

Serendipity in Diagnostic Imaging: Magnetic Resonance Imaging of the Breast

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Background

- Breast Cancer large burden of disease in U.S.
 - 175,000 new cases in 1999
 - 43,300 deaths, second leading cause of cancer death in women
 - 13% of women will be diagnosed with breast CA

Screening

- Screening for breast CA
 - Mammography & Clinical Breast Examination (CBE)
 - Reduce breast cancer mortality in women age 50-69 years by 25-30%
 - Mammography is moderately sensitive (~83-95%) and highly specific (~94-99%)
 - Low prevalence in screening population => Low positive predictive value

Evaluation of Abnormal Tests

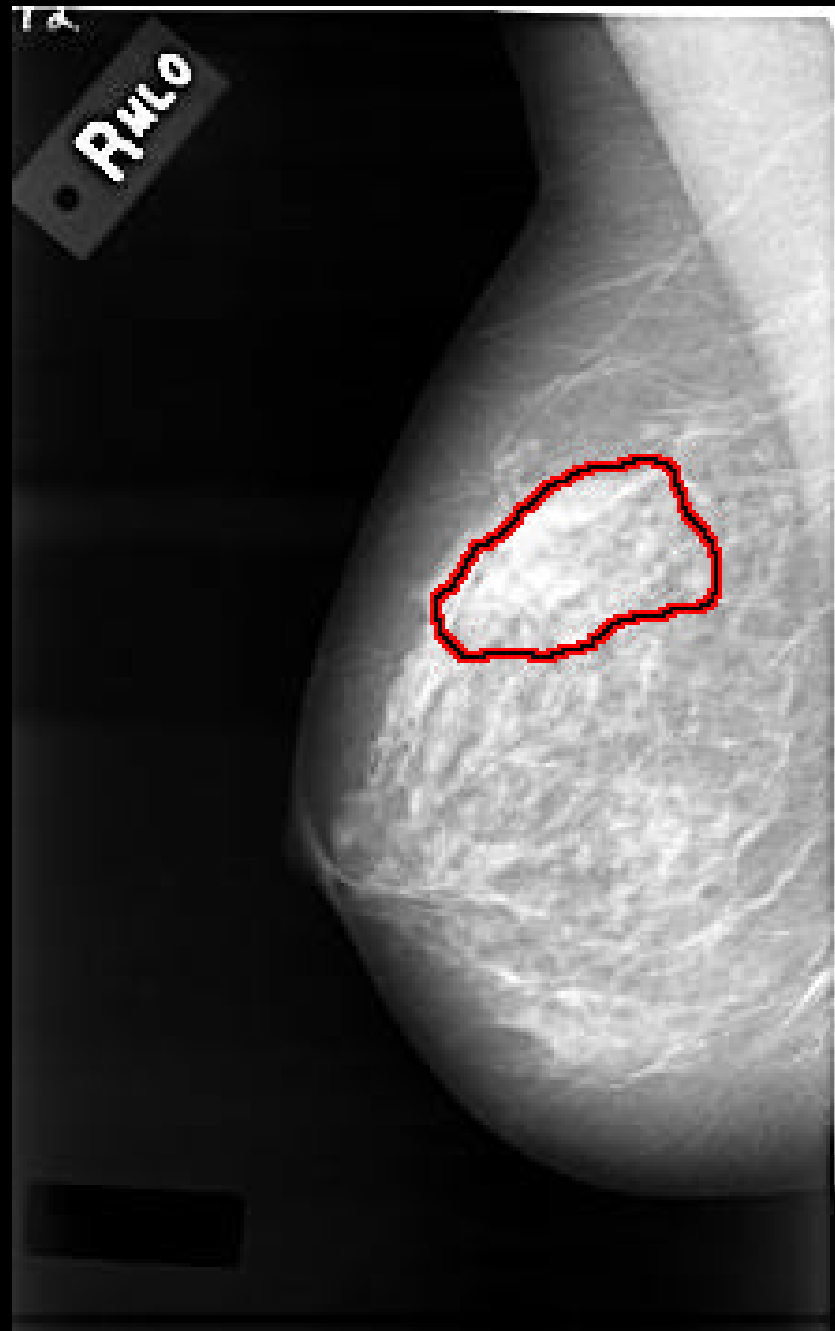
- Evaluation of an abnormal mammogram or CBE usually is biopsy - invasive
- 600,000 biopsies performed annually
- As many as 85% of biopsies yield benign findings
- Can anything non-invasive be done to decrease the chance of biopsy of benign disease without missing cancers?

