

# Benefits and Risks of MRI in Breast Screening

American Society of Breast Disease

*30<sup>th</sup> Anniversary Symposium*

April 27-29, 2006

*Alan B. Hollingsworth, M.D.*

*Medical Director, Mercy Women's Center*

*Oklahoma City, OK*

...as viewed by:



High Risk Clinic – n=1,000

Risk Assessment  
(tissue & F.H.)

Genetic counseling/testing

Risk Reduction

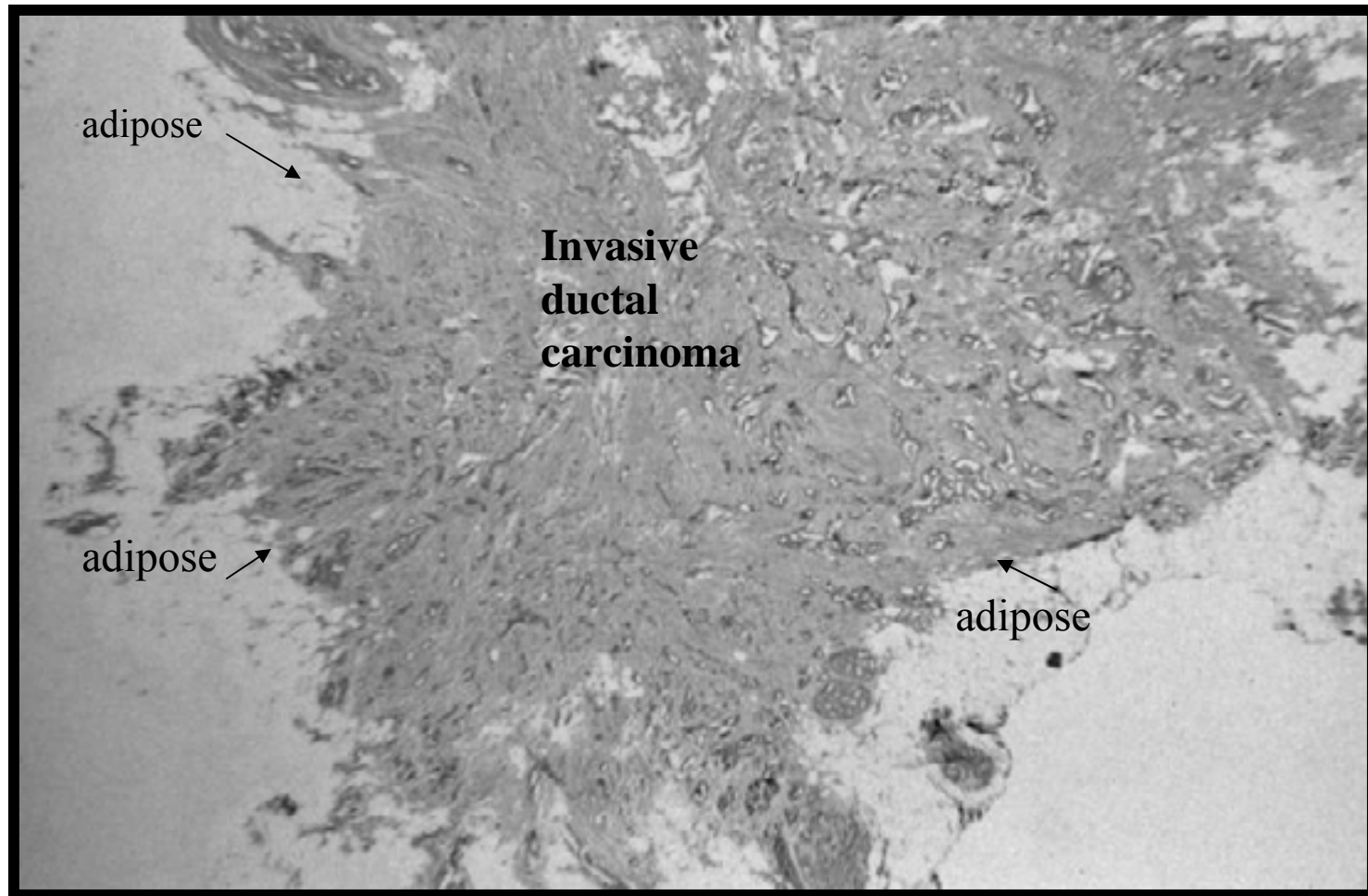
Multi-modality Imaging

Screening Research

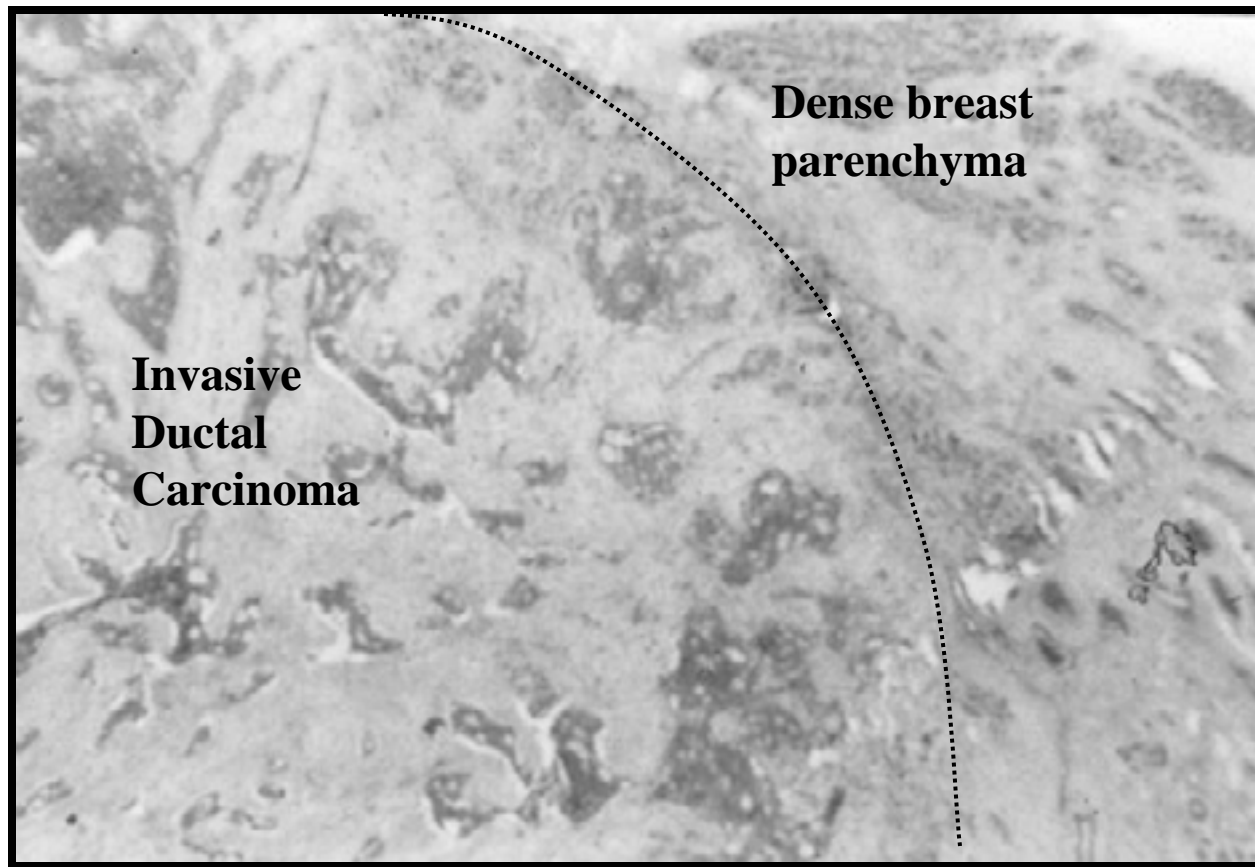
Mercy Women's  
Center radiologists



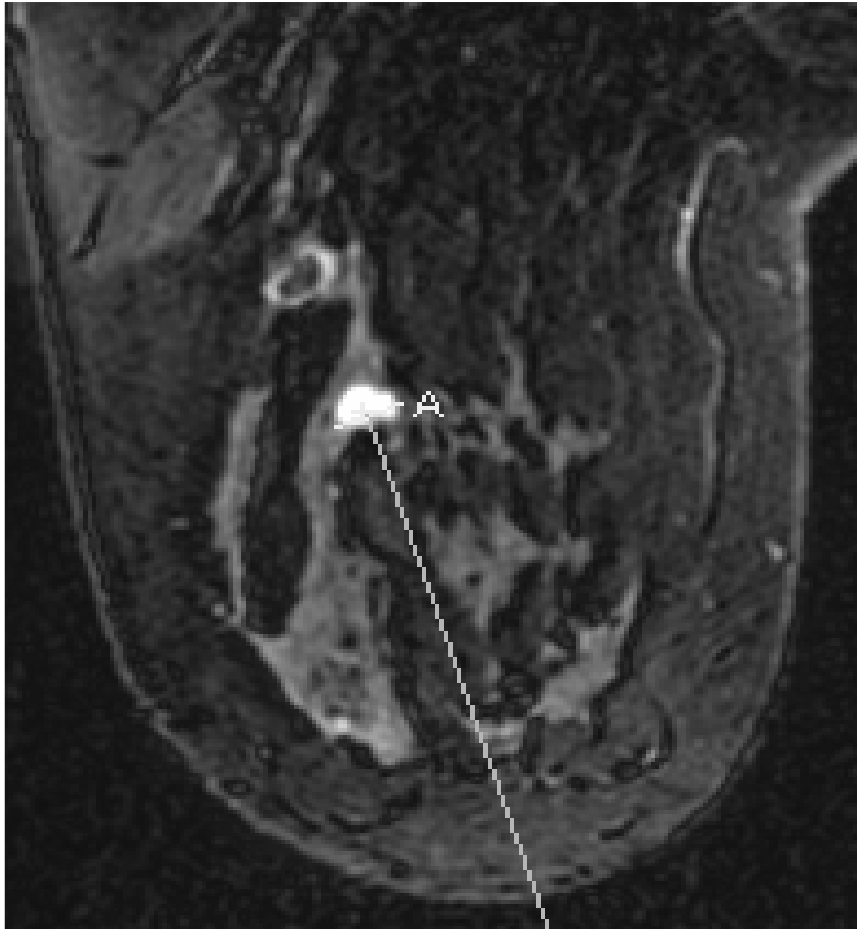
1.5 Tesla Breast-dedicated MRI  
