



SCREENING THE HIGHER RISK INDIVIDUAL

D David Dershaw

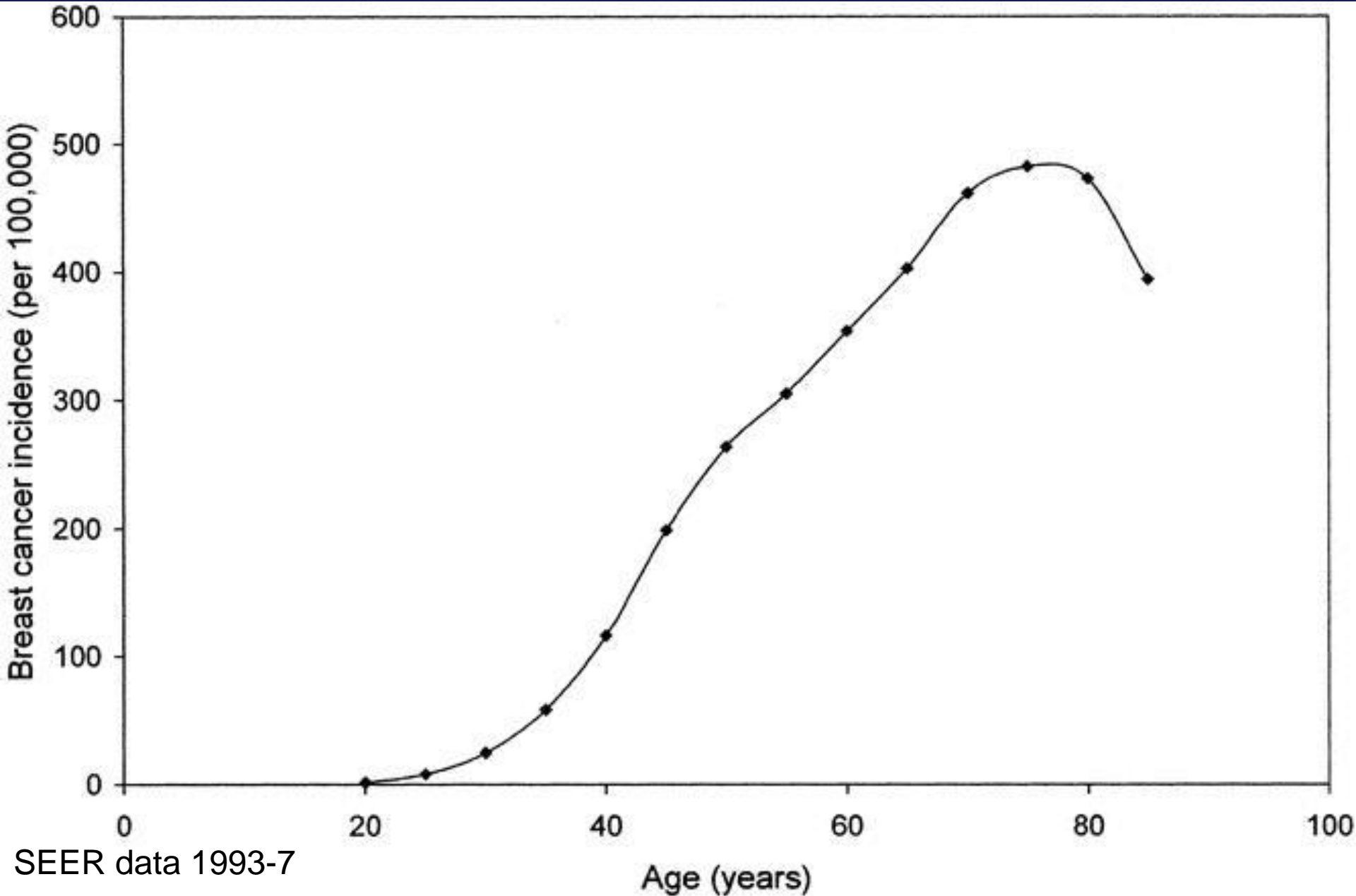
Memorial Sloan Kettering Cancer Center

New York, NY

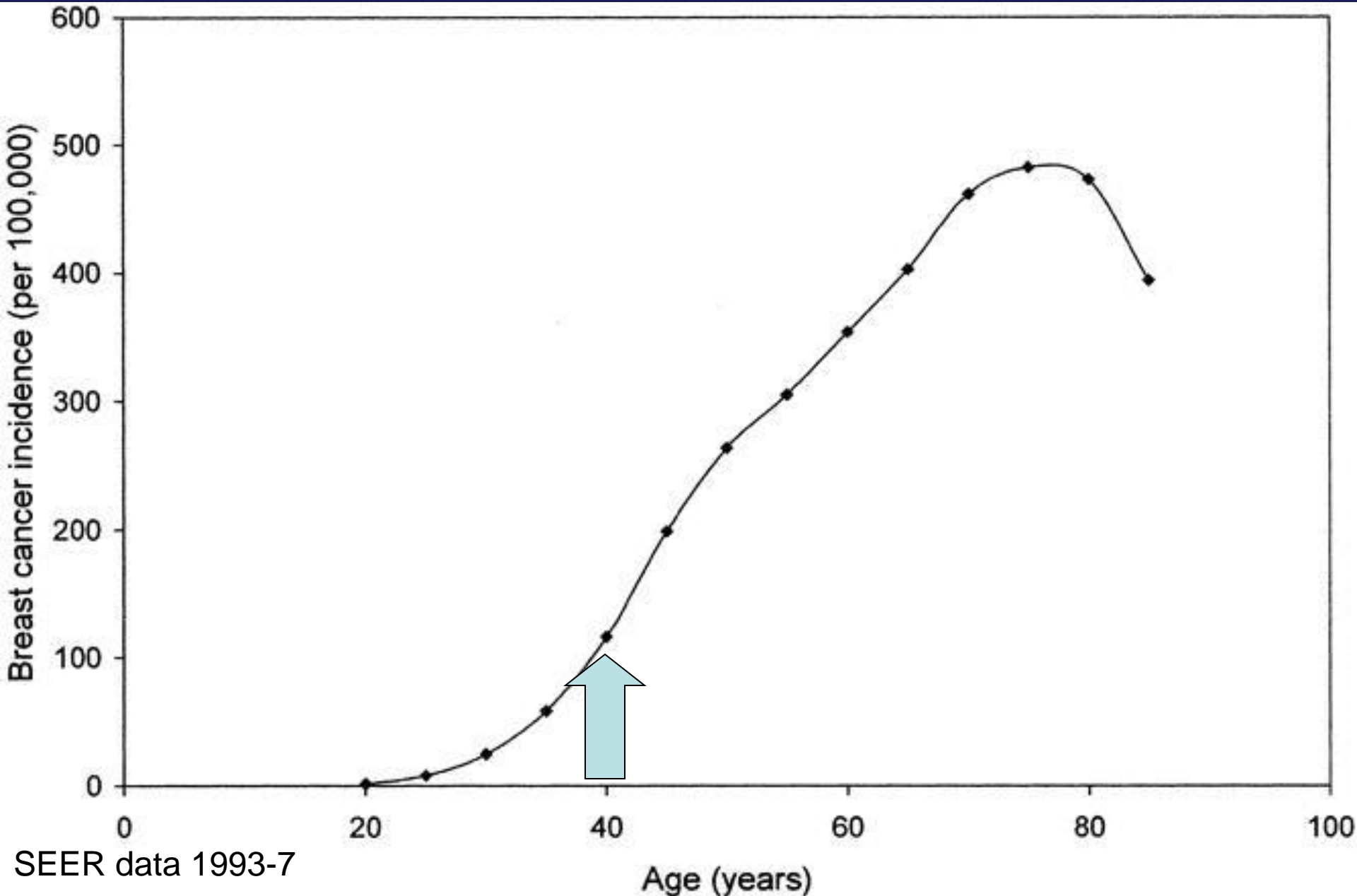
Routine Screening Recommendations: USA

Annual mammogram starting at
age 40

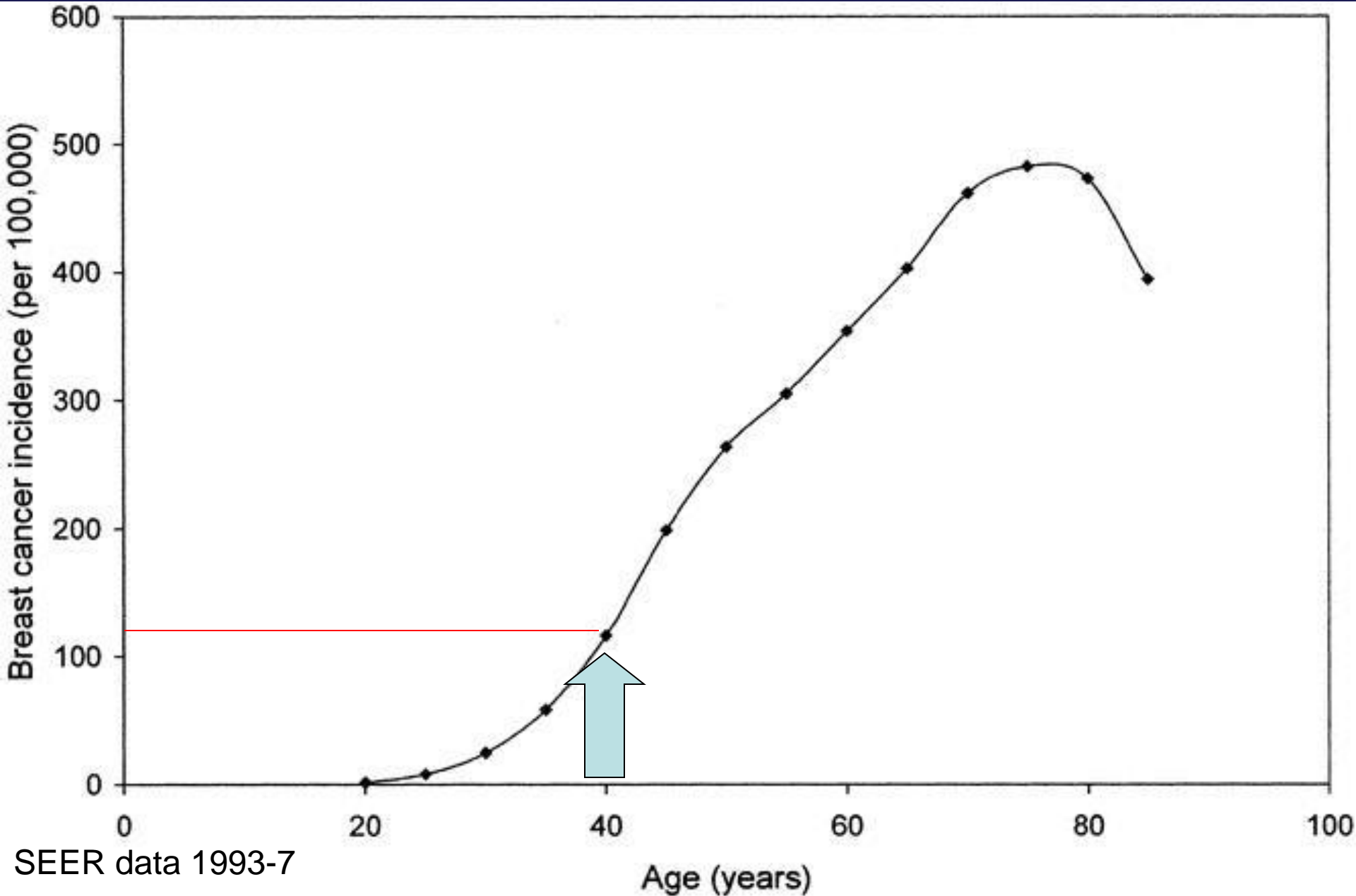
BREAST CANCER INCIDENCE VS AGE



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Age-Specific Probability of Developing Breast Cancer

If current age is...	Probability of developing breast cancer in next 10 years is...	Or 1 in:
20	0.05%	2,152
30	0.40%	251
40	1.45%	69
50	2.78%	36
60	3.81%	26
70	4.31%	23

Source: Am Cancer Soc 2003

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Source: Am Cancer Soc 2003

In US adequate risk for annual
mammographic screening set at
1.45% risk of developing breast
cancer in 10 years
(1 in 69 risk of developing breast
cancer over 10 years)

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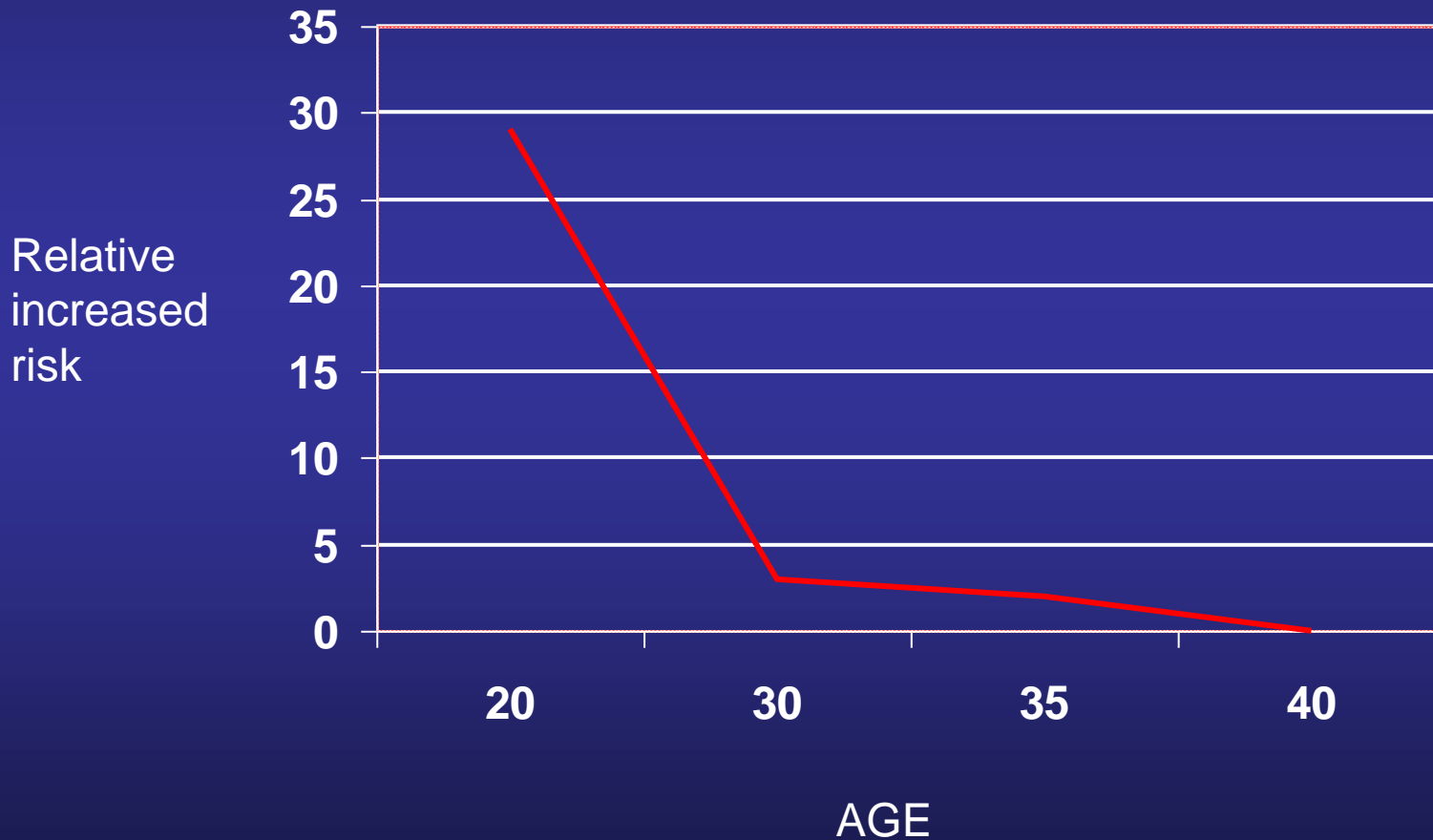
To increase risk to that of average 40 year old, risk must be increased by:

2x for 35 year old

3x for 30 year old

29x for 20 year old

Risk Increase vs Age to Meet Accepted Screening Risk Level



Relative Risk of Breast Cancer < 2x

- Alcohol intake 2 drinks/day
- Body mass index 80th percentile
- Repeated fluoroscopic radiation exposure
- Nulliparous or first child after 30
- First degree relative with post-menopausal breast cancer at age ≥ 50 years
- Second degree relative with breast cancer
- Biopsy showing ductal hyperplasia

Relative risk of breast cancer 2-4x

- Single first degree relative with premenopausal breast cancer
- Two first degree relatives with breast cancer

Relative risk of breast cancer 5-20x

- Radiation therapy for Hodgkin disease
- Personal history of breast cancer, invasive or DCIS
- Biopsy showing LCIS or atypia

Lobular Carcinoma in Situ

- No clinical or mammographic manifestations
- Found incidentally in 1.1% of breast biopsies
- Found in association with 5.7% breast cancers
- 90% premenopausal

Lobular Carcinoma in Situ

- Incidence of developing invasive cancer is 18-37%
- Relative risk = 8-10x general population
- Cancer risk is bilateral
- Histology usually ductal
- Most cancers develop > 15 years after diagnosis of LCIS

