

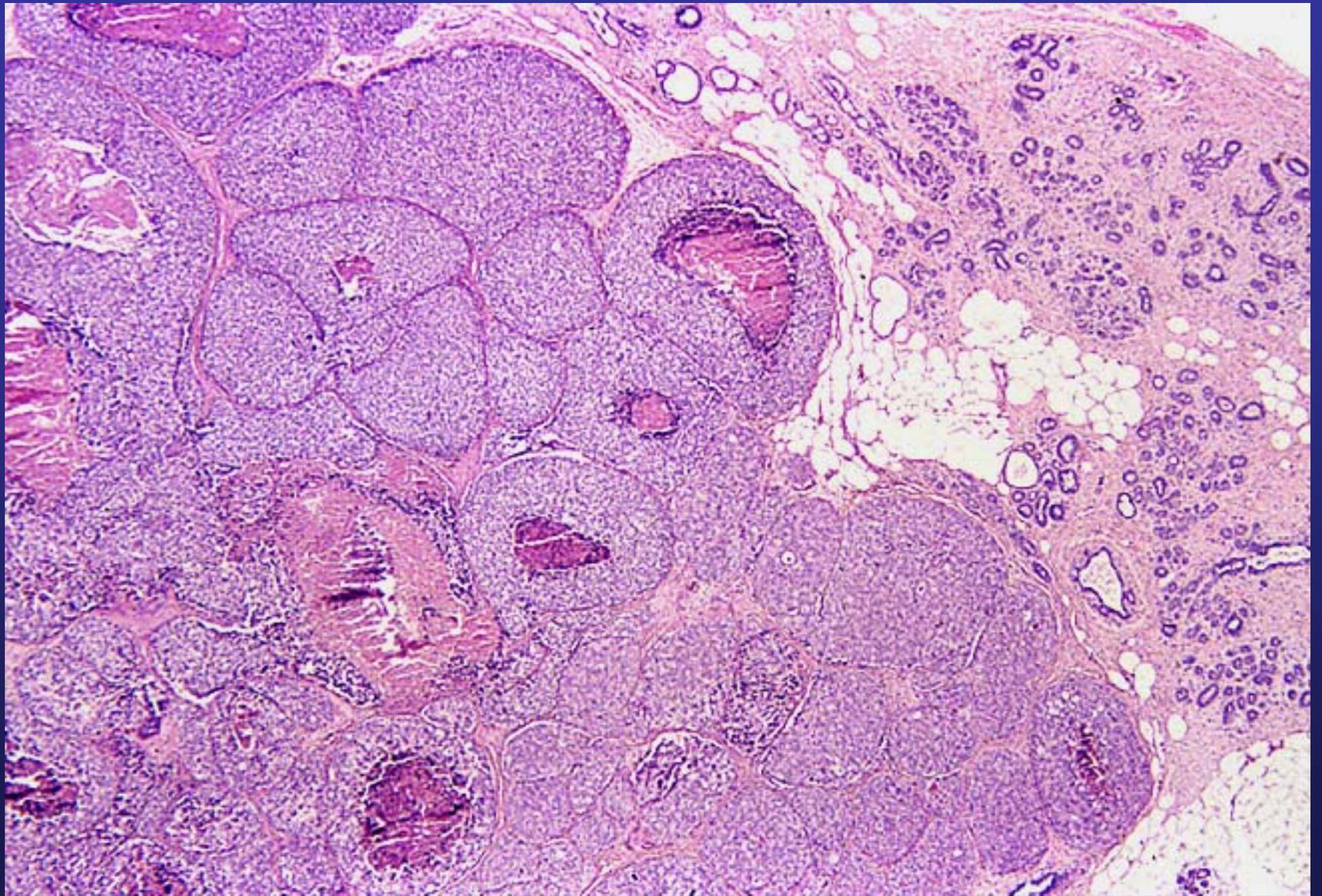
Ductal Carcinoma in Situ: Strategies for Integrating
Tumor Biology and Population Sciences
February 1-2, 2007, San Francisco, CA

Overview of the current definition of Ductal Carcinoma in Situ

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In the beginning...

