Breast and Ovarian Cancer: Risk Assessment and Prevention

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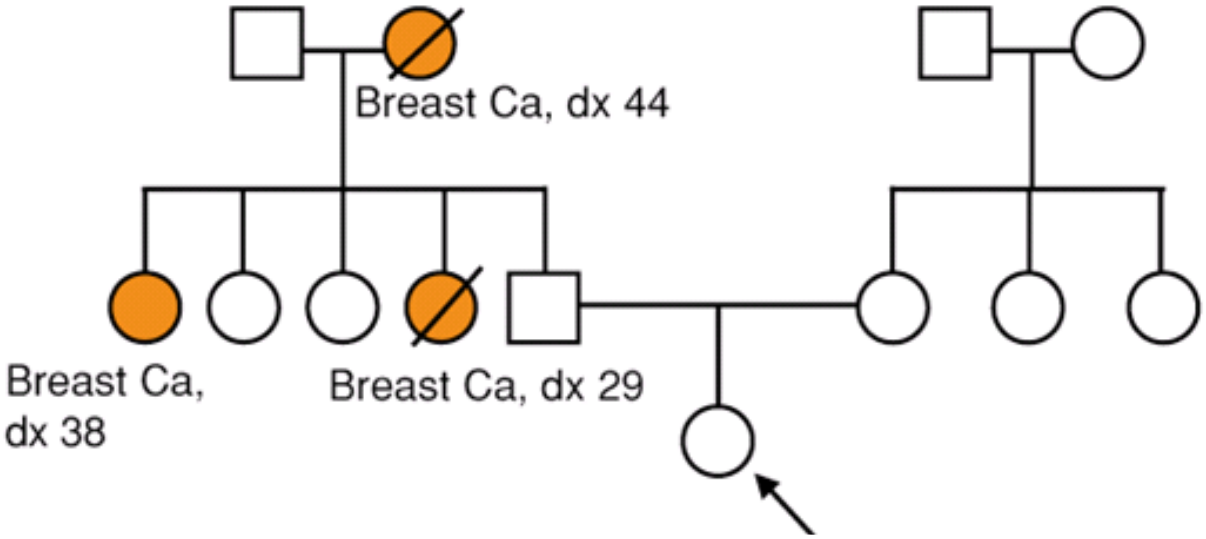
Case 1



Cancer Risk

- **Risk Assessment**
  - **Genetic testing referral ? (BRCA1/2 etc)**
  - If no inherited mutation- use models (e.g., Gail)

- **Risk Management**
  - Screening
  - Prevention medications
  - Prophylactic surgery
  - Lifestyle strategies

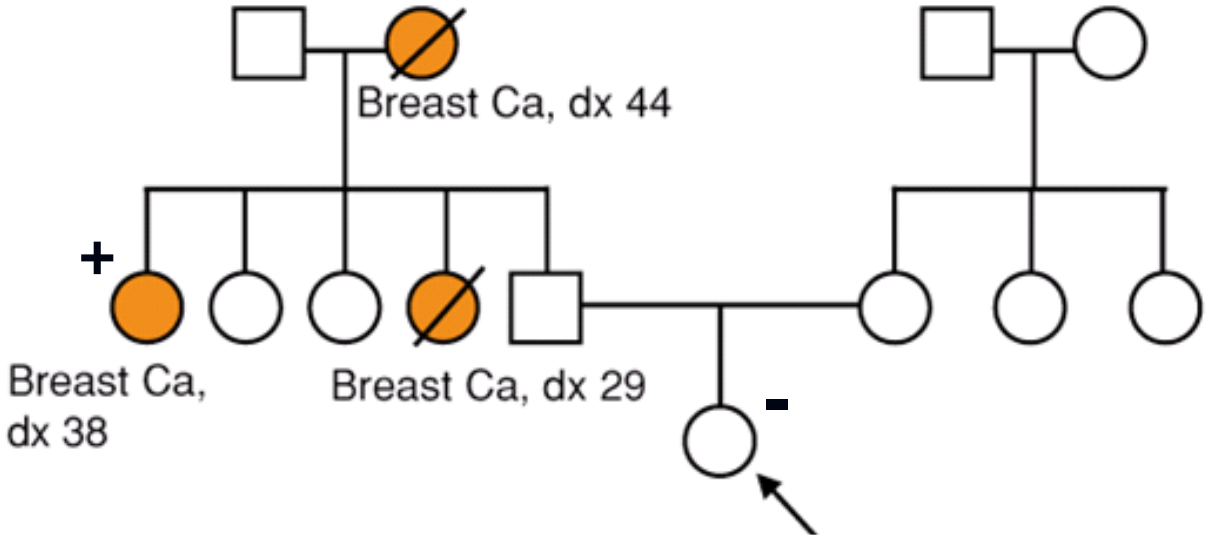
Models to select patients for BRCA1/2 testing

- Based on Family hx
  - NCCN criteria
- Statistical models based on family hx (> 10%?)
  - Ontario Family History Assessment Tool
  - Manchester Scoring System
  - Pedigree Assessment Tool
  - FSH-7

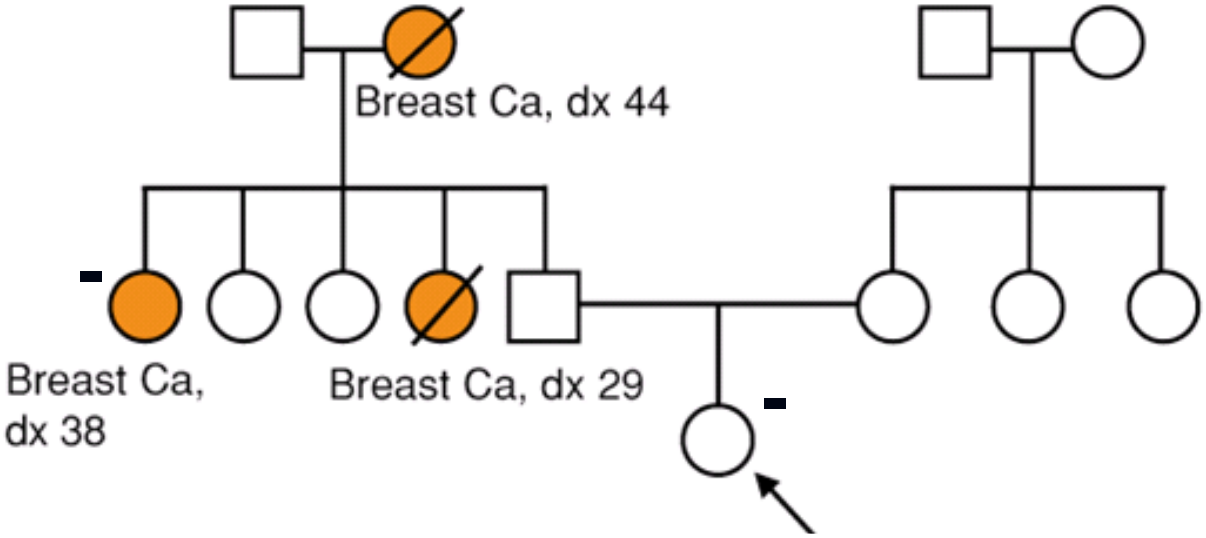
Features that Indicate an Increased Likelihood of *BRCA* mutation

- Ovarian cancer (any age)
- Young breast cancer (≤ 45 years; ≤ 50 if small family)
- Multiple cases of breast cancer in family (≥ 3 or ≥ 2 if one < age 50)
- Two breast cancers in the same woman, first < 50 yrs
- Ashkenazi Jewish heritage
- Male breast cancer
- Triple Negative Breast Cancer ≤ age 60
- Breast Cancer + 2 relatives: Pancreatic Cancer +/or Prostate Cancer (≥ Gleason 7)

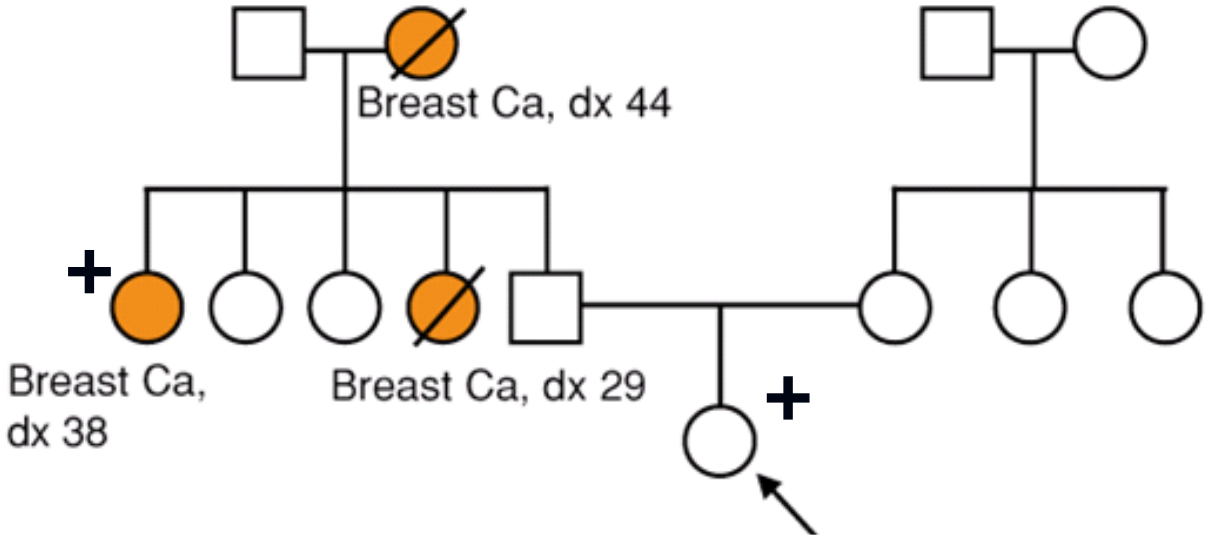
Benefit of negative result: true negative