Frykberg. Breast J 1999; 5:96

Hartmann. New Eng J Med 2014;372:78

Lobular Carcinoma in Situ

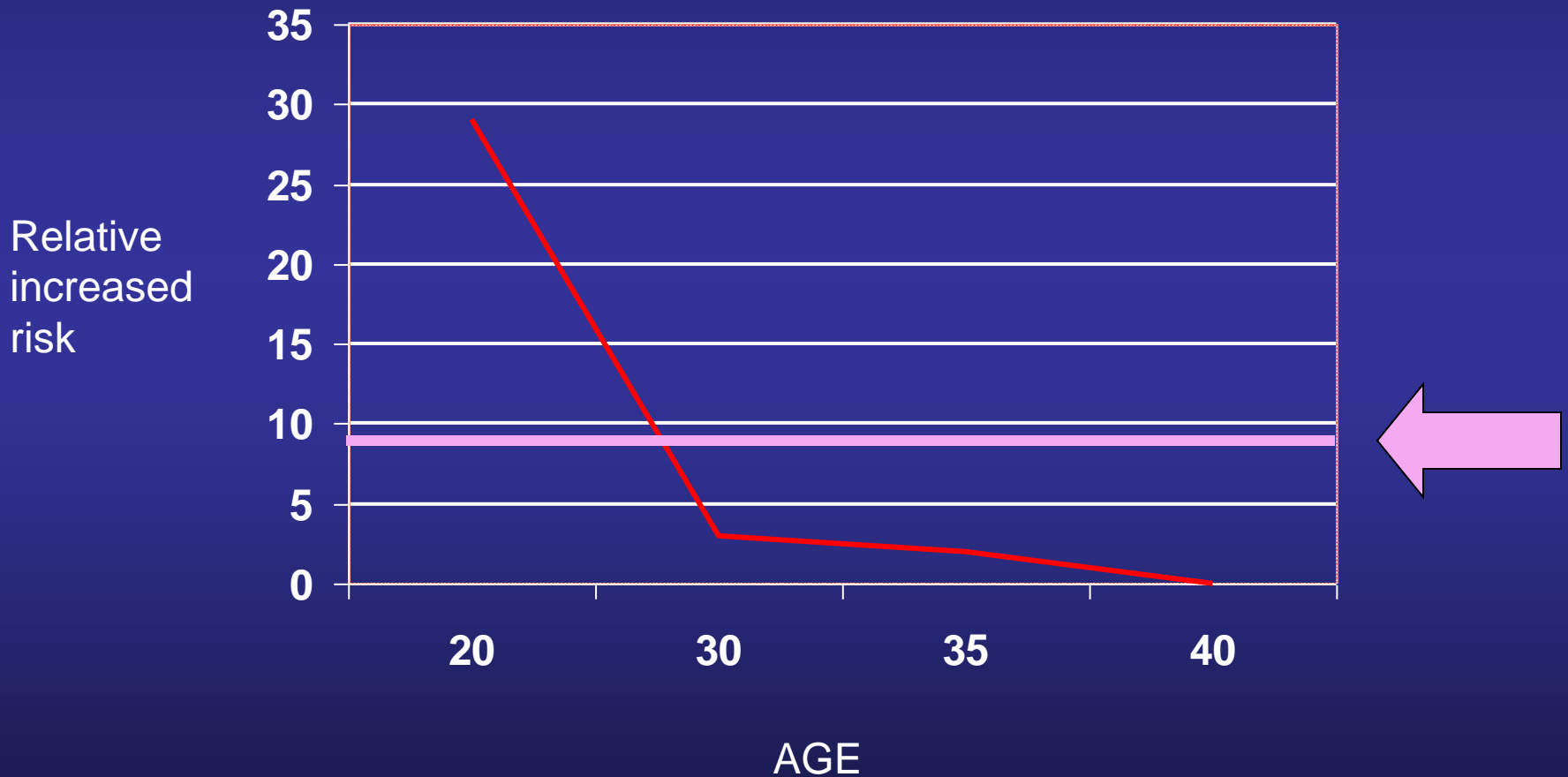
- Programs of routine surveillance have resulted in low mortality by managing LCIS as a high risk lesion not preinvasive carcinoma
- Comparable mortality in populations managed with surveillance or treated by prophylactic mastectomy

Lobular Carcinoma in Situ: Mammographic Screening Recommendation

- Mammographic surveillance:
 - Initial mammogram at time of diagnosis (preoperative)
 - Annual mammography thereafter

Risk Increase vs Age to Meet Accepted Screening Risk Level

LCIS



Atypical Lobular Hyperplasia

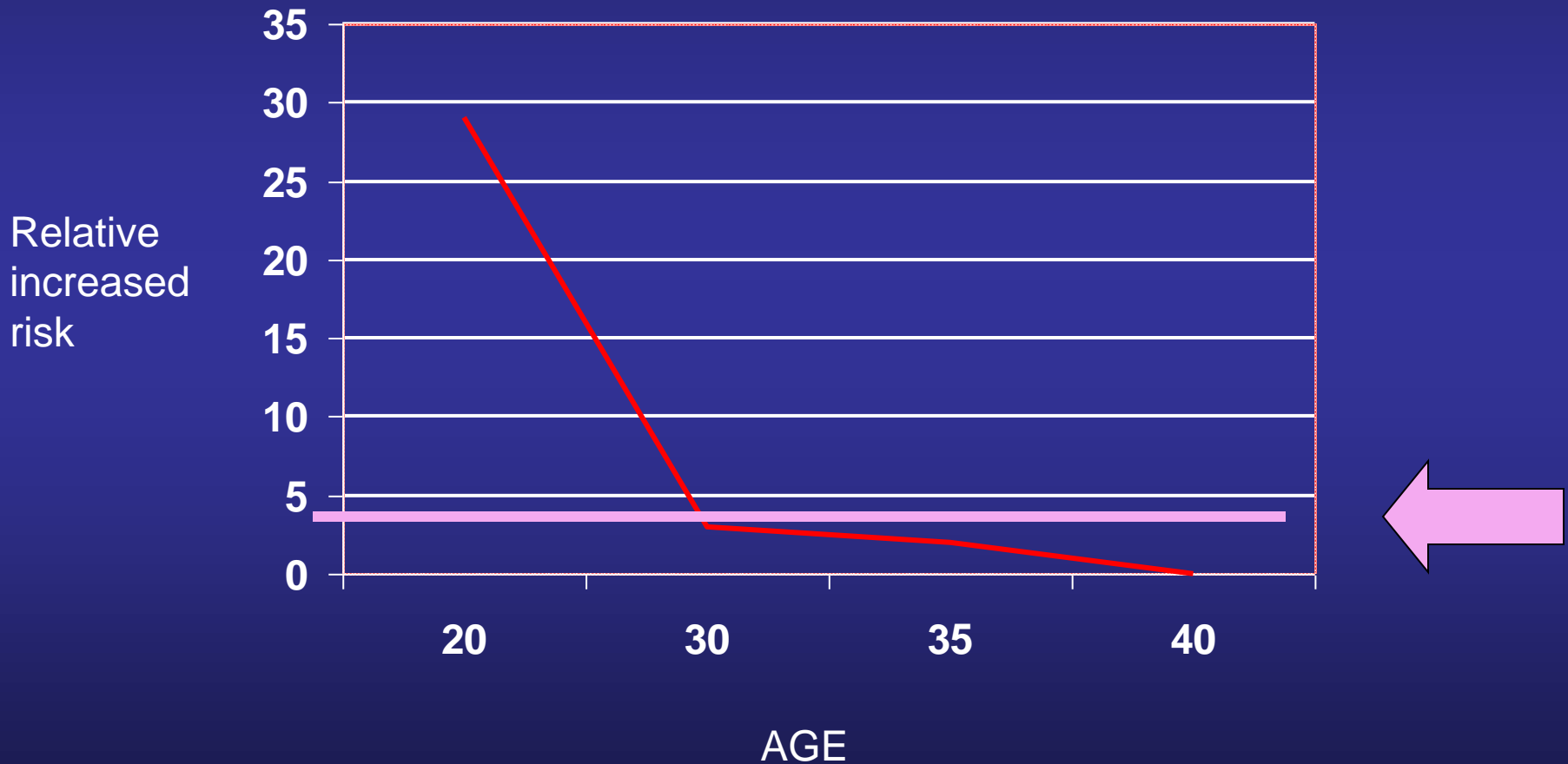
- Some but not all of the features of LCIS with involvement of the lobule not greater than 50-75% (definition varies with author)
- Lifetime risk of breast cancer: 10-20%

Atypical Lobular Hyperplasia

- Risk for developing cancer highest in women:
 - positive family history $rr = 8.4$
 - overall risk $rr \approx 4.0$
- Invasive carcinoma developed 2.6-21.0 (mean = 11.9) years after diagnosis of ALH

