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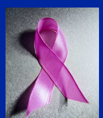
IBDC
International Breast Disease Centers

Screening: State of the Art

High risk and dense breasts

Robin Wilson



Smart Breast Screening ?

- 1 in 8 women in the will get breast cancer
- 8 in 9 will not
- 55% of breast cancers are not screen detected
- One breast cancer death prevented for every eight breast cancers detected by screening
- One breast cancer over-diagnosed for each breast cancer death prevented

- Can we target screening at those most at risk?

MAY 2004

THE LANCET

Screening with magnetic resonance imag[ing] mammography of a UK population at hig[h risk of] breast cancer: a prospective multicentre [cohort study] (MARIBS)

*MARIBS study group**

The classification and care of women at risk of familial breast cancer 1

NHS
National Institute for Health and Clinical Excellence

Issue date: October 2006

Familial breast cancer

The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care

This is a partial update of NICE clinical guideline 14

NICE clinical guideline 41
Developed by the National Collaborating Centre for Primary Care

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Improving Breast Screening

- **ACBCS – higher risk subgroup**
- **To advise the DH on what additional screening to adopt for increased risk groups**

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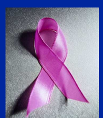
Improving Breast Screening

DRAFT REPORT OF THE WORKING PARTY FOR HIGHER RISK BREAST SCREENING

Prof. Lars Holmberg[1] (Chair), Prof. Ian Ellis[2], Dr. Louise Izatt[3], Dr. Michael Michell[4], Dr. Caitlin Palframan[5], Dr. Gillian Reeves[6], Dr. Robin Wilson[7], Prof. Ken Young[8]



Improving Breast Screening

- Assess ALL factors that increase risk
- Define a risk level above which breast screening can be expected to significantly reduce mortality and be cost effective
- Apply the same screening strategies to ALL women with the same risk

Improving Breast Screening

- Assess all factors that increase risk:
  - Family History
  - Mantle radiotherapy
  - HRT and OCP
  - Breast Density
  - Parity
  - Age at menopause
  - Alcohol
  - Obesity
  - Pathological risk factors
  - Previous breast cancer
  - Mammography

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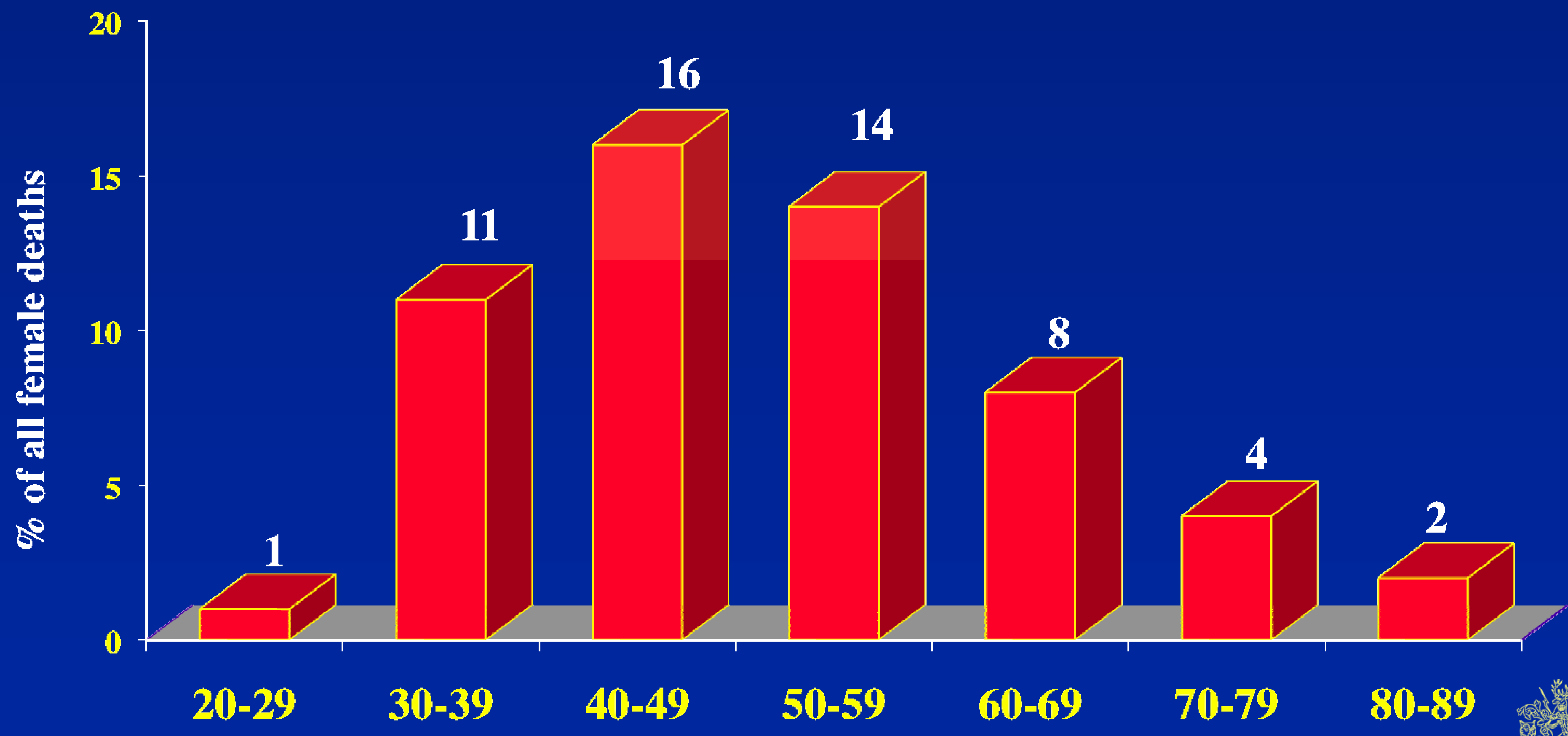
Percentage of All Female Deaths Attributable to Breast Cancer in England and Wales in 2005 (Office of National Statistics 2006. ISBN (10) 1-85774-644-4)



Improving Breast Screening

- Define a risk level above which breast screening can be expected to significantly reduce mortality and be cost effective:

- Three levels – normal, moderate and high

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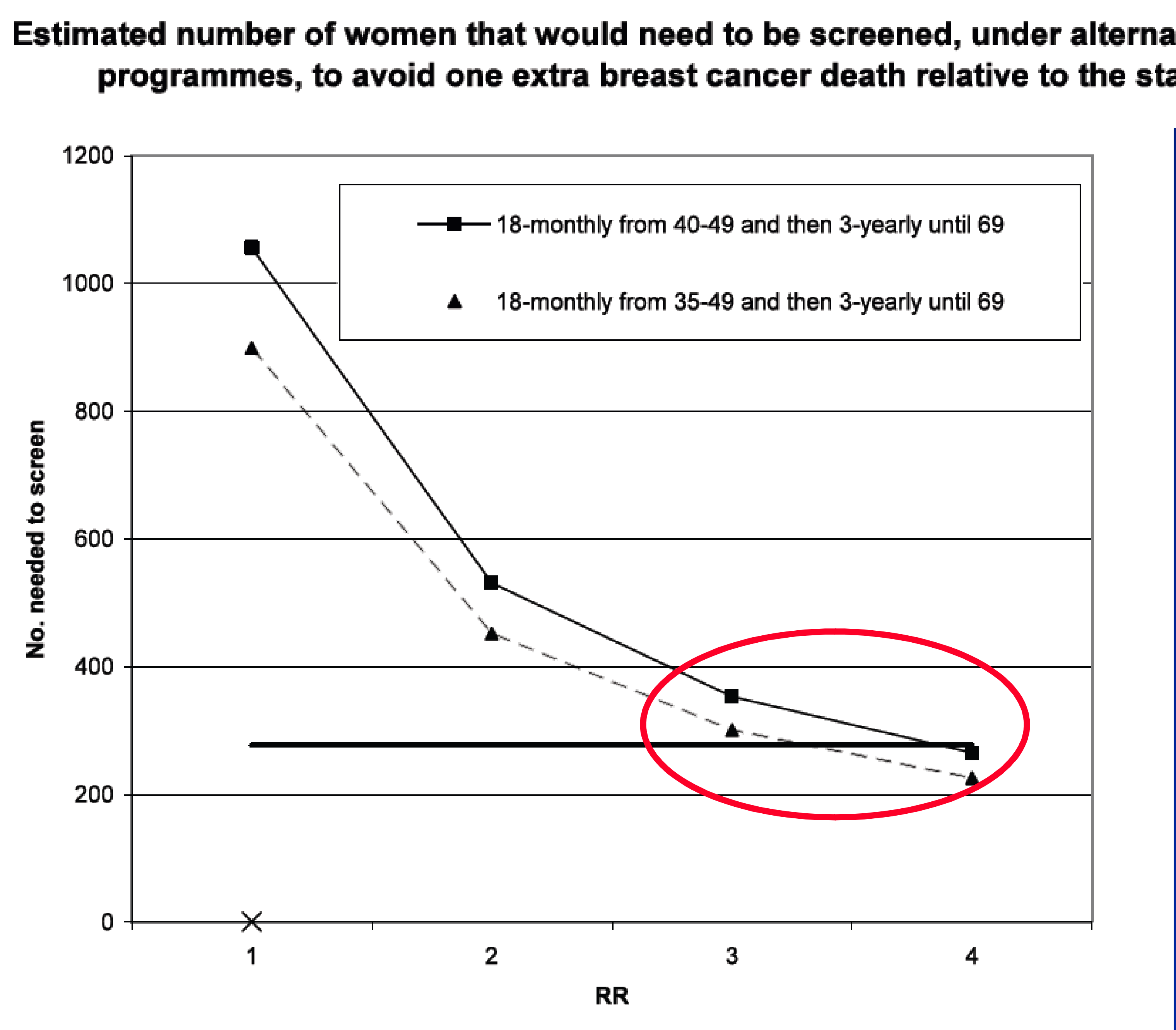
Age group 40

	RR <0.8	RR 0.8.-1.2	RR 1.2-1.9	RR 1.9-3.6	RR >3.6
Risk over 10 yrs (%)	1.0	1.5	2.2	3.6	6.2
% of population	48.1	28.3	19.8	3.8	0.1
% of cancers	33.8	28.2	28.5	9.2	0.3