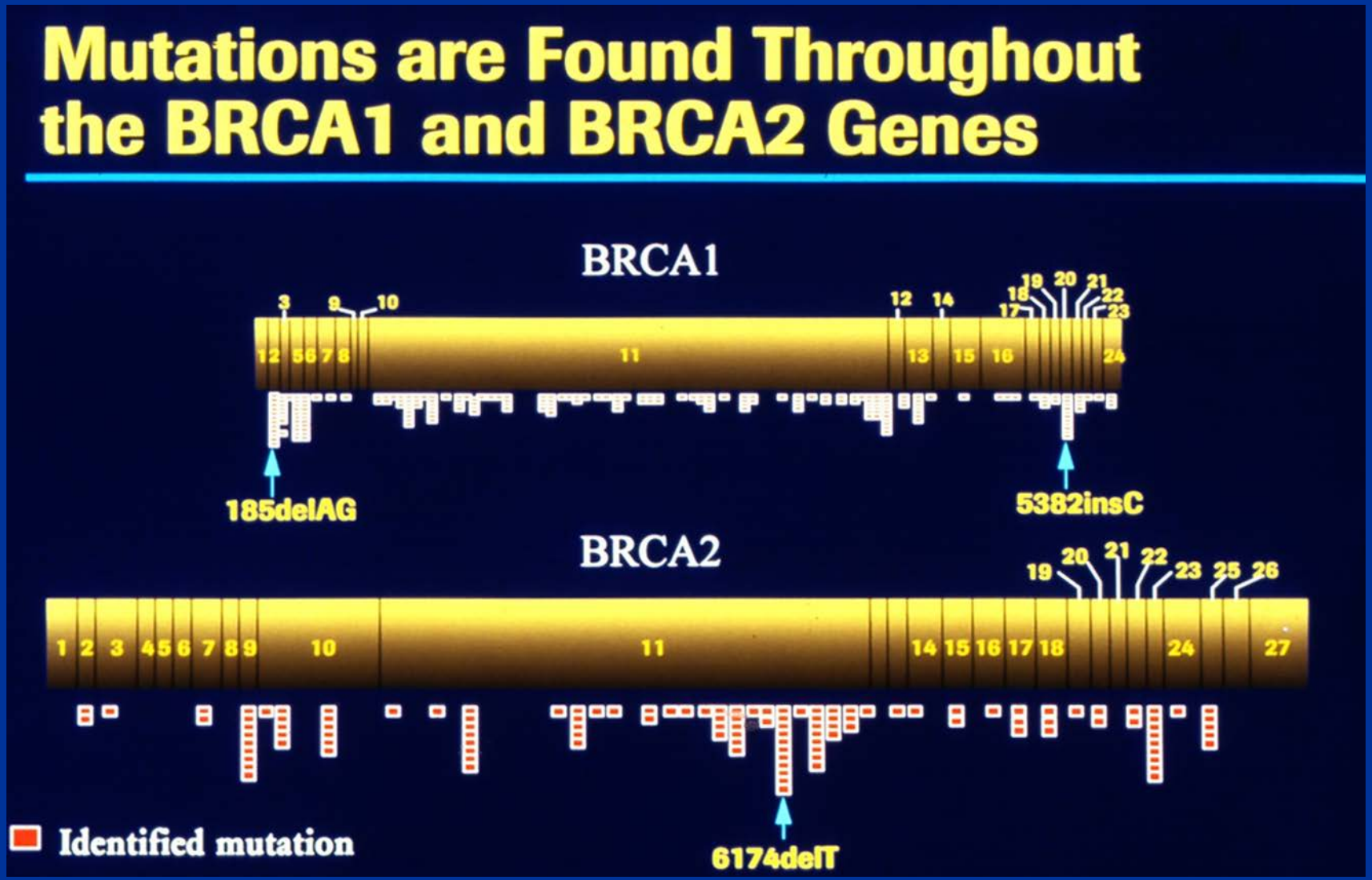
Uninformative negative



Case 1: BRCA1 or BRCA2+

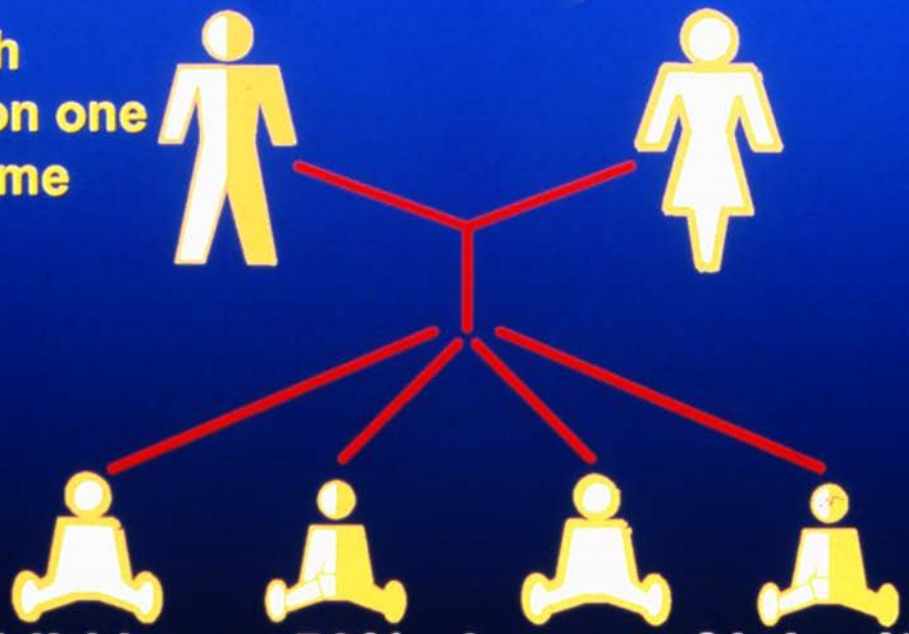


BR (Breast) CA (Cancer) Genes



Autosomal Dominant Inheritance

Father with mutation on one chromosome



Each child has a 50% chance of inheriting an autosomal dominant disorder

BRCA1-2 Mutations Increase the Risk of Early-Onset Breast Cancer

	By age 40	By age 50	By age 70
Population Risk	0.5%	2%	7%
Hereditary Risk	10% - 20%	33% - 50%	56%- 87%

BRCA1-2 Mutations Increase the Risk of Ovarian Cancer

By age 70

Population Risk	**< 2%**
Hereditary Risk	**28% - 59% (*BRCA1*)**
	27% (*BRCA2*)

Management of Breast and Ovarian Cancer Risk in *BRCA* mutation carriers

- Manage ovarian cancer risk
  - Screening- CA-125 and TVS: ineffective; "consider" > age 30
  - Prevention medications: Oral Contraceptives
  - Prophylactic surgery
    - BRCA+ : BSO age 35-40 (improves survival !)
- Manage breast cancer risk
  - Screening- begin age 25; MRI + mammogram (age 30)
  - Prevention medications- (e.g., tamoxifen) after childbearing
  - Prophylactic mastectomies

Risks of Other Cancers: *BRCA1/2*

- Male Breast Cancer *(BRCA2 > BRCA1)*
  - 7-8% by age 70 (< 1% in general population)
- Prostate Cancer *(BRCA2/BRCA1)*
  - 33-39% by age 70 (7% in general population)
- Pancreatic Cancer *(BRCA2 > 1)*
  - 2-8% by age 80 (< 1% in general population)
- Melanoma (*BRCA2/BRCA1*)
  - 5% (ocular as well)

Breast Cancer Linkage Consortium, JNCI 1999, 91:1310;
Thompson, JNCI 2002, 94:1358
Liede, JCO 2004, 22:735

