ATYPIA AND LOBULAR NEOPLASIA:
STILL A CHALLENGE, NEW OPTIONS FOR MANAGEMENT?

Danh Tran-Thanh, MD, FRCPC, Department of Pathology
Mona El Khoury, MD; Department of Radiology
Erica Patocskaí, MD; Department of Surgical Oncology
Centre Hospitalier de l’Université de Montréal (CHUM)
Disclosure

• The authors have no conflicts of interest to disclose (i.e. no industry funding received or other commercial relationships).

• The authors have no financial relationship or advisory role with pharmaceutical or device-making companies, or CME provider.
Why Flat Epithelial Atypia (FEA) and Lobular Neoplasia (LN)?

• Among all high risk breast lesions, FEA and LN lesions remain the most challenging

• For both (except pleomorphic LCIS), the optimal management after a percutaneous biopsy is still debatable

• Hence, uncertainty and variation in care of these patients
## Proliferative lesions arising in TDLU

<table>
<thead>
<tr>
<th>Benign</th>
<th>“Atypical”</th>
<th>“Malignant”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columnar cell change/Columnar cell hyperplasia</td>
<td>Flat epithelial atypia (FEA)</td>
<td></td>
</tr>
<tr>
<td>Ductal hyperplasia of “the usual type” (UDH)</td>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>Ductal carcinoma in situ (DCIS)</td>
</tr>
<tr>
<td></td>
<td>Atypical lobular hyperplasia (ALH)</td>
<td>Lobular carcinoma in situ (LCIS)</td>
</tr>
</tbody>
</table>
LOBULAR NEOPLASIA
Lobular neoplasia

- Atypical lobular carcinoma (ALH)
- Lobular carcinoma in situ (LCIS)

(With or without pagetoid involvement of terminal ducts – duct involvement by cells of atypical lobular hyperplasia (DIAL))
Pathologic criteria

- Cytomorphologic criteria
  - Monotonous proliferation of small, dyshesive neoplastic epithelial cells which fills and distends TDLU

- Extent criteria
  - 50% extent rule
ALH vs LCIS

Modified (with permission) from:

O’Malley, 2010
ALH vs LCIS


O’Malley, 2010
Lobular Neoplasia

ALH

LCIS
Lobular Neoplasia

- ALH vs LCIS… not always possible to differentiate
Clinical Features

- Diagnosed most commonly age 40-50 years
- Multicentric, bilateral
- Clinically non palpable, grossly invisible
Natural History

• Increase relative risk (RR) for invasive cancer
  – RR 4-5x for ALH
  – RR 8-9x for LCIS

• Early literature suggested risk is bilateral, whereas more recent reports suggest risk is higher in ipsilateral breast

• LCIS = high risk lesion AND non-obligate precursor
Low grade breast neoplasia family

Ellis, Mod Pathol, 2010
Differential Diagnosis

• In most cases the diagnosis of ALH/LCIS is straightforward
  • DCIS
  • Benign lesions
  • Invasive carcinoma

• It is often the ‘non-classical’ forms of LCIS that pose diagnostic difficulty
Variants of LCIS

- Pleomorphic LCIS (PLCIS)
- Apocrine PLCIS
- LCIS with comedo necrosis
- Carcinoma in situ with mixed DCIS/LCIS features
Pleomorphic LCIS
Pleomorphic LCIS
Management

• Which ALH/LCIS to excise?

1. Radiologic pathologic discordance – targeted lesion not represented
2. Another lesions for which excision is indicated (eg ADH)
3. Mass lesion or architectural distortion
4. Indeterminate features overlap with DCIS
5. “Non-classical”/variant forms of LCIS
Imaging guided core needle biopsy

- Alternative to open surgical biopsy in diagnosis of a breast anomaly
- It involves partial analysis of the lesion
- The larger the volume of tissue acquired, the lower the underestimation rate
  - Type of biopsy device
    - vacuum assisted probes better than spring loaded
  - Needle gauge
    - False negative rate of 11G (0.45%) v/s 14g (4.4%)
  - Number of samples

- Failure to adequately diagnose underlying pathology between 2% to 17%

Cohen et al. Radiology 2004; 231: 617-621
A non malignant biopsy result determines further recommendations:

- Close follow up
  - Radiology/pathology concordance i.e. benign result is expected

- Surgical excision
  - Radiology/pathology discordance
    - The expected malignant result not obtained or
    - The lesion was missed

For high risk lesions: the debatable question:

- How reliable is the non malignant biopsy result ? i.e. how important is it to excise these lesions?
Lobular Neoplasia

• When the pathologic diagnosis of LN is concordant with imaging?
• General belief that LN is an incidental pathologic finding without radiographic correlate
• If this is true, then all biopsy proven LN would be discordant and warrant surgical excision
• However, studies have shown that LN can manifest radiographically

• Hence, the statement that all LN is incidental is incorrect and a biopsy result of LN should not by itself indicate surgical excision

Georgian-Smith et al. AJR 2012;198:256-263
Lobular Neoplasia

- No specific radiologic presentation is typical for LN
- Most often LN is associated with microcalcifications 21-67%
- Less likely as a mass or an enhancement on MRI

Any radiologic abnormality classified as a BIRADS V is discordant with a pathologic diagnosis of LN

Li et al. Cancer 2006;106(10):2104-2112
Heller et al. AJR 2012;198;249-255
Linda et al. AJR 2012;198 : 272-280
What about MRI?

- No studies to date have focused specifically on the detection of LN on MRI
- No studies to date showed specific morphologic or kinetic characteristics for high risk lesions
- In a review of the literature published on MRI in high risk lesions, Heller et al. found no reliable features on MRI that could predict subsequent upgrade to malignancy
- Even the absence of enhancement on MRI can not be reliable since 20-60% of low grade DCIS do not enhance

Heller et al. AJR 2012;198:249-255
Strigel et al. AJR 2010; 195:792-798
What about MRI?

- In a prospective study (166 patients with 169 biopsy proven high risk lesions including 35 Lobular Neoplasia):

  - MRI showed Low NPV for malignancy for LN: 88% as compared to 97.4% (papilloma without atypia) and 97.6% (radial scar).

MRI cannot be recommended in the management decision of LN.

Linda et al. AJR 2012;198 : 272-280
• **No strict imaging features are reliable** for defining a subset of lobular neoplasia with an acceptable (< 2%) probability of upgrade to cancer like the BIRADS III

⇒ **Surgical excision is still recommended**
“Virtue for the prudent man lies in moderation between excess and deficiency”

✓ Neither underestimation nor overdiagnosis

✓ Making the right choice is still challenging since objective evidence is lacking
To achieve a rational clinical strategy for the care of patients

