Benign Breast Disease and Breast Cancer Risk

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Vanderbilt University
Nashville, Tennessee
December 1, 2011
Pre-malignant Breast Disease

- **1950-1980** confusing
  - "The female breast is a precancerous organ"
    - Fred Steward, AFIP fascicle
- **1980-1990** – risk defining
- **2000’s** – refining
  - Impact of breast imaging
  - Mimics
  - Molecular aspects
Risk Factors for Breast Cancer in Women with Proliferative Breast Disease
Dupont and Page, *NEJM* 1985

10,542 benign breast biopsies
1950-1968
85% follow up at 20 years

Nashville Breast Cohort Studies

• Specific histologically-defined terms linked to levels of later malignancy risk

• Regionality of risk, i.e. local vs. diffuse

Stratification of Breast Cancer Risk

• No proliferative disease = NO ↑ RISK

• Proliferative disease, no atypia = SLIGHT RISK

• Atypical hyperplasia = MODERATE RISK
Distribution of Breast Lesions
Nashville series (1950-1968)

Distribution of Mammographically Detected Lesions

Stratification of Breast Cancer Risk
- No proliferative disease = NO ↑ RISK
- Proliferative disease, no atypia = SLIGHT RISK
- Atypical hyperplasia = MODERATE RISK
Relative Risk

• Used to compare groups (not individuals), one group has characteristic, control group does not
• Slight increase risk = amount detectable in population
• Statistically significant, but not significant for patients

Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk

• Nurse’s Health Study
• Prospective observational study
• 105,986 women, entered 1980-2008

Chen et al. JAMA Nov 2, 2011

Nurse’s Health Study: risk of alcohol consumption

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<tr>
<th>alcohol per week</th>
<th>relative risk</th>
<th>CI</th>
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<td>3-6 drinks</td>
<td>1.15</td>
<td>(1.06-1.26)</td>
</tr>
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Chen et al, JAMA Nov 2, 2011

Slight increase in risk

Relative Risk for Developing Cancer After Benign Biopsy

- No increased risk
  - cysts
  - duct ectasia
  - adenosis
  - hyperplasia, mild

- Slightly increased risk
  - hyperplasia, moderate or florid, no atypia
  - sclerosing adenosis
  - solitary papilloma

- Moderately increased risk
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia

- Early menarche
- Late menopause
- Nulliparity

Relative Risk

Women with PD who develop breast cancer

Women with PD, no cancer development

RR = ______________________

Women in the general public who develop breast cancer

Women in the general public, no cancer development
Relative Risk

Women with PD who develop breast cancer

Women in the general public who develop breast cancer

Women in the general public, no cancer development

RR =

Women with PD, no cancer development

Women in the general public, no cancer development

RR =
Relative Risk Varies with Time Since Diagnosis

- Atypical Hyperplasia: 9.8
- Proliferative Disease without Atypia: 3.6
- No Proliferative Disease: 1.0

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<tr>
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<th>No Proliferative Disease</th>
<th>Proliferative Disease without Atypia</th>
<th>Atypical Hyperplasia</th>
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<td>4</td>
<td></td>
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<td>9.8</td>
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DCIS vs ADH vs FHWA: cytology and histology
Relative Risk for Developing Cancer After Benign Biopsy

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Minimum Criteria for DCIS

• Uniform population of cells, maintaining rounded, geometric configurations
• Even cell placement, without swirling or streaming
• **Fully** populating two adjacent spaces (3 mm)
Atypical Ductal Hyperplasia

• Uniform cytology
• Architecture
  – cribriform, micropapillary, solid
• Extent
Nashville Breast Cohort Study Design

• Define histologic categories that could be reproducibly recognized

• Perform patient follow up

• Assign risk based on cancer development

Relative Risk for Developing Cancer After Benign Biopsy

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Confirmatory Studies

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<tbody>
<tr>
<td>Proliferative disease without atypia</td>
<td>1.5-2X</td>
<td>1.6X</td>
<td>1.3X</td>
<td>1.9X</td>
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<tr>
<td>Atypical hyperplasia</td>
<td>4.5X</td>
<td>3.7X</td>
<td>4.3X</td>
<td>4.24X</td>
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Confounders

- Mammography
- Minimally invasive biopsy procedures
- Hyperplasia in unusual settings
**Underdiagnosis of ADH**

- Core needle biopsy: 41%
- Mammmotome: 15%
- Core needle biopsy (14 g): 44%
- Mammmotome (14 g): 39%
- Mammmotome (11 g): 19%


**Factors Influencing Underdiagnosis of ADH**

- Device used
- Extent of removal of mammographic lesion
- Microcalcifications vs mass

Jacobs et al, AM J Surg Pathol, 2002

**When to excise after core biopsy?**

- Diagnostic difficulty
- Sampling issues
Atypical Ductal Hyperplasia

- Uniform cytology
- Architecture
- Extent
Extent of ADH on Core Biopsy
(n=47)

Findings in Excised Specimen

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<th>benign</th>
<th>ADH</th>
<th>DCIS</th>
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<td>3</td>
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<tr>
<td>≥4</td>
<td>0</td>
<td>2</td>
<td>12</td>
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Extent of ADH on Core Biopsy
(n=42)

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ADH vs low grade DCIS

“At least atypical ductal hyperplasia, excision necessary to evaluate extent of the lesion”
**ADH vs DCIS**
- Differential diagnosis is LOW GRADE DCIS
- Extent of involvement is key
- Be conservative on core biopsy

**Biomarkers of ADH?**
- ADH is typically negative for HMW keratins (CK 5/6) and diffusely positive for ER
- Usual hyperplasia shows variable expression of HMW keratins and ER
- Expression of these markers is similar in ADH and low-grade DCIS
- None is sufficiently validated for routine clinical use

**Molecular analysis of ADH**
- LOH & CGH show common patterns of genetic alteration in ADH, low grade DCIS, and invasive carcinoma
- Frequent sites of LOH in ADH and invasive carcinoma: chromosomes 16q, 17p, and 11q13
- Studies of ADH are from cases of established cancer, both invasive and in situ
- Few studies of ADH as the most advanced lesion
- No studies have established significance of these changes through large, clinically validated patient cohorts.