Lobular Neoplasia, LCIS and ILC

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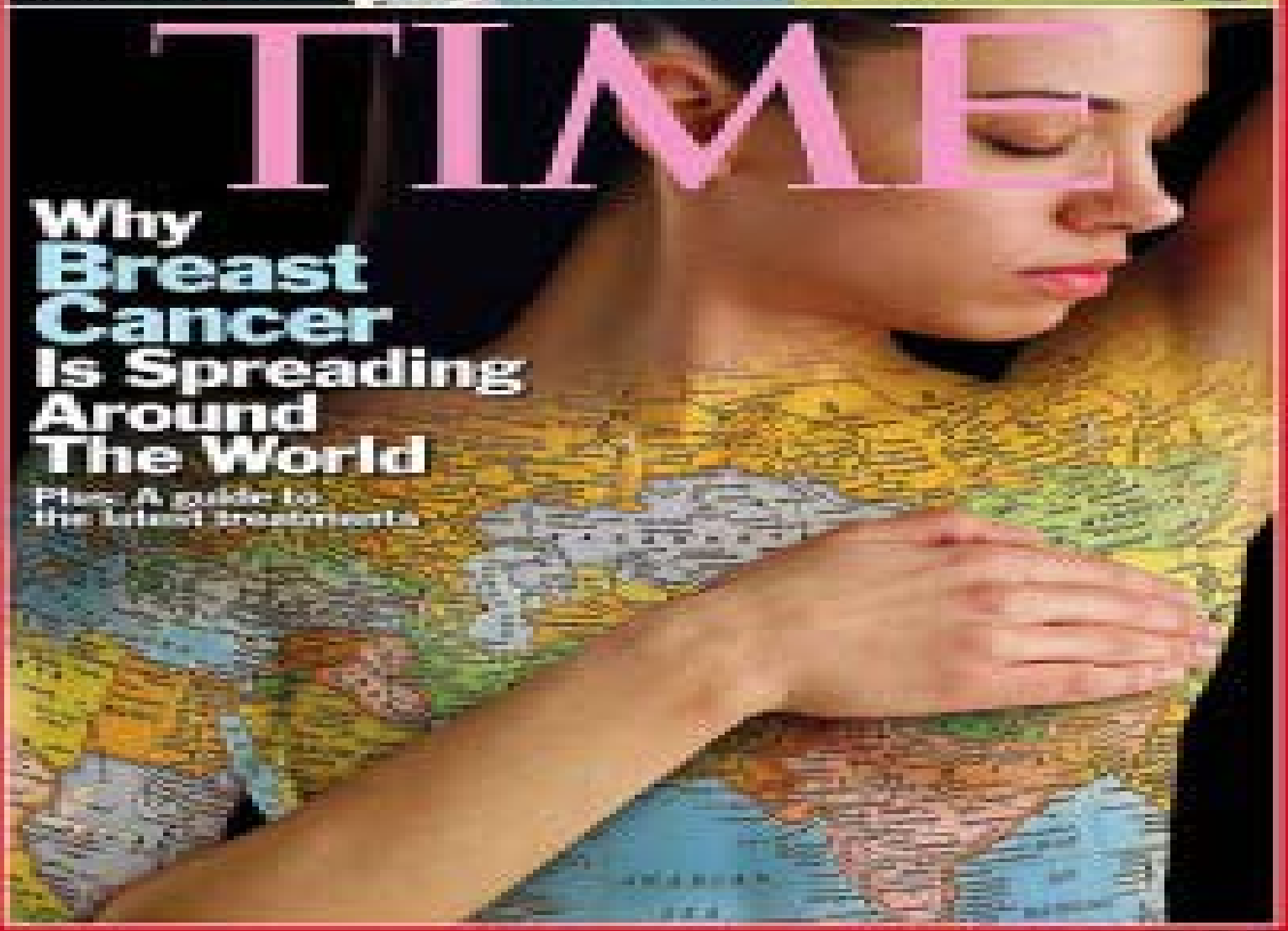
