Borderline Breast Disease: a Terminology that Minimize Over Diagnosis of Low-Grade Ductal Carcinoma In Situ in Core Needle
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The Plan

- To highlight the challenges associated with diagnosis of atypical proliferative lesions in breast pathology
- To discuss the critical need for a changing trend in diagnosis and management of these entities

Why the Emphasis on Atypical Proliferative Breast Lesions?
The Facts

- Screening mammography and image detected biopsy have increased the diagnosis of atypical proliferative breast lesions and ductal carcinoma *in situ*.

The Facts

- The number of invasive breast cancer cases has not decreased.
- The distinction between ADH and low-grade DCIS has remained a diagnostic challenge.
- This problem commonly leads to over-diagnosis and overtreatment:
  - More expense
  - More patient anxiety
- There is evidence suggesting that low-grade DCIS may not need cancer therapy.

The Story of Atypical Ductal Hyperplasia

The Facts

- Women who have a history of benign breast disease experience higher incidence of breast cancer.
- Fibrocystic change includes the spectrum of changes ranging from physiologic alterations to features approximating *in situ* lesions.
### Classification (Dupont and Page 1985)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-proliferative breast disease</td>
<td>Cysts, mild hyperplasia, simple fibroadenoma, papillary apocrine change</td>
</tr>
<tr>
<td>Proliferative breast disease without atypia</td>
<td>Complex fibroadenoma, moderate-florid hyperplasia, florid sclerosing adenosis, intraductal papilloma</td>
</tr>
<tr>
<td>Proliferative breast disease with atypia</td>
<td>Atypical ductal hyperplasia, Atypical lobular hyperplasia, Pagetoid extension to extralobular duct, Radial scar with atypia, Multiple papilloma syndrome</td>
</tr>
</tbody>
</table>

### Frequency and Risk Stratification

* Dupont and Page 1985 NEJM 312, 146-51

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Incidence</th>
<th>Relative Risk</th>
<th>Family History</th>
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</thead>
<tbody>
<tr>
<td>Non-proliferative breast disease</td>
<td>69.7</td>
<td>0.86</td>
<td>1.2</td>
</tr>
<tr>
<td>Proliferative breast disease without atypia</td>
<td>26.7</td>
<td>1.9</td>
<td>2.7</td>
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<tr>
<td>Proliferative breast disease with atypia</td>
<td>3.6</td>
<td>4.3</td>
<td>11.0</td>
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</table>

### Intraepithelial Neoplasia

<table>
<thead>
<tr>
<th>ER 10-30%</th>
<th>Ki-67 ≤ 1%</th>
<th>Proliferation and apoptosis balanced</th>
<th>Pro</th>
<th>Hyperplasia</th>
<th>Atypia</th>
<th>in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR=1</td>
<td>RR=2</td>
<td>RR=5</td>
<td>RR=10-20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-Proliferative Breast Disease

Proliferative Breast Disease without Atypia

Proliferative Breast Disease with Atypia, ADH
Low-Grade DCIS

ADH Versus DCIS

“An Entity Which Has Some but Not All The Features of Low Nuclear Grade Ductal Carcinoma in situ”

Morphologic Criteria for Low-Grade DCIS (Page and Anderson 1987)
- Two ductal spaces completely effaced in a single terminal ductal lobular unit
- Monomorphous population
- Non-polarized epithelium
- Cribriform bridges without attenuation
- Uniform lacunar spaces
**Morphologic Criteria for Low-Grade DCIS (Tavassoli and Norris 1990)**

- Minimum involvement of two duct spaces
- Sums of diameters of duct spaces must be $\geq 2\text{mm}$

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**Interobserver Variability**

*Hyperplasia versus low-grade ductal carcinoma in situ*

No Standardized Criteria:
10 Cases, 5 Pathologists

- Number of Pathologists in exact agreement/ Percent of Cases:
  - 5 of 5 agreed in 0% of cases
  - 4 of 5 agreed in 20% of cases
  - 3 of 5 agreed in 50% of cases


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**Interobserver Variability**

*Hyperplasia versus low-grade ductal carcinoma in situ*

Standardized Criteria:
24 Cases, 6 Pathologists

- Number of Pathologists in exact agreement/ Percent of Cases
  - 6 of 6 agreed in 58% of cases
  - 5 of 6 agreed in 71% of cases
  - 4 of 6 agreed in 92% of cases

Elmore conducted a study to assess the degree of agreement among expert breast pathologists and general pathologists. Overall, a set of 60 breast biopsies (240 total cases – 1 slide/case) were available. Concordance rate of diagnostic interpretations of participating pathologists was 75.3% with the highest level of concordance seen for invasive cancer. Lower level of concordance was seen for DCIS and atypia.


