1

Objectives

- Discuss the risk factors for breast cancer development
- Define the high-risk proliferative epithelial lesions of the breast
- Discuss the histologic criteria for the diagnosis of usual ductal hyperplasia, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and LCIS, classic and pleomorphic types
- Discuss the histologic criteria for the diagnosis of flat epithelial atypia (FEA)
- Appreciate the clinical significance of high-risk proliferative epithelial lesions of the breast

2

Outline

- Definition
- ADH
- ALH
- LCIS (and subtypes)
- Factors that modify risk in patients with atypias
- Issues with accuracy of diagnosis (interobserver variability)
- Molecular pathology/biomarkers in high risk lesions
- Genetic alterations in proliferative breast lesions
- Management of high risk lesions
- Columnar cell lesions of the breast (CCC, CCH, FEA)

3

Breast Cancer Risk Factors

- Age
- Gender
- Ethnic background
- Hormonal influences
- Reproductive history/Breast feeding
- Family history/Genetic predisposition
- Mammographic density
- Diet/Exercise
- Environmental factors
- Radiation exposure
- Pathologic findings in breast biopsies (high risk lesions):
  - Atypical hyperplasias (ADH, ALH)
  - Lobular carcinoma-in-situ (LCIS)

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High Risk Breast Lesions

- High risk breast lesions are lesions associated with an increased risk for future development of breast cancer based on results of long-term follow-up studies
- Implications on patient management, counseling and follow-up

Histologic Features	Relative Risk	Absolute Risk
Normal	1	10% by age 80
Proliferative lesions with no atypia	~1-2 x	~10% at 20y
Atypical hyperplasias (ADH and ALH)	~4-5 x	~1% per year (Mayo Cohort, 2015)
LCIS	8-10 x	~1% per year (MSKCC, 2015)

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Risk Factors in Women with Proliferative Breast Disease

- Retrospective cohort study (Dupont WD and Page DL, NEJM 312:146, 1985)
- 3,303 Nashville women, 3 hospitals, 10,366 benign breast biopsies, median follow-up: 17 years
- Strictly defined criteria
  - Nonproliferative lesions
  - Proliferative lesions without atypia
  - Atypical hyperplasia
- Risk of developing breast Ca determined for each group

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Nonproliferative Lesions

- Cysts
- Apocrine change
- Epithelial-related calcifications
- Mild hyperplasia of the usual type

70% of biopsy specimens

No increased risk

No effect of family history

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Proliferative Lesions without Atypia

- Moderate or florid usual hyperplasias
- Intraductal papillomas
- Sclerosing adenosis

26% of biopsy specimens

Slightly increased risk

- RR of 1.6
- RR of 2.1 with family history

8

Atypical Hyperplasias

- Atypical ductal hyperplasia
- Atypical lobular hyperplasia

4% of biopsy specimens

Moderately increased risk

- RR of 4.4
- RR of 8.9 with family history

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Incidence of Atypical Hyperplasias by Indication for Biopsy

- Biopsy for palpable mass:

  2 to 4%

- Biopsy for mammographic microcalcifications:

  12 to 17%

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Studies Looking into RR of Developing Breast Cancer by Pathologic Findings in Breast Biopsies

- Nashville Breast Cohort
  - Dupont and Page: NEJM 1985
- Nurses' Health Study (NHS)
  - London, Connolly, Schnitt and Golditz, JAMA 1992 (and updates)
- Breast Cancer Detection Demonstration Project (BCDDP)
  - Dupont, Parl, Hartmann et al, Cancer 1993
- Mayo Clinic
  - Hartmann, Sellers, Frost et al, NEJM 2005

These studies all found that proliferative lesions, especially those with atypia, confer an increased risk for future development of breast carcinoma

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No Increased Risk

- Adenosis (other than sclerosing adenosis)
- Duct ectasia
- Fibroadenoma without complex features
- Fibrosis
- Mastitis
- Mild usual ductal hyperplasia (without atypia)
- Cysts (gross or microscopic)
- Apocrine metaplasia
- Squamous metaplasia

Ref. Cancer Committee of the College of American Pathologists (CAP)

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Slightly Increased Risk (1.5 - 2 times)

