Intraductal Epithelial Proliferations of Breast
Classification, Diagnosis & Management

A. A. Sahin, M.D.
Professor of Pathology and Translation Molecular Pathology
Section Chief of Breast Pathology
Intraductal Epithelial Proliferations of Breast

- classification/definitions
- morphologic features
- practical issues
- clinical significance
Intraductal Epithelial Proliferations of Breast

- Frequently associated with microcalcifications
- Increasingly seen in the era of mammographic screening
- Further increase noted with introduction of digital mammography
• Heterogeneous group of lesions
• Diverse architectural and cytologic features
Intraductal Epithelial Proliferations of Breast

• May be clinically evident
  – Palpable mass
  – Mammographic abnormality

• Originates primarily in TDLUs and confined to ductal/lobular system
• Relationship to malignancy
  – Histologic co-existence
  – Long term studies
Intraductal Epithelial Proliferations of Breast

- Clinical considerations
  - Presence of an associated more advanced lesion
  - Risk of subsequent breast cancer
• Retrospectively reviewed >10,000 benign breast bx from >3000 pts.
• Related histologic findings in benign breast bx to subsequent breast ca. risk (med. f/u 17 yrs)
Intraductal Epithelial Proliferations of Breast

- Non-proliferative
- Proliferative without Atypia
- Atypical Hyperplasia
Relative Risk of Breast Cancer Among Women with Bx-Confirmed IEP

- Relative Risk (RR): 1.5-2x
- RR: 4-5x

Bar chart showing:
- NP
- PWA
- AH

Legend:
- Yellow: Nashville, 1985
- Light Blue: BCDDP, 1993
- Pink: Mayo, 2005
- Purple: NHS, 2006
Non Proliferative Lesions

- Apocrine metaplasia
- Cyst
- Adenosis
- Mild ductal epithelial hyperplasia
Intraductal Epithelial Proliferations of Breast

Non-proliferative

Proliferative Without Atypia

Atypical Hyperplasia
Intraductal Epithelial Proliferations of Breast

DH  ADH  DCIS
Intraductal Epithelial Proliferations of Breast

DH  ADH  DCIS
NON-PROLIFERATIVE LESIONS

- Cysts
- Apocrine metaplasia
- Papillary apocrine change
- Mild epithelial hyperplasia usual type
NON-PROLIFERATIVE LESIONS

- 70% of all biopsies
- No increase in risk of subsequent breast cancer development
PROLIFERATIVE LESIONS WITHOUT ATYPIA

- Hyperplasia without atypia
- Intraductal papilloma
- Sclerosing adenosis
- Fibroadenoma
DUCTAL HYPERPLASIA WITHOUT ATYPIA

Proliferation of heterogeneous cell population
DUCTAL HYPERPLASIA

Cytologic polymorphism

- epithelial
- myoepithelial
- apocrine metaplasia
DUCTAL HYPERPLASIA WITHOUT ATYPIA

Cell thickness

Mild: 3 - 5
Moderate: 5 - 10
Florid: > 10
DUCTAL HYPERPLASIA
DUCTAL HYPERPLASIA
DUCTAL HYPERPLASIA
CLINICAL FEATURES OF DH

• Age (years)
  range :  15 - 75
  mean :  45

• Clinical presentation
  Mammographic abnormality
  Palpable mass
  Incidental
ARCHITECTURAL FEATURES OF DH

Irregular and slit-like fenestration
Peripheral distribution of fenestration
Stretched epithelial bridges
Streaming or spindling of cells
Uneven distribution of nuclei
Hyperplasia without Atypia

- Frequency of genetic/molecular alterations much lower than in AH
- 7% show aneuploidy
- 15% show LOH
- 7% show chromosome loss or gains by CGH
Hyperplasia without Atypia

- 2.6% develop subsequent invasive breast carcinoma
- Average interval 14 years
ATYPICAL DUCTAL HYPERPLASIA

Definition
Intraductal epithelial proliferation with some, but not all features of low grade intraductal carcinoma
ATYPICAL DUCTAL HYPERPLASIA

Revised Definition
Intraductal epithelial proliferation with cytologic features identical to low grade intraductal carcinoma but lacks architectural features or quantitatively too small
FEATURES OF DCIS

• Uniform population of cells
• Smooth geographic spaces with even cellular placement
• Hyperchromatic nuclei
ATYPICAL DUCTAL HYPERPLASIA

Cytologic Features

• Monotonous, uniform rounded cell population
• Organized nuclear distribution
• Subtle increase in nuclear/cytoplasmic ratio
ATYPICAL DUCTAL HYPERPLASIA
ATYPICAL DUCTAL HYPERPLASIA
ATYPICAL DUCTAL HYPERPLASIA

Epithelial Proliferation

- Incompletely involved the duct space
- Completely involved duct space is too small
What is too small?
ATYPICAL DUCTAL HYPERPLASIA

