Breast Cancer Predisposition Gene
BRCA1    BRCA2

William Lodrigues
1990  Jeremy Irons wore a red ribbon pinned on his chest during the Tony Tony Awards. The ribbon was for AIDS awareness and the ribbons became very popular.

1991  Alexandra Penney, editor of Self Magazine, and Evelyn Lauder, VP of Estee Lauder were working on second annual Breast Cancer Awareness Month issue.

They worked with a Breast Cancer survivor named Charlotte Hayley, who was using peach colored ribbons and selling them to raise money. The three women came up with the concept of Pink Ribbons for breast cancer awareness. The ribbons were distributed to all the Estee Lauder stores in New York that year and promised to send them to all the stores in the country that year.
Breast Cancer

Prevalence

• Fifth leading cause of death of all cancers
• Second most common cancer
• Over 200,000 annual cases
• Over 1 million undiagnosed
• 1 in 8 women lifetime risk in Us

Symptoms

• Most breast cancers have no symptoms
• Breast lumps, many are benign
• Nipple discharge
• Skin changes, peau d’orange
Breast Cancer Genetic Etiology

- 75-80% Sporadic
- 15-20% Familial
- 5-10% Hereditary
Breast Cancer Genetic Etiology

- 60% Other known genes
- 10-30% PTEN
- 7% ATM
- 20-40% Other known genes
- 7% PTEN
- 7% ATM
- 7% Other known genes
- 7% BRCA1
- 7% BRCA2
- 7% Other known genes
- 7% Unknown Predisposing genes
<table>
<thead>
<tr>
<th>Treatments</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Tissue Sampling</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Core biopsy</td>
</tr>
<tr>
<td>Radiation</td>
<td>Skin biopsy</td>
</tr>
<tr>
<td>Endocrine Therapy</td>
<td>FNA</td>
</tr>
<tr>
<td></td>
<td>Ductal Lavage</td>
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</tbody>
</table>
BRCA GENES

- the maintenance of genomic stability
- cell cycle checkpoints
- remodeling of chromatin
- DNA damage response
- estrogen responsiveness
- is a coactivator of p53 responsive genes
BRCA1

Normally, the BRCA1 gene repairs a broken PTEN gene by "sewing" it back together. When BRCA1 is mutated it stops repairing the PTEN gene, which contributes to cancer tumors and metastasis.

NORMAL (Repair)  ABNORMAL (No repair)

Broken PTEN gene  Broken PTEN gene

BRCA1 gene repairs PTEN gene, which allows it to work

No repair of PTEN gene by BRCA1 gene results in: cell growth, cell death inhibition, cell migration, new blood vessels sprout, and metastasis

Image provided by Nancy Heim, Columbia University Medical Center © 2007
## BRCA Gene Mutation

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppressor gene on chromosome 17</td>
<td>Tumor suppressor gene on chromosome 13</td>
</tr>
<tr>
<td>Autosomal dominant transmission</td>
<td>Autosomal dominant transmission</td>
</tr>
<tr>
<td>Protein has role in genomic stability</td>
<td>Protein has role in genomic stability</td>
</tr>
<tr>
<td>~500 different mutations reported</td>
<td>~300 different mutations reported</td>
</tr>
<tr>
<td>Incomplete penetrance</td>
<td>Incomplete penetrance</td>
</tr>
<tr>
<td>Pathological Mutations</td>
<td>Polymorphisms</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>- Nonsense, frameshift and missense mutations</td>
<td>- Missence mutations</td>
</tr>
<tr>
<td>- Splicing sites mutations associated with pathology</td>
<td>- Splicing site mutations</td>
</tr>
</tbody>
</table>
Chromosome 17

BRCA1

17q25.2
17q24.3
17q24.1
17q23.2
17q22
17q21.32
17q21.2
17q12
17p12
17p13.2

Chromosome 13

13q33.3
13q33.1
13q32.2
13q31.3
13q31.1
13q22.2
13q21.33
13q21.31
13q21.1
13q14.2
13q14.12
13q13.3
13q13.1
13q12.2
13q12.12
13p11.2
13p12
13p13
BRCA1-Associated Cancers: Lifetime Risk