90 % of breast cancer in women under 50 occur in women at RR less than 2

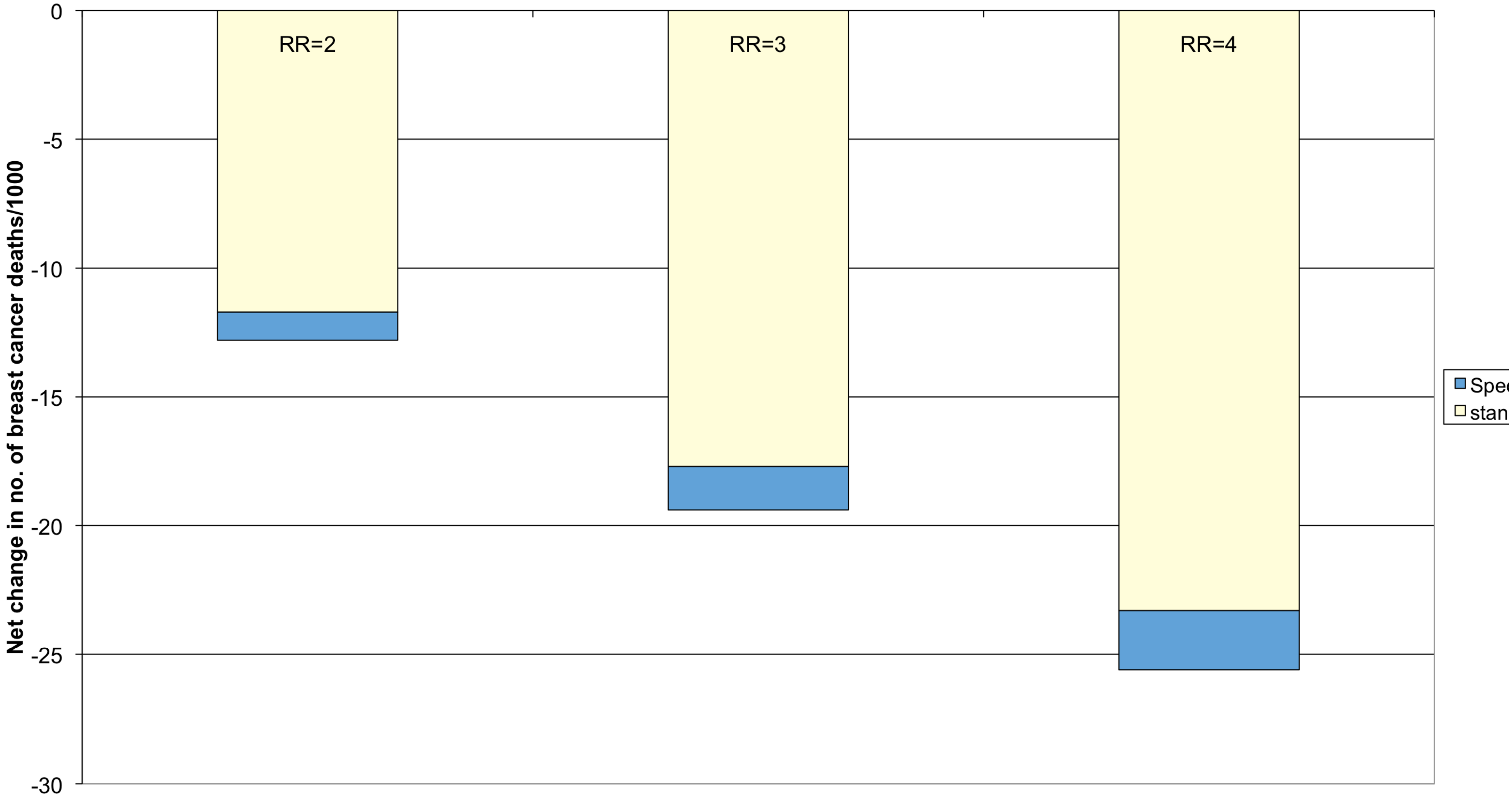
Table 5. Stratification of the population into risk categories based on parity, hormone use, breast density, alcohol consumption, obesity and benign breast disease.

Age		RR<0.8	RR 0.8-1.2	RR 1.2-1.9	RR 1.9-3.6	RR >3.6
40	Risk over next 10 years	1.0%	1.5%	2.2%	3.6%	6.2%
40	Percentage of population	48.1	28.3	19.8	3.8	0.1
40	Percentage of cancers	33.8	28.2	28.5	9.2	0.3
55	Risk over next 10 years	2.3%	3.1%	4.4%	7.0%	11.9%
55	Percentage of population	47.1	28.6	19.6	4.4	0.2
55	Percentage of cancers	32.6	28.0	28.0	10.5	1.0
70	Risk over next 10 years	2.5%	3.1%	5.2%	8.0%	16.7%
70	Percentage of population	41.1	37.6	16.2	4.6	0.5
70	Percentage of cancers	29.3	33.3	24.4	10.6	2.5

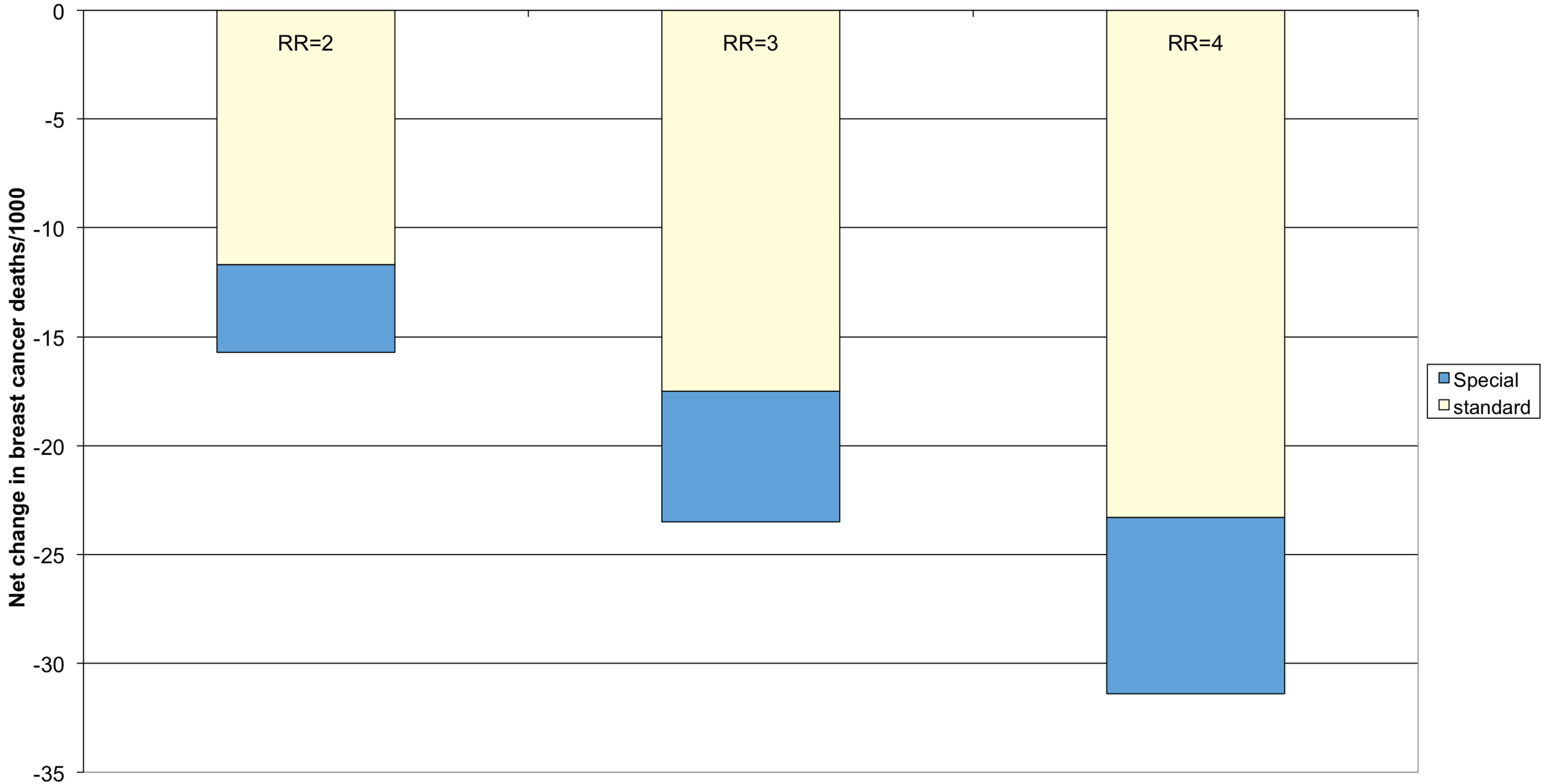


RR > 3 looks like a reasonable threshold

Additional net change in number of breast cancer deaths per 1000 screened women due to specialised (18-monthly 40-49 and 3-yearly thereafter) vs standard screening



Estimated additional net change in breast cancer deaths per 1000 screened women due to specialised (18-montly 40-73) vs standard screening



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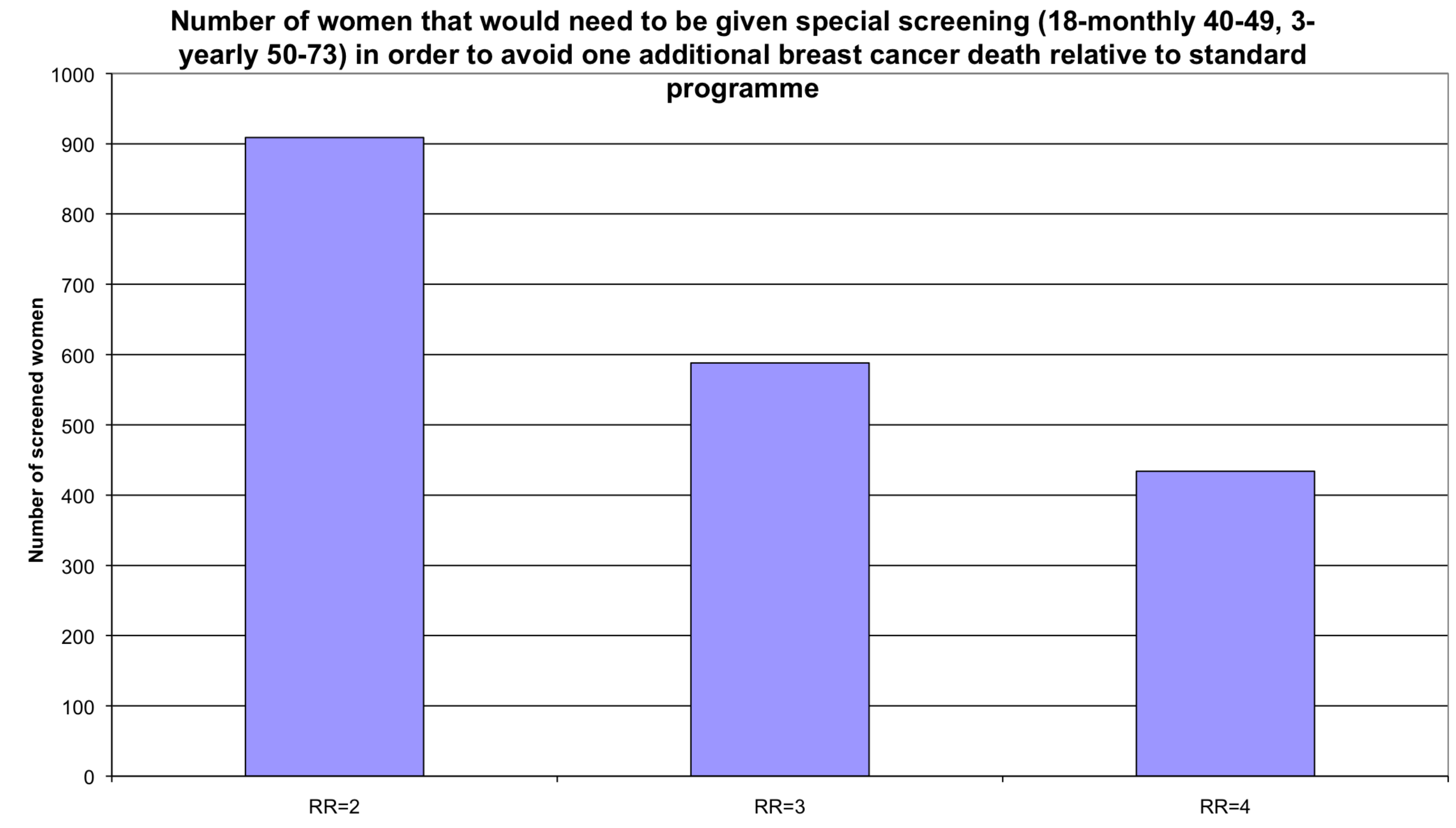

