MAYO CLINIC

Detection to Prediction: Imaging Markers of Breast Cancer Risk

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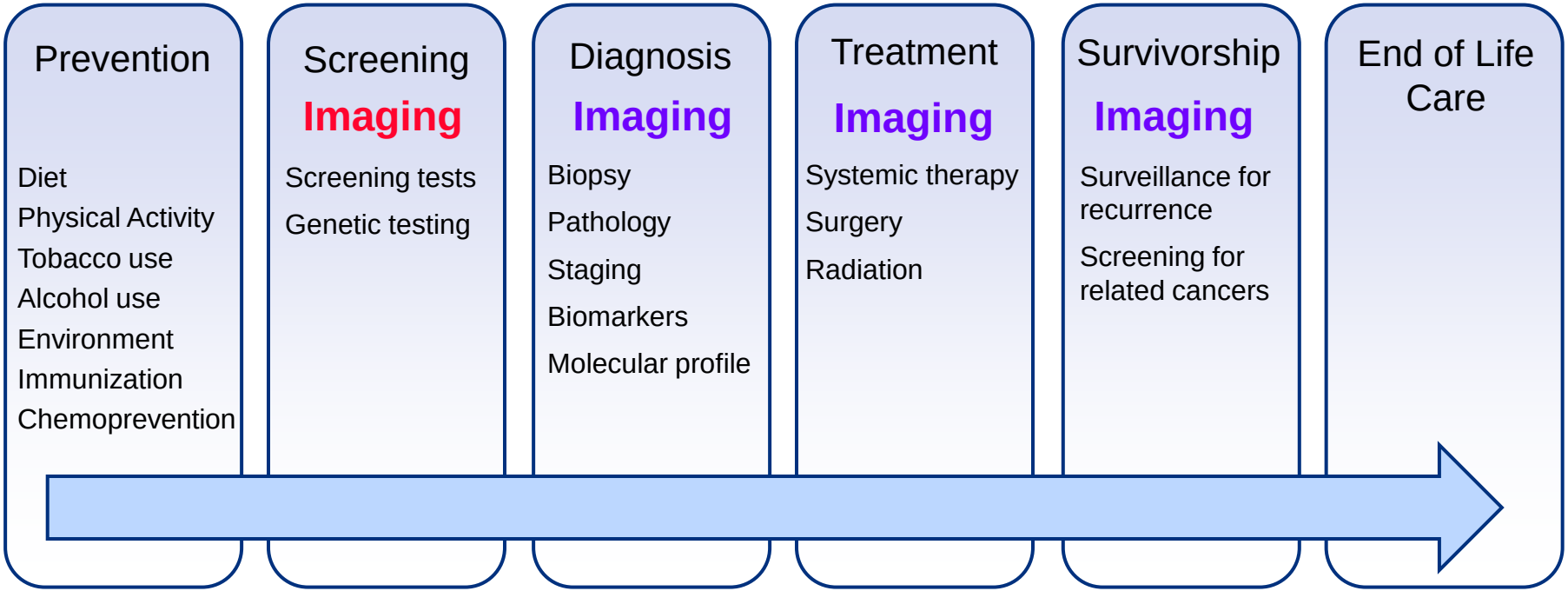
Disclosure

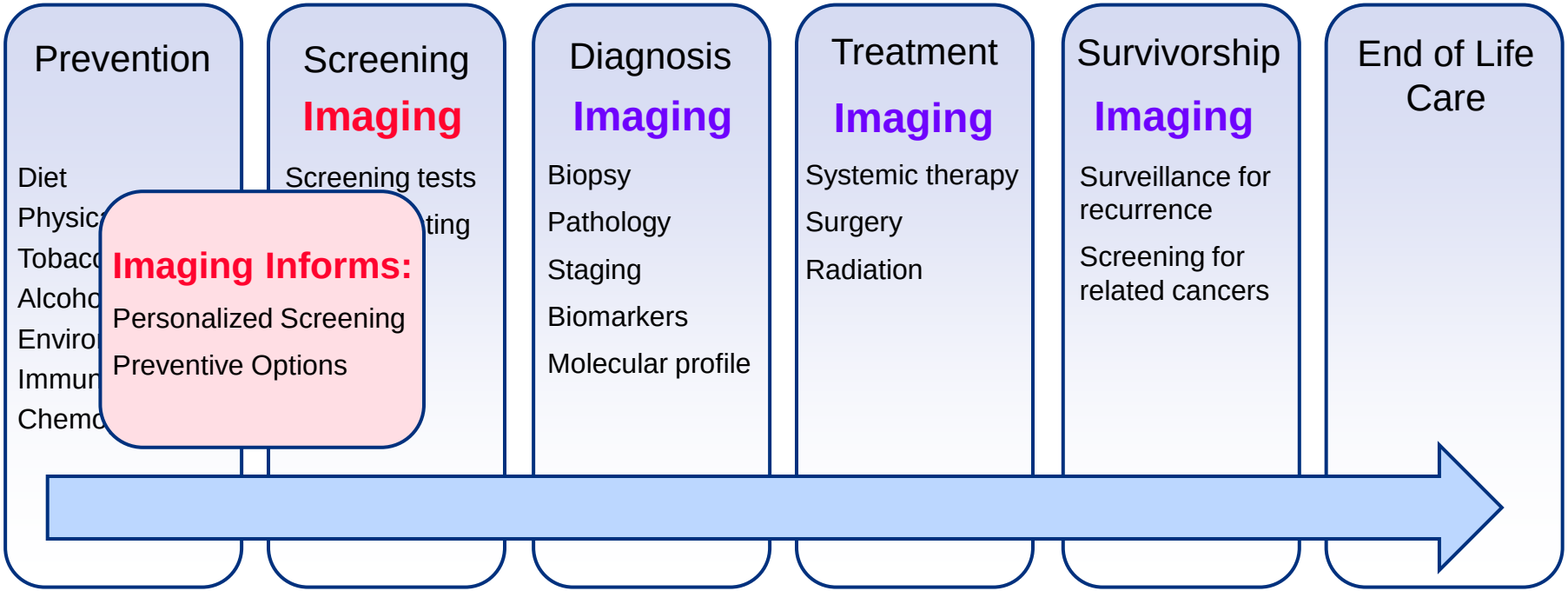
- Per agreement between Mayo Clinic and Gamma Medica, I receive royalties for licensed MBI technologies.

Cancer Care Continuum



Adapted from National Academies Press, 2013

Cancer Care Continuum



Adapted from National Academies Press, 2013

Screening Guidelines

Mammography for “Average Risk” Women:

	ACOG	ACR, SBI	ACS	AMA	NCCN	USPSTF
Age to start	40	40	45	40	40	50
Age to stop	Cont. as long as in good health	When life expectancy < 5-7 yrs	When life expectancy < 10 yrs	When life expectancy < 10 yrs	No limit	74
Frequency	Annual	Annual	Annual 45-54; 1-2 years 55+	Annual	Annual	Every 2 yrs

Annual screening MRI for Women at “Increased Risk”

Saslow, CA Cancer J Clin 2007

Risk models

- IBIS (Tyrer-Cuzick model)
- Claus Model

} Familial models to be used for determining appropriateness of MRI screening (> 20% lifetime)

- NCI Breast Cancer Risk Assessment Tool (Gail model)
  - FDA guideline: chemoprevention if 5-year-risk >1.67%
- Breast Cancer Surveillance Consortium model
  - Only model to include breast density

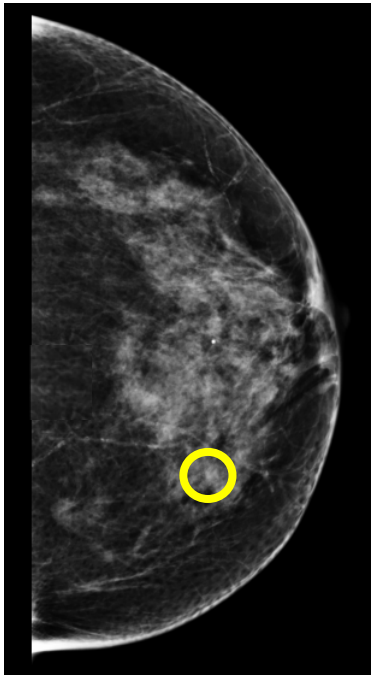
Mammographic Density

"The breasts are almost entirely fatty. …mammography is highly sensitive in this setting"

"The breasts are extremely dense, which lowers the sensitivity of mammography"

Breast composition categories, ACR BI-RADS 5th edition

Density masks breast cancer



What is the sensitivity of mammography in dense breasts?

- Studies only including mammography
  - 1 year of follow-up, until next screening mammogram
  - Estimate sensitivity of ~80%

Sensitivity, %§	
Almost entirely fat	78.3 (59.4–89.9)
Scattered fibroglandular densities	86.6 (80.3–91.1)
Heterogeneously dense	82.1 (76.6–86.6)
Extremely dense	83.6 (69.7–91.9)

Kerlikowske, Ann Intern Med, 2011

What is the sensitivity of mammography in dense breasts?

