

Update on Proliferative Breast Disease

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Proliferative Breast Disease: predictor or precursor?

- Review epidemiology, including histologic criteria
- Risk assessment
- Molecular analysis

“Mammary Fibrocystic Disease” - 1945

Most women undergoing breast biopsy have an elevated risk of subsequent carcinoma development, in the range of 3 times that of the population as a whole

Pre-malignant Breast Disease

- **1950-1980** -- confusion
“The female breast is a precancerous organ”
.....Fred Stewart, AFIP fascicle
- **1980-1990** -- risks defined
- **2000's** --↑ detection

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 Study Design

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

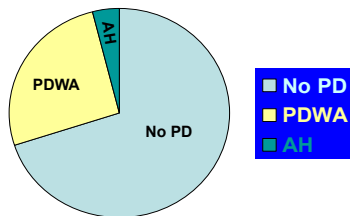
Nashville Breast Cohort Studies

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

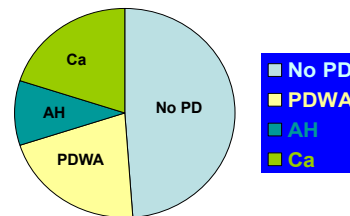
Stratification of Breast Cancer Risk

- 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

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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

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Slight increase in risk

Relative Risk for Developing Cancer After Benign Biopsy

- No increased risk
 - ectasia
 - adenosis
 - hyperplasia, mild
- Slightly increased risk
 - hyperplasia, moderate or florid, no atypia
 - sclerosing adenosis
 - solitary papilloma

Relative Risk for Developing Cancer After Benign Biopsy

- No increased risk
 - cysts
 - duct ectasia
 - adenosis
 - hyperplasia, mild
- Slightly increased risk
 - hyperplasia, moderate

- Early menarche
- Late menopause
- Nulliparity

- Atypical ductal hyperplasia
- Atypical lobular hyperplasia

Relative Risk

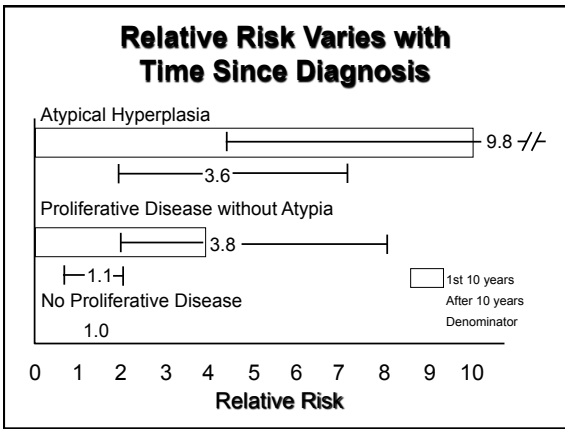
$$RR = \frac{\frac{\text{Women with PD who develop breast cancer}}{\text{Women with PD, no cancer development}}}{\frac{\text{Women in the general public who develop breast cancer}}{\text{Women in the general public, no cancer development}}}$$