with bil. RODEO™ High-Res-Plus  
3,800 studies since January '02



Cancer (without calcium) has to interface with lower density tissue (preferably fat) at some point in order to be seen on mammography. X-ray attenuation (stopping power) is low for fat, high for cancer.



If a cancer interfaces with dense breast parenchymal tissue around its surface area, it will NOT visualize on mammography (unless it contains calcium)...*indirectly* related to overall breast density



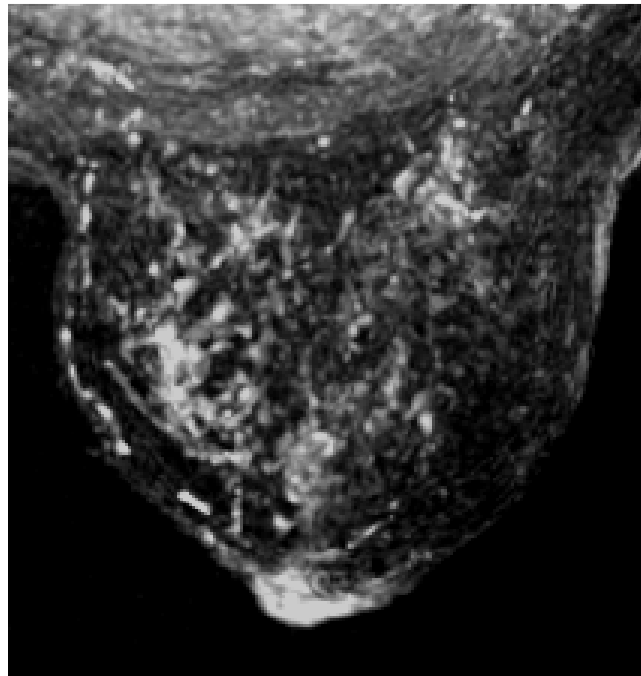
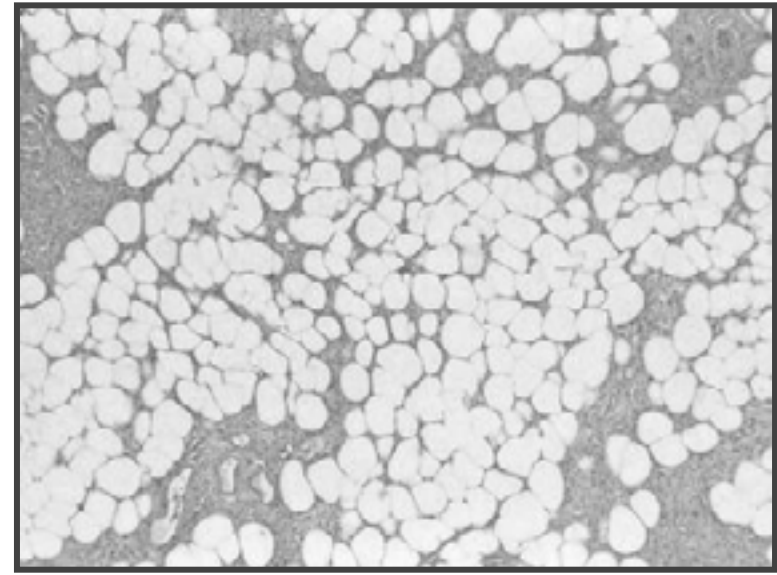
Incidental finding  
on RODEO™  
MRI.