- 1890's - Comedocarcinoma defined as a clinically palpable mass with foci of dilated ducts containing necrosis that can be expressed from the cut section of the tumor – not dependent on a microscopic evaluation
- Surgical pathologists were surgeons interested in describing the tissue or cellular basis of disease through visual and manual inspection of removed tissue for purposes of surgical decision making



Emergence of the basement membrane as a questionable defining feature

- 1911 - The cells of breast carcinoma were noted to look identical whether present in a duct or within the connective tissue
- 1913 - “Is it necessary to identify penetration of the basement membrane to establish a diagnosis of carcinoma?”
William MacCarty, Mayo Clinic
- 1920 - Surgery and Surgical Pathology diverge into distinct specialties

Recognition of DCIS as a subtype

- 1930's – well established that intraductal carcinoma existed but as a subtype of typical [invasive] carcinoma, CIS coined
- 1950's – intraductal carcinoma defined as a tumor with “at least 50% of tumor within ducts”, several patterns recognized, but all are “infiltrating and fully malignant” even though “actual infiltration” is not observed

State of the Art: mid 20th century

- Approximately 15% of carcinomas were the intraductal subtype [mixed DCIS and invasion]
- Deep mistrust of DCIS by surgeons,
 - even “pure forms” [only DCIS identified] metastasized and killed patients
 - 29% of “intraductal carcinoma” had axillary metastases
- The problem: mastectomy is routine treatment, large tumors were typically under-sampled with less than 10 sections examined - difficult to reliably exclude invasion

