Hereditary Breast Cancers

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Objectives

At the end of this presentation, participants should be able to --

1. Identify how genetics are becoming more important in determining who is at risk for breast and other related cancers
2. Predict which individuals would benefit most from hereditary breast cancer gene testing
3. Understand the benefits and risks of specific interventions once a genetic predisposition for breast cancer has been identified in an individual or a family, including surveillance, surgical prophylaxis and chemoprophylaxis
4. Recognize how breast cancer genomics are changing treatments for patients already diagnosed with breast cancer
All cancer is genetic or arises from changes in genes but not all cancer is hereditary or inherited.
Basic Facts About Breast Cancer

• In the US in 2017:
  – 255,180 new cases of invasive breast cancer among women
  – 63,410 new cases of non-invasive breast cancer among women
  – 40,620 women will die from breast cancer
  – 2,470 new cases of male breast cancer
• A woman’s risk of developing breast cancer in the US is 12% if she lives to age 85 years
• In contrast, men have a lifetime breast cancer risk of 0.13%, or about 1 in 1,000
• 50% of breast cancers occur after age 65
• Trends
  – From 1960 to 1999, the incidence rate ↑ 1 – 2% annually; since 1999, the incidence rate ↓ by 2% annually
  – Since 1999, the mortality rate has also declined due to
    • Better detection
    • Better awareness
    • Better adjuvant therapy

Causes of Breast Cancer

Risk factors
- Being female and ≥ age 35
Known HBOC Mutations – 2017

- **BRCA1**: 28%
- **BRCA2**: 24%
- **PALB2**: 10%
- **CHEK2**: 1%
- **TP53**: 9%
- **ATM**: 3%
- **PTEN**: 3%
- **CDH1**: 3%
- **MLH1**: 3%
- **MSH6**: 4%
- **PMS2**: 1%
- **RAD51C**: 1%
- **RAD51D**: 1%
- **BARD1**: 1%
- **BRIP1**: 3%

Other mutations:
- **FANCC**, **NBN**, **XRCC2**, **STK11**, **MSH2**, **BMPR1A**, **SMAD4**, **VHL**
Hereditary Breast Cancer

• Hereditary breast cancer is suspected when:
  – There is a strong family history of breast cancer
  – At least three first or second-degree relatives have been diagnosed with breast or ovarian cancer
  – Breast cancer is diagnosed at an early age
  – Breast cancer is bilateral
  – A male has breast cancer
Interpreting Gene Testing Results

- **Positive**
  - Clear disease association, protein dysfunction

- **Negative**
  - No sequence change consistent with mutation

- **Variant of uncertain significance (VUS)**
  - Often a change in a missense or non-coding region
  - 5% in US individuals of European ancestry
  - 20% African American, ethnic minorities
  - VUS are declining as the true clinical nature of these variants is being defined
What is BRCA+ Breast Cancer

- **BRCA1** and **BRCA2** are genes whose functions is to produce **tumor suppressor proteins**
  - These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of the cell’s genetic material
  - When either of these genes is mutated, or altered, such that its protein product is not made or does not function correctly, DNA damage may not be repaired properly
  - As a result, cells are more likely to develop additional genetic alterations that can lead to cancer
Basic Facts About BRCA Mutations

- Specific inherited mutations in BRCA1 and BRCA2 increase the risk of female breast and ovarian cancers, and have been associated with increased risks of several additional types of cancer.
- Together, BRCA1 and BRCA2 mutations account for ~ 50% of hereditary breast and ovarian cancer.
- Mutations in BRCA1 and BRCA2 account for ~ 5-7% breast cancers and ~8-13% of ovarian cancers.
- Breast cancers associated with BRCA1 and BRCA2 mutations tend to develop at younger ages than sporadic breast cancers.
Inheriting *BRCA* Mutations

- Harmful *BRCA1* or *BRCA2* mutations are inherited from a person’s mother or father in an autosomal dominant fashion.
  - i.e., only one mutated gene needs to be passed to inherit a BRCA mutation.
  - Each child of a parent with a *BRCA* mutation has a 50% chance of inheriting the mutation.