Quantitative Criteria

• Two membrane bound spaces
  (Page, et al)

• 2 mm in aggregate cross-sectional diameter (Tavassoli & Norris)
DCIS

1mm 1mm
A D H vs D C I S

- 2 mm
- 0.3 mm
ATYPICAL DUCTAL HYPERPLASIA

Controversies

• Definition
• Application of histologic criteria
• Clinical significance
ATYPICAL DUCTAL HYPERPLASIA

• Clinically silent lesion
• Either mammographic finding or incidental finding in biopsies done for clinically evident lesions
• Median age: 50 yrs (range: 15 - 78)
ATYPICAL DUCTAL HYPERPLASIA

- Usually less than 3-4 mm
- Confined to an individual ductal / lobular unit
- Commonly associated with microcalcifications
ATYPICAL DUCTAL HYPERPLASIA

80% of women DO NOT develop subsequent invasive carcinoma
Subsequent Invasive Cancer

- Majority in ipsilateral breast
- 25-40% in contralateral breast
ATYPICAL DUCTAL HYPERPLASIA

• Absolute risk for subsequent invasive cancer
  5.7% - 12.9%

• Average interval to subsequent invasive cancer
  8-10 years
• Is ADH merely a small example of non-comedo DCIS?

• Is ADH a biologically distinct lesions?
ATYPICAL DUCT HYPERPLASIA

The definition includes:

• Cytologic features
• Histologic pattern
• Some indication of size (extent)
Atypical Ductal Hyperplasia vs Intraductal Carcinoma
Benign

vs

Malignant
ADH vs low grade DCIS
Are they distinct entities?
Yes

- Magnitude of risk varies
- Laterality of risk different
- Type of subsequent ca. histology different

No

- Histologic criteria poorly defined difficult to have standard criteria
- Molecular/genetic features are similar
ADH vs DCIS

• ADH appears to be a neoplastic, clonal proliferation of cells identical to those of low grade DCIS

• Less completely developed
Changing Views of AH

- AH are “markers” of generalized increase in risk and not precursor lesions
- Family history more than doubles breast cancer risk among women with AH
- Among women with AH, risk highest in first 10 years after bx.
Atypical Hyperplasia

– Atypical ductal hyperplasia (ADH)
– Atypical lobular hyperplasia (ALH)
Atypical Hyperplasia

Ductal  Lobular
Atypical Hyperplasia

Ductal

Lobular

Is the breast cancer risk the same?
Relative Risk of Breast Cancer Among Women with Bx-Confirmed IEP

RR

NP  PWA  AH

1.5-2x  4-5x

<table>
<thead>
<tr>
<th>Category of Hyperplasia</th>
<th>No. Case</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>75</td>
<td>3.9 (2.7-5.7)</td>
</tr>
<tr>
<td>ADH</td>
<td>33</td>
<td>2.8 (1.7-4.4)</td>
</tr>
<tr>
<td>ALH</td>
<td>28</td>
<td>5.2 (3.0-9.1)</td>
</tr>
</tbody>
</table>
## Menopausal Status at Time of Benign Breast Biopsy and BC Risk

<table>
<thead>
<tr>
<th></th>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Atypical Hyperplasia</td>
<td>3.9 (2.5-6.1)</td>
<td>3.8 (1.7-8.5)</td>
</tr>
<tr>
<td>ADH</td>
<td>2.7 (1.6-4.7)</td>
<td>4.0 (1.7-9.8)</td>
</tr>
<tr>
<td>ALH</td>
<td>7.3 (3.7-14.2)</td>
<td>3.4 (1.1-10.8)</td>
</tr>
</tbody>
</table>

p=0.02  p=0.82
• While both ADH and ALH are associated with an increased breast cancer risk, level of risk may be higher for ALH, especially among pre-menopausal women
Marker vs. Precursor

- Marker (risk factor)
  - generalized (bilateral) increase in risk
- Precursor
  - ipsilateral breast cancer risk (at site of initial precursor lesion)
Evaluation of laterality of breast cancers in women with prior breast biopsy can provide insight into whether these lesions represent markers or precursors.
# Laterality of Breast Cancers

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>56%</td>
<td>55%</td>
<td>“an excess”</td>
<td>56%</td>
</tr>
<tr>
<td>ALH</td>
<td>69%</td>
<td>64%</td>
<td></td>
<td>63%</td>
</tr>
</tbody>
</table>
About 60% of the subsequent breast cancers in women with breast bx showing intraductal proliferations occur in the ipsilateral breast.

Excess of ipsilateral cancers within first 10 years after benign biopsy.
• Excess of ipsilateral cancers within first 10 years after benign breast biopsy

Figure 4. Comparison of the Number of Ipsilateral Breast Cancers with the Number of Contralateral Breast Cancers over Time, According to the Histologic Appearance of Benign Breast Disease.

