

Histoire naturelle des états pré-cancéreux

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Montpellier

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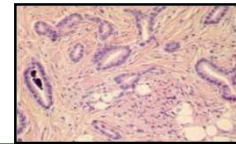
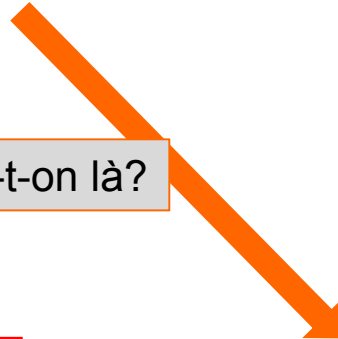
Epithelium Normal



Cellule épithéliale
+ Cellule Myoépithéliale
+ Membrane basale
+ Stroma

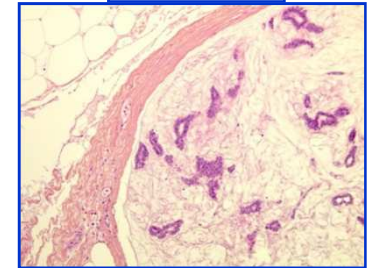
Comment arrive-t-on là?

Infiltrants

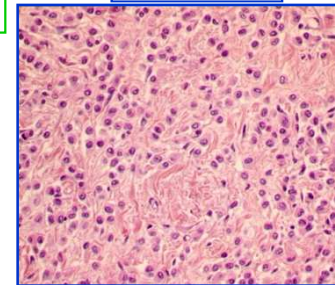


CCI
bas grade
1q+16q-
RO+ BCL2+

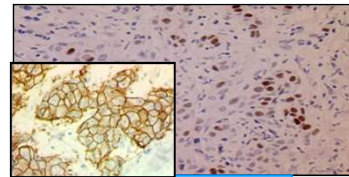
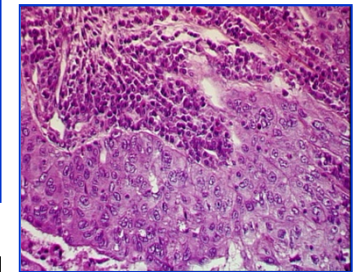
Mucineux



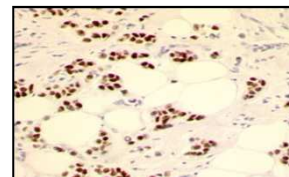
Lobulaire



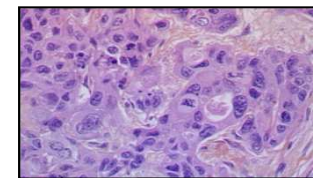
Médullaire



CCI
Luminal B
RO+
ERBB2+

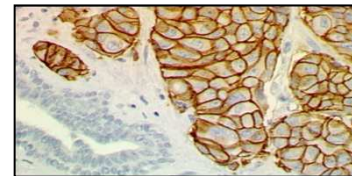
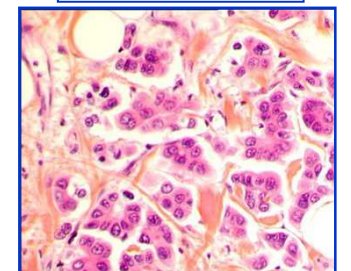


