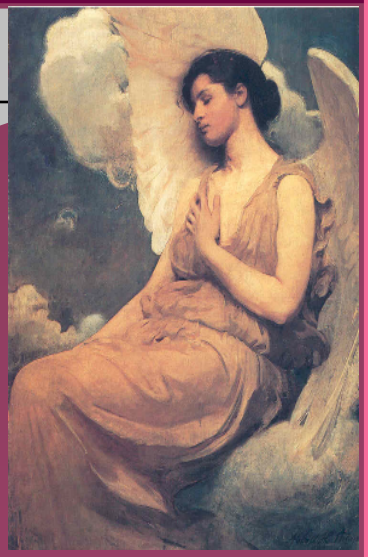


Breast Imaging: Now & the Future

Jennifer A. Harvey, M.D.
Professor of Radiology

Disclosures

- **Pending research agreement with Hologic and Dilon technologies**
- **Reader study for Naviscan**

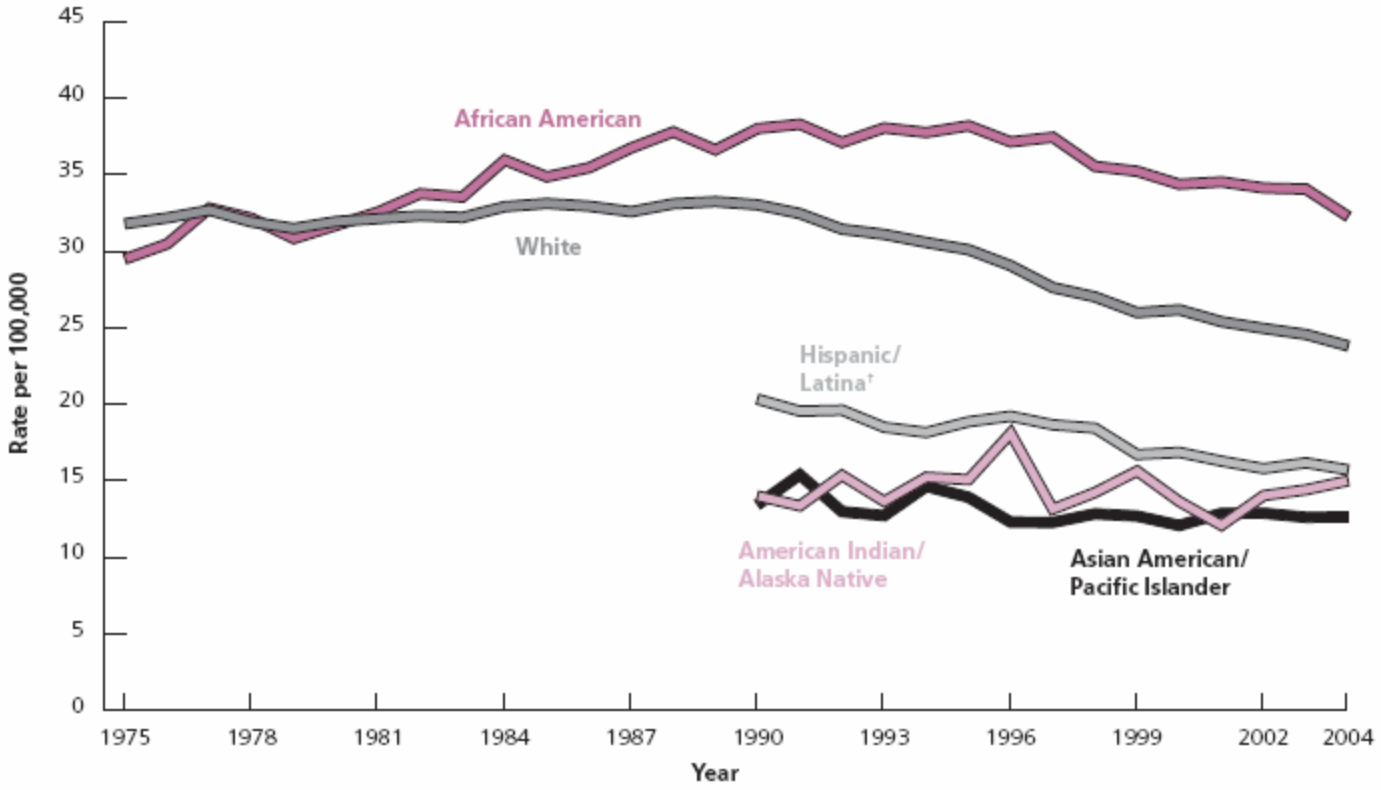
Objectives

- To understand the current state of breast imaging, including indications for imaging women at high risk for breast cancer
- To understand how screening of average risk women may be improved in the future
- To understand possible future roles of adjunct screening for women at moderate and high risk for developing breast cancer

American Cancer Society Guidelines: Average Risk Women

- Age 20-39
  - Clinical Breast Exam every 3 years
- Age 40 and older
  - Annual mammogram
  - Annual CBE

Figure 6. Trends in Female Breast Cancer Death Rates* by Race and Ethnicity, US, 1975-2004



*Rates are age-adjusted to the 2000 US standard population.

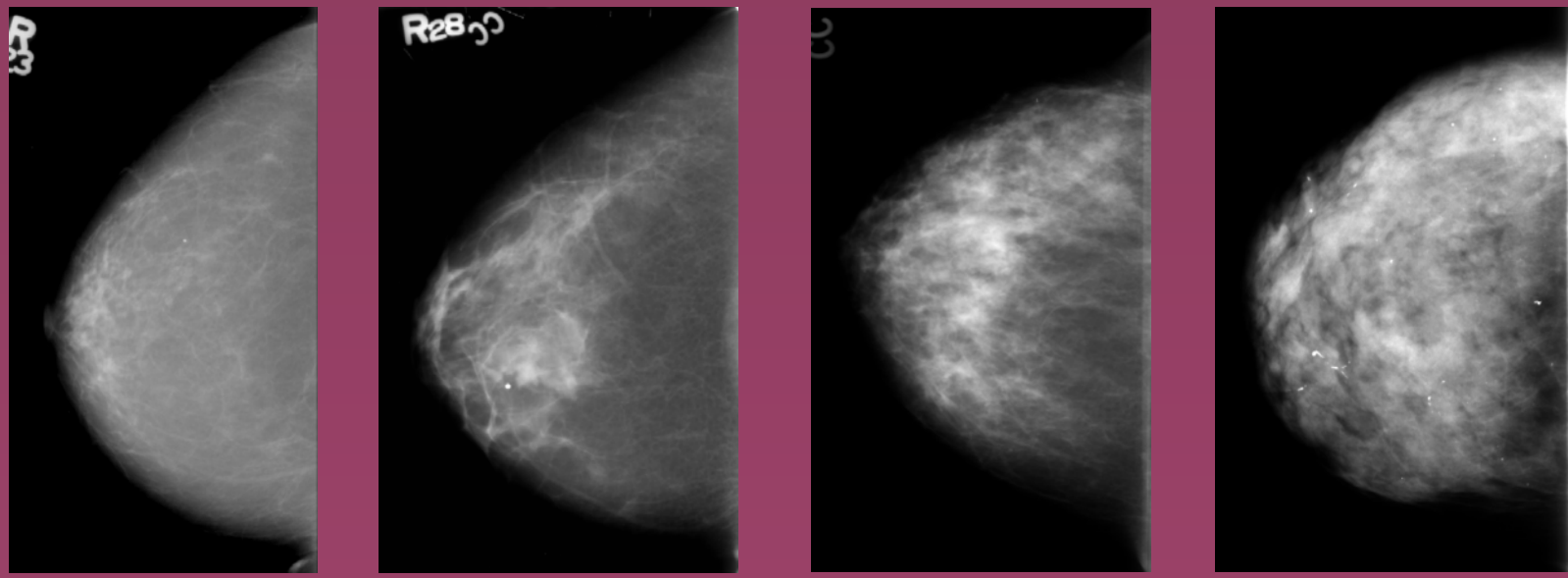
†Information is included for all states except Connecticut, Louisiana, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, Virginia, and Vermont.

Data source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2007.

