

# **Pre-neoplastic lesions of the Breast**

Forum of Pathology - February 2011

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# « PNL » of the Breast : Overview

- ⇒ I. Categories & definitions
- ⇒ II. Natural history & hypothesis
- ⇒ III. Clinical impact (NCB – Surgery)



- ⇒ IV. 8 cases



# I. « PNL » of the Breast : Categories & Definitions

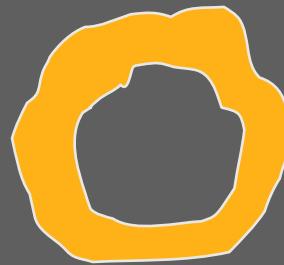
- ⇒ « Pre-neoplastic » not a good term
- ⇒ « In situ » neoplasia (clonal cell proliferation)
- ⇒ Real pre-invasive « malignant » neoplasia (in situ carcinoma)
- ⇒ Histologic risk factor for developing invasive carcinoma
- ⇒ Wide spectrum of lesions
- ⇒ Non obligate « precursor » of invasive carcinoma
- ⇒ Controversies .....

# I. ISN – Risk factor of the Breast : Categories & Definitions

- ⇒ Flat epithelial atypia – FEA (DIN 1a)
- ⇒ Atypical ductal hyperplasia – ADH (DIN1b)
- ⇒ Ductal carcinoma in situ (Van Nuys groupe I) – DCIS I (DIN1c)
- ⇒ Lobular neoplasia in situ – LIN 1 & 2
- ⇒ Pleomorphic lobular neoplasia in situ – LIN 3
- ⇒ DCIS II - III
- ⇒ Miscellaneous (stellate sclerosing adenosis, microglandular adenosis, papillary lesions, juvenile papillomatosis, mucocele-like lesions,....)

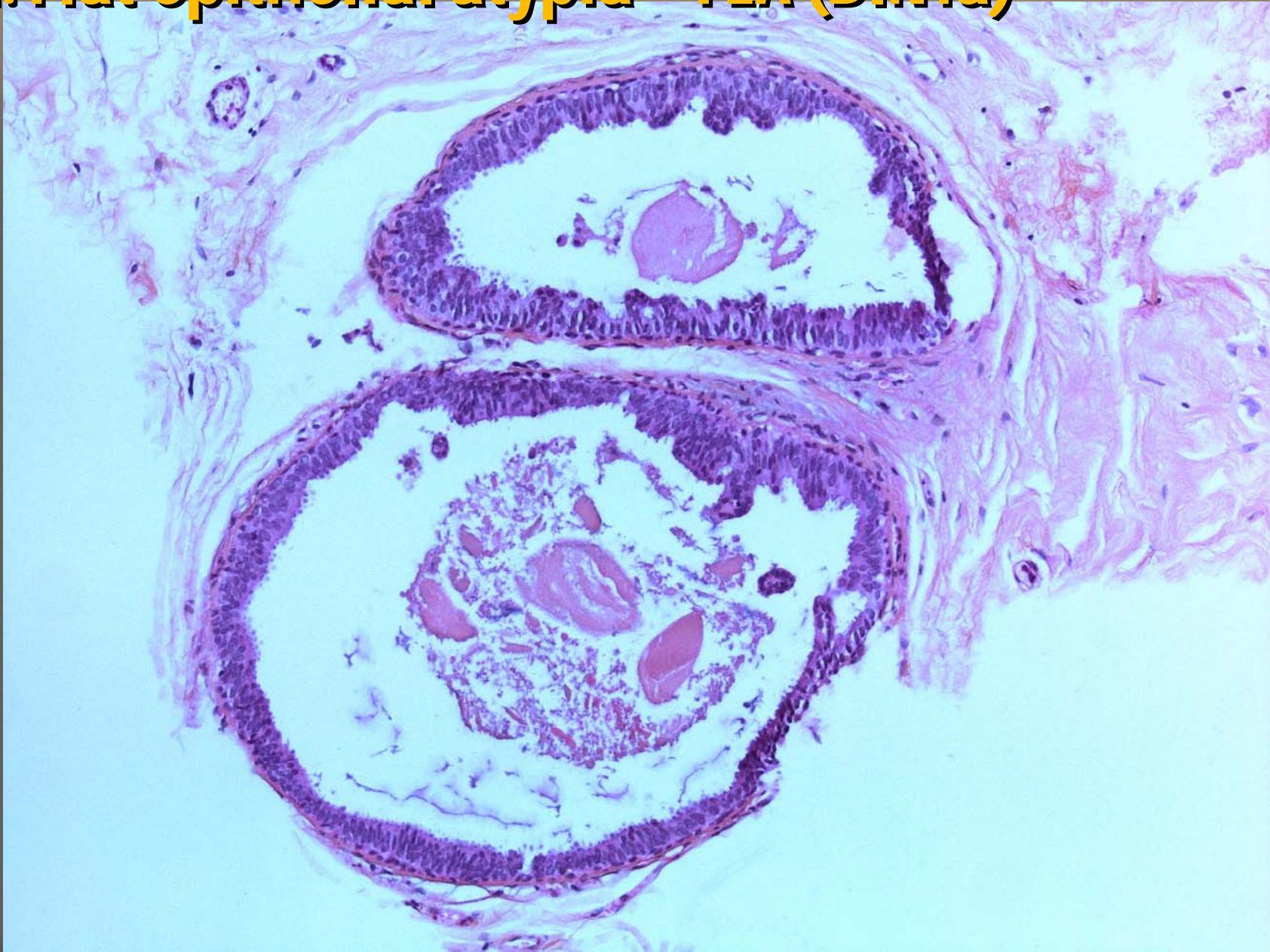
## I. Flat epithelial atypia – FEA (DIN1a)

Presumably neoplastic intraductal alteration characterized by a single or 3-5 layers of mildly atypical cells.

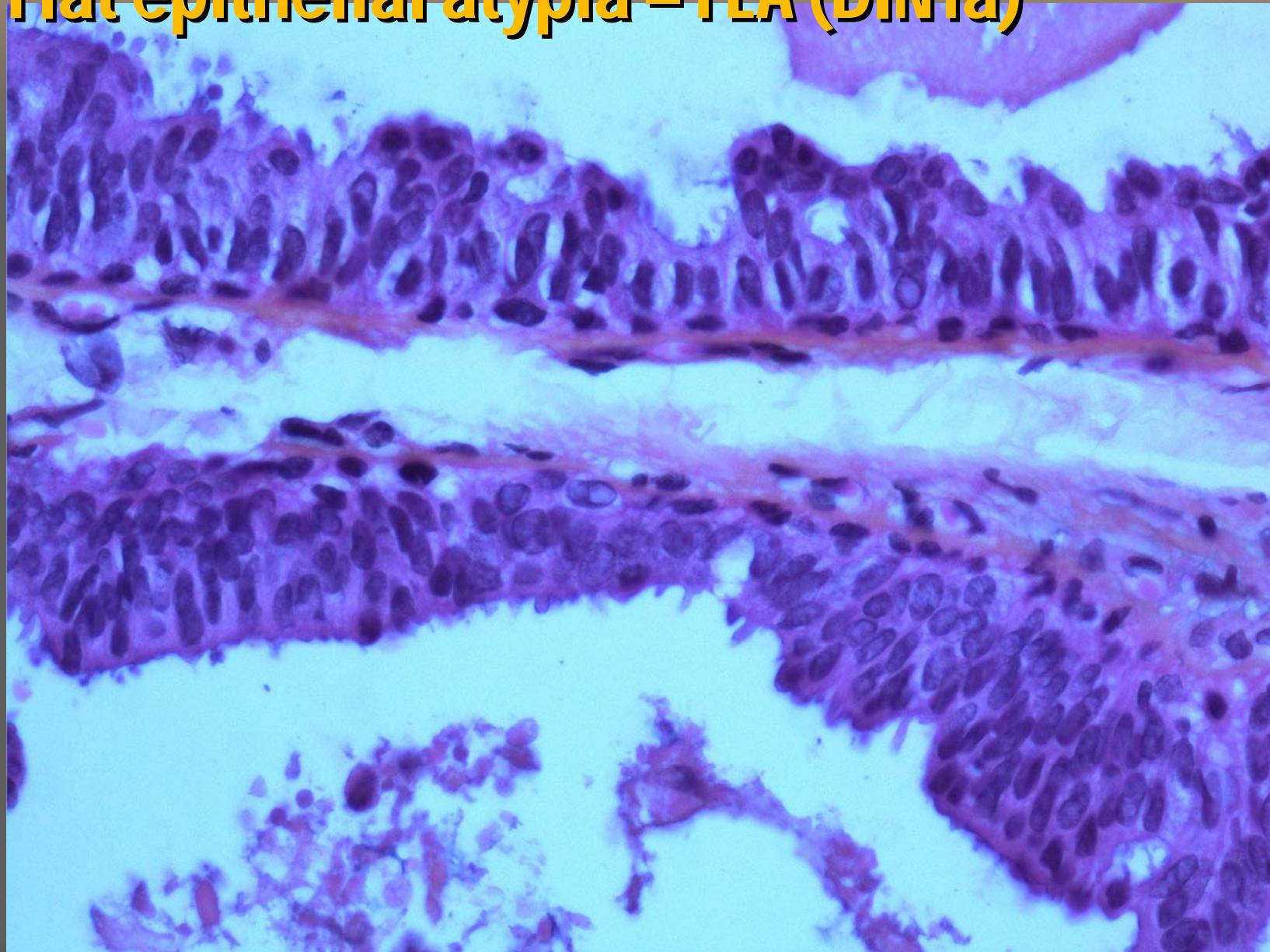


**WHO-blue book 2003**

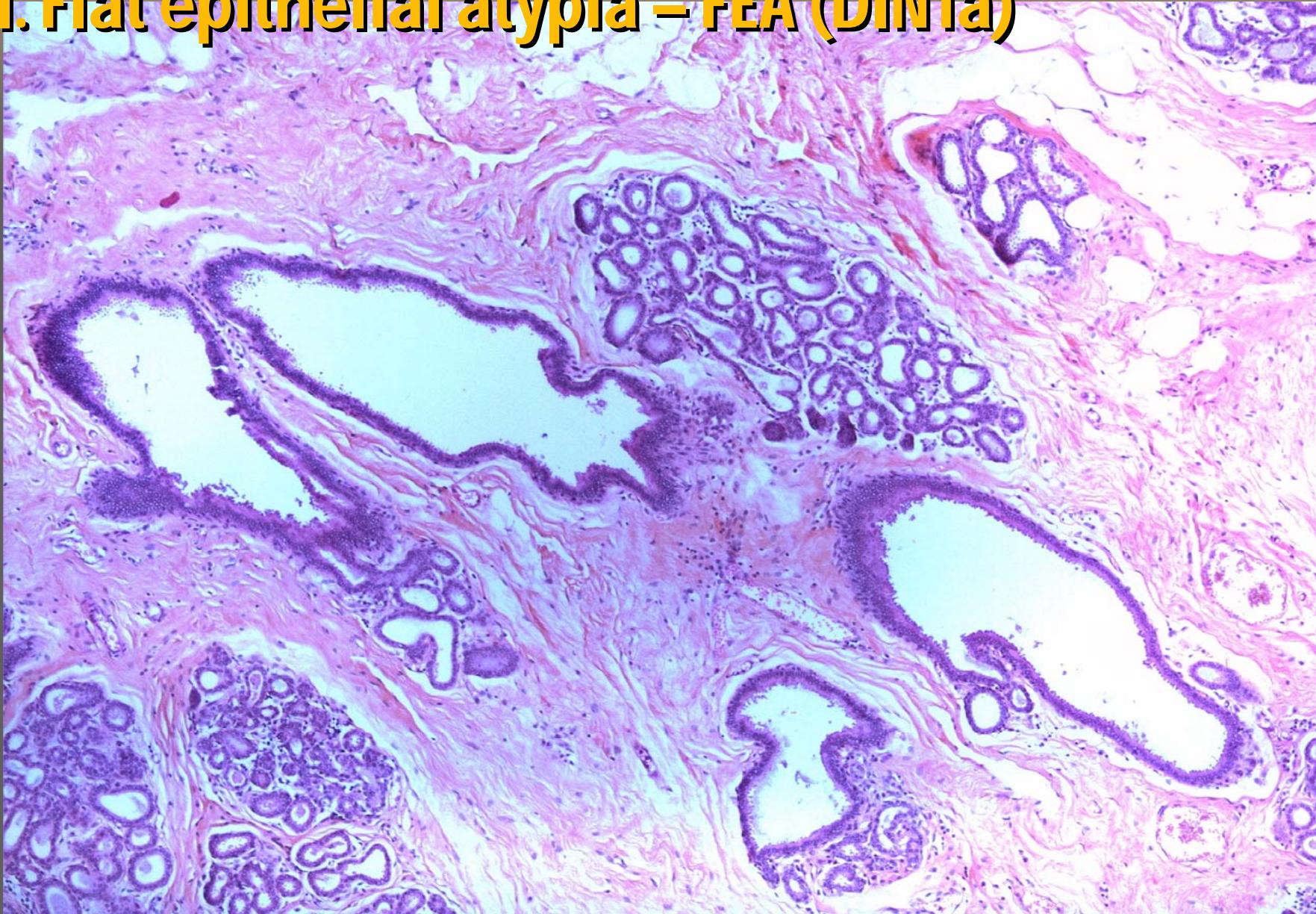
# I. Flat epithelial atypia – FEA (DIN1a)



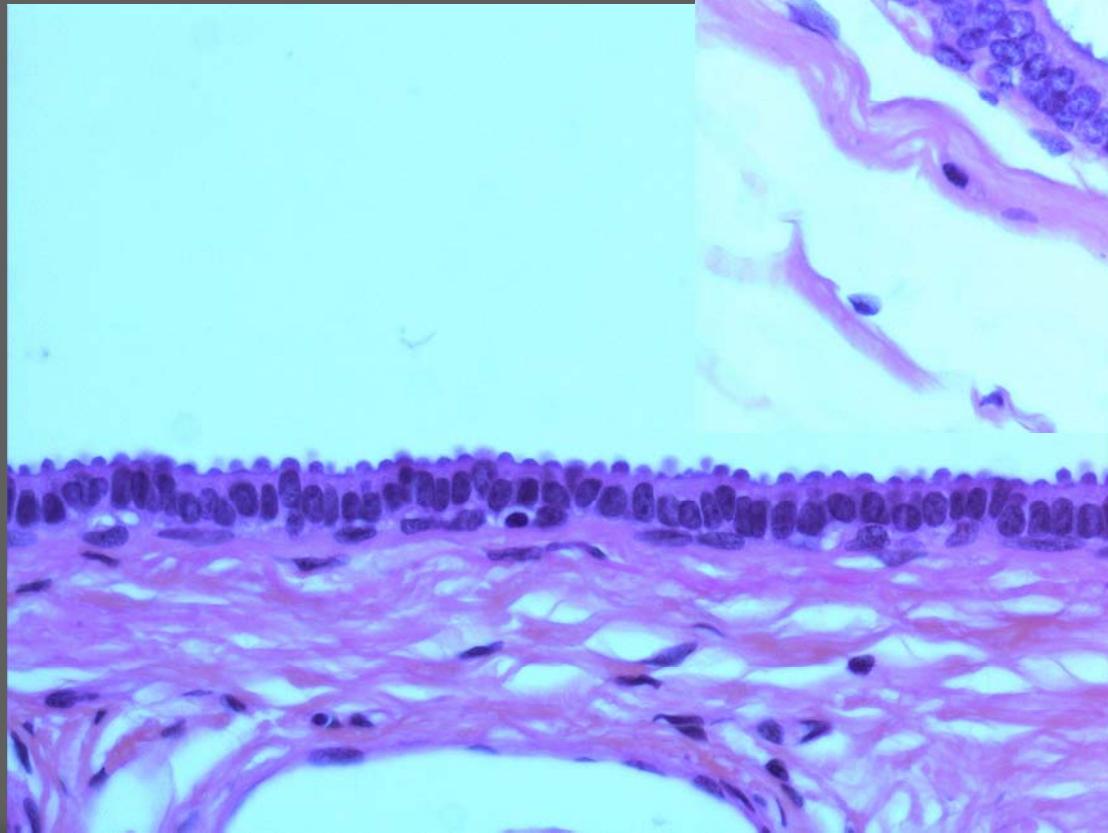
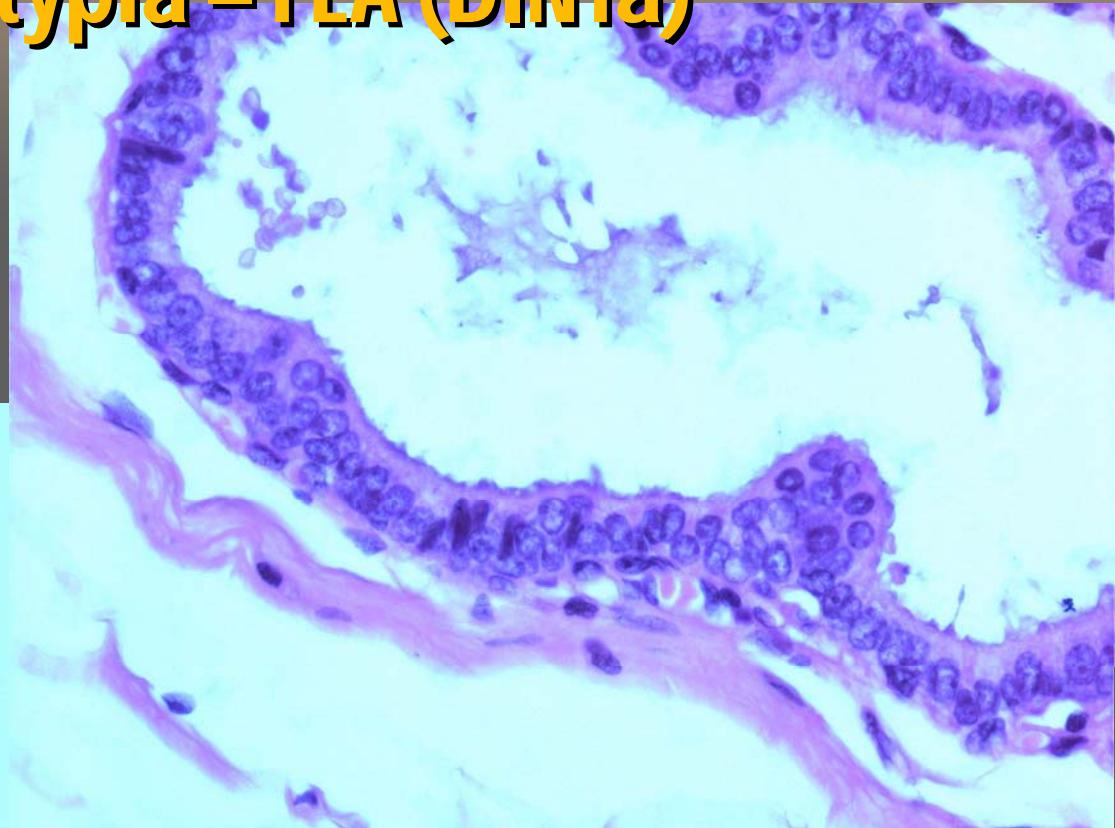
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# I. Flat epithelial atypia – FEA (DIN1a)



# I. Flat epithelial atypia – FEA (DIN1a)

- Atypical cystic lobules
- Atypical columnar lesions
- ADH clinging type (or DCIS)
- CAPSS (columnar alteration with prominent apical snouts & secretions)
- Métaplasie cylindrique atypique
- .....

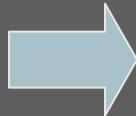
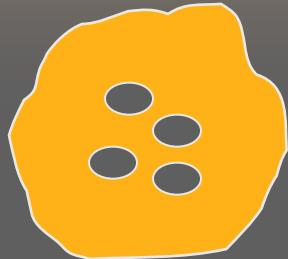
## I. Flat epithelial atypia – FEA (DIN1a)

Some cases may progress to invasive carcinoma but no quantitative epidemiological data are available for risk estimation .....



