Overdiagnosis: The Role of Pathology

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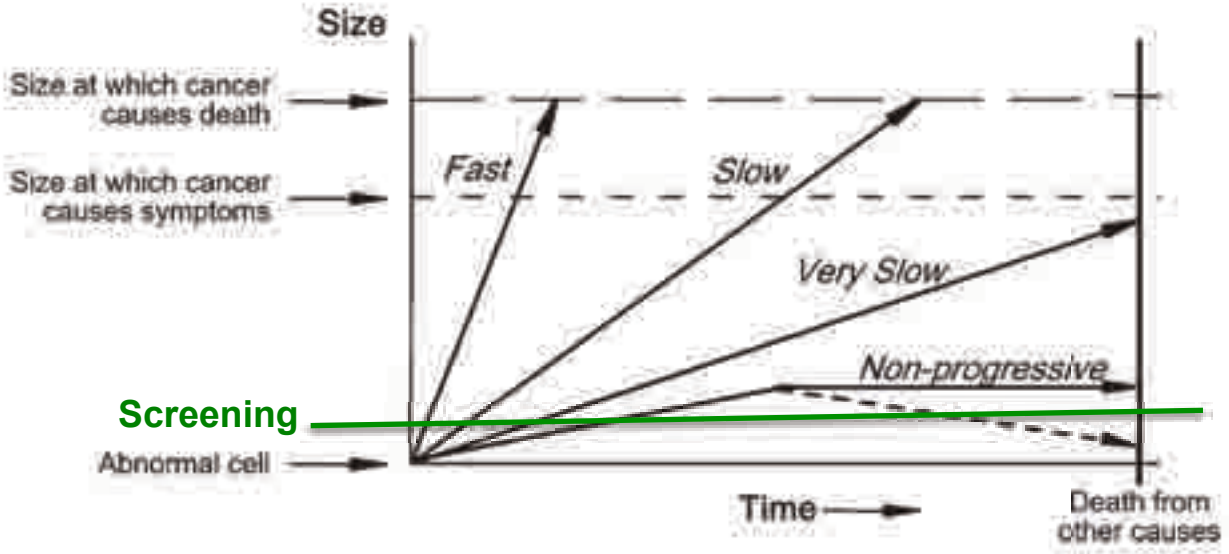
Overdiagnosis in screening mammography

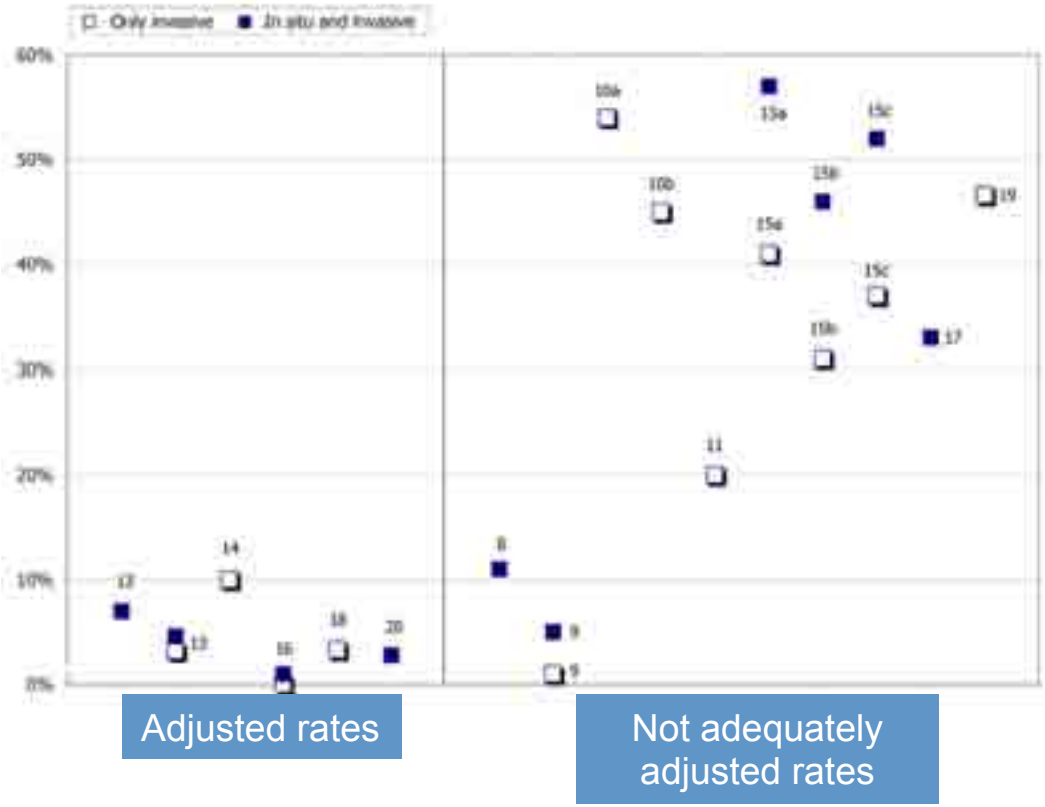
- **Definition:** Overdiagnosis is detection by screening of cancers that never would have come to clinical attention had screening had not taken place

Duffy, S. W. (2005). JMS, 12: 128–133.



Welch, H. G., & Black, W. C. (2010). JNCI, 102: 605–613.

Literature review of overdiagnosis estimates, adjusting for: incidence trends and lead-time



- Netherlands: 2.8%
- Italy: 4.6% / 1.0%
- Denmark: 7.0%
- England: 10% / 3.3%

Puliti, et al.: *JMS* 19 (2012): 42–56

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High expectations to the pathology diagnosis

- Objectively define the type of disease
- Comprehensively describe the individual situation
- Strictly follow standardized nomenclature
- Consider and interpret clinical and radiological findings
- Provide guidance to prognostic and predictive factors

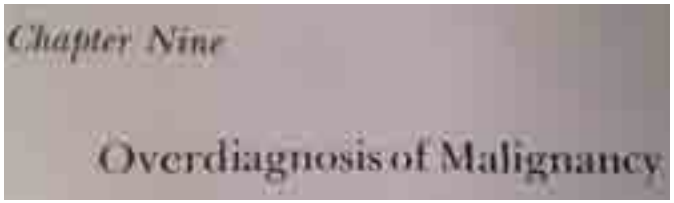
Situations leading to overdiagnosis (and overtreatment)

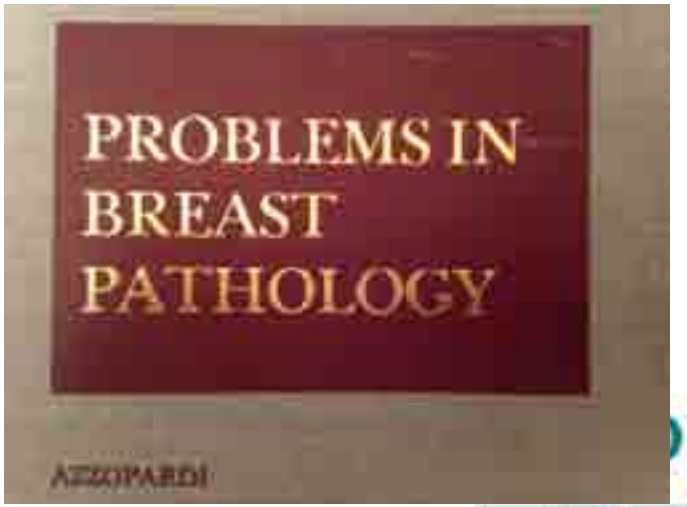
- Errors in interpretation
  - Diagnostic errors
  - Misclassification
- Terminology issues
  - Overinterpretation of B3 lesions
  - Communication problems
- Lesions with very low mortality
  - Low malignant tumors and lg-DCIS
  - Rare lesions

