Beyond BRCA: Hereditary Breast Cancer Genes

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MGH Center for Cancer Risk Assessment
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Overview

- Hereditary vs. sporadic breast cancer
- Features of hereditary breast cancer
- \textit{BRCA1/2}-history, features, medical management
- High risk breast cancer genes
- Moderate risk breast cancer genes
- Lower risk breast cancer genes
- Testing considerations
- Questions?
Breast Cancer Stats

- Most frequently diagnosed cancer globally
- Mostly diagnosed > age 50 (median age in U.S. is 62)
- 1 in 8 women will develop breast cancer (12% lifetime risk)
- In 2019, there will be 268,600 new cases
- Most breast cancer is not hereditary
Types of Breast Cancer

DCIS: Cancer contained in the milk ducts

IDC: ~80% breast cancer

ILC: ~10% start in lobules-milk producing glands

Other types: mixed lobular/ductal, inflammatory, sarcomas, phyllodes, angiosarcomas
WHAT FACTORS AFFECT BREAST CANCER RISK?

DECREASE RISK
- Maintaining healthy weight
- Exercising regularly, on average three to four hours a week
- One or more full-term pregnancies
- First full-term pregnancy before age 25
- Breast feeding for more than 15 months (total months across all children)
- Menopause before age 50

INCREASE RISK
- Being overweight or obese
- Sedentary lifestyle
- Drinking more than one alcoholic drink a day
- Exposure to high-dose radiation, particularly before age 40
- Aging
- Family history of breast cancer
- Inherited genetic mutations (e.g., BRCA1)
- Using hormone therapy after menopause

CityofHope.org/breast-cancer-environment
Causes of Hereditary Breast Cancer

Only 5-10% of breast cancer is hereditary

Adapted from http://www.ambyrgen.com/file/material/view/635/BRCAPlus_BreastNext_Slides_1117_web.pdf
Genetics 101

- About 20,000 genes
- Two copies of every gene in nearly every cell
- Every gene has a job to play in the body.
- Some genes prevent cancer by controlling cell growth and division—tumor suppressor genes

Image from the NIH: https://www.niaid.nih.gov/diseases-conditions/pidds-genetics-inheritance
Cancer Basics
Cancer Basics

2 normal genes

1 mutated gene
1 normal gene

2 mutated genes

Tumor develops
In hereditary cancer, one mutated gene is inherited and is in almost every cell of the body from the start.
‘Genetic’ is different from ‘Hereditary’

All cancer is genetic - caused by an accumulation of genetic damage leading to uncontrolled cell division

Most cancer is not hereditary!
Autosomal Dominant Inheritance

50% Unaffected

50% Affected
Features of Hereditary Breast Cancer

- Premenopausal breast cancer
- Individuals with more than one cancer diagnosis such as bilateral breast cancer or breast cancer and ovarian cancer
- Multiple women with breast cancer
- Multiple generations of breast cancer
- Presence of male breast cancer
- Presence of ovarian cancer
- Triple negative breast cancer
- Certain ancestries (Ashkenazi Jewish)
The Pedigree
Case Examples
Case #1: Low Risk
Case #2: High Risk

Guess Who???
BRCA1 mutation
**BRCA1/2: Hereditary Breast and Ovarian Cancer Syndrome**

**Incidence**
1:400-800 gen pop; 1:40 AJ

**Breast Cancer Risk**
- **BRCA1**: 50-80%
- **BRCA2**: 40-70%

**Ovarian Cancer Risk**
- **BRCA1**: 40-60%
- **BRCA2**: 15-20%

**Other Cancer Risk**
- Male Breast: <6-7%
- Pancreatic: 1.3-7%
- Prostate: <30-40%

*Figure 1. Probability of Breast Cancer and Ovarian Cancer during a 10-Year Period.*
Data were adapted from Chen and Parmigiani.¹⁰
Women
• Breast awareness (starting age 18)
• Clinical breast exams ev 6-12 months (starting at 25)
• Annual breast MRIs (starting at 25)
• Annual mammograms (starting at 30)
• Consider prophylactic double mastectomies
• Bilateral oophorectomies after childbearing, or between 35-40

Men
• Prostate cancer screening, starting at 45
• Clinical breast exams (starting at 35)
• Breast self exam training and education (starting 35)
BRCA1/2 History

Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21

Jeff M. Hall; Ming K. Lee; Beth Newman; Jan E. Morrow; Lee A. Anderson; Bing Huey; Mary-Claire King


- 1994: *BRCA1* cloned and patented
- 1995: *BRCA2* cloned and patented
- 1996: *BRACAnalysis* launched by Myriad
- 2006: BART available as add-on test
- 2013: Supreme Court rules patents invalid
Breast Cancer Gene Risk Categories

Figure from: Hollestelle et al. (2010). Discovering moderate-risk breast cancer susceptibility genes. Current Opinion in Genetics and Development Volume 20 (3) 268 - 276
Other High Risk Breast Cancer Genes

*BRCA1, BRCA2, PTEN, TP53, STK11, CDH1*

Figure from: Hollestelle et al. (2010). Discovering moderate-risk breast cancer susceptibility genes. Current Opinion in Genetics and Development Volume 20 (3) 268 - 276
Case Example: Barbara

- Barbara is a 42 year old woman that presented for genetic counseling. Her physician had advised her to seek testing for ‘the breast cancer gene’ given her family history.
Barbara’s family history

- **PTEN** (Cowden syndrome)
- **TP53** (Li-Fraumeni syndrome)
- **STK11** (Peutz-Jeghers syndrome)
- **CDH1** (Hereditary diffuse gastric cancer)
- **BRCA1/2** (HBOC)
### Cowden Syndrome AKA PTEN Hamartomatous Tumor Syndrome

Prevalence: 1/200,000

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>People who do not have a genetic mutation</th>
<th>Cowden syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer</td>
<td>10-12%</td>
<td>25-50%</td>
</tr>
<tr>
<td>Endometrial (uterine) cancer</td>
<td>2-3%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Thyroid cancer (typically follicular)</td>
<td>1%</td>
<td>3-10%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4.5%</td>
<td>9-16%</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>1-2%</td>
<td>Possibly increased</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2%</td>
<td>Possibly increased</td>
</tr>
</tbody>
</table>

*National Comprehensive Cancer Network, Version 1.2018*
Other features of Cowden Syndrome

- Oral papillomas (benign overgrowth of tissue on tongue, gums, inside nose) “cobblestone” appearance
  [Image](http://www.regionalderm.com/Regional_Derm/files/cowdens.html)

- (Facial) trichilemmomas (benign tumor of hair follicle)
  [Image](https://escholarship.org/content/qt916821pq/inner/2.jpg)

- (Palmar/plantar) acral keratoses (rough patches of skin often seen on extremities)
  [Image](https://goo.gl/images/cbmFt2)

- Lipomas (benign fatty tumors) and vascular anomalies
  [Image](https://www.laser-medica.eu/removal-of-fibromas-lipomas-sebaceous-cysts-and-other-skin-lesions/)

- Fibromas (overgrowth involving skin and connective tissue)

- Penile pigmentation (males)

- >80% macrocephaly
- Autism spectrum disorders
- Lhermitte Duclos disease (benign brain tumor)
High Risk Breast Cancer Genes: TP53

Li-Fraumeni Syndrome

Component Tumors:
- Sarcoma
- Breast Cancer
- Brain tumors
- Leukemia (childhood)
- Adrenal cortical carcinoma

CPC= choroid plexus carcinoma
RMS=rhabdomyosarcoma
OS=osteosarcoma
LK=leukemia
CNS=brain tumors
BR=breast cancer
Peutz-Jeghers syndrome

Prevalence: 1/25,000-1/280,000

Hamartomatous gastrointestinal polyps (often benign and in a tree-like configuration)

Mucocutaneous hyperpigmentation (often of mouth, lips, nose, eyes, genitalia, and fingers; fades with age)


https://emedicine.medscape.com/article/182006-overview
## Peutz-Jeghers syndrome

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>People who do not have a genetic mutation</th>
<th>Peutz-Jeghers syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer</td>
<td>10-12%</td>
<td>45-50%</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>5%</td>
<td>39%</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>&lt;1%</td>
<td>39%</td>
</tr>
<tr>
<td>Small intestinal cancer</td>
<td>&lt;1%</td>
<td>13%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1.5%</td>
<td>11-36%</td>
</tr>
<tr>
<td>Ovarian (benign sex cord/Sertoli cell)</td>
<td>1-2%</td>
<td>18-21%</td>
</tr>
<tr>
<td>Cervical (cervical adenoma malignum)</td>
<td>-</td>
<td>10%</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>2-3%</td>
<td>9%</td>
</tr>
<tr>
<td>Testicular (sex cord/Sertoli cell)</td>
<td>0.4%</td>
<td>Increased</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>6-8%</td>
<td>15-17%</td>
</tr>
</tbody>
</table>
High Risk Breast Cancer Genes: **CDH1**