- We should rely on clear, well conducted, unbiased studies
<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of LN (LCIS/ALH) on CNB</th>
<th>Diagnosis on CNB (cases with surgical biopsy)</th>
<th>Excision surgery after CNB (%)</th>
<th>Cancer on surgical biopsy</th>
<th>Cancer at surgical biopsy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Londero et al (2008)</td>
<td>21 LCIS</td>
<td>20</td>
<td>95</td>
<td>12/5 DCIS, 7 IC</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>14ALH</td>
<td></td>
<td></td>
<td>1 DCIS</td>
<td>13</td>
</tr>
<tr>
<td>El-Sayed et al (2003)</td>
<td>33 LN (unspecified)</td>
<td>33 LN (unspecified)</td>
<td>100</td>
<td>11 (6 DCIS, 5 IC)</td>
<td>33</td>
</tr>
<tr>
<td>O’Driscoll et al (2001)</td>
<td>7 LCIS</td>
<td>7 LCIS</td>
<td>100</td>
<td>3 (1 ILC, 2 DCIS)</td>
<td>43</td>
</tr>
<tr>
<td>Philpotts et al (2000)</td>
<td>5 LCIS</td>
<td>5 LCIS</td>
<td>100</td>
<td>1 DCIS</td>
<td>20</td>
</tr>
<tr>
<td>Burak et al (2000)</td>
<td>5 ALH</td>
<td>6ALH</td>
<td>80</td>
<td>1 DCIS</td>
<td>20</td>
</tr>
<tr>
<td>Berg et al (2004)</td>
<td>10 LCIS</td>
<td>8 LCIS</td>
<td>80</td>
<td>No carcinoma</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>15 ALH</td>
<td>7 ALH</td>
<td>47</td>
<td>1 DCIS</td>
<td>14</td>
</tr>
<tr>
<td>Lechner et al (1999)</td>
<td>89 LCIS</td>
<td>58 LCIS</td>
<td>65</td>
<td>26 (10 IDC, 8 ILC, 8 DCIS)</td>
<td>45</td>
</tr>
<tr>
<td>Shin and Rosen (2002)</td>
<td>NA*</td>
<td>8 LCIS</td>
<td>14</td>
<td>6 IC</td>
<td>35</td>
</tr>
<tr>
<td>Houssami et al (2007)</td>
<td>23 LN (unspecified)</td>
<td>23 LN (unspecified)</td>
<td>100</td>
<td>1 IDC</td>
<td>14</td>
</tr>
<tr>
<td>Bauer et al (2003)</td>
<td>13 LN (unspecified)</td>
<td>7 LN (unspecified)</td>
<td>54</td>
<td>5 (3 ICI – ipsi/2 ICI contralateral)</td>
<td>15</td>
</tr>
<tr>
<td>Crisi and Ricci (2005)</td>
<td>12 LCIS</td>
<td>21 LN</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Georgi-Smih and Lawton (2001)</td>
<td>10 LCIS+ALH</td>
<td>5 PLCIS</td>
<td>34</td>
<td>3 (2 DCIS, 1 IDC)</td>
<td>43</td>
</tr>
<tr>
<td>Dmytrasz et al (2003)</td>
<td>13 ALH</td>
<td>7 ALH</td>
<td>34</td>
<td>1 DCIS</td>
<td>14</td>
</tr>
<tr>
<td>Inman and Brem (2002)</td>
<td>NA</td>
<td>7 ALH</td>
<td>14</td>
<td>3 (2 DCIS, IDC)</td>
<td>44</td>
</tr>
<tr>
<td>Dillon et al (2007)</td>
<td>12 LN (unspecified)</td>
<td>9 LN (unspecified)</td>
<td>75</td>
<td>1 DCIS</td>
<td>7</td>
</tr>
<tr>
<td>Yeh et al (2003)</td>
<td>22 LN (unspecified)</td>
<td>15 LN (unspecified)</td>
<td>68</td>
<td>1 ILC</td>
<td>33</td>
</tr>
<tr>
<td>Meloni et al (2002)</td>
<td>NA</td>
<td>3 LCIS</td>
<td>54</td>
<td>No carcinoma</td>
<td>0</td>
</tr>
<tr>
<td>Pacelli et al (2001)</td>
<td>12 ALH</td>
<td>7 ALH</td>
<td>38</td>
<td>No carcinoma</td>
<td>0</td>
</tr>
<tr>
<td>Liberman et al (2000)</td>
<td>16 LCIS</td>
<td>14LCIS</td>
<td>88</td>
<td>3 (2 DCIS, 1 ILC)</td>
<td>22</td>
</tr>
<tr>
<td>Renshaw et al (2002)</td>
<td>5 PLCIS</td>
<td>5 PLCIS</td>
<td>100</td>
<td>3 ICI</td>
<td>60</td>
</tr>
<tr>
<td>Arpino et al (2004)</td>
<td>45 LN</td>
<td>21 LN</td>
<td>88</td>
<td>No carcinoma</td>
<td>0</td>
</tr>
<tr>
<td>Elsheikh and Silverman (2005)</td>
<td>45 ALH</td>
<td>4 ALH</td>
<td>100</td>
<td>3 ICI</td>
<td>60</td>
</tr>
<tr>
<td>Foster et al (2004)</td>
<td>15 LCIS</td>
<td>12 LCIS</td>
<td>80</td>
<td>4 (2 DCIS, 1 ILC, 1 IDC)</td>
<td>33</td>
</tr>
<tr>
<td>Mahoney et al (2006)</td>
<td>10 LCIS</td>
<td>20 LN (unspecified)</td>
<td>74</td>
<td>5 (2 DCIS, 3 ILC)</td>
<td>25</td>
</tr>
<tr>
<td>2 PLCIS</td>
<td>2 PLCIS</td>
<td>1 IC</td>
<td>50</td>
<td>3 IC</td>
<td>30</td>
</tr>
<tr>
<td>Zhang et al (2001)</td>
<td>10 LCIS</td>
<td>10</td>
<td>47</td>
<td>3 (1 DCIS, 2 IC)</td>
<td>14</td>
</tr>
<tr>
<td>Jacob et al (2002)</td>
<td>8 ALH</td>
<td>8</td>
<td>80</td>
<td>5 (4 DCIS, 1 ILC)</td>
<td>25</td>
</tr>
<tr>
<td>Lavoue et al (2007)</td>
<td>70 LN (unspecified)</td>
<td>42 LN (classic)</td>
<td>74</td>
<td>10 (5 DCIS, 3 ILC, 1 IDC)</td>
<td>19</td>
</tr>
<tr>
<td>Lee et al (2003)</td>
<td>18 LN (unspecified)</td>
<td>13 LN (unspecified)</td>
<td>72</td>
<td>6 (2 DCIS, 4 ICI)</td>
<td>46</td>
</tr>
</tbody>
</table>

