Update on Proliferative Breast Disease

Jean F. Simpson, M.D.
October 1, 2016

Proliferative Breast Disease: predictor or precursor?

- Review epidemiology, including histologic criteria
- Risk assessment
- Molecular analysis

“Mammary Fibrocystic Disease” - 1945

Most women undergoing breast biopsy have an elevated risk of subsequent carcinoma development, in the range of 3 times that of the population as a whole

Pre-malignant Breast Disease

- 1950-1980 -- confusion
  “The female breast is a precancerous organ” …………Fred Stewart, AFIP fascicle
- 1980-1990 -- risks defined
- 2000’s --† detection

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 Study Design

- Define histologic categories that could be reproducibly recognized
- Perform patient follow up
- Assign risk based on cancer development
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)

- No PD
- PDWA
- AH

Distribution of Mammographically Detected Lesions

- No PD
- PDWA
- AH
- Ca

Rubin et al, Cancer 1988

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

<table>
<thead>
<tr>
<th>alcohol per week</th>
<th>relative risk</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 drinks</td>
<td>1.15</td>
<td>(1.06-1.26)</td>
</tr>
<tr>
<td>6-10 drinks</td>
<td>1.15</td>
<td>(1.06-1.24)</td>
</tr>
<tr>
<td>13-19 drinks</td>
<td>1.28</td>
<td>(1.12-1.47)</td>
</tr>
<tr>
<td>&gt;19 drinks</td>
<td>1.50</td>
<td>(1.34-1.67)</td>
</tr>
</tbody>
</table>

Chen et al, JAMA Nov 2, 2011

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

Relative Risk

Women with PD who develop breast cancer

\[
RR = \frac{\text{Women with PD, no cancer development}}{\text{Women in the general public who develop breast cancer}}
\]

Women in the general public, no cancer development
Relative Risk

\[
\text{RR} = \frac{\text{Women with PD who develop breast cancer}}{\text{Women with PD, no cancer development}}
\]

\[
\text{RR} = \frac{\text{Women in the general public who develop breast cancer}}{\text{Women in the general public, no cancer development}}
\]

Relative Risk Varies with Time Since Diagnosis

<table>
<thead>
<tr>
<th>Time Since Diagnosis</th>
<th>Relative Risk</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>4</td>
<td>9.8</td>
</tr>
<tr>
<td>5</td>
<td>15.2</td>
</tr>
<tr>
<td>6</td>
<td>23.0</td>
</tr>
<tr>
<td>7</td>
<td>32.9</td>
</tr>
<tr>
<td>8</td>
<td>45.6</td>
</tr>
<tr>
<td>9</td>
<td>62.1</td>
</tr>
<tr>
<td>10</td>
<td>83.5</td>
</tr>
</tbody>
</table>

- **No Proliferative Disease**
  - **RR = 1.0**
- **Proliferative Disease without Atypia**
  - **RR = 3.6**
  - **Atypical Hyperplasia**
    - **RR = 9.8**

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

DCIS vs ADH vs FHWA:
cytology and histology

- Cribiform
- DCIS
- FHWA
- ADH
- Normal

These individual spaces are presented with each cytology retained within each space to show normal, atypical ductal hyperplasia, and adenosis in each space.
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
Relative risk confirmation

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<tr>
<th></th>
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</thead>
<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>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>4-5X</td>
<td>3.7X</td>
<td>4.3X</td>
<td>4.24X</td>
</tr>
</tbody>
</table>

Proliferative Mimics
Molecular studies of Proliferative Breast Disease

- Goal is to gain additional information beyond histologic risk factors
- Short list
- Focal lesions
- Most cases have concomitant carcinoma
- Not linked to long term outcome

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
Columnar Cell Lesions

CCL Clinical Presentation

Asymptomatic 45 yo female with round, non-branching Ca+2
Columnar Cell Lesions

**Columnar Cell Change**
- 1-2 cell layers
- Uniform, ovoid to elongated nuclei
- Polarized to BM
- Evenly dispersed chromatin
- Indistinct or no nucleoli

