Genetics of Hereditary Breast and Ovarian Cancer

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Goals of a Cancer Screening and Prevention Program (GCRA)

- Cancer Risk Assessment
  - Analysis of personal risk factors and pedigrees to identify individual and families at risk
- Medical Planning
  - Surveillance, prophylaxis and prevention
- Pre and post-genetic testing counseling
Risk Factors Associated with Breast Cancer

- Major risk factors increase the risk by >2 fold
- Minor risk factors increase the risk by up to 2 fold
**Major Risk Factors (>2 fold increase)**

- BRCA 1 and 2 Mutation: 20x
- Chest radiation before age 30: 10-20x
- DCIS: 20x
- LCIS: 10x
- ALH/ADH: 4-5x
- Age > 60 (vs age 30): 10x
- 1st degree relative < age 50: 2x
- Prior breast cancer: >2x
Minor Risk Factors (>1 and <2 fold) or Protectors (<1)

- Early Menarche: 1.05/year < age 12
- No births/1st birth > age 30 (vs 20): 2x
- No lactation: 0.96 per 12 months breast feeding
- Late menopause (>50): 1.05/year
- 5 years of CEE alone HRT: 0.75
- 5 years of CEE + MPR HRT: 1.25
- Obesity (vs 3 hrs/week): 1.3
- Inactivity (vs 3 hrs/week): 1.25
- Alcohol: 1.1/drink/day
The Human Genome

- Humans have 46 chromosomes (23 pairs)
- In every cell nucleus is DNA—the basis of heredity or the instructional manual for our body
- DNA makes up genes
- Genes are on the chromosomes
- The function of a gene is to code for a protein
- 3 billion base pairs
- 20,000 genes
- 2% of the genome is protein coding or contributing to function
Point Mutations Can Alter Protein Function

Point mutation: a change in a single base pair

Functional protein

Nonfunctional or missing protein
<table>
<thead>
<tr>
<th>Mutations</th>
<th>Mutation Example</th>
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<tbody>
<tr>
<td>Normal</td>
<td>THE BIG RED DOG RAN OUT</td>
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<tr>
<td>Missense</td>
<td>THE BIG RAD DOG RAN OUT</td>
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<tr>
<td>Nonsense</td>
<td>THE BIG RED ___</td>
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<tr>
<td>Frameshift (deletion)</td>
<td>THE BRE DDO GRA</td>
</tr>
<tr>
<td>Frameshift (insertion)</td>
<td>THE BIG RED ZDO GRA</td>
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Autosomal Dominant Inheritance (eg BRCA gene mutation)

- Phenotype is expressed in people heterozygous for a particular allele (translation=only 1 copy of a mutation is needed to express the condition)
- Each child has a 50% chance of inheriting the mutation
- Equally transmitted in men and women
- The mutation does not ‘skip generations’
- INDIVIDUALS INHERIT THE SUSCEPTIBILITY TO CANCER, NOT THE CANCER ITSELF
- Penetrance (or getting the cancer) is <100%
  - Highly penetrant
  - Moderately penetrant
  - Low penetrant
High-penetrance, rare cancer predisposition genes
(Relative risk ≥ 5)

Moderate risk alleles
(Relative risk ≥ 1.5 and < 5.0)

Low penetrance, high frequency risk alleles*
(Relative risk < 1.5)

Genome-wide Association Studies

Phenotypic Effect Size

PS3  APC  BRCA1  BRCA2
CDH1  MLH1  MSH2
STK11  PTEN
CDKN2A  MSH6
PMS2

ATM  CYP1A1
APC (11307K)  CHEK2
BRIP1  PALB2
BLM (BLM<sup>rep</sup>)
GSTM1
JAK2  KITLG
8q24 locus
MSMB  CHRNA3  CHRNA5  CHRN4
FGFR2
NUDT10  NUDT11

