Breast Density and Screening Ultrasound

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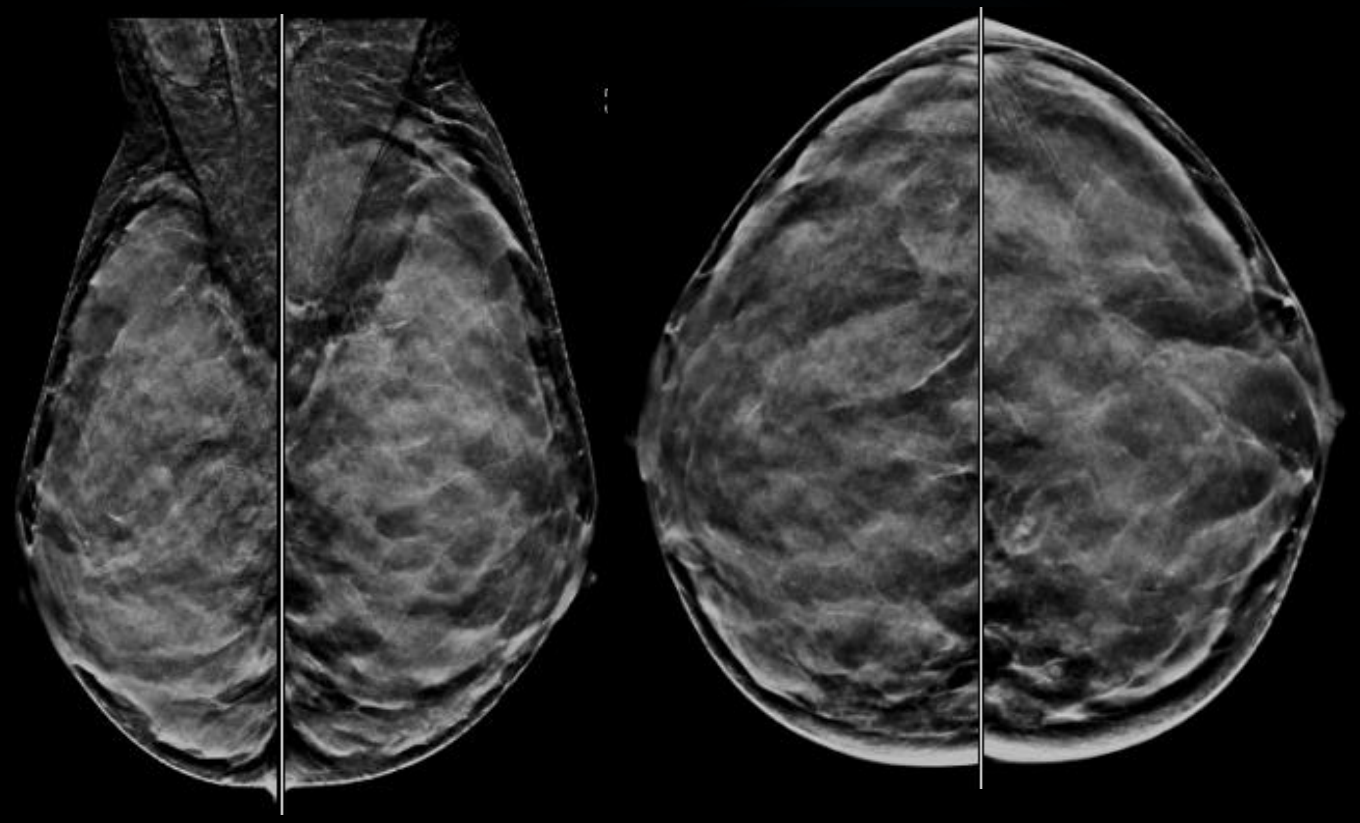
Breast Cancer Screening

- Numerous studies have shown that mammography screening leads to reduced mortality from breast cancer of greater than 30% - 40%
- Optimal screening protocol remains heavily debated
  - Screening and age intervals
- Up to now, screening protocols have been population-based, and have not been a personalized risk-based decision

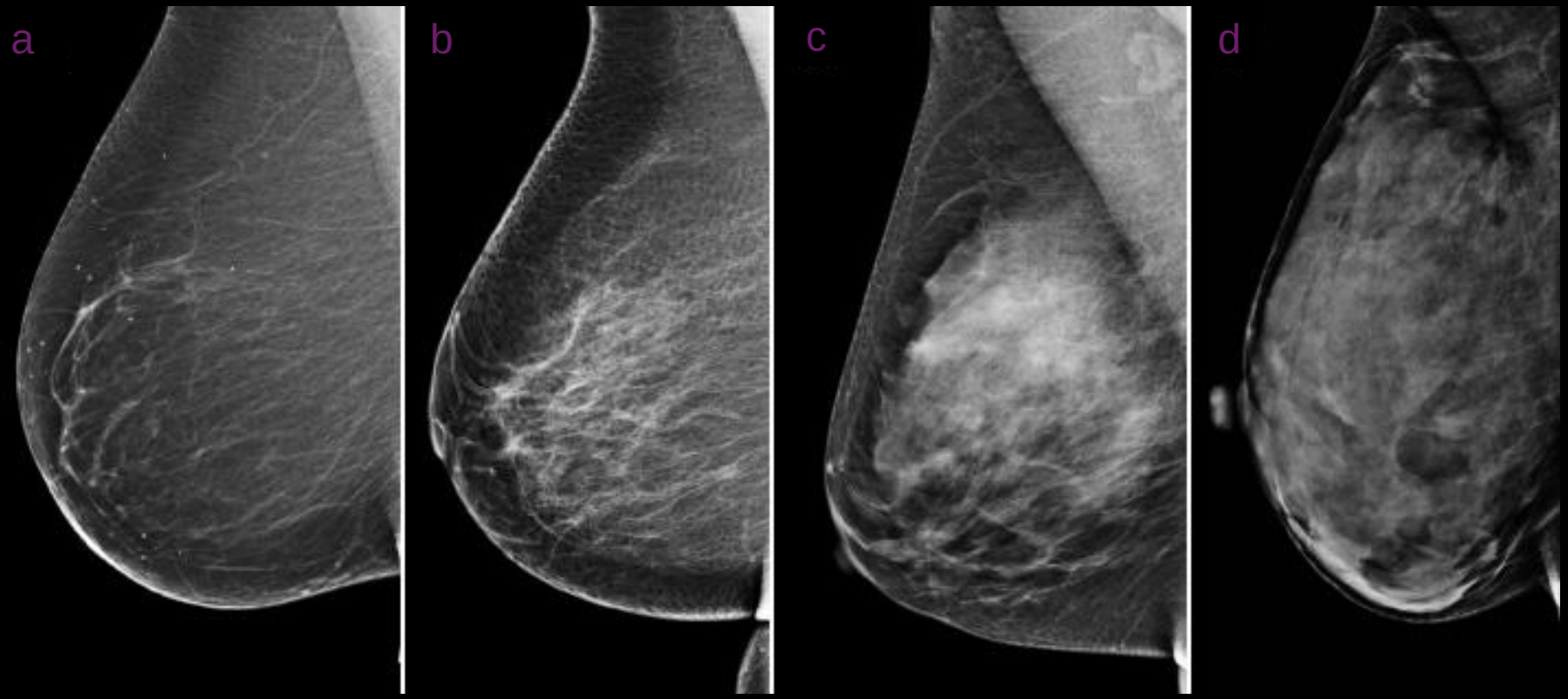
- Consider a woman's specific risk factors to determine the optimal screening regimen, family history, heritage, prior personal history, determine the need for supplemental screening – ***including breast density***

