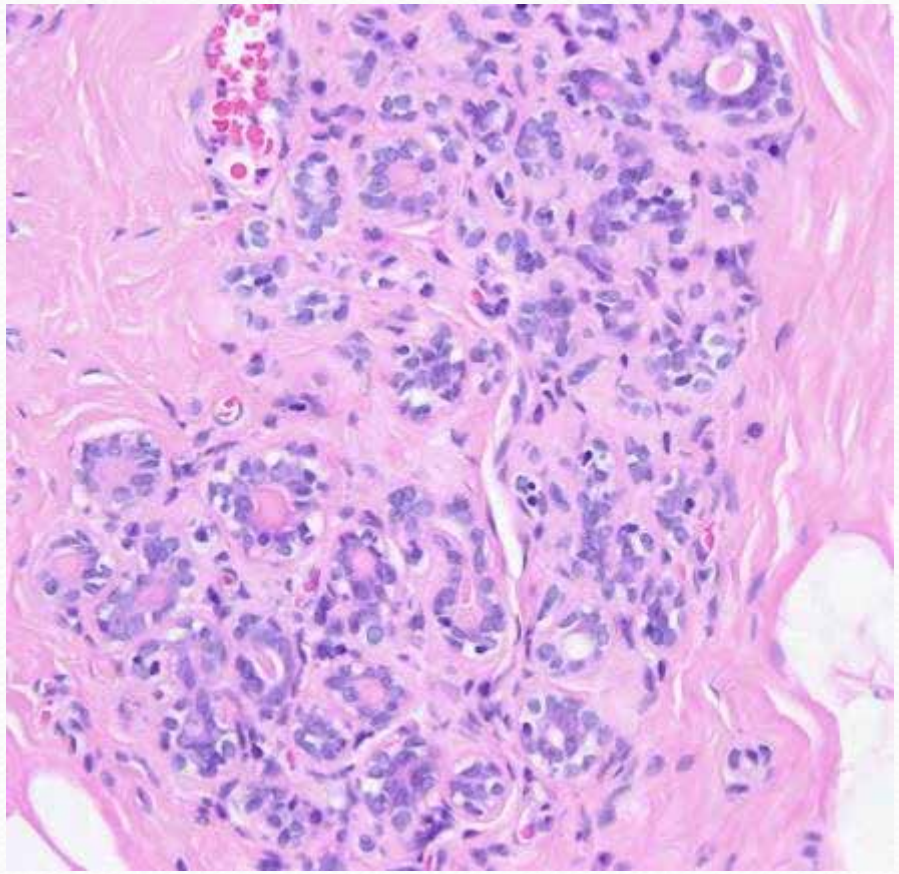
Wendy Raymond

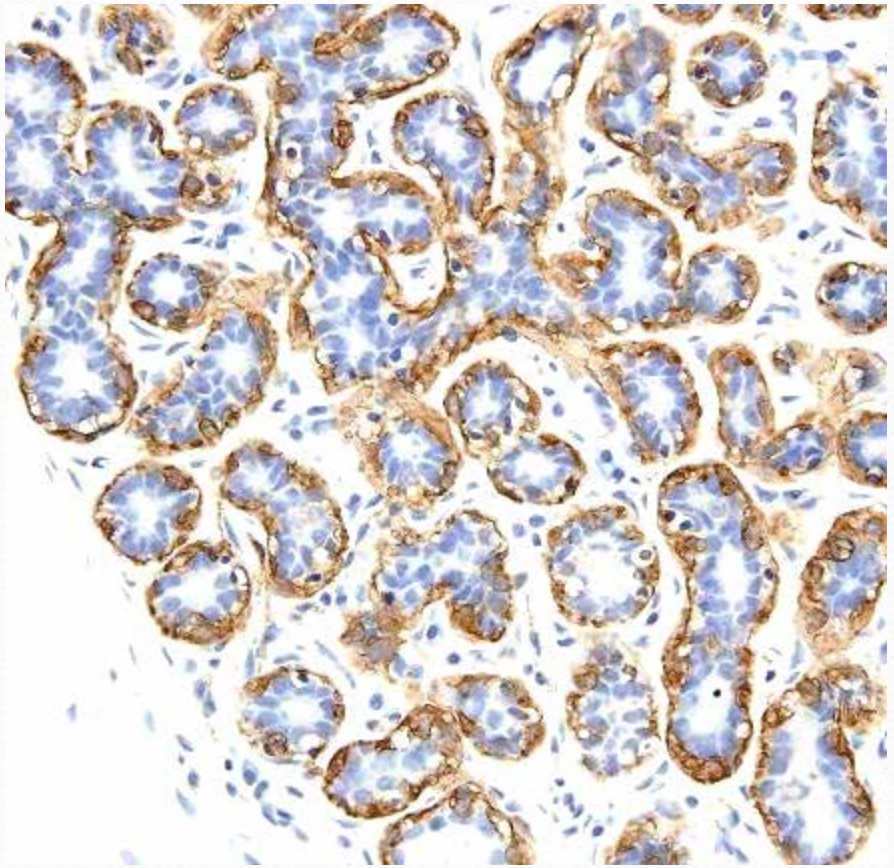
Consultant pathologist Flinders Medical Centre and Clinpath Pathology, Adelaide

The normal breast

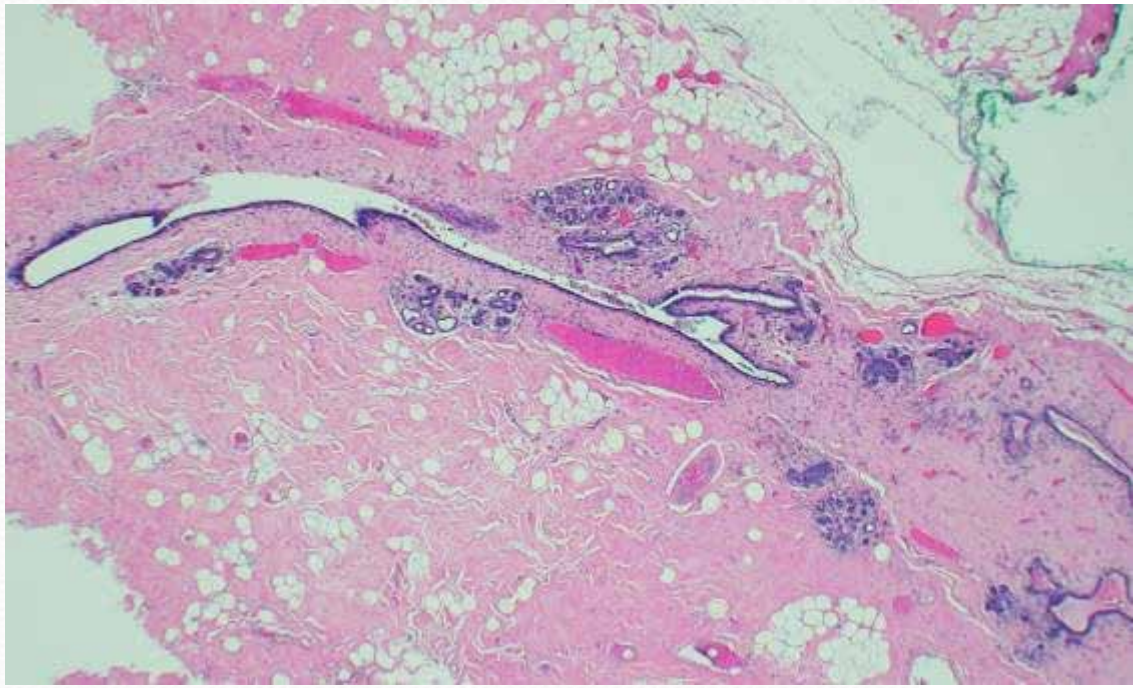
= A modified sweat gland

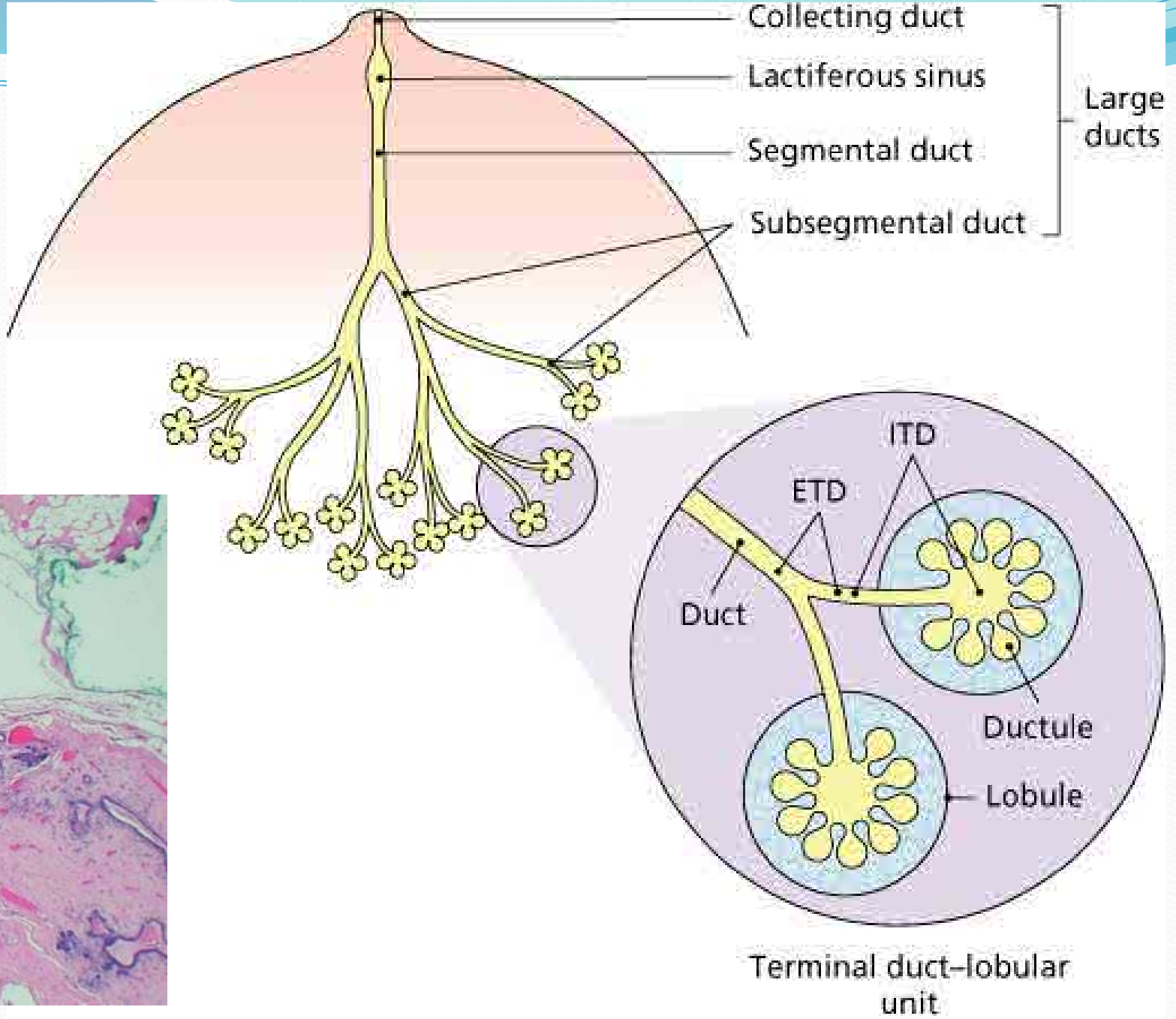


Myoepithelial layer



The normal breast





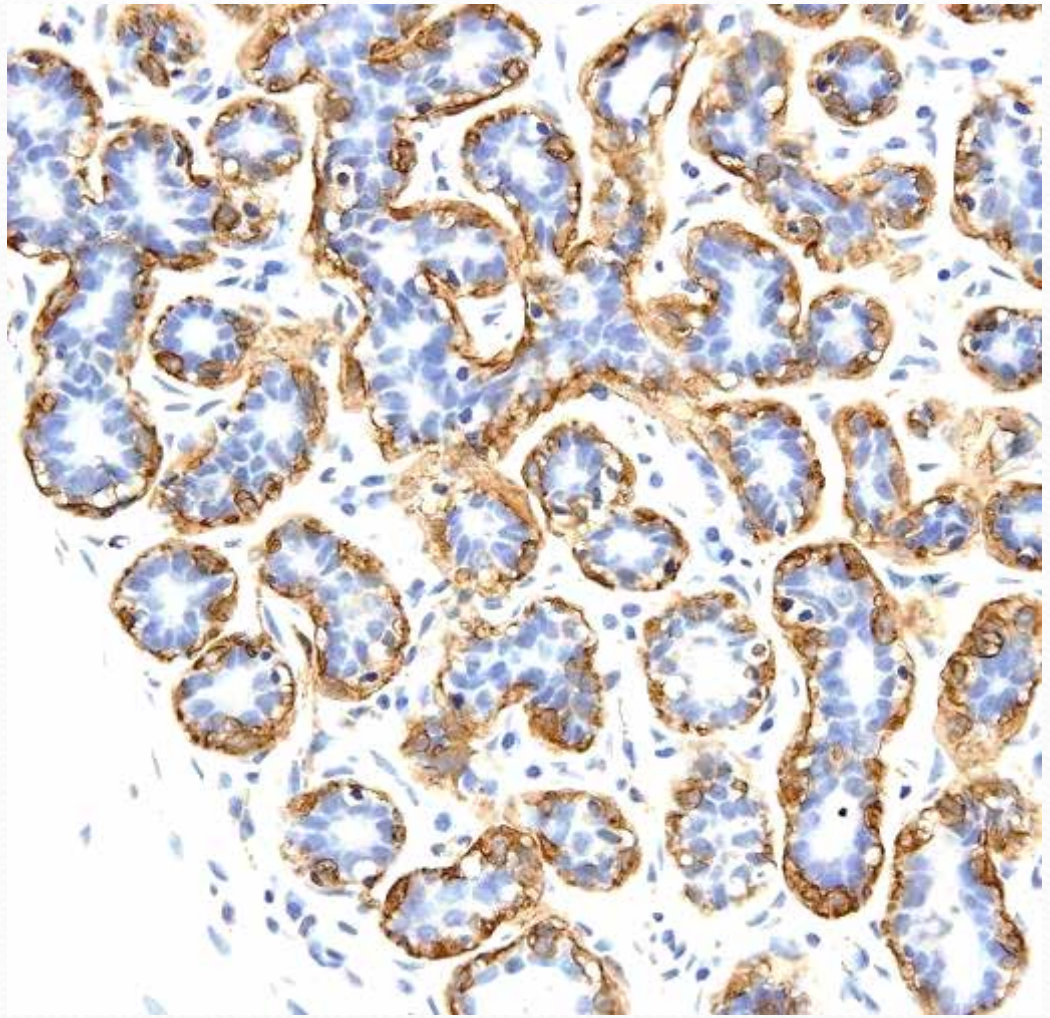
Terminal duct–lobular unit

Atypia in Breast pathology

Poorly defined morphological continuum for each of:

- Epithelial *
- Myoepithelial
- Stromal
- Endothelial

Difficulty in precisely defining à problems of interobserver concordance



“Atypia” = a (without) typia (type)

Different definitions for EPITHELIAL atypia:

- Ductal (usual type) hyperplasia v. Atypical DH (ADH)
- Low v. intermediate v. high grade DCIS
- Nuclear grade to assess invasive carcinoma

NB also

“*Reactive atypia*” refers to secondary insults (radiation, inflammation, trauma), prefer “nuclear changes”

Artefactual distortion – tissue preparation and quality (ischaemia etc)

Spectrum of Epithelial proliferation – a molecular continuum

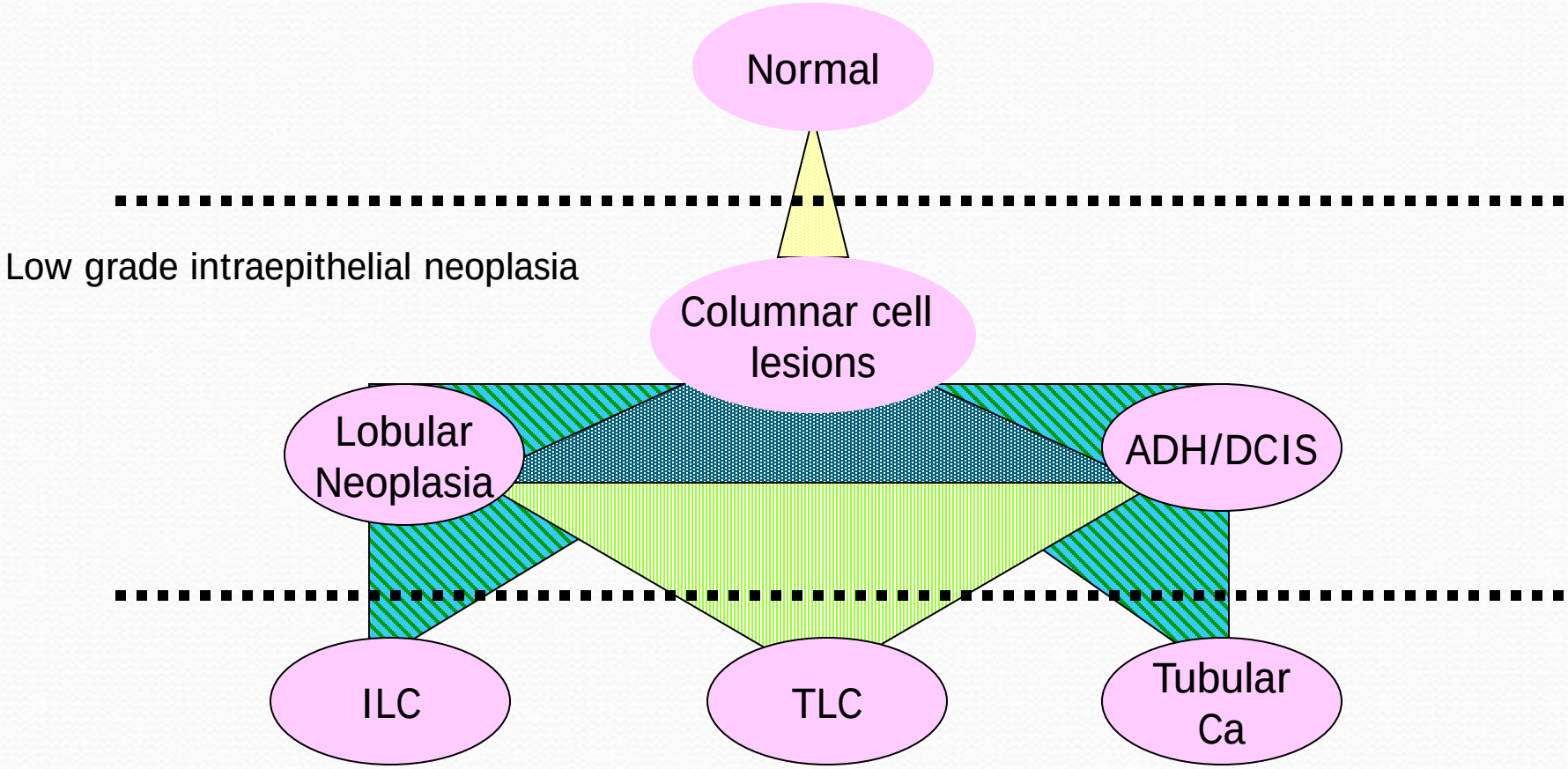
- Columnar cell change is clonal à Atypical Ductal hyperplasia (ADH)/ Flat epithelial atypia (FEA) à *Low grade Ductal carcinoma in Situ* (DCIS)

Most probably overlap with

- Lobular Neoplasia = atypical lobular hyperplasia (ALH) / lobular carcinoma in situ (LCIS) spectrum

High grade Ductal carcinoma in Situ = a distinct molecular entity

Low Grade Breast Neoplasia Family



Adapted from Ellis, Mod Pathol 2010, courtesy S Schnitt

- NO evidence breast epithelial atypia is reversible
- NO evidence of progression from low to high grade atypia (as different genetic alterations and pathways)…