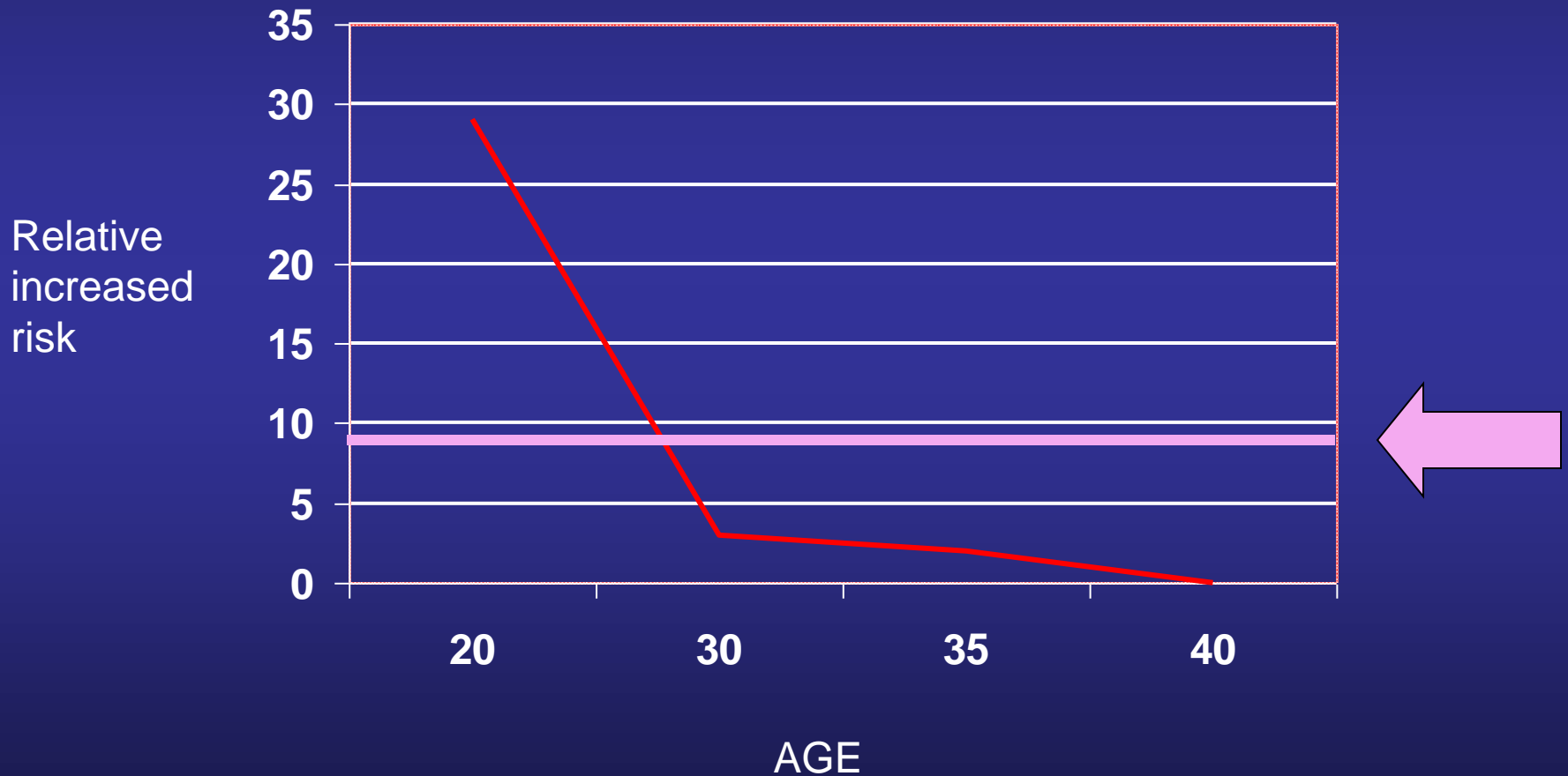
Risk Increase vs Age to Meet Accepted Screening Risk Level

ALH



Risk Increase vs Age to Meet Accepted Screening Risk Level

ALH WITH FAMILY HX



Atypical Ductal Hyperplasia

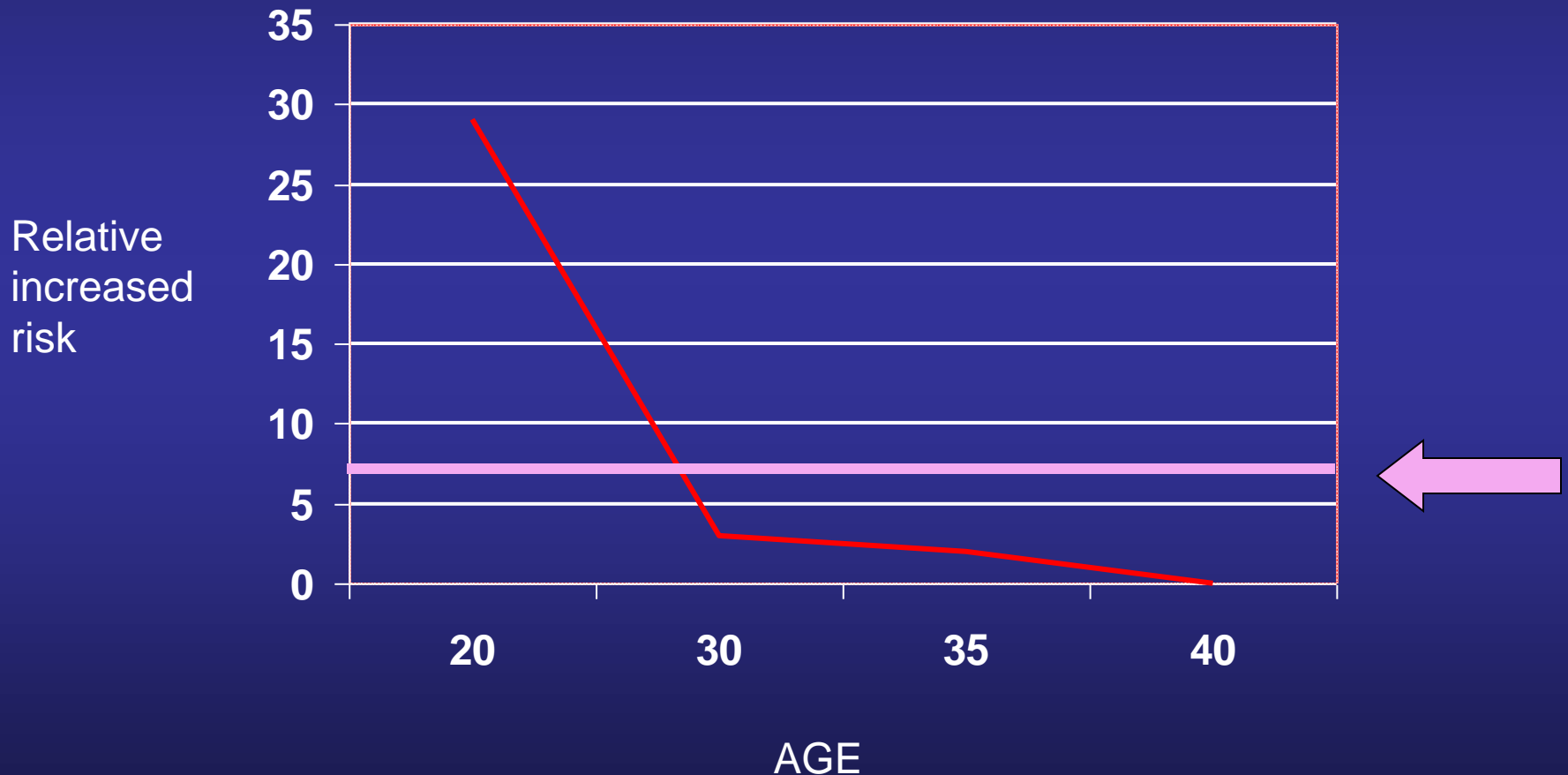
- Proliferation of ductal epithelium with some but not all of the features of DCIS
- It is considered the premalignant lesion of the breast

Atypical Ductal Hyperplasia

- Overall risk for developing invasive or in situ carcinoma is 27.5-30%
- Relative risk for development of carcinoma highest with:
 - Positive family hx rr=9.7
 - 20-30 years old rr=7.0
 - 31-45 years old rr=4.5
- Interval to develop carcinoma is 1.4-23.8 years, mean = 8.2 years

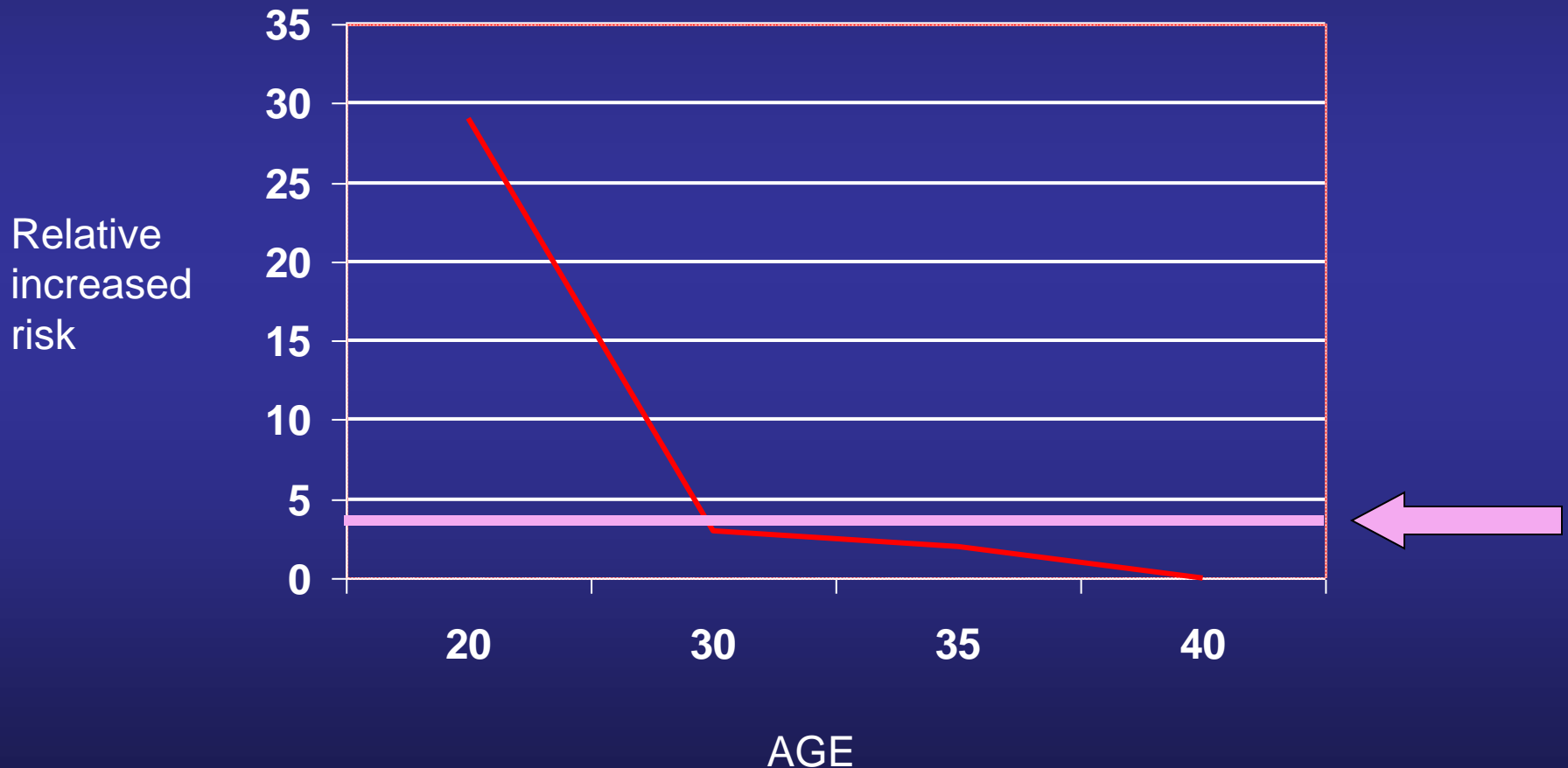
Risk Increase vs Age to Meet Accepted Screening Risk Level