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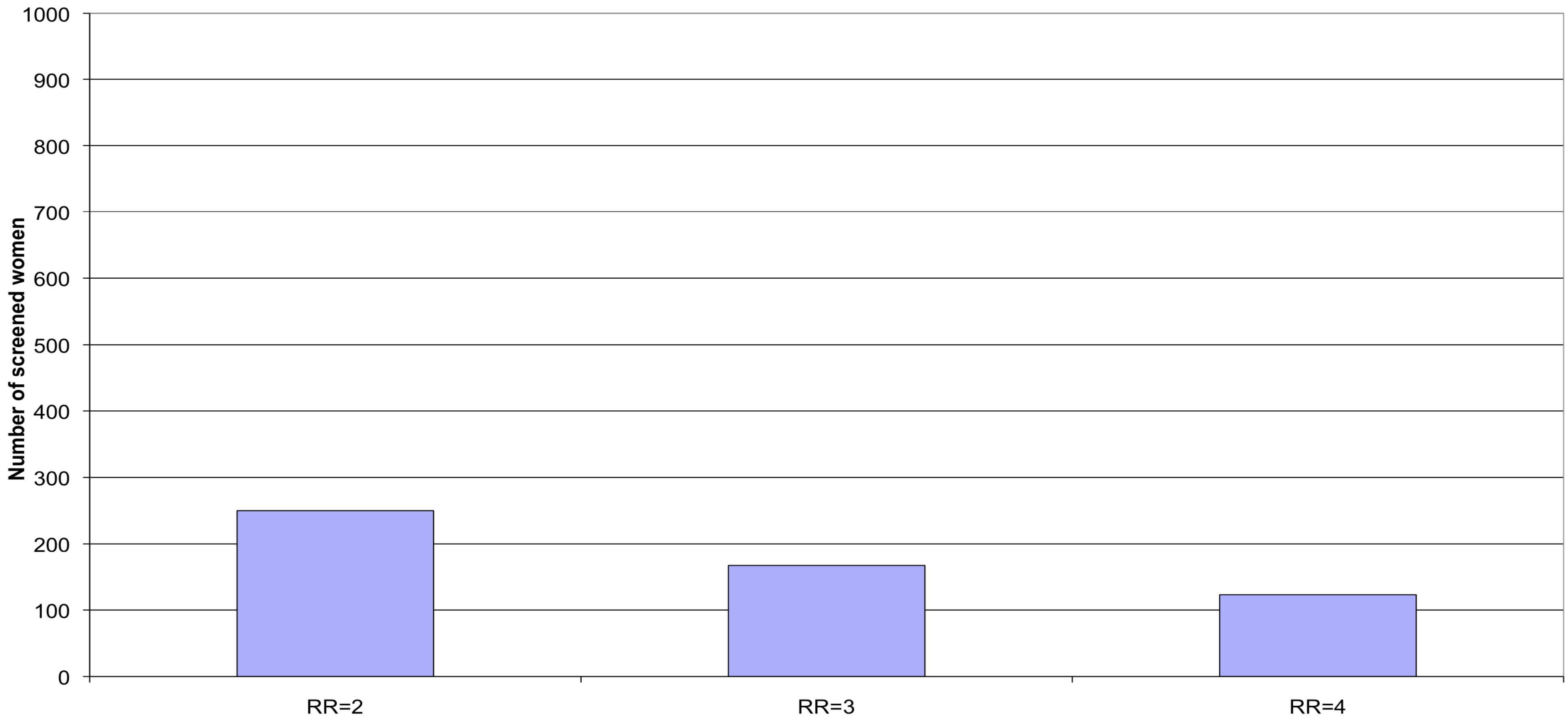
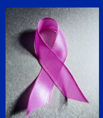
Number of women that would need to be given special screening (18-monthly 40-73) in order to avoid one additional breast cancer death relative to standard programme



Carry on with 18 month interval after age 50



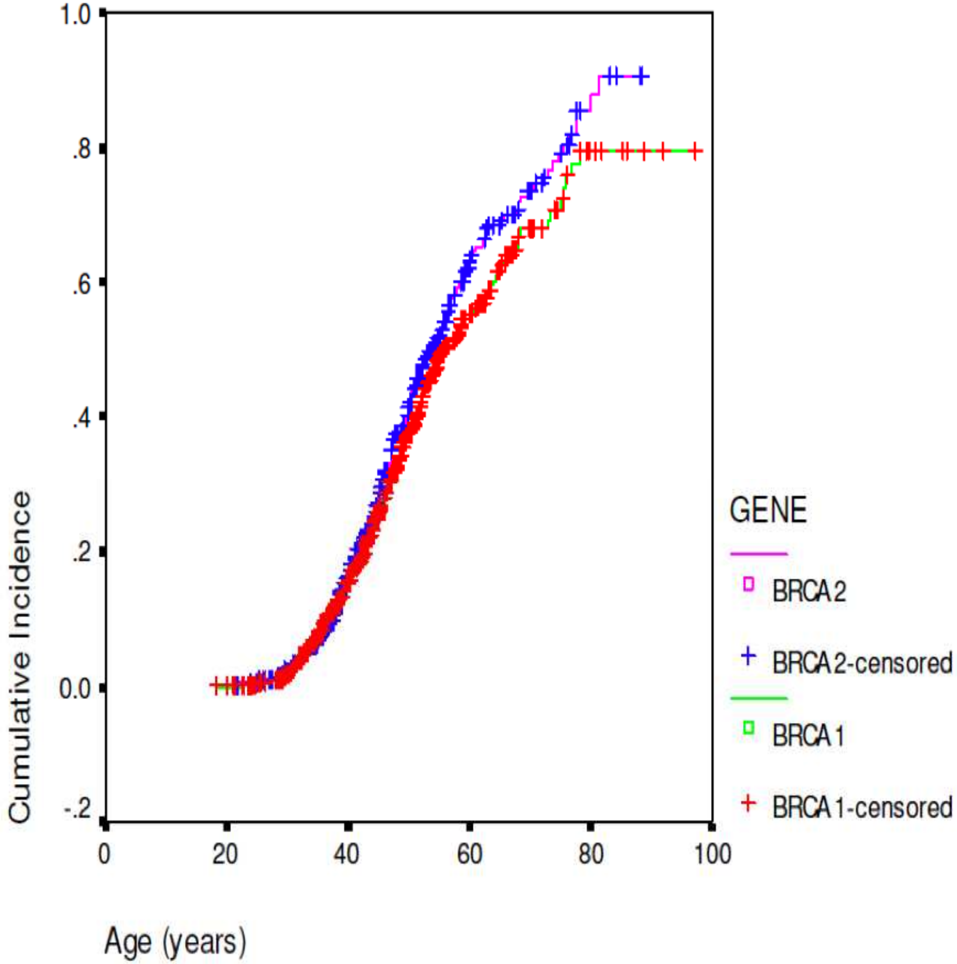

Cumulative Incidence
1.0
.8
.6
.4
.2
0.0
-.2
0
20
40
60
80
100
Age (years)
GENE
BRCA2
BRCA2-censored
BRCA1
BRCA1-censored

Table 3. Cumulative risk of breast cancer by 70 years for *BRCA1* and *BRCA2*

	Cumulative risk of breast cancer in *BRCA1* by 70 years	Cumulative risk of breast cancer in *BRCA2* by 70 years
Meta-analysis of population case series	65% (95% CI 44-78%) [3]	45% (95% CI 31-56%) [3]
Clinical genetics services	68% (95% CI 65-71%) [4]	75% (95% CI 72-78%) [4]
Breast Cancer Linkage Consortium	87% (95% CI 72-95%) [8]	84% (95% CI 43-95%) [5]

Table 4. Penetrance for breast cancer by age

Cancer risk to age	*BRCA1* Breast (standard error)	*BRCA2* Breast (standard error)
30	2%	2.5%
40	16.5% (0.015)	17% (0.019)
50	48% (0.023)	42% (0.027)
60	55% (0.027)	63% (0.031)
70	68% (0.033)	75% (0.033)
80	79.5% (0.04)	88% (0.037)

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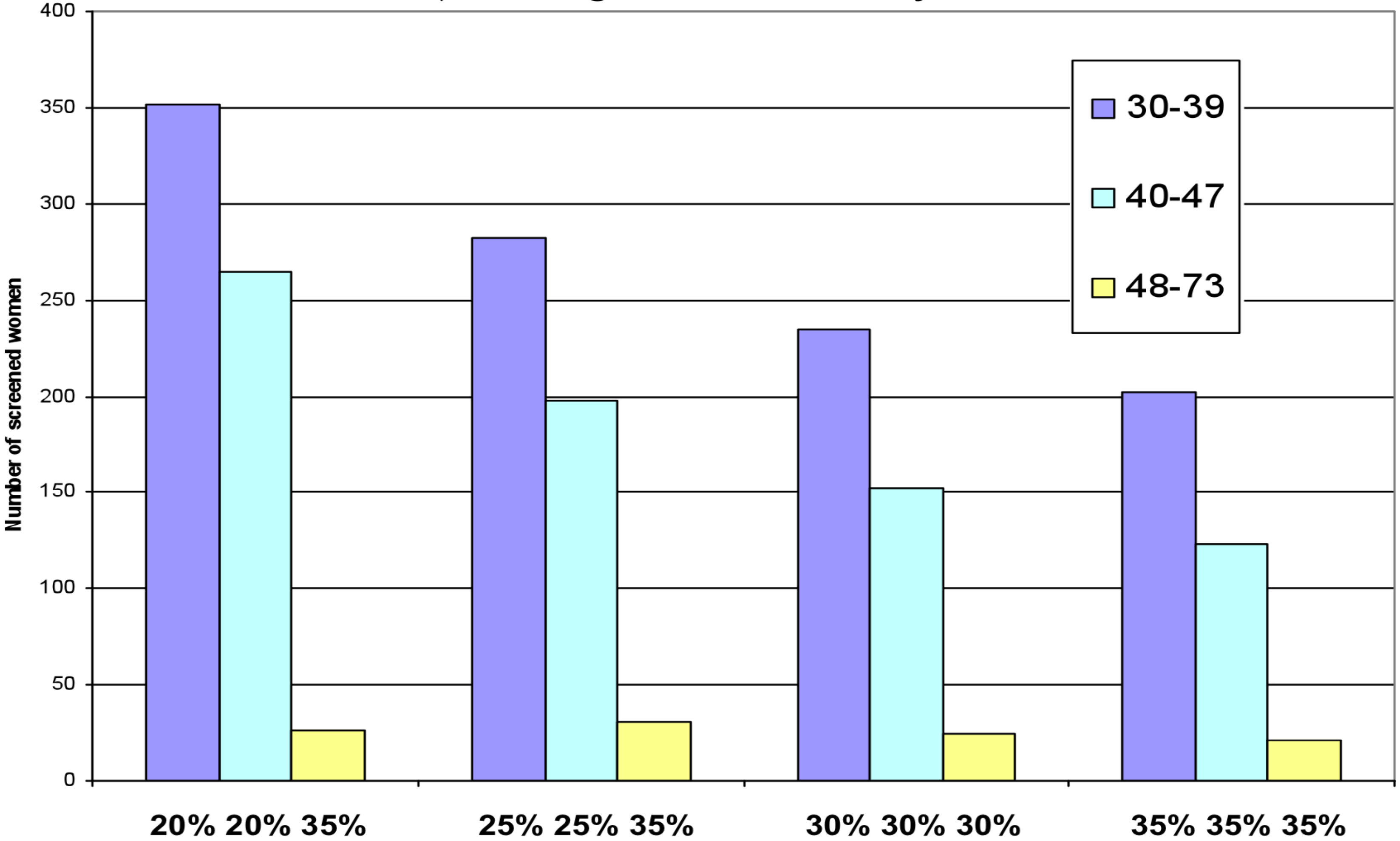
Figure 3. Number of women that would need to be screened in various components of high risk programme (RR=8) in order to avoid one breast cancer death, according to assumed mortality reductions

