

A Pathologist's Perspective on the Management of High-Risk Lesions

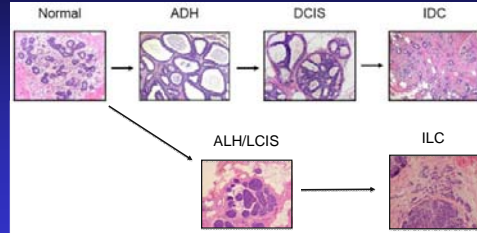
I think you already know what he's going to say ...

W. Fraser Symmans, M.D.

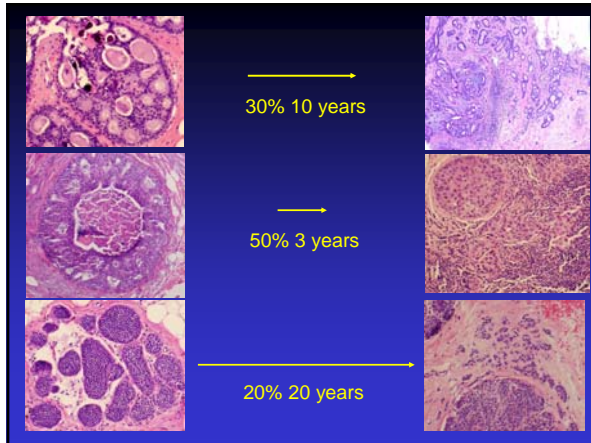


Pathogenesis of Breast Cancer (1990s)

Regional effect: most likely at or near the original site



Field effect: more common in ipsilateral breast, sometimes contralateral breast, but not necessarily the original site



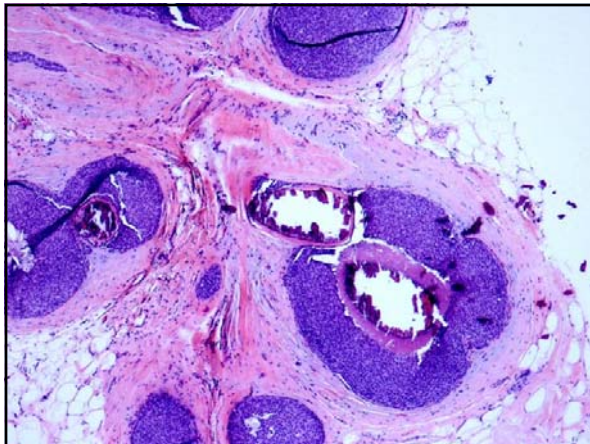
In situ carcinoma

Ductal carcinoma *in situ*

Excise if in CBX
Achieve negative surgical margins
Radiation therapy

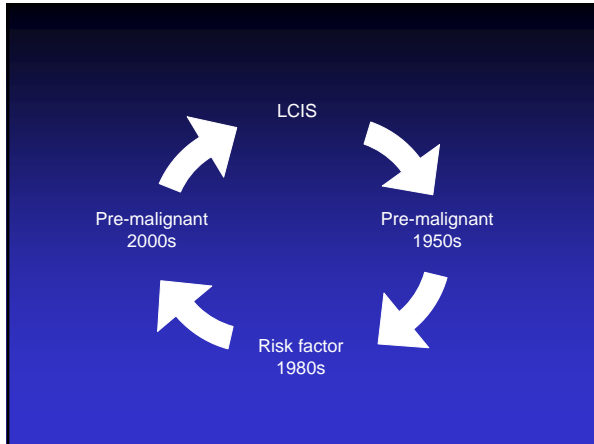
Pleomorphic lobular carcinoma *in situ*

Excise if on CBX
Achieve negative surgical margins
Radiation therapy?



Classic Lobular Carcinoma In Situ

- True incidence is unknown
 - lacks clinical and mammographic signs
- Page et al. reviewed 10,542 benign breast biopsies performed for clinical abnormalities
 - incidence of 0.5%
- Haagensen et al. reviewed results from 5,000 patients who had breast biopsies from 1932-1972
 - incidence of 3.6%