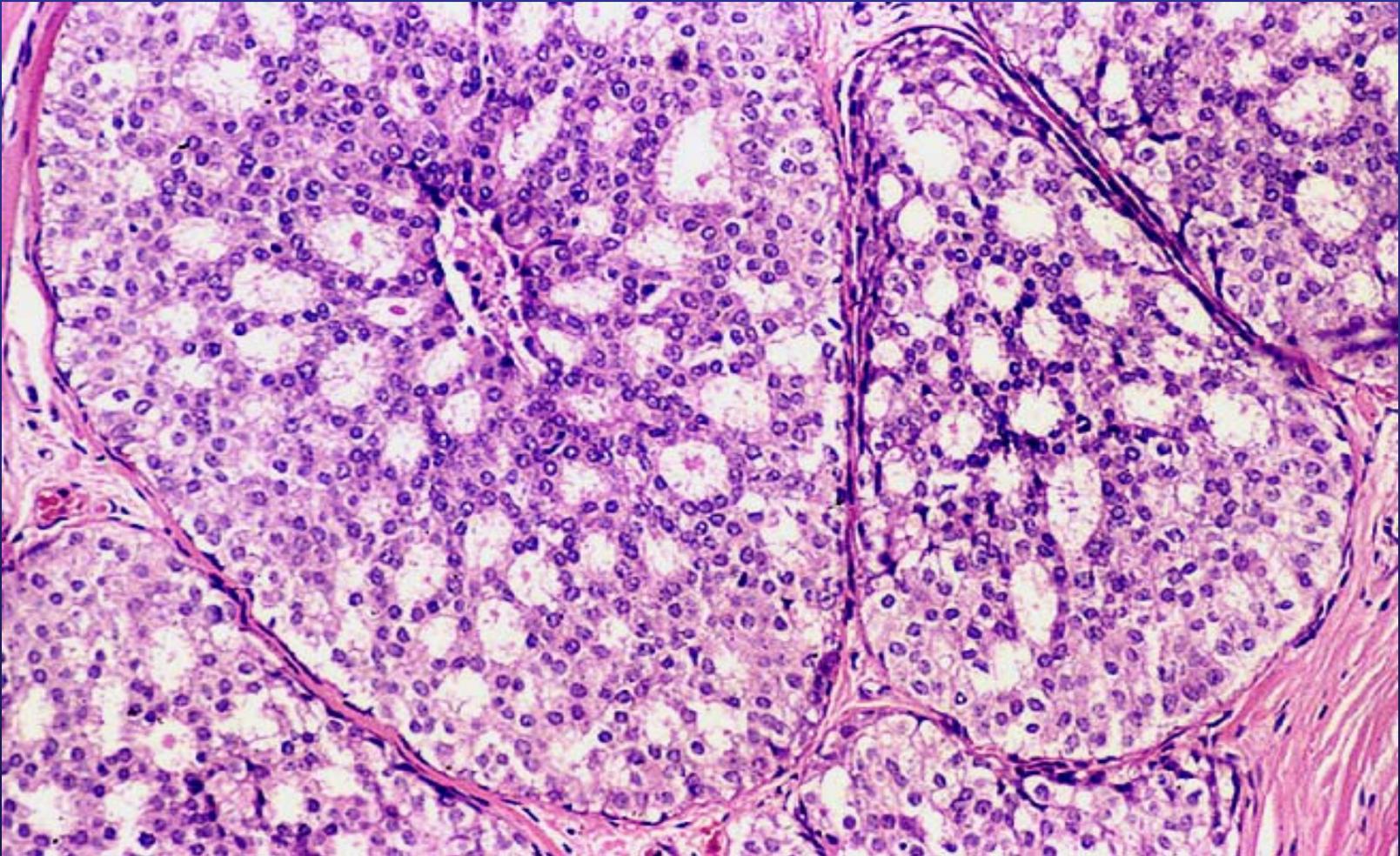
Pathology learning curve

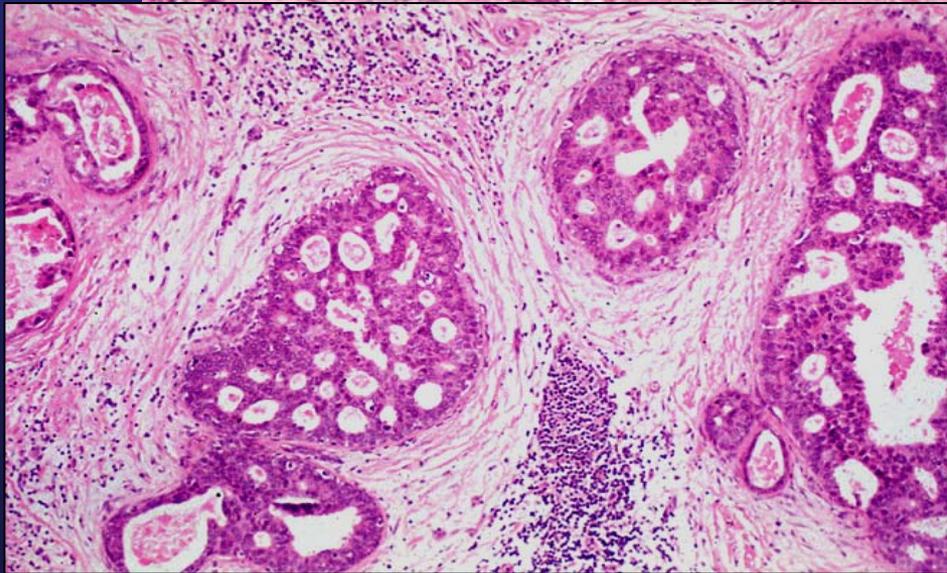
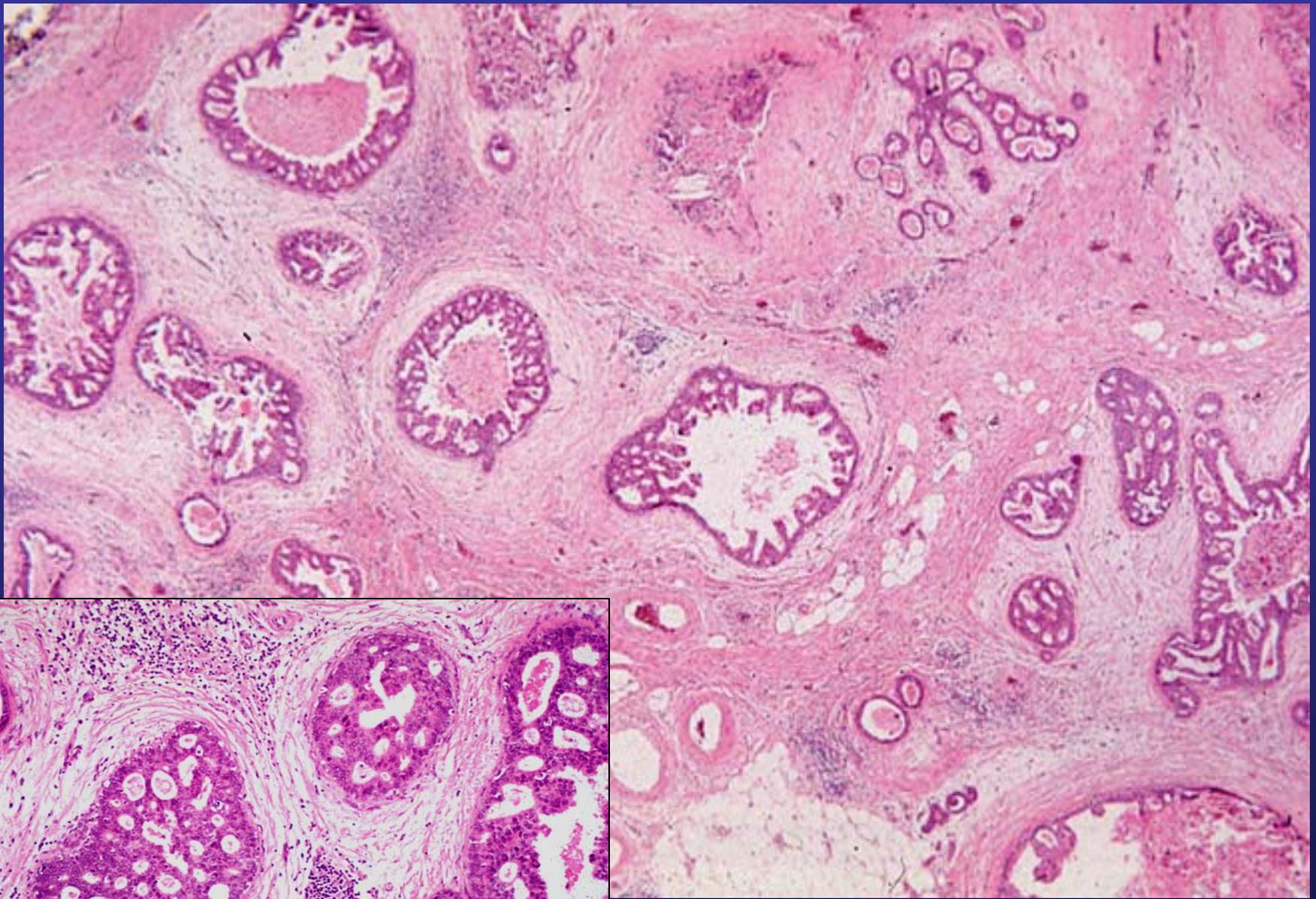
- Epidemiology
 - Median size of breast carcinoma is 3.4 cm
 - Median size of “intraductal carcinoma” is 3.3 cm
 - “intraductal carcinoma” noted to have a better outcome than carcinoma of no special type (eic)
- 1950 – 1970, evolution of DCIS
 - published incidence of node metastases decreases from 29% to 5% to <1%
 - [presumably as pathologists become better trained they are better able to distinguish between pure DCIS and invasion, sampling increased, also effect of other factors such as public awareness leading to decreasing tumor size]