American Cancer Society, Surveillance Research, 2007

Breast Cancer mortality declining 2.2%/year since 1990

Breast Density



87% → 63%

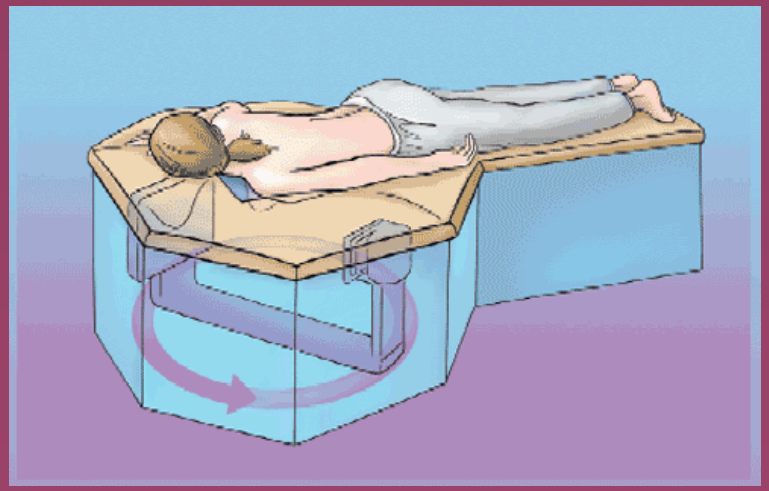
Sensitivity

97% → 89%

Specificity

Carney PA. Ann Int Med 2003

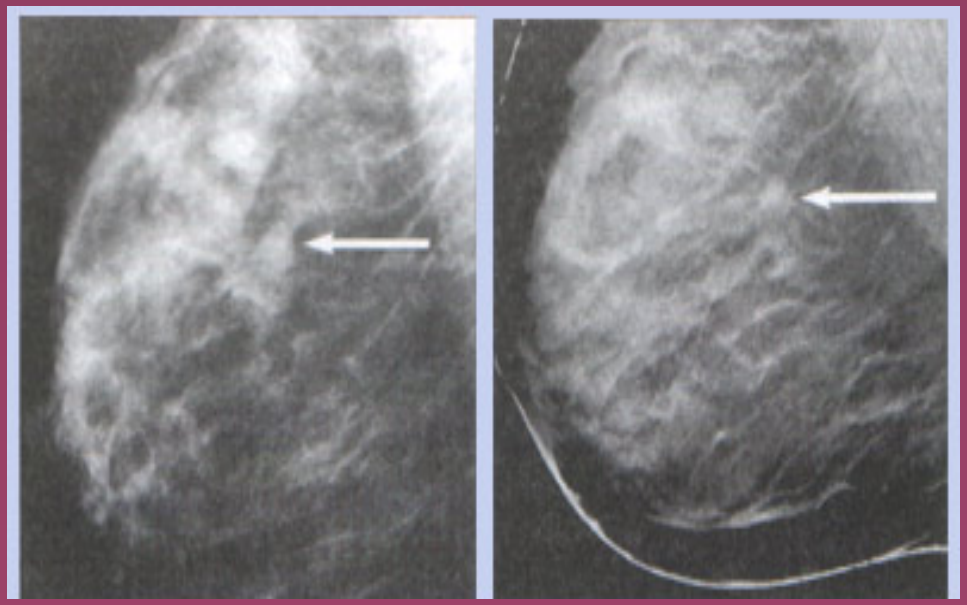
Improve Anatomic Imaging



UC Davis

Digital Breast Tomosynthesis

- **99 recalls from digital screening**
- **52% of lesions would not have been recalled based on tomo**
- **Recall reduction 40%**



Poplack SP. AJR 2007

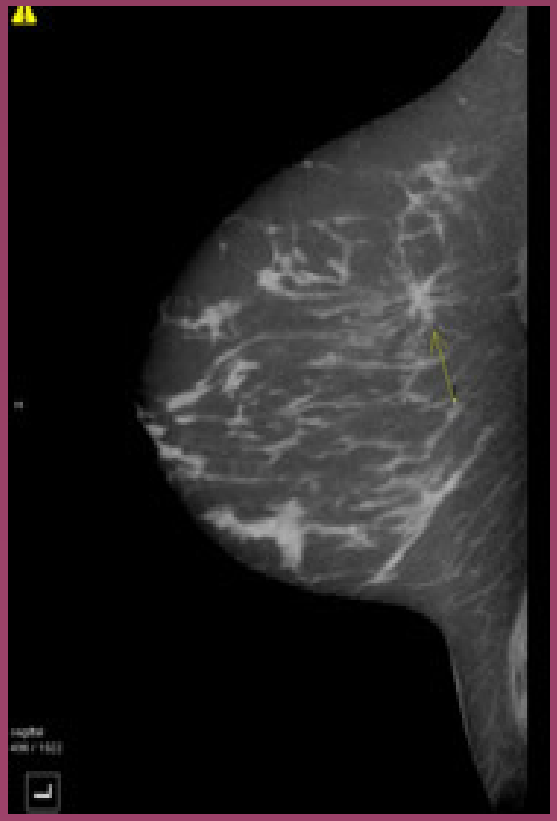
Tomosynthesis

- **190 women (39 cancers) scheduled for biopsy due to mass seen on mammo, US, or PE**
  - **4 additional lesions detected on tomo (2.1%); all IDC 6-14mm**
  - **2 fatty/scattered, 2 heterogeneous/dense**

Helvie M. RSNA 2008

Breast CT

- **Small studies to-date**
- **79 women**
- **CT significantly better for visualizing masses**
- **Mammo better for calcifications**



Lindfors KK. Radiology 2008

CA Cancer J Clin 2007;57:75–89

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)

ABSTRACT New evidence on breast Magnetic Resonance Imaging (MRI) screening has become available since the American Cancer Society (ACS) last issued guidelines for the early detection of breast cancer in 2003. A guideline panel has reviewed this evidence and developed new recommendations for women at different defined levels of risk. Screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease. There are several risk subgroups for which the available data are insufficient to recommend for or against screening, including women with a personal history of breast cancer, carcinoma in situ, atypical hyperplasia, and extremely dense breasts on mammography. Diagnostic uses of MRI were not considered to be within the scope of this review. *(CA Cancer J Clin 2007;57:75–89.)*

Dr. Saslow is Director, Breast and Gynecologic Cancer, Cancer Control Science Department, American Cancer Society, Atlanta, GA.

Dr. Boetes is Professor, Department of Radiology, University Medical Center Nijmegen, Nijmegen, The Netherlands.

Dr. Burke is Chair; and Professor of Medical History and Ethics, University of Washington, Seattle, WA.

Dr. Harms is Radiologist, The Breast Center of Northwest Arkansas, Fayetteville, AR; and Clinical Professor of Radiology, University of Arkansas for Medical Sciences, Little Rock, AR.

Dr. Leach is Professor of Physics as Applied to Medicine; Co-Chairman, Section of Magnetic Resonance; and Co-Director, Cancer Research; UK Clinical Magnetic Resonance Research Group, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Surrey, UK.

Dr. Lehman is Professor of Radiology; and Section Head of Breast Imaging, University of Washington Medical Center and the Seattle Cancer Care Alliance, Seattle, WA.

Dr. Morris is Director, Breast MRI, Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY.

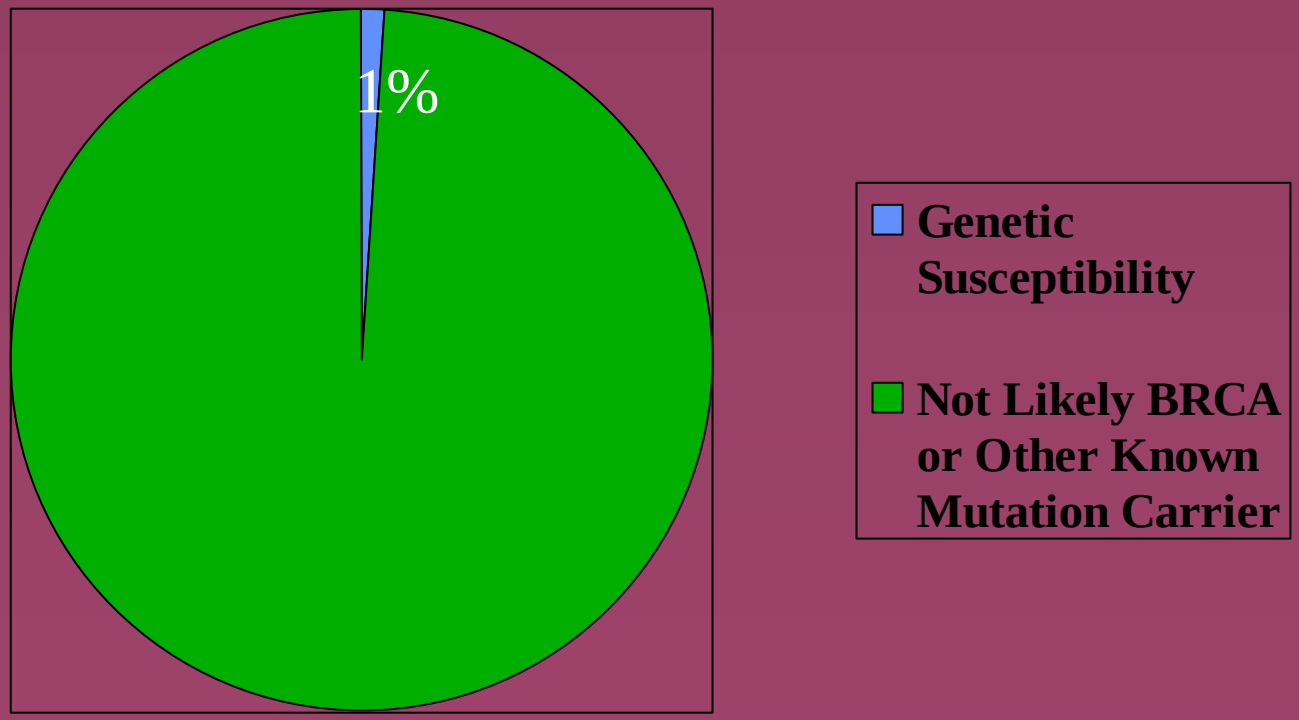
Journal for Clinicians

ACS: Annual Screening MRI

- **Women with ≥20% lifetime risk by BRCAPro or other model dependent on family hx**
- **BRCA mutation**
- **1st degree relative of BRCA carrier, but untested**
- **Li-Fraumeni, Cowden, and Bannayan-Riley-Ruvalcaba syndromes and 1st degree relatives**
- **Radiation to chest between age 10 and 30 years**