Diagnostic errors in breast pathology

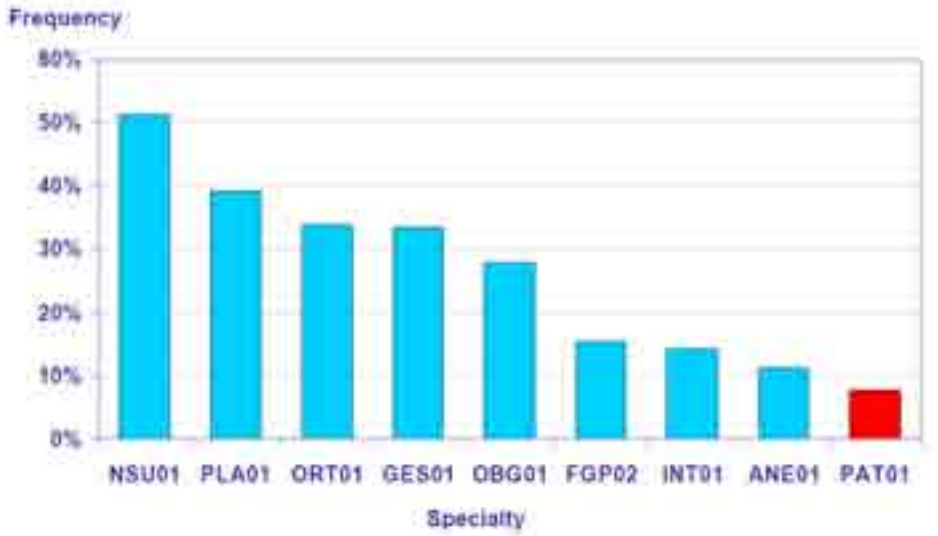
- Overdiagnosis may occur, especially with pathologists who are inexperienced or not subspecialized in breast pathology

- Azzopardi (1979):
  - Severe epitheliosis (florid ductal hyperplasia)
  - Sclerosing adenosis
  - Infiltrating epitheliosis (sclerosing lesions w/ hyperplasia)
  - Papilloma
  - Fibrosis, Elastosis
  - Pseudo-lobular carcinoma
  - Fat necrosis





Low frequency of diagnostic errors in pathology but high severity

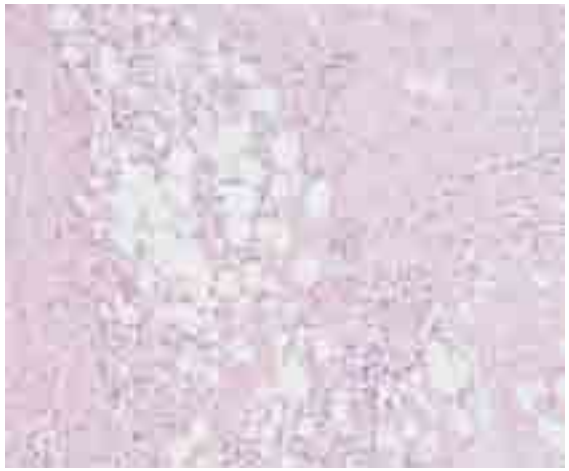


Number of medicolegal claims reported in the US each year per 100 insured phycicians (Troxel: USCAP 2006).

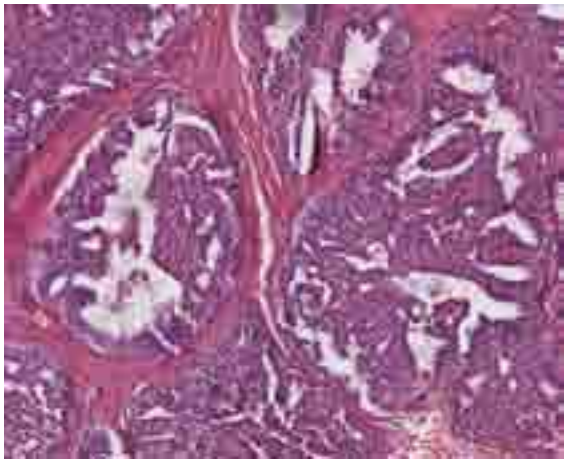
- Breast cases second most common to skin (melanoma)
- Average cost per claim: $453.200
- High due to failure to detect cancer
- False-negatives more frequent than false-positive cases

Troxel: *Arch Path Lab Med* 130 (2006): 617–19
Kornstein et al. *Arch Path Lab Med* 131 (2007): 615–18

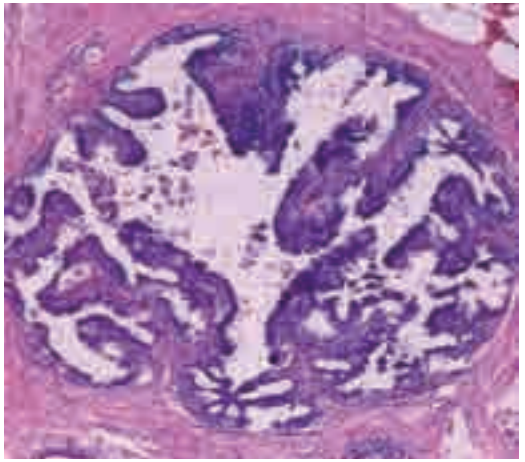
Examples of common diagnostic problems



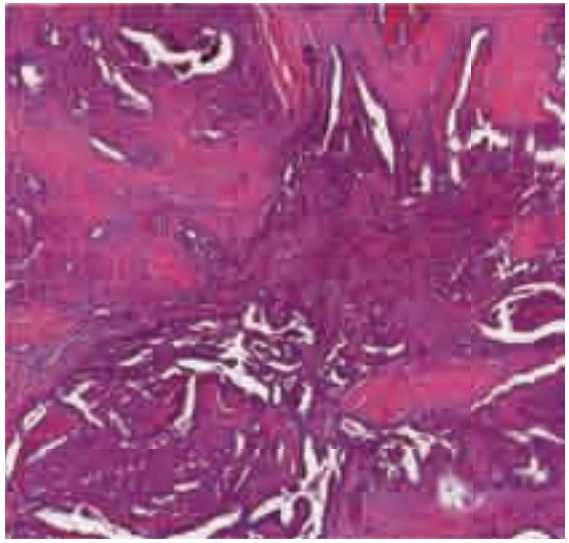
Fat necrosis



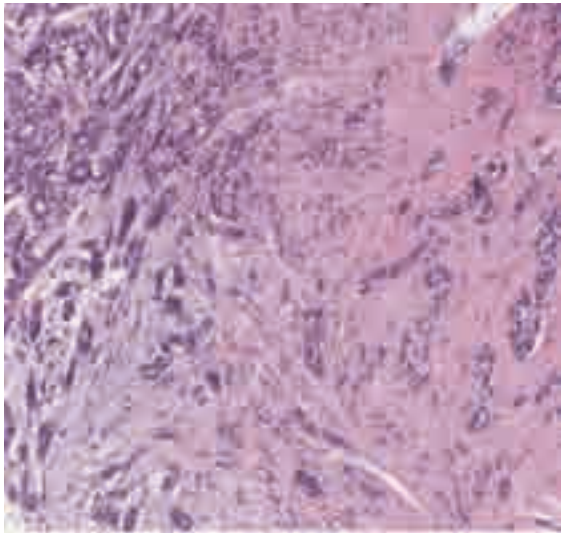
Florid ductal hyperplasia



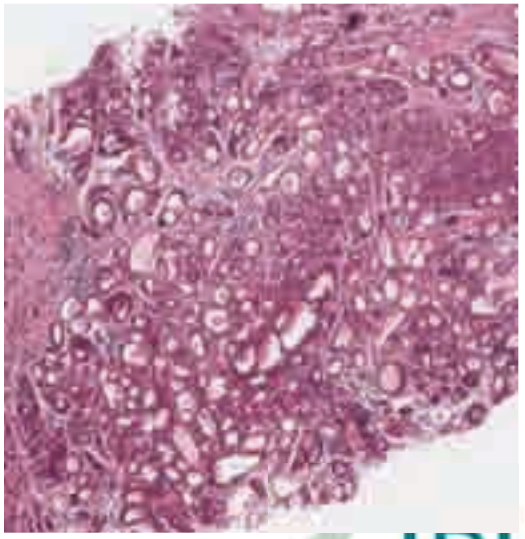
Papilloma



Sclerosing lesion



Sclerosing adenosis



Apocrine adenosis

Some sources of diagnostic errors in pathology

- „Hasty“ diagnosis
- Lack of experience
- Bad techniqual quality of tissue sections
- Mislabelling of specimen
- Incomplete / missing clinical information

