

Screening for Breast Cancer

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Working together to advance
breast cancer research

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Outline

- Criteria of good disease and test for cancer screening
- Screening mammography evidence based on age
 - When to start, how often, when to stop
- Risk-based screening
- Screening women with dense breasts

Criteria of disease good for cancer screening

- Common
 - Causes significant morbidity and mortality
 - Treatment more effective in early stage than late stage
-

Breast cancer risk or death in the next 10 years in U.S.

<u>Current Age</u>	<u>% diagnosed (or die)</u>	
20	.07---	1 in 2000
30	.46---	1 in 250 (1 in 1000)
40	1.49---	1 in 70 (1 in 300)
50	2.33---	1 in 44 (1 in 150)
60	3.47---	1 in 29 (1 in 100)

Lifetime women-- *12% or 12 in 100 (2.7%)*

Lifetime men-- *0.12% or 12 in 10,000 (0.03%)*

5-year breast cancer survival rates in U.S. by stage

Stage	Localized		Regional		Distant	
	<50	50+	<50	50+	<50	50+
2008-14	97	99	87	85	37	24
Percent	54	64	39	28	5	6

Criteria of good screening test

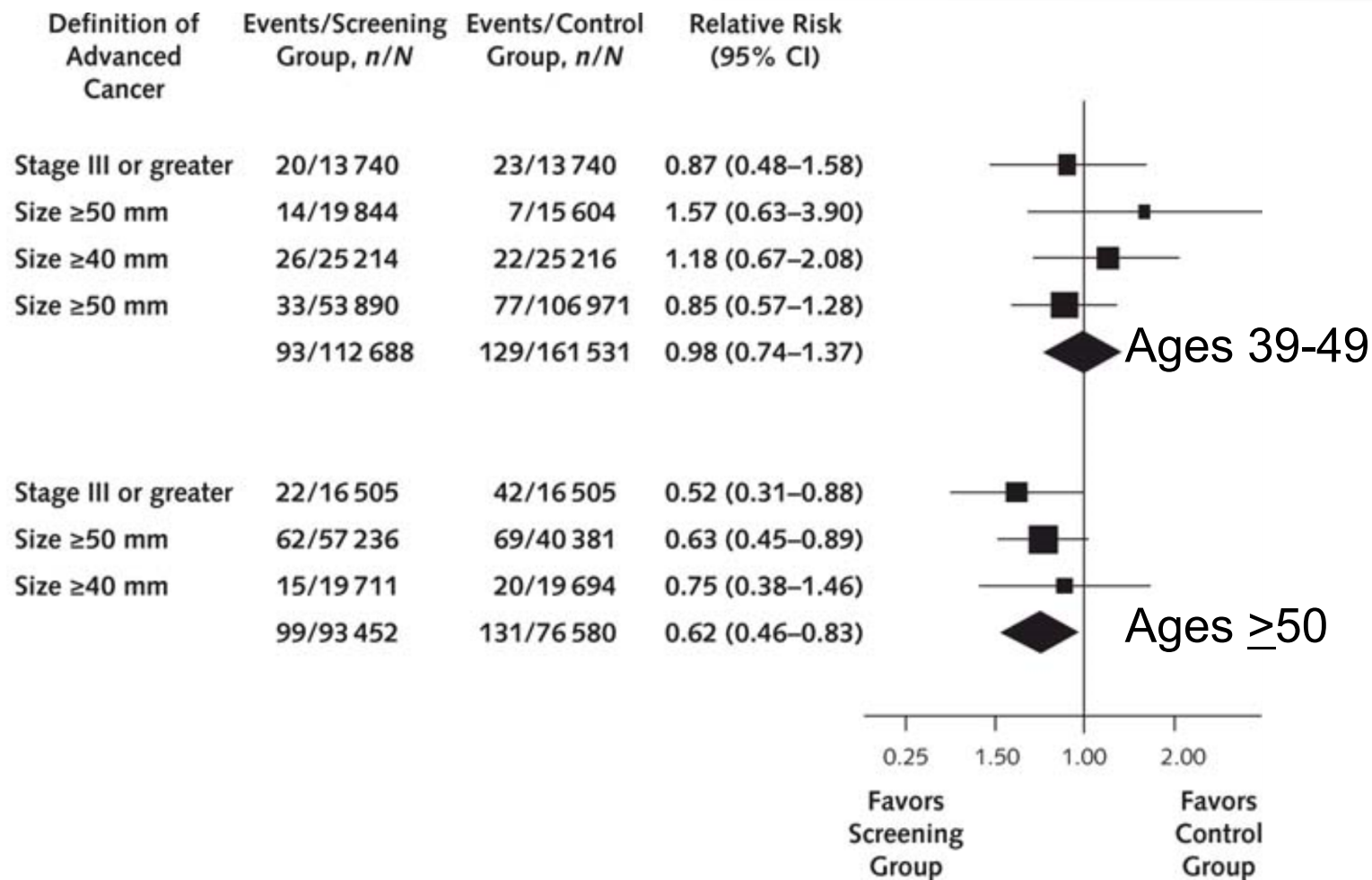
- Screening reduces disease specific mortality
- Identifies disease in an early stage, results in less advanced stage disease
- Disease identified by screening is biologically significant
- Test has high sensitivity & low false-positive rate
- Safe, cheap, & acceptable to patient

Meta-analyses of screening mammography trials -- *film*

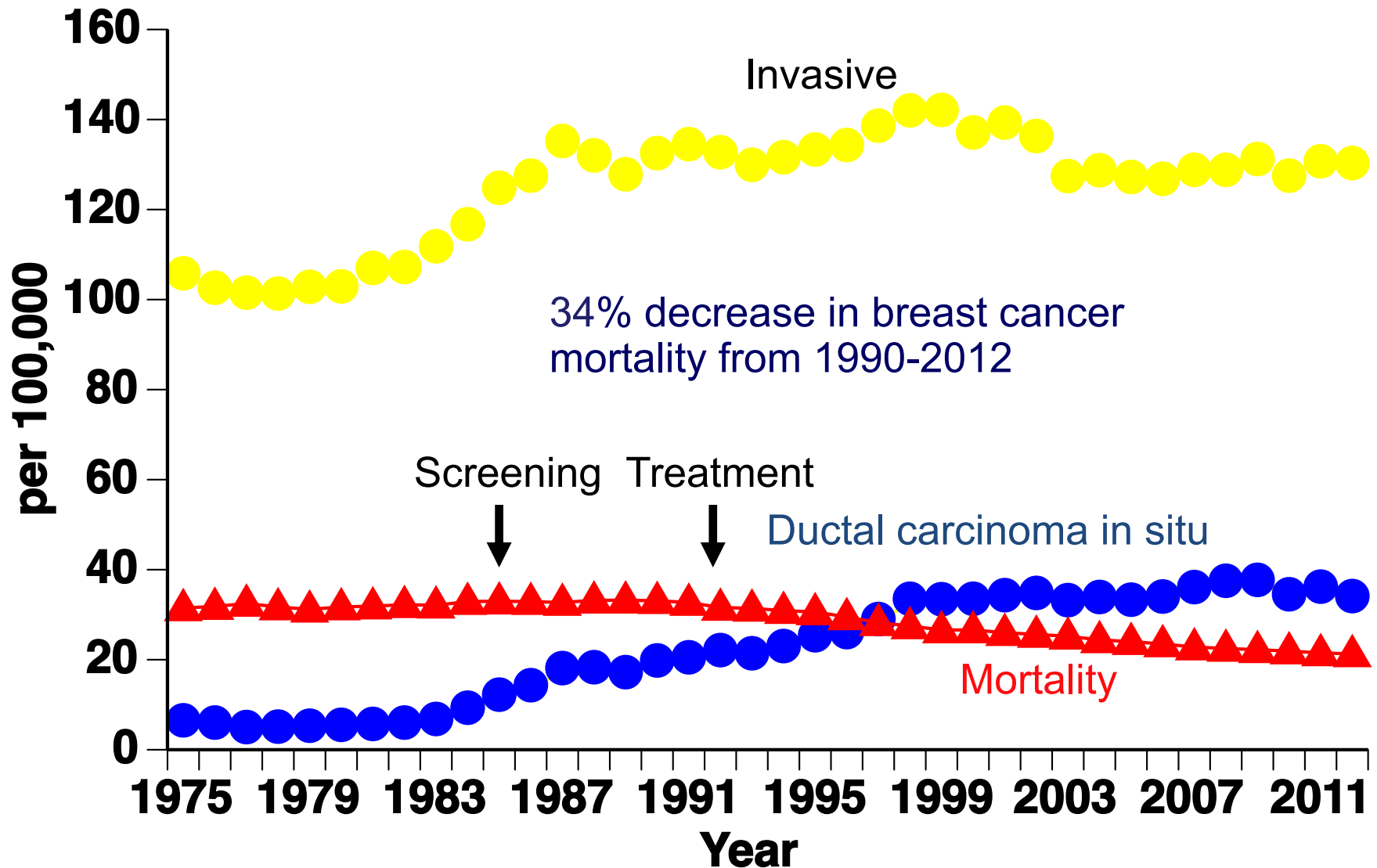
<u>Age</u>	<u>RR (95% CI)</u>	<u>NNS*</u>
39-49	0.92 (0.75-1.02)	3333
50-59	0.86 (0.68-0.97)	1300
60-69	0.64 (0.45-0.92)	470
70-74	0.80 (0.51-1.28)	800
All cause mortality	0.99 (0.97-1.002)	