- Fibroadenoma with complex features
- Moderate or florid hyperplasia without atypia
- Sclerosing adenosis
- Solitary papilloma

Ref. Cancer Committee of the College of American Pathologists (CAP)

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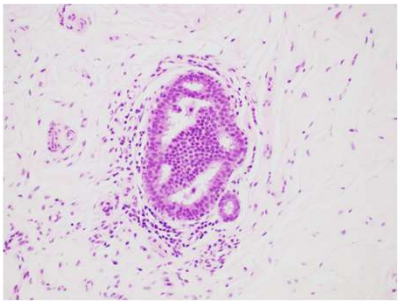
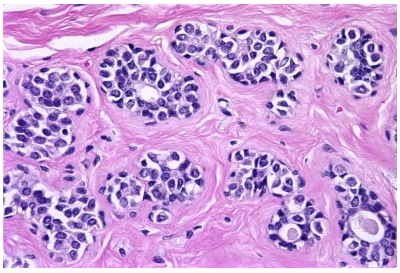
Moderately Increased Risk (4 to 5 times)

- Atypical ductal hyperplasia (ADH)



- Atypical lobular hyperplasia (ALH)



Ref. Cancer Committee of the College of American Pathologists (CAP)

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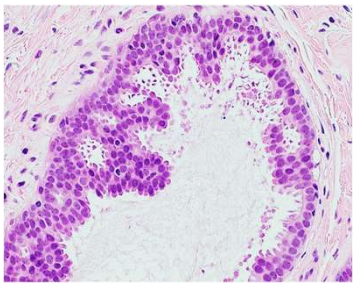
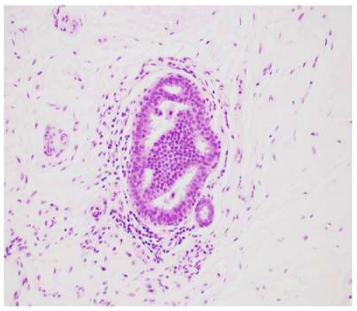
Histologic Criteria for Atypical Ductal Hyperplasia (ADH)

- Lesions have some of the architectural and cytologic features of DCIS, such as:
  - Nuclear monomorphism,
  - Regular cell placement,
  - Rigid/Roman arch-like epithelial formations and
  - Round regular spaces *in at least part of the involved space*





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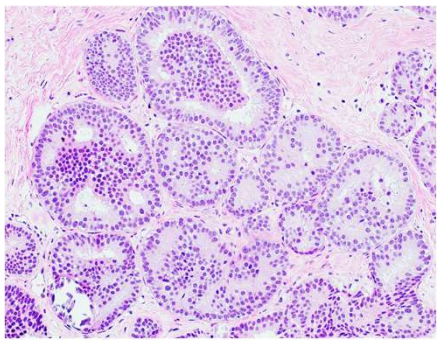
Histologic Criteria for Low Grade (Grade I) DCIS

- Uniform cell population
- “Punched out”, neatly rounded geometric spaces (cribriform pattern)
- Round, hyperchromatic, monotonous nuclei
- Complete involvement of the lesional spaces
- Area bound by basement membrane
- Microcalcifications



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ADH vs. DCIS
Quantitative Criteria

- At least 2 spaces of uniformly present atypical cells (Page et al.)
- 2mm rule (Tavassoli and Norris)
- Only apply to low grade lesions
- Do not use on core needle biopsy or reexcision specimens

Need for identification of reliable objective biologic markers in order to differentiate these two lesions

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Comparison between
ADH and Low Grade DCIS

- **Magnitude of risk:**
  - ADH: 4-5x
  - DCIS: 8-10x
- **Laterality of risk:**
  - ADH: either side
  - DCIS: ipsilateral
- **Type of subsequent cancer:**
  - ADH: any histology, any grade
  - DCIS: grade similar to DCIS

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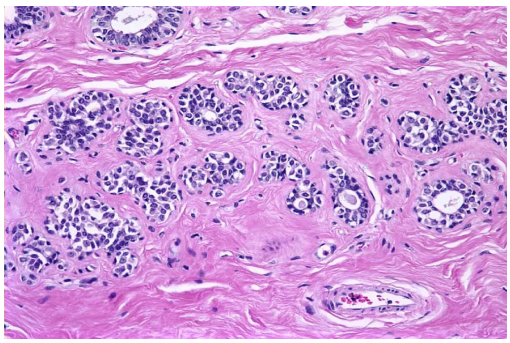
Histologic Criteria for Atypical Lobular Hyperplasia (ALH)

