Management of High Risk Lesions

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April 26, 2015

DISCLOSURE

- Support for research from GE Healthcare for GERRAF award

OBJECTIVES

- Describe high risk breast lesions.
- Discuss the management of high risk breast lesions.

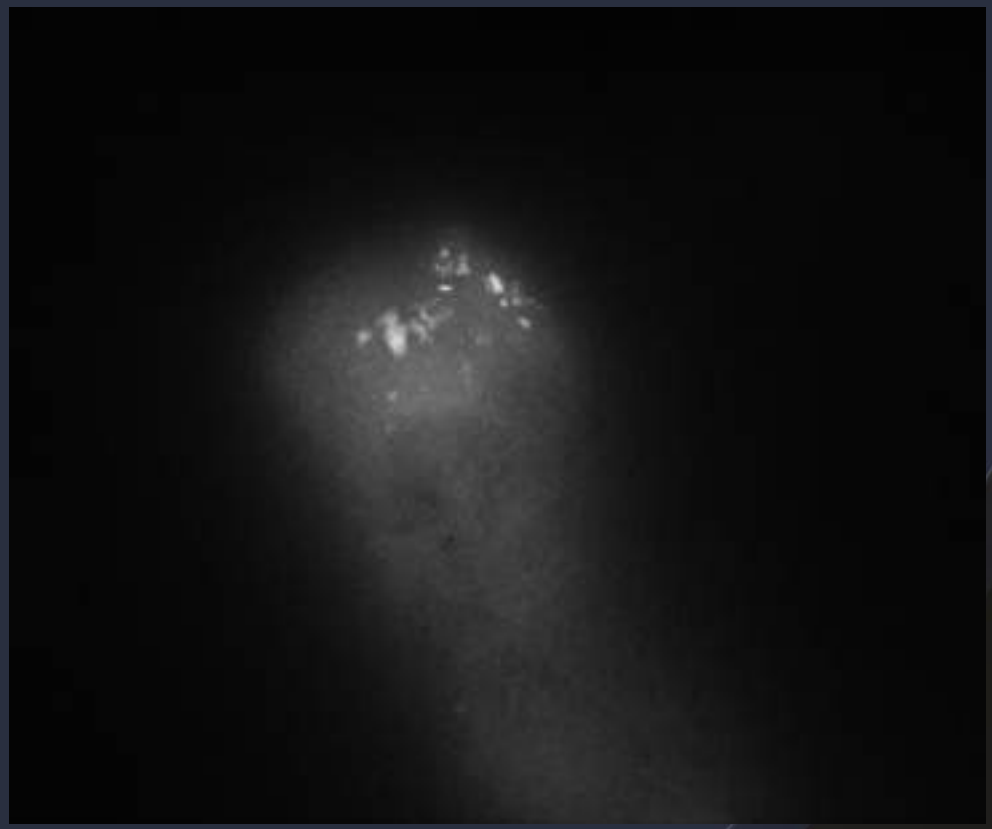
HIGH RISK BREAST LESIONS

- Lesions that increase a woman's risk to develop breast cancer in her lifetime

- Lesions sampled by percutaneous biopsy that have an increased rate of cancer with excisional biopsy

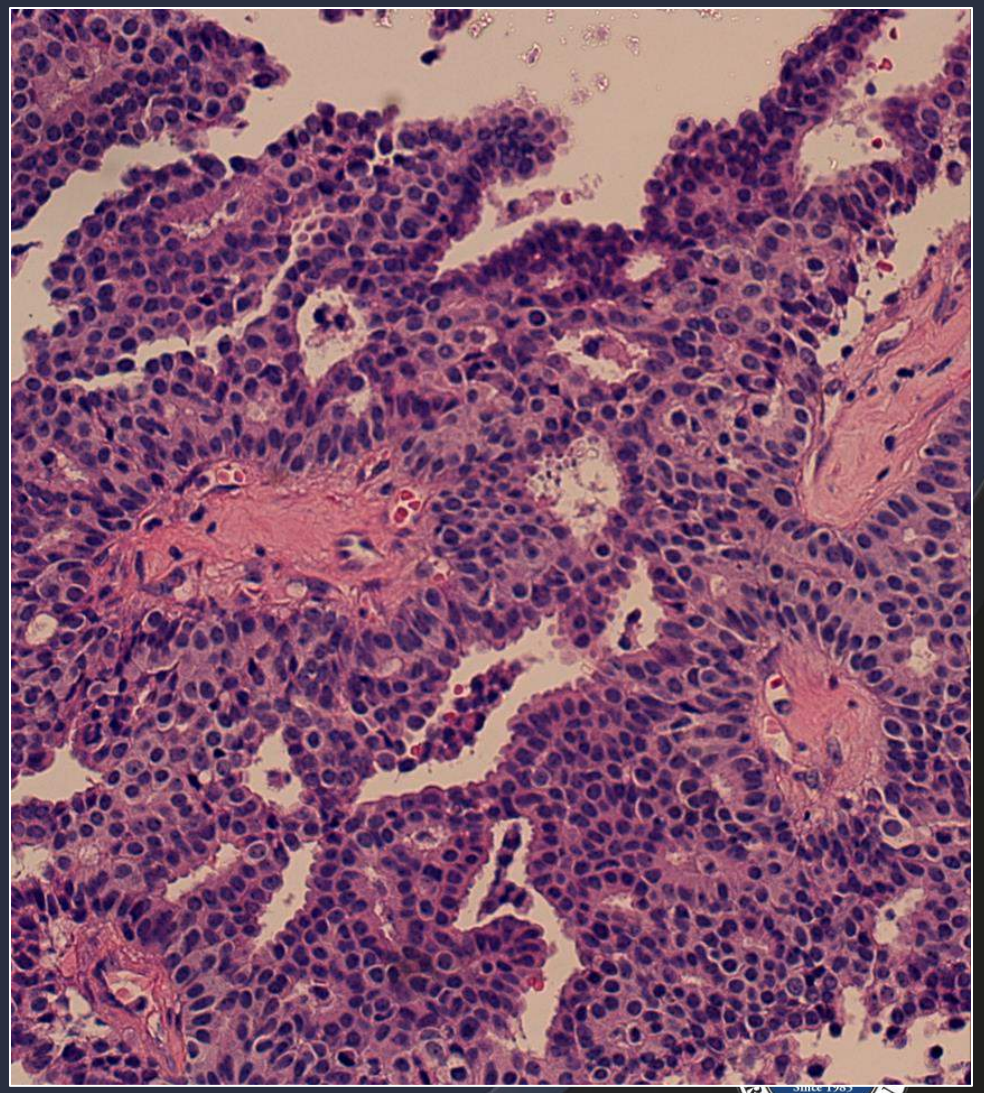
HIGH RISK BREAST LESIONS

- Optimize sample
  - Biopsy device
  - Number of cores
  - Assess technique
- Optimize pathology results
  - Specimen radiographs
    - Separate cores
    - Send imaging
    - Give pointers



