Breast Cancer Risk and Genetics

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- **No conflicts of interest to report**

LEARNING OBJECTIVES

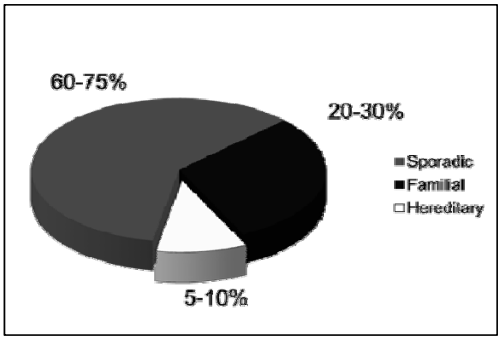
- **Differentiate between sporadic, familial, and hereditary cancer and review genetics basics**
- **Introduce cancer risk and surveillance / risk - reducing options for HBOC**
- **Present other conditions associated with breast cancer susceptibility**

LEARNING OBJECTIVES

- **Discuss pros and cons of multigene panels**
- **Explore the role of cancer genetic counselors**

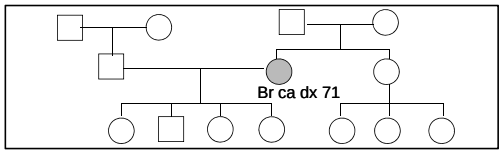
BREAST CANCER CATEGORIES

CANCER CATEGORIES



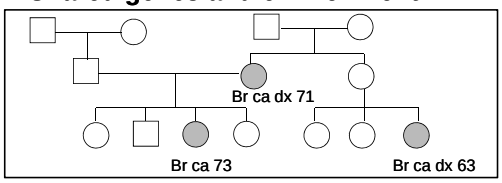
Sporadic Cancer

- Few family members with cancer
- Later age of onset
- Chance
- Environmental factors



Familial Cancer

- > 1 individual on the same side of the family with same type of cancer
- Typically later ages of onset
- Shared genes and environment

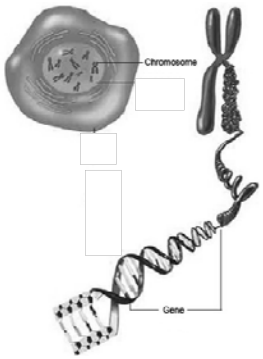


HEREDITARY CANCER RED FLAGS

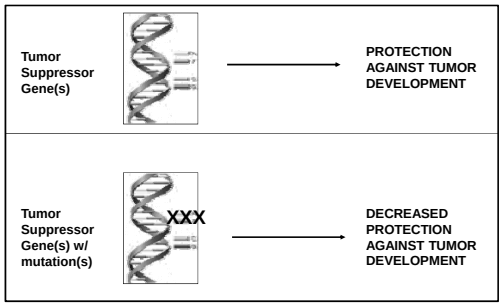
- Cancer at early ages
- Multiple primary cancers in one person
- Multiple cases of same or related cancers on the same side of the family
- Rare cancers
- Ethnic Background

CANCER GENETICS BASICS

GENETICS 101

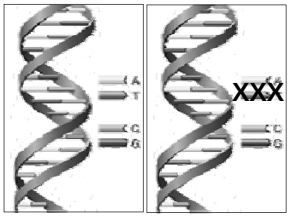


TUMOR SUPPRESSOR GENES



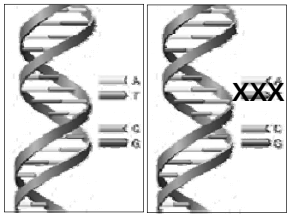
AUTOSOMAL DOMINANT

- 2 copies of each gene - one from each parent
- Mutation in one copy is enough to cause the condition

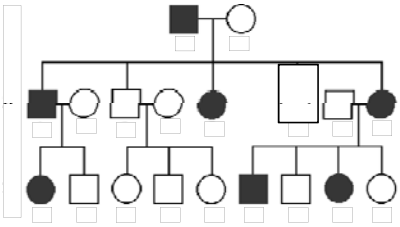


AUTOSOMAL DOMINANT

- 50% chance to pass copy with mutation in each pregnancy (sons and daughters)



