Screening for Breast Cancer

What are the benefits and harms?

Jonathan M. Ross, MD

October 7, 2005

Why discuss this?

- In screening for disease, early diagnosis will lead to improved survival or quality of life.
- The time and energy (and cost) to confirm the diagnosis and provide (lifelong) care are well spent.
- The frequency and severity of the target disorder warrants this degree of effort and expenditure.
  - Breast Ca affects >200,000 women yearly
  - Mortality from Breast Ca >40,000 women yearly

Current beliefs

- Screening for breast cancer saves lives
- Women should be (offered) screened between ages 50-69
  - and perhaps 40-49
  - and perhaps >69
  - and earlier than 40 for those at high risk
- Costs ($) are reasonable
- Harm is minimal (given the horror of Ca)

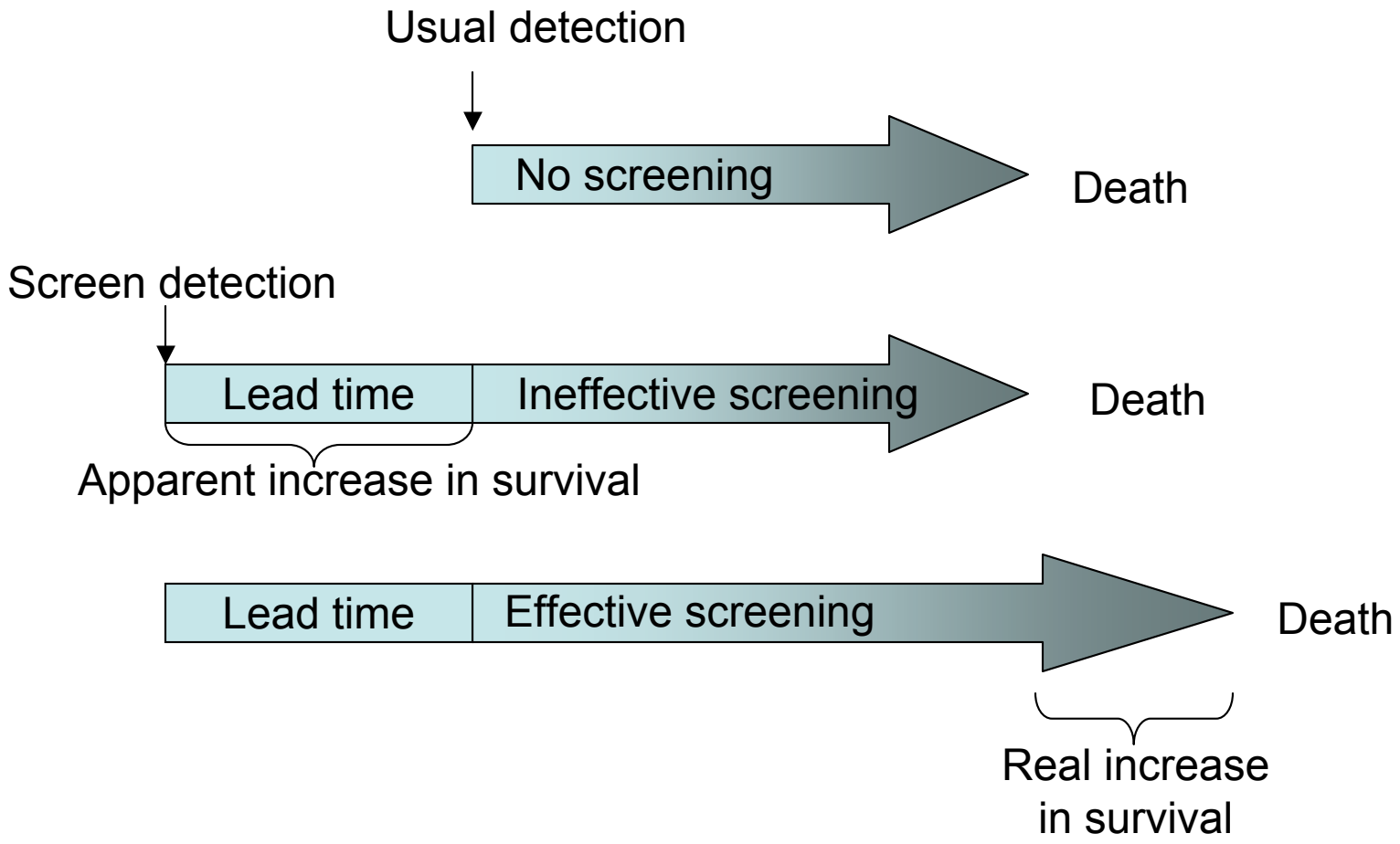
Breast Cancer Screening- Basics

- Screening is not meant for patients with symptoms
- Screening does not reduce the rate of breast cancer- detection is not prevention
- Early detection does not guarantee mortality reduction
- Not all breast cancers progress
- Early detection is not always a benefit

Biases in early detection

- Lead time bias- cancer is detected earlier
- Length time bias- cancer progresses less rapidly
- Overdiagnosis- cancer that is not really cancer

Lead time
(time between screening and usual detection)