- Supplemental screening in dense breasts
  - Cancers revealed that otherwise were not counted in mammography audit
  - Estimate sensitivity of 20-40%

Supplemental Screening Method	Sensitivity of Mammo alone	Sensitivity of Mammo + supplement
Automated whole-breast US (Kelly et al)	40%	81%
ACRIN 6666 – 3 yrs of radiologist-performed US (Berg et al)	52%	76%
ACRIN 6666 – MRI after 3 yrs mammo+US (Berg et al)	31%	100%
Molecular breast imaging (Rhodes et al)	24%	91%

Kelly et al Eur Radiol 2011; Berg et al, JAMA 2012; Rhodes et al, AJR 2015

Dual-risk of Density

1. Masking prevalent cancers (present at the time)
2. Greater likelihood of incident cancers (will develop later)
   - Mechanism linking density and cancer is unclear
     - Hypothesis that more glandular tissue, more likely to develop cancer
   - Extremely dense vs. fatty, RR of 4 to 6

Table 1. Risk Factors for Breast Cancer.*

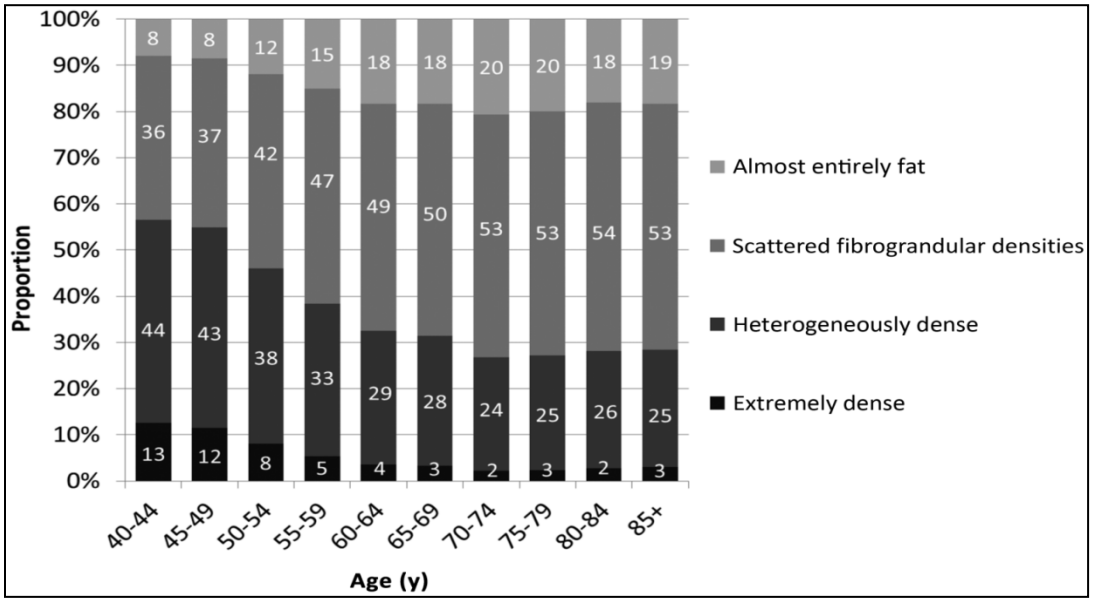
Risk Factor	Relative Risk
BRCA1 or *BRCA2* mutation	10.0–32.0
Family history of cancer (no known mutation)†	
1 first-degree relative	1.5–2.0
2 first-degree relatives	3.0
3 or more first-degree relatives	4.0
1 second-degree relative	1.2–1.5
Therapeutic radiation to chest at <30 yr of age‡	7.0–17.0
Hormonal factors	
Late (age >30 yr) parity or nulliparity	1.2–1.7
Early (age <12 yr) menarche or late menopause (age >55 yr)	1.2–1.3
Combined hormone-replacement therapy (e.g., for 10 or more yr)	1.5
Breast density (very dense vs. mainly fatty)	5.0
Atypical ductal or lobular hyperplasia or lobular carcinoma in situ on previous breast biopsy	4.0

Warner E. N Engl J Med 2011;365:1025-1032

Factors that impact density

- Age
- Menopause
- Hormone use
- BMI
- Anti-estrogen drugs
- Parity
- Genetics

Density by Age



Sprague et al, JNCI 2014

Density to predict risk

- Density alone does not have discriminatory accuracy to be a useful risk predictor
- 40-50% of women have dense breasts
- Should all be considered at “elevated risk”?
- Should all receive supplemental screening?

The NEW ENGLAND JOURNAL of MEDICINE
Perspective
FEBRUARY 12, 2015

Breast-Density Legislation — Practical Considerations

Priscilla J. Slanetz, M.D., M.P.H., Phoebe E. Freer, M.D., and Robyn L. Birdwell, M.D.

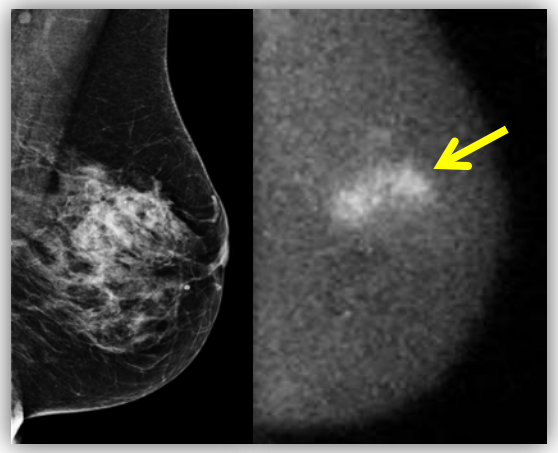
Ever since Nancy Cappello, a Connecticut woman who hadn’t been told that her mammograms showed dense breast tissue, was diagnosed with stage 3 breast cancer in 2004 and advocated for a new state law, there’s been a growing movement to educate women about breast density and the potential role of supplemen- with dense breasts of their status and others stipulating that supplemental screening be offered to such women. Most state laws, women about their breast density has been driven primarily by grassroots organizations and laypeople. The medical community has been more cautious because the ability to detect breast cancer is affected by many factors beyond the limitations of screening mammography, and evidence supporting supplemental screening

“**Risk stratification** will be an essential tool in determining the best screening plan for each woman.”

Slanetz, Freer, and Birdwell, NEJM 2015

Molecular breast imaging (MBI)

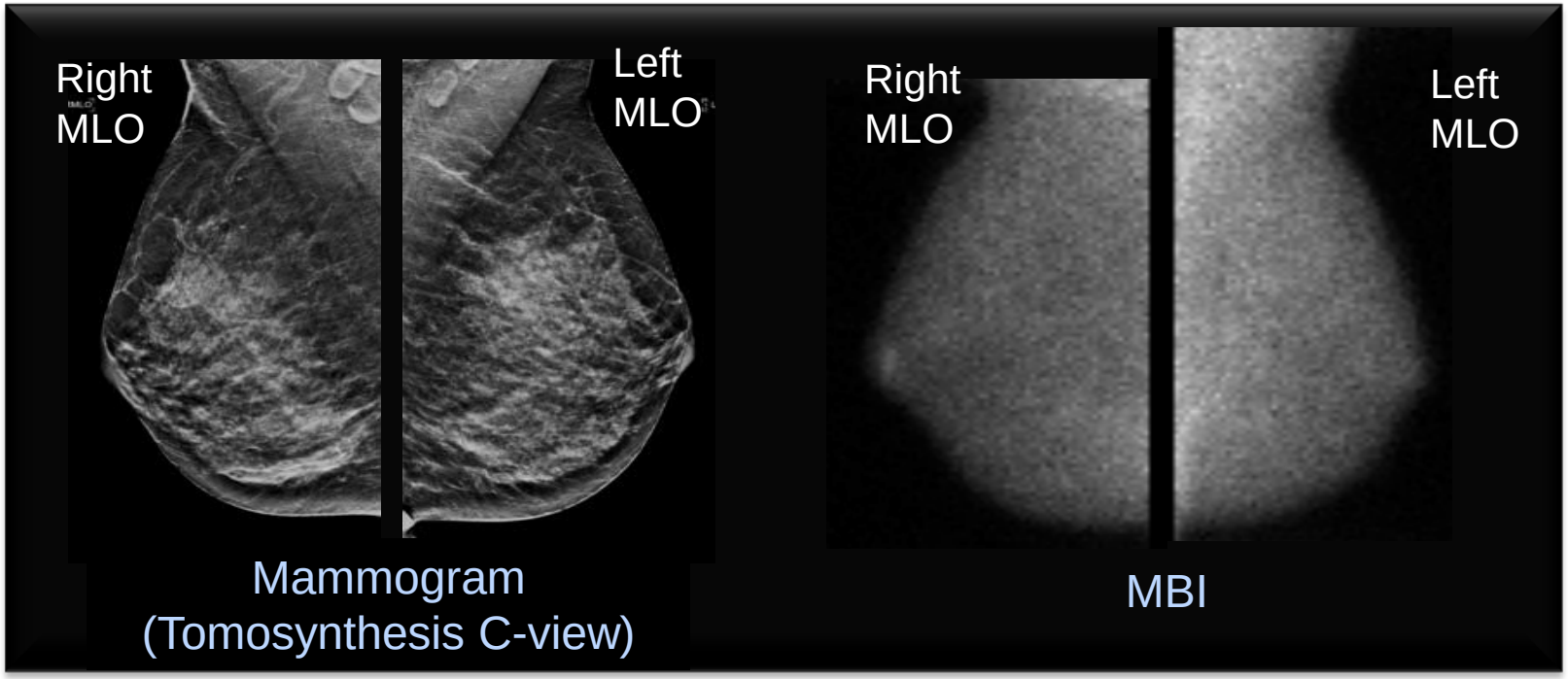
- Performed with injection of Tc-99m sestamibi and dedicated gamma camera
  - Dual-head CZT-based system capable of low-dose imaging
- Mayo experience
  - >5000 MBI exams since ~2004
  - Recommends MBI for supplemental screening
    - Women with dense breasts, intermediate risk
    - MR recommended, cannot be performed
- In dense breasts, MBI finds an additional 8 to 9 cancers per 1000 screened.



