Screening for Breast Cancer in High-Risk Women: Mammography, MRI, Ultrasound

Edward A. Sickles, M.D.

Learning Objectives

- Describe strengths / limitations of screening high-risk women using mammography, MRI, US
- Describe screening protocols for high-risk ♀
  - When to begin
  - How frequently
  - What modalities
  - How to sequence
  - When to end

Types of Evidence Supporting Screening

- Randomized controlled trials
- Case-control studies
- Prospective clinical studies
- Retrospective clinical studies
- Expert opinion
- Anecdotal reports

Data limited to randomized controlled trials involves screening only with mammography, only at ages 40-69, and only for average-risk women.

Mammography

At ages 40-69, for average-risk women, there is general consensus that the benefits of periodic screening with mammography exceed the “harms”.

At ages 70+, for average-risk women, there also is general consensus that benefits exceed “harms”, but not when life expectancy < 5 yrs or co-morbidity.

Benefits of Screening at Ages < 40

Cancers grow more rapidly

Very long life expectancy

Very infrequent co-morbidity

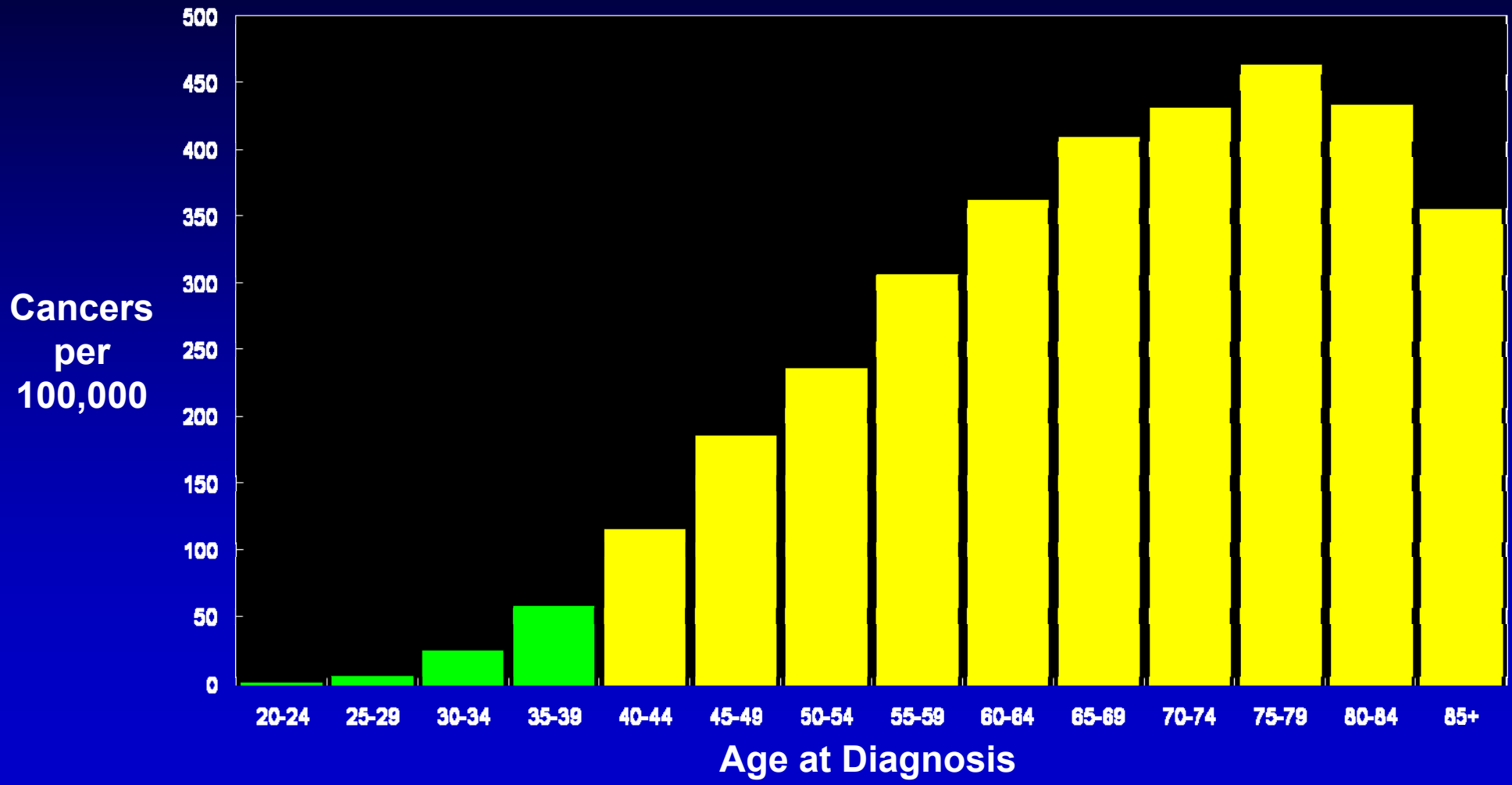
Limitations to Screening at Ages < 40

Reduced frequency of breast cancer

Somewhat reduced sensitivity

Slightly increased radiation risk

Age-Specific ♀ Invasive Breast Cancer Incidence, USA, 2000-2004



SEER Cancer Statistics Review (http://www.seer.cancer.gov/csr/1975_2004/results_single/sect_04_table.08.pdf)

To overcome this limitation for women at ages < 40, limit routine screening to high-risk subgroups of women.

Types of Evidence Supporting Screening

Randomized controlled trials

Case-control studies

Prospective clinical studies

Retrospective clinical studies

Expert opinion

Anecdotal reports

Cancer Detection Rate by Age at Screening

Age	Cancers	Exams	Rate/1000
30-39	8	2,476	3.2
40-49	193	58,873	3.3

UCSF Screening Mammography Practice, 1985-2007

Specific Indicators of High Risk