Relative Risk

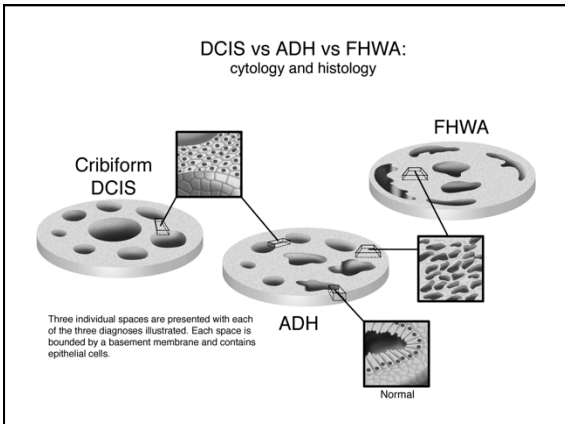
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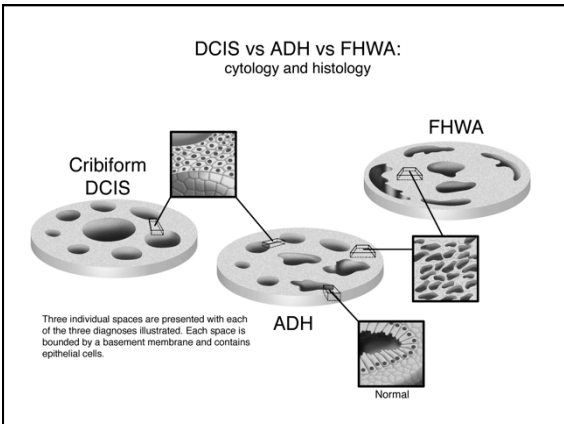
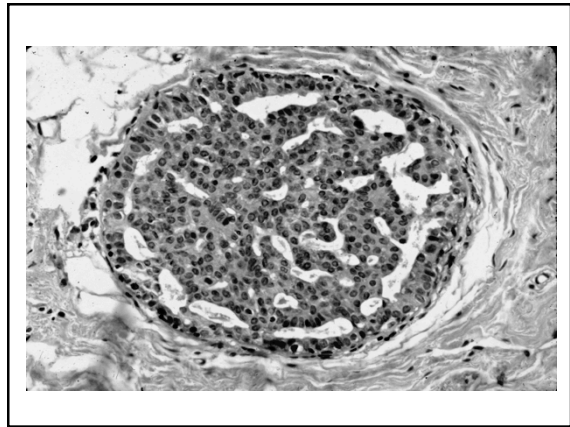
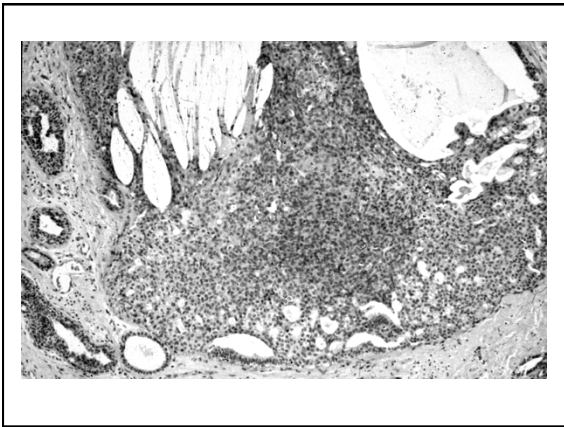
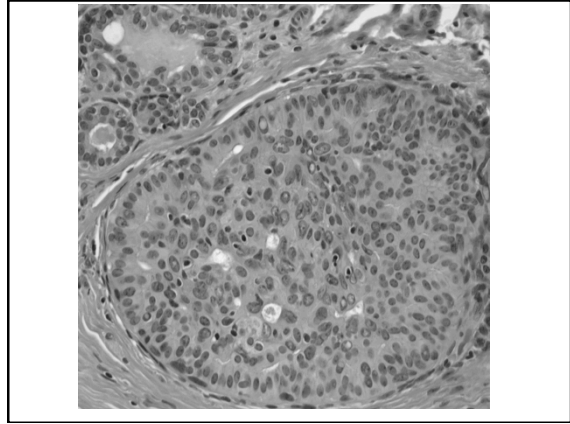
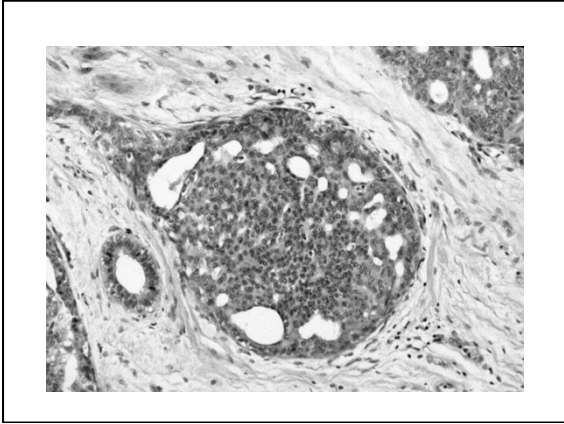
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- ### Relative Risk for Developing Cancer After Benign Biopsy
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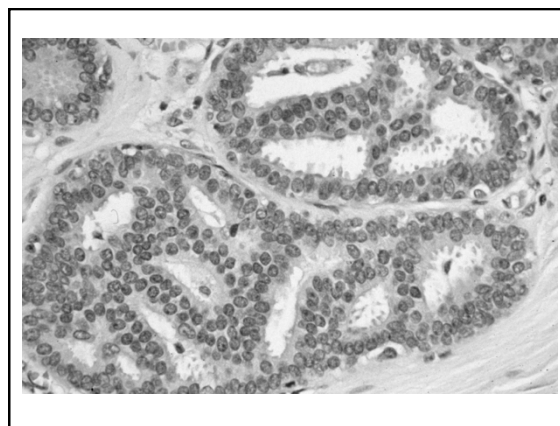