Breast Density as a Risk Factor

- Density on a mammogram can be responsible for the masking effect
  - Similar x-ray attenuation properties of dense tissue and breast tumors
  - Reduces sensitivity of mammography
- Breast density is an independent risk factor for breast cancer
  - Women in the highest breast density category are 4-6 times more likely to develop breast cancer than women with fatty breast tissue



Breast density is one of the risk factors associated with breast cancer, after gender and age



Breast Density as a Risk Factor

- *2017 Raghavendra* – in women with primary BC, breast density found to be a risk factor for contralateral BC [Cancer 2017; 123: 1935-1940]
- *2017 Destounis* – breast density only risk factor significantly associated with diagnosis of interval cancer v. screen-detected; quantitative VBD can capture potential masking risk of BD more precisely than visual BI-RADS assessment [AJR 2017; 208; 222-227]
- *2017 Wanders* – density strong marker of breast cancer risk, strong marker for predicting occurrence of tumors not detected during screening (interval cancers) [Breast Cancer Res 2017; 19:67]

Breast Density and Risk ACS Facts & Figures

- Some risk factors are a result of lifestyle choices
- Others cannot be altered as they are a part of our human characteristics
- Dense breasts, as seen on mammography, lie within the highest category of risk

Table 4. Factors That Increase the Risk for Breast Cancer in Women

Relative Risk	Factor
>4.0	• Age (65+ vs. <65 years, although risk increases across all ages until age 80) • Biopsy-confirmed atypical hyperplasia • Certain inherited genetic mutations for breast cancer (BRCA1 and/or BRCA2) • Mammographically dense breasts • Personal history of breast cancer
2.1-4.0	• High endogenous estrogen or testosterone levels • High bone density (postmenopausal) • High-dose radiation to chest • Two first-degree relatives with breast cancer
1.1-2.0	• Alcohol consumption • Ashkenazi Jewish heritage • Early menarche (<12 years) • Height (tall) • High socioeconomic status • Late age at first full-term pregnancy (>30 years) • Late menopause (>55 years) • Never breastfed a child • No full-term pregnancies • Obesity (postmenopausal)/adult weight gain • One first-degree relative with breast cancer • Personal history of endometrium, ovary, or colon cancer • Recent and long-term use of menopausal hormone therapy containing estrogen and progestin • Recent oral contraceptive use

Why Density Matters

- In clinical practice, risk stratification based on breast density is occurring and guides referral to supplemental screening
- There has been a simultaneous increase in the need for accurate and reproducible measures of breast density, as there are currently no recommendations for standardized breast density assessment

Importance of Accurate Assessment

- Very important to get it right…
  - Without subjectivity
  - Without variation
  - Temporal comparison for lifetime risk

- Implications for supplemental screening
  - US for those with dense breast tissue
  - MRI for those with dense breast tissue and other risk factors (family history/positive genetic testing)

Destounis, S., et al. "Qualitative versus quantitative mammographic breast density assessment: applications for the US and abroad." Diagnostics 7.2 (2017): 30.

Density Assessment Options

- Visual
  - Subjective
    - Considerable intra- and inter-observer variation
- Automated
  - Objective
  - Reproducible
  - Consistent

D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013

Visual Assessment

Table 1 Mammographic Density Assessment Methods

MD Assessment	Method	FDA Approval	Study
Visual			
Area			
Parenchymal pattern	Wolfe	Not applicable	Wolfe (1976)[35]
	TABAR	Not applicable	Gram et al. (1997)[36]
Qualitative	BI-RADS	Not applicable	Sickles et al. (2013)[37]
Semiqualitative	Boyd	Not applicable	Boyd et al. (1995)[38]
	Visual analogue scale	Not applicable	Duffy et al. (2008)[39]

Density Assessment - Visual

- Concern surrounding subjective nature of visual assessment
  - Inter-and intra-reader variability

- Guided by BI-RADS
  - 5th Edition (2013): assignment of descriptors that convey whether there are dense areas of tissue that could mask/obscure a cancer
    - Density category assigned based on densest region of breast tissue
    - Meant to capture the masking risk by locally dense areas regardless of size of dense area

Density Assessment: ACR® BI-RADS® Classifications

BREAST TISSUE ASSESSMENT
a. The breasts are almost entirely fatty
b. There are scattered areas of fibroglandular density
c. The breasts are heterogeneously dense, which may obscure detection of small masses
d. The breasts are extremely dense, which lowers the sensitivity of mammography

Most radiologists follow the ACR BI-RADS classifications for reporting purposes

Variation in Visual Assessment

- Wide variation among radiologists in the percentage of mammograms rated as showing dense breasts (range 6.3% to 84.5%)
- 17.2% of women with consecutive yearly mammograms interpreted by different radiologists had discordant assessments (dense vs nondense)
- Important implications – affect reporting density, clinical management

Sprague BL, et al. Variations in Mammographic Breast Density Assessments Among Radiologists in Clinical Practice. 2016

Automated Density Assessment

Semiautomated			
Area			
Quantitative	Cumulus	No	Byng et al. (1994)[40]
	Madena	No	Ursin et al. (1998)[41]
Fully automated			
Area			
Qualitative	DenSeeMammo	FDA approved to provide information on fifth edition BI-RADS density categories	
Quantitative	AutoDensity	No	Developed by the University of Melbourne
	Densitas	No	Abdolell et al. (2016)[42]
	ImageJ	No	Li et al. (2012)[43]
	iReveal	Yes	44
	STRATUS	No	Eriksson et al. (2016)[45]
	Libra	No	Keller et al. (2015)[46]
	MedDensity	No	Tagliafico et al. (2013)[47]
Volume			
Quantitative	BD_{SXA}	No	Shepherd et al. (2005)[48]
	Cumulus V	No	Alonzo-Proulx et al. (2010)[49]
	Quantra	Yes	50
	Spectral density	Yes	51
	Volpara	Yes	52

- Literature has shown that several automated methods are consistent and reliable means for determining breast density

Automated Assessment

- Objective and Reproducible
- Proper recommendation of ancillary screening tools depends on getting the breast density assessment correct
- Area vs. volumetric assessment

