



**“Borderline Breast Disease”
An Entity to Minimize Errors
in Over Diagnosis of Low-
Grade Ductal Carcinoma *in
situ* in Breast Pathology**

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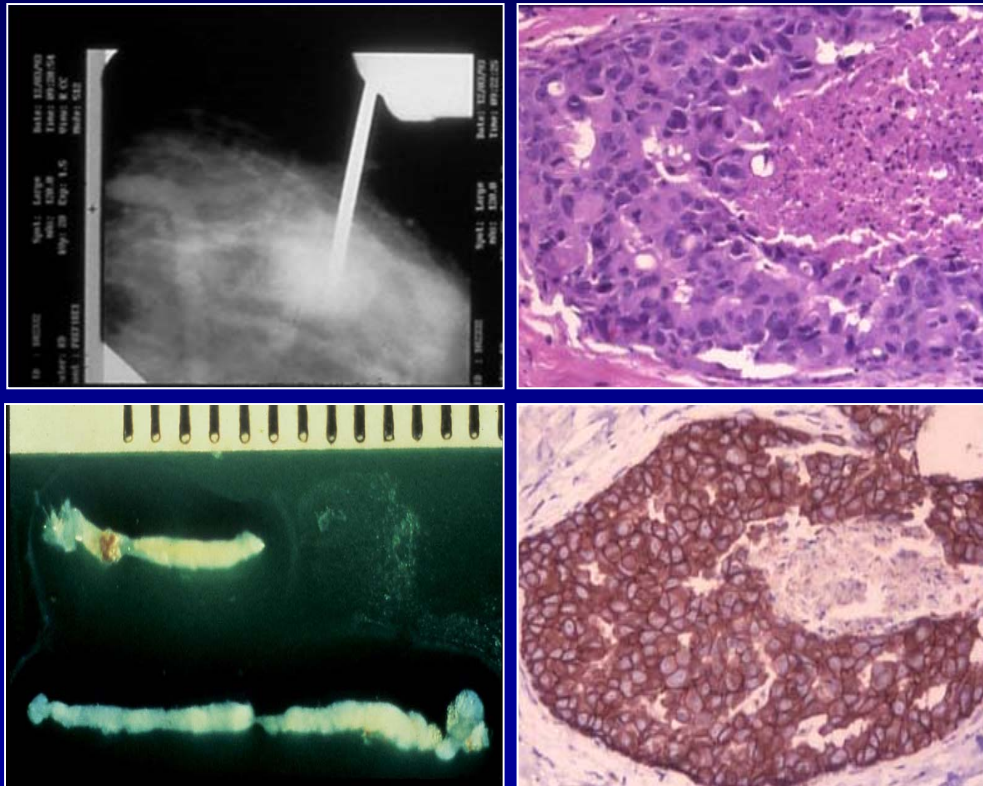
The Plan

- 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*



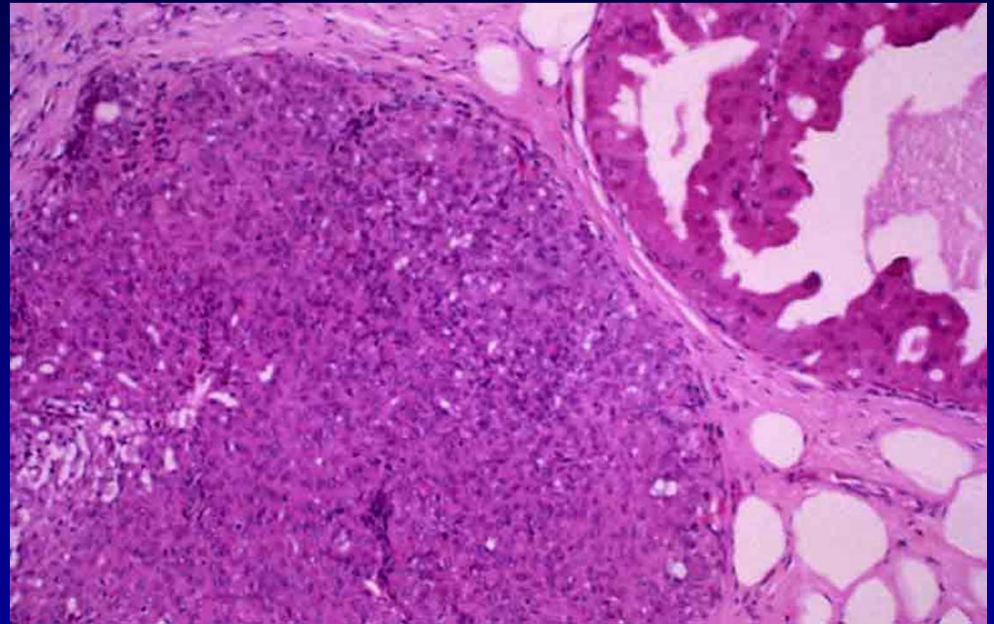
The Facts

- **The 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)

<p>○ Non-proliferative breast disease</p>	<p>– Cysts, mild hyperplasia, simple fibroadenoma, papillary apocrine change</p>
<p>○ Proliferative breast disease without atypia</p>	<p>– Complex fibroadenoma, moderate-florid hyperplasia, florid sclerosing adenosis, intraductal papilloma</p>
<p>○ Proliferative breast disease with atypia</p>	<p>– Atypical ductal hyperplasia</p> <p>– Atypical lobular hyperplasia</p> <p>– Pagetoid extension to extralobular duct</p> <p>– Radial scar with atypia</p> <p>– Multiple papilloma syndrome</p>

Frequency and Risk Stratification

* Dupont and Page 1985 NEJM 312, 146-51

<u>Subtype</u>	<u>Incidence</u>	<u>Relative Risk</u>	<u>Family History</u>
Non-proliferative breast disease	69.7	0.86	1.2
Proliferative breast disease without atypia	26.7	1.9	2.7
Proliferative breast disease with atypia	3.6	4.3	11.0