**WHO-blue book 2003**

# I. Flat epithelial atypia – FEA (DIN1a)



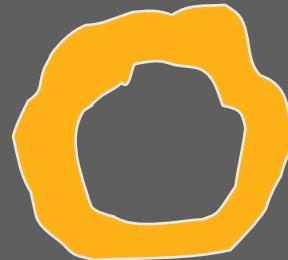
FEA

J. Azzopardi clinging low grade DCIS

Groupe I DCIS

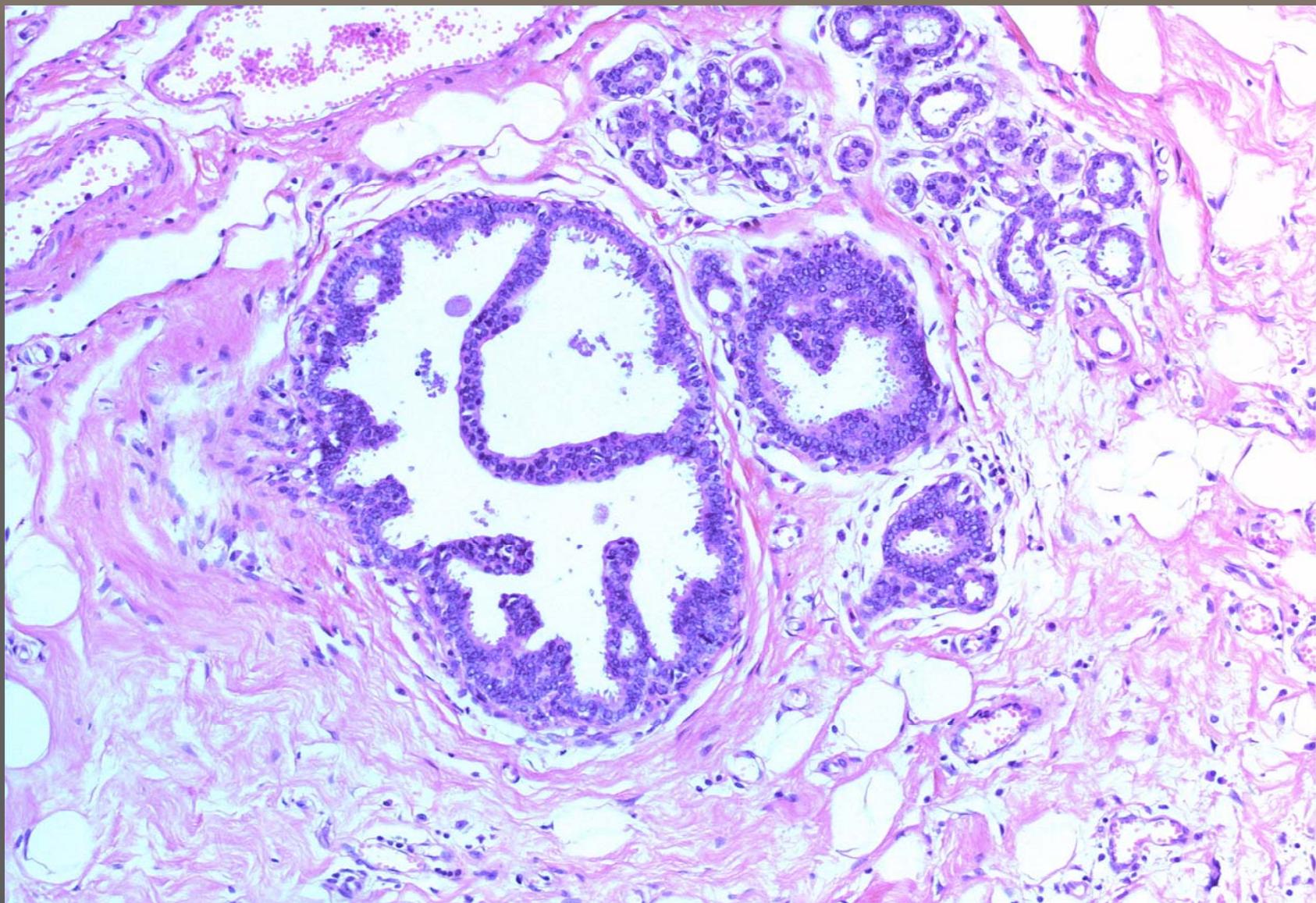
## I. Flat epithelial atypia – FEA (DIN1a)

« ...neoplastic cells limited to the periphery of the containing structures. The lesion can be easily missed since the alteration is cytological rather than anatomical »

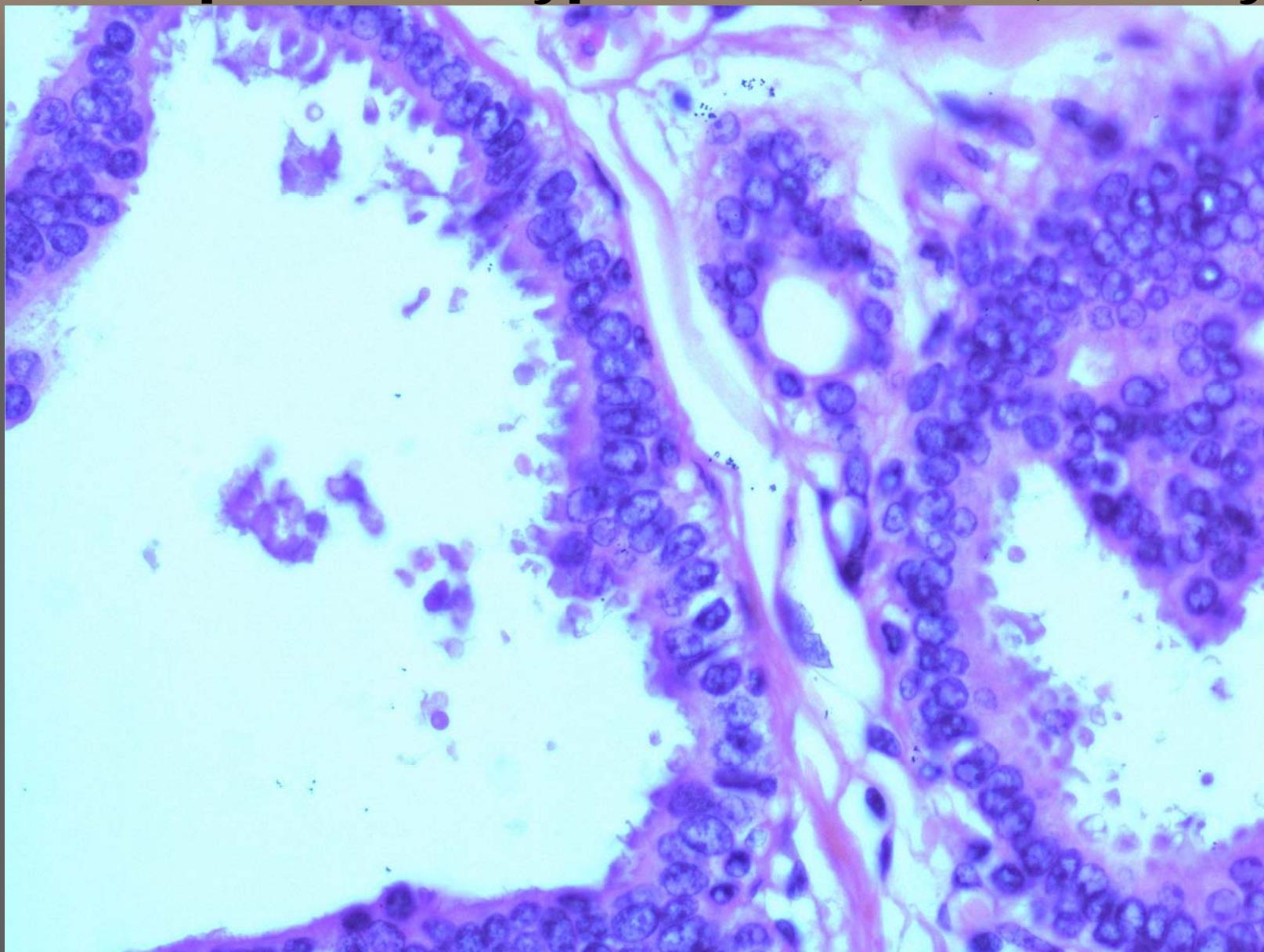


J. Azzopardi clinging low grade DCIS - 1979

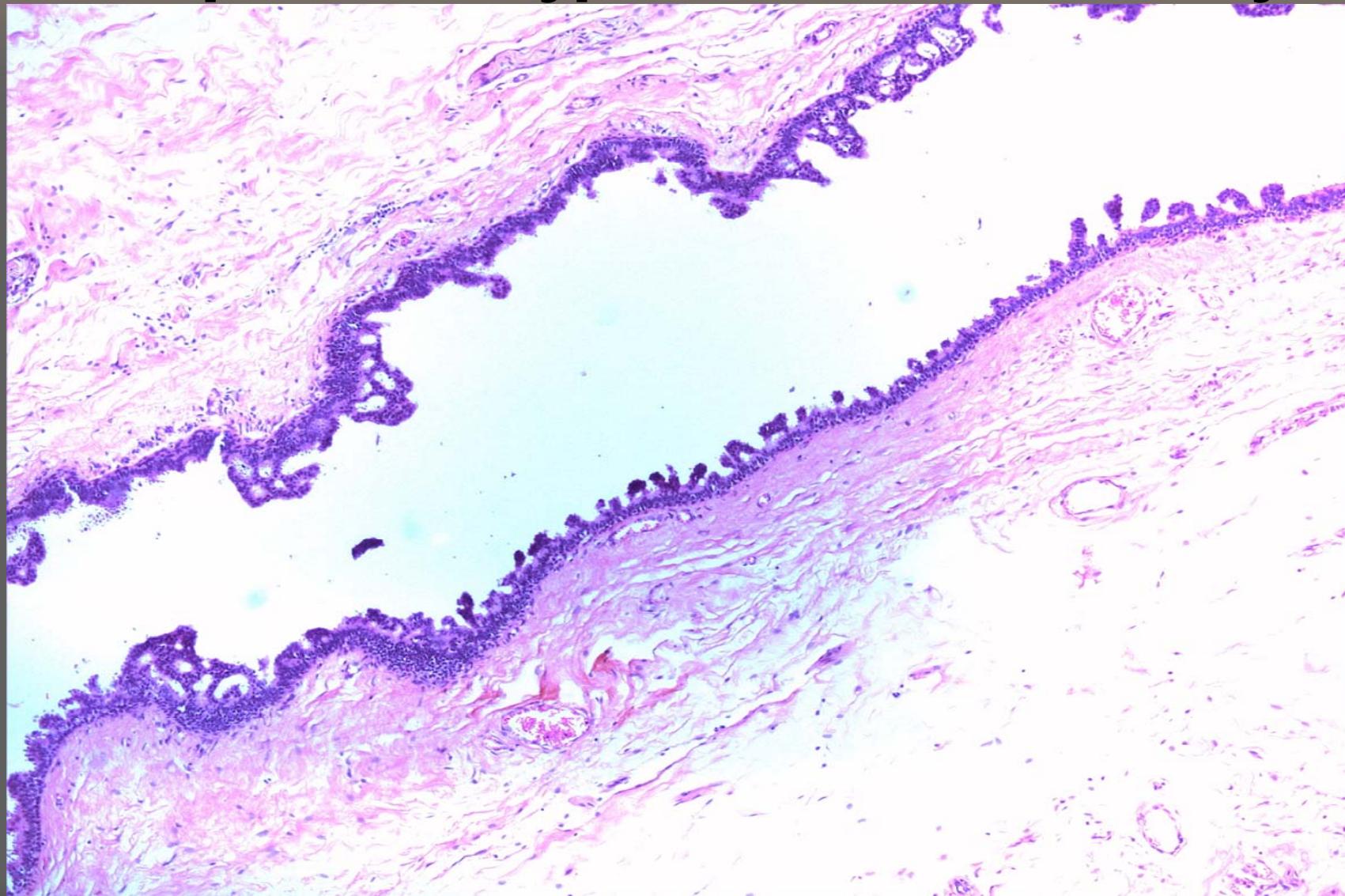
# I. Flat epithelial atypia – FEA (DIN1a) - ECstyle



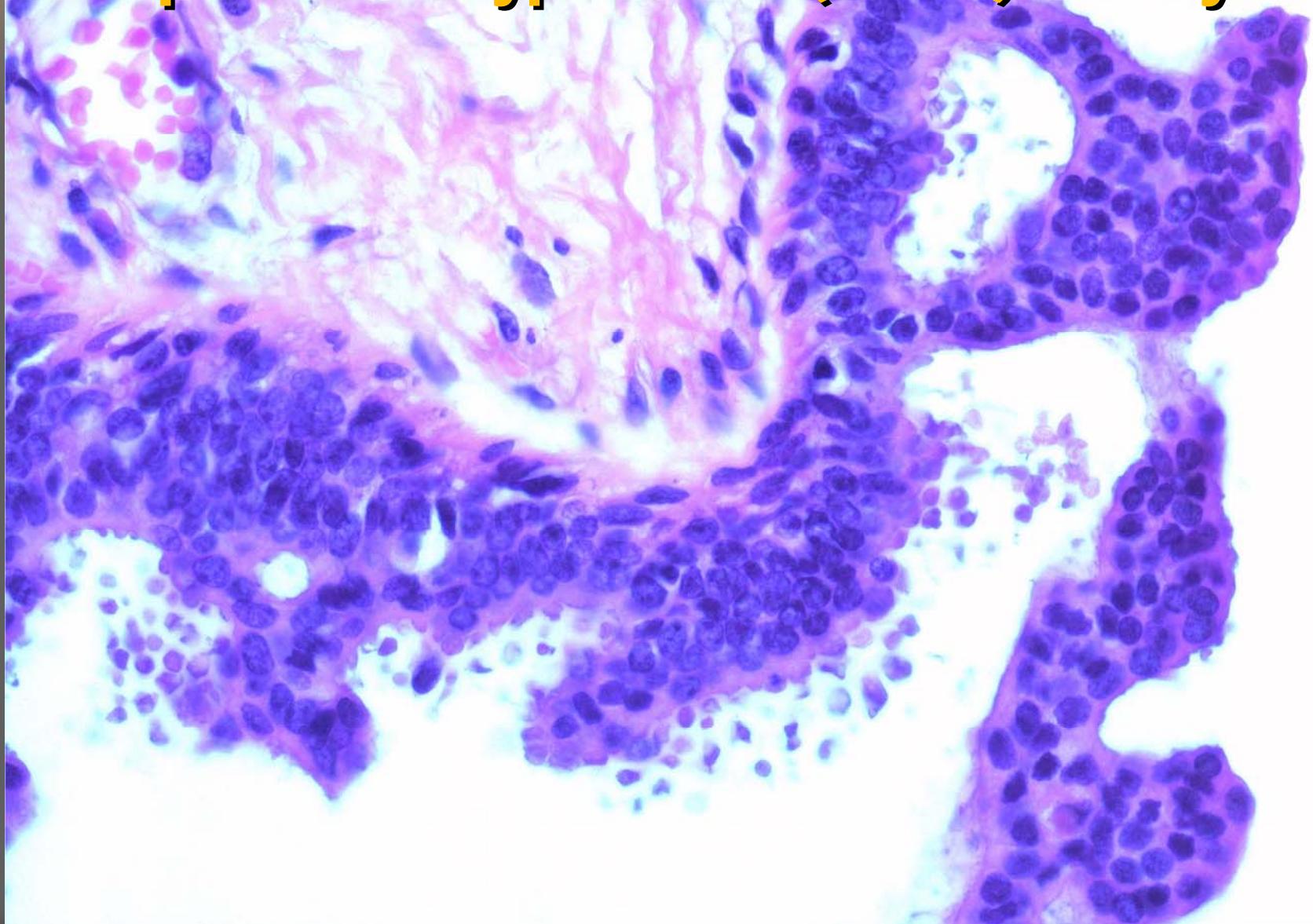
# I. Flat epithelial atypia – FEA (DIN1a) - ECstyle



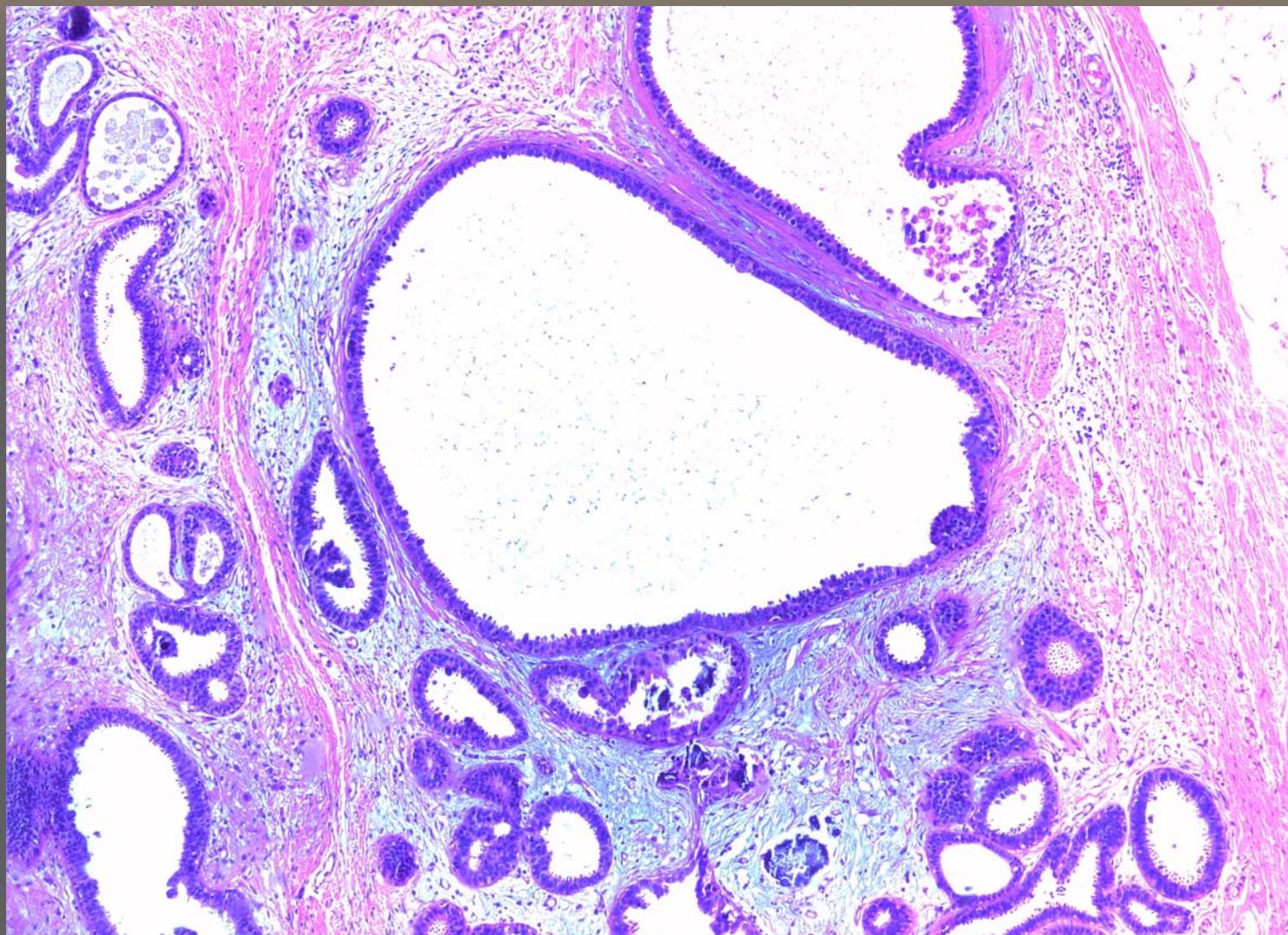
# I. Flat epithelial atypia – FEA (DIN1a) - ECstyle



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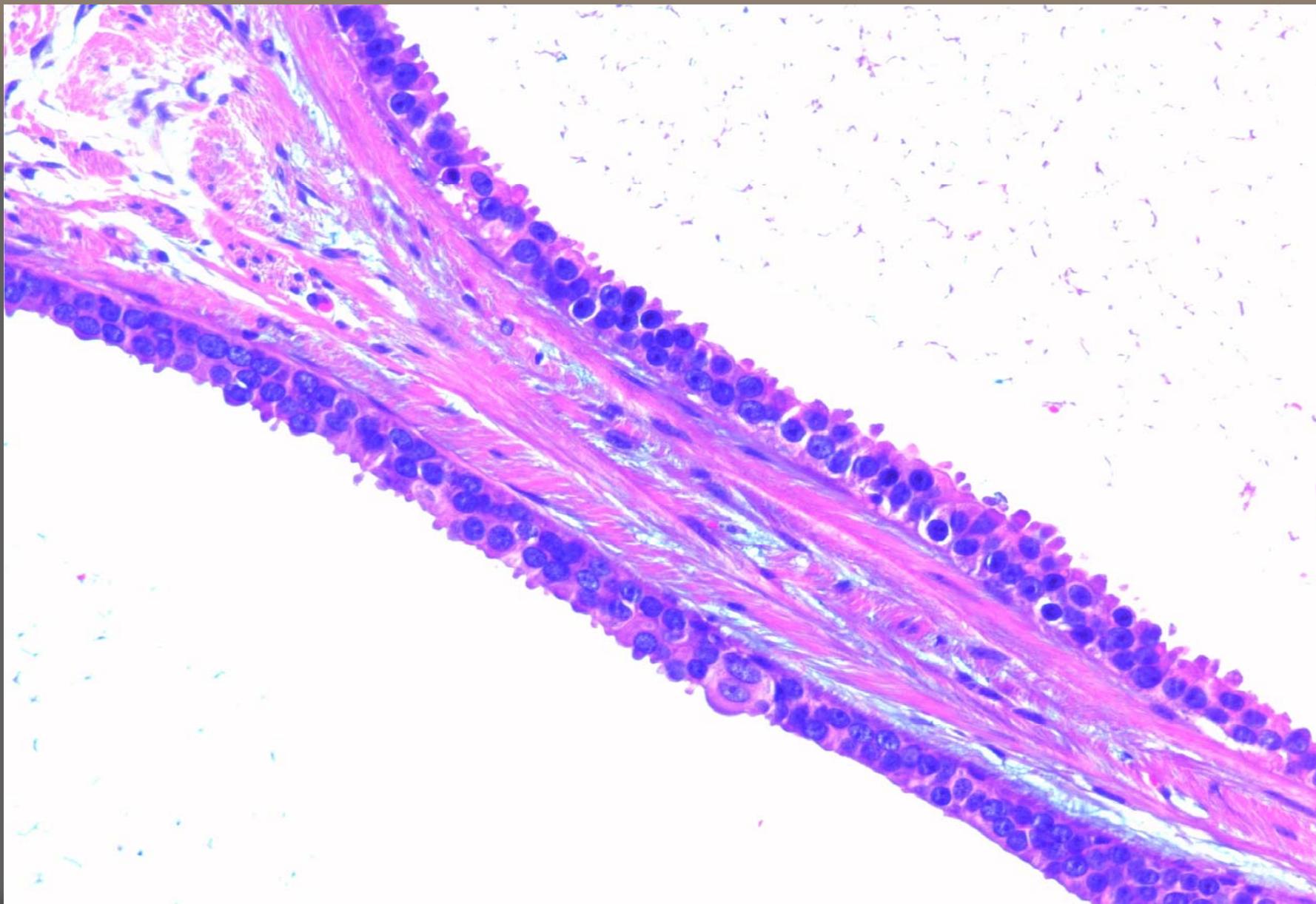