Beginning at age 25

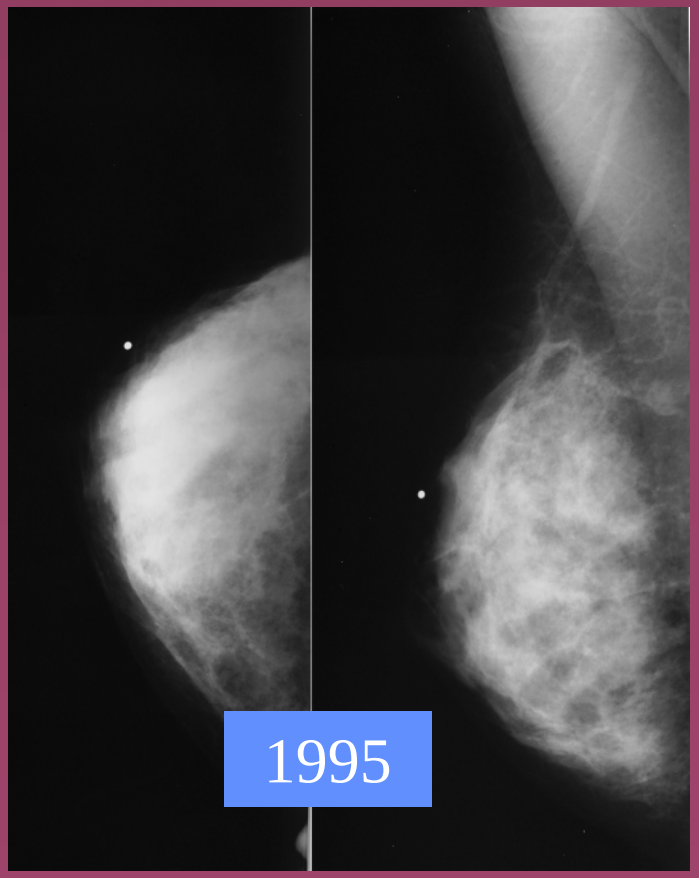
Genetic Risk in the Population

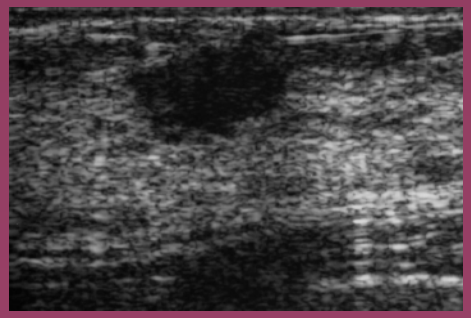


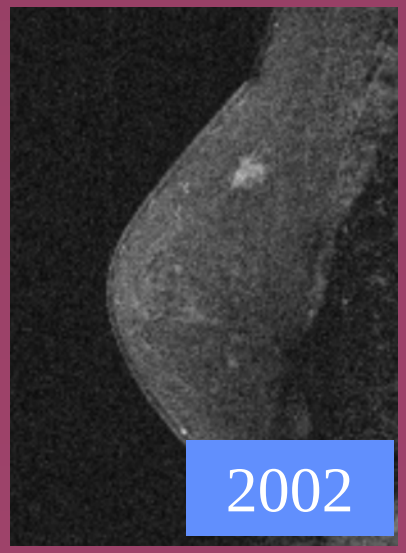
Genetic Syndromes

	Autosomal Dominant	Lifetime Risk	Other Cancers
BRCA1	X	55-85%	Ovary, liver, testis (male)
BRCA2	X	25-60%	Male breast, pancreas
Li-Fraumeni	X	60-90%	Leukemia, sarcoma, adrenal
Cowden Syndrome	X	30-50%	Thyroid (and B9), meningioma

BRCA Patient







Familial Breast Cancer

- **Tumor Doubling Time**
  - **BRCA carriers 45 days (CI 26-73)**
  - **Non-carriers 84 days (CI 58-131)**
- **Survival is hereditary**
  - **1277 mother-daughter breast cancer pairs showed daughter's length of survival correlated with mother's length of survival**

Tilanus-Linthorst MM. Eur J Cancer 2005
Hemminki K Br Cancer Res & Treat 2007

MR screening studies

	Investigator	Institution	N
1.	Kuhl ‘00	U Bonn	192
2.	Tilanus-Linthorst ‘00	Rotterdam	109
3.	Warner ‘01@	U Toronto	196
4.	Stoujesdijk ‘01	Nijmegen	179
5.	Lo/Schnall ‘01	U Penn	157
6.	Heerdt ‘01	MSKCC	124
7.	Morris ‘03	MSKCC	367
8.	Robson ‘01	MSKCC	54
9.	Kriege ‘04	Rotterdam	1909
10.	Warner ’04	U Toronto	236
11.	MARIBS ’05	UK	649
12.	Lehman ’05	Multi- North Am	390
			4562

High Risk MRI Screening Results

- 20 – 60 Cancers/1000 women screened
  - versus 3-7/1000 with mammography
- Mean tumor size 0.7-2.0 cm
- 65-100% node negative

Largest Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 29, 2004 VOL. 351 NO. 5

Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition

Mieke Kriege, M.Sc., Cecile T.M. Brekelmans, M.D., Ph.D., Carla Boetes, M.D., Ph.D., Peter E. Besnard, M.D., Ph.D., Harmine M. Zonderland, M.D., Ph.D., Inge Marie Obdeijn, M.D., Radu A. Manoliu, M.D., Ph.D., Theo Kok, M.D., Ph.D., Hans Peterse, M.D., Madeleine M.A. Tilanus-Linthorst, M.D., Sara H. Muller, M.D., Ph.D., Sybren Meijer, M.D., Ph.D., Jan C. Oosterwijk, M.D., Ph.D., Louk V.A.M. Beex, M.D., Ph.D., Rob A.E.M. Tollenaar, M.D., Ph.D., Harry J. de Koning, M.D., Ph.D., Emiel J.T. Rutgers, M.D., Ph.D., and Jan G.M. Klijn, M.D., Ph.D., for the Magnetic Resonance Imaging Screening Study Group*

Kriege M. NEJM 2004; 351:427-37

- **1909 women lifetime risk ≥15%**
  - **358 mutation carriers**
- **2.9 years f/u**
- **51 cancers**
- **Sensitivity for Inv CA:**
  - **CBE 17.9%**
  - **Mammo 33.3%**
  - **MRI 79.5%**

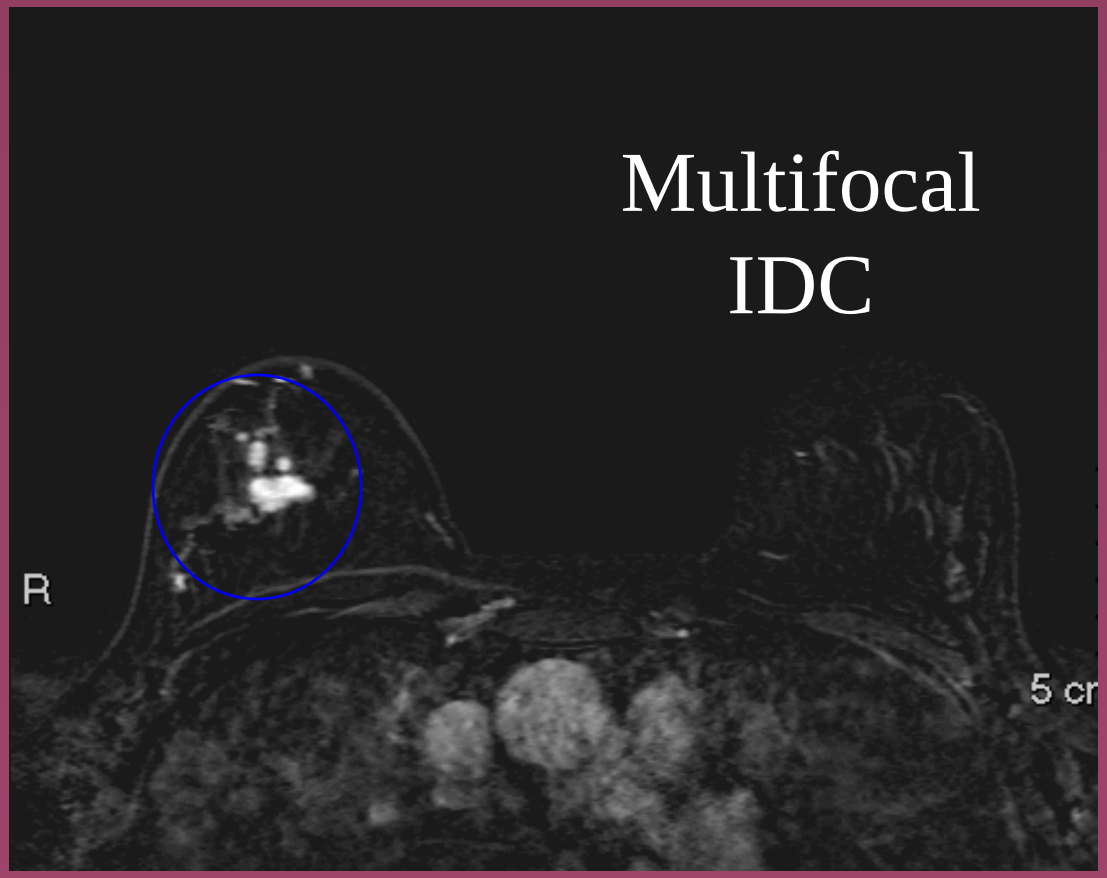
Kriege et al

- Compared to control groups (Cancer registry or prospective group), those undergoing MRI had:
  - Larger proportion of invasive cancers <10mm (43% compared to 14% and 12%)
  - Lower axillary metastasis (21% vs. 52% and 56%)
  - More DCIS cases (12% vs. 8% and 0%) (not significant)