The Issue

“Is it possible that ADH and low-grade DCIS are in reality representing the spectrum of the same entity?”
Suggested Terminologies

- “Intraepithelial Mammary Neoplasia”
- “Ductal Intraepithelial Neoplasia”
- “Low Nuclear Grade Breast Neoplasia Family”
- “Borderline Breast Disease”
- “Indolent Lesions of Epithelial Origin” (IDLE)

ADH vs. DCIS

- “There is no consensus presently on the criteria that should be adopted and how they should be applied for the distinction between atypical ductal hyperplasia and carcinoma in situ”


ADH vs. DCIS

- “Morphological criteria for the diagnosis of “atypia”, implying increased breast cancer risk, and in situ carcinoma may be improved when it is possible to relate proliferative lesions to specific genetic or biochemical markers”

Atypical Ductal Hyperplasia vs. Low-Grade Ductal Carcinoma \textit{in situ}

Diagnostic Challenge
- FNA biopsy
- Core needle biopsy
- Surgical biopsy

The story of a patient

The Story
- A self-referred newly diagnosed breast cancer patient was scheduled to undergo mastectomy and lymph node dissection
- The patient was 32 years old with no risk factors and discovered the mass when she was showering
- The breast mass was sampled by core needle biopsy and was diagnosed as an invasive cancer
- A palpable lymph node was found and was assumed to represent a lymph node metastasis
- The patient was advised to have mastectomy and axillary dissection followed by chemotherapy
Biopsy Original Diagnosis

- Invasive moderately differentiated ductal carcinoma
- Low-grade ductal carcinoma in situ

Review of the Biopsy at our Institution

Follow-up Excisional Biopsy
Consultant Reviews

- **Diagnosis #1**: Atypical apocrine adenosis with sclerosis and associated florid sclerosing adenosis
- **Diagnosis #2**: Low-grade apocrine ductal carcinoma *in situ*, with focal sclerosis, periductal and radial, involving multiples cores

The patient agreed to undergo close surveillance

New York Times Article: “Prone to Error: Earliest Steps To Find Cancer”
The Story of the Patient

The Question: Whose Fault is it?

- Are we overdiagnosing and overtreating our breast cancer patients?
- Do we know how to accurately distinguish between ADH and low-grade DCIS?
Atypical Proliferative Breast Lesions

- High molecular weight Cytokeratin 5/6
  - Distinction between florid ductal hyperplasia and ADH and low-grade DCIS
- E-cadherin
  - Lobular versus ductal lesions

The Use of Immunostains

Cytokeratin 5/6
The Use of Immunostains

Cytokeratin 5/6

Detection Rate for Cancer in Surgical Excision After Core Needle Biopsy

<table>
<thead>
<tr>
<th>Pathologic Factors</th>
<th>Increased Rate of Malignancy of Excision</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>13-66%</td>
</tr>
<tr>
<td>DCIS</td>
<td>Up to 20%</td>
</tr>
<tr>
<td>Flat Atypia</td>
<td>13-20%</td>
</tr>
<tr>
<td>Lobular Neoplasia</td>
<td>22-25%</td>
</tr>
</tbody>
</table>

“ADH vs. Low-Grade DCIS”
**Atypical Ductal Hyperplasia**

Morphologic Risk Factor
- Indicates increased risk to both breasts
- It is not a precursor for invasive breast cancer
- Does not need cancer therapy

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**Ductal Carcinoma in situ**

- May be a direct precursor to invasive cancer
- Rate of invasive transformation is dependent on grade
- Risk of invasion is limited to ipsilateral breast and generally same quadrant and site