Second-look  
ultrasound could  
not locate this  
lesion.

MRI-directed  
biopsy showed  
Invasive Ductal  
Carcinoma.

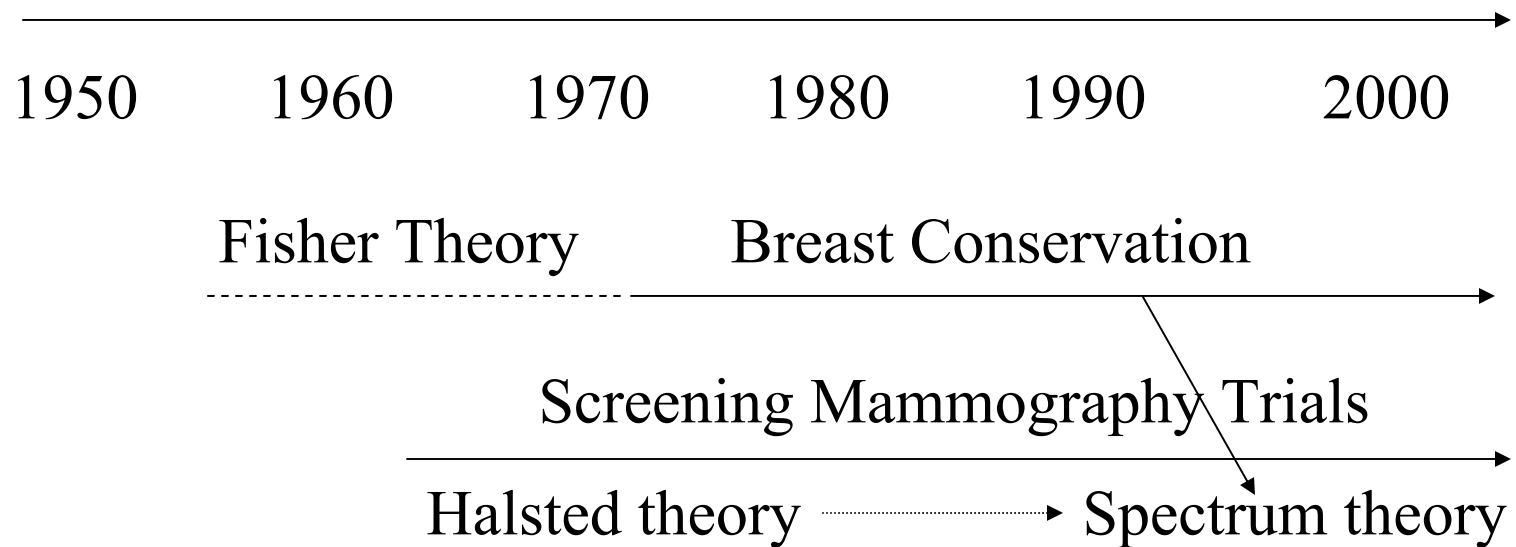
## DIFFUSE HISTOLOGY

LOBULAR OR DUCTAL  
E-cadherin = invisibility?



Although not 100%, MRI is  
the most sensitive imaging  
modality for ILC

# Does Early Detection Save Lives?



While widespread mammographic screening *facilitated acceptance* of breast conservation, the true foundation of lumpectomy rests in a competing biologic theory.

“Just because you’re finding cancer earlier with MRI does not mean you are saving lives...”

BIOLOGY – Fisher vs. Spectrum

premenopausal vs. post

bimodal theories

basal, luminal, etc.

*SOME* “biologies”  
are unaffected by  
early detection as we  
know it today

EPIDEMIOLOGY – *INHERENT BIAS* in retrospective studies and/or non-randomized prospective studies:

LEAD TIME bias

LENGTH TIME bias

The mortality reduction seen in the prospective mammography screening trials was not simply a victory for X-ray technology...

...but a victory for EARLY DETECTION.

**BIOLOGY & EPIDEMIOLOGY** were also on trial.

**TRIAD**

{ *Sensitivity* of the modality  
Biology/natural history  
Epidemiology

*Mammography was able to accomplish the 25-30% mortality reduction (15-20% for ages 40-49) with only “modest” sensitivity.*

Question:

What *is* the Sensitivity of Screening Mammography?

Evasive Answer:

It depends on how you: 1) define threshold of detection, 2) identify the invisible cancers (false negatives), & 3) account for age/breast density

“5-10% of cancers do not visualize on mammography”

This “90-95% sensitivity” is based on PALPABLE cancers and is not applicable to asymptomatic screening

For sensitivity data in asymptomatic screeners...

- 1) Follow up -- sensitivity declines in direct correlation to the duration – 6, 12, 24 months.
- 2) Simultaneous imaging (US and/or MRI) -- sensitivity approximates 12-24 month follow-up

***Threshold of detection: If an imaging technique were able to detect 100 malignant cells, sensitivity of MRI would likewise plummet.***

Dept. of Biostatistics MD Anderson (Yu Shen) &  
Harvard School of Public Health (Marvin Zelen)

## **Screening Sensitivity and Sojourn time from Breast Cancer Early Detection Trials: Mammograms & PE**

*J Clin Onc* 2001;19:3490-3499

**HIP – 39%**

**Malmo – 61%**

(Swedish Two-County – 40-49 = 53%; 50-59 = 75%; 60-64=69%; 70-74=92%)

**Stockholm 40-49 – 64%**

**50-59 – 89%**

**Edinburgh – 63%**

**Canada 1 (40-49) – 61%**

**Canada 2 (50-59) – 66%**

**Mammography  
Sensitivity**

# Diagnostic Performance of Digital versus Film Mammography for Breast-Cancer Screening

Pisano ED, Gatsonis C, Hendrick E et al. *New Engl J Med* 2005;353:

