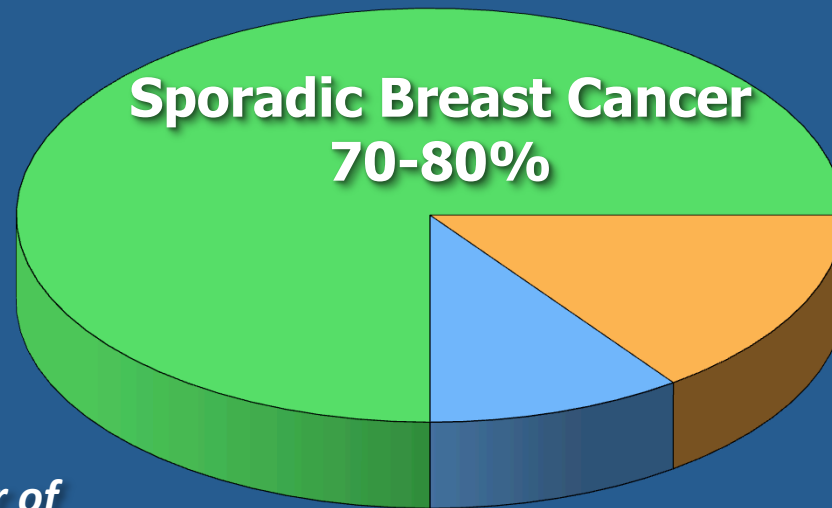


Evaluation and Management of Hereditary Breast Cancer

Kern Medical Center

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How much of breast cancer is hereditary?



Familial: 15% - 20%
(Interaction between lower penetrance genes and environment)

Hereditary: Number of recognized genes/syndromes:

- BRCA1/BRCA2
- Li Fraumeni (p53)
- Cowden (PTEN)
- Peutz-Jeghers (LKB1/STK11)
- Ataxia Telangiectasia (ATM)
- Diffuse hereditary gastric syndrome (CDH1/E-cadherin)

