The Genetics of Early-Onset Breast Cancer

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All cancers are genetic

BUT

Not all cancers are hereditary
Genetic breakdown of breast cancer

- Sporadic: 70-75%
- Familial: 15-20%
- Hereditary: 5-10%
Sporadic

Familial

Hereditary

Starting Genetic “Load”
Sporadic Cancer = Single occurrence of cancer in family

- Majority of cases
- Not usually inherited
- Onset later in life

Low or no increased risk to family members beyond general population risk
Familial Cancer = Cluster of Cancer within Families

- 2 or more affected 1st or 2nd degree relatives
- Later onset
- Unilateral (one breast)
- Unclear inheritance pattern:
  - Chance alone
  - Common environment
  - Genetic factors (minor)

“Modest” increase in risk to family members ~ 2 fold general population
Hereditary Cancer

- Multiple affected individuals in multiple generations
- Early age of onset
- Multiple primary tumors
- Dominant inheritance
- Specific cancer clusters

![Family Tree Diagram]

- Prostate Ca age 58
- Ov Ca age 52
- Bilat Br Ca ages 33, 38
- Br Ca age 46
- Br Ca age 40
- Br Ca age 31
- Br Ca age 48
- Br Ca age 35
## High Penetrance Breast Cancer Susceptibility Genes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene(s)</th>
<th>Breast cancer risks</th>
<th>Other associated cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast/Ovarian Cancer (HBOC)</td>
<td>BRCA1 &amp; BRCA2</td>
<td>20-35% by age 50, 50-85% lifetime</td>
<td>Ovarian, pancreatic, prostate, melanoma</td>
</tr>
<tr>
<td>Li-Fraumeni Syndrome</td>
<td>TP53</td>
<td>56% by age 45, &gt;90% lifetime</td>
<td>Soft tissue sarcomas, leukemias, brain tumors, osteosarcomas, adrenal</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>PTEN</td>
<td>30-50% lifetime</td>
<td>Thyroid, endometrial</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11</td>
<td>8% by age 40, 32% by age 60</td>
<td>Colorectal, gastric, pancreatic</td>
</tr>
<tr>
<td>Hereditary Diffuse Gastric Cancer (HDGC)</td>
<td>CDH1</td>
<td>(lobular) 39% lifetime</td>
<td>Diffuse gastric cancer</td>
</tr>
</tbody>
</table>
Moderate Penetrance Breast Cancer Susceptibility Genes

- **CHEK2, ATM, NBS1, RAD50, BRIP1, PALB2**
- Association with 2-4 fold increased risk for breast cancer
- Mutations more frequent in younger onset cases, but figures uncertain
- Account for 2-4% of familial breast cancers
- Unclear benefit of genetic testing
Low Penetrance Alleles

- SNPs associated with breast cancer in case control studies
- Common, probably 100’s-1000’s
- 1.1-1.4 fold relative risks
- Unclear relationship with early-onset breast cancer, but unlikely to be a major factor
- Genomic profiling available DTC has little to no clinical validity or utility
Features That Indicate Increased Likelihood of Having *BRCA* Mutations

- Early onset breast cancer (< age 50)
- Triple negative breast cancers (ER/PR/Her2)
- Multiple cases of breast and/or ovarian cancer in the same family
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer (at least one < age 50)
- Male breast cancer
- Ashkenazi Jewish heritage
Prevalence of *BRCA1/2* Mutations

The chart shows the prevalence of BRCA1 and BRCA2 mutations in the General Population and Women with Breast Cancer. The specific categories are:

- **General Population**
  - Gen Pop
  - Jewish
  - Dx any age
  - Jewish

- **Women with Breast Cancer**
  - Dx < 45
  - Fam Hist Br Ca
  - Fam Hist Ov Ca

The chart indicates that the prevalence of BRCA1 and BRCA2 mutations varies significantly across these categories, with the highest prevalence observed in Women with Breast Cancer with a known family history of ovarian cancer (Fam Hist Ov Ca).
## Woman with unknown family history

<table>
<thead>
<tr>
<th>Age of Diagnosis</th>
<th>Non-Jewish</th>
<th>Jewish</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ER/PR positive</td>
<td>ER/PR negative</td>
</tr>
<tr>
<td>25</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>35</td>
<td>2.5</td>
<td>17</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>45</td>
<td>1.4</td>
<td>9</td>
</tr>
</tbody>
</table>
BRCA1/2 Risks Over Time

