Benign Breast Disease
and
Breast Cancer Risk

Jean F. Simpson, M.D.
Vanderbilt University
Nashville, Tennessee
December 1, 2011

Nashville

Nashville

Lebanon

Cedars of Lebanon State Park

The American University of Beirut

Vanderbilt University

Pre-malignant Breast Disease

- **1950-1980**-confusing
  " The female breast is a precancerous organ"
  ……..Fred Steward, AFIP fascicle
- **1980-1990** – risk defining
- **2000's** –refining
  – Impact of breast imaging
  – Mimics
  – Molecular aspects

Risk Factors for Breast Cancer in Women with Proliferative Breast Disease

Dupont and Page, *NEJM* 1985

10,542 benign breast biopsies
1950-1968
85% follow up at 20 years

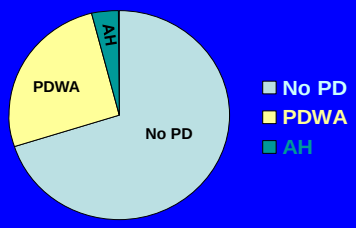
Nashville Breast Cohort Studies

- Specific histologically-defined terms linked to levels of later malignancy risk
- Regionality of risk, i.e. local vs. diffuse

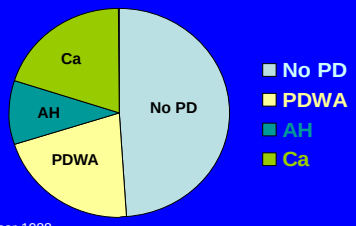
Stratification of Breast Cancer Risk

- No proliferative disease = NO ↑ RISK
- Proliferative disease, no atypia = SLIGHT RISK
- Atypical hyperplasia = MODERATE RISK

Distribution of Breast Lesions
Nashville series (1950-1968)



Distribution of Mammographically Detected Lesions



Rubin et al, Cancer 1988

Stratification of Breast Cancer Risk

- No proliferative disease = NO ↑ RISK
- Proliferative disease, no atypia = SLIGHT RISK
- Atypical hyperplasia = MODERATE RISK

Relative Risk

- Used to compare groups (not individuals), one group has characteristic, control group does not
- Slight increase risk = amount detectable in population
- Statistically significant, but not significant for patients

Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk

- Nurse's Health Study
- Prospective observational study
- 105,986 women, entered 1980-2008

Chen et al, JAMA Nov 2, 2011

Nurse's Health Study: risk of alcohol consumption

alcohol per week	relative risk	CI
3-6 drinks	1.15	(1.06-1.26)
6-10 drinks	1.15	(1.06-1.24)
13-19 drinks	1.28	(1.12-1.47)
>19 drinks	1.50	(1.34-1.67)

Chen et al, JAMA Nov 2, 2011

Nurse's Health Study: risk of alcohol consumption

alcohol per week	relative risk	CI
3-6 drinks	1.15	(1.06-1.26)
6-10 drinks	1.15	(1.06-1.24)
13-19 drinks	1.28	(1.12-1.47)
>19 drinks	1.50	(1.34-1.67)

Chen et al, JAMA Nov 2, 2011

Slight increase in risk

Relative Risk for Developing Cancer After Benign Biopsy

- No increased risk
  - cysts
  - duct ectasia
  - adenosis
  - hyperplasia, mild
- Slightly increased risk
  - •Early menarche
  - •Late menopause
  - •Nulliparity
- Moderately increased risk
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia

Relative Risk

$$RR = \frac{\text{Women with PD who develop breast cancer}}{\text{Women with PD, no cancer development}} \Big/ \frac{\text{Women in the general public who develop breast cancer}}{\text{Women in the general public, no cancer development}}$$

Relative Risk

$$RR = \frac{\dfrac{\text{Women with PD who develop breast cancer}}{\text{Women with PD, no cancer development}}}{\dfrac{\text{Women in the general public who develop breast cancer}}{\text{Women in the general public, no cancer development}}}$$