HIGH RISK BREAST LESIONS

- Correlate imaging with pathology
- Critique lesion sampling
- Correlate with clinical history
- Refer for risk assessment as appropriate



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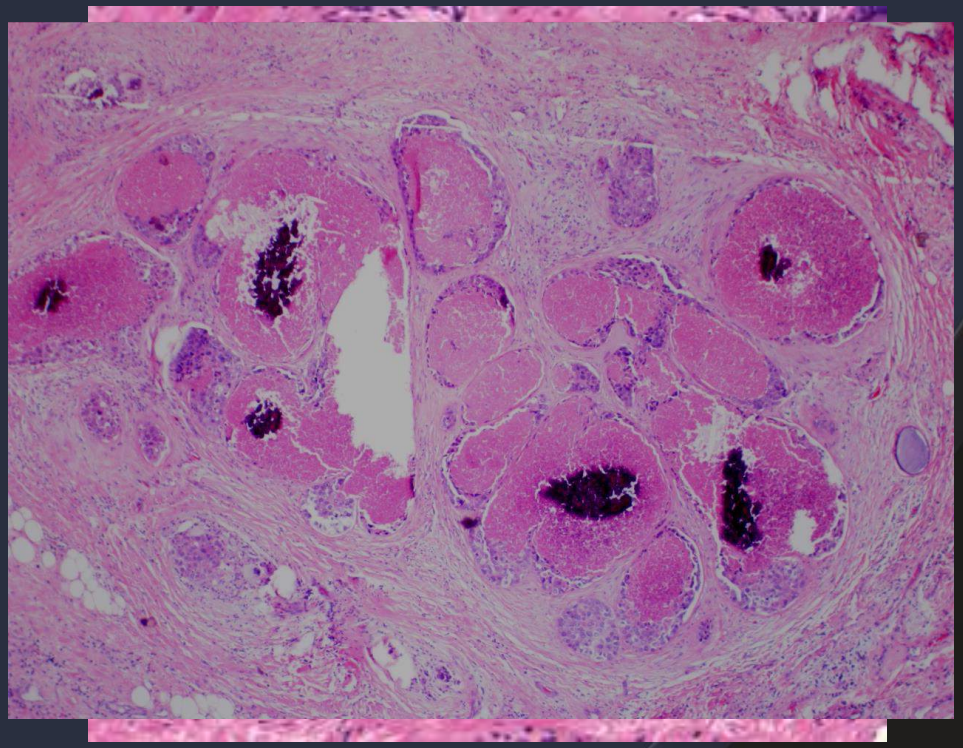


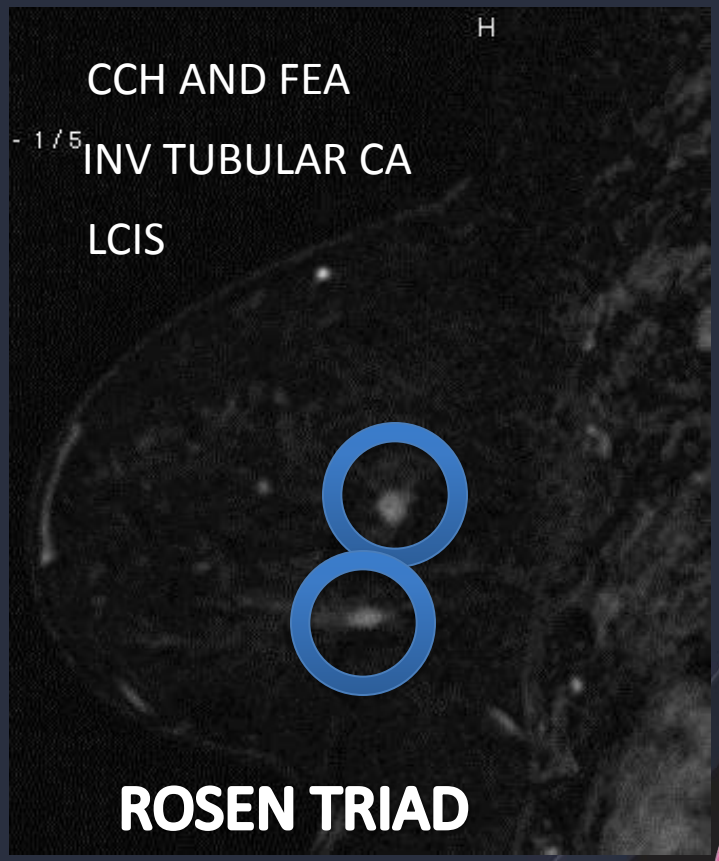
HIGH RISK BREAST LESIONS

- Correlate imaging with pathology
- Critique lesion sampling
- Correlate with clinical history
- Refer for risk assessment as appropriate

- Palpable mass
- Spontaneous, single duct bloody nipple discharge
- Family history

HIGH RISK BREAST LESIONS

- Correlate imaging with pathology
- Critique lesion sampling
- Correlate with clinical history
- Refer for risk assessment as appropriate