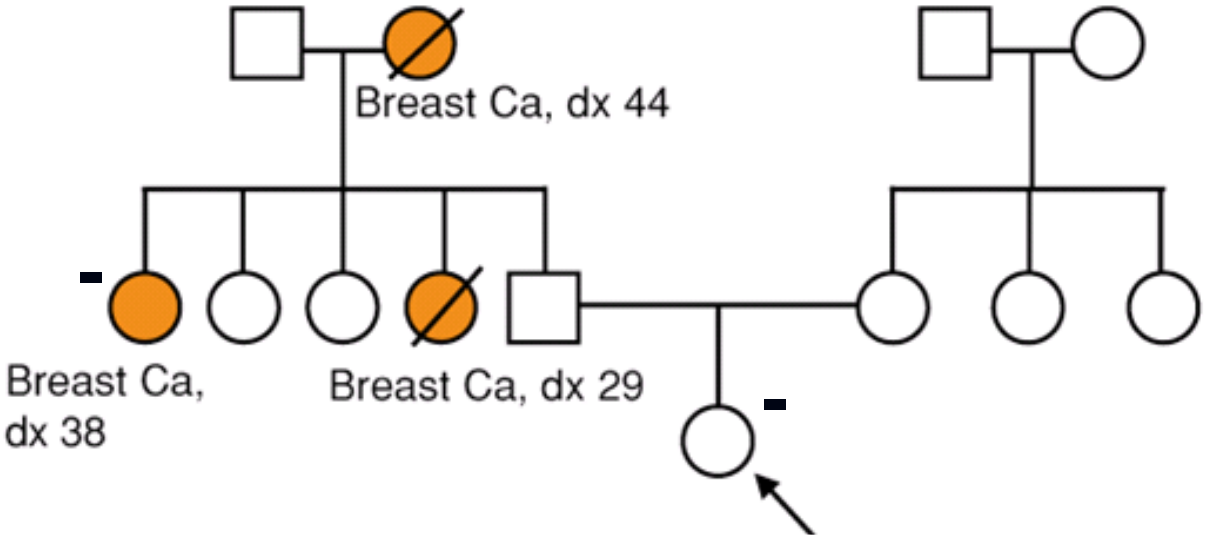
Has patient received the most "up-to-date" BRCA testing?

- ***BRCA* test changes**
  - **2006**: "**BART**" BRACAnalysis®Rearrangement Test
    - Since 2013: routinely included in *BRCA* testing

- **Remember to take family history each year**

Family history changes!!

Case 2: BRCA1/2 negative



Cancer Risk

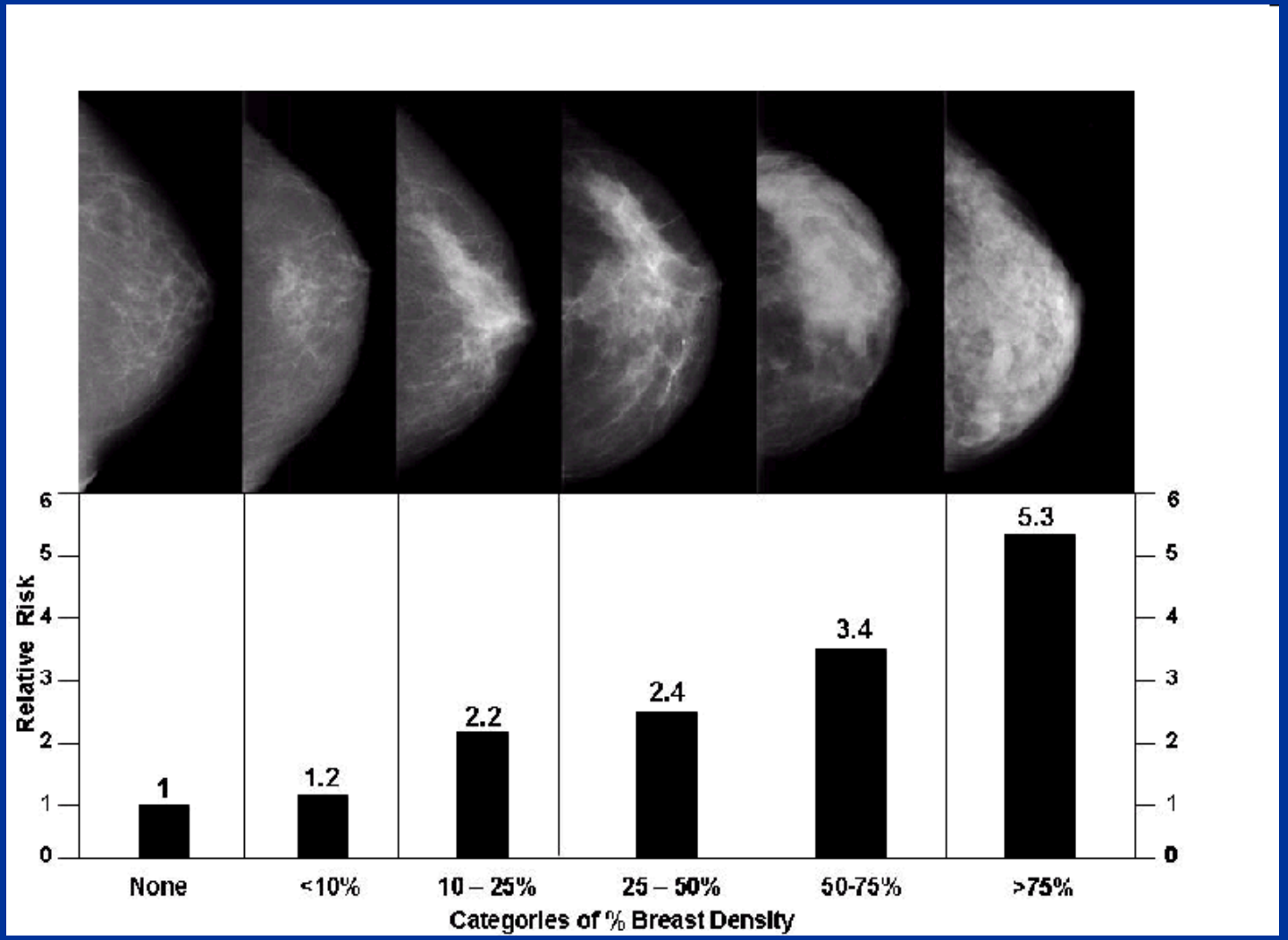
- **Risk Assessment**
  - Genetic testing referral ? (BRCA, etc)
  - **If no inherited mutation- use models (e.g., Gail)**

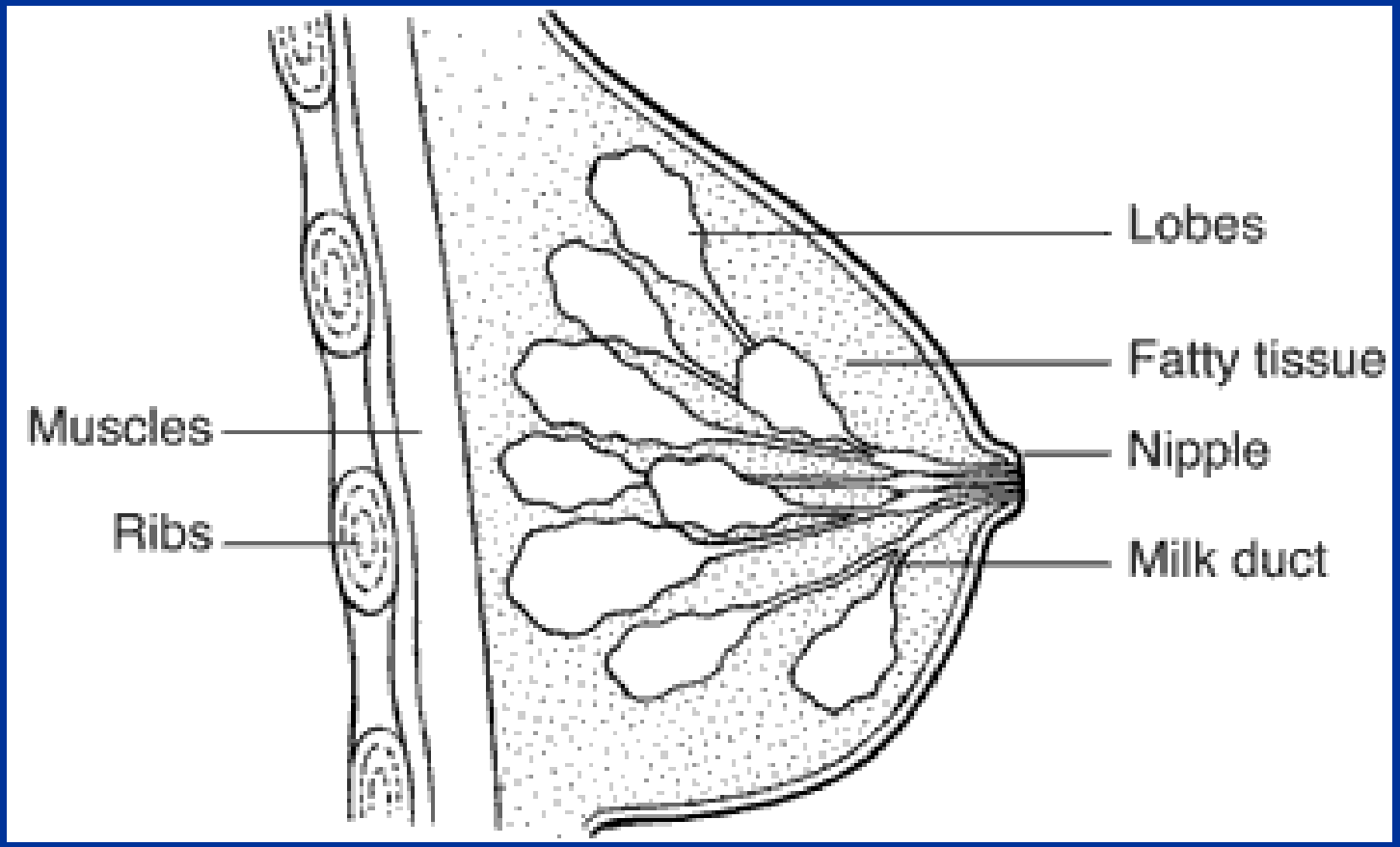
- **Risk Management**
  - Screening
  - Prevention medications
  - Prophylactic surgery
  - Lifestyle strategies