- The effects of mutations in *BRCA1* and *BRCA2* genes are seen even when a person’s second gene copy is normal.

- The presence of one mutated gene increases the risk of a 2nd gene mutation.
Who should be tested for *BRCA* mutations?

- **For individuals with breast cancer, *BRCA* testing is recommended if :**
  - BC diagnosed at age 45 or younger or in a family member 45 or younger
  - BC diagnosed in both breasts
  - 2 different breast cancers diagnosed in the same breast
  - Triple-negative breast cancer (ER-, PR-, HER2-) diagnosed at age 60 or younger
  - Prior personal or family history of ovarian, fallopian tube or peritoneal cancer
  - A close male relative has been diagnosed with BC
  - Two or more close relatives diagnosed with breast and/or ovarian, fallopian tube, primary peritoneal or pancreas cancers
  - Ashkenazi Jewish ancestry

*A close relative is defined as a parent, child, brother, sister, grandparent, aunt, uncle, niece, nephew, first cousin, great-grandparent, great-aunt or great-uncle*
Who should be tested for BRCA mutations?

- For individuals **without breast cancer**, testing is recommended if:
  - Patient diagnosed with ovarian, fallopian tube or primary peritoneal cancer
  - A male relative is diagnosed with breast cancer or a female relative is diagnosed with bilateral breast cancer
  - Patient has had pancreatic cancer and 2 close relatives have had breast and/or ovarian, fallopian tube or primary peritoneal cancer
  - There is a strong family history that fits one of the above criteria
BRCA Mutations in Ashkenazi Jews

- Approximately **2.65%** of Ashkenazi Jewish women have BRCA mutations compared with **0.2%** in the general population
- Three specific mutations, 2 in the **BRCA1** and 1 in the **BRCA2** genes account for 90% of variants within this ethnic group, suggesting a founder mutation
- In contrast, there are hundreds of unique **BRCA** mutations within the general non-Ashkenazi population
- Only **7%** of breast cancers in Ashkenazi women are caused by alterations in **BRCA1** and **BRCA2**
Facts About *BRCA1* Mutations

- **BRCA1**
  - Located on chromosome 17q21
  - >1,000 mutations
  - 57% (range 50-65%) risk of developing breast cancer by age 70
  - Contralateral breast cancer risk 83%
  - Ovarian cancer risk 40% (range 35-45%) at age 70 but NOT at an early age
  - Better prognosis with *BRCA1*+ vs sporadic OC
  - Undefined risk for breast and prostate cancers in males

Genetics Home Reference, 2007
Facts About BRCA2 Mutations

- **BRCA2**
  - Located on chromosome 13q12.3
  - > 800 mutations, usually caused by small insertions
  - 49% (range 40-57%) risk of developing breast cancer by age 70
  - Ovarian cancer risk 18% (13 to 23%) at age 70
  - Contralateral breast cancer risk 62%
  - Risk of uterine cancer ↑4x; ↑ risk pancreas cancer
  - Males with 10% lifetime risk of breast cancer and 5-7-fold ↑ risk of prostate cancer at an earlier age

Genetics Home Reference, 2007
HBOC Risks & BRCA Mutations

BRCA Mutation Increases the Risk of Cancer

- Breast cancer by age 50: 33-50% in BRCA mutation carriers, 2% in general population
- Breast cancer by age 70: 56-87% in BRCA mutation carriers, 7% in general population
- Ovarian cancer by age 70: 27-44% in BRCA mutation carriers, <2% in general population
**PALB2 and Hereditary Breast Cancer**

- **PALB2** = partner and localizer of **BRCA2**
- 10 different gene mutations have been identified in a recent study among 362 in 154 families with extensive histories of breast cancer
- The **PALB2** gene is located on chromosome 16
- Like **BRCA1/2**, wild type **PALB2** functions as a tumor suppressor gene
- With **PALB2** mutations
  - 14% of patients developed breast cancer by age 50
  - 35% of patients developed breast cancer by age 70
- 3.9% of breast cancers are **PALB2** mutated when **BRCA1/2** are negative
- Men with **PALB2** mutations have an 8-fold increased risk of developing breast cancer
- **PALB2** mutations also increase the risk of pancreatic cancer