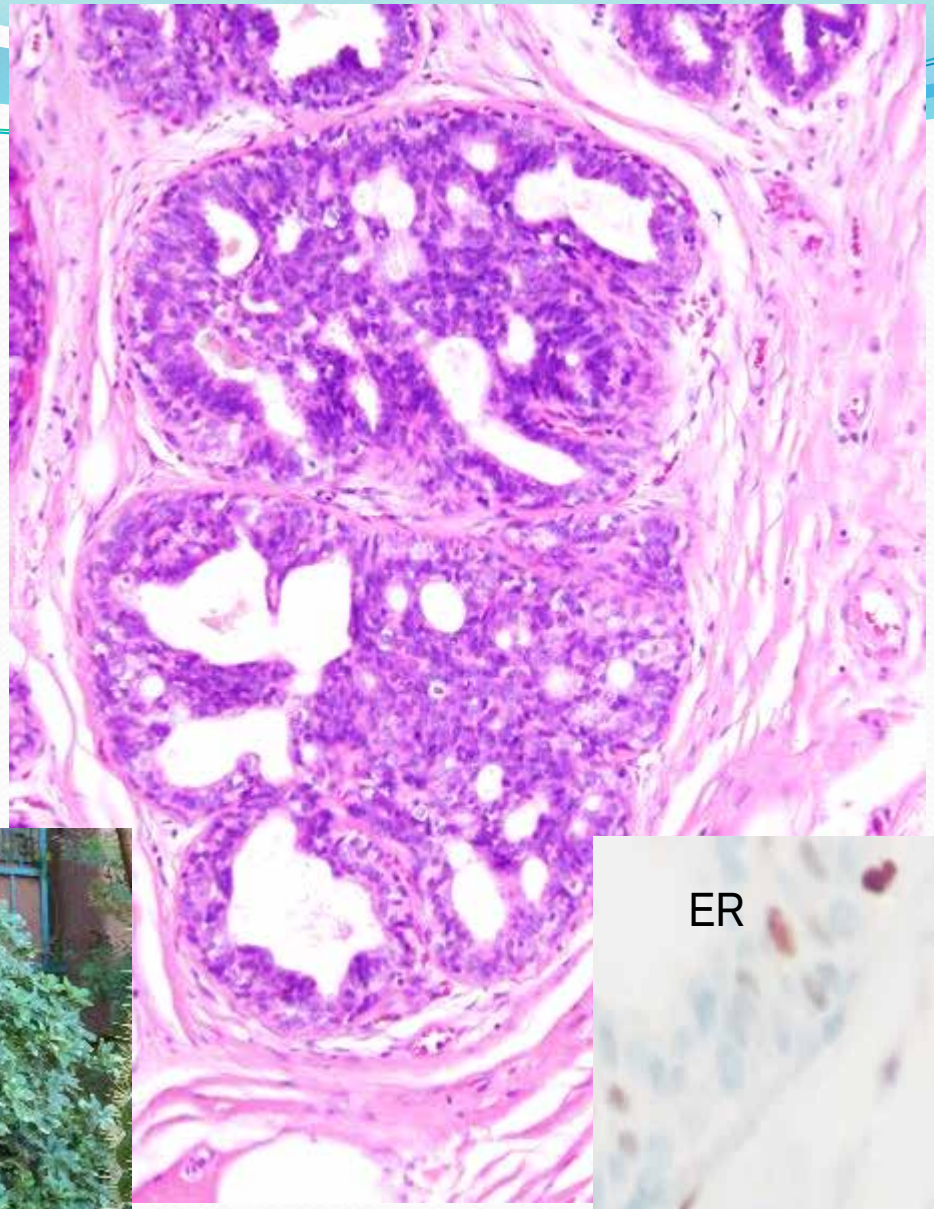
But frequently see both low-grade and high-grade DCIS in the same breast

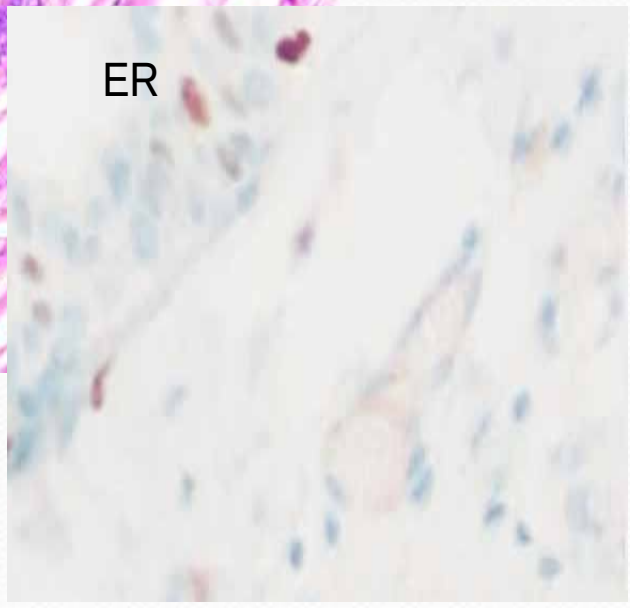
Usual type/Ductal hyperplasia

- Proliferation of epithelial cells:
  mild / moderate / florid
- Admixed myoepithelial cells

à *Swirls of overlapping cells*

- 2-3 x increased risk of breast cancer compared with women who have never had a breast biopsy *



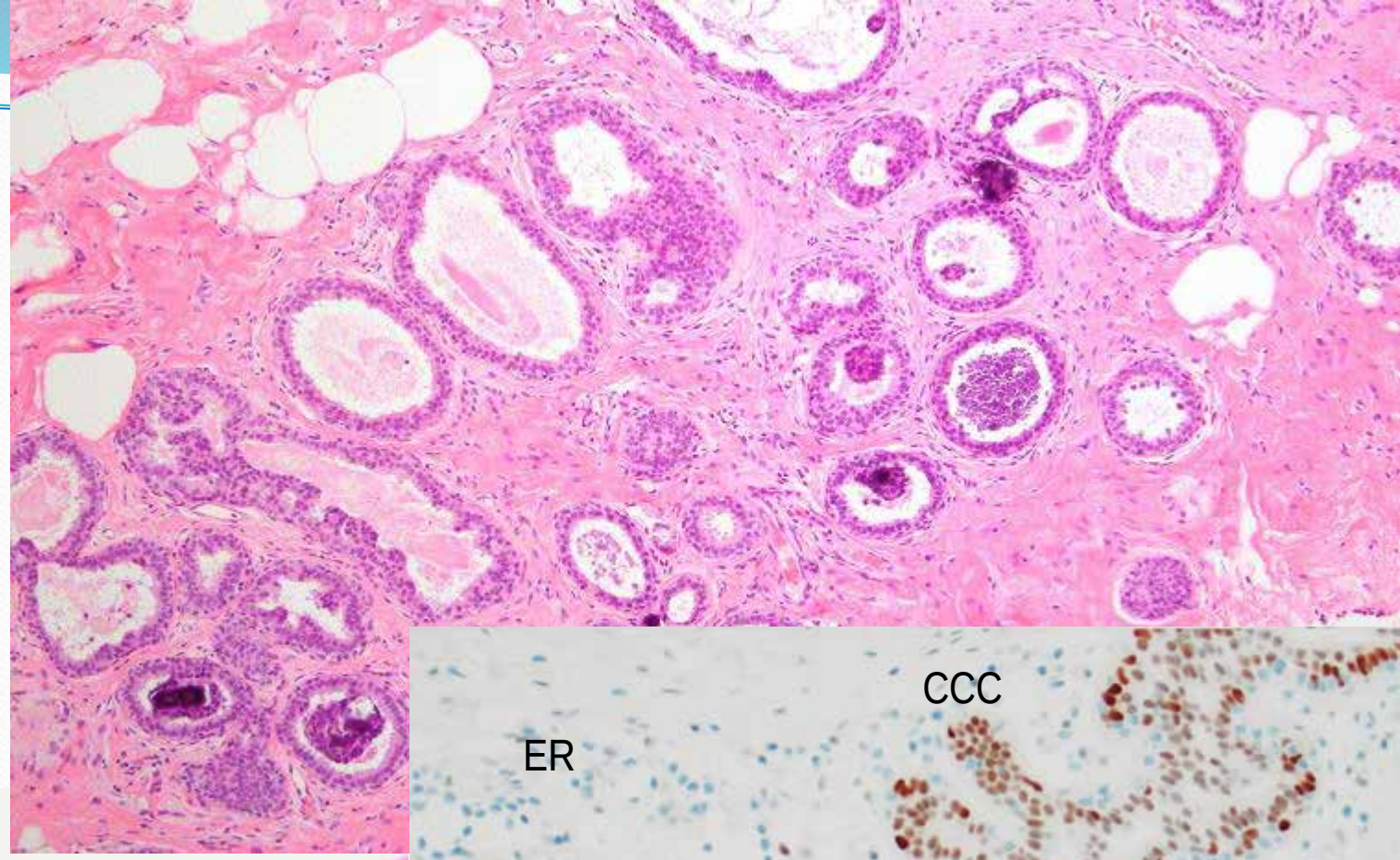


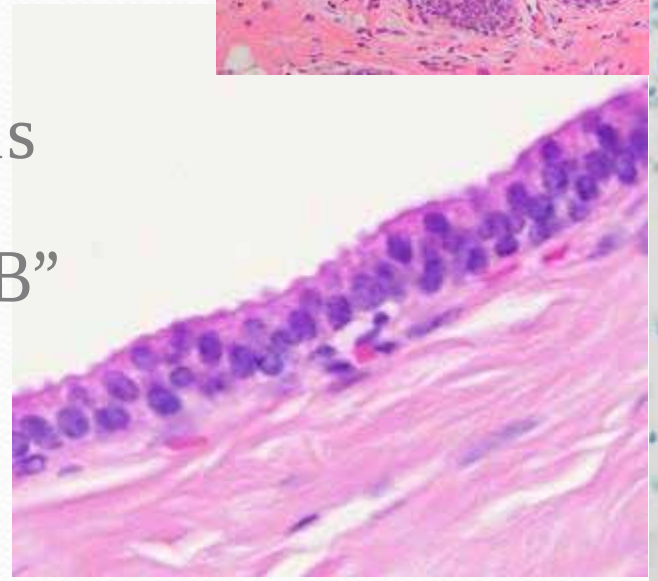
(*Page and Anderson,
Nurses health study,1985.)

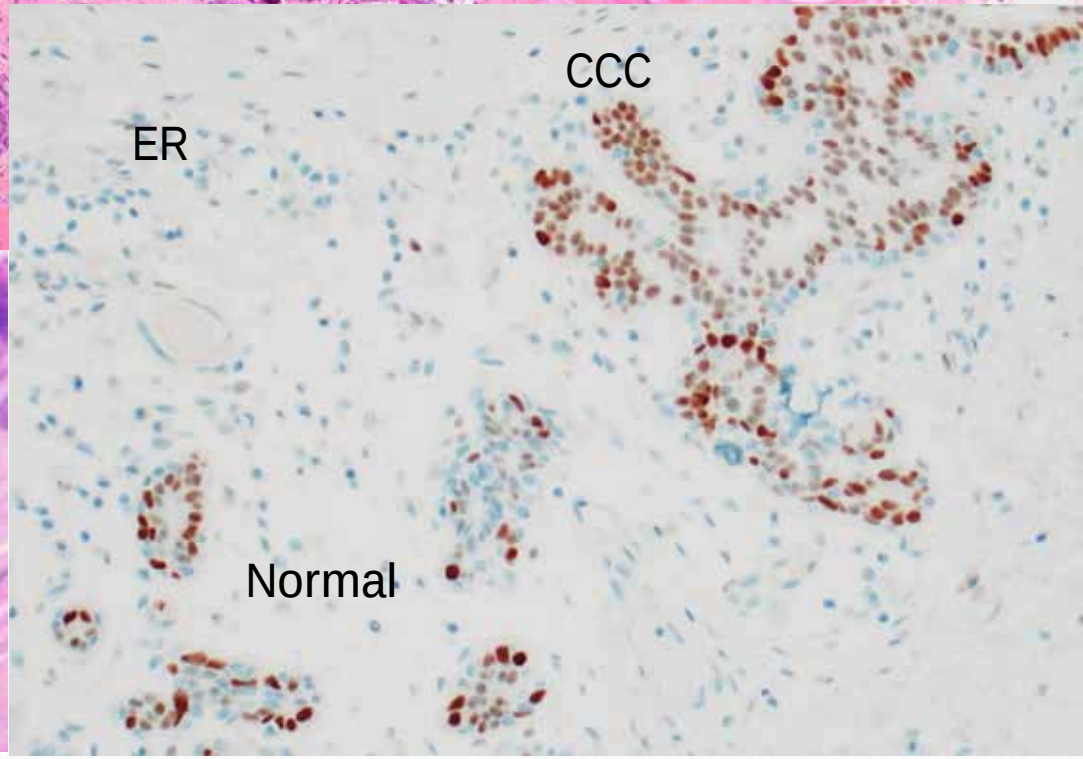
Columnar cell change

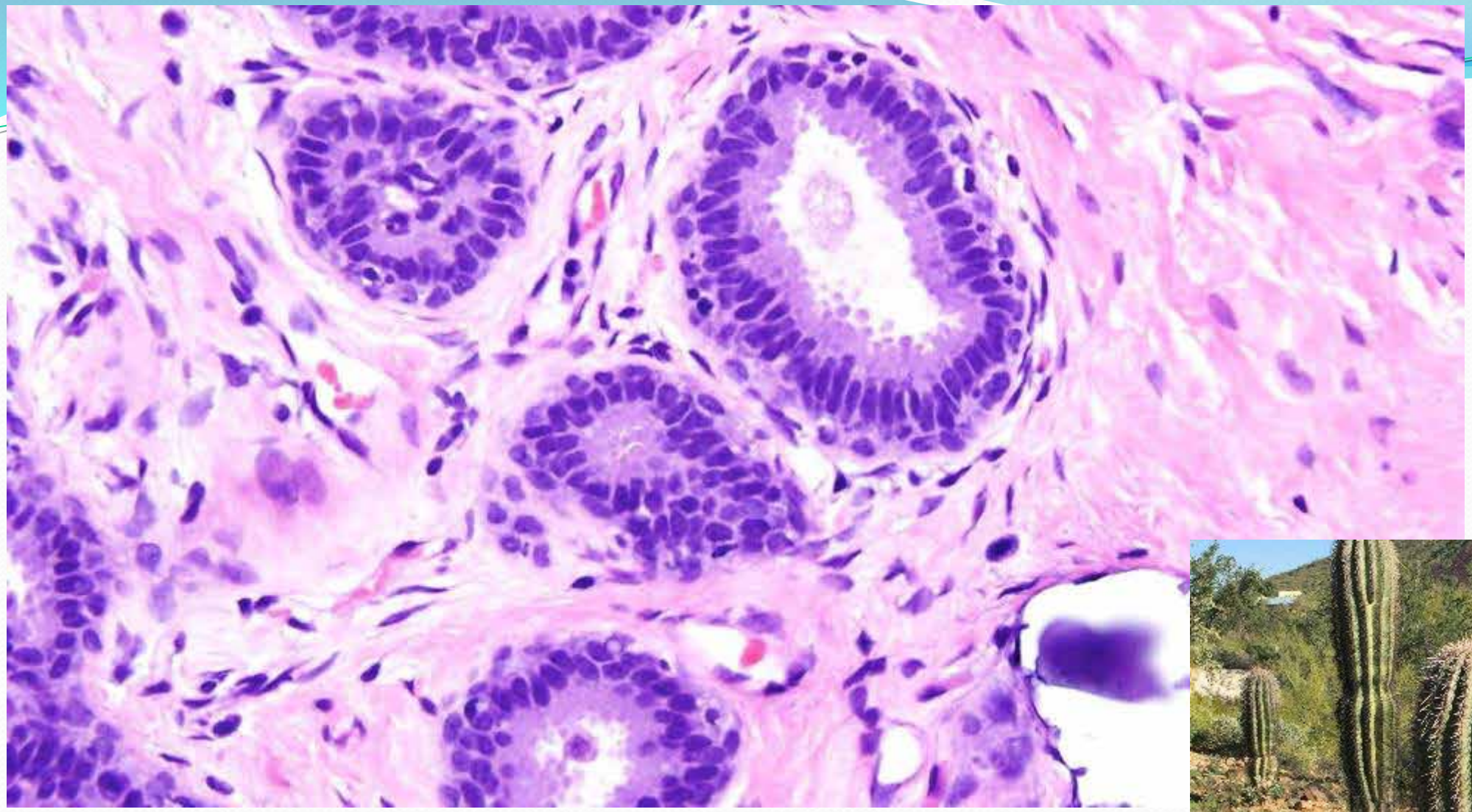
= a type of clonal metaplastic change

- Monolayer of cells with apical snouts
- +/- secretions
- No cytological atypia or architectural complexity
- Frequent calcifications – screening MMG detection(typically “3B” calcs)

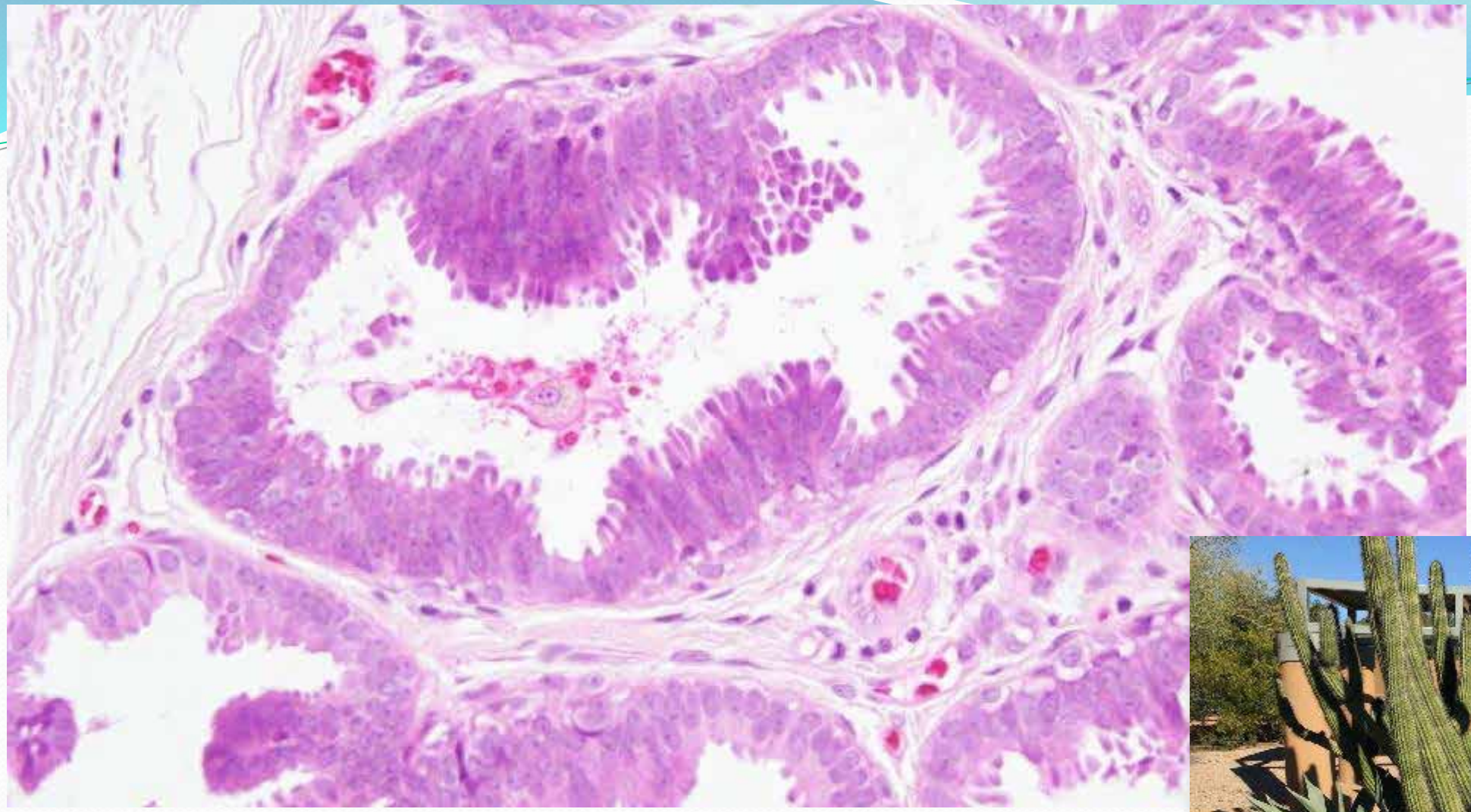




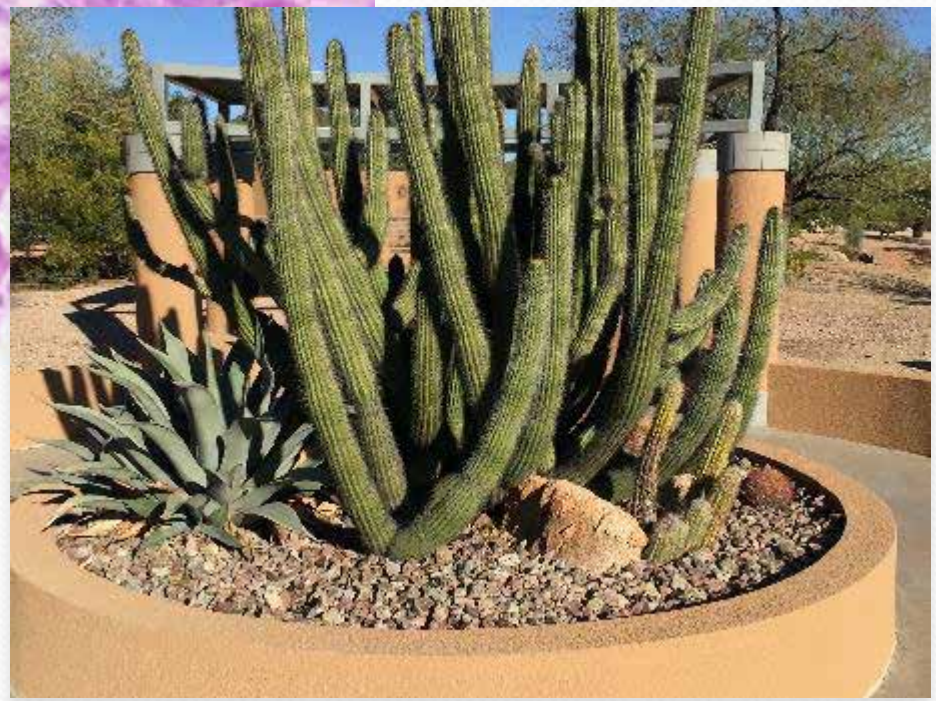




Columnar Cell Change



Columnar cell hyperplasia *(“bunch of bananas”)*



Atypical ductal hyperplasia (ADH)

