# Breast Density, Screening, and Prevention

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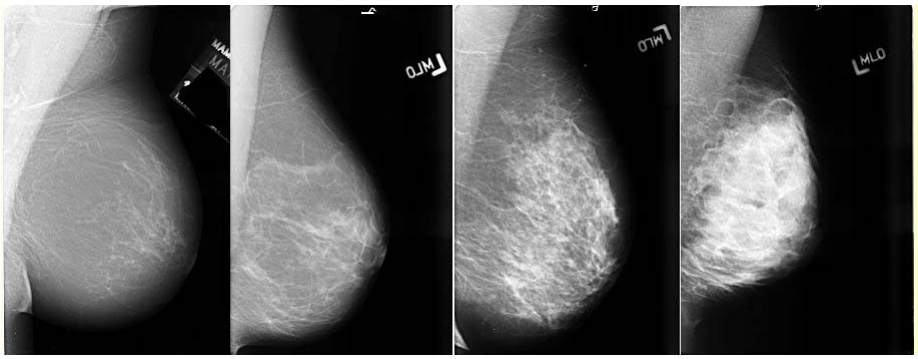
Fall 2017

## Outline

- Why is breast density so interesting to me?
- Factors that influence breast density
- BCERP project
- Tailoring screening based on density
- Summary: breast cancer prevention

# Mammographic Breast Density: risk of breast cancer increases with density



| Almost Entirely Fat | Scattered Densities | Heterogeneously Dense | Extremely Dense |
|---|---|---|---|
| RR=1 | RR = 2.2 | RR=2.8 | RR=3.9 |

Vacek and Geller. *Cancer Epidemiology, Biomarkers & Prevention* 13:715, 2004.

# Breast density fundamentally changes how we can study breast cancer

- Very strong risk factor
- Measured in a standardized way
- Available for large groups of women – not just in research settings or among breast cancer patients
- "Intermediate marker" – a change in density reflects a change in breast cancer risk
- Many studies show how both density and breast cancer are related to the same risk factors

Table 2. Age-specific Probability of Developing Invasive Breast Cancer for US Women

| Current age | 10-year probability: | or 1 in: |
|---|---|---|
| 20 | 0.1% | 1,567 |
| 30 | 0.5% | 220 |
| 40 | 1.5% | 68 |
| 50 | 2.3% | 43 |
| 60 | 3.4% | 29 |
| 70 | 3.9% | 25 |
| **Lifetime risk** | **12.4%** | **8** |

Note: Probability is among those free of cancer at beginning of age interval. Based on cases diagnosed 2012-2014. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.



https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html

## Breast Cancer Risk Factors

- Increased risk
  - Female sex
  - Older age
  - Family history of breast cancer
  - Dense breasts
  - Taller height
  - Radiation
  - Postmenopausal hormone use
  - Later age at 1st birth
  - Later age at menopause
  - Alcohol consumption
  - Obesity/weight gain
- Decreased risk
  - Later age at first menstruation
  - Full term pregnancies
  - Breast feeding
  - Physical activity
  - Tamoxifen (anti-estrogen)

## Estimating individual risk of breast cancer


BCSC Risk Calculator
https://tools.bcsc-scc.org/bc5yearrisk/calculator.htm


Breast Cancer Risk Assessment Tool
https://www.cancer.gov/bcrisktool/Default.aspx

# Breast cancer risk factors are also related to breast density

- Increased risk
  - Female sex
  - Older age (↓)
  - Family history of breast cancer
  - Taller height
  - Radiation
  - Postmenopausal hormone use
  - Later age at 1st birth
  - Later age at menopause
  - Alcohol consumption
  - Obesity/weight gain (↓)
- Decreased risk
  - Later age at first menstruation
  - Full term pregnancies
  - Breast feeding
  - Physical activity
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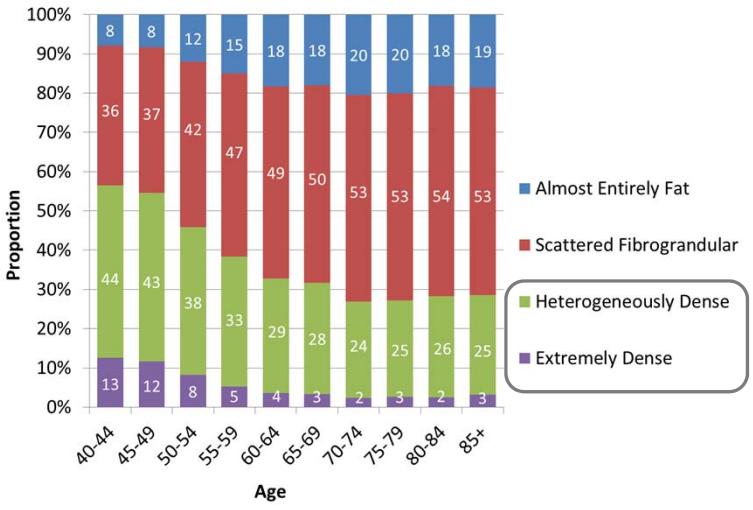
Factors in **black** are related to breast cancer
Factors in blue are related to both breast cancer and breast density, in the same direction
Red arrows indicate that as age and obesity increase, breast cancer risk increases but density decreases

