

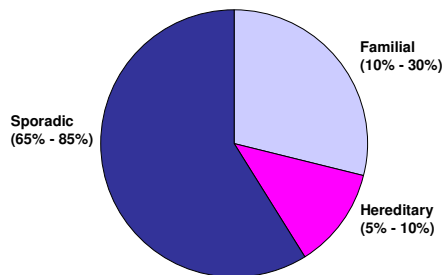
Identifying and Managing patients at High Risk for Hereditary Breast and Ovarian Cancer Syndrome

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Sutter Roseville Medical Center
April 27, 2008

Objectives

- Identification of appropriate patients for risk assessment of Hereditary Breast and Ovarian Cancer Syndrome
- Discuss genetic testing process, genes associated with Hereditary Breast and Ovarian Cancer Syndrome, and interpretation of genetic testing results
- Explain the clinical management options for patients with *BRCA1* and *BRCA2* mutations
- Discuss relevant insurance coverage issues regarding genetic testing

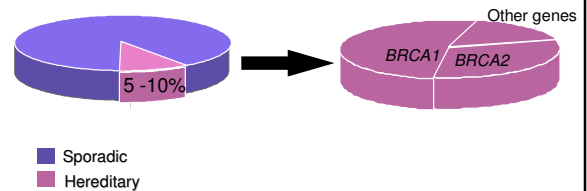
5%-10% of Breast & Ovarian Cancer is Hereditary



Blazer KR et al. *J Med Genet.* 2004;41:518-22.

Hereditary Breast and Ovarian Cancer

Most cases caused by a *BRCA1* or *BRCA2* mutation



ALMG 1998;62:676-89
JCO 2002;20:1480-14

Estimated Hereditary Breast & Ovarian Cases Annually

200,000 new cases of breast cancer

22,000 new cases of ovarian cancer

222,000 cancer cases/year

Estimated that 5-10% of these cancers are hereditary 20,000 - 25,000 cases per year

National Cancer Institute

“Red Flags” for Hereditary Breast and Ovarian Cancer

- Breast cancer before age 50
- Ovarian cancer at any age
- Male breast cancer at any age
- Multiple primary cancers
 - Bilateral breast cancer
 - Breast and ovarian cancer
- Ashkenazi Jewish ancestry
- Relatives of a *BRCA* mutation carrier



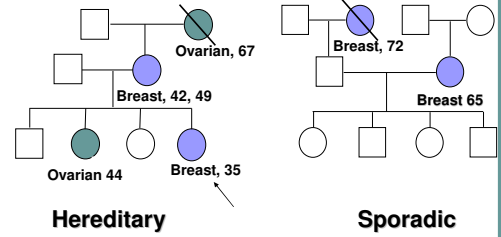
Science 2003;302:643-6
www.nccn.org

Family History Considerations

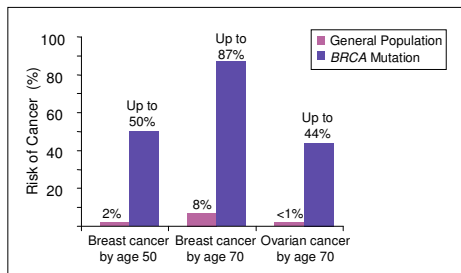
- History of breast and ovarian cancer on maternal or paternal side of family.
- Consider cancer history in first, second and third degree relatives
- Family history may appear insignificant because of small family size, male dominated families, or lack of knowledge about family history.

Cancer 2005 Dec; 15:104(12):2807-16
Science 2005;302:361-6
American Society of Breast Surgeons, June 12, 2006
www.asbs.org