BRCA1 / BRCA2 gene mutation, etc.

Untested 1° relative of mutation carrier

Very strong family Hx of breast cancer

Previous chest radiation therapy ≤30y

Histologic diagnosis of LCIS / atypia

Personal history of breast cancer

Routine Mammo Screening at Ages < 40

- Annually, starting after histologic diagnosis of BC, LCIS, or atypia
- Annually, starting 8 years after chest radiation therapy
- Annually, starting at age 30 (earlier if BC family history < age 40); starting at age 25 if BRCA1 / BRCA2

Limitations to Mammo (High-Risk Women)

Breasts more likely to be dense

Somewhat reduced sensitivity

Higher interval cancer rate

Limitation to Other Modalities (High-Risk ♀)

Possibility of substantial overdiagnosis

More false positives (recall / SIFU / biopsy)

Substantially higher cost

MRI

Types of Evidence Supporting Screening

Randomized controlled trials

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Retrospective clinical studies

Expert opinion

Anecdotal reports

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.)*

Ca Cancer J Clin 2007; 57:75-89

Screening MRI Results

	NL	CA	UK	DE	US	IT	AU
# centers	6	1	22	1	6	17	1
# women	1,909	236	649	529	171	377	327
Age range	25-70	25-65	35-49	≥30	≥25	≥25	≥22
# cancers	50	22	35	43	6	18	28
# Ca MRI only	22	7	19	19	4	6	12

Ca Cancer J Clin 2007; 57:75-89. Radiology 2007; 242:698-715. Radiology 2007; 244:381-388. Clin Cancer Res 2007; 13:6144-6152

Screening MRI Results

	NL	CA	UK	DE	US	IT	AU
Sensitivity (%)							
MRI	80	77	77	91	100	94	86
Mammo	33	36	40	33	33	59	50
Specificity (%)							
MRI	90	95	81	97	95	N/A	92
Mammo	95	>99	93	97	98	N/A	98

Ca Cancer J Clin 2007; 57:75-89. Radiology 2007; 242:698-715.
Radiology 2007; 244:381-388. Clin Cancer Res 2007; 13:6144-6152

Screening MRI Results (Netherlands)

	MRI	Mammo
Recalls	10.84%	5.40%
Biopsies	2.93%	1.30%
Cancers	1.04%	0.46%
False negatives	0.23%	0.81%

Ca Cancer J Clin 2007; 57:75-89

Screening MRI Results (U.K.)