ACRIN/DMIST Investigators Group

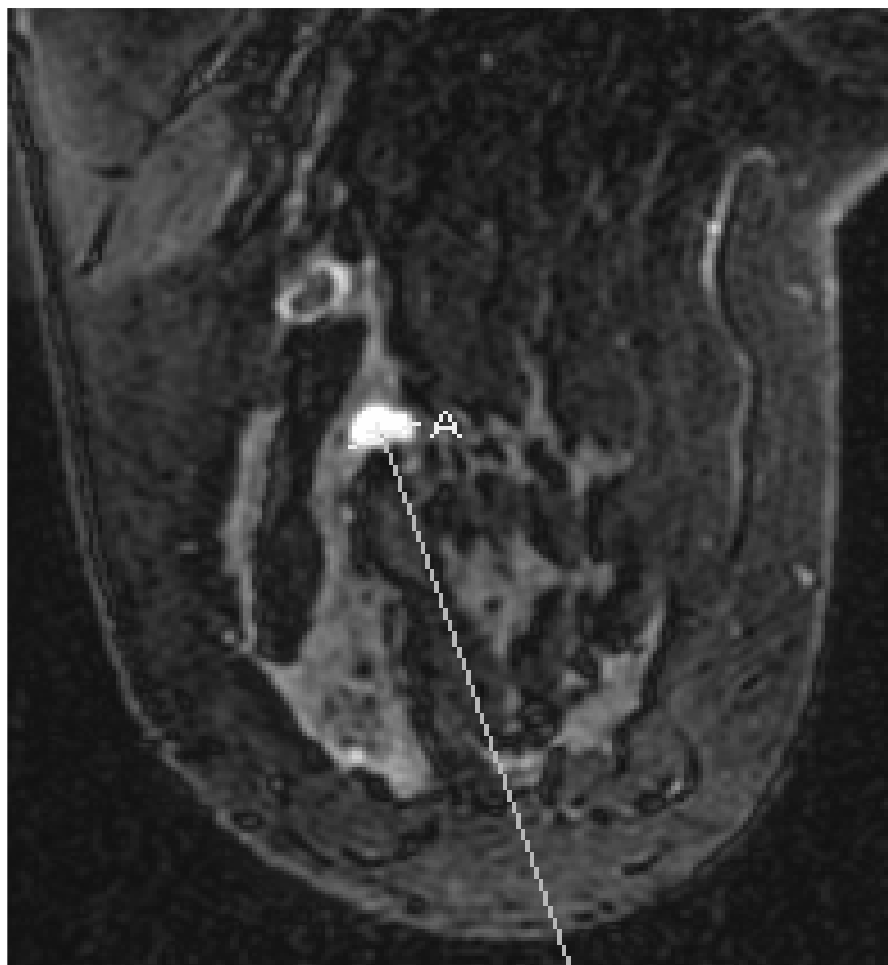
42,760 women @ 33 sites

*365 day follow-up:*

Overall Sensitivity = 70% digital 66% film

*455 day follow-up:*

Overall Sensitivity = 41% digital 41% film

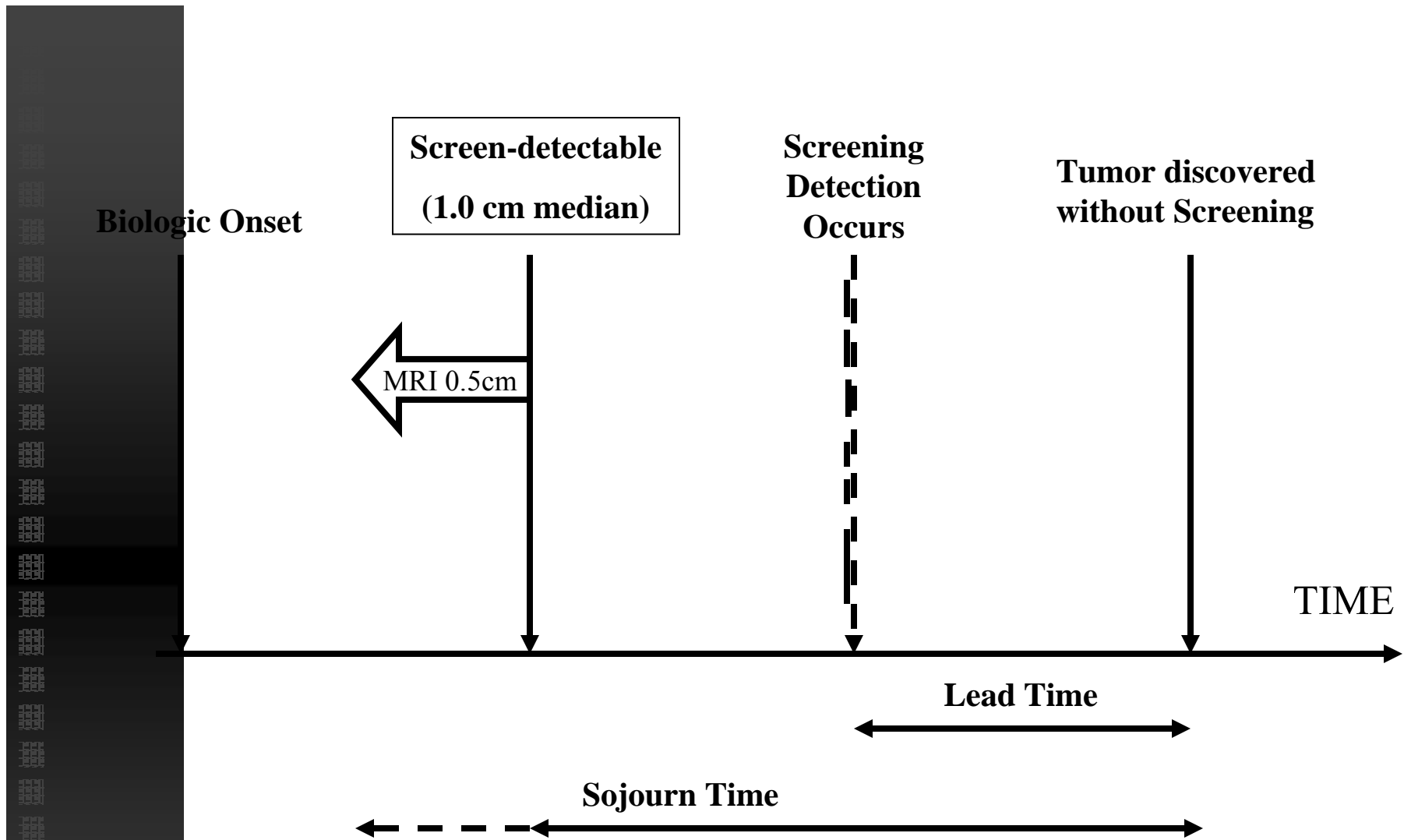


Mammographic “early detection” in 2007...  
but a “missed cancer” in 2006

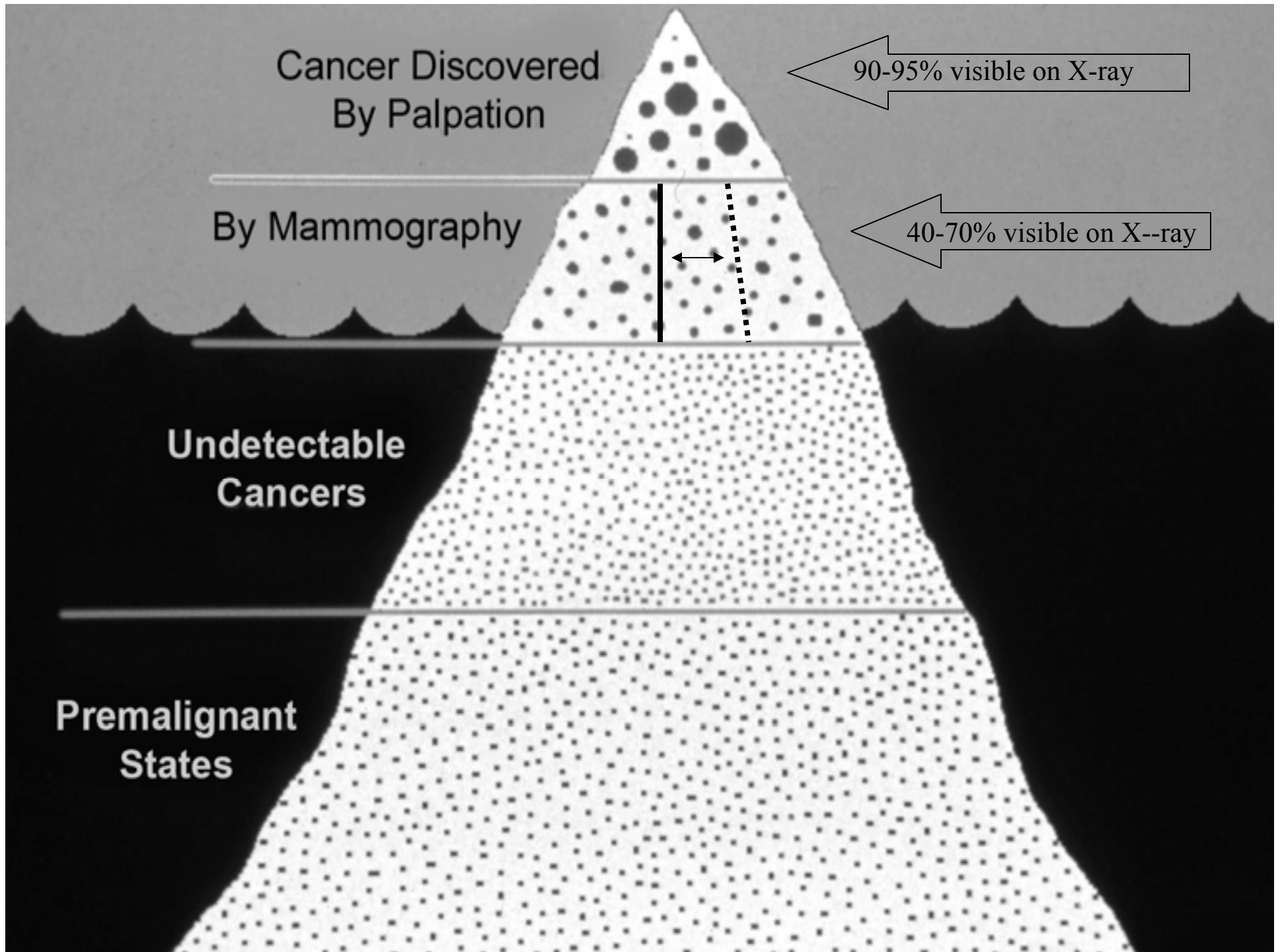
If “50% sensitivity” can reduce mortality...  