*Number women screened for 10 years to avert a breast cancer death

Advanced disease reduced in screened women ages ≥ 50



Invasive Cancer & DCIS Incidence & Breast Cancer Mortality, 1975-2012

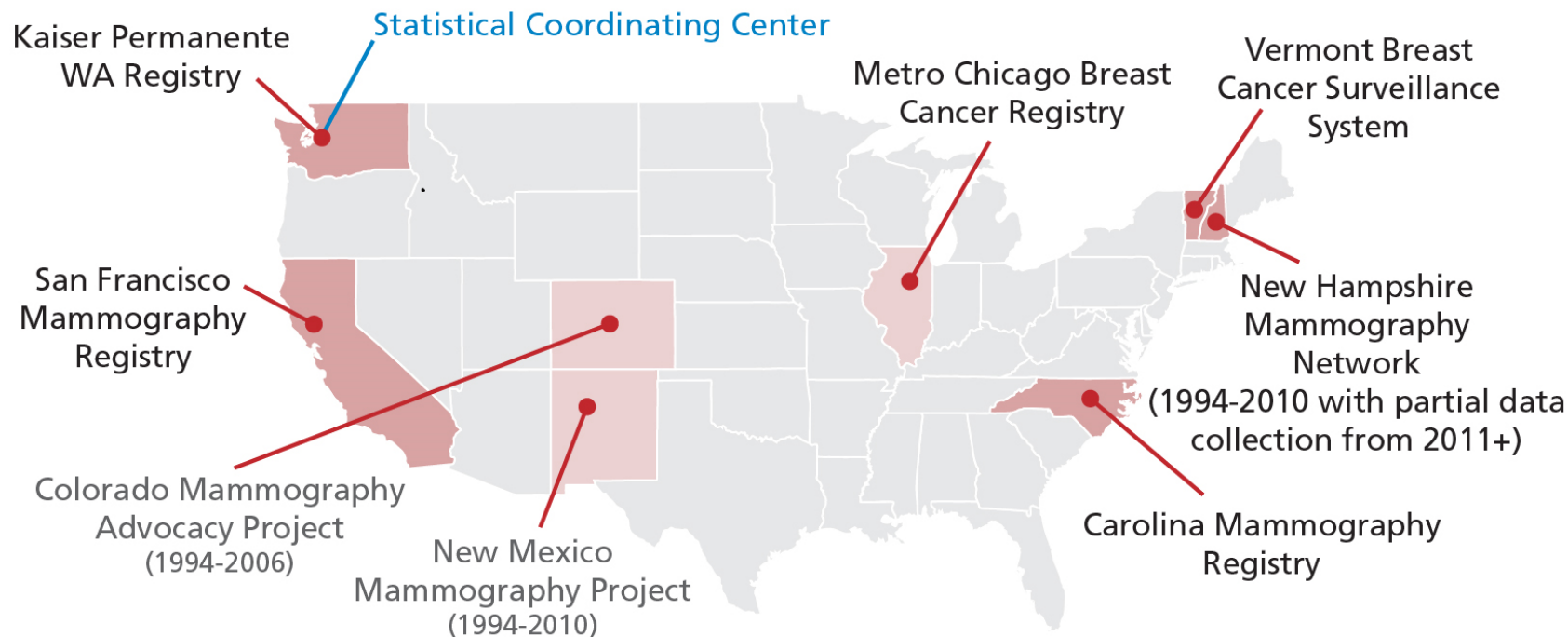


Overdiagnosis & overtreatment from screening mammography

- Cases not clinically detected in the absence of screening because of lack of progression or death from other causes
 - Canadian National Breast Screening Studies
 - 22% of invasive cancers
 - 37% invasive + DCIS
 - CISNET
 - 12% of detected cases
 - UK independent panel
 - 19% of detected cases

Breast Cancer Surveillance Consortium

BCSC data have been used for more than
475 publications and more than 70 grants



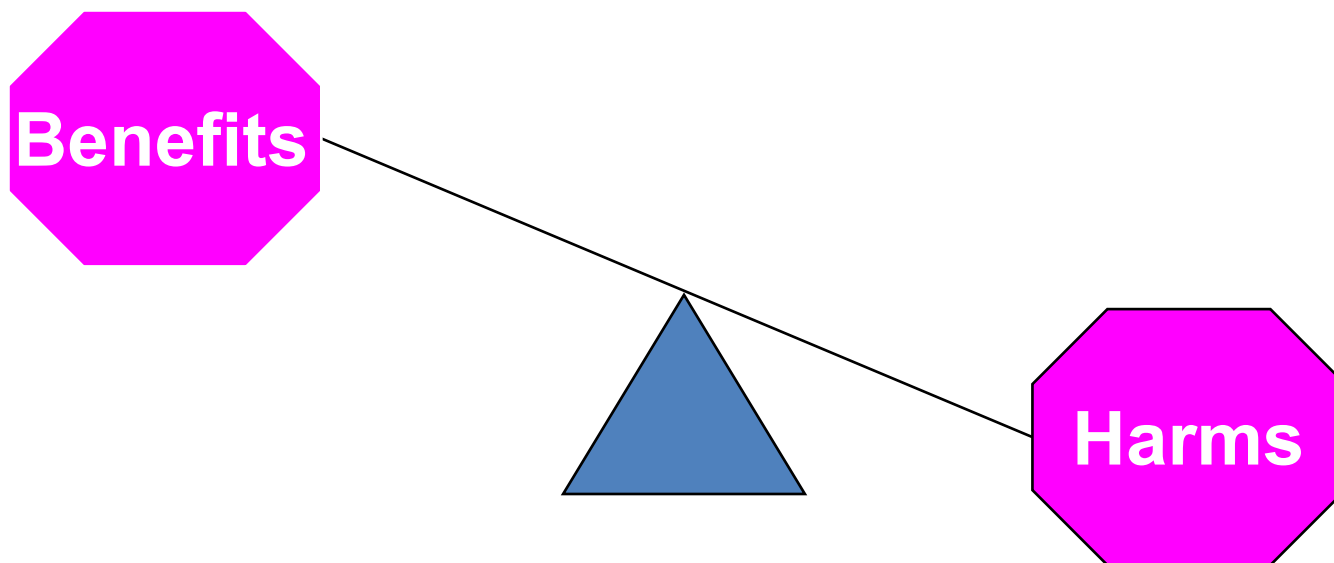
Active registries

Historic registries

BCSC outcomes per 10,000 *digital* screens

Outcomes	40–49	50–59	60–69	70–74
False-positives (false alarms)	1,212	932	808	696
No. biopsies per invasive breast cancer diagnosed	100	60	30	30
False-negatives (missed cancers)	10	11	12	13
Invasive cancer	22	35	58	72
DCIS	16	18	21	23

Do the benefits of screening outweigh the harms?