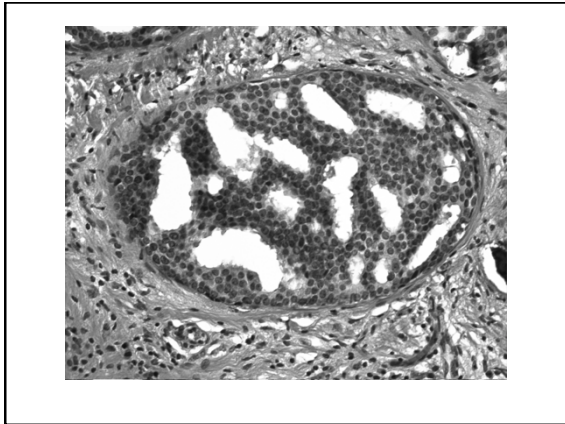
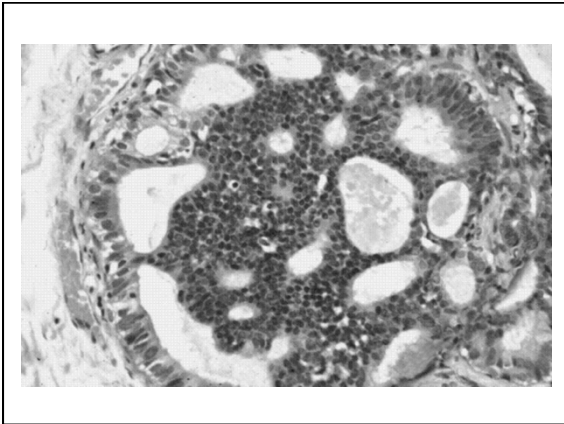


- ### Minimum Criteria for DCIS
- Uniform population of cells, maintaining rounded, geometric configurations
 - Even cell placement, without swirling or streaming
 - **Fully** populating two adjacent spaces (3 mm)

Atypical Ductal Hyperplasia

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

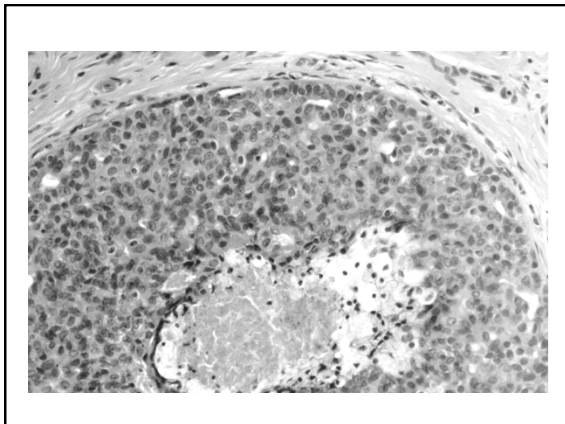
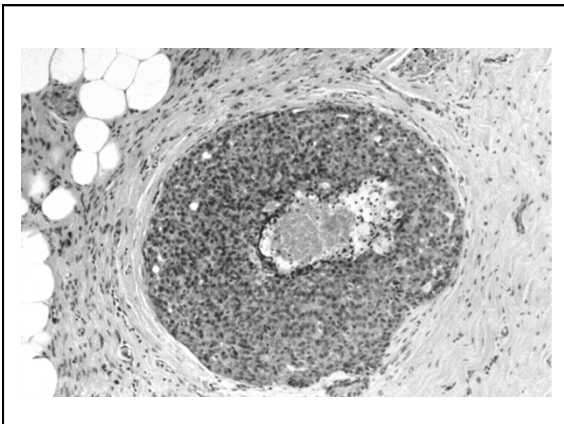