Total: 211/789, 27
Lobular Neoplasia

- These series, all retrospective, were limited as:
  - Not all patients with LN underwent excision
  - Not all cases with radio-pathologic discordance were excluded
  - In many cases, LN were not the only lesions identified in the core specimen
  - It is not clear if malignancy found at surgery was at the site of biopsy proven LN or an incidental finding elsewhere in the breast

- Thus creating an inherent selection bias and increasing the likelihood of finding an associated malignancy
Lobular Neoplasia

- How reliable is the upgrade rate reported in the literature?

- Studies reported recently after careful exclusion of:
  - Cases with radiology / pathology discordance
  - Cases of LN associated with other high risk lesions (ADH, papilloma & radial scar)

- Showed a significant drop in upgrade rate to malignancy at surgery

Chaudhary et al. Mod Pathol 2013;1-10
80 consecutive patients with biopsy proven LN underwent surgical excision

72 with concordant radiology/pathology
2 cancers
upgrade rate 2/72 3%

8 with discordant radiology/pathology
3 cancers
upgrade rate 3/8 38%

136 CNB proven LN underwent surgery

48 ALH
Upgrade rate 1/48
2%

39 LCIS
Upgrade rate 9/39
23%

49 LN + ADH
Upgrade rate 13/49
27%

After excluding cases where the upgrade was associated with nonclassic LCIS, upgrade rate was 1%.

After excluding cases with radio/pathology discordance, upgrade rate would be 4/87 LN = 5%.

Hwang et al. Mod Pathol 2008;21:1208-1216
93 consecutive with biopsy proven LN patients underwent surgical excision

68 patients with LN alone
- 3 cancers
- Upgrade rate 3/68 4.4%

25 patients with LN and ADH
- 4 cancers
- Upgrade rate 4/25 16%

108 CNB proven LN

87 CNB with no prior history of breast cancer

- 3 cancers
  - upgrade rate 3.4%

21 with prior history of breast cancer or biopsy proven risk factor for breast cancer

- 4 cancers
  - upgrade rate 19%

Chaudhary et al. Mod Pathol 2013;1-10
275 patients with 276 pure LN lesions followed up
Mean follow up of 5 years (range 0.6-12.2 years)

Cancer was diagnosed in 27 of the 275 cases (9.8%)
after a mean follow up of 3.9 years

Only 3 cancers (1.1%) occurred in the same quadrant of the biopsy proven LN

Lumpectomy of pure LN lesions may not prevent malignancy;
these patients should be followed up yearly
55 years; screening mammogram
Stereotactic guided biopsy reveals lobular neoplasia
Surgical excision after wire localization: invasive lobular carcinoma grade 2
77 years; screening mammogram
77 years; screening mammogram
77 years; screening mammogram
Stereotactic guided biopsy: lobular neoplasia (ALH)
No surgery but Tamoxifen
COLUMNAR CELL LESIONS
CCLs
Columnar cell lesions (CCLs)