- About 28 million women aged 40-74 in the United States have dense breasts
  - 44% of the breast cancer screening population
- Density decreases with age

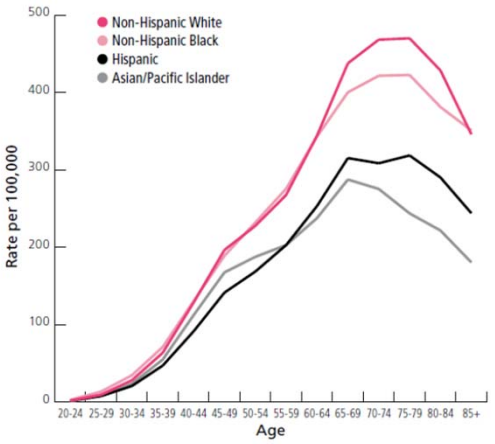



Data from the Breast Cancer Surveillance Consortium; Sprague et al., *JNCI* 2014

Puzzle: Breast cancer risk increases with age while density decreases

- Cumulative time living with dense breasts may be more important than density at a certain time point

Figure 1. Age-specific Female Breast Cancer Incidence Rates by Race/Ethnicity, 2010-2014, US

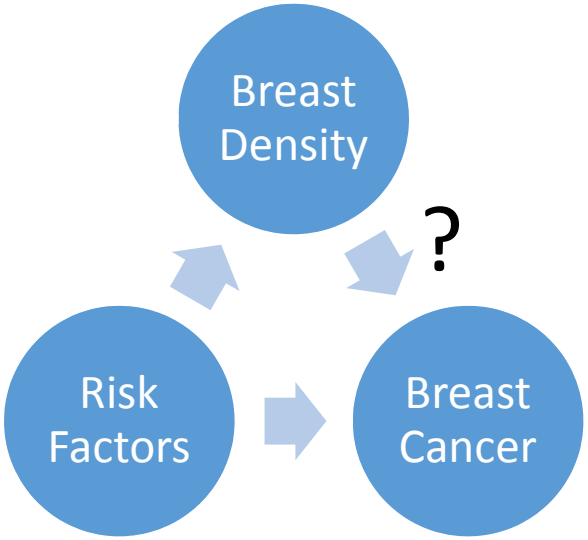



Note: Rates are per 100,000 and age adjusted to the 2000 US standard population.

**Sources:** Incidence: North American Association of Central Cancer Registries (NAACCR), 2017. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, 2017.

American Cancer Society, Inc., Surveillance Research, 2017

Association or Causation?



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# Breast Cancer and the Environment Research Program (BCERP)

- To focus science on the factors in our environment that may increase women's risk of developing breast cancer
- To bring together laboratory scientists with clinical researchers and community partners to determine risk factors for breast cancer
- To study windows of time over a woman's lifespan when she may be more vulnerable to environmental risks, or "Windows of Susceptibility"

➢ Visit www.bcerp.org

# The "Environment"

ANY NON-INHERITED FACTOR

- **Lifestyle and behavioral factors:** physical activity, body weight, dietary foods and beverages
- **Menstrual and reproductive factors**: age of first menstruation, use of postmenopausal hormones
- **Chemical agents:** pesticides used to kill bugs, ingredients in cosmetics, materials in food containers
- **Physical agents:** radiation, metals, and chemicals
- **Social factors:** how the government regulates chemicals, where you live, access to fresh foods, and access to health care, etc

# The Precautionary Principle

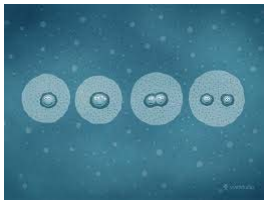
When an activity raises the threat of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.

