Breast Cancer Risk and Genetics

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LEARNING OBJECTIVES
• Differentiate between sporadic, familial, and hereditary cancer and review genetics basics
• Introduce cancer risk and surveillance / risk-reducing options for HBOC
• Present other conditions associated with breast cancer susceptibility

LEARNING OBJECTIVES
• Discuss pros and cons of multigene panels
• Explore the role of cancer genetic counselors

CANCER CATEGORIES

- 60-75%
- 20-30%
- 5-10%

• No conflicts of interest to report
Sporadic Cancer
- Few family members with cancer
- Later age of onset
- Chance
- Environmental factors

Familial Cancer
- > 1 individual on the same side of the family with same type of cancer
- Typically later ages of onset
- Shared genes and environment

HEREDITARY CANCER
RED FLAGS
- Cancer at early ages
- Multiple primary cancers in one person
- Multiple cases of same or related cancers on the same side of the family
- Rare cancers
- Ethnic Background

CANCER GENETICS BASICS

GENETICS 101

TUMOR SUPPRESSOR GENES
- Tumor Suppressor Gene(s) → PROTECTION AGAINST TUMOR DEVELOPMENT
- Tumor Suppressor Gene(s) w/ mutation(s) → DECREASED PROTECTION AGAINST TUMOR DEVELOPMENT
AUTOSOMAL DOMINANT

- 2 copies of each gene - one from each parent
- Mutation in one copy is enough to cause the condition

AUTOSOMAL DOMINANT

- 50% chance to pass copy with mutation in each pregnancy (sons and daughters)

HEREDITARY BREAST AND OVARIAN CANCER (HBOC)

HBOC RED FLAGS

- Cancer at early ages
  - Breast cancer < 50
- Multiple cancers in one person
  - Bilateral breast cancer
- Multiple cases of same or related cancers in a family

HBOC RED FLAGS

- Rare cancers
  - Male Breast Cancer
  - Triple negative breast cancer
- Ethnic Background
  - Ashkenazi Jewish ancestry and HBOC
**TUMOR SUPPRESSOR GENES**

BRCA1/BRCA2

PROTECTION AGAINST TUMOR DEVELOPMENT

BRCA1/BRCA2 w/ mutat.

DECREASED PROTECTION AGAINST TUMOR DEVELOPMENT

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**HBOC CANCER RISKS**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Gen. Pop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>46–63%</td>
<td>38–53%</td>
<td>12%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>34–44%</td>
<td>12–20%</td>
<td>1–2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>increased</td>
<td>20–30%</td>
<td>16%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>increased</td>
<td>7%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3–4%</td>
<td>2–5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>not increased</td>
<td>increased</td>
<td>2%</td>
</tr>
</tbody>
</table>


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**HBOC MANAGEMENT**

Breast

Non-Surgical

Medications (Tamoxifen)

Surgical

Bilateral Prophylactic Mastectomy

Ovarian

Non-Surgical

Screening:

Annual Transvaginal Doppler U/S (35)
Annual CA125 (35 yo)

Surgical

Prophylactic BSO

Melanoma

Annual Skin/Eye Exams


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**OTHER BREAST CANCER SUSCEPTIBILITY SYNDROMES**

- **COWDEN SYNDROME**
  - Caused by mutations in the PTEN gene
  - Associated cancers: breast, thyroid, uterine, renal, colon, melanoma

(Eng, 2012)
**COWDEN SYNDROME**

- Multiple benign findings:
  - Characteristic skin findings
  - Macrocephaly (larger head circumference)
  - GI polyps
  - Thyroid lesions (ex: goiter, nodules)
  - Autism, ID
- Rare: Lhermitte Duclos disease
  - (brain lesion)

**COWDEN**

<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>COWDEN syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female breast</td>
<td>12%</td>
<td>50-85%</td>
</tr>
<tr>
<td>Male breast</td>
<td>&lt;1%</td>
<td>increased</td>
</tr>
<tr>
<td>Thyroid (non-med.)</td>
<td>1%</td>
<td>10-35%</td>
</tr>
<tr>
<td>Uterine</td>
<td>3%</td>
<td>10-28%</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>2%</td>
<td>34%</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2%</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Eng, 2012; NSGC CA SIG, 2013)

**COWDEN**

- Caused by mutations in TP53 gene
- Core cancers
  - Sarcomas of bone and soft tissue
  - Premenopausal breast cancer (can be very early onset)
  - Brain tumors
  - Adrenocortical carcinoma

(Schneider, 2013)

**LI-FRAUMENI**

- Non - core cancers – colon, uterine, esophageal, gonadal germ cell, leukemias and lymphomas, lung, melanoma, neuroblastoma, ovarian, pancreatic, prostate, gastric, thyroid, renal

(Schneider, 2013)

**LI-FRAUMENI**

- Caused by mutations in TP53 gene
- Core cancers
  - Sarcomas of bone and soft tissue
  - Premenopausal breast cancer (can be very early onset)
  - Brain tumors
  - Adrenocortical carcinoma

(Schneider, 2013)

**LI-FRAUMENI**

- NCCN: TP53 testing should be considered for women diagnosed with breast cancer < age 35, especially after negative BRCA testing

(Schneider, 2013)
LI-FRAUMENI

- High risk of early-onset cancer
  - Risk of cancer ~50% by age 30, 90% by age 60 (~100% for women)
  - 0-10 yrs: soft tissue sarcomas, brain tumors, ACC
  - 11-20 yrs: bone sarcomas
  - >20 years: breast cancer, brain tumors