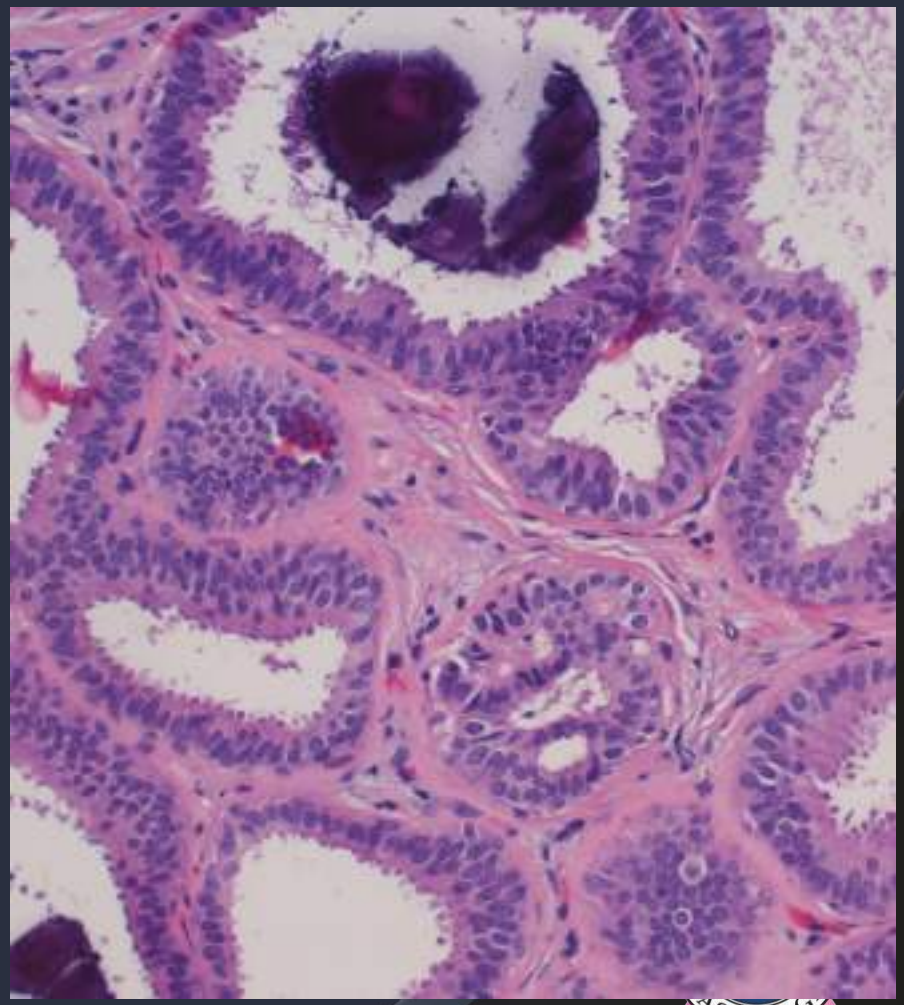


HIGH RISK BREAST LESIONS

- Lesions with Atypia
- Lobular Neoplasia
- Papillary Lesions
- Radial Scar/ Complex Sclerosing Lesions

FLAT EPITHELIAL ATYPIA

- Flat epithelial atypia (FEA)
  - Established in 2003 WHO
  - Suspicious calcifications
  - Nonmass enhancement
  - Columnar and cuboidal epithelial cells with low grade cellular atypia
  - Rare 3.8 to 10% bxs



Original Article

Flat Epithelial Atypia and Risk of Breast Cancer: A Mayo Cohort Study

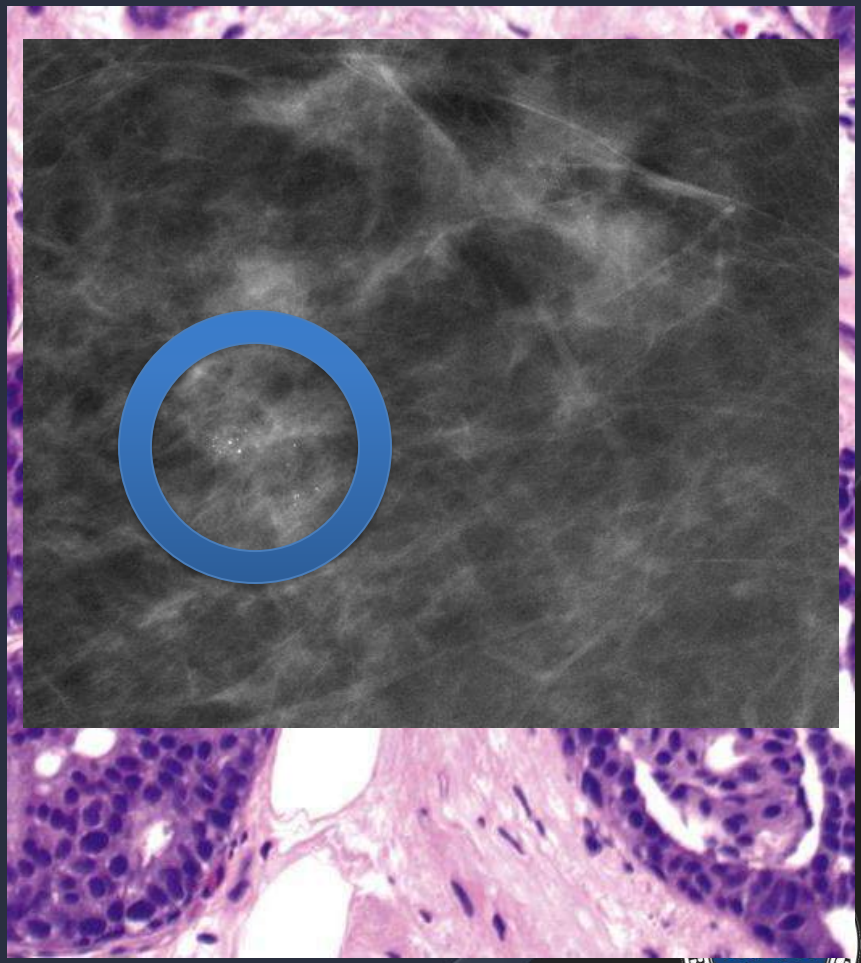
Samar M. Said, MD[1]; Daniel W. Visscher, MD[1]; Aziza Nassar, MD[2]; Ryan D. Frank, BA[3]; Robert A. Vierkant, MS[3]; Marlene H. Frost, PhD[4]; Karthik Ghosh, MD[5]; Derek C. Radisky, PhD[6]; Lynn C. Hartmann, MD[4]; and Amy C. Degnim, MD[7]

- 11, 591 women benign bxs 1967-2001
- Blinded review of pathology
- 282 FEA (46% AH) (54% PDWA)
- Median follow-up 16.8 yrs
- Standardized Incidence Ratios (SIRs)
  - AH with FEA 4.74 (95% CI, 3.17-8.81)
  - AH w/o FEA 4.23 (95% CI, 3.44-5.13)
  - PDWA with FEA 2.04 (95% CI, 1.23-3.19)
  - PDWA w/o FEA 1.90 (95% CI, 1.72-2.09)

Study	Core biopsies	Excisions	Upgrade Rate
Chivukula, 2009	39	35	14%
Guerra-Wallace, 2004	39	31	13%
Lavoue, 2011	60	60	13%
Khoumais, 2013	104	94	11%
Bianchi, 2012	190	190	10%
Peres, 2012	128	95	10%
Sohn, 2011	36	24	8%
Calhoun, 2014	94	73	7%
Noske, 2010	43	30	7%
Biggar, 2012	51	51	6%
Villa, 2013	142	121	6%
Ceugnart, 2013	63	52	4%
Uzoaru, 2012	145	95	3%
Senetta, 2009	41	36	0%
TOTAL	**1175**	**987**	**8%**

ATYPICAL DUCTAL HYPERPLASIA

- ADH
  - Page 1985
  - Localized intraductal proliferative lesion
  - Less than 2mm or 2 ductal spaces
  - Suspicious calcifications
  - Nonmass enhancement