Hypotheses and conflicts

- 1960's – progression theory: inexorable march of low grade DCIS to high grade DCIS to invasive carcinoma
- 1970's – electron microscopy demonstrates that DCIS has cytoplasmic extensions through gaps in the basement membrane, an observation thought to prove inevitable invasive behavior

Late 70's early 80's – lower grade, non-comedo forms of DCIS widely recognized

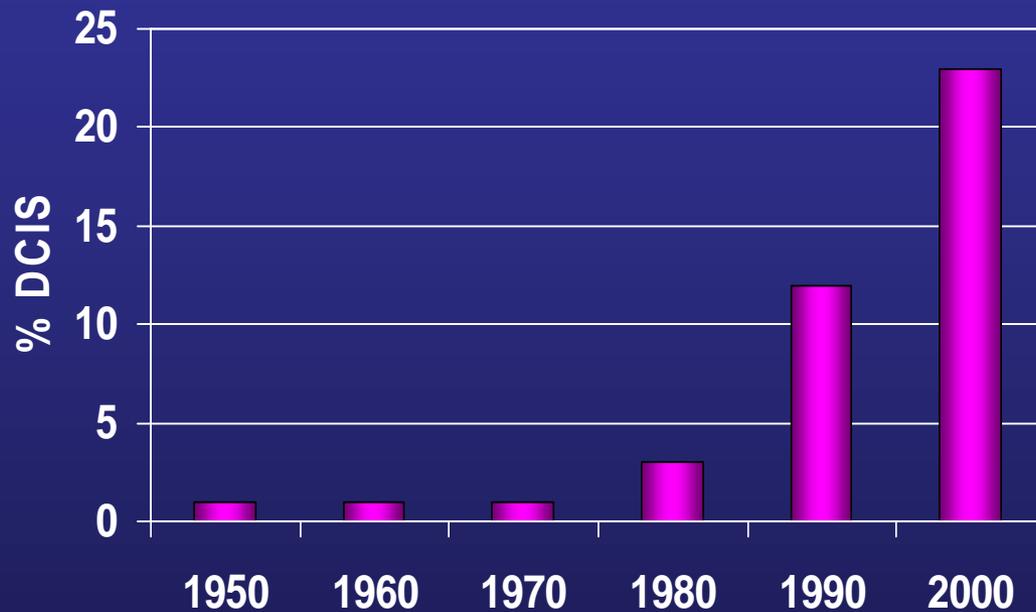




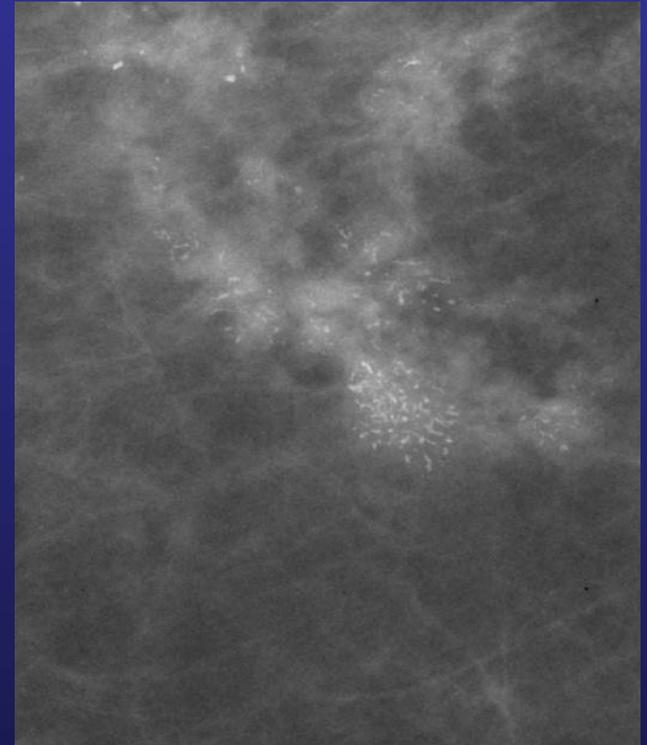
DCIS established as a distinctly different clinical-pathologic entity

- 1982 – Lagios demonstrates that small (<25mm) DCIS is unlikely to have associated invasion whereas 44% of DCIS >25mm had associated invasion
 - proof of principle that not all DCIS need be treated by mastectomy
- 1980's – Page and colleagues establish criteria for the diagnoses of usual hyperplasia, atypical ductal hyperplasia, and DCIS
 - Pre-neoplasia emerges

DCIS increases as a proportion of new breast cancer diagnoses

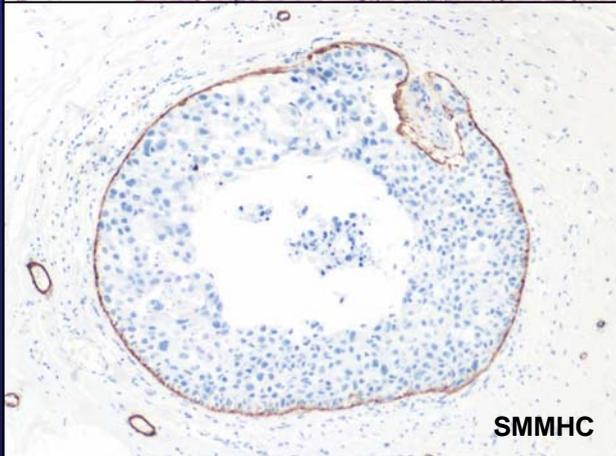
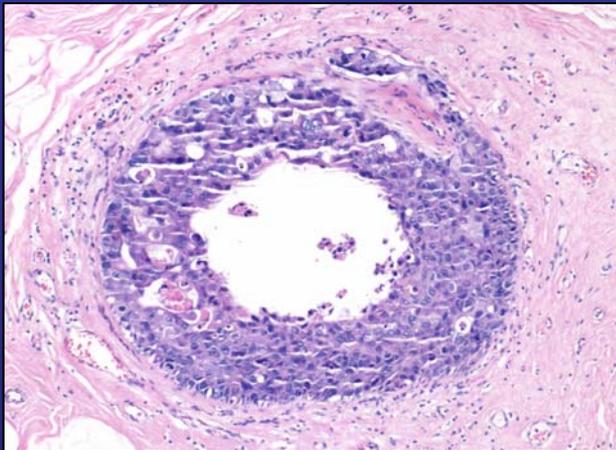