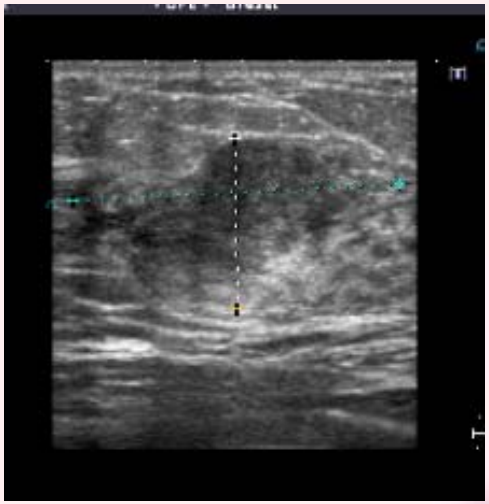
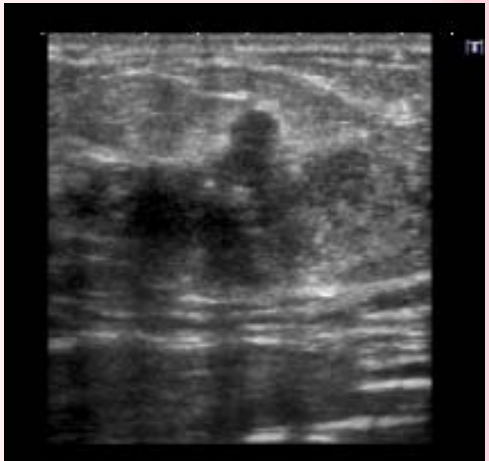
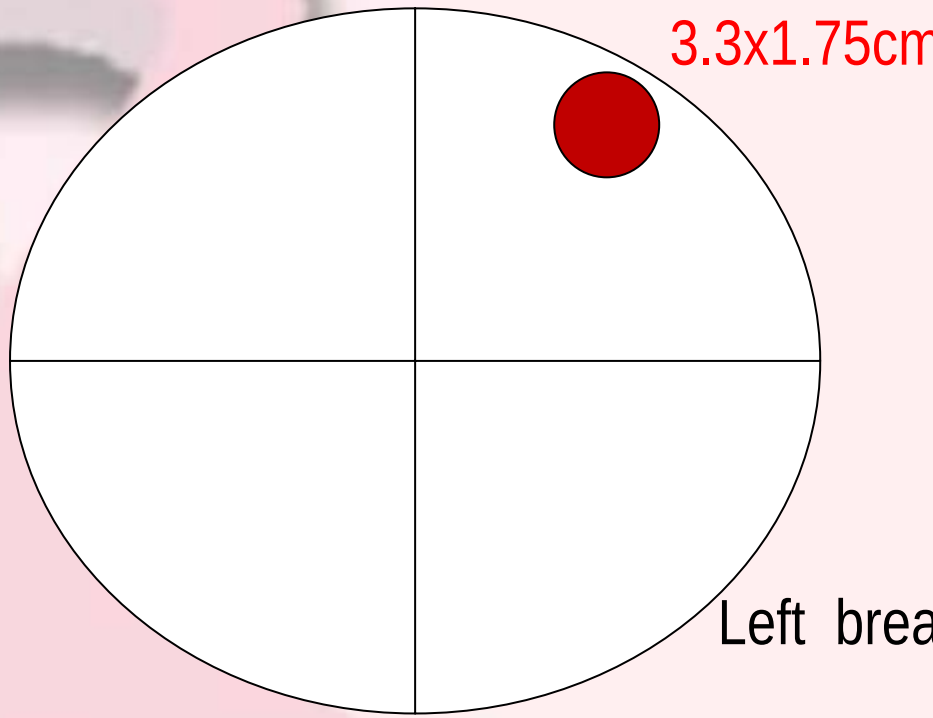