then EARLY DETECTION is a more powerful  
intervention than the mammography trials  
would suggest.

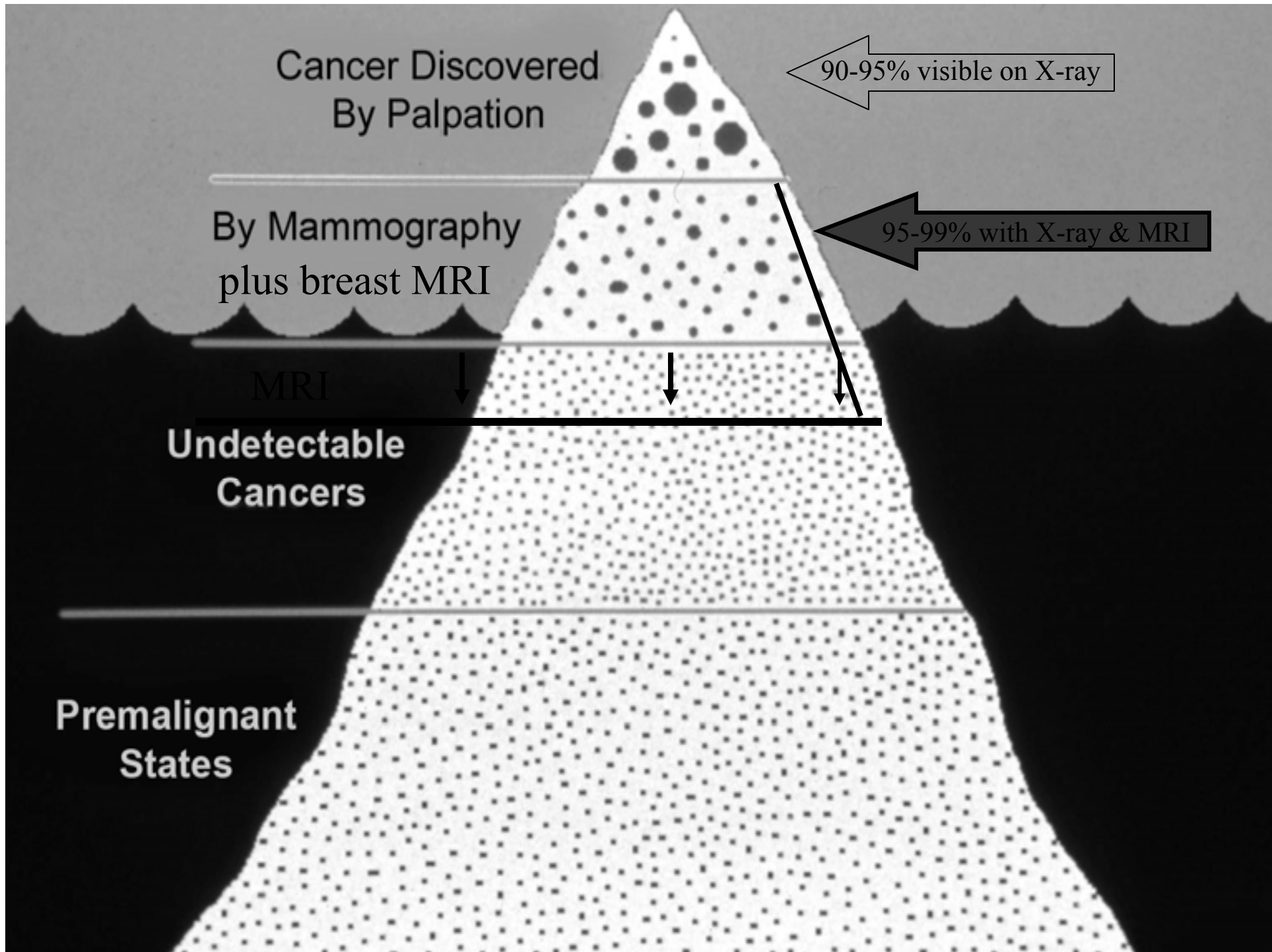
MRI sensitivity (*95% with high resolution*):

- 1) Detects the “detectable” cancers missed on X-ray
- 2) Earlier detection by lowering threshold of detection



Both ultrasound and MRI help close the dotted line above, thus improving detection, while MRI also lowers threshold of detection.