Hereditary Diffuse Gastric Cancer

Diffuse Gastric Cancer Risk in CDH1 carriers by Age

Lobular Breast Cancer Risk = 42-52%
High Risk Breast Cancer Genes: **CDH1**

*Hereditary Diffuse Gastric Cancer*

BR=breast cancer  
THY=thyroid cancer  
STO=stomach cancer  
OV=ovarian cancer  

**Courtesy of D. Patel, MGH**
Barbara’s family history

- **PTEN** (Cowden syndrome)
- **TP53** (Li-Fraumeni syndrome)
- **STK11** (Peutz-Jeghers syndrome)
- **CDH1** (Hereditary diffuse gastric cancer)
- **BRCA1/2** (HBOC)
Moderate Risk Breast Cancer Genes

BRCA1, BRCA2, TP53, PTEN, STK11, CDH1

PALB2, ATM, CHEK2
Moderate risk genes: **PALB2**

**PALB2**, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. **Partner and Localizer of BRCA2**

Nazneen Rahman, Sheila Seal, Deborah Thompson, Patrick Kelly, Anthony Renwick, Anna Elliott, Sarah Reid, Katarina Spanova, Rita Berfoot, Tasnim Chaghtai, Hiran Jayatilake, Lesley McGuffog, Sandra Hanks, D Gareth Evans, Diana Eccles, The Breast Cancer Susceptibility Collaboration (UK), Douglas F Easton & Michael R Stratton

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>People who do not have a genetic mutation</th>
<th>People who have a PALB2 gene mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer</td>
<td>10-12%</td>
<td>Up to 33% without a family history of breast cancer. Up to 58% with a family history of breast cancer.</td>
</tr>
<tr>
<td>Second primary breast cancer</td>
<td>Up to 15%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1-2%</td>
<td>Increased</td>
</tr>
</tbody>
</table>

National Comprehensive Cancer Network. Version 1.2018

**Cancer type** | **Surveillance recommendations**
--- | ---
Breast cancer (females) | Yearly mammogram with consideration of tomosynthesis and breast MRI with contrast beginning at age 30.
Pancreatic cancer | When applicable, discuss pancreatic cancer screening guidelines with your health care provider
Moderate risk genes: **CHEK2**

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>People who do not have a genetic mutation</th>
<th>People who have a CHEK2 gene mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer</td>
<td>10-12%</td>
<td>28-37%</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>4.5%</td>
<td>increased</td>
</tr>
</tbody>
</table>

*National Comprehensive Cancer Network, Version 1.2018*

- Other possible cancers: kidney, thyroid and prostate
- Most studies based on **CHEK2 1100delC** and I157T
## Moderate risk genes: *ATM*

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>People who do not have a genetic mutation</th>
<th>People who have an <em>ATM</em> gene mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast cancer</td>
<td>10-12%</td>
<td>27-38%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1-2%</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Ataxia Telangiectasia: Autosomal recessive condition involving neurologic deterioration, telangiectasias, immunodeficiency, and hypersensitivity to ionizing radiation.
So many breast cancer genes…

Figure from: Hollestelle et al. (2010). Discovering moderate-risk breast cancer susceptibility genes. Current Opinion in Genetics and Development Volume 20 (3) 268 - 276
### Lower risk/preliminary evidence genes: limited medical management