- 41 Y/O female.
- Nodule noted by patient on left breast about 2 -3 months before her visit to our clinic.







Surgery – Left MRM.
Lymph node, 4/9 .
ER : (-)
PR: (3+)
Her-2: (3+) by IHC

Questions

- 1. Is LCIS benign or malignant ?
- 2. Is LCIS precursor of ILC ? or just risk factor ?
- 3. How would LCIS develop into ILC ?
- 4. Is the term LCIS interchangeable with
- lobular neoplasm(LN) ?
- 5. How should we deal with LCIS ?
- 6. What is the major difference in surgical
- treatment between ILC and IDC ?

History of Lobular Neoplasia

- 1919, James Ewing , “Neoplastic Diseases” :
- Probably the first to identify and illustrate with 2 pictures of the lobular and ductal manifestations of these so-called “lobular lesions”.
- “ Atypical proliferation of acinar cells” and “Precancerous changes….atypical proliferation in a segment of a duct”

Foote and Stewart in 1941

- “Lobular carcinoma in situ” first defined in 2/300 mastectomy specimens, similar to those described by Ewing in 1919.

- 12/300 lobular proliferation + conventional infiltrating carcinoma

(Foote FW, Stewart SF, Am J Path 1941)

Cushman D. Haagensen at Columbia Physician & Surgeon

- Clinical Features:

1. Largely in premenopausal women and its lobular component regressed to some degree after menopause.
2. Multiple foci in one or both breasts
3. Does not form a palpable mass,
   lobules and ducts involved are so small
4. It does not metastasize
5. Predisposed to the subsequent development of carcinoma (LICS⟶ ILC)
6. Carcinoma as often as in contralateral breast
7. Carcinoma are usually of several special histology

(Haagensen, Bodian, Haagensen. Breast Carcinoma. 1981, Saunders Co.)

Nature History of LCIS to ILC

- 4% to 33% of LCIS will develop into ILC

10 years	**20 years**	**35 years**
13%	26%	35%

Bodian et al. Cancer 1996

- Data from SEER:

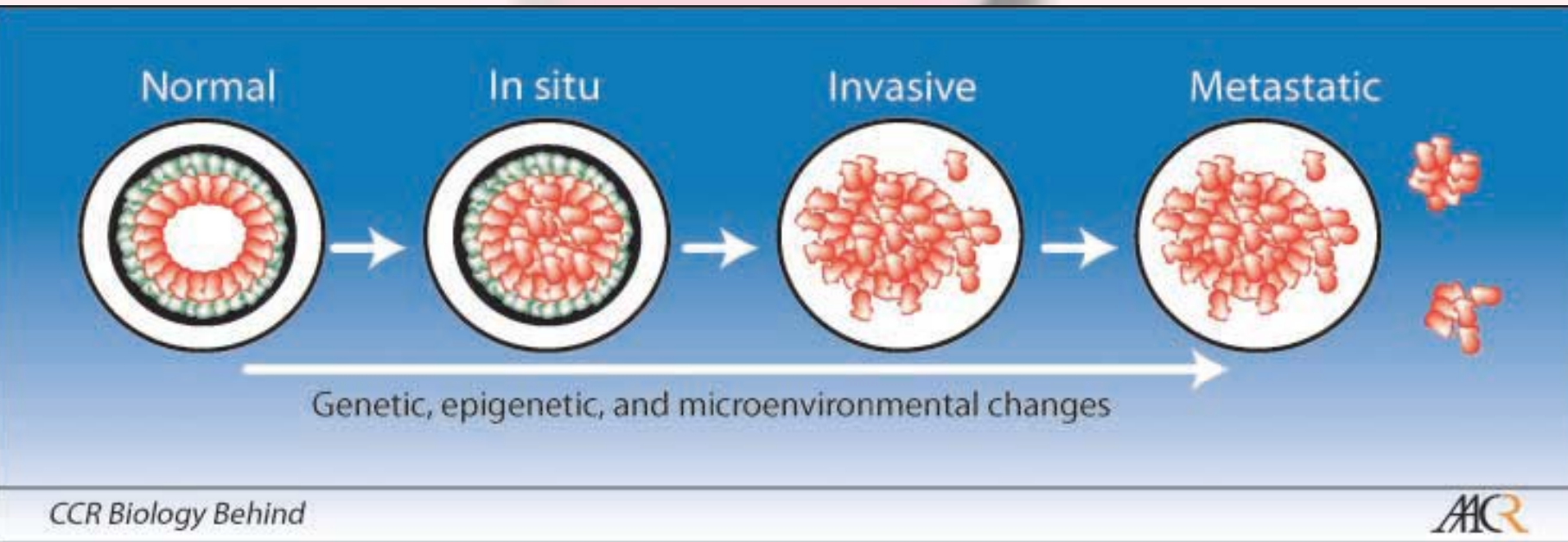
1973-1988	11% in 15 years
1988- 2003	6.2% in 15 years
	6.2% in 15 years
NSABP B-17	22.2% (Page, The Lancet 2003)
Population-based	12.5% in 25 years (Levi Int J Cancer 2005)