Established Risk Factors for Breast Cancer

Risk Factor	Relative Risk
Age (≥ 50 vs < 50)	6.5
Familial/Hereditary factors	
First degree relative	2 (1.4-13.6)
BRCA mutation	6-14
Reproductive and Hormonal	
Menarche < 12 or menopause ≥ 55	~ 1.5
Nulliparity	2.0
Age of FLB >30	1.3 – 2.2
Hormone replacement therapy (E + P)	1.0-1.5
Benign breast lesions (risk for either breast)	
LCIS	Absolute risk 1-2%/ year
atypical hyperplasia	4.0 - 4.4
Exposure to ionizing radiation (<30 yo)	1.4 (related to age)
Alcohol consumption (12g/d vs none)	1.1 -4.0
Increased body mass index (post-men)	1.3 -2.5

Mammographic Breast Density

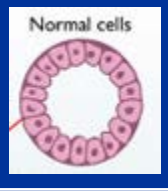



Lobes
Fatty tissue
Muscles
Nipple
Ribs
Milk duct

Risk of Breast Cancer with benign findings on breast biopsy

Lesion	Risk of breast cancer (RR)	Examples
Non-proliferative	none	▪ simple fibroadenoma ▪ fibrocyctic changes
Proliferative Without Atypia	1.5-2.0	▪usual ductal hyperplasia ▪ complex fibroadenoma ▪ Sclerosing adenosis ▪ papilloma ▪ radal scar
Proliferative With Atypia	> 2.0	▪ ADH ▪ ALH

Breast pathology and Risk of Breast Cancer

	Atypical Hyperplasia (AH)	Carcinoma in-situ (CIS)	Invasive Cancer (IC)
Ductal 	ADH 	DCIS 	IDC 
Lobular	ALH	LCIS	ILC

Breast pathology and Risk of Breast Cancer

	Atypical Hyperplasia (AH)	Carcinoma in-situ (CIS)	Invasive Cancer (IC)
Ductal	ADH 4x ↑ risk	DCIS Considered "cancer"	IDC
Lobular	ALH 4x ↑ risk	LCIS ≥ 1.3 % risk invasive cancer/year	ILC

Gail Model
(for woman without strong family hx)

- Calculates 5 yr and lifetime risk (to age 90) of breast cancer based on age, family history, reproductive history, previous breast biopsies (ADH/AHL) etc.

http://bcra.nci.nih.gov/brc/start.htm

Or google: Gail Risk Tool

Gail MH: J Natl Cancer Inst (1989); 81; 24; 1979-1886.

Risk Tool

(Click a question number for a brief explanation, or read all explanations.)

1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) or has she received previous radiation therapy to the chest for treatment of Hodgkin lymphoma? — Select

2. Does the woman have a mutation in either the *BRCA1* or *BRCA2* gene, or a diagnosis of a genetic syndrome that may be associated with elevated risk of breast cancer? — Select

3. What is the woman's age?
This tool only calculates risk for women 35 years of age or older. — Select

4. What was the woman's age at the time of her first menstrual period? — Select

5. What was the woman's age at the time of her first live birth of a child? — Select

6. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer? — Select

7. Has the woman ever had a breast biopsy? — Select

   7a. How many breast biopsies (positive or negative) has the woman had? — Select

   7b. Has the woman had at least one breast biopsy with atypical hyperplasia? — Select

8. What is the woman's race/ethnicity? — Select

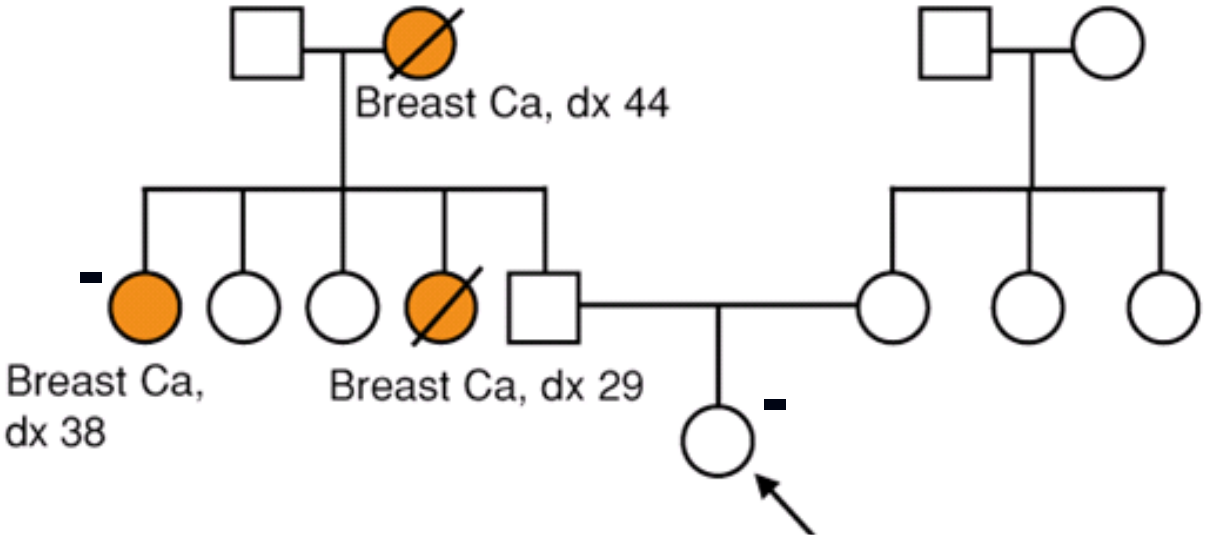
   8a. What is the sub race/ethnicity? — Select

Calculate Risk >

Gail Model Shortcomings (Family history questions)

- No paternal history
- No extended family- does NOT ask about 2nd degree relatives
- Does not ask age of breast cancer in relatives

Case 2: BRCA1/2 negative



Tyrer-Cuzick model (IBIS)

www.ems-trials.org/riskevaluator/

Google: Tyrer-Cuzick V 7.0

In addition to Family history, includes:

BMI (height/weight)

Age at menopause

HRT use

LCIS

NOT in Gail Model

	Gail		Tyrer-Cuzick
Family hx:			
Breast Cancer: FDR	**Yes**		**Yes**
Breast Cancer: SDR	**No**		**Yes**
Age of BC in relatives	**No**		**Yes**
Relative: Bilat BC	**No**		**Yes**
Relative: ovarian ca	**No**		**Yes**

Amir et al. JNCI 2010

What constitutes an increased risk of breast cancer?

- 5 year risk : > 1.66% (by any model)
  - Used as criteria for participation in breast cancer prevention medication trials
- Lifetime risk (by any model):
  - 15-30%: moderate risk
  - > 30%: high risk

Cancer Risk

- **Risk Assessment**
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  - If no inherited mutation- use models (e.g., Gail)

- **Risk Management**
  - **Screening**
  - Prevention medications
  - Prophylactic surgery
  - Lifestyle strategies

Women at high risk of breast cancer: When to start mammograms?

