

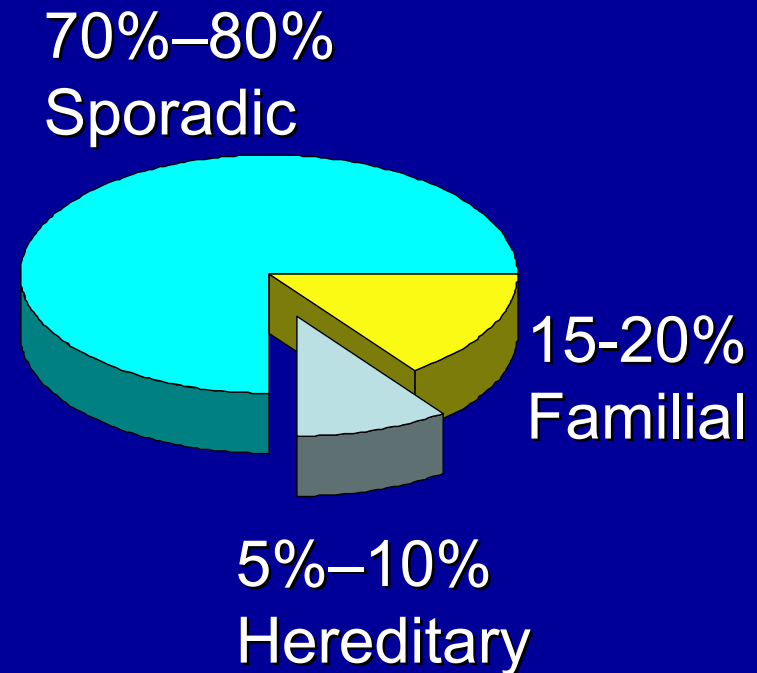
Comprehensive Breast Screening in Women at High Inherited Risk

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California Breast Cancer Research Program Symposium
September 9, 2005

Background: Breast Cancer and Hereditary Risk

- Breast Cancer:
 - >200,000 cases, 40,000 deaths annually in U.S.; ~1,000,000 cases yearly worldwide
- Sporadic Breast Cancer
 - No marked family history or early age
 - Non-hereditary risk factors
- Familial Breast Cancer
 - Shows familial clustering
 - Due to chance, shared environment, or
 - Lower-risk inherited genes
- Hereditary Breast Cancer
 - Early age of onset
 - Multiple relatives affected
 - Responsible inherited genes identified
 - 9,000-18,000 cases yearly in U.S.



Background: Hereditary Breast Cancer

- BRCA1 and BRCA2:
 - Genes which normally function in repair of damaged DNA
 - Show acquired dysfunction in some sporadic breast cancers
- BRCA1/2 mutations account for 60-70% of hereditary risk:
 - Autosomal dominant: 50% chance of inheritance from either parent
 - Estimated 550,000 BRCA1 mutation carriers in the U.S., fewer BRCA2
 - Some ethnic groups have higher risk (Ashkenazi Jewish, Icelandic)
 - Other responsible genes: P53, ATM, PTEN, CHEK-2, CDH1, unknown
- Cancer risk with BRCA1/2 mutation by age 70:
 - BRCA1: 65% (51-75%) breast cancer, 39% (22-51%) ovarian cancer
 - BRCA2: 45% (33-54%) breast cancer, 11% (4.1-18%) ovarian cancer
- Prophylactic bilateral salpingo-oophorectomy (BSO) recommended for all mutation carriers by age 40
- 20-55% of mutation carriers choose prophylactic mastectomy

Background: High-Risk Screening

- Breast screening is an emerging alternative to prophylactic mastectomy
- Standard screening:
 - Yearly mammogram, semi-annual clinical breast exam (CBE), monthly self-breast exam
 - Start early: age 25, versus 40 for mammography in general population
 - No established mortality benefit
 - Mammography less sensitive (25-40% range) in BRCA1/2 mutation carriers, young women with dense breast tissue

Background: Goals for Care of High-Risk Women

- Earlier breast cancer detection
 - Improve upon standard screening
 - Aim for stage-shift: earlier diagnosis, lower mortality
- More sensitive and specific breast screening tests
 - Fewer false-positives and false-negatives
 - Higher positive predictive value ($\% \text{ true positives} / \text{all test positives}$)
- More effective and tolerable medications to reduce risk
 - Preferable side effect profile to tamoxifen, only FDA-approved agent
 - More proven efficacy for women with BRCA1/2 and other mutations
- Fuller understanding of high-risk women's preferences
 - Quality of life with screening versus prophylactic surgeries or medications
- More appropriate targeting of interventions
 - When to initiate breast screening, chemoprevention or preventive surgery?
 - Which groups benefit most?