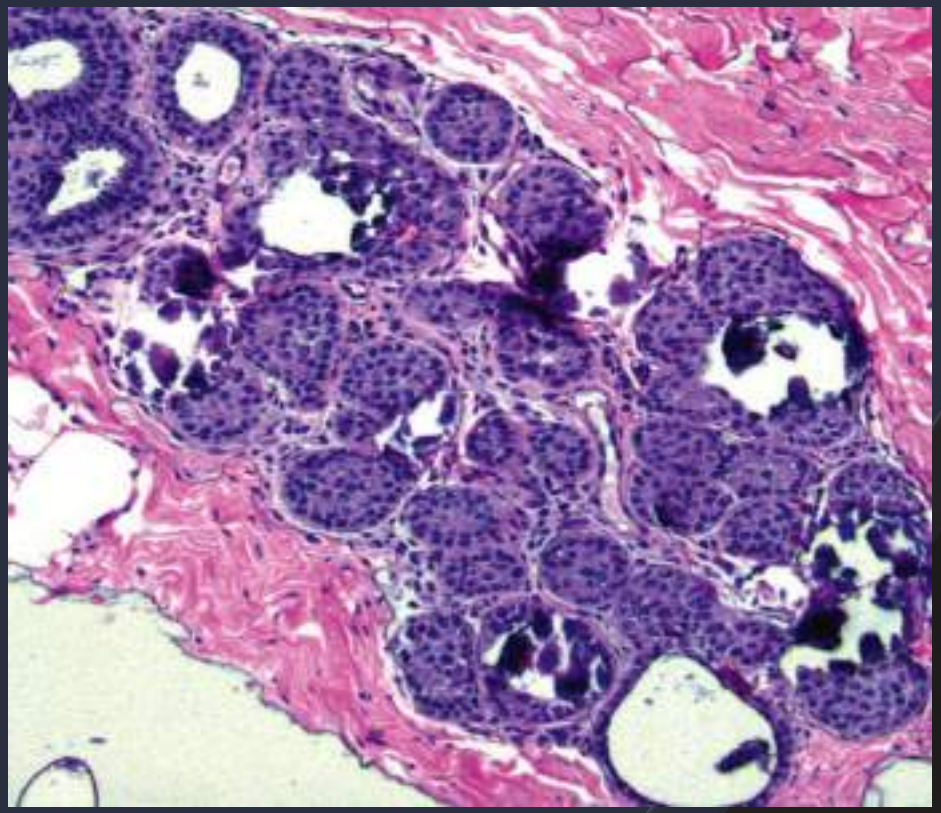


Dupont and Page. *N. Engl. J. Med.* 1985;312:146-151.

Lakhani, S., Ellis, I. O., Schnitt, S. J., Tan, P. H. & van de Vijver, M. J. (eds) *WHO Classification of Tumours of the Breast* 4th edn 77–89 (IARC Press, 2012).

ATYPICAL LOBULAR HYPERPLASIA

- 1978
- Proliferative changes within the TDLUs of poorly cohesive, monotonous cuboidal or polygonal cells
- ALH: < 50% acini affected
- Loss of E-cadherin



RELATIVE RISK ASSOCIATED WITH ATYPIA

Study	Patients	Median F/U	Outcome	ADH RR	ALH RR
Page, 1985	377	17 yrs	Invasive carcinoma	4.7 (2.5-8.9)	5.9 (3.0-11.0)
Page, 2003	252		Invasive carcinoma		3.1 (2.3-4.3)
Collins, 2007	395	9.1 yrs	Invasive carcinoma or DCIS	3.1 (2.0-4.8)	5.5 (3.3-9.2)
Degnim, 2007	331	13.7	Invasive carcinoma or DCIS	3.8 (2.5-5.6)	3.7 (2.5-54.3)

RISK ASSOCIATED WITH ATYPIA

- Mayo Benign Breast Disease Cohort
  - 698 ADH or ALH
  - Median follow-up 12.5 yrs
  - 143 cancers
  - 2:1 ipsilateral
  - Predominance of IDC with 69% moderate or high grade

Hartmann, L. C. *et al.* Understanding the premalignant potential of atypical hyperplasia through its natural history: a longitudinal cohort study. *Cancer Prev. Res. (Phila.)* 7, 211–217 (2014).

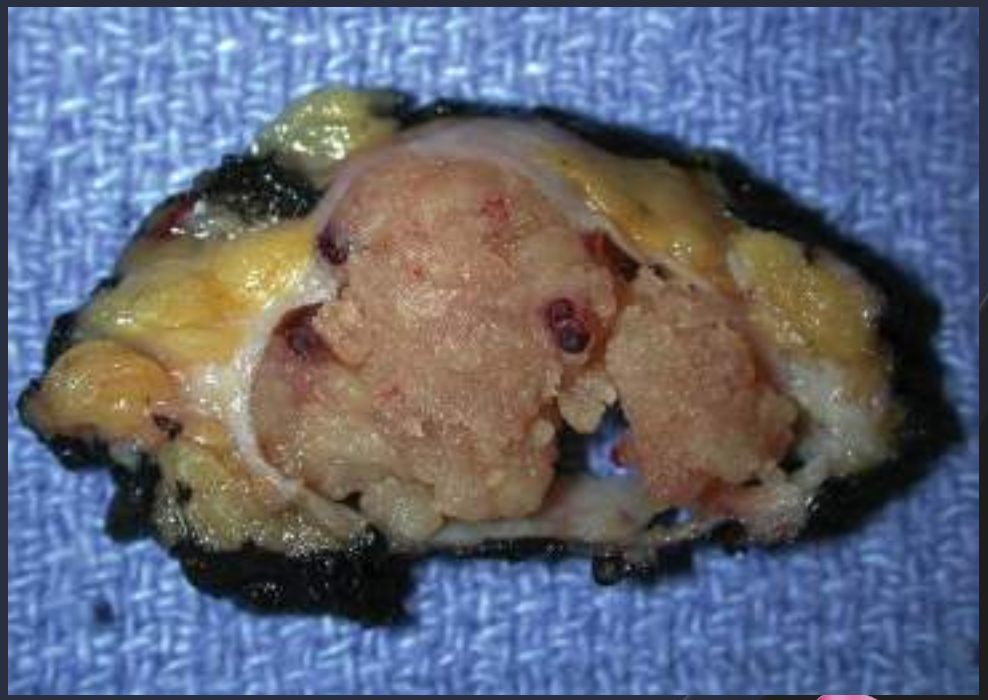
ADH UPGRADE

- Higher upgrade
  - Smaller needle
  - Linear, branching calcs
  - Micropapillary pattern
  - Increasing foci of ADH

Upgrade	N	Study
12%	9/78	Sohn, 2007
13%	5/40	Burak, 2000
17%	11/65	Winchester, 2003
21%	22/104	Jackman, 2002
31%	132/422	Deshaies, 2011

ATYPICAL PAPILLARY LESIONS

- Foci that meet the criteria for ADH or DCIS within a papilloma
  - Greater than 3mm then DCIS
  - Greater than 90% then DCIS