- "5-10 years earlier than the youngest breast cancer in the family"

- No mammograms until > age 30?
  - Lack of sensitivity of mammograms in very young women
  - Radiation exposure in developing breast

J Natl Cancer Inst 2009;101: 205 – 209
JCO 29: 2011 (suppl; abstr 1526)

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

- Lifetime risk of breast cancer > 20-25%

Saslow et al. CA Cancer J Clin 2007; 57:75-89

Breast Cancers detected with and without MRI in High Risk Women

	With MRI	Without MRI
≤ 1 cm	43%	12%
Negative nodes	79%	44%

NEJM 2004; Vol 351:427

MRI vs mammogram :
women at increased risk of breast cancer

	MRI	mammogram
sensitivity	95%	36%
specificity	95% *	99.8%

* **Specificity of MRI extremely operator (radiologist) dependent**

Warner et al. JAMA 2004; 292:1317

Drawbacks of Breast MRI

- Specificity lower than mammography: false positives (unnecessary biopsies)
- More difficult: claustraphobic; injection; longer
- Expensive
- No contrast if renal disease

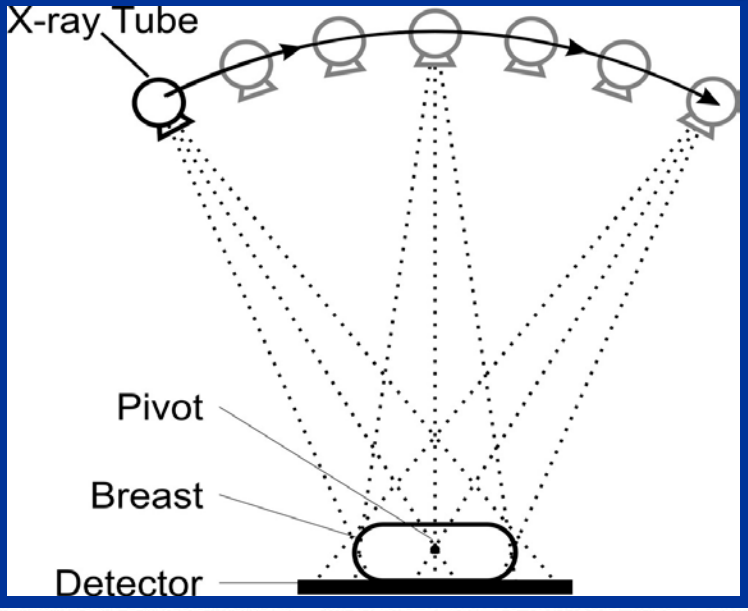
Who should have MRI screening?

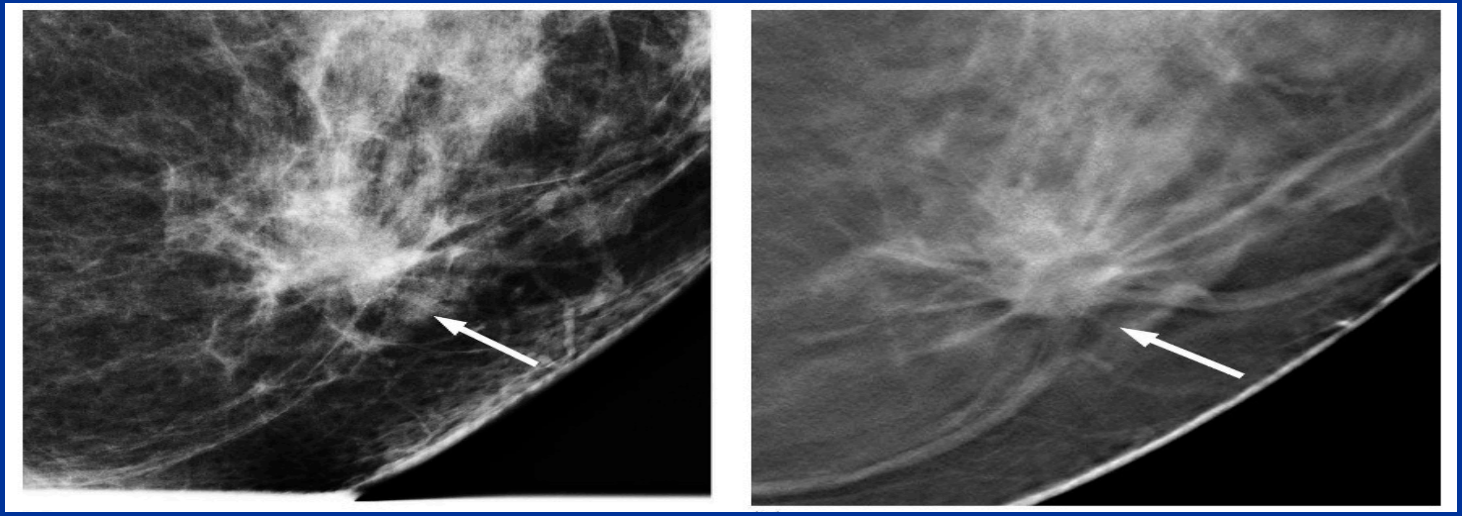
- BRCA+
- Hx of chest radiation (e.g., Hodgkins disease)
- > 20-25 % lifetme risk of breast cancer ?
  - if willing to accept false +
  - Especially if dense breasts on mammogram

MRI and mammogram

- MRI does not replace mammography
- Alternate annual mammogram and MRI every 6 months?

3D mammogram
(digital mammo + tomosynthesis)





Mammography: digital (2D) vs digital + tomosynthesis (3D)

	digital	tomosynthesis	p
	Per 1000 screens		
Breast cancer dx	4.2	5.4	< 0.001
--invasive	2.9	4.1	< 0.001
--DCIS	1.4	1.4	
Call back	107 (11%)	91 (9%)	< 0.001

Friedewald et al. JAMA 2014; 311: 2499-2507

Management of Breast Cancer Risk

- Screening
- Prevention medication
  - tamoxifen
  - raloxifene
  - aromatase inhibitor (e.g., exemestane)
- Preventative (Prophylactic) Surgery
- Lifestyle strategies

ASCO 2013 Guidelines for Breast Cancer Prevention Medicaion Use

- Discuss with women ≥ age 35 with 5 years risk (absolute) ≥ 1.66 (includes LCIS)
- Pre- menopausal: tamoxifen
- Post-menopausal:
  - Tamoxifen- 20 mg/day
  - Raloxifene- 60 mg/day
  - Exemestane- 25 mg/day
- Discuss Benefits vs Risks

Visvanathan et al. JCO 2013; 31: 2942-2962

Tamoxifen	**Raloxifene**	**Exemestane (Anastrazole)**
Pre and post menopausal women	Post menopausal women	Post menopausal women
Decreases breast cancer 49% (NSABP P-1 trial)	Decreases breast cancer: 37% (STAR trial)	Decreases breast cancer 65% (53%) (MAP-3) (IBIS-II)
Endometrial cancer About 1%	No increase	No increase
Blood clots About 1% Same as for HRT or birth control	Less	No increase
Cataracts- increase 20%	Less	No increase
Other side effects		
Hot flashes Vaginal dryness/discharge Menstrual irregularities Decreased libido	No significant difference	No significant difference
Not associated with arthralgias (joint stiffness)	Not associated with arthralgias	**Arthralgias (joint stiffness) and myalgias (muscle stiffness) in many women**
Good for bones	Good for bones	**Associated with bone loss**
Can decrease cholesterol	Can decrease cholesterol	Can increase cholesterol
+/-Weight Gain		Occasional hair thinning

Management of Breast Cancer Risk

- Screening
- Prevention medication
- **Preventative (Prophylactic) Surgery**
- Lifestyle strategies

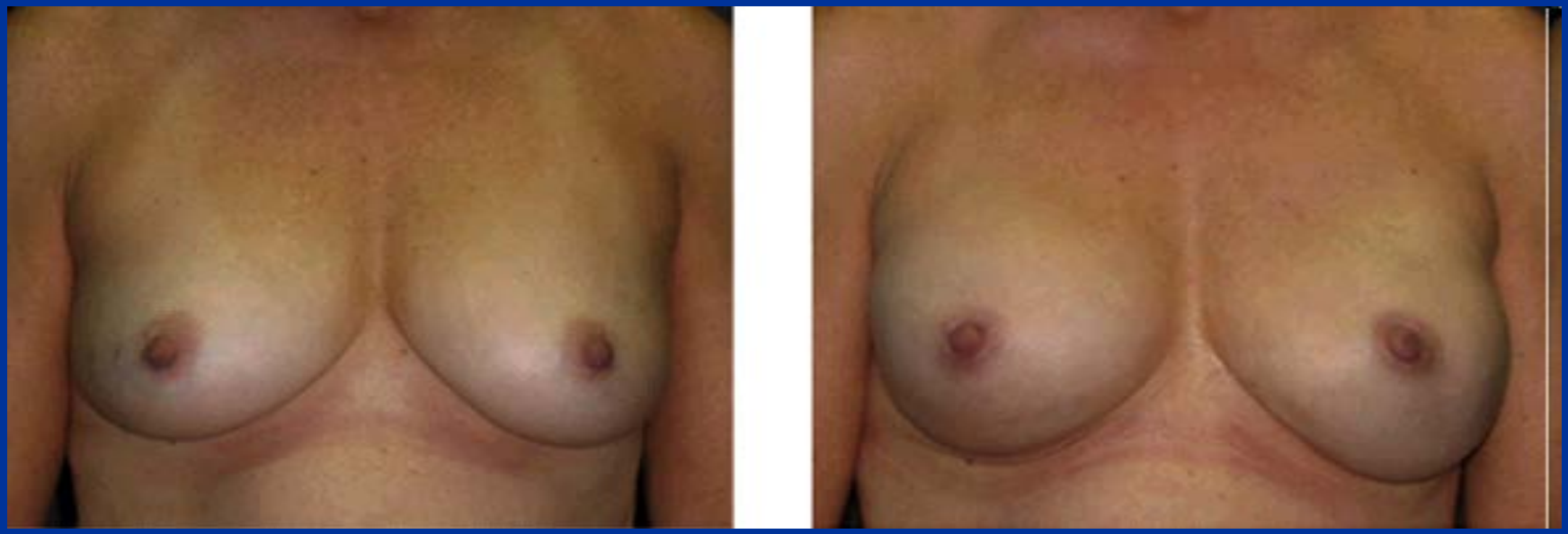
Breast Cancer after Prophylactic Mastectomy