Source: SEER, BCSC, historical literature



Prevalence of DCIS increases 587% compared to 34% for invasive

Defining features of DCIS: The end of the first 100 years

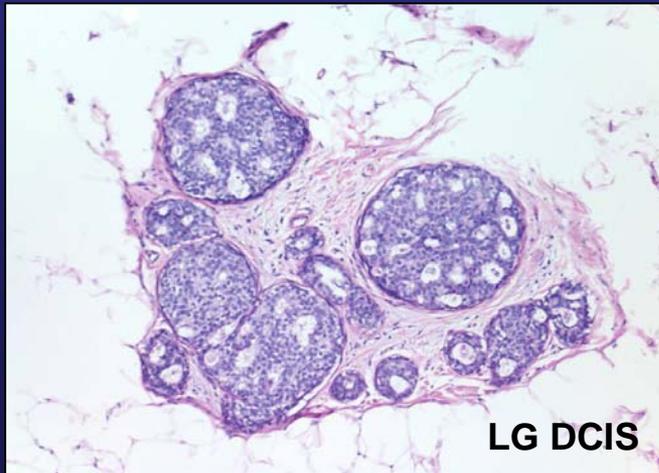
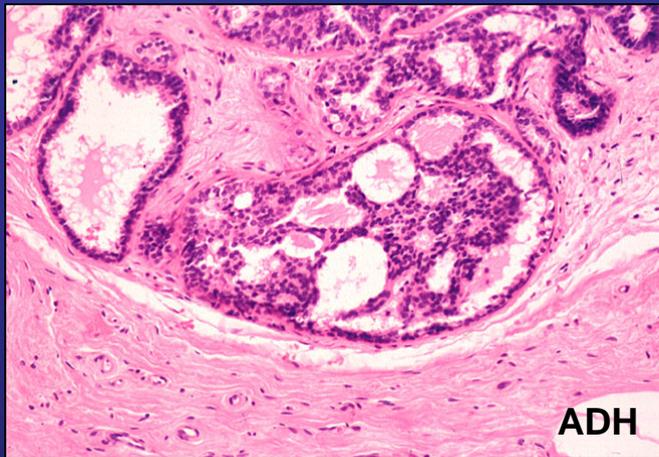


- Malignant Cytology
 - monomorphic or pleomorphic
- Volume
 - at least 2 duct cross sections (Page)
 - sum of involved duct diameters >2mm (Tavassoli)
- Architecture
 - confined to duct (lobule)
 - may be complex, no single cells or angular clusters outside specialized stroma of lobule
 - solid, cribriform [neolumens], papillary, arches, palisades

DCIS Grade

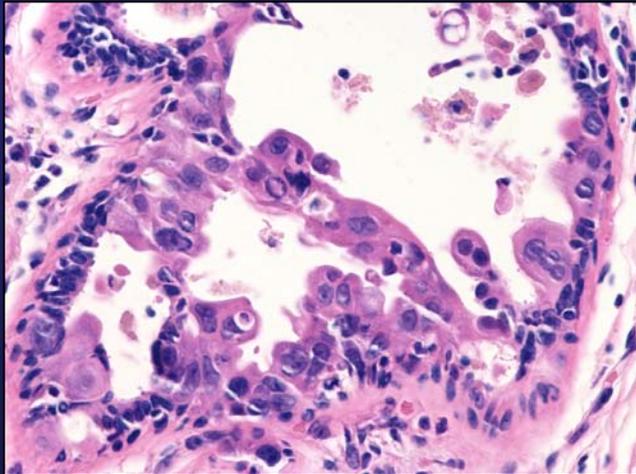
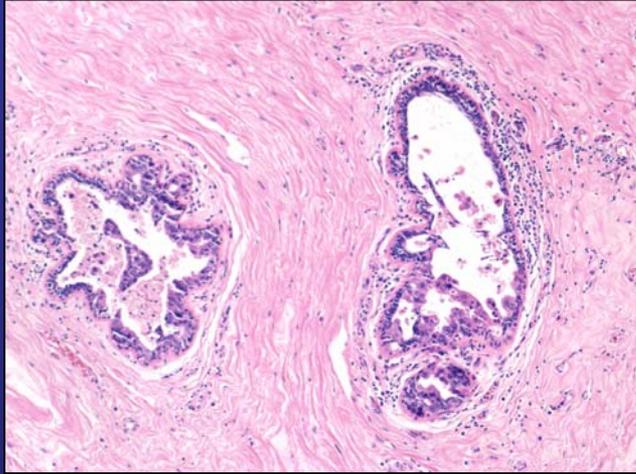
Nuclear grade	Necrosis	Overall grade
1	absent	low (well)
	present	intermediate (moderate)
2	absent	
	present	
	extensive	high (poor)
3	absent or present	