AUTOSOMAL DOMINANT



HEREDITARY BREAST AND OVARIAN CANCER (HBOC)

HBOC RED FLAGS

- Cancer at early ages
  - Breast cancer < 50
- Multiple cancers in one person
  - Bilateral breast cancer
- Multiple cases of same or related cancers in a family

HBOC RED FLAGS

  - Breast cancer in combination with ovarian cancer, pancreatic cancer, prostate cancer, melanoma
- Rare cancers
  - Male Breast Cancer
  - Triple negative breast cancer
- Ethnic Background
  - Ashkenazi Jewish ancestry and HBOC

TUMOR SUPPRESSOR GENES

BRCA1/ BRCA2 → **PROTECTION AGAINST TUMOR DEVELOPMENT**

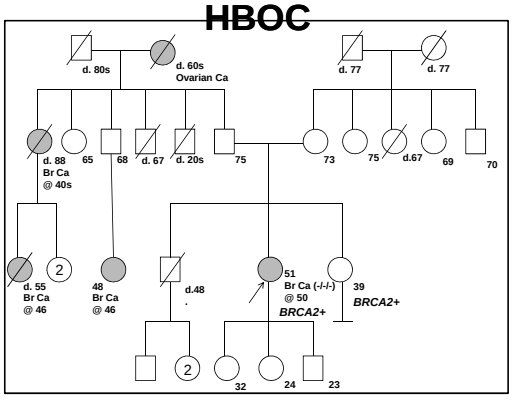
BRCA1/ BRCA2 w/ mutat. (XXX) → **DECREASED PROTECTION AGAINST TUMOR DEVELOPMENT**

HBOC CANCER RISKS

Cancer	BRCA1	BRCA2	Gen. Pop.
Breast	46-63%	38-53%	12%
Ovarian	34-44%	12-20%	1-2%
Prostate	increased	20-30%	16%
Male Breast	increased	7%	0.1%
Pancreatic	3-4%	2-5%	0.9%
Melanoma	not increased	increased	2%

(Graeser et al, 2009) (Chen and Parmigiani, 2007) (Liede, Karlan, and Narod, 2004) (Consortum TB, 1999)

HBOC



HBOC MANAGEMENT

Breast
- **Non-Surgical** → **Screening:** Annual Breast MRI (25 yo), Semiannual CBE (25 yo), Annual Mammogram (30 yo); **Medications** (Tamoxifen)
- **Surgical** → **Bilateral Prophylactic Mastectomy**

Ovarian
- Non-Surgical → **Screening:** Annual Transvaginal Doppler U/S (35), Annual CA125 (35 yo); **Medications** (OC Pills)
- Surgical → **Prophylactic BSO**

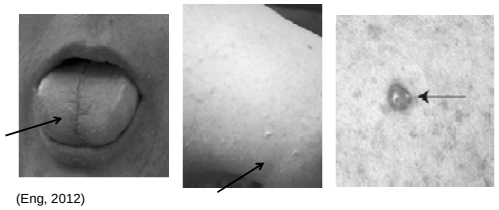
Melanoma → **Annual Skin/ Eye Exams**

NCCN Guidelines. (2015). *Breast cancer 3.2015.*

OTHER BREAST CANCER SUSCEPTIBILITY SYNDROMES

COWDEN SYNDROME

- **Caused by mutations in the PTEN gene**
- **Associated cancers: breast, thyroid, uterine, renal, colon, melanoma**



(Eng, 2012)

COWDEN SYNDROME

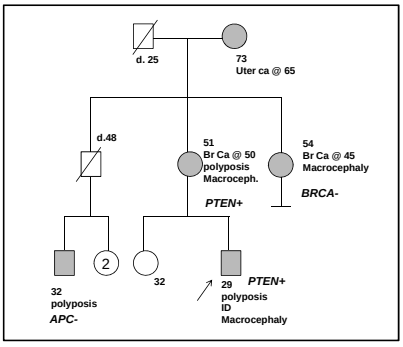
- **Multiple benign findings:**
  - **Characteristic skin findings**
  - **Macrocephaly (larger head circumference)**
  - **GI polyps**
  - **Thyroid lesions (ex: goiter, nodules)**
  - **Autism, ID**
- **Rare: Lhermitte Duclos disease**
  - **(brain lesion)**