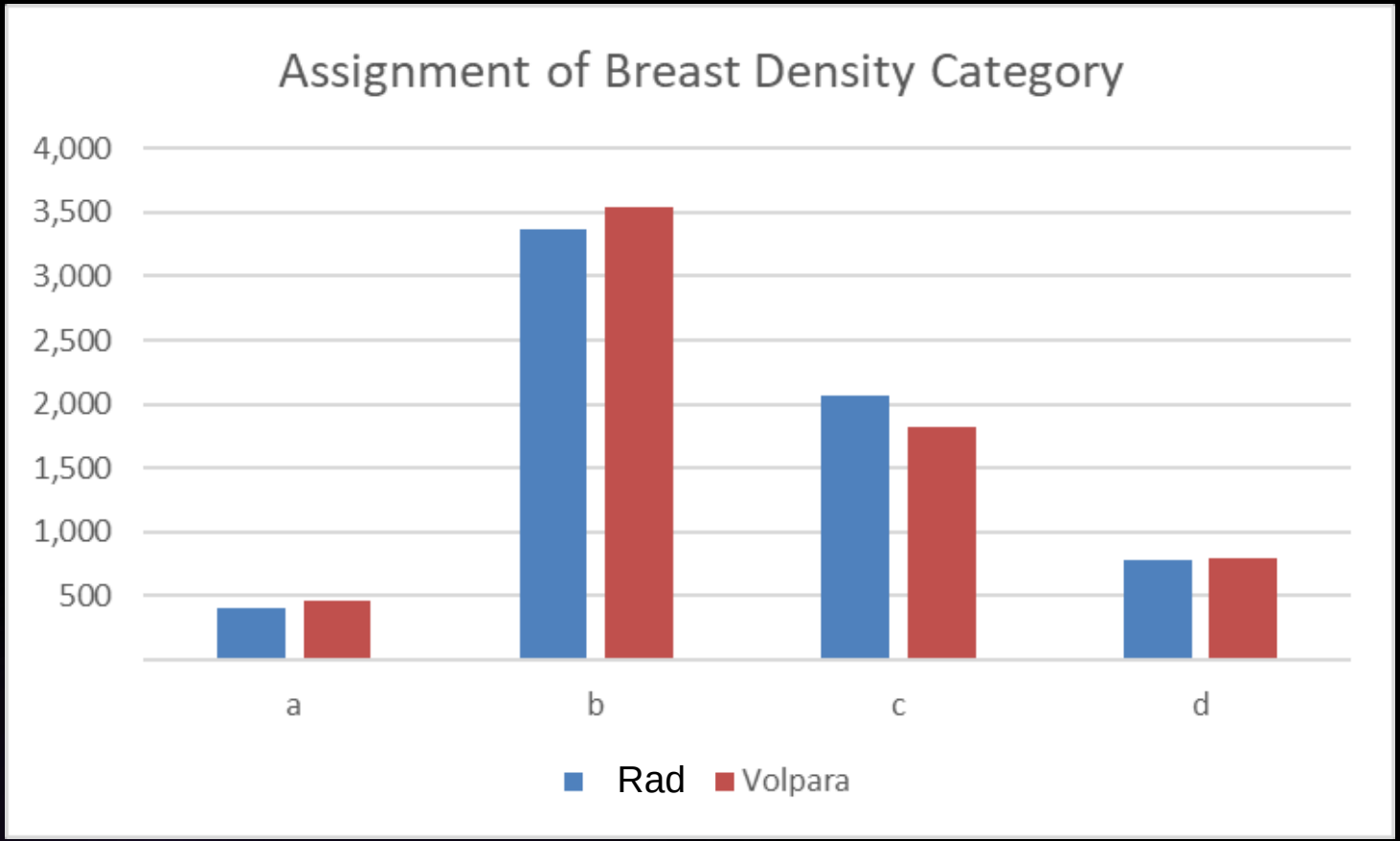
Comparison of Radiologist and Automated BD Category Assignment

- Study investigated the agreement of density category assignment between radiologists and automated breast density software

- Density assessments collected on consecutive patients at a breast imaging center during one calendar month (15 January to 14 February 2019) - study population n=6,629

Destounis et al. Results

- Radiologists agreed with Volpara density categories in 93.09% of cases
  - Disagreed by one density category in 6.82% of cases, and by two categories in 0.09% of cases
  - There were no instances where the radiologists disagreed with Volpara by three categories
- In 5.67% of cases the radiologist scored the mammogram as denser than Volpara; and less dense than Volpara in 1.24% of cases
- kappa showed almost perfect agreement between radiologists and Volpara (Fleiss Kappa > 0.889)



Rad > Volpara	376	5.67%
Volpara > Rad	82	1.24%
Rad > Volpara by 1	52	0.78%
Volpara > Rad by 1	-	0.00%

VBD% of 49 cases (0.74%) had VBD% within 10% of the threshold between the BI-RADS “b” and “c” density categories, the most common triage point for supplemental screening

Of those cases, 43 (0.65%) were cases in which the radiologist scored a breast as dense and Volpara scored the case as fatty; in 6 cases (0.09%) Volpara scored the case as dense and the radiologist did not

Supplemental Screening

- There has been increasing awareness on the limitations that exist with mammography imaging of women with dense breast tissue - growing number of women are in need of supplemental screening

- Frequently utilized screening tools are digital breast tomosynthesis, US and MRI

Current ACR Recommendation: US Screening

- For women with dense breasts, US may also be considered, but the balance between increased cancer detection and the increased risk of a false-positive examination should be considered in the decision

Revised 2017

American College of Radiology
ACR Appropriateness Criteria®
Breast Cancer Screening

Variant 1: **Breast cancer screening. Average-risk women: women with <15% lifetime risk of breast cancer.**

Procedure	Appropriateness Category	Relative Radiation Level
Mammography screening	Usually Appropriate	☢☢
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
FDG-PEM	Usually Not Appropriate	☢☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Monticciolo DL, et al. Breast Cancer Screening for Average-Risk Women: Recommendations From the ACR Commission on Breast Imaging. JACR 2017;14:1137-1143.

Recommendations from the ACR Commission on Breast Imaging

- Insufficient evidence to recommend use of ultrasound in average risk patients at this time
- Investigation of whole breast ultrasound screening in cohorts whose elevated risk is mainly or exclusively attributable to increased breast density show supplemental cancer detection from 1.9 - 7.7/1000
- Accompanied by more false positive examinations and lower PPP values for biopsy compared to mammography

Monticciolo DL, et al. Breast Cancer Risk for Average-Risk Women. Recommendations from the ACR Breast Commission JACR 2017;14:1137-1143.