CISNET models

Common inputs

Background
Trends -- SEER

Screening - BCSC

Treatment -- RCT

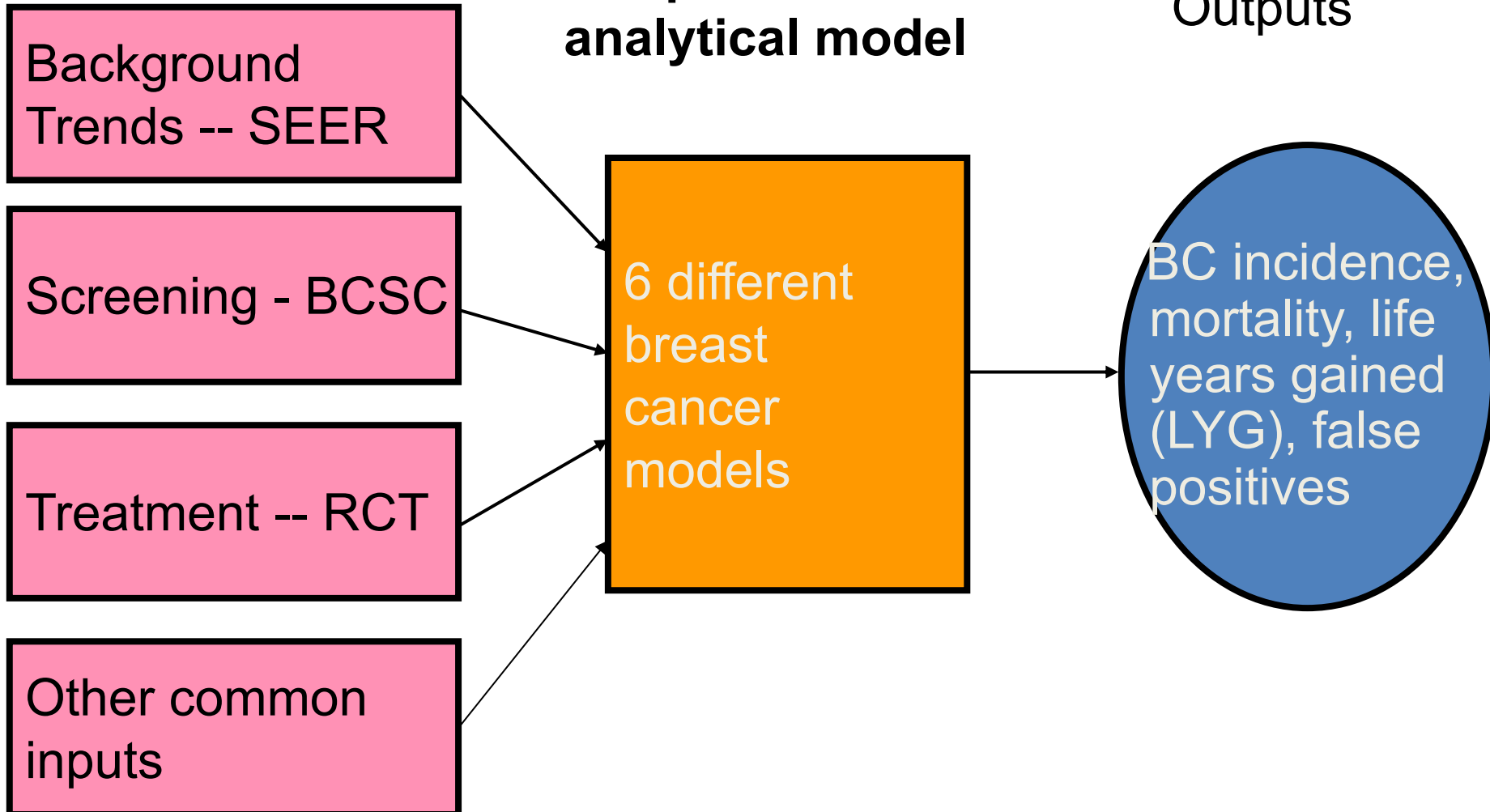
Other common
inputs

Unique simulation or analytical model

6 different
breast
cancer
models

Outputs

BC incidence,
mortality, life
years gained
(LYG), false
positives



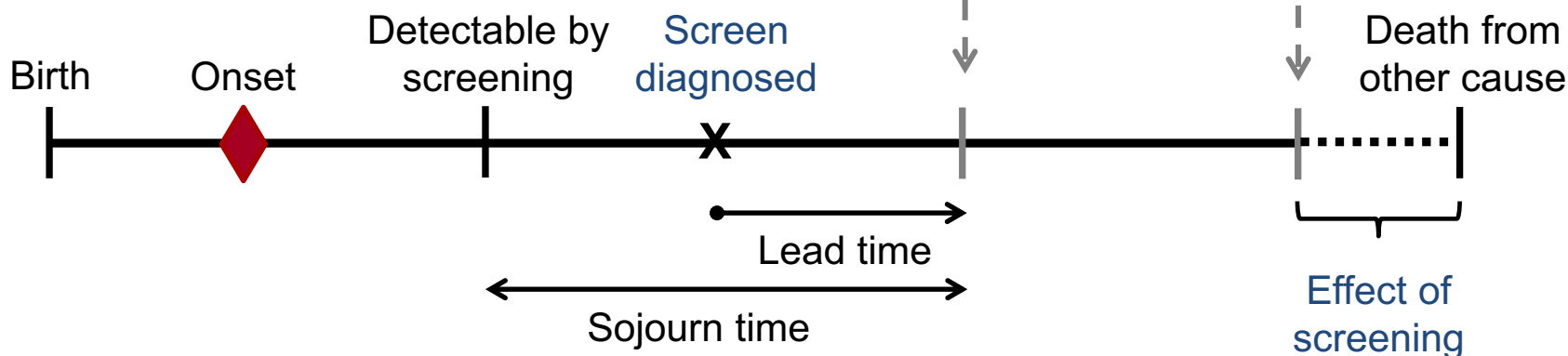
CISNET models

Models simulate events in individual life histories

No screening



Screening



Model estimates of *digital* screening mammogram effectiveness by interval

Age & Interval	Deaths*	Benign biopsy*	False-positive*	Overdiagnosis*
50-74 y				
1 y	9	228	1,798	25
2 y	7	146	953	19
40-49 y				
1 y	1.3	99	1,143	5
2 y	1.0	58	576	2

*per 1,000 women screened over screening period

When to start screening mammography

- ACR, SBI -- start at age 40
 - ACOG, ACS, USPSTF, ACP -- discuss 40-49, offer based on value of benefit vs. harm
 - ACS -- start at age 45
 - USPSTF, AAFP, WHO, ACOG, ACP – start at age 50
 - Most European countries and Canada start age 50
-

ACS rationale for starting screening at age 45

- Observational studies – 20-40% reduction in breast cancer mortality
- Breast cancer mortality similar 45 vs. 50
 - 40-44 -- 13.2 per 100,000
 - 45-49 -- 20.6 per 100,000
 - 50-54 -- 30.8 per 100,000
 - 55-59 -- 41.3 per 100,000
- Harms higher in women 40-44 vs. 45-49

How often to screen with mammography

- ACR, SBI – *annual*
- ACS – *annual* 45-54, *biennial* starting at 55
- ACOG – every 1-2 years
- USPSTF, WHO, AAFP, ACP – *biennial*
- Most European countries *biennial*; Canada *q2-3*; United Kingdom *q3*

Potential harms of screening; false-positive mammogram and biopsy, overdiagnosis

Risk of late stage disease with 2 vs. 1 year screening interval

	Advanced <u>stage†</u>	Tumor <u>>15mm</u>
Premenopausal	+28%*	+21%*
Postmenopausal	-5%	+11%*