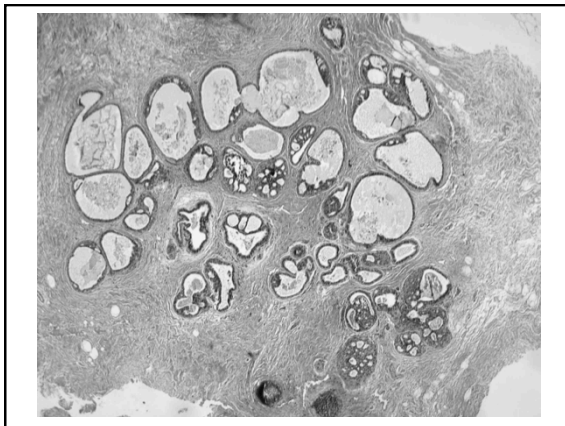
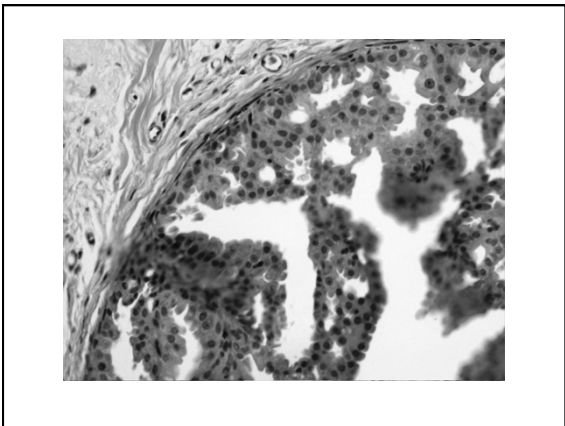
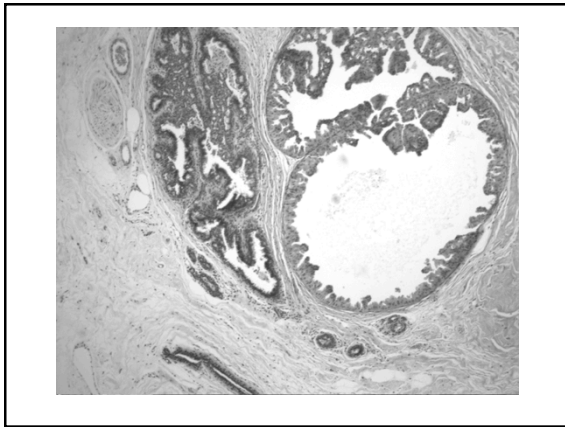
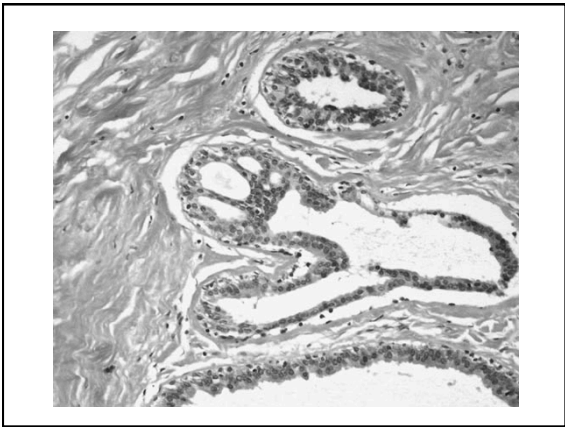
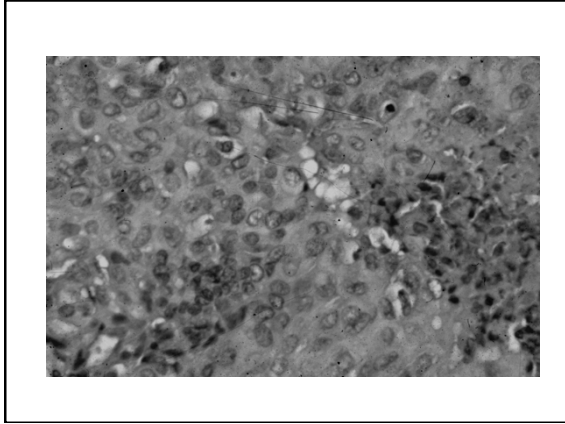