ADH AT 20-30 YEARS OLD



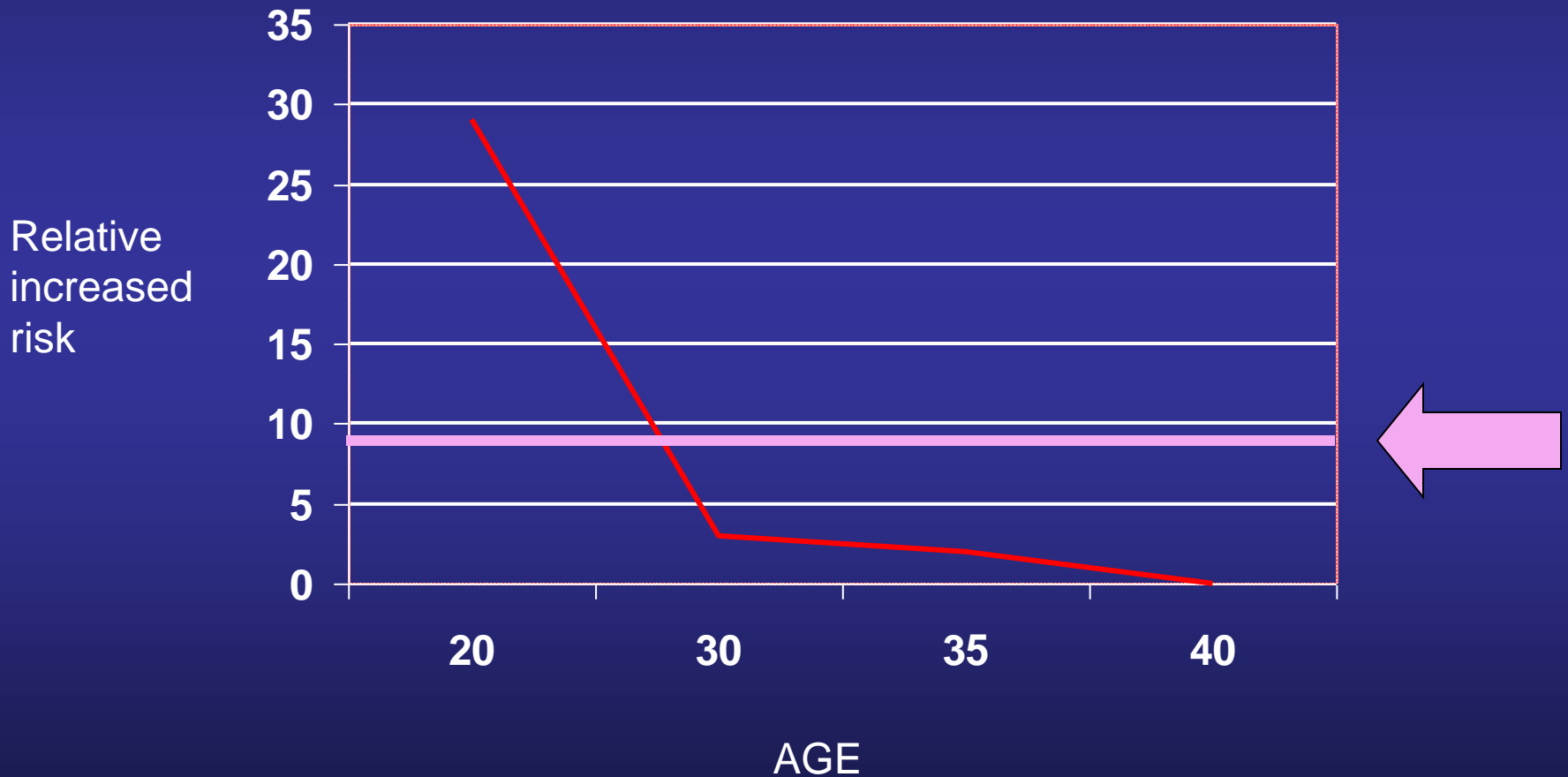
Risk Increase vs Age to Meet Accepted Screening Risk Level

ADH AT 31-45 YEARS OLD



Risk Increase vs Age to Meet Accepted Screening Risk Level

ADH WITH FAMILY HX



Treated Hodgkin Disease

- Risk is related to mantle field radiation and inversely related to age at treatment. When treated at age ≤ 10 and ≥ 30 years, minimal or no increased risk
- Breast cancer reported developing as early as 8 years post-radiation

Breast Cancer After Hodgkin's Disease (Mediastinal Radiation)

relative risk

Hancock	4x
Travis	3.2x vs those with <4Gy 8x vs those with >4Gy
Wolden	4.7x vs age matched cohort
Bhatia	75x (35% by age 40 yrs)

Hancock. J Natl Cancer Inst 1993; 85:25

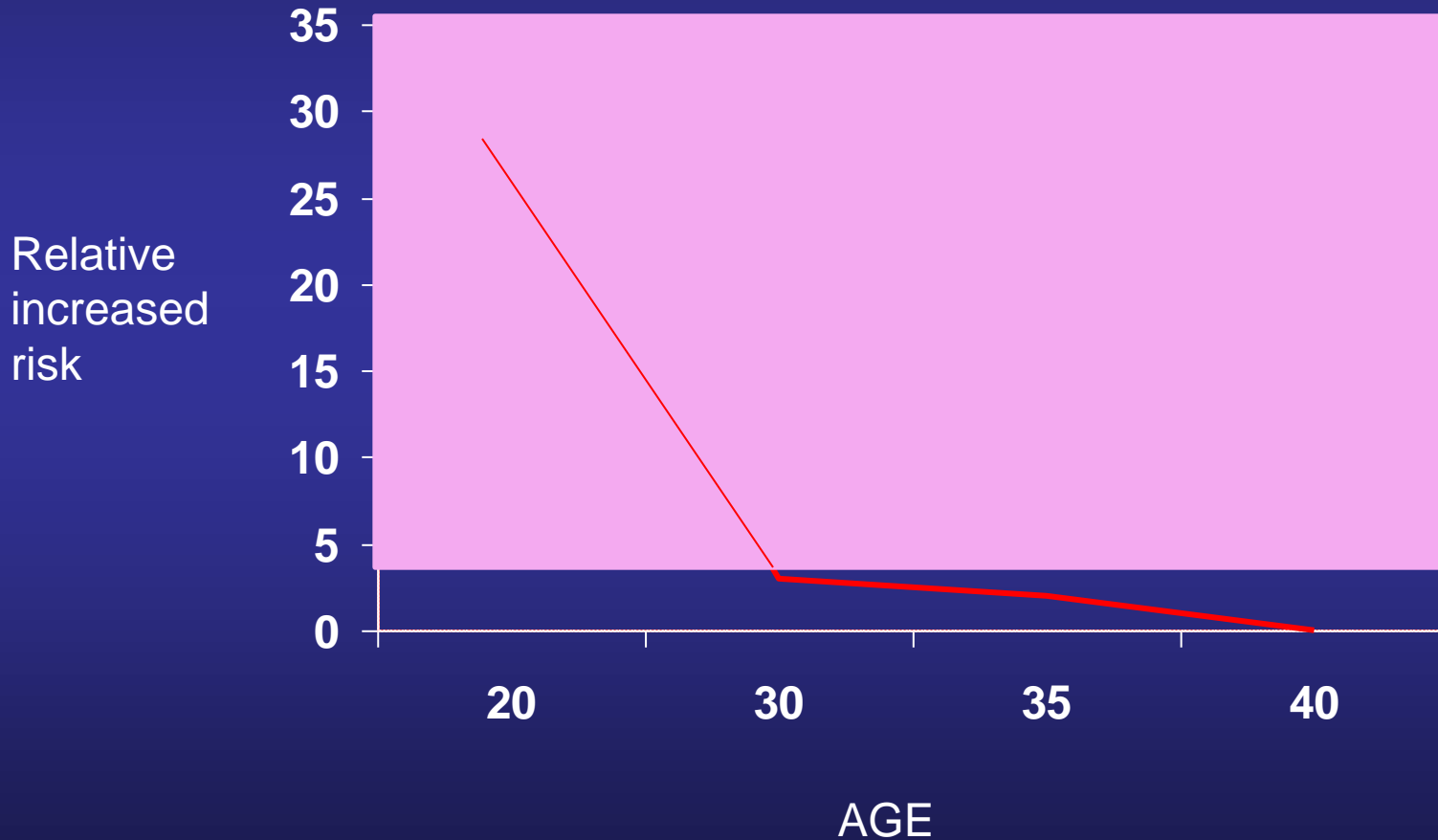
Travis. JAMA 2003; 290:465

Wolden. J Clin Oncol 2000; 18:765

Bhatia. N Engl J Med 1996; 334:745

Risk Increase vs Age to Meet Accepted Screening Risk Level

MEDIASTINAL RADIATION



Treated Hodgkin Disease: Mammographic Screening Recommendation

- Annual mammography commencing 8 years after successful treatment with radiation