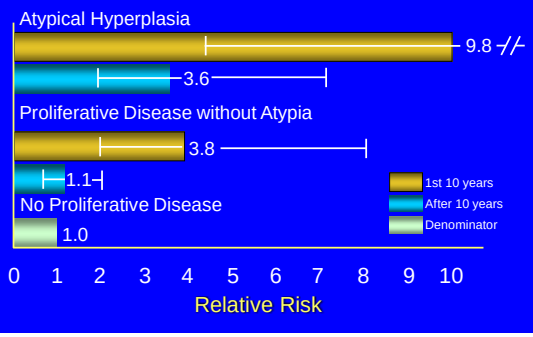
Relative Risk

$$RR = \frac{\dfrac{\text{Women with PD who develop breast cancer}}{\text{Women with PD, no cancer development}}}{\dfrac{\text{Women in the general public who develop breast cancer}}{\text{Women in the general public, no cancer development}}}$$

Relative Risk

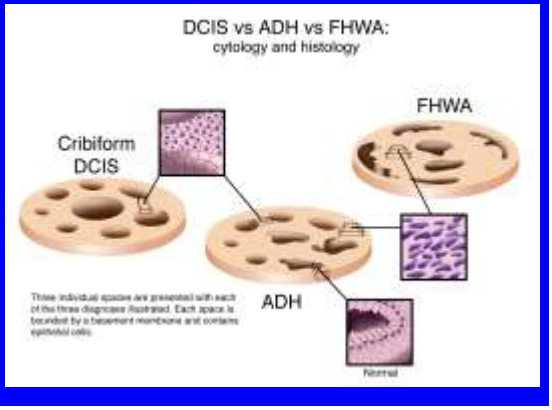
$$RR = \frac{\dfrac{\text{Women with PD who develop breast cancer}}{\text{Women with PD, no cancer development}}}{\dfrac{\text{Women in the general public who develop breast cancer}}{\text{Women in the general public, no cancer development}}}$$

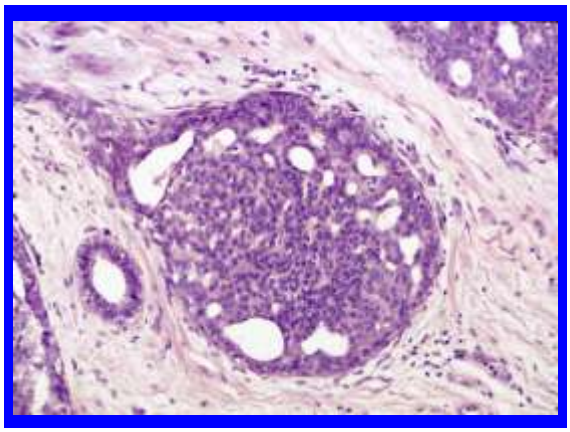
Relative Risk Varies with Time Since Diagnosis

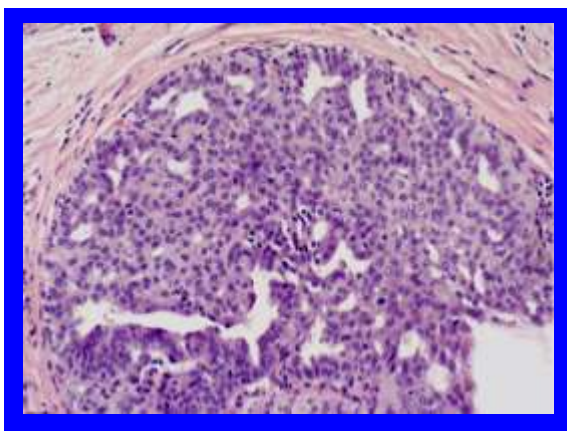


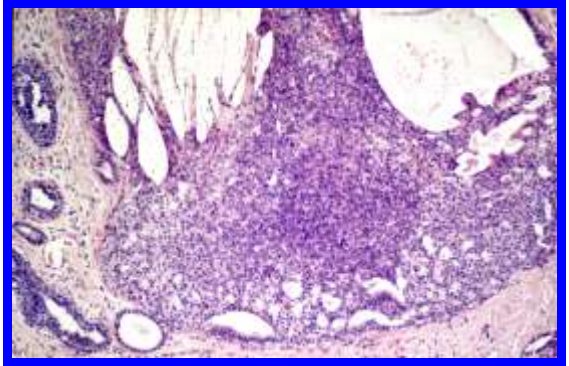
Relative Risk for Developing Cancer After Benign Biopsy

