No conflict of interest
Atypia

Figure 6: Breast cancer does not develop overnight. Gradually the cells become more abnormal-looking or atypical (see text). Eventually, the cells are recognized as being sufficiently abnormal to be called cancer cells that are initially inside the milk ducts (in situ cancer), and later become invasive breast cancer cells.
Definition of ADH or ALH

- Lesion defined by changes similar to DCIS or LCIS but lack the complete criteria for the diagnosis or are less than the fully developed form.
- Could be DCIS but only one microscopic duct involved.
- Absence of defined architectural and cytologic features of DCIS.
- Diagnostic reproducibility of ADH is poor.
- Hence there are inter-pathologist variations in interpretation.
Atypical Ductal Hyperplasia
Atypical Lobular Hyperplasia
Clinical presentation

- Mammographic abnormality (usually cluster of calcifications) - diagnosis made on stereotactic core biopsy or fine wire localization biopsy

- Palpable lesion - atypia in association with a benign lesion
Atypia diagnosis obtained from Core Biopsy
Diagnosis on core biopsy

- Ms K age 63
- Obese, diabetic woman of East Indian decent
- Screening mammogram shows calcifications
- Core biopsy atypical ductal hyperplasia
Ms. K fine wire biopsy
Ms K specimen radiograph
Ms K  final pathology

PATHOLOGY REVIEW

SLIDES FROM ST. PAUL’S HOSPITAL
W04-3994 (9) Sep. 9

7 X 3 X 1 CM FINE WIRE LOCALIZATION BIOPSY OF LEFT BREAST
- Low grade cribriform ductal carcinoma in situ extending within less than 1 mm of multiple biopsy margins.
- Overall size of ductal carcinoma in situ indeterminate, at least 1 cm.
- Additional microscopic foci of atypical duct hyperplasia, including atypical ductal hyperplasia within small intraductal papillomas.

Comment: Microcalcifications are seen within scattered small areas of low grade cribriform ductal carcinoma in situ and within atypical duct hyperplasia. There are also scattered small intraductal papillomas with varying degrees of ductal atypia. There are scattered small foci of low grade ductal carcinoma in situ extending within less than 1 mm of margins in a few foci within different sections, as designated in the outside hospital pathology report.
Atypia on core biopsy

- Most of the data comes from the radiological literature
- Long term follow up not easily found
- A core is only an 11 to 14 gauge needle and thus only represents a portion of the lesion
## ADH on Core Biopsy

<table>
<thead>
<tr>
<th>Author</th>
<th># Patients</th>
<th>ADH on Core</th>
<th>FWLB % Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao 2003</td>
<td>1036</td>
<td>53</td>
<td>50%</td>
</tr>
<tr>
<td>Winchester 2003</td>
<td>1750</td>
<td>77</td>
<td>17%</td>
</tr>
<tr>
<td>Eby 2008</td>
<td>991</td>
<td>141 focal ADH</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 8-susp dcis</td>
<td>44.4%</td>
</tr>
<tr>
<td>Wagoner 2009</td>
<td>123</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>Foster 2004</td>
<td>6081</td>
<td>75</td>
<td>17%</td>
</tr>
</tbody>
</table>
### DIN1A on Core Biopsy
(very difficult to find literature)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>CASES</th>
<th>UPGRADE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ladshimi 2007</td>
<td>14</td>
<td>3</td>
<td>21%</td>
</tr>
<tr>
<td>Purdy 2006</td>
<td>12</td>
<td>2</td>
<td>16.6%</td>
</tr>
<tr>
<td>Mairtza 2007</td>
<td>63</td>
<td>9</td>
<td>14.3%</td>
</tr>
<tr>
<td>Bogi (CCC change)</td>
<td></td>
<td></td>
<td>30%</td>
</tr>
</tbody>
</table>
Flat Epithelial Atypia -?DIN1a (columnar cell change)

<table>
<thead>
<tr>
<th>Study/Category</th>
<th>2006-2008</th>
<th>2009</th>
<th>Total (CNB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chivukula 2009</td>
<td></td>
<td>2009</td>
<td>8054 CNB</td>
</tr>
<tr>
<td>Follow-up excision FEA</td>
<td>FEA 190</td>
<td>FEA 35</td>
<td>ADH 45</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>8.4%</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>DCIS</td>
<td>7.9%</td>
<td>3%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Columnar Cell Lesions