Adapted from Straus, et al., Evidence-Based Medicine, 3rd edition, 2005

Breast Cancer Screening-2

- The reduction in mortality from screening all women over age 40 is ~25%
- Over 10 years, 1 out of 1000 women screened will be saved from dying from breast cancer (3 instead of 4/1000)
- NNS/10 years is ~1000
- Women who participate in screening from age 50-69 increase their life expectancy by an average of 12 days
- (Reducing the distance one drives each year by 300 miles is an equivalent mortality reducing strategy) Schmidt 1994

Breast Cancer Screening- 3

- There is little evidence that screening women age 40-50 reduces mortality
- There is no evidence that breast self exam reduces mortality
- Starting at age 50, screening every other year for 20 years reduces risk 27%, with a NNS ~ 270
- There is no difference in mortality with biennial vs annual screening

Breast Cancer Screening- 4 Some harms

- First mammogram: 1/10 positives had breast cancer (9/10 false positives)
- After 10 screenings, 1/3 to 1/2 women will receive at least 1 false positive
- Every year 300,000 women who do not have breast cancer undergo biopsy
- DCIS- estimates are 1-5/10 progress to invasive cancer within 20-30 years
- Early diagnosis can decrease quality of life

Breast Cancer Screening- 5 Costs

- In age group 50-69, screening biennially for 20 years results in costs of $21,000 per year of life saved.
- For every $100 spent on screening, $33 is spent on follow-up of false positive results.
- Radiation linked with dose and age at exposure
  - 2-4/10,000 exposed after age 40 develop cancer and 1 dies

Conveying information to people

- Patient autonomy
- Physician competence
  - Knowledge, methods, beliefs
- Financial implications
  - Government, private payers, uninsured
- Societal resources

But what about numeracy?

- Can physicians and patients appreciate numerical data? In the same way?
- What metrics are best used to convey such data?

Breast Imaging Reporting and Data System Assessment Categories Used in the United States for Mammography Examinations and Associated Likelihood Ratio for Breast Cancer Diagnosis*

Table 1. Breast Imaging Reporting and Data System Assessment Categories Used in the United States for Mammography Examinations and Associated Likelihood Ratio for Breast Cancer Diagnosis*

Assessment Category	Assessment	Definition	Likelihood Ratio for Breast Cancer Diagnosis†
1	Negative	Breasts appear normal	0.1
2	Benign finding	A negative mammogram result, but the interpreter wishes to describe a finding	0.1
3	Probably benign finding; short-interval follow-up suggested	Lesion with a high probability of being benign noted on mammogram	1.2
0	Need additional imaging evaluation	A lesion is noted for which additional imaging evaluation is needed; used almost always in a screening situation	7.0
4	Suspicious abnormality—biopsy should be considered	A lesion is noted for which the radiologist has sufficient concern to recommend a biopsy	125
5	Highly suggestive of malignancy; appropriate action should be taken	A lesion is noted that has a high probability of being cancer	2200

*Categories also include an assessment of 6, used when there is a known diagnosis of breast cancer before the mammogram.[53]
†Likelihood ratios for risk of breast cancer diagnosis at first screening mammography.[54]

Elmore, J. G. et al. JAMA 2005;293:1245-1256.

A moment for the math….

- Pre-test odds x LR = post-test odds

- If pre-test probability is 0.50,

  odds = p/(1-p) or 0.50/0.50 or 1

- If post test odds are 1,

  probability = odds/(1+odds) or 0.50

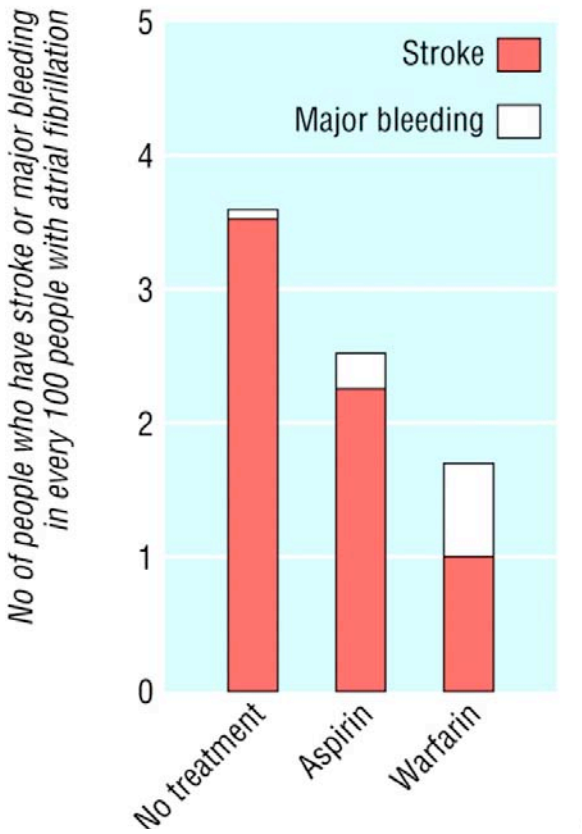
Therefore if pretest probability is 0.50 (0.50) and the LR+ is 10, the post-test probability is 0.91

Relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT)

Group		# Pts	# Events		RR	ARR	NNT
Placebo	1000	1	CER	50%	0.05%	2000	
Treated	1000	0.5	EER				
Placebo	1000	10	CER	50%	0.5%	200	
Treated	1000	5	EER				
Placebo	1000	100	CER	50%	5%	20	
Treated	1000	50	EER				
Placebo	1000	1000	CER	50%	50%	2	
Treated	1000	500	EER				

As the control event rate increases, the NNT decreases- populations with higher rates of events are more likely to benefit from interventions

Fig 2 Different representations of the same benefits of treatment: the reduction after treatment in the number of people who have a stroke or major bleeding looks much larger on the left, where the reference class of 100 patients who have not had a stroke or bleeding is not shown



Mammography efficacy assessment- patients given risk reduction information and asked to calculate risk of dying

1 There is a baseline risk of 12 in 1000 and a 33% reduction due to mammographic screening

2 There is a 33% risk reduction of death from breast cancer

3 There is a baseline risk of 12 in 1000 and a 4 in 1000 reduction with mammography

4 There is a 4 in 1000 risk reduction with mammography

- *Imagine 1000 women just like you…*

A How many will die from breast cancer without mammography?

B How many will die from breast cancer with mammography?

Schwartz, Ann Int Med 1997,127(1):966-72

Table 1

Characteristic	Study Sample (n = 287)
Median age (interquartile range), *y*	68 (48–74)
Highest level of education, %	
Not a high school graduate	4
High school graduate	60
Some college or greater	36
Household income, %	
<$10 000	26
$10 000–24 999	42
≥$25 000	32
White race, %	96
Employment status, %	
Employed	24
Unemployed	6
Homemaker or retired	70
History of breast cancer, %	9
Ever had a mammogram, %	85
Correct answers to numeracy measures, %	
Likely number of heads in 1000 coin flips	54
Convert 1% to 10 in 1000	54
Convert 1 in 1000 to 0.1%	20

* No statistically signficant differences were seen across the four study groups.

Table 1. Characteristics of the Study Sample
From: Schwartz: Ann Intern Med, Volume 127(11).December 1, 1997.966-972

