Proliferative Breast Disease: implications of core biopsy diagnosis

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Proliferative Breast Disease
Must be interpreted in clinical and epidemiologic framework

- Risks implications for later cancer development
- Risk implications for 'immediate' surgical procedures
Pitfalls of Core Bx Diagnosis

- Over-diagnosis
- Under-diagnosis

Consequences of ‘over’ diagnosis on core biopsy

- FEA; atypical ductal hyperplasia; DCIS
  - Unnecessary excision (or worse)
- Invasive carcinoma
  - Unnecessary sentinel lymph node biopsy
  - Unnecessary neoadjuvant chemotherapy
- Unnecessary patient anxiety

“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 (1.5-2x)

• Atypical hyperplasia = MODERATE RISK (4-5x)

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
Histologic Criteria for Proliferative Breast Disease

• Qualitative

• Quantitative
Minimum Criteria for DCIS

- Uniform population of cells
- Even cell placement, without swirling or streaming
- Rigid architecture, i.e. cribriform or micropapillary configurations
- **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>
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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>
</tr>
<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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</table>
ADH on core biopsy

- Uniform cytology
- Architecture
  - cribriform, micropapillary, solid
- Extent why ADH is excised

Upgrade of ADH

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

Factors Influencing ADH Upgrade

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

Jacobs et al, AM J Surg Pathol, 2002

ADH vs low grade DCIS

“At least atypical ductal hyperplasia, excision necessary to evaluate extent of the lesion”

Mimics

(or how to avoid over diagnosis)
Ancillary markers in assessing proliferative breast disease

- CK5/6
- Estrogen receptor
Ancillary markers

- CK5/6
  - absent in ADH
  - heterogeneous expression in usual hyperplasia

CK 5/6

- Absent in apocrine lesions
- Heterogeneous expression in intermediate grade DCIS
- Take results with ‘grain of salt’

CK 5/6

- IHC expression is reflection of CYTOLOGY
- Proliferative lesions require assessment of architecture, cytology, and extent
Biomarkers of ADH?

- ADH is 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

Hyperplasia detected in core biopsy specimen

- Usual patterns of hyperplasia
  - No excision

- Atypical ductal hyperplasia
  - Excision
Columnar Cell Lesions

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

CCL Without Atypia

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

“Flat” Epithelial Atypia
1+ layers, increased N/C ratio
Round or ovoid nuclei, loss of polarity
Low grade cytologic atypia

CCL With Atypia

No arches, papillae, cribriform spaces

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

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


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).

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>
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<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>
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CCL with atypia

- Rare lesion
- Associated with calcification
- 3 times more likely to have adjacent ADH, ALH, low grade DCIS, or low grade invasive carcinoma
- EXCISE if detected on core biopsy
- if none of those lesions is present, risk implications are the same as usual hyperplasia
CCL with atypia → ADH
Secretory change detected on core biopsy

 Core biopsy diagnosis

- Secretory change
  - No excision
- Columnar cell lesion without atypia
  - No excision
- Columnar cell lesion with atypia
  - Excision, because of sampling issues
Consequences of ‘over’ diagnosis on core biopsy
- Unnecessary sentinel lymph node biopsy
- Unnecessary mastectomy
  - Invasive carcinoma
- Unnecessary neoadjuvant chemotherapy
  - Invasive carcinoma

Consequences of ‘over’ diagnosis on core biopsy
- Unnecessary patient anxiety
  - Unnecessary pathologist anxiety
  - Unnecessary lawsuit

Radial scar diagnosed on core biopsy
Radial Scars

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

- Most recommend excision:
  - Rates of missed carcinomas 0-5%
  - Majority of "upgrades" had AH on Bx
  - no upgrades if:
    - RS < 1.0 cm
    - Sampled by 11 gauge needle or larger
    - ≥ 12 cores taken

Brenner 2002
Sohn 2010
Cawson 2003
Rajan 2011
Are Radial Scars at Core Biopsy High Risk Lesions?

? Radial scar high risk lesion?

- Literature review 1999-2014
  - 15 studies of upgrade rate
  - 831 patients with 38 upgrades (4.6%)
- All studies had at least 1 confounding factor

Radial scar studies: confounding factors
- No path/rad concordance, or inclusion of cases that were discordant
- Other risk lesions present on core bx (i.e. ADH)
- Considered discovery of risk lesion at excision (i.e. ADH) an upgrade
- No documentation of distance between bx and upgrade
- No breast pathologist review
UNC experience 2004-2014

- 53 patients had radial scar on core, followed by excision
- Eliminated any confounding factors
- 0 upgrades!

B Singer, T Lawton. UNC, USCAP 2015

Radial scar upgrade rate

- From literature review (831) plus UNC patients (53), if confounding factors are eliminated.....
- Upgrade rate is 3/884 (less than 0.5%)
- Distance to upgrade, 3 -10 mm

B Singer, T Lawton. UNC, USCAP 2015

Epidemiology of Radial Scar

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<tr>
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<th>Sanders (NBC)</th>
<th>Jacobs (NHS)</th>
<th>Berg (Mayo)</th>
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<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>
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<tr>
<td>PD or AH +/-RS</td>
<td>NS</td>
<td>RS [risk]</td>
<td>NS</td>
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Consequences of ‘over’ diagnosis on core biopsy

- Unnecessary sentinel lymph node biopsy
- Unnecessary mastectomy
  - Invasive carcinoma
- Unnecessary neoadjuvant chemotherapy
  - Invasive carcinoma
Phenotypic alterations in DCIS

• 101 cases of DCIS
• 7 different MEC markers
• Reduced expression in 85% of cases in at least one marker
• 85% of high grade DCIS lost markers

Core biopsy

• Be conservative
• Interpret myoepithelial markers with caution
• Know imaging findings
• Communication!