May 2003 – American Cancer Society  
breast cancer screening guidelines:

*Consider* ultrasound and/or MRI for  
high-risk patients

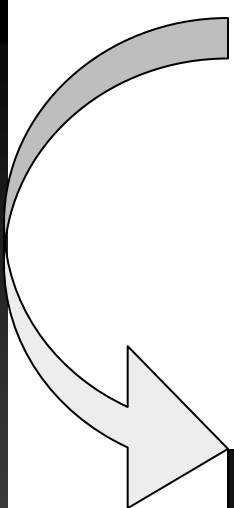
(no firm recommendations; no interval recs)

# Sensitivity of Breast MRI vs. Mammography

		<b>Mammo Sensitivity</b>	<b>MRI Sensitivity</b>
<i>Germany</i>	Kuhl et al. (n=192)	33%	100%
<i>Netherlands</i>	Tilanus-Linthorst et al. (n=109)	0%	100%
<i>Italy</i>	Podo et al. (n=105)	13%	100%
<i>Canada</i>	Warner et al. (n=236)	36%	77%
<i>Netherlands</i>	Kriege et al. (n=1909)	40%	71%
<i>Germany</i>	Kuhl update (n=529)	33%	91% (100% hi risk)
<i>U.S./U Penn</i>	Rosen et al (n=147)	12%	75%
<i>U.K.</i>	MARIBS study group (n=649)	40%	77%
<i>U.S./MSK</i>	Morris et al. (n=367 <i>retrospective</i> )	“normal”	14/367

## Breast MRI vs. Mammography %-age of patients who are BRCA+ in screening trials

Kuhl et al. (n=192)	18%
Tilanus-Linthorst et al. (n=109)	11%
Warner et al. (n=236)	<u>100%</u>
Kriege et al. (n=1,909)	19%
Kuhl (update – n=529)	8%
MARIBS (n=649)	19%
Morris (retrospective n=367)	5%



**Quadruple modality: 2/22 by exam (one interval cancer);  
8/22 detected by mammography; 7/22 by ultrasound;  
17/22 by MRI with 7/22 detectable by MRI alone**

# Detection of Cancers by MRI according to risk group:

Kuhl et al. n=529 (radiologists blinded)

MRI sensitivity overall = 91%

	<b>Mammo sens.</b>	<b>U.S. Sens.</b>	<b>Mammo + U.S.</b>	<b>MRI</b>
Prior CA	n=12/139	<b>33%</b>	<b>41%</b>	<b>66%</b>
<u>20%</u>	n= 6/110	<b>50%</b>	<b>83%</b>	<b>100%</b>
21-40%	n=20/241	<b>25%</b>	<b>45%</b>	<b>100%</b>
BRCA+	n=8/42	<b>25%</b>	<b>38%</b>	<b>100%</b>

Prior CA

20%

21-40%

BRCA+

## Kuhl et al (n=529)

Invasive tumor size, nodal status, shift to DCIS – used to be dismissed as “length time bias sampling”...but studies are now confirming these parameters as valid intermediate markers.

	Median size	+nodes	DCIS
Detected by mammography –	1.2cm	4/10	3/9
Detected by ultrasound –	1.3cm	5/12	0/9
Detected by mammo & u.s. –	1.3cm	5/16	3/9
Detected by MRI (overall) –	1.1cm	5/31	8/9
Detected by MRI alone –	0.75 cm	0/14	5/9

Volume of sphere with 1.2cm diameter = .90cc

Volume of sphere with 0.75cm diameter = .22cc

$$\text{Volume} = \frac{4}{3}\pi r^3$$

# Risks of MRI screening

- 1) Call-backs – 1/5 premenopausal & 1/10 post
- 2) One-half of call-backs = biopsy
- 3) Overtreatment of “subclinical” disease
- 4) Anxiety
- 5) Cost

*#1 & #2 deal with Specificity...*

*Specificity* of Mammography is greater than MRI in most studies...

	X-ray	MRI
Kriege et al. (Netherlands)	95.0%	89.8%
Warner et al. (Canada)	99.8%	95.4%
MARIBS (U.K.)	93.0%	81.0%

but not all...

## Kuhl et al. (Germany)

	Specificity	PPV
Mammography –	96.8%	23.7%
Ultrasound –	90.5%	11.3%
Mamm + U.S. –	89.0%	11.9%
MRI –	97.2%	50%
Mamm + MRI –	96%	42%

ACR guidelines for mammography PPV:

PPV-1 (based on abnormal screen) = 5-10%

PPV-2 (based on bx recommendation) = 25-40%

PPV-3 (actual bx's) = no guidelines (25-40%?)

## Biopsies and PPV in MRI screening trials

	%-biopsied based on MRI	PPV-3 of MRI-prompted biopsies
Kuhl et al.	7.3%	64%
Tilanus-Linthorst	4.6%	60%
Podo et al.	8.6%	89%
Morris et al.	16.0%	24%
Warner et al.	--	46%
Kriege et al.	2.9%	57%

While it is difficult to compare studies with regard to Specificity and PPV , confounded by different MRI techniques (*dynamic vs. high resolution*)...

The real challenge of triple-modality imaging is that the “false positives” are **ADDITIVE**.



# *Proposed* American Cancer Society Guidelines for Breast Cancer Screening: HEREDITARY RISK

## Annual screening MRI and mammography

- BRCA carriers
- Untested 1<sup>st</sup> degree relative of BRCA carrier
- 3 or more relatives on same side of family (at least one being 1<sup>st</sup> degree) with premenopausal breast cancer, or ovarian cancer at any age
- One of above with personal history of breast cancer

No special recommendations for moderately increased risk  
(15-25% lifetime; 2 first or second-degree relatives)


*Proposed* American Cancer Society  
Guidelines for Breast Cancer Screening:  
NON-HEREDITARY RISK

Annual Screening MRI and mammography  
Radiation exposure prior to age 30 (*no data*)

No special recommendations pending further  
research:

LCIS (low resolution MRI may not see ILC)

Moderately high risk: (15-25%): atypical  
hyperplasia, very dense breasts



Given that MRI is being superimposed on  
annual mammography, what is a  
reasonable interval for breast MRI?