Simple (total) mastectomy

Lifetime Risk decreased by 90%

Meijers-Heijboer et al. NEJM 2001;345:159
Rebbeck et al. JCO 2004; 22:1055

Breast Reconstruction (DIEP FLAP) after Prophylactic Mastectomies



BEFORE

AFTER

Other possible prevention strategies: lifestyle and supplements

- Exercise – yes
- Limit alcohol consumption- yes
- Maintain optimal weight- yes (especially post-menopausal)

- Soy ?
- Diet- probably no
- Vitamin D?
- Aspirin- no

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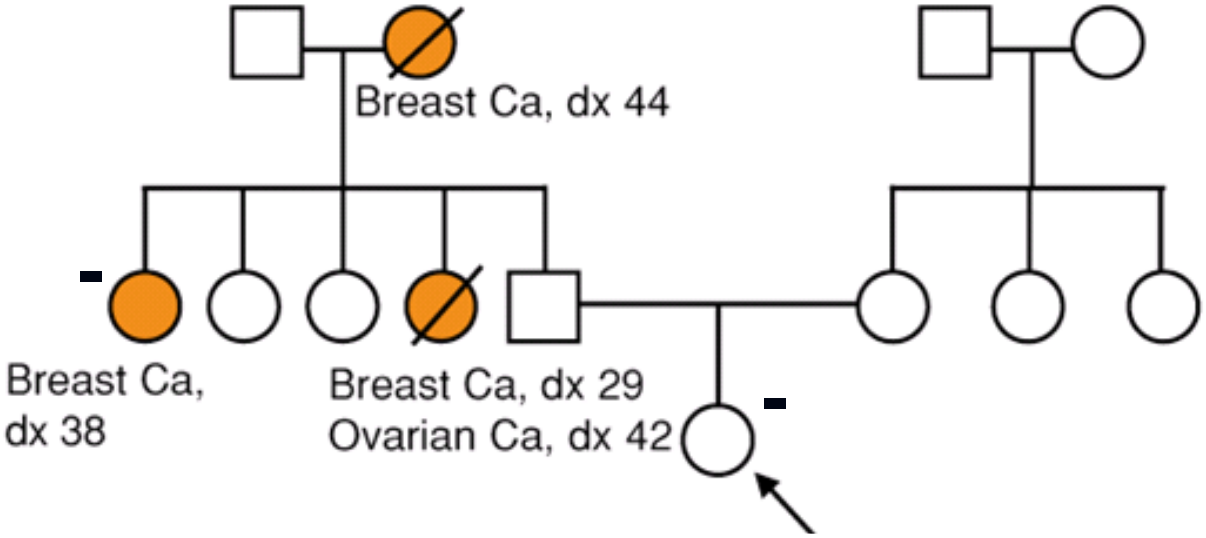
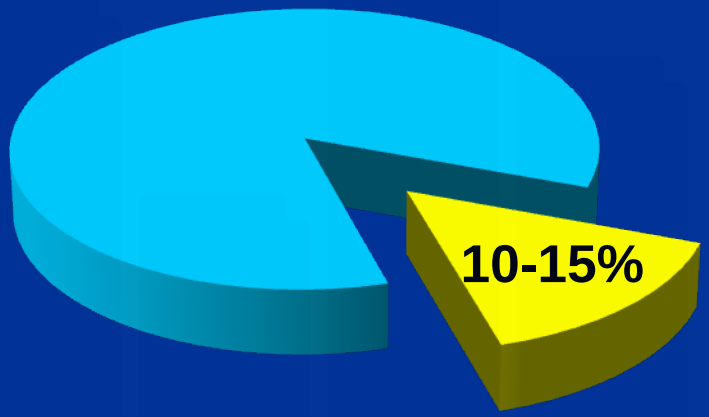
Other genetic testing

What about other genetic testing?

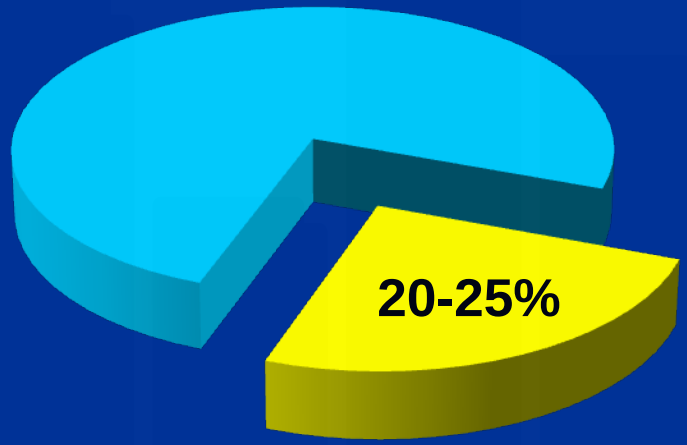


How Much Breast and Ovarian Cancer is Hereditary ?

Breast Cancer



Ovarian Cancer



Gene Mutations Associated with a Hereditary Predisposition to Breast Cancer

Gene	Syndrome	Breast Cancer Risk (by age 70)
High penetrance (RR ≥ 5; Lifetime Risk > 40%)		
BRCA1	Breast-ovarian	57-87%
BRCA2	Breast-ovarian	57-87%
TP53	Li-Fraumeni	> 90%
PTEN	Cowden Syndrome	25-50%
STK11/LKB1	Peutz-Jeghers	45-54%
CDH1	Diffuse gastric cancer	39%
Low-Moderate penetrance (RR 2-5; Lifetime risk 20-40%)		
PALB2	Pancreatic cancer	NA
ATM	Ataxia-telangectasia	NA
CHEK2	Li-Fraumeni variant	NA
BRIP1	Fancomi's anemia	NA

N Engl J Med 2007;357:154-62

Next-Gen sequencing: gene panels

Hereditary Multigene Panel Testing

Hereditary Cancer Next-Gen Panels by Gene

GENES	BreastNext	OvaNext	ColoNext	CancerNext
ATM	•	•		•
BARD1	•	•		•
BRIP1	•	•		•
MRE11A	•	•		•
NBN	•	•		•
RAD50	•	•		•
RAD51C	•	•		•
PALB2	•	•		•
STK11	•	•	•	•
CHEK2	•	•	•	•
PTEN	•	•	•	•
TP53	•	•	•	•
CDH1	•	•	•	•
MUTYH	•	•	•	•
MLH1		•	•	•
MSH2		•	•	•
MSH6		•	•	•
EPCAM		•	•	•
PMS2		•	•	•
PMS1		•	•	•
APC			•	•
BMPR1A			•	•
SMAD4			•	•

Consider multigene panel testing :

- Strong family history of cancer
- Diagnosed at young age
- Diagnosed with multiple cancers

The Mammography Controversy

US Preventive ServicesTask Force (USPSTF): 2009 update on mammogram recommendations

- Age 40-49: does not recommend routine screening
  - Except BRCA+ or hx of chest radiation (Hodgkins disease)
- Age 50-74: biennial screening
- ≥ Age 75: insufficient data to make recommendation

Recommendations for Mammography

- ACS/NCCN
  Amer Congr OB-Gyn
  - Age 40:
    Yearly mammogram

- USPSTF
  Canadian PHTF
  Swiss Medical Board
  - 50-74:
    mammogram: q 2 yrs
  - < 50:
    - BRCA1/2
    - Chest XRT (< 30)
    - Others ?- discuss

USPSTF: mammograms

Table 1. Pooled RRs for Breast Cancer Mortality From Mammography Screening Trials for All Ages

Age	Trials Included, *n*	RR for Breast Cancer Mortality (95% CrI)	NNI to Prevent 1 Breast Cancer Death (95% CrI)
39–49 y	8*	0.85 (0.75–0.96)	1904 (929–6378)
50–59 y	6†	0.86 (0.75–0.99)	1339 (322–7455)
60–69 y	2‡	0.68 (0.54–0.87)	377 (230–1050)
70–74 y	1§	1.12 (0.73–1.72)	Not available

Ann Intern Med. 2009;151:727-737.