CCI
Luminal A
RO+



CCI
Basal-like
RO-
ERBB2-

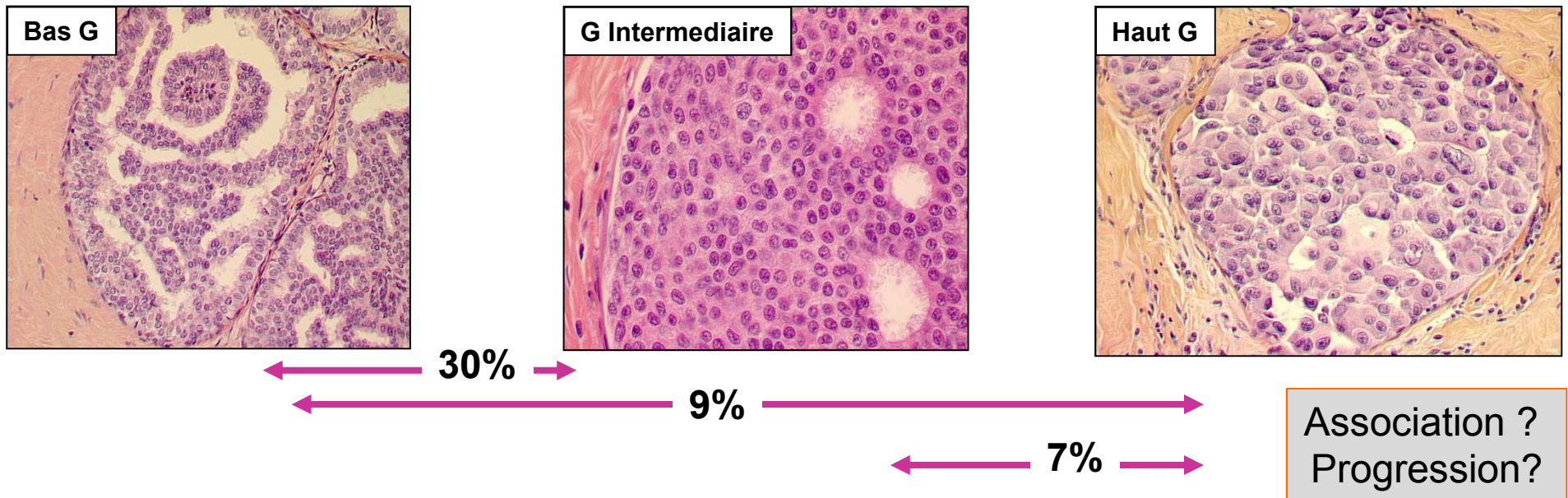
Micropapillaire



CCI
ERBB2+
RO-

Hétérogénéité des lésions de CCIS

- Grade nucléaire (trois classes)
- Autres paramètres
 - Nécrose
 - Architecture (micropapillaire, papillaire, cribriforme, solide ...)

