



29th Annual International Conference

*“Advances in the Application of Monoclonal Antibodies in
Clinical Oncology and Symposium on Cancer Stem Cells”*

25th-27th June, 2012, Mykonos, Greece

***Epithelial Columnar Breast Lesions:
Histopathology and Molecular Markers***

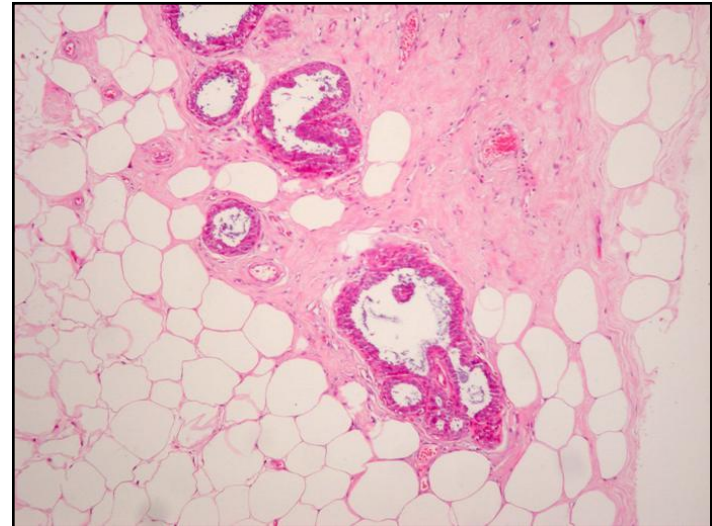
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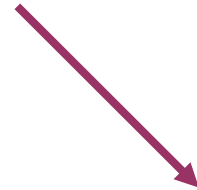
Columnar Cell Lesions (CCLs)

- CCLs are characterized by the presence of tightly packed columnar cells lining distended TDLUs
- Other morphologic features:
 - round to elongated nuclei, prominent apical snouts and intraluminal secretions or microcalcifications



Etiology-Incidence

- Etiology unknown
- Incidence increasing due to:



Screening mammography

Improved recognition

by Pathologists

Clinical profile of patients with CCLs

- Mean ages: 44 to 51 yrs
- Prevalence, demographic characteristics, distribution within the breast: unknown
- Present as nonpalpable lesions
- Calcifications in mammography

Intraepithelial breast lesions with columnar cell morphology have puzzled Pathologists for many years !!!

➤ No new lesions

➤ Other terms: "blunt duct adenosis", "columnar alteration with prominent apical snouts and secretions", "enlarged lobular units with columnar alteration", "clinging carcinoma of monomorphic type", "atypical cystic lobules", "well differentiated DCIS with a clinging architecture"

Classification Systems of CCLs

Initial classification of
Schnitt SJ, Vincent-
Salomon A, 2003



synthesizes and
simplifies the plethora
of terminology and
pathological
descriptions

Two broad categories

- Columnar cell change (CCC)
- Columnar cell hyperplasia (CCH)



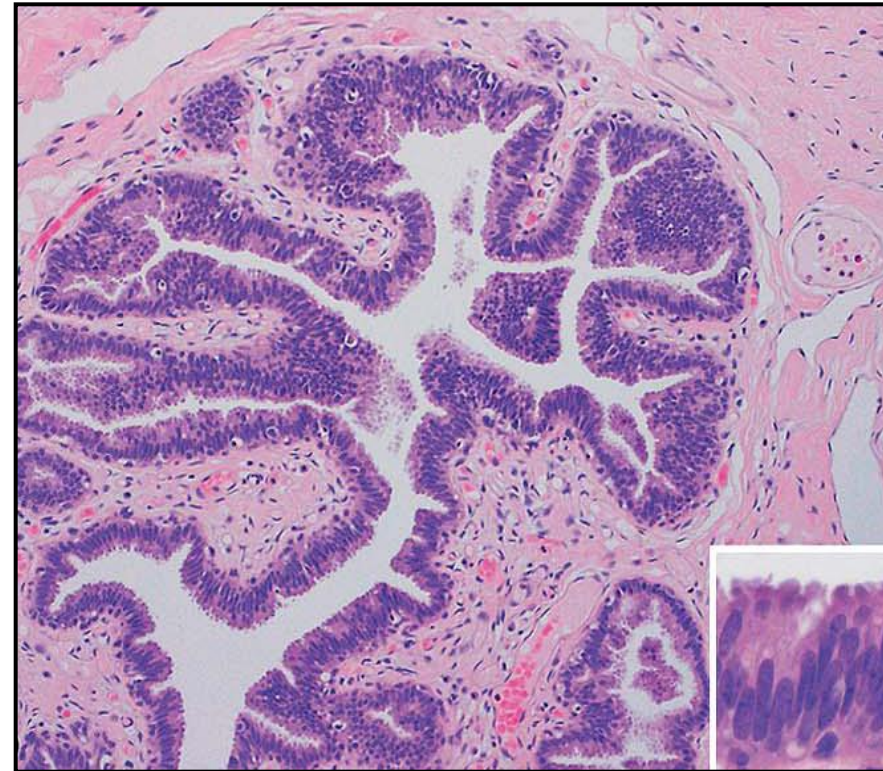
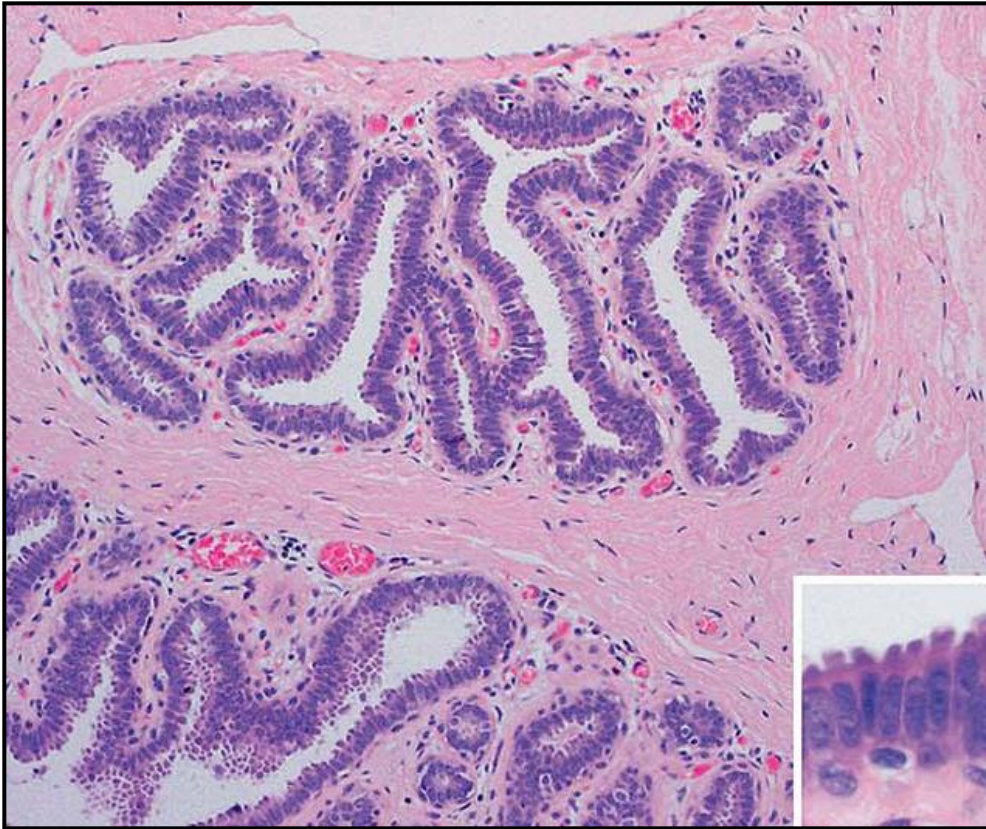
according to the number
of cell layers lining the
acini