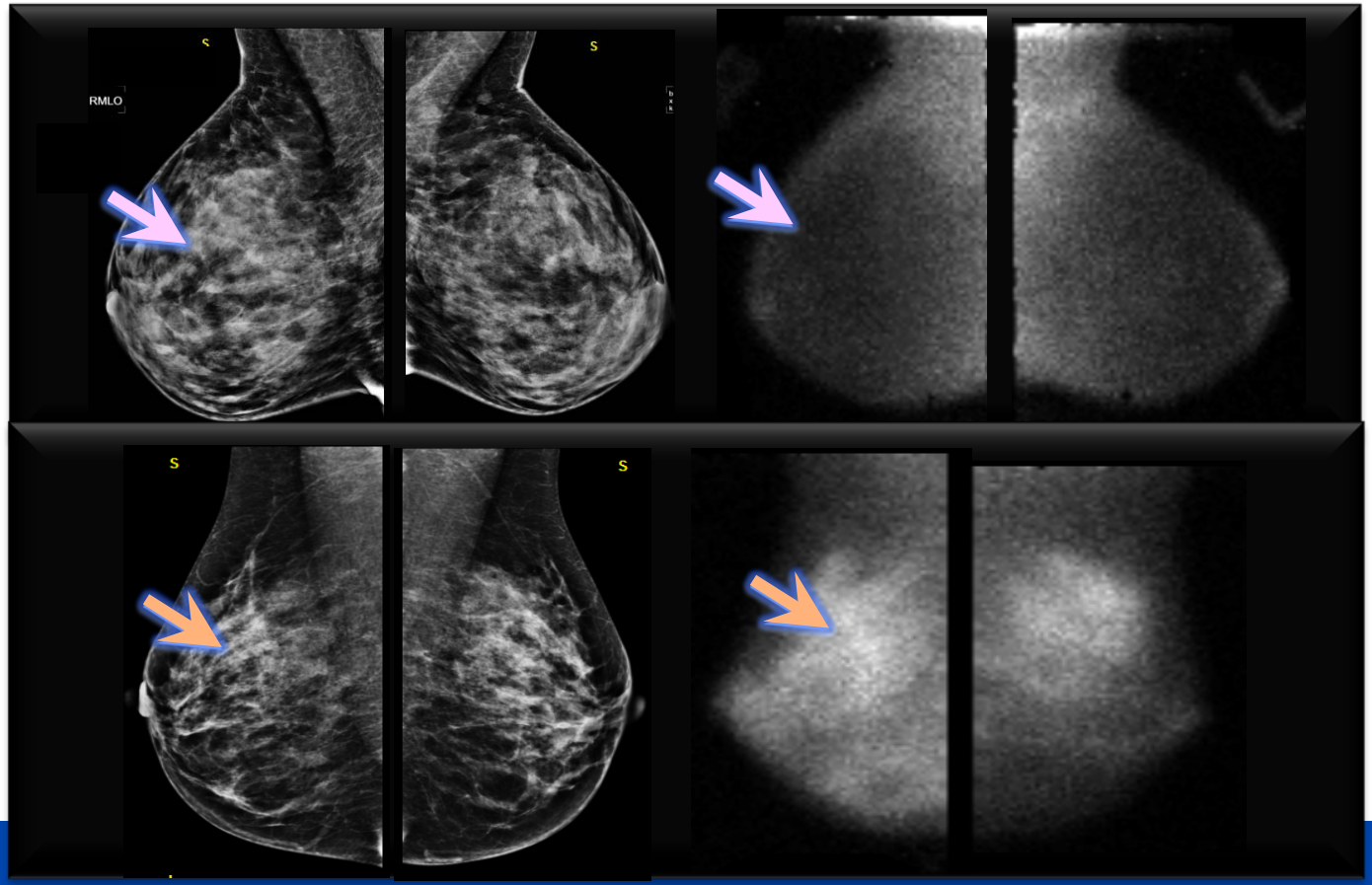
Mammographically-occult Invasive lobular carcinoma; 3.6 cm

Rhodes et al, *AJR* 2015

Typical Negative MBI Screening Exam



Variability in fibroglandular uptake

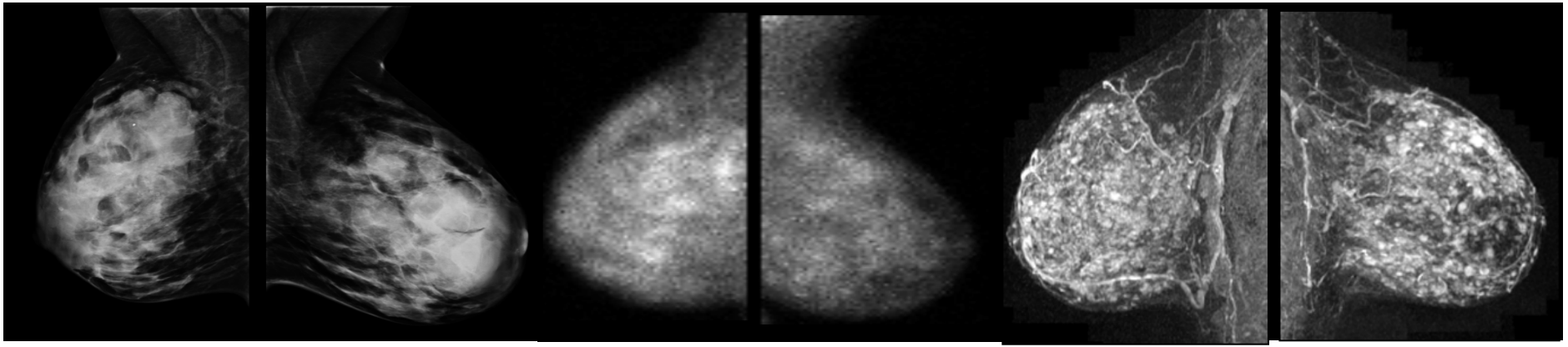


Lack of uptake:
Photopenia

Marked uptake

Masking cancer

49 yr old with extremely dense breasts, hx of multiple breast cysts



Extremely dense parenchyma with “innumerable large nodules”

MBI: “background activity makes the study non-diagnostic”

MRI: “small masses could be obscured”

Right breast: Scattered foci of DCIS throughout all 4 quadrants

Left breast:
Exuberant proliferative fibrocystic changes with multiple sclerosing papillary lesions and foci of ADH

Change our thinking about background

- Instead of just an occasional annoyance…
  - Should document consistently - potential to mask cancers
  - Termed “background parenchymal uptake (BPU)”

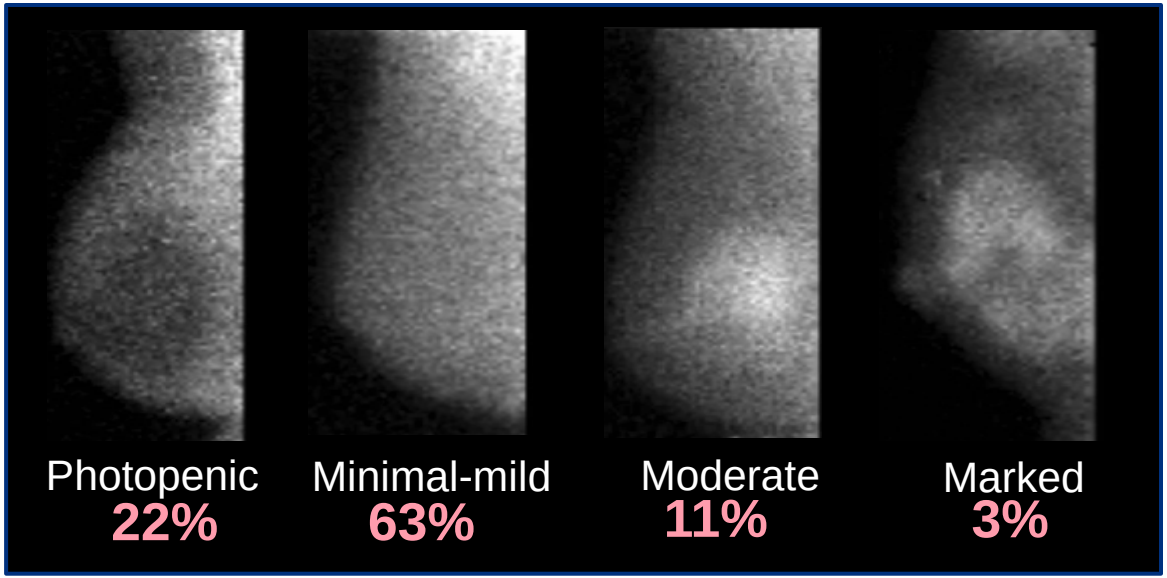
- What is the etiology of BPU?
  - Tc-99m sestamibi uptake in the breast is poorly understood
  - In cancer: related to angiogenesis, and sequestered in mitochondria