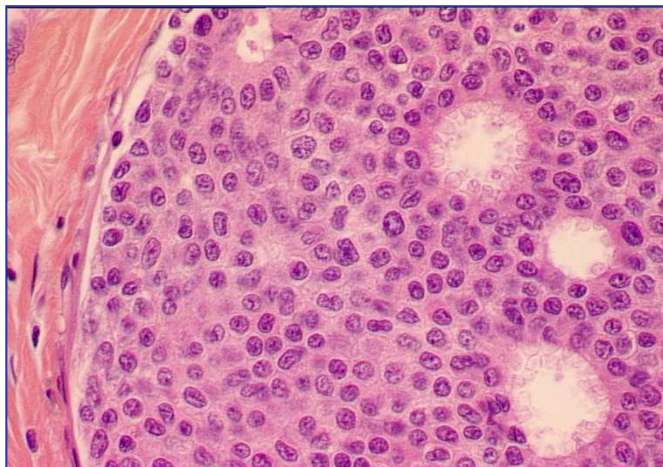


Alterations génomiques en fonction du grade

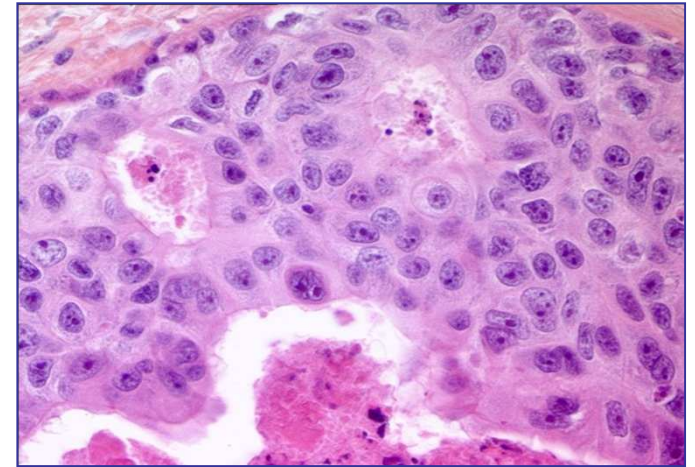
Bas grade



Grade intermédiaire



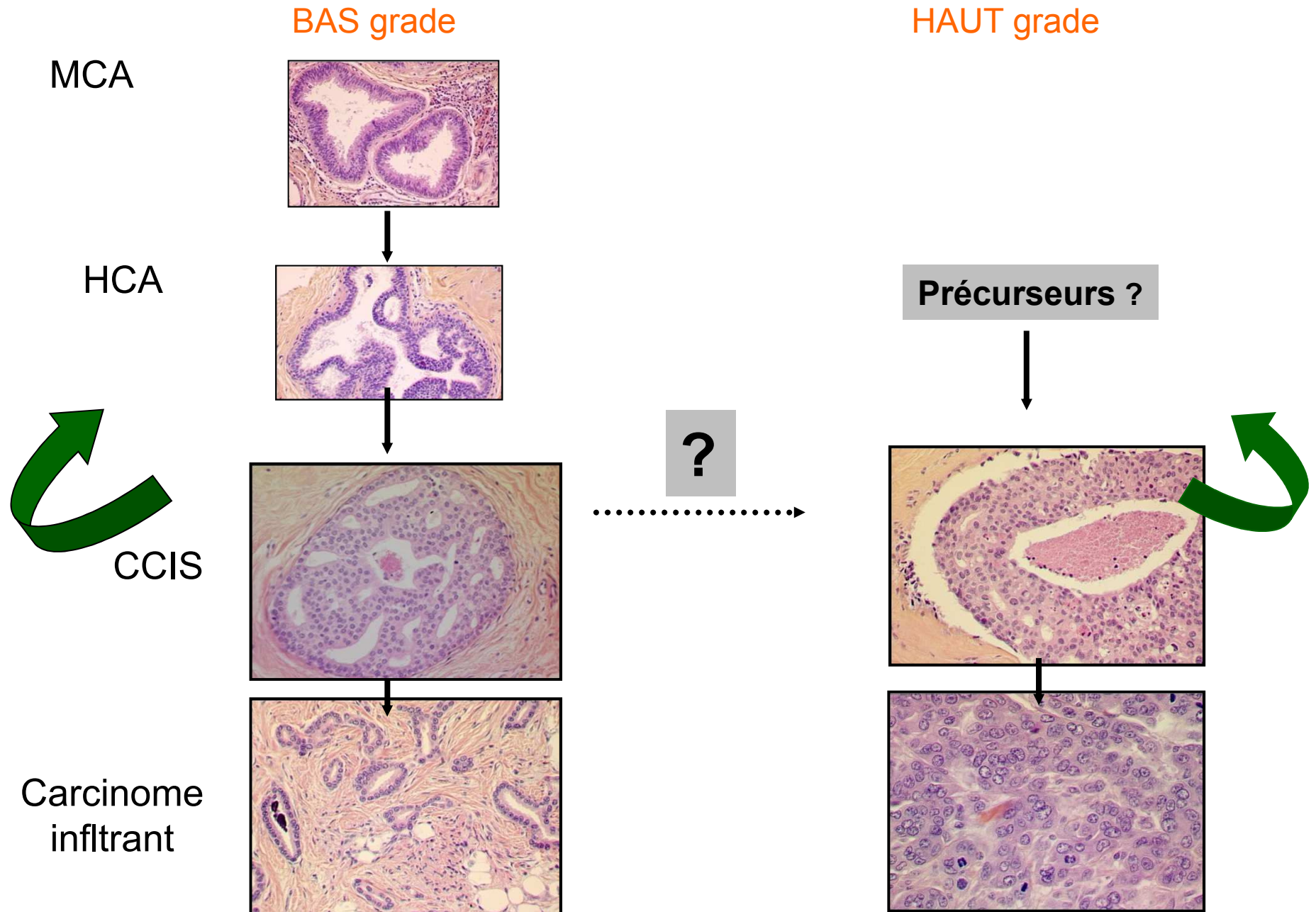
Haut grade



1q+, 16q-
CCND1 +
BCL2 +

1q+, 3q+, 17q+, 8q+, 11q-, 14q-, 8p-, 13q-
TP53 mutations
Amplification *ERBB2*
Amplifications 8q22, 11q13, 6q22
Prolifération (Ki67)

CCIS = précurseur des carcinomes infiltrants



Lésions précancéreuses in situ du sein à l'autopsie (mort sans lien avec un cancer du sein)

Nom (année)	Nb d'autopsies	Nbre de lésions in situ (%)	Nombre de CCIS (%)	Age moyen (ans)
Nielsen (1984)	77	14 (18)	–	67
Alpers and Wellings (1985)	185	–	11 (5,9)	–
Bhathal (1985)	207	27 (13)	21 (10%)	17 à 88
Nielsen (1985)	110	–	15 (13,6) 5,1% < 40 ans 33% 40-54 ans	20 à 54
Métanalyse (1997)			8,9%	

Welch HG, Black WC: Using autopsy series to estimate the disease “reservoir” for ductal carcinoma in situ of the breast: how much more breast cancer can we find? Ann Intern Med 127: 1023–1028, 1997

Lésions à haut risque sur les mastectomies prophylactiques

Table 2. Histopathologic Findings and Relevant Risk Indicators of Patients Younger Versus Older Than 40 Years of Age

	N = 67 (%)	< 40 years, n = 37 (%)	≥ 40 years, n = 30 (%)	p*
Overall presence of high-risk lesions	38 (57)	16 (43)	22 (73)	.01
ALH	25 (37)	8 (22)	17 (57)	.003
ADH	26 (39)	10 (27)	16 (53)	.03
LCIS	17 (25)	4 (11)	13 (43)	.002
DCIS	10 (15)	3 (8)	7 (23)	.08
Oophorectomy before mastectomy	17 (25)	5 (14)	12 (40)	.013
BRCA mutation carrier	44 (66)	29 (78)	15 (50)	.015
Previous breast cancer	26 (39)	7 (19)	19 (63)	.000

Signification biologique et clinique des MCA

= Précurseur des lésions d'hyperplasie canalaire atypique et de CCIS de bas grade

- Association fréquente
- Aspect cytologique identique
- Immunophénotype commun : RO/RP+++ Bcl2+, CK8/18+, CK5/6 –
- Altérations génomiques communes (1q+; 16q-)
- **Mais** taux de mutations de *PIK3CA* MCA >> Carcinome Infiltrant associé
- Mutations différentes entre lésions de MCA et les carcinomes associés

Troxell et al, Mod Path 2012

 Est-ce que les MCA sont vraiment des lésions précurseurs ??