CCC

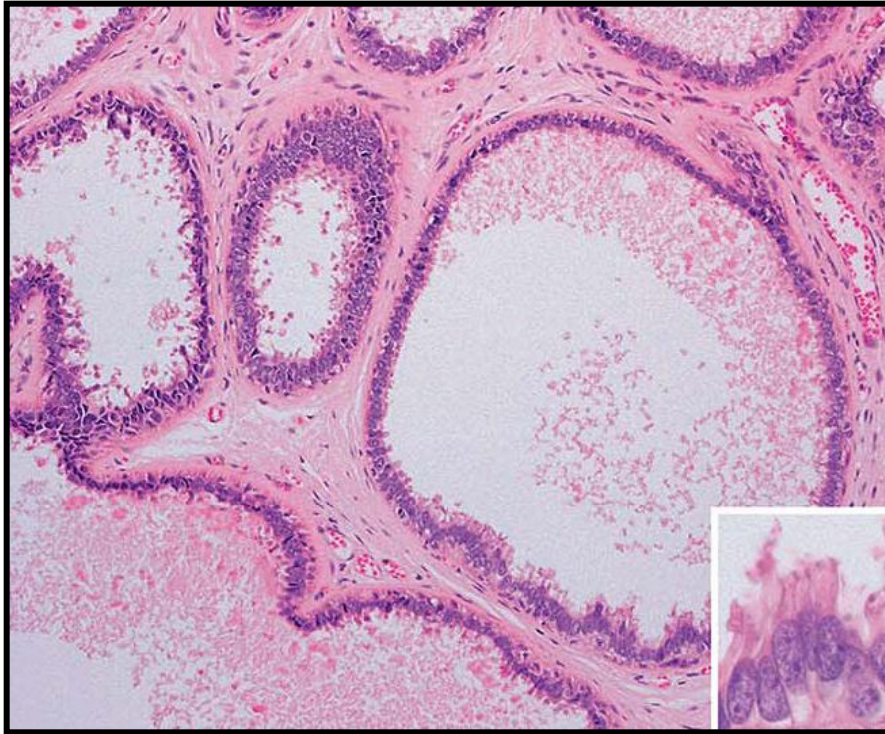
one to two cell layers

CCH

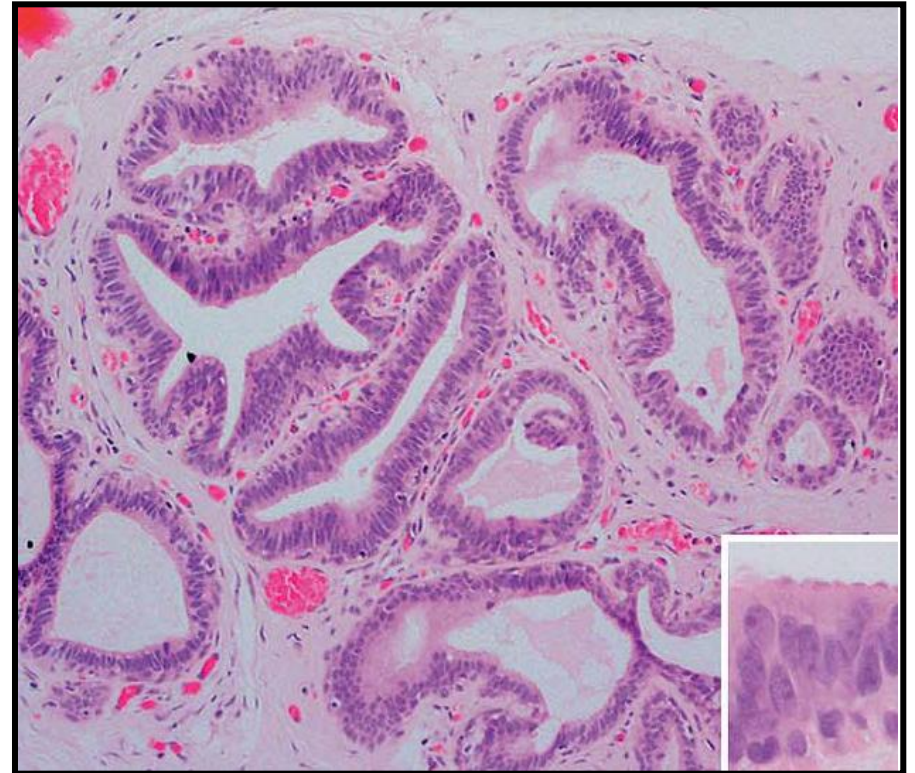
more than two cell layers
stratification, crowding,
overlapping