- Hypothesize that BPU could signify a tissue environment primed for breast cancer development

MBI Lexicon includes BPU Categories

- Inter-reader agreement: $\kappa = 0.84$
- Intra-reader agreement: $\kappa = 0.87$ to 0.94

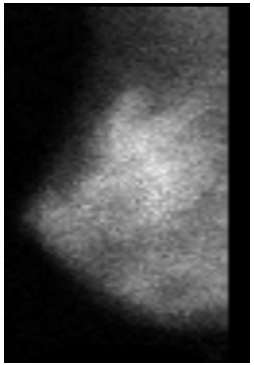
Prevalence of BPU categories in dense breasts →



Conners et al, AJR 2012; Hruska et al, AJR 2015

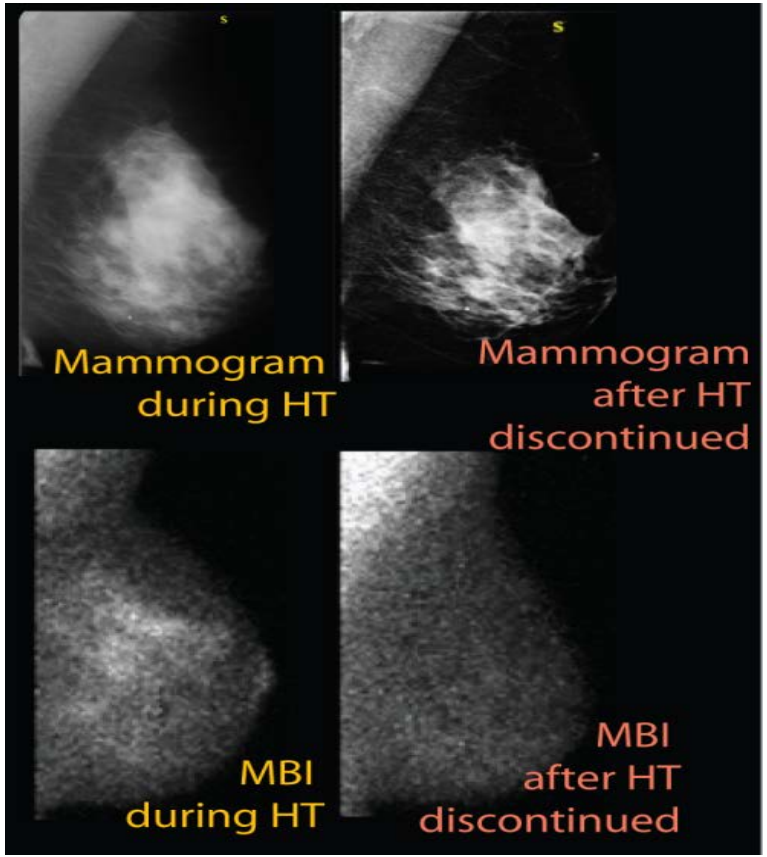
Association of BPU with clinical factors

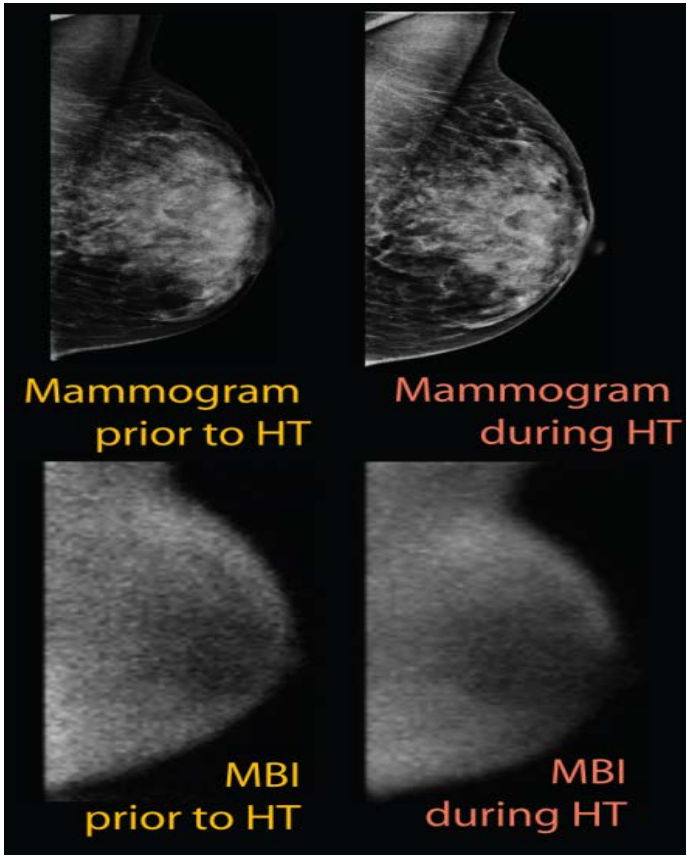
- Women with high background (moderate/marked) more likely to be
  - Younger (mean age 50 vs. 58)
  - Pre or perimenopausal
  - If postmenopausal, more likely using hormone therapy



Hruska et al, AJR 2015

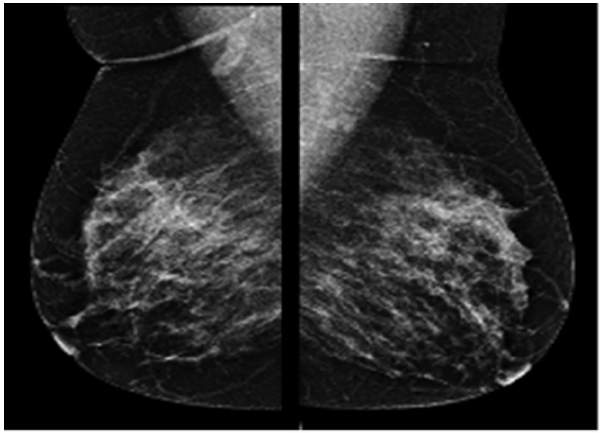
Hormone therapy can influence BPU



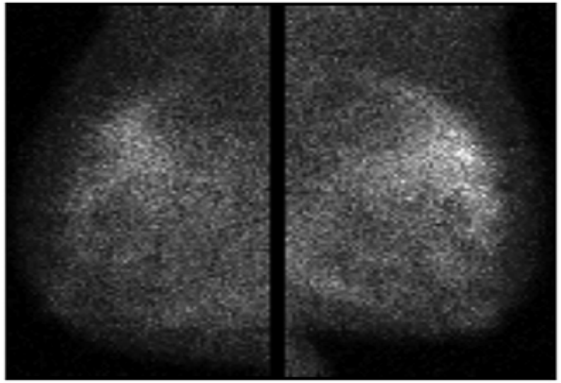


Menstrual cycle can influence BPU

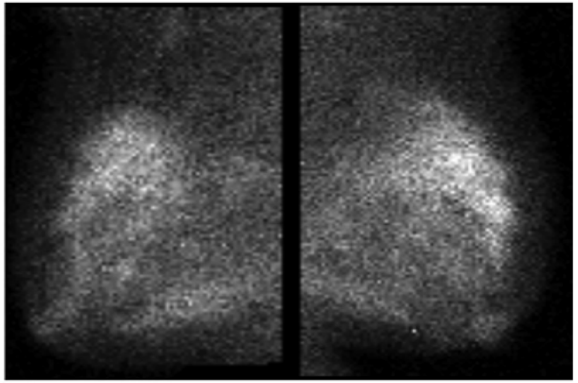
- BPU changes with cycle observed in about 30% of premenopausal women studied
  - Higher in luteal phase vs. follicular
  - Scheduling MBI in follicular phase (days 7-10) can minimize BPU