Beyond Hodgkin Disease: other childhood malignancies with breast cancer risk at age <40 years

Survivors of Wilms tumor treated with chest RT for lung mets

15% with BC by age 40

Chest RT for bone sarcoma, soft tissue sarcoma, non-Hodgkin lymphoma

median time for development of BC 19 years, range 6-26 years;

Childhood survivors of leukemia and brain tumors not treated with chest RT

95 women with BC with 19% 20-29; 64% 30-39 yo.

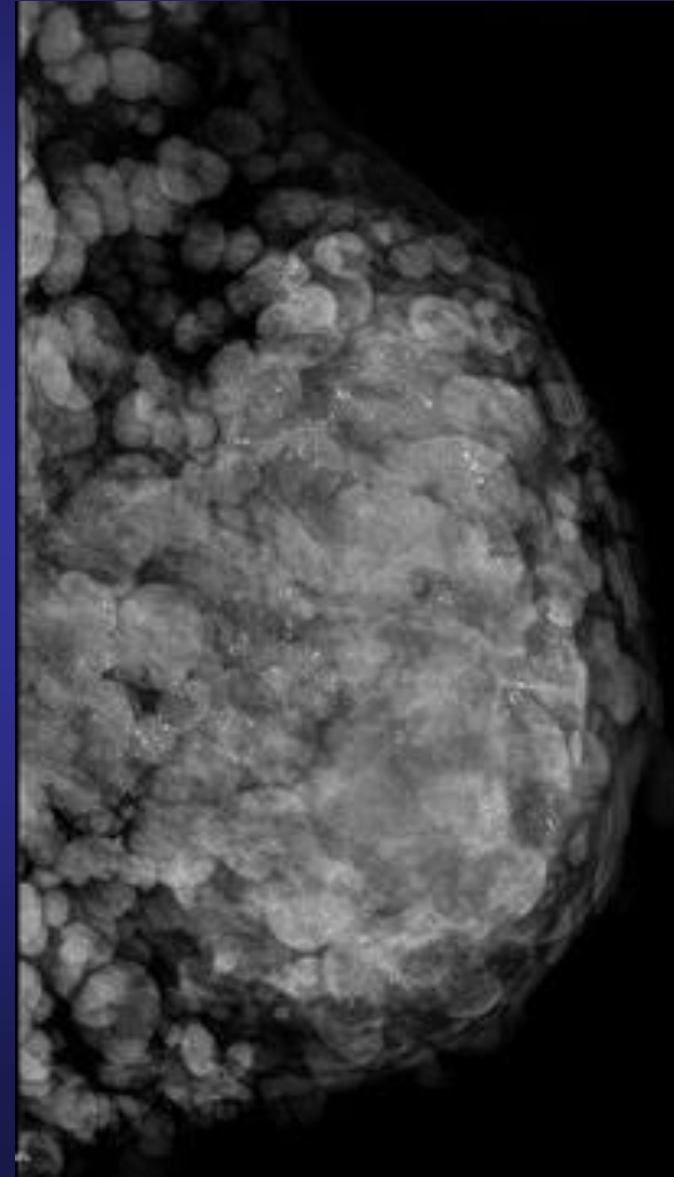
Lange JM et al. Breast cancer in female survivors of Wilms tumor. *Cancer* 2014; 120:37822

Kenney LB et al. Breast cancer after childhood cancer. *Ann Intern Med* 2004; 141:590

Neurofibromatosis

- Autosomal dominant transmission of NF1 gene
- For women 20-50 years old 3.5x risk for breast cancer with similar increase in breast cancer mortality compared to general population
- Mammogram may be compromised so additional screening with sono or MRI may be useful but is unstudied.

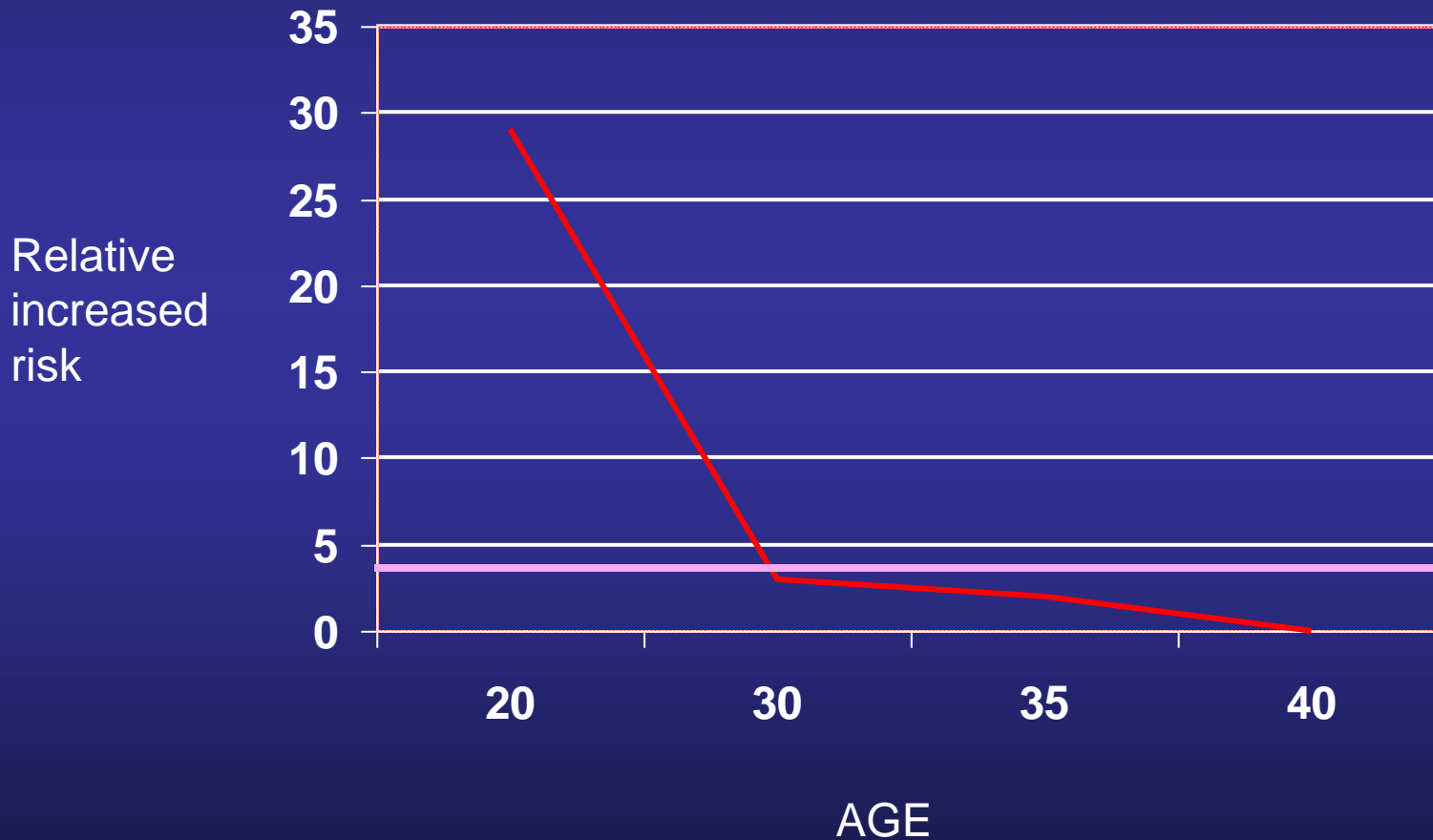
Neurofibromatosis



From DaSilva. BMC Cancer
Published online March 26, 2015

Risk Increase vs Age to Meet Accepted Screening Risk Level

NEUROFIBROMATOSIS



BRCA 1

- Accounts for half of familial breast cancer and 5-8% of all breast cancer
- 19% risk by age 40; 4% by age 30
- 85% risk by age 70
- (26-85% risk of ovarian cancer by age 70)

Hughes. Cancer 1999;86:1682

BRCA 2

- Similar risk to that of women with BRCA 1 but age of developing breast cancer may be somewhat delayed
- (10-16% ovarian cancer by age 70)
- Similar risk for development of breast cancer as in BRCA 1 but occurs about 5 yrs later