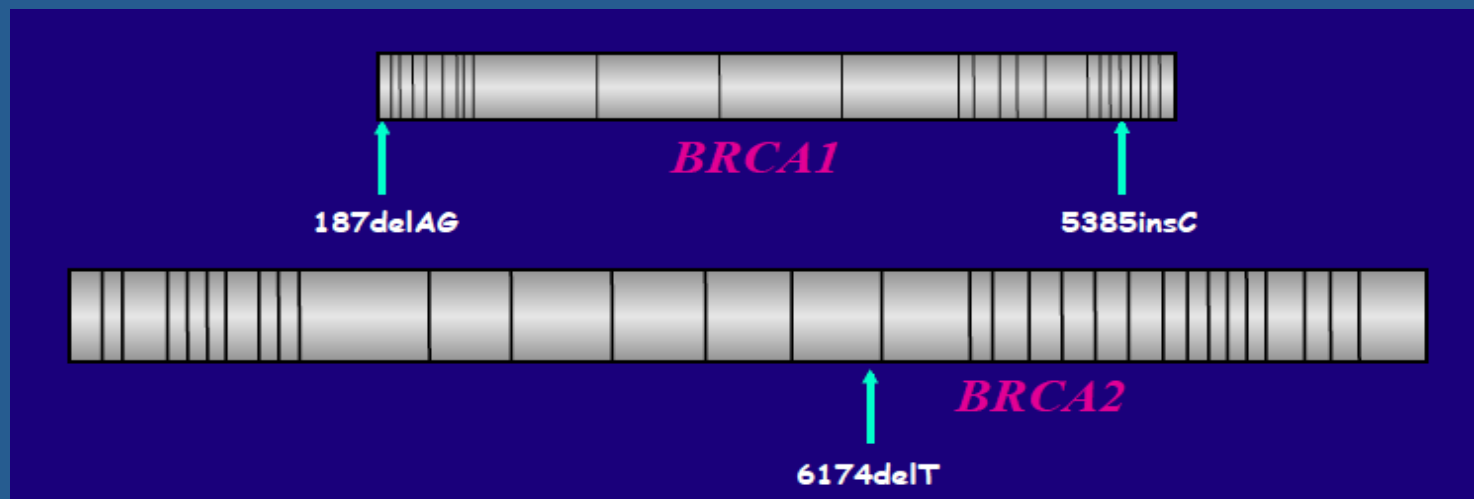
Hereditary: 5% - 10%

- Sporadic
- Family clusters
- Hereditary

Ovarian Cancers:
11% - 15%
BRCA1/2-related

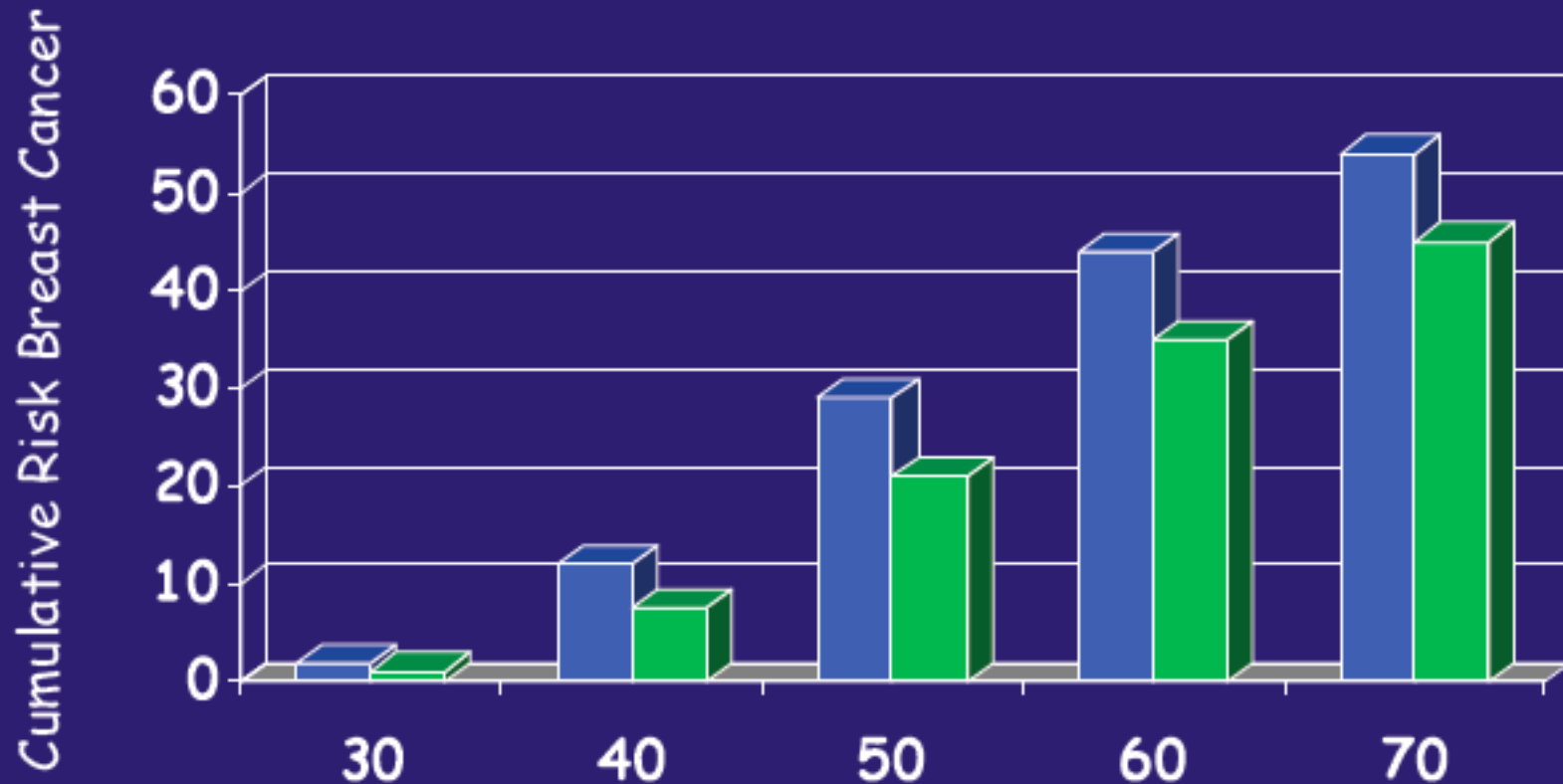
BRCA1* and *BRCA2

- Tumor suppressor genes on chr 17 and 13
- First identified in mid 1990's
- Autosomal dominant transmission
- Encode proteins which play key role in genomic stability
- Over 1,000 mutations distributed over each gene – most individually rare



Cancer Risk in BRCA1/2 Carriers

Cumulative Risk By Decade of Age



*Lifetime 60-80%
(vs. 13% Sporadic)*

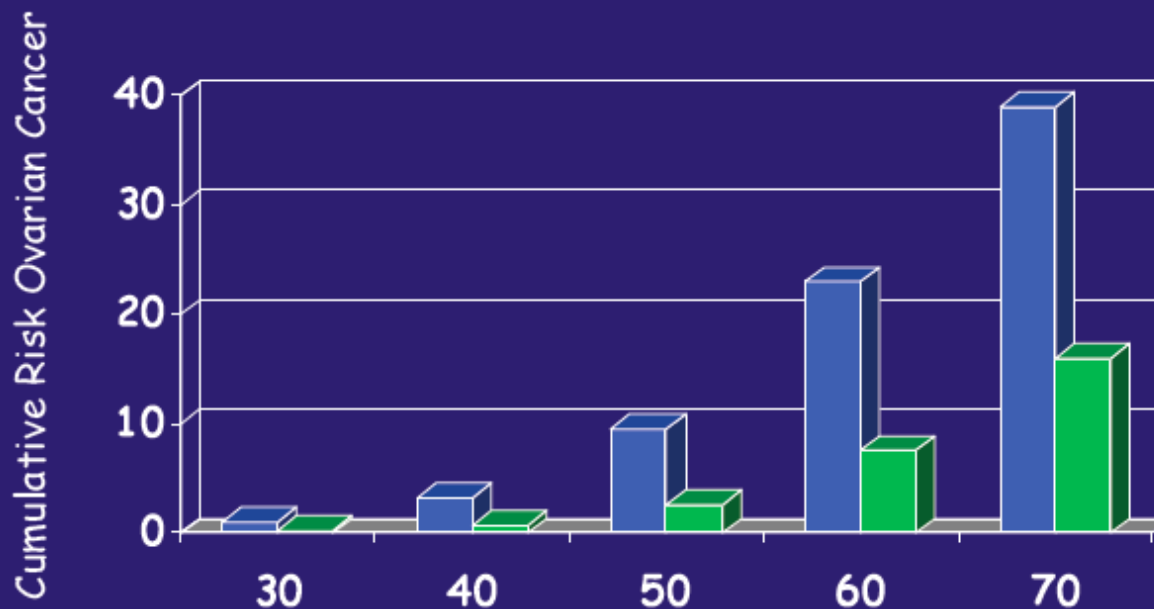
■ BRCA1 ■ BRCA2

Ov. Cancer Risk in BRCA1/2 Carriers

Cumulative Risk By Decade of Age

Cancer risks in BRCA1/2 carriers

Cumulative Risk Ovarian Cancer



Lifetime 20-50%
(vs. 1.4% Sporadic)

■ BRCA1 ■ BRCA2

Which of These Is An Indication for Genetic Counseling/Testing?