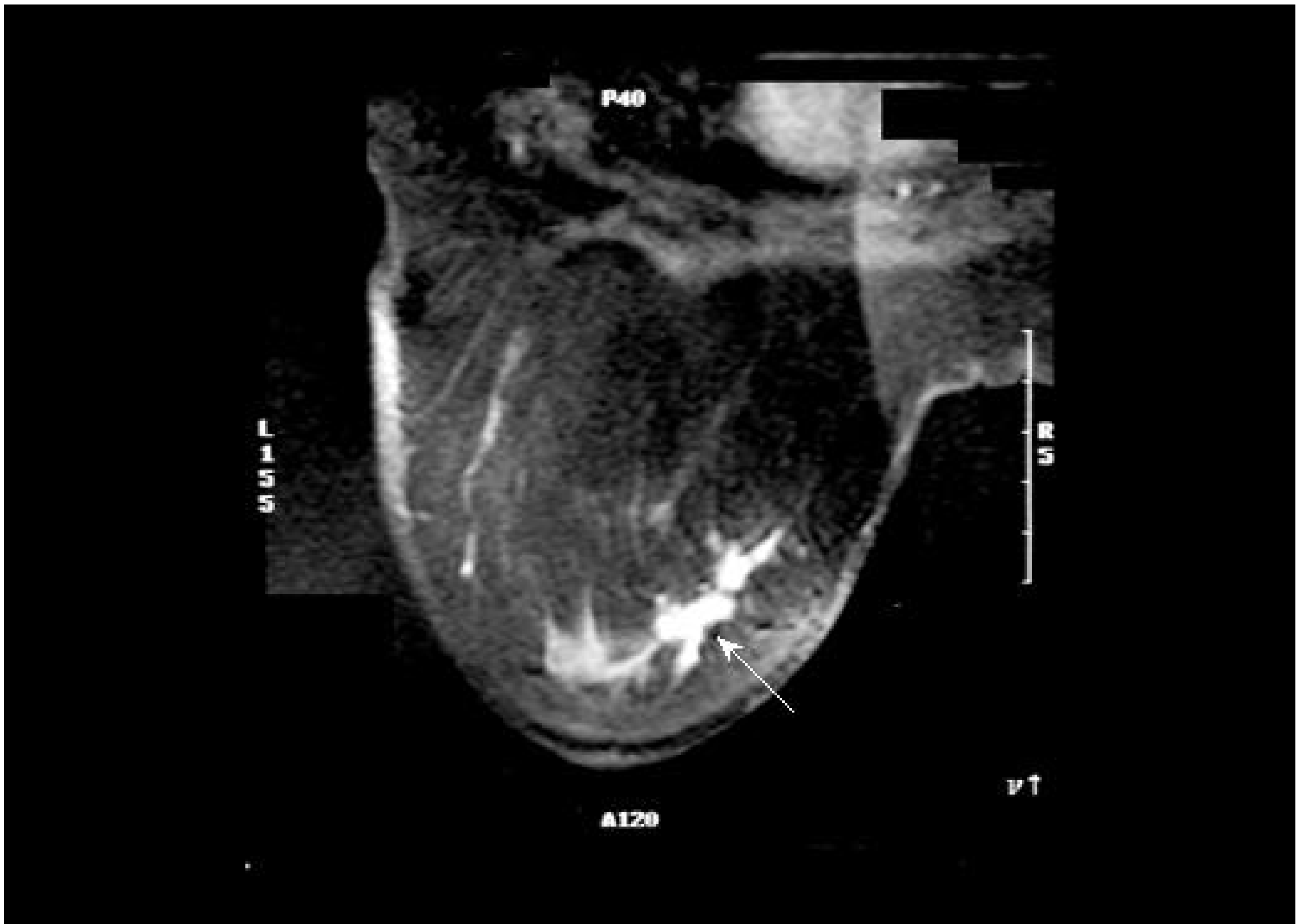
Intermediate Diagnostic Evaluation

- Use a diagnostic test to confirm suspicion of cancer in women with an abnormal mammogram or CBE
 - Analysis stems from study of testing (M Freedman, PI)
- Test should be highly sensitive and specific
- Several tests proposed, focus on Magnetic Resonance Imaging (MRI) of the breast