COWDEN

	General Population	Cowden syndrome
Female breast	12%	50-85%
Male breast	<1%	increased
Thyroid (non-med.)	1%	10-35%
Uterine	3%	10-28%
Renal Cancer	2%	34%
Colon Cancer	6%	9%
Melanoma	2%	6%

(Eng, 2012; NSGC CA SIG, 2013)

COWDEN



LI-FRAUMENI

- **Caused by mutations in TP53 gene**
- **Core cancers**
  - **Sarcomas of bone and soft tissue**
  - **Premenopausal breast cancer (can be very early onset)**
  - **Brain tumors**
  - **Adrenocortical carcinoma**

(Schneider, 2013)

LI-FRAUMENI

- **Non - core cancers – colon, uterine, esophageal, gonadal germ cell, leukemias and lymphomas, lung, melanoma, neuroblastoma, ovarian, pancreatic, prostate, gastric, thyroid, renal**

(Schneider, 2013)

LI-FRAUMENI

- **NCCN: TP53 testing should be considered for women diagnosed with breast cancer < age 35, especially after negative BRCA testing**

(Schneider, 2013)

LI-FRAUMENI

- High risk of early - onset cancer
  - Risk of cancer ~50% by age 30, 90% by age 60 (~100% for women)
  - 0-10 yrs: soft tissue sarcomas, brain tumors, ACC
  - 11-20 yrs: bone sarcomas
  - >20 years: breast cancer, brain tumors

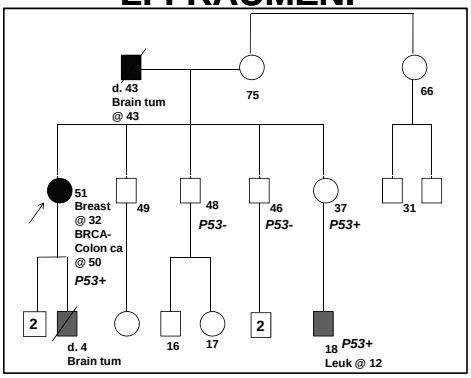
(Schneider, 2013)

LI-FRAUMENI

- Multiple primaries
  - Approximately 57% risk of second cancer
  - Approximately 38% risk for third cancer
  - 4th primaries have been reported
  - Survivors of childhood cancers at highest risk, likely related to treatment of previous cancers

(Schneider, 2013)

LI-FRAUMENI

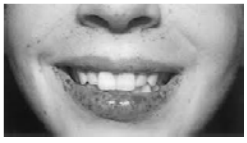


OTHER HEREDITARY BREAST CANCER SYNDROMES

- Hereditary Diffuse Gastric Cancer
  - Diffuse gastric cancer
  - Lobular breast cancer

OTHER HEREDITARY BREAST CANCER SYNDROMES

- Peutz - Jeghers Syndrome
  - Colon, gastric, pancreatic, breast, and ovarian cancers
  - Polyposis
  - Characteristic freckling



MULTI-GENE PANELS

MULTIGENE BREAST PANEL EXAMPLE

High Risk	Moderate Risk	Newer Genes
BRCA1/BRCA2 (HBOC: breast, ovary, prostate, pancreatic)	ATM (breast, colon, pancreatic)	BARD1/BRIP1 (breast, ovary)
CDH1 (HDGC: breast, gastric, colon)	CHEK2 (breast, colon, prostate, ovary)	RAD51C/RAD51D (breast, ovary)
PTEN (Cowden: breast, thyroid, endometrial)	PALB2 (breast, ovary, pancreatic)	FANCC (breast, pancreatic)
TP53 (LFS: breast, ovary, sarcoma, brain)	MUTYH (MAP: colon, breast)	NBN (breast, melanoma, NH-lymphoma, colon)
STK11 (PJS: colon, breast, pancreatic, gastric)		XRCC2 (breast, colon, pancreatic)