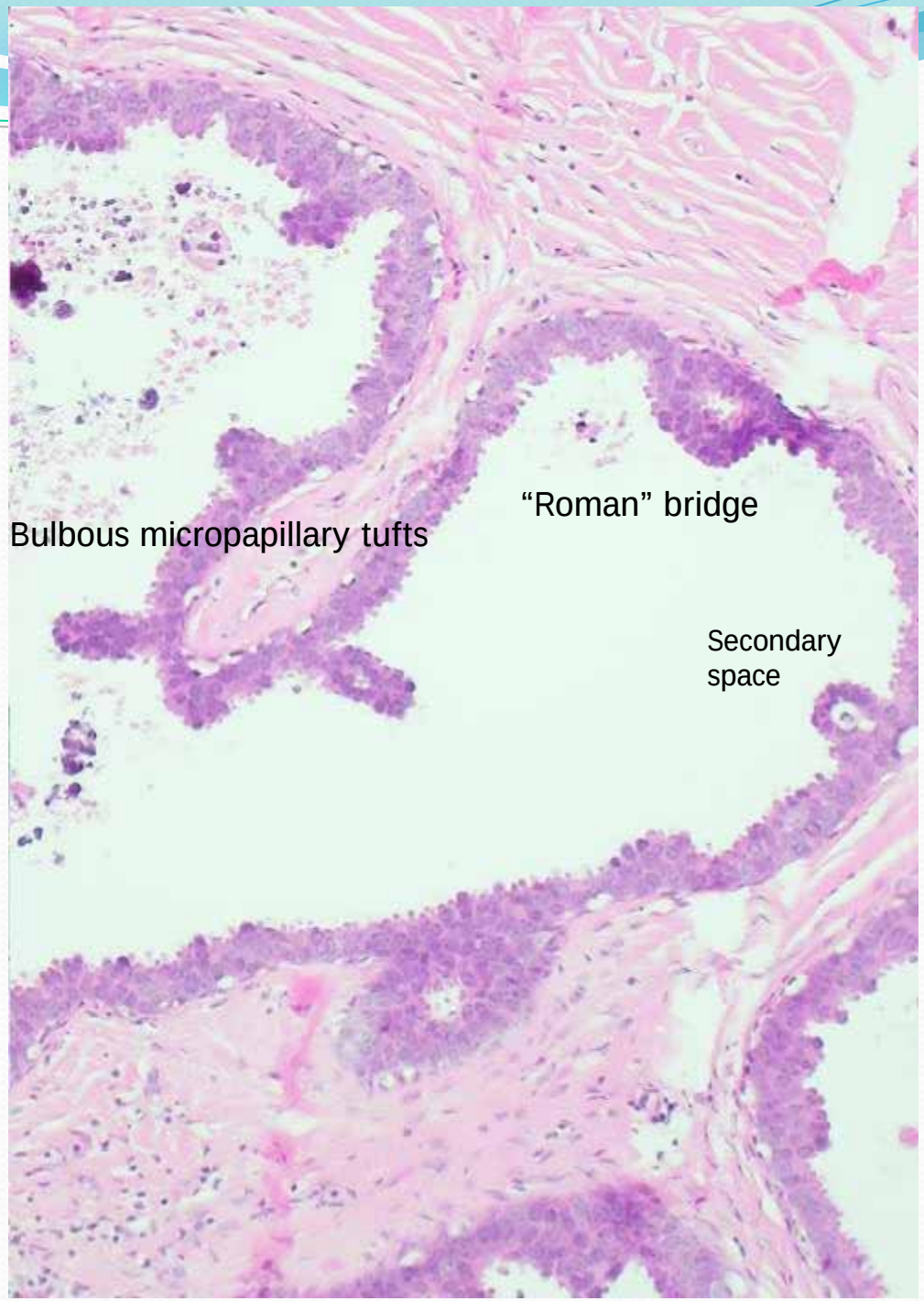
Defn = **epithelial proliferative lesion with cytological and architectural features similar to LGDCIS but less developed in architecture, degree of TDLU involvement and contiguous extent**

- Often associated with calcifications,
- May be incidental or in association with other lesions incl FA and papilloma

WHO, IARC, 2019

Atypical Ductal hyperplasia

- Monotonous cytology
- Rigid /traversing arcades "Roman" bridges
- Bulbous micropapillary tufts
- Sharply sculpted secondary spaces
- Fill only part of space



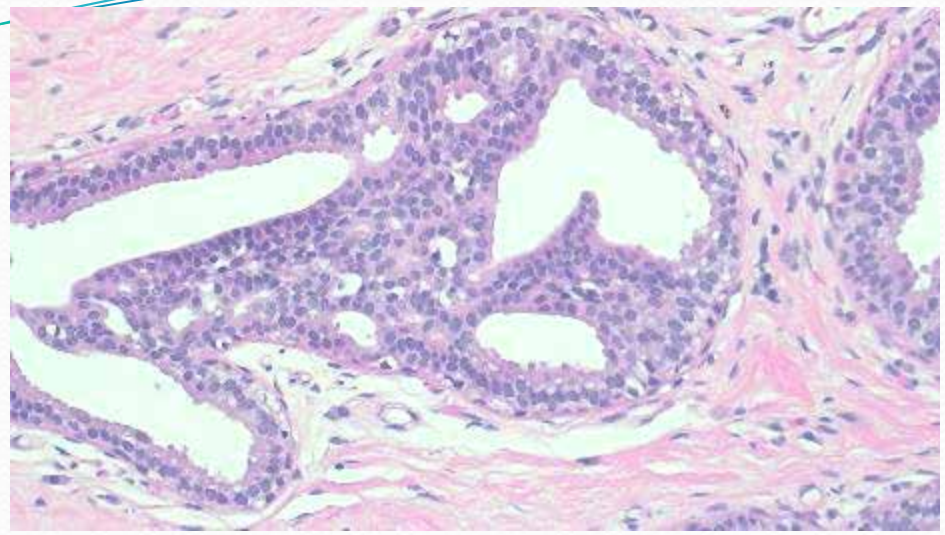
Atypical ductal hyperplasia (ADH)

- As specifically defined => increased risk of subsequent invasive carcinoma in EITHER breast, but higher in ipsilateral breast (4-5 x increased risk of Br Ca)

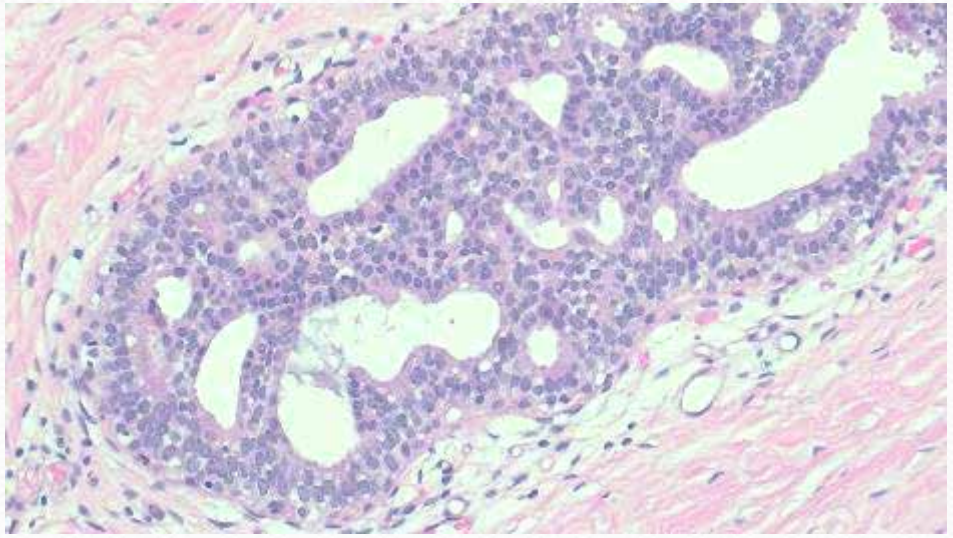
Problem of pathologist reproducibility

- As definition – ranges from focal areas cellular uniformity and even cell placement (ADH) to just short of cribriform/ micropapillary pattern low-grade DCIS
- 2 duct spaces (Page & Andersen) v. 2mm (Tavassoli and Norris) =arbitrary thresholds è requires caution in cores
- Use of AIDEP (atypical intraductal epithelial proliferation)

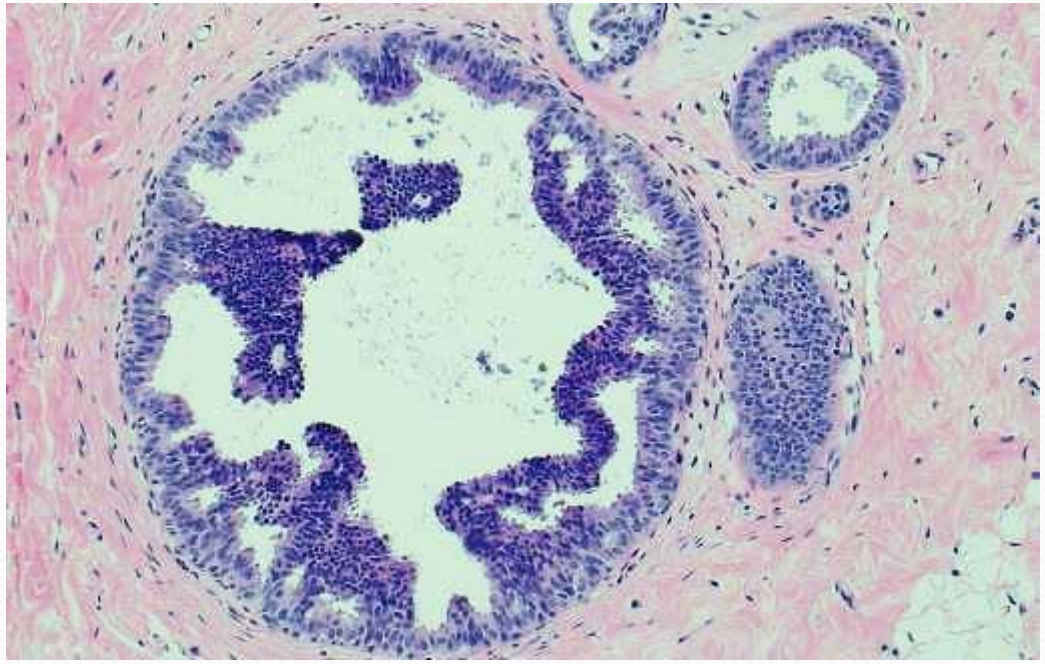
Almost ADH



Just ADH

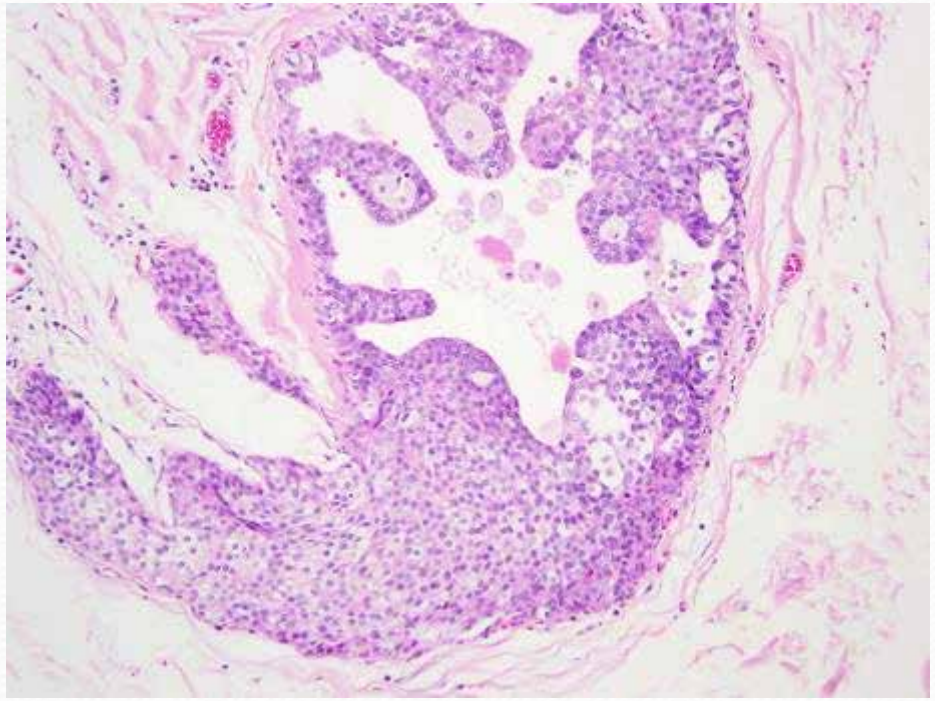


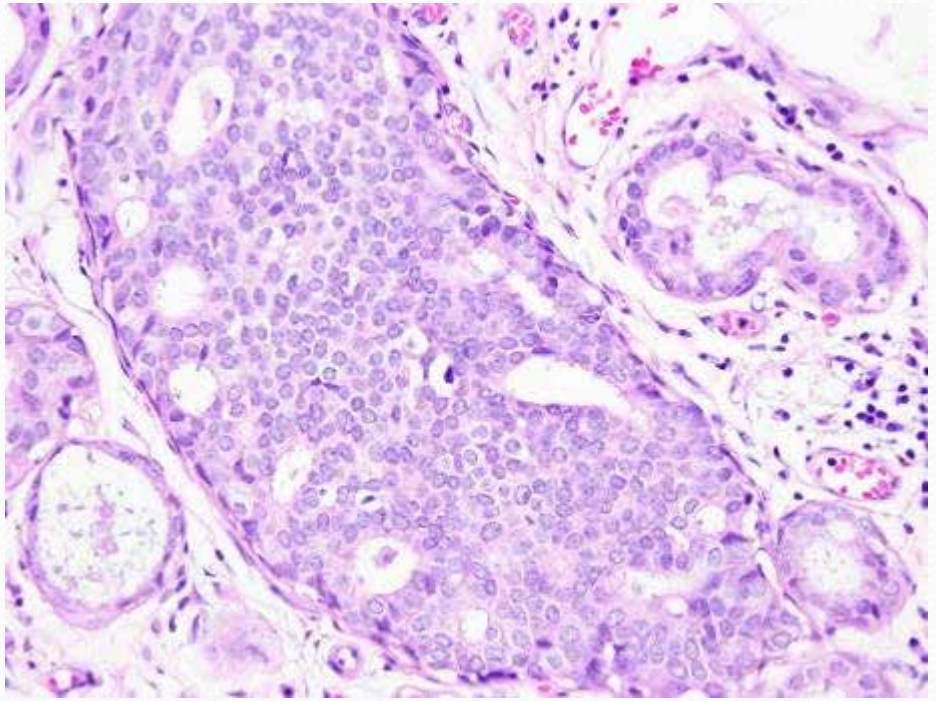
ADH with CCC



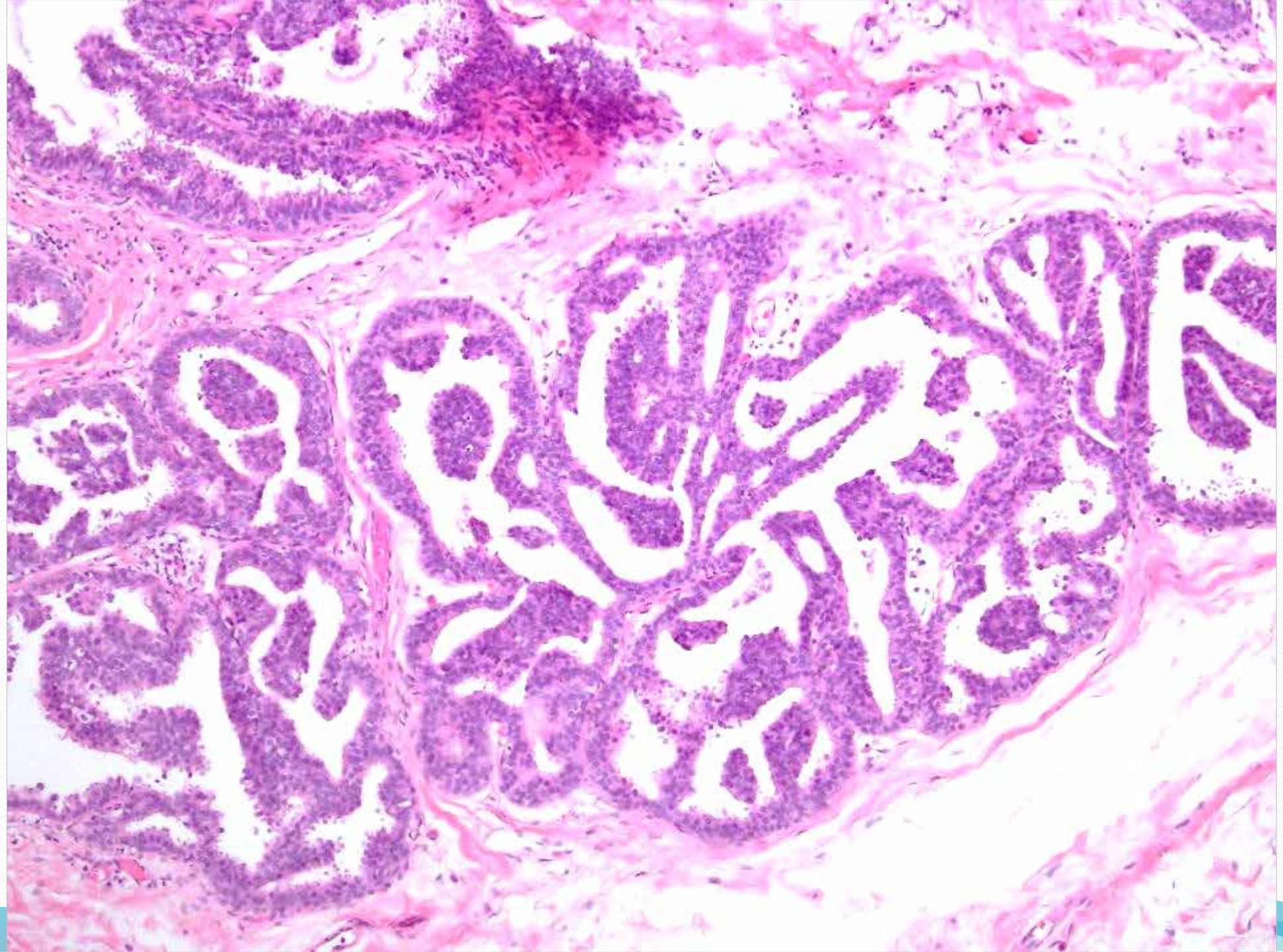
Low grade DCIS

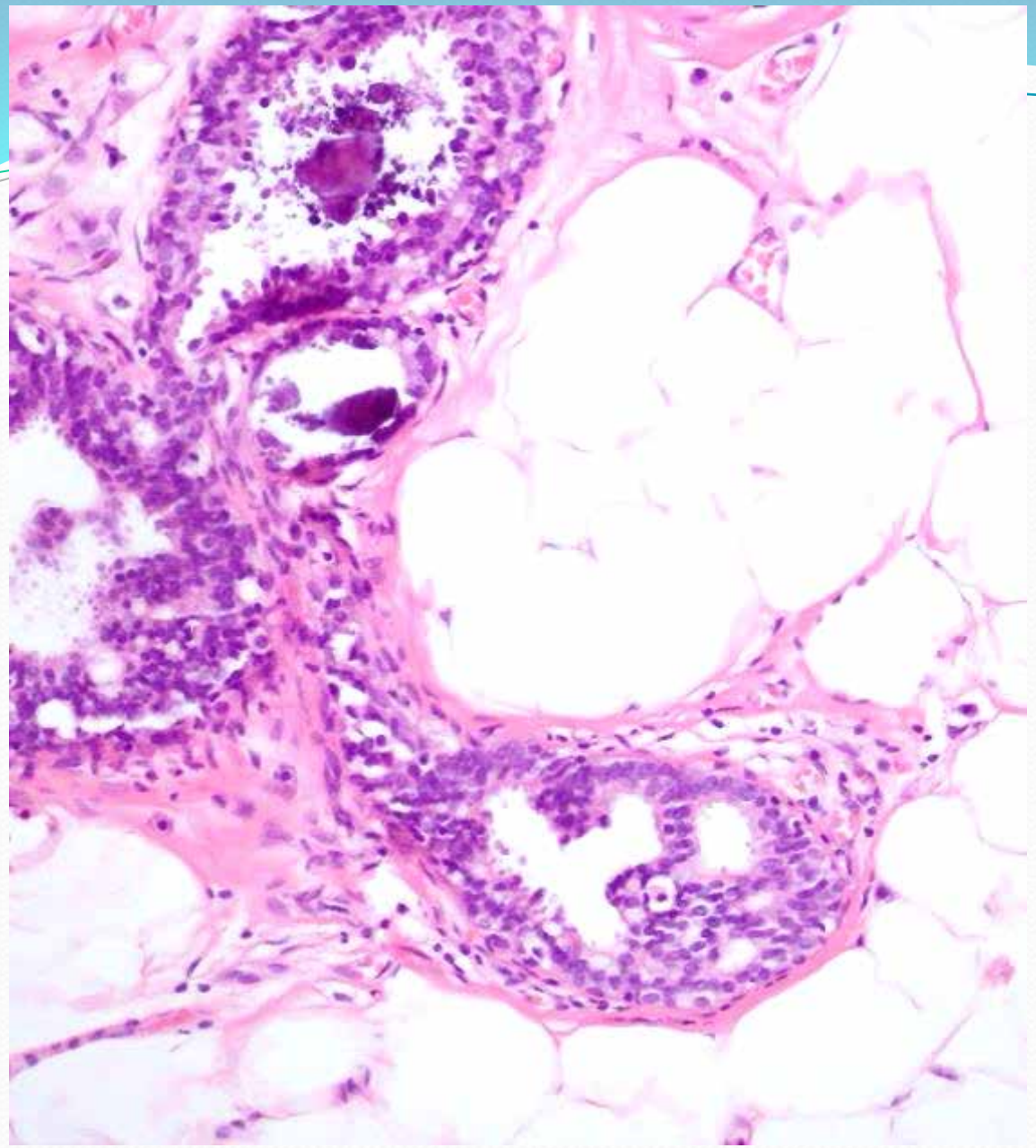
- Monotonous– low grade nuclear atypia
- Cribriform pattern
- Micropapillary pattern
- Solid areas => DCIS