The lower limit: ADH v LG DCIS



- Cytology similar or identical
 - Partial duct involvement
- Similar genetic abnormalities (16q-)
- Low risk if totally excised
- VOLUME defines

The lower limit: ~~ADH~~ v HG DCIS

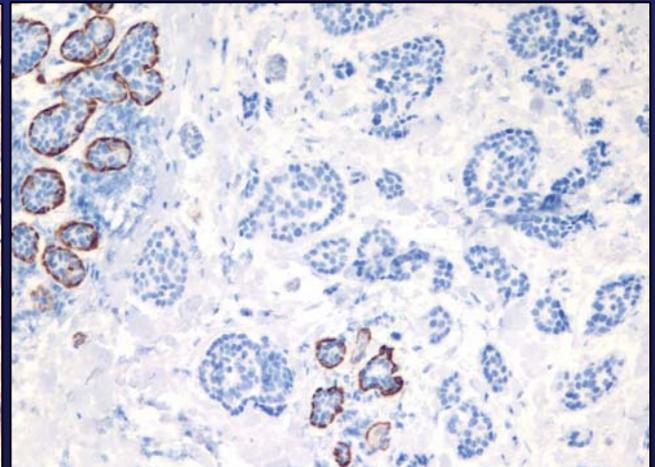
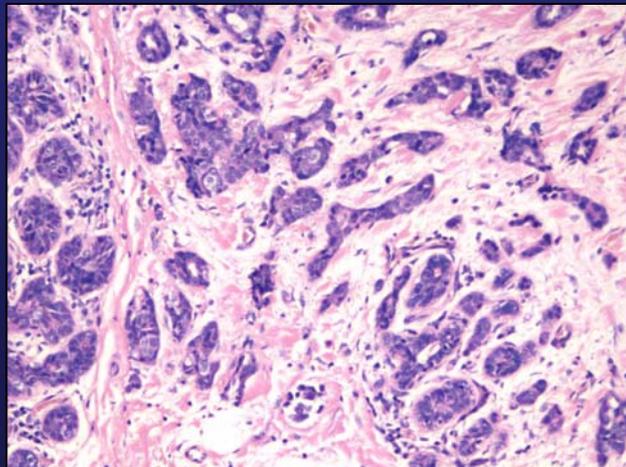
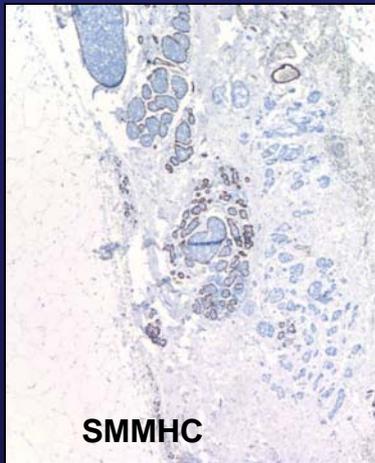


- High grade cytology trumps volume

The upper limit: DCIS to invasion



- Architecture
 - Violates lobular profile
- Special studies
 - Absence of basal myoepithelial layer



What are you likely to find documented in the medical record?

(What can we expect for population based studies?)