IntraEpithelial Neoplasia

Non-Proliferative



ER 10-30%

Ki-67 \leq 1%

**Proliferation
and
apoptosis
balanced**

RR=1

Hyperplasia



ER 60%

Ki-67 ~ 3%

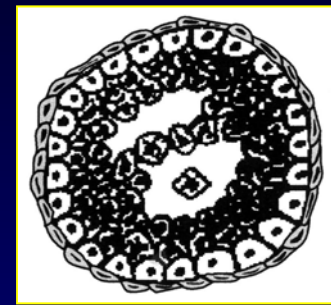
Atypia



ER 90%

Ki-67 ~ 5%

in situ



ER 50%

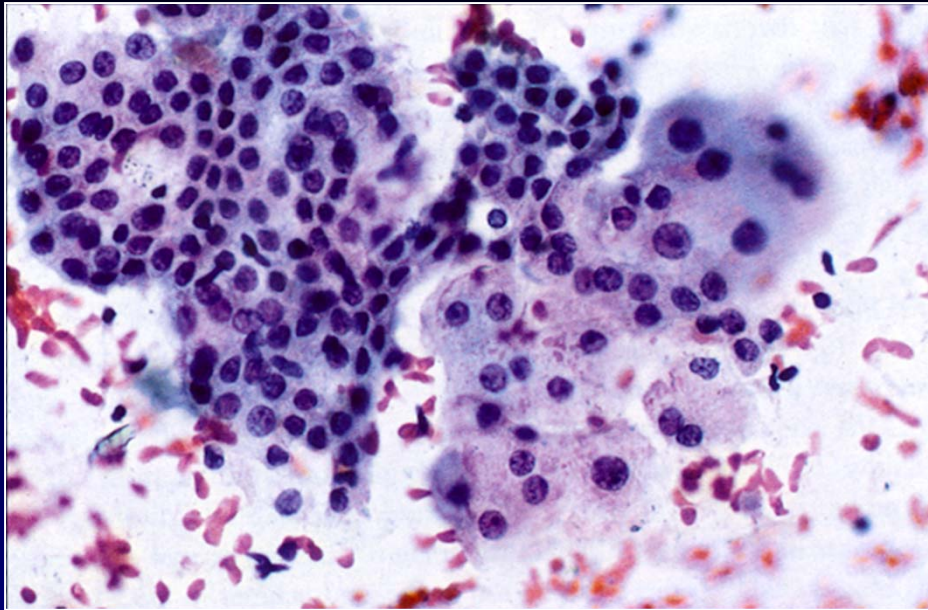
Ki-67 >10%

Proliferation and apoptosis