# I. Flat epithelial atypia – FEA (DIN1a) - USstyle

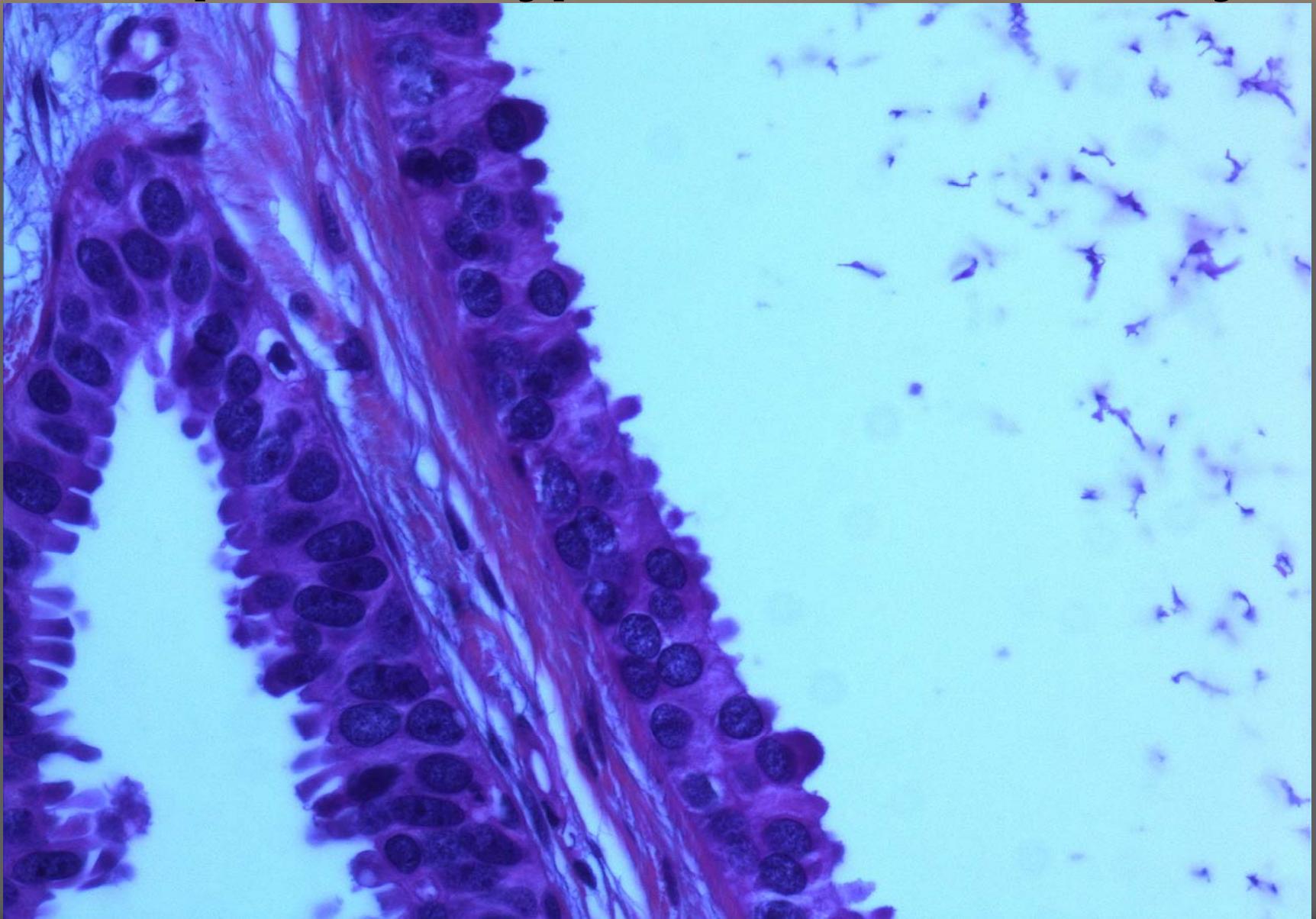


*S. Schnitt. Clinging carcinoma: an American perspective – Semin Diagn Pathol 2010*

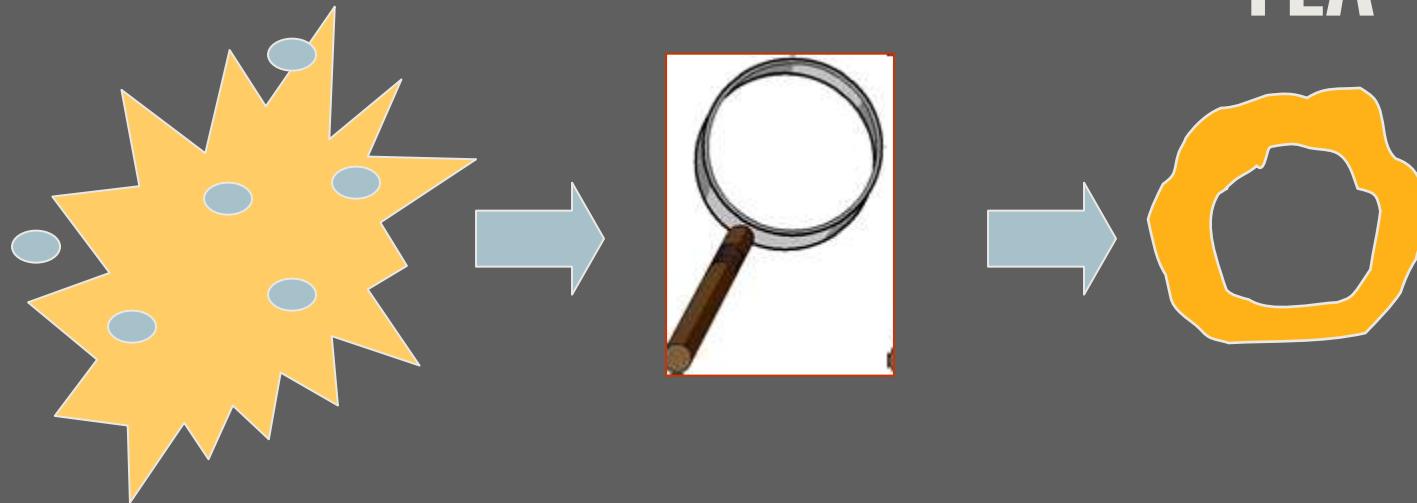
# I. Flat epithelial atypia – FEA (DIN1a) - USstyle



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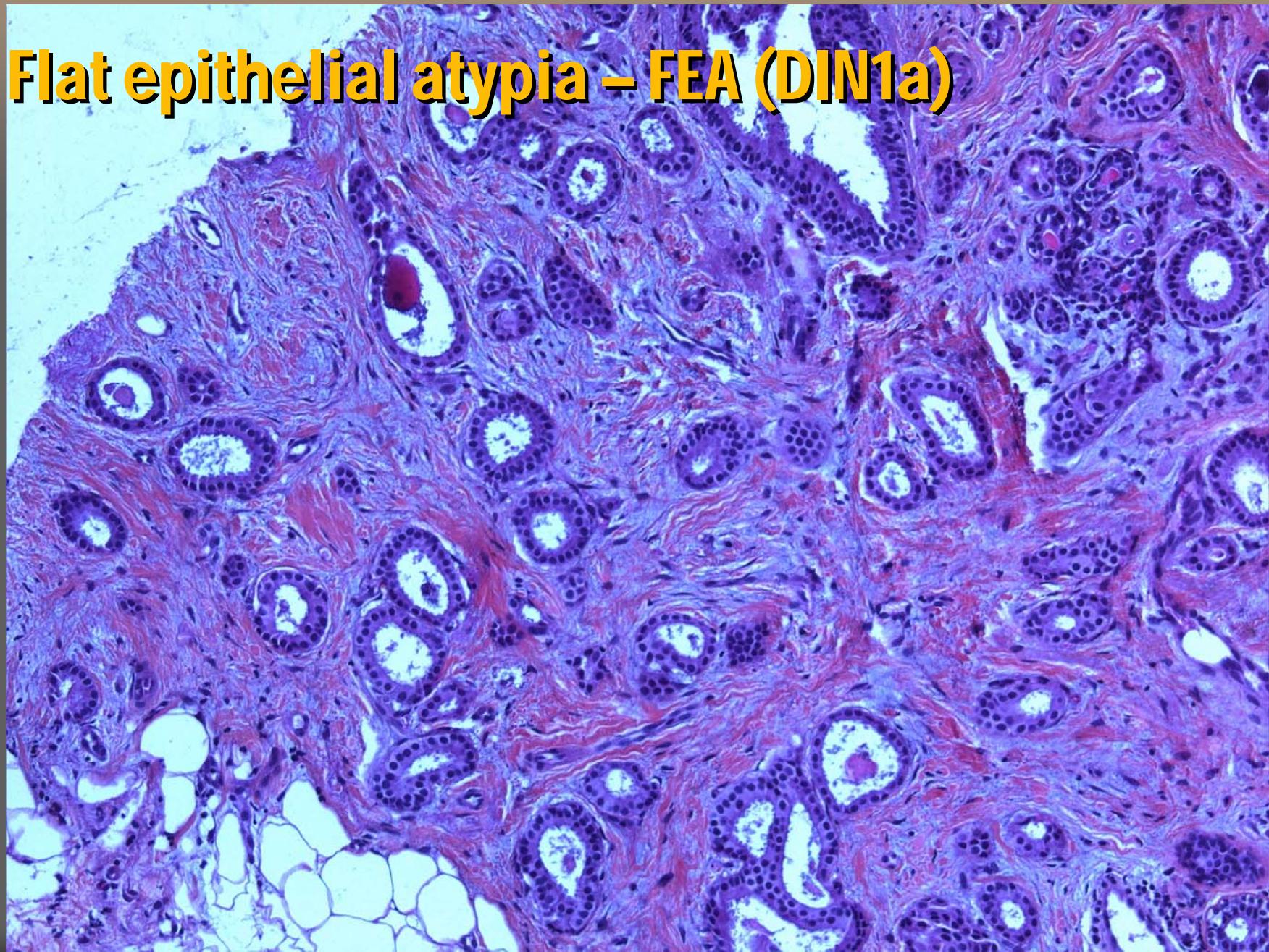


# I. Flat epithelial atypia – FEA (DIN1a)

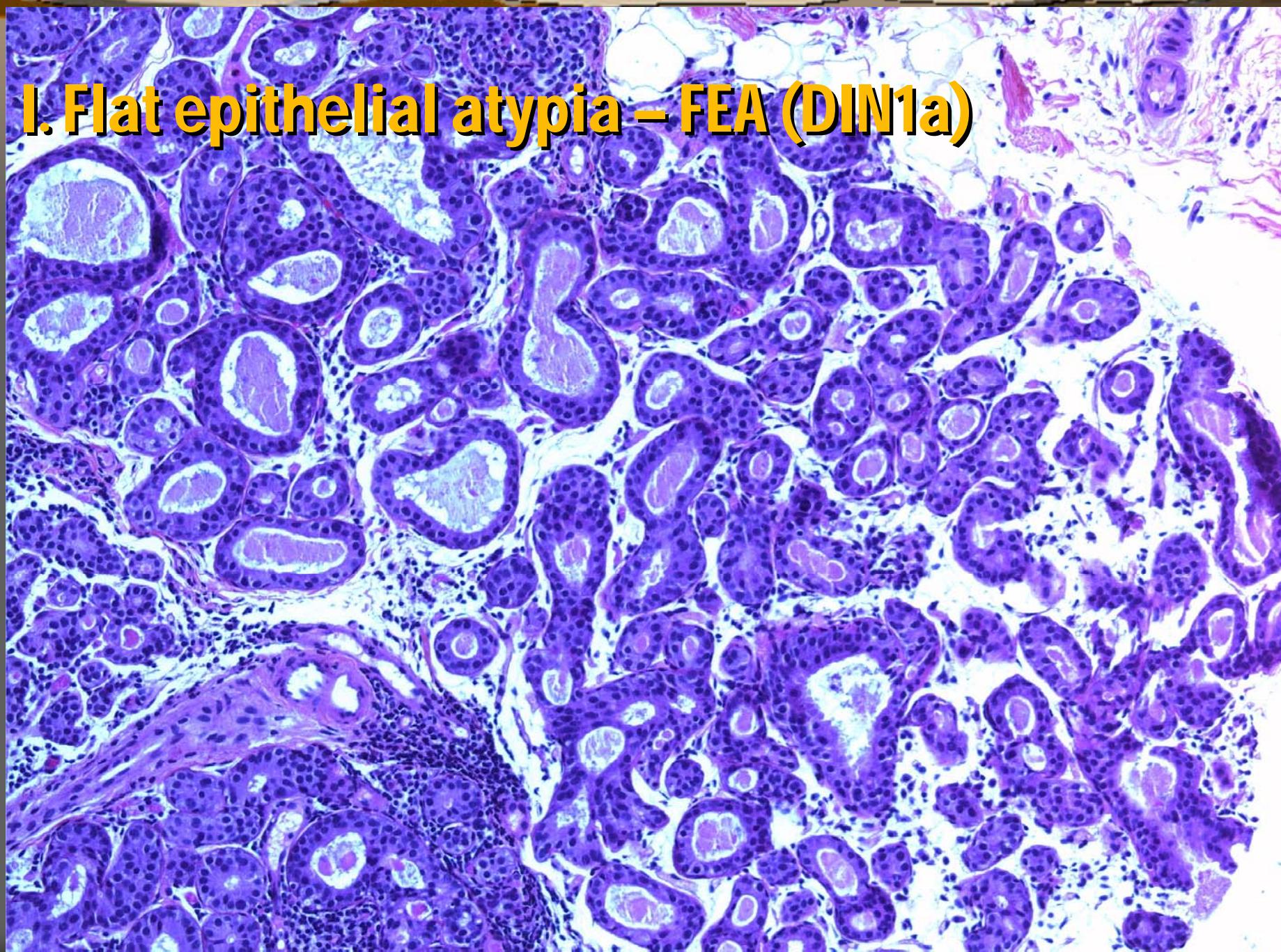


Invasive tubular carcinoma

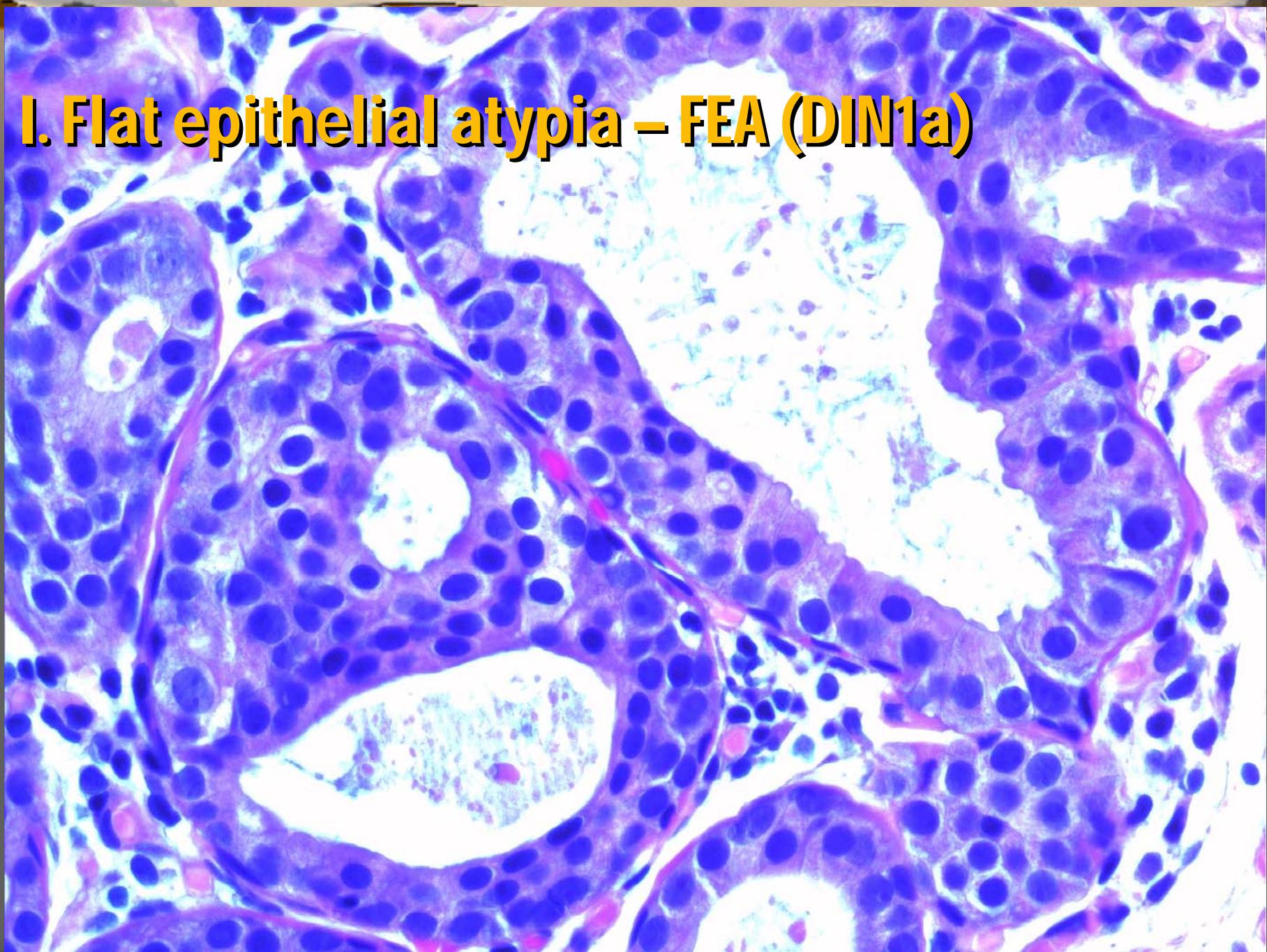
# I. Flat epithelial atypia – FEA (DIN1a)



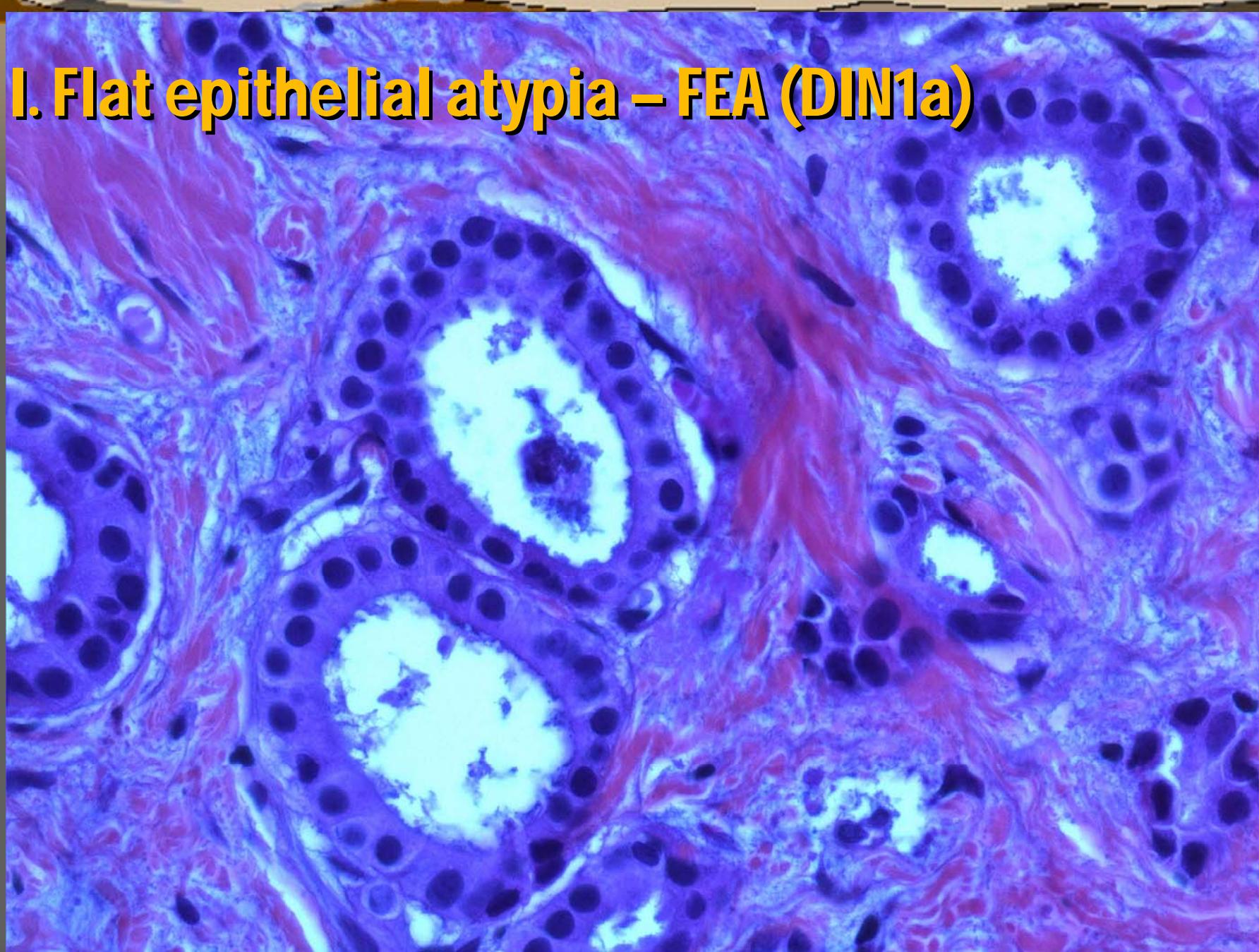
# I. Flat epithelial atypia – FEA (DIN1a)