DCIS

- Presents as linear ductal non-mass-like enhancement (NMLE)
- Mass-like enhancement less common
- Often with benign enhancement pattern

34 yo High Risk Screening



MRI Performance

- **Sensitivity**
  - **90-95% for invasive cancers**
  - **50-70% for DCIS**
- **Detection of DCIS varies by grade:**
  - **92% sensitivity for high grade**
  - **70% intermediate/low grade DCIS (Neubauer, Br J Rad 2003)**
- **Specificity 30-70%**

MR in BRCA 1 and 2 Carriers

- **23% of cancers were fibroadenoma-like (80% were in BRCA 1)**
  - **No internal septations**
  - **Not persistent enhancement**
- **BRCA 1- no calcifications**
- **BRCA 2- similar to sporadic breast cancer**

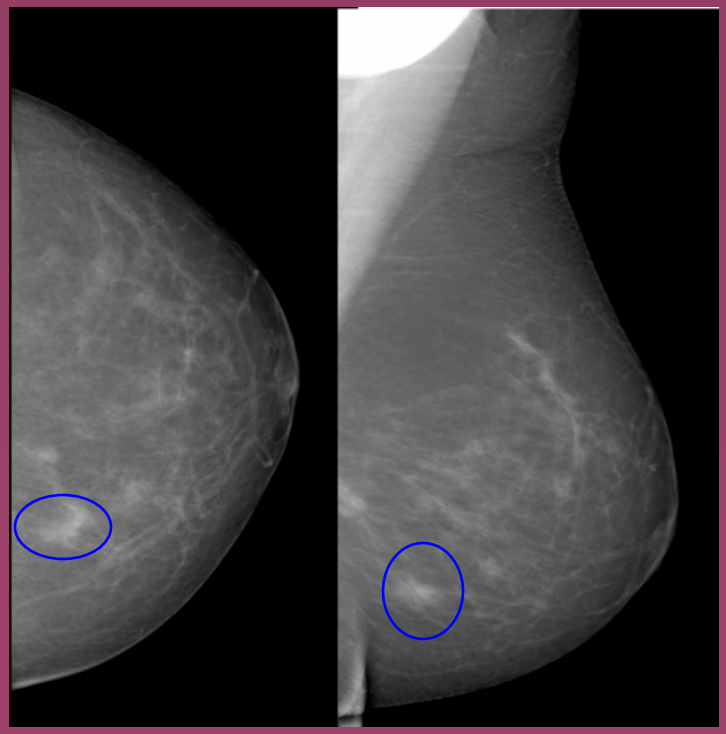
Schrading S and Kuhl CK. Radiology 2008

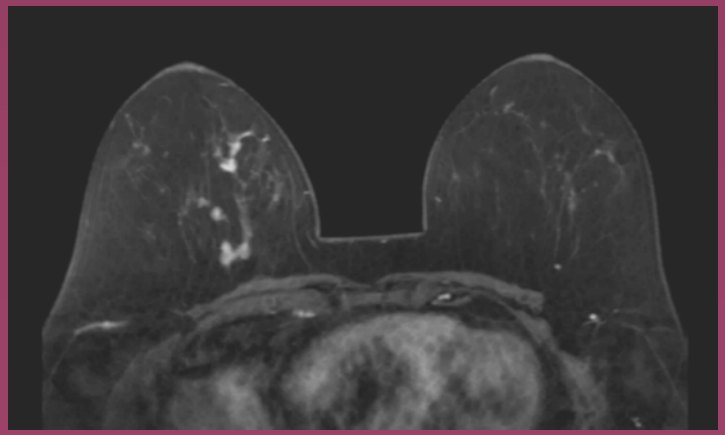
Is Mammography Adequate for Fatty Breasts?

	MRI	Mammo
Fatty	3/3 (100%)	1/3 (33%)
Scattered	14/15 (93%)	5/15 (33%)
Heterogeneous	22/25 (88%)	4/25 (16%)
Dense	2/3 (66%)	1/3 (33%)

Bigenwald RZ. Cancer Epid Biomark Prev; 2008

New IDC in fatty breast





Outcome Screening for BRCA1 Carriers

	Clinical	Mammo	MR	Mammo + MR
Cancer size, median	2.6 cm	1.9 cm	1.3 cm	1.1 cm
Ave Life Expectancy	71.2 yrs	+0.8 yrs	+1.1 yrs	+1.4 yrs
Decrease Rel Mortality		16.8%	17.2%	22.0%
FP		53.8%	80.2%	84.0%

Lee JM. Radiology 2008

Cost Effectiveness

- **BRCA 1**
- **QALY**
- **30-39 mammo 5,200 pds**
  - **MR 13,486**
- **40-49 mammo 2,913**
  - **MR 7,781**

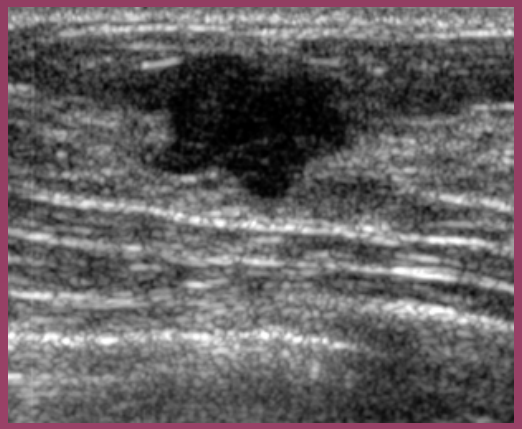
Norman RPA. Eur J Health Econ 2007

Radiation Exposure at Young Age

- **Hodgkins Disease treated with mantle radiation (RR 5.2)**
- **Risk of breast cancer increases beginning about 7-8 years after treatment, peaking at about 15 years post treatment**
- **Younger age at treatment = higher risk**
- **Many unaware of increased risk**
- **Begin intensive screening 6-7 years after treatment**

Clemons M. Cancer Treat Rev 2000
Goss PE. J Clin Onc 1998

Prior Radiation Therapy

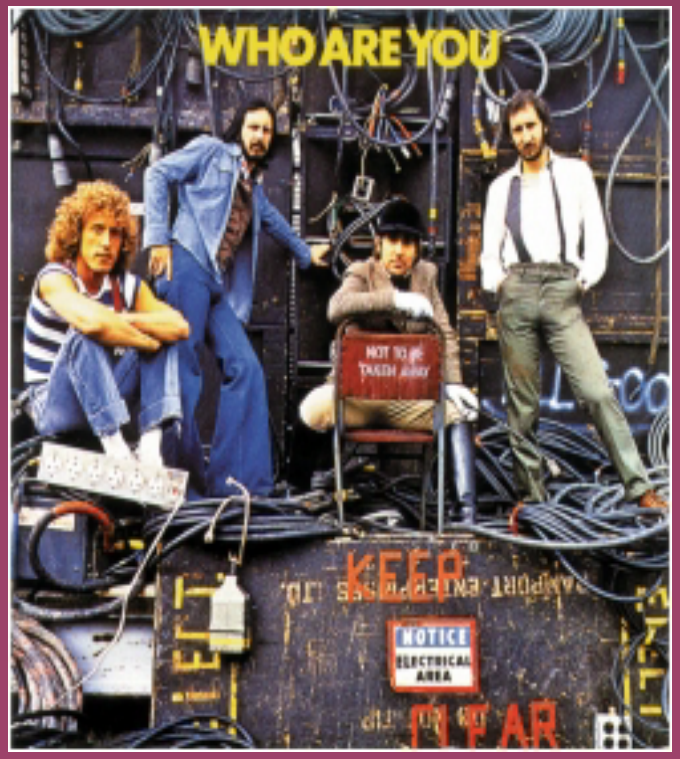


- 29 yo woman treated for Hodgkins dz 10 years ago
- Palpable lump left breast
- Biopsy showed invasive ductal carcinoma, grade III