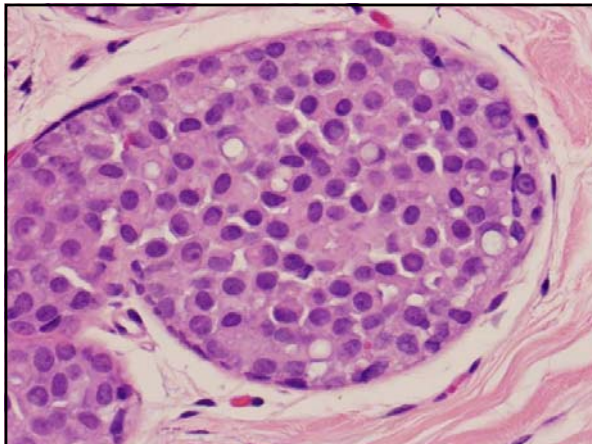
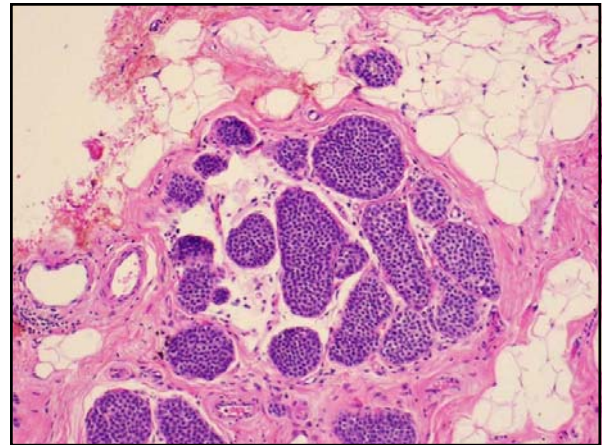


LCIS is a Risk Factor AND a Direct Precursor

- LCIS confers an increased risk for subsequent breast cancer
 - 7-10 fold higher than the index population
- Historically, the risk of subsequent breast cancer development was thought to be equal in both breasts
- Subsequent invasive ductal or invasive lobular cancers
 - ILC in 25-88%

LCIS is a Risk Factor AND a Direct Precursor

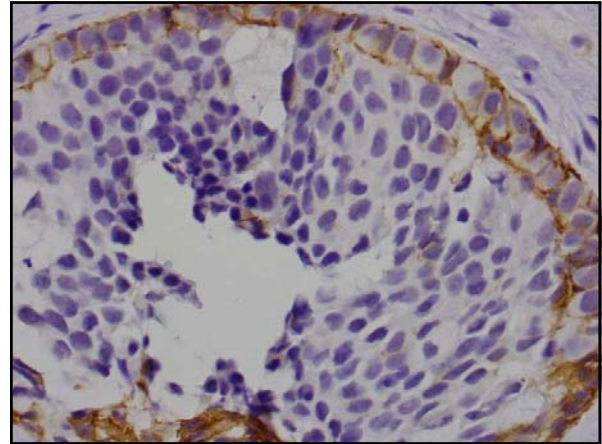
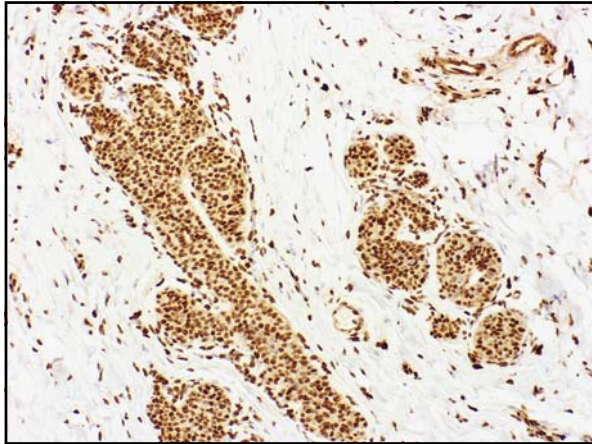
- LCIS is frequently seen in relationship to ILC
- Both lesions have similar IHC profiles
- Molecular studies also support that LCIS is a direct precursor to ILC
- Studies have demonstrated that subsequent invasive carcinomas are more common in the ipsilateral breast



Classic LCIS: Immunophenotype

| Biomarker | Usual Status | Rate of + Status |
|------------|--------------|------------------|
| E-cadherin | negative | <5% |
| ER | positive | 98% |
| PR | positive | 84% |
| Her 2 | negative | <5% |
| Ki67 | low | <5% |

Classic lobular = low-grade ductal – E-cadherin



Excisional Biopsy After CNB Diagnosis of LN

| Author | Pure ALH | | Pure LCIS | |
|----------------|----------|--------------|-----------|--------------|
| | CNB | Cancer on EB | CNB | Cancer on EB |
| Elsheikh | 20 | 5 | 13 | 4 |
| Liberman | | | 5 | 0 |
| Renshaw | 6 | 0 | 9 | 0 |
| Burak | 6 | 1 | | |
| Shin | 5 | 0 | 8 | 2 |
| Yeh | 12 | 1 | 3 | 0 |
| Middleton | 6 | 4 | 9 | 2 |
| O'Driscoll | | | 7 | 3 |
| Sapino | | | 10 | 4 |
| Bonnet | 24 | 2 | | |
| Georgian-Smith | | | 7 | 2 |
| Brown | 3 | 0 | | |
| Berg | 7 | 1 | | |
| Philpotts | | | 5 | 1 |
| Pacelli | 12 | 0 | 18 | 3 |
| Zhang | 8 | 0 | 10 | 3 |
| Dmytrasz | 7 | 3 | | |
| Bauer | | | 7 | 1 |
| Arpino | 17 | 1 | 4 | 2 |
| Foster | 14 | 2 | 12 | 4 |
| Total Cases | 238 | 39 (16.4%) | 255 | 50 (19.6%) |