Breast MRI

- Studies suggest quite sensitive, but may lack specificity (higher false positive rate)
- The problem: The MRI occasionally shows MORE lesions than the woman is referred for evaluation of
- What do we do with these “serendipitous” lesions?





Purpose

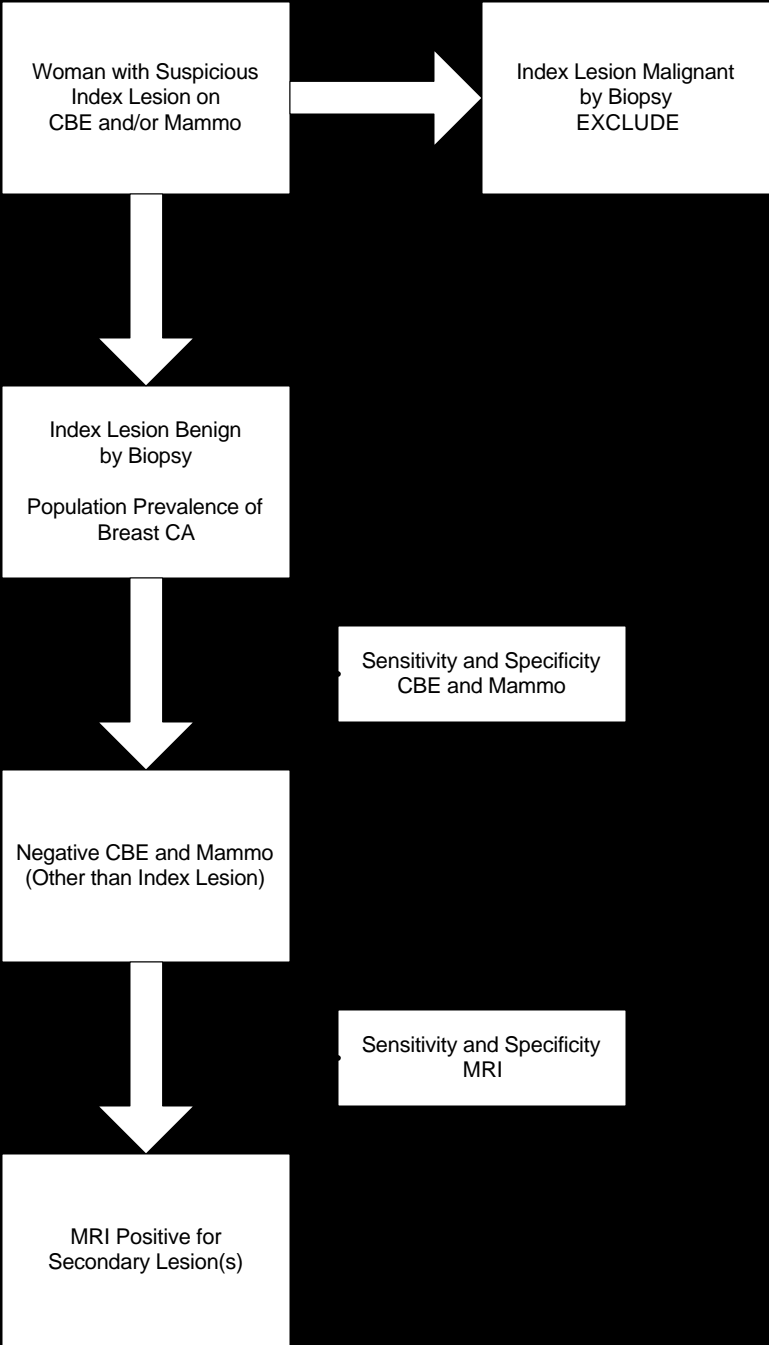
- To calculate the probability that a serendipitous lesion found on breast MRI is malignant given that the index lesion is found to be benign