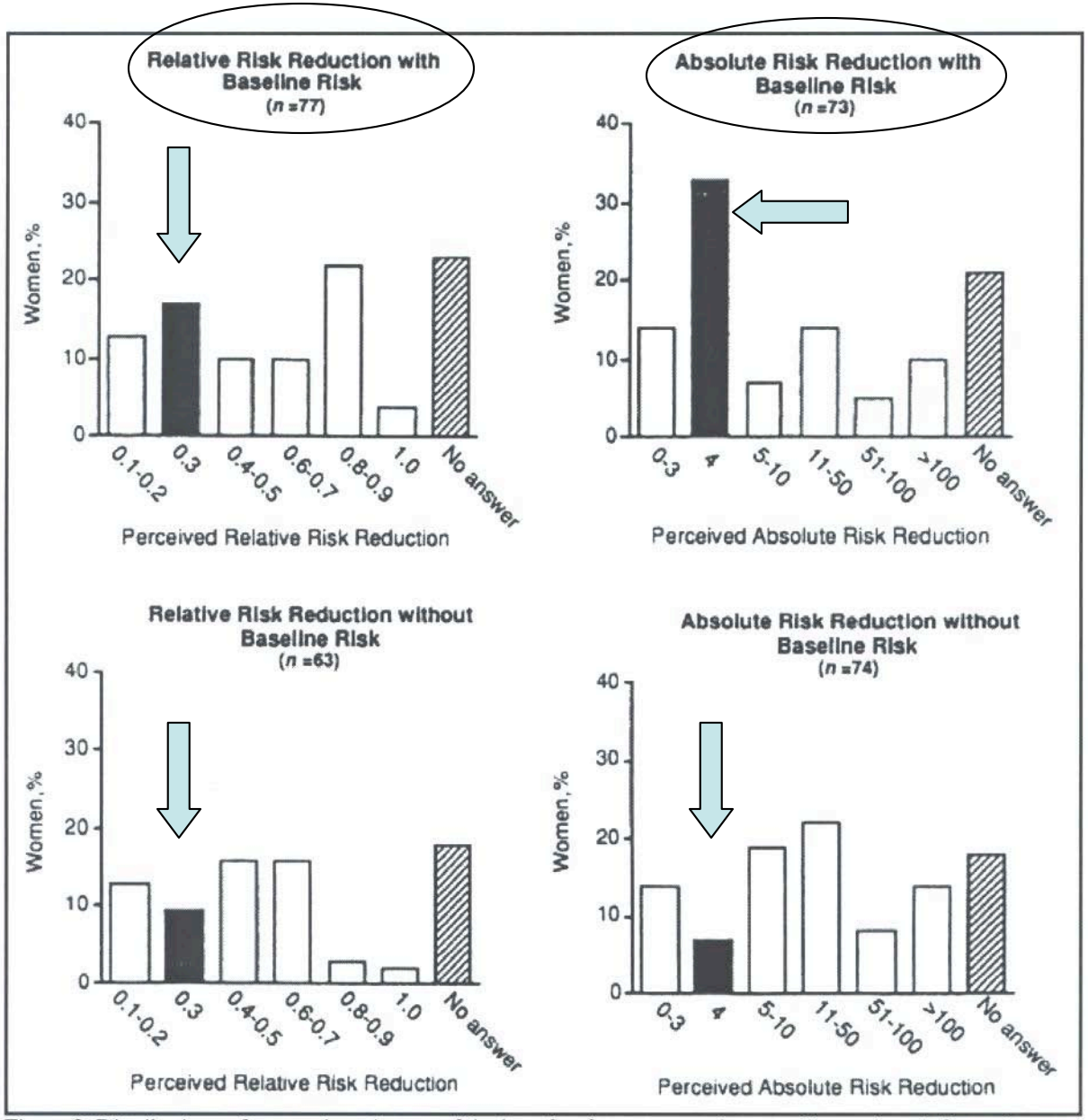


Figure 2. Distributions of women's estimates of the benefit of mammography according to how information on risk reduction was framed. Respondents provided numerical answers (___ out of 1000); these were summarized into ranges for presentation. The black bars represent the actual risk reduction given in the information presented.