- No increased risk
  - cysts
  - duct ectasia
  - adenosis
  - hyperplasia, mild
- Slightly increased risk
  - hyperplasia, moderate or florid, no atypia
  - sclerosing adenosis
  - solitary papilloma
- Moderately increased risk
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia



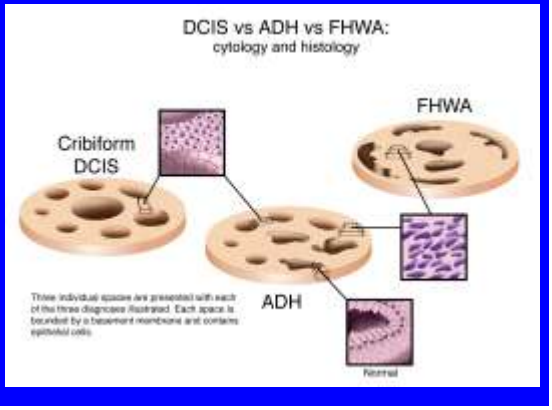






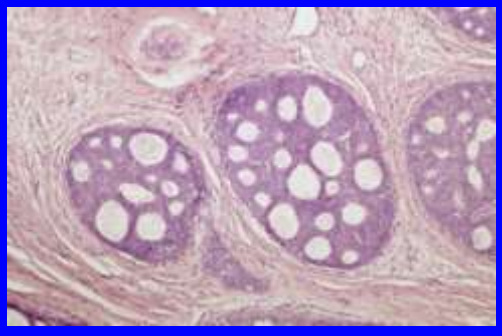
Relative Risk for Developing Cancer After Benign Biopsy

- No increased risk
  - cysts
  - duct ectasia
  - adenosis
  - hyperplasia, mild
- Slightly increased risk
  - hyperplasia, moderate or florid, no atypia
  - sclerosing adenosis
  - solitary papilloma
- Moderately increased risk
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia



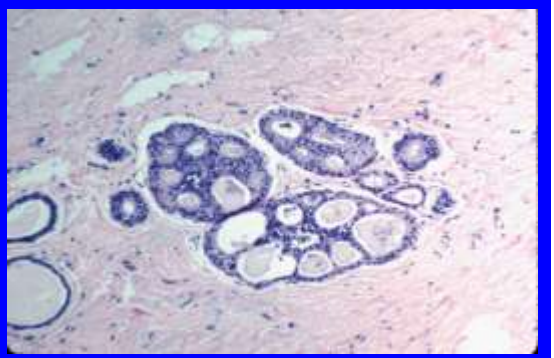
Minimum Criteria for DCIS

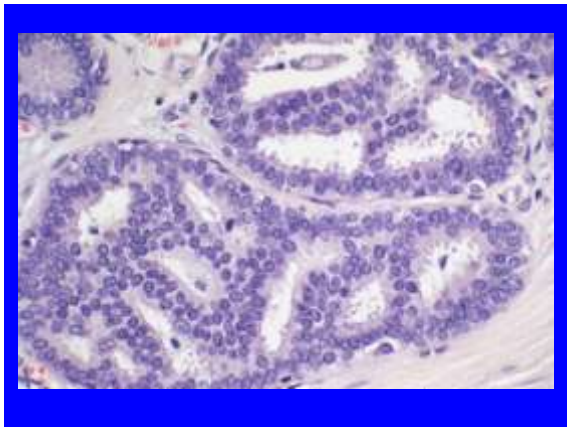
- Uniform population of cells, maintaining rounded, geometric configurations
- Even cell placement, without swirling or streaming
- **Fully** populating two adjacent spaces (3 mm)