- Lesions are characterized by changes similar to the LCIS but *they lack the complete criteria for that diagnosis*.
- Small, monomorphic, discohesive cells that fill <50% of acinar units without distension



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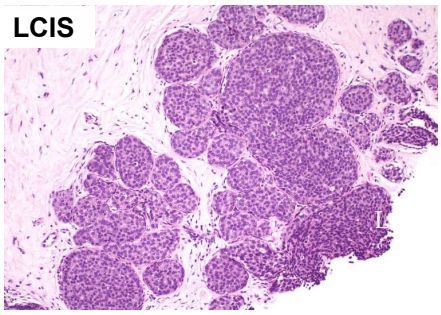
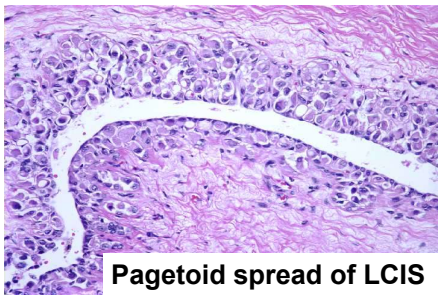
Histologic Criteria for LCIS (Classic Type)

- Characteristic, small uniform, monomorphic discohesive cells
- Filling of all the acini (no spaces between cells)
- Marked ***expansion/distension*** of at least half of the acini in the lobular unit
- Occasionally we see pagetoid spread of LCIS into ducts





Pagetoid spread of LCIS

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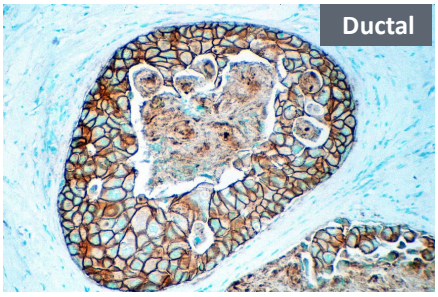
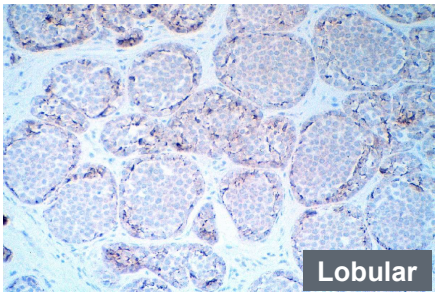
E-cadherin Expression

- Transmembrane glycoprotein involved in cell-cell adhesion
- CDH1 gene is located on chromosome 16q22.1
- 16q deletion/loss of function is an early event in the development of lobular neoplasia/ILC (also confirmed in the TCGA dataset)
- E-cadherin immunohistochemistry is commonly used to identify ALH/LCIS





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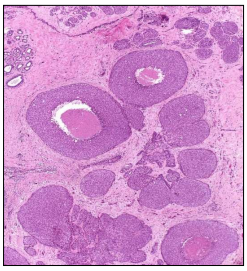
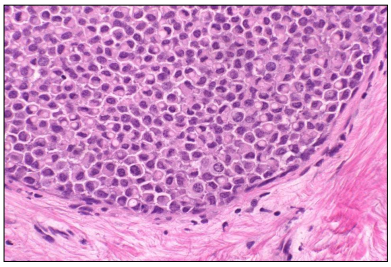
LCIS Pleomorphic Type

- Lobulocentric growth
- Discoherant cell population
- E-cadherin negative
- Central necrosis
- Nuclear pleomorphism
- Moderate to abundant cytoplasm, signet ring features
- Usually ER positive, GCDFP positive, and HER2 neg or pos
- Surgical excision required





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LCIS - Clinical Issues/Risk

- Usually multifocal (>50%) and bilateral (>30%)
- Present in up to 4% of benign breast biopsies
- Usually an incidental finding; rarely associated with microcalcifications
- Associated with 8-10x increased risk for future development of breast cancer (about 1%/year, steady over time)
- Cancer can be ipsilateral or contralateral (similar rates)
- 50% ILC, 50% IDC