a. Mammogram



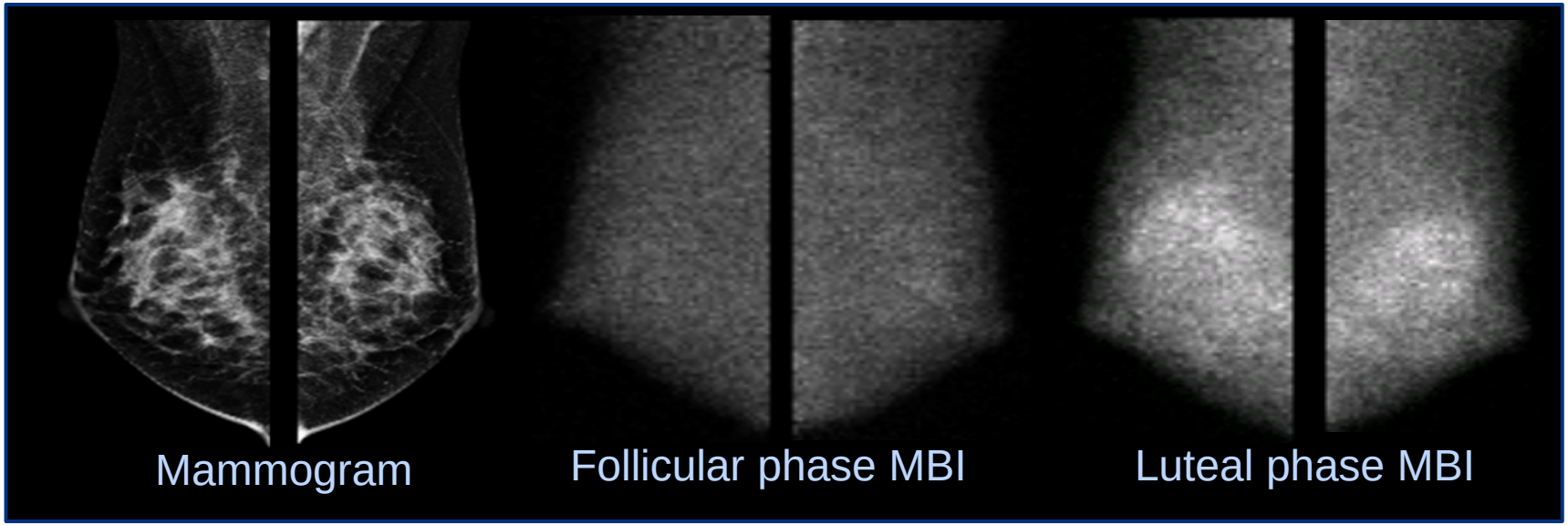
b. Follicular phase MBI



c. Luteal phase MBI

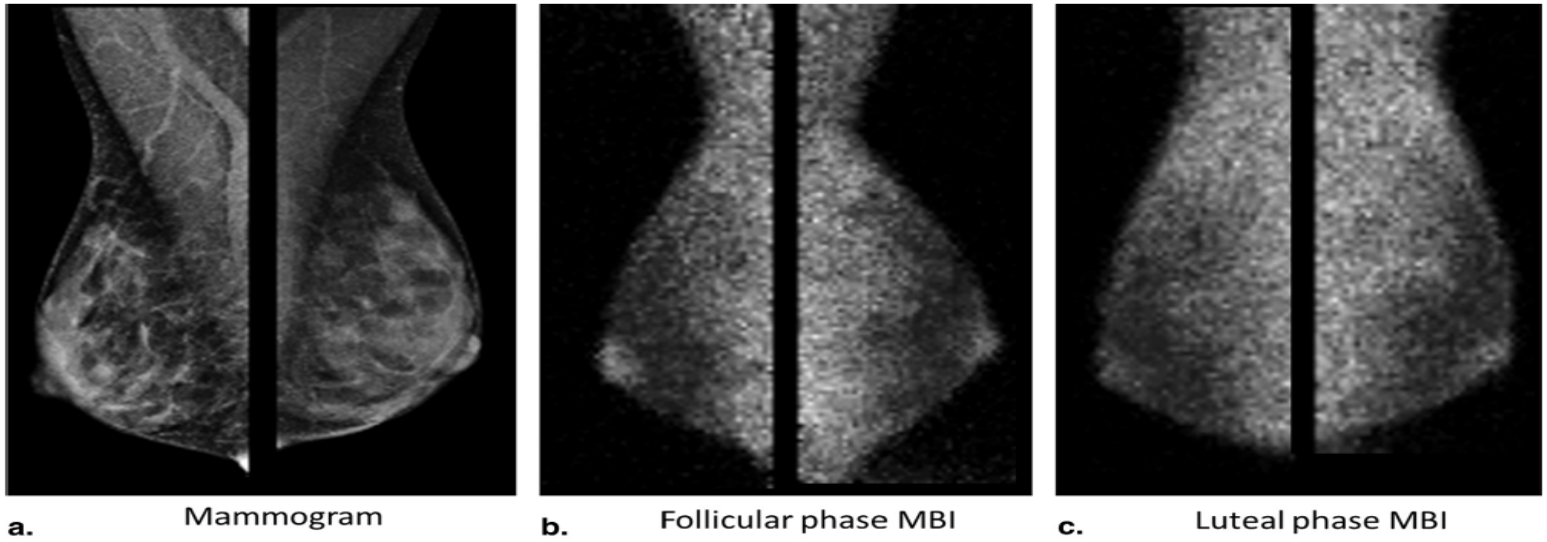
Menstrual cycle can influence BPU

- Dramatic increase at luteal phase



Menstrual cycle not influencing BPU

- Photopenic BPU at both phases



a. Mammogram

b. Follicular phase MBI

c. Luteal phase MBI

Hormonal effects on BPU

- Some patients show imaging changes with hormonal changes, others do not
- May reflect variability in hormone responsiveness of breast tissue
- May be differentiator in determining breast cancer risk?
  - Particularly important in guiding decisions to use hormone therapy

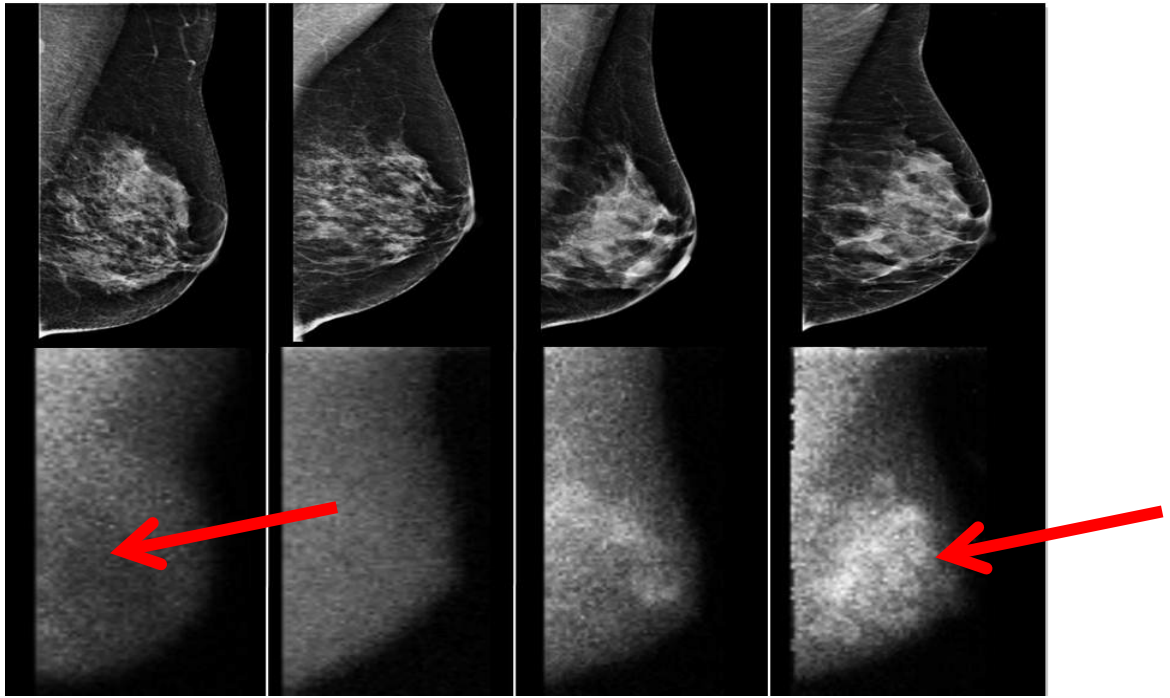
Beyond hormonal influence

4 different postmenopausal women, no exogenous hormones.