- Breast Cancer in mother and daughter
- Two sisters with breast cancer
- Breast cancer in a 45 year old
- Breast cancer and melanoma in same individual

Genetics Counseling & Testing

The Clues



- Cancer in multiple generations
- ≥2 people with cancer in 1 generation
- Earlier than average age of diagnosis (<50 y.o.)
- Individual >1 than one diagnosis of cancer
- Male Breast Cancer
- Cancers that run together
 - Example - Breast and ovarian, male breast cancer

Risk Assessment Tools

Risk of A Mutation	Lifetime Risk of Breast Cancer
BRCAPRO (breast, ovarian, colorectal, endometrial, pancreatic)	BRCAPRO
Tyrer-Cuzick	Tyrer-Cuzick
BOADICEA <i>(Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm)</i>	BOADICEA
Myriad	
	Claus and Gail Models (but underestimate risk in mutation carriers)

Myriad Risk Tables

Estimates Prevalence of BRCA1/2 Mutation

1. The Prevalence of Deleterious Mutations in BRCA1 and BRCA2 (Excludes Individuals of Ashkenazi Ancestry)

	Family History (Includes at least one first or second degree relative)					
Patient's History	No breast cancer <50, or ovarian cancer, in any relative. [†]	Breast cancer <50 in one relative; no ovarian cancer in any relative.	Breast cancer <50 in more than one relative; no ovarian cancer in any relative.	Ovarian cancer at any age in one relative; no breast cancer <50 in any relative.	Ovarian cancer in more than one relative; no breast cancer <50 in any relative.	Breast cancer <50 and ovarian cancer at any age. ^{††}
No breast cancer or ovarian cancer at any age	2.8%	4.5%	8.7%	5.6%	9.6%	12.2%
Breast cancer ≥ 50	2.9%	5.3%	11.4%	6.4%	12.2%	15.9%
Breast cancer <50	6.8%	15.8 %	30.1%	16.9%	27.3%	39.2%
Male breast cancer	12.8%	21.8%	41.9%	20.0%	40.0%*	61.9%
Ovarian cancer at any age, no breast cancer	8.8%	23.1%	42.3%	21.1%	33.2%	46.5%
Breast cancer ≥50 and ovarian cancer at any age	17.6%	26.1%	46.2%	30.3%	46.2%	60.0%
Breast cancer <50 and ovarian cancer at any age	39.1%	53.9%	67.2%	66.0%	70.8%	79.0%

Myriad Risk Tables

Estimates Prevalence of BRCA1/2 Mutation

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Breast cancer ≥ 50	2.9%	5.3%	11.4%	6.4%	12.2%	15.9%
Breast cancer <50	6.8%	15.8 %	30.1%	16.9%	27.3%	39.2%
Male breast cancer	12.8%	21.8%	41.9%	20.0%	40.0%*	61.9%
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Limitations of Models

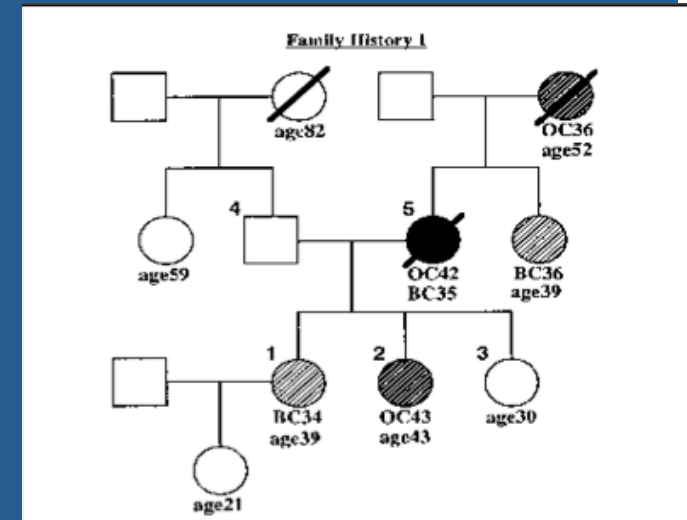
- Models underestimate risk if have few at-risk female relative. (e.g., small family or few females)
- Lack of inclusion of other associated cancers (e.g., melanoma)
- Models often do not include data on more distant relatives (e.g., Gail)

Where to Find The Models

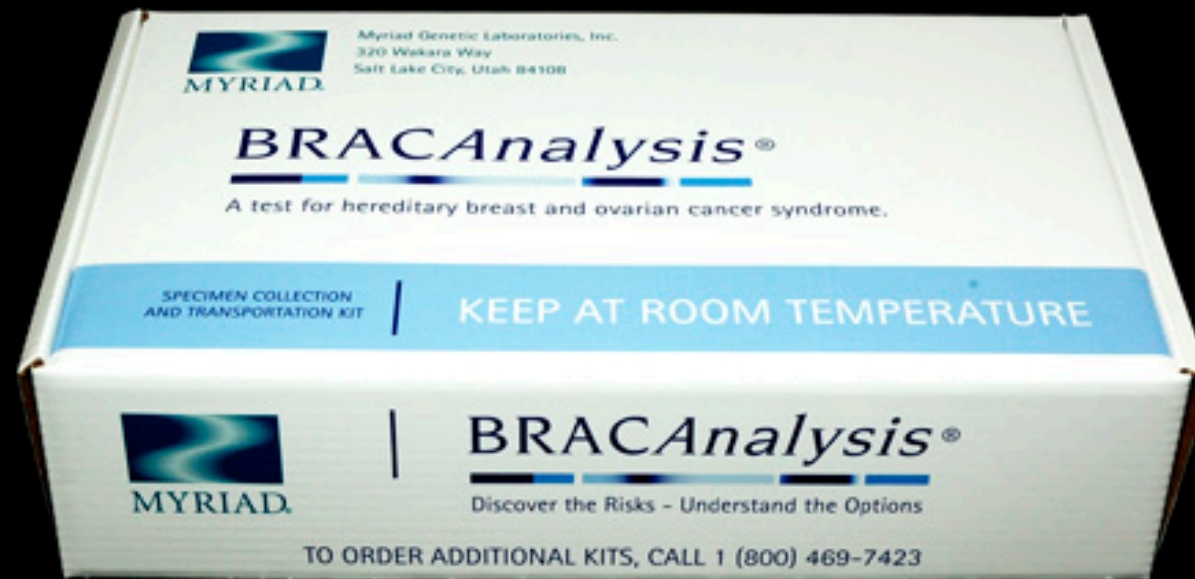
- BRCAPRO Version 4.3:
<http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp>
- Claus model (BreastCa for Palm, version 1.0, copyright 2001):
<http://www.palmgear.com/index.cfm?fuseaction=software.showsoftware&prodID=29820>
- Tyrer-Cuzick (IBIS Breast Cancer Risk Evaluation Tool, RiskFileCalc version 1.0, copyright 2004) Available by contacting IBIS: ibis@cancer.org.uk
- **BOADICEA:** http://www.srl.cam.ac.uk/genepi/boadicea/boadicea_intro.html
- Gail: www.cancer.gov/bcrisktool