Screening for *BRCA*+ Female Carriers

- **Breast cancer**
  - Monthly breast self-examination beginning at age 18
  - Clinical breast exam 2-4 times annually, beginning at age 25
  - Annual mammography/MRI (alternating every 6 months) beginning at age 25

- **Ovarian cancer screening**
  - Begin at age 35 OR 10 years earlier than the age of the youngest affected family member
    - Semi-annual ovarian cancer screening with pelvic exam
    - Transvaginal color Doppler ultrasound
    - CA-125 tumor marker

NCCN Guidelines 2012
Screening for *BRCA*+ Male Carriers

- Monthly breast self-examination
- Semi-annual clinical breast examination
- Baseline mammogram with annual mammogram if baseline study +
  for gynecomastia or parenchymal/glandular breast density
- Appropriate prostate cancer screening
- Prophylactic mastectomies are considered experimental in *BRCA1*+
  or *BRCA2*+ males since there is no evidence of breast cancer risk reduction

NCCN Guidelines 2012
Surgery and BRCA+ Patients

• Bilateral prophylactic mastectomy:
  • Decreases breast cancer risk by 90-95%
  • Has no effect on ovarian cancer risk
  • Famous BRCA1/2 mutation carriers who have opted for bilateral prophylactic mastectomies include A. Jolie, C. Applegate, S. Osbourne

– Bilateral prophylactic oophorectomy
  • Decreases ovarian cancer risk by 85-95%
  • Reduces breast cancer risk:
    – 29% in BRCA1-positive carriers
    – 72% in BRCA2-positive carriers
    – This difference in risk reduction between BRCA1 and BRCA2 patients due to the fact that TNBCs are much more frequent in BRCA1 carriers

NCCN Guidelines, Version 7, 2012
Do all *BRCA*+ BC Require Mastectomies?

- Retrospective analysis of 655 women with *BRCA*-related breast cancer treated at centers in the U.S., Australia, Israel and Spain
  - 302 patients treated with breast-conserving surgery plus radiation therapy
  - 353 treated with mastectomy (103 of whom also had radiation therapy)
- At a median follow up of ~ 8 years,
  - Rate of local recurrence in the BCT group increased from 4.7% at 5 years to 10.5% at 10 years, 23.5% at 15 years and 30.2% at 20 years
  - The comparative rates of local recurrence in the mastectomy group were 1.4% at 5 years, 3.5% at 10 years, 5.5% at 15 years and 5.5% at 20 years (*P*<0.0001)
  - However, when BCT was followed by chemotherapy, the incidence rate of recurrent breast cancer was no different than the mastectomy group (*P*=0.082)

Conclusion: If you opt for breast preservation, you should probably be treated with chemotherapy!

Pierce L, *EBCC* 2010; Abstract 7N.
Chemoprevention and BRCA+ BC

• **Chemoprevention** - the use of drugs, vitamins, or other agents to reduce the risk of or delay the development of cancer

• Although two chemopreventive drugs (tamoxifen and raloxifene) have been approved by the U.S. Food and Drug Administration (FDA) to reduce the risk of breast cancer in women at increased risk, the role of these drugs in preventing BC for carriers with BRCA1 or BRCA2 mutations is not definitive

• Data from 3 small studies suggest that tamoxifen may lower the risk of breast cancer in BRCA1 and BRCA2 mutation carriers among women previously diagnosed with breast cancer.