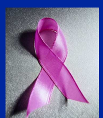


Improving Breast Screening

- Assess all factors that increase risk

- Define a risk level above which breast screening can be expected to significantly reduce mortality and be cost effective

- Apply the same screening strategies to all women with the same risk



Improving Breast Screening

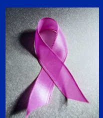
- Apply the same screening strategies to all women with the same risk:
  – Normal risk 3 yearly 50 – 70 (7 screens)
  – Moderate risk digital mammography only from age 40 – 70 every 18 months (20 screens)
  – High risk group – annual MRI only before 40 then add mammography to age 70
  – Post-treatment - stay on the same screening strategy
  – Post Rx risk stratified into the same three risk groups

Ref	Risk	Ages	Surveillance Protocol	Frequency	Notes
1	BRCA 1 or 2 carrier or not tested and equivalent risk	20-29 30-39 40-49 50+	n/a MRI MRI + Mammo Mammo ± MRI	 Annual Annual Annual	Review MRI annually on basis of background density
2	TP53 (Li-Fraumeni)	20-29 30-39 40-49 50+	MRI MRI MRI +Mammo Mammography± MRI	Annual Annual Annual Annual	Review MRI annually on basis of background density
3a	A-T homozygotes	25+	MRI	Annual	No mammography
3b	A-T heterozygotes	40-50 50+	Mammography Mammography	18 monthly Routine screening (3 yearly)	Routine screening from 50
4a	Supradiaphragmatic radiotherapy irradiated below age 20.	25-39 40-50 50+	MRI MRI +/- Mammography Mammography	Annual Annual Routine screening (3 yearly)	Surveillance commences at 25 or 8 years after first irradiation whichever is the later
4b	Supradiaphragmatic radiotherapy irradiated 20-35	40-50 50+	Mammography Mammography	18 monthly Routine screening (3 yearly)	Surveillance commences at 40 or 8 years after first irradiation whichever is the later

Premalignant breast disease

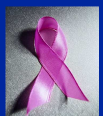
- Atypical ductal hyperplasia
- Atypical lobular hyperplasia
- Lobular carcinoma in situ

All confer an RR of 4 and more



Post-treatment breast cancer

- Most women who have had invasive breast cancer have a RR of 4 and more for developing another breast cancer
- UK HTA mammography surveillance assessment shows mortality benefit for detecting recurrence and second cancer (Gilbert et al. 2011)



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Higher Risk Breast Screening

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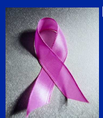
These data suggest:

- **Most breast cancer does not occur in women that are at ‘increased risk’**
- **Much of the benefit from screening those at increased risk occurs after the age of 50**
- **But:**
- **Screening younger women confers greater life years gained**



The Royal Marsden

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Higher Risk Breast Screening

These data suggest:

- **Very high risk groups can be offered MRI from age 30**
- **All higher risk women must be told that there is only theoretical mortality benefit for screening**
- **There is no evidence as yet from randomised trials that screening reduces mortality in these women**
- **MRI screening = high false positives**

Improving Breast Screening

What does this all mean ?

- Much more mammography
- Much more MRI
- More false positives
- More over-diagnosis ?

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Radiology 2011; 260:621–627

Radiology

Is Mammographic Screening Justifiable Considering Its Substantial Overdiagnosis Rate and Minor Effect on Mortality?

Karsten Juhl Jørgensen, MD
John D. Keen, MD, MBA
Peter C. Gøtzsche, MD

Radiology 2011; 260:621–627

[1] From the Nordic Cochrane Centre, Rigshospitalet, Department 3343, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark (K.J.J., P.C.G.); and Department of Radiology, John H. Stroger Jr Hospital of Cook County, Chicago, Ill (J.D.K.). Received April 1, 2011; revision requested April 11; revision received April 12; final version accepted April 14. **Address correspondence to** K.J.J. (e-mail: *kj@cochrane.dk*).

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Radiology 2011; 260:616–620

Radiology

Mammographic Screening and "Overdiagnosis"[1]

Daniel B. Kopans, MD
Robert A. Smith, PhD
Stephen W. Duffy, MSc

Radiology 2011; 260:616–620

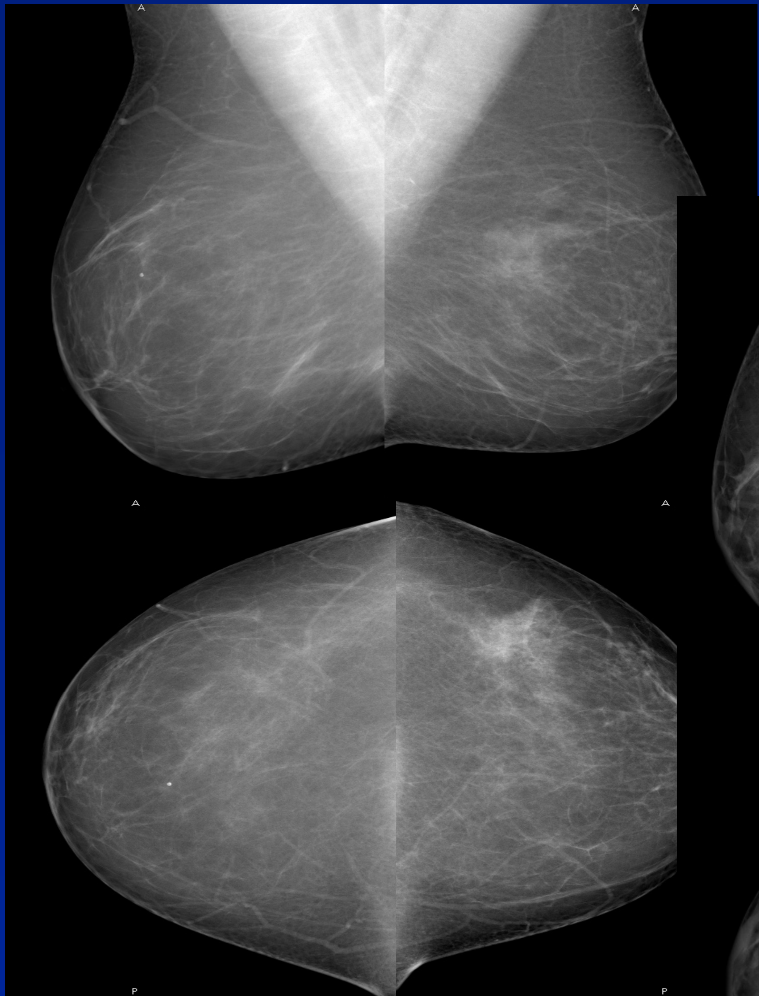
[1] From the Department of Radiology, Massachusetts General Hospital, Harvard Medical School, 15 Parkman St, Ambulatory Care Building, Suite 219, Boston, MA 02114 (D.B.K.); Cancer Control Sciences Department, American Cancer Society, Atlanta, Ga (R.A.S.); and Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, England (S.W.D.). Received April 6, 2011; revision requested April 11; revision received May 4; final version accepted May 5. **Address correspondence to** D.B.K. (e-mail: *dkopans@partners.org*).

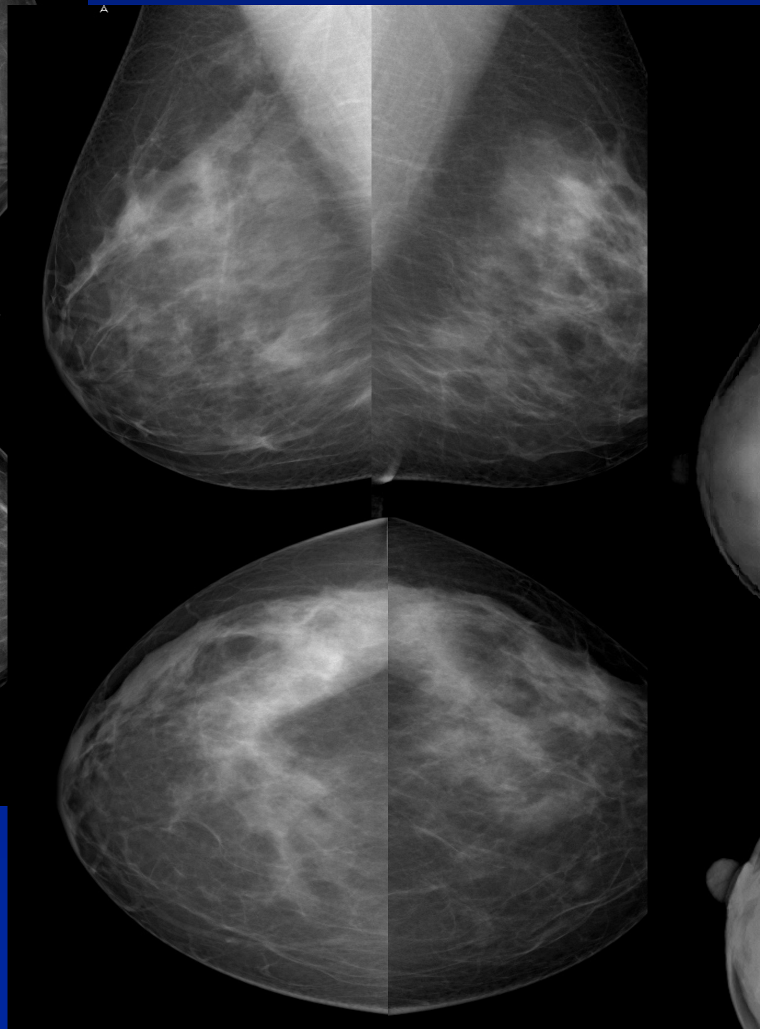
Improving Breast Screening

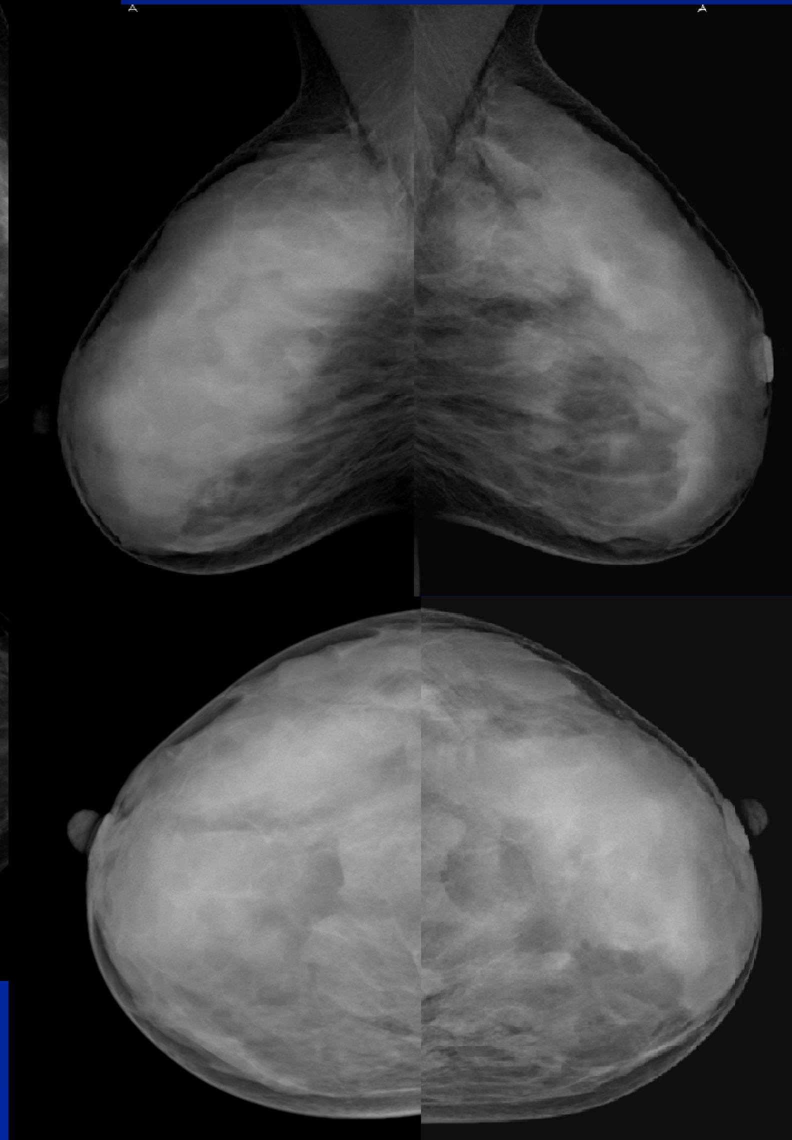
What about breast density?