In other words, "better safe than sorry", "look before you leap", "an ounce of prevention is worth a pound of cure", etc.

## Windows of Susceptibility (WOS)

**Key Times of Hormone Changes and High Cellular Activity:**

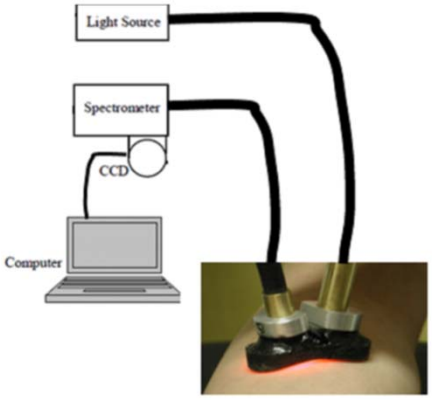
- Prenatal
- Puberty
- Pregnancy
- Menopause



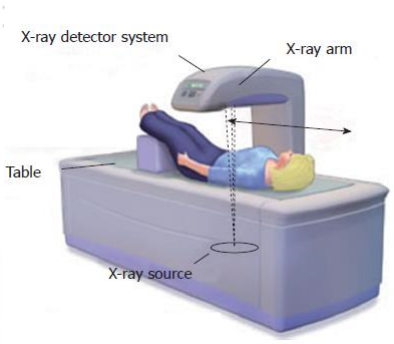
➢ Density provides a method for research across the lifespan, even during puberty

## Approaches for evaluating breast density and other breast tissue features in BCERP

Mammography

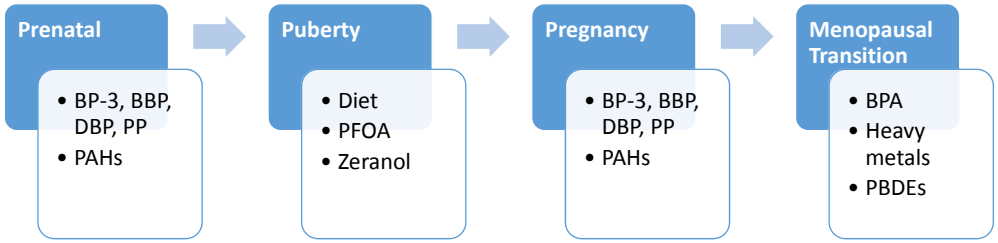



Optical Spectroscopy




DXA

# BCERP Research Projects




- Density and other breast tissue evaluated during puberty and menopausal transition, and in mother-daughter pairs
- Rodent experiments to examine the mechanisms by which chemical exposure at certain time points may cause mammary cancer

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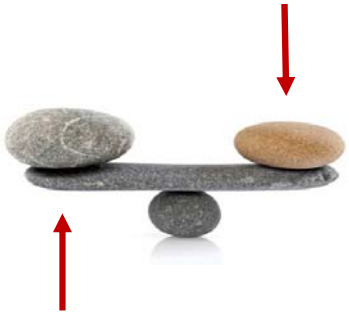
# Shared decision making for mammography