Population Frequency
Important Dates in Cancer Genetics

1953  Watson and Crick describe the DNA double helix
1982  First gene patent was issued
1988  Human Genome project was initiated
1994  BRCA 1 sequence was reported
1995  BRCA 2 sequence was reported
1996  BRAC Analysis test launched
2000  Completion of the Human Genome project
2013  US Supreme Court rules that genes cannot be patented
BRCA1 and BRCA2 Associated Cancers: Lifetime Risk

- Breast cancer (often early of onset)  50-85%
- Second primary breast cancer        40-60%
- Ovarian cancer                      15-45%
BRCA 1 and BRCA 2

- BRCA1 is on chromosome 17
- BRCA2 is on chromosome 13
- Autosomal dominant transmission
- Proteins have a role in genomic stability
- >2000 different mutations and variants distributed over these genes
Cancer ‘causes’

- Sporadic cancer doesn’t have obvious reasons for occurring
- Familial cancer is likely caused by a combination of environmental risk factors and possible genetic factors
- Hereditary occurs when there is an altered or mutated gene that is passed down in the family from parent to child
Breast/Ovarian cancer ‘causes’

- Breast cancer
  - 5% hereditary
  - 15-20% familial
  - 75-80% sporadic
- Ovarian cancer
  - 15% hereditary
  - 85% sporadic
GCRA

- Identify individuals with inherited cancer risks
- Recommend high risk screening and preventive care
- Reduce cancer burden
Consultation for Risk Assessment

- Engage the patient and assess concerns/motivations
- Document patient and family cancer history
- Explain principles of heredity and cancer genetics
- Facilitate informed consent and possibly initiate testing
Test Results Disclosure

- Interpret/communicate the genetic test results
- Help provide personalized risk management recommendations and resources
- Facilitate adaptation and coping with impact of test result
- Assist with communication of results to at-risk family members
Comprehensive Cancer Family History

- GCRA is dependent on gathering accurate, detailed and relevant information and the family history is a fundamental
- Family history is the basis for:
  - Making a diagnosis
  - Determining risk
  - Making recommendations for medical management
  - Assessing the needs for patient education and psychosocial support
Taking a Comprehensive Family History

- At least 3-generations for each lineage
- Specify exact biological relationship
- Age, or age/cause of death
- All cancers and age of diagnosis (determine if primary, recurrence or metastatic)
- Location of primary cancer (stage, laterality, treatment)
- Pertinent chemoprevention/surgeries (tamoxifen, OCPs, hysterectomy, oophorectomy, mastectomy, colectomy, gastrectomy, thyroidectomy)
- Race/ethnicity
Draw a Pedigree

- Quick and accurate visual record assisting in providing genetic counseling and disease risk assessment

NCCN, 2014
Degree of Relatives

- Probability of hereditary cancer predisposition
- Cancer risk for patient and other family members
- Cancer cases needing confirmation or documentation
- Genetic testing—who to test/who has been tested
- Need for screening/prevention
Reliability

- Reports of breast cancer in a first degree relatives are highly reliable (>90%)
- Tendency to over-report with multiple relatives
- Reports of ‘female’ gynecologic cancers are often inaccurate
- Metastatic and recurrent cancers are often reported as a new primary cancer
- **Accuracy matters!!!**
  - Which genes to test
  - Who to test
  - Is risk reduction treatment really necessary
**SPORADIC**
- Few affected family members
- Caused by an accumulation of mutations throughout life
- Not hereditary

**FAMILIAL**
- Clusters of cancer in a family
- Genetic predisposition is not evident in the family history

**HEREDITARY**
- Cancer in more than 2 generations
- Caused by mutations in genes
- Bilateral breast cancer
- Multiple related cancers
When to Suspect Hereditary Cancer

- Earlier age at diagnosis than expected
- Multiple generations with cancer
- Multiple cancers in one generation
- Rare types of cancer
- Bilaterality
- Constellation of tumors characteristic of a specific syndrome
Limited Family Structure for Breast/Ovarian Cancer

- May make it harder to determine there is a hereditary cancer risk
- Defined as fewer than 2 first or second degree female relatives older than age 45 in one lineage (maternal or paternal)
Who Should Be Tested?