USPSTF: Benefit of Mammography

However:

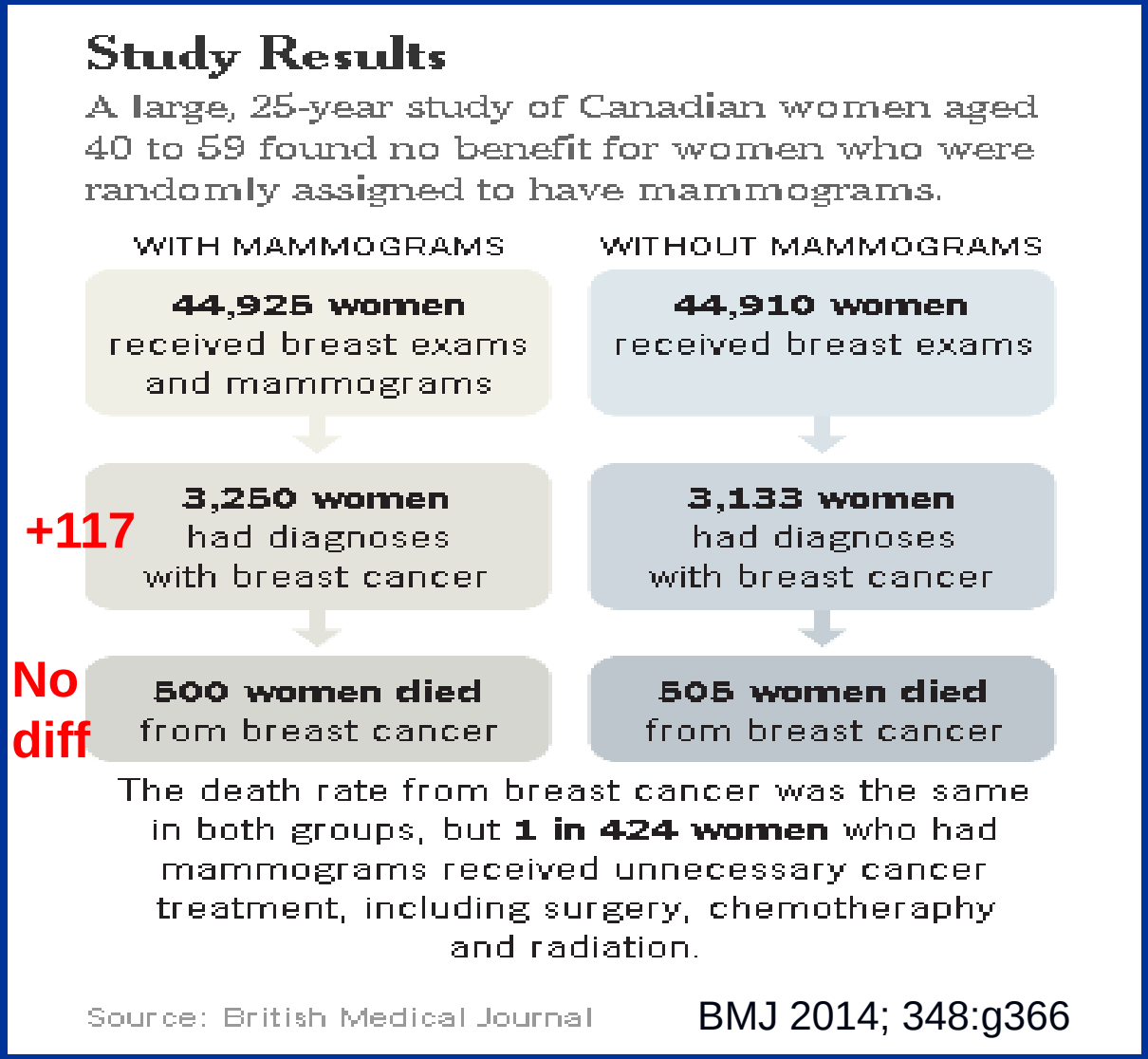
- Better results with modern technology?
  - Not all studies used digital mammography (some used single view)
- Better results if analyze just those who screened?
  - Screening compliance only 70%

In order to save one breast cancer death…

Age	↓ in Breast Cancer Death	# Women Needed to be Invited to Screen
39-49	15%	1904
50-59	15%	1339
60-69	32%	377
70-74	------	------

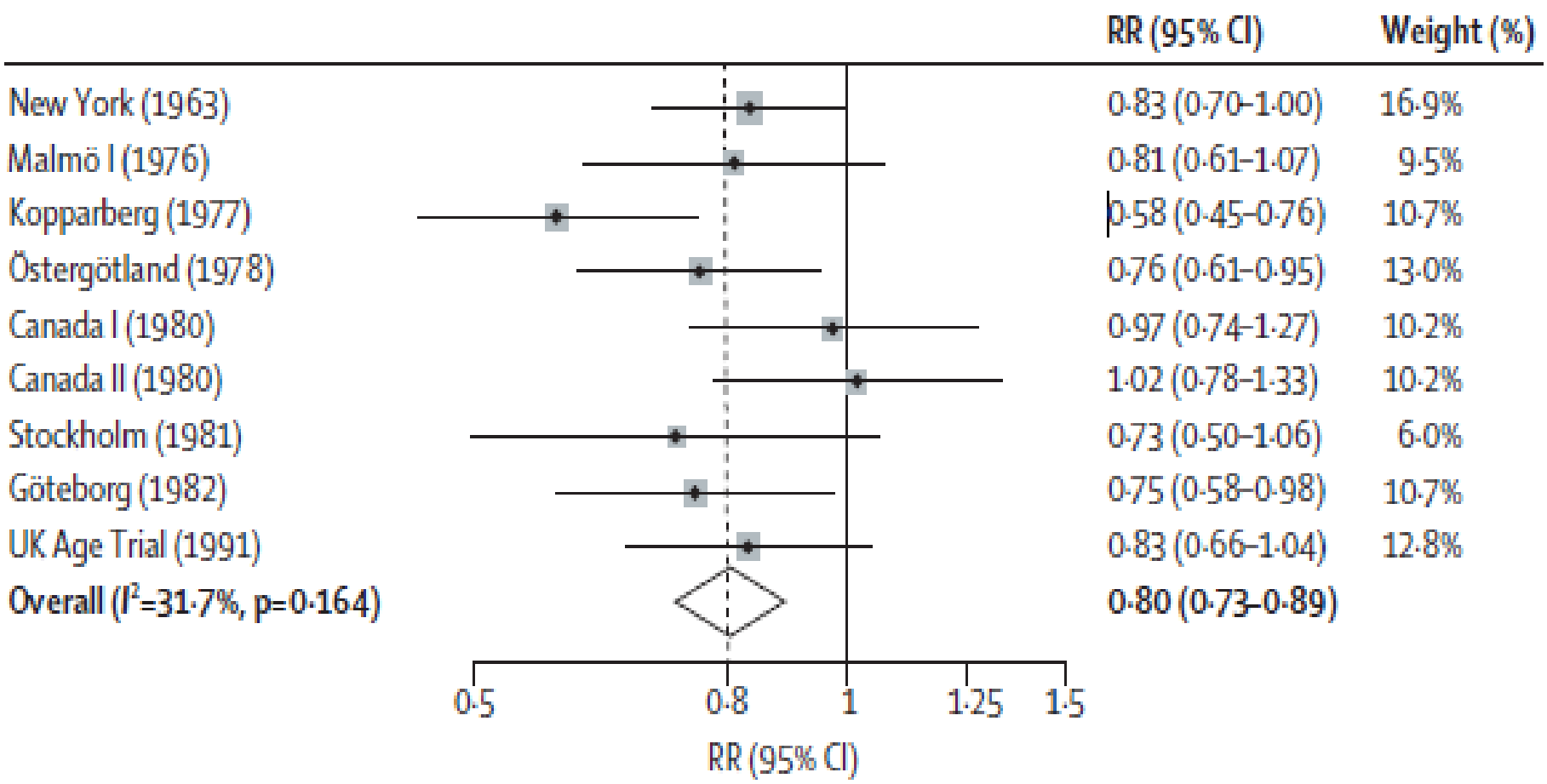
Ann Intern Med. 2009;151:727-737.