Breast Density Inform Movement

- 2003- Diagnosed with Stage III breast cancer, within months of normal mammogram, later discovered after diagnosis that she had dense breast tissue

- Dr. Nancy Cappello launched Are You Dense
  - Inform patients about breast density, advocate for patients to know their breast density, the risks that come with having dense breast tissue
  - Instrumental along with JoAnn Pushkin in adoption of breast density legislation across United States

Are You DENSE?
exposing the best-kept secret®

Breast Density Inform Law

- Mammography reports must include information about breast density based on the four BI-RADS® density categories; patient letter in easy to understand terms

- Mammography report states: the state law requirement for reporting breast density, what was reported to the patient and that the patient may be contacting their physicians to discuss breast cancer risk and other useful screening tests

Implications of Density Notification Legislation

- Patient awareness of density allows them to make personal screening choices

- ACR statement (2012) - warned about potential unintended harms of mandatory breast density notification - in part due to the lack of reproducibility of visual density assessment and inconsistent utilization of computerized methods to assess breast density

Increase in Supplemental Screening

- As more states mandate breast density notification, more patients will learn of the implications on screening and potential for additional screening
- Mammography has inherent limitations in imaging dense tissue
  - Reduced sensitivity in dense tissue, reportedly 47.8-64.4%
- Solutions for more effective screening in this population have emerged – most frequently ultrasound

Supplemental Screening: Ultrasound

- US promising adjunct screening modality due to its low costs and availability
- For women whose only risk was dense breast tissue, a systematic review showed an incremental cancer detection rate of 3.2 per 1,000 [Nothacker, BMC Cancer 2009]
- US detected cancers are often smaller, lower grade and node negative

Critiques Against Breast Ultrasound for Cancer Detection

- Detection has come at the cost of additional health care expense and false-positive interpretations
- Critics have pointed to a lack of evidence proving a survival benefit from screening ultrasound that is analogous to the mortality reduction data from randomized controlled trials of screening mammography
- Although ultrasound finds small invasive carcinomas 1 cm or less
- Studies of supplemental screening with ultrasound show an ICDR

Screening US Literature Review – Scheel 2015

- Systematic review of all articles (clinical trials and observational studies) regarding screening US (handheld and ABUS) in women with dense breast tissue (2000 – 2013)

- Review of the literature identified 189 studies on breast US (handheld and automated) as an adjunct to screening mammography - 12 studies included in analysis

Scheel JR, et al. Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts. Am J Obstet Gynecol 2015; 212(1): 9-17.

Scheel Literature Review – Biopsy Rate

- HHUS biopsy rate ranged from 11.7 – 106.6 per 1000 exams
  - In addition to the approx. 10.2 biopsies / 1000 recommended based on screening mammography findings alone
  - US exceeding the mammography biopsy rate 5-fold
- Automated US biopsy rate (Kelly et al) – 11.7 / 1000

Scheel Literature Review – Cancer Detection

- Added cancer detection in HHUS studies – 0.3 – 6.8 cancers / 1000 exams
- Automated US added CDR:
  - Kelly et al – 3.6 / 1000
  - Guiliano et al – 12.3 / 1000
    - Includes cancers also detected by mammography
    - Control group CDR (mammography only) 4.6/1000
      - resulting in CDR from adjunct screening US of approx. 7.7 /1000
- The median cancer detection rate for all adjunct breast US studies was 4.2 cancers per 1,000 examinations

Scheel Literature Review – Cancer Characteristics

- The median node negative cancers detected by all US studies were 89%
- Median rate of additional invasive cancer detection 91%
- Lesion size
  - Range 6.5 – 19mm
  - Mean size ≤ 1cm

Scheel Literature Review Summary

- Reporting of breast cancer risk factors varied across studies; however, the study populations tended to be at greater than average risk for developing breast cancer
- In depth comparison was made to the ACRIN 6666 study with the Connecticut studies (first state to pass legislation requiring direct patient notification and also insurance coverage)
- Screening US detects more invasive cancers compared to mammography alone
- No evidence of associated long-term breast cancer mortality reduction

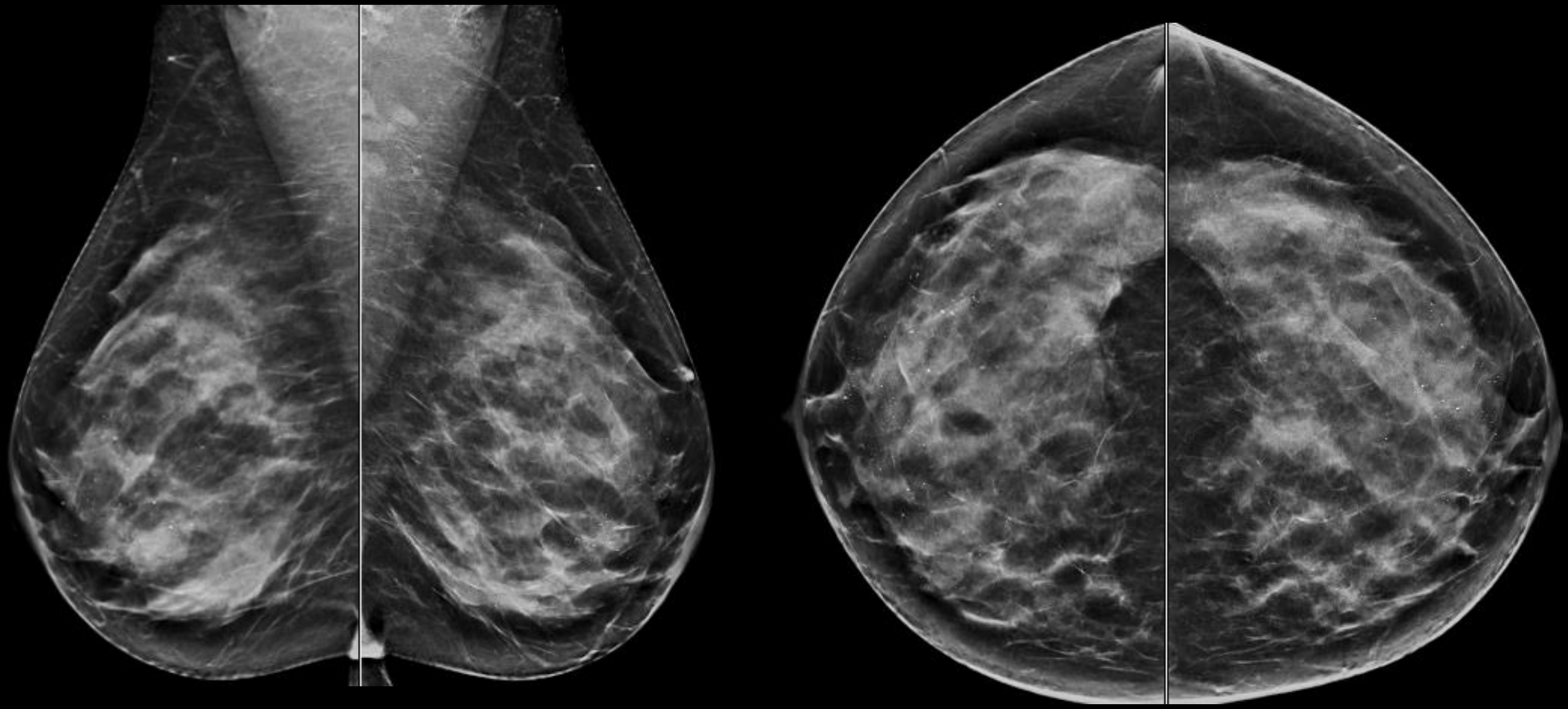
Final Comments on Scheel

- ACRIN 6666 was a prospective multi-institutional trial and the women had additional risk factors not just dense breasts, radiologists performed the exam, added 4.2 cancers per 1000 by performing adjunct ultrasound