	MRI	Mammo
Recalls	10.70%	3.90%
Biopsies	3.08%	1.33%
Cancers	1.44%	0.69%
False negatives	0.43%	1.52%

Ca Cancer J Clin 2007; 57:75-89

Breast MRI: Probably Benign Outcomes

	Number	Frequency	PPV
Kuhl 2000	198	12.4%	2.4%
Liberman 2003	367	24.3%	10.1%
Kriege 2004	1909	6.6%	1.1%
Sadowski 2005	473	16.7%	5.1%
Eby 2009	1735	7.6%	1.0%
TOTAL	7941	9.4%	2.8%

Radiology 2000; 215:267-279. Cancer 2003; 98:377-388. NEJM 2004; 351:427-437. JMRI 2005; 21:556-564. AJR 2009; 193:861-867.

Additional Indication for MRI Screening

One-time screening of contralateral breast (newly diagnosed breast cancer)

8 published studies involving 2626 women

Range of cancer detection rates: 3% to 9%

Average cancer detection rate: 4%

Clinical efficacy not yet demonstrated

Basics to Successful MRI Screening

Partner with high-risk screening expertise

High-quality MRI equipment & techniques

Moderate-to-high volume experience

MRI-guided biopsy capability / partnering

Audit recall, biopsy, cancer detection rates

Despite the increased sensitivity and cancer yield of screening MRI compared to screening mammography, the sensitivity and cancer yield of both is greater than those for MRI alone.

Hence annual screening MRI should be provided in addition to, not instead of, annual screening mammography.

Screening with Mammography and MRI

- Staggering mammo and MRI every 6 months may reduce the rate of interval cancers
- Performing both exams on the same day allows both tests to be interpreted / reported together
- No data to support one or the other approach

Screening MRI Cost-Effectiveness (/QALY)

	BRCA1	BRCA2
Mammo ages 25-69	$ 18,952	$ 28,421
+ MRI ages 40-49	$ 43,484	$111,600
+ MRI ages 35-54	$ 71,401	$158,839
+ MRI ages 30-59	$124,820	$198,429
+ MRI ages 30-69	$164,762	$266,334
+ MRI ages 25-69	$475,932	$731,553

JAMA 2006; 295:2374-2384

Defining the High-Risk Threshold

≥ 20% to 25% lifetime breast Ca risk

15% to 20% lifetime breast Ca risk

< 15% lifetime breast Ca risk

Ca Cancer J Clin 2007; 57:75-89

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Specific Indicators of High Risk

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Untested 1° relative of mutation carrier