• **Oral contraceptives** (birth control pills) may lower the risk of ovarian cancer in women with harmful BRCA1 or BRCA2 mutations, but this can increase the risk of BC
Other Mutations and Lifetime BC Risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>Estimated lifetime risk of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>55-65%(^{10})</td>
</tr>
<tr>
<td>BRCA2</td>
<td>45-47%(^{13})</td>
</tr>
<tr>
<td>TP53</td>
<td>49-60%(^{36})</td>
</tr>
<tr>
<td>PTEN</td>
<td>25-50%(^{61,62})</td>
</tr>
<tr>
<td>PALB2</td>
<td>33-58%(^{55})</td>
</tr>
<tr>
<td>STK11</td>
<td>30-50%(^{58,63,64})</td>
</tr>
<tr>
<td>CDH1</td>
<td>39-52%(^{65,66})</td>
</tr>
<tr>
<td>ATM</td>
<td>15-52%(^{67-70})</td>
</tr>
<tr>
<td>CHEK2</td>
<td>20-44%(^{71-74})</td>
</tr>
</tbody>
</table>
PTEN Mutations

- The *PTEN* (phosphatase and tensin homolog) gene acts as a tumor suppressor gene
- There is a high frequency of somatic *PTEN* mutations found in a variety of sporadic human cancers, including breast, thyroid, endometrial, kidney cancer
- The most common inherited *PTEN* Hamartoma Tumor Syndrome (PHTS) disorder is **Cowden Syndrome**
  - Autosomal dominant inheritance
  - Associated with disorganized growth of benign tumors called hamartomas in multiple organ systems
  - Mucocutaneous lesions (trichilemmomas and papillomas of the face, lips, tongue and oral mucosa) and acral keratoses
- Confers a lifetime risk of breast cancer between 25-50%
Cowden Syndrome

- Incidence: 1 in 200,000—although this figure is probably an underestimate
- Autosomal dominant inheritance
- \textit{PTEN} gene on chromosome 10q23
- Pathognomonic mucocutaneous lesions
  - Facial trichilemmomas (Fig 1)
  - Papillomas of face, lips, tongue, oral mucosa (Figs 2 and 3)
  - Acral keratoses (Fig 4)
- Lifetime risk of breast cancer estimated to be between 25% and 50%
TP53 Mutations

- *TP53* mutations are the most frequent genetic alterations in human cancers
- There are more than 35,000 *TP53* mutations described in different types of cancer
- *TP53* mutations associated with Li Fraumeni Syndrome
Li-Fraumeni (LFS)

• Autosomal dominant disorder
• Predisposition to multiple early onset cancers
  ▪ Bone and soft tissue sarcoma
  ▪ Premenopausal breast carcinoma
  ▪ Brain tumors
  ▪ Adrenocortical carcinoma
  ▪ Acute leukemia
  ▪ Gastric cancer
  ▪ Colorectal cancer
  ▪ Pancreatic cancer
  ▪ Choroid plexus papilloma
  ▪ Wilms tumor
Li-Fraumeni Family

- Bilateral breast cancer, 40 y
  - Brain tumor, 32 y
  - Breast, 40 y
  - Osteosarcoma, 42 y
  - Breast cancer, 35 y
  - Soft tissue sarcoma, 7 y
    - Leukemia, 6 y

- Gastric cancer, 33 y

Noncarrier

Affected with cancer

ASCO
CDH1 Mutations

- The *CDH1* gene encodes the E-cadherin protein, a member of the trans-membrane glycoprotein family
- Loss of *CDH1* expression is associated with cancer cell invasiveness
- E-cadherin loss also associated with lobular breast cancer
- Men and women with *CDH1* mutations have an 80% risk of being diagnosed with diffuse gastric cancer – and the majority diagnosed before age 40
- Women with *CDH1* mutations have a 60% risk of developing lobular breast cancer
- Inheritance is autosomal dominant
STK11 Mutations

• The STK11 (also known as LKB1) gene acts as a tumor suppressor

• Mutations in the gene have been associated with Peutz-Jehgers syndrome
  – Autosomal dominant inheritance
  – Hamartomatous polyps in the gastrointestinal tract, especially in the small intestine, but also found in the stomach, large bowel, stroma and extra-intestinal sites
  – Gastrointestinal polyps can lead to chronic bleeding, resulting in anemia and increased risk of malignant transformation
  – Pigmented mucocutaneous lesions
STK11-Peutz-Jehgers syndrome