- Characterized by the presence of columnar epithelial cells lining enlarged TDLUs
- Spectrum of lesions with a variety of different names historically:
  - Blunt duct adenosis
  - Columnar alterations of lobules
  - Atypical lobules type A
  - DIN flat monomorphic type
  - CAPSS
  - Atypical cystic lobules
  - Clinging carcinoma
Terminology for columnar cell lesions

• Columnar cell change (CCC)

• Columnar cell hyperplasia (CCH)

• Flat epithelial atypia (FEA)
  • (Columnar cell change with atypia)
  • (Columnar cell hyperplasia with atypia)
Clinical Features

- Pre-menopausal years
- Associated with calcifications – identified with increasing frequency
- Often seen part of proliferative fibrocystic changes
- No specific gross features
Columnar Cell Change (CCC)
Columnar Cell Change (CCC)
Columnar Cell Hyperplasia (CCH)
Flat Epithelial Atypia (FEA)

- Histologic hallmarks of FEA:
  - Low-grade (monomorphic) cytologic atypia
  - Nuclei usually round rather than elongated
  - Flat growth pattern (no architectural complexity)
  - Features do not fulfill combined architectural and cytologic criteria for diagnosis of ADH or DCIS
Flat Epithelial Atypia (FEA)
Flat Epithelial Atypia (FEA)
Flat Epithelial Atypia (FEA)
Columnar Cell Lesions
How do we make the diagnosis?

Columnar cell change

Hyperplasia

No

Cytologic atypia

Yes

Simple

Cytologic atypia

Complex

Cytologic atypia

No

Columnar cell change (CCC)

Yes

Flat epithelial atypia (FEA)

No

Columar cell hyperplasia (CCH)

Yes

ADH/DCIS
Columnar Cell Lesions
How reproducible are we?

• Interobserver variability studies

  • Poor agreement: Tan, J Clin Pathol, 2005
    • « …the lowest numbers of complete agreement were in the
categories of CCC with cytological atypia … This underscores
the fact that cytological atypia is subjective, and the threshold
between pure CCC and that with cytological atypia is difficult to
delineate »
    • Interobserver kappa = 0.48

  • ‘Excellent’ agreement: O’Malley, Mod Pathol, 2006
    • « The diagnosis of FEA and its distinction from CCLs without
atypia is highly reproducible with the use of available diagnostic
criteria »
    • Interobserver kappa = 0.83
Differential Diagnosis

- CCLs vs FEA
- FEA vs ADH/LG DCIS
- CCLs vs apocrine cysts/microcysts
- CCLs vs UDH
Flat Epithelial Atypia

• The “missing link” in breast cancer progression?

• Molecular studies
  • Spectrum of genetic changes of CCLs through DCIS and invasive carcinoma
  • FEA is a clonal proliferation
Low grade breast neoplasia family

Ellis, Mod Pathol, 2010
FEA – Clinical Significance

- Data limited
- FEA often seen associated with:
  - Tubular carcinoma
  - ADH/low grade DCIS
  - Lobular neoplasia
- Risk is low
- Non-obligate precursor
FEA – Practical issues

• CCLs on Core Biopsy
  • CCLs without atypia
    • No additional pathology w/up
    • Not excised
  • CCLs with atypia (FEA)
    • Additional levels – r/o ADH low grade DCIS
    • Excise?
FEA – Practical issues

- CCLs on Excision Biopsy
  - CCLs without atypia
    - No further treatment
  - CCLs with atypia (FEA)
    - Additional levels – r/o ADH low grade DCIS
    - Submit all tissue
    - Manage as per most developed lesion
Flat Epithelial Atypia (FEA)

- **At mammography**, FEA typically demonstrate clustered, amorphous, or fine microcalcifications that are deposited within the duct lumina of the TDLUs.
- CCLs are frequently associated with ADH, in situ and low grade invasive carcinomas in excision specimens.
- Like LN, several studies have reported on the underestimation rate of a core needle biopsy of FEA.