# I. Flat epithelial atypia – FEA (DIN1a)



# I. Flat epithelial atypia – FEA (DIN1a)



# I. Flat epithelial atypia – FEA (DIN1a)

*CK5 -*

*Nofech S et al. Role of CK5 as a diagnostic tool in NCB. Int J Surg Path 2008*

# I. Flat epithelial atypia – FEA (DIN1a)

ER+++



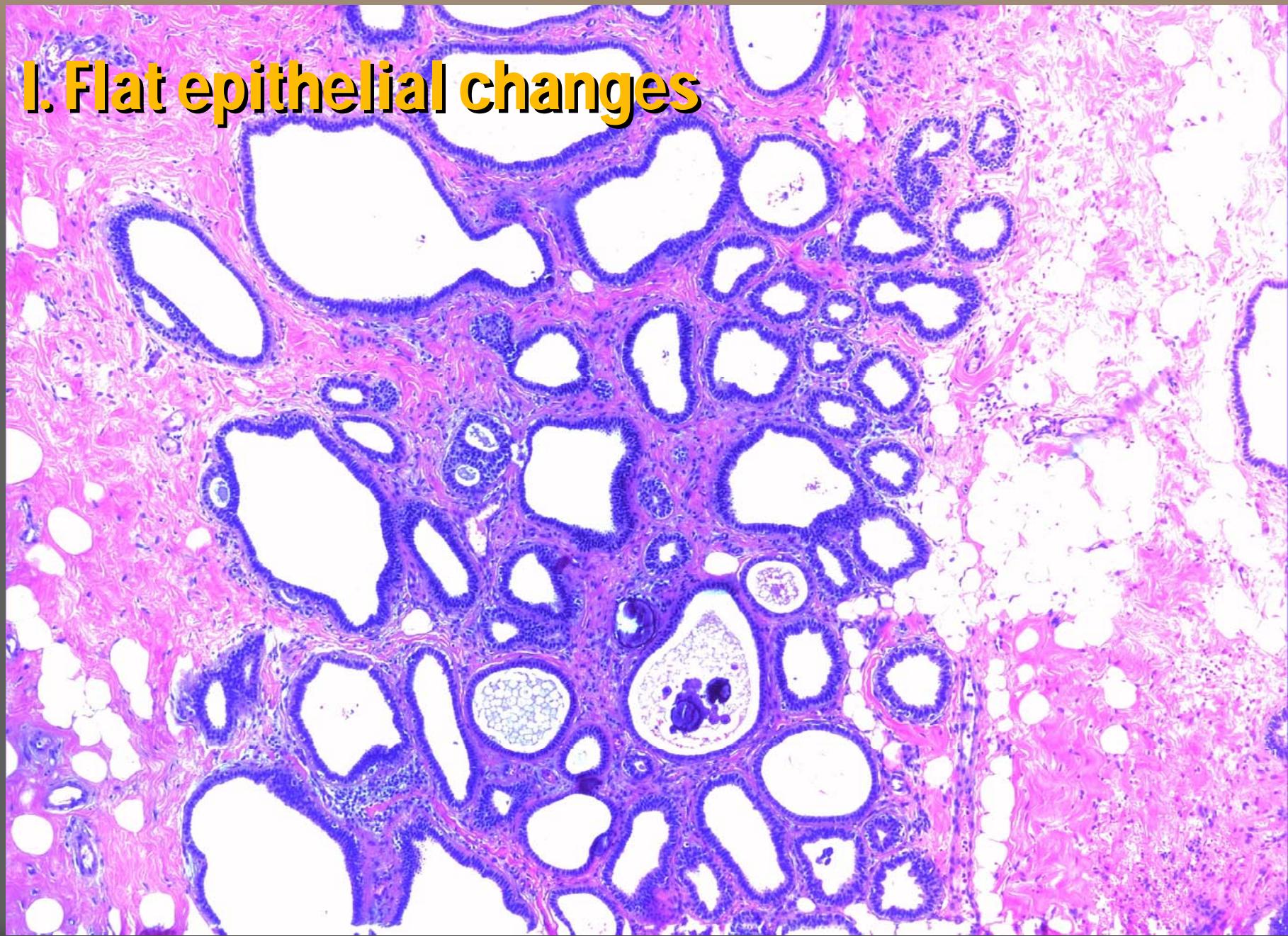
*S. Pinder & I. Ellis. ADH – DCIS definitions. Breast Cancer Res 2003*

# I. Flat epithelial atypia – FEA (DIN1a)

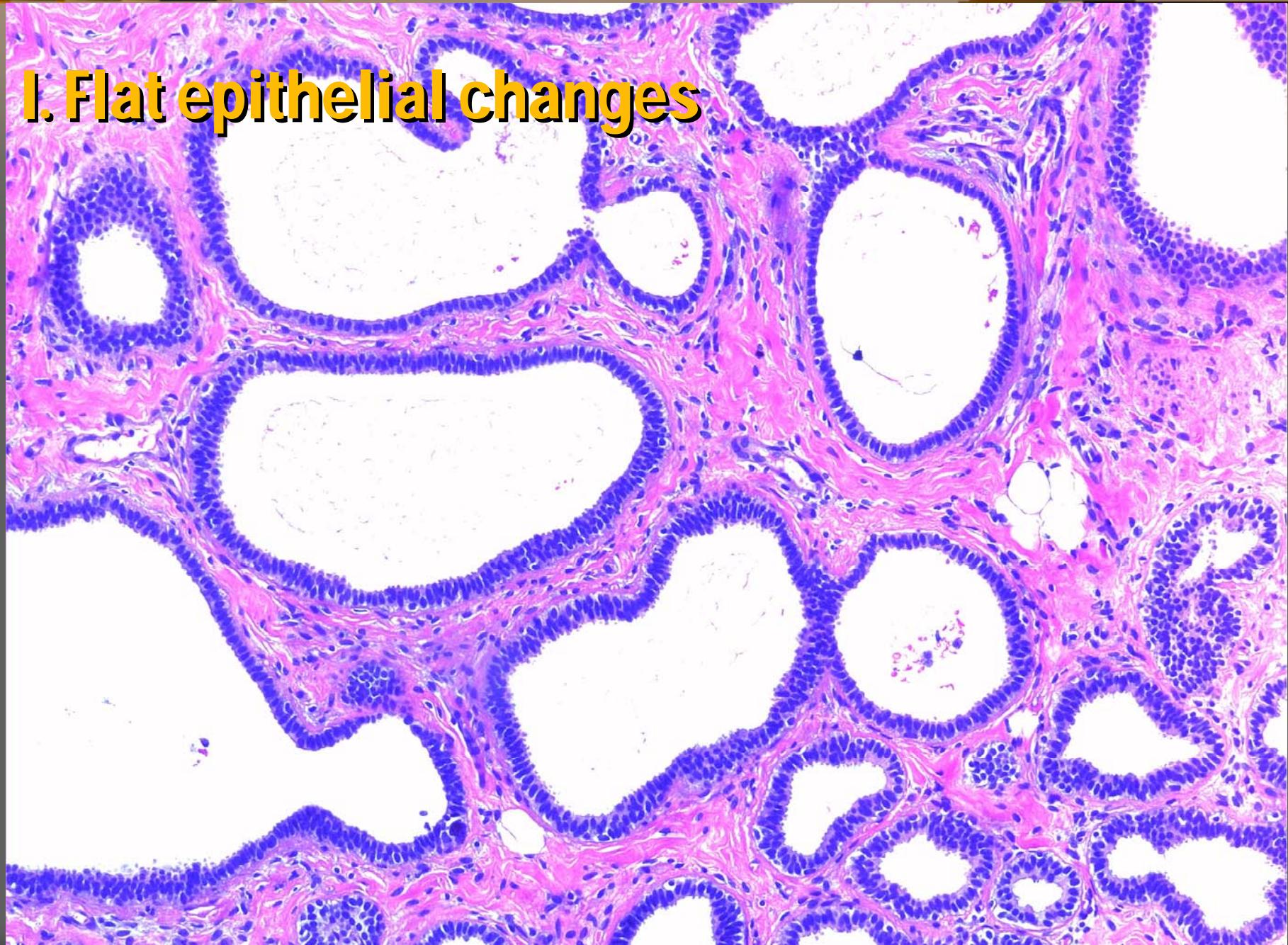
## Differential diagnosis

- Flat epithelial changes
- Blunt duct adenosis
- Métraplasie cylindrique simple
- Cylindrical ductal hyperplasia
- .....

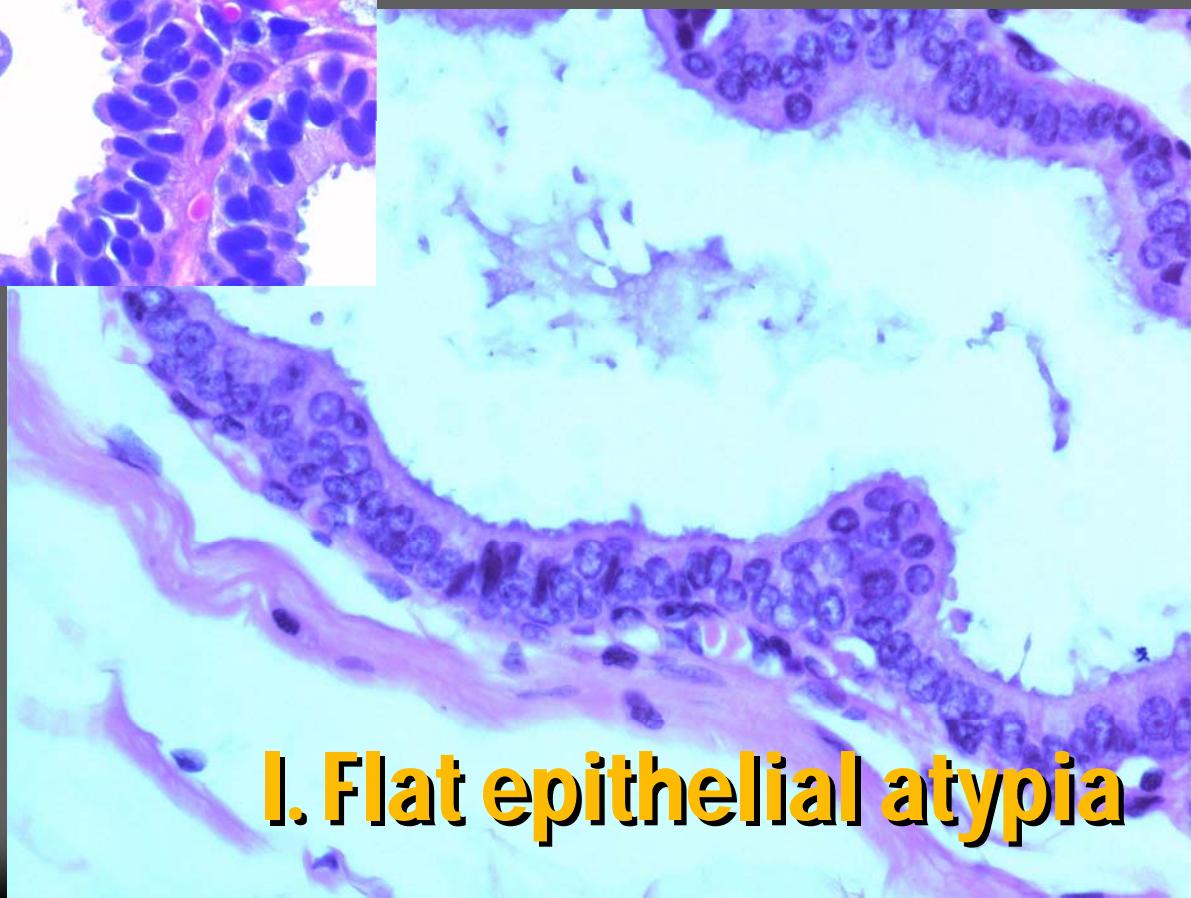
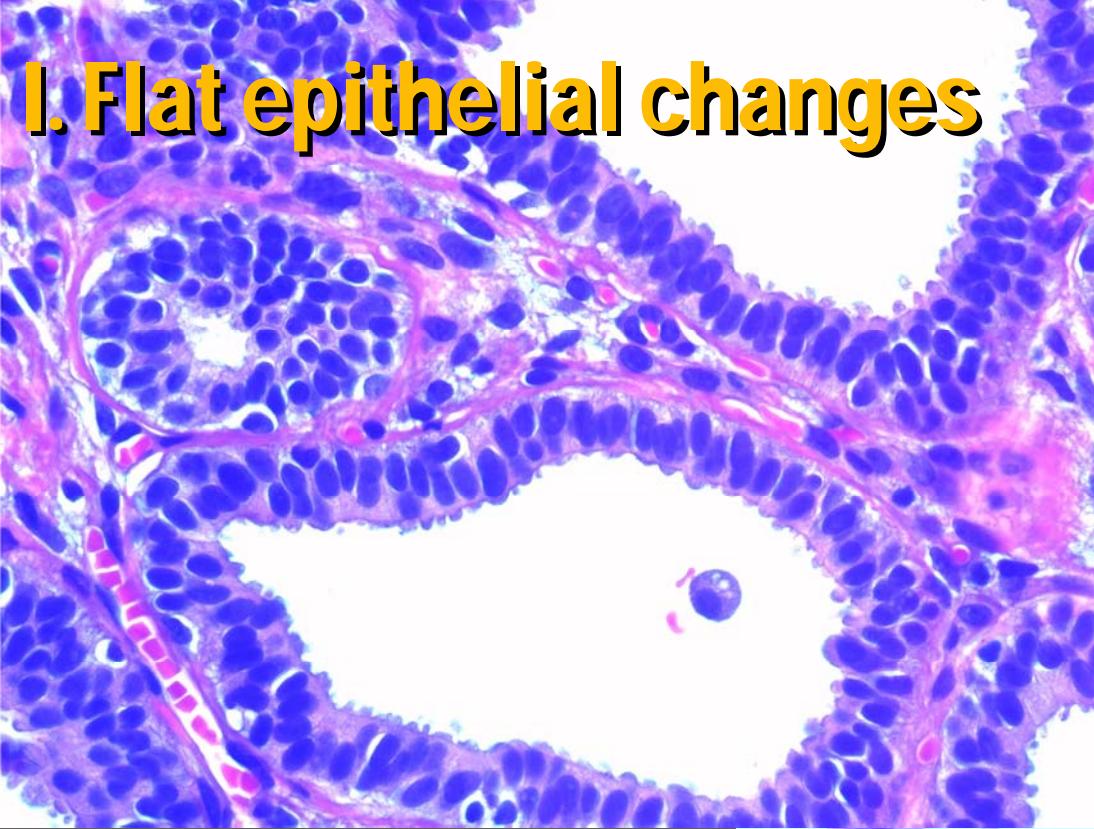
# I. Flat epithelial changes



# I. Flat epithelial changes



# I. Flat epithelial changes



# I. Flat epithelial atypia

# I. Flat epithelial atypia – Why ?

- ⇒ Impact on mammography screening
- ⇒ Fine granular calcifications
- ⇒ Most common subtype in NCB-B3 (35%)...
- ⇒ Association with other *in situ* neoplastic lesions
- ⇒ Increasing incidence of surgical resection
- ⇒ Controversies .....

*Noske A. FEA in B3 breast lesions. Hum Pathol 2010*

## I. Atypical ductal hyperplasia – ADH (DIN1b)

A neoplastic intraductal proliferation of evenly distributed monomorphic cells associated with a moderately elevated risk (RR 4 to 5) for progression to invasive carcinoma



**WHO-blue book 2003**

# I. Atypical ductal hyperplasia – ADH (DIN1b)

Native definition (Page): based on exclusion criteria. Some but not all features of DCIS ....



*Page DL et al. Atypical hyperplastic lesion of the female breast. Cancer 1985*

# I. Atypical ductal hyperplasia – ADH (DIN1b)

Updated definition (Page): cellular changes of DCIS are present but occupy fewer than 2 separate duct spaces... or DCIS less than 2 mm being classified as ADH .....



*Page DL et al. Criteria for the diagnosis of mammary atypical hyperplasia. Hum Pathol 1992*

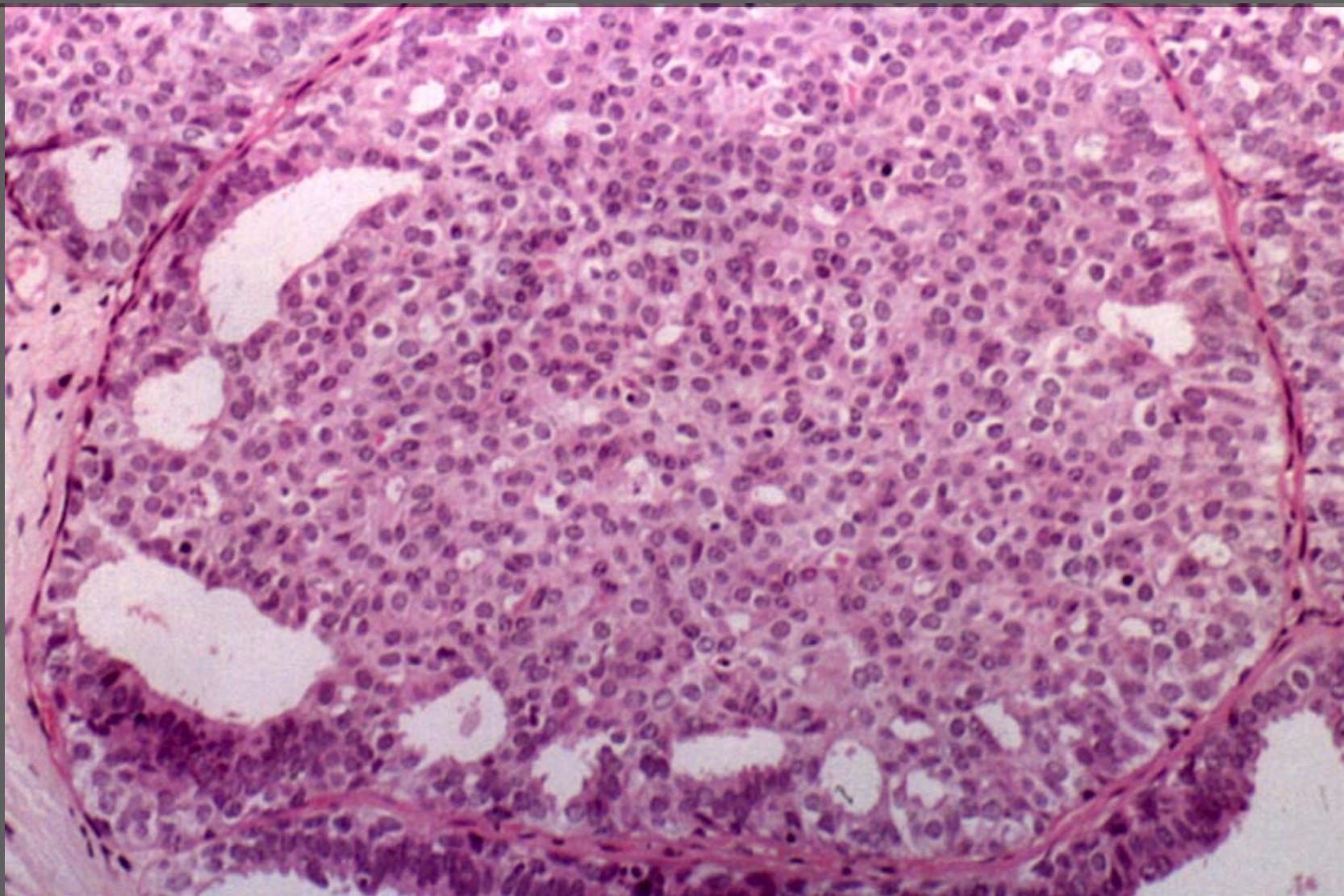
# I. Atypical ductal hyperplasia – Facts

- ⇒ Rare in symptomatic benign biopsies (4%)
- ⇒ But till 33% of NCB in screen-detected microcalcifications
- ⇒ RR higher in premenopausal women (6x)
- ⇒ RR cumulative if first-degree relative with breast cancer (10x)
- ⇒ Worse kappa score in EQA programme (0.2-0.3)
- ⇒ Controversies .....