Some CCLs show cytological atypia: round or ovoid nuclei lacking the normal perpendicular orientation to the basement membrane, variable presence of nucleoli, occasional mitotic figures and mildly increased nuclear to cytoplasmic ratio

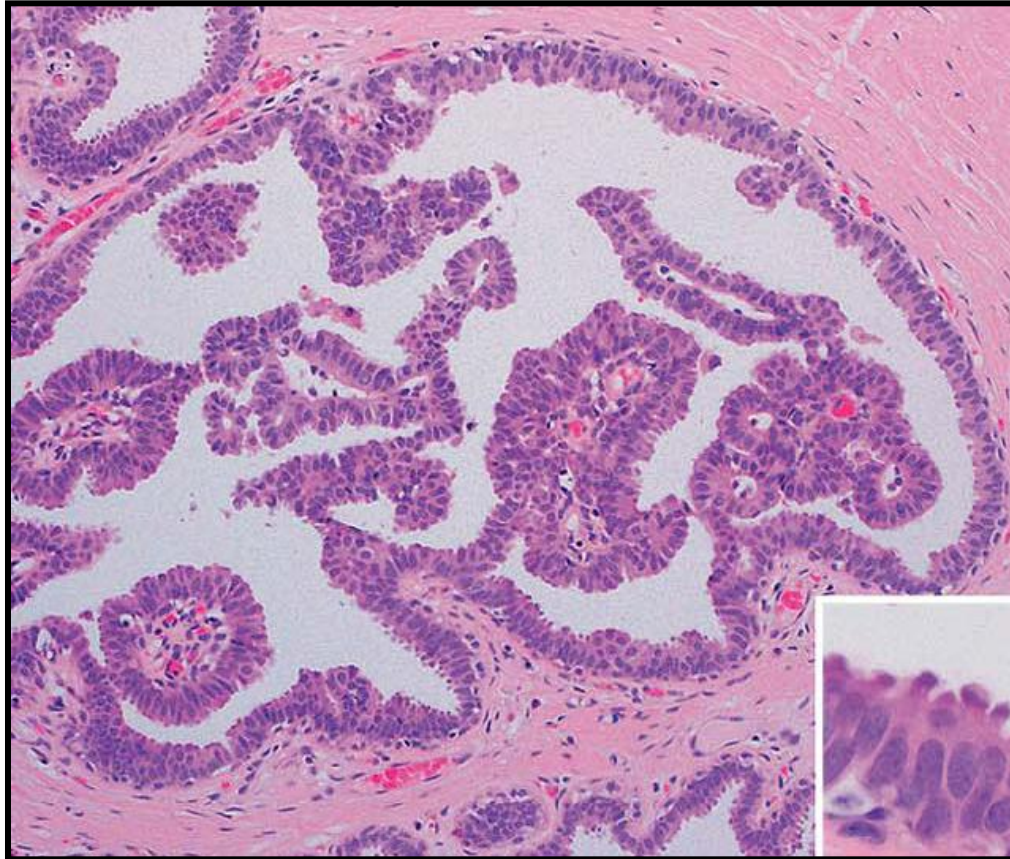


CCC with cytological atypia



CCH with cytological atypia

Some CCLs, especially CCH, show architectural atypia: complex architectural patterns including tufts, fronds, short micropapillae, bridge formation, early cribriform features



CCH with architectural atypia

Classification of Simpson PT et al, 2005

Six categories of CCLs

➤ Without atypia

columnar cell change (CCC)

columnar cell hyperplasia (CCH)

➤ With atypia (architectural, cytological)