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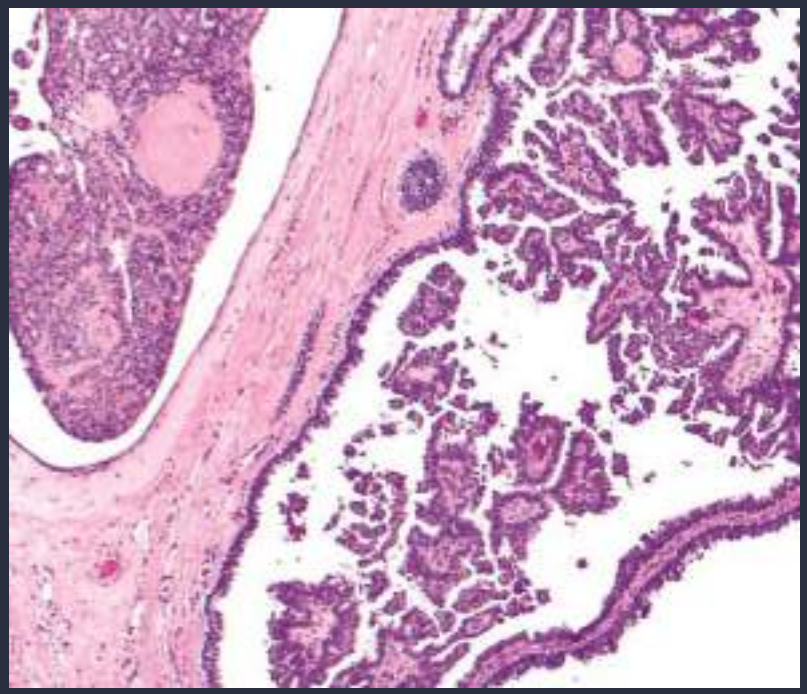
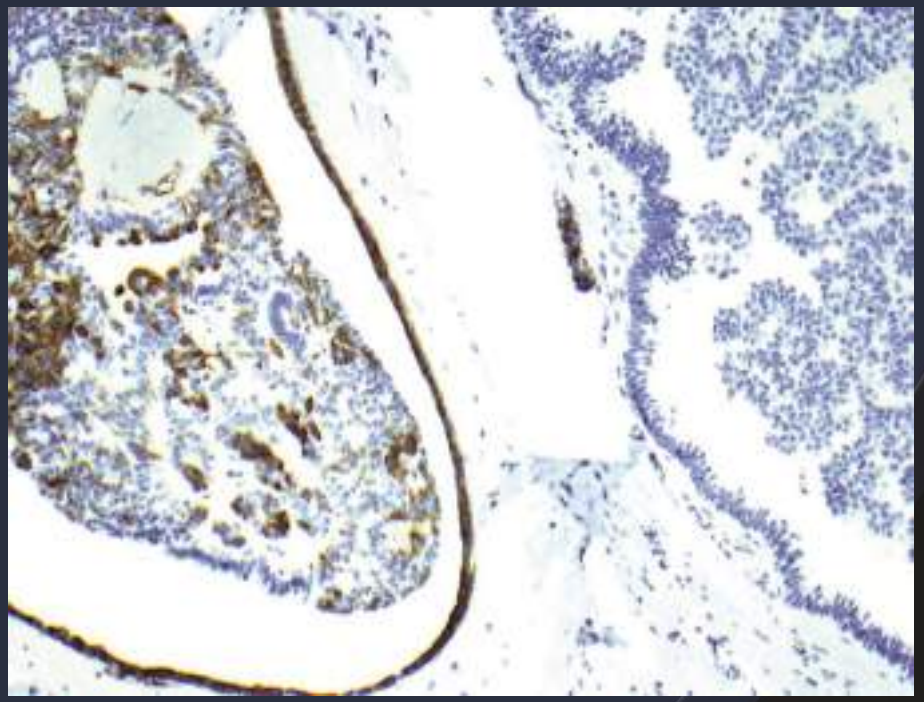
PAPILLARY LESIONS



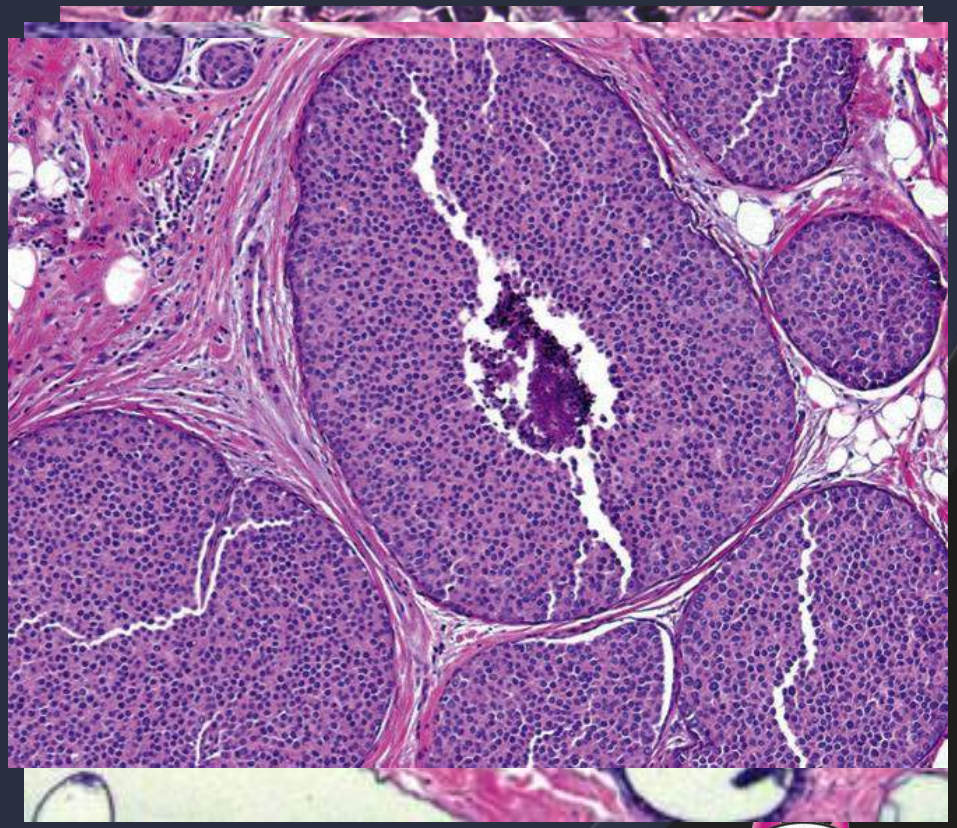


LOBULAR NEOPLASIA

- Atypical Lobular Hyperplasia (ALH)
- Lobular Carcinoma in Situ (LCIS)
- Pleomorphic Lobular Carcinoma in Situ

LOBULAR NEOPLASIA

- 0.5 to 3.8% benign bx
- ALH, LCIS, PLCIS
- ALH and LCIS
  - Loss of E-cadherin expression (CDH1)
  - Strong ER
  - Low proliferation