Family History and Clinical Characteristics of HBOC

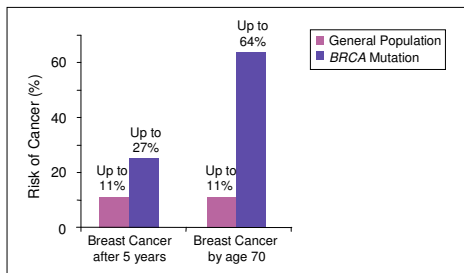


A BRCA Mutation Increases Breast and Ovarian Cancer Risks



Lancet 1994;343:692-695
NEJM 1997;336:1401-1408
AJHG 2003;72:1117-1130

A BRCA Mutation Increases Risk of Second Breast Cancer

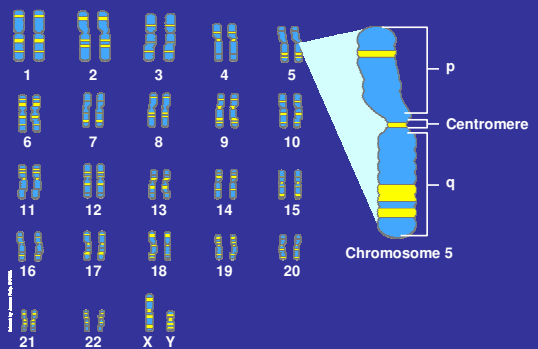


JNCI 1999;15:1310-8
JCO 1998;16:2471-6
Lancet 1998;351:316-21
JCO 2004;22:2089-95
Lancet 1994;343:692-5

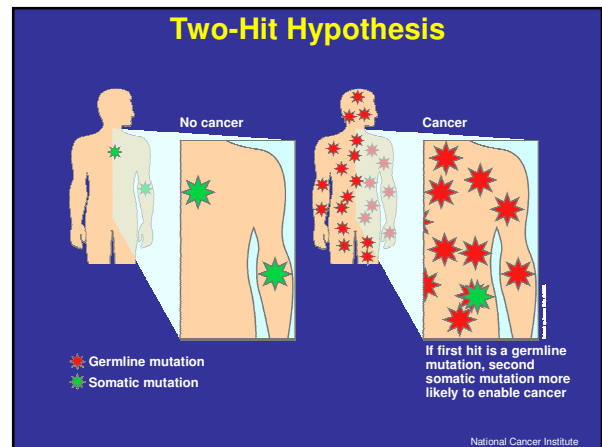
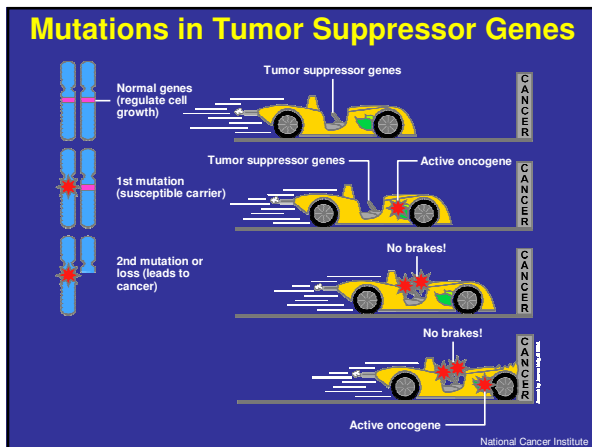
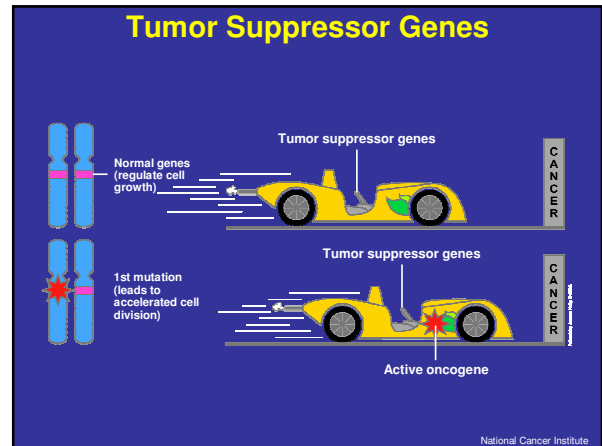
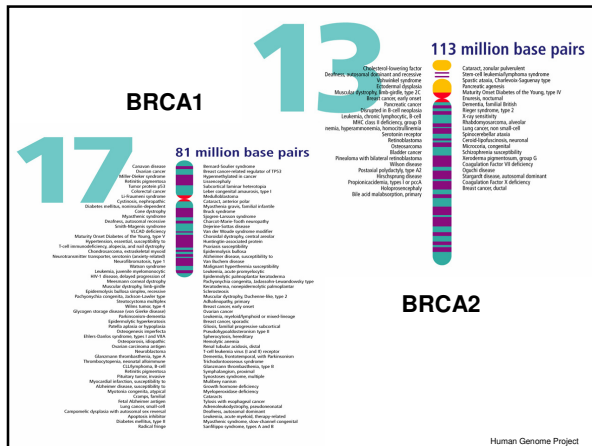
Other Cancers Associated with BRCA mutations