imbalanced

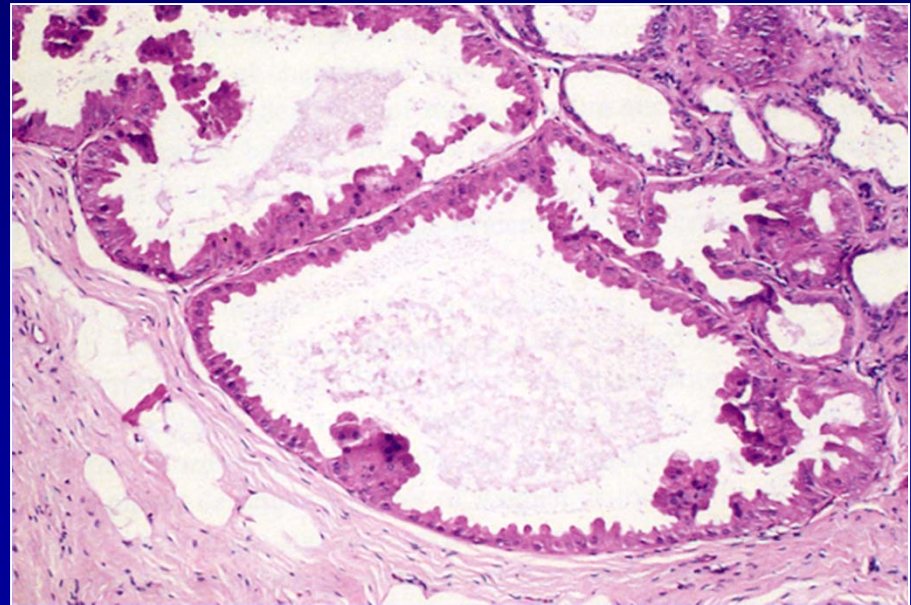
RR=2

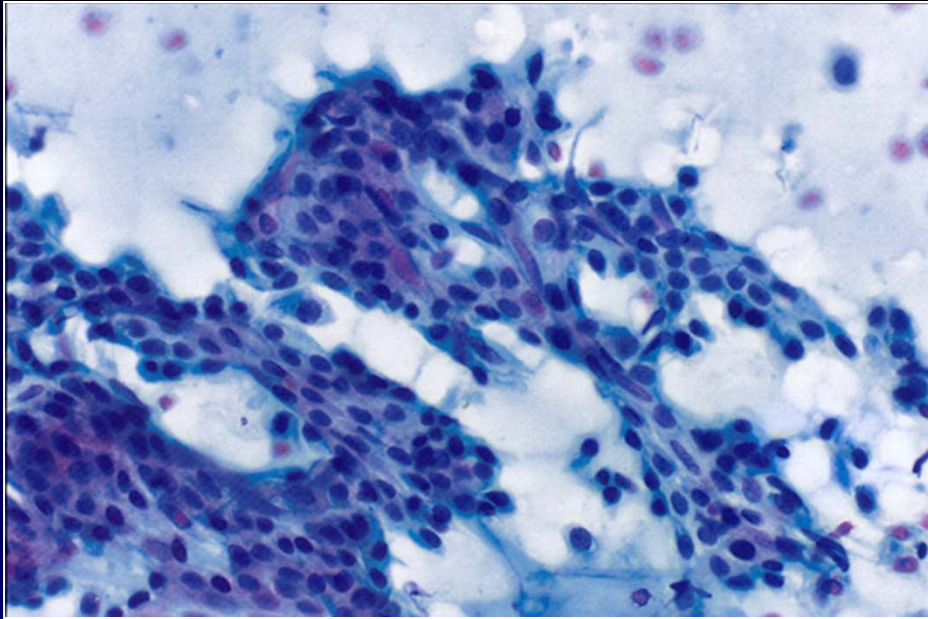
RR=5

RR=10-20

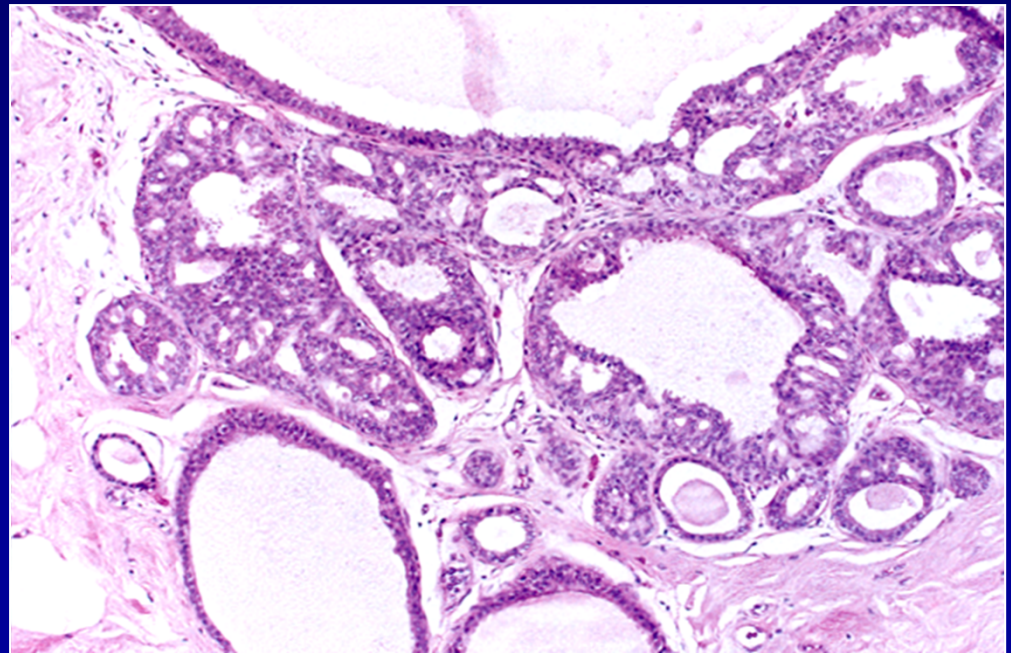


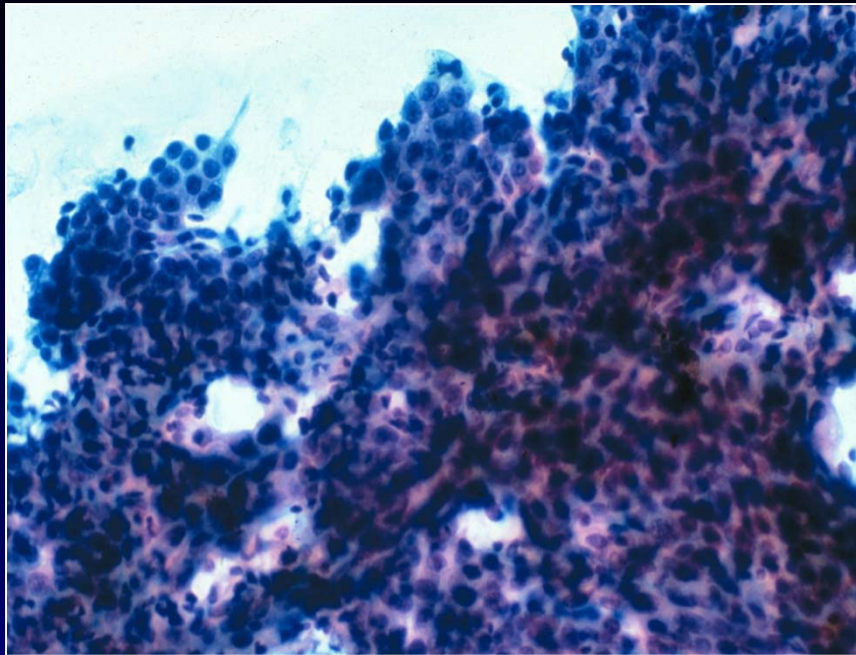
**Non-Proliferative
Breast Disease**



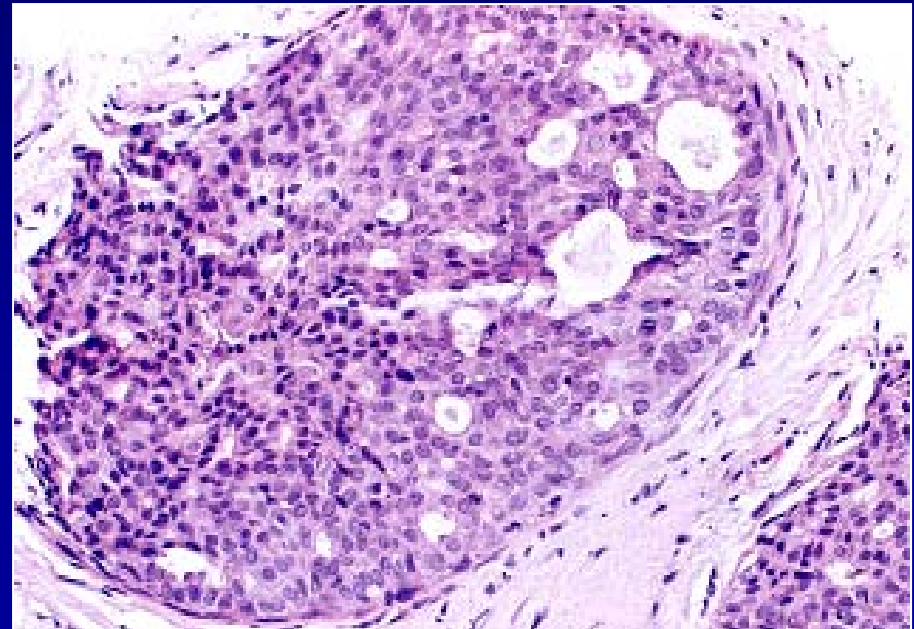


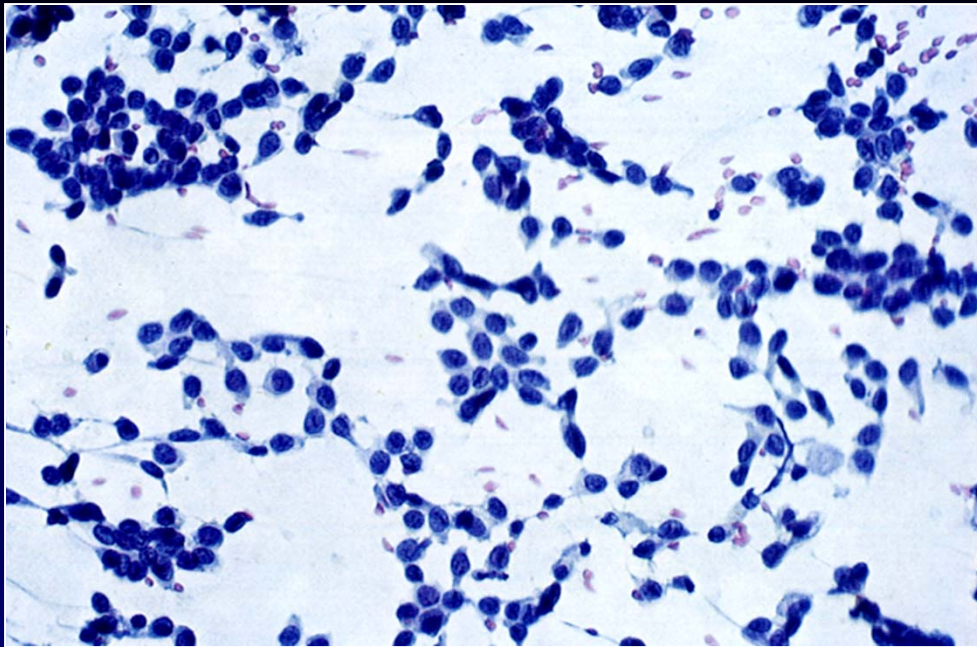
