Hereditary Breast Cancer and New Options in Genetic Testing
Melanie J. Cortman, MS, LCGC
Licensed Certified Genetic Counselor
Atlantic Regional Osteopathic Conference
April 18, 2015

Learning Objectives
• Learn to recognize referral indications for genetic counseling for cancer predisposition assessment
• Overview of the basic features of hereditary breast cancer syndromes
• Update on new genes associated with hereditary breast cancer
• Impact of genetic test results on breast cancer screening and treatment

Cancer Risk
Family History  Lifestyle
Environment  Genes
Who is high-risk for ovarian cancer?

- Accurate family history is key

Gilda Radner
Stage IV @ 40

The Importance of Family History

"it is quite possible that even with our ability to measure hundreds and thousands of genes and environments we may find that family history is the best, low-cost way to identify the at-risk subgroups in the population"

Kardia, SLR. Am J Prev Med
2003: 24: 143-51

Did you know?

- Family history is a risk factor for most chronic illnesses in the general population: diabetes, cardiovascular disease, certain cancers, osteoporosis & asthma.
- In general, family history affords relative risks 2-5 x's the population risk
  - Relative risks increase with multiple affected family members & young ages of diagnosis
Breast Cancer Patterns

- 70% Sporadic
- 5-10% Hereditary
  - 5% BRCA1
  - 3% BRCA2
  - 2% Other
- 15-20% Familial

1st-, 2nd-, and 3rd-Degree Relatives

Sporadic Family History

OVARY, 75

BREAST, 71
Hereditary Breast Cancer and New Development in Genetic Testing

All cancer is genetic
but
most cancer is NOT inherited
All Cancers Have Genetic Origins

**Somatic Mutations**
- Occur in non-germline tissues (breast, colon, lung, blood cells, etc.)
- NOT inherited
- “Sporadic cancer”
- 90-97% of cancer

**Germline Mutations**
- Occur in eggs and sperm
- Are heritable
- Cause cancer family syndromes
- Account for 3-10% of cancer in the population

Cancer Risk Counseling – Indications for Referral

- Individual risk factors
  - Bilateral primary tumors
  - Multifocal tumors
  - Atypical age/sex/site
  - Rare tumor
  - Tumor associated with a birth defect, genetic disease or precursor lesion
- Family risk factors
  - 1 first-degree relative with a cancer having any of the individual risk factors
  - 2 first-degree relatives with the same or related cancers

Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer
- Basal phenotype (BRCA1only)ER- PR- her2neu-
Hereditary Breast Cancer and New Development in Genetic Testing

Breast Cancer Patterns

- ~10% Hereditary:
  - ~5% BRCA1
  - ~5% BRCA2
  - ~2% Other
- ~20% Familial
- ~70% Sporadic

Chromosomes

Chromosomes to Gene to Protein

Cell → Chromosome → Gene → Protein

International Breasts Cancer
Hereditary Breast Cancer and New Development in Genetic Testing

Hereditary Breast Ovarian Syndrome (HBOC)
- BRCA1 and BRCA2 – DNA repair genes
- About 50% of hereditary breast cancer
- About 90% of hereditary breast / ovarian cancer
- Incidence is approximately 1/500 – 1/800 among those of European, African and Asian descent
- Incidence is 1/40 among Ashkenazi Jews (Jews of Eastern European descent)

BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

An estimated 1 in 40 Ashkenazi Jews carries a BRCA1 or BRCA2 mutation

185delAG
Prevalence ~1%

5382msC
Prevalence ~0.15%

6174delT
Prevalence ~1.5%
Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- No "skipped generations"
- Equally transmitted by men and women

Lifetime Risk for Cancer

Women

Risk of Cancer with Family History

King MC et al 2003
Hereditary Breast Cancer and New Development in Genetic Testing

Risk of Second Breast Cancer
After Initial Breast Cancer Diagnosis

- General Population
- BRCA Alteration

Within 5 years
By age 70

General Population
BRCA Alteration
Carriers

Lifetime Risk of Cancer
Men

- General Population
- BRCA Alteration Carriers

Breast Cancer
Prostate Cancer

Medical Management
BRCA1/2 carrier - woman

**Breast**
- Screening
  - Breast awareness
  - Clinical breast exam
  - Mammogram
  - Breast MRI
- Prevention
  - Preventive mastectomy
  - Chemoprevention

**Ovary**
- Screening
  - Transvaginal ultrasound
  - CA-125
  - Limited usefulness!
- Prevention
  - Preventive oophorectomy
  - Chemoprevention
Reducing Cancer Risks