Genetic Counseling

- Review family tree (pedigree)
- Assess personal risk of BC
- Assess risk of hereditary of BC
- Determine need for testing
- Initiate testing
- Pre- and post-test counseling



BRACAnalysis®



Blood Draw or Oral Rinse

CONFIDENTIAL

Comprehensive BRCAAnalysis®
BRCA1 and BRCA2 Analysis Result

PHYSICIAN	SPECIMEN	PATIENT
John Smith, MD Comprehensive Medical Center 1100 Grand Ave Away, GA 12345	Specimen: Blood Draw date: Aug 01, 2010 Accession date: Aug 02, 2010 Report Date: Jun 22, 2011	Name: Doe, Jane Date of Birth: April 1, 1492 Patient ID: 000000 Gender: Female Accession #: 00000000-BLD Requisition #: 000000

Test Results and Interpretation

POSITIVE FOR A DELETERIOUS MUTATION

<u>Test Performed:</u>	<u>Result:</u>	<u>Interpretation:</u>
BRCA1 sequencing 5-site rearrangement panel	No Mutation Detected No Mutation Detected	No Mutation Detected No Mutation Detected
BRCA2 sequencing	S1970X (6137C>A)	Deleterious

It is our understanding that this patient was identified for testing due to a personal or family history suggestive of hereditary breast and ovarian cancer. Analysis consists of sequencing of all translated exons and immediately adjacent intronic regions of the BRCA1 and BRCA2 genes and a test for five specific BRCA1 rearrangements. There are additional large genomic rearrangements in BRCA1 and in BRCA2, which are not detected by this test, but can be identified with the BRCAAnalysis Rearrangement Test (BART). The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information becomes available.

The results of this analysis are consistent with the germline BRCA2 mutation S1970X, resulting in premature truncation of the

Levels of Testing

- BRCA Analysis Full Sequence Testing (\$3,400)-
 - 90% Detection Rate
 - Testing for Known Family Mutation (only \$450)-Fully informative
 - Ashkenazi (3 common founder mutations)-(only \$550)-97% Detection Rate
- BART-BRCA Analysis® Rearrangement Test (BART),
 - detects rare, large cancer-associated rearrangements of the DNA in the BRCA1 and BRCA2 genes (2-3% additional detection)
 - Performed routinely only when certain criteria are met
 - Otherwise, \$700 if ordered otherwise
 - Performed if "no mutation detected" but strongly suspicious
 - Or if results show "genetic variant of uncertain significance" or "genetic variant, favor polymorphism"

Genetic Testing Standard Practices

- Test youngest at-risk individual or Youngest person with breast cancer
- Test Living Cancer Survivor First,
 - If proven BRCA1/2+, Test relatives only for specific mutation
 - If BRCA1/2-, may still consider testing, or add BART
- If no living/accessible cancer Survivor
 - Full Sequence or Ashkenazi

Possible outcomes of BRCA1/ BRCA2 testing

■ Definitive

- True positive: deleterious mutation identified**
- True negative: no mutation identified in an individual from a family with a known deleterious mutation**

■ Uninformative

- True “Negative”: No mutation identified after full sequencing in a family in which no mutation has been identified**
- “False Positive” Mutation of uncertain significance**