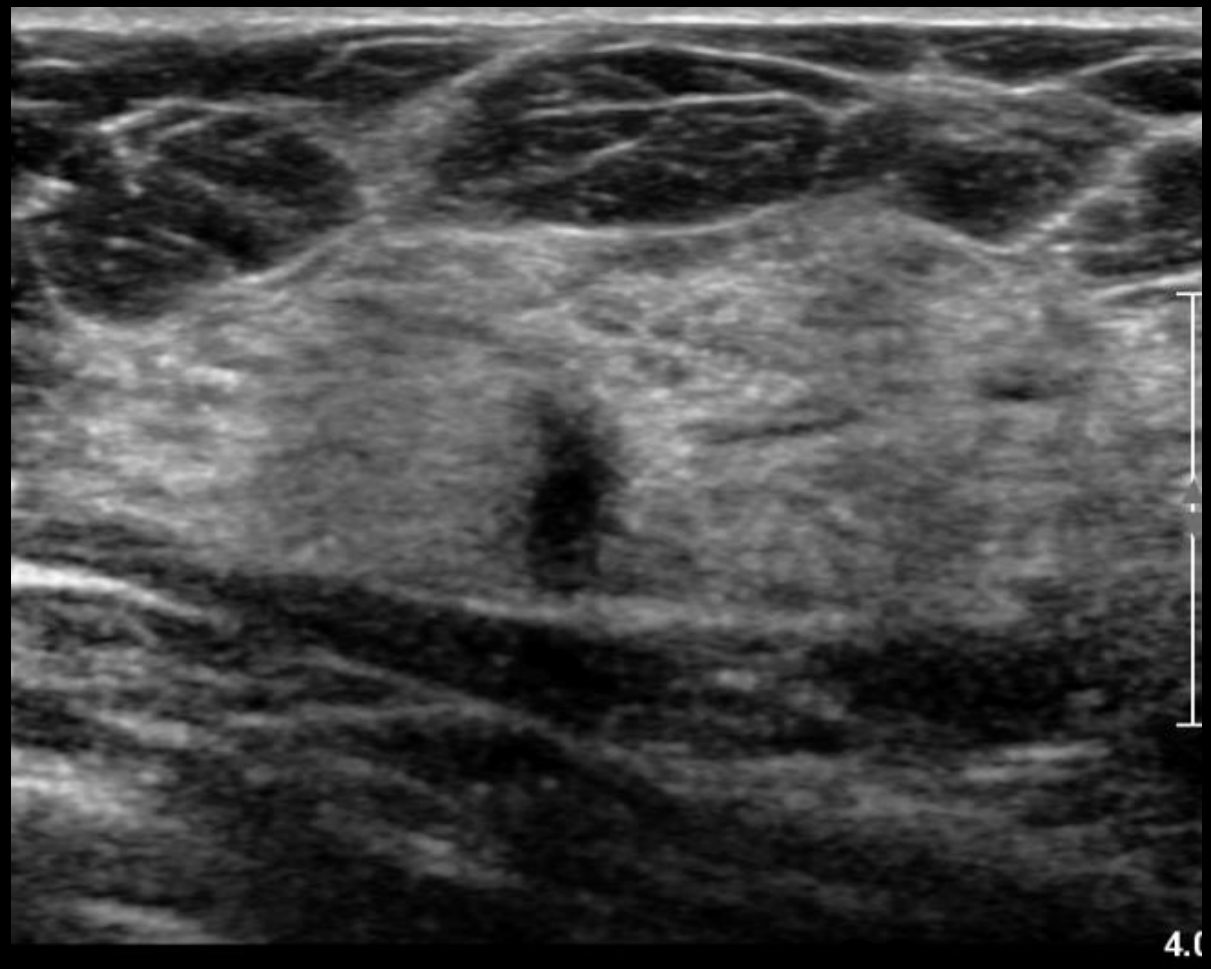
- The Connecticut studies were retrospective, and cancer detection closer to 2/1000 leading us to believe in an average risk population with technologists performing examination we will be at the lower end of the cancer detection rate

Case:

52 year old patient with extremely dense breast tissue. No family history of BC. Mammography with DBT + screening US performed



Negative mammogram



Grade 1 Invasive ductal carcinoma

US as Primary Screening Test- Analysis from ACRIN 6666

- 2809 participants enrolled at 20 sites
- 2662 participants completed three annual screens total of 7473 examinations
- 110 women had 111 cancers
- The number of US screens to detect one cancer was 129 and for mammography it was 127, cancer detection was comparable at 58/111 and 59/111
- Second and third screening incident rounds, recall rate and biopsy rate was higher and PPV3 lower than for mammography
- US had higher proportion of invasive and node negative cancers

US as Primary Screening Test-Analysis from ACRIN 6666

Table 5. Cumulative unique participants recalled or biopsied because of ultrasound or mammography for 2662 women during the three-year period

Performance characteristic	US		Mammography		Absolute percent difference US vs mammography	
	No./total participants	Rate (95% CI*)	No./total participants	Rate (95% CI*)	Estimate	P†
Overall recall rate	877/2662	32.9 (31.2 to 34.7)	657/2662	24.7 (23.1 to 26.3)	8.26	<.001
Cancer patients recalls	58/110‡	52.7 (43.5 to 61.8)	59/110	53.6 (44.3 to 62.7)	-0.91	1.00
Cancer patients recalls for wrong reason§	9/110	8.2 (4.4 to 14.8)	7/110	6.4 (3.1 to 12.6)	1.82	.79
Noncancer patients recalls	810/2552	31.7 (30.0 to 33.6)	591/2552	23.2 (21.6 to 24.8)	8.58	<.001
Overall biopsy rate	447/2662	16.8 (15.4 to 18.3)	157/2662	5.9 (5.1 to 6.9)	10.89	<.001
Noncancer patients biopsy (at least one)	390/2552	15.3 (13.9 to 16.7)	100/2552	3.9 (3.2 to 4.74)	11.36	<.001

* 95% Wilson confidence limits for simple proportions. CI = confidence interval; US = ultrasound.