Terms

- Index Lesion - Abnormality found on Mammogram and/or CBE for which woman is undergoing diagnostic testing
- Serendipitous lesion - Abnormality found on MRI in area where Mammogram and CBE are normal

Methods

- Decision model to calculate the revised probability of cancer in a serendipitous lesion in cases where the index lesion is benign
- Monte Carlo Stochastic simulation to determine positive predictive value for women by age and race, with confidence intervals on the estimates



Assumptions

- Not applicable if index lesion biopsy proven malignancy
- If index lesion is benign, then probability of cancer = U.S. population average for age and race
- Conditional independence of MRI and Mammography/CBE

Odds Form of Bayes' Theorem

$$\text{Posttest Odds (CA|Test+)} = \text{Pretest Odds(CA)} \times \text{LR}_{\text{test}^+}$$

Where:

$$\text{Odds} = \frac{P}{1-P} \quad \text{and} \quad \text{LR}_+ = \frac{\text{Sens.}}{1 - \text{Spec.}}$$

Positive Predictive Value of MRI

Post-test Odds =

$$\text{Pre-Test Odds} \times \text{LR}_{\text{MAM,CBE}^-} \times \text{LR}_{\text{MRI}^+}$$

Breast Cancer Prevalence

- Incidence rates will underestimate breast cancer prevalence - not all breast cancer detected in year of onset
- Use simulation model (Chang, et al., 1992) to estimate prevalence of cancer by age and race based upon cancer incidence
- Incidence by age and race from SEER registry

Likelihood Ratio for MRI

- Meta-analysis of published literature on sensitivity and specificity of MRI
- Inclusion criteria
 - Article in English
 - Sample size > 10
 - Data available on MRI results and breast cancer
 - Sample: women at risk for breast cancer
 - MRI readers blinded to diagnosis

Meta-Analyses

- Independent estimation of sensitivity and specificity may underestimate true accuracy
- Summary Receiver-Operating Characteristic (ROC) curve (*Littenberg and Moses. Med Decis Making. 1993;13:313*)
- Likelihood ratio analogue of Mantel-Haenszel estimator - provides operating point for analysis
- Confidence interval using jack-knife estimation

Likelihood Ratio Estimator

$$LR_{MRI^+} = \frac{\sum_{i=1}^{12} \frac{TP_i}{TP_i + FN_i}}{\sum_{i=1}^{12} \left[1 - \frac{TN_i}{TN_i + FP_i} \right]},$$