Very strong family Hx of breast cancer

Previous chest radiation therapy ≤30y

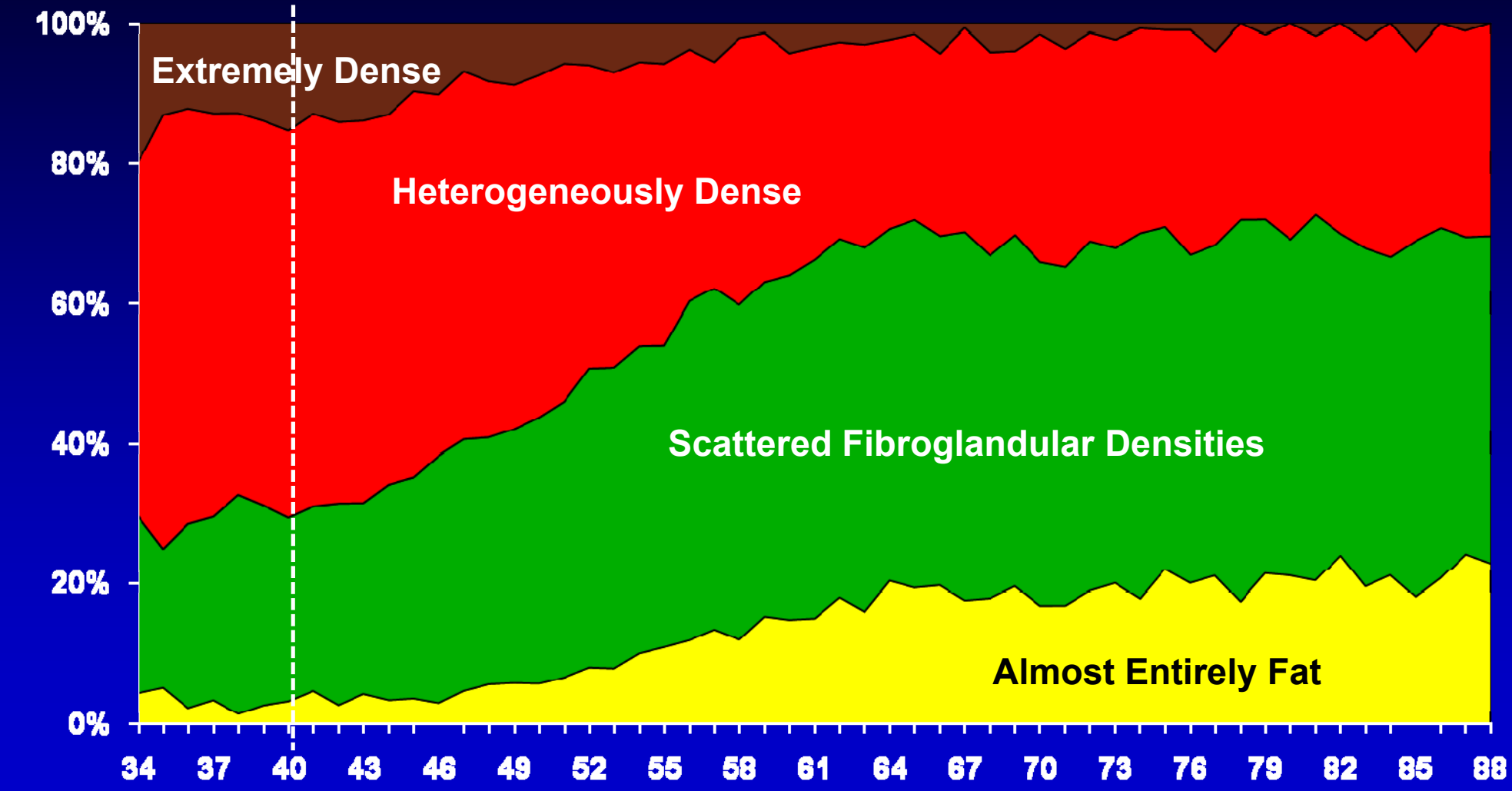
Strong family history of breast cancer

Histologic diagnosis of LCIS / atypia

Personal history of breast cancer

Very dense breasts at mammography

Breast Density as a Function of Age



UCSF Mammo Screening, 1985-2007

Ultrasound

Types of Evidence Supporting Screening

Randomized controlled trials

Case-control studies

Prospective clinical studies

Retrospective clinical studies

Expert opinion

Anecdotal reports

S.I. Screening Ultrasound Results

Author	# Exams	Bx (%)	Ca (PPV_3)
Gordon	12,706	279 (2.2)	44 (15.8%)
Buchberger	8,103	362 (4.5)	32 (8.8%)
Kaplan	1,862	102 (5.5)	6 (6.6%)
Kolb	13,547	358 (2.6)	37 (10.3%)
Crystal	1,517	38 (2.5)	7 (18.4%)
Leconte	4,236	N/A	16
Corsetti	7,615	486 (7.5)	36
TOTAL	49,586	1,625 (3.7) *	178

Radiol Clin North Am 2007; 45:895-906

Other S.I. Screening Ultrasound Results

Cancer detection rate: 0.36% (178/49586)

Biopsy yield (PPV_3): 11.1% (126/1139)

Probably benign rate: 6.3% (range 3%-10%)

US-only cancers: 94% invasive, 6% DCIS

US-only cancers: more than 70% ≤ 10 mm

US-only cancers: 86% node-negative

Radiol Clin North Am 2007; 45:895-906

Selected Screening Outcomes

	US	Mammo
Prevalence Ca rate	0.36%	0.8%
Biopsy rate	>3.7%	1.5%
Short-Intvl F/U Rate	6.3%	1.5%
PPV_3	11.1%	25%-40%