Background: Breast Magnetic Resonance Imaging (MRI)

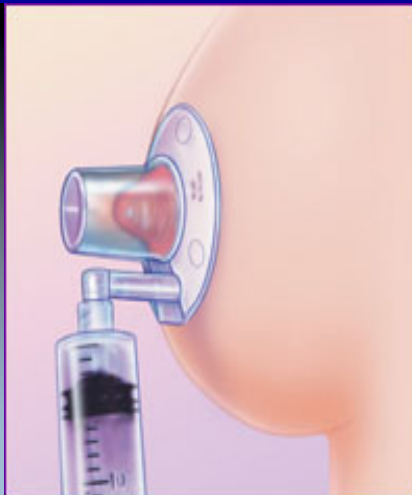
- Increases sensitivity of screening mammography
- Detects small cancers, most lymph node-negative
- No data yet on mortality impact
- High rate of false-positive biopsies (40% range)
- High cost (\$1400-\$3000 per MRI, more for biopsies)
- Emerging as standard of care, with increasing insurance coverage

Background: Ductal Cytology

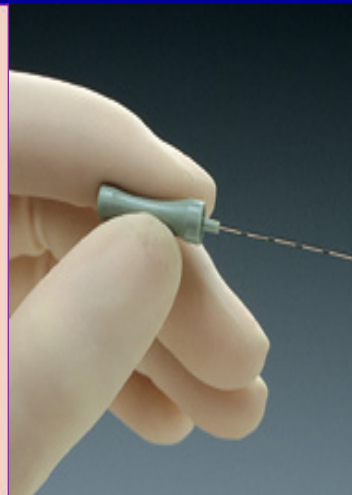
- Breast Duct Cell Analysis:
 - Atypical breast duct cells in women at increased risk:
 - 2 to 5-fold cancer increase when found via suction or needle aspiration
 - Ductal lavage (DL): uses small catheter inserted in nipple ducts
 - Prior reports of atypical or malignant cells found in ~23% on DL
 - Less reported to date about women with BRCA1/2 mutations
 - Might have promise as a risk assessment technique