MULTIGENE PANELS

BENEFITS	CHALLENGES
More cost-effective and efficient if considering multiple syndromes. Insurance may only allow one genetic test per lifetime.	More expensive than single gene testing
May identify rarer genetic causes of cancer in an individual/family	May identify mutation in gene for which there is limited info/guidance • Tumor Spectrum • Cancer risk estimates • Management recommendations
May identify genetic causes in "non-textbook" cases of well known cancer syndromes	Inconclusive test results more likely

GENETIC COUNSELING

GENETIC COUNSELING DEFINITION

- **Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:**

(NSGC, 2006)

GENETIC COUNSELING DEFINITION

- **Interpretation of family and medical histories**
- **Education about inheritance, testing, management, prevention, resources and research**
- **Counseling to promote informed choices**

(NSGC, 2006)

WHEN TO CONSIDER TESTING

- **American Society of Clinical Oncology: "Genetic counseling and testing should be offered if…"**
  - **An individual has personal or family history features suggestive of cancer predisposition**

(ASCO, 2003)

WHEN TO CONSIDER TESTING

- The test can be adequately interpreted
- The test will influence medical management

(ASCO, 2003)

GENETIC COUNSELING GOALS

- Contracting
- Risk assessment
- Education
- Informed consent
- Results
- Medical Management Recommendations
- Support

CONTRACTING

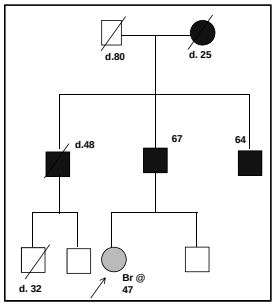
- Motivations - Patients often want to gain a better understanding of:
  - Personal cancer risks
  - Options and considerations for participation in genetic testing or research
  - Screening and cancer prevention

CONTRACTING

- Implications / recommendations for family members
- What can we offer?

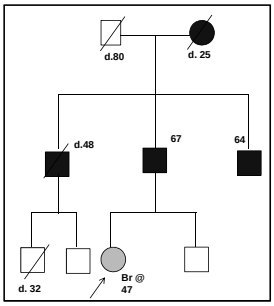
RISK ASSESSMENT

- Methods
  - Medical and family history analysis
  - Risk models



RISK ASSESSMENT

- Challenges
  - Limited information
  - Family structure
  - Variability



PT CONCERNS REGARDING TESTING

- Cost
- Timing / Impact on treatment
- Childbearing considerations
  - Age at hysterectomy / ovary removal
  - Risk to current/future children

PT CONCERNS REGARDING TESTING

- Quality of life
  - Perceived cancer risk
  - Body image; self - esteem
  - Surgery impact on quality of life
  - Management of surgical menopause
- Discrimination

TESTING

- Testing Options
- Informed Consent
  - Benefits
  - Limitations
  - Possible outcomes
  - Risks
- Test Interpretation
- Result Explanation

MANAGEMENT

- Recommendations for patient and family
  - NCCN guidelines if exist
  - Use studies and customize to medical / family history otherwise
  - Take limitations into account (insurance coverage, location, etc.)

SUPPORT

- Facilitate decision - making
  - Discuss how each test option and potential results might impact patient
  - Identify what is most important to patient
  - Listen to concerns and help them come to a decision
- Psychosocial counseling
- Provide support / resources

TAKE HOME MESSAGE

- 5 - 10% of breast cancers are due to underlying hereditary cause
- 20 - 30% of breast cancers are due to combination of genetic and environmental factors
  - Increased surveillance may still be appropriate!

TAKE HOME MESSAGE

- **A genetic counselor can review medical and family histories to determine:**
  - **whether testing is appropriate**
  - **who the best person is to test in a family**
  - **what testing is indicated**
  - **how test results and family history may affect medical management for patient and family**

Contact Information

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