**Proliferative
Breast Disease
without Atypia**



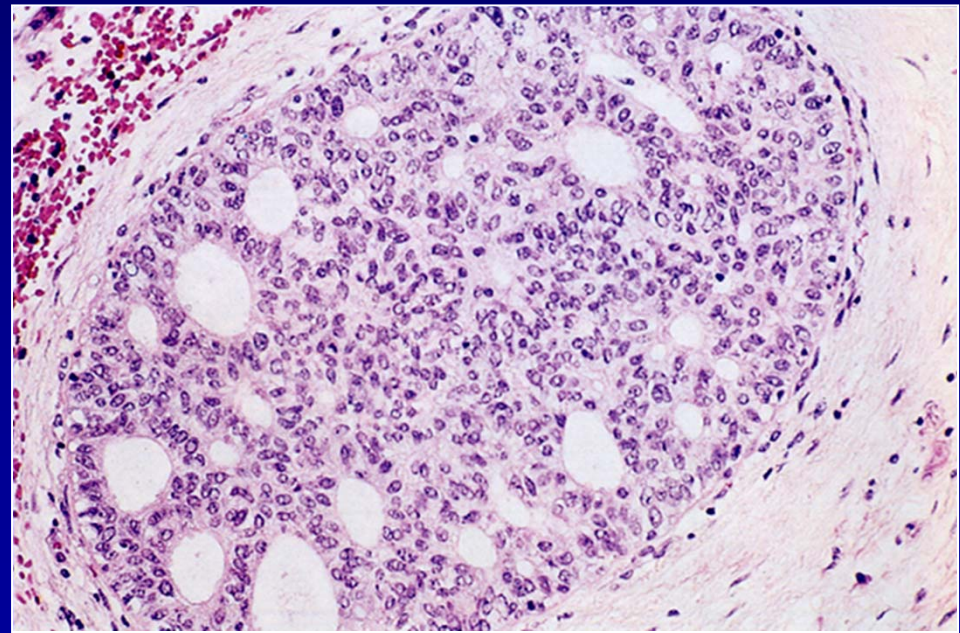


**Proliferative Breast
Disease with Atypia,
ADH**

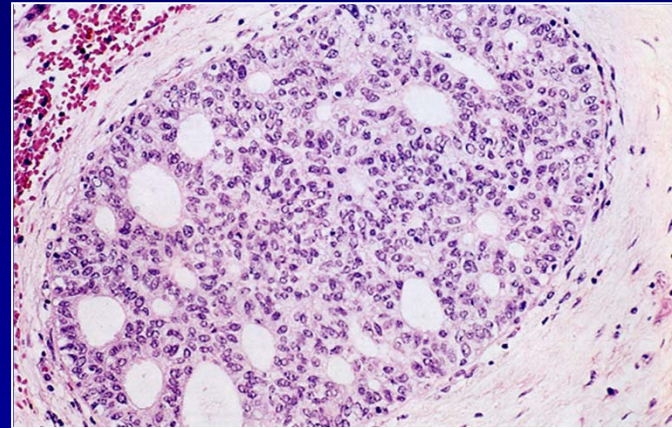
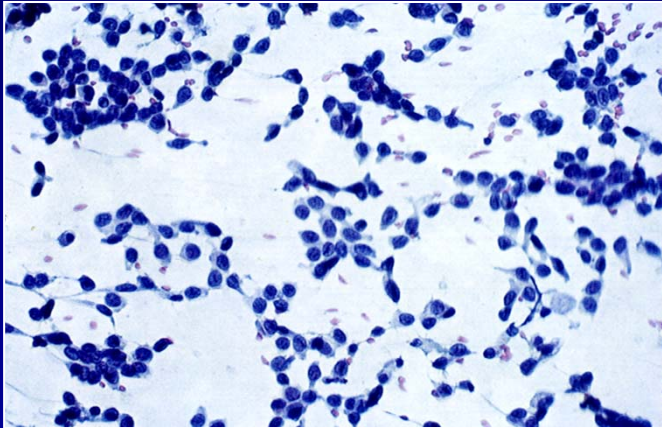
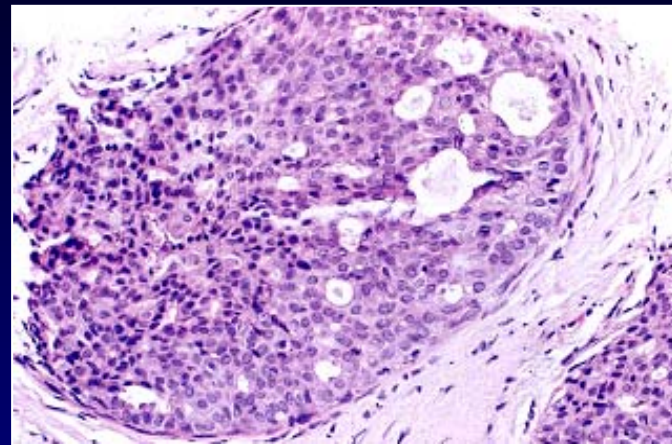
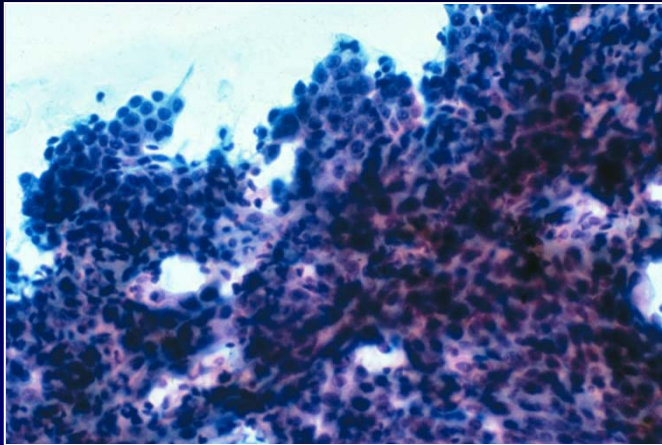