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Significance of High Risk Breast Lesions

Histologic Lesion	Type of Risk
ADH and ALH	Markers of generalized increase in risk
LCIS	Marker and non-obligate precursor to ER+ breast cancer
DCIS	Non-obligate precursor to invasive cancer usually of similar grade

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Factors that Modify the Breast Cancer Risk in Patients with Atypical Hyperplasia

	Family history	Time since biopsy	Risk based on type of AH and age
Nashville Cohort	Increases risk	Risk is greatest during first 10 years, then decreases	Risk for ALH>ADH Constant with age/menopausal status
NHS	No effect	Constant over time	Risk for ALH>ADH more so in young /premenopausal pts
Mayo Clinic	No effect	Constant over time	Risk for ALH=risk for ADH Risk higher in younger pts

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Concerns in Categorizing Proliferative Breast Lesions

- Study by Rosai J., AJSP, 1991 15:209
  - 5 breast pathologists reviewed 17 proliferative breast lesions
  - Application of criteria used in their daily practice
  - Complete agreement: 0% of cases
  - 4 out of 5 agree: 18% of cases
- Study by Schnitt et al., AJSP, 1992 16:1133
  - 6 breast pathologists reviewed 24 proliferative breast lesions
  - Specific set of criteria (by Page et al.) and a set of 15 teaching slides
  - Complete agreement (6/6): 58%
  - 5 out of 6 agree: 71%
  - 4 out of 6 agree: 92%

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Diagnostic Accuracy of DCIS Diagnosis; ECOG 5194 Trial

- 693 pts with DCIS
- Aim: Compare the agreement between original pathologist (OP) and central pathologist (CP) review
- 92.9% overall agreement
- 49/693 (7.1%) change of diagnosis by CP
- Biggest discrepancy between LG-DCIS and ADH (28/49 cases)
- Similar disagreement rates between academic vs community practices

Ref: Simpson, Sanders and Page: USCAP meeting abstract, 64A, 2011

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Interobserver Agreement & Uncertainty in Medicine

- **Treatment recommendations for breast cancer patients**
  - 43% disagreement between multidisciplinary panels and outside physicians (Ref 1)
  - 20.3 % disagreement re: surgical management after a second opinion (Ref 2)
- **Mammography interpretation by radiologists**
  - 8.9% false positive rates (Ref 3)
  - Fair agreement in overall BI-RADS categorization (k=0.28) (Ref 4)
  - Moderate agreement on BI-RADS 5 (k=0.56) (Ref 4)
- **DCIS diagnosis disagreement by pathologists: 7.1 %** (Ref 5)

Ref: 1. Chang et al. Cancer, 91:1231, 2001
2. Clauson et al. Proc ASCO 19:91a, 2000
3. Elmore et al. Radiology, 253: 641, 2009
4. Lazarus et al. Radiology, 239:385, 2006
5. Simpson et al. USCAP meeting abstract, 64A, 2011

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Biomarkers in Proliferative Breast Lesions

- Although it provides valuable information, classic histologic classification has limitations in accurately predicting risk, especially for an individual patient
- There is a need to further refine risk by using molecular biomarkers
- Long list of biomarkers are studied in proliferative breast disease (ER, HER2, p53, Ki-67, COX-2, stem cell markers, chromosomal and genomic abnormalities, various expression signatures and others)
- Very few studies try to correlate biomarkers with the risk of future development of breast cancer
- Most are observational, have a few numbers of cases, or even in larger studies very few cancer events were observed
- Currently we still do not have a validated list of what set of biomarkers we should look for to accurately categorize these proliferative lesions and predict future risk

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Genetic Alterations in Proliferative Breast Lesions

- Usual ductal hyperplasia
  - LOH in 0-15%
  - Abnormalities of 17q, 16q, 9p and 13q
- ADH
  - LOH for at least one marker in 42%
  - Abnormalities of 16q and 17p (similar to that of low grade DCIS)
- ALH
  - Loss of material from 16p, 16q, 17p and 22q
  - Gain from 6q (similar to LCIS)