Risk Reduction: High Risk Women

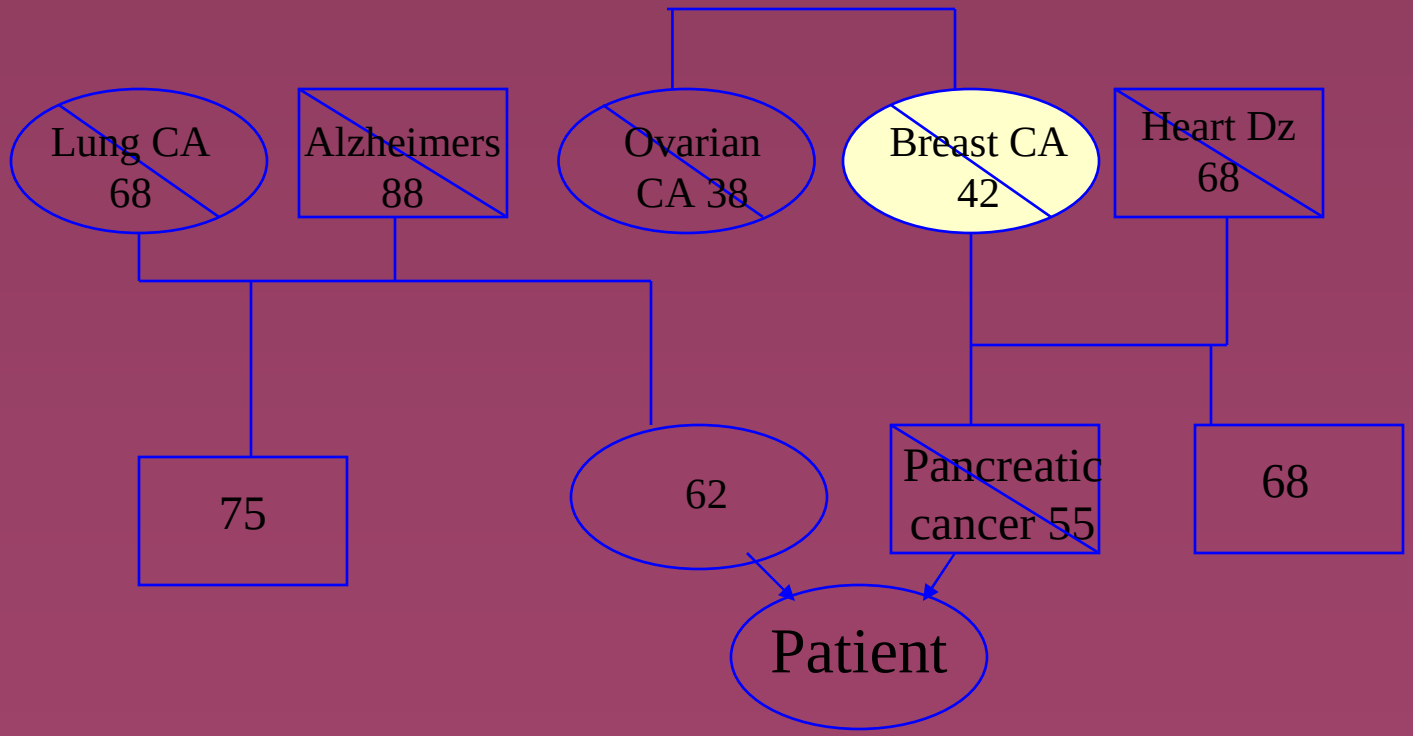
- Early detection- Modified/intensive screening
- Pharmacologic- Tamoxifen, Raloxifene, aromatase inhibitors?
- Surgical- Prophylactic mastectomy, oophrectomy

Risk Evaluation: Identifying Women at Elevated Risk



- Young at onset
- Bilateral breast cancer
- Other cancers in family
- Multiple or male relatives

Family History



This family history is worrisome for hereditary breast and ovarian cancer on the paternal side

Breast Cancer Risk Factors

Personal

- **Parity**
- **[illegible]**
- **[illegible]**
- **[illegible]se**
- **[illegible]**
- **therapy**
- **Obesity**

Breast Disease

- **ALH**
- **ADH**
- ***DCIS***
- **Breast density**

Genetic

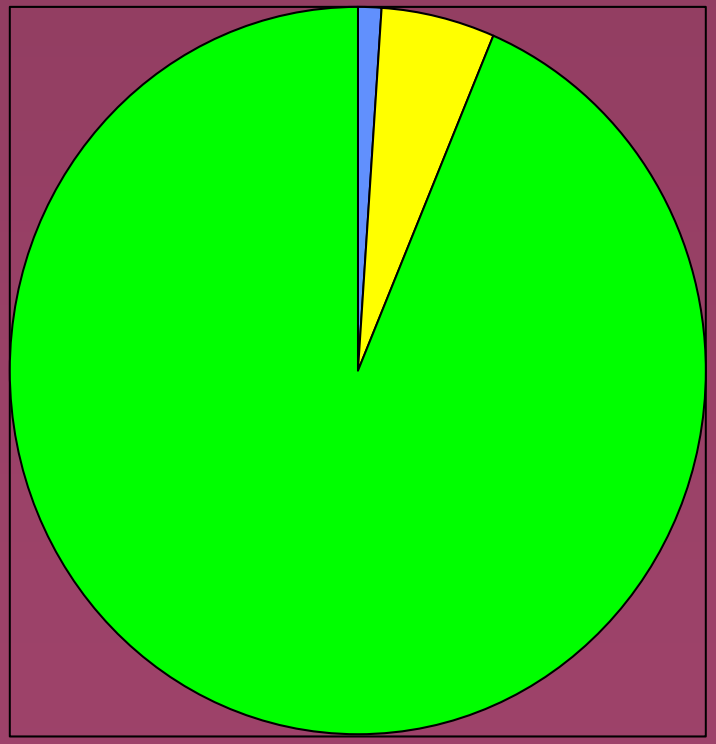
- **BRCA**
- **[illegible]**
- **[illegible]**
- **Syndrome**