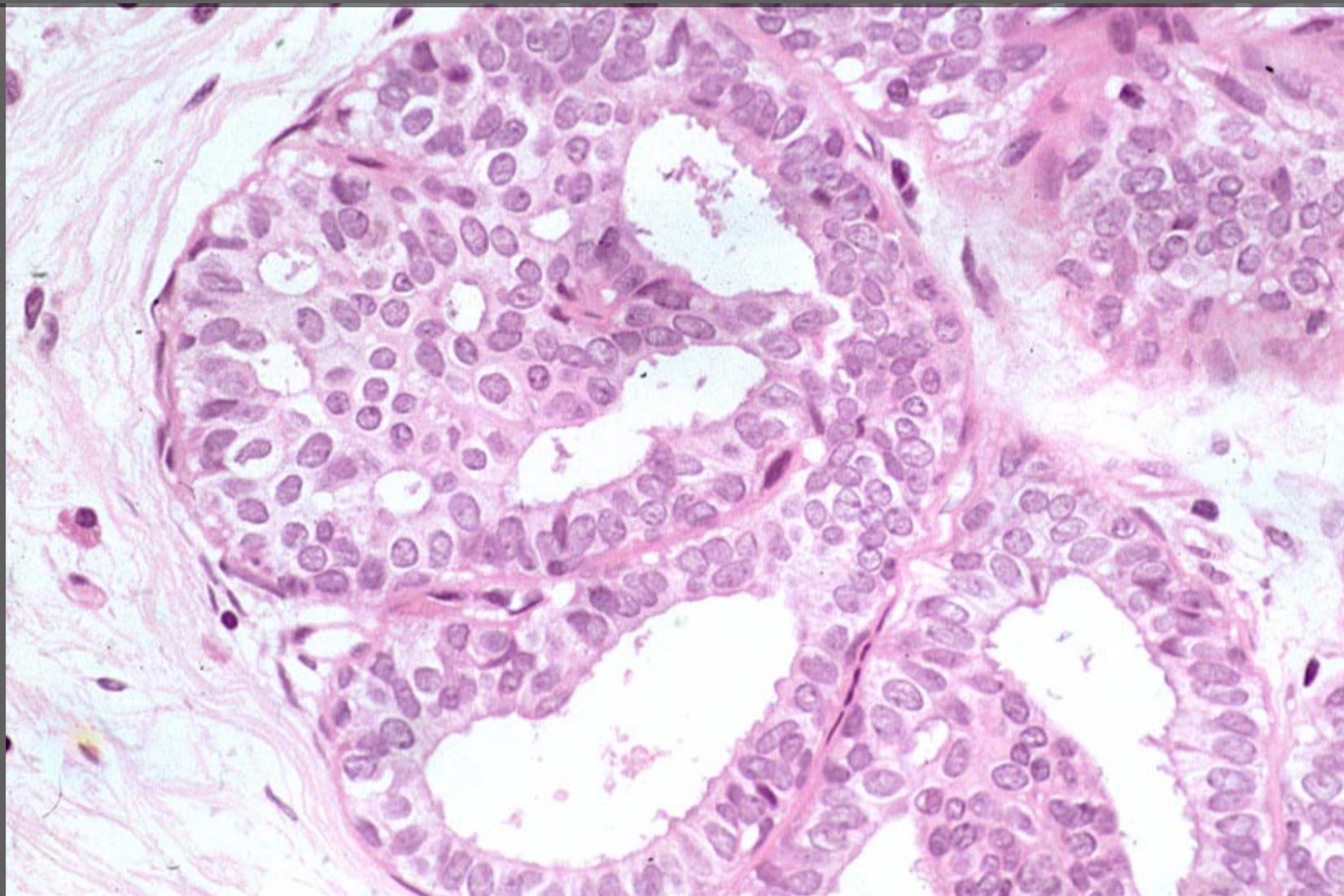
*S. Pinder & I. Ellis. ADH – DCIS definitions. Breast Cancer Res 2003*

*J. Sloane (ECWGBSP). Consistency achieved by 23 european pathologists in diagnosing breast disease. Virchows Archiv 1999*

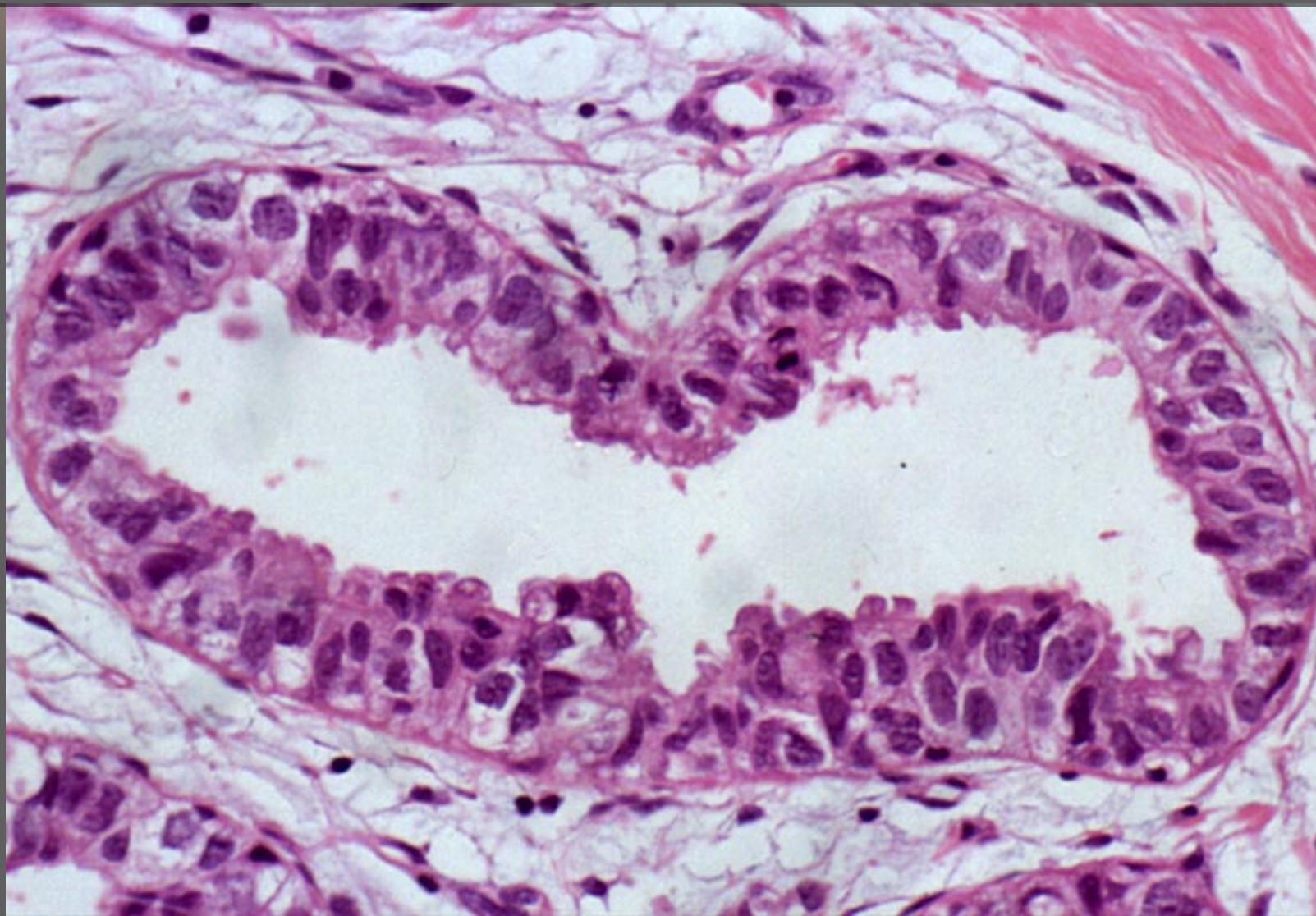
# I. Atypical ductal hyperplasia - ECWGBSP



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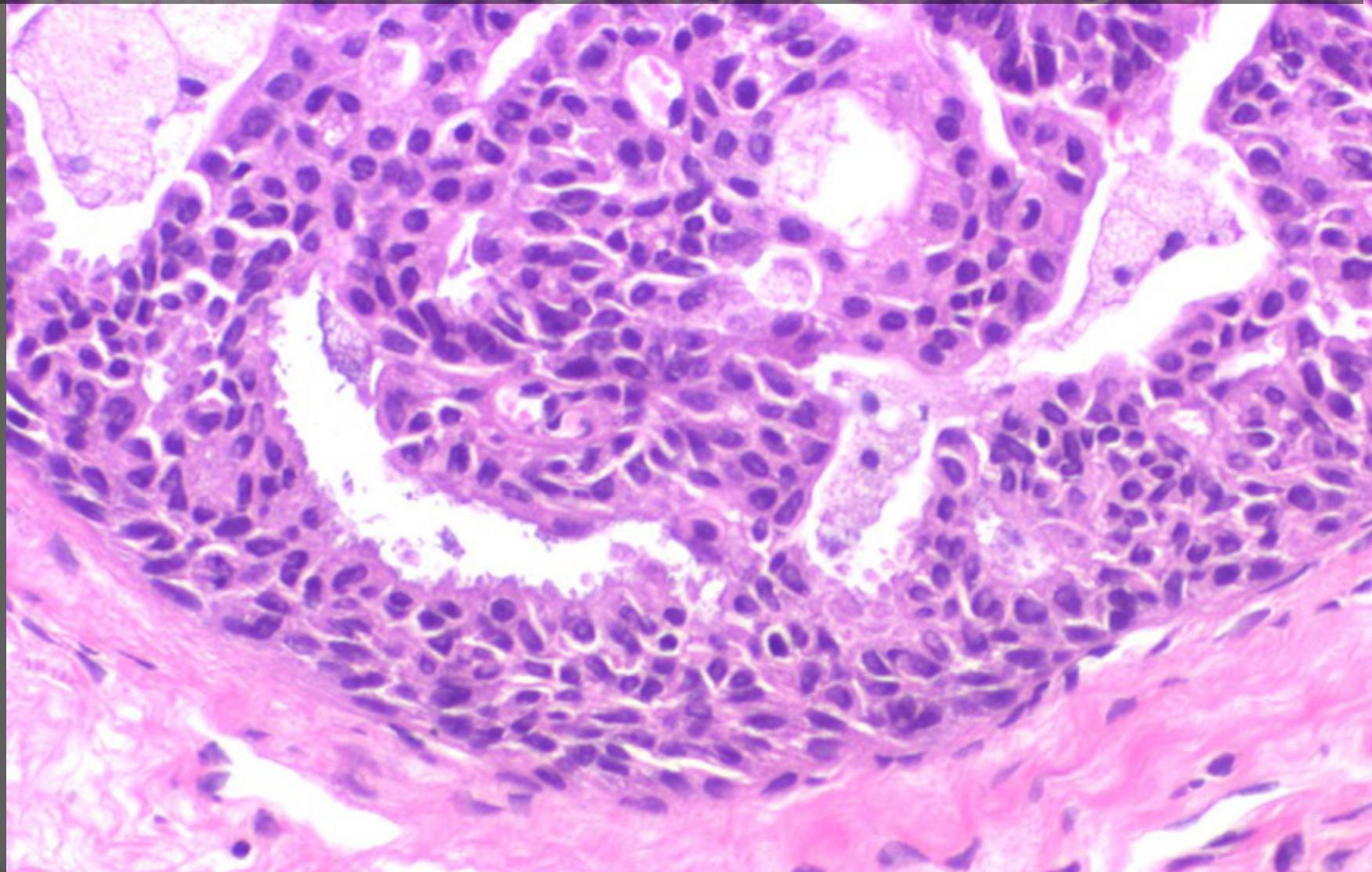


# I. Atypical ductal hyperplasia- (DIN1b)

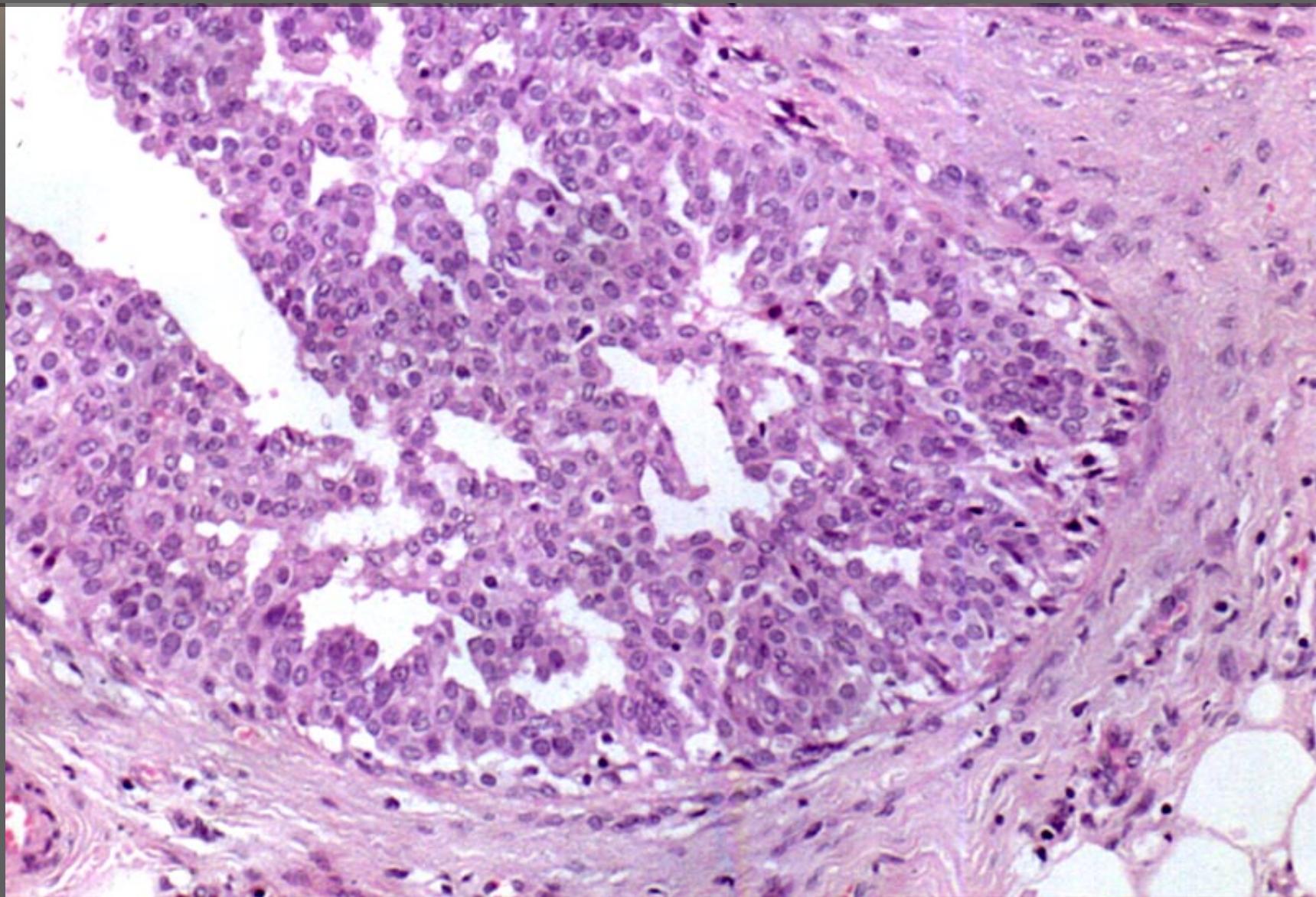
## Differential diagnosis

- Usual type ductal hyperplasia
- Florid « papillary » hyperplasia
- FEA !
- .....

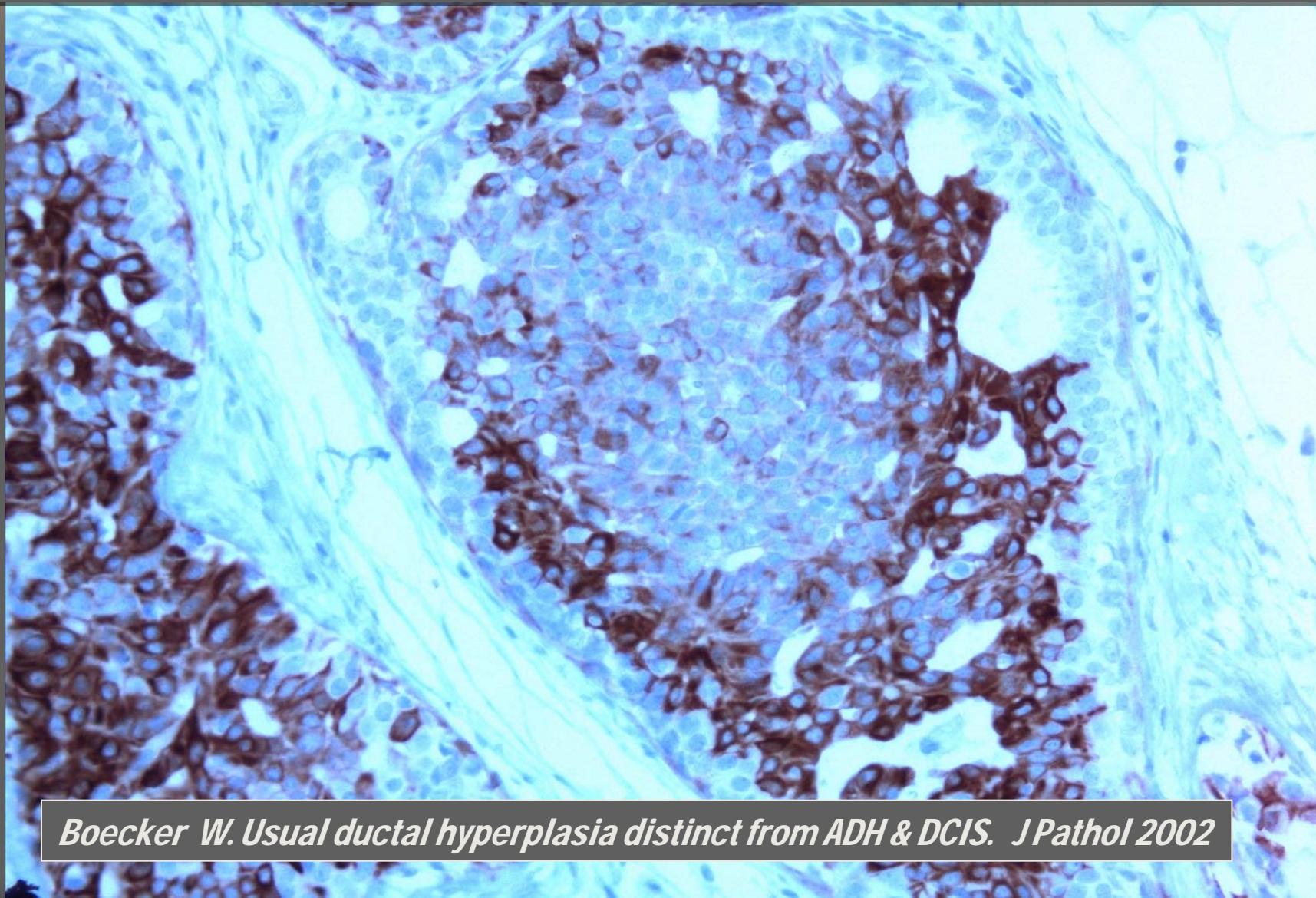
# I. Usual type ductal hyperplasia



# I. Usual type ductal hyperplasia



# I. Usual type ductal hyperplasia



*Boecker W. Usual ductal hyperplasia distinct from ADH & DCIS. J Pathol 2002*

# I. Lobular in situ neoplasia – LIN

Atypical lobular hyperplasia - ALH (LIN1) and lobular carcinoma in situ – LCIS (LIN2) under the same umbrella.