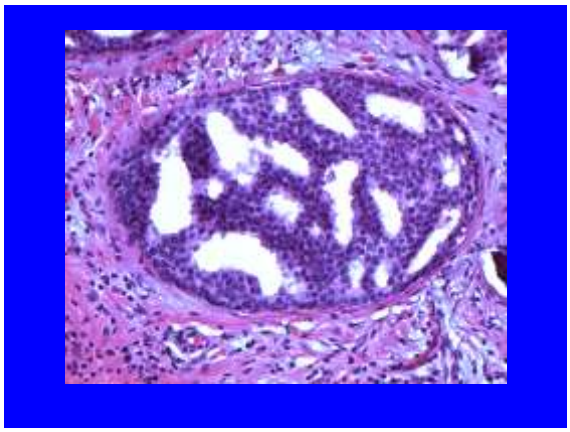


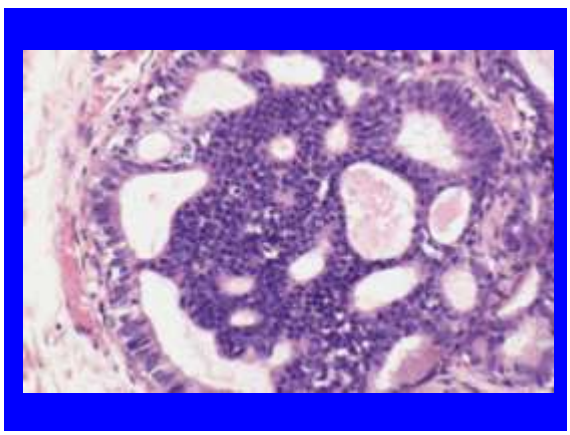
Atypical Ductal Hyperplasia

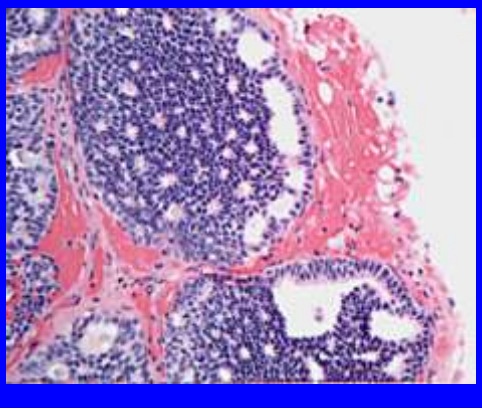
- Uniform cytology
- Architecture
  - cribriform, micropapillary, solid
- Extent











Nashville Breast Cohort Study Design

- Define histologic categories that could be reproducibly recognized
- Perform patient follow up
- Assign risk based on cancer development

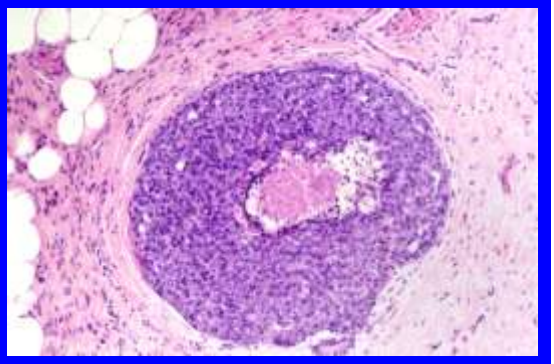
Relative Risk for Developing Cancer After Benign Biopsy

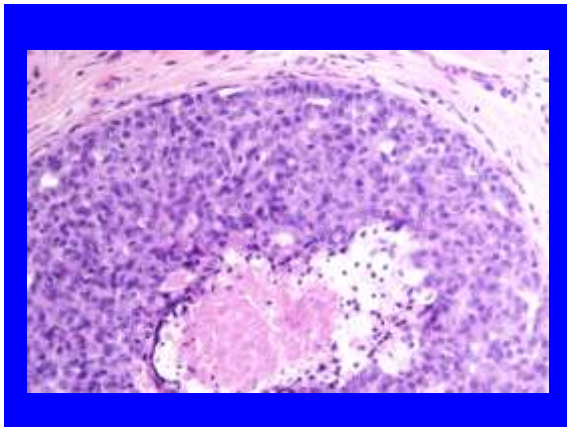
- No increased risk
  - cysts
  - duct ectasia
  - adenosis
  - hyperplasia, mild
- Slightly increased risk
  - hyperplasia, moderate or florid, no atypia
  - sclerosing adenosis
  - solitary papilloma
- Moderately increased risk
  - Atypical ductal hyperplasia
  - Atypical lobular hyperplasia