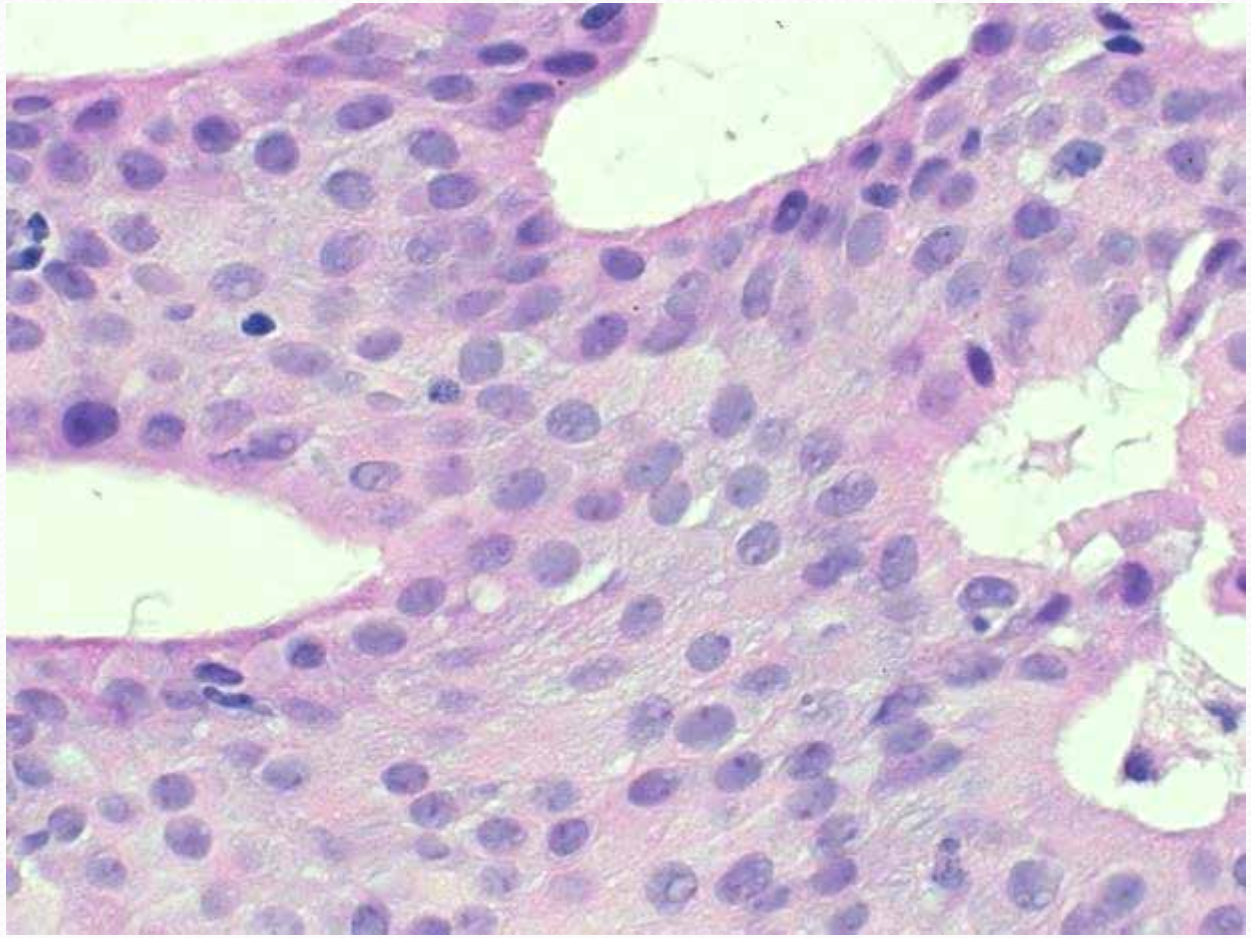


ADH v
LG DCIS?

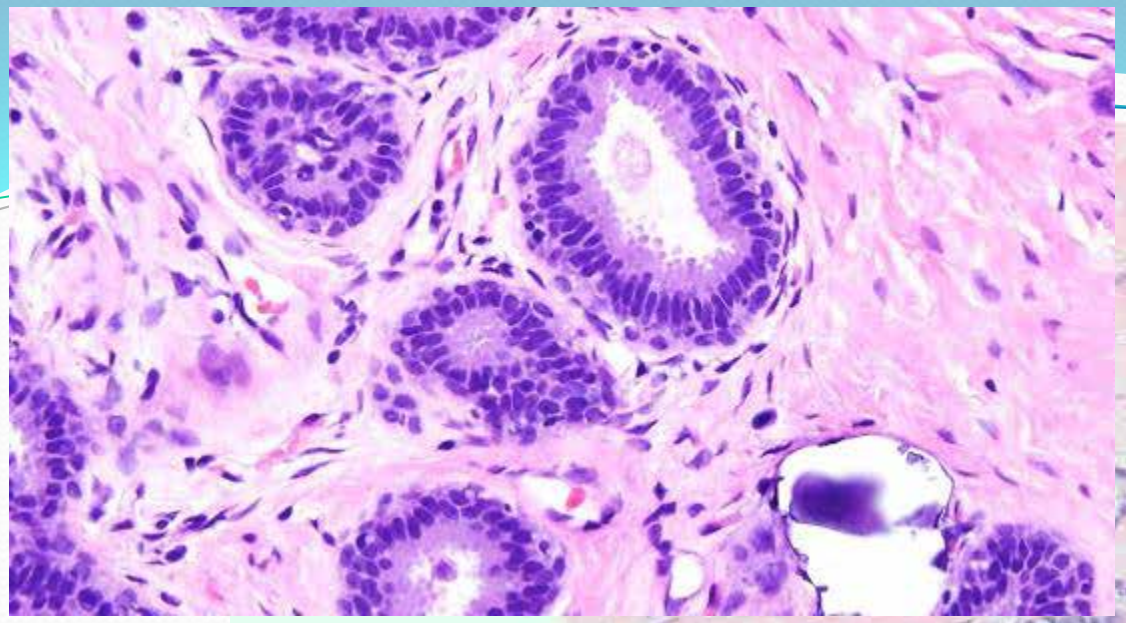


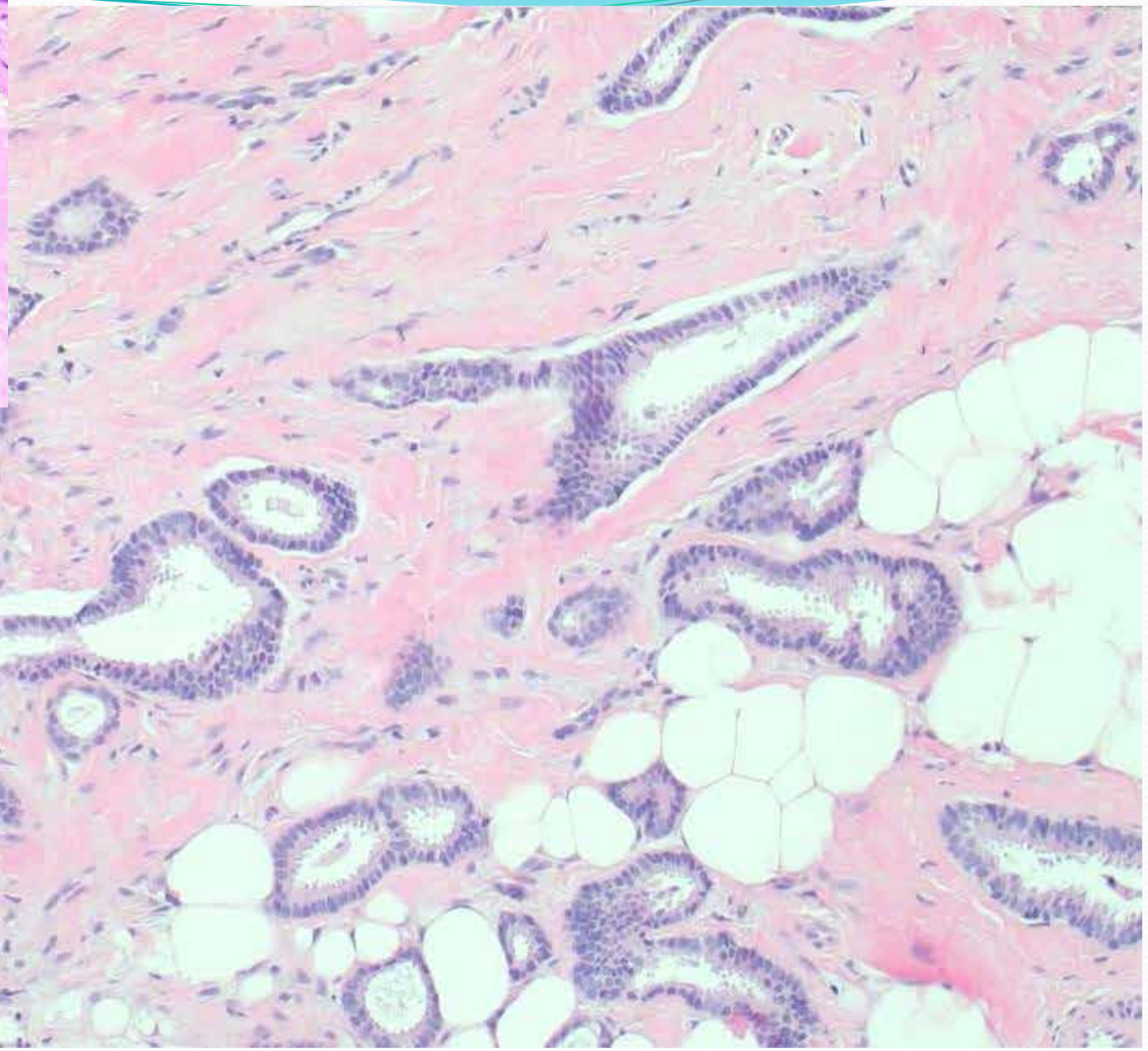


UDH and CCC and ?? ADH



Cf Intermediate grade DCIS



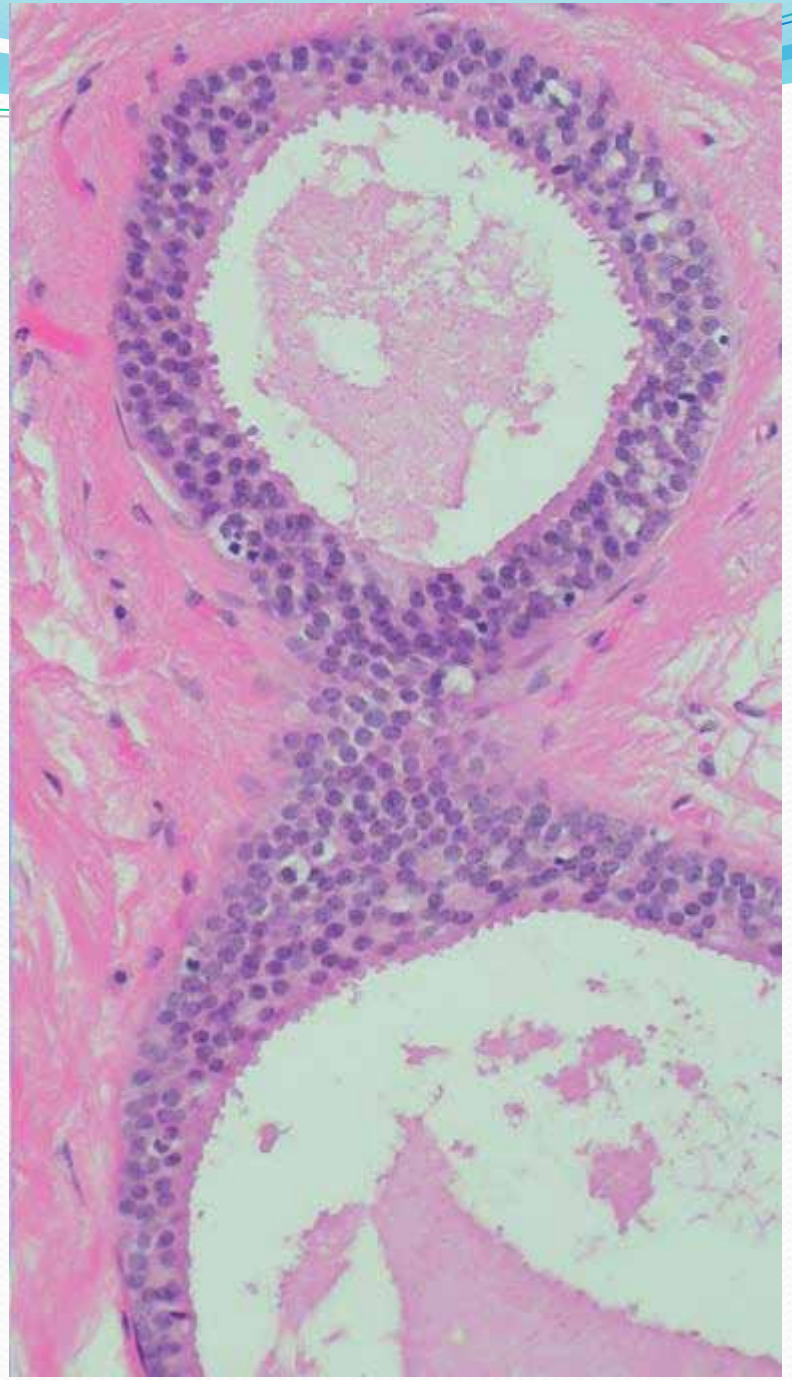


Tubular ca

Flat epithelial atypia (FEA)

- A clonal monomorphic neoplastic proliferation of low grade and a continuum with ADH and LGDCIS
- *May be termed columnar cell change/hyperplasia with atypia*
- Risk of progression < ADH or ALH

(WHO, IARC, 2019)



Risk of developing invasive carcinoma in ATYPICAL DUCTAL PROLIFERATIONS

- Mild usual/ductal hyperplasia – no clinical sig
- Mod – florid hyperplasia – minimal increased risk (1.5 - 2x) for 10 – 15 yrs post biopsy, bilateral
- **Atypical ductal hyperplasia – 4-5 x** (no Fam Hx), absolute risk approx 10% - (BILATERAL)
- **Low grade DCIS – 10x**, absolute risk approx 25% - UNILATERAL (true precursor)
- **ADH and Fam Hx = LG DCIS**

(Page and Anderson, Nurses health study,1985.)

Carcinoma Risk with Dx of ADH

- Hartmann (2015) – ADH and ALH – 30% à invasive ca in 25 yrs = risk markers
- 1% per year for at least 25 years
- Monoclonality recognized in ADH, FEA, ALH and LCIS

but = non-obligate precursors

cf

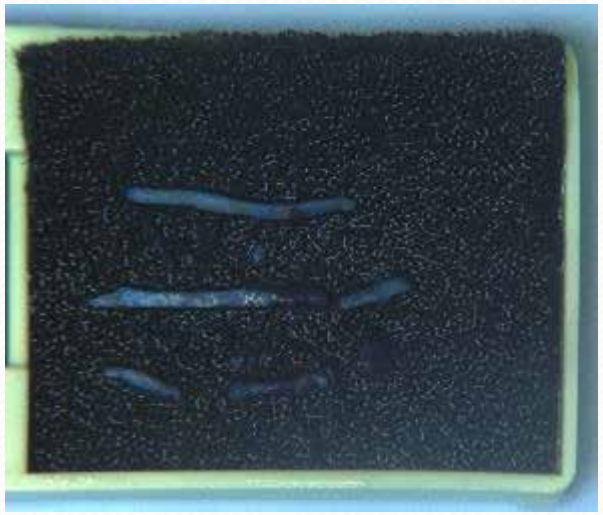
LG DCIS= low risk precursor

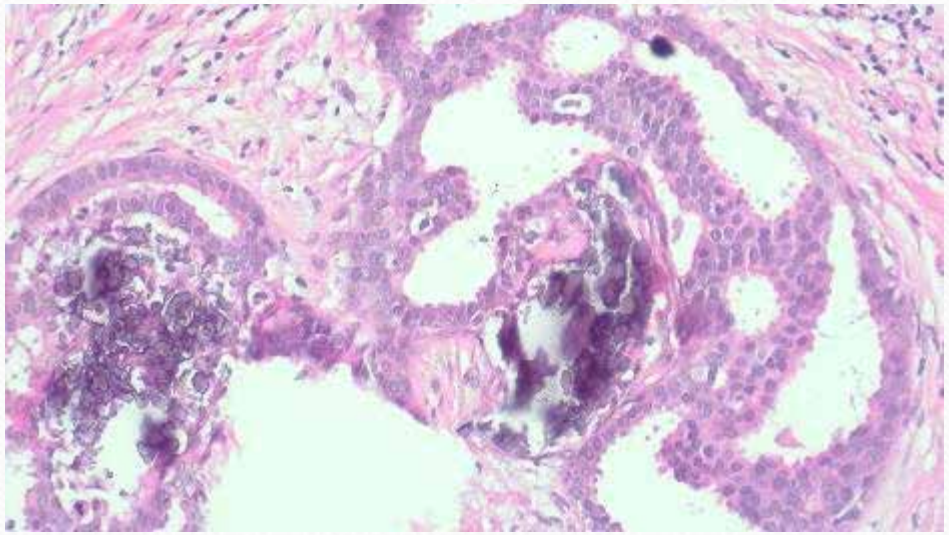
HG DCIS= high risk precursor

Upgrade rate for ADH on core biopsy à carcinoma (DCIS or invasive)

- **Overall - 18-20%**
- Stanford – 9% of cores; UCLA (Mod Pathol 2016) – 18%
- Upgrades mostly to Low or Intermediate Grade DCIS or tubular/G1 invasive ca

PROBLEM: Interobserver variation and spectrum of ADH diagnosis

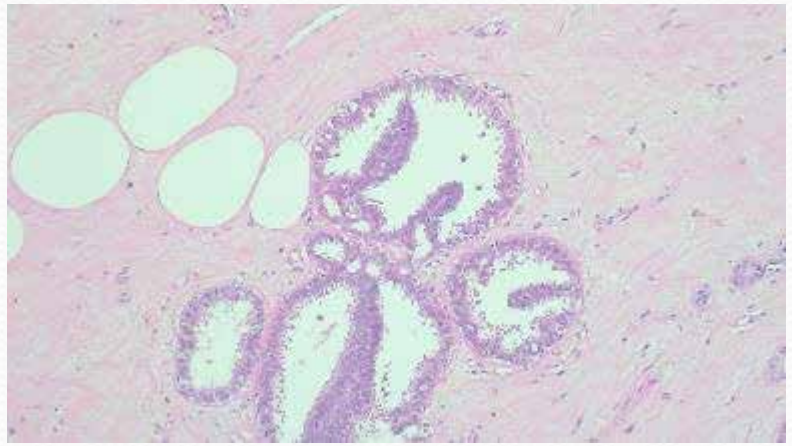




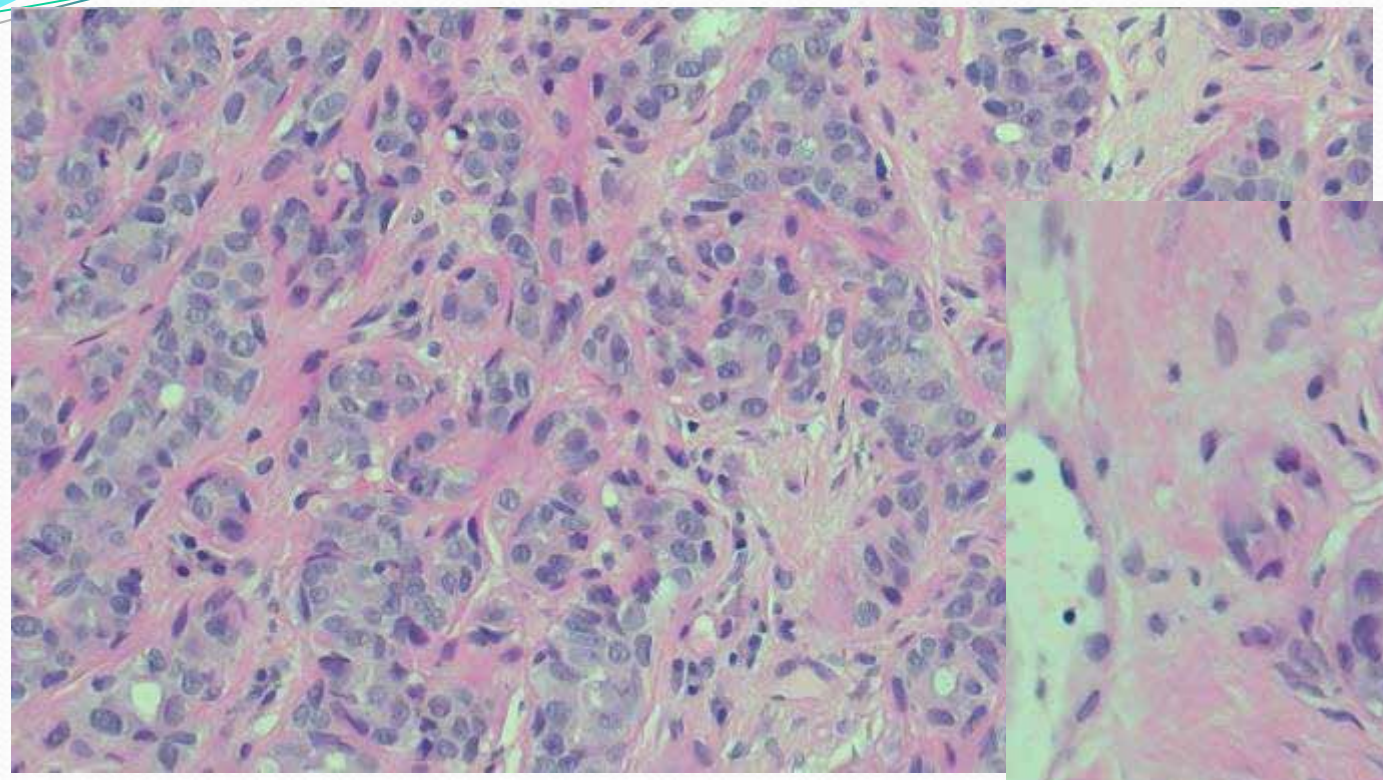
à Recommendation: excise area of calcifications if ADH present on core Bx