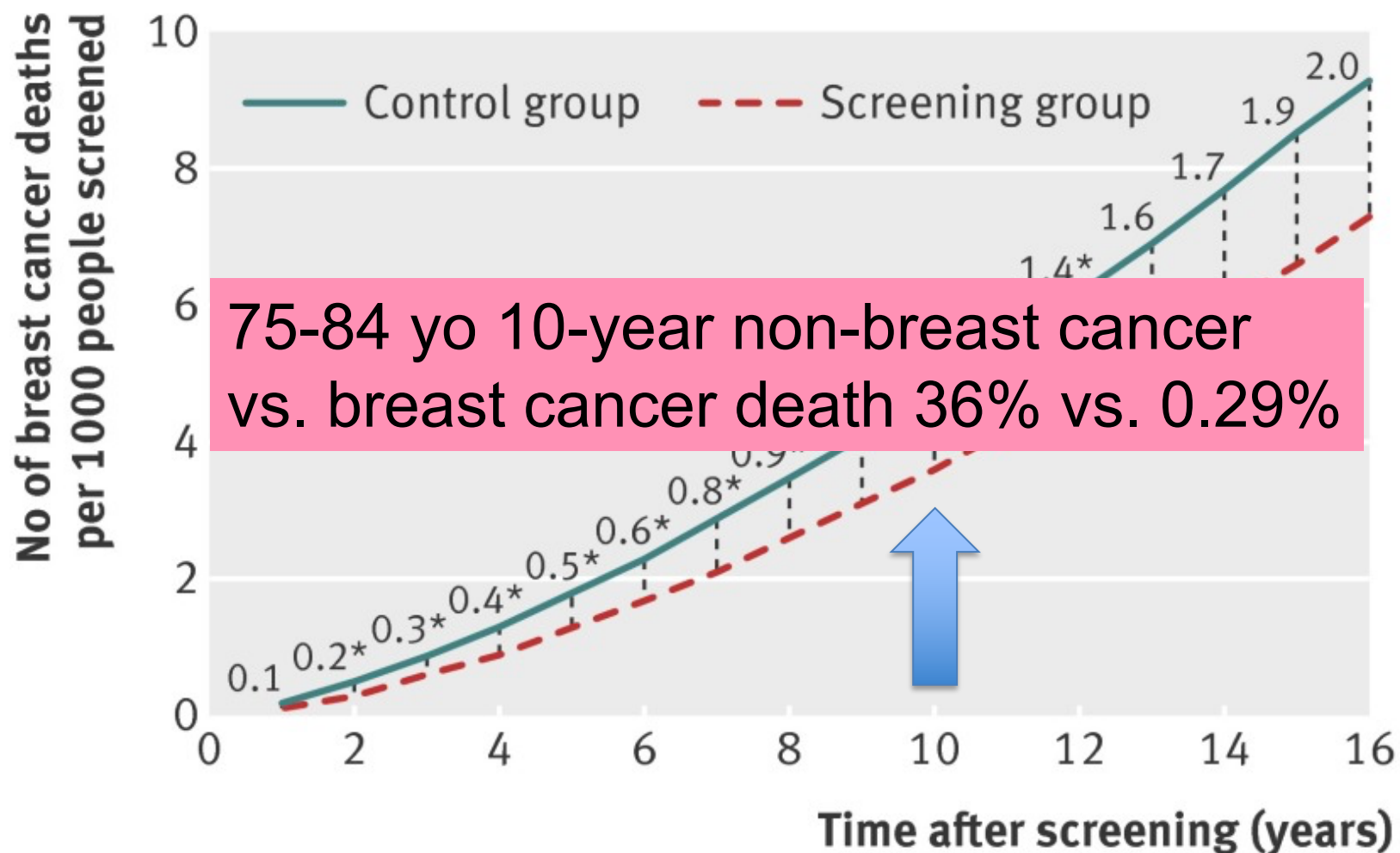
†Stage IIB or higher

*P< 0.05

When to stop screening mammography

- ACR, SBI -- if life expectancy <5-7 years
 - ACS -- if life expectancy <10 years
 - ACOG – to age 75, shared decision-making
 - USPSTF, WHO, AAFP, ACP – age 75
 - Most European countries and Canada stop at age 70-75
-

Breast cancer deaths averted per 1000 women screened



Stopping ages based on comorbidities

	Comorbidities				
	<u>Ref</u>	<u>None</u>	<u>Mild</u>	<u>Moderate</u>	<u>Severe</u>
Age stop	74	76	72	70	64-66
Deaths	1.0	1.0	0.8	0.9	0.6
averted*					
Overdiag- nosis*	0.5	0.7	0.6	0.9	0.7

*per 1,000 women screened

- Mild: history of MI, acute MI, ulcer, or rheumatologic disease
- Moderate: vascular disease, cardiovascular disease, paralysis or diabetes, or combinations of diabetes with MI, ulcer, or rheumatologic disease
- Severe: AIDS, COPD, mild to severe liver disease, chronic renal failure, dementia, or congestive heart failure

Lifetime risk of breast cancer death

	<u>Risk %</u>	<u>Deaths averted†</u>
● Overall	2.70	
● 50-74 biennial	2.00	7
● 40-74 biennial	1.88	8
● 45-49 annual, 50-74 biennial	1.90	8

†per 1,000 women screened

Improving benefit-harm ratio with risk-based screening

- Screening most efficient if strategy based on risk
 - Target fixed number of women at high risk
 - Decreases harms for low risk women
 - Decreases costs
- Breast cancer risk used to determine
 - When to start screening
 - Screening frequency
 - Supplemental imaging



Breast cancer risk assessment models

General

- Breast cancer risk assessment tool

- BCSC model highest calibration and discrimination > Gail > TC in average-risk population
- Tyrer

*includes breast density measure

Family risk

- BRCAPro – BRCA carrier
- Tyrer-Cuzick* – 10y – BRCA carrier + ovarian cancer

BCSC Risk Calculator

FREE iPhone & iPad app

Breast Cancer Surveillance Consortium
BCSC
Working together to advance
breast cancer research



+ Get ▾

This app is designed for both
iPhone and iPad

Rating: 17+

LINKS

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[Developer Website](#)

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BCSC Risk Calculator 17+

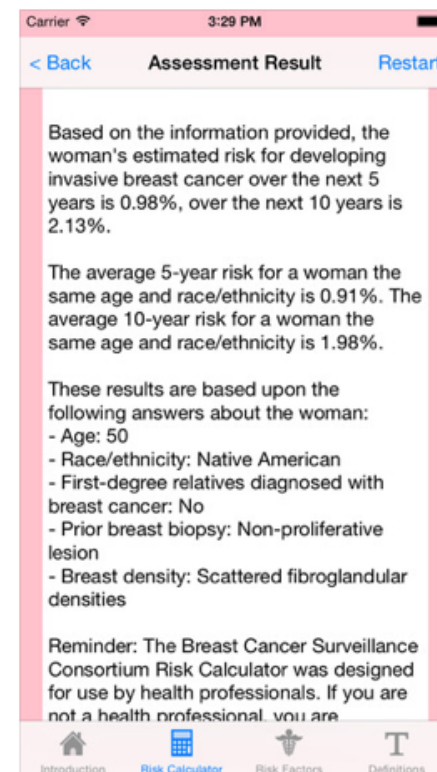
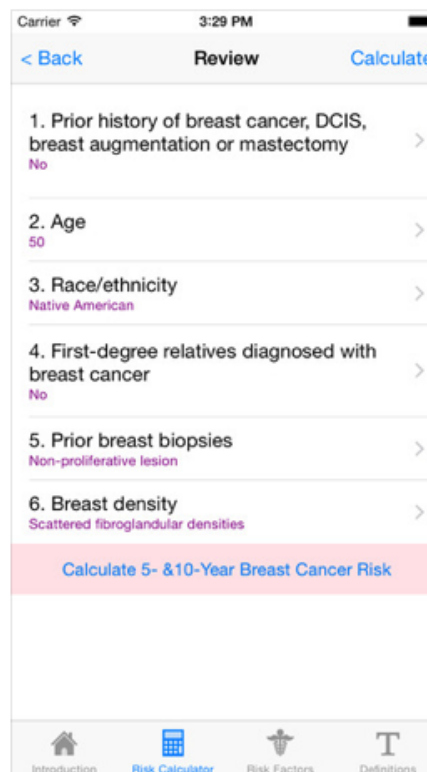
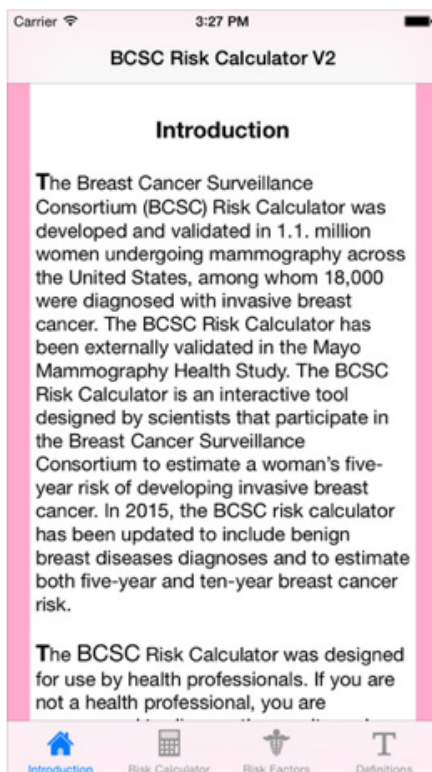
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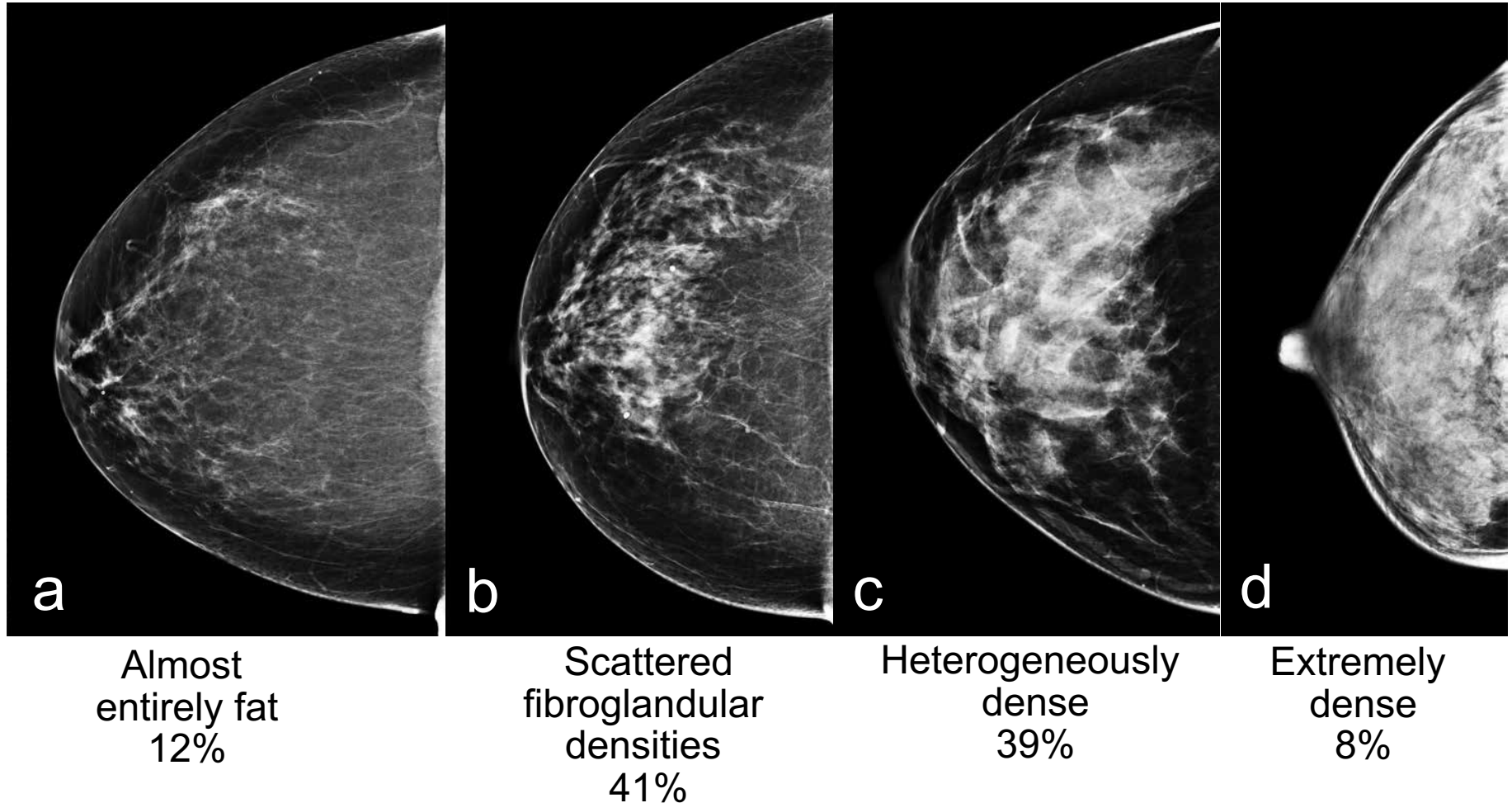
Screenshots