Schwartz, Ann Int Med 1997,127(1):966-72

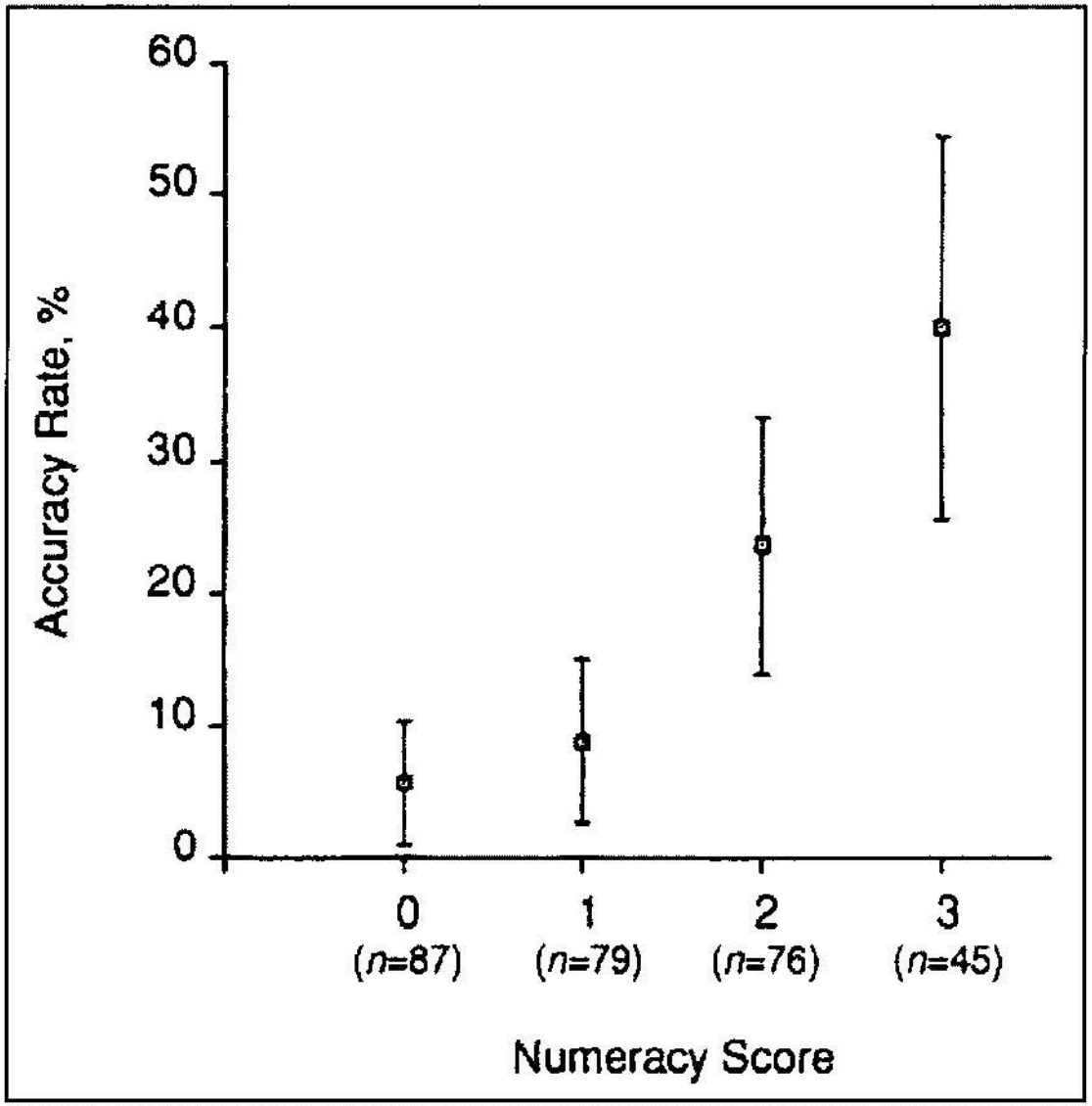


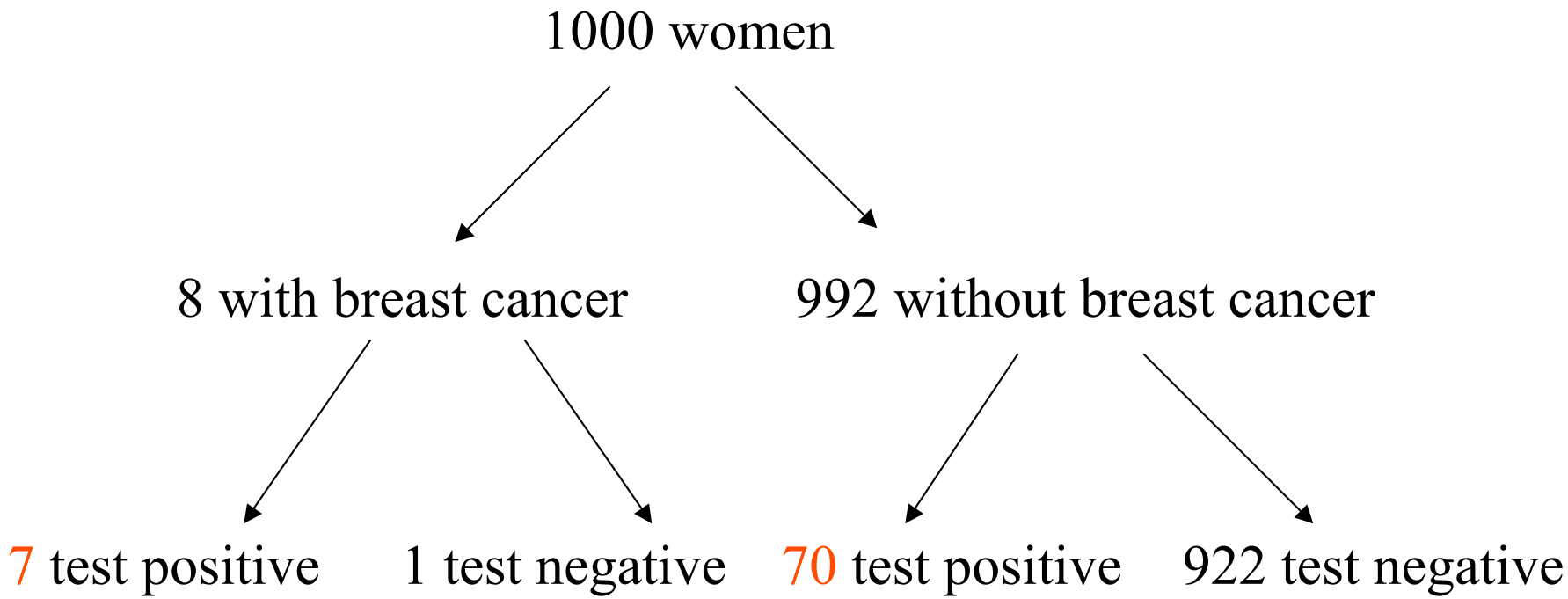
Figure 3. Accuracy rate for each numeracy score. Bars represent 95% CIs; numbers in parentheses are the number of study participants with the given score.

Schwartz, Ann Int Med 1997,127(1):966-72

So, we need to be very clear with the language we use, e.g…..

- Eight out of every 1000 women have breast cancer. Of these 8 women, 7 will have a positive mammogram. Of the remaining 992 women who don't have breast cancer, 70 will still have a positive mammogram. Imagine a sample of women who have positive mammograms in screening. How many of these women actually have breast cancer?

Breast cancer screening



Thus the probability of having cancer when the test is positive is 7/77, or 9.1%

- Anyway, what do the studies show?

Risks (%) of Developing and Dying of Invasive Breast Cancer

Age	Risk of Breast Cancer	Risk of Dying of Breast Cancer
35-95+	13.3	3.0
35-55	2.9	0.40
*50-75	8.0	1.4
65-85	7.3	1.6

Your risk of developing breast cancer over the next 25 years is 8%, or about 80 women out of 1000 will develop breast cancer. Your risk of dying from breast cancer over the next 25 years is 1.4%, or about 14 women in a thousand will die of breast cancer.

SEER data, 2002

Efficacy of Mammography- Women Over 50

Study	**RR**	**ARR**	**NNS**
HIP	.604	.00155	645
S2C	.613	.00087	1,151
Malmo	.680	.00062	1,619
Edinburgh	.810	.00075	1,335
Stockholm	.530	.00082	1,217
Canada	.974	.000052	19,069
Total with Canada	.655	.00089	1,122

Baseline risk of death from breast cancer in this age group is 0.00271.

Based on 301/116,387 deaths in control group - 247/145,711 deaths in screened group = ARR

NNS to prevent one death from breast cancer is 1122.

Women under 50?

