Hereditary Cancer Predisposition

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Cancer is a Genetic Disease

Normal

Tumor
Cancer Arises From Gene Mutations

**Germline mutations**

- Present in egg or sperm
- Are heritable
- Cause hereditary cancer syndromes

**Somatic mutations**

- Occur in nongermline tissues
- Are nonheritable
- Later onset

**Parent**

Mutation in egg or sperm

**Child**

All cells affected in offspring

Somatic mutation (e.g., breast)
All Cancer is Genetic, Not All Cancer is Inherited

Sporadic Cancer
- Normal cell
- First mutation
- Second mutation
- Third mutation
- Fourth + mutation
- Malignant cell

Hereditary Cancer
- First mutation
- Second mutation
- Third mutation
- Fourth + mutation
- Malignant cell
Hereditary Versus Sporadic Cancer

**Hereditary**
- Onset of breast cancer usually < 50
- Ovarian cancer at any age (not always present)
- Breast and ovarian cancer in the same individual
- Male breast cancer
- Ashkenazi ancestry

**Sporadic**
- None of the breast cancer is diagnosed before 60 yrs
- No ovarian cancer
- No clear pattern on one side of family or the other
The Key to Identification: Family History

- Maternal and paternal family history
- Accurate risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
When to Suspect Hereditary Cancer Syndrome

- Cancer in 2 or more relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (e.g., breast and ovary)
- Evidence of autosomal dominant transmission
- Ancestry
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...your DNA chip will tell us if you have a predisposition to certain illnesses, our lab techs are trying to isolate "the willing to work long hours for little pay" gene...
How Much Breast and Ovarian Cancer Is Hereditary?

Breast Cancer

- Sporadic: 5%–10%
- Family clusters: 15%–20%
- Hereditary: >10%

Ovarian Cancer

- Sporadic: 5%–10%
- Hereditary: >10%
Inheritance Pattern: Autosomal Dominant with Incomplete Penetrance

- Penetrance is often incomplete
- May appear to “skip” generations
- Individuals inherit altered cancer susceptibility gene, not cancer
BRCA1-Associated Cancers: Lifetime Risk

- Breast cancer 50%–85% (often early age at onset)
- Second primary breast cancer ~60%
- Ovarian cancer 40%–60%

Possible increased risk of other cancers (eg, male breast, colon)
BRCA2-Associated Cancers: Lifetime Risk

- Breast cancer: 50%–85%
- Male breast cancer: 6%
- Ovarian cancer: 10%–27%
- Second primary breast cancer: ~50%
- Increased risk of prostate and pancreatic cancers (magnitude unknown)
BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

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

BRCA1

185delAG
Prevalence = ~1%

5382insC
Prevalence = ~0.15%

BRCA2

6174delT
Prevalence = ~1.5%

Breast Cancer Management Options

• Surveillance:
  – Self breast exam, Clinical breast exam, Mammogram, Breast MRI, and Breast Ultrasound.
  – MRI has been shown to have higher sensitivity in BRCA carriers (77-91% for MRI vs. 33-36% for mammography)

• Chemoprevention:
  – Tamoxifen

• Prophylactic Surgery:
  – Bilateral Mastectomy is associated with ~90% reduction of breast cancer risk in women with BRCA mutations
  – Bilateral Salpingo-Oophorectomy is associated with ~50% reduction in breast cancer risk when done prior to menopause.

Ovarian Cancer Management Options

- **Surveillance:** CA-125, Pelvic exams, Transvaginal ultrasound

  “There are no data demonstrating that screening these high-risk women reduces their mortality from ovarian cancer. Nonetheless, [the above screening measures] are recommended...” - NIH Consensus Guidelines, JAMA 1995;273:491-7

- **Chemoprevention:**
  - Oral Contraceptives

- **Prophylactic Bilateral Salpingo-Oophorectomy:**
  - Ovarian cancer risk reduction of ~95%
  - Breast cancer risk reduction of ~50% (premenopausal)

References:

Genetic Predisposition Testing Is a Multi-Step Process

- Identify at-risk patients
- Provide pretest counseling
- Provide informed consent
- Select and offer test
- Disclose results
- Provide post-test counseling and follow-up
Psychological Issues in Testing

- Anxiety/fear
- Guilt
- Self-esteem
- Depression
- Stigmatization
- Grief
- Anticipatory loss
- Changes in family dynamics
- How/when to inform at risk children/relatives
Genetic Testing Has Implications for the Entire Family

- Consider the impact of testing on all family members
- Ultimately, testing is the individual’s choice
Questions???