- Prostate
- Pancreatic
- Colon
- Melanoma
- Fallopian tube

A Sample Human Genome



National Cancer Institute



Medical Management of BRCA Mutation Carriers

- Surveillance
- Chemoprevention
- Surgery

Cancer 2004;100:479-89
NEJM 2004;351:427-37
www.nccn.org

Surveillance for Breast Cancer

Procedure	Age to begin	Frequency
Breast self-exam	18 yrs	Monthly
Clinical breast exam	25 yrs	Every 6 months
Mammography	25 yrs	Yearly
MRI	25 yrs	Yearly

JAMA 1997; 277:987-1003
Cancer 2004;100:479-89
NEJM 2004;351:427-37
www.nccn.org

Chemoprevention - Tamoxifen

- Data is limited to support use of Tamoxifen in an unaffected *BRCA* mutation carrier
- In patients with breast cancer who are *BRCA* mutation positive, Tamoxifen has been shown to decrease breast cancer in the contralateral side by 50%

Br J Cancer. 2006;115(9):2281-4
Lancet. 2006;368:1878-81
JAMA. 2001;286:2251-6
JCO. 1996;14(12):3171-86

Bilateral Risk Reducing Mastectomy

- Reduces risk of breast cancer by 90% for *BRCA* carriers
- Remove all breast tissue
- Multidisciplinary approach

NEJM. 1999;340:77-84
JNCI. 2001;93:1033-7
JCO. 2004;22:1052-62

Surveillance for Ovarian Cancer

- CA-125
- Pelvic exams
- Transvaginal ultrasound
- Every 6-12 months starting at age 25-35 depending on the family history

J Clin Oncol. 2005 Mar 10; 23(8): 1656-63

Ovarian cancer screening in *BRCA* mutation carriers

- Studies have not demonstrated that ovarian cancer screening is effective in women with *BRCA* mutations

Study	High risk women	Number of screening events	Number of positive screening tests	Cancers detected
Oei et al. (2006)	512	4143	378	2 (1 during BSO)
Olivier et al. (2006)	312	2319	130	9 (5 during BSO)

- Ovarian cancers detected with screening are typically later stage, and there is a high rate of false positives
- Research continues in an effort to develop improved methods of early detection and screening for ovarian cancer

Br J Cancer. 2006;94(6):814-9.
Gynecol Oncol. 2006;100(1):20-6.

Chemoprevention of Ovarian Cancer

Oral Contraceptives

- Up to 50% risk reduction for ovarian cancer for oral contraceptives taken over a period of 5 years.
- Current literature supports there is no evidence that current low-dose oral contraceptive formulations increase the risk of early onset breast cancer for mutation positive individuals
- Oral Contraceptives would be most appropriate for a woman without cancer at an early age (20-30s)

NEJM. 2001;345:255-60
JNCI. 2002;94:1773-9
Cancer Epidemiol Biomarkers Prev. 2003;12(4):520-3

Risk Reducing Salpingo-Oophorectomy

Recommend bilateral salpingo-oophorectomy (BSO) at age 35 or after childbearing is complete

- 96% ovarian cancer risk reduction in *BRCA* carriers
- Can reduce breast cancer risk in premenopausal women up to 50%