iPhone

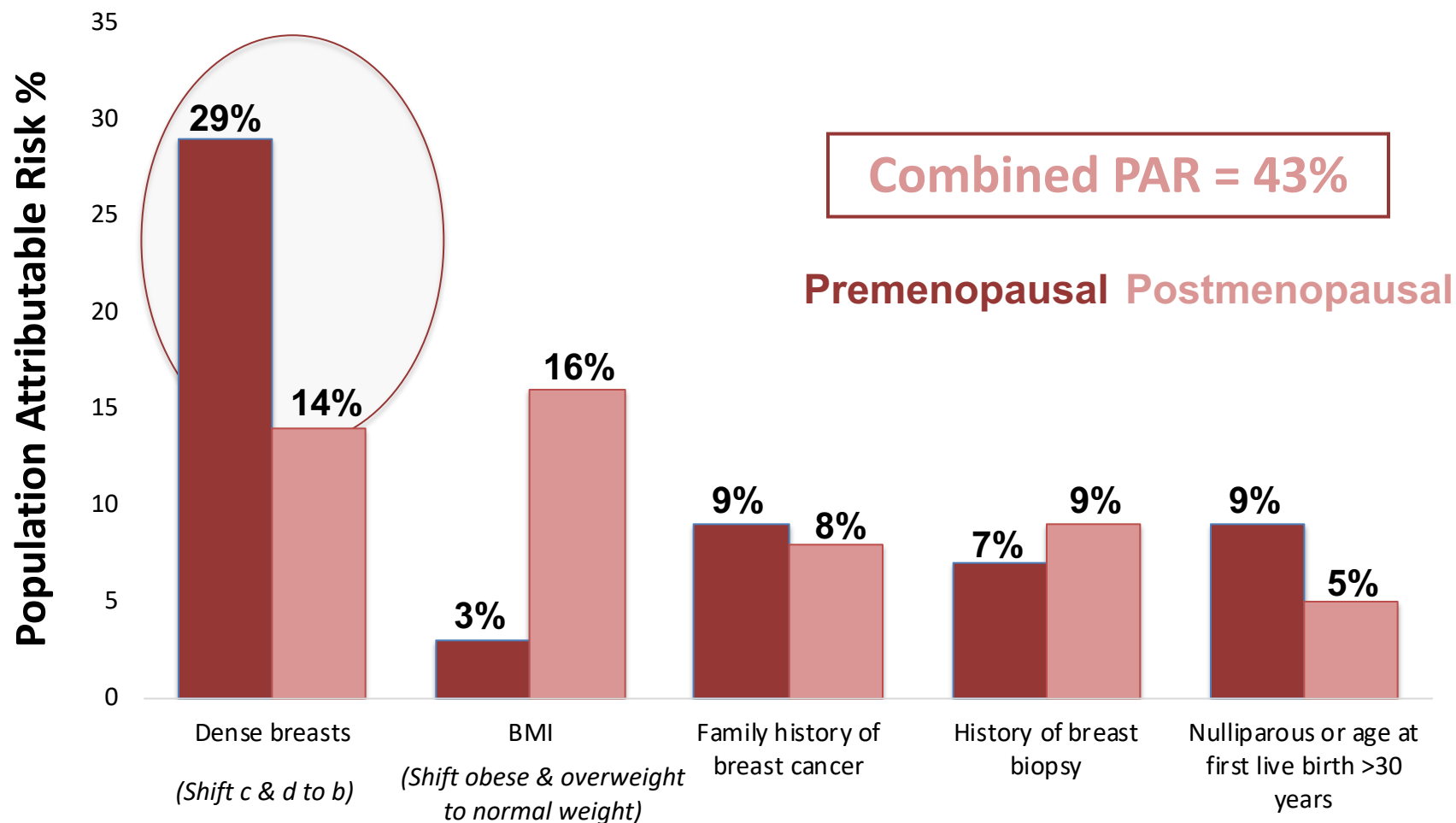
iPad



Breast Imaging Reporting and Data System (BI-RADS)



Common risk factors account for breast cancers



5-year risk (%) for 45-49y women

<u>Density</u>	BCSC	<u>No Family Hx</u>		<u>Family Hx</u>	
	<u>5-yr risk</u>	<u>No bx</u>	<u>Bx</u>	<u>No bx</u>	<u>Bx</u>
a	.4	.3	.5	.5	.8
b	0.8	0.7	1.0	1.0	1.7
c	1.2	1.0	1.7	1.6	2.6
d	1.6	1.3	2.1	2.1	3.3