Summary of Excisional Biopsy after CNB Diagnosis of LCIS

238 cases pure ALH → 39 (16.4%) CA

255 cases pure LCIS → 50 (19.6%) CA

When cases are SELECTED for surgical excision

Lobular Carcinoma *in situ*

Excise after diagnosis of LCIS on CBX, if there is:

- overlapping features of DCIS
- an associated mass lesion
- pathologic/radiologic discordance
- residual worrisome calcification
- strong family history ??

ALH as a Predictor of Future Breast Cancer Risk

- 252 women with ALH
- 50 (20%) developed IBC
- Ipsilateral in 34 (68%)
- IBC after ALH is 3X more likely to develop in same breast

Page et al Lancet 2003;361:125-9

ALH and ADH as Predictors of Future Breast Cancer Risk

- Nurses' Health Study
 - 395 cases (subsequent cancer) and 1610 controls, matched for age and surgery date
- Odds ratio for future breast cancer (*in situ* or invasive)
 - Proliferative FCC 1.5
 - AH 4.1
 - ADH 3.0
 - ALH 5.8
- Cancer was ipsilateral in 60% (ADH or ALH)

Collins et al Cancer 2008;132:615-21

Atypical Lobular Hyperplasia

Excise after diagnosis of ALH on CBX, if there is:

- overlapping features of DCIS
- an associated mass lesion
- pathologic/radiologic discordance
- residual worrisome calcification
- strong family history ??

Atypical Ductal Hyperplasia

ADH

Excise if in CBX

Surgical margins not relevant in excision specimens

Differential diagnosis from low-grade DCIS is an issue

Cytologic Atypia on Needle Biopsy 1990s

- Fine needle aspiration lost popularity
 - Non-diagnostic results
 - Atypical diagnoses that did not correspond to ADH, ALH, *in situ* or invasive carcinoma when radiologic lesion was excised
- Core needle biopsy became favored
 - Almost never provides a non-diagnostic result
 - Less frequent and more specific atypical diagnoses, i.e. ALH or ADH
- Vacuum assisted core biopsy overtook
 - Larger and more numerous tissue cores
 - Probe does not require re-positioning

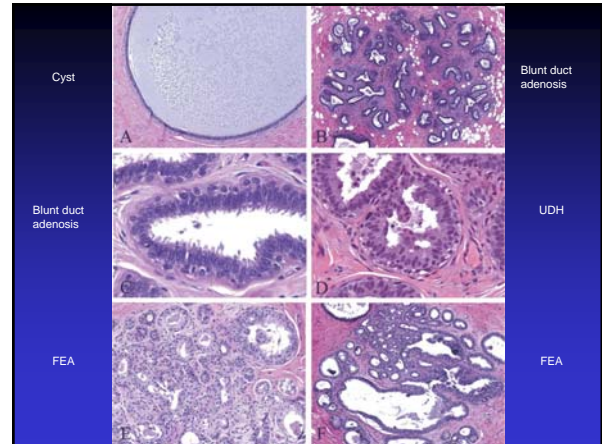
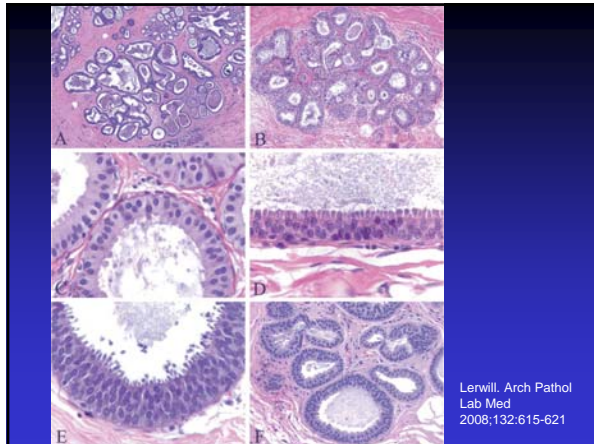
Non-specific atypical diagnoses for needle biopsies create problems

- Increase patient anxiety
- Lead to "unnecessary" operations
- Induce surgeon frustration
- Diminish confidence in the pathologist
- Diminish confidence in the procedure

Flat Epithelial Atypia

oh no, here we go again ...