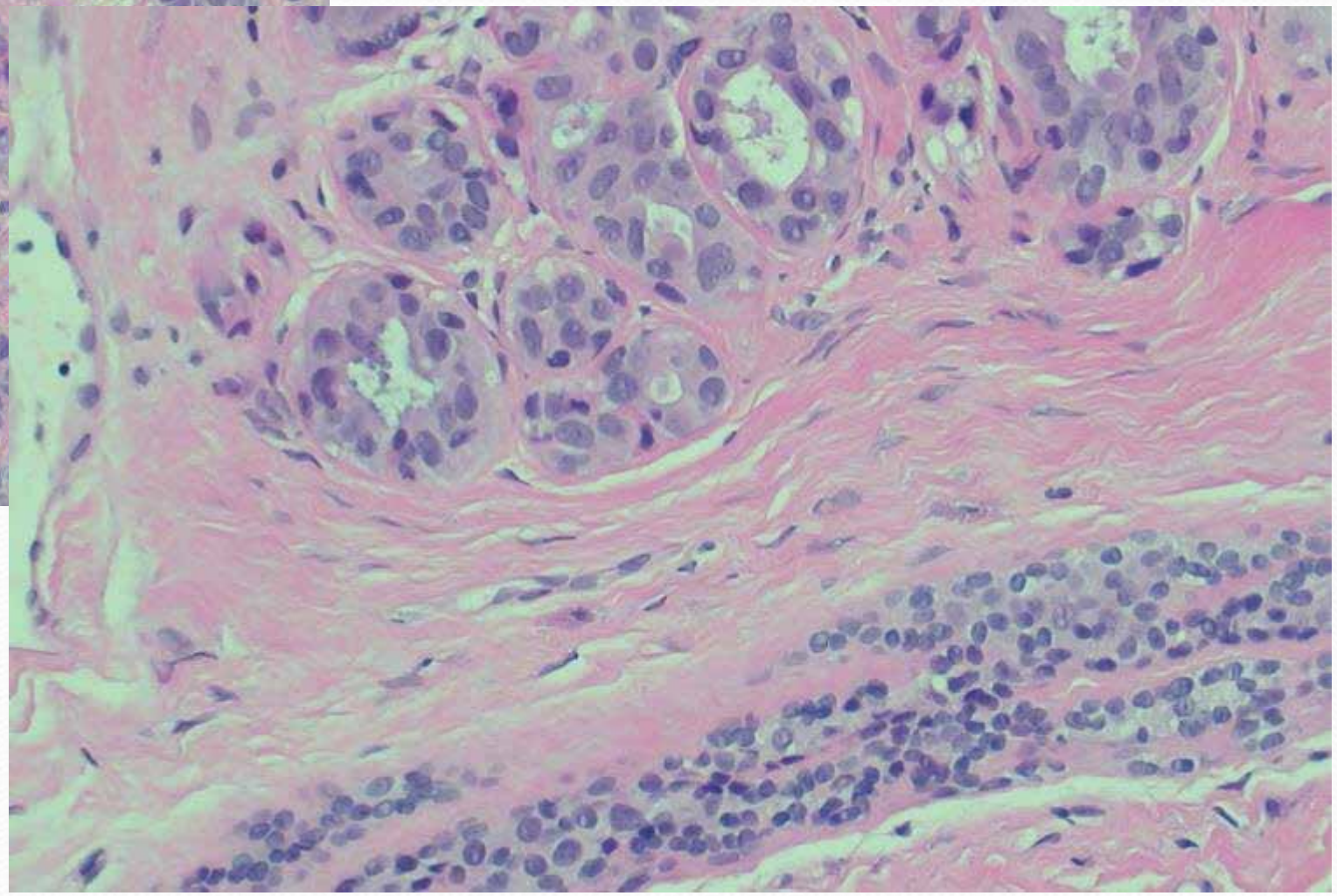
Upgrade rate for FEA (or CC lesion with atypia) on core biopsy – controversial

- Reported up to 30% - but frequently associated with other lesions eg ADH/LN
- Recent studies – 0-15% (UCLA – 11%)
- Cf increased breast cancer risk 1-2X
- Some suggest excise calcifications, others consider observation reasonable if no ADH/other lesion



Atypical intraductal epithelial proliferation (AIDEP) – *don't quite fulfill the criteria for a specific diagnosis of FEA/ADH/DCIS*

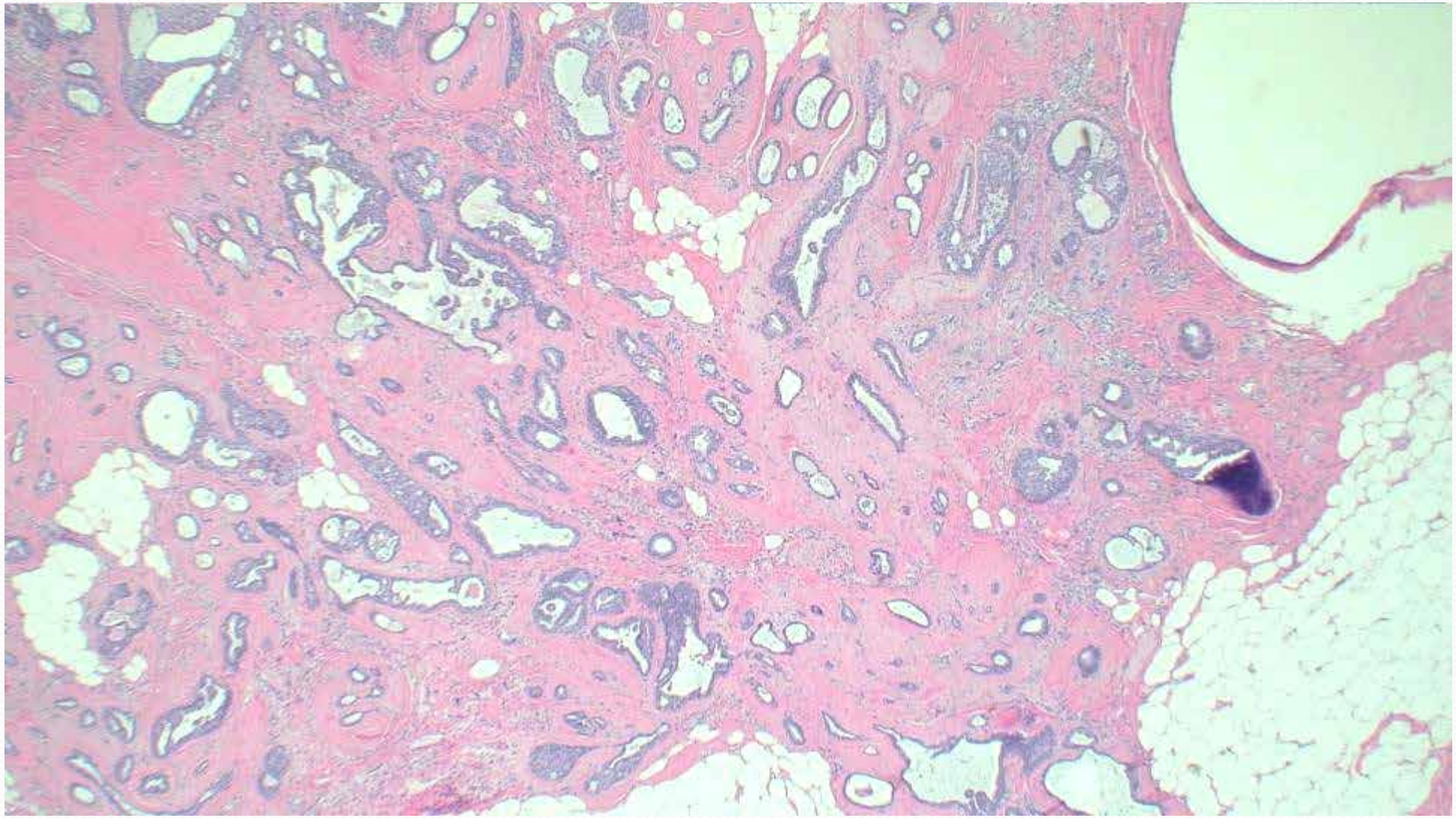




Atypical Intraductal epithelial proliferation (AIDEP) – Upgrade rate reported up to 28% - probably reflects a proportion actually show features of LGDCIS

Radial Scar/radial sclerosing lesions/complex sclerosing lesion –

suggested secondary to chronic ischaemia/localized inflammation (??)



Upgrade rate (to malignancy) of radial scar on core biopsy

-Reflects associated atypia

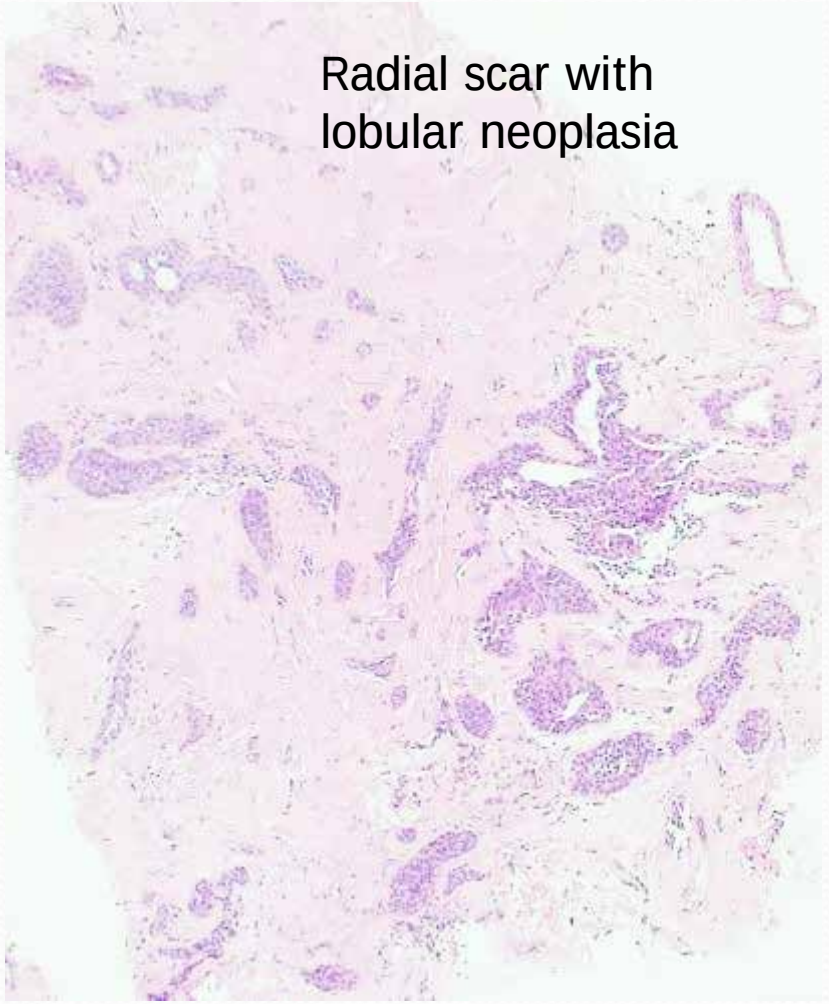
-Upgrade rate depends on epithelial component

- 0-6 % if no atypia**

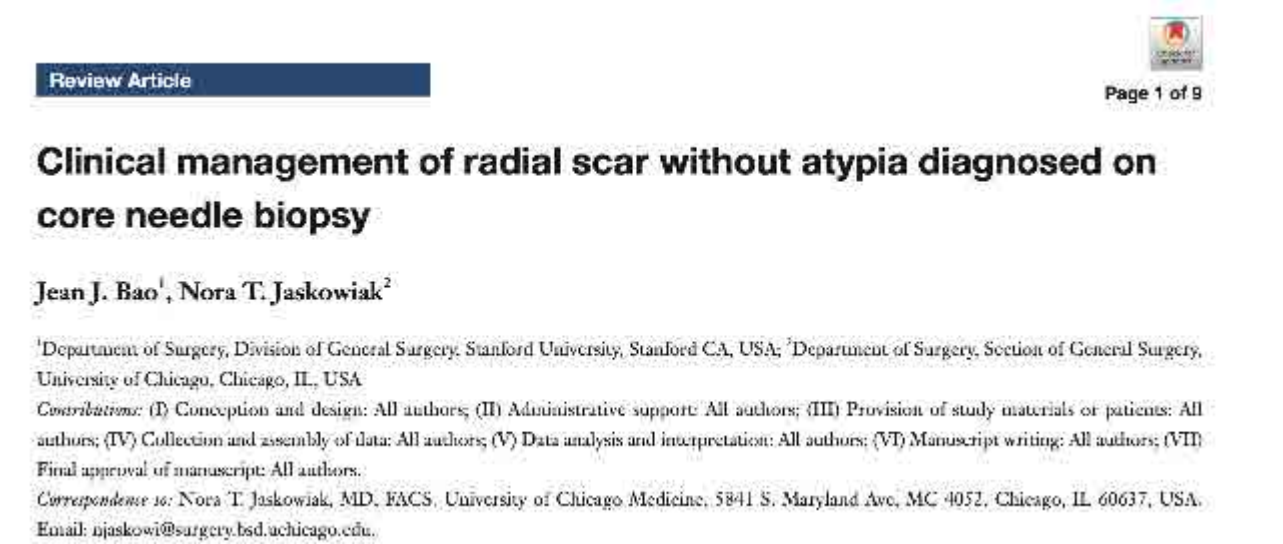
- up to 18 % (? to 29-32%) with atypia*

Risk of developing cancer with a radial scar in a benign Bx = 1-2X ie no greater than mild ductal hyperplasia

(**Yan et al. Radiology 2021; *Catanzariti et al. Insights Imaging, 2021; Farshid & Buckley. Breast Cancer Res Treatment 2019)*



Radial scar - Changing consensus to excise vs. VAE



Review Article

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Clinical management of radial scar without atypia diagnosed on core needle biopsy

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nora T. Jaskowiak, MD, FACS. University of Chicago Medicine, 5841 S. Maryland Ave, MC 4052, Chicago, IL 60637, USA. Email: njaskowi@surgery.bsd.uchicago.edu.

- Review, Annals of breast surgery, 2021
- Recent studies <5% if no atypia
- Lower upgrade rates likely related to larger gauge sampling
- Upgrade rates to a HRL (high risk lesion = ADH or LN): 12-26%
- Management with an individualised algorithmic approach based on size of lesion, age of patient, potential for risk reducing strategies or option for VAB/VAE with observation.

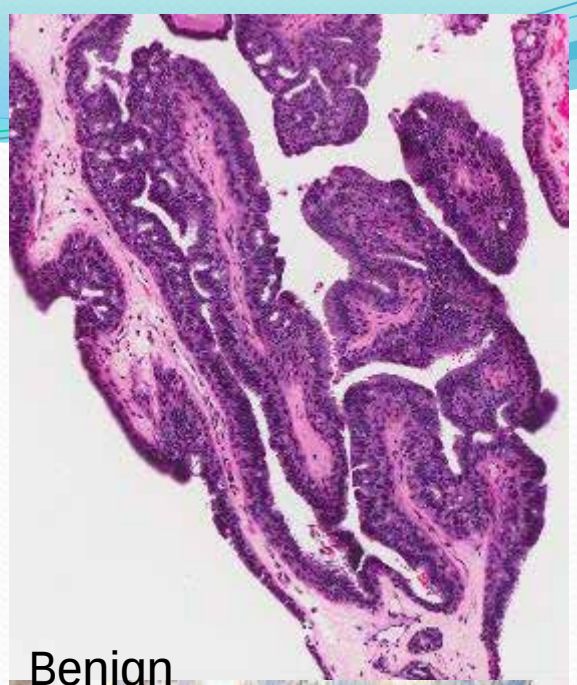
Victor Harbor SA

Papillary neoplasms – Benign

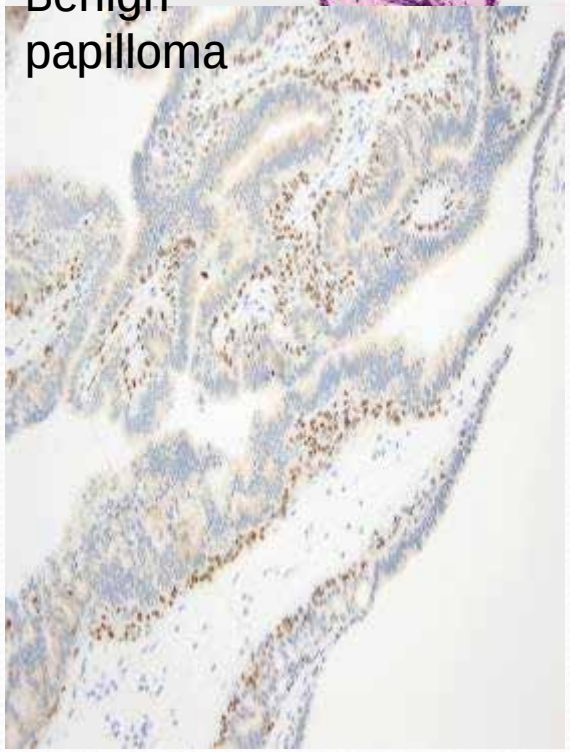
Intraductal papilloma => MEs along papillae (most monoclonal – PIK3CA/AKT1 pathway point mutations)

- **Papilloma without atypia**
- **Papilloma with atypical hyperplasia/ADH** in papilloma/Atypical papilloma = *low grade nuclei, < 3mm total area*
- **Papilloma with DCIS** = *monotonous population with low grade nuclei, cribriform bridges/rigid arcades >=3mm. Frequently extends into surrounding ducts*

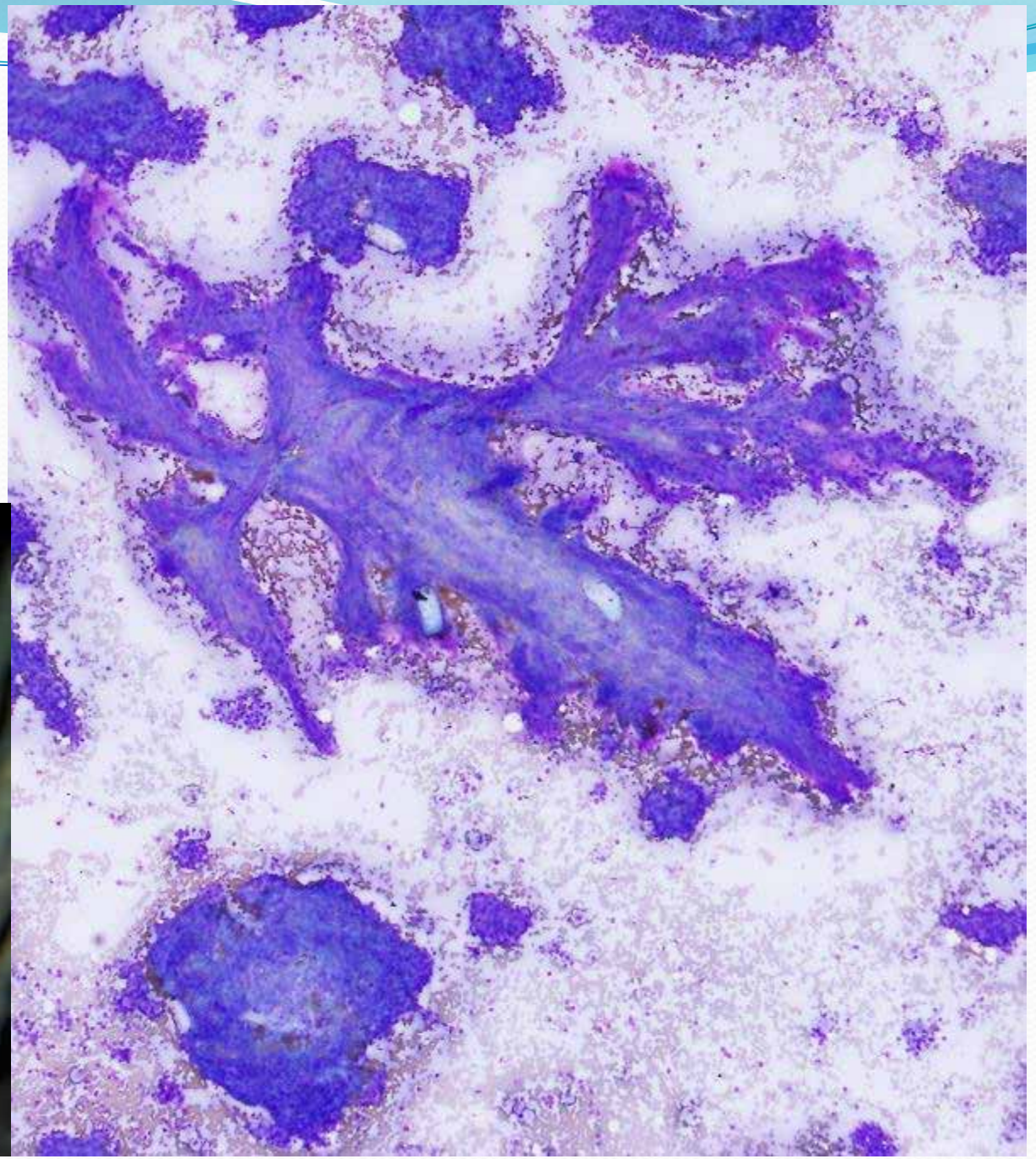
(NB :If intermediate or HG nuclei of any size à DCIS)