<u>Benefits</u>

Reduced morbidity and mortality from breast cancer



<u>Harms</u>

Inconvenience

Pain

Radiation

Anxiety

"Unnecessary" Biopsies

Over-diagnosis

Costs

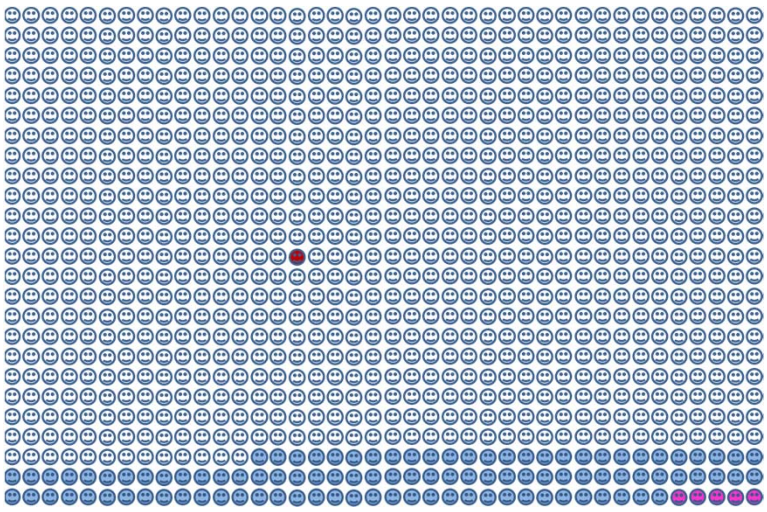
# 1000 Screening Mammograms

True negative

False positive

True positive

False negative



Data from the Breast Cancer Surveillance Consortium

## How can we optimize the benefit/harm balance of breast cancer screening?

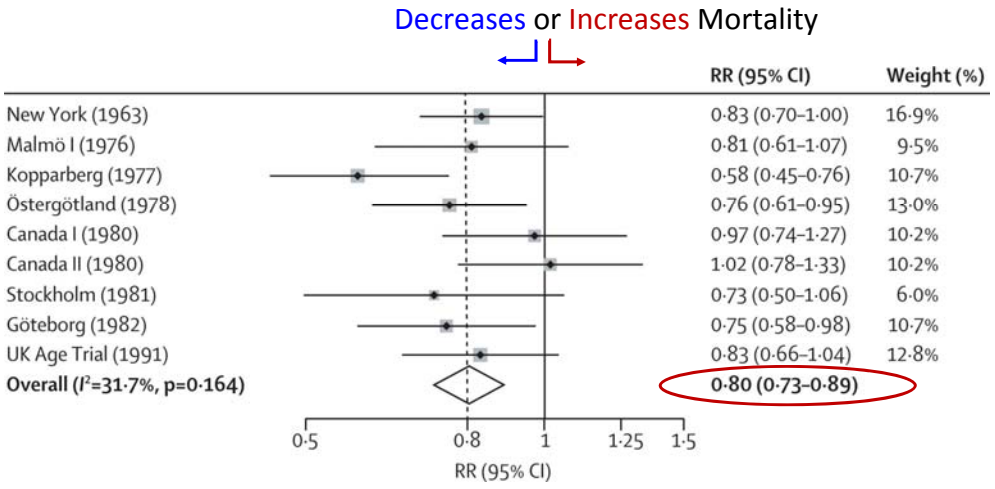
- Who should get screened?
- How often?
- With which modality (or modalities)?
  - Mammography
  - MRI
  - Ultrasound

## Mammography screening for breast cancer has had a long history of debate

- Reasonable people disagree over interpretation of the same evidence
- "Strong political forces" are present

| Guideline | American Cancer Society | US Preventive Services Task Force |
|---|---|---|
| 1983-1991 | 35-39 Baseline<br>40-49 Every 1-2 years<br>50+ Yearly | 1989: 50-74 Every 1-2 years.<br>Recommends against "baseline" <50 |
| 1992-1997 | 40-49 Every 1-2 years<br>50+ Yearly | 1997: 50-74 Biennial, <50 Take patient context into account, 75+ Insufficient |
| 1997-2003 | 40+ Yearly | 2002: 40-70 Every 1-2 years |
| 2003-2015 | 40+ Yearly, for as long as a woman is in good health | 2009: 50-74 Biennial, <50 Take patient context into account, 75+ Insufficient evidence |
| 2015-present | 45-54 Yearly<br>55+ Every 2 years, annual if they want, for as long as a woman is in good health with life expectancy ≥10 years | 2016: 50-74 Biennial, <50 Take patient context into account, 75+ Insufficient evidence |