Tyrer-Cuzick Model

Gail Model

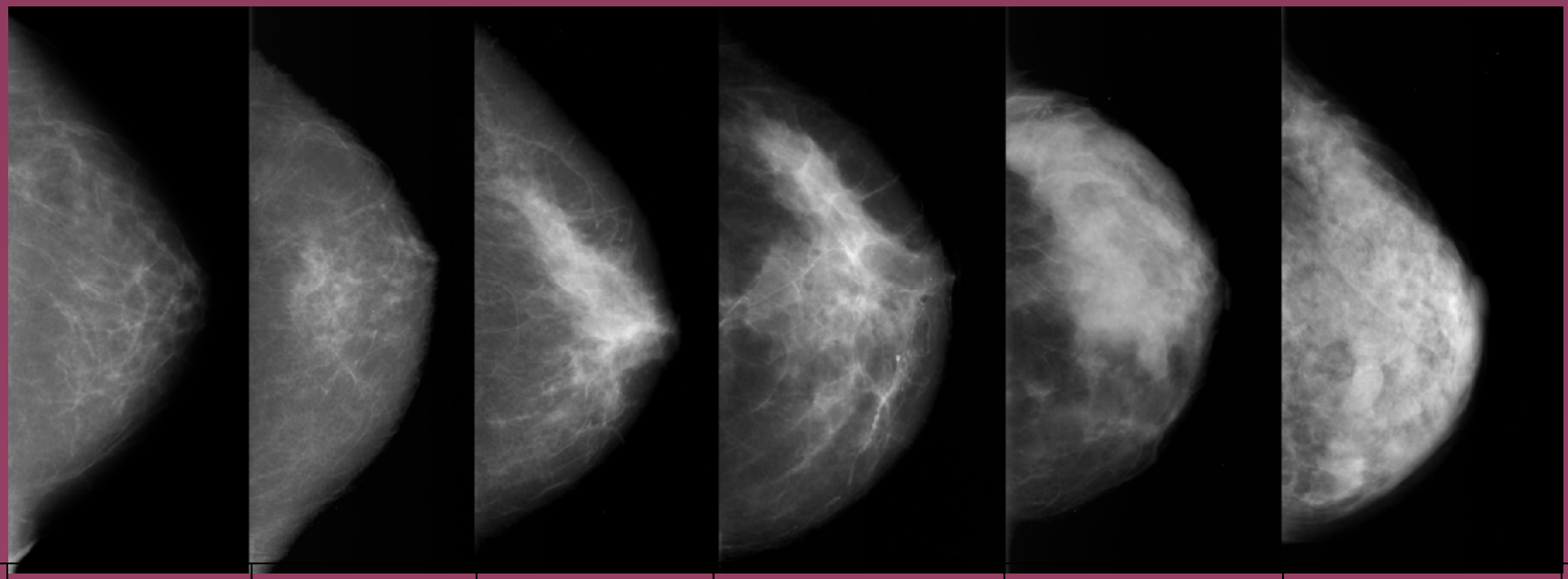
Claus or BRCA Pro Model

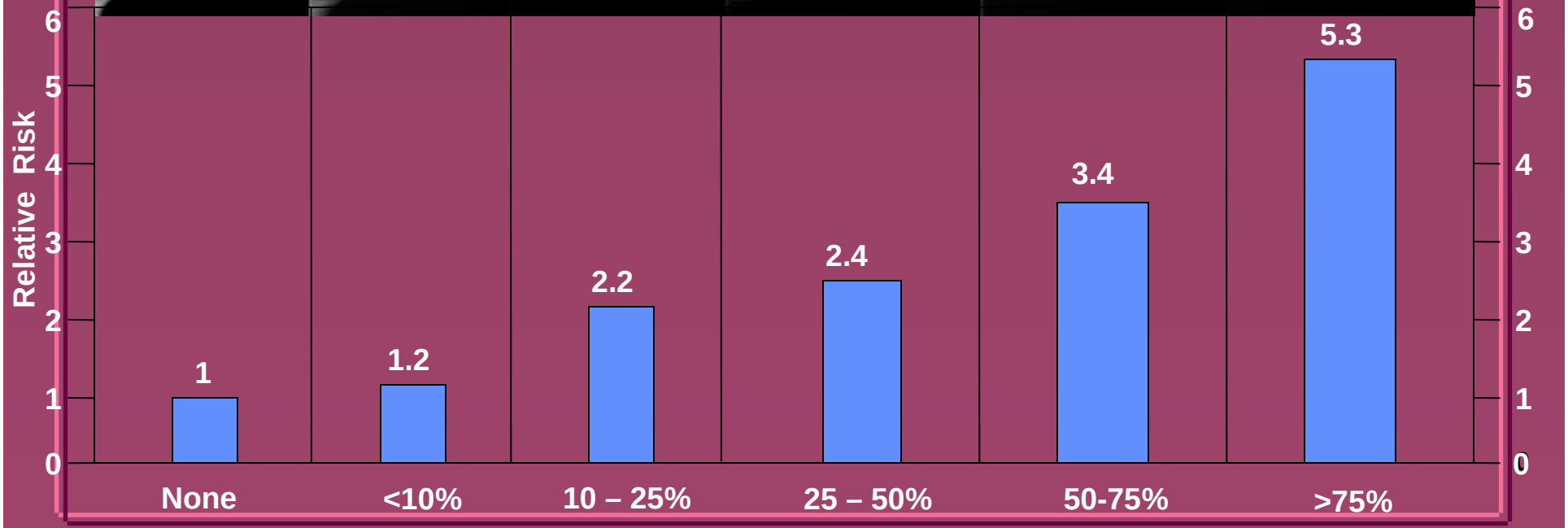
Breast Cancer Risk in the Population



- **Genetic Susceptibility** → MRI
- **High Risk Due to Combination of factors**
- **Average Risk**

Boyd Classification

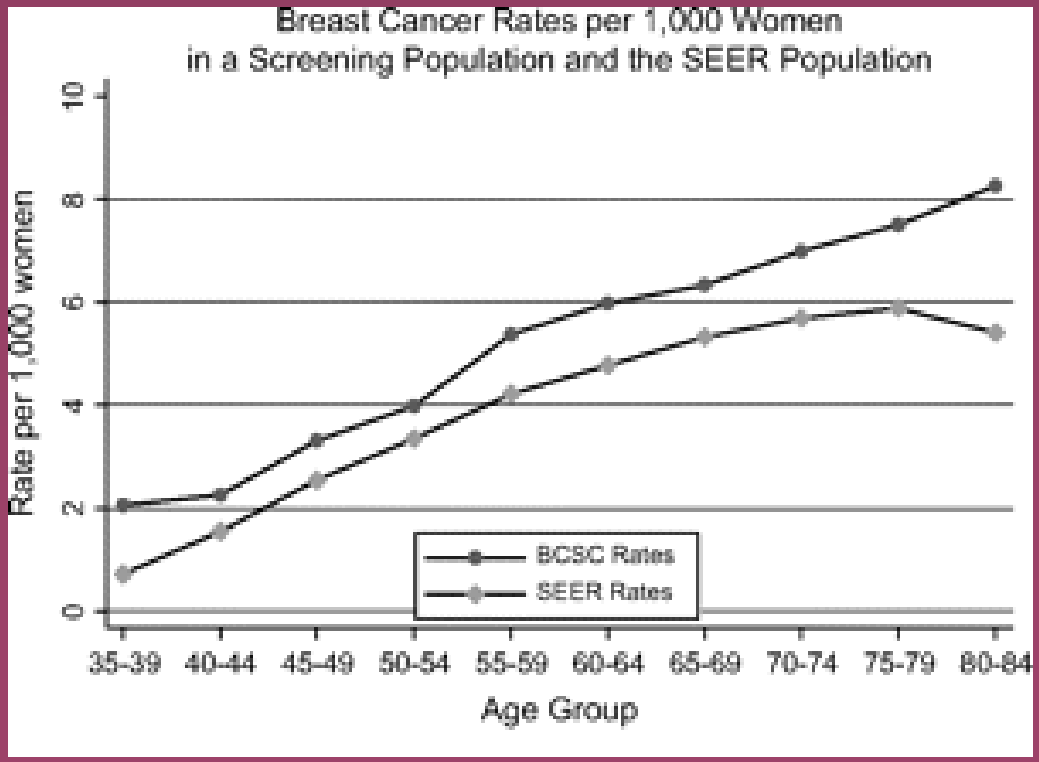




Boyd, 1995

Models that Incorporate Breast Density Improve Accuracy

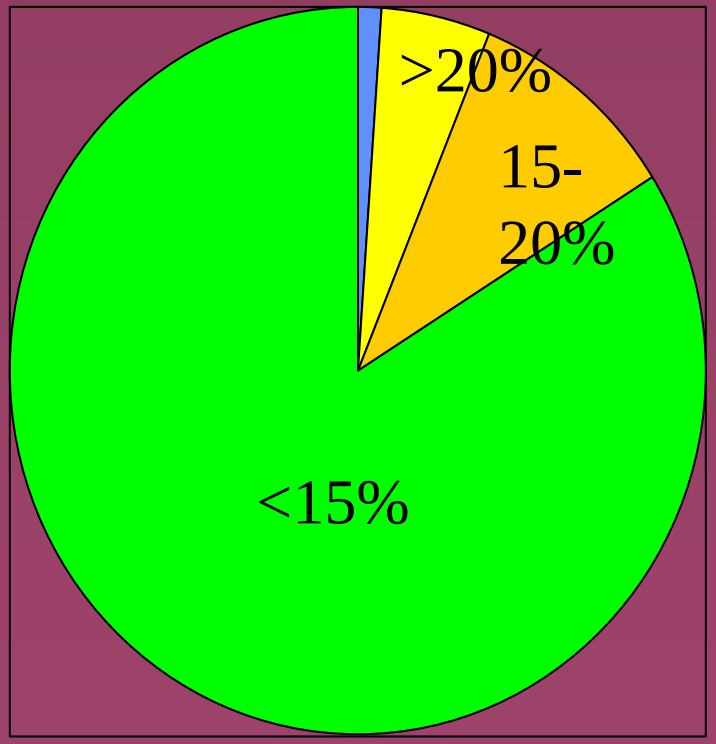
- **Breast Cancer Screening Consortium (BCSC) (Barlow WE. JNCI, 2006).**
- **BCDDP (Chen J. JNCI 2006)**



Insufficient Evidence for Screening MRI

- 15-20% lifetime risk (moderate risk)
- LCIS, ADH, or ALH on prior biopsy
- Heterogeneous or dense breast tissue
- Personal history of breast cancer, including DCIS

Personalized Breast Cancer Screening

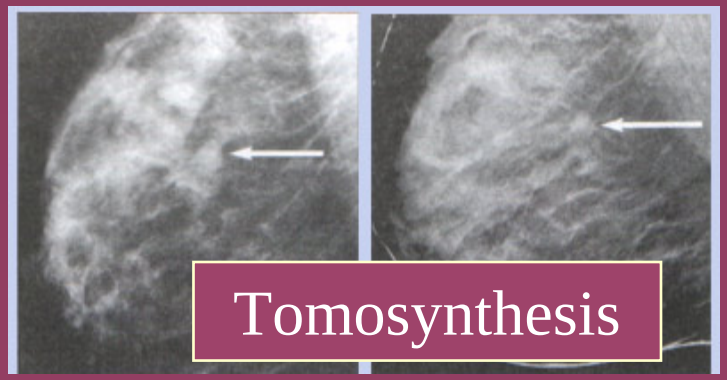


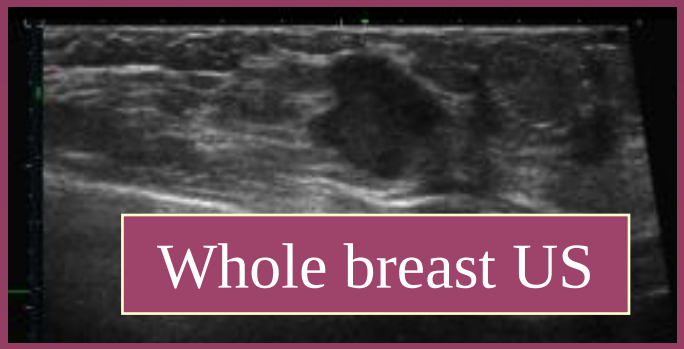
- **Genetic Susceptibility** → MRI
- **High Risk Due to Combination of factors**
- **Moderate Risk** → BSGI PEM CT
- **Average Risk**