**WHO-blue book 2003**

# I. Lobular in situ neoplasia LIN – Facts

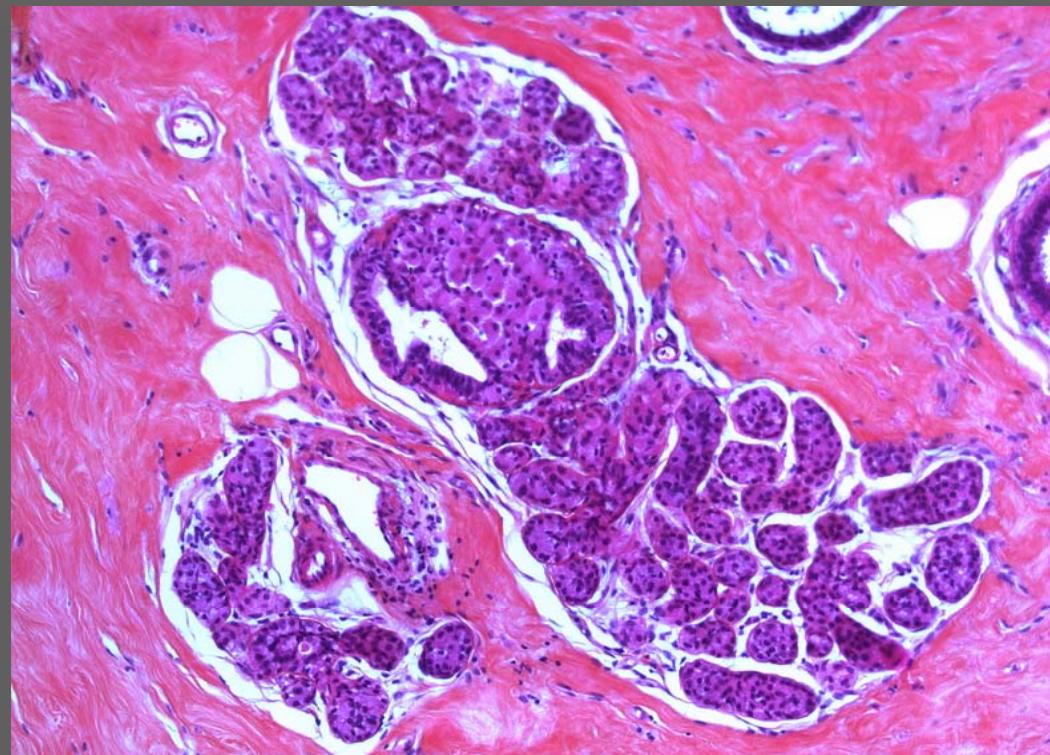
- ⇒ Most frequently diagnosed between 40-50 years
- ⇒ Asymptomatic, usually incidental finding in NCB or surgery
- ⇒ Incidence in benign breast biopsies from 0.5 to 3.8%
- ⇒ RR LIN1 4 to 5x & 8 to 10x for LIN2
- ⇒ Absolute risk of IC at 15 years 15% for LCIS

*P. Simpson et al. Pathology of ALH & LCIS. Breast Cancer Res 2003*

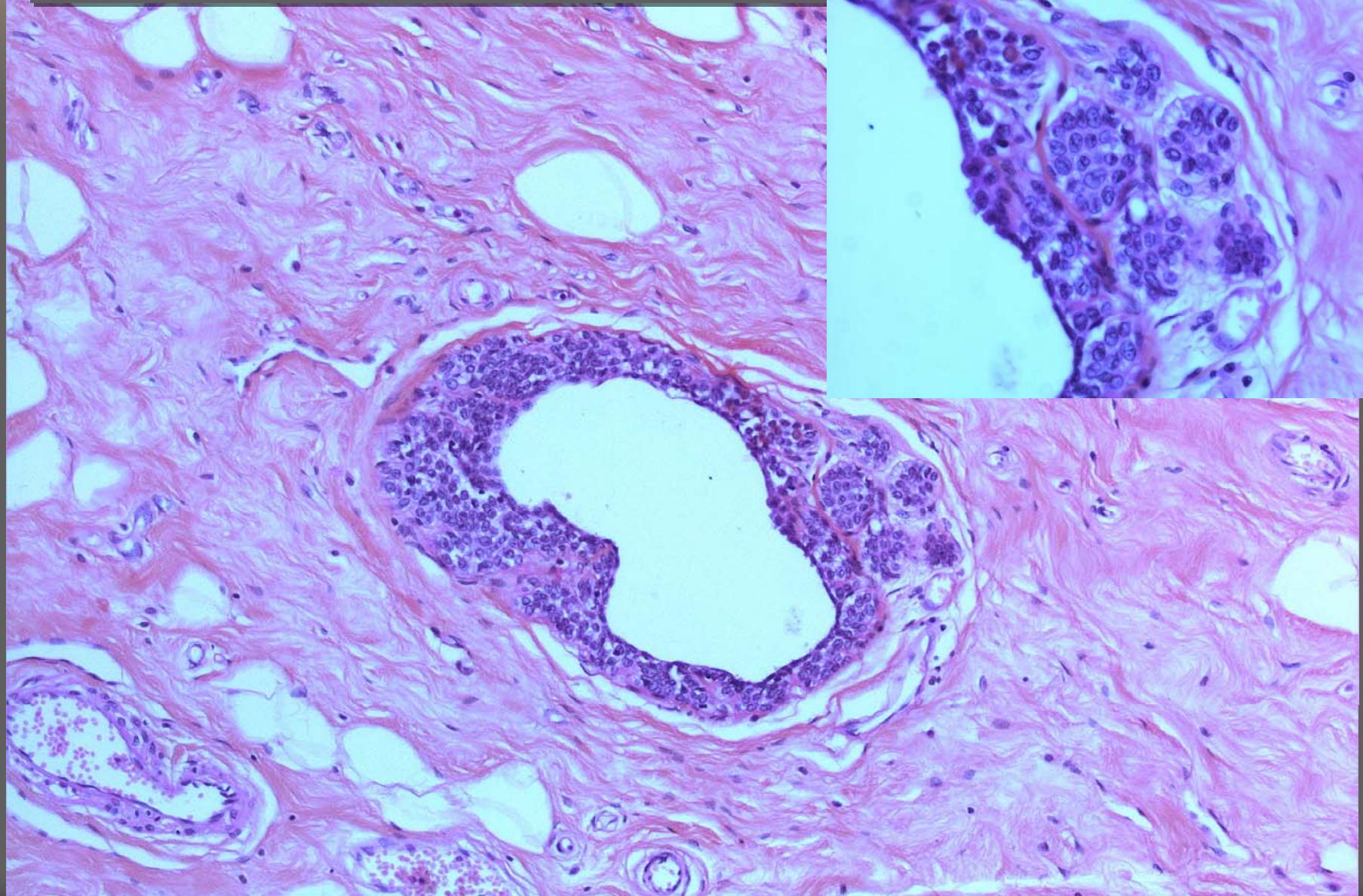
*F. O'Malley. Lobular neoplasia. Mod Path 2010*

# I. Lobular in situ neoplasia – ALH- LIN 1

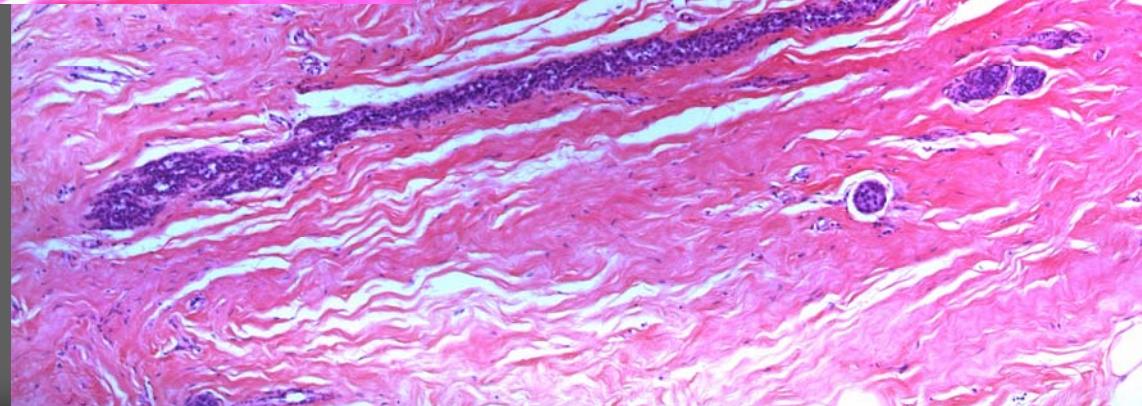
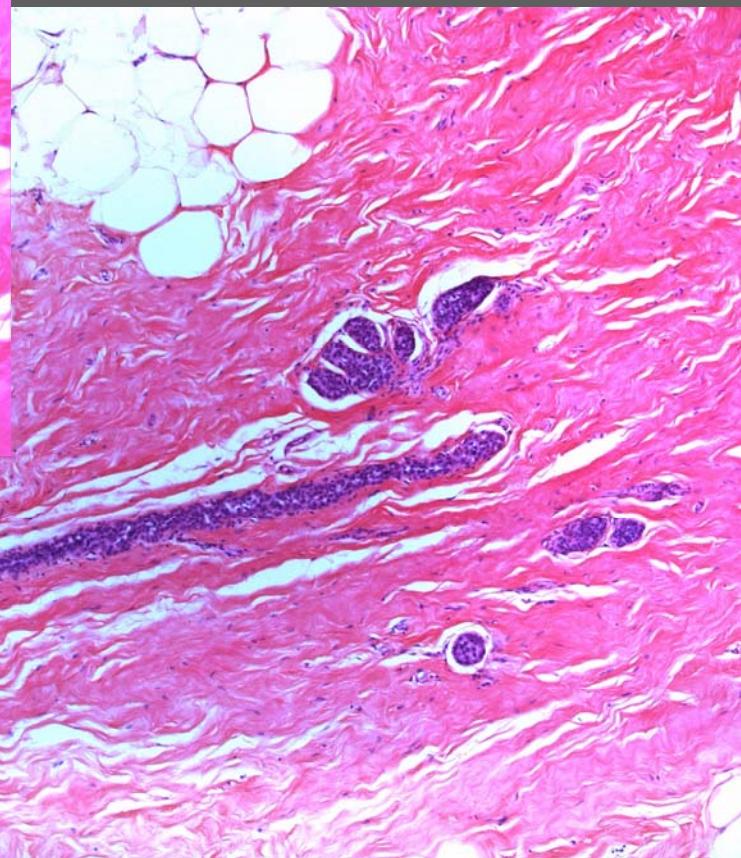
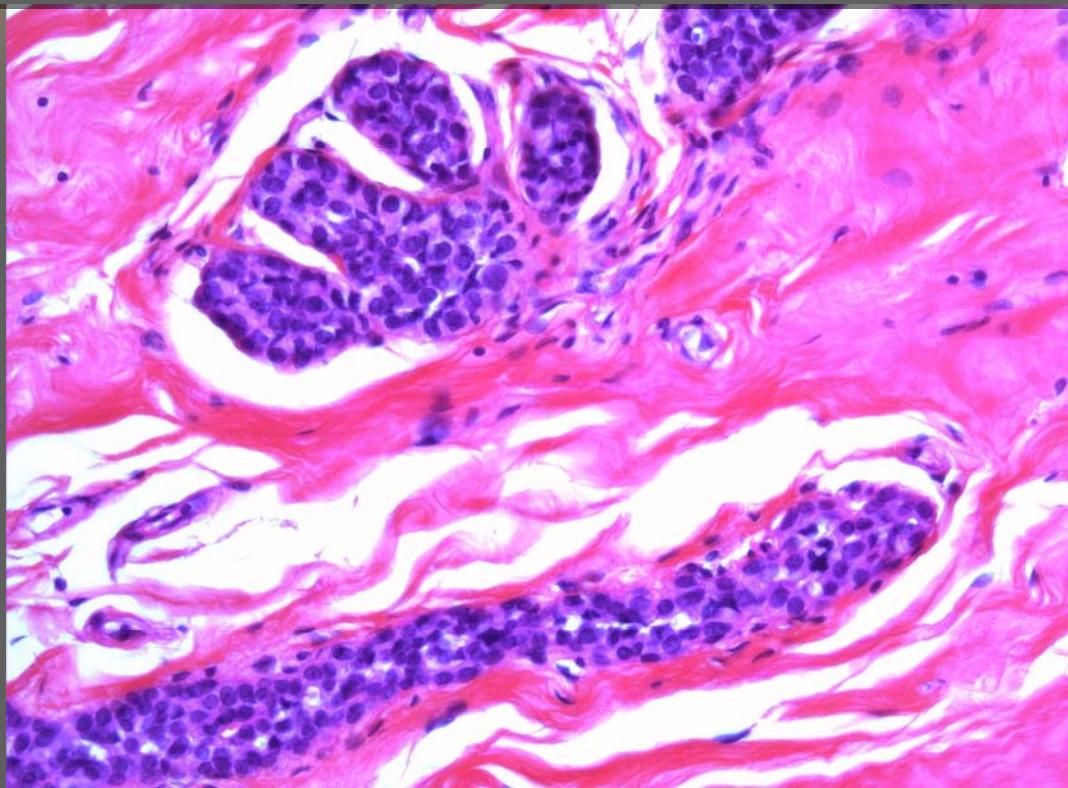
- ⇒ Less than one half of a lobular unit involved
- ⇒ No enlargement of lobule
- ⇒ Remaining lumen
- ⇒ Criteria for DD between LINI & II somewhat arbitrary



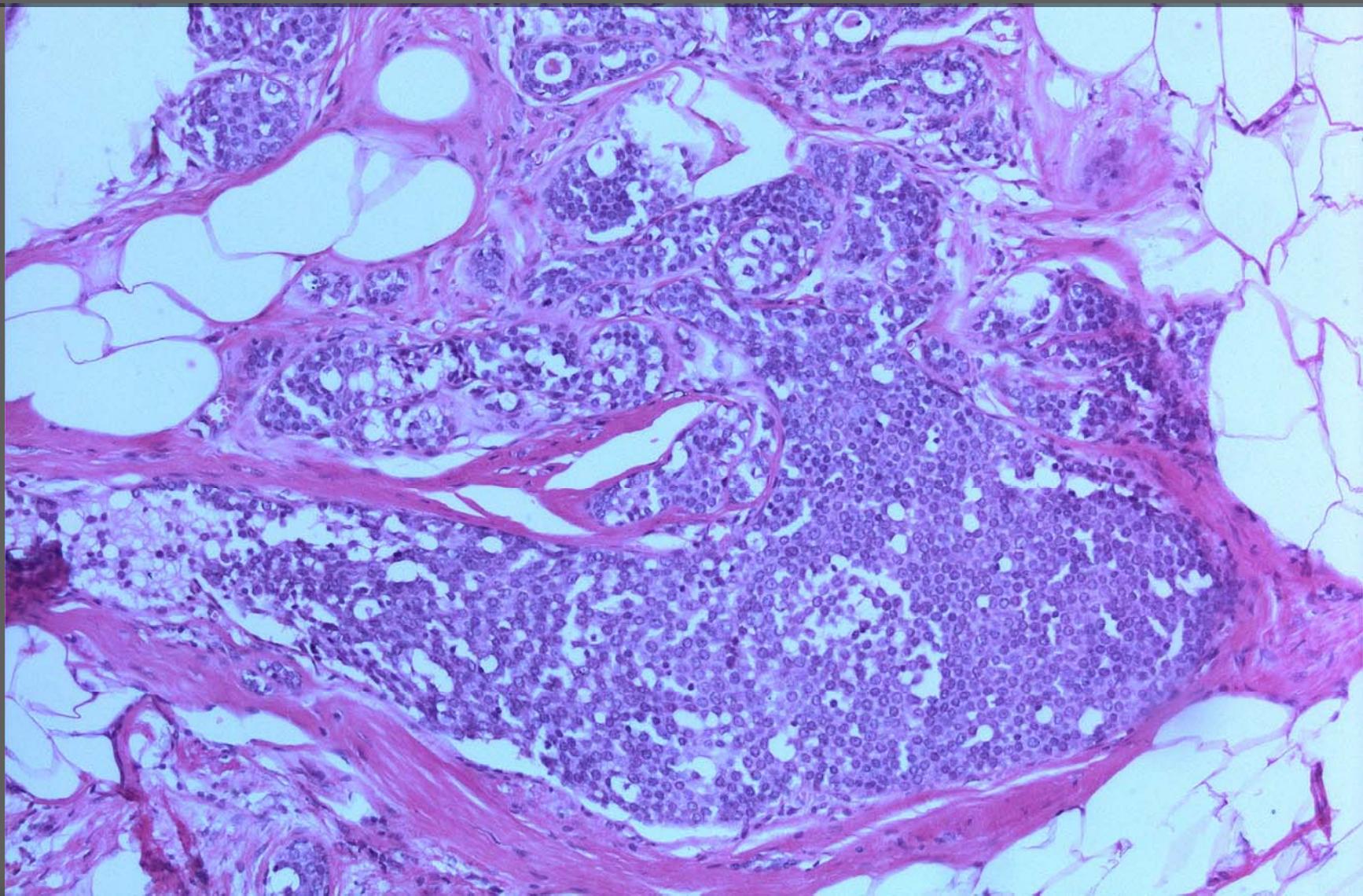
# I. Lobular in situ neoplasia – ALH- LIN 1



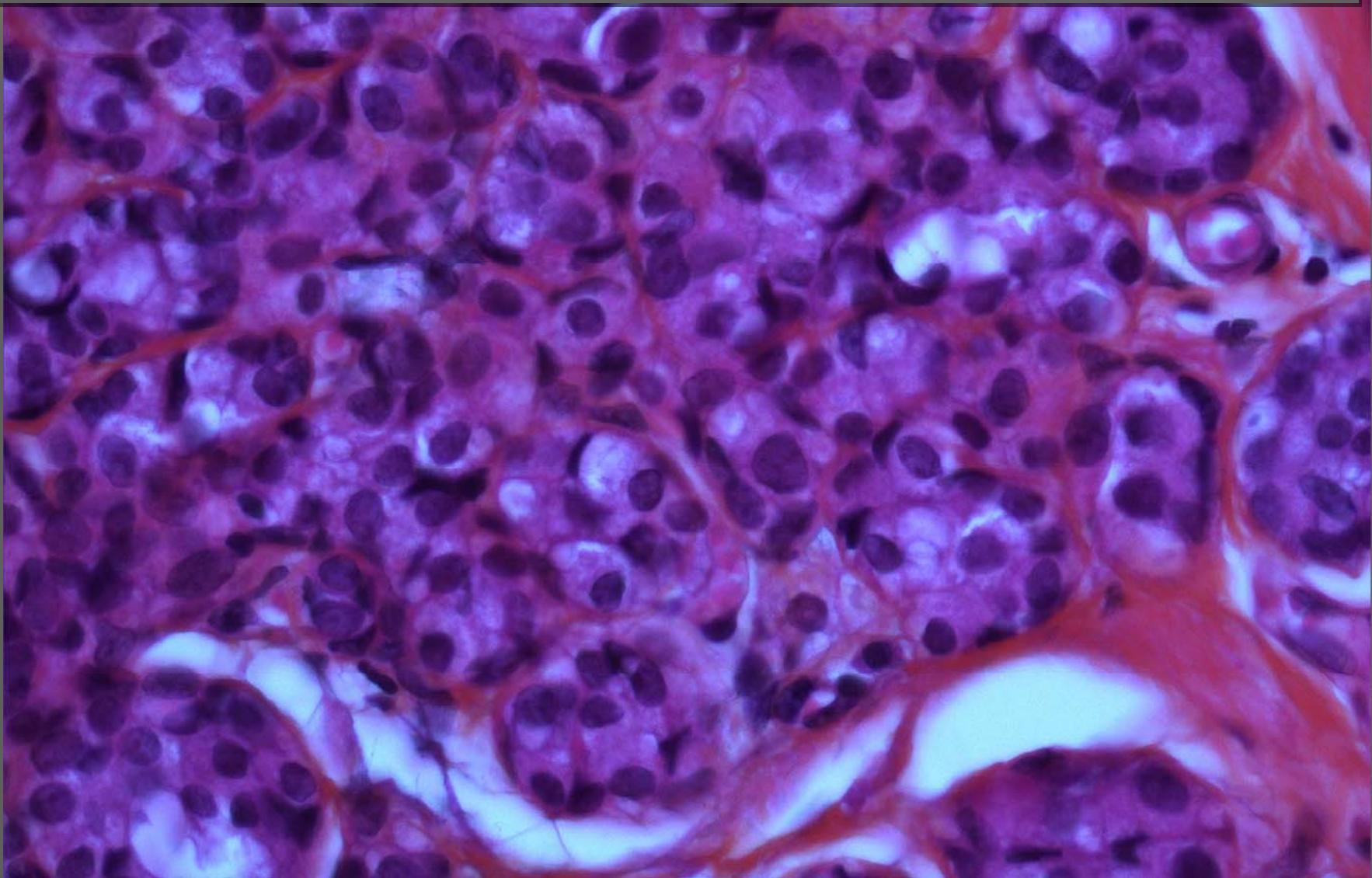
# I. Lobular in situ neoplasia – ALH- LIN 1