# BREAST DENSITY

the “Rodney Dangerfield of Risk Factors”

RR = 2.0 or greater in all studies since Wolfe in 1976  
Gail still wrestling, but adopted by IBIS-II (*50% or greater*)

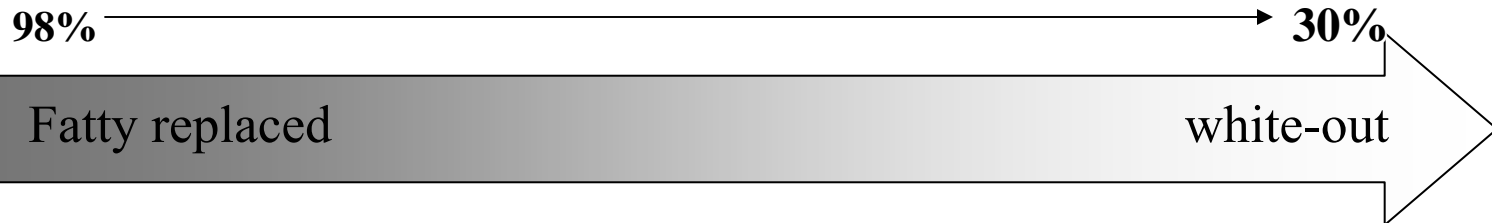
Lifetime Risk of breast cancer with dense  
mammography (est. 20%) would have allowed entry  
into the 2 largest MRI screening trials mentioned.

THESE ELEVATED-RISK PATIENTS ARE  
THE VERY PATIENTS IN WHOM WE ARE  
MOST LIKELY TO MISS CANCER ON  
MAMMOGRAPHY.

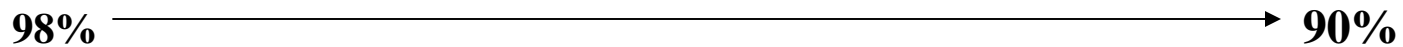
RISK – %/yr *regardless* of risk origin

DENSITY – dictates %-age of missed cancers

X-ray



MRI



Proposal: Breast density should be an integral part of recommendations for auxiliary screening (MRI or U.S.)

*Back-of-the-envelope calculations suggest density as a more helpful parameter than level of risk...*

“Thought experiments in breast screening” based on  
RISK and DENSITY

$N = 1,000$  at a particular risk level

Risk *incidence* as %/yr

Calculate # cancers in 10 years

Pick a density level & corresponding sensitivities

Calculate # of cancers that will be detected by X-ray

Calculate # of cancers that will be detected by MRI

Calculate # of cancers detected by MRI alone

- a) n=1,000 40 y/o BRCAs with fatty replacement on mammography  
3%/year = 300 cancers in 10 yrs. 98% X-ray and MRI sensitivity = 294 by X-ray; 294 by MRI; 0 by MRI alone
- b) n=1,000 40 y/o with LCIS and white-out on mammography  
1%/year = 100 cancers in 10 yrs. 30% X-ray/90% MRI sens. = 30 by X-ray; 90 by MRI; 60 by MRI alone
- c) n=1,000 40 y/o with no risk factors other than white-out  
0.5%/year = 50 cancers in 10 yrs. 30% X-ray/90% MRI sens. = 15 by X-ray; 45 by MRI; 30 by MRI alone

# Mercy Women's Center Screening Protocol for Auxiliary Imaging

Uses a RISK + DENSITY index for  
recommendations and interval.

# **3 RISK LEVELS based on “Current Comprehensive Assessment and Management of Women At Increased Risk for Breast Cancer”**

*Am J Surg* 2004; 187:349-362

## **■ STEERING COMMITTEE**

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**■ Rebecca Garcia, PhD**

**■ Joyce O’Shaughnessy, MD**

**■ S. Eva Singletary, MD**

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**Lisa Newman, MD**

“Average Risk” = 1 point  
“Elevated or High Risk” = 2 points  
“Very High Risk” = 3 points

Examples of “Very High Risk”:

BRCA+

2 or more 1<sup>st</sup> degree relatives with breast/ovarian

Breast irradiation prior to age 20

LCIS

ADH/ALH or cellular atypia AND 1<sup>st</sup> degree relative

# ACR – BIRADS guidelines for *DENSITY*

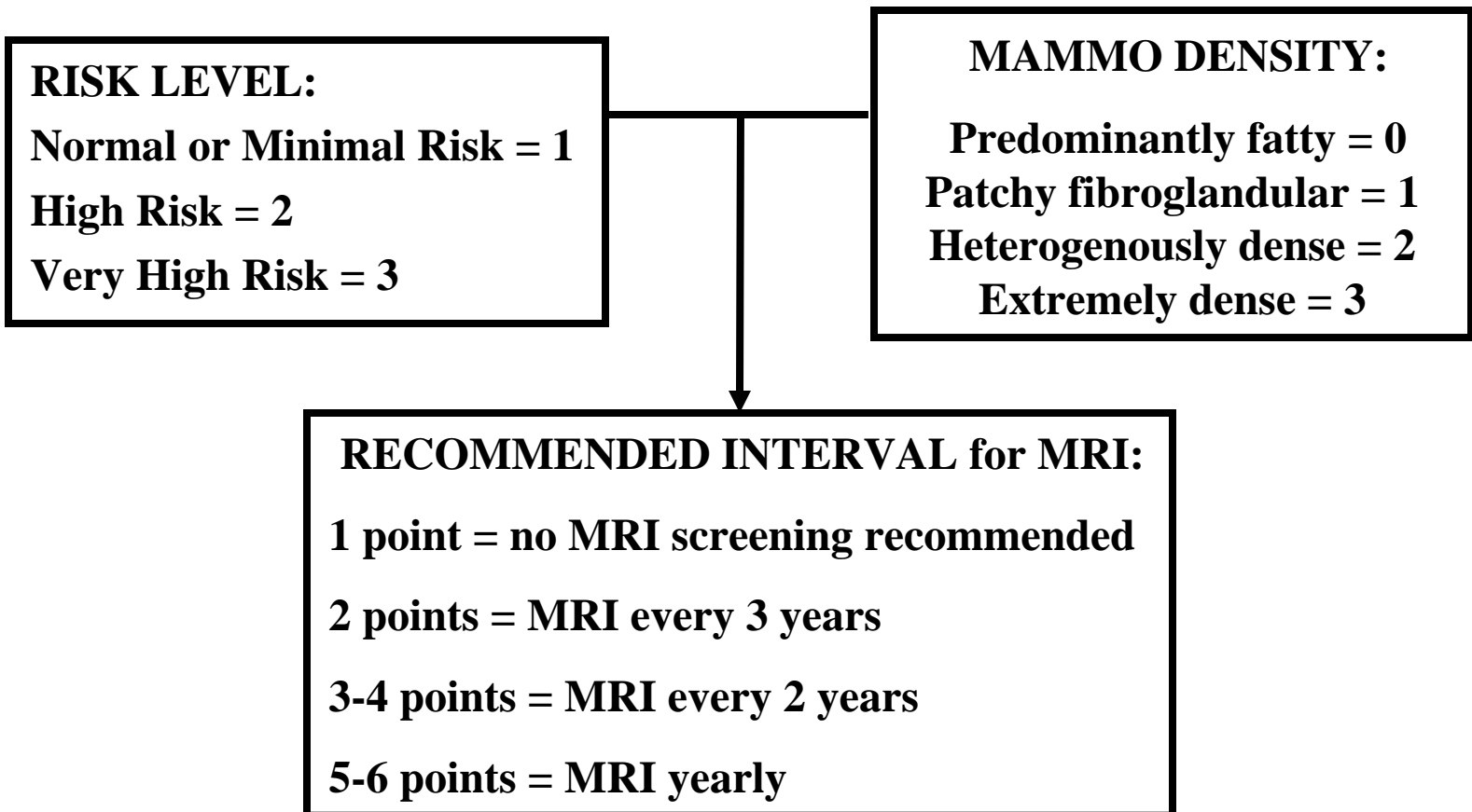
0-25% -- “predominantly fatty” (0 points)