Stragegies for Minimizing Errors in Breast Pathology

- Quality assurance programs
  - Consensus slide conference
  - Adherence to established guidelines
  - Accreditation, external audits
- Review of outside pathology slides and reports before the initiation of cancer therapy
- Seeking a second opinion in difficult cases

After: Masood ICBDC 2013

Major and minor changes after seeking second opinion in breast pathology

TABLE 1. *Major changes in pathologic diagnosis*

Initial diagnosis	Second-opinion diagnosis	n[a]	% Total cases
DCIS	Benign	1	.3
DCIS	Invasive cancer	6	1.7
Invasive cancer	DCIS	7	2.0
Margins positive	Margins negative	10	4.1
Margins negative	Margins positive	6	2.5

DCIS, ductal carcinoma-in-situ.

[a] Includes three cases that had both a margin change and another major change. Thus, major changes occurred in 7.8% of cases.

- Change in surgical therapy in up to 7.5% of cases

TABLE 3. *Minor changes in prognostic information*

Change	n	%
Prognostic changes		
Grade 1 to other		
Invasive	18	7.4
DCIS	9	11.1
Other grade change		
Invasive	32	13.2
DCIS	8	9.9
No grade on first pathologic report		
Invasive	42	17.4
DCIS	29	35.8
Histological changes		
Change in subtype		
Invasive	61	25.2
Tubular/colloid to other	18	7.4
DCIS	36	44.4
Invasive to invasive + DCIS	43	17.8
No subtype on initial pathologic report		
Invasive	4	1.7
DCIS	9	11.1

DCIS, ductal carcinoma-in-situ.

- Additional prognostic information in 40% of cases

Staradub et al. *Ann Surg Oncol* 9 (2002): 982–87

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Situations leading to overdiagnosis (and overtreatment)

- Errors in interpretation
  - Diagnostic errors
  - Misclassification

- Terminology issues
  - Overinterpretation of precancerous lesions
  - Communication problems

- Lesions with very low mortality
  - Low malignant tumors and lg-DCIS
  - Rare lesions