Management Options For Mutation Carriers

Management Options

- Screening Measures to facilitate early detection

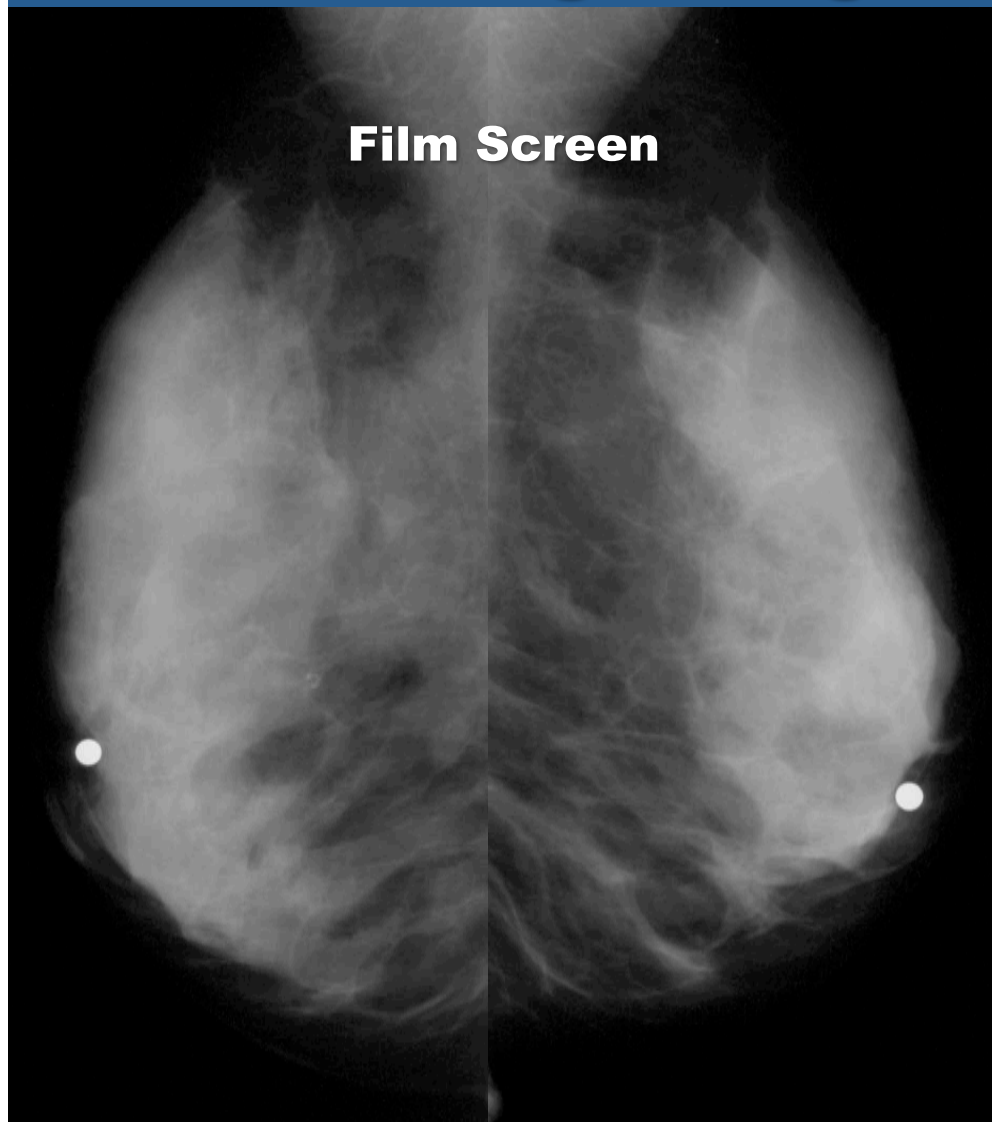
And/Or

- Prevention Measures to reduce risk & incidence

Breast Cancer Screening for Mutation Carriers

- **Monthly BSE beginning at age 18**
- **Clinician exam q6mos beginning age 25**
- **Mammogram and MRI annually beginning age 25, or individualized based on earliest age of onset in family**
 - **For MRI need high quality study with dedicated breast coil, experienced radiologist, ability to perform MRI guided biopsy.**
 - **To minimized false positive MRI, perform MRI on day 1-15 of menstrual cycle**
 - **Optimal imaging interval not yet defined (e.g., alternate @ 6 months)**

Analog vs Digital Mammography



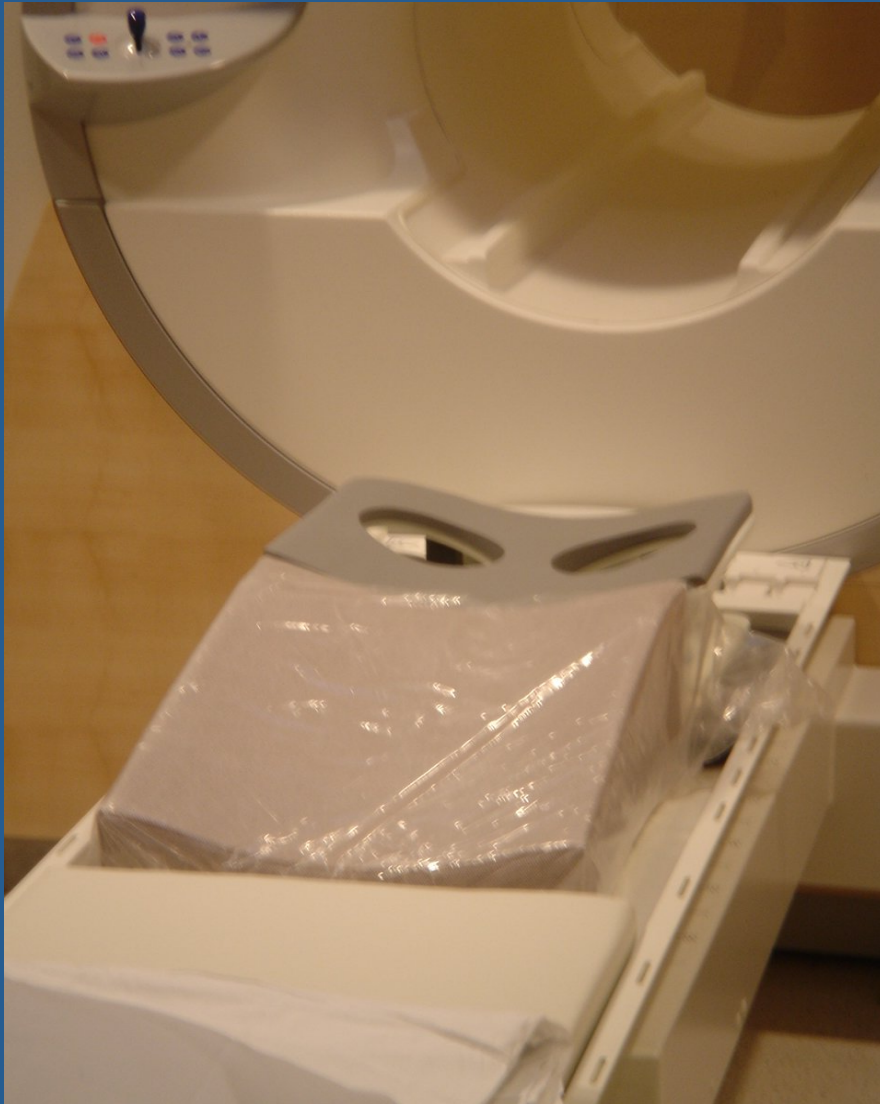
Digital Mammographic Imaging Screening Trial (D-MIST) 2005

Digital Mammographic Imaging Screening Trial (2005)

- Digital Mammography more sensitive
 - In pre – and peri menopausal women
 - Women with mammographically dense breasts (any age)
- Equal sensitivity
 - Post-menopausal women
 - Women with fatty breasts
- Applies to general population