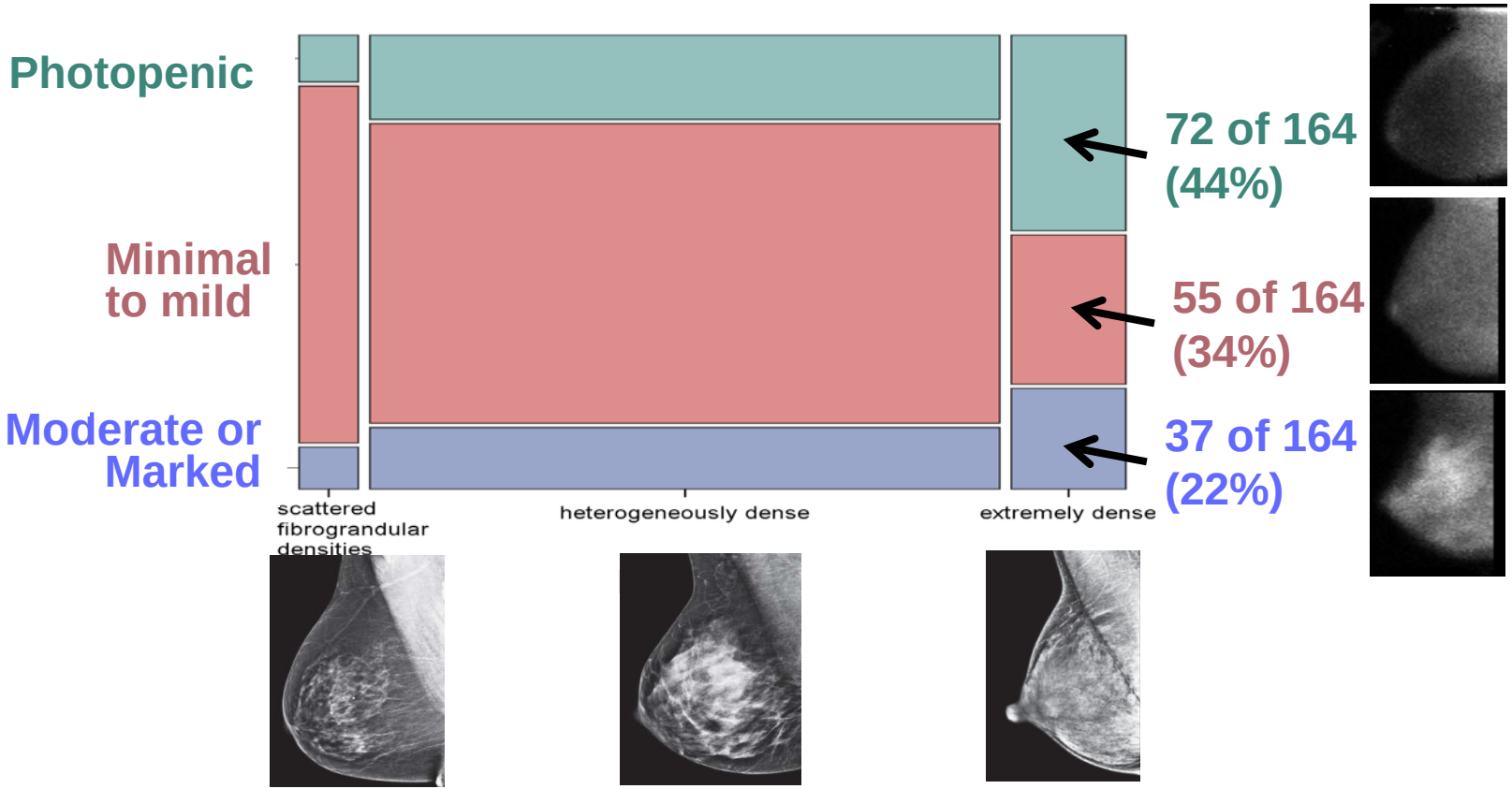
Mammograms

Similar density

Corresponding MBI Exams

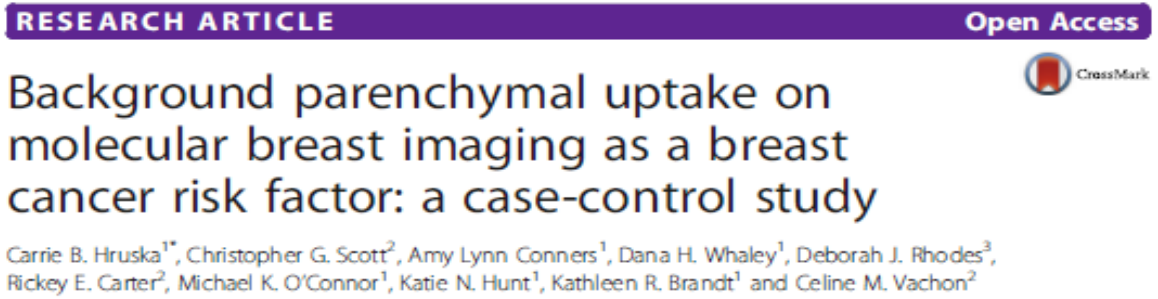


BPU prevalence varies across density categories



Case-Control Study

- Purpose: To investigate whether BPU on MBI is a risk factor for incident breast cancer



RESEARCH ARTICLE Open Access

Background parenchymal uptake on molecular breast imaging as a breast cancer risk factor: a case-control study

Carrie B. Hruska[1*], Christopher G. Scott[2], Amy Lynn Conners[1], Dana H. Whaley[1], Deborah J. Rhodes[3], Rickey E. Carter[2], Michael K. O'Connor[1], Katie N. Hunt[1], Kathleen R. Brandt[1] and Celine M. Vachon[2]

Hruska et al. Breast Cancer Research 2016

Case-Control Study

- Reviewed institutional MBI database
  - >3000 women with screening MBI performed between 2005-2014
  - Earliest (index) MBI used for analysis
- Excluded
  - Prevalent breast cancer cases
  - Women with breast implants
- Participants followed for breast cancer through
  - Review of medical records
  - Linkage to Mayo Clinic Tumor Registry

Cases and Controls

- 62 incident breast cancer cases
  - 45 (73%) were invasive and 17 (27%) were DCIS
  - Median time to diagnosis: 3.3 years (range 0.5 to 8.8 years) after index MBI.
- 179 controls randomly selected
  - Matched on
    - Age (within 5 yrs)
    - Menopausal status
    - MBI year
  - Required to be followed at least as long as matched case
- Two breast radiologists read all MBIs independently
  - Blinded to case status

Case-Control Study Results

- Women with high BPU more likely to develop breast cancer than women with low BPU.

BPU as dichotomous variable	Odds Ratio†, adjusted for BMI†
Reader 1	
Photopenic or Minimal-mild	1.0
Moderate or Marked	**3.4 (1.6, 7.3)**
P-value	0.002
Reader 2	
Photopenic or Minimal-mild	1.0
Moderate or Marked	**4.8 (2.1, 10.8)**
P-value	< 0.001

†Numbers in parentheses are 95% confidence intervals

Case-Control Study Results

- Association remained with adjustment for density

BPU as dichotomous variable	Odds Ratio†, adjusted for BMI†	Odds Ratio†, adjusted for BMI and BI-RADS density
Reader 1		
Photopenic or Minimal-mild	1.0	1.0
Moderate or Marked	**3.4 (1.6, 7.3)**	**3.3 (1.6, 7.2)**
P-value	0.002	0.002
Reader 2		
Photopenic or Minimal-mild	1.0	1.0
Moderate or Marked	**4.8 (2.1, 10.8)**	**4.6 (2.1, 10.5)**
P-value	< 0.001	< 0.001

†Numbers in parentheses are 95% confidence intervals

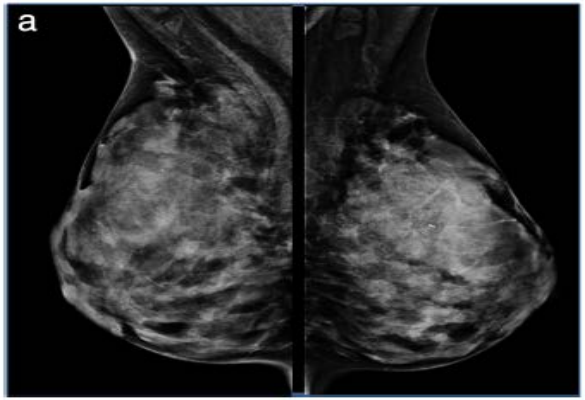
Case-Control Study Results

- Association remained with adjustment for postmenopausal HT

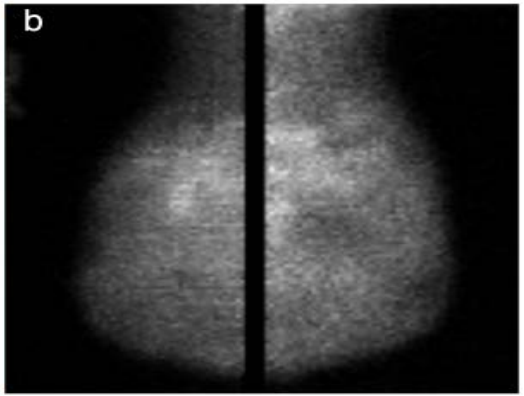
BPU as dichotomous variable	Odds Ratio†, adjusted for BMI†	Odds Ratio†, adjusted for BMI and BI-RADS density	Odds Ratio†, adjusted for BMI and postmenopausal HT
Reader 1			
Photopenic or Minimal-mild	1.0	1.0	1.0
Moderate or Marked	**3.4 (1.6, 7.3)**	**3.3 (1.6, 7.2)**	**3.6 (1.7, 7.7)**
P-value	0.002	0.002	0.001
Reader 2			
Photopenic or Minimal-mild	1.0	1.0	1.0
Moderate or Marked	**4.8 (2.1, 10.8)**	**4.6 (2.1, 10.5)**	**5.0 (2.2, 11.4)**
P-value	< 0.001	< 0.001	< 0.001

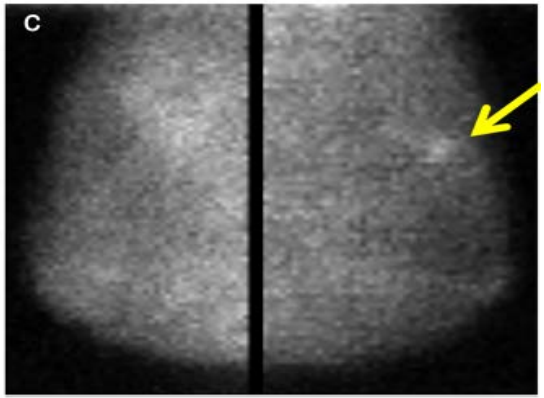
†Numbers in parentheses are 95% confidence intervals