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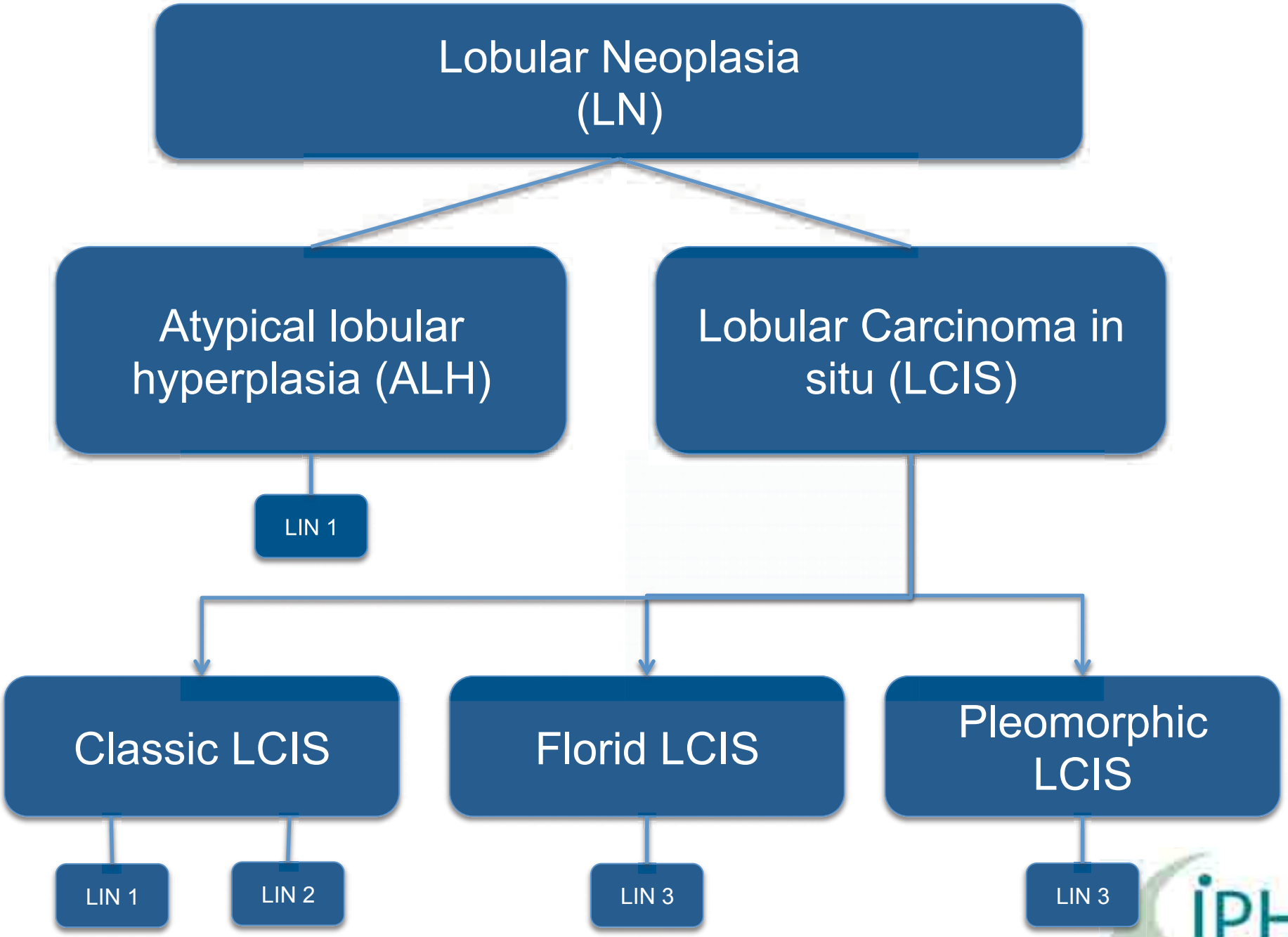
Lobular Neoplasia (LN)
Atypical lobular hyperplasia (ALH)
Lobular Carcinoma in situ (LCIS)
LIN 1
Classic LCIS
Florid LCIS
Pleomorphic LCIS
LIN 1
LIN 2
LIN 3
LIN 3
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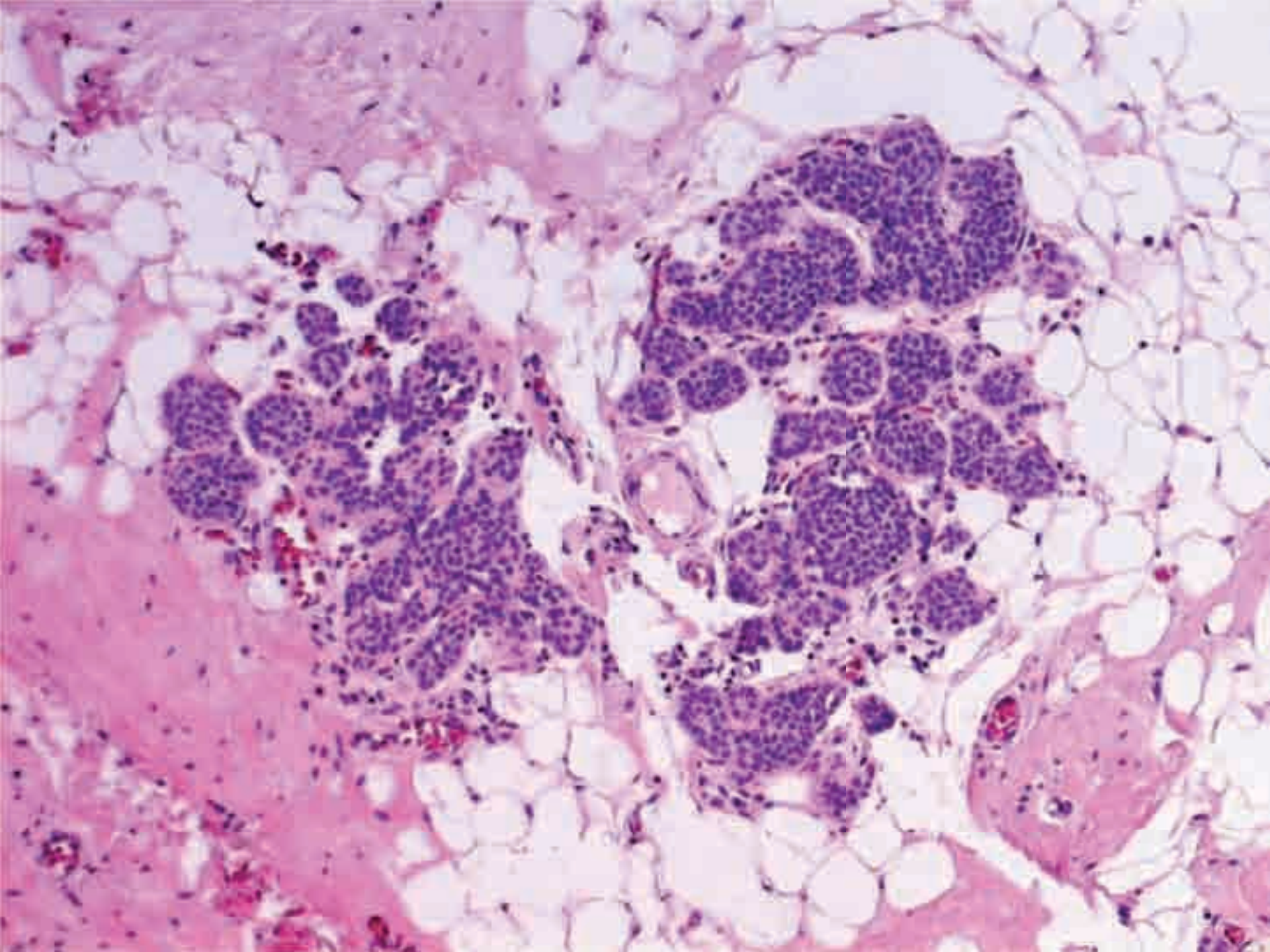
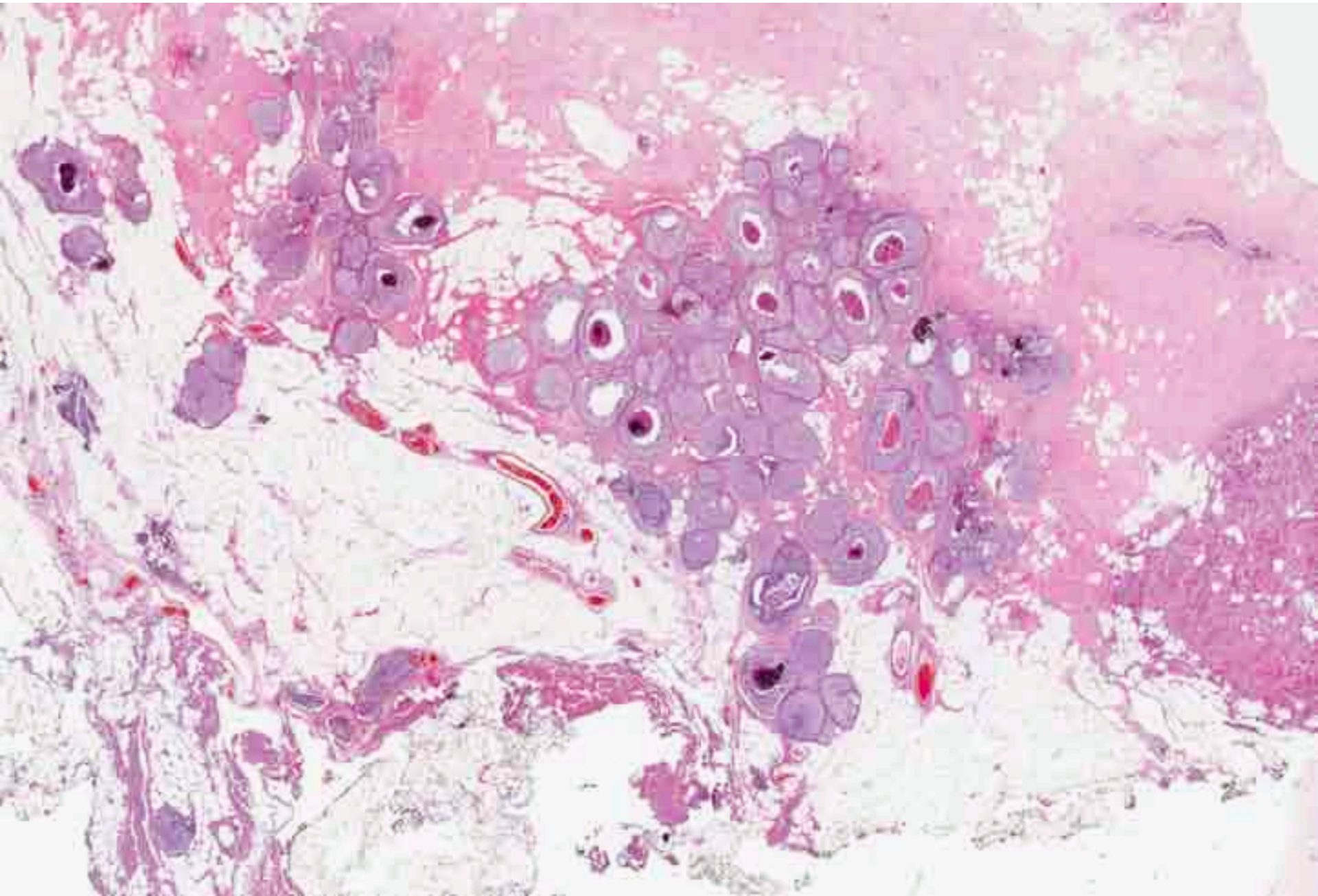


Natural history: ALH vs. LCIS

- ALH:
  - 4 - 5x increased risk for invasive breast ca.
  - Individual risiko (15 years): ~8%
- LCIS
  - LCIS: 8 - 9x increased risk for invasive breast ca.
  - Individual risiko (15 years): ~15-20%
- Cofactors
  - Extent / number of lobules involved
  - History of previous breast biopsies
  - Family history