US data in high-risk ♀; mammo data in average-risk ♀

Limitations to S.I. Screening US Data

Examiners not blinded to mammo findings

Investigators all highly skilled, experienced

Case experience ~ prevalence screening

Interpretive criteria not fully described

False pos outcomes reported incompletely

Patients high-risk, most with dense breasts

No data on breast cancer mortality

Rationale for a Trial of Screening Breast Ultrasound: American College of Radiology Imaging Network (ACRIN) 6666

Wendie A. Berg[1]

Mammography is the only screening test to date that has been shown to reduce death rates due to breast cancer. In a report commissioned by the United States Preventive Services Task Force, Humphrey et al. [1] recently reviewed eight randomized controlled trials of mammography and two of breast self-examination. The Edinburgh trial was excluded because of lower socioeconomic status, higher all-cause mortality in the control group, and the lack of masking when evaluating cause of death. Overall, across the seven remaining trials, in women 50 years old or older, a 22% reduction (95% confidence interval [CI], 13–30%) in breast cancer mortality rates was found among women screened at 14 years of observation [1]. In women 40–49 years old, the summary risk reduction was 15% (95% CI, 1–27%) [1] at 14 years of observation. The decrease in mortality rates was almost entirely attributable to a decrease in the size distribution of cancers detected on screening mammography [2]. In the analysis of Tabar et al. [3], 73% of breast cancer deaths in women with cancers smaller than 15 mm at diagnosis were attributable to cancers manifested as branching casting calcifications on mammography. Such calcifications are usually due to ductal carcinoma in situ (DCIS), often of high nuclear grade with comedonecrosis [4].

Despite the proven benefits of mammography, results have been less promising when the tissue is dense. Dense tissue is common, especially in younger women. In the series of Stomper et al. [5], approximately 62% of women in their 30s, 56% of women in their 40s, 37% of women in their 50s, and 27% of women in their 60s had at least 50% parenchymal densities evident on mammography. Kerlikowske et al. [6] reported results of 27,281 screening mammograms and found the sensitivity to cancer was 98.4% in women 50 years old or older with fatty breasts and 83.7% in women with dense breasts ($p = 0.01$). In women less than 50 years old, the sensitivity was 81.8% in fatty breasts and 85.4% in dense breasts (p = not significant), although the number of cancers was small [6]. In women less than 50 years old with a family history of breast cancer, mammographic sensitivity decreased to 68.8% [6]. Thus, in women with dense breasts, and particularly those at increased risk because of a family or personal history of breast cancer or atypia, methods to supplement mammography are sought.

Although breast self-examination intuitively seems worthwhile, randomized controlled trials have not shown a reduction in mortality rates. The effect may have been too small to measure within the power and conditions of the trials. The Shanghai trial of 133,000 women randomized to receive instruction in breast self-examination or control groups found no difference in mortality rates; women in the breast self-examination group were 84% more likely to undergo an unnecessary breast biopsy with benign results [7].

No randomized controlled trials have been conducted to evaluate the impact of screening sonography on breast cancer mortality rates. However, in several single-center studies, whole-breast bilateral sonography has been shown to depict small nonpalpable invasive breast cancers not seen on mammography, particularly in dense breasts [8–12]. The survival of patients diagnosed with invasive breast cancer is a direct, but imperfect, function of tumor size [13], and although we presume that this early detection is of benefit, this benefit has not been proven. Until such "surrogate" end points are further validated to reliably predict mortality rates, the efficacy of any new screening test can only be shown if it reduces breast cancer deaths in the setting of a randomized controlled trial. Any population-based screening test to be recommended must be held to a high standard of proof of

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AJR 2003;180:1225–1228 0361–803X/03/1805–1225 © American Roentgen Ray Society

Features of ACRIN 6666 Trial Data

Examiners blinded to mammo findings

Investigators moderately-to-highly skilled

Prevalence (1) + incidence (2) screening

Interpretive criteria fully described

False pos outcomes reported completely

Patients quite high-risk, dense breasts

No data on breast cancer mortality

Selected Screening Outcomes (ACRIN 6666)

35% increase in breast cancers

US-only cancers: 92% invasive

US-only cancers: median size, 10 mm

US-only cancers: 89% node-negative

Higher-risk ♀, dense breasts. JAMA 2008; 299:2151-2163.