Possible mode of how LCIS developed into ILC

轉移機制

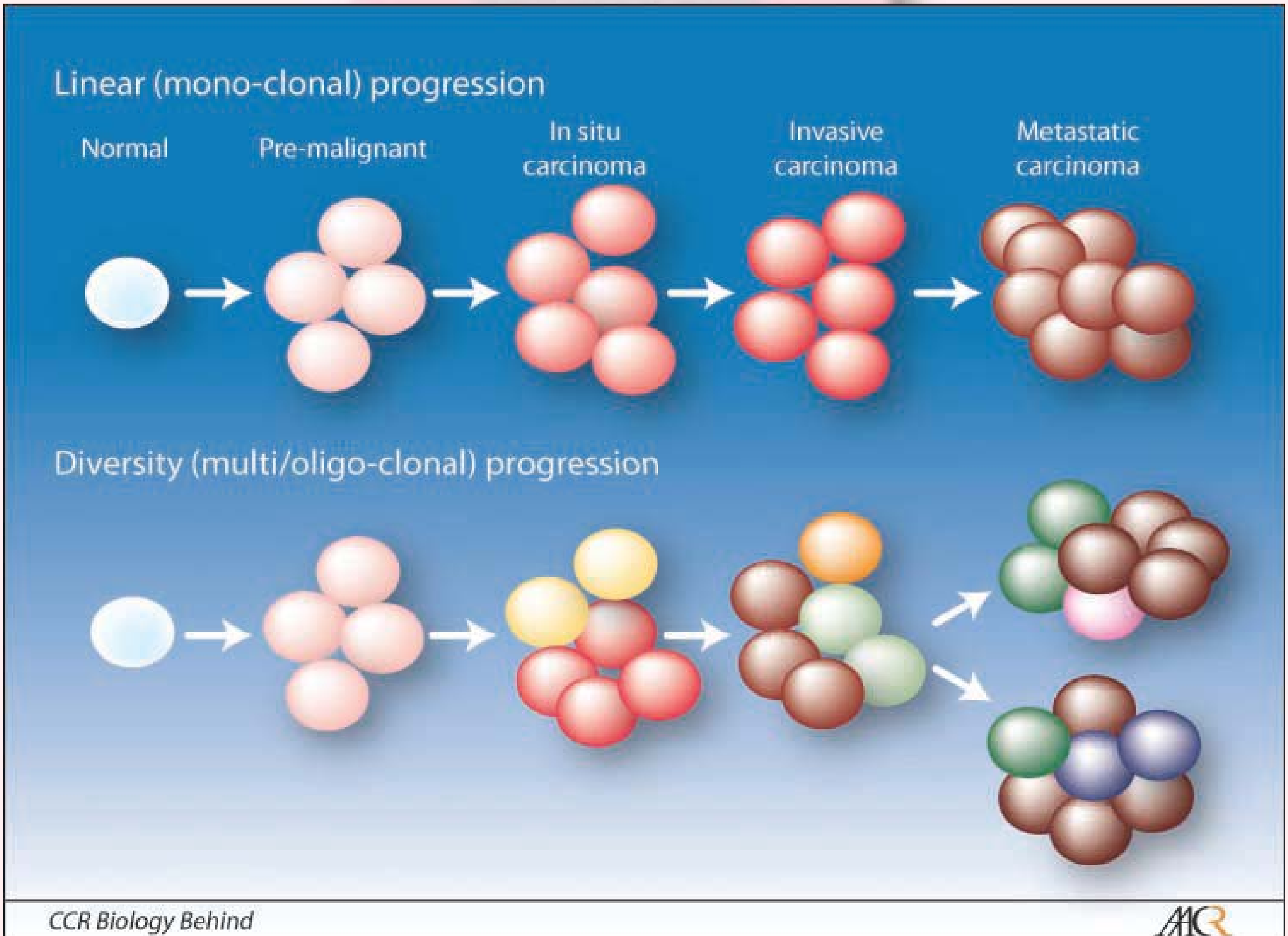
Vogelstein & Fearon Theory

Normal cell → Dysplasia → Adenoma → In situ → Cancer → Metastases



圖片來源：Kornelia. Is breast tumor progression really linear? Clin Cancer Res 2008;14(2):339-341.

數學分析模式(Mathematic Analysis Model)