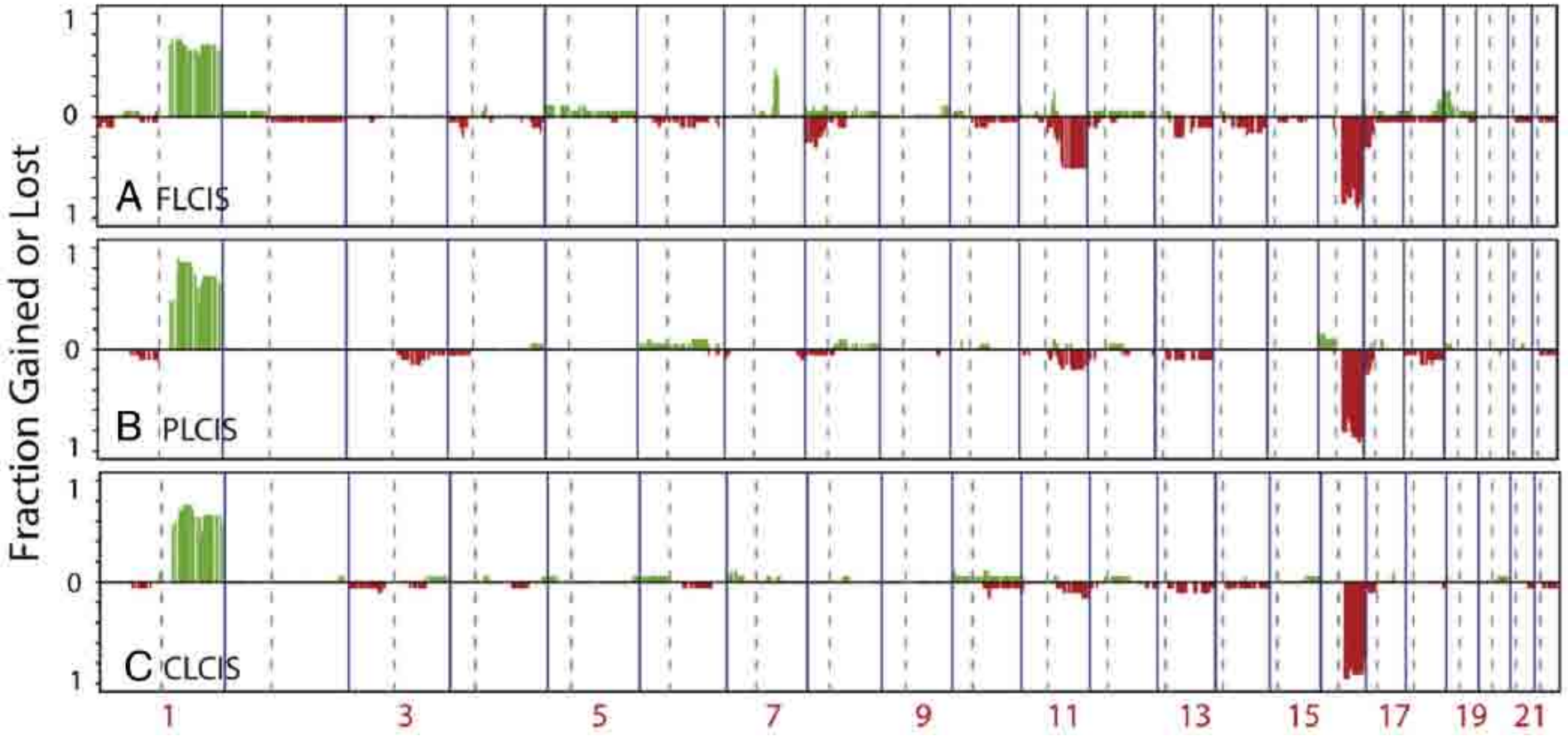
Nashville Breast Cohort
Nurses Health Study

Florid LCIS



aCGH comparison of fLCIS, pLCIS, and cLCIS

Shin et al. *Hum Pathol* 44 (2013): 1998–2009



- **fLCIS in situ shares the cytologic features, E-cadherin loss, and the lobular genetic signature loss found in classic lobular carcinoma in situ.**
- **fLCIS is genetically more advanced compared with the indolent phenotype of classic lobular carcinoma in situ.**

European guidelines

- The pathologist is a key member of the specialist multidisciplinary team and has a primary role in the pre- and postoperative conferences. Patient management is largely based on the pathological findings. They should be sufficiently detailed and accurate.

European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. N Perry, M Broeders, C de Wolf, S Törnberg, R Holland, and L von Karsa (eds.) 2008, p. 214

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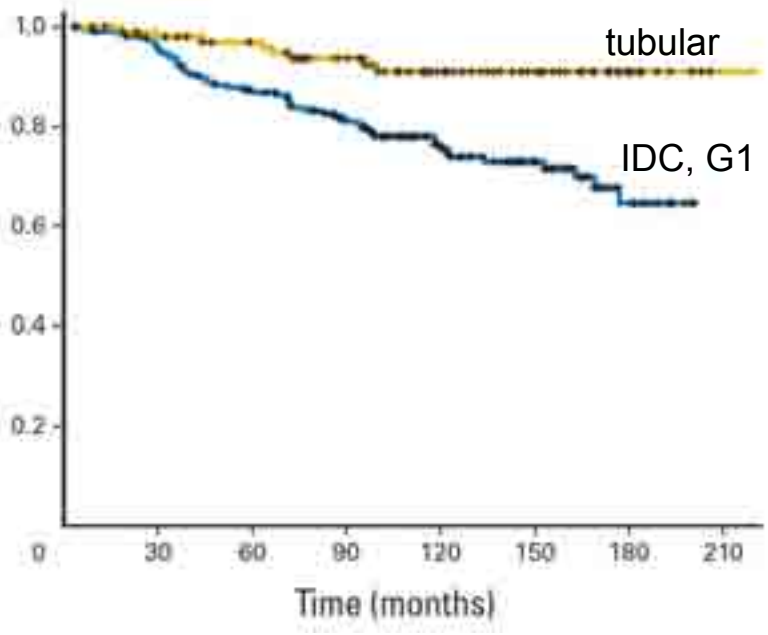
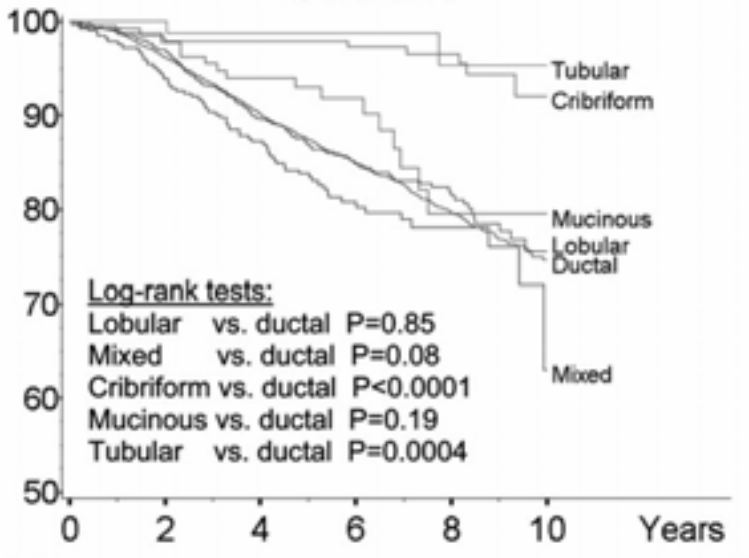
Invasive tubular carcinoma

Clinicopathological characteristics (Rakha 2009)

- 68% screen detected
- 59% ≤ 1 cm
- 91% node negative
- 100% good Nottingham prognostic index