Myriad Genetic Laboratories

Other Cancers Associated with BRCA Alterations

- Absolute risk likely to be less than 10%
  - Fallopian Tube Cancer
  - Pancreatic Cancer
- Risk association unclear
  - Melanoma
  - Colon Cancer
  - Gastric Cancer
  - Other sites

Hereditary Breast Cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBOC</td>
<td>BRCA1 and BRCA2</td>
</tr>
<tr>
<td>Li Fraumeni</td>
<td>TP53</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
</tr>
<tr>
<td>Hereditary Diffuse Gastric Cancer (lobular pathology)</td>
<td>CDH1</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
</tr>
<tr>
<td>CHEK2</td>
<td>CHEK2</td>
</tr>
<tr>
<td>HNPCC (Lynch)</td>
<td>MMR genes</td>
</tr>
<tr>
<td>Ataxia Telangiectasia</td>
<td>ATM</td>
</tr>
<tr>
<td>Bloom's syndrome</td>
<td>BLM</td>
</tr>
</tbody>
</table>
Other Genetic Conditions Associate with Increased Breast Cancer Risk

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Fraumeni</td>
<td>TP53</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>ATM</td>
</tr>
<tr>
<td>(heterozygous carriers)</td>
<td></td>
</tr>
</tbody>
</table>

Li-Fraumeni Syndrome

- Rare syndrome
- Mainly associated with germline mutations in the TP53 gene on chromosome 17 or, rarely, mutations in CHK2 on chromosome 22
- 50% risk of cancer by age 40 years; 90% by age 60 years
  - Breast (most frequent cancer in women)
  - Other syndrome-related malignancies, often seen in children: bone and soft tissue sarcomas, brain tumors, adrenocortical tumors, and leukemia
  - Risk of multiple primary cancers
  - Risk of radiation-related second cancers within radiation treatment field

Keep in mind . . .

- Germline TP53 mutations are thought to account for less than 1% of breast cancer cases
- 5-7% of women with breast cancer <30 who test BRCA1/2 negative will have TP53 mutations
- TP53 mutations are found in 2-10% of patients with childhood brain tumors and 2-3% osteosarcomas
- Only 70% of families meeting the classic diagnostic criteria have an identifiable TP53 mutation, and CHK2 mutations are seldom detected

Li-Fraumeni Syndrome

- Rare syndrome caused by germline mutations in TP53 gene on chromosome 17
- 50% risk of cancer by age 35
- Lifetime risk of cancer ~90% for women; ~70% for men
  - breast (most frequent cancer in women, often very early onset)
  - other: sarcoma, brain, leukemia, childhood adrenocortical tumors, and other early onset cancers (SBLA syndrome)

Cancer Risks with LFS

- 50% with cancer by age 40 yo
- 80-90% with cancer by age 60 yo
- 15% with 2 primary cancers (lifetime)
- 4% with 3 primary cancers (lifetime)
Cowden Syndrome – PTEN Multiple Hamartoma Syndrome

- Autosomal dominant transmission
- Features include:
  - Macrocephaly
  - Trichilemmomas and papillomatous papules – usually by late 20’s
  - Lhermitte-Duclose disease (LDD) – cerebellar dysplastic gangliocytoma
  - Rare benign brain tumor presenting typically 30-40’s, may present as hydrocephalus

Cowden Syndrome – associated cancers

- Associated cancers:
  - Breast (25-50% lifetime risk), often onset in 30’s and 40’s
  - Thyroid (usually follicular, rarely papillary) 10% lifetime risk
  - Uterine (endometrial) 5-10% lifetime risk

Cowden Syndrome

- Incidence: 1 in 200,000—although this figure is probably an underestimate
- Autosomal dominant inheritance
- PTEN gene on chromosome 10q23
- Pathognomonic mucocutaneous lesions
  - Facial trichilemmomas (Fig. 1)
  - Papillomas of face, lips, tongue, oral mucosa (Figs. 2 and 3)
  - Acral lacteals (Fig. 4)
- Lifetime risk of breast cancer estimated to be between 25% and 50%
Hereditary Breast Cancer and New Development in Genetic Testing

Cowden Syndrome:
Major and Minor Diagnostic Criteria

**Major criteria**
- Breast cancer
- Thyroid cancer, usually follicular
- Macrocephaly
- Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma)
- Endometrial cancer

**Minor criteria**
- Other thyroid lesions
- Mental retardation
- Hamartomatous intestinal polyps
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- GU tumors or malformations