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LCIS AND RISK

Study	Follow-up	Patients	Developed invasive cancer	RR
Haagensen, 1978	16.3 yrs	287	18%	6.9
Rosen, 1978	24.0 yrs	99	34.5%	9.0
Salvadori, 1991	5.0 yrs	80	6.3%	10.3
Otteson, 1993	5.0 yrs	69	11.6%	11.0
Chuba, 2005	10.0 yrs	4853	7.1%	
Choopey, 2012	10.0 yrs	296	23.7%	

LOBULAR NEOPLASIA

ALH

Upgrade	N	Study
0	0/56	Subhawong, 2010
1	1/81	Shah-Khan, 2012
3	1/40	Renshaw, 2006
8	5/63	Karabakhtsian, 2007
22	21/97	Brem, 2008

LCIS

Upgrade	N	Study
3	2/72	Murray, 2012
4	3/68	Rendi, 2012
4	2/52	Renshaw, 2006
25	17/67	Brem, 2008

MANAGEMENT OF RISK: ATYPIA AND LOBULAR NEOPLASIA

- Risk Assessment
- Active surveillance
- Chemoprevention
- Bilateral prophylactic mastectomy
  - 5% LCIS cohort MSKCC

ACTIVE SURVEILLANCE

- Screening mammography
  - Sensitivity similar in high risk group
  - Specificity lower in high risk group
- MRI screening
  - Based on risk assessment
- Clinical breast exam q 6 to 12 months
- Modification of lifestyle factors ?

Houssami, N. *et al.* Accuracy of screening mammography in women with a history of lobular carcinoma *in situ* or atypical hyperplasia of the breast. *Breast Cancer Res. Treat.* 145, 765–773 (2014).

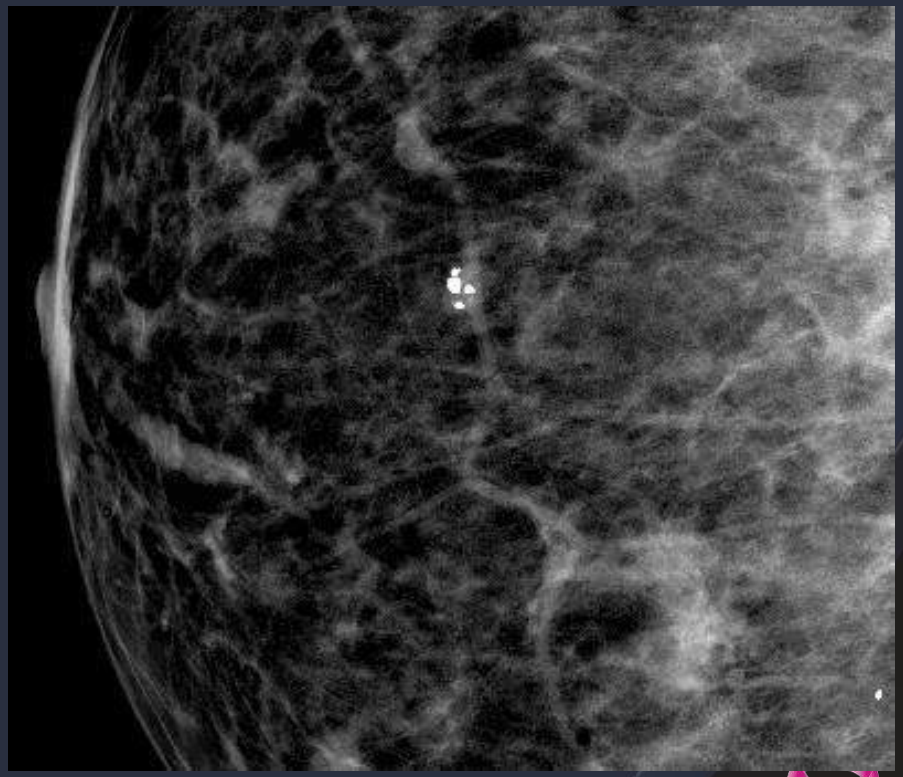
CHEMOPREVENTION

- NSABP Breast Cancer Prevention P1 trial
  - Tamoxifen treatment in high risk women decreased risk of developing invasive cancer
- NSABP STAR (P-2) trial
  - Raloxifene was as effective as Tamoxifen in reducing risk in post menopausal high risk women
- Women with LCIS
  - NSABP P-1 6.2%
  - STAR 9.2%

Fisher B et al. J Natl Cancer Inst 1998;90(18):1371-88.
Vogel VG et al. JAMA 2006; 295(23):2727-41