- In women 40-49, does annual screening with mammography, clinical breast examination (CBE), and breast self-examination (BSE) instruction reduce breast cancer mortality to a greater extent than a single CBE and BSE instruction?
- Miller, et al. The Canadian National Breast Screening Study. Ann Int Med. 2002;137:305-12 [PubMed ID 12204013]

The Canadian National Breast Screening Study-1: breast cancer mortality after 11-16 years of follow up. A randomized screening trial of mammography in women age 40-49.

- Randomized (allocation concealed), blinded (outcome assessors, controlled trial with mean 13 year follow up.
- 15 centers in Canada
- 50,489 women, no previous dx of breast Ca and had not had mammography in previous year. 99.9% included in analysis.
- All received initial CBE and BSE instruction, allocated to annual screening comprising mammography, CBE and instruction and evaluation on BSE (25,214) or to usual care (25,216)
- Intention to treat
- 105 breast cancer deaths in mammography group, 108 in usual care group.
- The study had 80% power to detect 40% difference after 5 years

Results

Years of f/u	Cumulative breast cancer mortality rates/10,000 persons		Rate Ratio (95% CI)
	Mammography	Usual Care	
2 to 5	2.26	2.12	1.07 (0.75 to 1.52)
6	2.55	2.51	1.01 (0.73 to 1.41)
7	3.04	2.90	1.05 (0.78 to 1.42)
8	3.29	3.15	1.04 (0.78 to 1.40)
=/>9	3.72	3.82	0.97 (0.74 to 1.27)

Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening- a summary of the evidence for the USPSTF. Ann Intern Med. 2002;137:347-60.

Screening with mammography vs usual care to prevent breast cancer mortality at mean 14-year follow-up

Age groups	Number of trials	RRR (95% CrI)	NNS (CrI)
All ages (39 to 74 y)	7	16% (9 to 23)	1224 (665 to 2564)
< 50 y	7	15% (1 to 27)	1792 (674 to 10 540)
≥ 50 y	7	22% (13 to 30)	838 (494 to 1676)

8 RCTs (479,987 women) (154 publications) met the selection criteria:
4 evaluated mammography, and 4 evaluated mammography plus CBE.
7 trials were rated fair quality, and 1 was rated poor quality.
The mean follow-up period was 14 years.

Calculating risk

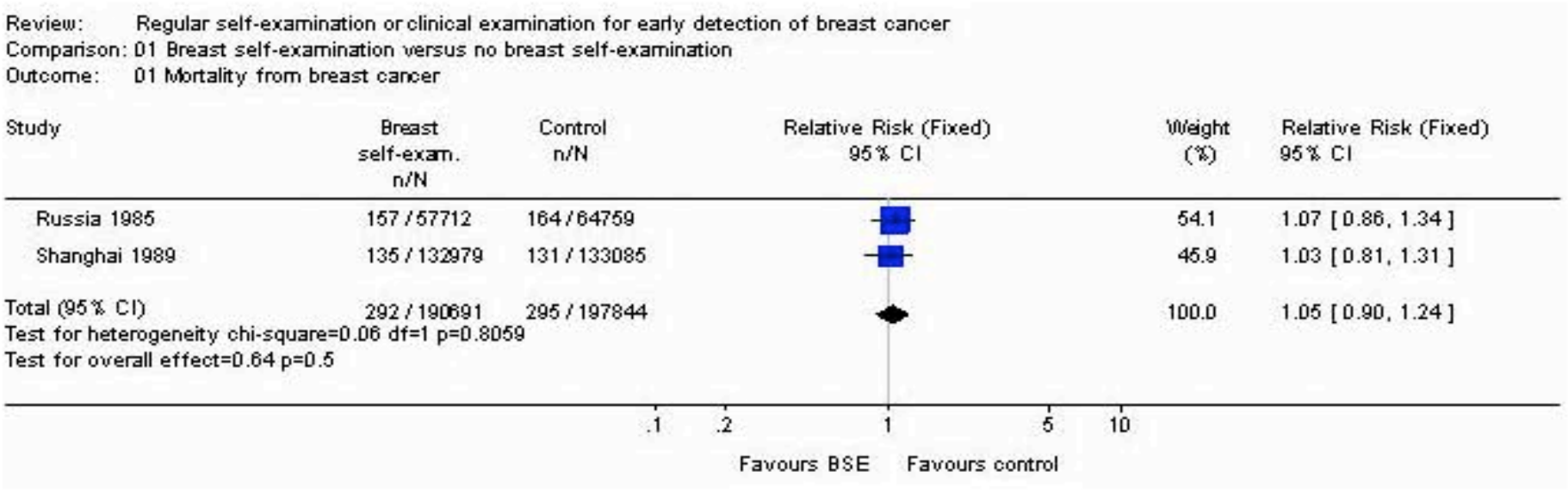
- Breast Cancer
  - http://bcra.nci.nih.gov/brc/start.htm
- Multiple conditions
  - http://www.yourdiseaserisk.harvard.edu/

Breast self-examination

- Main results: Two large population-based studies (388,535 women) from Russia and Shanghai that compared breast self-examination with no intervention. There was no statistically significant difference in breast cancer mortality: relative risk 1.05 (95% confidence interval (CI) 0.90 to 1.24) (587 deaths in total). In Russia, more cancers were found in the breast self-examination group than in the control group (relative risk 1.24, 95% CI 1.09 to 1.41), while this was not the case in Shanghai (relative risk 0.97, 95% CI 0.88 to 1.06). Almost twice as many biopsies (3406) with benign results were performed in the screening group compared to the control group (1856), relative risk 1.88, 95% CI 1.77 to 1.99.