Cumulative Risk (%) vs. Age (years)

- BRCA1-Br
- BRCA1-Ov
- BRCA2-Br
- BRCA2-Ov
Breast Cancer Risks for 20 yo *BRCA1* or 2 Mutation Carrier

<table>
<thead>
<tr>
<th>Chance of Developing Cancer by age:</th>
<th>BREAST CANCER RISK</th>
<th>POPULATION RISK (non-carriers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1</td>
<td>BRCA2</td>
</tr>
<tr>
<td>30</td>
<td>1-2%</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>40</td>
<td>10-14%</td>
<td>6-10%</td>
</tr>
<tr>
<td>50</td>
<td>24-35%</td>
<td>17-26%</td>
</tr>
<tr>
<td>60</td>
<td>37-52%</td>
<td>28-42%</td>
</tr>
<tr>
<td>70</td>
<td>46-63%</td>
<td>38-53%</td>
</tr>
</tbody>
</table>
Importance of Paternal Family History

Probability of a BRCA1/2 mutation

<3%

Probability of mutation with paternal history

35-70%
The Problem of Limited Family Structure

BRCA1/2: < 2%

BRCA1/2: 5-10%
Impact of Genetic Test Results

**Bonnie:**
- Risk for second breast cancer
- Risk for ovarian cancer

**Sara:**
- No increased risk for breast or ovarian cancer beyond anyone in the general population.

BRCA1 mutation

Bonnie: Breast, dx 42
Sara: Breast, dx 36

Breast, dx 45
Ovarian dx 49
72 73 68 71
d. 52

Bonnie: Negative for BRCA mutation found in sister
Sara: No increased risk for breast or ovarian cancer beyond anyone in the general population.

= true negative
Impact of Genetic Test Results

Bonnie:
Risk for 2nd breast cancer or ovarian cancer is uncertain.

Sara:
Risk for breast cancer is still increased 3-4 times population risk.

Not tested
Management Options for \textit{BRCA1/2} Mutation Carriers

- Early clinical surveillance (begin at age 20-25) annual or semi annual:
  - clinical breast exam, mammogram, breast MRI
  - CA125, transvaginal ultrasound (uncertain efficacy)
- Chemoprevention
  - tamoxifen
  - oral contraceptives
Breast MRI vs. Mammogram in “High Risk” Women

- Kriege-04
- Warner-04
- MARIBS-05*
- BRCA 1/2 carriers*

Legend:
- MRI
- Mammo
Management Options for BRCA1/2 Mutation Carriers

• Prophylactic mastectomy – 90%+ reduction in breast cancer risk

• Prophylactic bilateral salpingoophorectomy
  • 80-96% reduction in ovarian/fallopian tube cancer risk
  • 50%+ reduction in breast cancer risk
Impact of Identifying a \textit{BRCA1/2} mutation in a young woman with newly diagnosed breast cancer

- Surgical management – bilateral mastectomy vs. lumpectomy
  - 10 year risk for contralateral breast cancer 20-30%

- Risk for ovarian cancer

- Emerging therapies – PARP2 inhibitor trials

- Implications for family members

- Availability of support network (e.g. FORCE)
What Is Cancer Genetic Counseling?

• Cancer genetic counseling is **NOT** genetic testing!
• It is a *process* of information gathering, risk assessment and education.
• The goal of cancer genetic counseling is to provide the individual, family and their health care providers with accurate cancer risk information to facilitate personal management decisions.
Cancer Genetic Counseling

Preparation
- Obtain personal and detailed family medical histories
- Collect and review medical records
- Calculate risk probabilities
- Assess patient’s risk perception

Education
- Cancer genetics and inheritance
- Personal cancer risks and likelihood for hereditary involvement

Discussion
- Appropriateness of genetic testing
- Risks, benefits, and limitations of testing
- Screening and management options
- Risk reduction strategies
- Psychosocial adjustment to cancer/genetic risks
“Marry me, Virginia. My genes are excellent and, as yet, unpatented.”
Resources:

- facingourrisk.org
- BeBrightPink.org
- nsgc.org/FindaGeneticCounselor/tabid/64/Default.aspx
- cancer.gov/search/geneticsservices/

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