NEJM. 2002;346:1609-15

BSO vs TAH/BSO

- Prophylactic oophorectomy surgical options
 - BSO w/combined estrogen/progesterone replacement
 - BSO w/short term estrogen replacement
 - TAH-BSO with unopposed estrogen
 - BSO +/- TAH without HRT
- Optimal combination is controversial
 - Unopposed estrogen – increases uterine cancer risk
 - Estrogen/progesterone – possible increase breast cancer risk
 - Tamoxifen – decreases the risk of breast cancer, but increases the risk of uterine cancer
 - Excess fallopian tube carcinoma risk – consideration of TAH
 - Possible increase risk of uterine cancer – consideration of TAH
 - TAH has an added recovery time

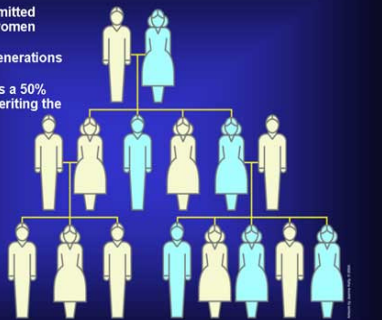
J Natl Compr Canc Netw. 2006;4(2):177-82.

Genetic Risk Assessment

- Personal history
- Family history
- Discuss features of the hereditary cancer syndrome, genetic testing process, medical management options, potential impact on family and provide an estimation of risk.
- Provide informed consent for genetic testing
- Determine insurance authorization for genetic testing

Autosomal Dominant Inheritance

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



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Insurance Coverage of Genetic Testing

- All major carriers provide coverage for genetic testing
- Established guidelines
 - Medicare
 - Most major carriers

Genetic Discrimination

- Federal and state laws prohibit genetic discrimination for patients in group health insurance plans
 - Federal HIPAA legislation
 - The majority of states have additional laws
- Pending Federal legislation that would eliminate distinction between patients in group and individual policies
- No documented cases of genetic discrimination

Prevalence of *BRCA* Mutations

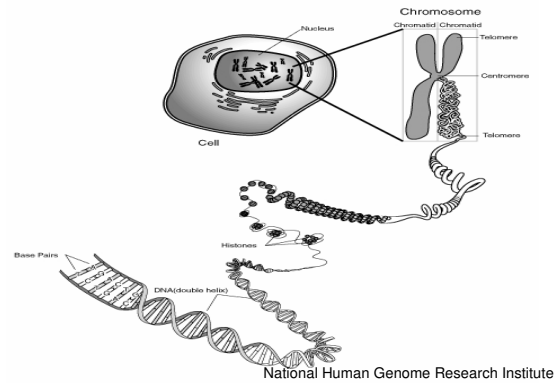
Patient's History	Family History		
	No breast cancer <50 or ovarian cancer	Breast cancer <50, no ovarian cancer	Ovarian cancer in one relative, no breast cancer <50
No breast or ovarian cancer	3.1%	4.2%	5.0%
Breast cancer <50	6.9%	16.3%	17.6%
Ovarian cancer, no breast cancer	9.0%	22.9%	19.5%

www.myriadtests.com/brcacalculator

BRCA1 & BRCA2 Genetic Testing

- Comprehensive BRCA Analysis
 - Full sequence and large rearrangement analysis of *BRCA1* and *BRCA2* genes
- Single Site testing
- Multisite 3 Analysis
 - Ashkenazi Jewish descent

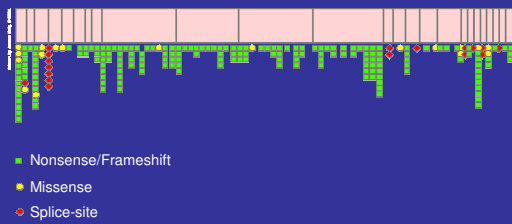
GENETIC TESTING FOR *BRCA1* & *BRCA2*



Mutations in Cancer Susceptibility Genes: *BRCA1*

On chromosome 17
Autosomal dominant transmission

Protein has role in genomic stability
~500 different mutations reported



National Cancer Institute

Mutations in Cancer Susceptibility Genes: *BRCA2*

On chromosome 13
Autosomal dominant transmission

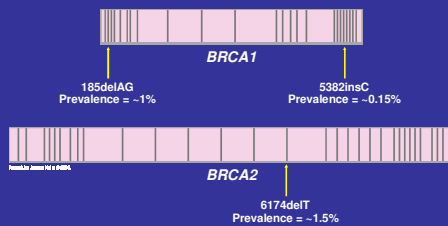
Protein has role in genomic stability
~300 different mutations reported