Canadian study



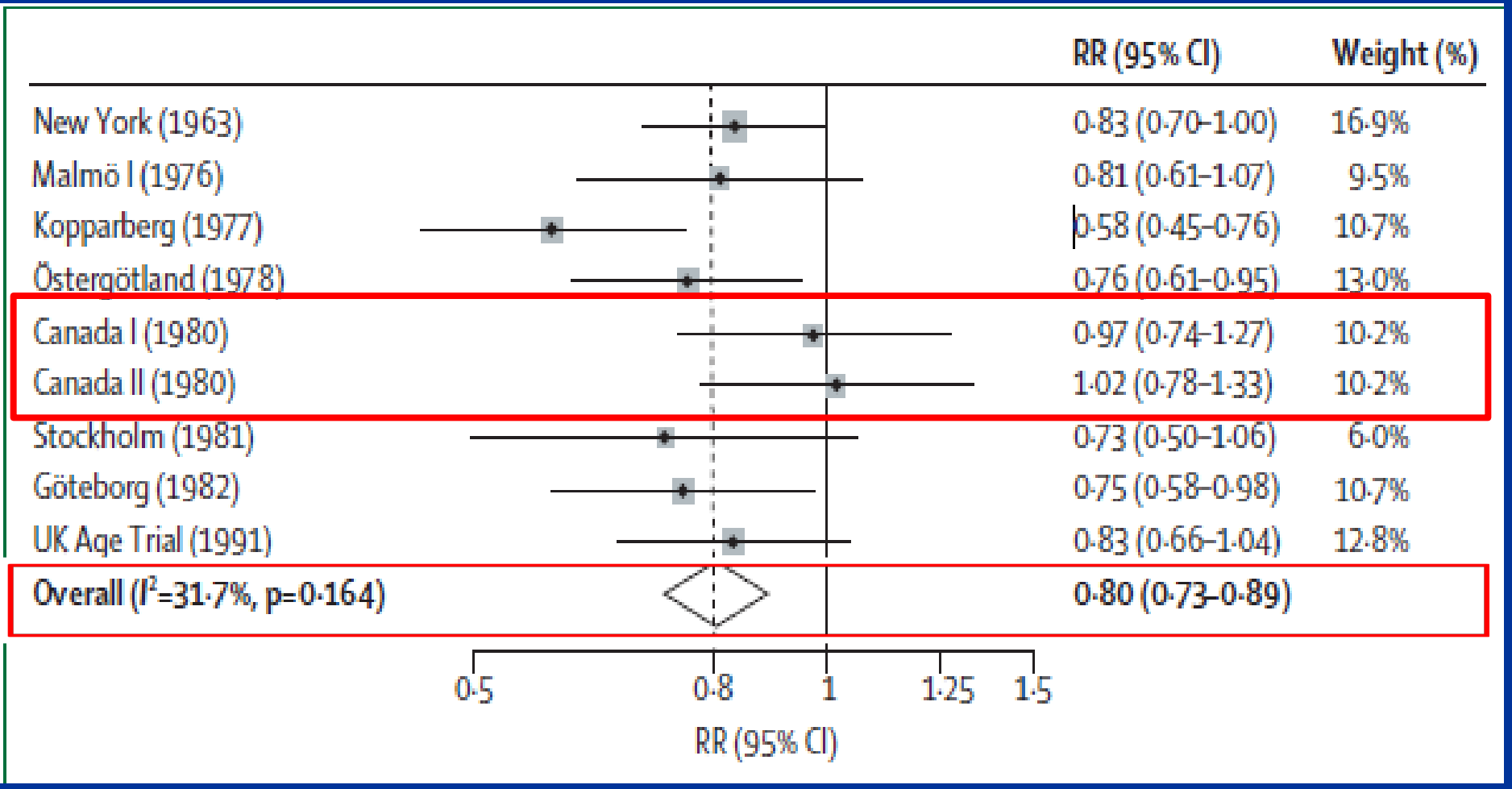
BMJ 2014; 348:g366

Odds Ratio for breast cancer death 8 randomized trials: 13 yr F/U



Adapted from Cochrane review 2011

Odds Ratio for breast cancer death 8 randomized trials: 13 yr F/U



Adapted from Cochrane review 2011

What are the possible drawbacks of mammography?

- False + (call back, anxiety)
- Overdiagnosis (DCIS, indolent invasive cancers)

Which women age 40-49 have RR $\geq$ 2 ?

- **Family hx**
  - 9% have FDR with breast cancer
- **Breast density**
  - 13% have the highest level of breast density
- **Prior breast biopsy**
  - Atypical hyperplasia, LCIS etc.

Annals Int Med, 2012; 157: 597-8

- Extra

How Long do the benefits of tamoxifen last? The IBIS-1 Trial

- European breast cancer prevention trial: tamoxifen x 5 yrs vs placebo
- The breast cancer risk reduction was constant for 10 years
- Most of the side effects only lasted while on tamoxifen

J Natl Cancer Inst 2007;99: 272 – 82

How Much Breast and Ovarian Cancer Is Hereditary?

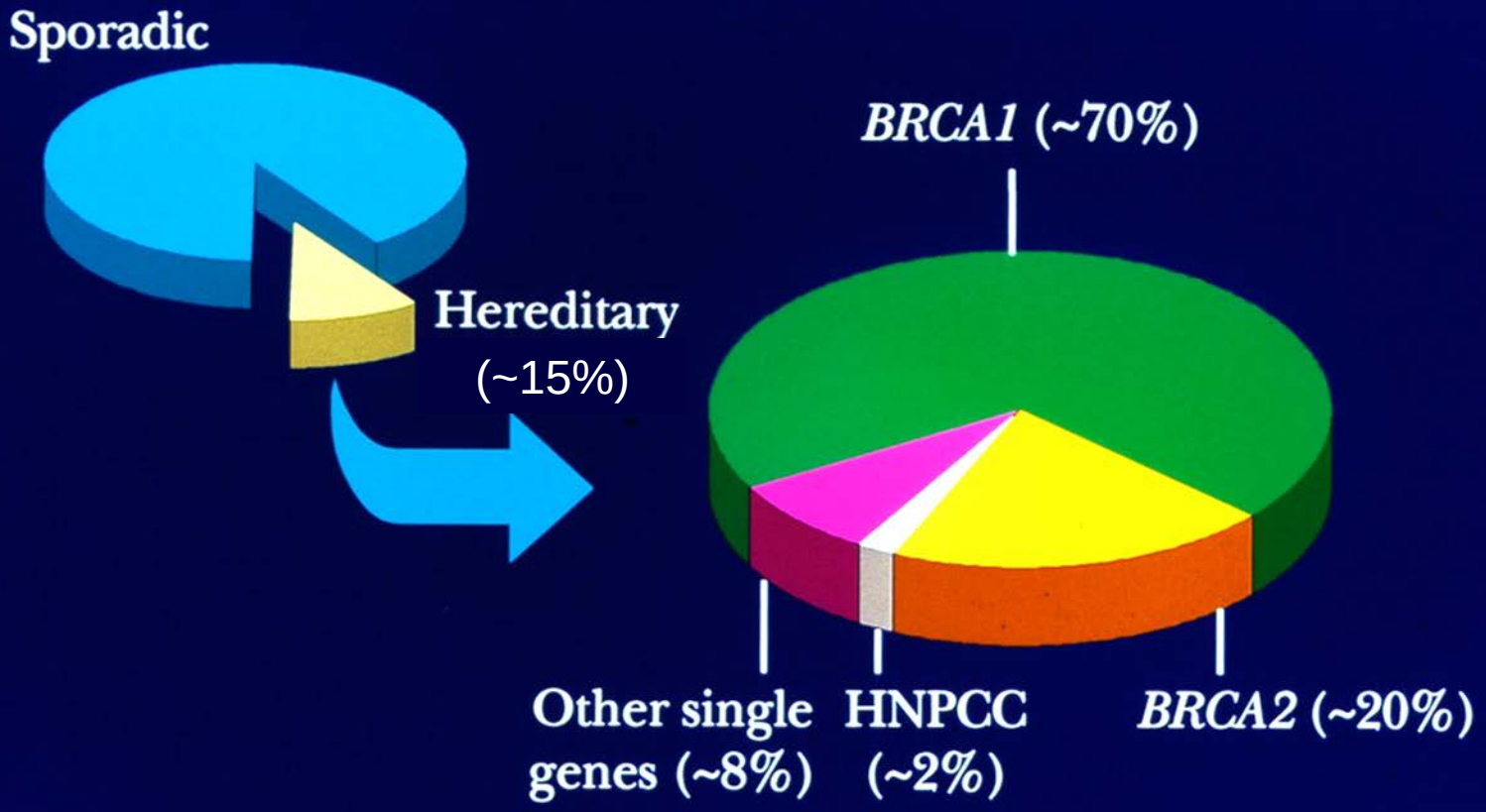
Breast Cancer

- Sporadic
- Family clusters
- Hereditary

Next-Gen sequencing: gene panels

- But:
  - Who should test? All BRCA-negative?
  - VUS (Variants of Uncertain Significance): nonpathogenic or deleterious mutation?
  - Not clear how to counsel families for lower penetrant mutations or mutations in rarer genes just being discovered.

Causes of Hereditary Susceptibility to Ovarian Cancer



Lynch syndrome (HNPCC)

- Mutations in *MLH1, MSH2, MSH6, PMS2*
- Colon cancer
- Endometrial Cancer: 45% risk
- Ovarian Cancer: ~10% risk
- Cancers of upper GI tract (bile ducts, SI)
- Cancers of urinary system- transitional cell ca of renal pelvis and ureter

- Think of Lynch when multiple colon cancers or colon ca < age 50 or endometrial cancer < 50 or coexistence of colon cancer and other Lynch cancers