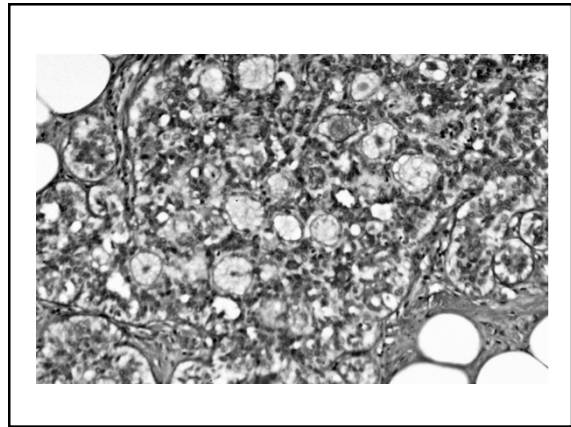
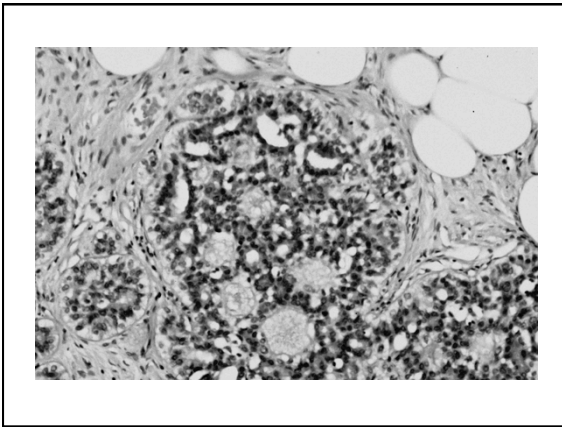
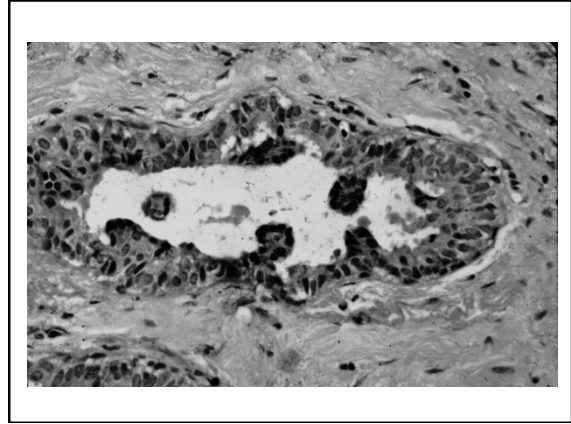
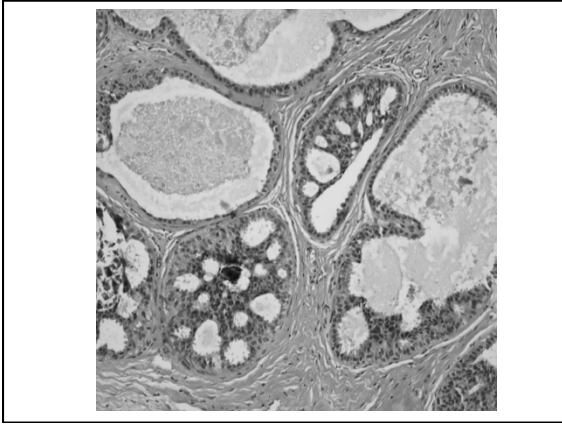
Relative risk confirmation