- The core biopsy version of cytologic atypia
 - Mild atypia
 - No architectural (histologic) change
 - Associated with calcification
 - Involves the terminal ductular-lobular units
- Ignored by pathologists in the 1990's, but embraced by pathologists in the 2000's



Flat Epithelial Atypia

- Synonymous with columnar cell change with atypia, CAPSS with atypia, DIN-1, clinging *in situ* carcinoma flat type.
- FEA is observed in association with LOW GRADE carcinomas
 - Tubular, tubulo-lobular, mixed tubular-ductal, lobular, low-grade ductal carcinomas
 - Low-grade DCIS
 - Lobular neoplasia
- Similar molecular aberrations in FEA as in low-grade cancers

Flat Epithelial Atypia as a CBX Diagnosis

- Preliminary small studies suggest that 15-30% of core biopsies with FEA as the main diagnosis are associated with carcinoma in the excision specimen
 - Selection bias?
 - Need larger series
 - Undoubtedly will have subjective variation with this diagnosis

Quite similar to the malignant FNA diagnoses of ATYPIC

Flat Epithelial Atypia as a Surgical Resection Diagnosis

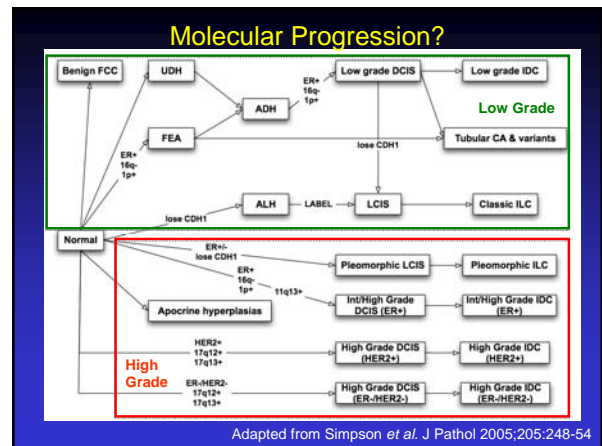
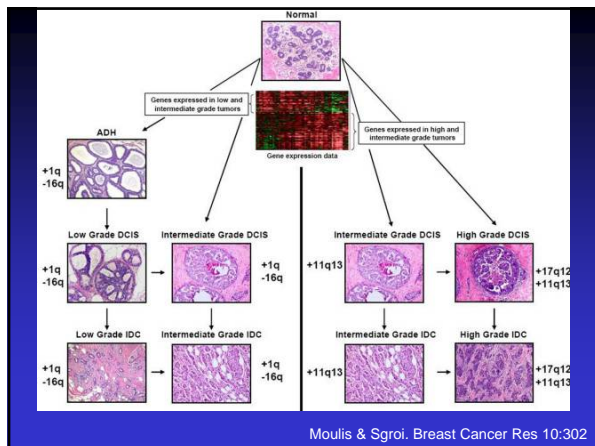
- Negligible data from small retrospective studies suggest a minor risk for subsequent cancer
 - Need larger series
 - Need long follow up
 - Problem is that these diagnoses were essentially introduced into diagnostic practice within the last 10 years

Flat Epithelial Atypia

Management Recommendations:

Excise if diagnosed in CBX

Surgical margins not relevant for FEA



Are High Risk Lesions Associated With Low-Grade Cancers A Medical, Rather Than Surgical Condition?

- Incidental findings or indeterminate calcifications
- Low grade, low proliferation, always strongly ER+
- Minimal or moderate long-term risk ($\leq 20\%$, 30 years) for subsequent invasive cancer
 - What proportion of those are ER+?
- Would hormonal chemoprevention halt their progression?
 - NSABP P-01 & STAR trials

Conclusions (Opinions)

- The risk lesions that cause the most radiologic-pathologic confusion are associated with low-moderate risk of low-grade invasive cancer
 - Excise if on core biopsy
 - Probably a field effect, so margins might not be critical
- Maybe those FNA diagnoses of cytologic atypia (without corresponding ALH, ADH, or cancer at excision) were not so wrong, since surgical pathologists have recently realized the same issue in flat epithelial atypia
- Current evidence indicates that the molecular pathogenesis of low-grade breast cancer and high-grade breast cancer are probably very different
 - Low-grade pathogenesis is influenced by hormones
 - High-grade pathogenesis is poorly understood