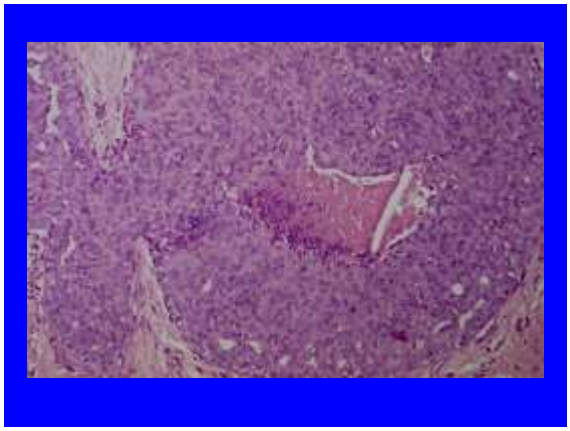
Confirmatory Studies

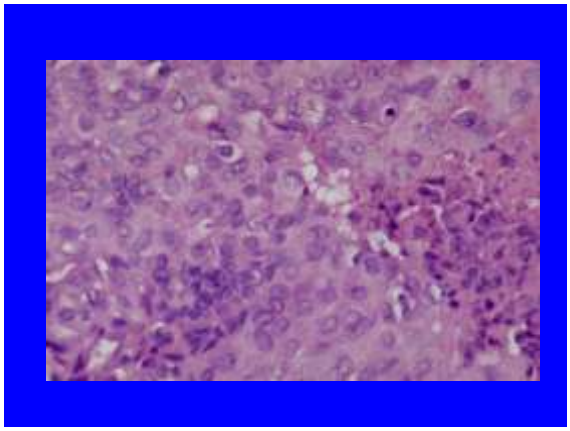
Pathologic finding	Nashville Cohort (1985)	Nurse's Health Study (1992)	Breast Cancer Detection Project (1993)	Mayo Clinic (2005)
Proliferative disease without atypia	1.5-2X	1.6X	1.3X	1.9X
Atypical hyperplasia	4-5X	3.7X	4.3X	4.24X