† Two-sided exact McNemar's test.

‡ One hundred ten women were diagnosed with 111 cancer events (one woman diagnosed in year 1 was diagnosed with contralateral cancer in year 3).

§ Women recalled prior to the appearance of the confirmed cancer or because of finding in a cancer-free location.

Conclusions for US as Primary Screening Test

- Breast cancer is a global issue and developing countries don’t have ability to have mammography screening but US equipment could be obtained at low cost

- Authors acknowledge the barriers to any screening program implementation are the false positives and suggest that as the recall rate decreased in years 2 and 3 from the first year of screening having comparison examinations could reduce false positive recalls

Screening US as Adjunct to Mammography Across Risk Levels

- BCSC registries – prospective data on screening mmg with and without same-day breast ultrasound

- 6,081 screening mammograms plus same-day screening US exams in 3,385 women were propensity score matched 1:5 to 30,062 screening mammograms without screening US in 15,176 women from a sample of 113,293 mammograms

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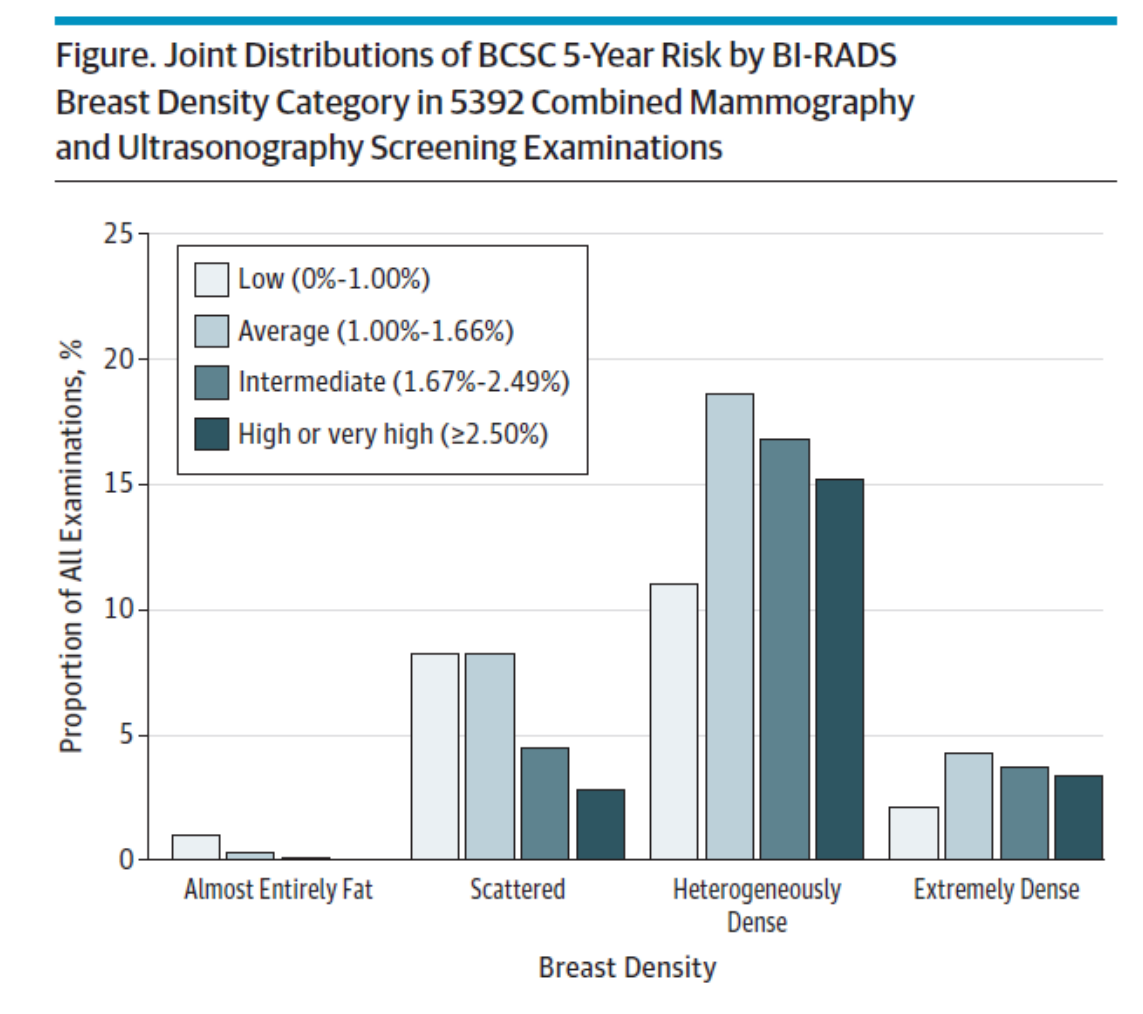
Performance of Screening US - Lee



- Screening mammo with US vs without were performed more often in women:
  - with dense breasts (74% vs 36% in overall sample)
  - who were younger than 50 years (50% vs 32%)
  - with a family history of breast cancer (43% vs 15%)
- 21% of screening US exams were in women with high / very high (>2.50%) BCSC 5-year risk scores
  - 53% had low / average (<1.67%) risk

Performance of Screening US - Lee

	CDR	Interval Cancer Rates	FP Biopsy Rates	Short Interval follow up Rates	PPV2
MMG alone	5.5	1.9	22.2	1.1	21.4
MMG + US	5.4	1.5	52.0	3.9	9.5