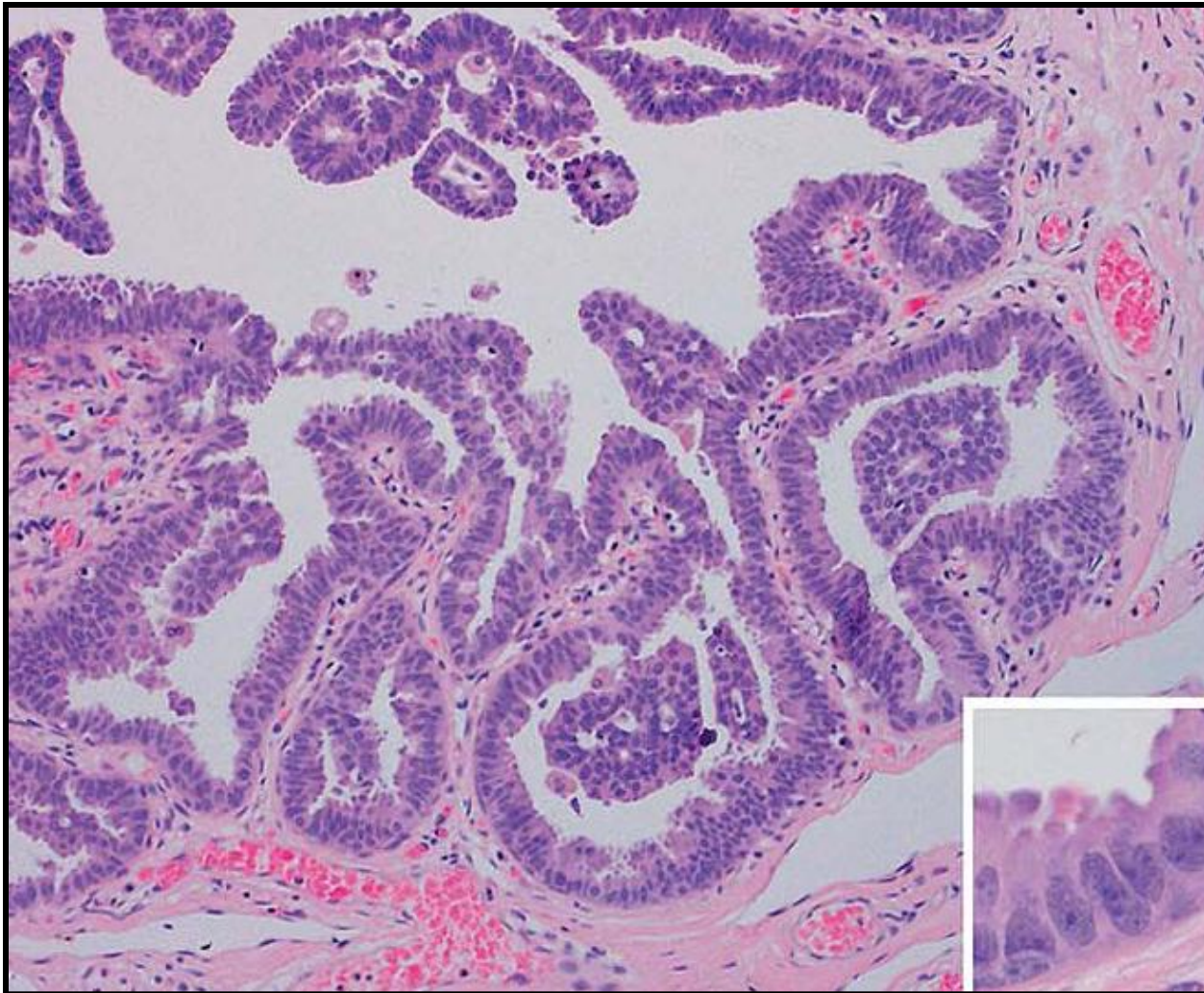
CCC- cytological atypia

CCH- cytological atypia

CCH- architectural atypia

➤ CCH- cytological atypia and architectural atypia

Columnar Cell Hyperplasia -architectural and cytological atypia-

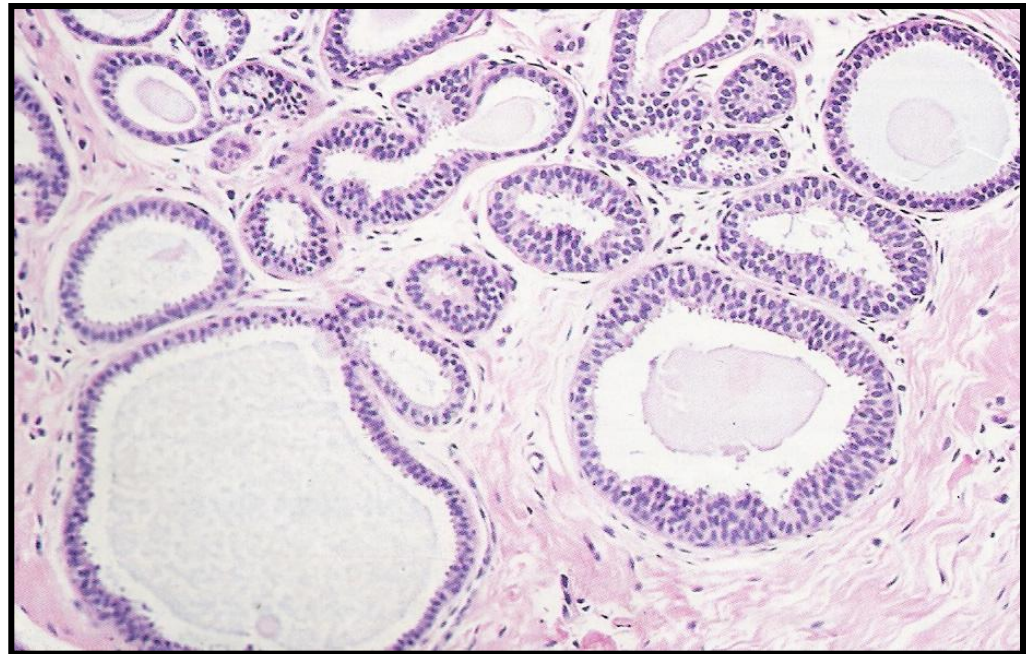


In the current WHO classification

- CCLs with cytological atypia are referred as:

“flat epithelial atypia (FEA)”

in order to describe
“*a presumably neoplastic intraductal alteration characterized by replacement of the native epithelial cells by a single or 3-5 layers of mildly atypical cells*”.

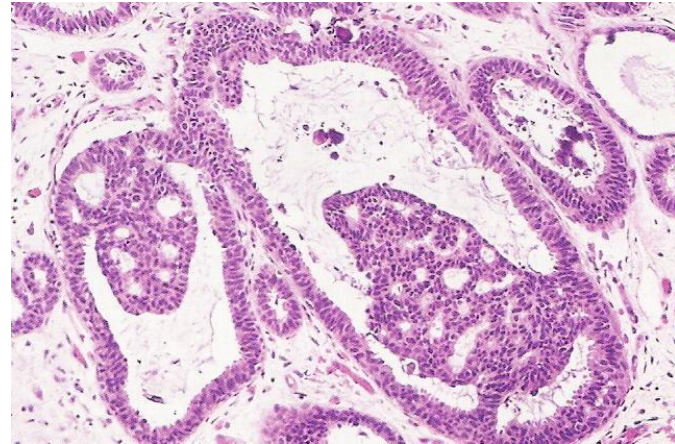


In the latest revision of **DIN** (ductal intraepithelial neoplasia) system, FEA is designated as **DIN1a**

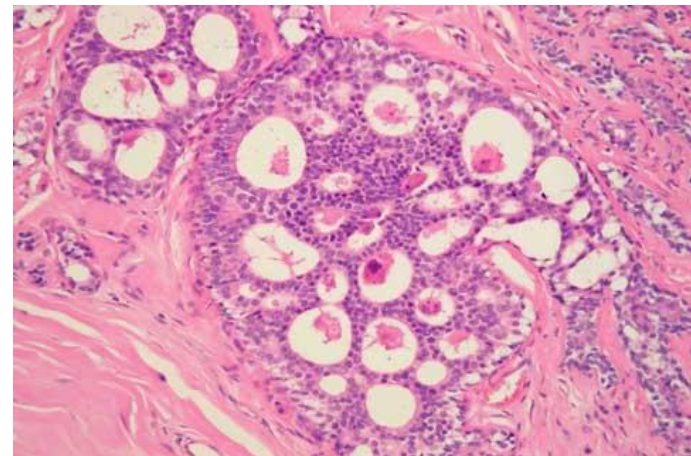
Traditional terminology	Ductal intraepithelial neoplasia (DIN) terminology
Usual ductal hyperplasia (UDH)	Usual ductal hyperplasia (UDH)
Flat epithelial atypia	Ductal intraepithelial neoplasia, grade 1A (DIN 1A)
Atypical ductal hyperplasia (ADH)	Ductal intraepithelial neoplasia, grade 1B (DIN 1B)
Ductal carcinoma in situ, low grade (DCIS grade 1)	Ductal intraepithelial neoplasia, grade 1C (DIN 1C)
Ductal carcinoma in situ, intermediate grade (DCIS grade 2)	Ductal intraepithelial neoplasia, grade 2 (DIN 2)
Ductal carcinoma in situ, high grade (DCIS grade 3)	Ductal intraepithelial neoplasia, grade 3 (DIN 3)