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Conclusions from Recent Genetic Studies

- Usual ductal hyperplasia (UDH) has some similarities to ADH, DCIS and invasive cancer
- ADH has many similarities to low grade DCIS and the exact cut off is somewhat arbitrary
- UDH-ADH-LG-DCIS is a histologic and molecular continuum without distinct boundaries
- Low grade DCIS and high grade DCIS appear to be genetically distinct lesions that lead the development of distinct forms of invasive breast cancer
- Implications for the paradigm of breast cancer progression

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Traditional Breast Cancer Progression Model

Normal epithelium

↓

Usual ductal hyperplasia

↓

Atypical ductal hyperplasia (ADH)

↓

DCIS

↓

Invasive cancer

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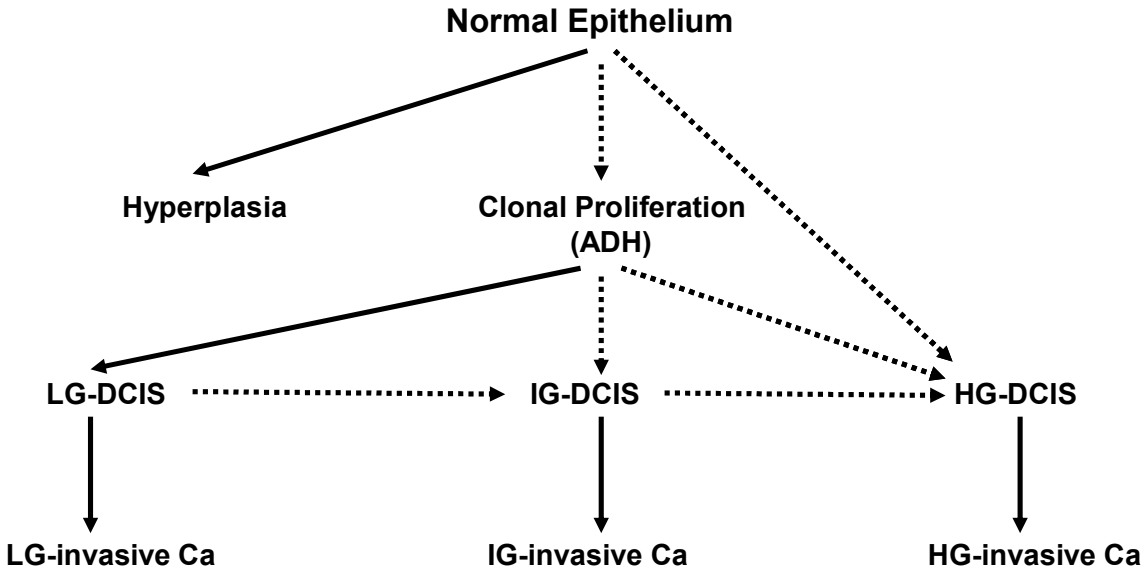
Current Breast Cancer Progression Model



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Management of High-Risk Lesions Found on Core Biopsy

The American Society of Breast Surgeons Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions (2016)

Lesion	Recommendation	Notes
ADH	Surgical Excision	If ADH is focal and completely excised on core biopsy may be observed based on risk assessment and multidisciplinary discussion
ALH/LCIS	Surgical Excision or Observation with Clinical and Imaging follow up	Excision is needed if limited sampling, other high risk lesion is present and pathology/imaging correlation is discordant. No margin assessment
Pleomorphic LCIS	Surgical Excision	Assess margins; try to obtain clear margins

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Columnar Cell Lesions of the Breast

DEFINITION:

- Represent a spectrum of lesions that have in common the presence of columnar epithelial cells lining variably dilated terminal duct lobular units (TDLUs)
- Range from those that show no cytologic or architectural atypia to those that show sufficient features to warrant a diagnosis of atypical ductal hyperplasia or low-grade ductal carcinoma in-situ

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Columnar Cell Lesions of the Breast

- Previously described under a variety of names:
  - Columnar metaplasia
  - Columnar alteration with apical snouts
  - Atypical cystic lobules
  - Pretubular hyperplasia
  - Hypersecretory hyperplasia with atypia
  - Clinging carcinoma

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Columnar Cell Lesions of the Breast