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







Molecular studies of Proliferative Breast Disease

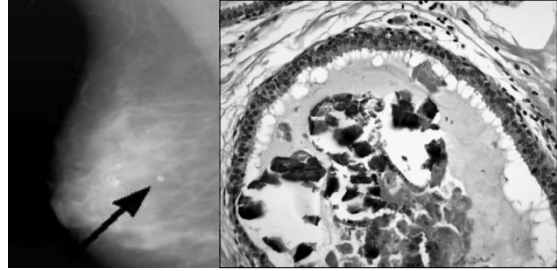
- Goal is to gain additional information beyond histologic risk factors
- Short list
- Focal lesions
- Most cases have concomitant carcinoma
- Not linked to long term outcome

Biomarkers of ADH?

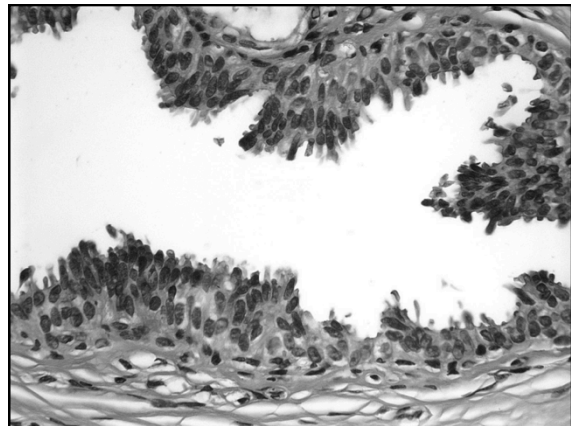
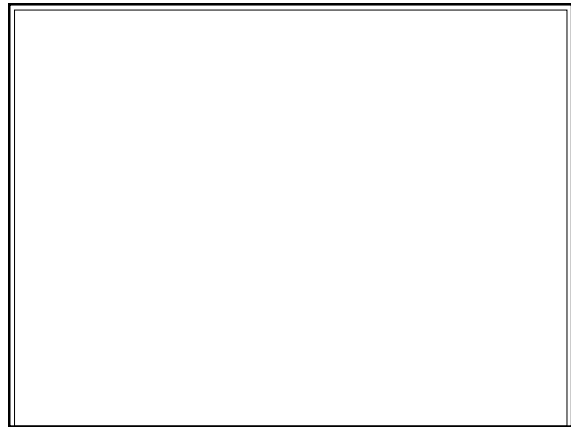
- ADH is typically negative for HMW keratins (CK 5/6) and diffusely positive for ER
- Usual hyperplasia shows variable expression of HMW keratins and ER
- Expression of these markers is similar in ADH and low-grade DCIS
- None is sufficiently validated for routine clinical use