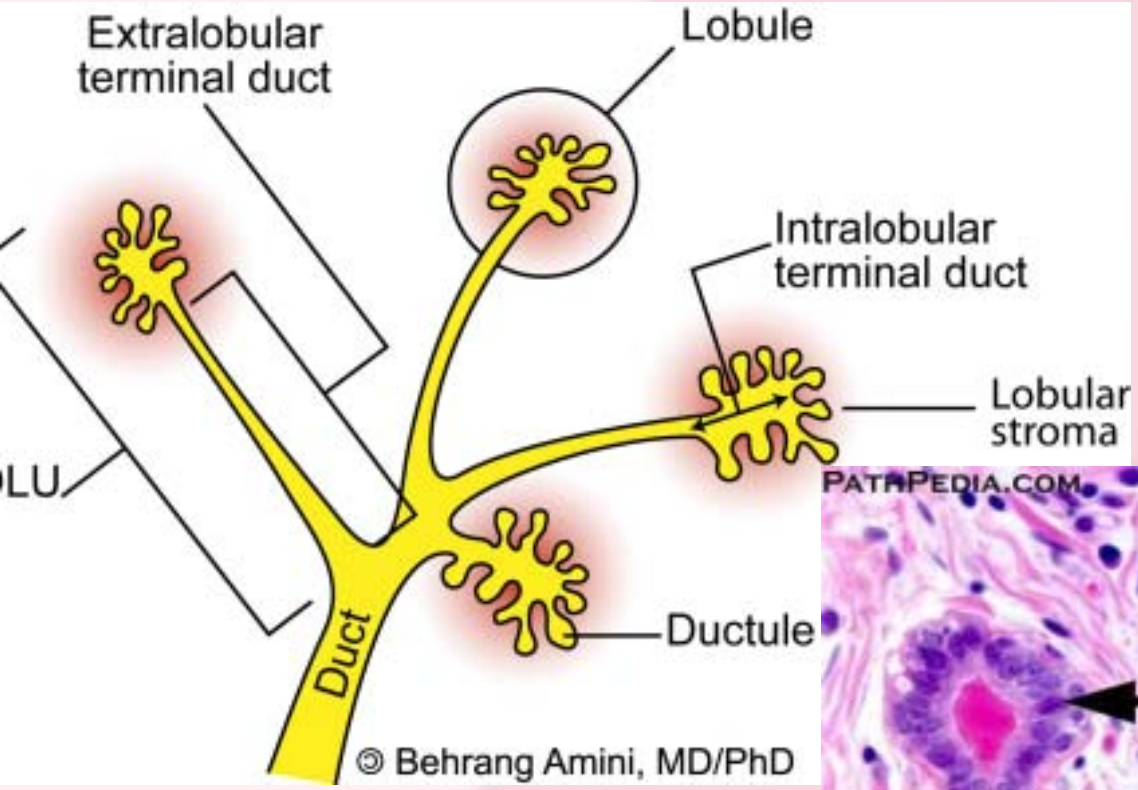


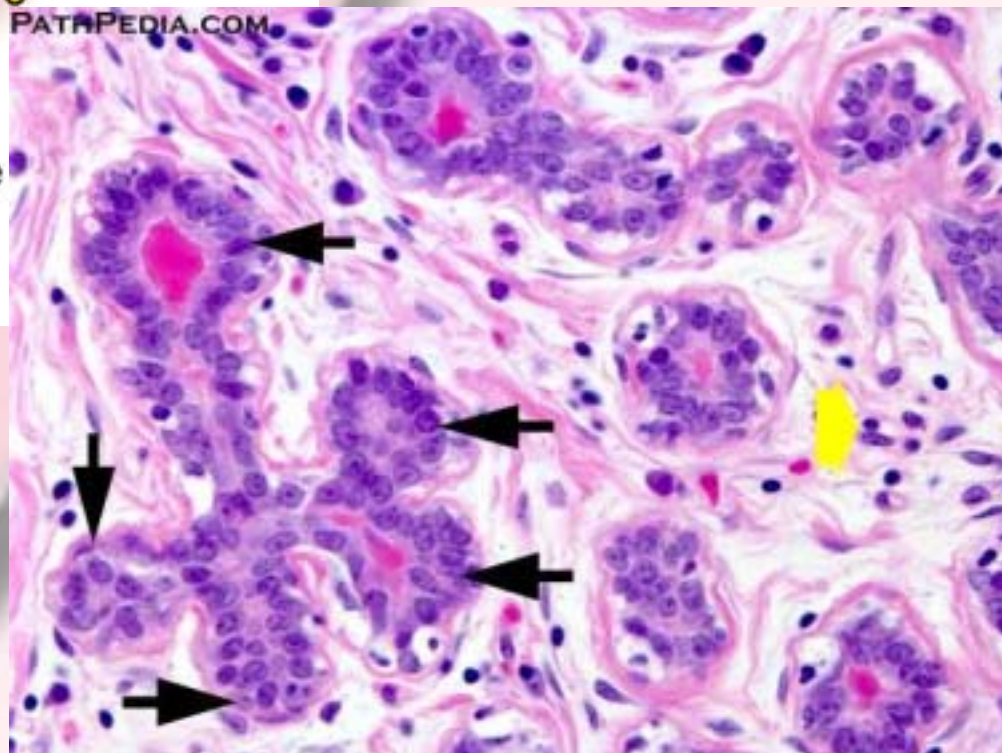
圖片來源：

Pathology of Lobular Neoplasia

- The mammary acini are lined by 2 types of cells.
  - 1. epithelial cells
  - 2. myoepithelial cells
- Presence of cells containing clear vacuoles, known as intracytoplasmic lumina or magenta bodies.
- Differentiation between ALH and LCIS
- Pleomorphic LCIS(PLCIS)

Pathology


Extralobular terminal duct
Lobule
Intralobular terminal duct
Lobular stroma
LU
Duct
Ductule
© Behrang Amini, MD/PhD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Molecular Pathology

1. Immunophenotype
2. E-Cadherin Immunochemistry in lobular neoplasia
3. Molecular aspect of E-cadherin inactivation
4. Whole genome molecular genetics of lobular neoplasia

Immunophenotype

1. ER (+), PgR (+)
2. HER-2 (-) epidermal growth factor receptor
3. P53 >10%(tumor suppression gene)
4. Ki 67 <15%(cell proliferation gene)