- Schnitt SJ, Vincent-Salomon A.
  Columnar cell lesions of the breast. *Advances in Anatomic Pathology* 2003;10:113-124.
- Scheme for classification:
  - Columnar cell change
  - Columnar cell change with atypia
  - Columnar cell hyperplasia
  - Columnar cell hyperplasia with atypia
- In 2003 the WHO working group on the Pathology and Genetics of Tumors of the Breast introduced the term “flat epithelial atypia” to describe the columnar lesions with atypia creating 3 instead of 4 categories

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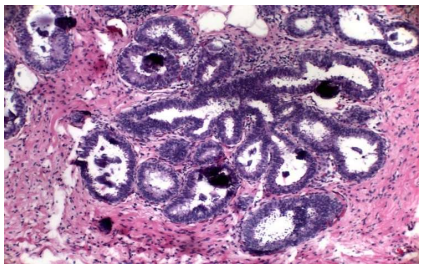
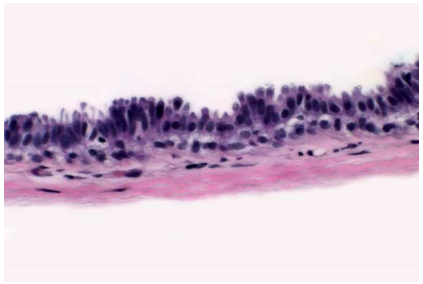
Columnar Cell Change





- Characterized by TDLUs that display variably dilated acini lined by only 1or 2 layers of columnar epithelial cells
- Apical cytoplasmic blebs or snouts are often present at the luminal surface of the epithelial clefts
- Intraluminal calcifications may be present
- Flocculent intraluminal secretions frequently seen

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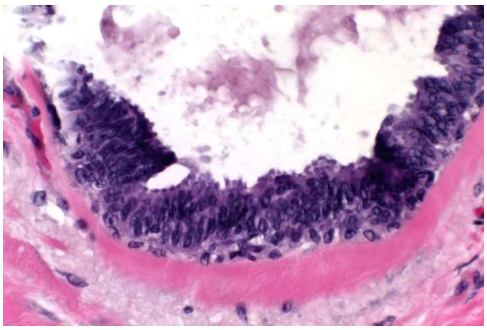
Columnar Cell Hyperplasia

- Composed of TDLUs with variably dilated acini lined by columnar epithelial cells showing cellular stratification more than 2 cell layers; however, despite the stratification the cells maintain their orientation perpendicular to the basement membrane
- Exaggerated apical cytoplasmic snouts and abundant flocculent intraluminal secretions are often seen
- Intraluminal calcifications are frequently present



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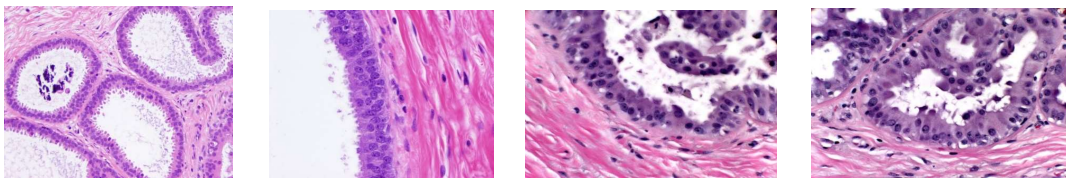
Flat Epithelial Atypia (FEA)

- Composed of TDLUs with variably dilated acini lined by columnar epithelial cells showing some cellular stratification (more than 2 cell layers)
- Cytologic atypia present
  - usually low-grade
  - complex architectural patterns are NOT present
- Features of cytologic atypia
  - nuclei of the columnar epithelial cells are round or ovoid
  - not oriented perpendicular to the basement membrane (loss of polarity)
  - slight increase in the nuclear/cytoplasmic ratio



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Columnar Cell Lesions of the Breast

- Not uncommon for various combinations of columnar cell lesions to coexist:
  - in the same breast
  - in the same terminal duct lobular unit
  - within the same acini
- Therefore, these columnar cell diagnoses should not be considered mutually exclusive

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Interobserver Reproducibility in the Diagnosis of FEA