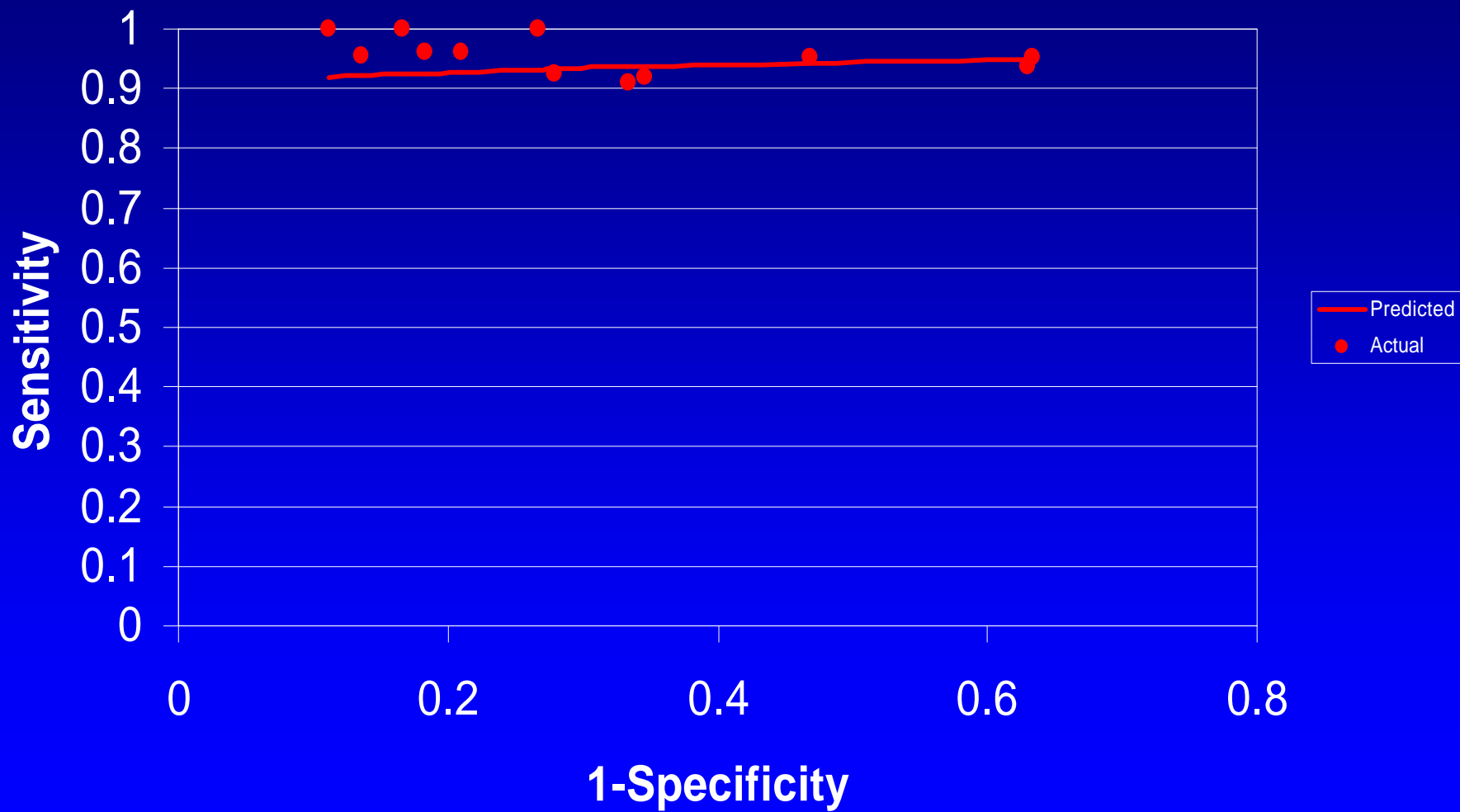
Mammo/CBE Likelihood Ratio

- Estimate joint likelihood ratio negative for Mammography/CBE
- 4 Randomized trials employing CBE + 2-view Mammography
- Detection method of sensitivity
- Meta-analysis on likelihood ratio

Results - MRI

- 360 MEDLINE entries identified - 12 studies eligible
- Sensitivity 91-100%, average 95.6%
- Specificity 37-89%, average 68.6%
- LR+: 3.05 (95% CI 2.0-4.1)
- In comparison, LR+ of mammography estimated at 69

MRI Summary ROC Curve



Results - Mammo/CBE

- 4 Randomized trials eligible
- Sensitivity 74 - 88%, average 82.2%
- Specificity 98.1 - 99.6%, average 95.6%
- LR-: 0.18 (95% CI 0.12-0.24)

Probability of Cancer

- Prevalence of cancer approx. 3 X incidence
 - 35 y.o.: 0.24%
 - 80 y.o.: 1.67%

- But for baseline analysis:

$$\text{Product of } LR_{\text{MAMCBE}^-} \times LR_{\text{MRI}^+} = 0.55$$

- Since product < 1 , Posterior probability is less than starting probability!