25-50% -- “scattered f-g densities” (1 point)

50-75% -- “heterogenously dense” (2 points)

75-100% -- “extremely dense” (3 points)

# Mercy Women's Center MRI Screening Recommendations



## Mercy Women's Center experience to date:

Out of 107 first-screens (11% BRCA+)...3 invasive cancers detected by MRI only (13 call-backs; 7 biopsies):

#1 – Risk: Sister with postmenopausal breast CA – 1.1cm Gr 3 IDC

#2 – Risk: Hx of ADH – 1.0cm Gr 1 IDC in the contralateral breast

#3 – Risk: prior hx of low grade DCIS – 1.0cm Gr. 2 IDC in contralateral breast

Second screens:

#1 – Risk = 34 y/o BRCA2+ – large area of hi-grade DCIS; normal MRI one year earlier.

In newly diagnosed breast cancer patients, the contralateral breast can be considered screening. From March 2003 thru December 2004, 334 consecutive patients with newly diagnosed breast cancer underwent pre-op staging MRI at MWC.

### Contralateral “normal” breast:

12/334 (3.6%) had occult cancer on MRI alone

14/367 (3.8%) in prevalence screen at MSK retro study

11/12 were invasive (9 of 11 ductal)

8/12 – occult cancer had same or worse stage

3/12 – primary was DCIS, but contralateral was Stage I in 2 patients, Stage IIA in 1.

Mercy Women's Center  
Contralateral Cancers in Pre-op Staging with MRI  
(continued)

18/334 (5.4%) total contralateral cancers

4/18 detected by mammo – 22.2% sensitivity

16/18 detected by MRI – 88.9% sensitivity

(2 false negatives on MRI – both ILC on 0.5 Tesla)

12/16 detected by MRI alone

## Informed Consent prior to MRI screening:

- 1) Risk assessment (BRCA testing if indicated) & discussion of all options
- 2) Review of actual films for density level
- 3) Discussion of calculated interval for MRI
- 4) Discussion of benefit
- 5) Discussion of risk
- 6) 1 in 5 call back for premenopausal (50% bx)
- 7) 1 in 10 call back for postmenopausal (50% bx)
- 8) Risk of false-pos lower on subsequent screens

# Recommendations of the International Working Group on Breast MRI – Screening Group

Constance Lehman, MD, PhD (group leader) Schnall MD, Kuhl CK, Harms SE

High Risk only – 15% min. 25% preferred

Experience in Diagnostic MRI prior to screening program

MRI-guided bx capability

Partner with high-risk clinic or risk expert

Informed consent for “false positives” and alternatives

Track data

Technical requirements (1.5 Tesla preferred)

# Reimbursement

BC/BS TEC (2003) recommends reimbursement for BRCA+ and patients at high risk of BRCA+

Private insurance – unpredictable

Medicare – screening not covered in guidelines

Private Pay – reduced charges

*Mammographic* screening is NOT cost-effective  
(insurance coverage for screening was legislated)  
estimates range from \$500,000 to \$1.2 million to save one life

Since breast MRI is 5-10X the cost of  
mammography, we need better patient  
selection for screening.

Beyond Risk...Beyond Density...

Low Cost Screening Blood Test to complement  
mammography, efficiently selecting patients for the other  
modalities (Ultrasound and/or MRI)

Ferritin-bearing lymphocytes and T-cell levels in  
peripheral blood of patients with breast cancer.

Moroz, C, Shamai G, Kupfer B, Urca I. Cancer  
Immunology, Immunotherapy (1977). Vol. 3:101-105.

Rogoff-Wellcome Medical  
Research Institute & Dept.  
of Surgery, Beilinson Med  
Center & Tel-Aviv  
University Medical School

circa 1992





Over 4,000 serum aliquots on 850 patients ( -80C freezer), *tied to breast MRI results* and a pathology database, through an IRB-approved program.

# Blood Test Collaborations

1992-1998	Beilinson Med Center	(Tel Aviv, Israel)
2000-present	Matritech	(Newton, MA)
2003-2005	CeMines	(La Jolla, CA)
2003-2005	Fred Hutchinson	– Dr. N. Urban
2004-present	Power3 Medical	(The Woodlands, TX)
2005-present	A&G Pharm	(Columbia, MD)
2006	DiaGenic	(Oslo, Norway)

If he signs a research agreement with one more group, I'm going to scream!!



Sharon Nall, RN, MS, CNS, OCN, formerly a medical technologist, carries out the blood test research. She is also a Certified Breast Nurse Navigator, her primary role at Mercy Women's Center

# Matritech Cancer Detection Product Pipeline

	Discovery	Preclinical	Clinical	Market
Bladder: NMP22 Microtitre format				
Bladder: NMP22 BladderCheck™				
Bladder: NMP22 Automated format (DPC)				
Cervical: NMP179				
Breast: NMP66				
Prostate: NMP48				
Colon: NMP35				

**Cover:** Dr. Rosemary Duda, surgical oncologist at Beth Israel Deaconess Medical Center, Boston, MA, with patient Jill Brown. Dr. Duda and physicians at six other breast cancer centers in the United States are participating in the NMP66 trial designed to confirm its clinical utility in improving the detection of breast cancer in their patients.

## *Preliminary Results for NMP66:*

**Proof of Concept Data (Mass Spectrometry):** In Stage 0 (n=5), I (n=5), & II (n=14) patients, Sensitivity was 96% and Specificity was 93%.

23/24 cancers detected...only miss was 1/5 DCIS

26/28 “benign” controls were Negative.

### **RT-PCR:**

14 cancers/26 controls

Sensitivity = 93%

Specificity = 53%

### **Immunoassay:**

14 cancers/26 controls

Sensitivity = 50%

Specificity = 75%

# The Future of Breast Cancer Screening?

Mammography – Negative  
Blood Test – Negative



Re-check 1 year  
Hi-risk – blood test q 6mo.

Women under 40  
Women who decline mammography  
Countries without X-ray screening

Mammography – Positive  
Blood Test – Pos. or Neg.



Standard w/u...  
though blood test might  
guide decision for biopsy

Mammography – Negative  
Blood Test – *POSITIVE*



**MRI**



Mercy Health Center – Oklahoma City, OK

*Where the wind comes sweeping down the plains...*