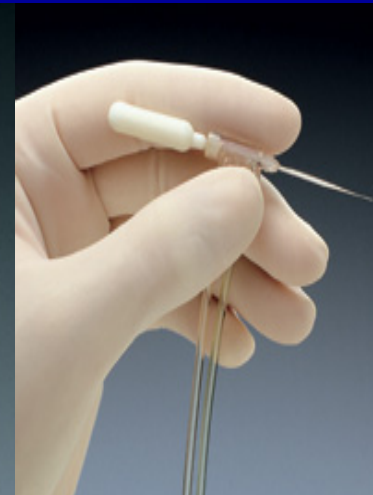
Suction aspirator



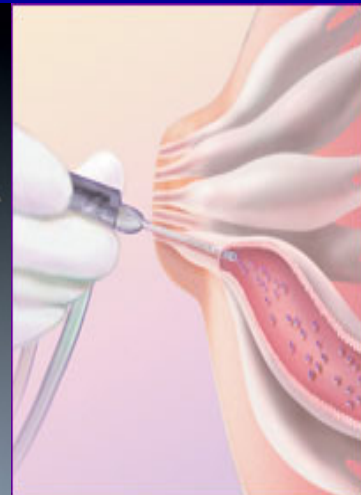
Nipple aspiration



Duct dilator



Catheter



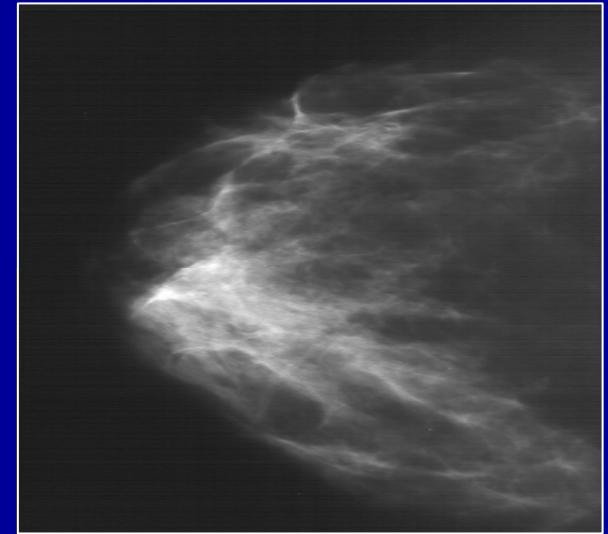
Ductal lavage

Methods: Study Aims and Design

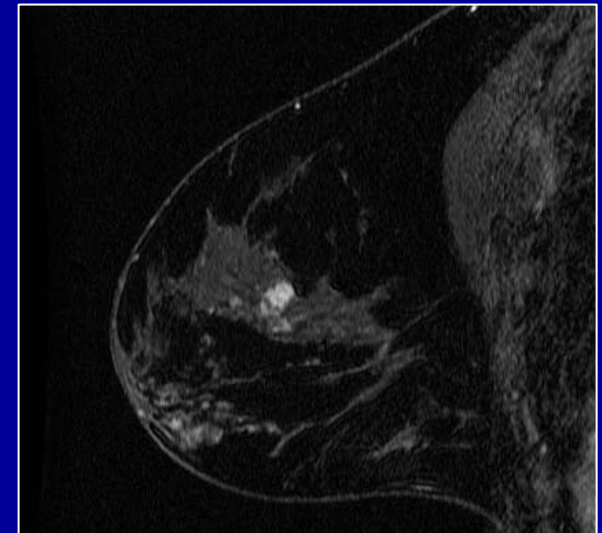
- Study Aims:
 - Assess contribution of breast MRI and DL to early detection of cancer and high-risk lesions
- Study Design:
 - A pilot study of women at high inherited risk:
 - Age \geq 25 yrs
 - BRCA1/2, other mutation or \geq 10% risk over 10 years
 - >1 year after adjuvant therapy for any prior cancer
 - Participants underwent:
 - Annual MRI, mammogram and DL, biannual CBE
 - 6 month follow-up (f/u) if clinically indicated
 - Evaluation of screening experience via questionnaire

Results: MRI Screening

- 127 women had 1 or more screening MRIs
- Median age 42 years; median f/u 16 months
- 79% mutation carriers, 24% prior breast cancer
- 28 biopsies due to MRI, 2 due to mammogram; 24 6 month f/us on MRI, 4 on mammogram
- 5 malignant lesions found, 3 DCIS
- 3 DCIS found by MRI only; 5 high-risk lesions by MRI (atypical hyperplasia, radial scar), 1 by CBE
- 1 cancer found by mammogram only, 1 by CBE only
- Trend toward lower positive predictive value in women risk-reduced via tamoxifen or oophorectomy (5 vs. 25%, $p=0.16$)