Benign papilloma

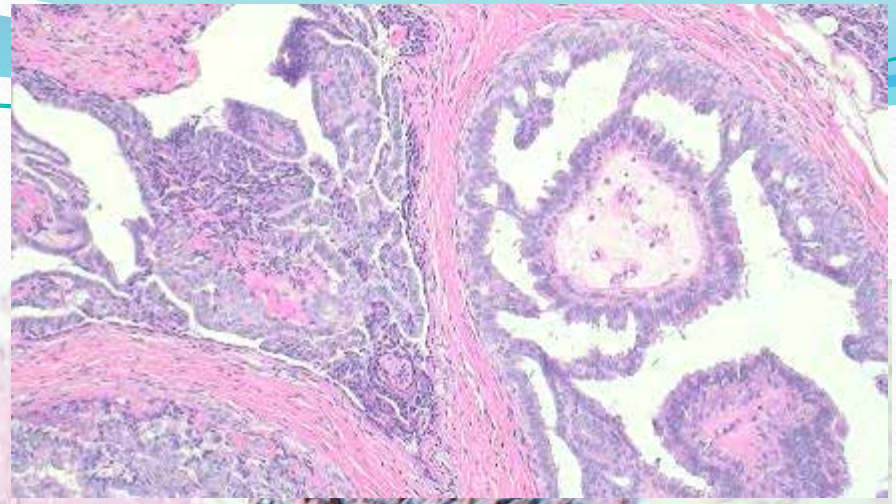


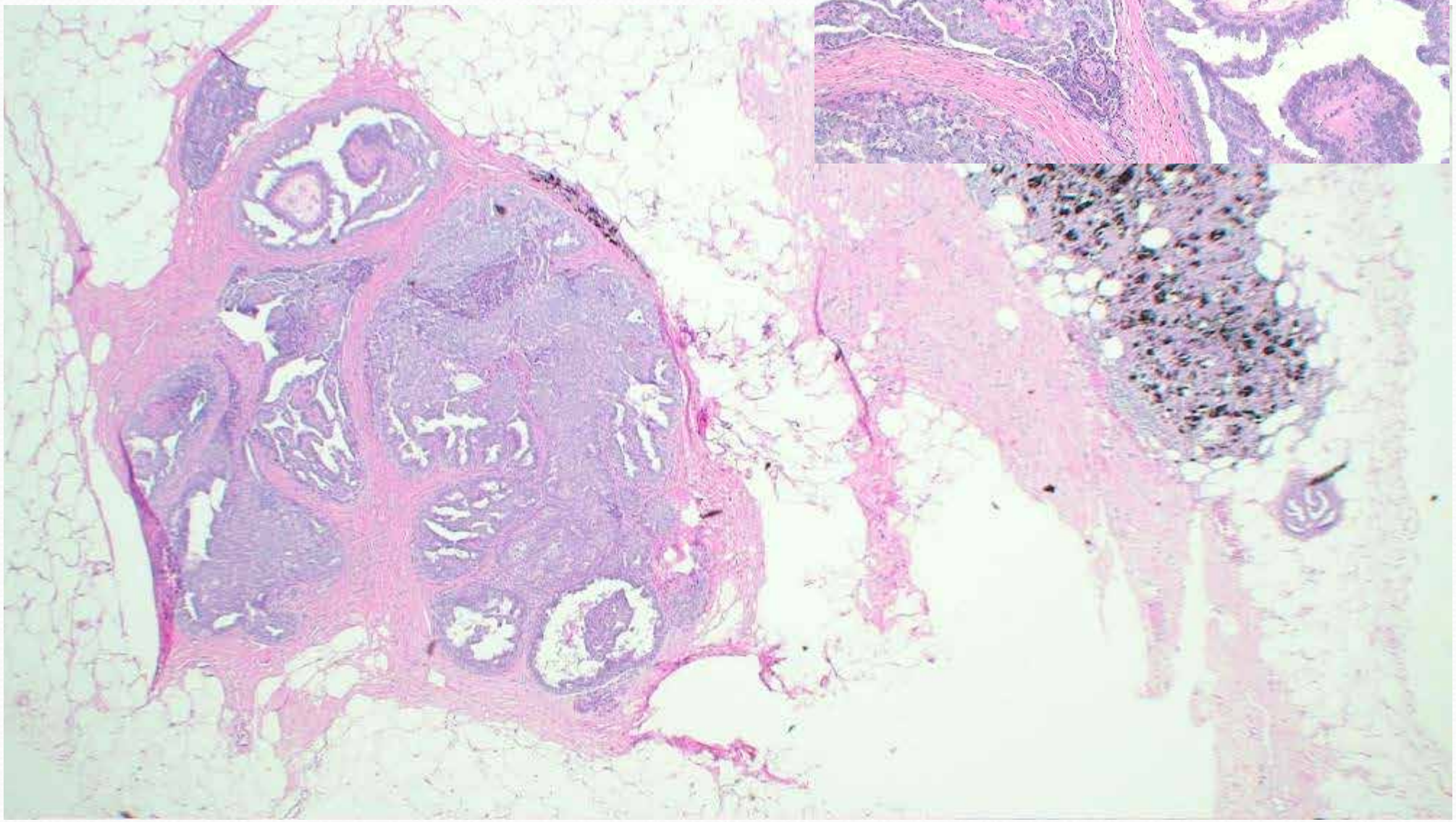
Papillary lesion on FNA



Leafy sea dragon, SE Australia

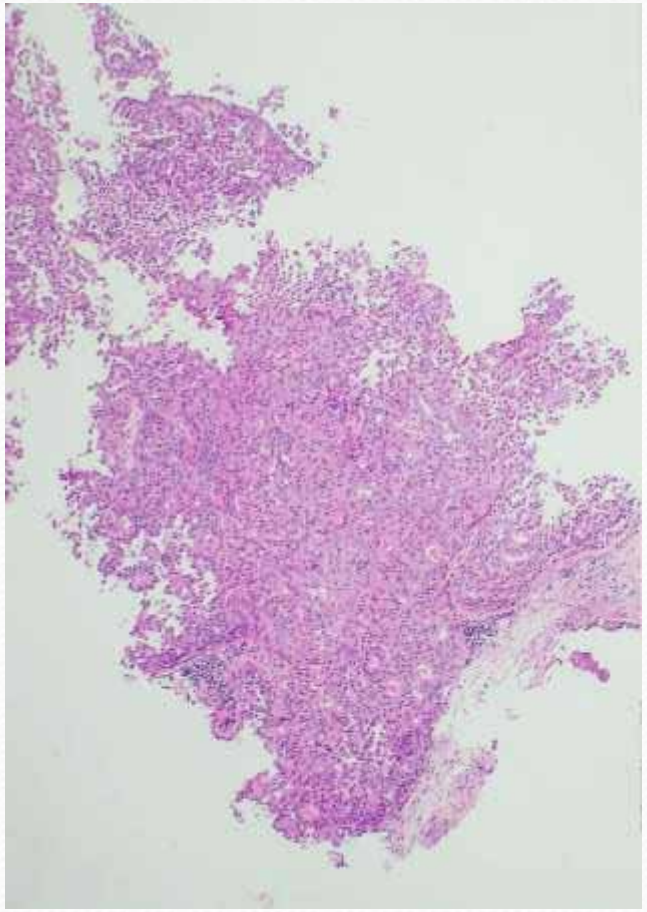
Benign complex sclerosing papillary lesion



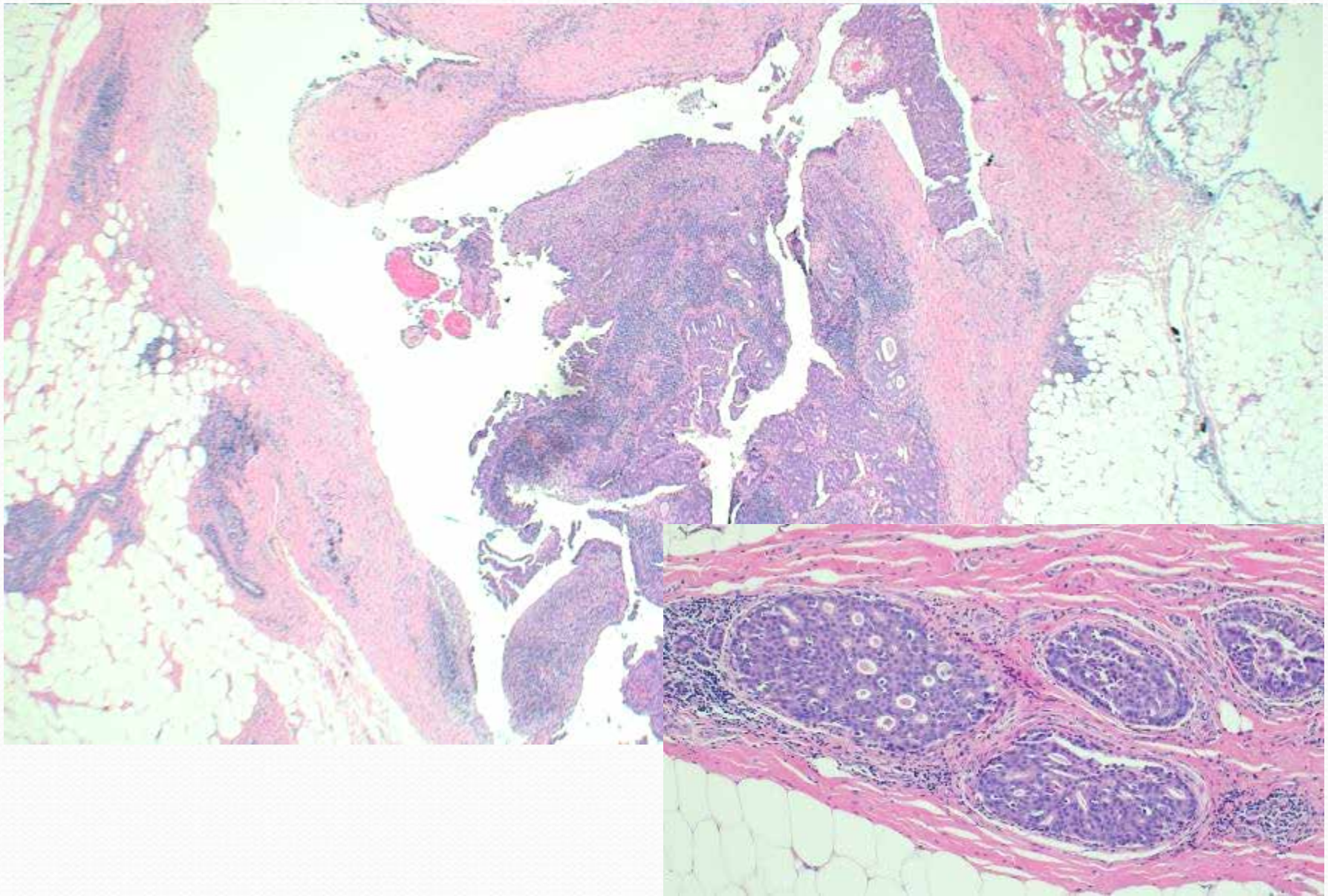


Papilloma with atypia

Core biopsy



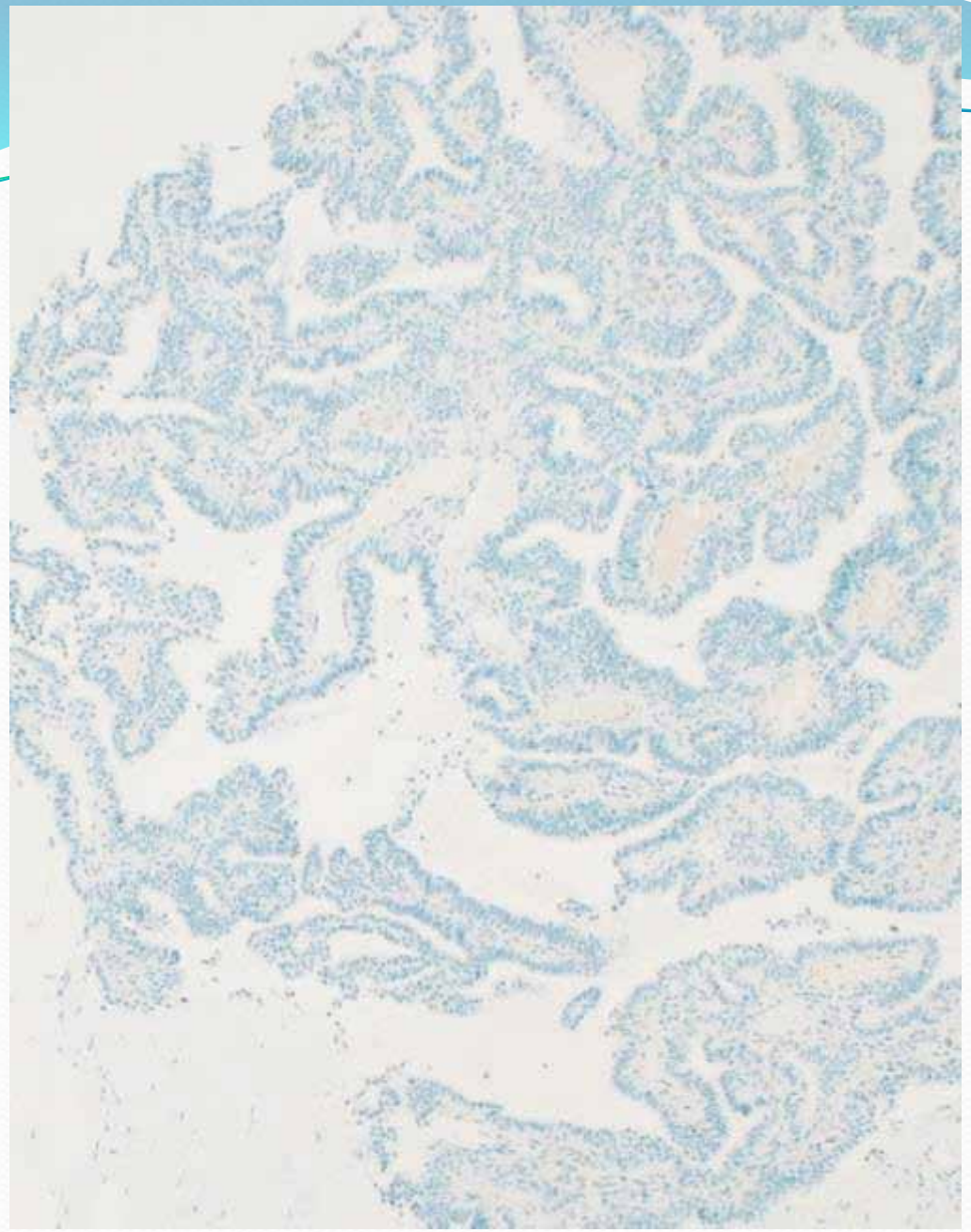
Papilloma with and extensive DCIS on excision



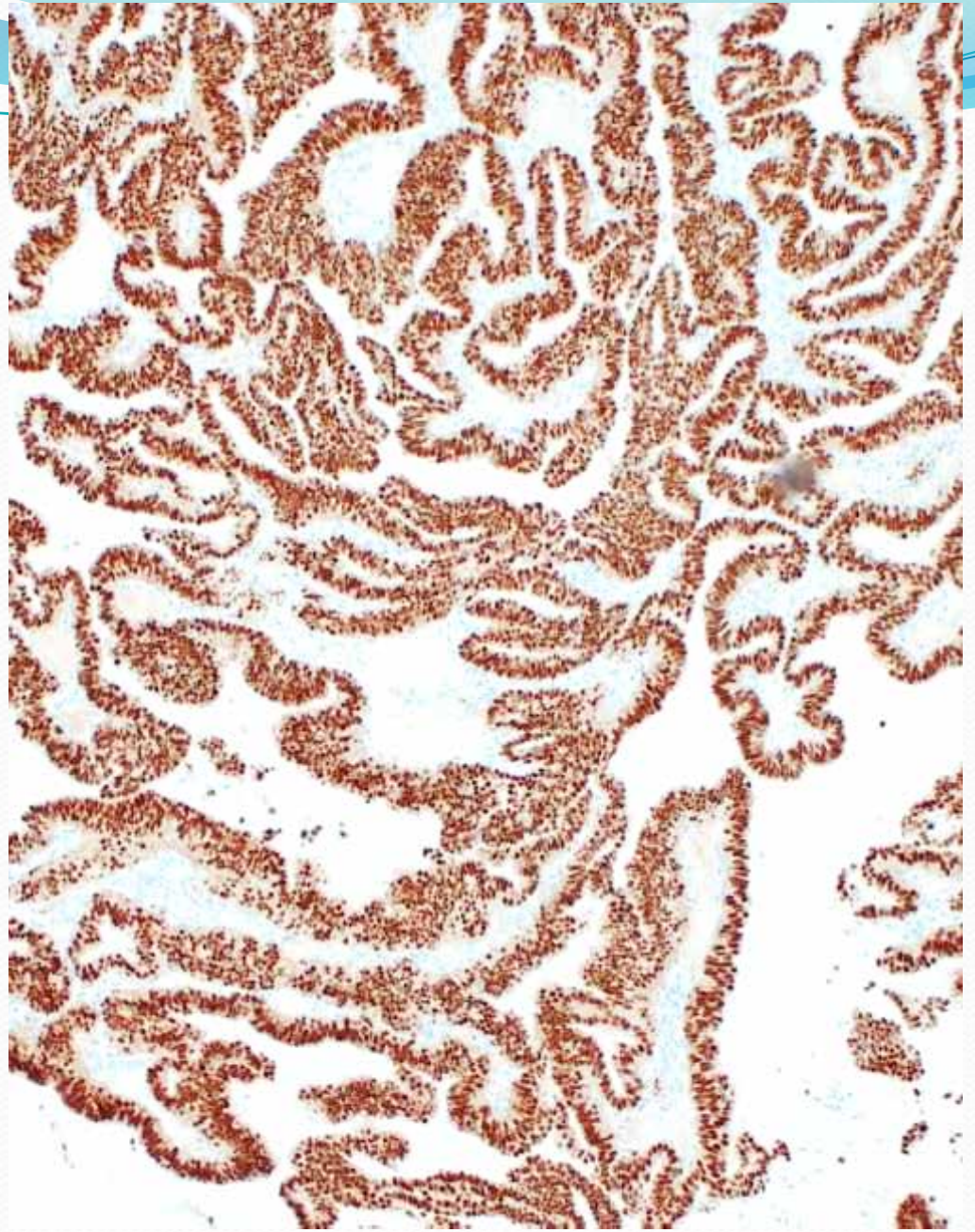
Papillary neoplasms - malignant

- **Papillary DCIS -** ME cells rim outside of duct = “true” DCIS
- **Encapsulated Papillary carcinoma –** no ME cells around duct **(**formerly intracystic or encysted Papillary ca**)**
- **Solid Papillary Carcinoma (in situ or invasive) –** may be ME cells
- **Invasive Papillary carcinoma** – very rare

Papillary DCIS (intraductal papillary ca)