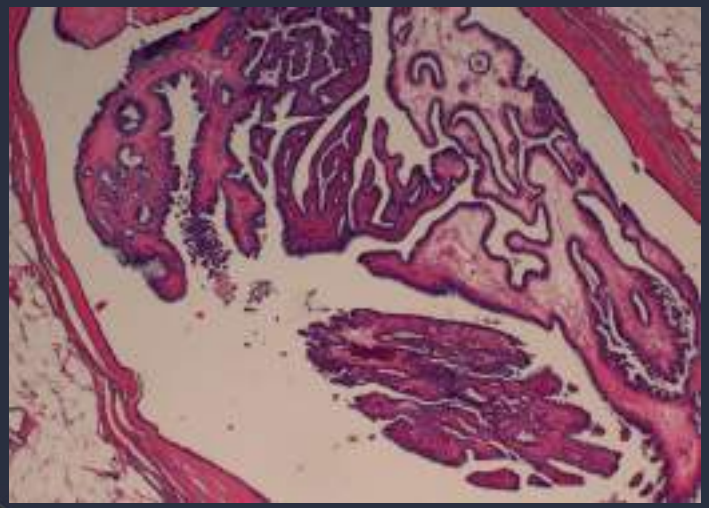
PAPILLARY LESIONS

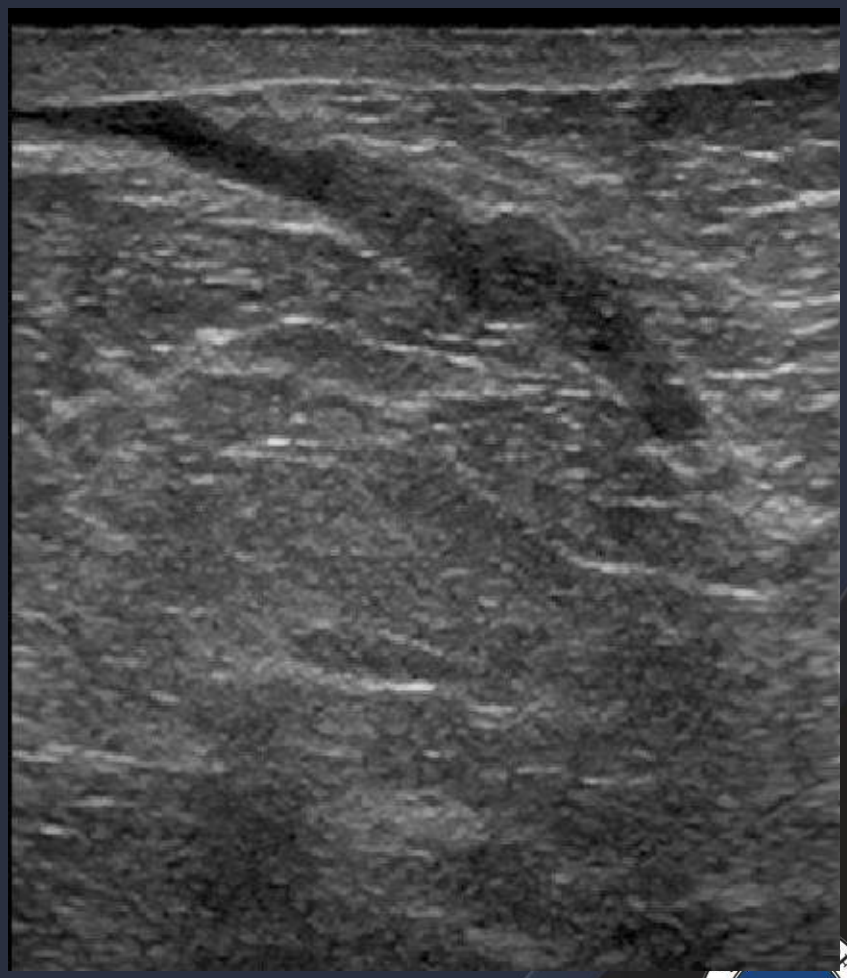
- Heterogeneous group of breast lesions
- Relatively uncommon
  - Less than 10% of benign
  - Invasive papillary ca 0.5 to 2% of all breast malignancies
  - Up to 5% of all breast lesions undergoing biopsy



BENIGN PAPILLOMA

- Benign Papillary Lesions
  - Central or peripheral papillomas
  - Multiple papillomas





Meta-analysis of non-malignant papillary lesions

- Meta-analysis of 34 studies
- Upgrade rate 15.7%
- Assoc factors with upgrade
  - Atypical papillary lesions
  - Positive mammographic findings
  - Article publication year prior to 2005

Wen X, Cheng W. Ann Surg Oncol 2013; 20(1):94-101.

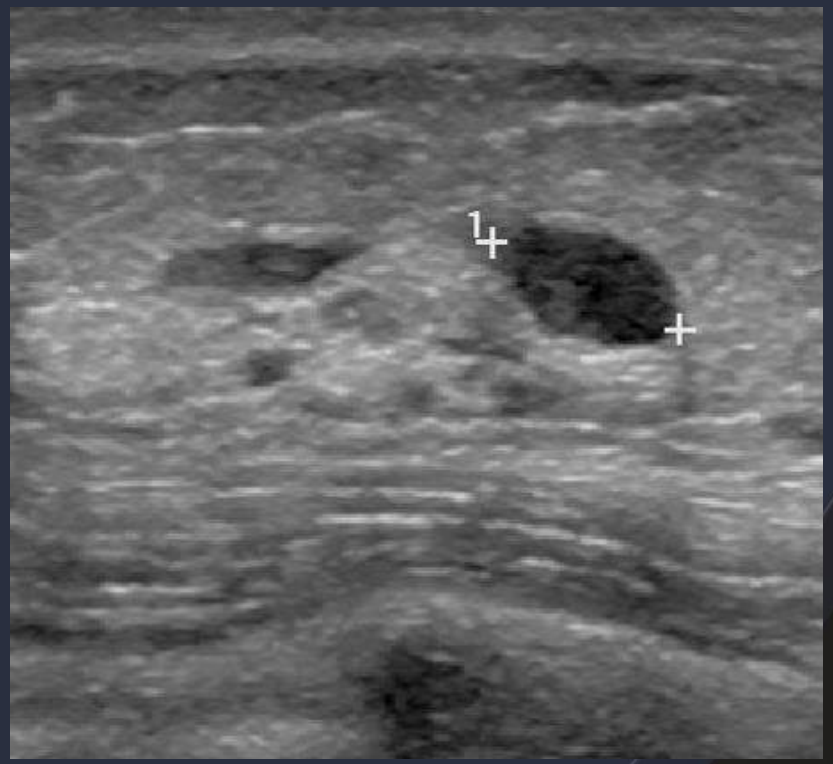
Papillary Lesion Upgrade Rate

Upgrade	N	Study
10%	13/125	Rizzo, 2008
17%	15/87	Gendler, 2004
24%	19/80	Vaides, 2006
37%	14/38	Renshaw, 2004

Benign papillomas at core biopsy upgrade rate ranges from 0- 29%.

BENIGN PAPILLOMA

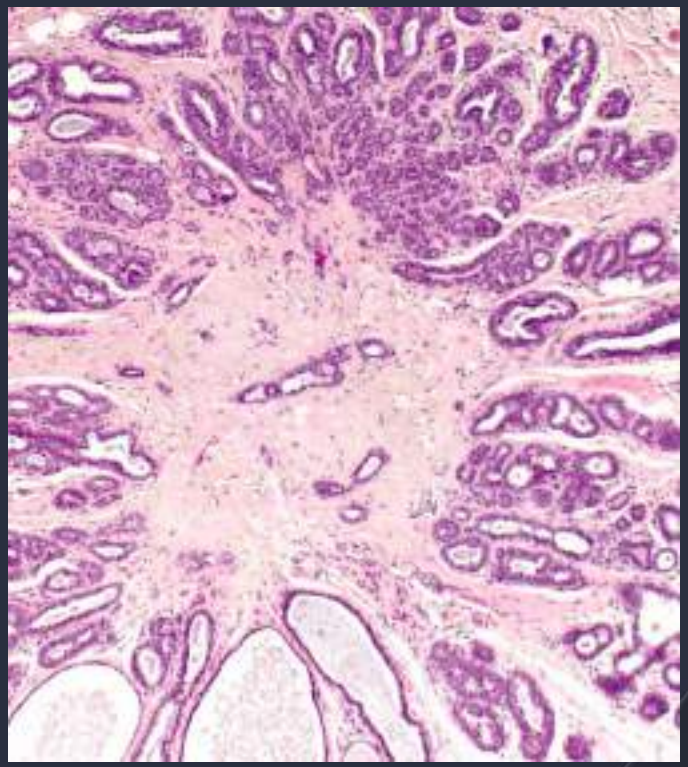
- Benign Papilloma US guided 14 G core needle bx
- 160 cases with Sx
- 5% (8/160) upgrade
- Assoc with malig
  - Age
  - Lesion size (mean 19mm)
  - Distance from nipple
  - Discordance
  - Multiplicity



Youk JH et al. 2011 Radiology 258:81-88.