Results are shown for 616 cancers (342 ipsilateral and 274 contralateral cancers). The remaining 91 cases include women with bilateral benign or malignant lesions or for whom the side of the benign or malignant lesion was unknown. CI denotes confidence interval.

Hartmann et al, 2005
Laterality of Breast Cancers According to Time Since Benign Biopsy

Nurses Health Study 2006

% Ipsilateral
% Contralateral

Years after biopsy
Insights from Molecular/Genetic Studies

- ADH shares genetic abnormalities with low grade DCIS and low grade invasive breast cancers
  - Losses at 16q and 17p
  - Gains at 1q
- Suggests that ADH maybe direct precursor to low grade DCIS and low grade invasive ca. and is an early lesion in a low grade neoplasia pathway of breast tumorigenesis
Newer Insights

- Risk factors associated with intraductal epithelial proliferations
- Risk factors for different molecular subtypes
• Most prior studies evaluating risk factors have considered breast cancer as a single group
Breast Cancer Subtypes Determined by Gene Expression Profiling

Sorlie, 2001
Breast Cancer Risk Factors

• Some risk factors differ for ER+ and ER- breast cancer
• Not yet known if risk factors differ across the recently described molecularly-defined breast cancer types
• Neither HRT nor alcohol consumption add to the risk associated with AH

• ? Risk factors such as FH, HRT, and alcohol promote development of AH but no longer represent risk factors in women with established AH
Differences in Risk Factors for Breast Cancer Molecular Subtypes in a Population-Based Study


Risk of Luminal B, HER2 and Basal-like Cancers Relative to Risk of Luminal A for Several Breast Cancer Risk Factors

- * significant increase
- + significant decrease
• Increased BMI associated with reduced risk of luminal A ca. among pre-menopausal women (OR 0.71)
• Later age at menarche associated with greatest reduction in risk for basal-like ca. (OR 0.78)
• Magnitude of effect of family history on increasing risk greatest among basal-like ca.
Summary

- Impact of several established breast cancer risk factors may differ according to the molecularly-defined category of breast cancer.

- The identification of risk factors for these different breast cancer types could be of value in patient risk assessment and prevention.
Classification of Intraductal Epithelial Proliferations

• Evolving concept
• Likely to be modified with additional molecular/ genetic data
Goal

To have a biologically based classification system with clinical application for risk assessment
Intraductal Epithelial Proliferations of Breast

Clinical Management
Multidisciplinary Approach
Pathology
Radiology
Surgery
Medical Oncology
Recent studies have provided new insights into the relationship between IDEP and have raised questions about the prevailing views of influence on breast cancer risk of:

- Type of atypical hyperplasia
- Family history
- Time since biopsy
Conclusions

• Some benign breast lesions appear to represent direct breast cancer precursors rather than just “markers” of increased risk.

• However, for the purposes of risk assessment and clinical management, these lesions are still best viewed as markers of a generalized (bilateral) increase in breast cancer risk.
INTRADUCTAL CARCINOMA

Proliferation of malignant epithelial cells within ductal lobular system without invasion into surrounding stroma
Heterogeneous

• mode of presentation
• histologic appearance
• clinical behavior
<table>
<thead>
<tr>
<th>Comedo</th>
<th>Non Comedo</th>
</tr>
</thead>
<tbody>
<tr>
<td>cribiform</td>
<td>papillary</td>
</tr>
<tr>
<td>micropapillary</td>
<td>solid</td>
</tr>
<tr>
<td>Traditional</td>
<td>Current</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>• cribiform</td>
<td>• low grade</td>
</tr>
<tr>
<td>• micropapillary</td>
<td>• intermediate grade</td>
</tr>
<tr>
<td>• papillary</td>
<td>• high grade</td>
</tr>
<tr>
<td>• solid</td>
<td></td>
</tr>
<tr>
<td>• comedo</td>
<td></td>
</tr>
</tbody>
</table>
• Clinically relevant
• Reproducibly applicable by different observers
1999 Consensus Conference of the Classification of DCIS

• No single system is endorsed
• Histologic grading should include
  - nuclear grade
  - architectural pattern
  - presence of necrosis
Size / Extent Correlates

- Occult invasion
- Axillary nodal metastases
INTRADUCTAL CARCINOMA

Final Pathology Report

- Histologic classification
  - nuclear grade
  - histologic pattern
  - necrosis
- Size
- Margin status
Evaluation of Margin

Careful assessment of
- Specimen x-ray
- Histopathologic review
Contents of Surgical Pathology Report

Histologic features -
- nuclear grade
- arch. pattern
- necrosis

- Size (extent)
- Status of margin
D C I S of Breast

- Accounts 20-30% of BC
- 65,000 pts annually
- Most diagnosed on screening
- Primary aim of treatment is prevention of invasive BC
D C I S of Breast

Fundamental Issues

• Over diagnosis
• Over treatment
Multidisciplinary approach is essential

- Pathologists
- Surgeons
- Oncologists
- Molecular Biologists
Thank You!