- Any individual at any age with a known pathogenic (or likely pathogenic variant) within the family (including first, second and third degree relatives)
- An individual diagnosed at any age with the following cancer:
  - Ovarian
  - Pancreatic
  - Metastatic prostate cancer
  - Breast cancer or high grade prostate cancer of Ashkenazi Jewish ancestry
Who Should Be Tested?

- Any individual with breast cancer with the following:
  - Breast cancer diagnosed at or younger than age 50
  - Triple-negative breast cancer diagnosed at or younger than age 60
  - 2 breast cancer primaries
  - Breast cancer at any age and 1 or more blood relatives with
    - Breast cancer at or younger than age 50
    - Invasive ovarian cancer
    - Male breast cancer
    - Pancreatic cancer
    - High grade or metastatic prostate cancer
  - Breast cancer at any age and 2 or more blood relatives with breast cancer
Who Should Be Tested?

- An individual who has not had cancer, but has a first- or second-degree relative with any of the following:
  - Breast cancer at or younger than age 45
  - Ovarian cancer
  - Male breast cancer
  - Pancreatic cancer
  - Metastatic prostate cancer
  - 2 or more breast cancer primaries in a single individual
  - 2 or more breast cancer primaries on the same side of the family with at least 1 diagnosed at or younger than age 50
Who Should Be Tested?

- An individual with a personal and/or family history on the same side of the family of 3 or more of the following (especially if diagnosed at or before age 50):
  - Breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia (LIFR)
  - Colon cancer, endometrial cancer, thyroid cancer, kidney cancer, certain GI polyps (COWD)
  - Lobular breast cancer, diffuse gastric cancer (CDH1)
  - Breast cancer, GI cancer, certain GI polyps, pancreatic cancer, testicular tumors (STK11)
Possible Genetic Test Results

- Positive results
- Inconclusive results
- Negative results
  - Uninformative vs. Informative
ASCO Guidelines Risk Reduction Counseling Update

- Tamoxifen should be discussed with a premenopausal or postmenopausal woman at increased risk for breast cancer with a 5 year Gail model of >1.66%
- Raloxifene or exemestane should be discussed in a postmenopausal woman with a 5 year Gail model of >1.66%
- <5% of eligible women take any of the above
**Standard Risk Reduction**

- **Very High Risk or ~2%/year (BRCA mutation)**
  - Prophylactic surgery

- **High Risk or ~1%/year (LCIS, AH +FH)**
  - SERMS, AIs, Prevention trials

- **Moderate Risk or >0.33 to <1%/year (FH alone)**
  - Possibly tamoxifen under age 50
  - Possibly raloxifene postmenopausal
  - Healthy behaviors only
Summary of Standard Risk Reduction Medications

- **Benefits** - reduce risk by:
  - Raloxifene ~ 40%
  - Tamoxifen ~ 40-50%
  - Aromatase Inhibitor (AI) 50-65%

- **Side Effects**
  - Menopausal symptoms
  - Blood clots (SERMS)
  - Bone Density loss and joint pain (AIs)
Risk Reduction Behaviors

- Avoid alcohol (RR 1.10/drink/day)
- Avoid weight gain over age 30
- Exercise > 150 minutes/week
- (Maybe) Vitamin D – achieve level of 50 ng/ml
- (Maybe) Lignans (flaxseed) – 50 mg/d
- (Maybe) Omega-3 Fatty Acids – DHA+EPA 3.4 g/d
Early Detection

- Mammograms
  - Generally recommended annually > age 40
- Tomosynthesis or 3D MMG annually
  - Dense breasts
  - Family history of breast cancer
  - Chest wall radiation
  - History of call backs
- MRI annually
  - Lifetime breast cancer risk >20%
Thank you!