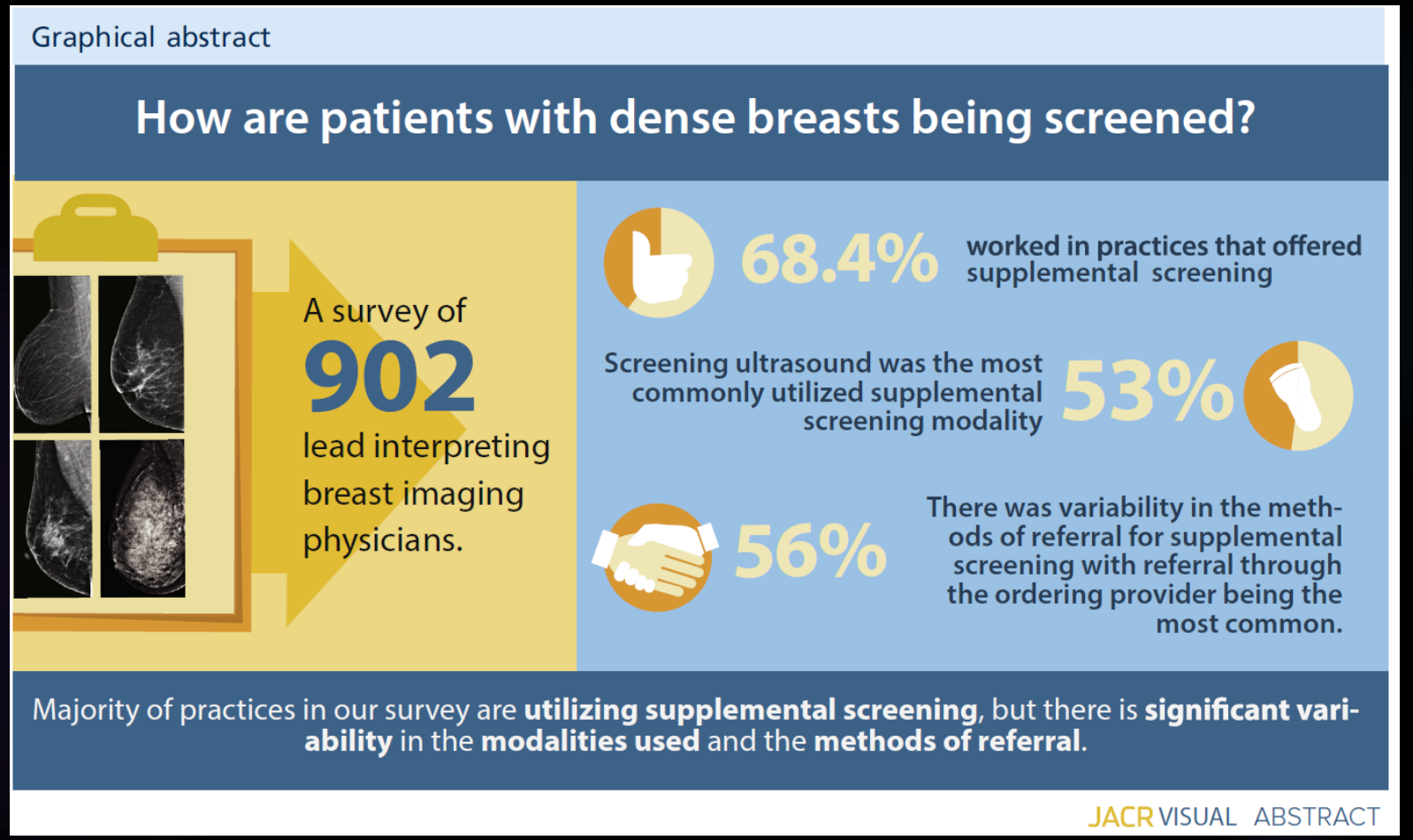
In a relatively young population of women at low, intermediate, and high breast cancer risk, our results suggest that the benefits of supplemental ultrasound screening may not outweigh associated harms

Performance of Screening US - Lee

- In this cohort study, for women whose breast cancer risk ranged from low to very high, there were significantly higher short-interval follow-up exams and biopsy recommendation rates with screening mammography plus same-day ultrasonography compared with mammography alone

- However, no significant increase in cancer detection or decrease in interval cancer rates was observed

Supplemental Screening In Practice – ACR Survey



Choudhery S, et al. Trends in Supplemental Screening in Women With Dense Breasts. *JACR* 2020; 24: S1546-1440(20)30038-7.

Results in Practice

- Most practices are offering supplemental screening
- Wide variation in availability of screening modalities and mode of referral
- Academic and private practices with breast specialization and in the Northeast more likely to provide supplemental screening
- Use of automated breast density assessment software and patient education brochures about density and supplemental screening had significant relationships with availability of supplemental screening ($P < .05$)

Table 5. Multivariate analysis assessing supplemental screening modalities by region, practice type, and state legislation

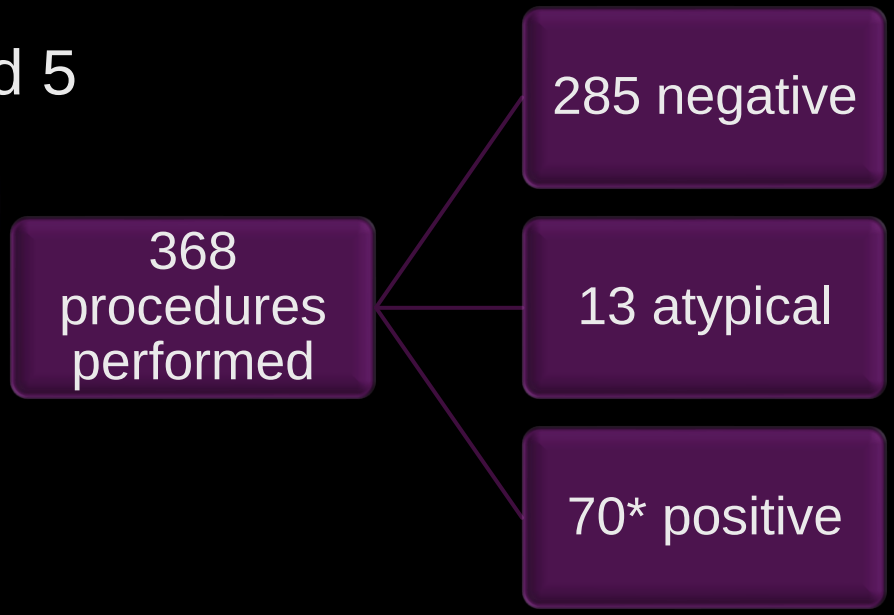
Supplemental Screening Modality	Variable	*P*
Supplemental screening tomosynthesis	Region*	.05
	Practice type†	.04
	State legislation‡	.10
Screening ultrasound	Region	<.001
	Practice type	.003
	State legislation	.003
Screening MRI	Region	.25
	Practice type	.02
	State legislation	.77
Any supplemental screening	Region	<.001
	Practice type	<.001
	State legislation	.06

*South, West, Midwest, and Northeast.
†Academic, private practice with breast specialization, private practice without breast specialization, Veterans Affairs, and others.
‡State law requiring some form of notification of breast density to

EWBC Screening US Outcomes

- Performed 25,000+ screening US exams since 2013 in over 14,000 patients
- 97% BI-RADS 1 and 2
- 1% BI-RADS 3
- 2% BI-RADS 4 and 5