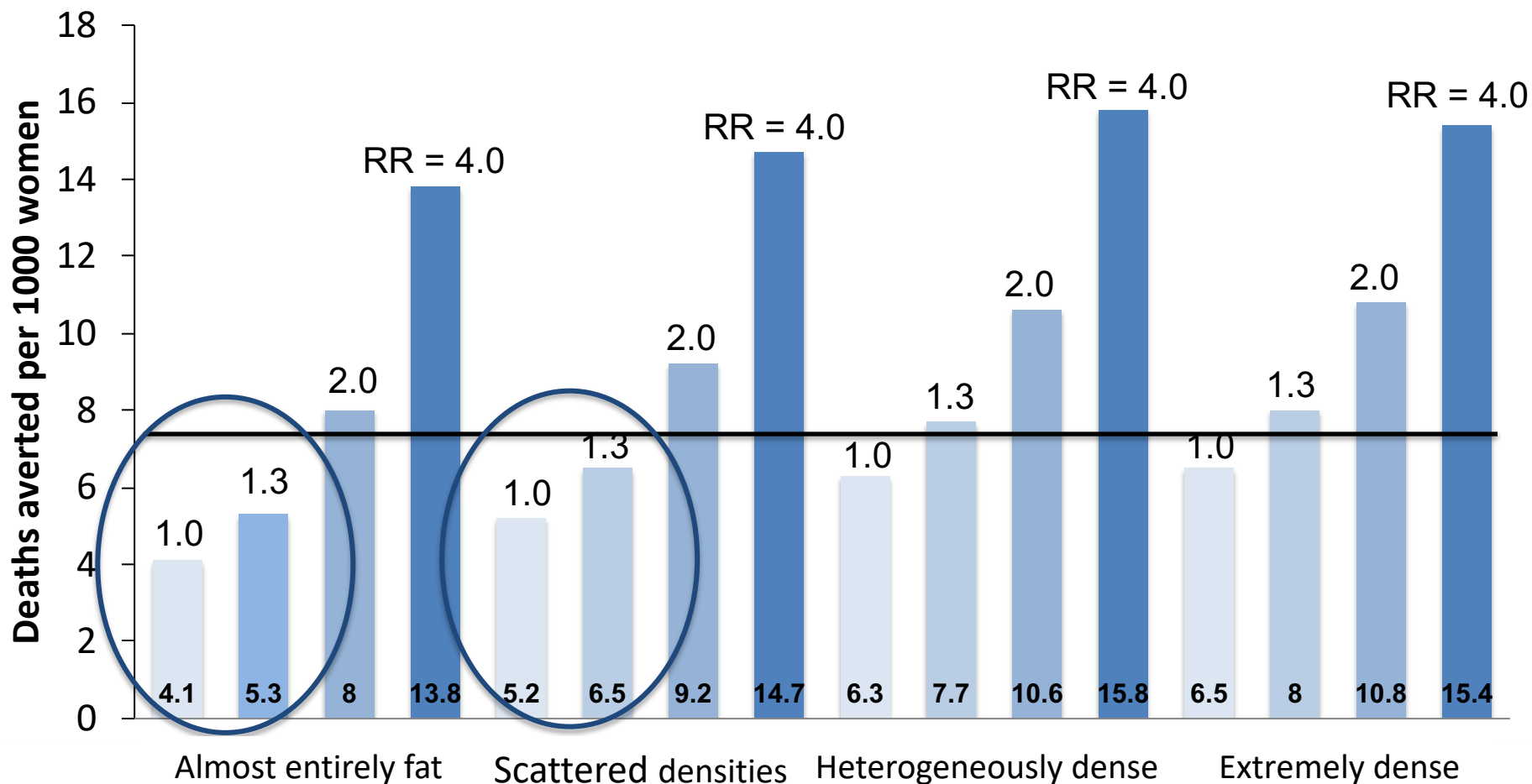
Average 5-year risk >1.3% for 50-year-old – 16% of women 40-49

5-year risk (%) for 50-54y women

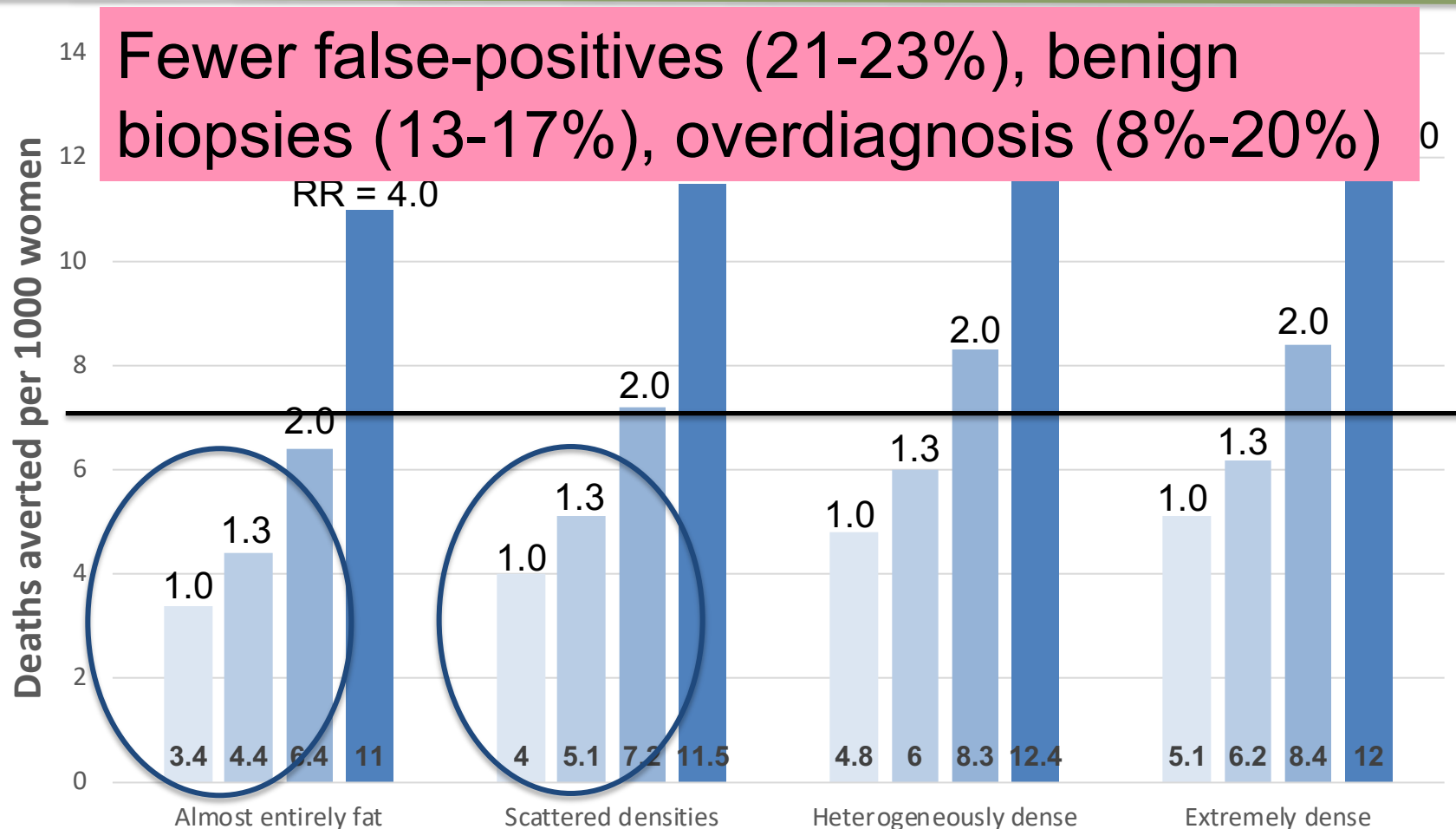
<u>Density</u>	BCSC	<u>No Family Hx</u>		<u>Family Hx</u>	
	<u>5-yr risk</u>	<u>No bx</u>	<u>Bx</u>	<u>No bx</u>	<u>Bx</u>
a	.5	.4	.7	0.7	1.1
b	1.0	0.9	1.4	1.4	2.2
c	1.6	1.3	2.2	2.1	3.4
d	2.1	1.7	2.8	2.7	4.4