Low-Grade DCIS



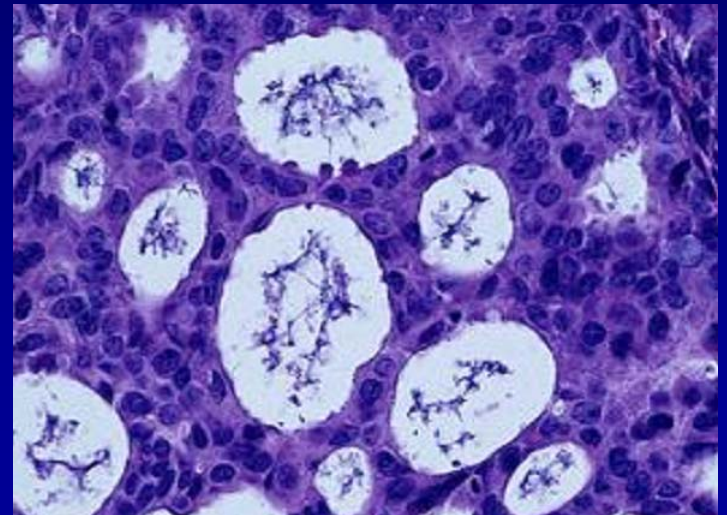
ADH Versus DCIS



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

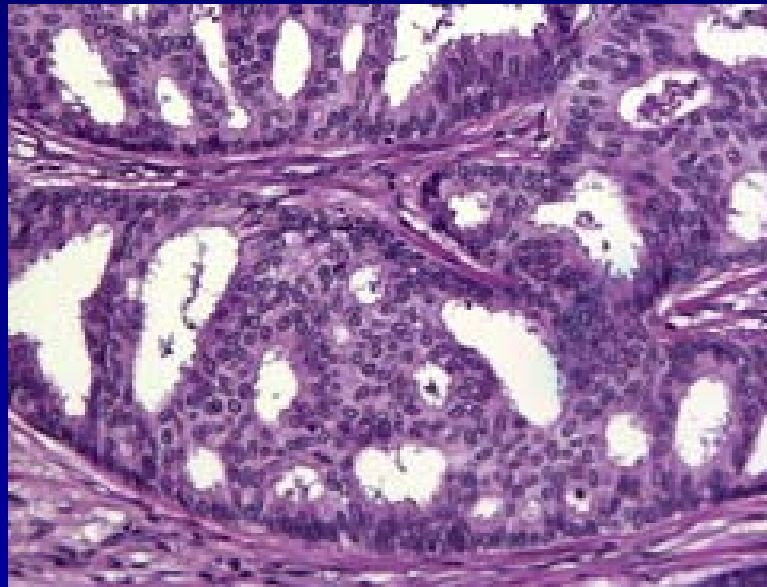
Morphologic Criteria for Low-Grade DCIS (*Page and Anderson 1987*)

