td>
<td>Single gene tests</td>
</tr>
<tr>
<td>2013</td>
<td>Many labs offer cancer genetics panels – variability in cost and number of included genes</td>
</tr>
<tr>
<td>Now</td>
<td>Targeted therapies: need to add to bulk testing, too</td>
</tr>
</tbody>
</table>

June 2013

NCCN guidelines Genetic/Familial High Risk Assessment: Breast and Ovarian v.1.2017
Multigene panel testing
- Genes other than BRCA1/BRCA2
- Current NCCN recommend multigene panel
  - When more than one syndrome suspected
  - When a person is negative for BRCA gene mutations but personal/family history is still highly suggestive
- Consider referral/consultation with genetic experts in the context of pre and post test counseling

Genetic testing
- Next generation sequencing: multi-gene panel testing
  - More labs and more options
  - Prices range from $249 - $4,500
  - Number of genes included ranges from 2-90**
  - Turn-around time ranges from 3-12 weeks
- Advantages:
  - Multiple genes tested
  - Lower costs that older techniques
  - Options to customize
- Disadvantages:
  - Finding of unknown gene mutations
  - Higher chance of ambiguous results
  - More genes≠better

Multigene panel testing
- Approximately 6-10% of patients who test negative for BRCA may have another known gene mutation
  - RAD51C
  - RAD51D
  - BRIP1
  - BARD1
  - PALB2
  - May or may not have evidence to support increased risk for hereditary cancer
  - Controversy with multi-gene panel testing versus BRCA specific testing
Non BRCA related ovarian cancer risks

<table>
<thead>
<tr>
<th>Gene</th>
<th>Relative Risk</th>
<th>Lifetime Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIP1</td>
<td>8-11</td>
<td>10-15%</td>
</tr>
<tr>
<td>RAD51D</td>
<td>6-12</td>
<td>8-15%</td>
</tr>
<tr>
<td>RAD51C</td>
<td>4-8</td>
<td>5-10%</td>
</tr>
<tr>
<td>PALB2</td>
<td>3-8</td>
<td>5-10%</td>
</tr>
<tr>
<td>Lynch Syndrome genes</td>
<td>Varies greatly by gene</td>
<td>5-10%</td>
</tr>
</tbody>
</table>

Knowledge continues to evolve – prospective follow up needed

Norquist et al. 2015; Rafnar et al. 2011, Ramus et al. 2015; Loveday et al. 2011, Peltari et al. 2011, Song et al. 2015, Loveday et al. 2012

Multigene panel mutations

- Breast MRI
- Discuss risk reducing mastectomy
- Recommend or consider risk reducing BSO

Brca1, Brca2, ATM, PTEN, CDH1, STR11, CHEK2, TP53, PALB2

NCCN in Annual Genes/Familial High Risk Assessment: Breast and Ovarian v.2.2016

Germline versus somatic mutations

- Germline genetic testing looks for inherited mutations
  - Usually a blood or saliva test
- Somatic genetic testing looks for mutations that occurred in the cancer cells
  - Tumor tissue tests/Liquid biopsies
  - No impact on family members
  - No known risk of other primary cancers
- Both may be important for therapeutic options
  - Germline or somatic BRCA mutations and PARP inhibitors
  - MSI high tumors and immunotherapy
Genetic Information Non Discrimination Act (GINA) 2008

- Prevents health insurers from denying coverage, adjusting premiums, or otherwise discriminating on the basis of genetic information.
- Group and self-insured policies
- Insurers may not request that an individual undergo a genetic test
- Employers cannot use genetic information to make hiring, firing, compensation, or promotion decisions
- Sharply limits a health insurer’s or employer’s right to request, require, or purchase someone’s genetic information

Conclusions and potential future directions

- Accurate family history is critical: Verify and update
- Genetic testing
  - Surveillance
  - Chemoprevention or risk reducing surgery
  - Cascade testing
- Identify targeted therapeutics based on mutation status
  - Better outcomes/less toxicities
- All cancer is genetic but may not be inherited
- Benefit of testing all women for BRCA mutations?
  - May prevent breast/ovarian cancer cases
  - Challenges: Penetrance differences, new genes/tests, invasive actions to reduce risk

A CANCER-FREE WORLD BEGINS HERE