Regular self-examination or clinical examination for early detection of breast cancer
[Review] Cochrane Database of Systematic Reviews (3), 2005
Kosters, JP; Gotzsche, PC
Date of Most Recent Update: 16-November-2004
Date of Most Recent Substantive Update: 01-February-2003

Mortality from Breast Cancer and Breast Self Examination

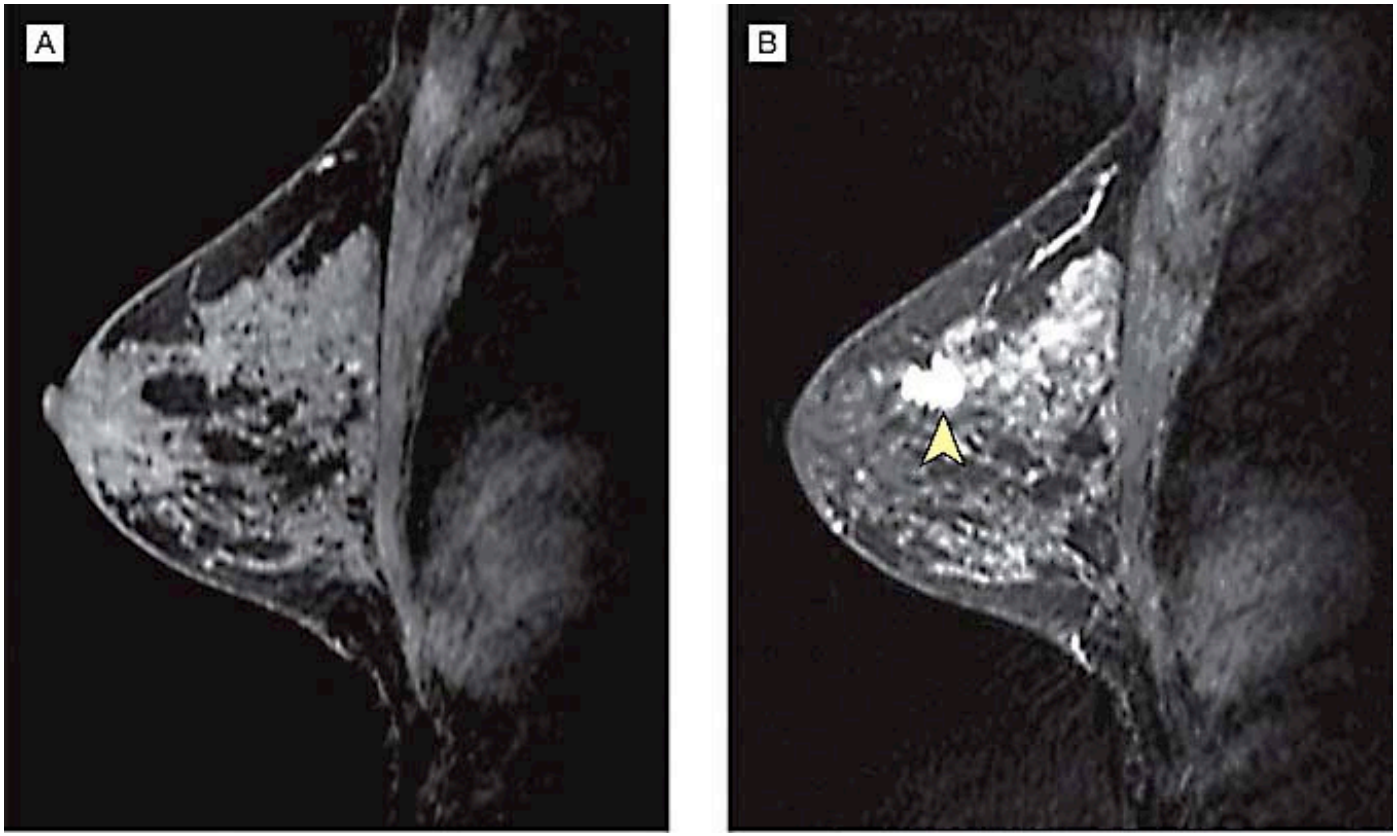


Is MRI more sensitive than standard mammography for detecting breast cancer in high risk women?

Test	Sensitivity (95% CI)	Specificity	+LR	LR
Mammography	40% (33 to 49)	95%	8.0	0.63
MRI	71% (65 to 73)	90%	7.1	0.32

EBM Reviews - ACP Journal Club **Magnetic resonance imaging was more sensitive than mammography for detecting breast cancer in high-risk women** [Diagnosis] *ACP Journal Club. v142(1):23, January/February, 2005.*

Magnetic Resonance Imaging Examination of the Breast



Elmore, J. G. et al. JAMA 2005;293:1245-1256.