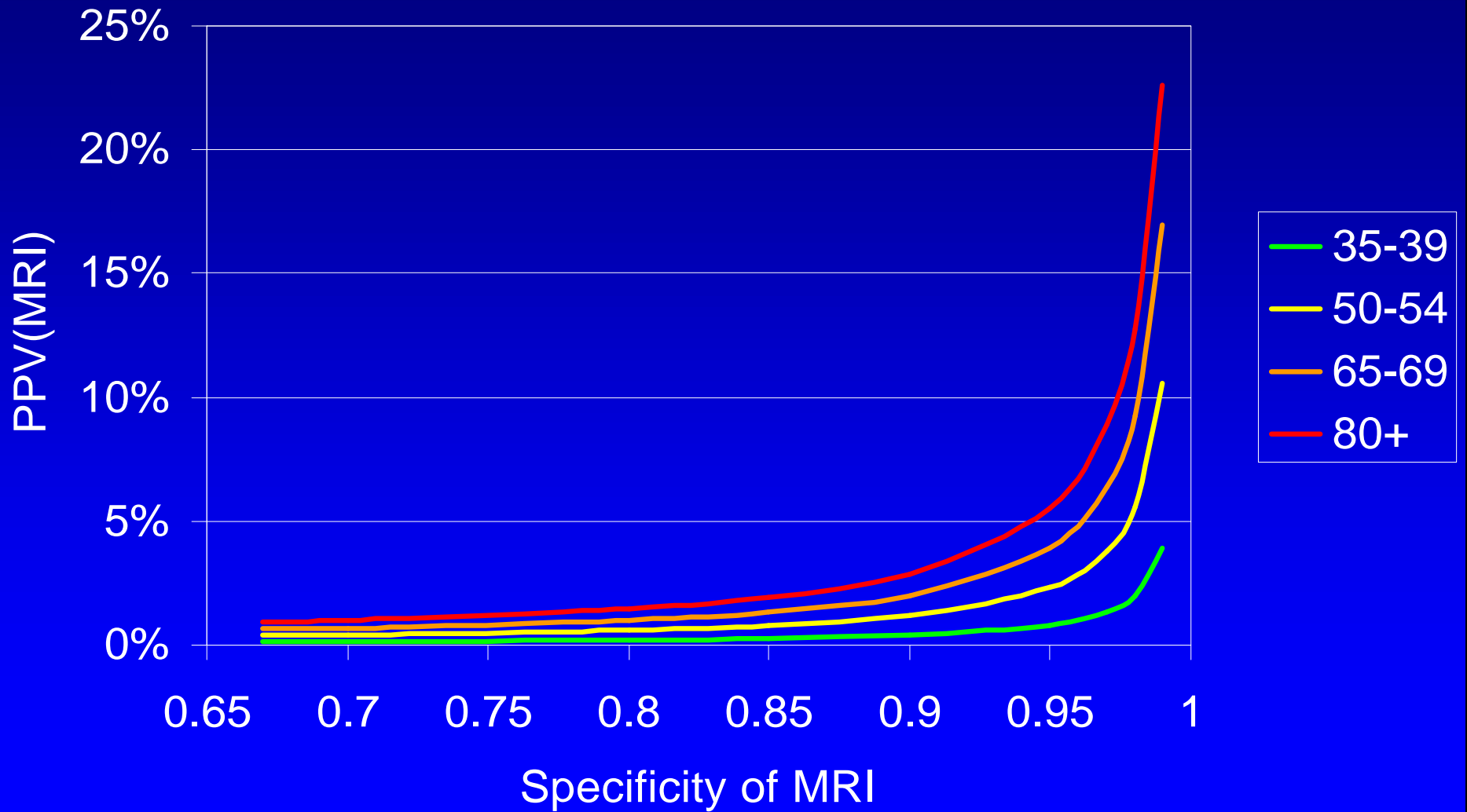
Probability of Cancer - Serendipitous Lesions

Age	Prevalence (Total Pop.)	Prob. Of Cancer
50-54	0.68%	0.38% (0.21-0.58)
65-69	0.98%	0.65% (0.34-0.99)
80+	1.67%	0.93% (0.51-1.4)