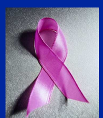
- Breast density is an independent risk factor for breast cancer

- Mammography is much less effective in the dense breast









Ultrasound and Screening

Radiology

Breast Imaging

Comparison of the Performance of Screening Mammography, Physical Examination, and Breast US and Evaluation of Factors that Influence Them: An Analysis of 27,825 Patient Evaluations[1]

Thomas M. Kolb, MD
Jacob Lichy, MD
Jeffrey H. Newhouse, MD

Index terms:
Breast, US, 00.129, 00.12989
Breast neoplasms, diagnosis, 00.30
Breast radiography, 00.11
Cancer screening, 00.11, 00.129, 00.12989

Published online before print
10.1148/radiol.2251011667
Radiology 2002; 225:165–175

Abbreviations:
BI-RADS = Breast Imaging Reporting and Data System
HRT = hormonal replacement therapy
PE = physical examination

[1] From 222 E 68th St, New York, NY 10021 (T.M.K., J.L.) and Department of Radiology, Columbia-Presbyterian Medical Center, New York, NY (T.M.K., J.H.N.). From the 1998 RSNA scientific assembly. Received October 11, 2001; revision requested December 5; final revision received April 11, 2002; accepted April 18. **Address correspondence to** T.M.K. (e-mail: tkolb@pipeline.com).

Author contributions:
Guarantor of integrity of entire study, T.M.K.; study concepts, T.M.K., J.L., J.H.N.; study design, T.M.K.; literature research, T.M.K.; clinical studies, T.M.K.; data acquisition, T.M.K.; data analysis/interpretation, T.M.K., J.H.N.; statistical analysis, T.M.K.; manuscript preparation, editing, and final version approval, T.M.K., J.H.N.; manuscript definition of intellectual content and revision/review, T.M.K., J.L., J.H.N.

PURPOSE: To (*a*) determine the performance of screening mammography, ultrasonography (US), and physical examination (PE); (*b*) analyze the influence of age, hormonal status, and breast density; (*c*) compare the size and stage of tumors detected with each modality; and (*d*) determine which modality or combination of modalities optimize cancer detection.

MATERIALS AND METHODS: A total of 11,130 asymptomatic women underwent 27,825 screening sessions, (mammography and subsequent PE). Women with dense breasts subsequently underwent screening US. Abnormalities were deemed positive if biopsy findings revealed malignancy and negative if findings from biopsy or all screening examinations were negative.

RESULTS: In 221 women, 246 cancers were found. Sensitivity, specificity, negative and positive predictive values, and accuracy of mammography were 77.6%, 98.8%, 99.8%, 35.8%, and 98.6%, respectively; those of PE, 27.6%, 99.4%, 99.4%, 28.9%, and 98.8%, respectively; and those of US, 75.3%, 96.8%, 99.7%, 20.5%, and 96.6%, respectively. Screening breast US increased the number of women diagnosed with nonpalpable invasive cancers by 42% (30 of 71). Mammographic sensitivity declined significantly with increasing breast density ($P < .01$) (48% for the densest breasts) and in younger women with dense breasts ($P = .02$); the effects were independent. Mammography and US together had significantly higher sensitivity (97%) than did mammography and PE together (74%) ($P < .001$). Tumors detected at mammography and/or US were significantly smaller ($P = .01$) and of lower stage ($P = .01$) than those detected at PE.

CONCLUSION: Mammographic sensitivity for breast cancer declines significantly with increasing breast density and is independently higher in older women with dense breasts. Addition of screening US significantly increases detection of small cancers and depicts significantly more cancers and at smaller size and lower stage than does PE, which detects independently extremely few cancers. Hormonal status has no significant effect on effectiveness of screening independent of breast density.

© RSNA, 2002

Mammography and palpation are the currently accepted breast cancer screening tests. Their effectiveness is imperfectly known due to differences among the reported series, less-than-ideal standards for defining true-negative and false-negative examination findings, lack of analysis of patient subgroups, and variation in risk factors and characteristics of the normal breast tissues.

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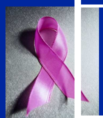
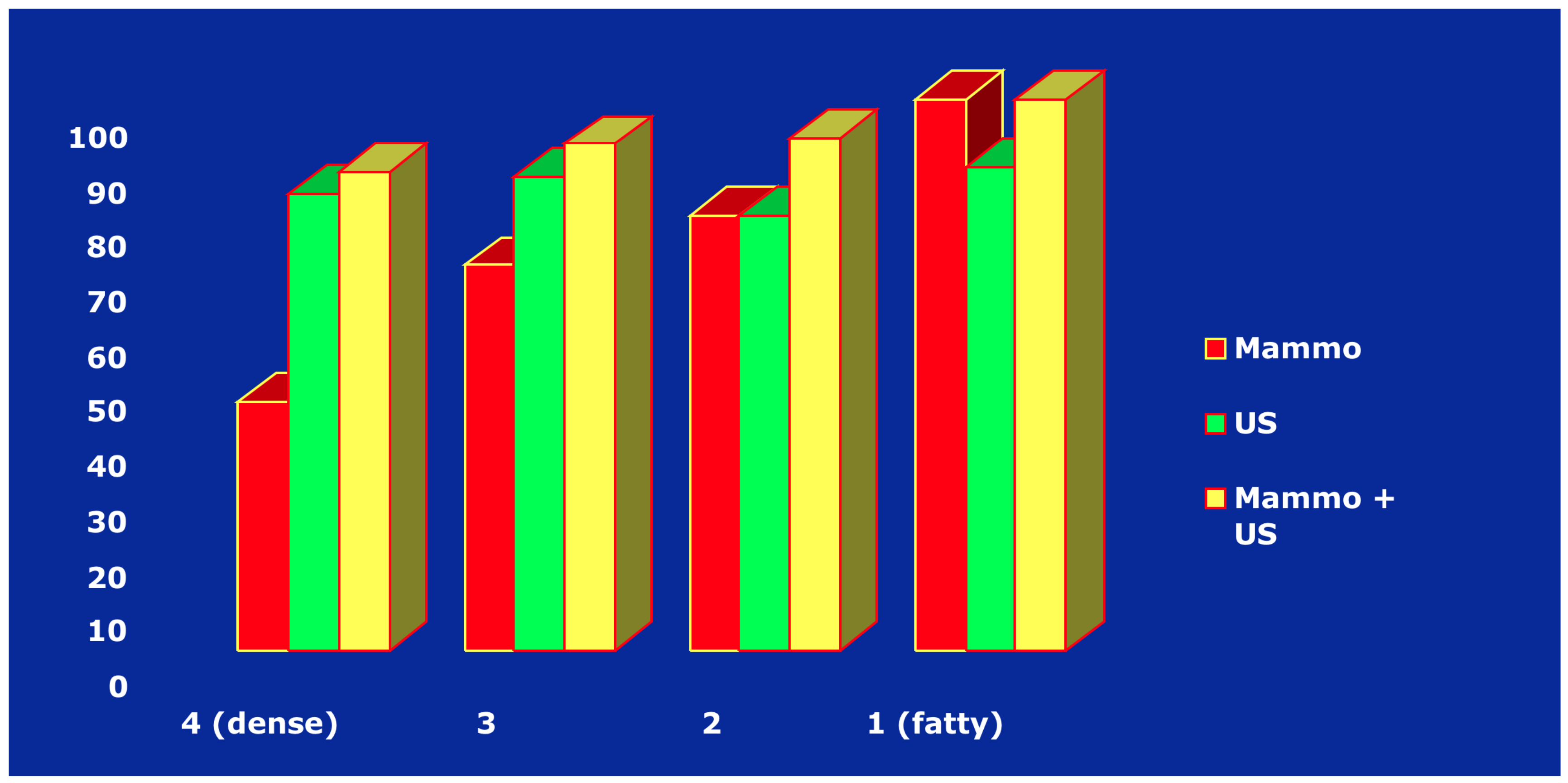
G Rizzatto - EBCC5
Summary of US Detection Studies
Average Risk Women

Investigator	Cancer detected
Gordon and Goldenberg 1995	44/12706 (0.35)
Buchberger et al 2000	32/ 8103 (0.39)
Kaplan et al 2001	6/1862 (0.32)
Kolb et al 2002	37/13547 (0.27)
Rizzatto et al 2002	8/2500 (0.32)
Crystal et al 2003	7/1517 (0.46)
LeConte et al 2003	16/4236 (0.38)
Total	154/44471 (0.34)



Mammography and Ultrasound: comparative sensitivity



Berg et al Radiology 2004;233:830-849

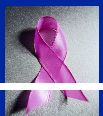
Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations

Kolb TM, Lichy J, Newhouse JH. Radiology 2002; 225: 165-175

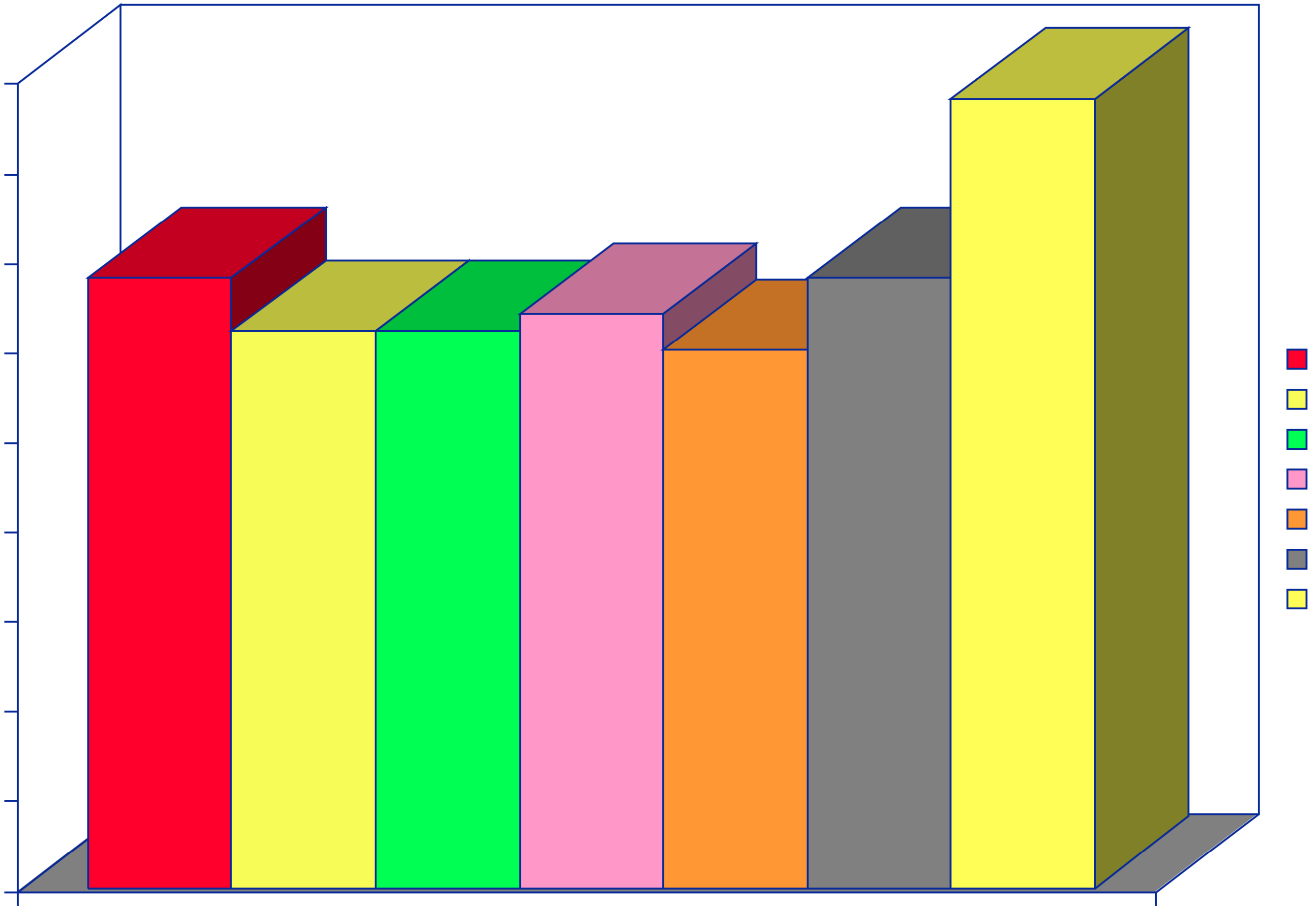
- **11,130 women and 27,825 screening events (mammography and physical examination)**
- **13,547 ultrasounds in 5,418 women with dense breasts**
- **246 cancers in 221 women**
- **Ultrasound increased the diagnosis of non-palpable breast cancer by 42% (30 of 71 cases)**

Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations
Kolb TM, Lichy J, Newhouse JH. Radiology 2002; 225: 165-175

	Sensitivity	Specificity	NPV	PPV	Accuracy
Mammography	77.6	98.8	99.8	35.8	98.6
Examination	27.6	99.4	99.4	28.9	98.8
Ultrasound	75.3	96.8	99.7	**20.5**	96.6



Rizzatto EBCC5: US and Screening



ACRIN 6666

Screening Breast US in High-Risk Women

Aim

- Diagnostic yield of screening mammography + US compared to mammography alone
- Independently read and blinded

Results

- Adding ultrasound to mammography will add an additional 1.1 to 7.2 cancers detected per 1000 higher risk women but will also substantially increase the risk of false positive results

Berg WA et al. ACRIN 6666", JAMA 2008; 299:2151-2163

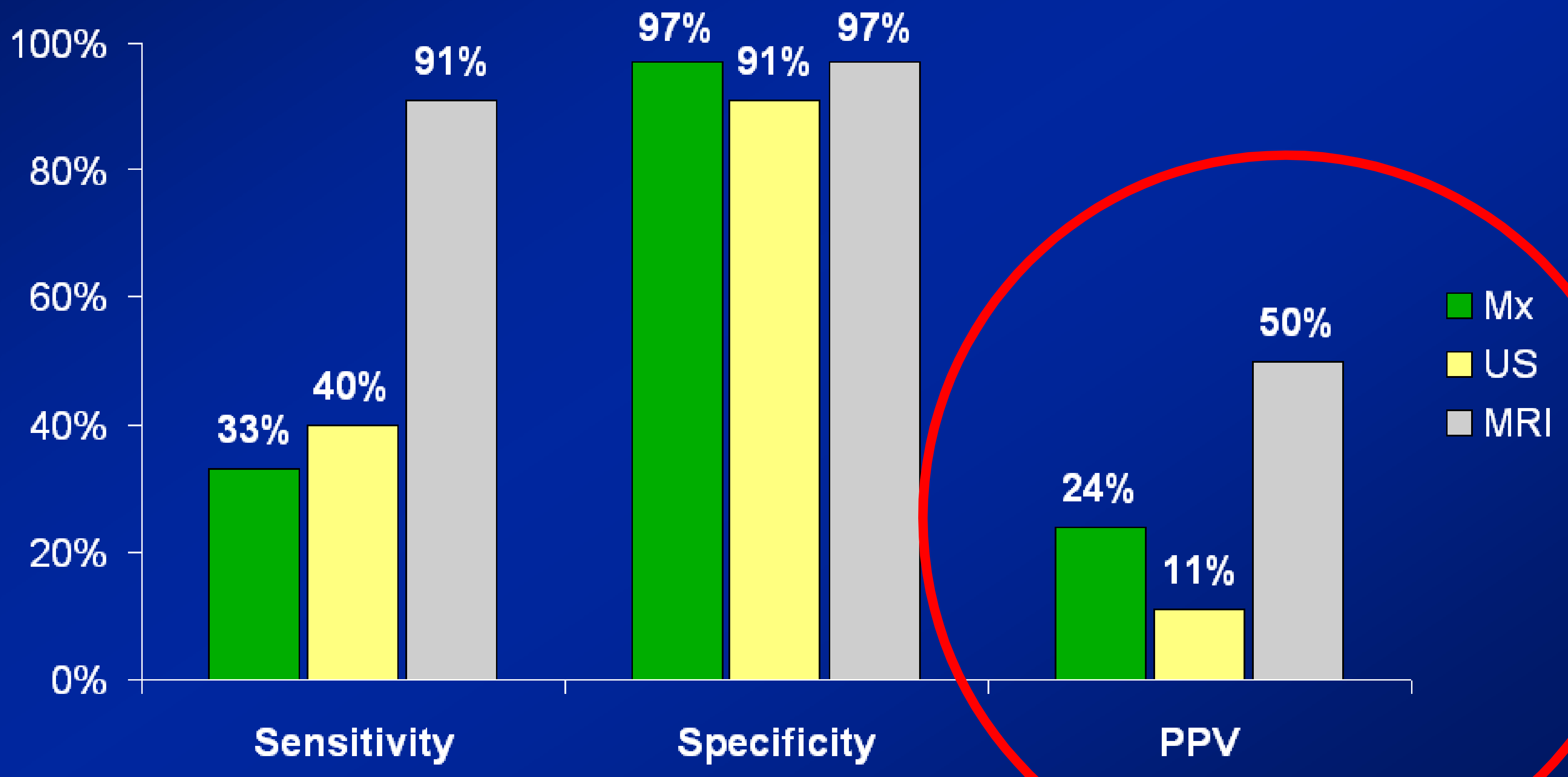
G Rizzatto - EBCC5

US Screening: interventional procedures

Author	Exams	Biopsies	Cancer
Gordon	12,706	279 (2.2)	44 (16)
Buchberger	8,103	362 (4.5)	32 (8.8)
Kaplan	1,862	102 (5.5)	6 (6.6)
Kolb	13,547	358 (2.6)	37 (10)
Crystal	1,517	38 (2.5)	7 (18)
Overall	37,735	1139 (3.0)	126 (11.1)

C Kuhl - EBCC5

Major Prospective Trials for MRI Surveillance of Women at High Genetic Risk



The NEW ENGLAND JOURNAL of MEDICINE

Diagnostic Performance of Digital versus Film Mammography for Breast-Cancer Screening

Etta D. Pisano, M.D., Constantine Gatsonis, Ph.D., Edward Hendrick, Ph.D., Martin Yaffe, Ph.D., Janet K. Baum, M.D., Suddhasatta Acharyya, Ph.D., Emily F. Conant, M.D., Laurie L. Fajardo, M.D., Lawrence Bassett, M.D., Carl D'Orsi, M.D., Roberta Jong, M.D., Murray Rebner, M.D., for the Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group

NEJM October 2005; 353 (17) :1773-1783

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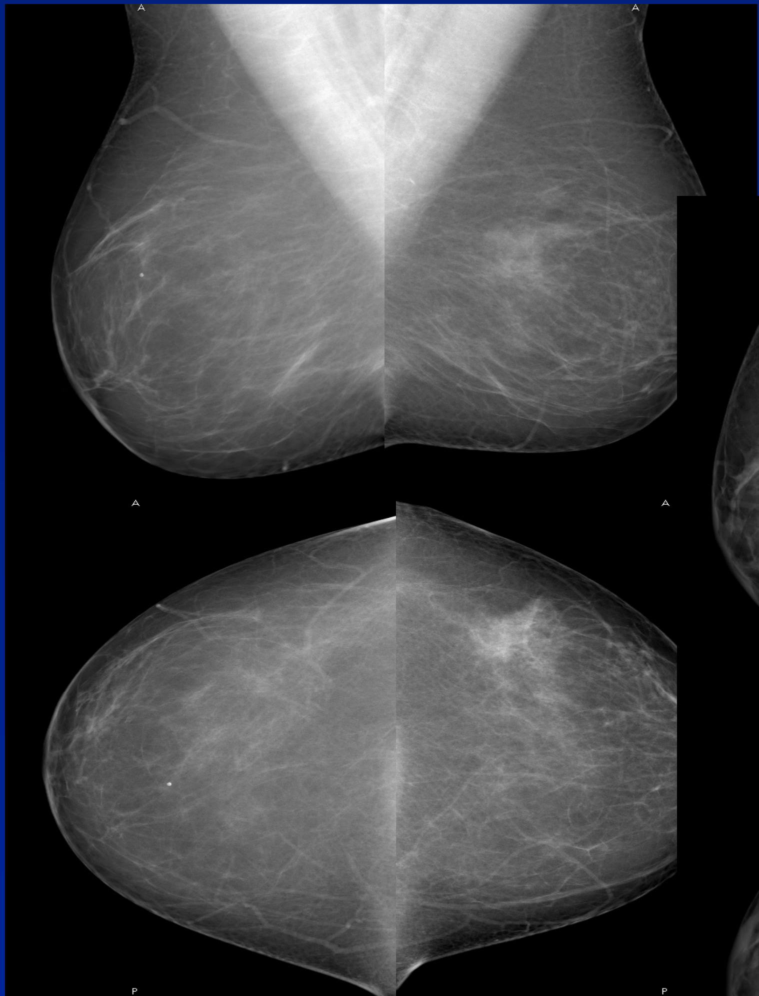
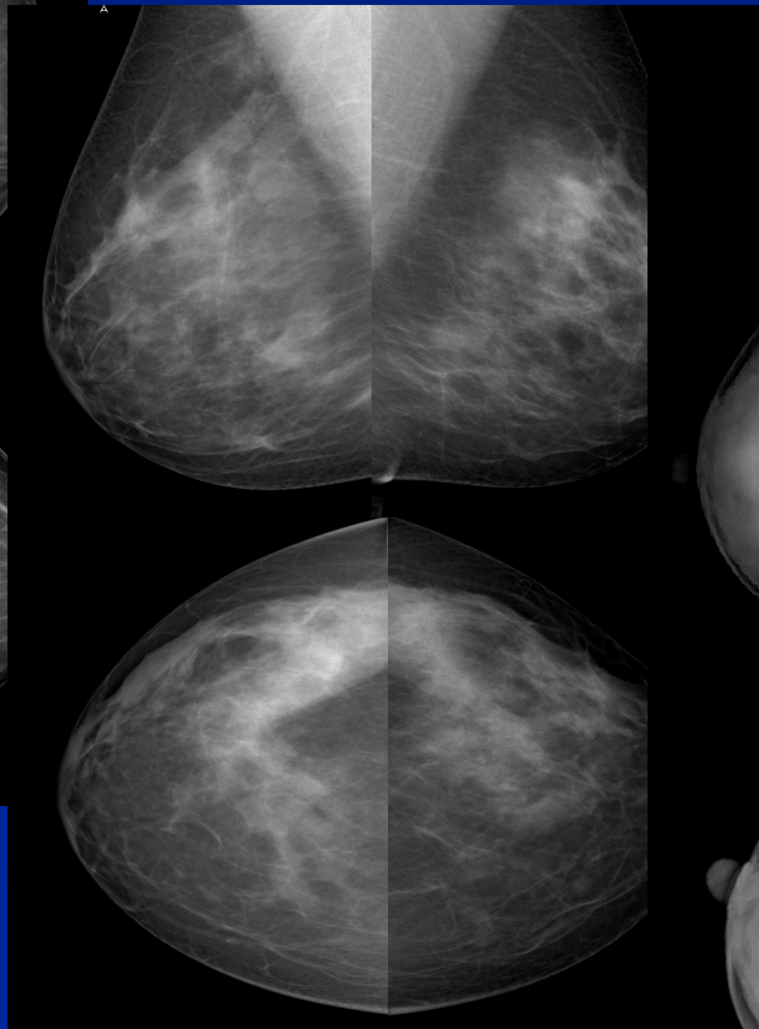
The NEW ENGLAND JOURNAL of MEDICINE