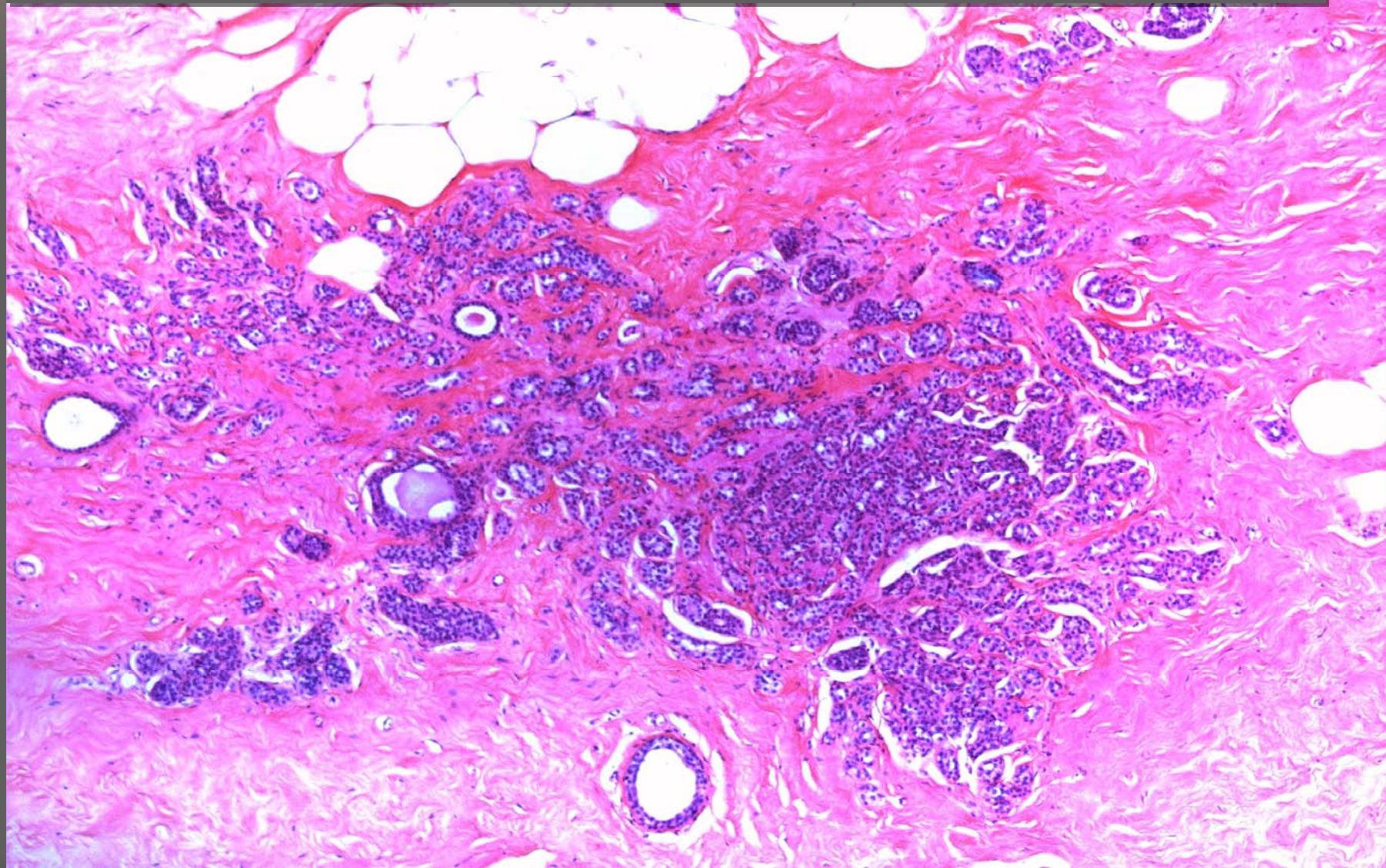
# I. Lobular in situ neoplasia – LCIS- LIN 2



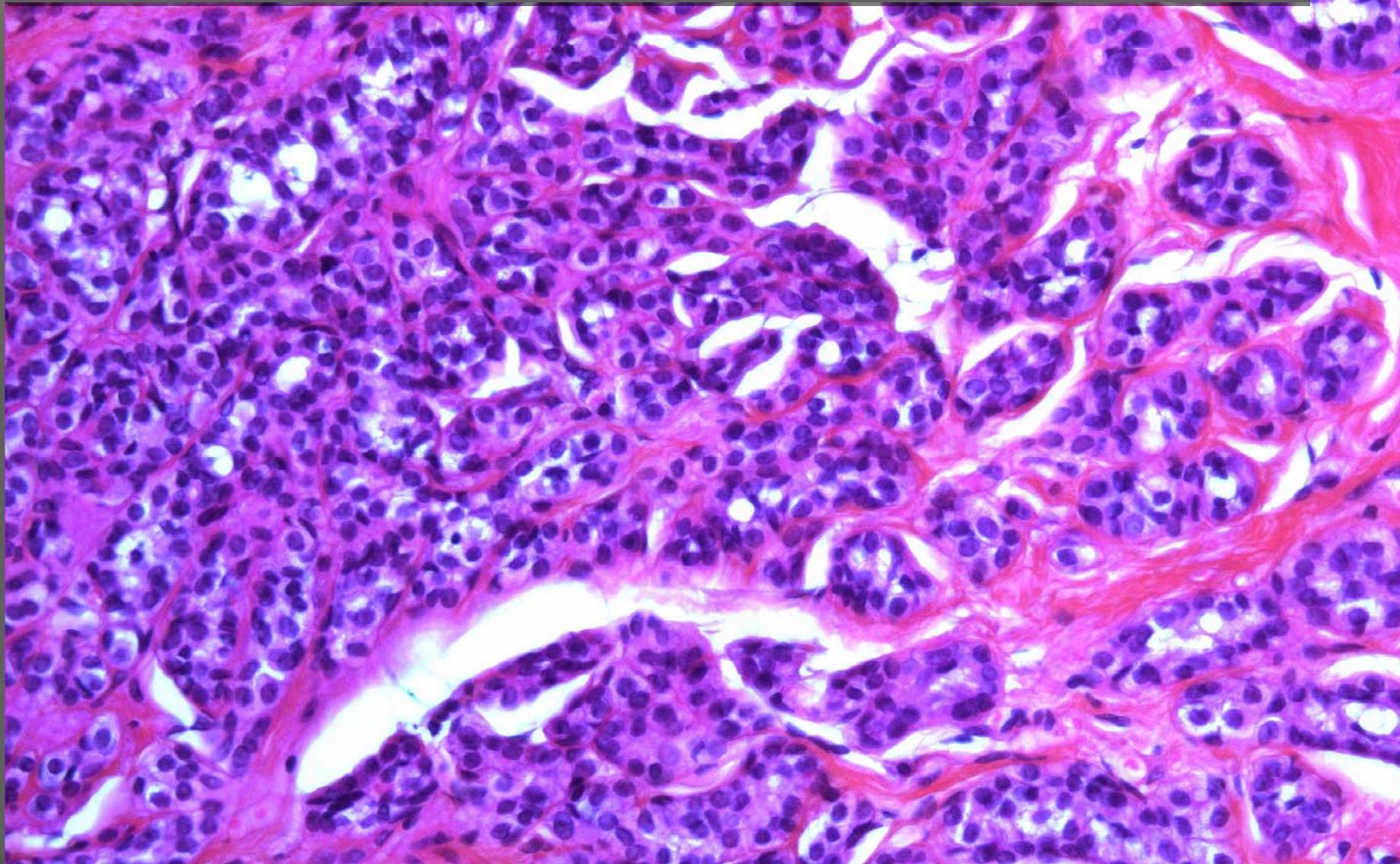
# I. Lobular in situ neoplasia – LCIS- LIN 2



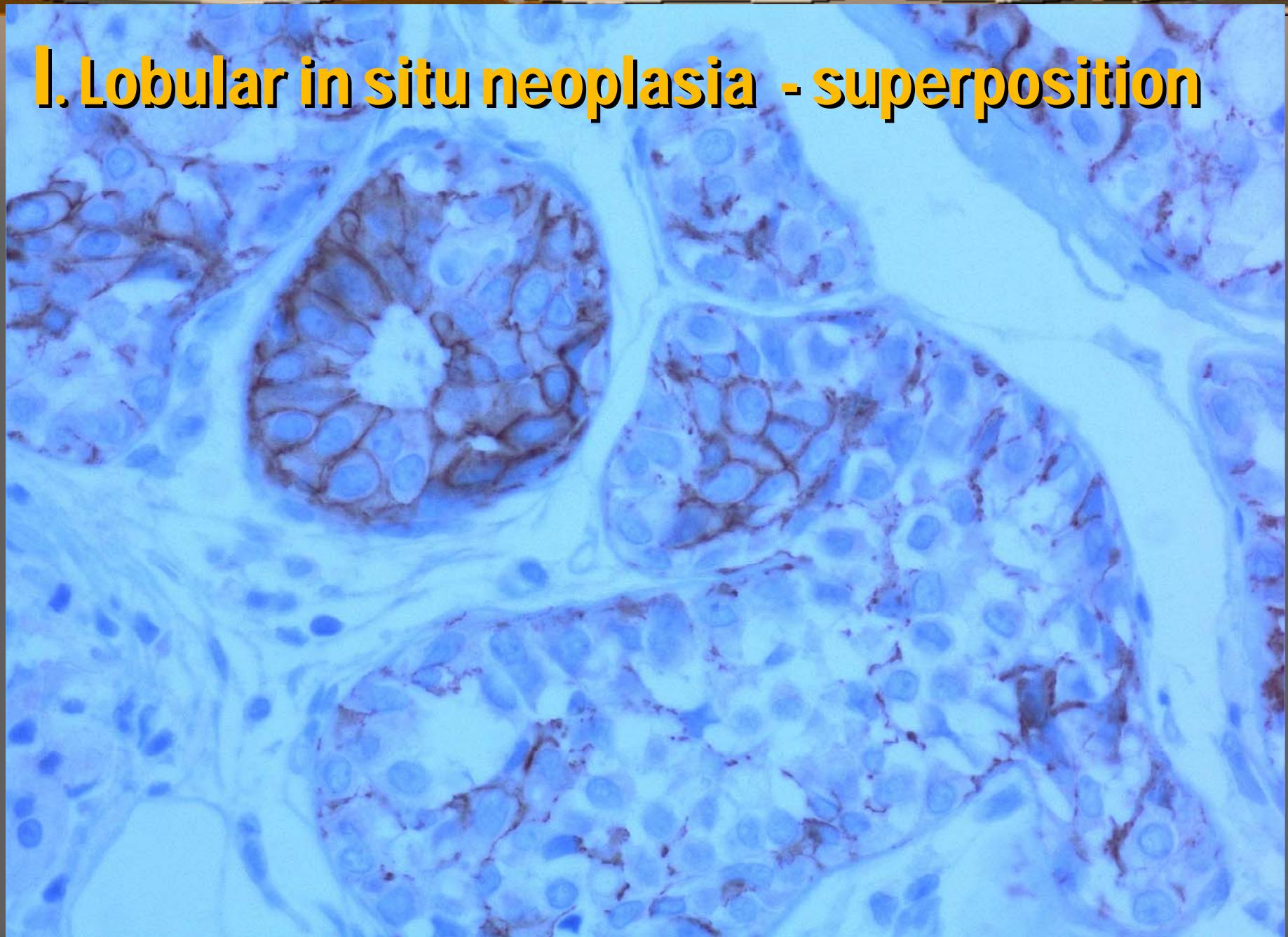
# I. Lobular in situ neoplasia - superposition



# I. Lobular *in situ* neoplasia - superposition



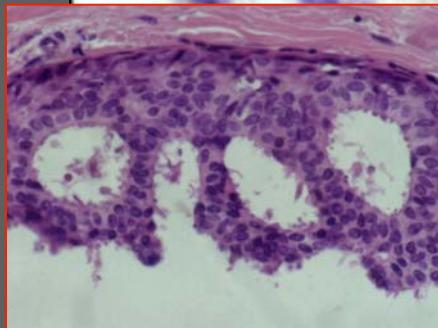
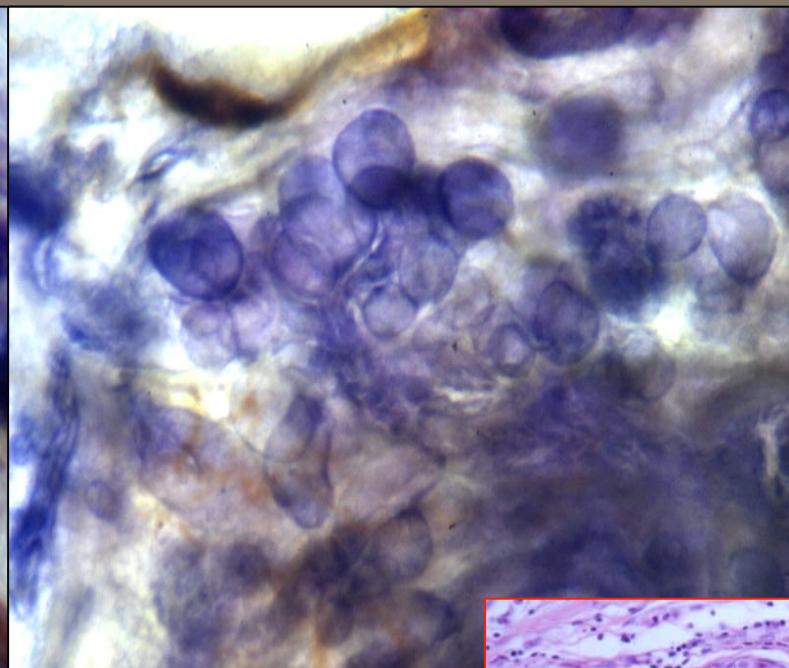
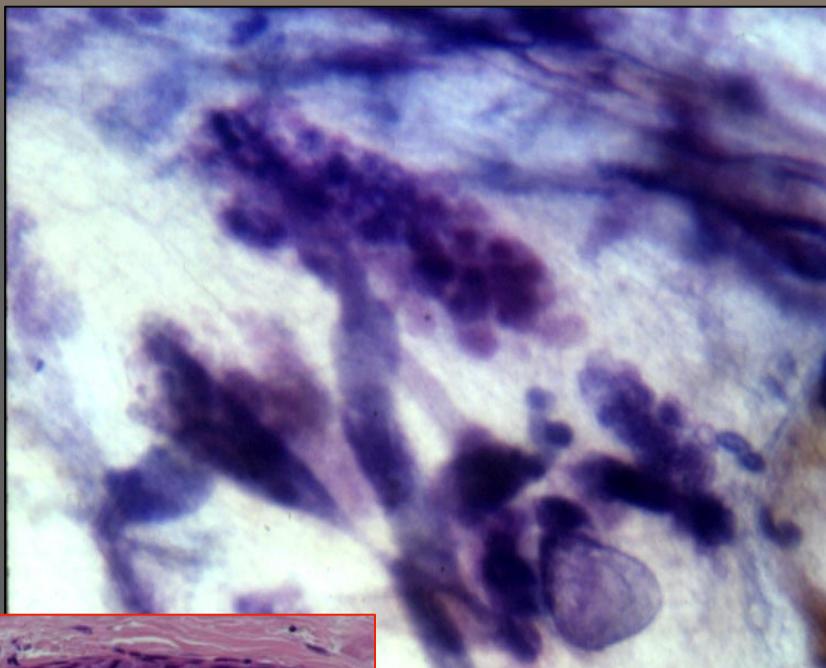
# I. Lobular *in situ* neoplasia - superposition



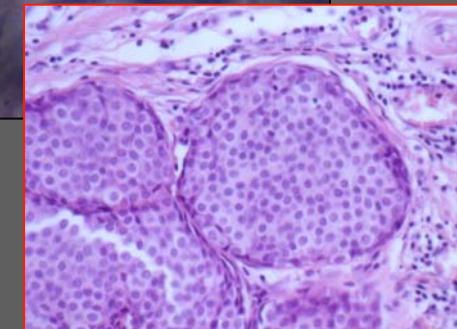
## **II. ISN of the Breast : models and hypothesis**

- ⇒ Distribution and growth pattern
- ⇒ The LIN model
- ⇒ The DIN model
- ⇒ The multifocal model
- ⇒ The single hit model
- ⇒ A wide spectrum of possibilities

## II. ISN of the Breast : models and hypothesis

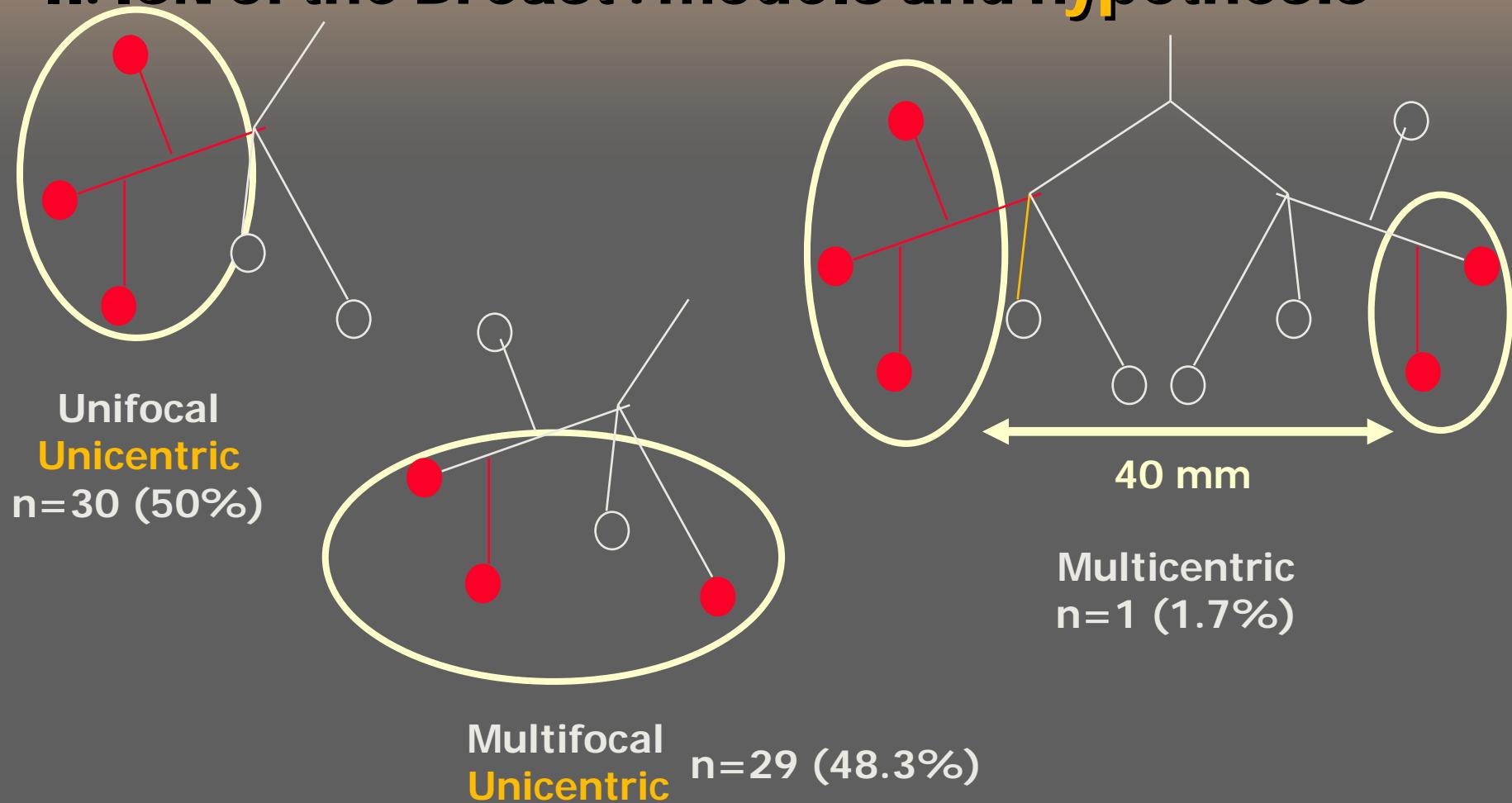


*TDLU: terminal duct-lobular unit*



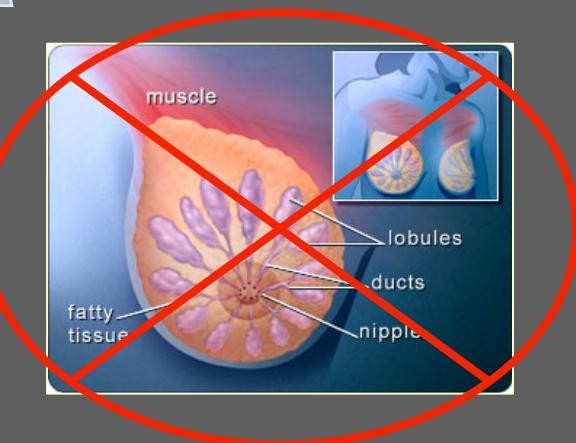
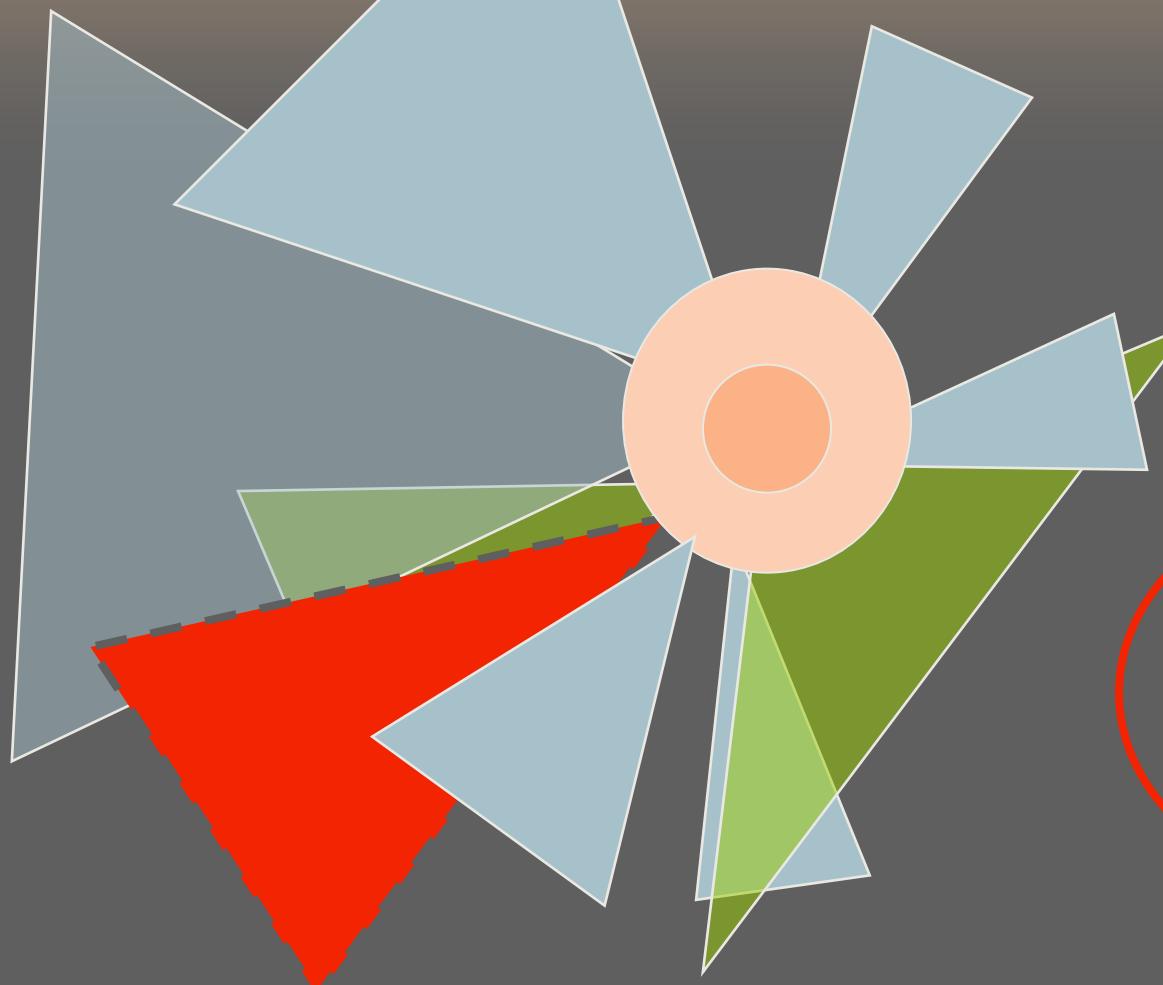
*Wellings SR, Jensen HM. On the origin and progression of ductal carcinoma in situ of the human breast.  
J Natl Cancer Inst 50: 1111-1118, 1973*