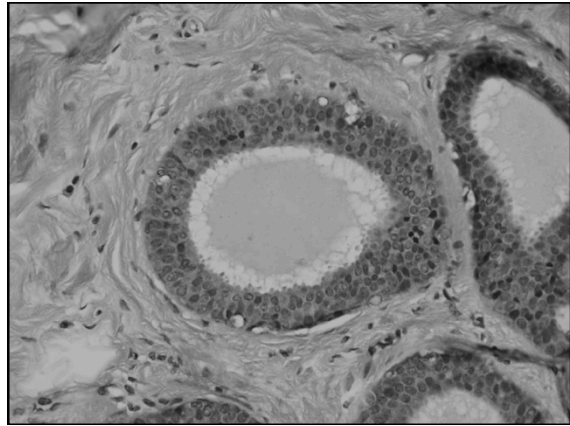
Columnar Cell Lesions

CCL Clinical Presentation



Asymptomatic 45 yo female with round, non-branching Ca²⁺





Columnar Cell Lesions

<p>Columnar Cell Change 1-2 cell layers Uniform, ovoid to elongated nuclei Polarized to BM Evenly dispersed chromatin Indistinct or no nucleoli</p>	}	CCL Without Atypia
<p>Columnar Cell Hyperplasia >2 cell layers, overlapping nuclei Mounds, tufts, abortive micropapillae</p>	}	
<p>“Flat” Epithelial Atypia 1+ layers, decreased N/C ratio Round or ovoid nuclei, loss of polarity Low grade cytologic atypia No arches, papillae, cribriform spaces</p>	}	CCL With Atypia

**Columnar Cell Lesions of the Breast:
 The Missing Link in Breast Cancer
 Progression? A Morphological and
 Molecular Analysis**

P. Simpson, T Gale, J. S. Reis-Filho, C. Jones,
 S. Parry, J. Sloane, A. Hanby, S. Pinder, A
 Lee, S Humphreys, I. Ellis, and S. Lakhani

Am J Surg Pathol 2005;29:734–746)

Columnar Cell Lesions of the Breast

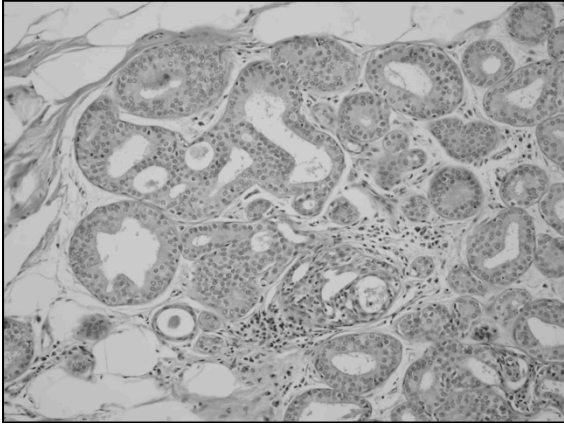
- 18 cases of columnar cell lesions
- High resolution comparative genomic hybridization
- Expanded CCL into 6 categories, with category 5 having overlap with ADH

P Simpson et al. Am J Surg Pathol 2005;29:734–746

Columnar Cell Lesions of the Breast:

- 8 cases had synchronous DCIS or invasive carcinoma
- All categories of CCL showed a range of gross chromosomal copy number gains and losses
- Recurrent changes were identified (loss on 16q, 17p, and X and gain on 15q, 16p, and 19).

P Simpson et al. Am J Surg Pathol 2005;29:734–746



Columnar Cell Lesions

- Co-exist with ALH/LCIS, ADH, LG DCIS, and tubular carcinoma
- common cytologic and immunophenotypic features
- CCLwA has genetic alterations (-16q, -11q) as do low grade DCIS, and tubular carcinoma