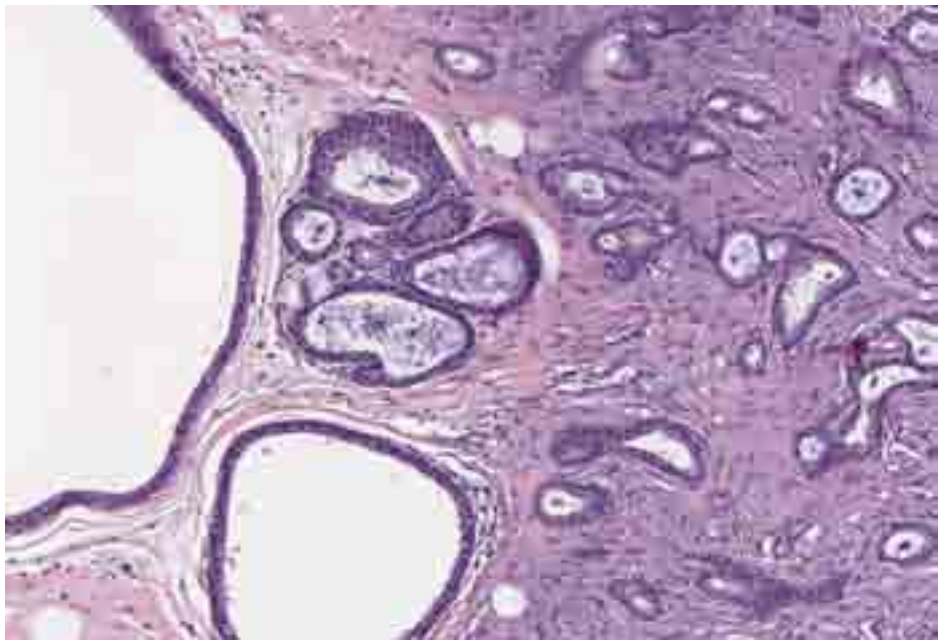
Rakha et al. JCO 28 (2009): 99–104



Colleoni et al: *Ann Oncol* 23 (2011): 1428–36

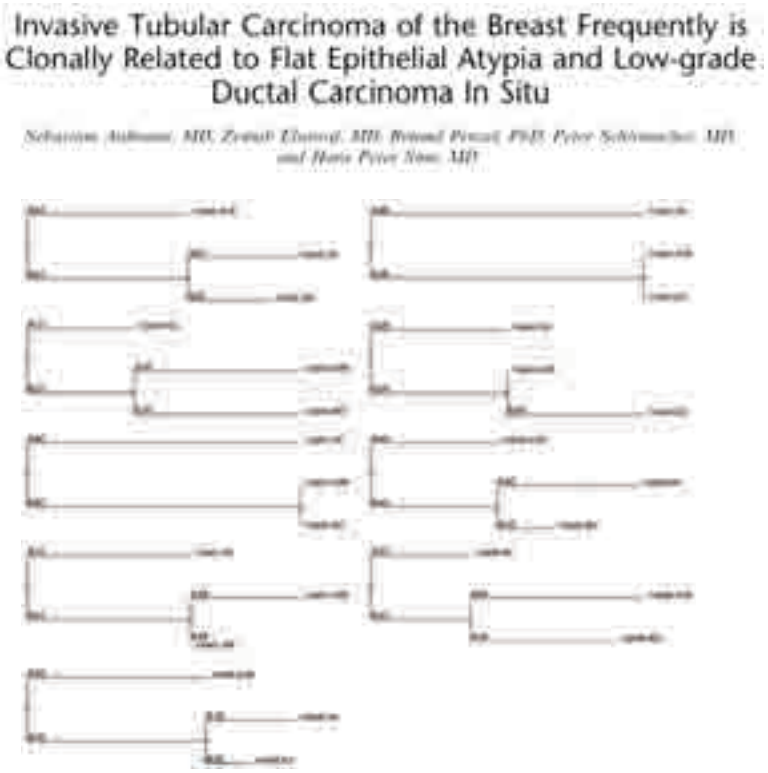
Invasive tubular carcinoma – Origin from low grade columnar cell lesions