FEA is not necessarily "flat", but rather does not form complex architectural patterns such as cribriform or micropapillary

- cases previously categorized as CCH with architectural atypia, due to the presence of cribriform spaces or micropapillae, are now proposed by several Pathologists to be **classified as ADH or low grade DCIS**, depending on the severity and extent of changes



ADH



LG-DCIS

Important diagnostic criteria

- CCLs are low-grade lesions in terms of cytological appearance



High grade cytological atypia = should be called high-grade DCIS

- CCLs are not so complex lesions in terms of architectural appearance



Cribriform or micropapillae or bridge formations = it's better to be called ADH or DCIS depending on the severity of the findings

Biological and clinical significance

CCLs, in particular those with cytological atypia may be biologically significant, possibly representing a **very early stage** in the evolution of low-grade DCIS and invasive carcinoma

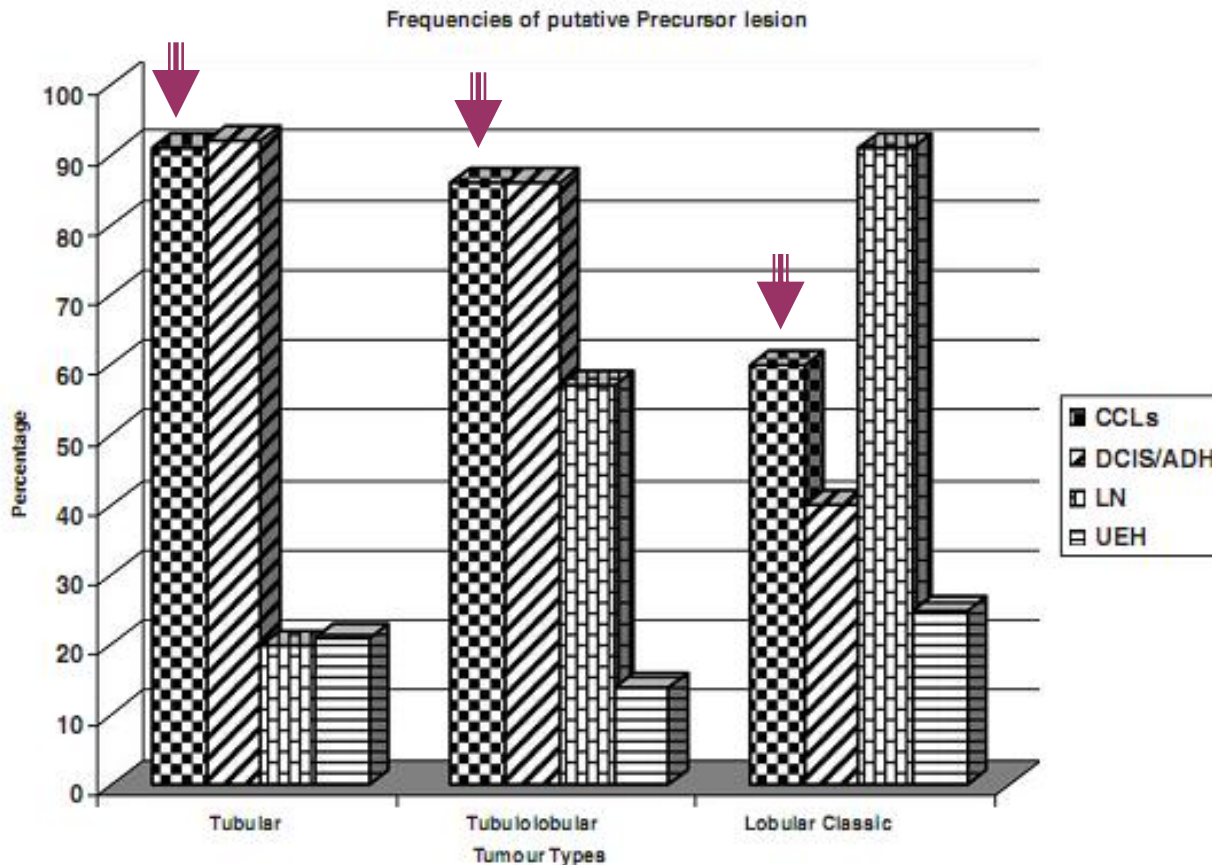
- Observational studies
- Follow-up studies
- Immunohistochemical studies
- Molecular studies

Observational studies

- CCLs have been observed in association with LCIS (86.5%), ADH (60%), low-grade DCIS (42%) and with low-grade invasive carcinomas
- Low grade invasive carcinomas: tubular, tubulolobular and lobular carcinomas

Abdel-Fatah TMA et al, Am J Surg Pathol, 2007; Abdel-Fatah TMA et al, Am J Surg Pathol, 2008; Lerwill M, Arch Pathol Lab Med, 2008; Sudarshan M et al, Am J Surg, 2011

Presence of CCLs in 90% of tubular carcinomas, 85% of tubulolobular carcinomas, 60% of lobular carcinomas