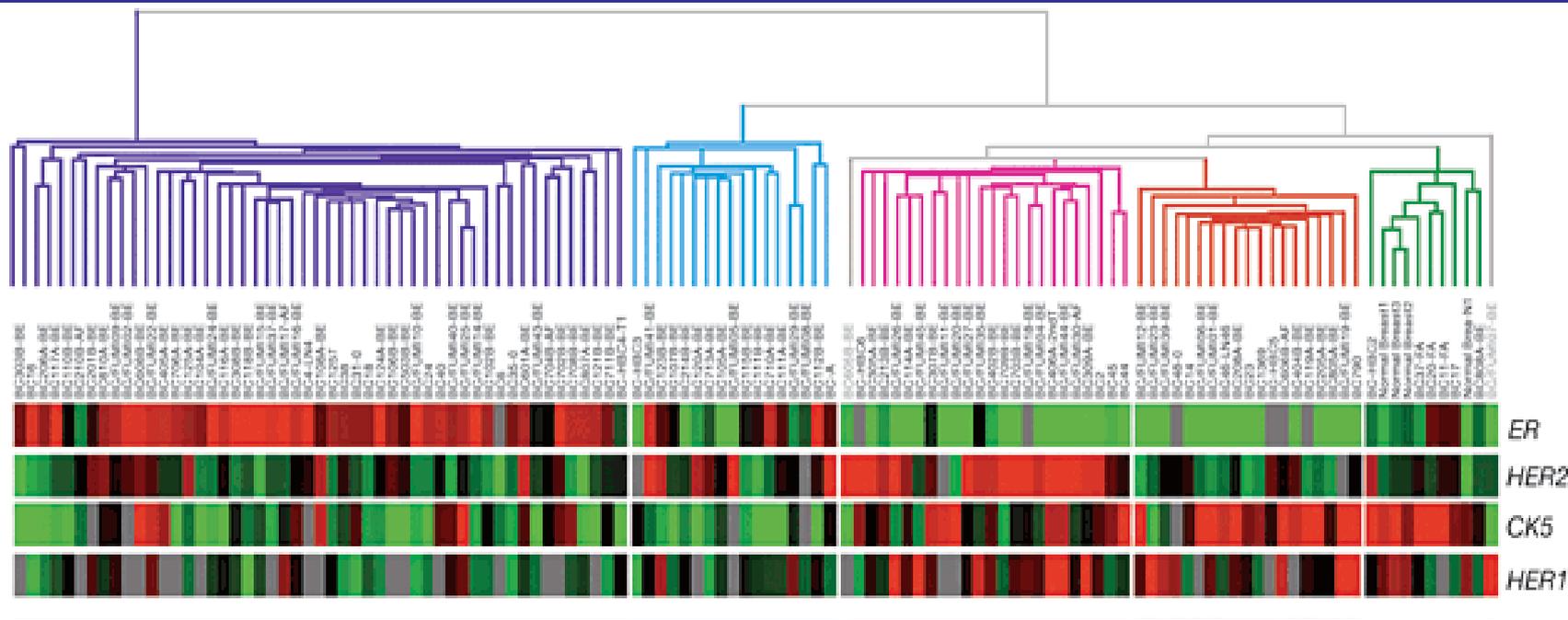
- Diagnosis (DCIS)
- Grading schemes
 - Comedo/non-comedo
 - Architectural patterns
 - Necrosis
 - Nuclear grade
- Margins
 - No mention
 - Negative/positive
 - Distance to closest
- Poor documentation of volume
- Future efforts
 - CAP checklists
 - Improved volume
 - Improved margins
- Data will still be heterogeneous and of variable quality

How might studies of invasive carcinoma help? (and why?)

Phenotype is conserved in breast cancer

- DCIS grade/cytology similar to invasive
- Recurrent cancer similar to original
- ER preserved in metastases/recurrences
- Her2 preserved in metastases/recurrences

classification of DCIS may mirror invasive



Microarray-Based Breast Cancer Subtype^{15, 17}

Luminal A

Luminal B

HER2+/ER-

Basal-like

Normal Breast-like

Immunohistochemical Profile

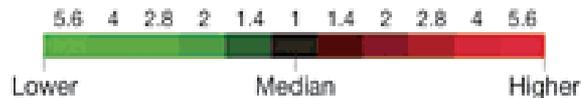
ER+ and/or PR+,
HER2-

ER+ and/or PR+,
HER2+

ER-, PR-,
HER2+

ER-, PR-, HER2-,
CK5/6+ and/or HER1+

Gene Expression
(Fold Difference Relative to Median Level of Expression Across All Samples)



Progenitor Cell Concept [adapted from W Boecker and colleagues]