Case example: 41 yr old woman with strong family hx



Screening mammogram
Negative, Extremely dense





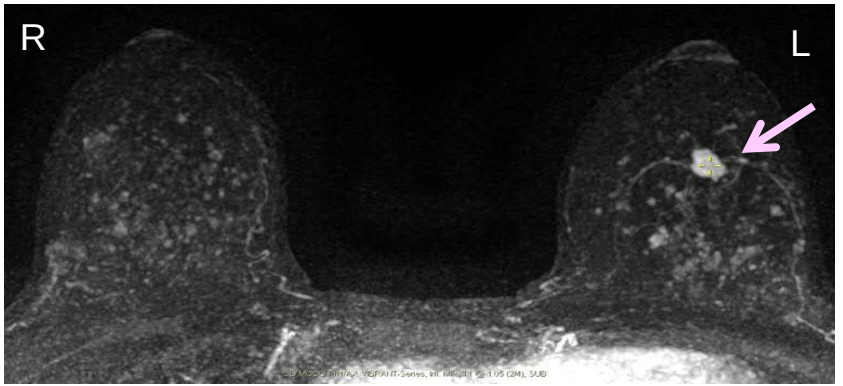
Screening MBI, Marked BPU

2 years later,
Presented with clinical symptoms (nipple retraction)

MRI performed:

Right breast: atypia

Left breast: Grade I, 0.9 cm invasive ductal carcinoma, node negative



Case-control study Conclusions

- BPU on MBI is an imaging biomarker associated with breast cancer risk; OR 3.4 to 4.8
- Associations remained
  - With adjustment for mammographic density
  - With adjustment for hormone therapy use
  - When limited to postmenopausal women only
    - Suggests risk factor is not just cyclic effect artifact
  - When limited to invasive cancer cases only

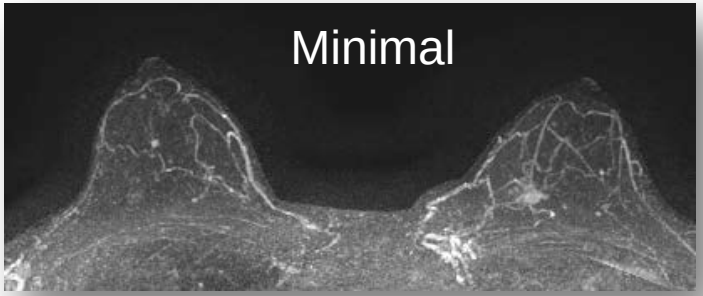
Background parenchymal enhancement (BPE) at breast MR imaging

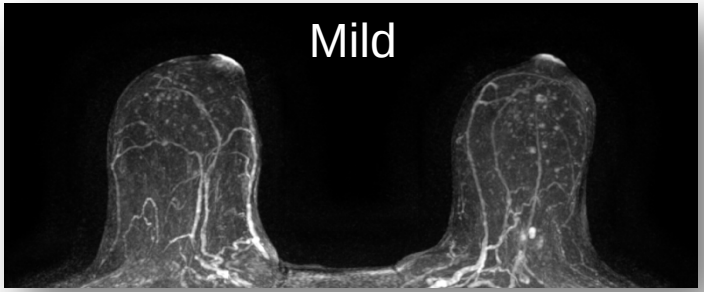
- Associated with hormonal influences
  - Menopausal status (King, Eur Radiol 2012; Hegensheid, Eur Radiol 2012)
  - Menstrual cycle phase (Kuhl, Radiology 1997; Delille, Breast J 2005)
  - Hormone therapy use (Delille, Radiology 2005)
  - Tamoxifen and AI use (King, Radiology 2012)

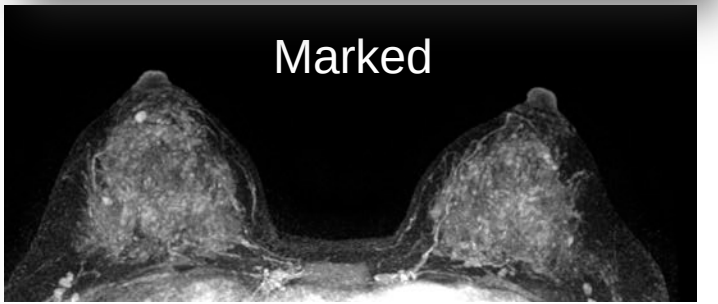
- Variable background among women with similar
  - Mammographic density (Kuhl et al, JMRI 2014)
  - MR-depicted fibroglandular tissue (King et al, Radiology 2011)

MRI background parenchymal enhancement (BPE)

Post-contrast maximum intensity projections





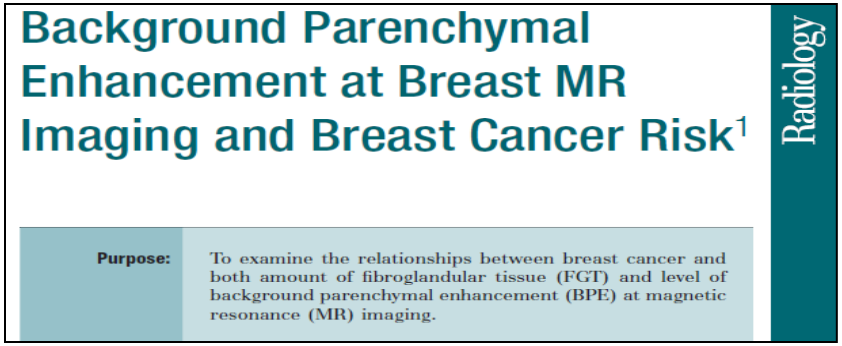


Per ACR BI-RADS:

“visually estimated enhancement of fibroglandular tissue of the breasts”

Refers to the volume and intensity of enhancement

MRI BPE association with breast cancer



Background Parenchymal Enhancement at Breast MR Imaging and Breast Cancer Risk[1]

Radiology

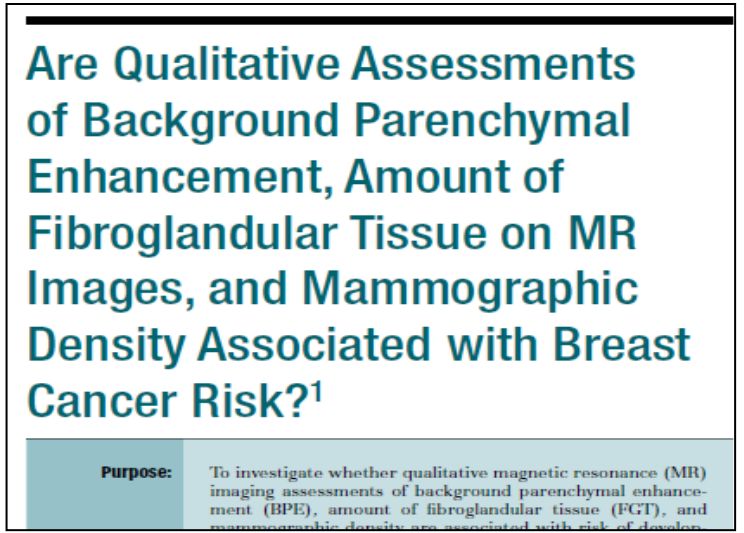
Purpose: To examine the relationships between breast cancer and both amount of fibroglandular tissue (FGT) and level of background parenchymal enhancement (BPE) at magnetic resonance (MR) imaging.

- Case-control analysis
  - 39 prevalent breast cancer cases
  - High vs. Low BPE: ORs = 3.7 to 10.1
  - Associations remained significant after adjustment for amount of fibroglandular tissue seen on MR

King et al, Radiology 2011

MRI BPE association with breast cancer

- Case-control analysis
  - 23 breast cancer cases
    - 6 prevalent
    - 17 incident
  - High vs. Low BPE: OR = 9.0



Are Qualitative Assessments of Background Parenchymal Enhancement, Amount of Fibroglandular Tissue on MR Images, and Mammographic Density Associated with Breast Cancer Risk?[1]

Purpose: To investigate whether qualitative magnetic resonance (MR) imaging assessments of background parenchymal enhancement (BPE), amount of fibroglandular tissue (FGT), and