Histoire naturelle des MCA

- Bijker, *EORTC Trial 10853* : 59 cas : pas de rechute (suivi de 5,4 ans)
- *Eusebi* : 25 cas : 1 rechute (suivi > 17 ans)
- de Mascarel : 115 cas : 7 rechutes (Suivi de 160 mois)
 - 3 CCI ----- à 1, 7 et 12 ans
 - 3 MCCA----- à 4 et 5 ans
 - 1 CCIS contro-latéral----- à 10 ans
- *Verschuur-Maes* : sur 27 cas non opérés et suivi ~ 100 mois: pas de rechute sous forme de CCIS ou CCI, un cas de néoplasie lobulaire
- *Boulos (Nashville cohort)* : Parmi 13 cas de MCA qui ont développé un cancer :
 - 6 ipsilatéraux / 7 controlatéraux
 - Grade 1 : 3/13; Grade 2 : 4/13; Grade 3 : 6/13

CCIS : hétérogénéité moléculaire

Luminal A (56 à 61%)

RO +++

Bas grade >>> haut grade

1q+, 8p+, 16q-,

*TP53** 3%

Pathways des oestrogènes et anti-apoptotique

Luminal B

+/- ERBB2 3+

RO +

*TP 53** 10%

ERBB2 (16 à 37%)

RO -

HG>>>NHG

4p-, 8p-, 3q-, 17q+

*TP53** 35%

Pathways de l'adhésion cellulaire, métabolisme des acides grade et des kinases

Triple négatifs / basal-like

(5 à 8%)

HG;

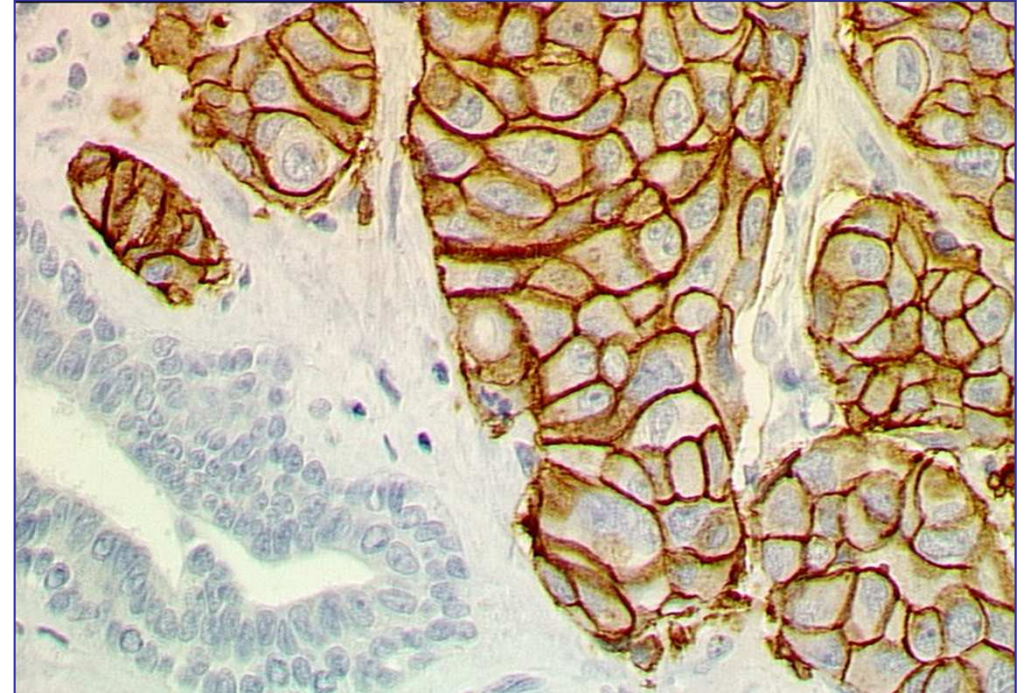
*TP53** 33%

Paradoxe de l'amplification de ERBB2

CCIS



Carcinome infiltrant



28 à 60% des CCIS

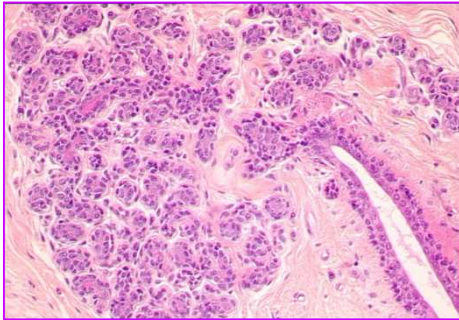
>>

15 à 20% des c. infiltrants

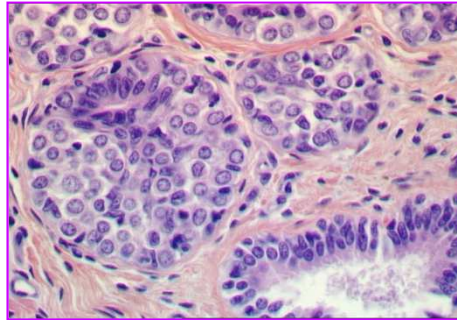
ERRB2 est associé à un pronostic défavorable dans les c infiltrants et
Pourquoi est il amplifié si fréquemment dans les CCIS ?