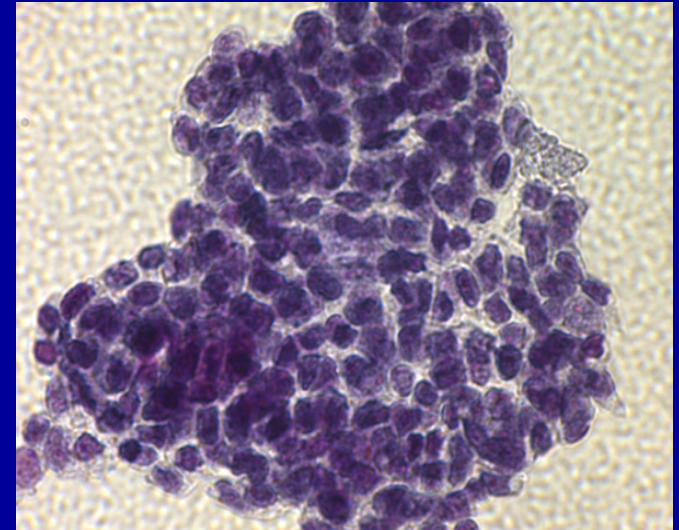
Normal Mammogram



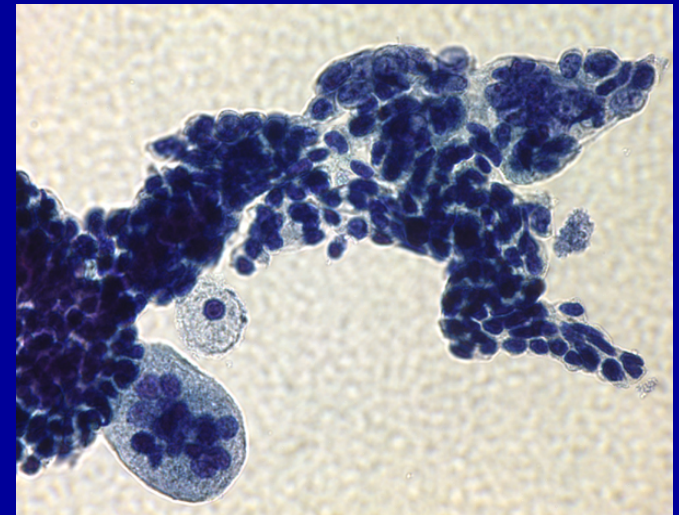
Abnormal MRI (same patient)

Results: Ductal Lavage

- 79 women underwent DL, 75% BRCA1/2 mutation carriers
- DL more successful in younger women (median age 41 vs. 53 years) with nipple fluid on suction (45% in successful group vs. 13% in unsuccessful, $p=0.037$)
- Atypical cell rate similar to other studies using DL, suction or needle aspiration (28%, 95% confidence interval (CI) 19-40%)
- Atypical cells found more often in breast ducts with no nipple fluid on suction (72% vs. 28%, $p=0.02$)
- 1 patient had high-grade DCIS 4 months after atypia; no other concurrent biopsy findings
- Longer follow-up planned to assess prognostic significance of atypical duct cells



Normal breast duct cells



Atypical breast duct cells

Results: Participants' Preferences

- Tolerance of MRI / DL screening assessed by questionnaire in subset of early participants
- Of 36 responding participants (84% response rate):
 - 85% (CI 69-95%) were not more likely to choose prophylactic mastectomy (PM) after experiencing MRI / DL screening protocol
 - 15% (CI 5-31%) more likely to choose PM; $p=0.017$
- Most patients tolerated screening well; 9 out of 127 (7%) have chosen PM after experiencing screening

Conclusions

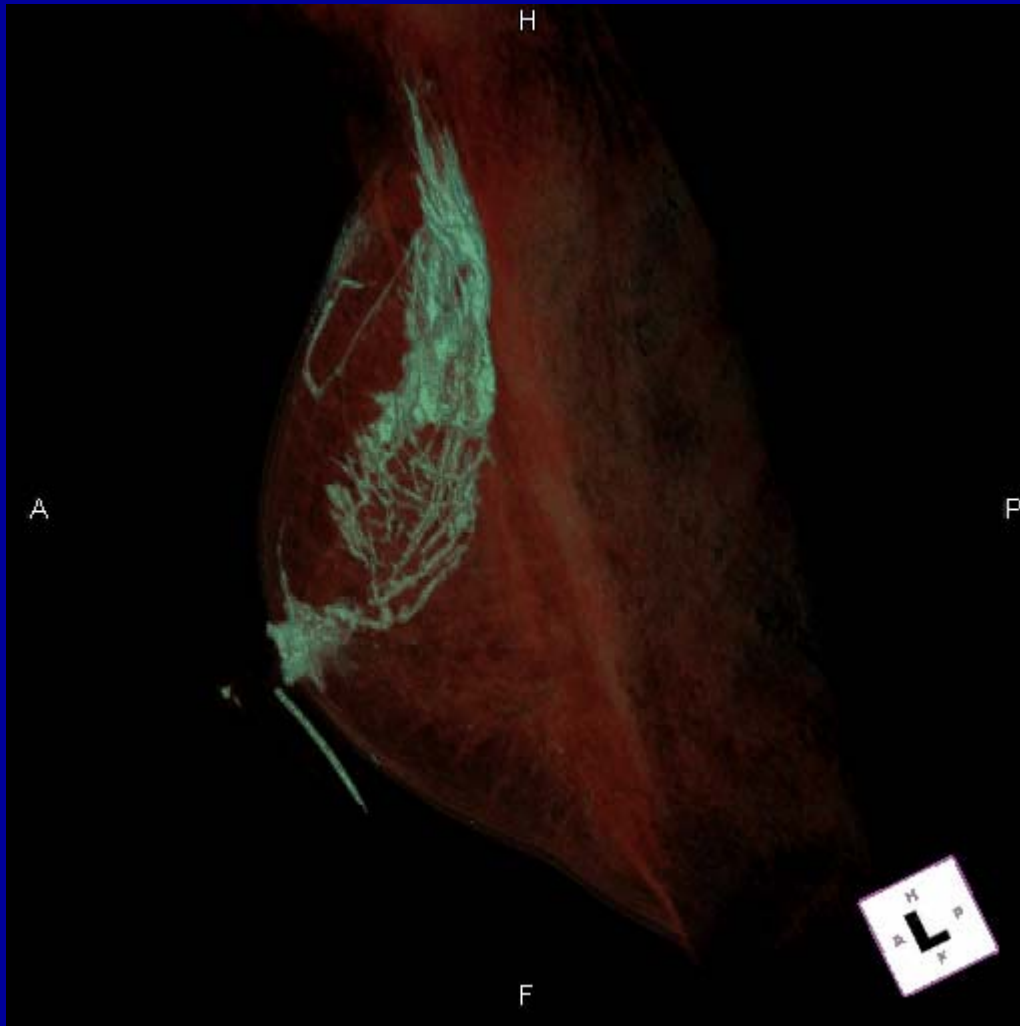
- MRI can detect malignant and high-risk breast lesions not seen on mammography, as shown by other studies, but does not have perfect sensitivity
- Low positive predictive value (thus high false-positive biopsy rate), especially after risk reduction, of concern
- Atypical breast duct cells found in 28% of this high-risk cohort on DL, more often in ducts without fluid production; clinical importance not yet known
- Intensive breast screening including MRI appears to be a well-tolerated alternative to prophylactic mastectomy