- 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 $\geq 2\text{mm}$



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

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

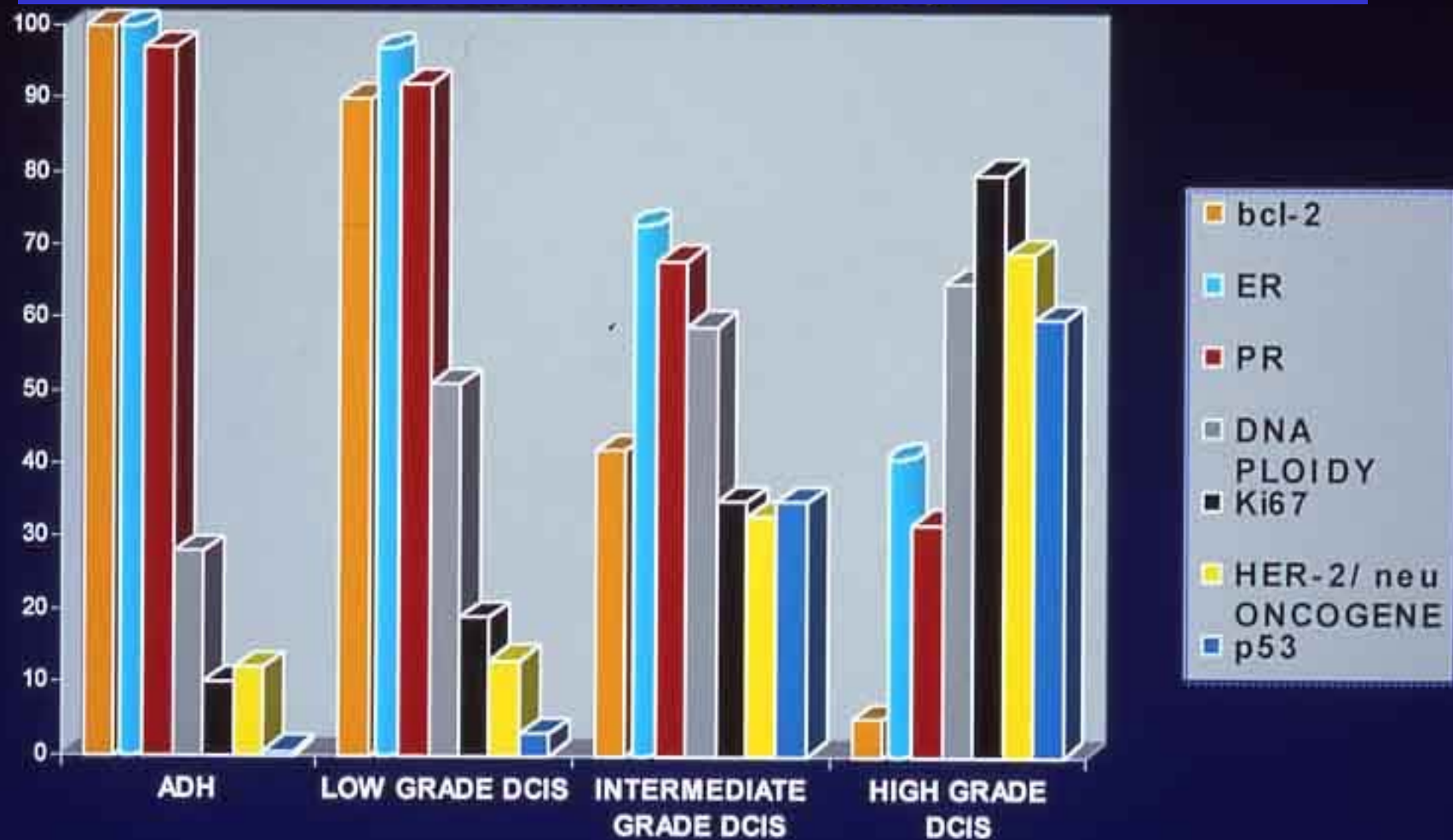
Schnitt SJ, et al. *Am J Surg Pathol* 16:1133-1143, 1992.

Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens

- 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 highest level of concordance seen for invasive cancer
- Lower level of concordance was seen for DCIS and atypia

Elmore JG, Longton GM, Carney P, et al. Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens. *JAMA Oncol.* 2015;313(11):1122-1132.

PATTERN OF EXPRESSION OF VARIOUS BIOMARKERS IN ATYPICAL DUCTAL HYPERPLASIA (ADH) AND DUCTAL CARCINOMA *in situ* (DCIS)



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”**

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*”

Rosen P: *Rosen Breast Pathology*: Third Edition. 264-284, 2008.

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 *in situ*

Diagnostic Challenge

- FNA biopsy
- Core needle biopsy
- Surgical biopsy



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**

Ductal Carcinoma *in situ*

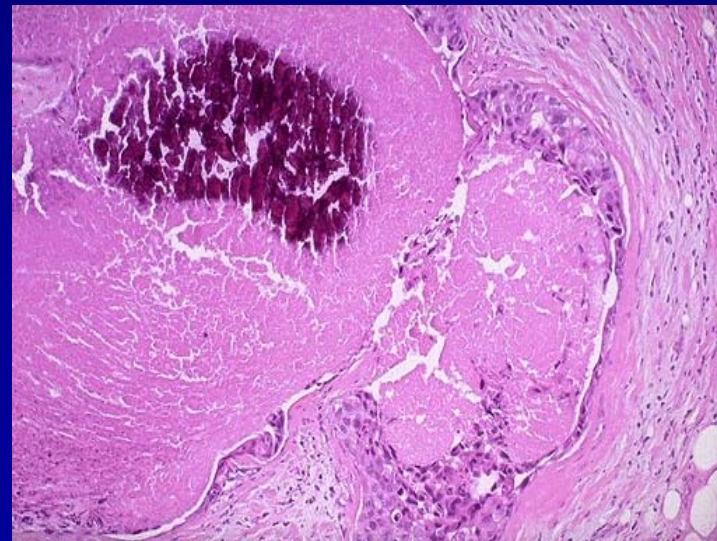
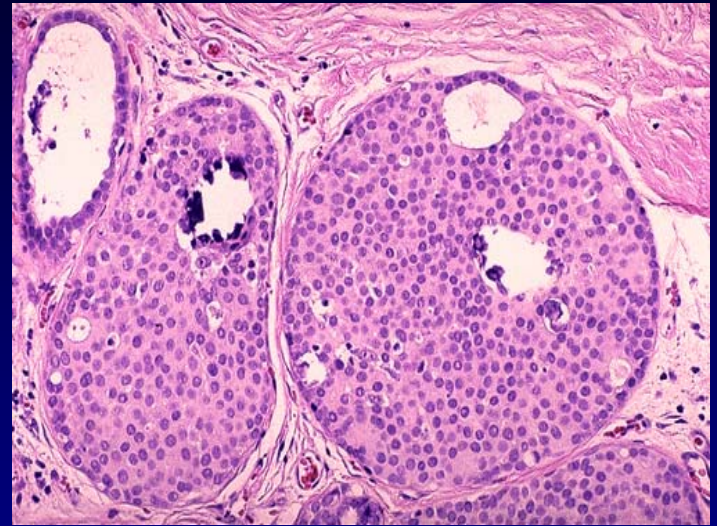
- **May be a direct precursor to invasive cancer**
- **Rate of invasive transformation is dependent on grade**
- **Risk of invasion is limited to ipsilateral breast and generally same quadrant and site**