# Sources of Evidence: Randomized Trials



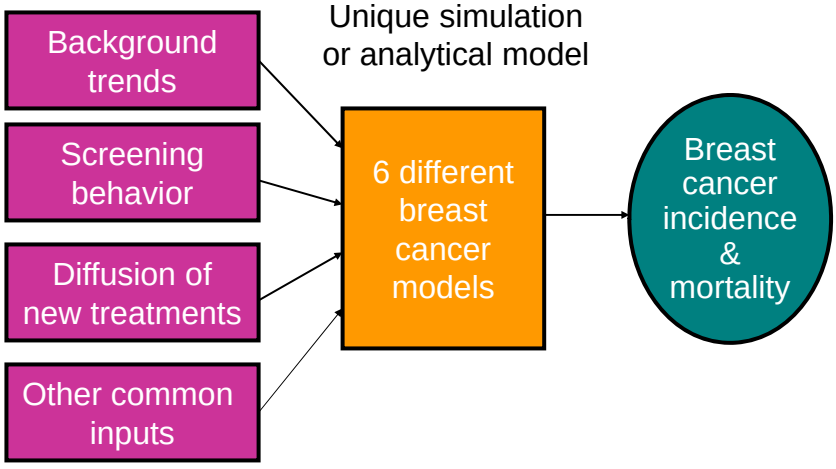

Overall, mammography reduces risk of death from breast cancer by about **20%**

Independent UK Panel on Breast Cancer Screening *Lancet* 2012

# Conceptual view of computer models

Common inputs

Unique simulation or analytical model



## CISNET Analysis Conclusions

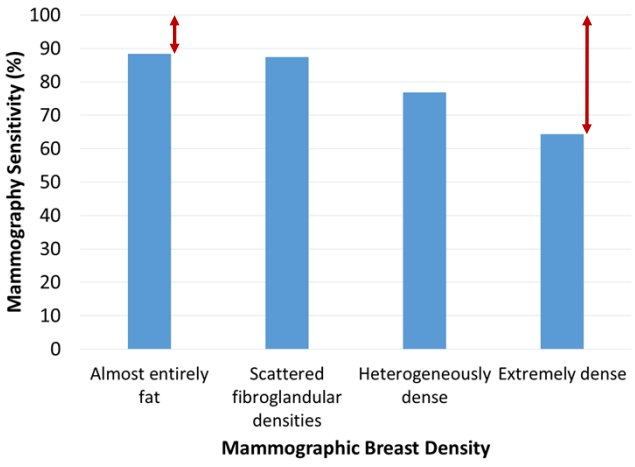
- Results consistent across 6 models
- Biennial strategies achieve good balance of benefits and harms
  - Modeling uniquely is able to assess screening intervals
- All models estimated some benefit for starting at age 40; benefits are generally small
  - Consistent with evidence review of trials

| | *IF GOAL* | *THEN* |
|---|---|---|
| 1 | % mortality reduction per screen | 50-79 every 2 years |
| 2 | Life years gained per screen | 40-79 every 2 years |
| 3 | Maximum % mortality reduction | 40-84 annually |
| 4 | Least false positives | Start later |
| 5 | Less detection of invasive tumors that would not become symptomatic before death other causes | Stop earlier |

## Breast density impairs mammography performance

"Sensitivity" is a measure of the probability that the mammogram finds a breast cancer if it is present

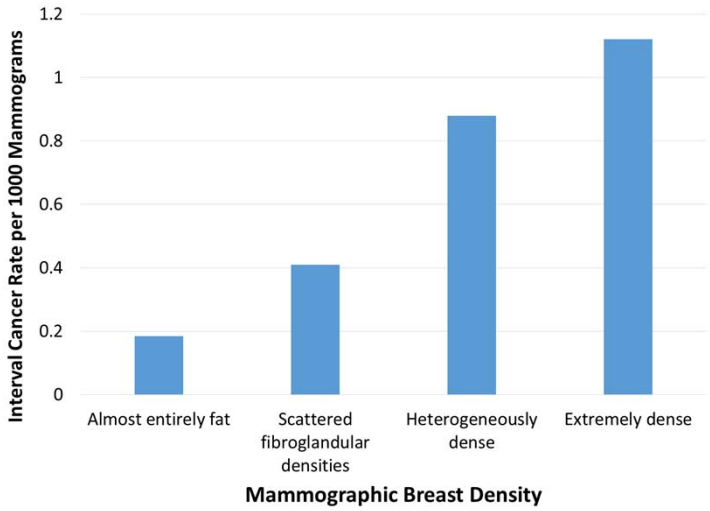
Sensitivity of mammography is better in women with fatty (less dense) breasts




Based on data from the Breast Cancer Surveillance Consortium

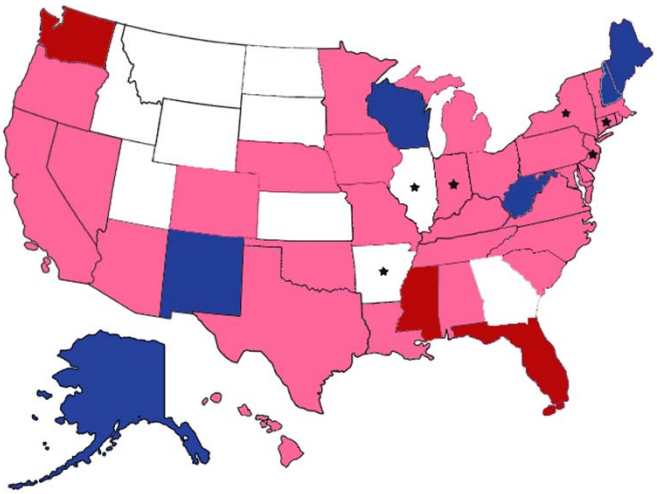
"Interval" cancers are more likely among women with dense breasts