Lésions lobulaire in situ

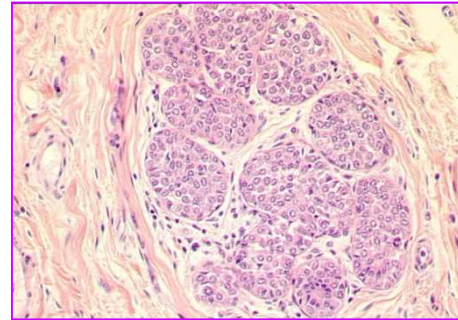
Normal



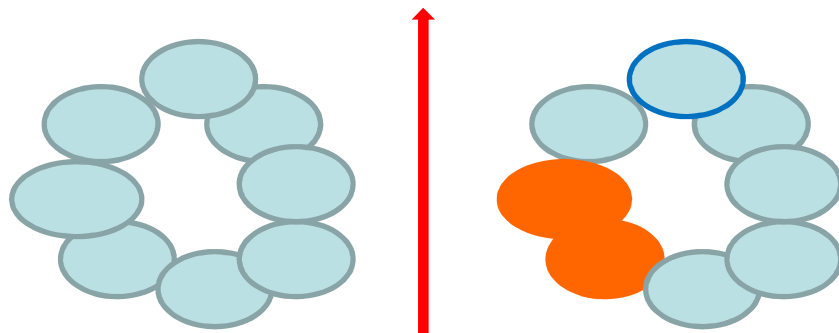
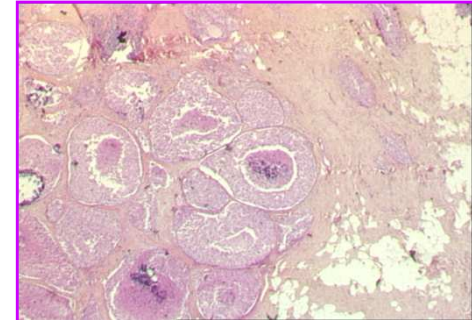
Hyperplasie Lobulaire atypique