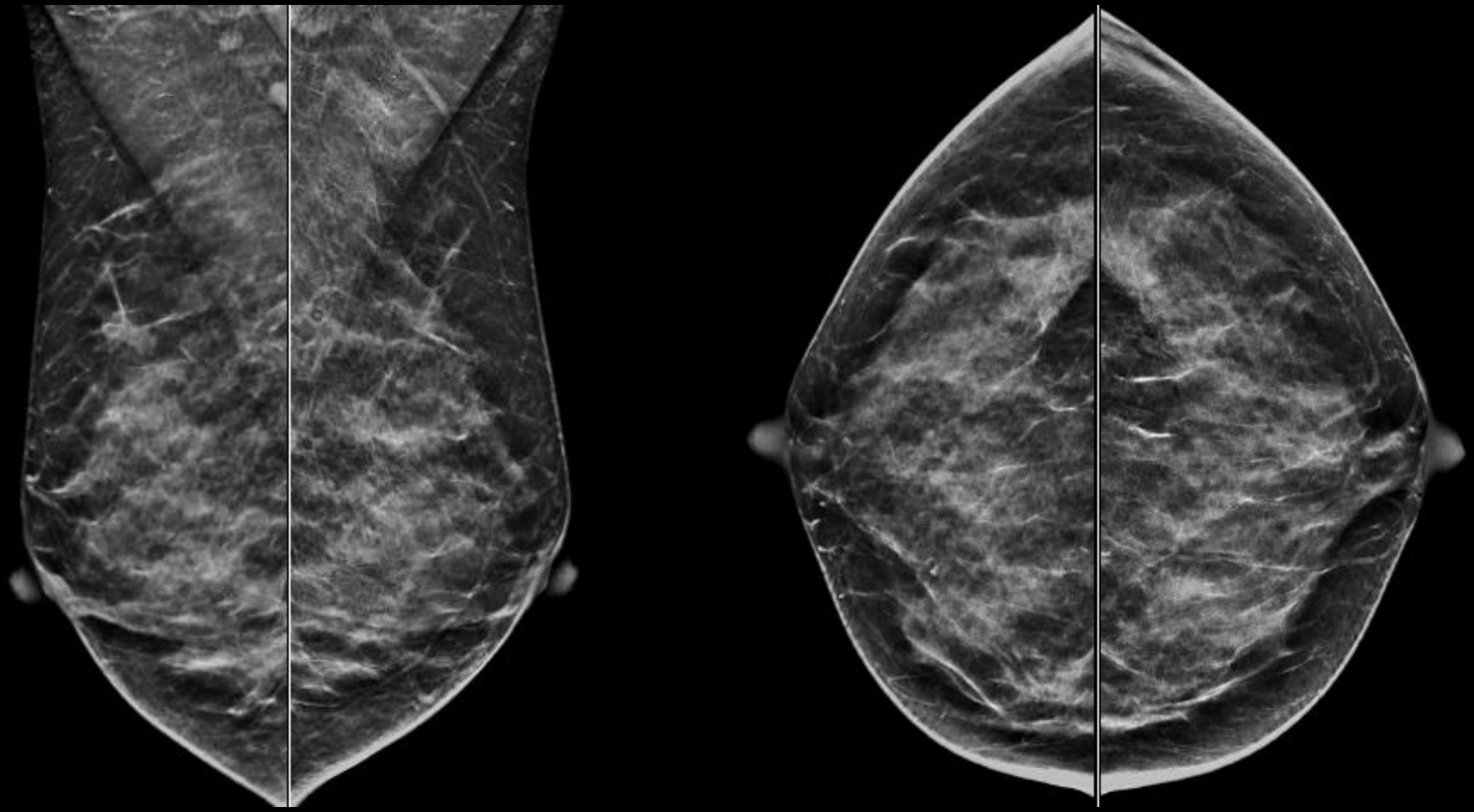
US only findings

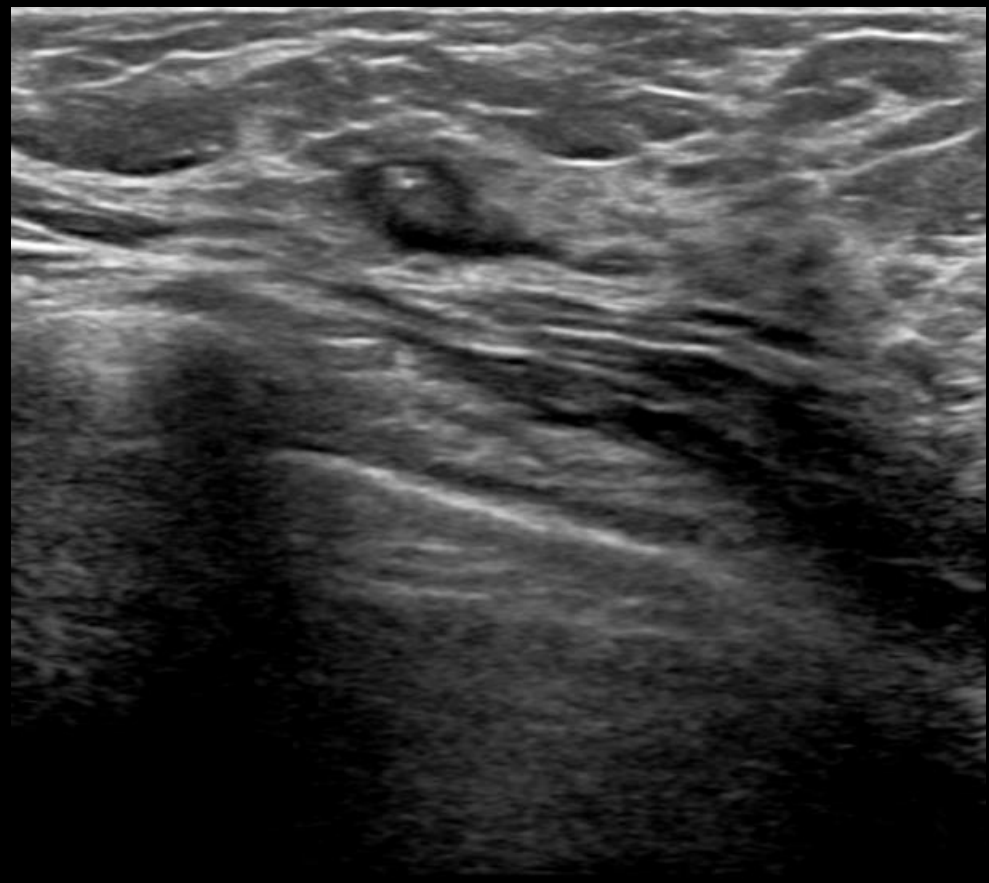


*70 positive includes 2 recurrence in mastectomy, and 5 non-breast malignancies

Case:

43 year old patient with heterogeneously dense breast tissue. 26% calculated lifetime risk. Mammography with DBT + screening US + screening MRI





Grade 1 Invasive ductal carcinoma

Looking Forward: Tailored Screening

- Should certain populations with dense breast tissue be targeted?
  - Dense tissue in combination with other factors
    - Personal history
    - >20% lifetime BC risk
    - Age
- Ex. For women with personal histories of breast cancer AND dense breast tissue annual surveillance with breast MRI is recommended-ACR/SBI [JACR 2018]

Summary

Over 40% of women have heterogeneously or extremely dense breast tissue

- Difficult to detect cancer on mammography
- It is a risk factor

Screening Breast US plays important role in detecting mammographically occult carcinomas in dense breasts

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Thank You!

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