Model of outcomes of screening mammography: information to support informed choices BMJ.330:936-938,4/23/2005

- Assumptions
  - RRR benefit due to screening
    - 37% for women age 50-79
    - 23% for women age 40-49
  - Benefit accrues linearly to maximal level over first 5 years screening. Benefits decline linearly after stopping screening.
  - Mortality from causes other than breast Ca are equal among screened and unscreened
  - Screening is biennial (q 2 years)

Screen q2y x 10 y, start age 40

Results are # out of 1000 women over 10 years

	Screen	vs No screen
Recall for more tests	251	
Bx	60	
Total invasive Ca	17.6	13.2
DCIS	3.4	0.3
Total breast Ca	21	13.5
Die breast Ca	2.0	2.5
Die other causes	10.8	10.8
Total who die	12.8	13.3

Screen q2y x 10 y, start age 50

Results are # out of 1000 women over 10 years

	Screen	vs No screen
Recall for more tests	242	
Bx	64	
Total invasive Ca	28.1	19.8
DCIS	4.9	0.4
Total breast Ca	32.9	20.2
Die breast Ca	4	5.9
Die other causes	25.3	25.2
Total who die	29.3	31.1

Screen q2y x 10 y, continue at age 60

Results are # out of 1000 women over 10 years

	Screen	vs No screen
Recall for more tests	185	
Bx	56	
Total invasive Ca	32.5	23.9
DCIS	5.5	0.5
Total breast Ca	38	24.4
Die breast Ca	5.1	8.1
Die other causes	68.5	68.4
Total who die	73.6	76.5

Screen q2y x 10 y, continue age 70

Results are # out of 1000 women over 10 years

	Screen	vs No screen
Recall for more tests	167	
Bx	56	
Total invasive Ca	35.1	25.1
DCIS	5.7	0.5
Total breast Ca	40.8	25.6
Die breast Ca	6.2	8.4
Die other causes	199.5	199.3
Total who die	205.7	207.8

Screen v No screen q 2 yrs
(number out of 1000 over 10 years)

Event	Age 40	Age 40	Age 50	Age 50	Age 60	Age 60	Age 70	Age 70
Screen	**+**	**-**	**+**	**-**	**+**	**-**	**+**	**-**
Recall	**251**		**242**		**185**		**167**	
Bx	**60**		**64**		**56**		**56**	
Invasive Ca	**18**	**13**	**28**	**20**	**33**	**24**	**35**	**25**
DCIS	**3.4**	**0.3**	**5**	**0.4**	**5.5**	**0.5**	**5.7**	**0.5**
Death Breast Ca	**2**	**2.5**	**4**	**6**	**5**	**8**	**6**	**8.4**
Any Death	**12.8**	**13.3**	**29.3**	**31.1**	**73.6**	**76.5**	**206**	**208**
“Benefit”	**-0.5**		**-1.8**		**-2.9**		**-2.1**	

Is screening for breast cancer with mammograpy justifiable?

Gotzsche and Olsen. Lancet. 355:129-134, 2000

Study	Screen	Control	Death Screen	Death Control	Relative Risk (95%CI)
Malmo	21,088	21,195	63	66	0.96(068-1.35)
Canada	44,925	44,910	120	111	1.08(0.84-1.40)
Total	66,013	66,105	183	177	1.04(0.84-1.27)
Goteborg	11,724	14,217	18	40	0.55(0.31-0.95)
Stockholm	40,318	19,943	66	45	0.73(0.50-1.06)
Kopparberg	38,589	18,582	126	104	0.58(0.45-0.76)
Ostergotland	38,491	37,403	135	173	0.76(0.61-0.95)
New York	30,131	30,565	153	196	0.79(0.64-0.98)
Edinburgh	22,926	21,342	156	167	0.87(0.70-1.08)
Total	182,179	142,052	654	725	0.75(0.67-0.83)

Randomization adequate

Randomization not adequate

Is screening for breast cancer with mammograpy justifiable? Goetsche and Olsen. Lancet. 355:129-134, 2000

- **We conclude that screening for breast cancer with mammography is unjustified.**

- **On the one hand, those who believe that the Swedish trials are unbiased have to accept from the data that screening for breast cancer with mammography causes more deaths than it saves. The total mortality in the five Swedish trials was 10%, the relative risk of death was 1·06, and the Swedish meta-analysis showed a difference in breast-cancer mortality of 0·1% after 12 years of followup. The data therefore show that for every 1000 women screened throughout 12 years, one breast-cancer death is avoided but the total number of deaths is increased by six.**

- **On the other hand, those who believe the Swedish trials (apart from the Malmö trial) are biased have to accept that there is no reliable evidence that screening decreases breast-cancer mortality.**

Conclusions

- Screening for breast cancer is widely recommended
- Screening with clinical breast examination is recommended by some (American Cancer Society) and not by others (USPSTF).
- Screening with mammography has many advocates, but some have expressed reservations
- It is likely that screening will continue, will be imperfect, will introduce individual benefits and harms
- Physician and patient facility with numeracy remains problematic
- Newer imaging modalities are being studied
- Targeting individuals for screening is not yet feasible