E-Cadherin IHC in lobular neoplasia

- E-Cadherin mediates calcium-dependent cell-cell adhesion and loss of its function will result in cell discohesiveness.
  - E-Cadherin (+) : DCIS
  - E-Cadherin (-) : LCIS
  - Mixed lesions
- Lack or display aberrent E-Cadherin expression : triple negative or basal-like breast cancer

Molecular aspect of E-cadherin inactivation

- Loss of chromosome arm 16q : common finding
  - lobular
  - low- grade ductal proliferation
- E-cadherin inactivation or down-regulation occurs via a combination of
  - genetic
  - Epigenetic(transient reversible changes):
  - transcriptional mechanisms: signaling pathway lead to transcription of new gene---cell growth, cell differentiation, cell death and other biological effects

- Gene mutations have been identified in:
  - ALH
  - LCIS
  - PLCIS
  - ILC
  - rare in bona fide(genuine, real) IDC.

Clinical Implications

1. ***Calcification*** may be up to 40% of ALH and LCIS (contrary to traditional concept).

2. Only 0.5%-2.9% of biopsy as sole ***LN in CNB***
3. LN should be perceived as "***high risk***" and recommended excision of all cases due to the ***underestimation of cancer up to 33% of LN*** diagnosed on CNB

4. ***PLCIS***, more associated with aggression, should be subjected to further excision(pleomorphic LCIS)

Quantitative Variations in Lobular Neoplasia

1. Loss of cohesiveness: E- cadherin (-).
2. Increase in cell size
3. Macroacini
4. Hyperchromatic, closely packed cell masses
5. Microscopic types of carcinoma developed following lobular neoplasia :
   - 90% well differentiated
   - 10% undifferentiated

Infiltrating(invasive) Lobular Carcinoma

1. postmenopausal
2. non-cohesive cell proliferation, E-cadherin (-) 90%
3. low histologic grade
4. 80%-90% ER(+), low HER/2(+),
   (Arpino et al. Breast Cancer Res 2004)
5. multicentric and multiple metastasis
6. high rate of visceral, CSF, serosal surface, retroperitoneum, ovary and bone marrow metastasis
7. bilateral, 20%-29%, combined with IDC 3%-7%
8. poor response to chemotherapy
   (not good to consider neoadjuvant chemotherapy)
9. treatment outcome is similar to IDC. (Pestalozzi et al. JCO 2008)
10. different molecular entity from that of IDC

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Conclusions

1. LN(lobular neoplasm), LCIS not only the risk factor but more importantly also the precursor of ILC.
2. Approximately, 1% of LN or LCIS will develop into ILC per year.
3. Further surgery will be necessary if ductal carcinoma mixed in the process of CNB for LN or LCIS (no further surgery needed vice versa)

Conclusions

4. Mastectomy rather than BCS is more appropriate for ILC due to the nature of multicentric and multifocal lesions to reduce the rate of recurrence, 6% vs 29%

(Sarron et al., Cancer 2001)

5. The incidence of bilateral ILC is about 20%-29% (IDC 3%-7%), thus prophylact bilateral mastectomy has to be considered.

Invasive Lobular Carcinoma
vs
Invasive Ductal Carcinoma

- Database: 263,408 women diagnosed as breast cancer from SEER during 1993-2003

	size>2cm	LN(+)	ER(+)
ILC	43.1%	36.8%	93.1%
IDC	32.6%	34.4%	75.6%

- $p<0.001$

5-year disease-specific survival(DSS)

- Before stage-matched :

ILC	IDC	
90%	88%	p<0.001

- After stage- matched:

	T1N0	T2N0	T3N0
ILC	98%	94%	92%
IDC	96%	88%	83%

p<0.001

5-year DSS for Nodal Metastasis

	T1N1	T2N1	T3N1
ILC	89%	81%	72%
IDC	88%	73%	56%
p value:	NS	<0.001	<0.001

Multivariate analysis: identified 14% survival benefit for ILC (HR 0.86).

Wasif N. et al. Invasive lobular vs ductal breast cancer: A stage-matched comparison of outcome. Ann Surg Oncol 2010;17:1862-69