Histology



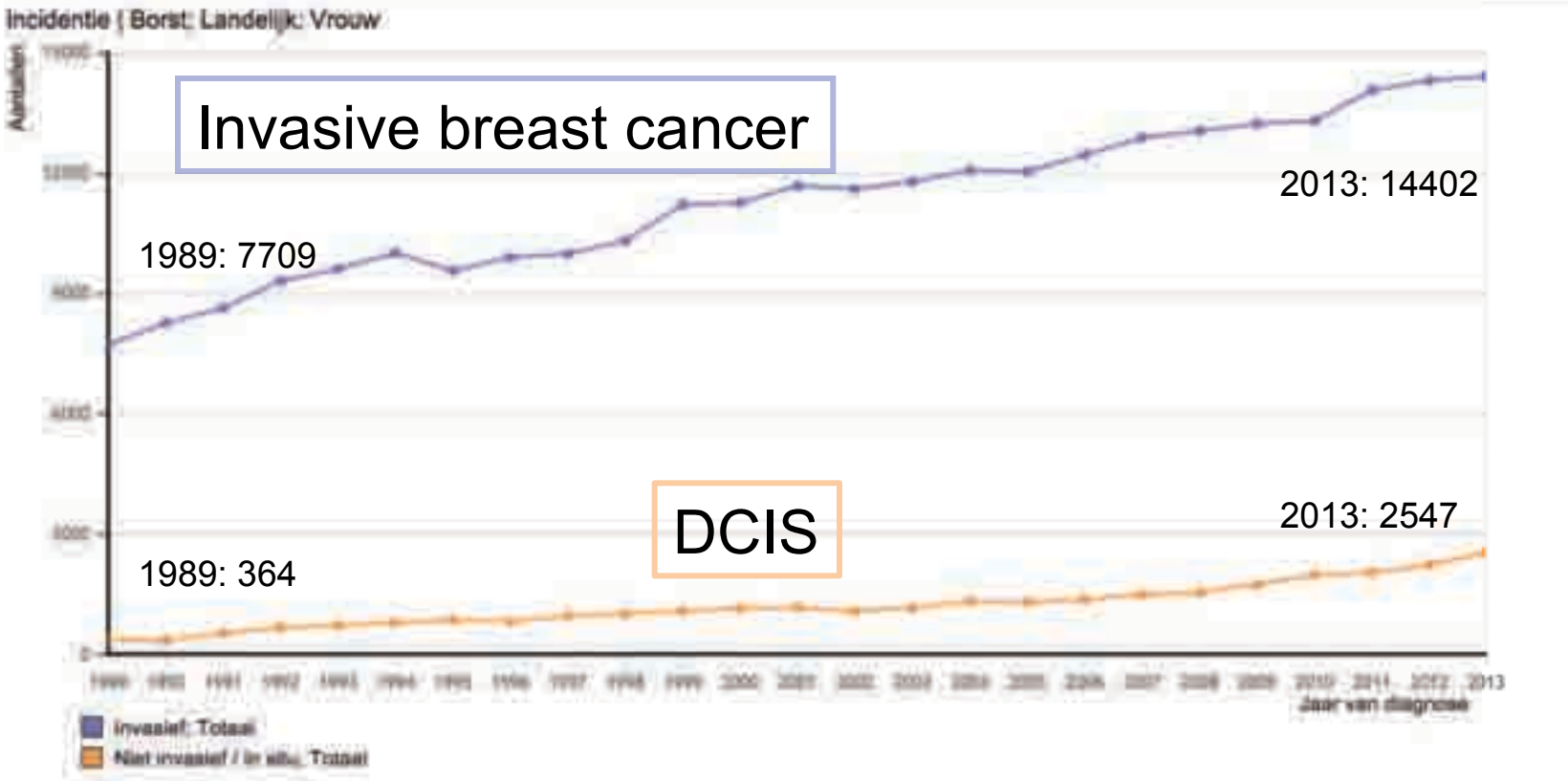
CCC → FEA → Inv. tubular Carcinoma

Molecular biology



Clonal relationship of FEA and ITC

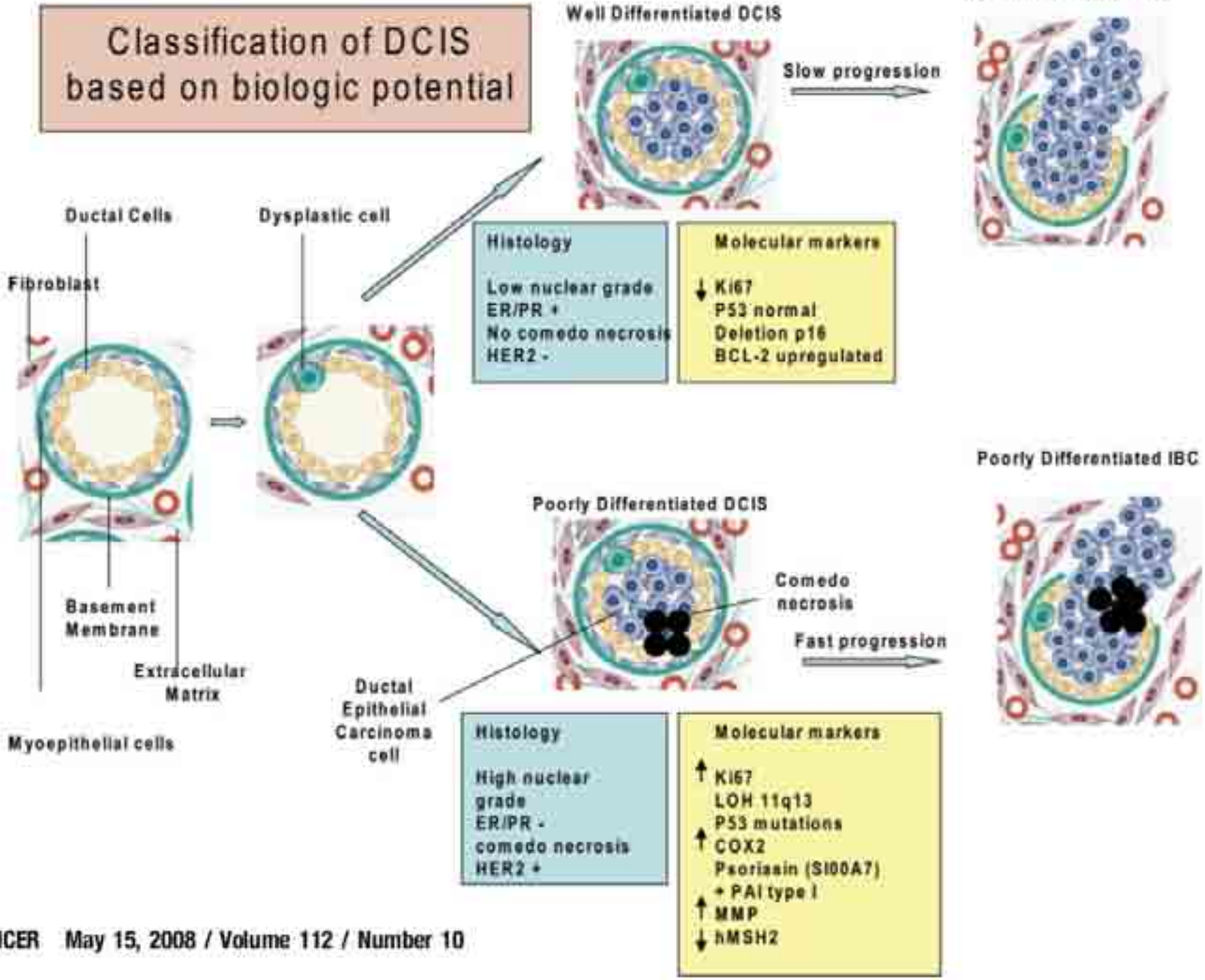
Annual incidence of invasive ca. and DCIS



Continuous incidence of invasive breast cancer, despite increased detection of DCIS

Source: www.cijfersoverkanker.nl/

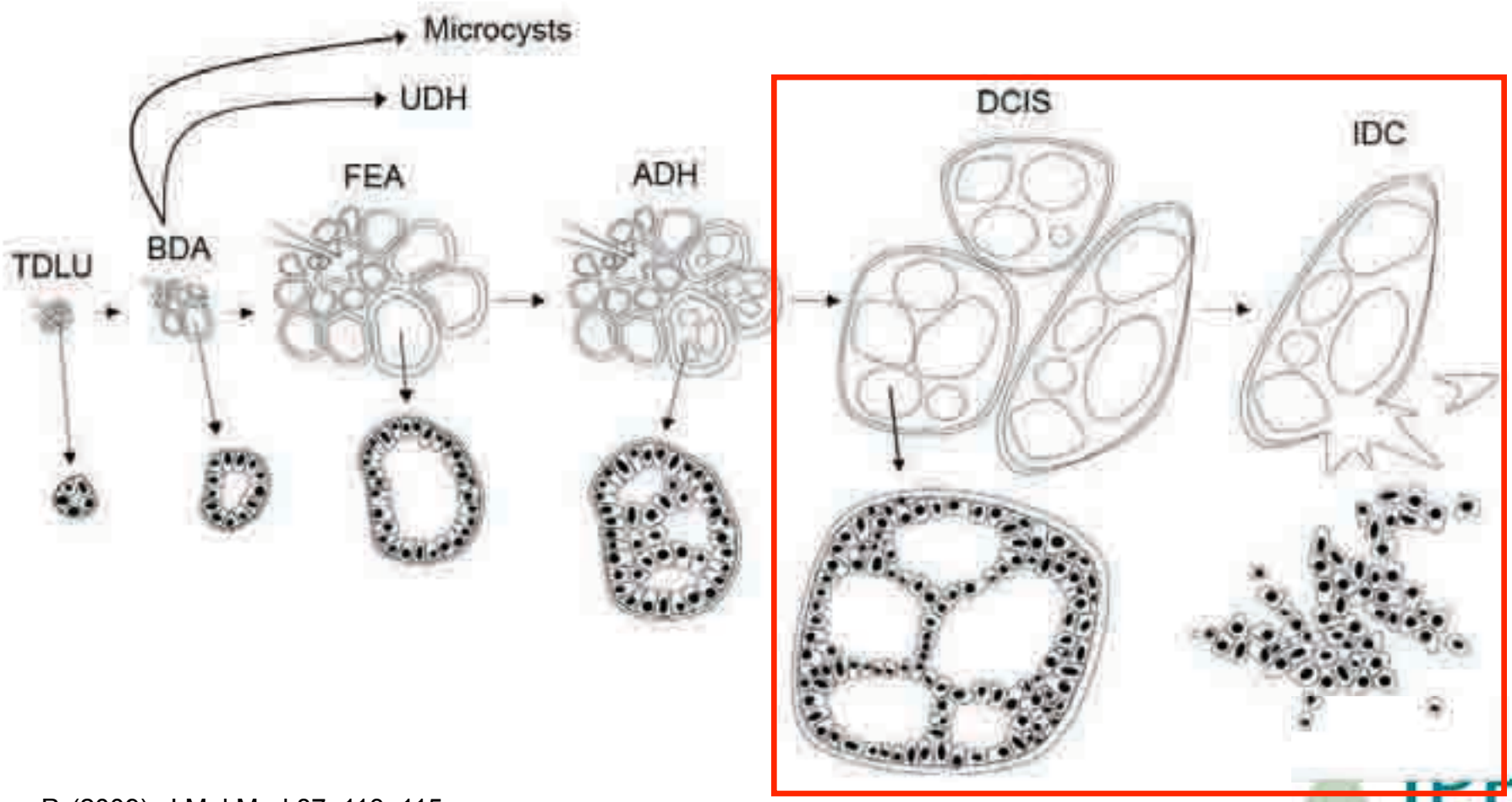
Classification of DCIS based on biologic potential



CANCER May 15, 2008 / Volume 112 / Number 10

Screen detected Ig-DCIS

- How likely is it progression to clinically overt breast cancer during life time?