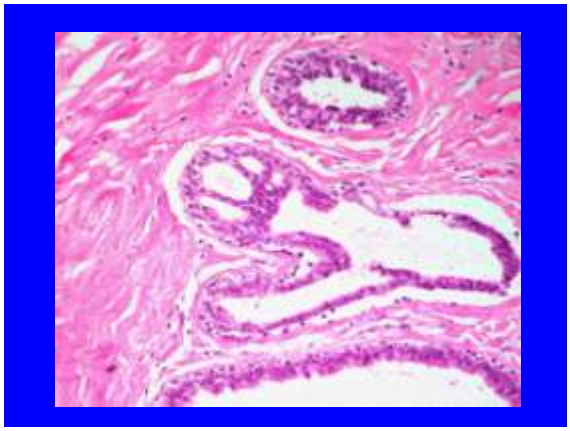
Proliferative Mimics

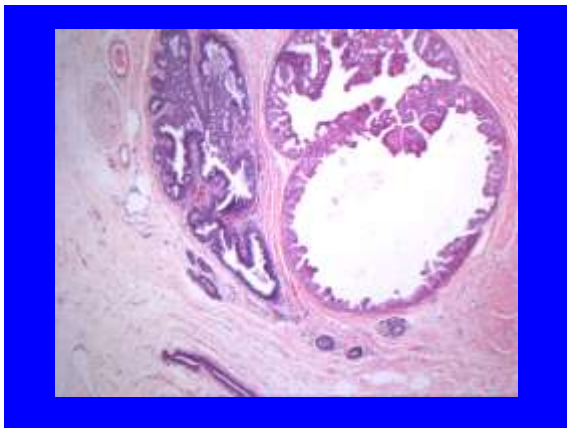


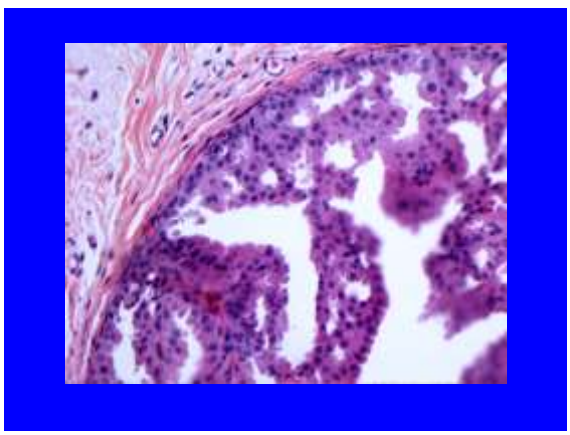


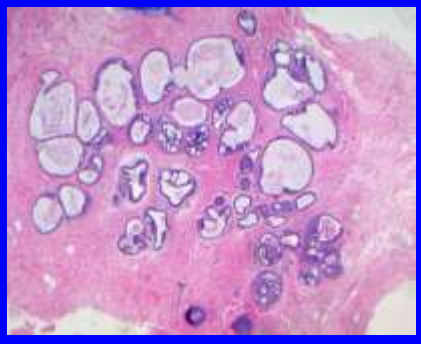


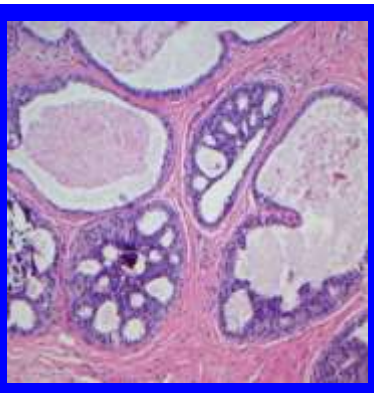


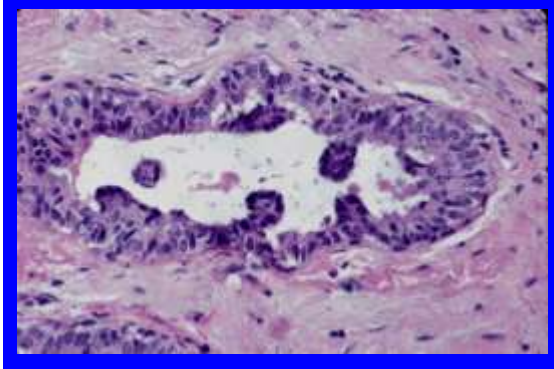


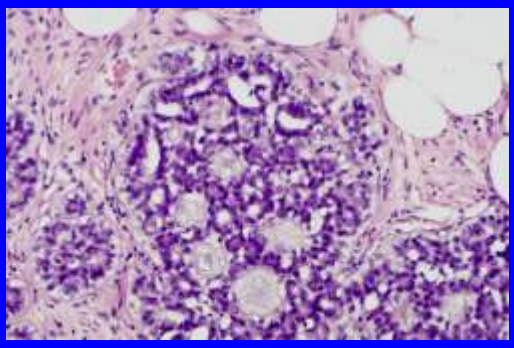


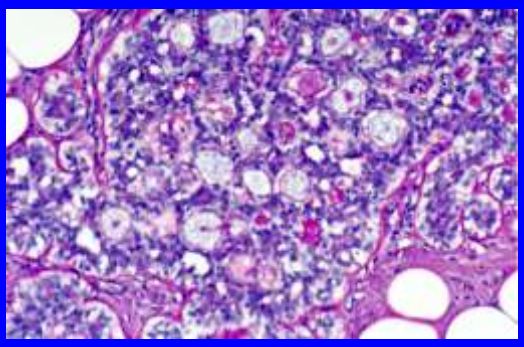












Confounders

- Mammography
- Minimally invasive biopsy procedures
- Hyperplasia in unusual settings

Underdiagnosis of ADH

- Core needle biopsy 41%
- Mammotome 15%

- Core needle biopsy (14 g) 44%
- Mammotome (14 g) 39%
- Mammotome (11g) 19%

Jacobs et al, Am J Surg Pathol, 2002

Factors Influencing Underdiagnosis of ADH

- Device used
- Extent of removal of mammographic lesion
- Microcalcifications *vs* mass