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer Risk</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRIP1</strong></td>
<td>Breast</td>
<td>Consider RRSO by 45-50y</td>
</tr>
<tr>
<td></td>
<td>Ovarian (5.8% by age 80)</td>
<td></td>
</tr>
<tr>
<td><strong>MLH1, MSH2, MSH6, PMS2, EPCAM</strong></td>
<td>Uterine (up to 60%), ovarian (up to 24%); possibly breast (with MLH1, PMS2) Lynch syndrome-related cancers</td>
<td>TAH/BSO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no guidelines for breast screening</td>
</tr>
<tr>
<td><strong>NBN</strong></td>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>annual mammogram starting at 40, consider breast MRI, RRM based on fmhx</td>
</tr>
<tr>
<td><strong>NF1</strong></td>
<td>Breast (8.4% by age 50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 1-related findings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>annual mammogram starting at 30, consider breast MRI, RRM based on fmhx, refer to NF clinic</td>
</tr>
<tr>
<td><strong>RAD51C and RAD51D</strong></td>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ovarian (1.5% RAD51C; 2.6% with RAD51D)</td>
<td>Consider RRSO by 45-50y</td>
</tr>
<tr>
<td><strong>BARD1</strong></td>
<td>Breast</td>
<td>no formal guidelines</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td></td>
</tr>
<tr>
<td><strong>RAD50</strong></td>
<td>Breast</td>
<td>no formal guidelines</td>
</tr>
<tr>
<td></td>
<td>Ovarian</td>
<td></td>
</tr>
<tr>
<td><strong>SMARCA4</strong></td>
<td>Sm. cell carcinoma of ovary (hypercalcemic) Central nervous system and kidney tumors</td>
<td>no formal guidelines</td>
</tr>
<tr>
<td><strong>DICER1</strong></td>
<td>Ovarian sex cord-stromal tumors Pleuroplumonary blastoma, kidney cysts, thyroid goiter, thyroid cancer</td>
<td>no formal guidelines</td>
</tr>
</tbody>
</table>
# Medical Management Guideline Differences

<table>
<thead>
<tr>
<th>Genes</th>
<th>HIGH RISK GENES</th>
<th>MODERATE RISK GENES</th>
<th>ELEVATED RISK GENES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td><em>BRCA1, BRCA2, CDH1, PTEN, TP53, STK11</em></td>
<td><em>ATM, CHEK2, PALB2, NF1</em></td>
<td><em>BARD1, BRIP1, NBN, RAD50, RAD51C, RAD51D</em></td>
</tr>
<tr>
<td>Lifetime Breast Cancer Risk</td>
<td>45-87%</td>
<td>20-58%</td>
<td>Increased, but not well defined</td>
</tr>
<tr>
<td>Medical Management</td>
<td>• Established guidelines for screening and prevention based on genetic test result</td>
<td>• Established guidelines for screening and prevention based on genetic test result and family history</td>
<td>• Screening and/or prevention guidelines may or may not be established • Management based on family history and estimated cancer risk</td>
</tr>
</tbody>
</table>

Both parents need to be carriers to have a child affected with a condition.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Recessive condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<td>PALB2</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>NBN</td>
<td>Nijmegen breakage syndrome</td>
</tr>
<tr>
<td>RAD50</td>
<td>Nijmegen breakage syndrome-like disorder</td>
</tr>
<tr>
<td>RAD51C/D</td>
<td>Fanconi anemia</td>
</tr>
</tbody>
</table>
Evolution of Genetic Testing

1996-2006
• Single gene testing
• Single syndrome testing

2006-2013
• Improvements in gene coverage sensitivity

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

Present
Multi-Gene Panels

Consider updated testing if it’s been more than 4 years!
Why would I want to know this??

✓ To better understand the reasons for my personal and/or family history of cancer

✓ To clarify my risk of future cancer development

✓ To learn if my children/grandchildren/relatives are at increased risk to develop cancer
### Genetic Testing Considerations

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May provide explanation for the history of cancer</td>
<td>• Psychological impact</td>
<td>• Negative result is most informative when familial mutation is known</td>
</tr>
<tr>
<td>• Results may assist with medical management decisions</td>
<td>• A normal result could give false reassurance</td>
<td>• Testing may not be able to detect all gene changes</td>
</tr>
<tr>
<td>• May provide information for family members</td>
<td>• Possibility of insurance or employment discrimination</td>
<td>• Variants of unknown significance</td>
</tr>
</tbody>
</table>

Greenwood Genetic Center
Can I just get my cancer testing through 23 and Me?

- Yes but we don’t recommend it

- 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 *BRCA1/2*,
  - NOT comprehensive testing for other genes associated with hereditary breast cancer risk

- Direct-to-consumer genetic testing is best for recreational use only, not for clinical purposes
Questions?

Thank you!

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

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