Relative risk of Subsequent Breast Cancer Case-Control Studies of Women with CCL

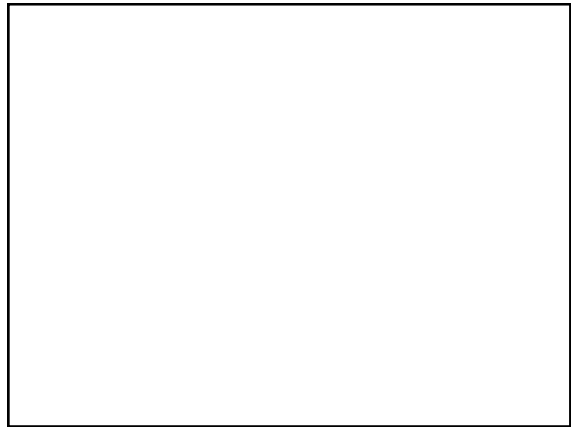
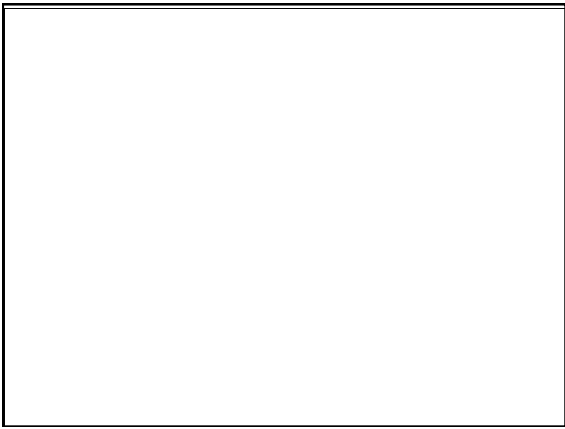
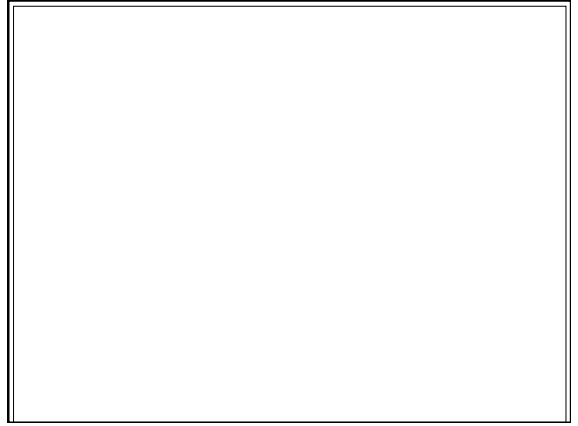
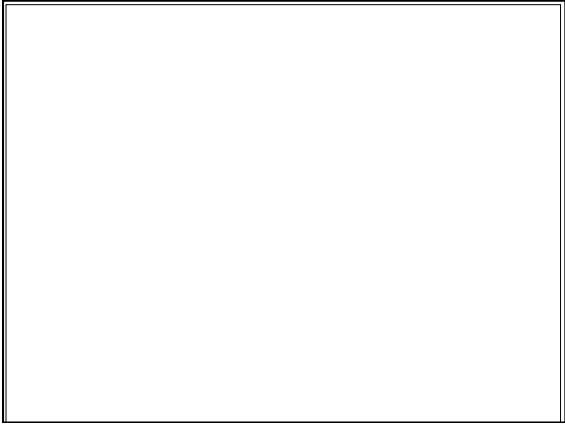
	Boulos (NBC)	Collins (NHS)
Cases/Control	77/152	140/448
Design	Nested CC	Nested CC
Treatment	Bx only	Bx only
Follow-up	17 yrs	12 yrs
RR (95%CI)	1.47 (1.0-2.2)	1.44 (1.4-1.83)

Radial scar

- Histologic features
- Core vs excision
- Indicator of increased risk?

Radial Scars

- Incidental findings in bx
- Less than 1 in a 1000 women screened
- Mammographically spiculated
- Usually associated BPD



p63	SMMHC
calponin	

Radial Scar

- Most recommend excision:
 -
 -
 - no upgrades if :
 - RS < 1.0 cm
 - Sampled by 11 gauge needle or larger
 - ≥ 12 cores taken

Bx

*Brenner 2002
Sohn 2010
Cawson 2003
Rajan 2011*

Epidemiology of Radial Scar

	Sanders (NBC)	Jacobs (NHS)	Berg (Mayo)
Years	1950-1986	1976-1992	1976-1991
Cohort Design	Retrospective	Case-Control	Retrospective
# RS	880 (9.2%)	99 (7.1%)	439 (4.7%)
Ave size	4.8 mm	4.0 mm	≤ 5.0 mm
# Cancers	62 (IMC)	24 (IMC+DCIS)	52 (IMC+DCIS)
Follow-up	20.4 yrs	12 yrs	17 yrs
RR (95%CI)	1.82 (1.2-2.7)	3.0 (1.7-5.5)	1.88 (1.36-2.53)
PD or AH +/-RS	NS	RS \uparrow risk	NS

Cancer 2005
NEJM 1999
Br Can Res Treat 2008