Hereditary Diffuse Gastric Cancer (HDGC) & Lobular breast cancer

- **CDH1** (16q22.1)
- Protein: e-cadherin
- Autosomal dominant
- Risks for diffuse gastric cancer (linitis plastica) & lobular breast cancer

HDGC: e-cadherin

<table>
<thead>
<tr>
<th>Diffuse Gastic Cancer</th>
<th>Lobular breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>women: 83%</td>
<td>39% lifetime risk</td>
</tr>
<tr>
<td>men: 67%</td>
<td></td>
</tr>
<tr>
<td>mean age: 38 yo</td>
<td></td>
</tr>
<tr>
<td>range: 14-69 yo</td>
<td></td>
</tr>
</tbody>
</table>

? Colon cancer
Since we know that there are multiple genes that can cause an increased risk for breast cancer, can we test for them at the same time?

• New beginnings, new opportunities……
Hereditary Breast Cancer and New Development in Genetic Testing

### NGS Panels - Ovary

Walsh et al., 2011
- 360 newly diagnosed ovarian, fallopian tube and primary peritoneal patients
- BROCA Panel (49 genes)
  - 24% mutation rate
    - 18% BRCA1/2
    - 6% 10 other genes
- >30% had no family history of br/ov
- >35% diagnosed >60y


### NGS Panels - Breast

Walsh et al. 2013 (ASHG Platform Presentation)
- Resolved 206 of 800 families with wild-type results from BRCA1/2 testing (26%)
- BROCA panel
- 39% (80/206) had BRCA1/2 mutations (BART or other rare mutations)
  - 37% carried mutations in CHEK2, PALB2, or TP53
  - 20% carried mutations in 10 less characterized genes
Hereditary Breast Cancer and New Development in Genetic Testing

High Risk Breast Cancer Genes

BRCA Plus

<table>
<thead>
<tr>
<th>BRCA1/BRCA2</th>
<th>CDH1</th>
<th>PTEN</th>
<th>TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast/Ovarian Cancer</td>
<td>Hereditary Diffuse Gastrointestinal Cancer</td>
<td>Cowden Syndrome</td>
<td>Li-Fraumeni Syndrome</td>
</tr>
<tr>
<td>Breast</td>
<td>Breast</td>
<td>Breast</td>
<td>Breast</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Diarrhoeal Cancer</td>
<td>Thyroid</td>
<td>Renal</td>
</tr>
<tr>
<td>Rectal</td>
<td>Colorectal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Kidney</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BRCAplus Gene Specific Lifetime Breast Cancer Risks

<table>
<thead>
<tr>
<th>Gene</th>
<th>General Population</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>CDH1</th>
<th>PTEN</th>
<th>TP53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5%</td>
<td>45%</td>
<td>8%</td>
<td>8%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*Based on the risk assessment in concert with BRCA mutations, although the lifetime risk calculation alone, not in isolation, is a key component.

Lifetime Breast Cancer Risk

- Average
- Family
- Moderate Risk Gene
- High Risk Gene

*Specific risk not dependent on moderate family history of breast cancer
**Specific risk not depend on the gene involved
Hereditary Breast Cancer and New Development in Genetic Testing

Types of Alterations

- Alterations known to increase risk for cancer
  - Also known as deleterious mutations

- Alterations not associated with an increased cancer risk
  - Alterations are neutral and called polymorphisms

- Alterations when cancer risk is not currently known
  - Also known as variants of uncertain significance (VUS)
Possible Results
Comprehensive Analysis

- **Positive**
  - A deleterious mutation was identified that is associated with an increased risk to develop specific cancers
- **Negative**
  - Not a carrier of deleterious mutation that was previously identified in your family
- **Indeterminate**
  - No alterations were detected in you and no alterations have been previously identified in the family
- **Inconclusive**
  - A variant of uncertain significance was detected

What Do My Test Results Mean?

- GENETIC TEST RESULTS
  - BRCA1
  - BRCA2
  - Low, Moderate, High Risk
  - Negative
  - Positive
  - Indeterminate

- RESULT MEANING
  - Positive
  - Indeterminate
  - Negative

- IMPLICATIONS
  - Medical management based on genetic result
  - Medical management based on personal family history

Summary

- BRCA genes discovered in 1994 and 1995
- Breast cancer gene panel testing available in 2012
- High, moderate and low risk genes
- Guidelines have not been established for moderate and low risk genes
- Family history is still important!
To find a genetic counselor

- National Society of Genetic Counselors Website
- [www.nsgc.org](http://www.nsgc.org)
- Click on find a counselor and insert your zip code
- Search for a genetic counselor who specializes in cancer genetics
Hereditary Breast Cancer and New Development in Genetic Testing