Questions for Future Study

- What is the role of screening MRI in high-risk women who have been medically or surgically risk-reduced?
 - Goal: fewer false-positive biopsies
 - Longer intervals between MRI scans?
 - Different starting / stopping ages for MRI screening?
- Is there a clinical role for ductal cytology evaluation?
 - Prognostic significance of atypical cells on DL?
 - Utility of other breast duct cell collection techniques?
- How can high-risk women's preferences be integrated into the development of screening guidelines?

Ongoing Research: Novel Imaging

- MRI-galactography: MRI of breast using contrast in ducts, via DL catheter
- Might permit localization of breast lesions in ducts yielding atypical cells on DL
- Pilot study: procedure performed in 4 high-risk women to date



Ongoing Research: Chemoprevention

- An early-stage chemoprevention study using lovastatin
- Statins widely used to treat high cholesterol; known to be safe
- Appear promising for reduction of breast cancer risk in observational studies, cell line and animal data
- Participant eligibility: BRCA1/2 or other high risk mutation, family history conveying $\geq 20\%$ lifetime breast cancer risk
- Primary Study Endpoint: change in proportion of women with atypical breast duct cells on random periareolar fine needle aspiration after 6 months of lovastatin
- Secondary Study Endpoints: change in other risk-associated biomarkers including mammographic density, Ki-67, ER, PR, and DNA damage response

Ongoing Research: Targeting Screening

- Study of cost-effectiveness and quality-adjusted life years saved by screening breast MRI
- Focus on groups of women with increased risk:
 - High inherited risk, with / without risk-reduction
 - Dense breasts on mammography
- Computer-based simulation modeling, using clinical data:
 - Results of screening breast MRI studies
 - Measurement of utilities: women's quantified preferences about management of breast cancer risk
 - Including women's measured preferences will significantly influence the outcome of the cost-effectiveness analysis
- Supported by the California Breast Cancer Research Program

Acknowledgments

Stanford Cancer Genetics

James M. Ford, M.D.
Meredith A. Mills, B.A.
Nicolette M. Chun, M.S.
Kerry E. Kingham, M.S.

Stanford Radiology

Sylvia K. Plevritis, Ph.D.
Bruce L. Daniel, M.D.
Bronislava M. Sigal, Ph.D.
Robert J. Herfkens, M.D.

Stanford Pathology

Kent W. Nowels, M.D.
Erich Schwartz, M.D., Ph.D.

Stanford Breast Surgery

Frederick M. Dirbas, M.D.

Dana-Farber Cancer Institute

Anne-Renee Hartman, M.D.
Judy E. Garber M.D., M.P.H.
Laura C. Collins, M.D.
Margo Jaffee, B.S.
Sylvia Baedorf, B.S.

FORCE

Sue Friedman, D.V.M.

Research Support

California Breast Cancer Research
Program

Dr. Susan Love Research Foundation
The V Foundation

Department of Defense Breast Cancer
Research Program

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