*Pandey et al. Radiographics, 2007; 27: S79*
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Journal</th>
<th>Number patients</th>
<th>Number patients surgery</th>
<th>Number upgrade after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Bibeau et al</td>
<td>Ann Pathol</td>
<td>8</td>
<td>3</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>2003</td>
<td>Bonnett et al</td>
<td>Mod Pathol</td>
<td>9</td>
<td>9</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>2006</td>
<td>David et al.</td>
<td>Radiol</td>
<td>59</td>
<td>40</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>2006</td>
<td>Lim et al.</td>
<td>J Clin Pathol</td>
<td>8</td>
<td>5</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>2007</td>
<td>Datrice et al.</td>
<td>Am Surg</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>Kunju et al.</td>
<td>Hum Pathol</td>
<td>14</td>
<td>12</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>2007</td>
<td>Martel et al.</td>
<td>Virchows Arch</td>
<td>63</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>De Mascarel et al</td>
<td>Virchows Arch</td>
<td>101</td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>2008</td>
<td>Kumaroswamy et al</td>
<td>J Clin Pathol</td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>Chivukula et al.</td>
<td>Am J Clin Pathol</td>
<td>39</td>
<td>35</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>2009</td>
<td>Darvishian et al</td>
<td>Ann Clin Lab Sci</td>
<td>12</td>
<td>12</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>2009</td>
<td>Hayes et al.</td>
<td>J Clin Pathol</td>
<td>8</td>
<td>8</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>2009</td>
<td>Noel et al</td>
<td>Surg Oncol</td>
<td>60</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>Piubello et al</td>
<td>Am J Surg Pathol</td>
<td>33</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>Senetta et al</td>
<td>Mod Pathol</td>
<td>41</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>Tomasino et al</td>
<td>J Cell Physiol</td>
<td>54</td>
<td>6</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>2010</td>
<td>Ingegnoli et al</td>
<td>Breast J</td>
<td>18</td>
<td>15</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>2010</td>
<td>Noske et al</td>
<td>Hum Pathol</td>
<td>43</td>
<td>30</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>2010</td>
<td>Flegg et al</td>
<td>J Surg Oncol</td>
<td>5</td>
<td>5</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>2010</td>
<td>Lee et al</td>
<td>Breast J</td>
<td>15</td>
<td>7</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>2011</td>
<td>Lavoué et al</td>
<td>Breast Cancer Res Treat</td>
<td>60</td>
<td>60</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>2011</td>
<td>Vershuur- Maes et al</td>
<td>Int J Cancer</td>
<td>69</td>
<td>24</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>2011</td>
<td>Rajan et al</td>
<td>J Clin Pathol</td>
<td>38</td>
<td>37</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>2012</td>
<td>Uzoaru et al</td>
<td>Virchows Arch</td>
<td>145</td>
<td>95</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>2012</td>
<td>Bianchi et al</td>
<td>Virchows Arch</td>
<td>190</td>
<td>190</td>
<td>18 (9.5%)</td>
</tr>
<tr>
<td>2012</td>
<td>Biggar et al</td>
<td>Breast J</td>
<td>51</td>
<td>51</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>2012</td>
<td>Peres et al</td>
<td>Breast cancer Res Treat</td>
<td>128</td>
<td>95</td>
<td>10 (10.5%)</td>
</tr>
<tr>
<td>2013</td>
<td>Khoumais et al</td>
<td>Ann Surg Oncol</td>
<td>104</td>
<td>94</td>
<td>10 (9.6%)</td>
</tr>
</tbody>
</table>
Biopsy proven Columnar Cell lesions (CCL)

- CCL without Atypia
  - N=630
  - Surgery N=70; 11%
  - 10 cancers 15%
  - Pooled underestimation risk for all patients 1.5%

- CCL with Atypia
  - N=668
  - Surgery N=389; 58%
  - 57 cancers 17%
  - Pooled underestimate risk for all patients 9%

- CCL with ADH
  - N=374
  - Surgery N=310; 89%
  - 61 cancers 26%
  - Pooled underestimate risk for all patients 20%

Flat Epithelial Atypia (FEA)

• When a biopsy result shows FEA:
  • Technical parameters:
    • **Biopsy device:** Needle gauge, vacuum assisted…
    • **Size of the target:** large cluster with residual microcalcifications
  ! Removal of all the mammographic target does not imply definitive removal of the pathologic anomaly