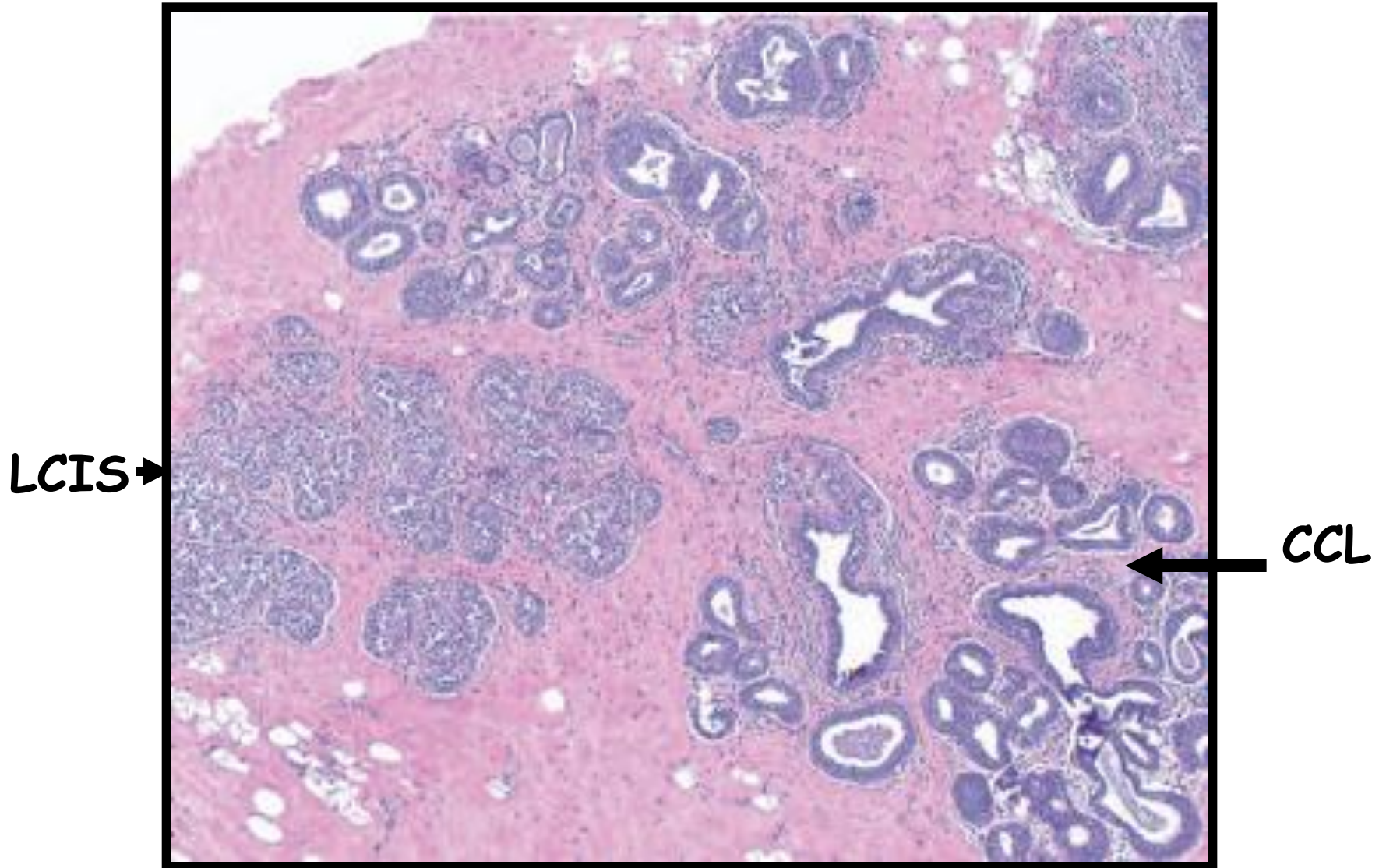


Abdel-Fatah TMA et al, Am J Surg Pathol, 2007

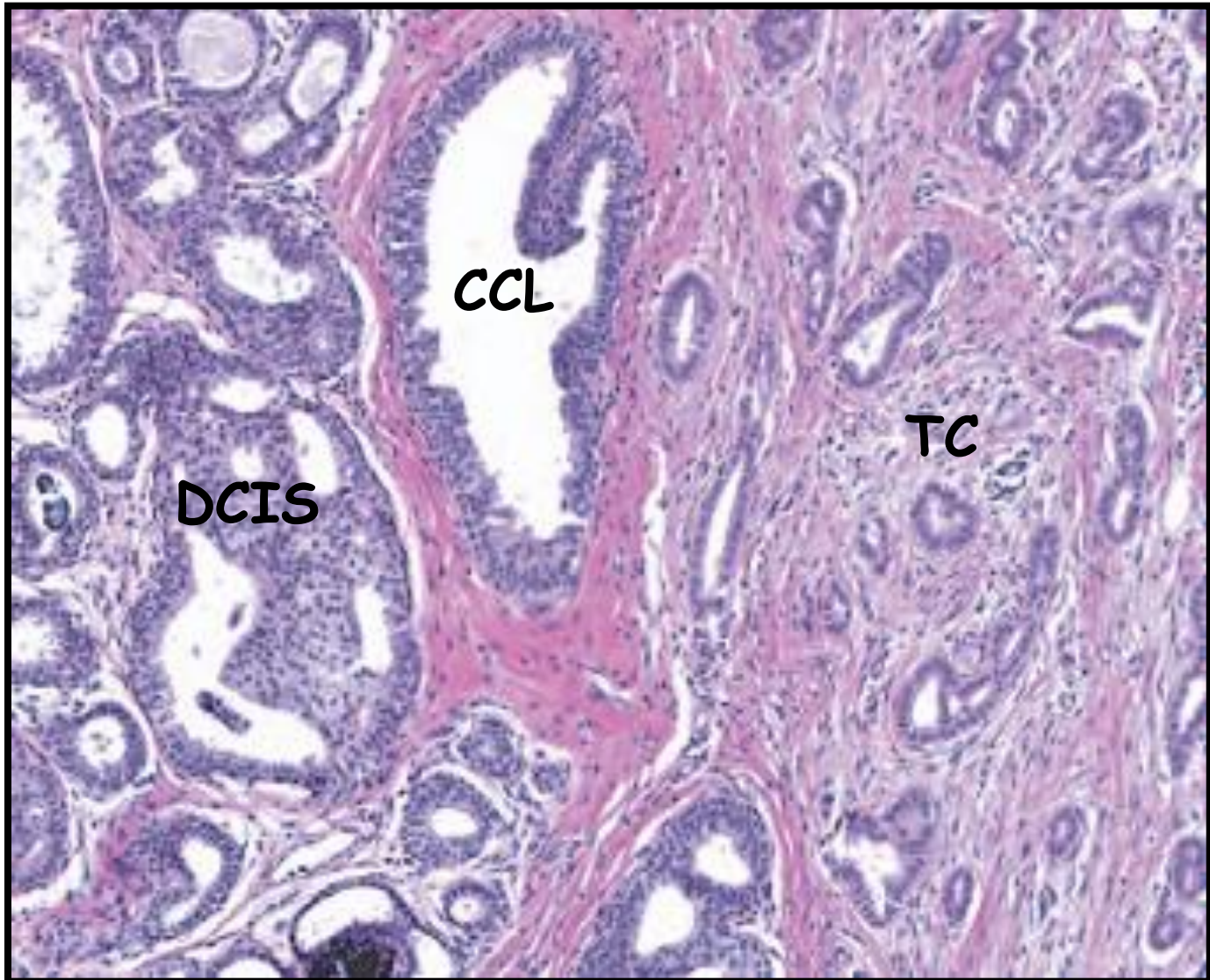
CCL with atypia merging into low-grade DCIS