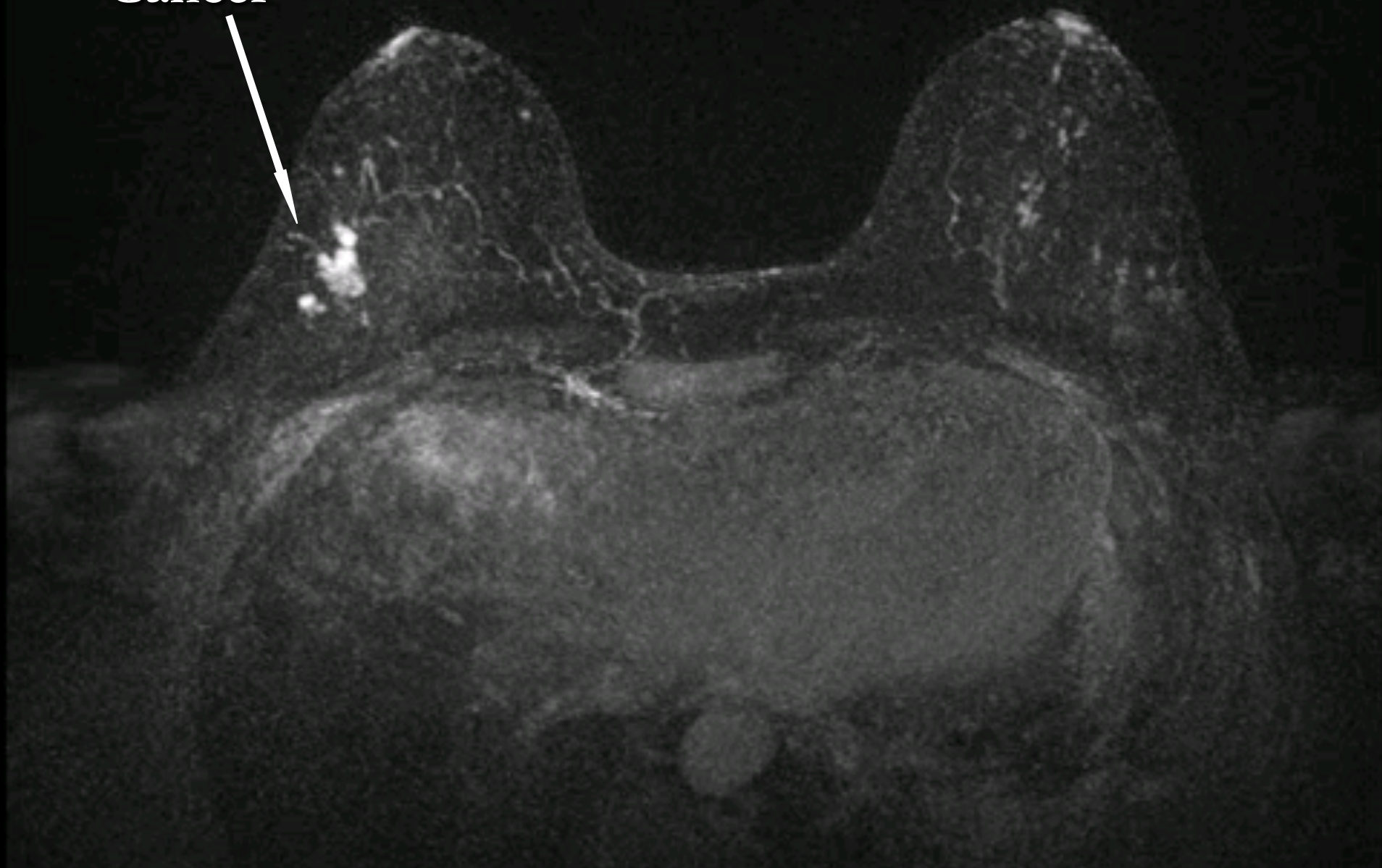
Pisano ED. N Engl J Med 2005; 353:1773-1783

Breast Magnetic Resonance Imaging



Contrast Enhanced Breast MRI using Gadolinium

Cancer



American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography

Debbie Saslow, PhD; Carla Boetes, MD, PhD; Wylie Burke, MD, PhD; Steven Harms, MD; Martin O. Leach, PhD; Constance D. Lehman, MD, PhD; Elizabeth Morris, MD; Etta Pisano, MD; Mitchell Schnall, MD, PhD; Stephen Sener, MD; Robert A. Smith, PhD; Ellen Warner, MD; Martin Yaffe, PhD; Kimberly S. Andrews; Christy A. Russell, MD (for the American Cancer Society Breast Cancer Advisory Group)

Indications for Annual Breast MRI

From American Cancer Society

■ Based on Evidence

- BRCA 1 or BRCA 2 Mutation**
- 1st Degree Relative with BRCA 1 or 2 Mutation**
- Lifetime Risk of Breast Cancer >20%**

■ Based on Expert Opinion

- Radiation to chest between ages 10-30**
- Personal history of hereditary breast cancer (or 1st Degree Relative)**
 - Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome**

Mammo vs MRI Screening

Dutch MRI Screening Study

Rijnsburger A, JCO 2010; pub ahead of print Nov 15, 2010

- 2,157 women screened with CBE q6mos and simultaneous mammo and MRI, Median f/u 4.9 yrs
- Sensitivity of MRI > MMG (77 v 35% p<0.00005) for invasive cancer, but not for DCIS

Risk Group	BRCA1	BRCA2	High Risk 30-50% Risk	Moderate Risk 15-30% Risk
Mammo Sensitivity	25%	62%	46%	47%
MRI Sensitivity	67%	69%	77%67%	67%

**BRCA1 carriers had highest incidence of interval cancers
(32% vs ~6% in other groups)**

Breast Screening

	Sensitivity	Specificity
Mammography	32% (14-59%)	98.5% (91-99%)
MRI	75% (51-100%)	96.1% (75-97%)
MRI + Mammo	84% (60-100%)	95.2% (73-97%)

■ Limitations

- Studies non-randomized
- Each study detected relatively few cancers
- Performed in populations previously screened by mammogram
- No data on impact on mortality