National Cancer Institute

Example: Founder Effect in Ashkenazi Jewish Population

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



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Interpreting Test Results

- Positive for a deleterious mutation
- No mutation detected
 - Mutation previously identified in the family
 - No known mutation in the family
- Genetic Variant of Uncertain Significance

Case Study

- 40-year-old woman of Ashkenazi Jewish with invasive ductal carcinoma. ER/PR + Her2 -
- S/P Neoadjuvent chemotherapy and lumpectomy right breast.
- Family history: Mother diagnosed with breast cancer at age 42, now deceased.
- Patient has two sisters, a brother and a 12 year old daughter.
- How would knowing her BRCA mutation status change her medical management?

Positive vs. Negative Result

	Positive BRCA1/2	Negative BRCA1/2
Patient 2 nd breast ca	•27% within 5 years	•0.5-1% per year
Patient ovarian cancer	10-fold increase over general population	Not significantly increased
Management considerations	BSO; bilateral mastectomy; use of MRI if breast conserved	Breast conserving surgery. Consider mammogram for relatives at younger age
Relatives' risk	High – breast and ovarian cancer, offer genetic testing	Moderately increased for breast cancer only

Prevalence of Mutations in the Ashkenazi Jewish Population

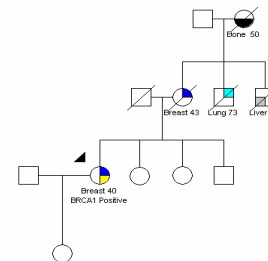
Patient's History	Family History		
	No breast cancer <50 or ovarian cancer	Breast cancer <50, no ovarian cancer	Ovarian cancer in one relative, no breast cancer <50
No breast or ovarian cancer	6.6%	20.8%	15.3%
Breast cancer <50	12.2%	39.5%	39.6%
Ovarian cancer, no breast cancer	23.1%	69.2%	42.7%

www.myriadtests.com/brcacalculator

Ashkenazi family

9/26/2006

■ BRCA1 Test Results = 1
 ■ Cancer History/Cancer Diagnosis = Lung
 ■ Cancer History/Cancer Diagnosis = Bone
■ Cancer History/Cancer Diagnosis = Breast
 ■ Cancer History/Cancer Diagnosis = Liver



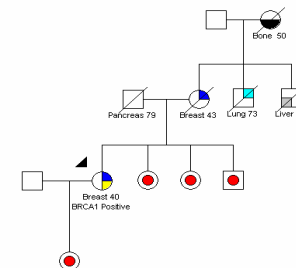
Management Considerations

- Bilateral Mastectomy vs. breast surveillance
- BSO vs. TAH + BSO vs. ovarian surveillance
- Single Site testing for family members

BRCA1 Family2

9/26/2006

■ BRCA1 Test Results = 1
 ● Appropriate for BRCA testing = yes
 ■ Cancer History/Cancer Diagnosis = Liver
■ Cancer History/Cancer Diagnosis = Breast
 ■ Cancer History/Cancer Diagnosis = Lung
 ■ Cancer History/Cancer Diagnosis = Bone



Societal Standards and Guidelines

- ACCC- Association of Community Cancer Centers
- AMA- American Medical Association
- ASBS- American Society of Breast Surgeons
- ASCO- American Society of Clinical Oncology
- NCCN- National Comprehensive Cancer Network
- ONS- Oncology Nurses Society
- SGO- Society of Gynecologic Oncologists
- SSO- Society of Surgical Oncology
- USPSTF- U.S. Preventive Services Task Force

Impact of Hereditary Breast and Ovarian Cancer in Your Practice

- Mutations in *BRCA* dramatically increase the risk for breast and ovarian cancer
- Specific medical management options are available to reduce cancer risks
- Who are the patients in your practice setting appropriate for counseling and testing?
- How can you help patients gain access to Hereditary Cancer Assessment services?

