Identifying your risk for hereditary breast or ovarian cancer

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Outline

• Genetics and biology of hereditary cancer syndromes
• BRCA1 and BRCA2
• Genetic counseling and testing
• Genes related to breast cancer
• What to do with a positive genetic testing result
• Your questions

What causes cancer?

Random chance
DNA damage to genes regulating cell growth
Environment
Genetics

Genetics 101

• Genes contain the instructions for building and regulating all living organisms
• Genes are encoded by long strings of chemical “letters” (base pairs) in molecules of DNA found in the nucleus of each cell
Genetic variation

- Subtle differences in DNA sequences give rise to the diversity of life.
- Variations can be:
  - Wild type – the most common variant
  - Benign – less common but not harmful
  - Deleterious – giving rise to disease

Hereditary Mutations

Examples
- The fat cat ate the rat (Normal)
- The fatty cat ate her rat (deletion)
- The fatty cat ate her rat (insertion)
- The fat cat ate the rat (point mutation)
- The cat fat ate the rat (Rearrangement)
- The fat cat (stop codon)

How can cancer be inherited?

BRCA1 and BRCA2

- Involved in DNA repair
  - DNA needs to be copied in its entirety each time a cell divides
  - BRCA1, BRCA2, and many other proteins correct DNA damage that occurs over time
- Deleterious mutations in BRCA1 or BRCA2 cause cells to accumulate more errors in DNA
BRCA1 and BRCA2

- Many errors are benign variants.....
- ..... But occasionally an error can alter genes responsible for cell growth
- It is these secondary mutations that ultimately give rise to cancer

BRCA1 and BRCA2

- You only need 1 defective copy of BRCA1 or BRCA2 to increase cancer risk
- Cancers arise later in life (because it takes decades for the right combination of errors)
- Some patients with BRCA1 or BRCA2 mutations never develop cancer (because there is some random chance involved in which errors occur)

BRCA mutations and Ashkenazi Jews

- BRCA1 and BRCA2 mutations are found in people of all ethnic/racial backgrounds
- 3 specific mutations are found with greatly increased frequency in Ashkenazi Jews
  - BRCA1: 185delAG, 5382insC
  - BRCA2: 6174delT
  - 1:33 to 1:56 affected individuals
- BRCA1 founder mutation also found in other Jewish populations

The founder effect

- A very small population may become enriched for rare genetic variants by chance
  
  Genetic "bottleneck"
  600-800 years ago
  350 individuals
Ashkenazi Jewish genetic history

Cancer genes with Jewish founder mutations:
- BRCA1
- BRCA2
- CHEK2
- GREM1
- APC

You may have seen....

- Familial, 15-20%
- Hereditary, 5-10%
- Sporadic, 70-80%
Sporadic Cancer

Breast (65)

Familial Cancer

Breast (61)

Breast (69)

Breast (72)

When do we suspect hereditary cancer?

2 or more primary cancers in the same person
3 or more cancers on the same side of the family
10 or more colorectal polyps in a person’s lifetime

Multiple

Young

Rare

Ancestry

Any of the following cancers diagnosed early:
Breast, colorectal, uterine

Cancer of small bowel, uterus, wall breast cancer, ovarian cancer

Ashkenazi Jewish and history of breast or pancreatic cancer

Hereditary Cancer

Uterine (30)

Breast (45)

Ovarian (60)

Pancreas (52)

Colon (45)

Colon (35)
Genetic Counseling vs. Genetic Testing

- **Genetic counseling:**
  - Appointment to assess cancer risks
  - Discuss genetic testing options
  - Interpret genetic testing results
  - Create a personalized management/screening plan

- **Genetic testing:**
  - Blood or saliva test that can show if you inherited an abnormal gene (mutation) that increases your risks for certain cancers
  - Testing is performed by a specialized laboratory
  - Results take ~ 3 – 4 weeks

How do we estimate breast cancer risk?

- Genetic testing may not be needed by everyone
- Can still use family history / personal history to estimate risk
- May qualify for increased screening
**Genetic Test Results**

- **NEGATIVE**
  - Negative for the genes tested. Important to consider if there is a known mutation in your family.

- **VUS**
  - Variants of Undetermined Significance.
  - Unknown at this time if change identified is harmful.

- **POSITIVE**
  - Positive for a gene that increases the risk of cancer.

**GINA**

**Genetic Information Non-Discrimination Act**

- GINA protects most patients from discrimination with health insurance or an employer. Active duty military personnel are an exception.

**Colorado has protections for long-term and short-term disability insurance, but NOT life insurance**
**BRCA1/BRCA2 Management in Women**

### Breast
- **Annual Screening**
  - Self breast exam - start at 18
  - Clinical breast exam - start at 18
  - Breast MRI – start at 25
  - Mammogram – start at 30
- **Risk Reduction**
  - Consider bilateral mastectomy
  - Chemoprevention (Tamoxifen)

### Ovarian
- **Screening**
  - Transvaginal ultrasound
  - CA-125
  - **Limited usefulness**
- **Risk Reduction**
  - Oophorectomy:
    - BRCA1 35-40
    - BRCA2 40-45
  - Chemoprevention (birth control)

### Considerations
- Screening during pregnancy
- Nursing
- Recovery from mastectomy
- Insurance coverage

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**BRCA1/BRCA2 Management in Men**

### Breast
- **Annual Screening**
  - Self breast exam – start at 35
  - Clinical breast exam – start at 35
  - Consider mammogram

### Prostate
- **Annual Screening**
  - PSA and prostate exam – start at 45

**Men and women:**

No specific guidelines for **pancreatic cancer** or **melanoma**, but may be individualized based on family history.

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**Recent Updates**

- American College of Radiology (ACR) and Society of Breast Imaging (SBI) now recommend that **ALL** women should be evaluated for breast cancer risk no later than age 30.
  - Specifically names populations at higher risk:
    - Black women
    - Women of Ashkenazi Jewish
Recent Updates – 23andMe

23andMe Granted First FDA Authorization for Direct-to-Consumer Genetic Test on Cancer Risk
March 8, 2018

Authorization allows 23andMe to report on BRCA1- and BRCA2-related genetic risk for breast, ovarian, and prostate cancer.

- Only analyzes the 3 AJ founder mutations in BRCA1 and BRCA2.
- Hundreds of other known BRCA mutations are **NOT** analyzed.
- FDA states “the test does not diagnose cancer or any other health conditions and should not be used to make medical decisions. Results should be confirmed in a clinical setting before taking any medical action.”
- The test has a minimum analytical sensitivity of 95%.

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