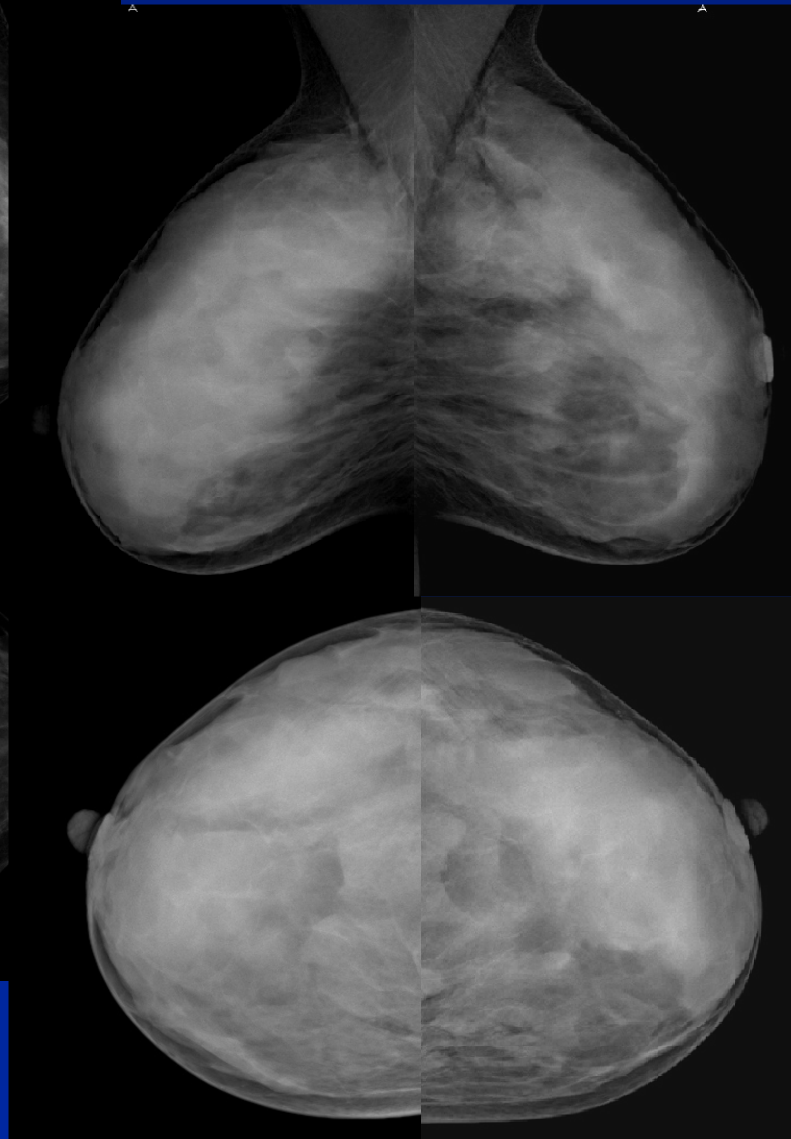
DMIST Study - 49,528 asymptomatic women

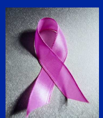
- **FFDM no better than conventional mammography for the non-dense breast (p = 0.18)**
- **FFDM significantly more accurate in women under 50 (p = 0.002)**
- **FFDM more accurate for the heterogenously dense and very dense breast at all ages (p = 0.003)**
- **FFDM more accurate for pre- and perimenopausal women (p = 0.002)**

NEJM October 2005; 353 (17) :1773-1783







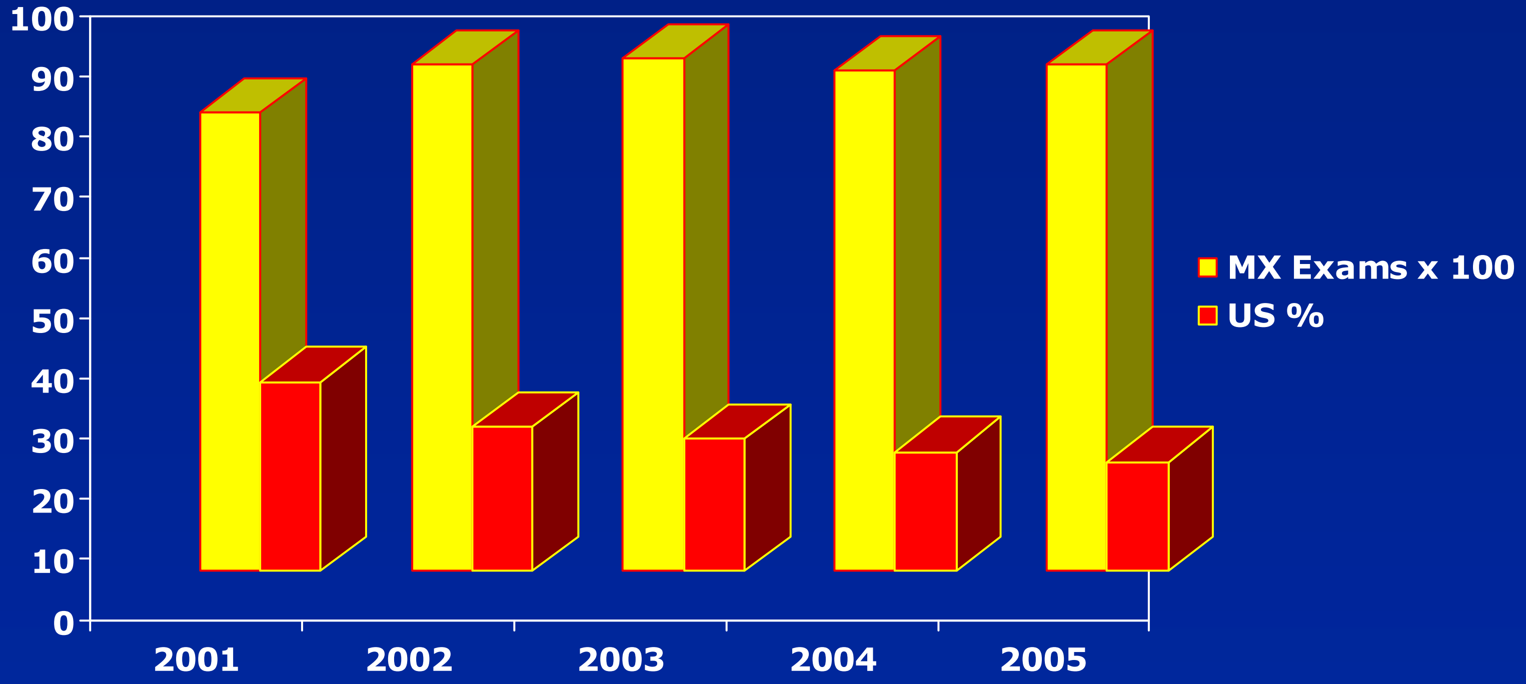


2nd International Congress of Breast Disease Centers 2012

IBDC

G. Rizzatto - EBCC5

Ultrasound screening of the dense breast



42% reduction in 2nd look ultrasound examinations

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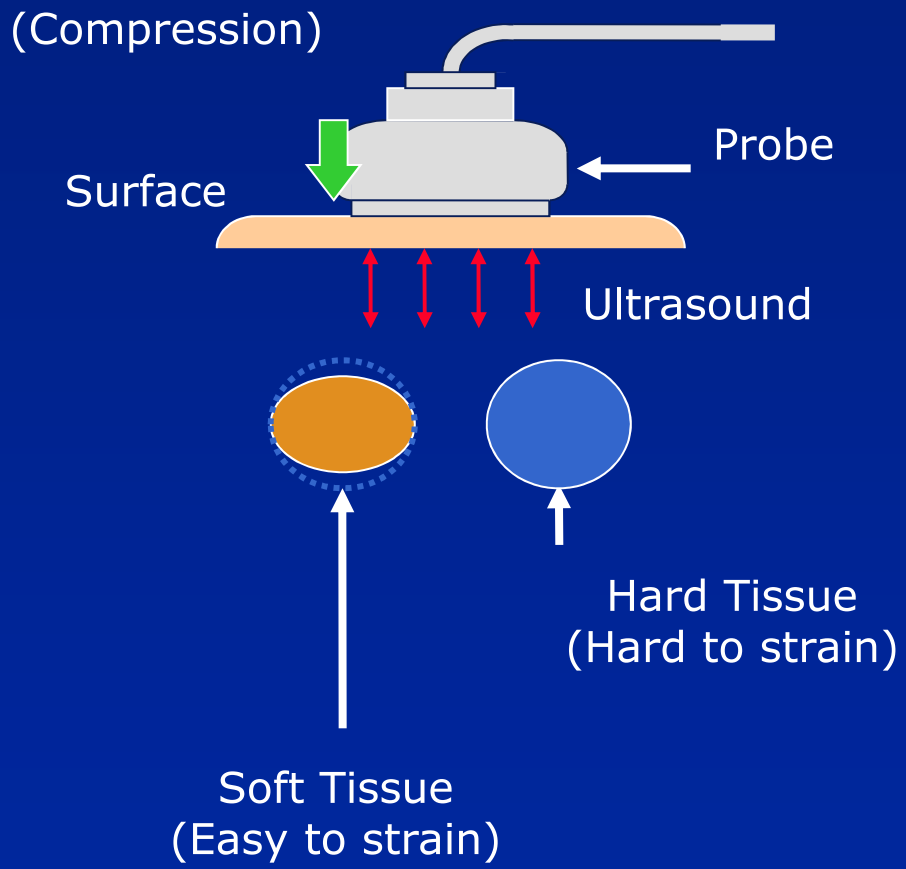
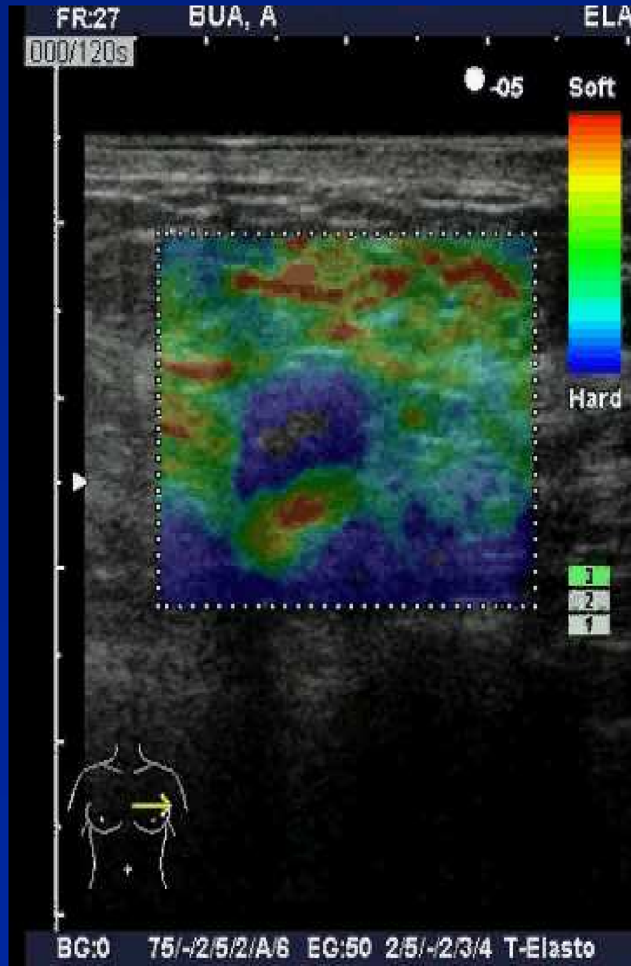
ELASTOGRAPHY