Senetta 2009

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL without atypia</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>FEA</td>
<td>55</td>
<td>1.8%</td>
</tr>
</tbody>
</table>
BC study on DIN1a

In process. No firm data yet
About 150 cases on core biopsy
Few DCIS
one invasive (prev inv ca same breast)
Clinical case of atypia

- 50 yr old slim, healthy female with history of grandmother and great aunt with breast ca
- Multiple previous screening mammos with known dense breasts
- Feb 09 Calcifications R breast - core biosy DIN1a,1b and susp for 1c
- MRI done showing susp lesion L breast
Left side fine wire
Right side fine wire-atypia
Clinical case of Atypia-cont

- US guided core biopsy-invasive ca-L
- Apr 09 R Fine wire biopsy and 2 L fine wire biopsies plus L SLNB
- Din1a anb b on both sides. Nodes neg
- Cancer missed
Clip insertion under US
Clinical case Atypia cont

- June 09 repeat FWLB and successful removal or cancer
- Patient chose radiation
  - Without the MRI, this patient would have presented in the future with a breast cancer when it would have become large enough to detect
## ALH on Core Biopsy

<table>
<thead>
<tr>
<th>Author</th>
<th># patients</th>
<th>ALH on core</th>
<th>FWLB % Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster 2004</td>
<td>6081</td>
<td>20</td>
<td>10%</td>
</tr>
<tr>
<td>Dymtrasz 2003</td>
<td>766</td>
<td>13</td>
<td>50%</td>
</tr>
<tr>
<td>Elsheikh 2005</td>
<td>20</td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td>Polom 2009</td>
<td>4326</td>
<td>17</td>
<td>29.4%</td>
</tr>
</tbody>
</table>
ALH or ADH on core bx

- If atypia of any type is found on core biopsy, then
- 10 to 50% will have cancer (insitu or invasive) found on excision of the area
- All authors recommend fine wire localized excision
What is the Significance of ADH and ALH from open biopsy?

A progressive lesion or simply a risk marker?
Relative risk for invasive ca

- No increased risk in non proliferative disease as cysts, duct ectasia
- Slight (1.5-2X) increased risk in hyperplasia of usual type, sclerosing adenosis, papilloma
- Moderate risk (4-5X) in atypical hyperplasia
- High risk (8-10X) in LCIS
Atypia and risk of invasive ca

- Dupont and Page 1985 NEJM
- Previous open biopsy followed for 17 yrs
- 3303 women-1925 with proliferative disease
  - cysts: 1.3
  - Proliferative disease: 1.9
  - ADH: 5.3
  - AH with Family history: 11
Atypia and risk of invasive ca

Figure 1. Proportion of Patients Free of Invasive Breast Cancer, as a Function of the Time since the Entry Biopsy.
Atypia and risk of invasive ca

- London et al 1992
- 8 yr follow up

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No proliferation</td>
<td>1</td>
</tr>
<tr>
<td>Proliferative disease</td>
<td>1.6</td>
</tr>
<tr>
<td>AH</td>
<td>3.7</td>
</tr>
</tbody>
</table>
Atypical Lobular Hyperplasia

- Page et al 2003 (lancet)
- Retrospective analysis of 252pt (261) biopsies 1952-1985
- 50 (20%) developed invasive ca
- 68% in same breast
- 24% in contralateral breast
- ALH risk intermediate between local process and overall risk
Nurses Health Study-ADH

- Mean age at biopsy 43.5 yrs
- Correlations with ADH
  - More women were:
    - Older
    - More ETOH use
    - More likely to use HRT
    - More likely to have fam hx of breast ca
## Nurses Health Study (1976-1995) risk of breast ca

<table>
<thead>
<tr>
<th>Type</th>
<th>All breast ca</th>
<th>Invasive breast ca</th>
<th>Pre-men at dx</th>
<th>Post-men at dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non proliferative</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Proliferative no atypia</td>
<td>1.5</td>
<td>1.58</td>
<td>1.39</td>
<td>1.89</td>
</tr>
<tr>
<td>Atypia</td>
<td>4.9</td>
<td>4.04</td>
<td>3.89</td>
<td>4.04</td>
</tr>
<tr>
<td>Ductal</td>
<td>3.99</td>
<td>2.77</td>
<td>2.72</td>
<td>4.04</td>
</tr>
<tr>
<td>Lobular</td>
<td>5.78</td>
<td>5.72</td>
<td>7.3</td>
<td>3.41</td>
</tr>
<tr>
<td>Ductal &amp; lobular</td>
<td>6.95</td>
<td>8.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nurses Health Study cont