- Study by O'Malley et al., Modern Pathology, 2006, 19: 172-179.
  - 8 breast pathologists
  - Power Point Tutorial with written set of criteria and representative images of CCLs with and without FEA
  - Images in Power Point format from 30 CCLs; asked to categorize each as either FEA or not atypical
  - Complete agreement: 91.8% (kappa value of 0.83, excellent); slightly better agreement for the absence of FEA than for the presence of it

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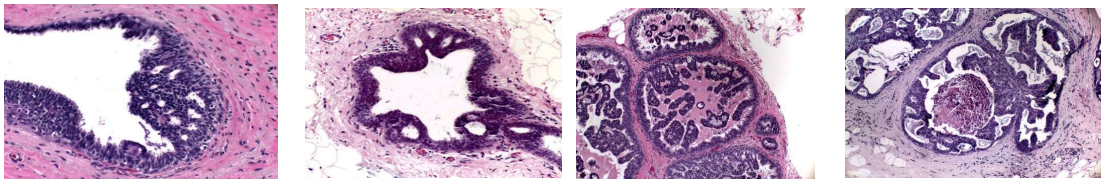
Differential Diagnosis

- Atypical ductal hyperplasia & Ductal carcinoma in-situ:
  - Some lesions composed of columnar epithelial cells show more complex architectural patterns such as well-developed micropapillations, rigid cellular bridges, and sieve-like fenestrations
  - Others show high-grade cytologic atypia with nuclear pleomorphism
- The presence of such complex architectural patterns or high grade nuclear features merits the designation of ADH or DCIS



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Clinical Significance

- Some authors have concluded that columnar cell lesions represent an early phase in the development of low-grade DCIS
  - Investigators have noted that the cells comprising some columnar cell lesions are cytologically similar or identical to the cells comprising forms of DCIS
  - Cells comprising some columnar cell lesions are immunophenotypically identical to coexistent low-grade DCIS cells (the cells of both lesions are positive for estrogen receptor, progesterone receptor, keratin 19, and cyclin D1)

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Practical Considerations

- **In a Needle Core Biopsy**
  - Columnar cell change
  - Columnar cell hyperplasia
    - Neither additional pathology work-up nor excision are required
  - Flat epithelial atypia (FEA)
    - Recent data have suggested subsequent excision shows a more advanced lesion in about one-third of cases, which is sufficiently frequent to recommend excision

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Practical Considerations

- **In an Excisional Biopsy**
  - Columnar cell change
  - Columnar cell hyperplasia
    - Neither additional pathology work-up nor additional treatment
  - Flat epithelial atypia (FEA)
    - Prompt a careful search for areas with diagnostic features of ADH or DCIS by obtaining additional levels from the block, and the submission of the remainder of the tissue

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Practical Considerations

- **In an Excisional Biopsy**
  - Is the presence of an atypical columnar cell lesion at the excision margins sufficient to consider the margins "positive" requiring further surgical resection?
  - Should an atypical columnar cell lesion be taken into consideration in determining the size or extent of the DCIS lesion?

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Practical Considerations

- FEA is associated with a very low risk of recurrence or progression to invasive carcinoma
- Therefore, this lesion should **not** be taken into consideration when determining the size of a coexistent DCIS lesion or in the evaluation of the status of the margins of excision

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Summary

- Definition
- ADH
- ALH
- LCIS (and subtypes)
- Factors that modify risk in patients with atypias
- Issues with accuracy of diagnosis (interobserver variability)
- Molecular pathology/biomarkers in high-risk lesions
- Genetic alterations in proliferative breast lesions and their implications in the current breast cancer progression model
- Management of high-risk lesions
- Columnar cell lesions of the breast

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Summary

In high-risk proliferative lesions of the breast newer insights and new recommendations continue to challenge our pre-existing concepts and our understanding of their significance in increasing future breast cancer risk and are expected to lead to improved patient management and outcomes.

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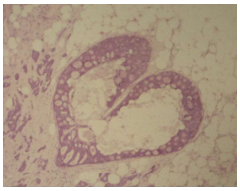
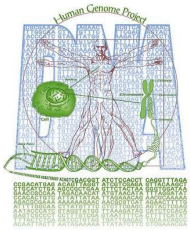
Thank you !





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Questions?

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