32% of 50 year olds average risk less than average risk 40-year old

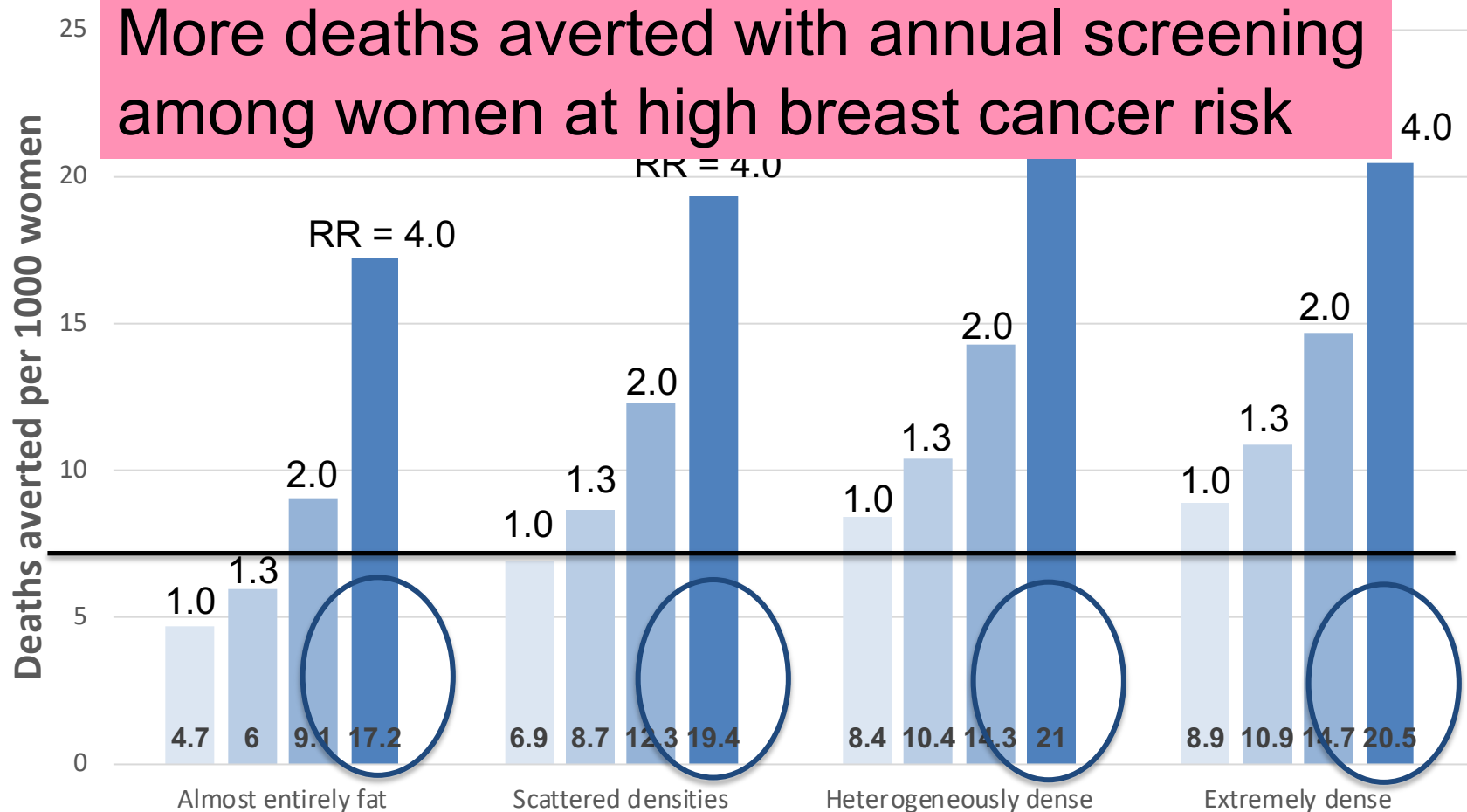
Deaths averted vary by risk if screen women 50-74 biennial



Deaths averted vary by risk if screen women 50-74 triennial



Deaths averted vary by risk if screen women 50-74 annual



Breast Cancer Risk Factors

RR= 1.3-1.9

- >25g alcohol/day
- Postmenopausal HT
- Nullparity or age first birth ≥ 30
- Body mass index ≥ 30 kg/m²
- First-degree relative with breast cancer
- Hx of breast biopsy

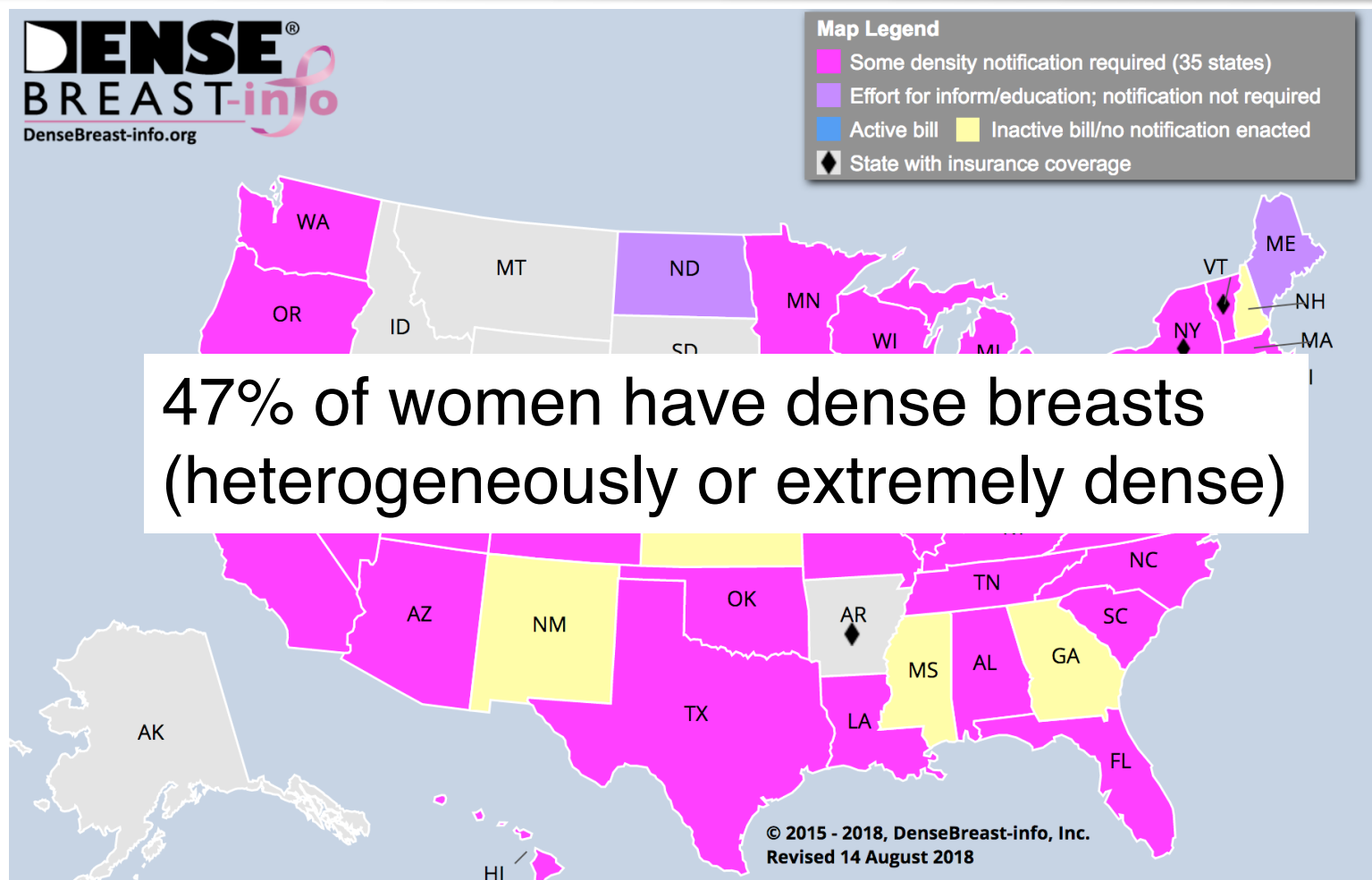
RR= 2.0

- Two first-degree relatives with breast cancer
- History of proliferative disease without atypia

RR= >2.0 to 4.0

- LCIS or ADH

New federal law for breast density notification - 2019



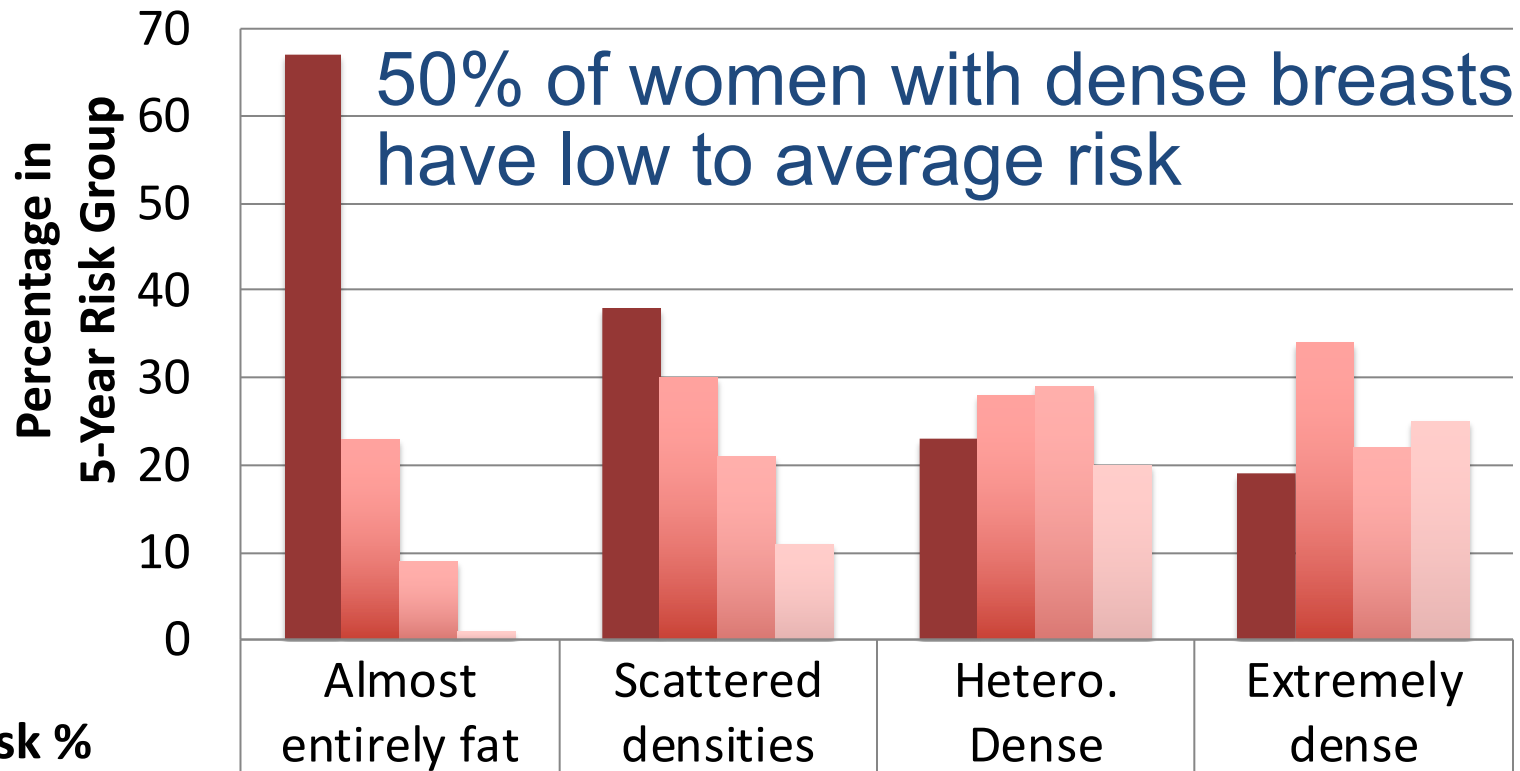
High breast density masks interval invasive tumors