Hughes. Cancer 1999;86:1682

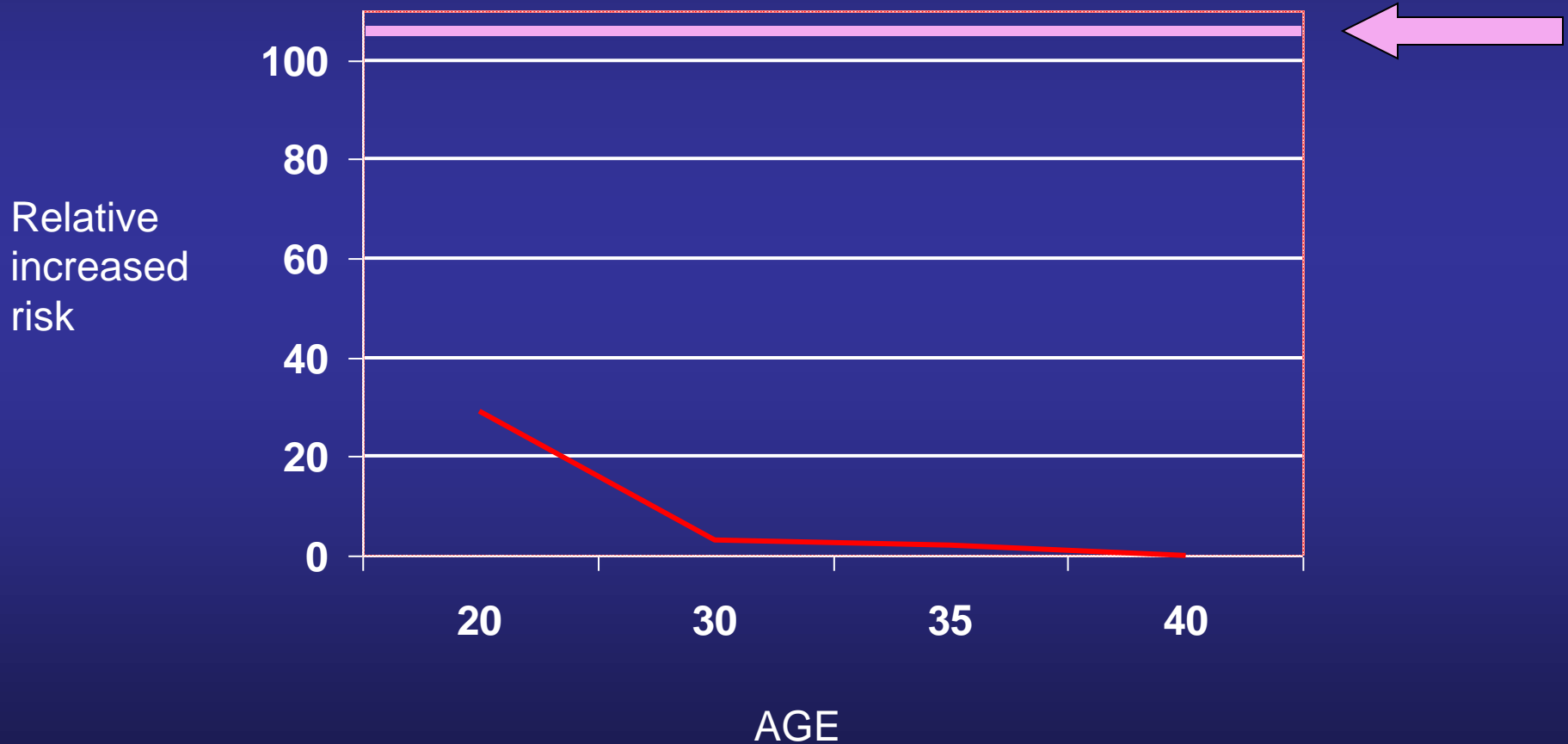
BRCA Breast Cancer Risk

	BRCA1	BRCA 2
Risk by age 70	39-87%	29-91%
RR at age 20-29	106	46

Most of these cancers develop ≥ 25 yo

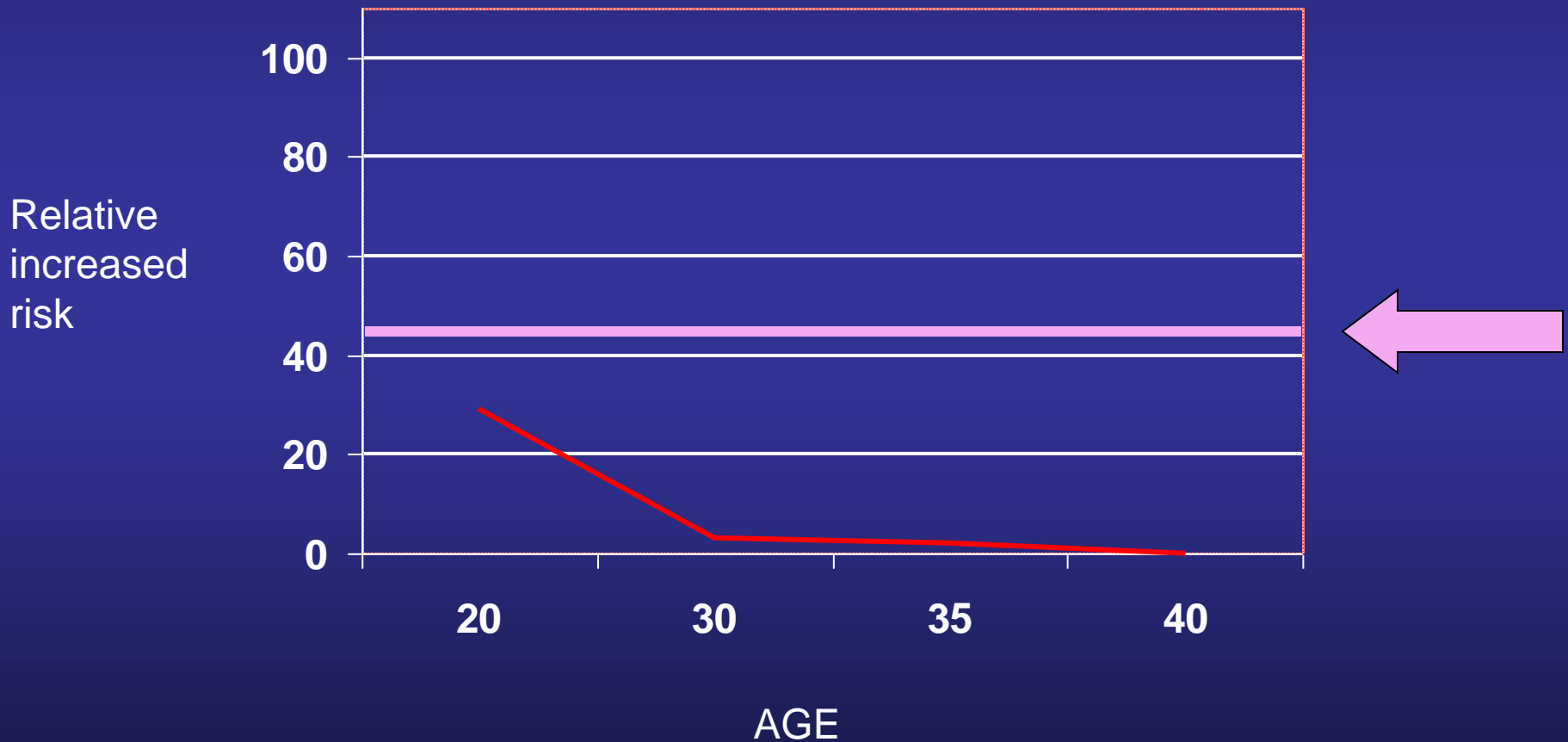
Risk Increase vs Age to Meet Accepted Screening Risk Level

BRCA 1 CARRIER



Risk Increase vs Age to Meet Accepted Screening Risk Level

BRCA 2 CARRIER



BRCA+ Mammo Screening Issues

- Cancers less frequently calcified than in BRCA – women¹
- “Benign” pattern often seen on mammo²
- Rapid tumor growth: estimated time from tumor inception to mammographic detection is 1000 days (2.7 yr) and from mammo detection to palpability 500 days (1.35 yrs)
→ *1 year window for mammo detection*³

¹Armes JE. Pathology 34:309;2002

²Sun CC. Lancet 353:2070;1999

³Spratt. J Surg Oncol 1996; 61:68

Change in Risk for BRCA + Women with Risk Reducing Intervention

- Tamoxifen and raloxifene have shown no risk reduction in BRCA + women¹
- Salpingo-oophorectomy reduces risk by inducing menopause; risk reduction = ?. If menopausal symptoms treated with low dose estrogen, then reduction may be cancelled
- Prophylactic mastectomy eliminates need for imaging screening

¹ Kirchhoff. Clin Cancer Res 2004; 10:2918. Fisher. J Natl Cancer Inst 1998; 90:1371. Gronwald. Int J Cancer 2006; 118:2281. King. JAMA 2001; 286:2251.

Therefore:

no change in screening for BRCA
+ women with risk reduction
intervention except for bilateral
mastectomy.