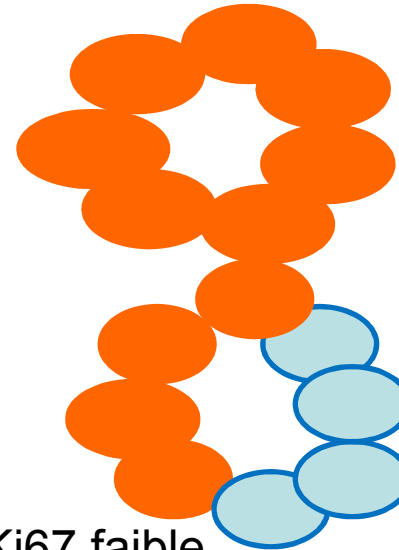
Carcinome lobulaire In situ classique



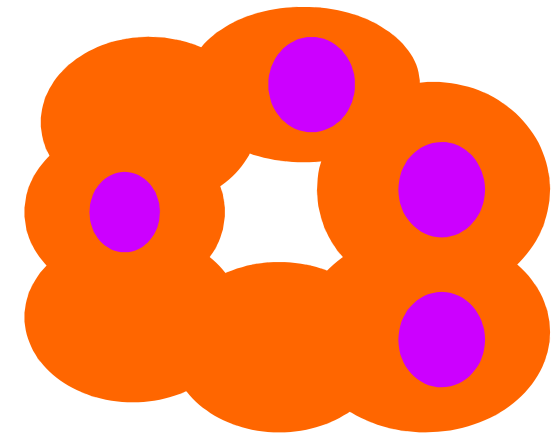
Carcinome lobulaire Pléomorphe in situ



Mutation E-cadhérine

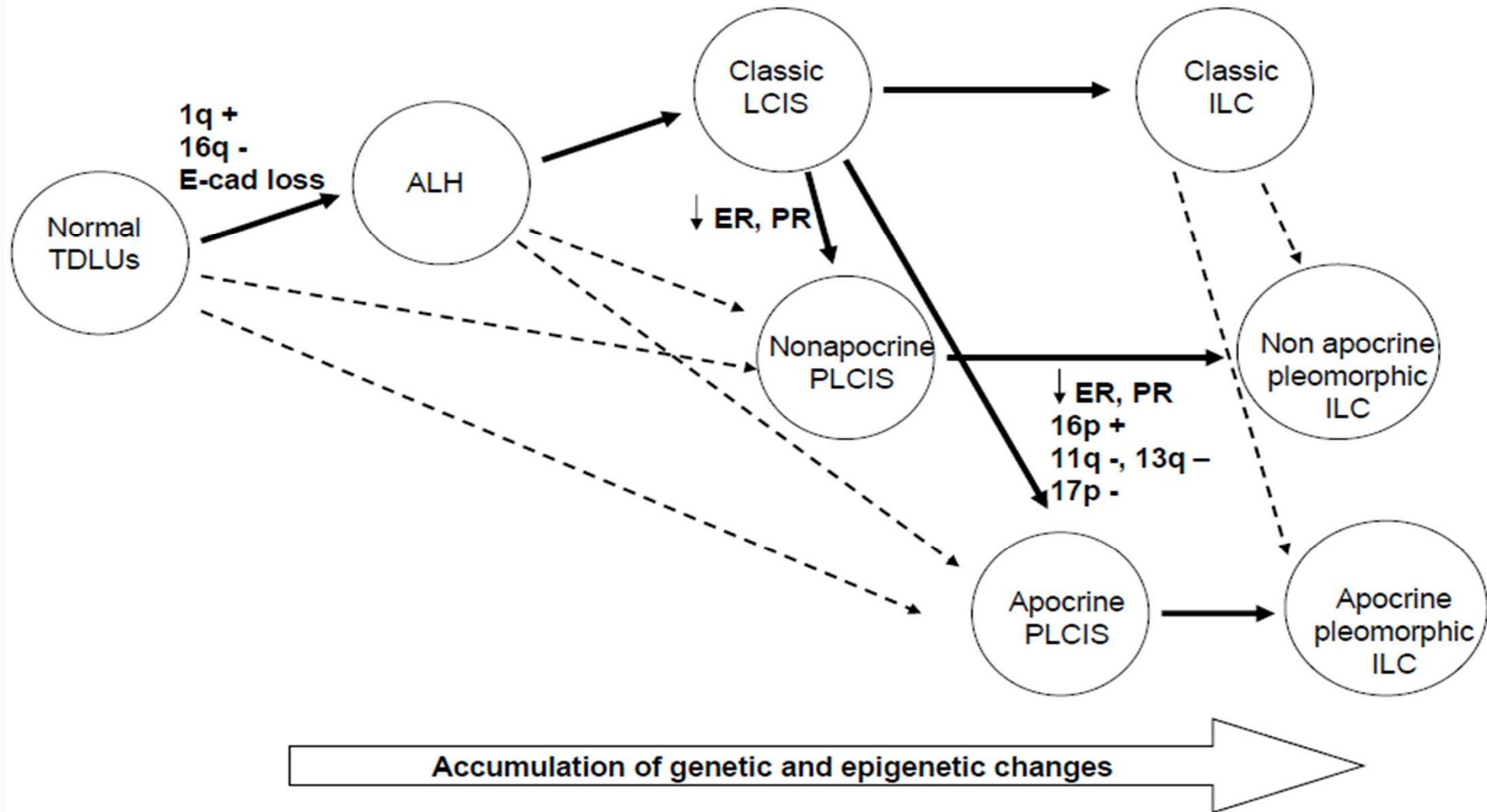


Ki67 faible,
RO +,
HER2-
E-cadhérine



Ki67 plus élevé
RO -/+
HER2-/+
E-cadhérine -

Histoire naturelle des lésions lobulaires



Facteurs biologiques pour prédire la progression des lésions pré-cancéreuses (canalaires et lobulaires)

BJC FULL PAPER
British Journal of Cancer (2013) 108, 1593–1601 | doi: 10.1038/bjc.2013.147

Keywords: ductal intraepithelial neoplasia; DCIS; Ki-67; prognosis; radiotherapy; low-dose tamoxifen

Tailoring treatment for ductal intraepithelial neoplasia of the breast according to Ki-67 and molecular phenotype

M Lazzeroni^{1,8}, A Guerrieri-Gonzaga^{1,8}, E Botteri², M C Leonardi³, N Rotmensz², D Serrano¹, C Varricchio¹, D Disalvatore², A Del Castillo⁴, F Bassi⁴, G Pagani⁴, A DeCensi^{1,5}, G Viale^{6,7}, B Bonanni¹ and G Pruner^{6,7}

DOI:10.1093/jnci/djt067
Advance Access publication May 2, 2013

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A Multigene Expression Assay to Predict Local Recurrence Risk for Ductal Carcinoma In Situ of the Breast

Lawrence J. Solin, Robert Gray, Andrew J. Baehner, Steven M. Butler, Lorie L. Hughes, Carl Yoshizawa, Diana B. Cherbavaz, Steven Shak, David L. Page, Robert W. Sliemers Jr, Nancy E. Davidson, James N. Ingle, Edith A. Perez, William C. Wood, Joseph A. Sparano, Scott Hunsberger

Cancer Cell
Article

Abrogated Response to Cellular Stress Identifies DCIS Associated with Subsequent Tumor Events and Defines Basal-like Breast Tumors

Mona L. Gauthier,^{1,6,7} Hal K. Berman,^{1,6,7,8} Caroline Miller,¹ Krystyna Kozakeiwicz,¹ Karen Chew,² Dan Moore,^{3,4} Joseph Rabban,¹ Yunn Yi Chen,¹ Karla Kerlikowske,^{3,5} and Thea D. Tlsty^{1,2,*}

Gènes de prolifération & Ki67

Biomarker Expression and Risk of Subsequent Tumors After Initial Ductal Carcinoma In Situ Diagnosis

Karla Kerlikowske, Annette M. Molinaro, Mona L. Gauthier, Hal K. Berman, Fred Waldman, James Bennington, Henry Sanchez, Cynthia Jimenez, Kim Stewart, Karen Chew, Britt-Marie Ljung, Thea D. Tlsty