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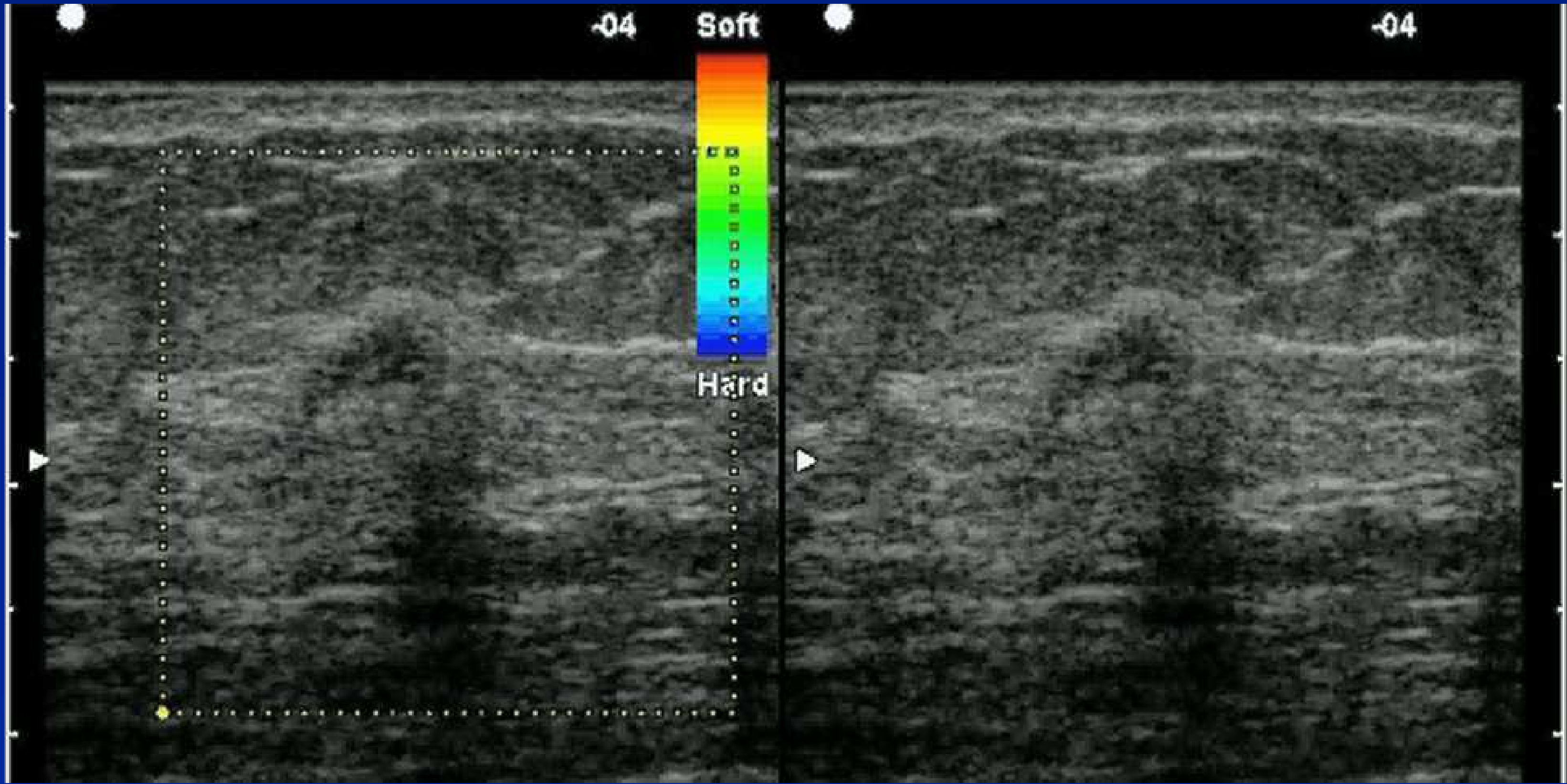

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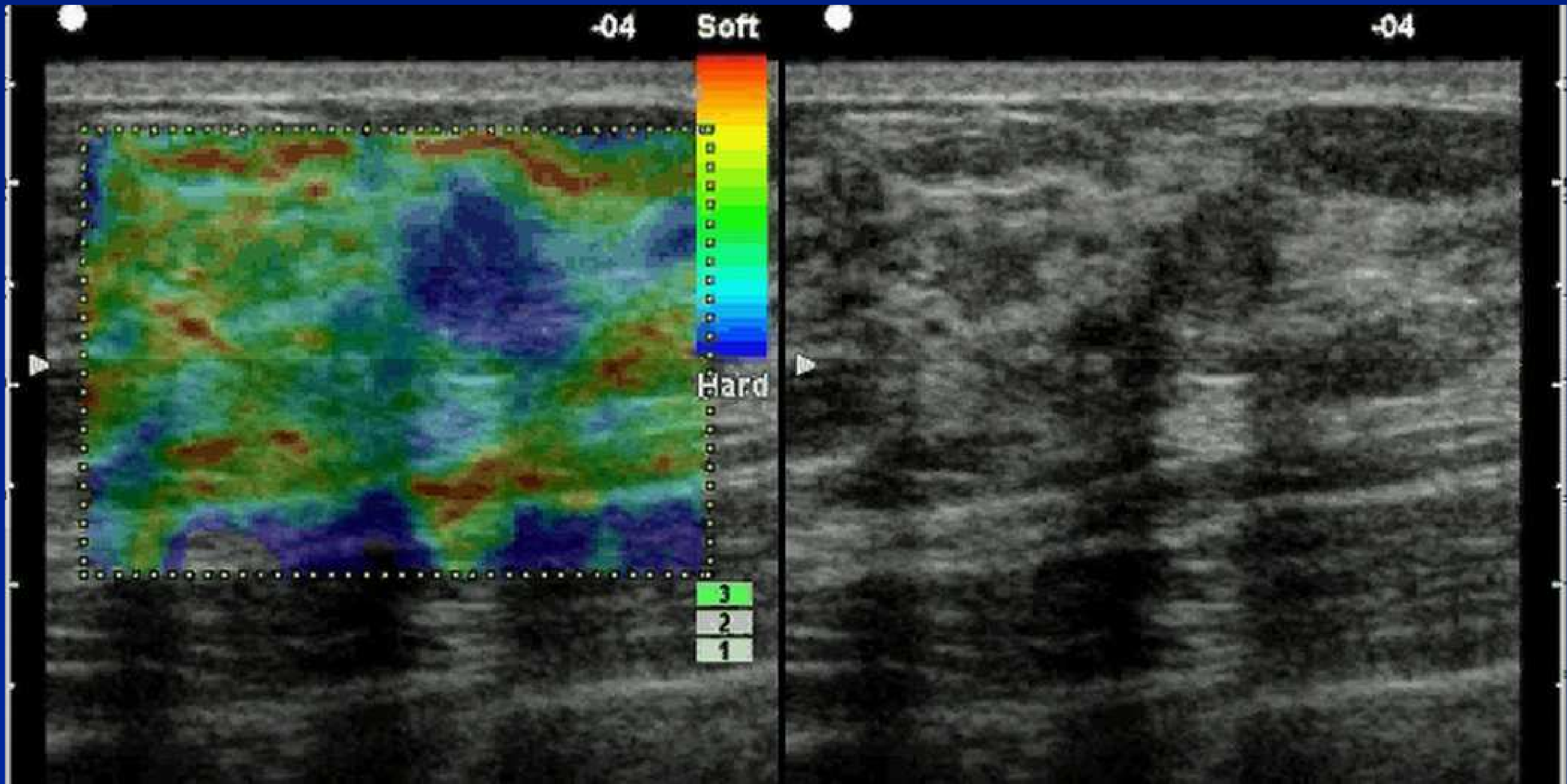
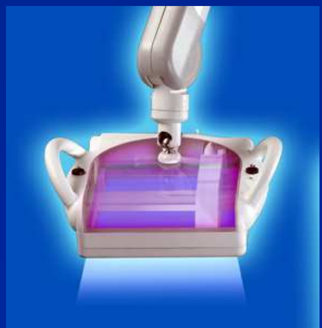
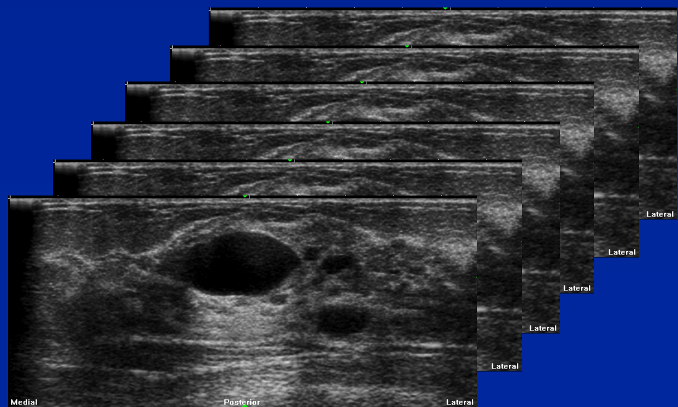


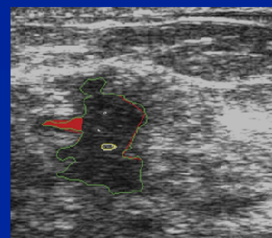
The Royal Marsden

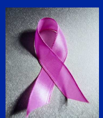


Volumetric Ultrasound Data Set



Self extraction





G.Rizzatto

Screening strategy for the future

- **Mammography supplemented by targeted ultrasound of those with dense breasts**
- **MR for high risk**
- **New ultrasound technology suggests an increasing role for US in screening**

Higher Risk Breast Screening

- Most breast cancer does not occur in those that are at increased risk
- Much of the benefit for screening those at increased risk occurs after the age of 50
- Both MRI and ultrasound may have a role in screening but as yet there is no proven mortality benefit
- Screening younger women does confer greater life years gained