• **Radiology/pathology concordance: FEA is discordant when:**
  • BIRADS V lesion
  • Mass / distortion / asymmetric density

• **Family history**
Ultrasound guided biopsy of both lesions: FEA
Surgical excision after wire localization: invasive carcinoma grade 1
50 years old, mag views after Screening mammogram
50 years old, mag views after Screening mammogram
50 years old, mag views after Screening mammogram
Stereotactic guided biopsy: FEA
Surgical excision after wire localization: Invasive tubular carcinoma
DOES THE PATIENT WITH ALH & LCIS ON CORE NEEDLE BIOPSY REQUIRE A SURGICAL EXCISION?
Standard Reponse in 2013

• YES! Excision Recommended

• « 10-15% of ALH/LCIS on Core Needle Biopsy are upstaged to DCIS or Infiltrating Carcinoma on Excisional Biopsy »

• This recommendation may change with newer studies showing less upstaging
NCCN Guidelines for LCIS 2013
(National Comprehensive Cancer Network)
But...the risk benefit ratio is always patient specific

« I have a 90% chance of not having cancer... »

« No one in my family has ever had breast cancer »

« Will my breast be deformed? »
When is close follow-up reasonable?

- Radiologic abnormality is concordant with pathology
- Patient is willing to assume the small risk of malignant neoplasia remaining unexcised
Breast Cancer Risk Reduction

• Stop hormone therapy if possible
• Limit alcohol consumption to 1 drink per day
• Exercise
• Weight Control
• Pharmacologic Intervention
American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction

Exemestane for Breast-Cancer Prevention in Postmenopausal Women

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., José E. Alés-Martínez, M.D., Angela M. Cheung, M.D., Ph.D., Rowan T. Chlebowski, M.D., Ph.D., Jean Wactawski-Wende, Ph.D., Anne McTiernan, M.D., John Robbins, M.D., Karen C. Johnson, M.D., M.P.H., Lisa W. Martin, M.D., Eric Winquist, M.D., Gloria E. Sarto, M.D., Judy E. Garber, M.D., Carol J. Fabian, M.D., Pascal Pujol, M.D., Elizabeth Maunsell, Ph.D., Patricia Farmer, M.D., Karen A. Gelmon, M.D., Dongsheng Tu, Ph.D., and Harriet Richardson, Ph.D., for the NCIC CTG MAP.3 Study Investigators*
Relative Risk Reduction in Randomized Trials in Which Eligibility: 5 yr Gail Risk >1.6 or LCIS

Pre menopausal women (age 35 & up) → Tamoxifen (50%)

Post menopausal women → Tamoxifen (50%)
Raloxifene (40%)
Exemestane (65%)

Reduction in ER+ but not ER- cancer
No survival advantage

Side Effects of Preventive Agents

Tamoxifen

- Hot flashes & vaginal discharge
- DVT, PE
- Uterine carcinoma and sarcoma (1.6% at 7 years)
- ?Cataracts

Raloxifene

- Hot flashes & vaginal dryness
- DVT, PE

A few Caveats

- Contraindications to tamoxifen or raloxifene:
  - history of DVT or PE
  - thrombotic stroke, TIA
  - known inherited clotting trait

- American Cancer Society lists tamoxifen as a known carcinogen

- « Use should not be avoided in cases where the risk of breast cancer without the drug is higher than the risk of developing uterine cancer with the drug »
Side Effects of Preventive Agents

Exemestane
• Hot flashes & vaginal dryness
• Joint and muscle pain
• Bone density loss
• Fatigue

*therapy influenced by osteoporosis

Goss NEJM 2011 363:2381
What if patient asks for a mastectomy?
(NCCN Guidelines)

• Discussion of risk reduction mastectomy in high-risk women with:
  • BRCA1/2
  • other strongly predisposing gene mutation
  • compelling family history
  • prior thoracic radiation therapy <30 y of age
  • possibly women with LCIS
Conclusions

- Surgeons suggest surgical excision for ALH/LCIS
- Counsel patients concerning risk reduction
- Prophylactic mastectomies for LCIS extremely rare