<u>BI-RADS Density</u>	<u>Screen- detected*</u>	<u>Interval cancer*</u>
a	1.8	0.21
b	3.3	0.38
c	4.8	0.84
d	5.1	1.11

64% of interval cancers in women
with BI-RADS c or d

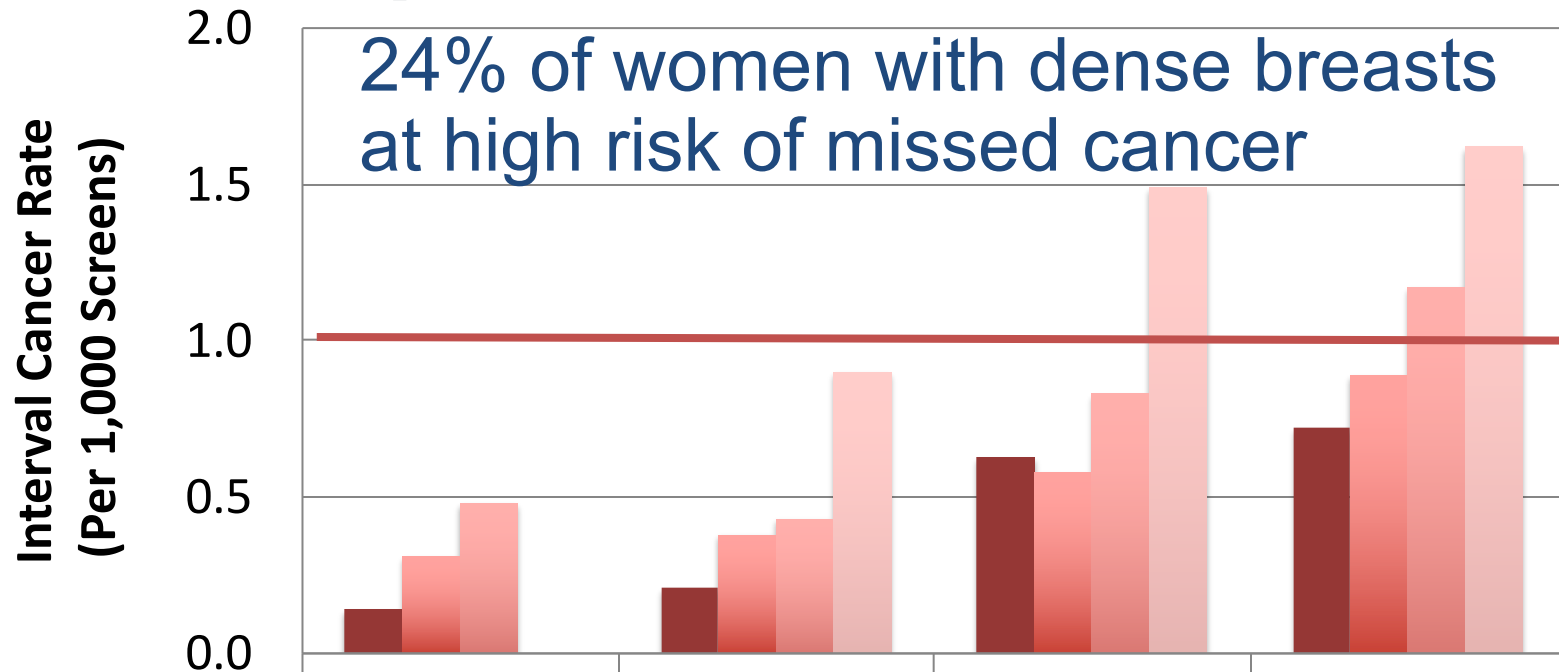
*per 1,000 women 40-74 screened

Half of women with dense breasts have low 5-year risk



BCSC 5-year risk %	Almost entirely fat	Scattered densities	Hetero. Dense	Extremely dense
Low: 0-1	67	38	23	19
Average: >1-1.66	23	30	28	34
Intermediate: 1.67-2.49	9	21	29	22
High: >2.5	1	11	20	25

High risk, high density – interval cancer rate >1 per 1000 exams



BCSC 5-year risk %

Low: 0-1

Average: >1-1.66

Intermediate: 1.67-2.49

High: >2.5%

Almost
entirely fat

Scattered
densities

Hetero.
dense

Extremely
dense

0.14

0.21

0.63

0.72

0.31

0.38

0.58

0.89

0.48

0.43

0.83

1.17

N/A

0.90

1.48

1.62

Alternative imaging strategies for women with dense breasts

- Change screening frequency
 - Tomosynthesis (3D)
 - Screening ultrasound -- hand held; whole breast
 - Breast MRI
-

Odds of advanced stage with 2 vs. 1yr screening interval

<u>Age group</u>	<u>Heterogeneously dense</u>	<u>Extremely dense</u>
40-49	1.32 (0.93-1.88)	1.89 (1.06-3.39)

Higher advanced stage with biennial vs. annual screening in extremely dense group

Cancer detection by extent of density for digital vs. DBT

	<u>Digital</u>	<u>Digital + DBT</u>
Exams	278,906	173,414
Invasive cancer rate*		
Non-dense	• Decrease recall and increase cancer detection -- mostly density b and c • No difference in interval cancer rate overall or by breast density category	
Dense		
Recall rate*		
Non-dense		
Dense	127	109

*per 1,000 exams, $P < 0.001$

*Biopsy rate: 18.1 vs. 19.3

J-START ultrasound trial

- Randomized trial of average-risk women age 40-49 years
- Annual digital mammography + screening ultrasound vs. annual digital mammography
- Outcome = interval cancer
- 18 interval cancers in intervention group vs. 35 in control group
 - Rate of 0.5 per 1000 vs. 0.97 per 1000

MRI in women with dense breasts

- RCT of women with extremely dense breasts
- Age 50-75 years (mean 54 years)
- 59% participation (N=4756)
- Negative mammogram
- Biennial MRI vs. biennial mammography
- Outcome= 2.5 vs. 5.0 interval cancer/1000 screens – node positive rate no different
- False-positive rate MRI group 79.8/1000 screens

Supplemental breast imaging

Test	Incremental breast cancer detection per 1,000 exams	Biopsy rate per 1,000 exams	Radiation dose (location)
Digital mammography	NA	22	0.5 mSv (breast)
Ultrasound	2 to 4	50 to 57	None
Digital breast tomosynthesis	1 to 2	28	1.0 mSv (breast)
Breast MRI	10 to 16	44	None
Molecular breast imaging	8 to 9	32 to 37	2.4 mSv (whole body)

Summary

- Women undergoing screening mammography based on age has a modest impact on breast cancer mortality and results in substantial harms
- Risk-based screening maximizes the potential benefits and minimizes the harms of screening
- Assessment of BCSC 5-year risk can identify women at high and low breast cancer risk for targeted screening and supplemental screening
- Targeted strategies consider breast cancer risk, screening frequency, and imaging modality

Thank you