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**Ductal Carcinoma in situ**

"DCIS is a heterogeneous disease characterized by neoplastic proliferation of ductal epithelial cells with no evidence of stromal invasion"
Determinant of Biology of Ductal Carcinoma in situ

- Architectural pattern
- Nuclear grade
- Presence or absence of necrosis

Molecular Biology of DCIS

- High-grade lesions are often associated with unfavorable biological markers
- Genetic alterations and loss of heterozygosity at various chromosomal loci differ according to DCIS pattern and grade
- Low-grade lesions are associated with the “Low Nuclear Grade Breast Neoplasia Family”
Ductal Carcinoma *in situ*

**Treatment Options**
- Local wide excision with and without radiation therapy
- Mastectomy

ADH vs. Low-Grade DCIS

**Breast Cancer Mortality After a Diagnosis of DCIS**
- The study was designed to estimate 10-20 years mortality rate from breast cancer following the diagnosis of DCIS and standard cancer therapy
- This observational study used the information registered in the SEER database from over 100,000 women

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ADH vs. Low-Grade DCIS

**Breast Cancer Mortality After a Diagnosis of DCIS**
- The risk of dying from breast cancer in these patients was 3.3%
- At 20 years, this risk was higher for the following patients
  - Young age (before age 40)
  - Black ethnicity
  - High-grade DCIS
    - Large size >5cm
    - ER negative status
    - HER-2/neu oncogene positive status

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**ADH vs. Low-Grade DCIS**

Breast Cancer Mortality After a Diagnosis of DCIS

- The issue in question:
  - Do the patients with low-grade DCIS need to undergo cancer therapy?
  - Do we need to abandon the use of the term “carcinoma” for lesions that may not be biologically malignant?


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**ADH vs. Low-Grade DCIS**

- Current data suggests that:
  - Low-Grade DCIS should be considered a “risk factor” for invasive breast cancer and an opportunity for targeted prevention
  - Radiation therapy should not be routinely offered after lumpectomy for DCIS lesions that are not high risk because it does not affect mortality


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**ADH vs. Low-Grade DCIS**

- Current data suggests that:
  - We should continue to better understand the biological characteristics of the highest-risk DCIS (large, high-grade, hormone receptor negative, HER2 positive, especially in very young and African American women) and test targeted approaches to reduce death from breast cancer

ADH vs. Low-Grade DCIS
The Natural History

- Identified from a large prospectively identified study 28 patients with low-grade DCIS were identified
- The follow-up study ranged from 20 to 23/24 years


ADH vs. Low-Grade DCIS
The Natural History

- Seven out of twenty-eight women were diagnosed with invasive cancer within 10 years
- One was diagnosed within 12 years
- Five women who developed invasive cancer after 29 years developed distant metastasis resulting in death 1-7 years after diagnosis


ADH vs. Low-Grade DCIS
The Conclusion

- The natural history of low-grade DCIS can extend greater than 4 decades with invasive cancer developed at the same site at the DCIS
- The natural history of low-grade DCIS is markedly different from high-grade

ADH vs. Low-Grade DCIS

- The study was designed to assess the rate of upgrade of DCIS cases during a 15-year period.
- This retrospective study identified 2943 cases of which 229 cases (8%) were upgraded to invasive breast cancer upon excision.


ADH vs. Low-Grade DCIS

- Apparently, one-half of the upgrades were associated with high-grade DCIS with necrosis.
- The other half of the upgrades were due to low- or intermediate-grade DCIS.
- Axillary lymph node metastasis was seen in 3% (7 out of 218 of invasive cancers).
- Caution is needed when DCIS is diagnosed on core needle biopsy.


Borderline Breast Lesions

The Suggestions

- Abandon the term of “Low-Grade Ductal Carcinoma in situ.”
- Use the term of “Borderline Breast Disease.”
- Completely remove the entire lesion.
- Offer risk assessment/risk reduction options.

The Models to Follow

- Offer the options of “wait and watch” for borderline lesions/low-grade DCIS similar to low-grade prostate cancer
- Continue to search for malignancy associated biomarkers that can find more aggressive tumors