CCL with atypia and coexistent LCIS

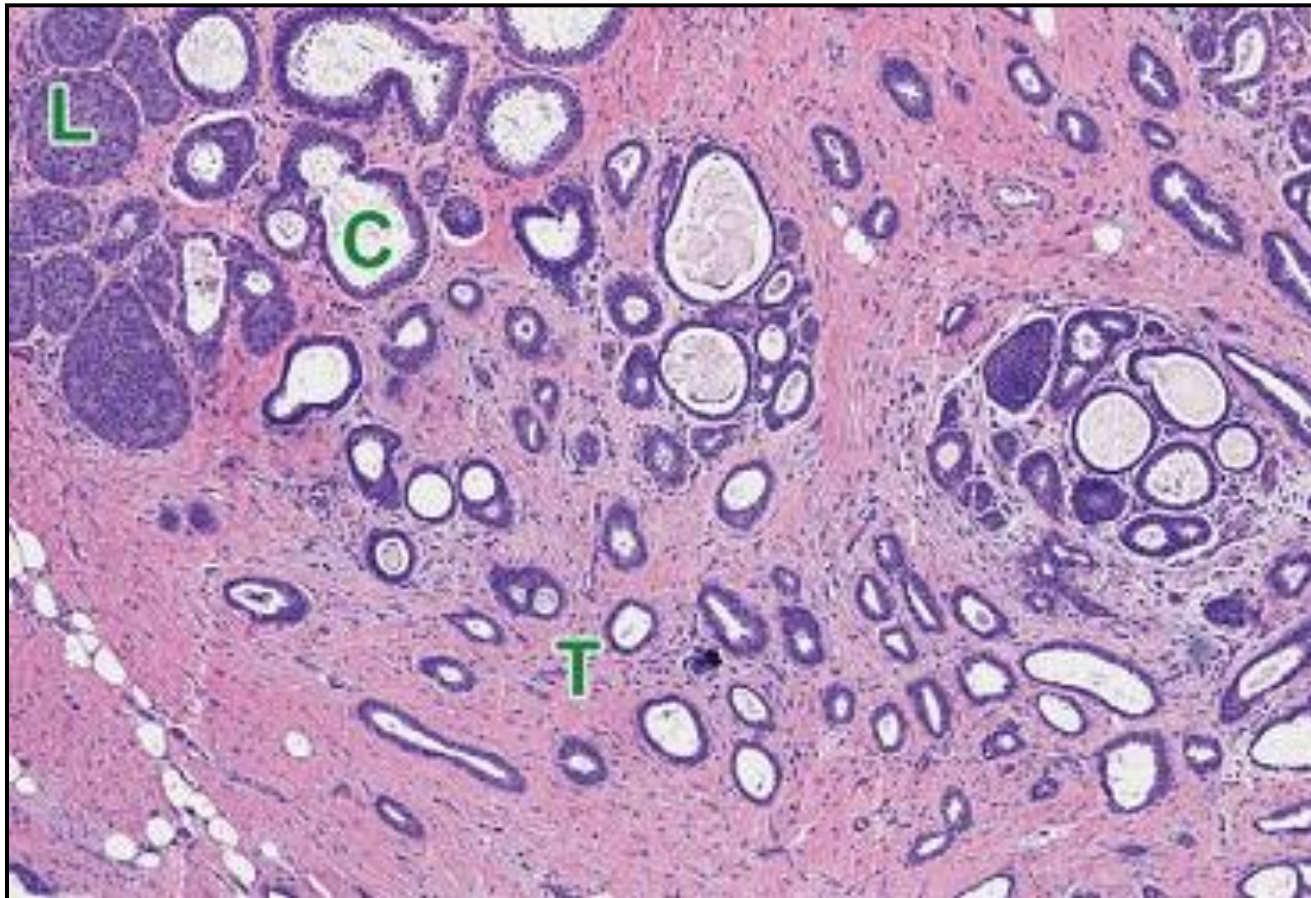


CCL with atypia associated with low-grade DCIS
and invasive tubular carcinoma



"Rosen triad" has been proposed for breast lesions consisting of **CCL + LCIS + tubular carcinoma** (this co-existence has been described initially by the eponymous

Pathologist P. Rosen)



Brandt S et al, Adv Anat Pathol, 2008

Follow-up studies

Information on the natural history of CCLs is scarce

Guerra-Walace M et al, Am J Surg, 2004

- 18.3% of patients with CCLs with atypia developed invasive carcinoma (follow-up period: 5 yrs)
 - *David N et al, J Radiol, 2006*
- All patients with CCLs with atypia and lesions > 10mm developed invasive carcinoma

In practice, the size of *CCLs* is not routinely determined by Pathologists, since it is not a safe procedure

- Determining the size of *CCLs*, especially in core biopsies or determining their completeness of excision is difficult
- Moreover, it is not known if the carcinoma that subsequently developed came from the incompletely excised *CCLs* or from other atypical or malignant changes that were not included in the breast tissue
- Therefore, the management of patients based on the size of the *CCLs* is not practical