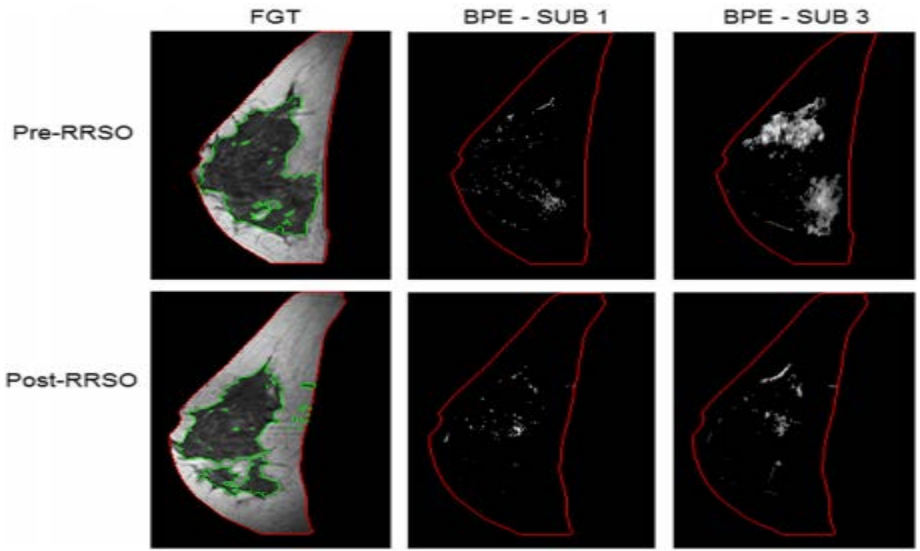
Dontchos et al, Radiology 2015

MRI background enhancement in BRCA carriers

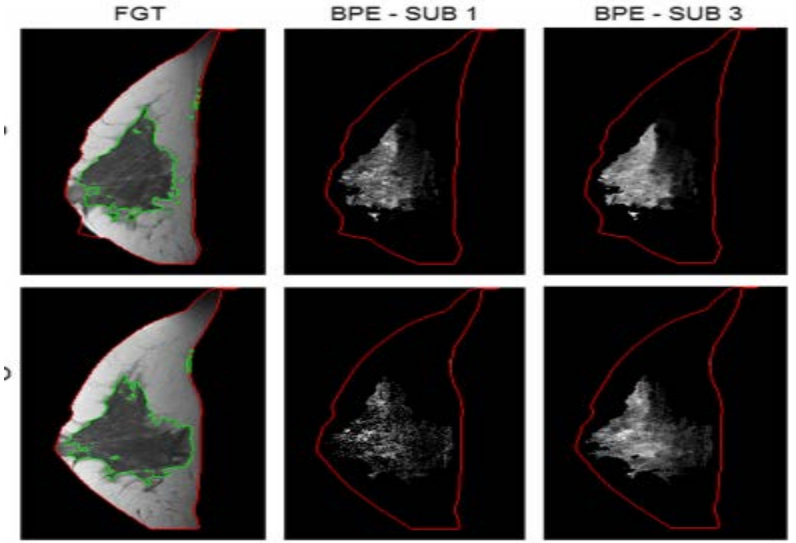
- UPenn researchers developed quantitative BPE measurement tools for MRI
- 50 BRCA1/2 carriers who underwent risk reducing oopherectomy
  - Pre and post-oopherectomy MRI performed
  - Median 4.8 yrs follow-up
  - 44 with no breast cancer: BPE was reduced after oopherectomy
  - 6 developed breast cancer: BPE was not reduced after oopherectomy

Wu et al, Breast Cancer Res 2016

MRI background enhancement in BRCA carriers



40 yrs old
No cancer at 9 years follow-up
Decrease in MRI-measured FGT
Decrease in BPE

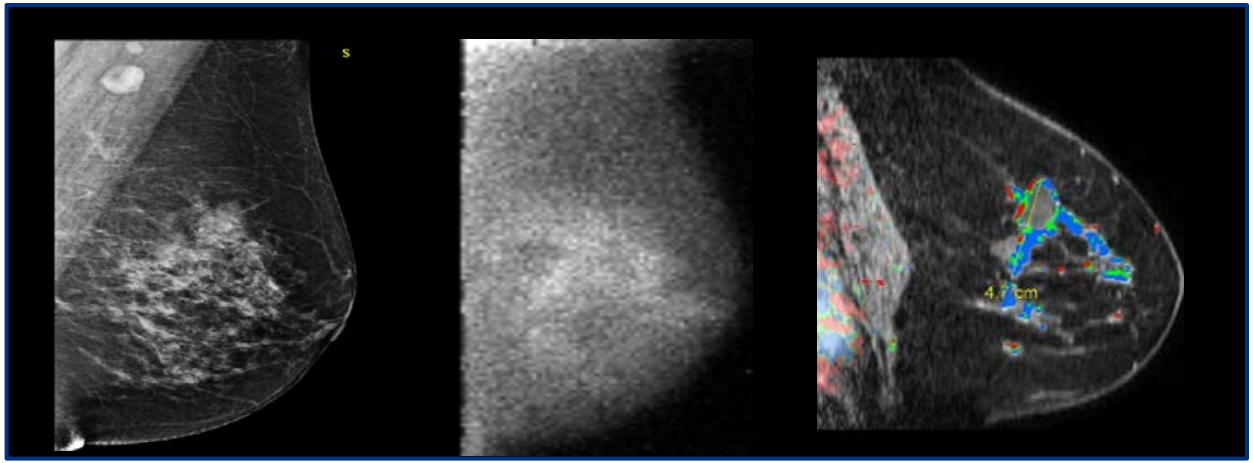


36 yrs old
Cancer diagnosed at 6 years follow-up
No decrease in MRI-measured FGT
No decrease in BPE

Wu et al, Breast Cancer Res 2016

MBI and MRI background

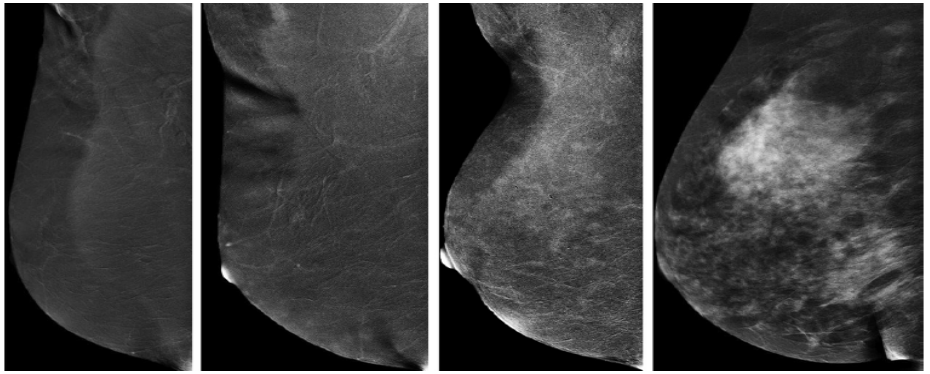
- Gadolinium contrast enhancement and sestamibi uptake have similar functional mechanism
  - Perfusion, angiogenesis and vascular permeability



Mammogram MBI MRI

Background on Contrast-enhanced Mammography

- Associated with
  - Menopausal status
  - Prior radiation therapy
  - Hormonal treatment
  - Density
  - MR fibroglandular tissue

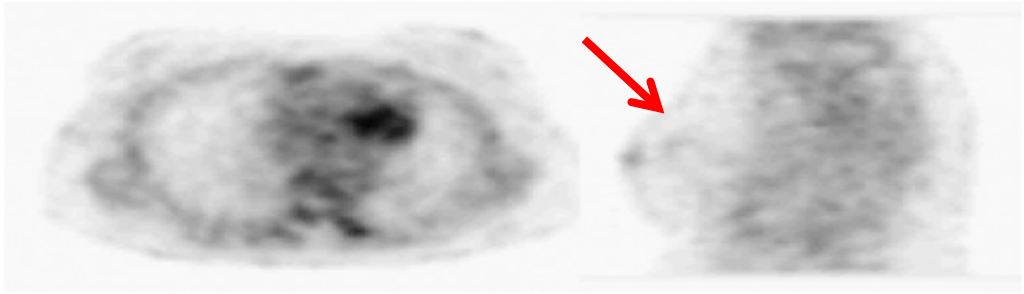


- Agreement between MR and CEDM background
  - $\kappa = 0.66$

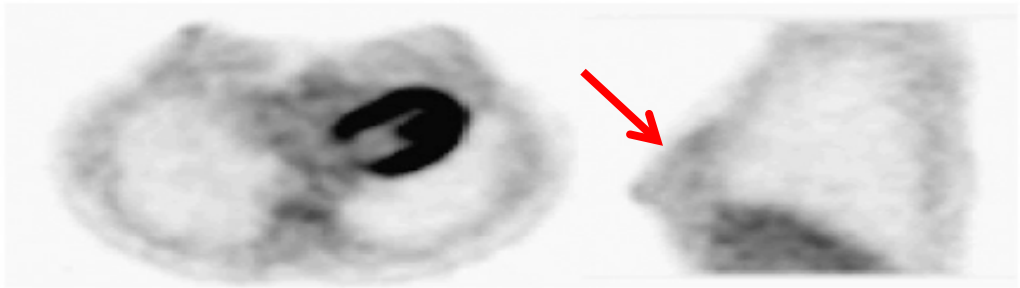
Sogani et al, Radiology 2016

Background uptake on PET

- Evidence of variability in FDG uptake in breast fibroglandular tissue



Non-dense on mammography
Low FDG uptake



Dense on mammography
High FDG uptake

Mavi et al, J Nuc Med 2010

Summary

- Functional imaging techniques show variability among fibroglandular tissue that appears similar on a mammogram
  - Provide additional risk information beyond mammographic density
  - May depict fibroglandular tissue primed for cancer development

- Functional imaging biomarkers could identify the subset of women with dense breasts who are
  - at greatest risk of breast cancer, and
  - most likely to benefit from tailored screening or risk-reduction strategies

Thank you

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