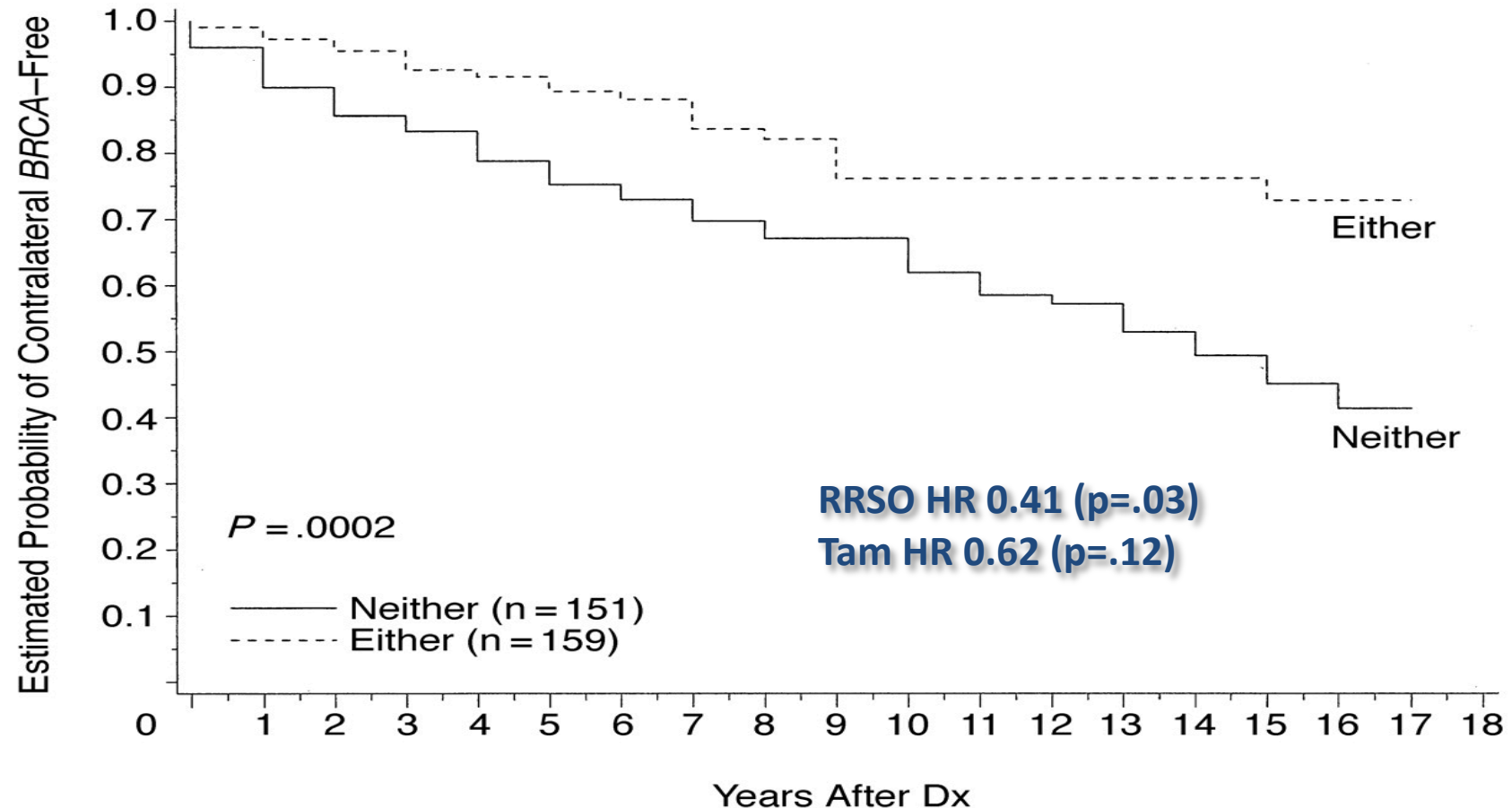
Chemoprevention

- Tamoxifen reduces risk of contralateral breast cancer in BRCA1/2 carriers
- Debate about benefit in BRCA1 carriers given predominance of ER negative disease
- No data on other agents (e.g., Raloxifene)

JAMA 2001;286:2251; Lancet 2000;356:1876; JCO 2004; 22:2328;
JCO 2006;24:2437; Int J Cancer 2006;118: 2281

Risk of CBC in BRCA1/2 Patients

Impact of BSO and Tamoxifen



For women diagnosed < 50 y.o, HR for combination BSO and Tam 0.09

Prophylactic Surgery

ASSOCIATION OF RISK- REDUCING SURGERY IN BRCA1 AND BRCA2 MUTATION CARRIERS WITH CANCER RISK AND MORTALITY

Domchek SM, Friebel TM, Singer CF, et al.
Journal of the American Medical Association
2010;304(9):967-975

Objective

- To estimate risk-reduction and mortality reduction of
 - Prophylactic Mastectomy
 - Prophylactic Oophorectomy
- Stratified by mutation and prior cancer status

Methods

- Prospective, non-randomized, multicenter, cohort study, 22 centers internationally
- 2482 Women with BRCA 1 or BRCA 2
- Ascertained between 1974-2008, following to 2009
- Endpoints: Breast & Ovarian Cancer risk, cancer specific mortality, overall mortality

Prophylactic Mastectomy

- Risk-reducing Mastectomy reduced risk of breast cancer (median F/u 3 yrs)

0% (0/247) BRCA1/2 BPM

Vs

7% (98/1372) in No BPM

Bilateral Salpingo-oophorectomy

(median F/u 6 yrs)

- BSO reduced risk of Ovarian Cancer
 - 7.4% → 1.8 % in BRCA1 (HR 0.31)
 - 3.2% → 0% in BRCA2
- BSO reduced risk of Breast Cancer
 - 20.4% → 13.6 % in BRCA1
 - 23.4 → 7.0% in BRCA2

Risk Reducing Salpingo-Oophorectomy

Mortality Reduction

	No RRSO	RRSO	HR [95% CI]
All cause mortality	10%	3%	0.40 [95% CI, 0.26-0.61]
Breast cancer specific mortality	6%	2%	0.44 [95% CI, 0.26-0.76]
Ovarian cancer specific mortality	3%	0.4%	0.21 [95% CI, 0.06-0.80]

Domchek S et al. JAMA 2010; 304;967

Summary of Study Results

- Among BRCA1 and 2 Mutation Carrier,
 - Risk-reducing mastectomy virtually eliminated risk of breast cancer
 - BSO was associated with lower Ovarian cancer risk and mortality in BRCA1 and BRCA2
 - BSO was associated with lower Breast Cancer incidence and mortality in BRCA1 and BRCA 2 with h/o BC, but did not benefit BRCA1/2 with prior h/o BC (tx effect?)
 - BSO was associated with improved all-cause mortality (better if no prior h/o BC)