Molecular Biology of DCIS

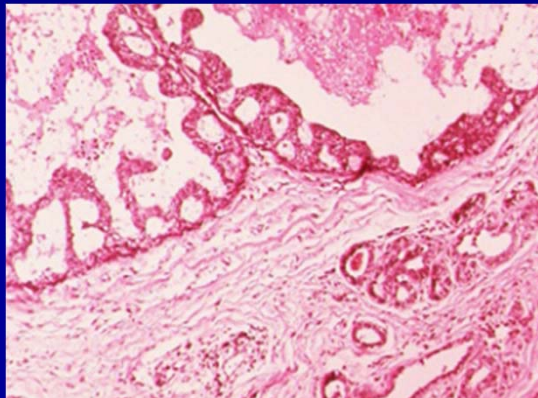
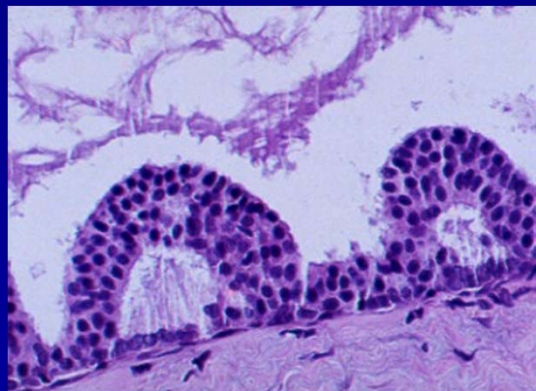
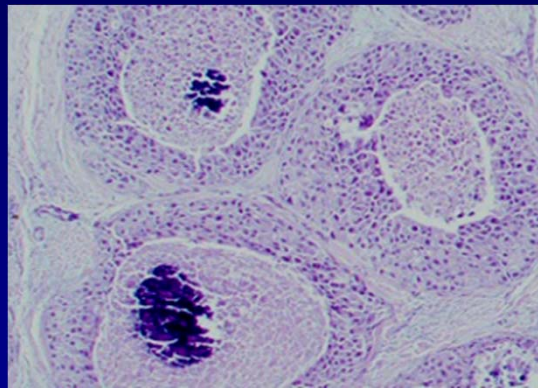
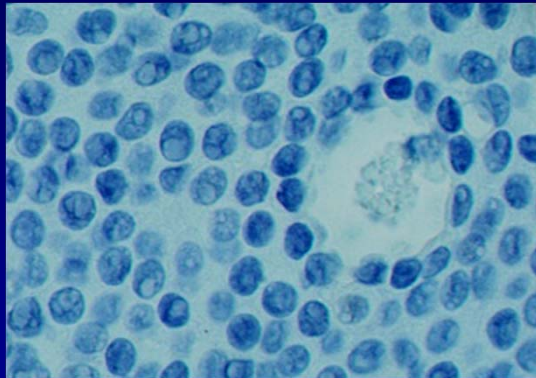
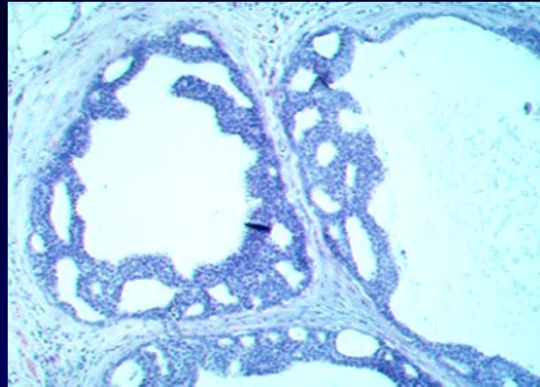
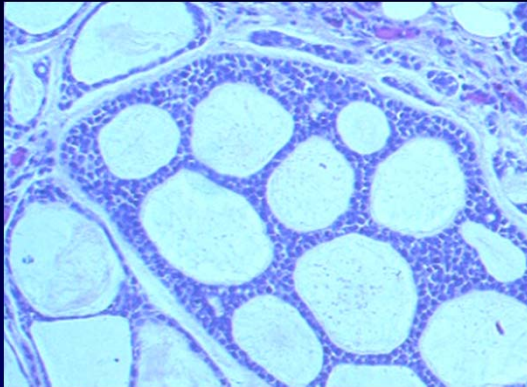
- High-grade lesions are often associated with unfavorable biological markers**
- Genetic alterations and loss of heterozygosity at various chromosomal loci differ according to DCIS pattern and grade**
- Low-grade lesions are associated with the “Low Nuclear Grade Breast Neoplasia Family”**

Ductal Carcinoma *in situ*

“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*

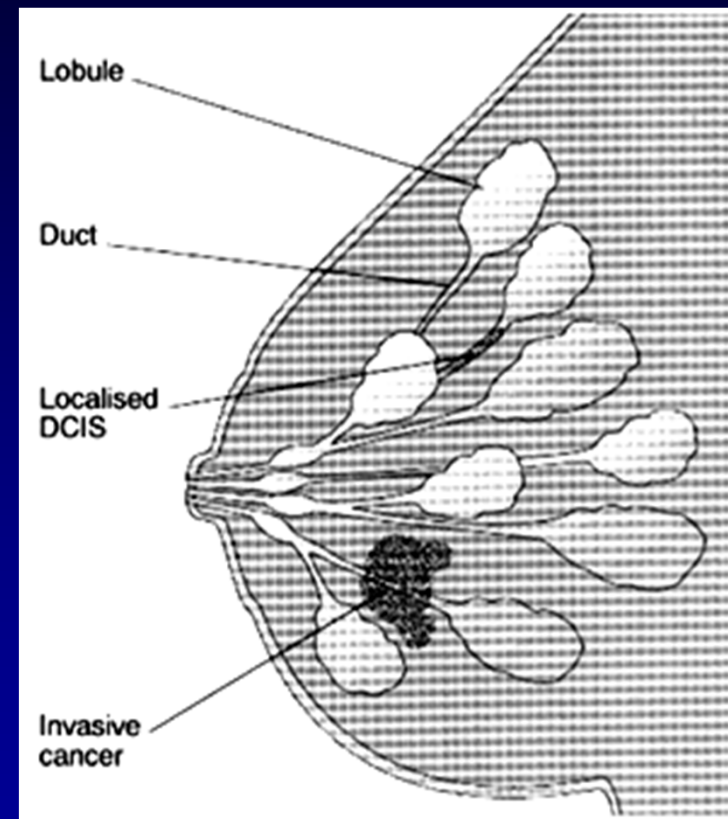


- Architectural pattern
- Nuclear grade
- Presence or absence of necrosis

Ductal Carcinoma *in situ*

Treatment Options

- Local wide excision with and without radiation therapy
- Mastectomy



“ADH vs. Low-Grade DCIS”



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**

Narod SA, Iqbal JI, Ginnakeas V. Breast Cancer Mortality After a Diagnosis of DCIS. *JAMA Oncol.* 2015;1(7):888-896.