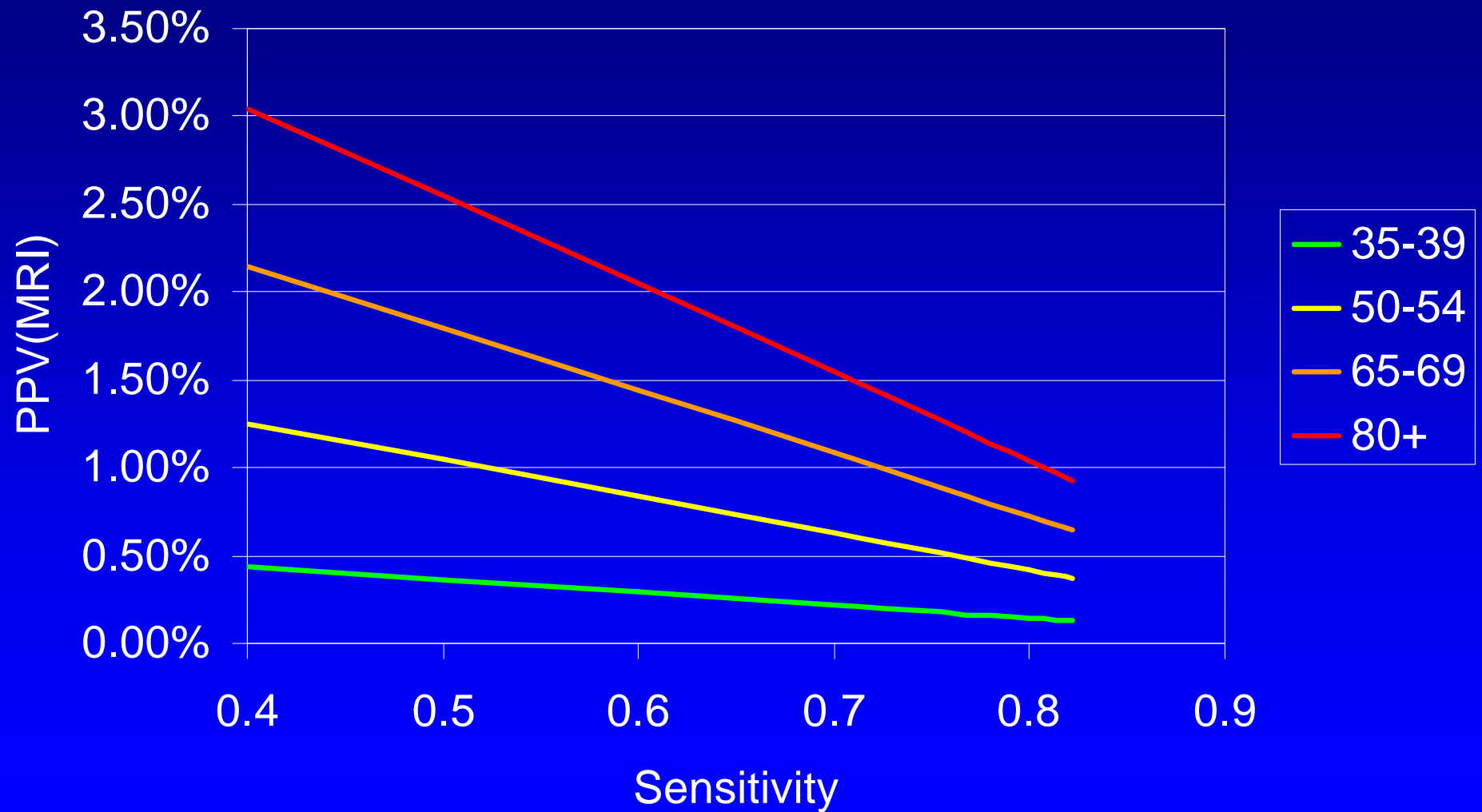
Sensitivity Analysis - High Risk Women

- What happens if the woman is at “high risk” for cancer? E.g. 1st degree relative with CA
- RR (breast cancer) ~ 2
- P(CA) = 0.29% (35 y.o.) - 1.9% (80+)
- Does NOT include women with BRCA1/2 susceptibility mutations

Specificity of MRI



Sensitivity of Mammography



Limitations

- Based upon MRI sens and spec for index lesions, not serendipitous lesions
- Person-level instead of lesion-level analysis, could impact on women with multiple serendipitous lesions
- Do not include DCIS
- What is the optimal threshold PPV for which biopsy should be performed?

Conclusions

- Probability of breast cancer in a serendipitous lesion, if the index lesion is benign, is extremely low...
- ...Enough lower than the 15-35% probability of finding cancer at biopsy that immediate biopsy is unlikely to be beneficial
- Future MRI research: Increasing specificity while maintaining sensitivity

Where to from here?

- Costs and outcomes of using MRI as a confirmatory test for evaluation of abnormal mammogram/CBE, compared to immediate biopsy