- Increases risk for colorectal, gastric, breast, gynecologic, pancreatic, testicular and lung cancers
- Average age at diagnosis is 42 years
- Most patients who are diagnosed with PJS have a causative mutation in STK11
- The clinical diagnosis of PJS is made when a patient meets at least 2 of the following criteria:
  - 2 or more Peutz-Jeghers polyps of the small intestine
  - Typical mucocutaneous hyperpigmentation
  - Family history of PJS
How Are We Doing So Far????
Breast Cancer Genetics Are Quite Complex

- **Wellcome Trust Sanger Institute (outside Cambridge, UK):**
  - Has identified over 200,000 mutations in 21 breast cancers via whole gene sequencing
  - Different mutational processes act at different times in the lifespan of a breast tumor; some act throughout the evolution of cancer and others act only late in the development of a cancer cell
  - Most mutations accumulate slowly in breast cancer cells over many years, but in 13 of the 21 breast cancer genomes evaluated, sporadic mutations bursts were observed
  - This newly discovered phenomenon is called *kataegis*, from the Greek word for *thunderstorm*
  - In *kataegis*, a large number of mutations occur very close together in the genome
  - These mutation patterns DO NOT appear to be due to external exposures like tobacco smoke or sunlight, all which are known to cause mutations and cancer, but are more likely due to defective internal cellular machinery

Single Nucleotide Polymorphisms (SNPs)

• Common genetic variants (BRCA+) account for a small amount of familial cancer risk
• SNPs are sequence variations in DNA due to a single substitution of an amino acid base pair (A-T, G-C)
• SNPs occur more often in non-coding vs coding regions
• Natural selection acts to fix an allele of any SNP that codes for the most favorable genetic adaptation
• The majority of SNPs are not associated with functional changes in genes located near them
• Clusters of SNPs may account for some of the familial cancers without clearly defined causes
iCOG Testing

• The Collaborative Oncologic Gene–Environment Study has combined the research of 250,000 people around the world to create a more complete genetic map than a smaller study could by itself, with the goal of providing substantial insights into how common genetic variants contribute to breast, prostate and ovarian cancer.

• The custom Illumina COG SNP (iCOGs) array can evaluate ~211,000 SNPs at one time, and has identified 74 new susceptibility loci for breast, ovarian or prostate cancer, nearly doubling the number of known susceptibility loci, and study groups are currently calculating the impact of these common variant SNPs on each of these tumor types.

Bahcall, O. Nature Genetics. 45; 343 (2013)
SNPs and Penetrance

• Many groups are currently studying the impact of SNPs on BRCA1/2 expression, also known as penetrance

• Preliminary reports indicate that low, moderate and high-penetrance SNPs likely account for the differences in BC and OC risk among various studies
The Real Picture of Hereditary Cancers

Breast cancer

Ovarian cancer

Prostate cancer
The Future of BC Risk Assessment

• Genotyping more carriers for more accurate risk assessment based on personal and family risk factors
• Employing multi-gene panels/new generation sequencing for those diagnosed with BC
• Conducting genomic sequencing for “mystery” families
• Continuing to identify moderate penetrance genes
• Calculating risk of multiple low penetrance genes
• Continuing to decipher genetic variants of unknown significant (VUS) among ethnic and racial groups
So What Does This All Mean?

• We need to do better a better job identifying individuals at greatest risk for developing breast cancer
  – The NCCN Gail Model can identify women at increased risk for breast cancer
  – We must gather more detailed family cancer histories
  – Order appropriate genetic testing, provided insurance carries are willing

• Once identified, these patients should be urged to consider
  – Prophylactic chemoprevention
  – Prophylactic surgery
  – Active surveillance for various cancer types
  – Minimizing risk factors
Gail Model Components

- Age
- Age at first period
- Age at birth of first child (or has not given birth)
- Family history of breast cancer (mother, sister or daughter)
- Number of past breast biopsies
- Breast biopsies with atypical hyperplasia, DCIS and LCIS (automatically qualify as high risk)
- Race/ethnicity

Women with a five-year risk of 1.67% or higher are classified as "high-risk."

That's all Folks!