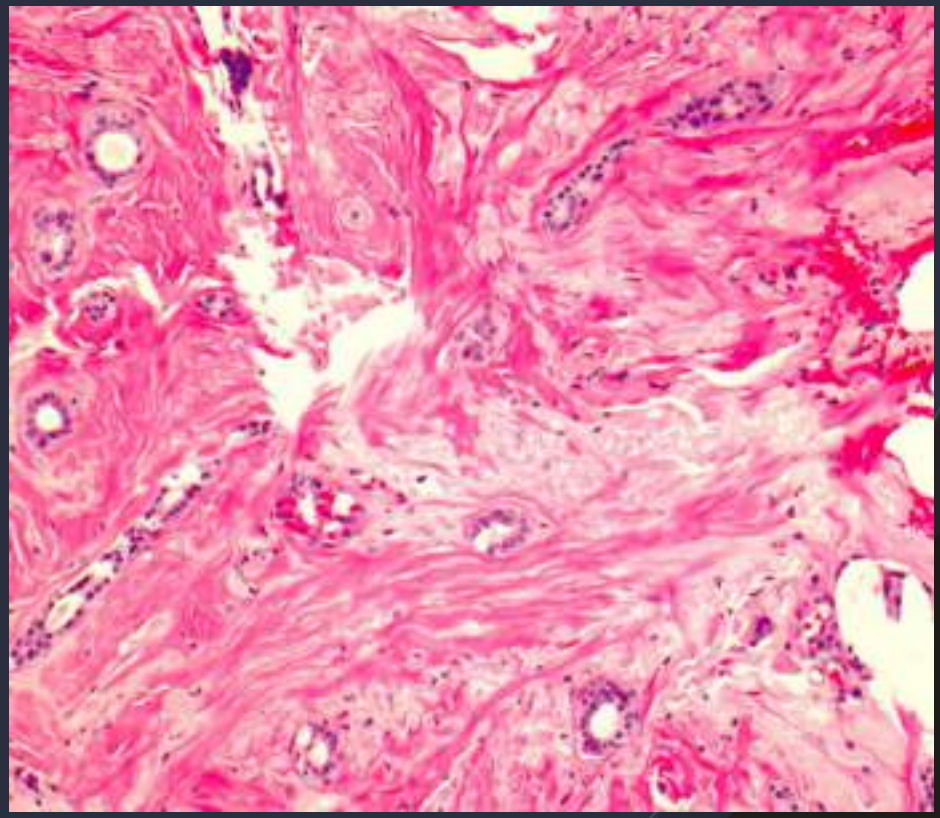
RADIAL SCAR /COMPLEX SCLEROSING LESIONS

- Radial scar < 1 cm
- Complex sclerosing Lesion > 1cm
- Benign lesion with stellate architecture, prominent fibroelastosis and epithelial hyperplasia
- ~RR 2x
- Differential diagnosis IDC and tubular carcinoma
  - Lack myoepithelial cells (negative for CD10 and p63 staining)
- Rare rates of 0.03–0.09%



RADIAL SCAR/ COMPLEX SCLEROSING LESION

- Upgrade rate 0% to 34%
- Upgrade rate 0% to 12% without atypia



Incidental Papillomas or Radial Scars?

- Microscopic papillomas and radial scars at percutaneous biopsy
- 35 pts
- Incidental RS 18
- Incidental papilloma 17
- No cancer at surgical follow-up

Lee KA et al. AJR 2012;198:W141-145.

Lesions found at percutaneous biopsy that have an increased rate of cancer with excisional biopsy.

Histology	Management
ADH	Surgical consultation with excision
Lobular neoplasia (ALH/LCIS/PLCIS)	Surgical consultation with excision
FEA	Surgical consultation with excision
Papillary lesions	Surgical consultation
Radial Scar/Complex Sclerosing Lesions	Surgical consultation
Mucocele-like Lesion	Surgical consultation with excision

DIAGNOSTIC CONCORDANCE AMONG PATHOLOGISTS

Diagnostic Concordance Among Pathologists Interpreting Breast Biopsy Specimens. Joann G. Elmore,MD, MPH; GaryM. Longton, MS; Patricia A. Carney, PhD; Berta M. Geller, EdD; Tracy Onega, PhD; Anna N. A. Tosteson, ScD;Heidi D. Nelson, MD, MPH; Margaret S. Pepe, PhD; Kimberly H. Allison, MD; Stuart J. Schnitt, MD; Frances P. O'Malley, MB; Donald L.Weaver,MD

- 3 consensus panel members unanimous agreement of independent diagnosis 75% and concordance with consensus-derived reference 90.3%.

Consensus Reference Diagnosis	Total, No.	Rate, % (Range)[b]		
		Rate of Overinterpretation or Underinterpretation vs Consensus Diagnosis		Overall Concordance Rate vs Consensus Diagnosis
		Overinterpretation	Underinterpretation	Concordance
Benign without atypia	72	9 (3-13)		91 (87-97)
Atypia	72	12 (7-17)	8 (1-15)	80 (75-87)
DCIS	73	1 (0-1)	2 (0-4)	97 (95-100)
Invasive carcinoma	23		3 (0-4)	97 (96-100)

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	Pathologist Interpretation vs Consensus-Derived Reference Diagnosis, % (95% CI)			
Consensus Reference Diagnosis	No. of Interpretations	Overall Concordance Rate	OverInterpretation Rate	UnderInterpretation Rate
Benign without atypia	2070	87 (85-89)	13 (11-15)	
Atypia	2070	48 (44-52)	17 (15-21)	35 (31-39)
DCIS	2097	84 (82-86)	3 (2-4)	13 (12-15)
Invasive carcinoma	663	96 (94-97)		4 (3-6)

		Participating Pathologists' Interpretation				
		Benign without atypia	Atypia	DCIS	Invasive carcinoma	Total
Consensus Reference Diagnosis[a]	Benign without atypia	1803	200	46	21	2070
	Atypia	719	990	353	8	2070
	DCIS	133	146	1764	54	2097
	Invasive carcinoma	3	0	23	637	663
	Total	2658	1336	2186	720	6900

High risk lesions that increase a woman's risk to develop breast cancer in her lifetime.

Histology	Relative Risk
FEA	~1.7-2.1 (min data)
Papillary lesions	~2
Radial scar/ complex sclerosing lesion	~2
ADH or ALH	~4
LCIS	~10

Summary

- High risk lesions require radiology pathology correlation to determine concordance and adequate tissue sampling.
- While the majority of high risk lesions may require excisional biopsy given retrospective data upgrade rates, close observation may be appropriate in certain selected cases, and prospective data is needed to better direct patient care.
- ADH, ALH and LCIS are likely non-obligate precursors and increase the patient's risk for the development of breast cancer. Risk assessment and management plans should be discussed.
- Research focused on imaging and molecular biomarkers is needed to advance precision medicine in breast care.

Thank you!

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