The Age of
Personalized Medicine

A Service o

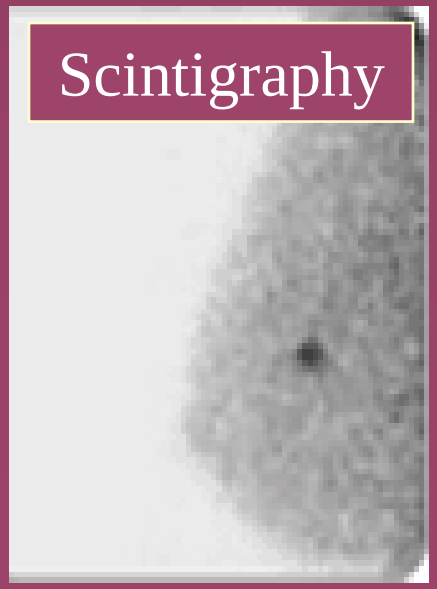
Home | Personalized Medicine Today & Tomorrow | View of the Experts | Knowledge C

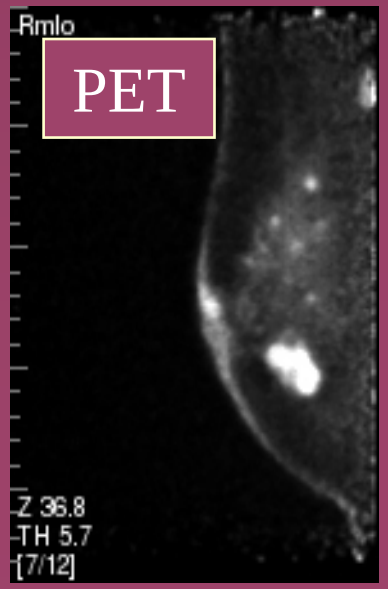

Tomosynthesis


Whole breast US


MRI


CT


Scintigraphy


PET
Rmlo
Z 36.8
TH 5.7
[7/12]

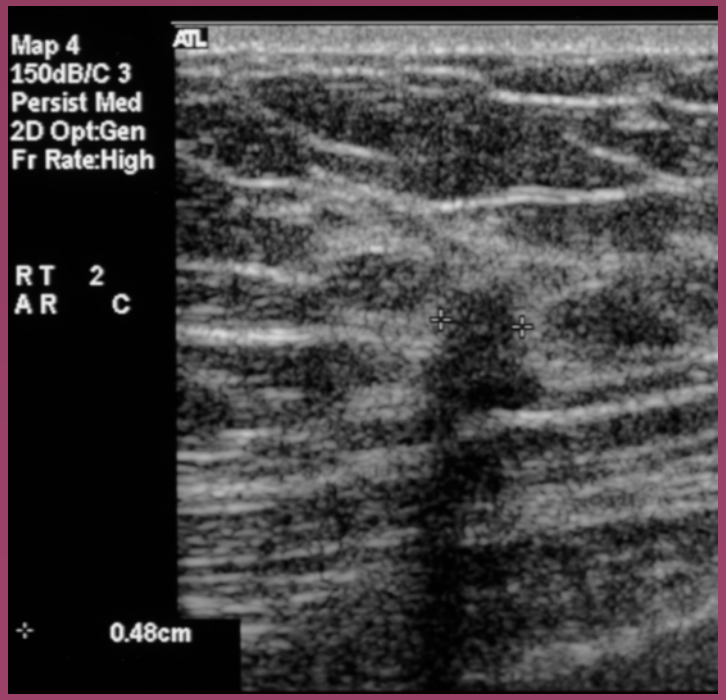
New Modalities

- **Anatomic**
  - **Tomosynthesis**
  - **CT**
  - **US**
- **Functional**
  - **MRI**
    - **Spectroscopy**
    - **Diffusion weighted imaging**
  - **Gamma imaging**
  - **PET**

Screening US

ACRIN 6666/Avon trial

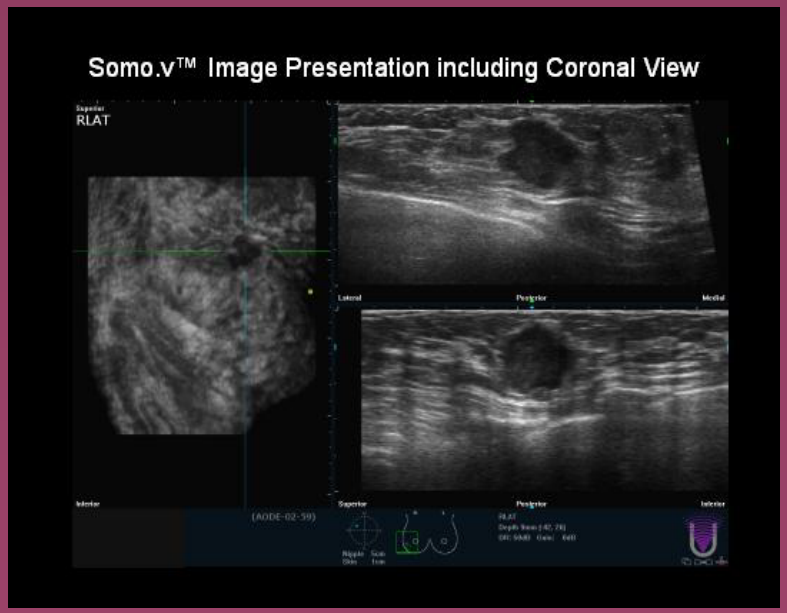
- **2809 high-risk women had mammo + screening US, 1 year follow-up**
- **40 women (41 breasts) with CA**
- **Additional 4.2 CA/1000**
- **8.9% PPV for US lesions**



Berg WA. JAMA 2008

Automated Whole Breast US

- **61 women with 14 cancers detected on screening hand-held US**
  - **Sensitivity of Automated Breast US 57-78%**
- **101 breasts/87 women had both HH and ABUS**
  - **71/78 (91%) lesions on HH also on ABUS**
  - **9/11 additional BI-RADS 4-5 lesions on ABUS not reproducible on HHUS**



Chang J. RSNA 2008

Hovanessian L. RSNA 2008

Cancer Detection by Modality

	Mammo	US	MRI
Lehman, 2007	0.6%	1.2%	3.5%
Kuhl, 2000	1.6%	1.6%	4.7%
Warner, 2004	3.4%	3.0%	7.2%
Italian Multi-Center, 2002	1.0%	1.0%	7.6%

MR vs. Mammo/US

- **195 high risk women, 171 completed all studies**
- **6 cancers, 3.5%**

	Cancers detected	Diagnostic Yield	Biopsy	PPV
MRI	**6**	**3.5%**	**8.2%**	**43%**
Mammo	**2**	**1.2%**	**2.3%**	**50%**
US	**1**	**0.6%**	**2.3%**	**25%**

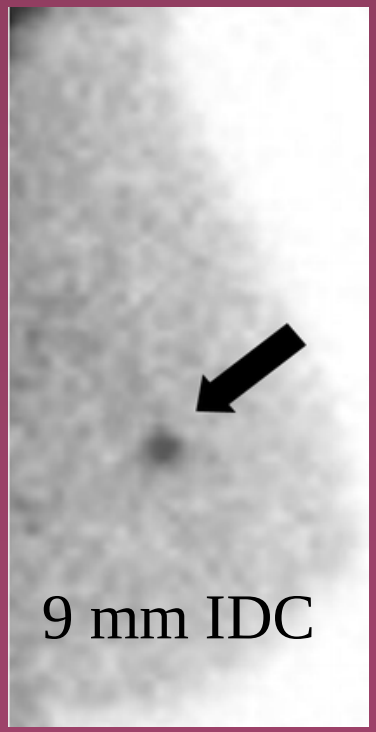
Lehman CD. Radiology; 2007

Breast Specific Gamma Imaging (BSGI)

- Dedicated detector
- Inject 20-30 mCi ^{99m}Tc sestamibi
- Wait 10 minutes
- Image each breast (about 10 min per view)

Breast Specific Gamma Imaging (BSGI)

- 94 high risk women with negative mammo and CBE
- 16 abnormal BSGI (17%)
  - 2 with invasive cancer at biopsy (PPV 12%)



Brem RF. Radiology 2005

BSGI Performance

- **146 patients with 167 lesions undergoing biopsy (83 cancers)**
  - **BSGI 80/83 cancers (sensitivity 96%). Smallest IDC and DCIS each 1mm**
  - **50/84 true negative benign lesions (specificity 60%)**
  - **PPV 69%, NPV 94%**

Brem RF. Radiology 2008

BSGI Detection of ILC

- **Invasive lobular carcinoma**
  - **26 women**

	Sensitivity
Mammo	79%
US	68%
Gamma	93%
MRI	83%

Brem R. AJR 2009

BSGI compared to MRI

- **48 patients with 63 indeterminate lesions on mammography underwent both BSGI and MRI**
  - **21 cancers, 5 high-risk**
  - **Sensitivity of BSGI 96%, MRI 88%**
  - **Specificity of BSGI 46%, MRI 27%**