(Schneider, 2013)

LI-FRAUMENI

- Multiple primaries
  - Approximately 57% risk of second cancer
  - Approximately 38% risk for third cancer
  - 4th primaries have been reported
  - Survivors of childhood cancers at highest risk, likely related to treatment of previous cancers

(Schneider, 2013)

OTHER HEREDITARY BREAST CANCER SYNDROMES

- Hereditary Diffuse Gastric Cancer
  - Diffuse gastric cancer
  - Lobular breast cancer

OTHER HEREDITARY BREAST CANCER SYNDROMES

- Peutz-Jeghers Syndrome
  - Colon, gastric, pancreatic, breast, and ovarian cancers
  - Polyposis
  - Characteristic freckling

MULTI-GENE PANELS
MULTIGENE BREAST PANEL EXAMPLE

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Newer Genes</th>
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</thead>
<tbody>
<tr>
<td>BRCA1/BRCA2</td>
<td>ATM</td>
<td>BRCA1/BRCA2</td>
</tr>
<tr>
<td>HBOC: breast, ovary, prostate</td>
<td>ATM: breast, colon, pancreatic</td>
<td></td>
</tr>
<tr>
<td>CDH1 (HDGC: breast, gastric, colon)</td>
<td>CHEK2: breast, colon, pancreatic</td>
<td></td>
</tr>
<tr>
<td>PTEN (Cowden: breast, thyroid, gonadal)</td>
<td>PALB2: breast, ovary, pancreatic</td>
<td></td>
</tr>
<tr>
<td>TP53 (LFS: breast, ovary, sebaceous, brain)</td>
<td>MUTYH (HNPCC: colon, breast)</td>
<td></td>
</tr>
<tr>
<td>STK11 (Cowden, breast, pancreatic, gastric)</td>
<td>XRCC2: breast, colon, pancreatic</td>
<td></td>
</tr>
</tbody>
</table>

MULTIGENE PANELS

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>CHALLENGES</th>
</tr>
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<tbody>
<tr>
<td>More cost-effective and efficient if considering multiple syndromes.</td>
<td>More expensive than single gene testing</td>
</tr>
<tr>
<td>Insurance may only allow one genetic test per lifetime.</td>
<td>May identify rare genetic causes of cancer in an individual/family</td>
</tr>
<tr>
<td></td>
<td>May identify mutation in gene for which there is limited info/guidance</td>
</tr>
<tr>
<td></td>
<td>• Tumor Spectrum</td>
</tr>
<tr>
<td></td>
<td>• Cancer risk estimates</td>
</tr>
<tr>
<td></td>
<td>• Management recommendations</td>
</tr>
<tr>
<td></td>
<td>May identify genetic causes in “non-textbook” cases of well known cancer syndromes</td>
</tr>
</tbody>
</table>

GENETIC COUNSELING DEFINITION

- Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

  (NSGC, 2006)

GENETIC COUNSELING DEFINITION

- Interpretation of family and medical histories
- Education about inheritance, testing, management, prevention, resources and research
- Counseling to promote informed choices

  (NSGC, 2006)

WHEN TO CONSIDER TESTING

- American Society of Clinical Oncology: “Genetic counseling and testing should be offered if…”
  - An individual has personal or family history features suggestive of cancer predisposition

  (ASCO, 2003)
WHEN TO CONSIDER TESTING

- The test can be adequately interpreted
- The test will influence medical management

GENETIC COUNSELING GOALS

- Contracting
- Risk assessment
- Education
- Informed consent
- Results
- Medical Management Recommendations
- Support

CONTRACTING

- Motivations - Patients often want to gain a better understanding of:
  - Personal cancer risks
  - Options and considerations for participation in genetic testing or research
  - Screening and cancer prevention

- Implications / recommendations for family members

RISK ASSESSMENT

- Methods
  - Medical and family history analysis
  - Risk models

- Challenges
  - Limited information
  - Family structure
  - Variability
PT CONCERNS REGARDING TESTING

• Cost
• Timing / Impact on treatment
• Childbearing considerations
  – Age at hysterectomy / ovary removal
  – Risk to current/future children

PT CONCERNS REGARDING TESTING

• Quality of life
  – Perceived cancer risk
  – Body image; self-esteem
  – Surgery impact on quality of life
  – Management of surgical menopause
• Discrimination

TESTING

• Testing Options
• Informed Consent
  • Benefits
  • Limitations
  • Possible outcomes
  • Risks
• Test Interpretation
• Result Explanation

MANAGEMENT

• Recommendations for patient and family
  – NCCN guidelines if exist
  – Use studies and customize to medical / family history otherwise
  – Take limitations into account
    (insurance coverage, location, etc.)

SUPPORT

• Facilitate decision-making
  – Discuss how each test option and potential results might impact patient
  – Identify what is most important to patient
  – Listen to concerns and help them come to a decision
• Psychosocial counseling
• Provide support / resources

TAKE HOME MESSAGE

• 5 - 10% of breast cancers are due to underlying hereditary cause
• 20 - 30% of breast cancers are due to combination of genetic and environmental factors
  – Increased surveillance may still be appropriate!
TAKE HOME MESSAGE

- A genetic counselor can review medical and family histories to determine:
  - whether testing is appropriate
  - who the best person is to test in a family
  - what testing is indicated
  - how test results and family history may affect medical management for patient and family

Contact Information

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