Annual Screening Commencing Before Age 40

- Personal history of breast cancer
- BRCA + and other high risk mutations
- First degree relative with premenopausal breast cancer or other family history with similar risk
- Treated Hodgkin disease and some other childhood malignancies
- LCIS, ALH
- Ductal atypia

High Risk (*BRCA* + or Family Hx) Screening Results: Sensitivity

<i>Study</i>	<i># Cancer</i>	<i>CBE</i>	<i>Mammo</i>	<i>MRI</i>
Stoutjesdijk 2001	13		93%	100%
Warner 2001	7	29%	43%	86%
Scheuer 2002	12	50%	50%	
Brekelmans 2001	26	54%	81%	15%
Kriege* 2004	44	18%	33%	90%
Sardanelli 2007	18	50%	59%	94%
Kuhl 2000	9		33%	100%

*invasive only; additional 6 DCIS not included

MR Discovered Breast Cancers in High Risk Women: PPV

AUTHOR	# PTS	MEAN AGE	BX (%)	PPV
Kuhl	192	39	14 (7)	64%
Lo	157	43	28 (18)	18%
Warner	196	43	23 (12)	26%
Stoutjesdijk	179	---	30 (17)	43%
Tilanus	109	43	9 (8)	33%
Sardanelli	278	46	24 (9)	63%
Morris	367	50	64 (17)	24%
TOTAL	1478		192 (13)	36%

MR Discovered Breast Cancers in High Risk Women: TUMOR SIZE

AUTHOR	# PTS	% WITH MRI FOUND CANCER	DCIS	INVASIVE
Sardanelli 2007	278	4.8%	22%	57% ≤ 10 MM
Morris 2002	367	4%	57%	4 MM MEDIAN; RANGE: 1-12 MM

Axillary nodal involvement in high risk women developing breast cancer as a function of screening technique

- In screening done with mammo, positive nodes reported in 30-45%¹
- In screening done with MRI, positive nodes reported in 0-21%²

¹Chart PJ. CMAJ 157: 1235;1997.
Lallo F. Eur J Cancer 34:937; 1998.
Brekelmans CTM. J Clin Oncol 19:924; 2001.

²Kuhl CK. Radiology 15:267; 2000.
Kreige M. N Engl J Med 351: 427;2004.

Does MRI screening work after the first round?

	% sensitivity		% specificity	
	MAMMO	MRI	MAMMO	MRI
Dutch MRI ¹ 1 st round:	36	82	94	87
Subsequent rounds:	29	77	95	92
Canadian ² 1 st round:	38	85	99	93
Subsequent rounds:	43	71	100	97
UK Royal College ³ 1 st :	40	75	93	82
Subsequent rounds:	40	80	94	81

Table from Kriege et al. *Cancer* 2006; 106:2324.

1. Kriege. *NEJM* 2004;351:427

2. Warner. *JAMA* 2004;292:1317

3. Leach. *Lancet* 2005; 365:1796

COMPARISON OF MAMMO, SONO AND MRI FOR HIGH RISK SCREENING

Mammography Sonography MRI
sens spec sens spec sens spec

Kuhl	33	93	33	80	100	95
Warner	43	99	50	93	86	91
Podo	13	100	13	100	99	100
TOTAL	29	98	30	91	96	94

from Liberman. NEJM 2004; 351:497-500

MR Screening: Post-Hodgkins radiation

Ng. J Clin Oncol 2103:31:2282

Sensitivity for detection of breast cancer:

mammo: 68%

MRI: 67%

mammo + MRI: 94%

Conclusion: both mammo and MRI should be used in followup for best results

High Risk Screening with MRI

Family HX

Chest RT¹

LCIS²

# women		91	220
% biopsied	13%	11%	9%
% malign bx	36%	23%	20%
% minimal CA	~80%	89%	100%
% women with cancer only found by MRI/	4-5%	4.4%	4.5%

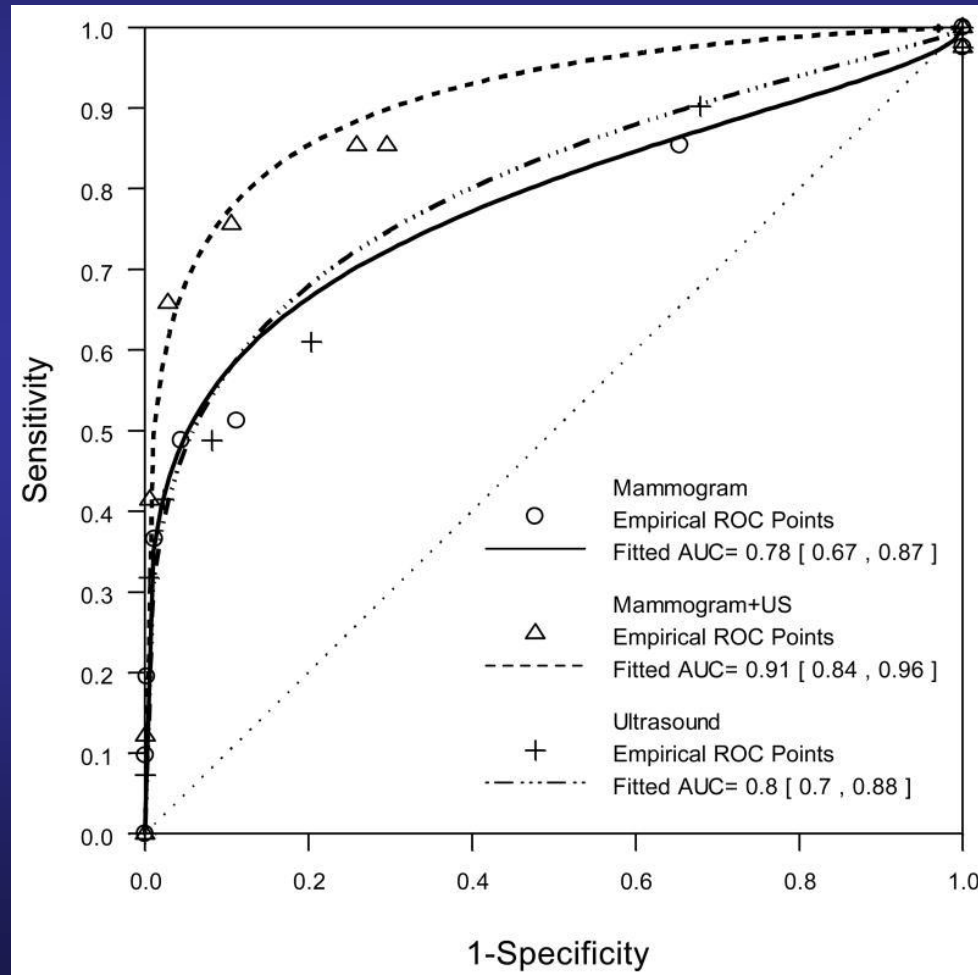
1. Sung. Radiology 2011; 259:65
2. Sung. Radiology 2011; 261:414

ACRIN 666: One year of Mammo + Sono screening of at least heterogeneously dense breasts (dense in at least one quadrant; physician performed screening).

Berg. JAMA 2008; 303:1482

N = 2809

Ca = 41



ACRIN 666: Mammo + Sono screening. Berg. JAMA 2008; 303:1482

Mammo: 7.6 cancers/1,000

Sono + Mammo: 11.8 cancers/1,000

Addition of sono increased diagnostic accuracy of screening from 0.78 to 0.91

Of 12 additional cancers diagnosed by sono, 11 were invasive, median = 10 mm, range 5-40mm

ACRIN 666: Mammo + Sono screening. Berg. JAMA 2008; 303:1482

Likelihood of cancer in women undergoing biopsy
(PPV):

Mammo $19/84 =$ 22.6%

Sono $21/235 =$ 8.9%

Mammo + Sono $31/276 =$ 11.2%

Author conclusion:

“Adding a single screening ultrasound to mammography will yield an additional 1.1 to 7.2 cancers per 1000 high risk women, but will also substantially increase the number of false positives.”

ACRIN 666: Mammo + Sono screening.
Berg. JAMA 2008; 303:1482

612 women agreed to undergo MRI
screening after mammo and sono
screening

MRI in this group found 9 additional
cancers:

$9/612 = 15 \text{ cancers}/1,000 \text{ screening}$

Additional Cancers Found with Sono Screening of BI-RADS 3-4 density breasts

2.0-4.2/1000 screenings

PPV=7-38%; 5% of all screenings resulted
in biopsy

Screening done by technologist or physician
with same results

Brem. AJR 2015; 204:234

What should I do with the
patient who cannot or will
not get an MRI but falls
within that higher risk
group
?

No MRI options:

sono screening

tomosynthesis

contrast mammography

BSGI

No MRI options:

sono screening

useful in denser breasts

improved detection of 3-

4 cancers/1,000

screens

low PPV with biopsy rate

of about 5%

No MRI options:

tomosynthesis

significant reduction in
recall rate

no value in adding to
sono with mammo

reported increase

cancer detection

rate by 2-3/1000 in at

least two studies

No MRI options:

contrast mammography
comparable to MRI in
detecting index
cancers although may
be slightly inferior in
staging
no data in screening
requires IV iodine contrast

No MRI options:

BSGI

comparable to MRI in
cancer detection with
some reports showing
slight superiority
high radiation dose to entire
body including
radiosensitive organs
probably nullifies its
usefulness for
screening

No MRI options:

sono screening

tomosynthesis

contrast mammography

BSGI



thank you