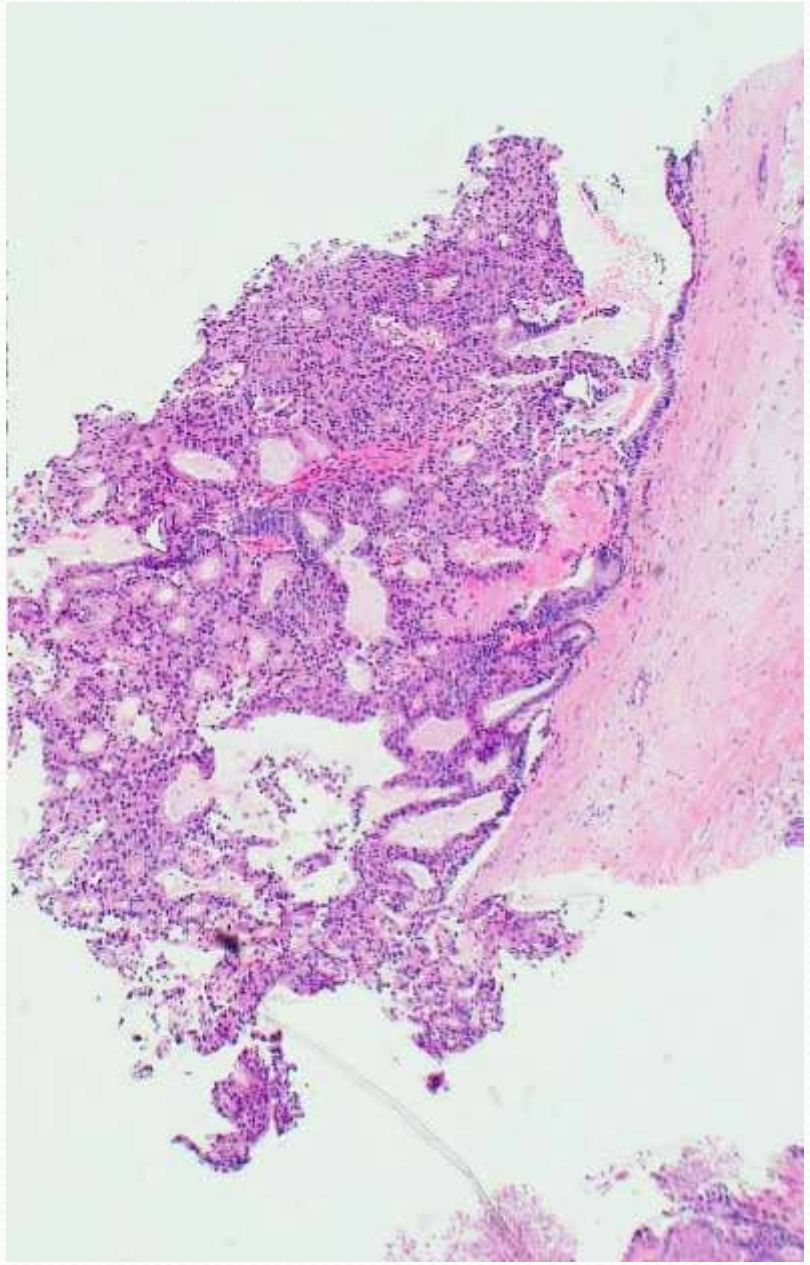
P63/calponin – No ME cells



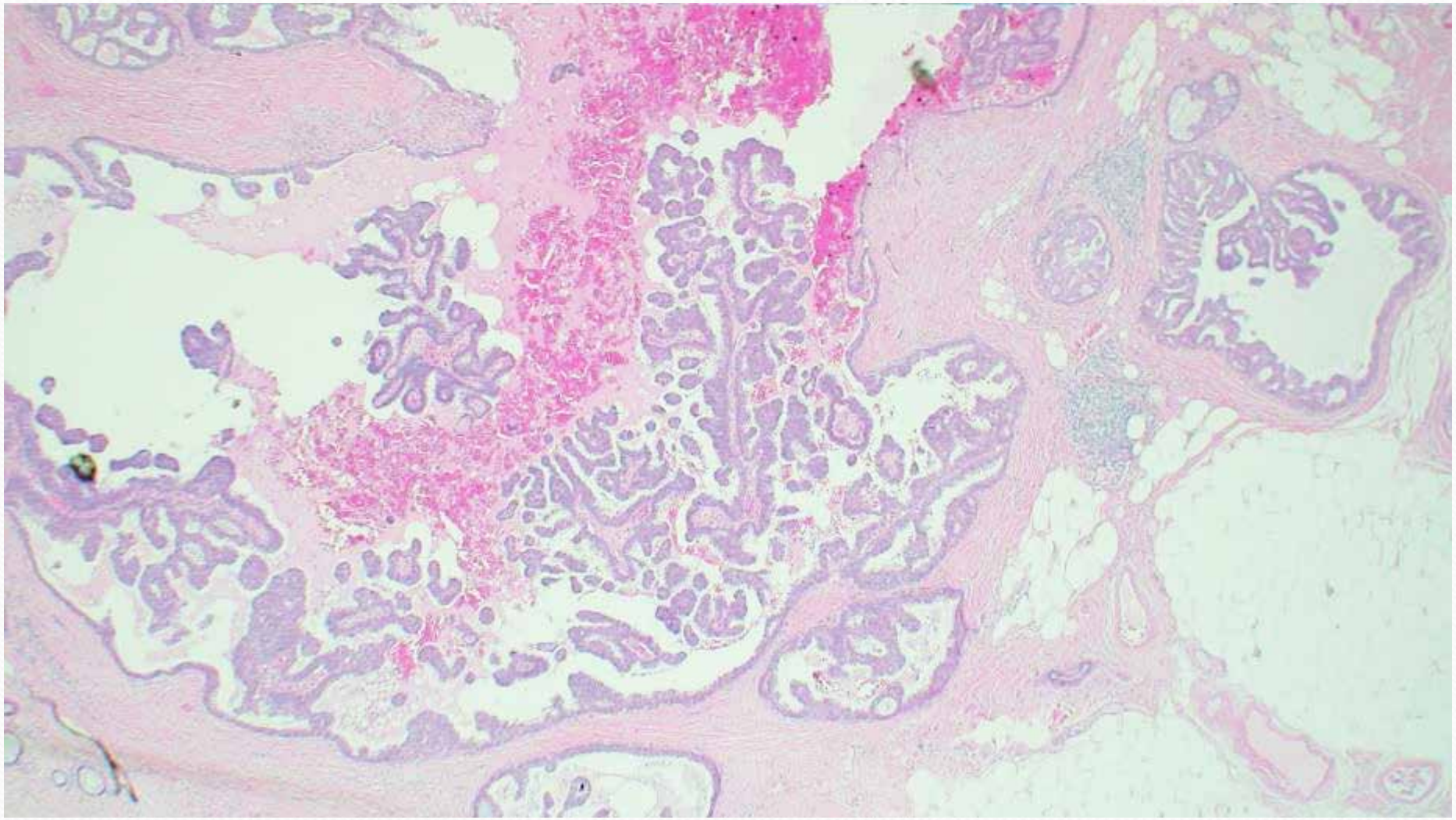
ER (monoclonal)

Encapsulated papillary carcinoma

- Surrounding fibrous capsule. NO myoepithelial cells along the papillae and generally no peripheral myoepithelial layer.
- Grade as nuclear grade (low or intermediate)
- Similar genomic signature to low grade ER – positive IBC
- Regard as equivalent to in situ carcinoma (stage 0) ("current *assumption* is this is an indolent invasive carcinoma with a prognosis similar to DCIS").



Encapsulated Papillary carcinoma



Encapsulated Papillary Carcinoma of the Breast: An Invasive Tumor With Excellent Prognosis

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AJSP 2011

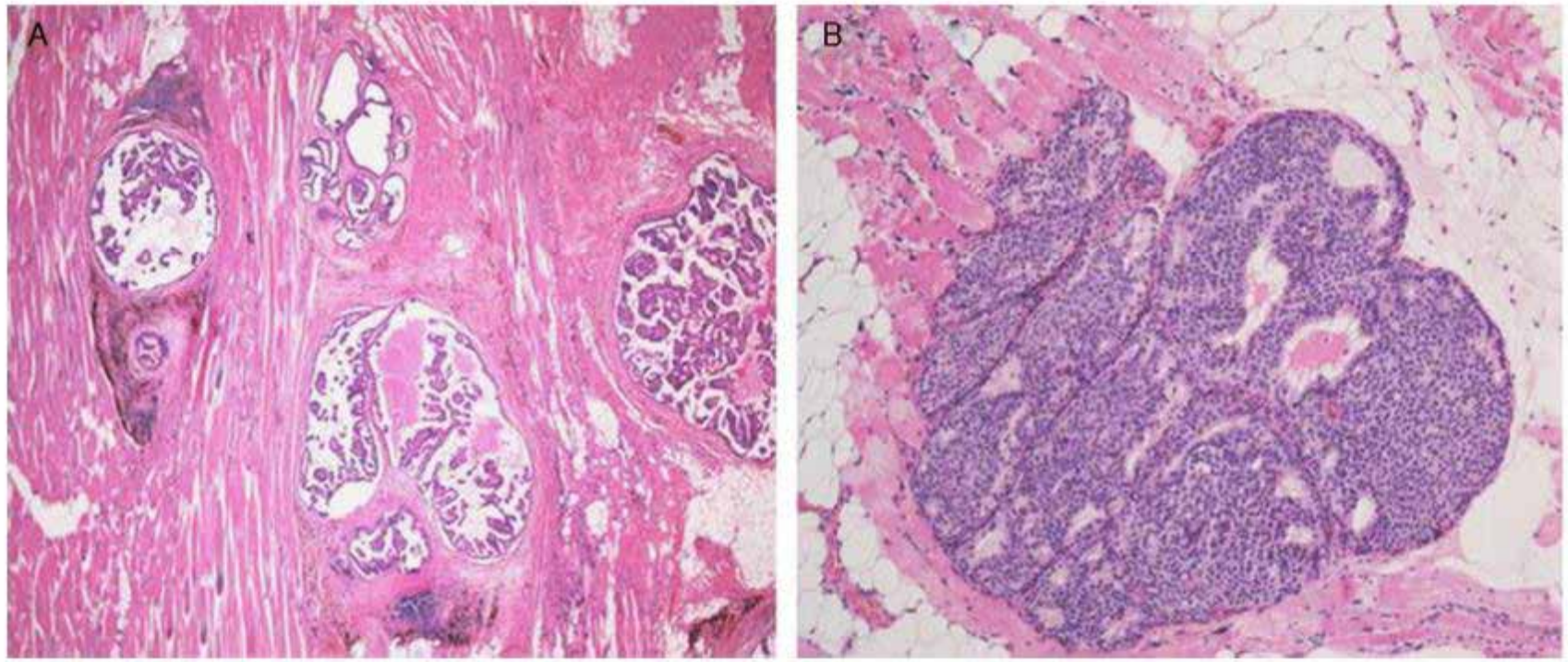
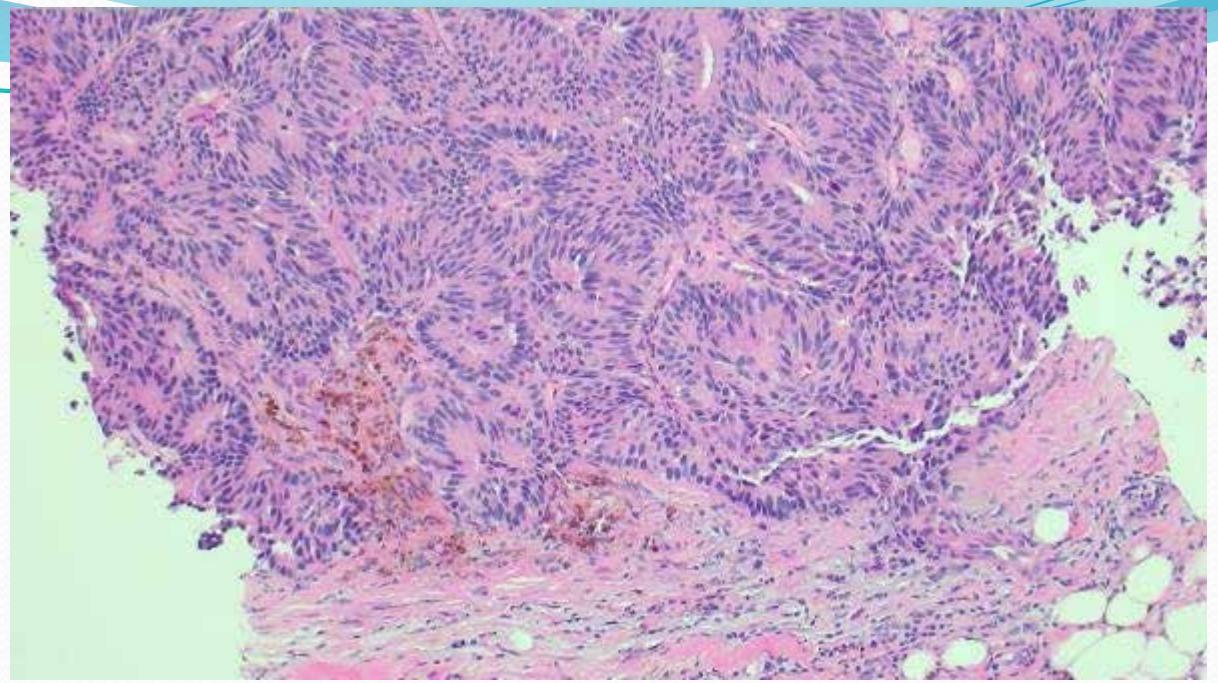
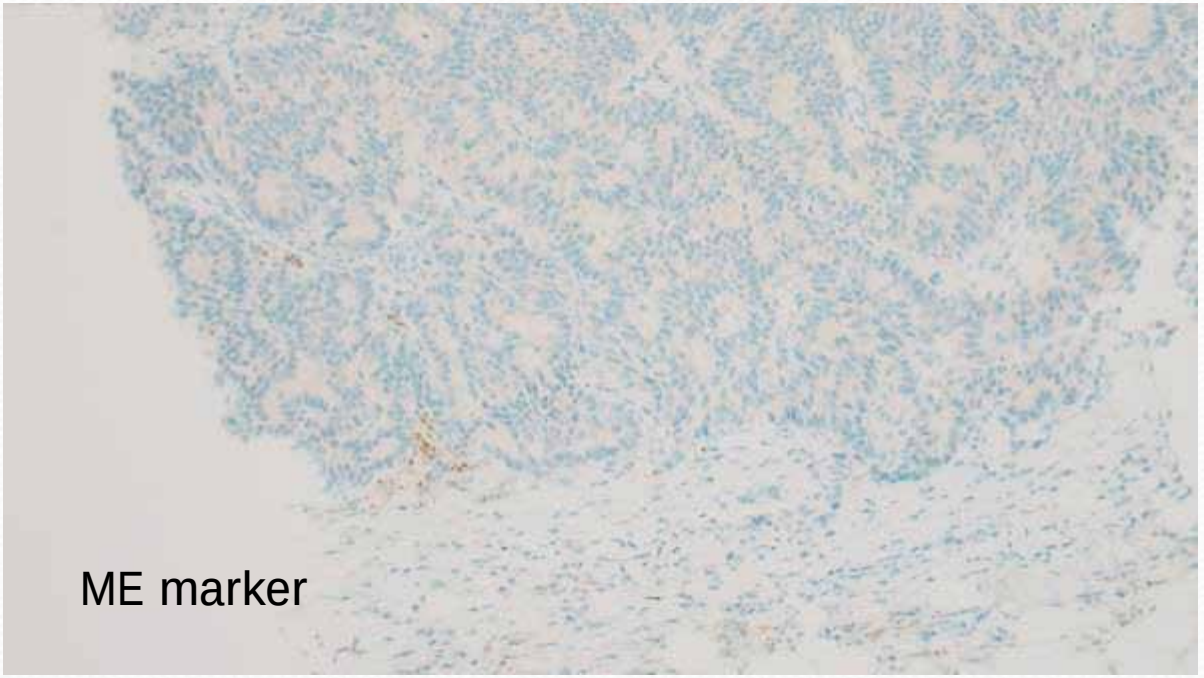


FIGURE 2. EPC showing skeletal muscle invasion with (A) or without (B) the peripheral fibrous capsule. full color online

Encapsulated papillary carcinoma

- Frank invasion is generally of no special type and extends beyond the capsule
- IHC for myoepithelial cells allows diagnosis on core biopsy in many cases
- *NOTE: If there are high grade nuclear features and/or triple negative or HER 2 Pos à grade, stage and manage as invasive carcinoma*





Solid papillary carcinoma

All have solid growth with delicate fibrovascular cores. Frequently show neuroendocrine differentiation, biologically indolent. Low grade atypia. +/- ME cells

- **Solid papillary carcinoma in situ**
- **Solid papillary carcinoma with invasion**
- **Invasive solid papillary carcinoma (rare)**

Upgrade rate of papilloma on core biopsy

- *Papilloma WITHOUT atypia*: low (0-7%) and <2% if no mass or symptoms, no ADH or LCIS in same core, and no Hx B Ca. Lower rate if VABB.

?? need excision if imaging concordant

Management shifting -excise if imaging >1-1.5 cm –endorsed in USA but not uniformly followed. vs VAE

Micropapillomas (<2 mm) do not need excision (incidental)

Upgrade usually à DCIS, mostly papillary DCIS, invasion rare (? Role of misclassification)

Up to 20% excisions have atypical proliferations ie ADH (atypical papilloma)/LN (not regarded as upgrade to cancer).

(Brogi & Whittemore, Review of 24 studies -Modern Pathology, 2021; 1.7% - *Naklis et al. Ann Surg Oncol 2021, prospective trial).)*

Upgrade rate of papilloma on core biopsy

-*Papilloma WITH atypia*: Upgrade rate up to 27% - 32%*. Upgrade includes all types of Papillary DCIS.

– Consensus to excise.

*(*Hsu Lin et al. Hum Pathol 2021; Catanzariti et al Insights Imaging, 2021)*

Potential problems with papillary lesions on core biopsy

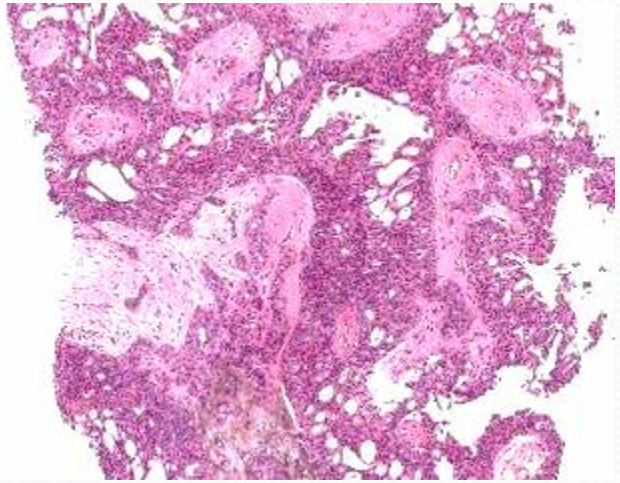
- Heterogeneity of lesion
- Frequently fragmented

à *Cautious about designation as benign or malignant unless clearly encapsulated papillary/papillary DCIS type on IHC*

- Freq Dx as atypical papillary lesion if IHC not conclusive
- Complete excision required for definite Dx

BUT note problems of previous core biopsy in excision specimen:

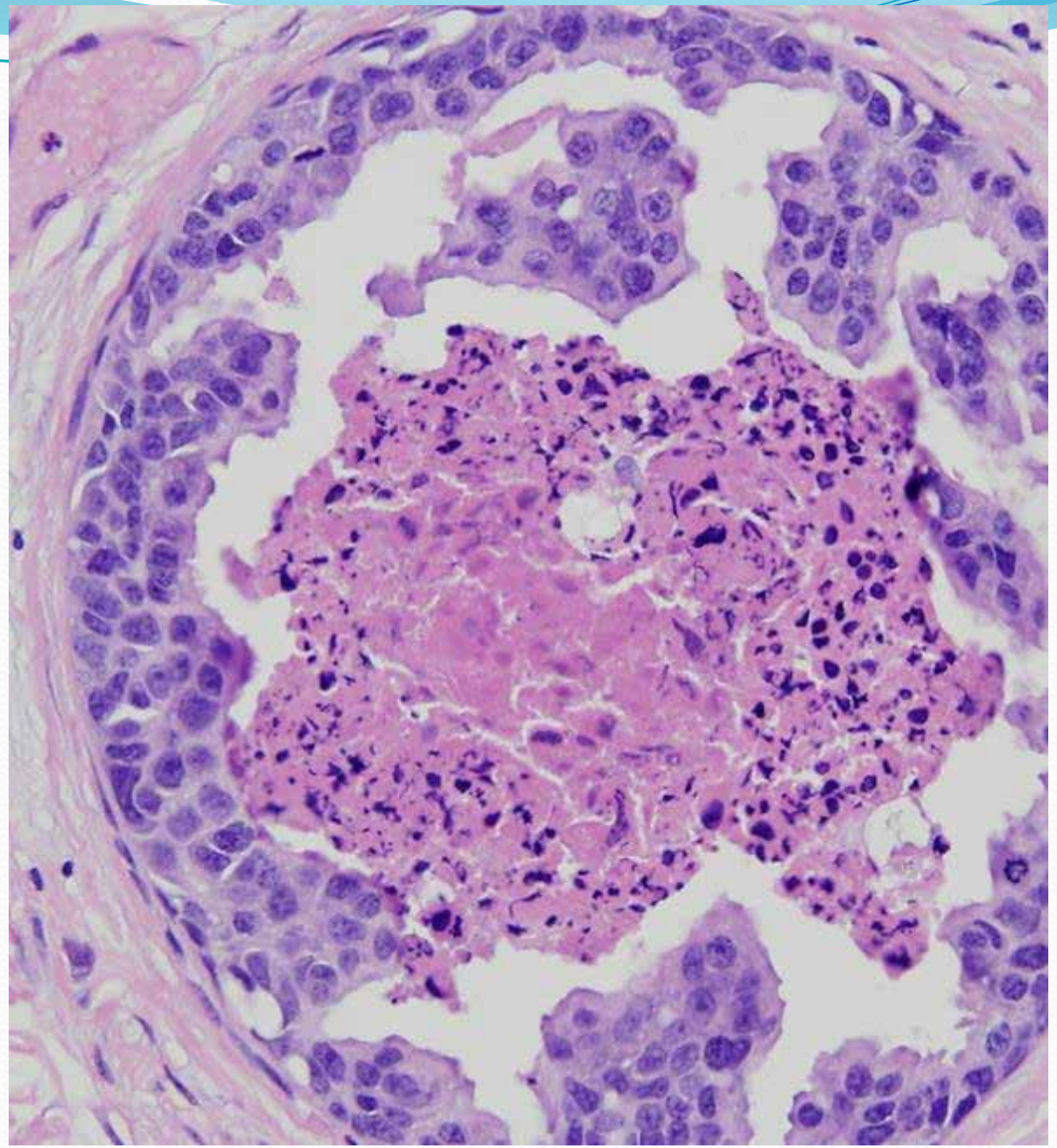
- misplaced epithelium (mimic invasion)
- haemorrhage into lesion à obscuring
- infarction à obiterates