- 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, colon)
BRCA2-Associated Cancers:
Lifetime Risk

- breast cancer (50%-85%)
- ovarian cancer (10%-20%)
- male breast cancer (6%)

Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)
Genetic Testing

- Identify at risk patients
- Provide pretest counseling

- Provide informed consent
- Select and Offer test

- Disclose results
- Provide post-test counseling and follow up
BRACAnalysis
Myriad Genetic Laboratories

**BRCA1**

Blood samples are bar coded for robotic tracking

DNA is extracted and purified from white cells isolated from sample

Full sequence determination, forward and reverse, 5,400 base pairs comprising 22 coding exons and 750 adjacent base pairs, introns

Wild type of BRCA1 - 1863 amino acids

**BRCA2**

Blood samples are bar coded for robotic tracking

DNA is extracted and purified from white cells isolated from sample

Full sequence determination, forward and reverse 10,200 base pairs comprising 26 coding exons and 900 adjacent base pairs, introns

Wild type of BRCA2 – 3418 amino acids
## BRACAnalysis

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1% incidence of a false report of a genetic variant or mutation resulting from errors in specimen handling and tracking</td>
<td>&lt; 1% incidence of failure to detect a variant or mutation in the analyzed DNA</td>
</tr>
</tbody>
</table>
Performance

Overall Test Accuracy

With 10% probability of mutation, the BRACAnalysis is >99% accurate

Limitations

Analysis includes testing of only 5 specific large genomic rearrangements

Will not detect some types of errors in RNA transcription processing
Breast Surveillance for Genetic Risk

- Monthly self-examination of the breast (18 years)
- Clinician breast exam, every 6 months (25 years)
- Annual mammography and MRI starting age 25 (or based on earliest family case)

Reductions in breast cancer mortality in general population attributable to screening mammography.
- 25-30% in women in their 50s
- 18% in women in their 40s

For men, breast self-exam training and regular monthly practice
If gynecomastia, mammogram
Adhere to prostate guidelines

NCCN Guidelines 2008
Ovarian Surveillance

- Pelvic examination annually (>18 years)
- Transvaginal ultrasound, every 6 months (25-35 years)
- Serum Ca 125, 6-12 months (25-35 years)
Prophylactic Surgery

- **Salpingo-oophorectomy upon completing childbearing (age 35-40)**
  Should reduce BC risk by at most 50%
  Should reduce OC risk by at least 95%

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**Drug Therapy**

- Tamoxifen
- Raloxifene

- **Bilateral prophylactic mastectomy (total or skin-sparing)**
  Should be limited to women at very high risk (such as patients with lobular carcinoma in situ (LCIS) or those who are known carriers of BRCA1/BRCA2 mutations)
  Expected BC risk reduction is 90%
<table>
<thead>
<tr>
<th>Case</th>
<th>Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 y/o female was recently told mother has BRCA mutation</td>
<td>50-85% lifetime risk of breast cancer</td>
</tr>
<tr>
<td>Does she get tested?</td>
<td>15-40 % lifetime risk of ovarian cancer</td>
</tr>
<tr>
<td>Effects on ability to get employment, insurance?</td>
<td>Early Screening is imperative</td>
</tr>
<tr>
<td></td>
<td>Prophylactic surgery reduces risk</td>
</tr>
<tr>
<td>Plan</td>
<td>Professional Code</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Bilateral Breast MRI and pelvic exam</td>
<td>Counseling for probability</td>
</tr>
<tr>
<td>Insurance?</td>
<td>Order screening test</td>
</tr>
<tr>
<td>Employment?</td>
<td>Offer Genetic Testing</td>
</tr>
</tbody>
</table>
Beneficence

- Prevent harm
- Remove harm
- Promote good
Legal Issues

• Results placed in medical records might not be kept private

• Results of genetic testing may affect an applicant’s ability to access insurance, decrease medical coverage, and raise insurance premiums

• Failure to provide truthful information is considered fraud and result in loss of insurance and employment
Legal Issues

Some protections

Americans with Disabilities Act

Protection from discrimination with employers

Equal Employment Opportunity Commission

Expanded definition of disabled to include individuals who carry genes that increase risk of genetic disorders
References