**Columnar Cell Hyperplasia**
- >2 cell layers, overlapping nuclei
- Mounds, tufts, abortive micropapillae

**“Flat” Epithelial Atypia**
- 1+ layers, decreased N/C ratio
- Round or ovoid nuclei, loss of polarity
- Low grade cytologic atypia
- No arches, papillae, cribiform spaces

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**Columnar Cell Lesion of the Breast: The Missing Link in Breast Cancer Progression? A Morphological and Molecular Analysis**

P. Simpson, T Gale, J. S. Reis-Filho, C. Jones, S. Parry, J. Sloane, A. Hanby, S. Pinder, A Lee, S Humphreys, I. Ellis, and S. Lakhani


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**Columnar Cell Lesions of the Breast**

- 18 cases of columnar cell lesions
- High resolution comparative genomic hybridization
- Expanded CCL into 6 categories, with category 5 having overlap with ADH


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**Columnar Cell Lesions of the Breast**

- 8 cases had synchronous DCIS or invasive carcinoma
- All categories of CCL showed a range of gross chromosomal copy number gains and losses
- Recurrent changes were identified (loss on 16q, 17p, and X and gain on 15q, 16p, and 19).

Columnar Cell Lesions

- Co-exist with ALH/LCIS, ADH, LG DCIS, and tubular carcinoma
- Common cytologic and immunophenotypic features
- CCLwA has genetic alterations (-16q, -11q) as do low grade DCIS, and tubular carcinoma

Relative risk of Subsequent Breast Cancer Case-Control Studies of Women with CCL

<table>
<thead>
<tr>
<th></th>
<th>Boulos (NBC)</th>
<th>Collins (NHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/Control</td>
<td>77/152</td>
<td>140/448</td>
</tr>
<tr>
<td>Design</td>
<td>Nested CC</td>
<td>Nested CC</td>
</tr>
<tr>
<td>Treatment</td>
<td>Bx only</td>
<td>Bx only</td>
</tr>
<tr>
<td>Follow-up</td>
<td>17 yrs</td>
<td>12 yrs</td>
</tr>
<tr>
<td>RR (95%CI)</td>
<td>1.47 (1.0-2.2)</td>
<td>1.44 (1.4-1.83)</td>
</tr>
</tbody>
</table>

Radial Scar

- Histologic features
- Core vs excision
- Indicator of increased risk?

Radial Scars

- Incidental findings in bx
- Less than 1 in a 1000 women screened
- Mammographically spiculated
- Usually associated BPD
Radial Scar

- Most recommend excision:
  - Bx

- no upgrades if:
  - RS < 1.0 cm
  - Sampled by 11 gauge needle or larger
  - ≥ 12 cores taken

Epidemiology of Radial Scar

<table>
<thead>
<tr>
<th></th>
<th>Sanders (NBC)</th>
<th>Jacobs (NHS)</th>
<th>Berg (Mayo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort Design</td>
<td>Retrospective</td>
<td>Case-Control</td>
<td>Retrospective</td>
</tr>
<tr>
<td># RS</td>
<td>880 (9.2%)</td>
<td>99 (7.1%)</td>
<td>439 (4.7%)</td>
</tr>
<tr>
<td>Ave size</td>
<td>4.8 mm</td>
<td>4.0 mm</td>
<td>≤ 5.0 mm</td>
</tr>
<tr>
<td># Cancers</td>
<td>62 (IMC)</td>
<td>24 (IMC+DCIS)</td>
<td>52 (IMC+DCIS)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>20.4 yrs</td>
<td>12 yrs</td>
<td>17 yrs</td>
</tr>
<tr>
<td>RR (95%CI)</td>
<td>1.82 (1.2-2.7)</td>
<td>3.0 (1.7-5.5)</td>
<td>1.88 (1.36-2.53)</td>
</tr>
<tr>
<td>PD or AH +/- RS</td>
<td>NS</td>
<td>RS</td>
<td>NS</td>
</tr>
</tbody>
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