Lanzkowsky L RSNA 2008

BSGI: Detection of DCIS

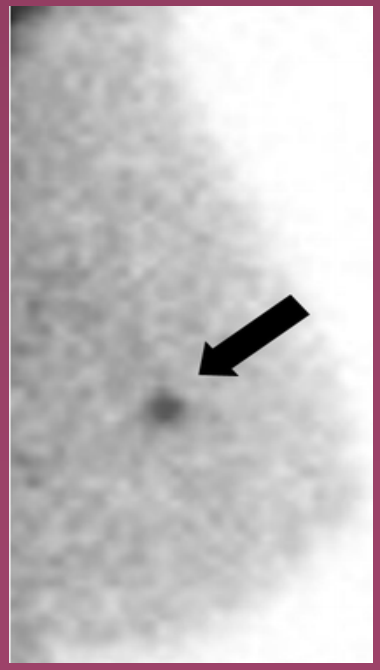
- **20 women with 22 DCIS lesions**
  - **Mammo, MRI, BSGI**
  - **2-21 mm**
  - **2 lesions only on BSGI in contralateral breast**

	Detection
Mammo	**18/22 (82%)**
MRI	**7/8 (88%)**
BSGI	**20/22 (91%)**

Brem R. Acad Rad 2007

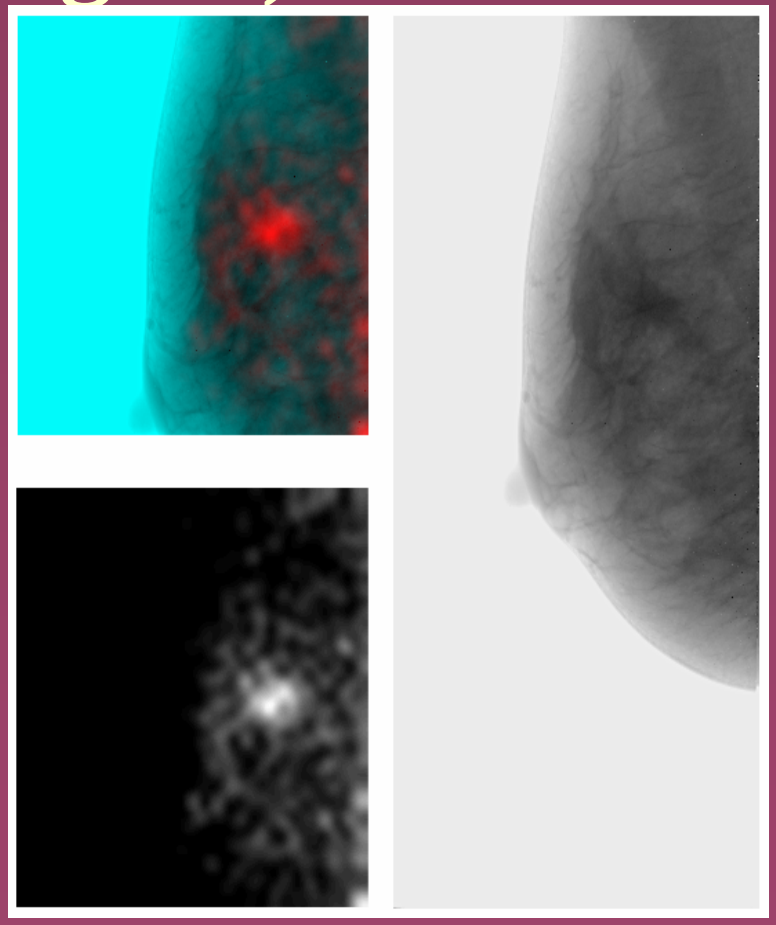
Limitations of BSGI

- **Hot lab**
- **No Biopsy capability**
- **Small series by a limited number of investigators**



Hybrid Imaging (BSGI-Digital)

- **Fused BSGI and digital mammogram**

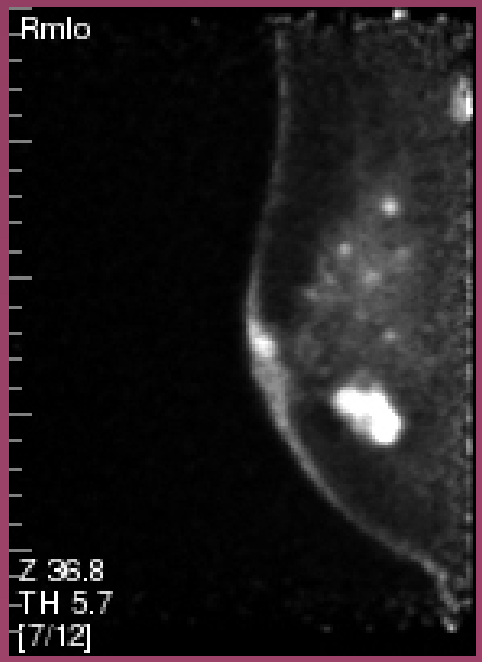


Positron Emission Mammography (PEM)

- Fasting 4-6 hours
- Inject ^{18}F-FDG IV
  - 1 Rad whole body dose
  - Shielding
- Wait one hour (not active)

Positron Emission Mammography (PEM)

- **Small Studies to Date**
- **23 BI-RADS 5 lesions**
  - **Sensitivity 86%**
  - **Specificity 33%**
  - **PPV 90%**



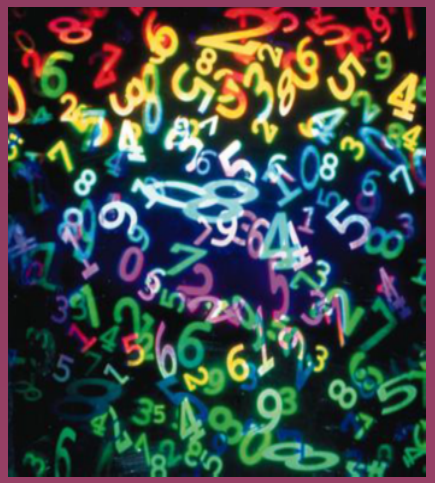
Rosen EL. Radiology 2005

PEM

- **113 women (133 breasts) with biopsy proven cancer**
- **PEM detected 107/119 cancers**
  - **Sensitivity 90%**

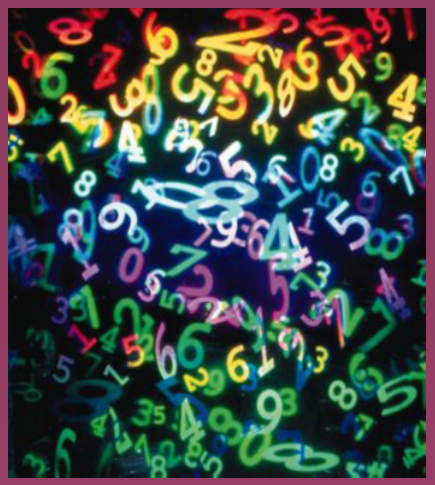
Schilling K. RSNA 2008

Lifetime Risk



	>20%	15-20%	<15%
Mammo	X	X	X
MRI	X	?	
HH US	X	?	

Lifetime Risk: Future Strategies?



	>20%	15-20%	<15%
Tomo/CT	X	X	X
MRI	X		
ABUS		X	
BSGI	?	?	
PEM	?	?	

Conclusions

- **Breast MRI highly sensitive for detection of invasive cancer in a high risk population**
- **Moderate specificity and lower pre-test probability make MRI less useful for screening moderate risk women**
- **Other modalities, such as whole breast US, BSGI and PEM may play a role in adjunct screening in moderate risk women**

Cancer Risk by Site for BRCA Carriers

Table 5. Population relative risks and 95% confidence intervals of cancer by mutation status and cancer site*

Cancer site	BRCA1	BRCA2
Ovary	21 (12 to 36)	7.0 (3.1 to 16)
Breast		
Females	11 (7.5 to 15)	4.6 (2.7 to 7.8)
Males	–†	102 (9.9 to 1050)
Colorectum	–†	1.3 (.35 to 5.1)
Stomach	4.8 (1.5 to 15)	3.4 (.87 to 13)
Lung	1.3 (.30 to 5.6)	.46 (.020 to 11)
Kidney, bladder	4.4 (1.5 to 13)	–†
Leukemias, lymphomas, etc	3.7 (1.5 to 9.5)	–†
Liver, gallbladder, bile duct	8.1 (2.0 to 33)	4.6 (.73 to 28)
Prostate	.65 (.051 to 8.3)	2.7 (1.1 to 7.1)
Pancreas	3.1 (.45 to 21)	6.6 (1.9 to 23)
Uterus	1.7 (.17 to 17)	1.6 (.15 to 16)
Testis	17 (1.3 to 230)	–†
All cancers		
Females	6.7 (5.0 to 8.8)	3.0 (2.0 to 4.5)
Males	1.6 (.87 to 2.9)	1.6 (.85 to 2.9)

From Risch et al. JNCI 2006.