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**

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?**

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

Esserman L. Rethinking the Standard for Ductal Carcinoma *in situ* Treatment. *JAMA Oncol.* 2015; 1(7):881-883.

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**

Esserman L. Rethinking the Standard for Ductal Carcinoma *in situ* Treatment. *JAMA Oncol.* 2015; 1(7):881-883.

**“The Current
Challenges Associated
with the Practice of
Breast Pathology”**

Current Issues In Breast Pathology

- Diversity in tissue handling, processing and reporting
- Insufficient evidence-based correlation between morphology and patient outcome
- Significant interobserver variability in diagnosis and test results
- Communication barriers among physicians involved in breast care

Current Issues In Breast Pathology

- There are no uniform guidelines to measure the rate of diagnostic errors
- Fear of disclosure and medicolegal issues limits the reporting of diagnostic errors
- There are many look-alikes in breast pathology that can mimic cancer

Current Issues in Breast Pathology

- Breast pathology is considered as a component of general surgical pathology
- Breast pathology fellowships are not accredited by ACGME
- Referral of pathology samples to commercial laboratories impairs communication

Suggestions

- To acknowledge the challenges associated with the current practice of breast pathology
- To design studies that can appropriately analyze the problems and quantitate their impact on therapy, patient outcome and health economy

Suggestions

- **Establishment of quality assurance programs**
 - **Internal quality measures**
 - **Consensus slide conference**
 - **Mandatory second review of cancer cases**
 - **Mandatory adherence to established guidelines**
- **Second opinion**
 - **The review of outside pathology slides and reports by a local pathologist before the initiation of cancer therapy**
- **Involvement in external quality assurance programs**

Clinically Significant Discrepancies in Breast Pathology During Second Review Process

<u>Author</u>	<u># of Cases</u>	<u>Rate of Discrepancy</u>
Khazai et al 2015	1,970	10%
Kennecke et al 2010	405	20%
Price et al 2012	100	11%

Multidisciplinary Case Review

The Impact

	Imaging	Pathology
Interpretive Change	45%	29%
Surgical Management Change	16%	9%

Newman EA, et al: *Cancer* 2006, 107:2346-2351.

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

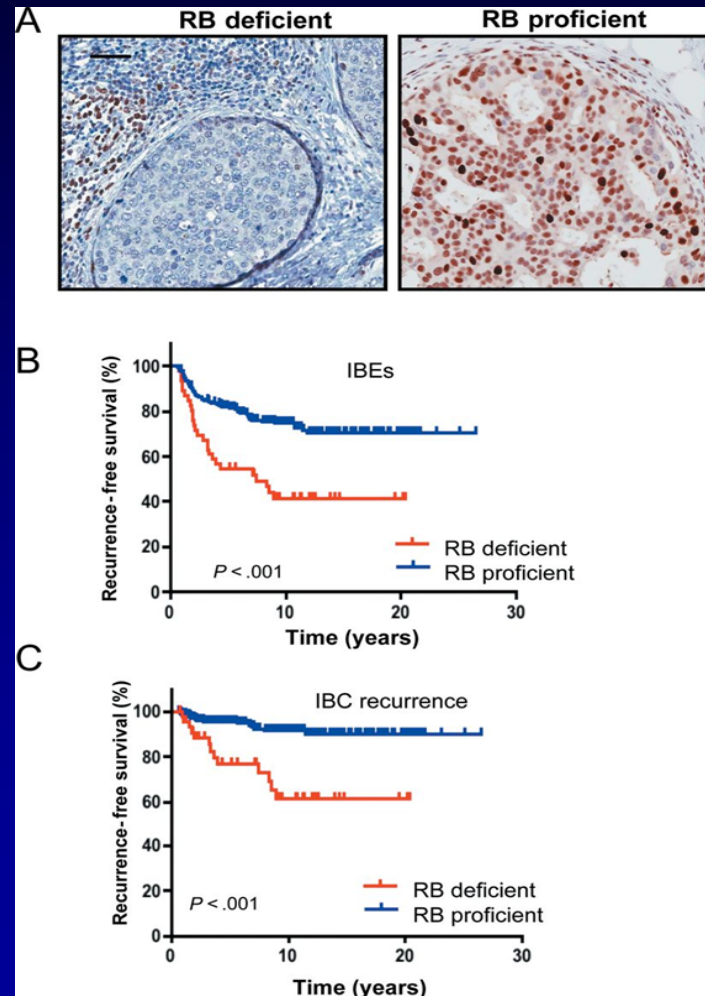
- Offer the options of “wait and watch” for borderline lesions/low-grade DCIS similar to low-grade prostate cancer
- Continue to search for malignancy associated biomarkers that can find more aggressive tumors

Masood S. Focusing on breast cancer overdiagnosis and overtreatment: the promise of molecular medicine. *The Breast Journal* 2013;19(2):127-129.

Loss of Tumor Suppressor Genes Linked to DCIS Breast Cancer Progression

Knudsen E S et al. Retinoblastoma and phosphate and tensin homolog tumor suppressors: impact on ductal carcinoma *in situ* progression. *JNCI J Natl Cancer Inst* 2012;104:1825-1836

Retinoblastoma (RB) status is associated with ductal carcinoma *in situ* (DCIS) recurrence and invasive progression.



The Urgent Need

- Better define the morphologic and biologic characteristics of spectrum of high risk proliferative and precursors breast lesions
- Change the concept, terminology, and the pattern of practice

Masood S. Focusing on breast cancer overdiagnosis and overtreatment: the promise of molecular medicine. *The Breast Journal* 2013;19(2):127-129.

The Significance?

- **Over 1.1 million women are diagnosed with breast cancer each year across the globe**
- **Estimated diagnostic errors in breast pathology may be about 2%**
- **It appears that a significant number of women will receive under/over treatment**

The Message

Raising the Bar:

**A plea for standardization and improved
quality of breast pathology**

Masood S: *The Breast Journal* 12(5):409-412, 2006.