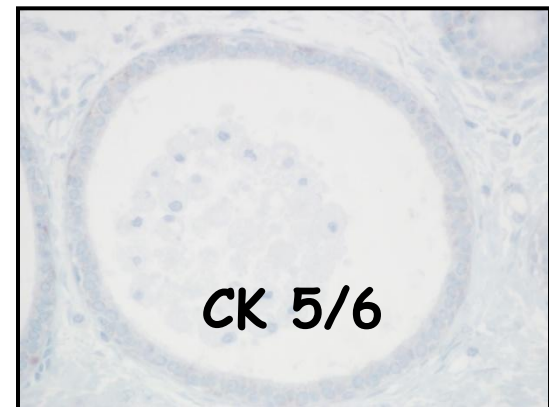
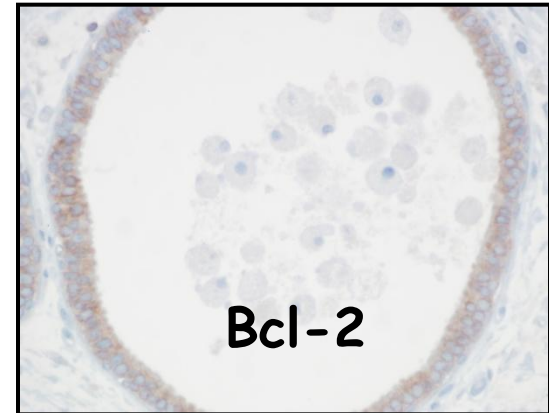
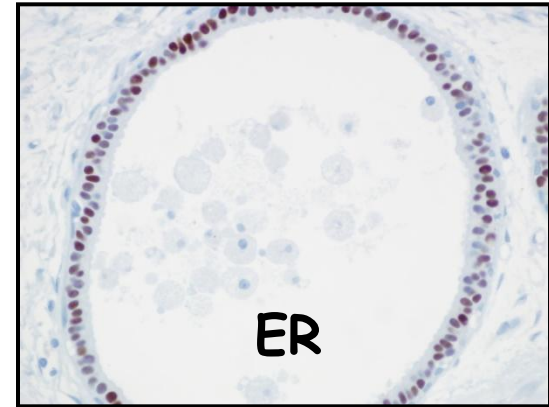
Immunohistochemical/Molecular studies

- ✓ ER, PR, Bcl2, CK19 (+)
- ✓ CK5/6, CK14, p53, HER2/neu (-)
- ✓ Ki67 (- or low)
- ✓ loss on 9q, 10q, 16q, 17p
- ✓ gain on 15q, 16p, 19
- ✓ LOH at 11q, 16q, 3p
- Profile resembles that seen in ADH & low-grade DCIS
- Molecular changes analogous to that seen in low-grade DCIS & low-grade invasive carcinoma







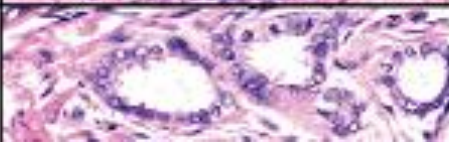
Immunohistochemistry

- ER positive
- Bcl2 positive
- CK 5/6 negative

CCL



Proposed evolutionary pathway of tubular carcinoma on the basis of the reported morphological genetic changes for each stage

Lesions		Reported Genetic Changes					
		Loss			Gain		
CCC ↓		-16q	-19q	-11q	+16p +7	+19	+20 +15q
CCC with atypia ↓		-16q	-17p -22 -12q		+16p +7		
CCH with atypia ↓		-16q	-17p -22 -12q		+16p +7	+8q	
CCH complex architectural & atypia ↓		-16q -6q	-17p -22 -12q		+16p +7 +17q	+8q +19	+15q +12p +3p +3q
ADH ↓		-16q -6q -8p	-17p -22q 12q	-11q -1p -13q -11q	+17q	+1q +8q	+12q +6q +3q +2p
Low grade DCIS ↓		-16q -6q -8p	-17p -19q -22 -12q	-13q -14q -11q	+16p +7p +17q	+8q +19 +1q	+15 +20 +12p +3p
Tubular Carcinoma		-16q -6p -8p	-17p	-11q	-16p +7 +17q	+8q +19 +1q	+20

Biological and clinical significance

- CCLs seems to be biologically significant lesions, since the co-existence with more advanced entities may suggest that CCLs probably represent a very early form of malignant changes
- The concept of a family of "low-grade nuclear breast neoplasia" has been reported recently, based on the significant coexistence of precursor (ADH), in situ (DCIS, LCIS) and invasive lesions (tubular, tubulolobular and lobular carcinoma) along with CCLs
- It has been suggested that CCLs are the earliest morphologically identifiable, non-obligate precursor lesion of low-grade nuclear breast neoplasia.

- Whether the risk for subsequent development of breast cancer is due to the presence of CCLs alone or whether CCLs predict the development of higher risk lesions is not currently known
- The risk of cancer development appears to be low

in a recent retrospective study with 1,261 pts with CCLs and a follow-up period of 17 yrs



risk of cancer development 1.47

Boulos F et al, Cancer, 2008;

Aroner S et al, Breast Cancer Res, 2010;

Sudarshan M et al, Am J Surg, 2011

CCLs on needle core biopsy

- Whether further tissue excision should be recommended for CCLs with atypia detected in core biopsies remains controversial
- There are limited outcome data which indicate that subsequent excision shows a more advanced lesion in 20-30% of cases when CCLs with atypia is identified in core biopsy

CCLs on needle core biopsy

- The lack of consensus and the need for guidelines in managing these lesions is highlighted by a study, which found that 21% of the pathologists would recommend excisional biopsy, when multiple ducts showing CCL with atypia

Ghofrani M et al, Virchows Arch, 2006

CCLs on excision breast specimen

- A careful search from the Pathologist with multiple levels of sectioning for more advanced lesions is very critical
- If CCLs with atypia close to resection margins - do not recommend further excision
- However in practice, most clinicians agree that close monitoring is deemed satisfactory

Conclusions

- ❖ CCLs are being identified with increasing incidence in breast tissue specimens undertaken for the assessment of mammographic microcalcifications
- ❖ CCLs with atypia are seen frequently in relation to ADH, low-grade DCIS, LCIS and low-grade invasive carcinomas
- ❖ Despite these associations, the risk of developing subsequent carcinoma after the diagnosis of CCLs with atypia is not exactly known; however it seems to be very low

Conclusions

- The management of patients with CCLs with atypia remains controversial since there are very limited clinical data and therefore, their significance is still unclear
- A multidisciplinary evaluation tailored to each patient appears to be the most feasible approach, taking account the family history, the personal history (previous breast biopsies) and the mammographic findings

Thank you very much!



Mykonos, Greece