- Risk of ca increased after 10 yrs
- Risk constant with ALH but increased with ADH
- Among all women with AH who developed breast ca 56% developed in the ipsilateral breast
- With ALH 61-70% occurred in the ipsilateral breast
Atypia at surgical margin—should re excision be done?
Case of 42 yr old

- Healthy, no risk factors
- Somewhat difficult patient
- Aug 2007 palp mass R breast
- Mammo and US – cyst but bilateral calcs
- Nov 08 Core bx L -ADH
- Dec 08 FWLB L ADH(margins clear)
- Feb 09 new calcs seen on digital L and core biopsy done showing DCIS
Left Breast mammo
Case 42 yr old continued

- June 09 MRI show susp lesion R
- Core biopsy under us invasive ca at 6 and DIN 1a at 8:30
Right susp on MRI
Right Core biopsy under US
42 yr old continued

June 29/09 bilateral mastectomies, right SLNB and bilateral reconstruction
PATH: DCIS on left
12 mm invasive ca right
2/2 nodes positive
Atypia at margin

- Arora et al. NY 2008
- 2001-2006 44 pts with ca with ADH at margins
- 24 pts re excision
- 14 had residual ADH or ca (58%)
- 25% with ADH only at margins had DCIS or Invasive ca
- Re-excision recommended
Atypical Hyperplasia

- Does the entire lesion need to be excised?
  - Yes, if you believe this is a progressive lesion
  - No, if you believe it is simply a risk marker
LCIS and cancer risk

- LCIS is considered a marker for increased risk of ca in both breasts
- Risk assessed at increasing at 1% per year for a lifetime risk of up to 30%
- Higher risk if associated family history (up to 50%)
## Clinical Management of ALH and LCIS

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>LCIS is designated as “carcinoma” and mastectomy is recommended</td>
</tr>
<tr>
<td>1941–1970</td>
<td>Mastectomy with contralateral biopsy is favored over observation</td>
</tr>
<tr>
<td>1970</td>
<td>Introduction of mammographic screening and increased public awareness of breast cancer</td>
</tr>
<tr>
<td>1978</td>
<td>Rosen and colleagues reported that invasive carcinoma subsequent to LCIS was exceptional</td>
</tr>
<tr>
<td>1985</td>
<td>NSABP legitimized breast preservation as alternative to mastectomy</td>
</tr>
<tr>
<td>1986</td>
<td>Haagensen reports that the majority of patients with LCIS never develop invasive carcinoma</td>
</tr>
<tr>
<td>1996</td>
<td>Observation is favored over mastectomy with contralateral biopsy</td>
</tr>
</tbody>
</table>
LCIS and risk of breast ca

- NSABP data 2004
- 180 pt with 12 year follow up
- 26 (14%) ca in same breast, 9 were invasive (8 lobular invasive)
- 96% in the same quadrant
- 14 (8%) ca in contralateral breast, 8 were invasive (6 were lobular inv.)
Management of lobular neoplasia

- Anderson 2006 review (Seattle)
- ALH and LCIS ob core biopsy need FWLB
- Found on surgical biopsy do not require further intervention even if at margins
- Consider bilateral mastectomies in special circumstances
Treatment options for ADH and ALH

- Excise entire lesion (if possible)
- Close follow up with yearly mammograms and 6 mo clinical exam
- Tamoxifen for 5 years - 49% risk reduction in prevention trials
- Raloxifene 50% risk reduction
- Aromatase inhibitors under study in post menopausal women only
- Bilateral mastectomies (consider with family history)
BCPT Results: Cumulative Rate of Invasive Breast Cancer

<table>
<thead>
<tr>
<th>Events</th>
<th>Rate per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>175</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>89</td>
</tr>
</tbody>
</table>

Rate/1000

$P < 0.00001$

Prophylactic mastectomies
Conclusions

- ADH, LDH and LCIS are lesions that the surgeon will frequently encounter.
- If detected on core biopsy, surgical excision biopsy is appropriate.
- There is a significant increased risk of developing in situ or invasive cancer in the future with the risk increasing over time.
- Patients need to be counselled on the long term risk and on the options of treatment.