Elevated risk + decreased sensitivity → interval cancers




Based on data from the Breast Cancer Surveillance Consortium

## 31 states have enacted breast density notification laws



Pink: Enacted Law

Red: Introduced Bill

Blue: Working on Bill

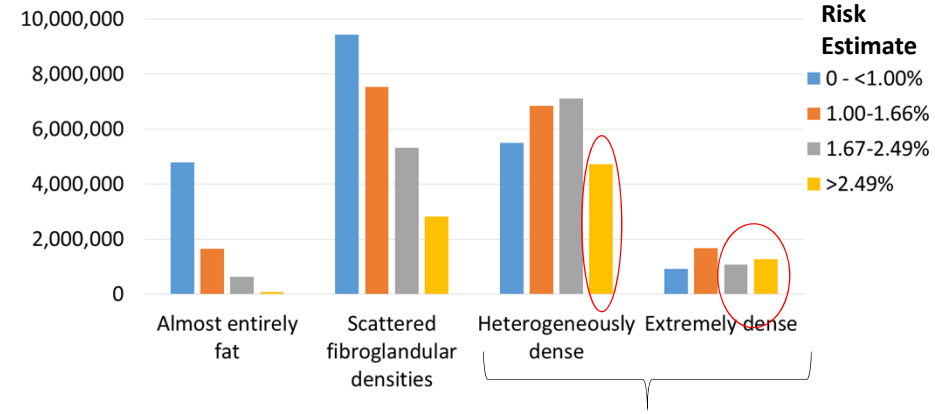
*Insurance coverage law

# What to do?

- "…individuals with dense breasts should talk with their physicians about whether they would benefit from additional tests."
- There is very limited evidence regarding the comparative effectiveness of supplemental screening strategies for women with dense breasts.
  - MRI? Prohibitively expensive to offer to 40% of population; also specificity concerns.
  - Ultrasound? Widely available but sensitivity (~55%) is modest and benign biopsy rate is high (6%).

## Can we identify subsets of women with dense breasts who might benefit most from supplemental screening?


Data from the Breast Cancer Surveillance Consortium
Kerlikowske et al, *Ann Intern Med* 2015 May 19; 162(10): 673-81




28 million women aged 40-74 have dense breasts.

7 million have combination of density and risk that result in interval cancer rate > 1 per 1000.

Based on data from the Breast Cancer Surveillance Consortium

# Digital Breast Tomosynthesis (DBT, or 3D mammography)

- Multiple x-rays from multiple angles
  - 10 to 15 images over 10 to 20 seconds
- Trade offs
  - Increase invasive breast cancer detection
    - Especially in young women with dense breasts
  - Decrease recall rates
  - Possible increase in biopsies
  - Increased radiation exposure, especially if paired with digital mammography
    - "Synthetic" 2D image may replace mammography if concerns are alleviated about missing calcifications
- No clinical trial evidence yet, although a study is just getting started

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# Conclusions

- Reasonable people can disagree on issues related to breast cancer screening and risks associated with environmental factors
- Know your (estimated) risk of breast cancer
- Reduce your risk of breast cancer
  - Follow physical activity recommendations – get those steps in!
  - Minimize alcohol
  - Avoid weight gain
  - Breastfeed your babies
  - These approaches also help reduce risk of other major health conditions
- Reasons for optimism
  - We are now having a more nuanced conversation
  - We're making progress

# Acknowledgements

**University of Wisconsin-Madison**
Natalia Arroyo
Mary Pat Berry
Christopher Bradfield
Ronald Gangnon
Mia Gaudet
Michael Gould
John Hampton
Sara Lindberg
Kristin Malecki
Julie McGregor
Eileen McGuine
Betsy Rolland
James Shull
Mark Thornquist

**University of Vermont**
Brian Sprague

**Uniformed Services University**
Celia Byrne

**Mayo Clinic**
Celine Vachon

**Funding**
NIEHS/NCI U01 ES026127
NCI U01 CA199218