JNCI 2010

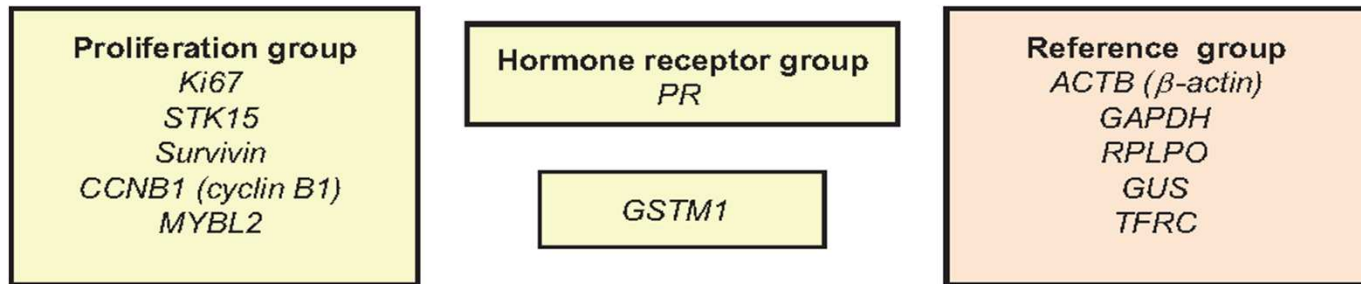
1162 patientes
CCIS traités par chir conservative seule
Entre 1983 et 1994

324 rechutes (Infiltrantes ou in situ)
Revue centralisée des CCIS
avec analyse IHC

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) from final multivariable models of clinical and histopathologic characteristics and molecular markers independently associated with subsequent tumor events*

Variable	Récidive inf HR (95% CI)
Age at diagnosis, y	1.0 (0.8 to 1.3)
Detection by palpation (vs mammography)†	2.7 (1.4 to 5.5)
Nuclear grade	
High vs low	1.0 (0.4 to 2.3)
Intermediate vs low	1.9 (0.8 to 4.3)
p16/COX-2/Ki67	
Positive/positive/positive	2.2 (1.1 to 4.5)
All other groupings	1.0 (referent)
Variable†	Récidive IS HR (95% CI)
Age at diagnosis, y	0.9 (0.7 to 1.1)
Margins ordinal (per category increase)‡	1.3 (1.1 to 1.7)
Nuclear grade	
High vs low	1.7 (0.6 to 4.8)
Intermediate vs low	1.3 (0.4 to 4.1)
p16/COX-2/Ki67	
Positive/negative/positive	3.7 (1.7 to 7.9)
All other groupings	1.0 (referent)
ER/ERBB2/Ki67	
Negative/positive/positive	5.8 (2.4 to 14)
All other groupings	1.0 (referent)

Oncotype DCIS®



327 patientes Essai ECOG E5194, chirurgie sans radiothérapie
 RO+ (97%), HER2 – (86%) et avec berges à > de 3mm (> 96%)

46 rechutes : 20 infiltrantes et 26 in situ

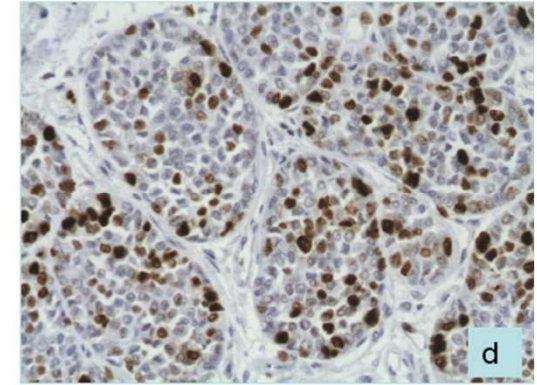
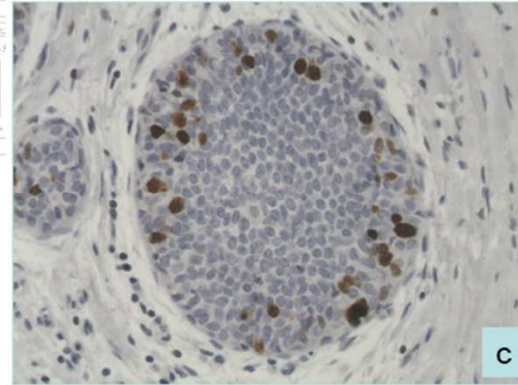
Table 4. Multivariable Cox proportional hazards models for the risk of an ipsilateral breast event

Analyses and variables	Hazard ratio (95% CI)*	P†
Multivariable analysis of significant clinical and pathologic factors, excluding the DCIS Score		
Menopausal status		.02
Premenopausal	1.00 (referent)	
Postmenopausal	0.49 (0.27 to 0.90)	
Tumor size‡	1.54 (1.14 to 2.02)	.006
Multivariable analysis of significant clinical and pathologic factors, including the DCIS Score		
Menopausal status		.02
Premenopausal	1.00 (referent)	
Postmenopausal	0.49 (0.27 to 0.90)	
Tumor size‡	1.52 (1.11 to 2.01)	.01
DCIS Score‡	2.37 (1.14 to 4.76)	.02