Selected Screening Outcomes (ACRIN 6666)

	US	Mammo
Prevalence Ca rate	0.42%	0.76%
Biopsy rate (excl asps)	5.2%	2.6%
Short-Interval F/U Rate	8.6%	2.2%
PPV_3 (excl cyst asps)	8.8%	33.3%

Higher-risk ♀, dense breasts. JAMA 2008; 299:2151-2163.

Selected Screening Outcomes (ACRIN 6666)

	US	Mammo
Prevalence Ca rate	0.42%	0.76%
Biopsy rate (incl asps)	6.8%	2.8%
Short-Interval F/U Rate	8.6%	2.2%
PPV_3 (incl cyst asps)	6.7%	31.3%

Higher-risk ♀, dense breasts. JAMA 2008; 299:2151-2163.

Screening Ultrasound + MRI Results

	NL	CA	UK	DE	US	IT	AU
Sensitivity (%)							
MRI	80	77	77	91	100	94	86
Ultrasound		33		40		65	43
Mammo	33	36	40	33	33	59	50
Specificity (%)							
MRI	90	95	81	97	95	N/A	92
Ultrasound		96		91		N/A	98
Mammo	95	>99	93	97	98	N/A	98

Ca Cancer J Clin 2007; 57:75-89. Radiology 2007; 242:698-715.
Radiology 2007; 244:381-388. Clin Cancer Res 2007; 13:6144-6152

Screening Ultrasound + MRI Results

	NL	CA	UK	DE	IT	AU
# women	1909	236	649	529	278	327
# cancers	45	22	35	43	14	28
Ca @ mammo	33%	36%	40%	33%	57%	50%
Ca @ US	N/A	32%	N/A	40%	57%	43%
Ca @ MRI	64%	77%	77%	91%	93%	86%

Ca Cancer J Clin 2007; 57:75-89; Radiology 2007; 242:698-715
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Screening Ultrasound + MRI Results

	NL	CA	UK	DE	IT	AU
# women	1909	236	649	529	278	327
# cancers	45	22	35	43	14	28
Ca @ mammo	33%	36%	40%	33%	57%	50%
Ca @ US	N/A	32%	N/A	40%	57%	43%
Ca @ MRI	64%	77%	77%	91%	93%	86%
Ca @ mam + US	N/A	55%	N/A	49%	64%	50%
Ca @ mam + MRI	89%	91%	94%	93%	100%	93%

Ca Cancer J Clin 2007; 57:75-89; Radiology 2007; 242:698-715
Radiology 2007; 244:381-388. Clin Cancer Res 2007; 13:6144-6152