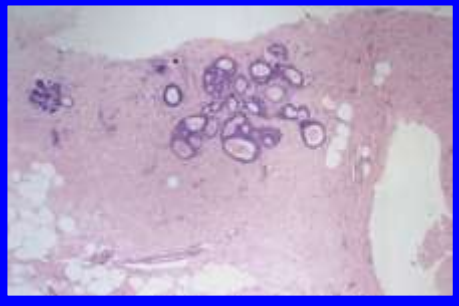
Jacobs et al, AM J Surg Pathol, 2002

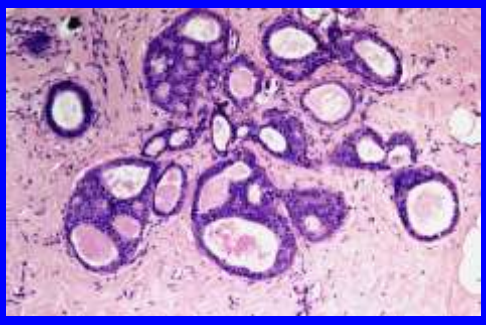
When to excise after core biopsy?

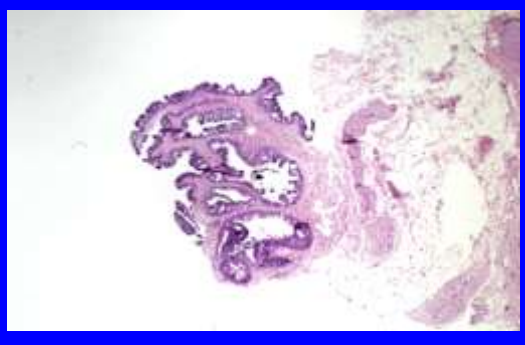
- Diagnostic difficulty
- Sampling issues

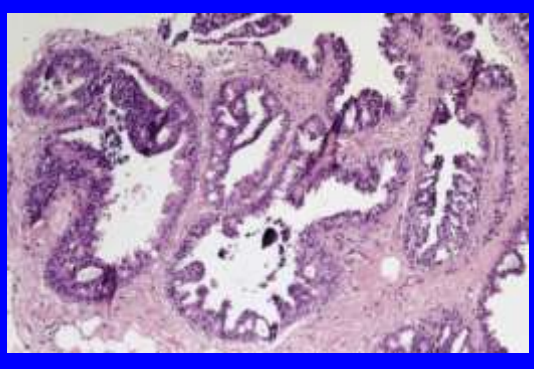
Atypical Ductal Hyperplasia

- Uniform cytology
- Architecture
- Extent









Extent of ADH on Core Biopsy (n=47)

	Findings in Excised Specimen		
	benign	ADH	DCIS
# ADH foci			
≤2	14	7	0
3	0	4	3
≥4	0	2	12

Ely et al, Am J Surg Pathol, 2001

Extent of ADH on Core Biopsy (n=42)

	Findings in Excised Specimen		
	benign	ADH	DCIS
# ADH foci			
1	14	7	0
2	2	5	0
3	3	1	1
≥4	5	2	2

Sneige et al, Am J Clin Pathol, 2003

ADH *vs* low grade DCIS

"At least atypical ductal hyperplasia, excision necessary to evaluate extent of the lesion"

ADH vs DCIS

- Differential diagnosis is LOW GRADE DCIS
- Extent of involvement is key
- Be conservative on core biopsy

Biomarkers of ADH?

- ADH is typically negative for HMW keratins (CK 5/6) and diffusely positive for ER
- Usual hyperplasia shows variable expression of HMW keratins and ER
- Expression of these markers is similar in ADH and low-grade DCIS
- None is sufficiently validated for routine clinical use

Molecular analysis of ADH

- LOH & CGH show common patterns of genetic alteration in ADH, low grade DCIS, and invasive carcinoma
- Frequent sites of LOH in ADH and invasive carcinoma: chromosomes 16q, 17p, and 11q13
- studies of ADH are from cases of established cancer, both invasive and in situ
- Few studies of ADH as the most advanced lesion
- No studies have established significance of these changes through large, clinically validated patient cohorts.