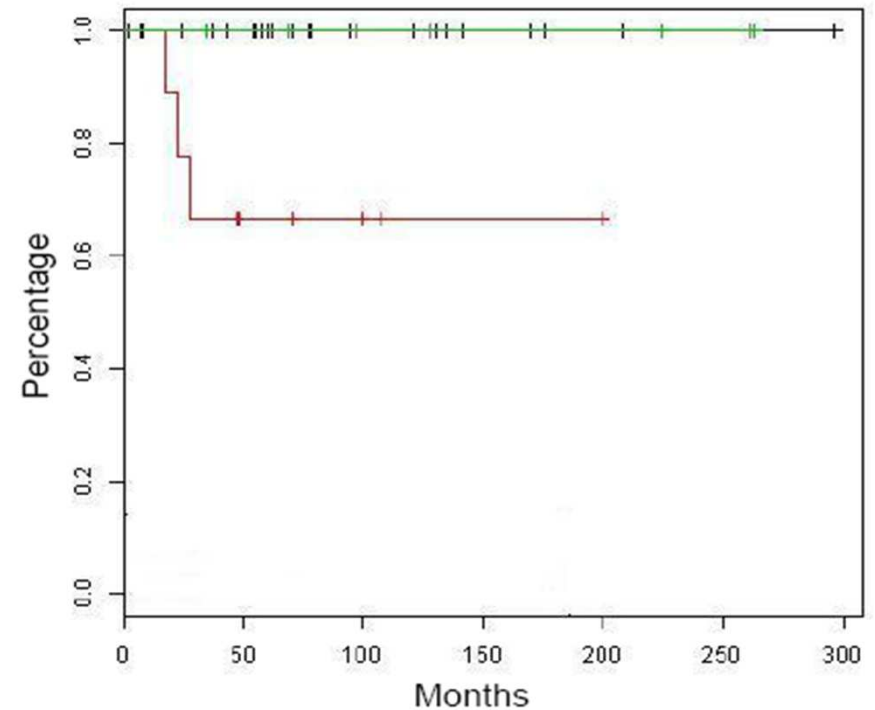
Original article

High Ki67 expression is a risk marker of invasive relapse for classical lobular carcinoma *in situ* patients

Anne Vincent-Salomon^{a, b, *}, David Hajage^c, Alexandre Rouquette^a, Aurélie Cédenot^a, Nadège Gruel^b, Séverine Alran^d, Xavier Sastre-Garau^a, Brigitte Sigal-Zafrani^a, Alain Fourquet^e, Youlia Kirova^e



- 47 patientes,
- Age moyen 51.3 ans
- CLIS classique (97%)
- E-cadhérine négative (71%) ou faible (29%)
- 34 cas RO + et Ki67 $\leq 10\%$ (79%),
- 9 cas RO + et Ki67 $> 10\%$ (21%),
- 1 cas RO – RP – et EGFR +
- A 5 ans:
- Rechutes:
 - 1/34 RO+ et Ki67 bas
 - 3 / 9 RO+ et Ki67 élevé
 - 2 IDC; 1 ILC ($p = 0.0054$).





Progression tumorale : Rôle des anomalies biologiques

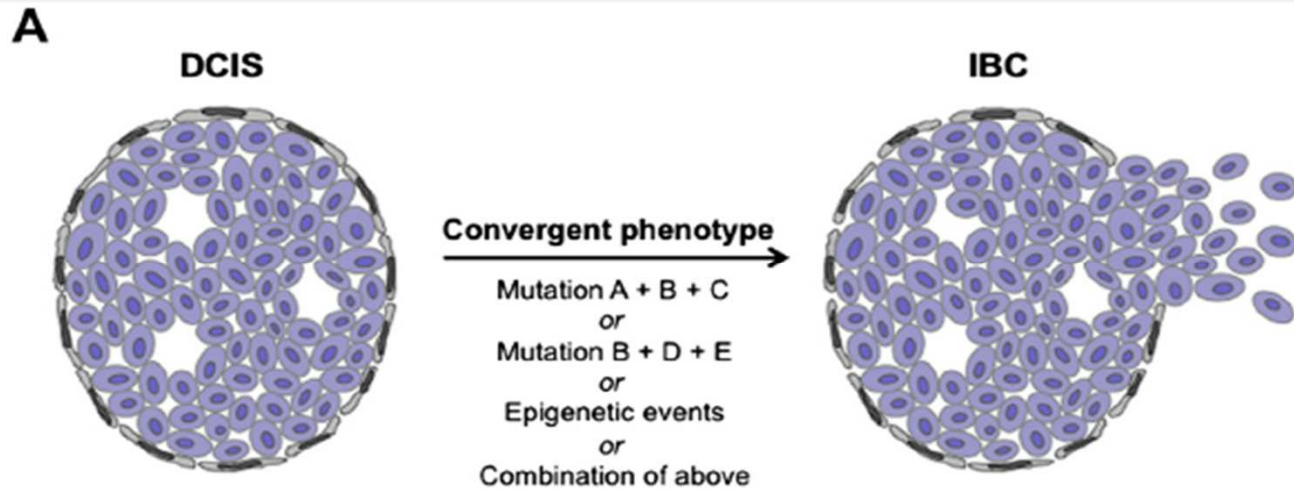
des cellules tumorales

- Perte de PTEN et Rb
- Prolifération (gènes de prolifération et Ki67)
- Sécrétion de métalloprotéinases (MT1-MMP9 ...)
- Cellules souches (ALDH1, CD44+/CD24- ...)

du stroma tumoral (fibroblastes)
dans la progression tumorale?

des cellules myoépithéliales?
CXCL12/ CXCL14
Col1A1, Col3A1...

Marqueurs constitutionnels de la patiente ?



Hétérogénéité moléculaire intra-tumorale des CCIS
1 altération “driver”?