Sinn, P. (2009). J Mol Med 87: 113–115

Invasive Cancer Risk				Options
	10 yr ipsilateral	5 yr ipsilateral	Lifetime (either breast)	Offered / preferred
LCIS		3-6%	20-40%	Active surveillance
Atypia		4-7%	20-40%	Active surveillance
DCIS Score 10	5,0%	2.5%	10-20%	• Lumpectomy • Lumpectomy + XRT +/- Tamoxifen • Mastectomy
DCIS Score 30	10,0%	3.5%	10-20%	
DCIS Score 65	15,0%	7.5%	15-30%	
BRCA 1/2		5-7%	50-85%	• Active surveillance/ screening • Prophylactic mastectomy and/or oophorectomy

After: Essermann ASCO 2012

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DCIS Score 65	15,0%	7.5%	15-30%	
BRCA 1/2		5-7%	50-85%	• Active surveillance/ screening • Prophylactic mastectomy and/or oophorectomy

With treatment !

After: Essermann ASCO 2012

Risk of invasiv cancer after biopsy of DCIS alone

		N	All	%
Lewis	1938	(8)	6	75
Farrow	1970	(25)	5	20
Haagensen	1971	(11)	8	73
Millis	1975	(8)	2	25
Rosen	1980	(15)	8	53
Eusebi	1994	(80)	11	14
Page	1995	(28)	9	32
			Mean =	28 %

After: Schnitt USCAP 2009

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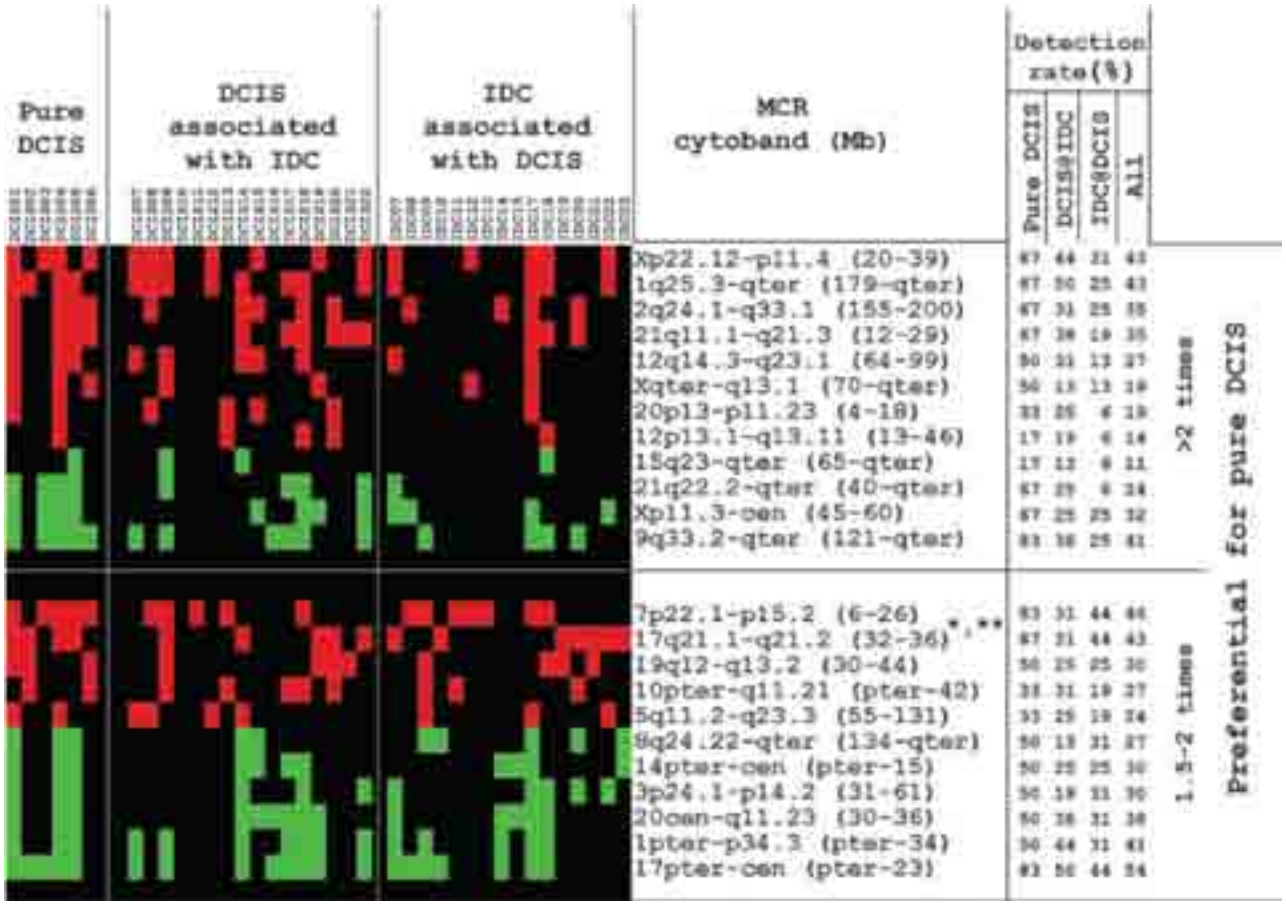
Genomic Differences Between Pure Ductal Carcinoma *In Situ* of the Breast and that Associated with Invasive Disease: a Calibrated aCGH Study

Vladimir V. Iakovlev,[1] Nona C.R. Arneson,[1] Vietty Wong,[1] Chunjie Wang,[1] Stephanie Leung,[3,6] Galiane Iakovleva,[6] Keisha Warren,[1] Melania Pintilie,[7] and Susan J. Done[1,2,4,5]

Clin Cancer Res 2008;14(14) July 15, 2008

- ***DCIS associated with IDC is genomically similar to the invasive component and therefore may represent either a clone with high invasive potential or invasive cancer spreading through the ducts.***



Low Grade DCIS (LORD) Trial

- Hypothesis: Asymptomatic, low-grade DCIS detected by microcalcifications only can safely be managed by active surveillance
- Aim: To show non-inferiority of active surveillance as compared to standard treatment in low-grade DCIS patients
- Primary end-point: Ipsilateral invasive breast cancer-free rate (IBCF rate) at five years
- Study design:
  - Randomized, non-inferiority trial
  - Age $\geq$ 49 year
  - Asymptomatic, low grade DCIS w/ microcalcifications

Wesseling, EBCC-9, 2014

Should lg-DCIS and LCIS be considered as a precursor lesions or as risk indicators?

- Histologic and molecular evidence indicate the lg-DCIS and LCIS are both precursor lesions and also risk indicators
- However, due to the slow progression of the lesions, they may never evolve into an agressive cancer

Personal view:

- Possibly, there is a balance of progression and regression with low-grade lesions, due to the low proliferation rates of the neoplastic cells, and this may explain for the low risk to the patients.

Summary

Overdiagnosis may occor in three different settings:

- Pathology overdiagnosis (misclassification)
- Terminologic overdiagnosis (overinterpretation)
- Academic overdiagnosis (low mortality lesions)