## II. ISN of the Breast : models and hypothesis



*Holland R, Faverly D. The local distribution of DCIS of the breast.  
Silverstein M, 2nd edition 2002*

## II. ISN of the Breast : models and hypothesis



T. Tot. *The theory of the sick lobe*. Semin Diagn Pathol 2010

## **II. ISN of the Breast : models and hypothesis**

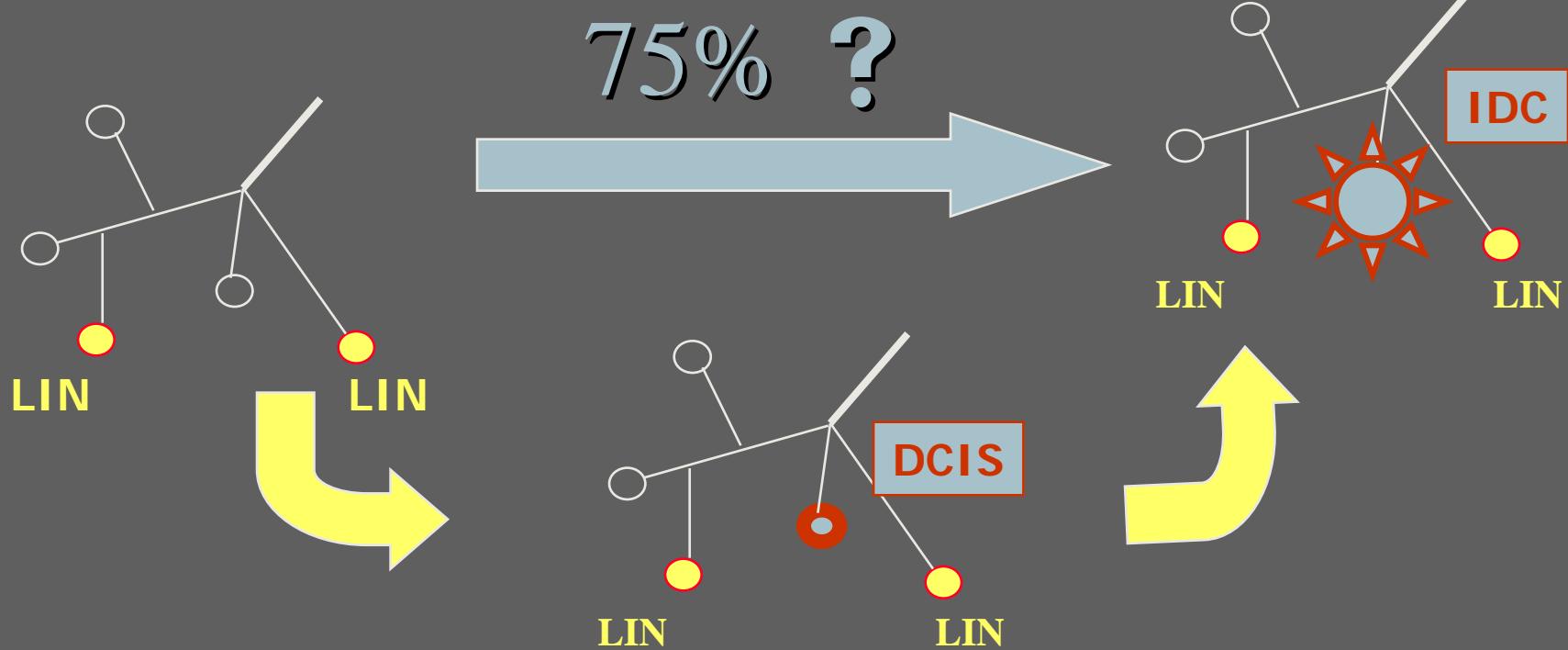
- ➲ « Segmental, unicentric or lobar » distribution of DCIS is a validated model
- ➲ Clinically validated : Both & local recurrences
- ➲ Precursor lesions also unicentric distribution ?

## III. ISN of the Breast : the LIN model -facts

- ⇒ LIN an unicentric lesion ?
- ⇒ LIN is multifocal, over 50% of patient with LIN contain mutiple foci in the ipsilateral breast (where?) and 30% will have further LIN in the contralateral breast (multicentric)
- ⇒ 10 to 20% of patients with LIN develop IC after an average interval of 20 years
- ⇒ The risk is bilateral but 15% of the patient developped IC in the breast diagnosed with LIN versus 9.3% in the contralateral breast
- ⇒ The histotype of IC was not lobular in 2/3 of the cases

## II. ISN of the Breast : the LIN model -facts

### The LIN paradox

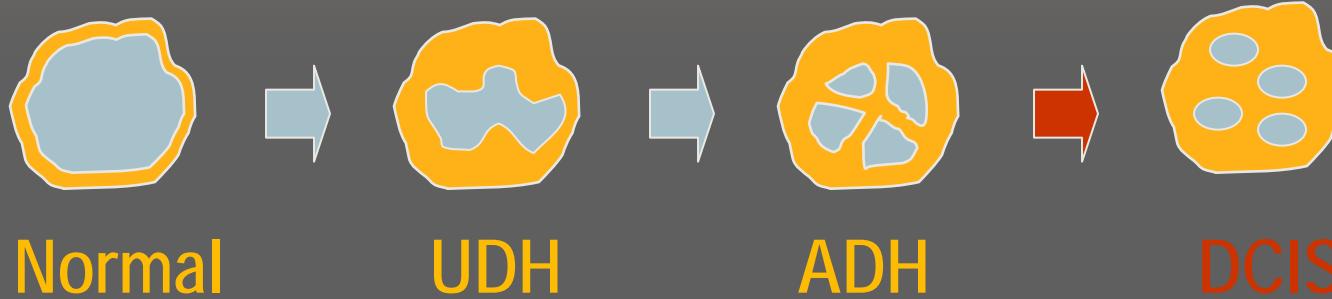


## III. ISN of the Breast : the LIN model -facts

- ⇒ LIN is regarded as an histologic risk factor for developping invasive carcinoma (bilateral risk, not the precursor because predominantly IDC phenotype, 80% of patient are safe & well after 20 years ....) with a multicentric distribution ?
- ⇒ But LIN might also be a real pre-invasive « malignant » neoplasia (precursor of ILC, light balance for the ipsilateral breast) with an unicentric distribution ?

## II. ISN of the Breast : the DIN model

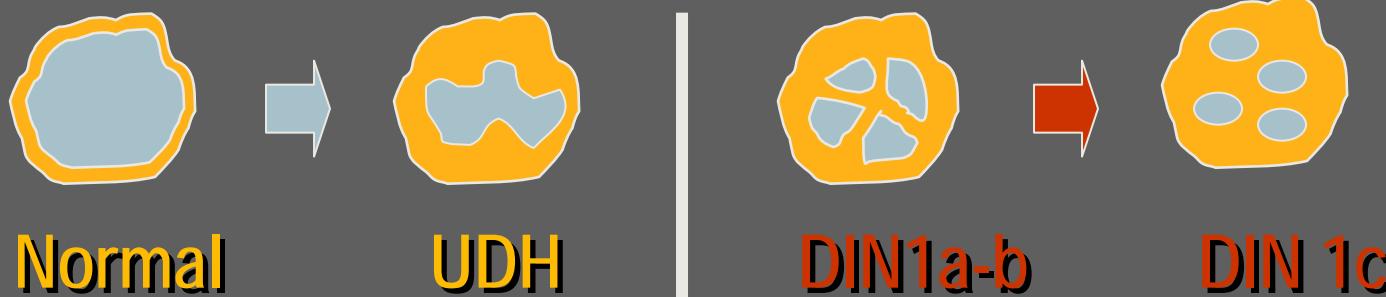
### The tradition



Benign neoplasia

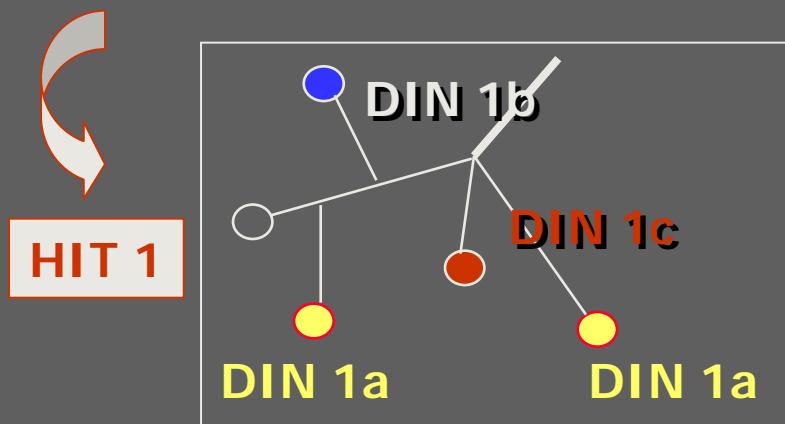
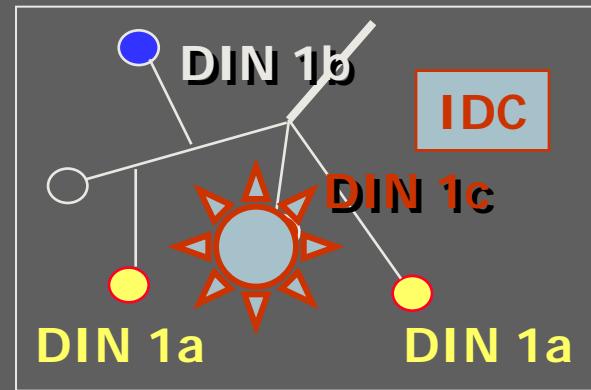
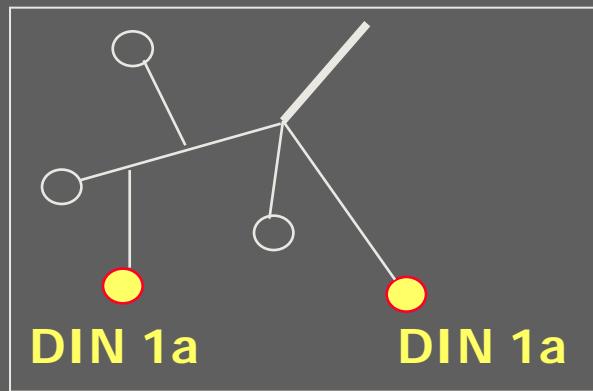
In situ malignancy

### The DIN (ductal intraepithelial neoplasia)



## II. ISN of the Breast : the DIN model

The multistep pathway yes but linear ?



## II. ISN of the Breast : the mixed LIN - DIN model

DIN 1a



LIN 1

LIN 2



HIT 1

DIN 1a



LIN 1

DIN 1c

LIN 2

DIN 1a



LIN 1



DIN 1c

IDC

LIN 2

ILC



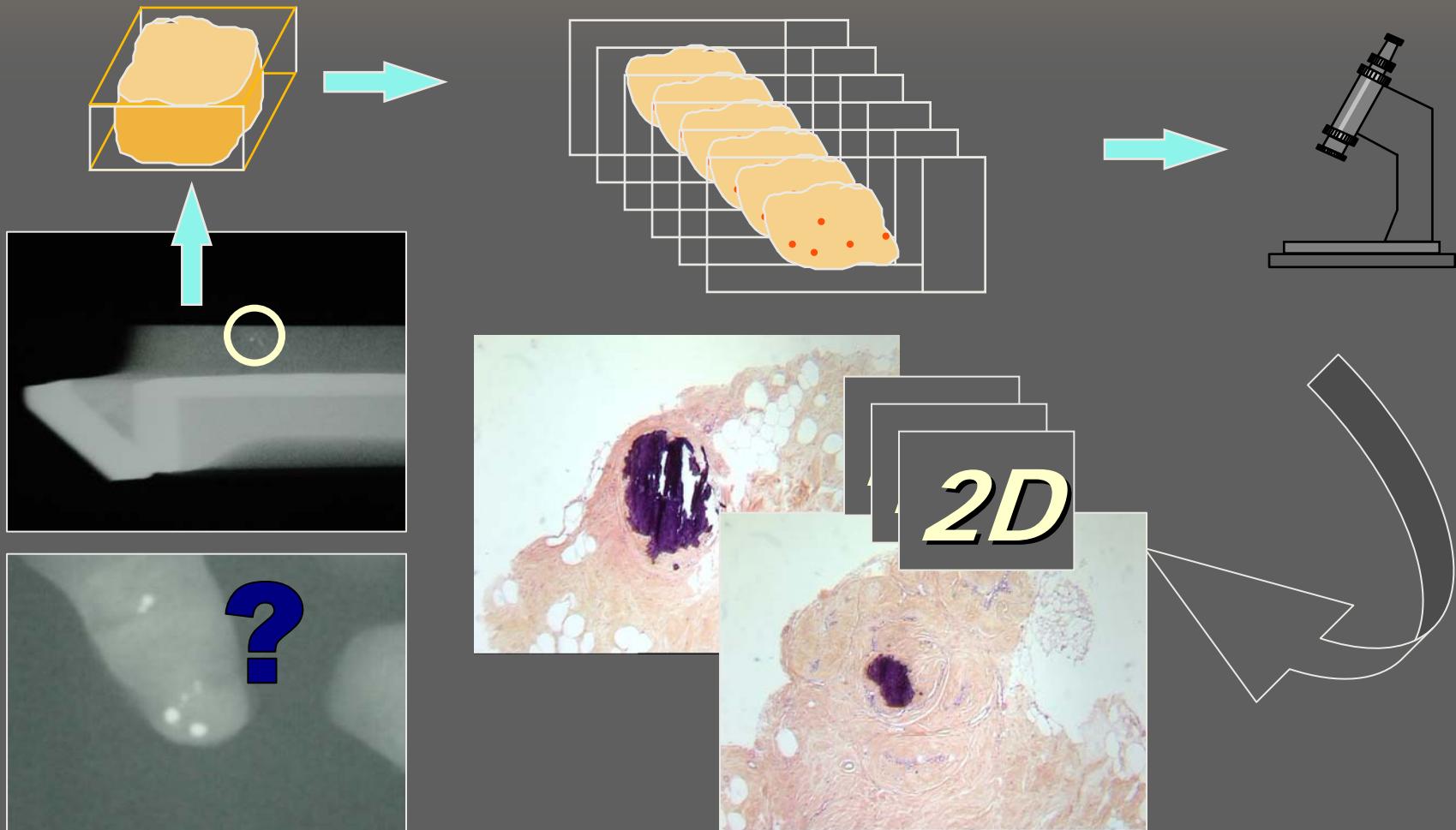
HIT 2

Abdel – Fatah et al. High frequency of coexistence of columnar cell lesions, LIN, DIN 1c with Invasive tubular and lobular carcinoma . Am J Surg Pathol 2007

## **II. ISN of the Breast : the short single hit model**

- ⇒ IDC poorly differentiated grade III, triple negative, basal-like more frequent in BRCA1 mutation carrier
- ⇒ Precursor lesions not frequently seen (not extended) in the close vicinity of the IC
- ⇒ Mixture with multifocal LIN, DIN is rare
- ⇒ Suggest a « short » *in situ* stage with rapid evolution to IC (unicentric and unifocal)

### III. Clinical impact of ISN – VANCB



## **III. Clinical impact of B3 – VANCB**

ECWGBSP classification: B3 lesion of unpredictable behaviour  
Incidence : 5 to 12% of NCB

- ⇒ What to do with B3 ?
- ⇒ Impact of the team work approach (breast clinic, multidisciplinary meeting,...)
- ⇒ State-of-the-art medical imaging set-up (primary & secundary)
- ⇒ Radiomorphologic diagnosis (imaging correlation with histology)
- ⇒ The risk of surgery is high !

### **III. Clinical impact of B3 – VANCB**

*S. Bianchi et al. PPV of B3 for malignancy of VANCB – Breast 2011*

- ⇒ 3107 B3 out of 26165 VANCB
- ⇒ 54% underwent surgery
- ⇒ PPV for malignancy: 21%
- ⇒ Consider surgery for B3 patient

*Rakha et al. Outcome of B3 NCB. Int J Cancer 2010*

- ⇒ 1025 B3 underwent surgery
- ⇒ 25% of cases where malignant (17% DCIS – 8% IC)
- ⇒ PPV of ADH 50%
- ⇒ Consider surgery for B3 patient

### **III. Clinical impact of B3 – VANCB**

*Flegg KM et al. Surgical outcome of B3 – World J Surg Oncol 2010*

- ⇒ 94 surgical excision
- ⇒ 55% remain borderline, 24% malignant
- ⇒ No definite criteria can exclude surgery

*Hayes B et al. B3 NCB & surgery. J Clin Pathol 2009*

- ⇒ 141 underwent surgery
- ⇒ 16% of cases where malignant (17% DCIS – 8% IC)
- ⇒ PPV of LIN 50%
- ⇒ Consider surgery for B3 regarding subtype

### **III. Clinical impact of LIN – VANCB**

*Hussain et al. Eur J Surg Oncol 2011– LIN in NCB*

- ⇒ 1229 LIN diagnosed on CNB
- ⇒ 64% underwent surgery
- ⇒ underestimation 27%
- ⇒ Consider surgery for all NCB LIN patient

*Nagi CS et al. LIN on NCB not require excision. Cancer 2008*

- ⇒ 92 patients fup 1 to 8 years
- ⇒ 50% underwent surgery but 93 % only LIN
- ⇒ All patients OK

# **III. Recommandations Institut National Cancer**

## *LIN 1*

- ➲ *Une surveillance est recommandée*
- ➲ *Identique à celle des CCIS après conservateur*
- ➲ *Si facteurs de risques (atcd familiaux, personnels, autres lésions histologiques à risques) ou discordance radio-morphologique (NCB non représentatifs): une biopsie chirurgicale peut être discutée*

## *LIN 2*

- ➲ *Biopsie chirurgicale puis surveillance*
- ➲ *Une surveillance est recommandée*

## *LIN 3 type 1*

- ➲ *Biopsie chirurgicale puis surveillance*
- ➲ *Pas de reprise si berges positives (idem LIN1 & 2)*

## **III. LIN vs LCIS – WHO 2003 vs TNM ?**

*TNM Classification of Malignant  
Tumor UICC 2009 (7th edit) :*

*pTis (LCIS)*

- ⇒ *What about LIN (WHO 2003) ?*
- ⇒ *What about LIN 1 ?*

### **III. Clinical impact of DIN1a – VANCB**

*Noske A et al. Hum Pathol 2010– FEA in NCB not associated with IC after surgery*

- ⇒ 1845 NCB – 6.6% B3 - 66% were operated
- ⇒ FEA 35% - ADH 20%
- ⇒ After FEA – FEA some DCIS I, no IC

*Noel JC et al. Pure FEA on NCB followed by surgery . Surg Oncol 2010*

- ⇒ 20 cases out of 62 FEA – surgery for residual microcalcifications
- ⇒ No DCIS, No IC

**Not yet the end ..... !**

### **III. ISN in margin of BCTh specimen for IC**

*Fowble B et al. Int J Radiat Oncol 1998*

⇒ AH (ISN) was not associated with an increased risk of ipsilateral breast tumor recurrence or contralateral breast cancer in this study of patients with invasive breast cancer treated with conservative surgery and radiation. Therefore, the presence of proliferative changes with atypia in background benign breast tissue should not be a contraindication to breast-conservation therapy

*Stolier A et al. Am Surg 2004*

⇒ The growing body of literature suggests that in patients undergoing breast-conserving therapy, LCIS in the surgical margin does not impact the risk of local recurrence and therefore may not require reexcision for close or involved surgical margins



or