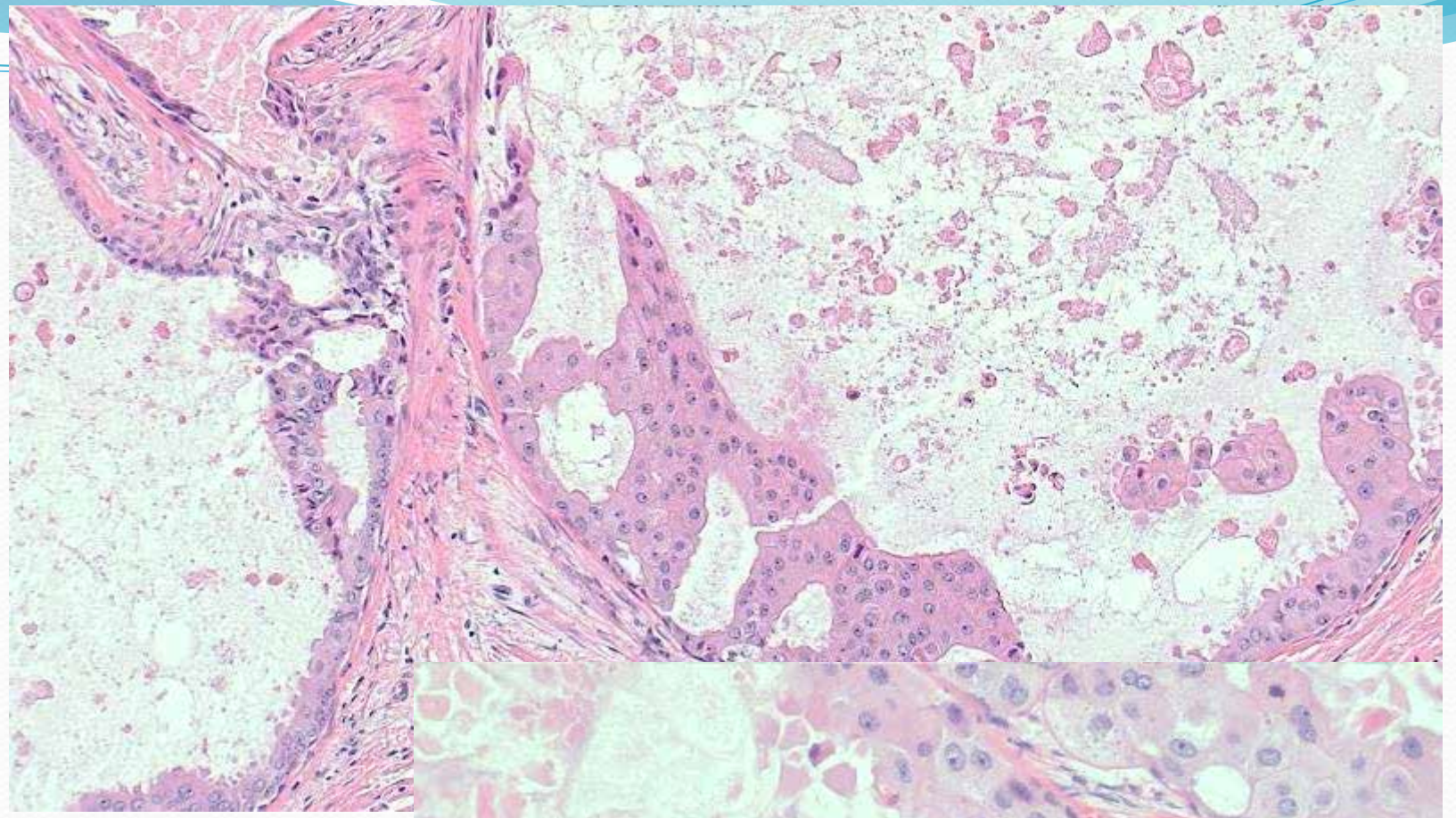
High grade DCIS

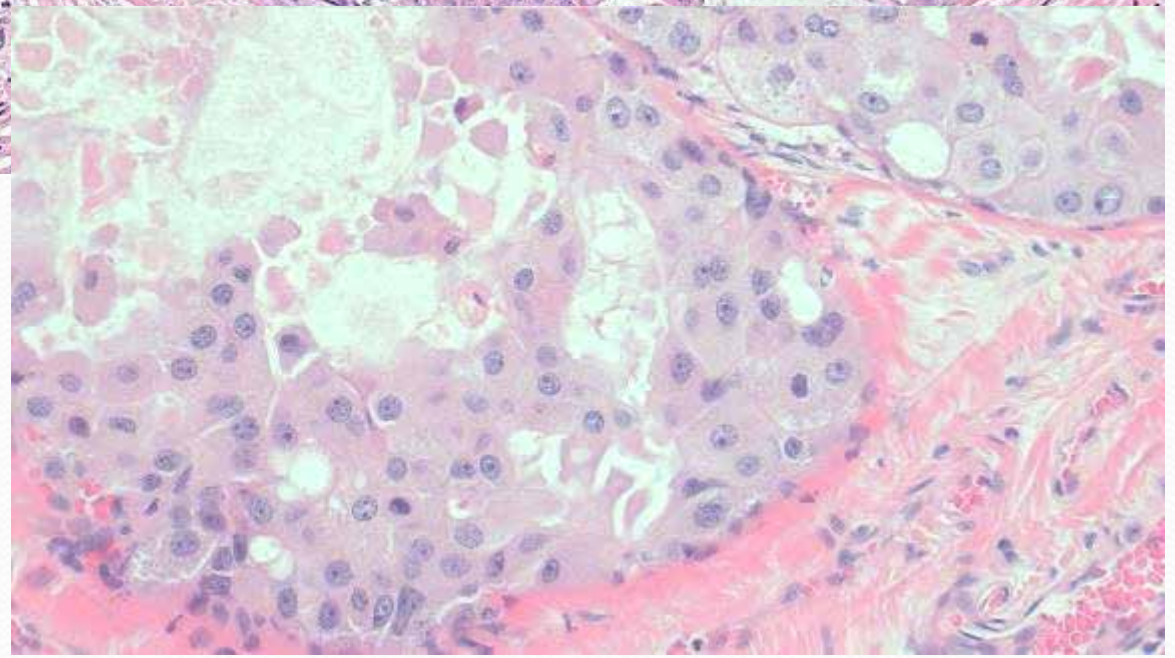
- High nuclear grade atypia
- Prominent nucleoli
- Solid, cribriform, comedo – type (with central necrosis)
- Often calcifications
- Often HER 2- positive
- ? 20 – 25% à develop invasive breast cancer

(10-12 x risk)



Challenges in apocrine DCIS –Intermediate or high grade, but may be subtle involvement of ducts in cores

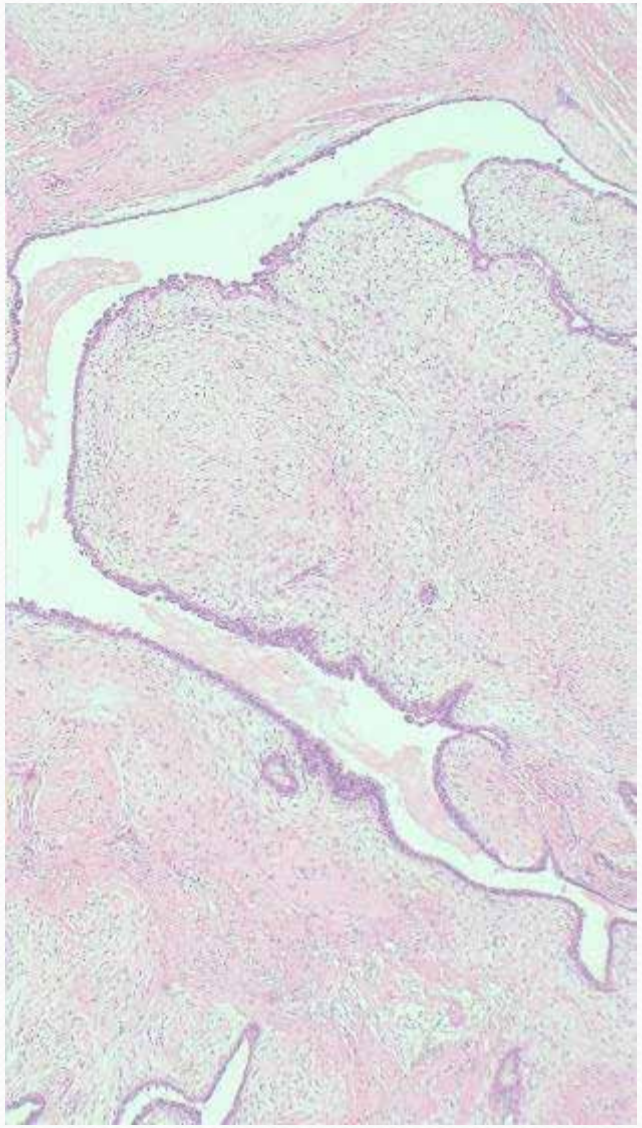




- Insidiously track along ducts into lobular acini
- Generally non-calcifying
- Maybe admixed hyperplasia

Fibroepithelial lesions - Phyllodes tumour (PT)

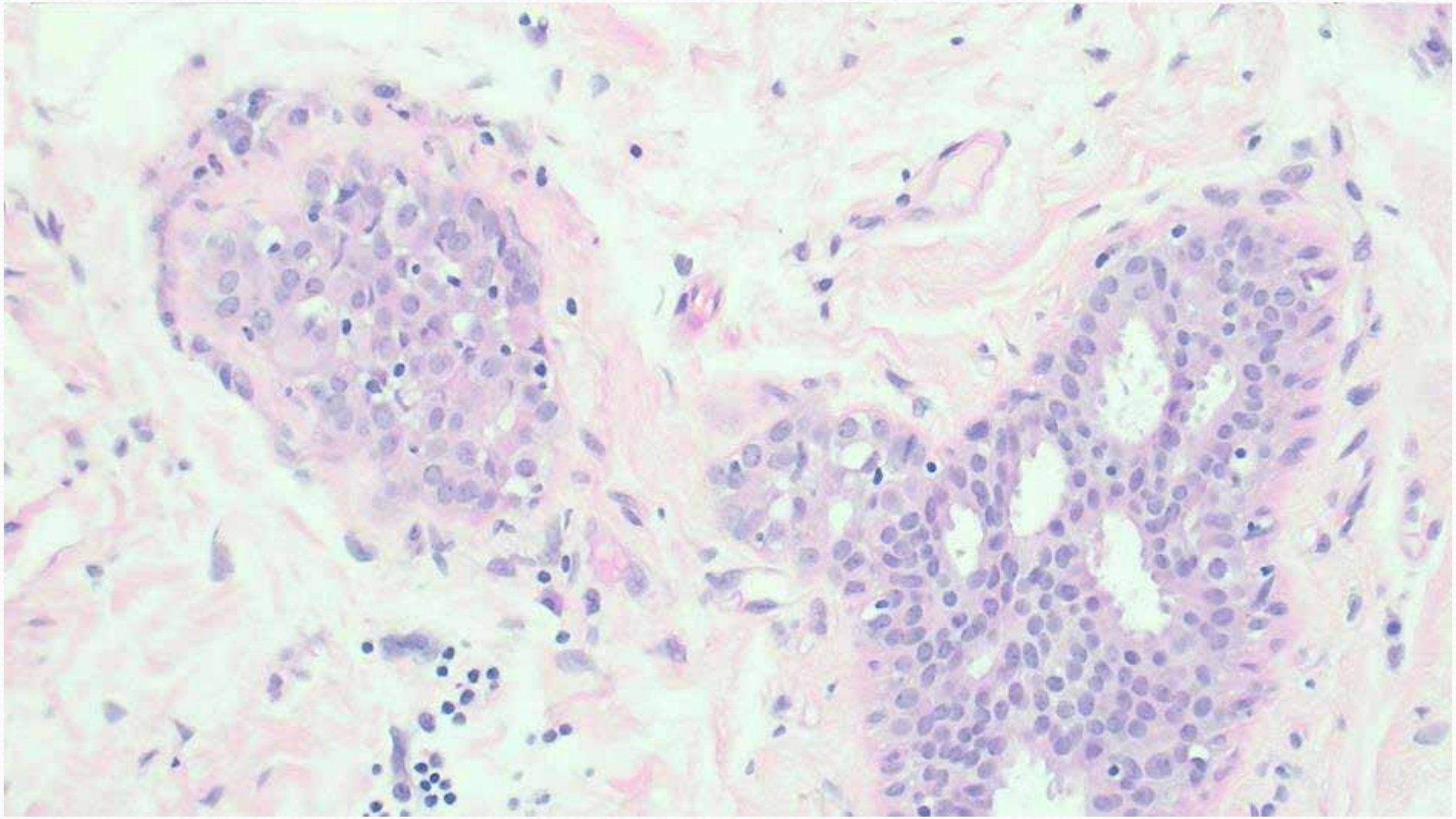
- Challenges in distinguishing FA and benign PT on core Bx à reported *underestimation of PT ~20% on CNB*
- Distinction between benign and borderline PT – generally not possible on CNB
- Malignant PT



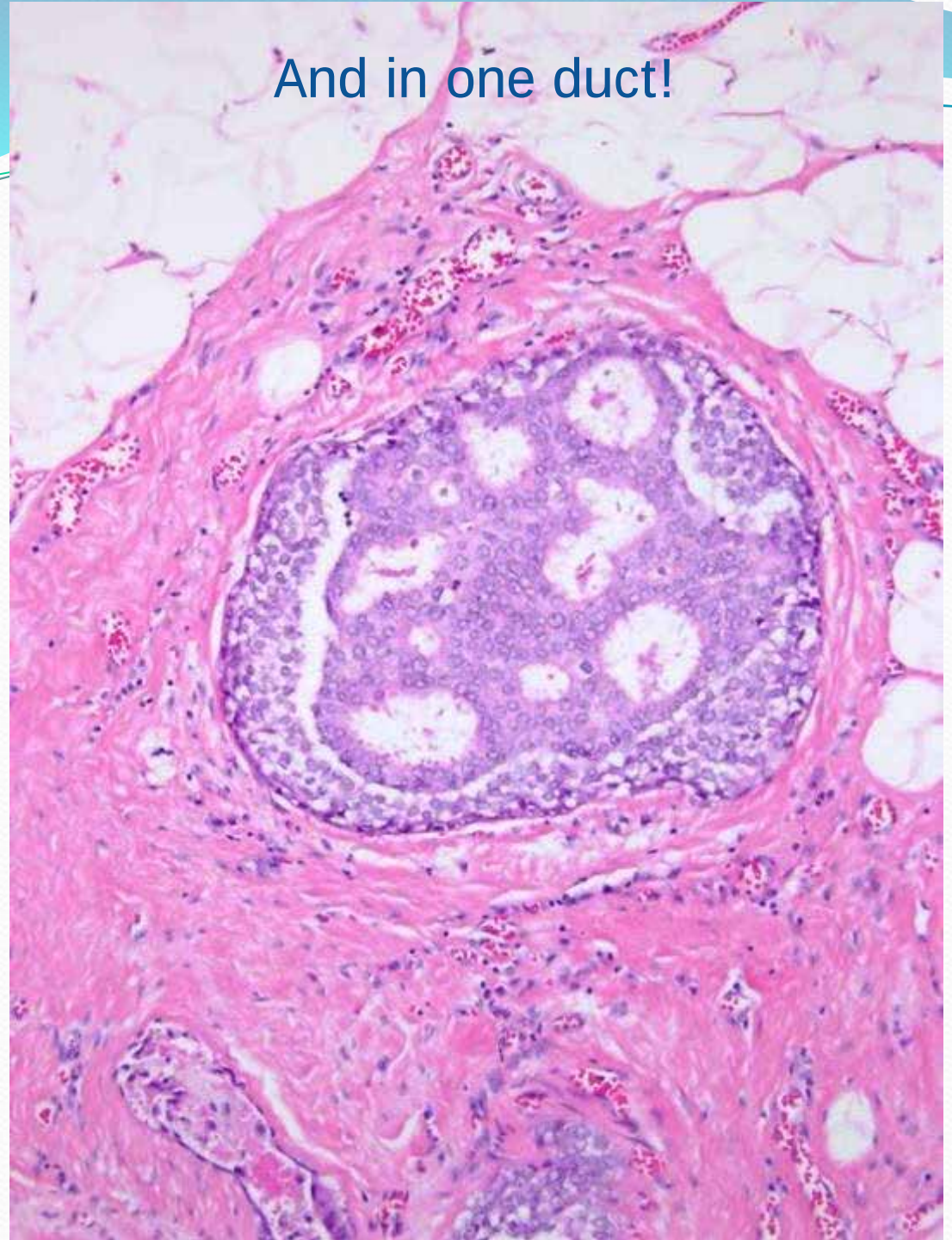
ALH/LCIS

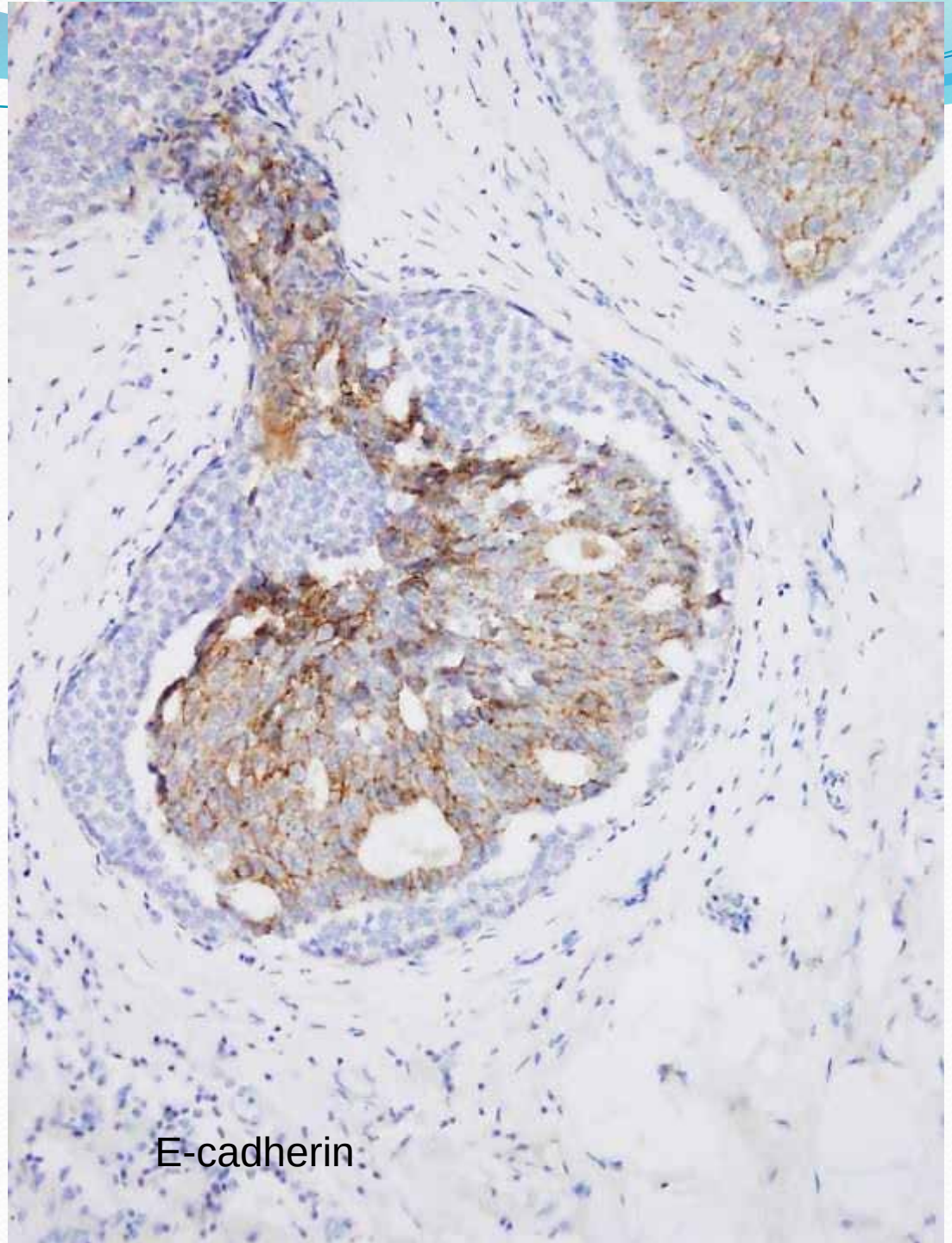
- A risk factor and a non-obligate precursor
- Classic LN Risk of developing invasive breast carcinoma = 4-5 (ALH)-10x (LCIS) = >20% at 20 years/lifetime risk 30-40% (Page and Anderson, 1985)
- ILC > IDC
- Ipsilateral > contralateral

All in one case!



And in one duct!





E-cadherin


Thank you