Integration of Results

- First time BSO has been shown to provide a mortality benefit; Emphasizes the importance of BRCA testing
- Underscores the value of BPM and BSO in both BRCA 1 and 2 subgroups, particularly in individuals not yet affected by cancer
- Benefits of BC risk reduction less in women who have reached natural menopause or are post-menopausal due to prior breast cancer treatment, but benefits persists for Ovarian cancer risk reduction
- These data do not apply to non-BRCA 1 or 2 Carriers

Satisfaction with CPM

Mayo Clinic - - 10 yr follow-up

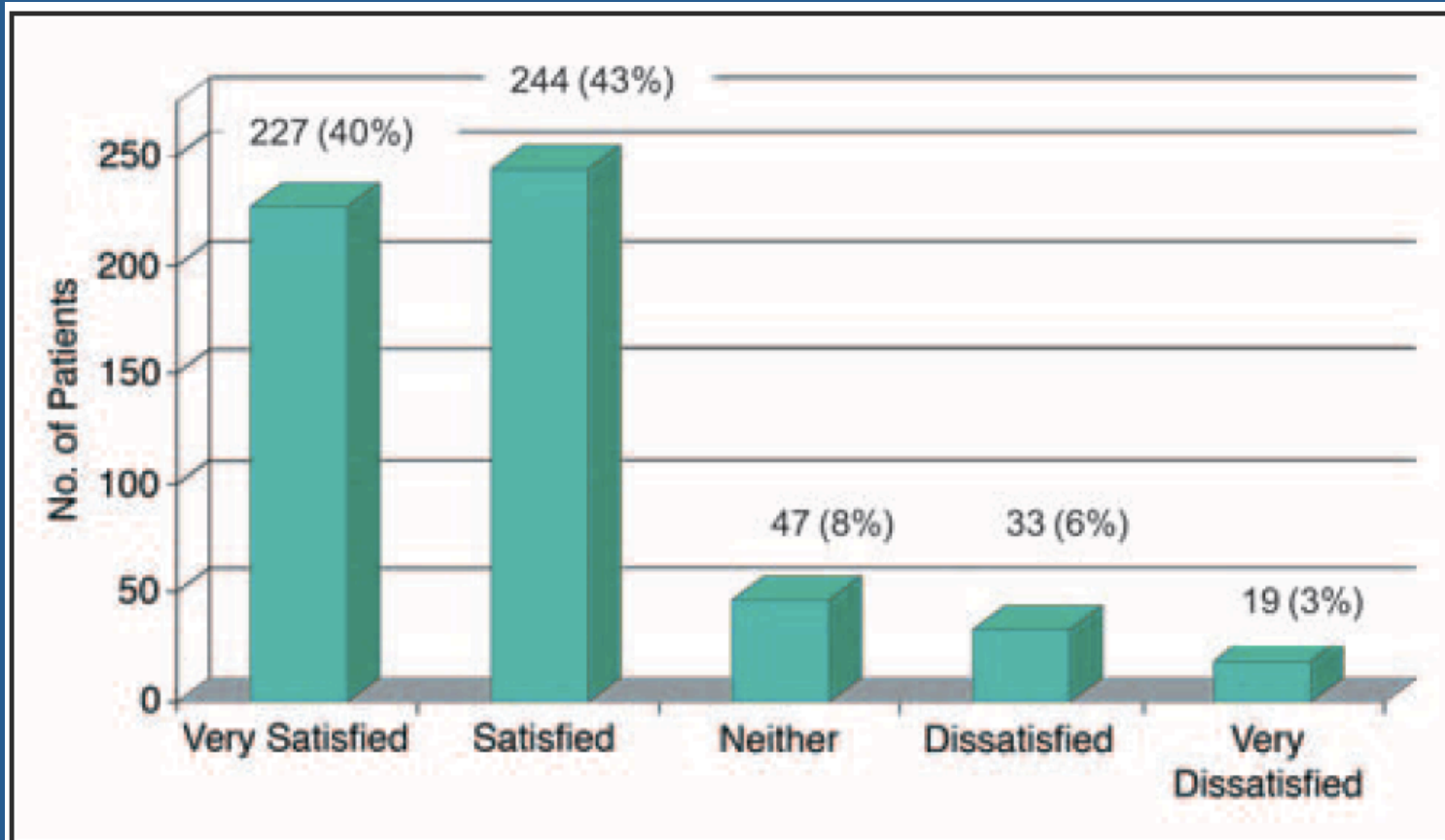


Fig 1. Satisfaction with contralateral prophylactic mastectomy.

Breast Cancer in Mutation Carriers

Local Therapy Issues

- BCT results in good local control
 - Over long term, carriers have increased risk ipsilateral breast cancer
- High rate of contralateral breast Cancer

Pierce JCO 2000; Pierce SABCS 2003;
Robson Cancer 2004; Haffty Lancet 2002;
Metcalf JCO 2004; Seynaeve Eur J Can 2004; Pierce et al. JCO 2006;24:2437

Contralateral Breast Cancer

Cumulative Risk Influenced by Age at Diagnosis

- Slightly higher risk for BRCA1 than BRCA2 carriers
- Annual risk ~ 0.5%/yr in age matched non-carriers

Time since diagnosis	5 yrs	10 yrs	25 yrs
< 40 at diagnosis (n=379)	12%	28%	62%
40-50 at diagnosis (n=338)	8%	12%	45%
> 50 at diagnosis (n=325)	6%	8%	20%

Graeser et al. JCO 2009;27:5887;
Malone et al. JCO 2010;28:2404

Male Breast Cancer/BRCA

Overall Incidence 1%	
BRCA1	BRCA2
~4%	15%
	Lifetime Risk of BC = 6% Life
Associated Cancers	
Prostate (RR 1-3)	Prostate (RR 4.6)
	Pancreas (4-7%; 10% AJ)
	Melanoma (RR 3.2)
	Pancreas (RR 2-8)
	Stomach (RR 2.6)

Screening in Male Carriers

- Annual Prostate Specific Antigen and DRE
- Regular Breast Self Exam
- Annual Skin Exams
- Annual Eye Exam

Management of Mutation Carriers

- Review of surveillance and prevention options
- Strong recommendation for RRSO for women between 35-40 or when have completed childbearing
- Individualized choice about risk reducing mastectomy vs more intensive screening
- Discuss implications for other family members