Advantages of Mammo + US Screening

US more widely available than MRI

US far less expensive than MRI

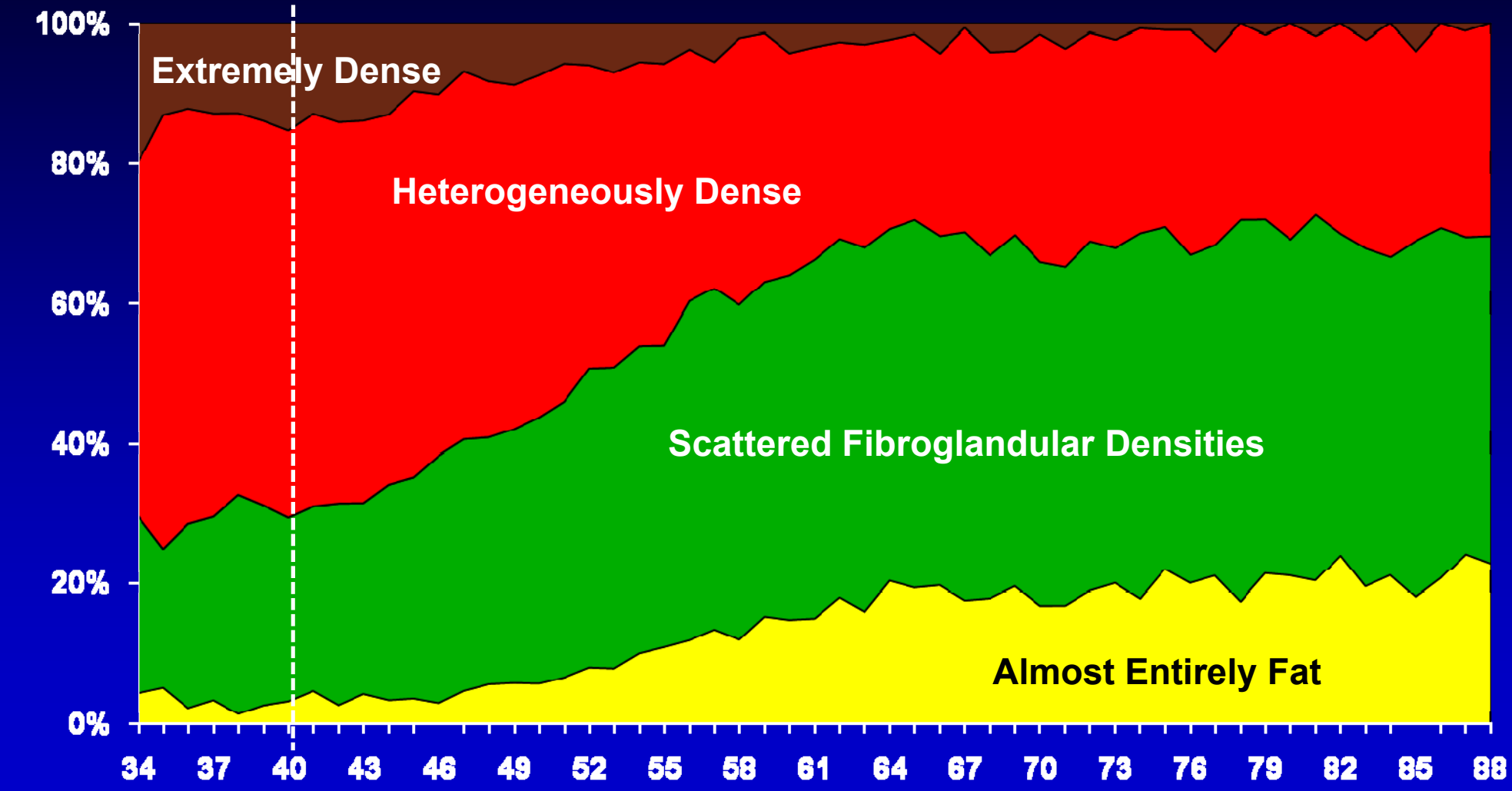
US better tolerated by patients

US requires no IV contrast injection

Ultimate Use of US Screening

- Very high-risk / dense breasts / no MRI
- High-risk women with dense breasts
- All women with dense breasts

Breast Density as a Function of Age



UCSF Mammo Screening, 1985-2007

Ultimate Use of US Screening

- Risk-benefit analyses
- Cost-benefit analyses

Selected Screening Outcomes

	Prev.	ACRIN
Prevalence Ca rate	0.36%	0.42%
Biopsy rate	>3.7%	6.8%
Short-Intvl F/U Rate	6.3%	8.3%
PPV_3	11.1%	6.7%

Single-institution versus multi-institution studies

Ultimately, if US is used to screen all women with dense breasts, the current model of physician-performed scanning using hand-held transducers must change (inadequate physician workforce).

This will require demonstration that either technologist-performed scanning or automated scanning has equal efficacy to physician-performed hand-held scanning.

Learning Objectives

- Describe strengths / limitations of screening high-risk women using mammography, MRI, US
- Describe screening protocols for high-risk ♀
  - When to begin
  - How frequently
  - What modalities
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  - When to end